CHINESE ACADEMY of MEDICAL SCIENCES OXFORD INSTITUTE

NUFFIELD DEPARTMENT of MEDICINE

UNIVERSITY OF OXFORD

CSC-COI SCHOLARSHIP DPHIL PROJECT PROPOSALS

Enrolment Year: 2027

1 Program Available

- ☑ MSD Program: 1 Program

53 Projects Available

- ☑ Cancer Biology, Immunology & Immunotherapy: 12 Projects
- ☑ Cardiovascular: 6 Projects
- ☑ Genomic Medicine & Data Science: 9 Projects
- ☑ Infection Immunology & Disease: 7 Projects
- ☑ Inflammation & Autoimmune Disease: 4 Projects
- ☑ Neuroscience: 2 Projects
- ☑ Public Health and Population Health: 6 Projects
- ☑ Other Themes: 7 Projects

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PROGRAMME 1: MSD PROGRAMME

Genomic Medicine and Statistics DPhil Programme

Prof. Gavin Band *well-gms-administrators@well.ox.ac.uk*

PROGRAMME OVERVIEW

There is a unique opportunity for students to be trained in the rapidly growing area of genomic medicine, and the related areas of bioinformatics, big data science and statistics. Scholarship funding is available to support two students from China each year to join the highly prestigious DPhil programme in Genomic Medicine and Statistics at the University of Oxford.

Overview of The Programme

This is a four-year DPhil programme aiming to train future scientific leaders who will work at the cutting edge of genomics in biomedical research and the clinic. Students from a diverse range of academic backgrounds are encouraged to apply, from analytical sciences (including maths, physics, computer science) to wet lab biomedical sciences (including molecular biology, human genetics, biology, and medicine).

The course is part of the University of Oxford Medical Sciences Division Doctoral Training Centre and hosted by the Centre for Human Genetics.

The first year includes taught modules focused within the first term. First-year students then undertake short research projects in up to three laboratories in three-month rotations, with further training and teaching sessions tailored to the needs of individual students. The research projects and lab visits help inform the choice of DPhil project to be undertaken over the subsequent three years of the programme. The final three years of the course will comprise a doctoral research project under the supervision of two named supervisors and a doctoral committee. Students do not need to choose a research project in advance of applying to the course, this decision is made at the end of their first year after the rotations.

The programme is focused on genomic and -omic technologies, functional genomics, genome biology, genomics of disease, genomic analysis, drug discovery and application of genomics in the clinic. The names of principal investigators currently affiliated with the programme are shown here together with current research projects.

For further details see https://www.ox.ac.uk/admissions/graduate/courses/dphil-genomic-medicine-and-statistics

Student Candidates / Selection Criteria

Eligible students

Chinese students eligible for the program include those enrolled on an eight-year MD course (20 Scholarships) or undergraduates of non-medical courses (5 Scholarships) from 14 China's top Medical Universities. Scholars must demonstrate exceptional academic merit and/or potential prior to commencing a full-time DPhil course of study in any subject within the Medical Sciences Division of the University. Scholars shall meet the standard selection criteria of the University and the specific course requirements here.

Shortlist and Interview

CSC and COI will be responsible for sending out the advertisement and checking students against their own eligibility criteria for shortlisting. The University will shortlist and interview candidates of the Programme using the University's own entry requirements for this course. Successful candidates will have passed both the University and CSC application process.

Course Coordinators

Oxford: Professor Julian Knight

CSC: Xiaopeng Hu

Application and Selection Process

Only candidates who are recommended by three Professors in China and subsequently offered admission to study at the University of Oxford, having applied through the normal admissions process, and meet the criteria for funding by CSC, can be considered for scholarships of the Programme. Applying students will select the Genomic Medicine and Statistics course option on the form and then be assessed as part of a gathered field with other students applying to the Genomic Medicine and Statistics course who have not applied for this scholarship scheme. The selection of candidates for the scholarships will be the joint responsibility of the CSC and the University. Final selection will be based solely on academic merit and/or potential.

Graduate Destinations

The interdisciplinary nature of the programme is reflected in the destination of graduates which includes academic research in prestigious laboratories worldwide together with biotech, spin-outs, consulting and working in health care settings.

Key Dates (tentative and subject to change)

Mid Oct 2026	CSC/COI/NDM begin advertising for applications.
15th Nov 2026	Deadline for candidates to submit their CV, cover letter, list of three projects, references and other required documents to CSC
1st Dec 2026	Deadline for candidates to apply directly to the University of Oxford for admission.
4th - 8th Jan 2027	The University will shortlist candidates for the Programme.
11th - 15th Jan 2027	Interviews by Oxford University for the Genomic Medicine and Statistics course.
Late Feb 2027	Interviews by CSC.
Mid - Late Mar 2027	Successful candidates will be notified.

DISEASE RELVEANCE

The Genomic Medicine and Statistics course is designed to provide world class training and the opportunity to conduct research in the rapidly developing field of genomic science and its application to human health. The research opportunities for the doctoral research are very broad and interdisciplinary, with collaboration highly encouraged. Disease areas span the breadth of clinical medicine, from infection and immunity to cardiovascular disease, metabolism, rare disease and cancer across Departments in the Medical Sciences Division.

KEY TECHNOLOGY

The programme is focused on the following themes:

1) Genomic and -omic technologies (including method development, single cell genomics, imaging, model systems, CRISPR screens, genome engineering, proteomics, metabolomics, high throughput screening)
2) Functional genomics (gene regulation and epigenetics)
3) Genome biology (genetic variation, recombination, human history, evolution, palaeogenomics, pathogen genomes)
4) Genomics of disease (Mendelian, multifactorial traits, cancer)
5) Genomic analysis (bioinformatics and statistical genetics)
6) From genes to clinical proof of concept (integrated drug development pipeline spanning genetic-led target discovery, structural biology, medicinal chemistry)
7) Application of genomics in the clinic (rare disease diagnostics, cancer therapeutics, personalised medicine and genome therapies).

Teaching modules combine theoretical and practical classes, with further skills training available through the Medical Sciences Doctoral Training Centre.

TRAINING OPPORTUNITIES

GMS Teaching Overview

The GMS DPhil programme includes a first term of teaching and up to three lab rotations before deciding on the final DPhil project. Students offered a place on the programme come from diverse academic disciplines and the teaching gives a broad introduction to a variety of genomic and statistical topics. The research projects and lab visits help inform the choice of DPhil project to be undertaken over the subsequent three years of the programme.

The aims of the first term are to:

- Provide cross-discipline skills training in genome biology, statistics and bioinformatics
- Introduce the latest genomic techniques and applications
- Emphasise the tight integration of lab and computational work in genomic research
- Discuss research activity in the wider context of clinical genomic medicine
- Familiarise students with research areas, potential supervisors and projects

The final three years of the course will comprise doctoral research under the supervision of two named supervisors and a doctoral committee. Applicants are advised to visit the Doctoral Training Centre course webpage for further information about supervisors connected to this programme.

Students receive world-class training, supervision, mentorship and pastoral support. Promoting excellence in research culture underlies all aspects of the programme with a commitment to support creativity, prioritise diversity and inclusion, and promote best practice.

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THEME 1: CANCER BIOLOGY, IMMUNOLGY & IMMUNOTHERAPY

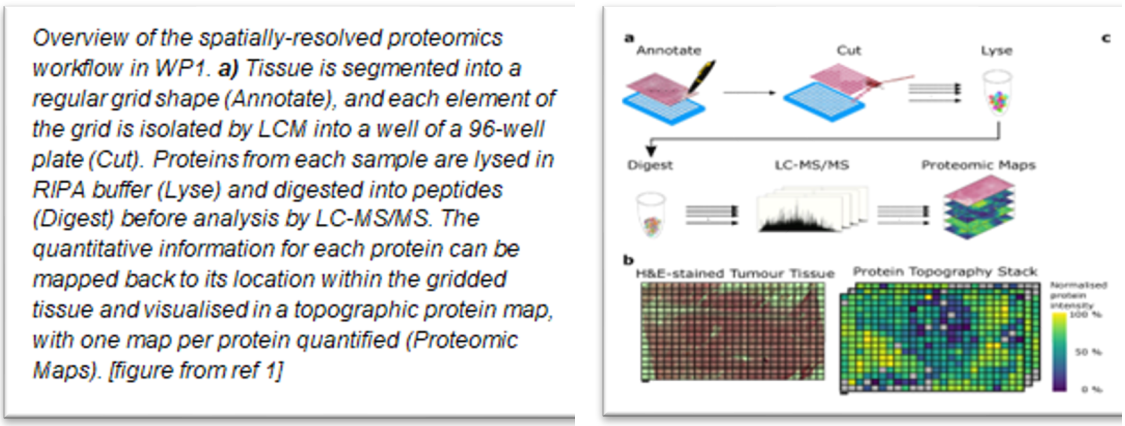
1.1 Expanding Deep Topographic Proteomics into the 3rd Dimension to Enable Ovarian Pre-Cancer Grading

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Dr. Sarah Blagden patosarahblagden@oncology.ox.ac.uk

PROJECT OVERVIEW

This PhD project aims to tackle a significant gap in understanding ovarian cancer by developing a new grading system for its precursor lesions, serous tubal intraepithelial carcinoma (STIC). Ovarian cancer is the sixth most common cancer in the UK, affecting approximately 7,500 women annually. It is known to be preceded by a non-invasive pre-cancerous phase, specifically STIC lesions which can develop into invasive high-grade serous ovarian cancer (HGSOC). However, unlike other pre-cancers that can be classified into mild, moderate, and severe dysplasia, there is currently no such differentiation for STIC lesions. This lack of understanding about the biological diversity of STICs at a cellular level represents a missed opportunity for developing early, grade-specific treatments and even identifying time windows for potential reversal.

The core of this project is to address this challenge by defining the hallmarks of different STIC lesion grades using state-of-the-art methodology. The research will use novel LCM-LCMS (Laser Capture Microdissection combined with topographic proteomics) to analyse the proteome of STIC lesions with single-cell and spatial resolution. This method, developed in Professor Fischer's lab, can characterize over 5,000 proteins within individual cells or microscopic tissue regions, providing unbiased information about protein expression and spatial dependencies.



*Overview of the spatially-resolved proteomics workflow in WP1. **a)** Tissue is segmented into a regular grid shape (Annotate), and each element of the grid is isolated by LCM into a well of a 96-well plate (Cut). Proteins from each sample are lysed in RIPA buffer (Lyse) and digested into peptides (Digest) before analysis by LC-MS/MS. The quantitative information for each protein can be mapped back to its location within the gridded tissue and visualised in a topographic protein map, with one map per protein quantified (Proteomic Maps). [figure from ref 1]*

The project is structured into three main work packages.

Work Package 1 will involve using LCM to micro dissect tissue blocks from patients with ovarian cancer, pre-cancer, and adjacent normal tissue, followed by LC-MS to identify proteins unique to the pre-cancerous state.

Work Package 2 will build upon this by expanding the methodology into a 3D space, aiming to map the entire proteome of STIC lesions. This involves developing and applying spatial machine learning algorithms to predict high-resolution proteome distribution and bridge the gap between MS sensitivity and minute sample size at a single-cell level. The data generated will be used to predict spatial proteome expression and will inform about the spatiotemporal molecular development of STICs into invasive tumours, ultimately leading to a grading system for these lesions.

Work Package 3 will focus on validation and characterization. Candidate proteins and pathways will be validated using ovarian cancer cell lines and organoids, and their impact on tumorigenesis will be explored using molecular techniques like CRISPR and siRNA. The project will ultimately correlate multi-omics data with functional and phenotypic queues to establish a novel grading system for STIC lesions and identify potential therapeutic interventions to disrupt their progression to invasive cancer.

DISEASE RELVEANCE

Ovarian cancer is a lethal gynaecological malignancy that is often diagnosed at an advanced stage. Its mortality rate is high because pre-cancerous lesions, known as serous tubal intraepithelial carcinoma (STICs), are clinically “invisible” on standard scans and blood tests, such as the tumour marker CA125. This makes early detection and prevention extremely challenging, as we cannot identify who has these lesions and remove them before they become invasive.

The lack of a defined grading system for STIC lesions, unlike other pre-cancers, represents a critical knowledge gap. Without understanding the biological heterogeneity of STICs, we miss opportunities for grade-specific treatment and early intervention. This project aims to fill this void by defining a grading system at a molecular level, providing unbiased proteomic characterization of these pre-invasive lesions for the first time. Understanding the specific pathways that drive STICs toward invasive ovarian cancer has enormous clinical potential, as it could lead to new interventions like preventive vaccines. The success of this project could have a transformative impact on the prevention and treatment of this disease and the methodologies developed could be applied to other pre-cancer types.

KEY TECHNOLOGY

This project will leverage several cutting-edge technologies to achieve its goals. The primary methodology is

LCM-LCMS, which combines Laser Capture Microdissection (LCM) with Liquid Chromatography-Mass Spectrometry (LC-MS). This allows for the detailed characterization of over 5,000 proteins within microscopic regions of tissue or even single cells. This provides unbiased, spatially resolved proteomic information about STIC lesions. The workflow involves annotating tissue into a grid or phenotypical features down to single cell level, using LCM to isolate each section, and then analysing the proteins via LC-MS to create a topographic protein map that shows protein intensity across the tissue.

Beyond this core technique, the project will expand the existing methodology to enable 3D mapping of the proteome in STIC lesions. To achieve this, the project will explore the use of spatial machine learning algorithms. These algorithms will be used to predict high-resolution proteome distribution and correlate spatial protein expression from mass spectrometry with other spatial methodologies such as MALDI imaging, spatial transcriptomics and immune histochemistry (IHC). The project will also use basic molecular techniques to validate candidate proteins and their pathways, including CRISPR, siRNA, and construct-driven re-expression to determine their impact and relevance to tumor formation. Finally, the research will utilize ovarian cancer cell lines and organoids as models to further explore the applicability of the developed models at a single-cell level.

TRAINING OPPORTUNITIES

This interdisciplinary project, a collaboration between Prof. Sarah Blagden's and Prof. Roman Fischer's labs, offers a wide range ofTRAINING OPPORTUNITIES. The successful candidate will receive hands-on training in core lab techniques for sample preparation and analysis. This includes the preparation and mapping of tissue specimens for laser microdissection.The student will gain expertise in operating state-of-the-art mass spectrometry instruments, such as the Orbitrap Astral and timsTOF Ultra 2, along with other cutting-edge equipment like CellenOne and Leica LMD7. The project will also provide a solid foundation in cell culture techniques, including maintaining cancer cell lines and working with organoid models, as well as basic wet lab procedures.

Beyond practical lab skills, the student will develop a deep understanding of several advanced scientific fields. They will gain insights into machine learning, systems biology, and biomarker development, learning how to apply these concepts to biological research. The project will also offer training in understanding drug and target discovery and provide a comprehensive understanding of tumorigenesis biology. This holistic training will equip the

student with both the practical and theoretical knowledge required for a successful career in academic or industrial research.

KEY PUBLICATIONS

1. Davis S, Scott C, Oetjen J, Charles PD, Kessler BM, Ansorge O, Fischer R. Deep topographic proteomics of a human brain tumour. Nat Commun. 2023 Nov 24;14(1):7710. doi: 10.1038/s41467-023-43520-8.
2. Labidi-Galy SI, Papp E, Hallberg D et al. High grade serous ovarian carcinomas originate in the fallopian tube. Nat Commun. 2017 Oct 23;8(1):1093. doi: 10.1038/s41467-017-00962-1.
3. Menon U, Gentry-Maharaj A, Burnell M, et al. Ovarian cancer population screening and mortality after long-term follow-up in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. Lancet. 2021 Jun 5;397(10290):2182-2193. doi: 10.1016/S0140-6736(21)00731-5

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1.2 A New Protein-Dynamics Mechanism for Editing the Cancer Immunopeptidome

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PROJECT OVERVIEW

Classical HLA-A, -B and -C molecules present peptides for immune surveillance, yet closely related allotypes can differ markedly in their dependence on the peptide-loading factor tapasin (tapasin dependence, TD). This project will test the hypothesis that such divergence is partly explained by an active displacement (AD) mechanism in which local rearrangements of conserved intramolecular hydrogen bonds alter peptide-binding dynamics and HLA conformational stability.

The study will combine molecular dynamics, experimental mutagenesis, biochemical and cell-based assays, immunopeptidomics and structural analysis. Dimorphic HLA pairs with divergent TD will first be analysed using 150 ns REST2 simulations to quantify regional hydrogen-bond frequencies and identify candidate AD targets. Matched control pairs in which the same dimorphism is not associated with TD divergence will test whether the mechanism depends on the HLA structural chassis.

Candidate residues will then be tested experimentally by site-directed mutagenesis, recombinant HLA peptide-binding assays and HLA-transfected .220 cells, including pulse-chase measurements of peptide loading. Immunopeptidomics will quantify repertoire size and stability/off-rate and affinity distributions, providing measures of strongly versus lightly edited repertoires. Pocket-specific peptide-binding free-energy contributions will be evaluated to test whether primary selection occurs in a pocket distal to the main AD site, with secondary selection at the AD-proximal pocket.

Finally, peptide:MHC molecular-dynamics trajectories will be examined for conformations resembling tapasin-stabilised open intermediates, and informative allotypes with unusual anchor-pocket chemistry will be studied to address defined knowledge gaps. The project will establish a mechanistic framework linking HLA polymorphism, protein dynamics, peptide loading and immunopeptidomic repertoire selection.

DISEASE RELVEANCE

The project is directly relevant to cancer immunotherapy because tumour-derived peptides presented by classical HLA class I molecules form the basis for immune recognition and are potential targets for therapeutic cancer vaccines and other T-cell-based approaches. Tapasin-dependent peptide loading shapes which peptides are presented at the cell surface, while differences between HLA allotypes can alter peptide selection and therefore the composition of the immunopeptidome. By determining whether active displacement of conserved hydrogen bonds is a mechanism governing tapasin dependence and repertoire refinement, the project aims to explain how HLA polymorphism influences antigen presentation. The resulting mechanistic understanding may improve interpretation of tumour antigen presentation and help identify HLA-dependent determinants of peptide display that are relevant to cancer vaccine and immunotherapy design.

KEY TECHNOLOGY

The project uses an integrated computational-experimental platform. Molecular dynamics will use 150 ns REST2 simulations to quantify conserved H-bond frequencies, identify candidate active-displacement sites, analyse conformational states and compare peptide:MHC trajectories with tapasin-stabilised open intermediates. Pocket-specific peptide-binding free-energy decomposition will test the proposed pocket-focus model.

Experimental validation will use site-directed mutagenesis and recombinant HLA peptide-binding assays, including fluorescence-polarisation approaches. Selected variants will be studied in .220 transfectants using tapasin-dependence and pulse-chase assays. Immunopeptidomic analyses will quantify repertoire size, peptide stability/off-rate and affinity distributions, providing quantitative measures of repertoire editing. Structural analysis will extend to informative allotypes with distinctive anchor-pocket chemistry, linking sequence variation to structure and functional peptide selection.

TRAINING OPPORTUNITIES

Training will span molecular dynamics, computational chemistry, molecular and cellular biochemistry, immunology, immunopeptidomics and structural biology. The student will be trained in REST2 simulations, trajectory and hydrogen-bond analysis, conformational-state analysis and peptide-binding free-energy calculations; site-directed mutagenesis, recombinant HLA production and fluorescence-polarisation peptide-binding assays; and functional analysis in

HLA-transfected .220 cells, including tapasin-dependence and pulse-chase experiments.

Immunopeptidomics training will cover repertoire analysis, peptide stability/off-rate and affinity-distribution measures and interpretation of HLA ligand datasets. General graduate training will include statistics, bioinformatics, reproducible workflows, data visualisation, research data management, version control and scientific communication. The candidate should have strong quantitative problem-solving ability and an interest in integrating computational and experimental evidence.

KEY PUBLICATIONS

1. Turner S, Darley R, Essex JW, Sim MJW, van Hateren A, Elliott T. “Atom-level mechanism of tapasin-independent peptide editing by Major Histocompatibility Complex class I molecules.” bioRxiv (2025), 2025.06.20.660712. doi:10.1101/2025.06.20.660712

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1.3 Homeostatic Niche Reinforcement to Prevent Colorectal Neoplasia

Prof. Simon Leedham *simon.leedham@well.ox.ac.uk*
Prof. Christian Siebold *christian.siebold@strubi.ox.ac.uk*

PROJECT OVERVIEW

Homeostatic niche reinforcement to prevent colorectal neoplasia Rationale and objectives. Colorectal cancer initiation depends not only on epithelial mutations but also on the ability of mutated cells to remodel the surrounding tissue microenvironment. Cancer can be viewed as a dynamic cellular ecosystem in which mutated epithelial cells interact with the surrounding stroma and immune system. Although cancer-associated mutations are frequently present in histologically normal colorectal epithelium, only a minority of mutated cells progress to neoplasia, indicating that mutation alone is insufficient for tumour initiation. Instead, early lesions must acquire functional capabilities that allow them to overcome homeostatic mechanisms, including stromal signals that normally restrain epithelial proliferation and promote differentiation.

Remodelling of the tissue microenvironment to establish a supportive cellular ecosystem is therefore likely to be critical for tumour development. Importantly, tumour initiation represents a transient state in which mutated epithelial cells exist before a fully supportive microenvironment has been established. During this window, mutant cells may remain dependent on, and vulnerable to, homeostatic signals from the surrounding niche, creating an opportunity for preventative intervention.

This project will test the hypothesis that failure to establish a supportive microenvironment limits early lesion progression and that reinforcing protective BMP-mediated niche signalling can suppress tumour initiation. We will: (1) define how APC-mutant epithelial cells remodel and respond to their local stromal and immune niche; (2) determine how niche-derived BMP signals regulate mutant epithelial fate and plasticity; and (3) test whether therapeutically reinforcing BMP signalling can prevent colorectal lesion initiation.

Research Plan

1-Define microenvironmental changes during tumour initiation.

Our preliminary data suggest that APC mutation causes changes not only within epithelial cells but also in surrounding stromal populations. In particular, we observe expansion of sub-epithelial myofibroblasts (SEMFs), which express BMP ligands that normally maintain intestinal homeostasis, restrict proliferation and promote epithelial differentiation. We hypothesise that SEMF expansion represents an active protective response to abnormal epithelial growth rather

than simply a consequence of tumour formation. For tumours to progress, APC-mutant cells may therefore need to overcome or subvert these signals, potentially through inflammatory and wound-healing pathways.

We will use 10X Xenium spatial transcriptomics to map epithelial, stromal and immune states in human and mouse colorectal polyps while preserving their spatial organisation. Combined with MuSpAn computational spatial analysis, this will allow us to determine how APC-mutant cells alter neighbouring stromal populations, identify spatially restricted signalling interactions, and establish how these relationships change during early lesion development.

2-Determine how stromal BMP signalling regulates APC-mutant epithelium.

We will next test whether the stromal changes identified above functionally constrain mutant epithelial cells. Human and mouse epithelial–stromal organoid co-cultures will model communication between these compartments during tumour initiation. RNA and ATAC sequencing will define how fibroblast co-culture alters the transcriptional and chromatin states of APC-mutant epithelium and identify pathways controlling epithelial fate and plasticity.

To directly determine whether BMP signalling suppresses APC-mutant behaviour, wild-type and APC-mutant organoids will be exposed to BMP2, BMP4 and BMP7. We will assess effects on proliferation, differentiation and stem-cell activity, establishing whether different niche-derived BMP ligands can drive mutant cells away from tumour-promoting states. Finally, genetically engineered mouse models that disrupt BMP signalling specifically in Apc-mutant epithelial cells will test whether loss of this homeostatic signal accelerates tumour development in vivo. Together, these experiments will establish whether SEMF expansion represents a functional tumour-suppressive response to cancer-initiating mutation.

3-Test therapeutic reinforcement of homeostatic signalling.

If endogenous BMP signalling constrains mutant epithelial cells, therapeutically strengthening this response may prevent their progression to established neoplasia. We will therefore evaluate newly developed BMP receptor-activating nanobodies in collaboration with Professor Christian Siebold. These agents provide a targeted means of activating BMP receptors and offer an opportunity to reinforce the tissue's endogenous protective response rather than directly targeting the initiating mutation.

We will test BMP receptor activation in organoid systems to determine whether it suppresses stem-like properties and promotes differentiation of APC-mutant cells. Promising agents will then be evaluated in genetically engineered mouse models of intestinal polyposis to determine whether reinforcing BMP signalling suppresses or prevents polyp formation. These experiments will establish

whether manipulation of the homeostatic niche can be exploited as a precision prevention strategy for colorectal neoplasia.

DISEASE RELVEANCE

Translational potential. This project targets the earliest stages of colorectal carcinogenesis, shifting the therapeutic focus from treatment of established disease towards cancer interception and prevention. If successful, BMP receptor activation could provide a prevention strategy for individuals at high colorectal cancer risk, including patients with Familial Adenomatous Polyposis. Characterising stromal and immune regulation of early lesions may additionally identify biomarkers of lesion behaviour and therapeutic targets

KEY TECHNOLOGY

1) Spatial transcriptomics and MuSpAn analysis
2) Mouse and organoid models of intestinal neoplasia
3) Bioinformatics

TRAINING OPPORTUNITIES

This project will provide the student with multidisciplinary training across cancer biology, spatial biology, organoid technology, computational analysis, and translational preclinical modelling. The student will gain experience in both wet-laboratory and computational approaches within a highly collaborative translational research environment. This environment will provide broad exposure to both fundamental cancer biology and clinically relevant translational research. KeyTRAINING OPPORTUNITIES will include:

1) Spatial transcriptomics using advanced platforms such as 10X Xenium to study cellular interactions within intact human and mouse tissues.
2) Computational spatial biology analysis using MuSpAn to quantify cellular ecosystems, stromal remodelling, and immune interactions within tumours.
3) Human and mouse intestinal organoid culture, including epithelial–stromal co-culture systems to model tumour–microenvironment interactions.
4) Use of genetically engineered mouse models of colorectal cancer and intestinal polyposis for in vivo studies of tumour initiation and prevention.
5) Preclinical therapeutic testing of novel BMP receptor-targeting nanobody agents in both organoid and mouse systems.

6) Bioinformatic analysis and integration of spatial, transcriptomic, and epigenetic datasets.

7) Exposure to translational research pipelines linking mechanistic discovery with therapeutic development and precision cancer prevention strategies.

KEY PUBLICATIONS

1. Mulholland EJ, Belnoue-Davis HL, Valbuena GN, Gunduz N, Ligeza A, Lin M, Biswas S, Gil Vasquez E, Omwenga S, Nasreddin N, Hodder MC, Wang LM, Ng AS, Jennings E, Midwood KS, Dedi N, Irshad S, Ridgway RA, Phesse TJ, East J, Tomlinson IP, Davies GC, Sansom OJ, Leedham SJ. Epithelial GREMLIN1 disrupts intestinal epithelial-mesenchymal crosstalk to induce a wnt-dependent ectopic stem cell niche through stromal remodelling. *Nat Commun*. 2025 Jun 4;16(1):5167.

2. Gil-Vasquez E, Nasreddin N, Valbuena GN, Mulholland EJ, Belnoue-Davis HL, Eggington HR, Schenck RO, Wouters VM, Wirapati P, Gilroy K, Lannagan TRM, Flanagan DJ, Najumudeen AK, Omwenga S, McCorry AMB, Easton A, Koelzer VH, East JE, Morton D, Trusolino L, Maughan T, Campbell AD, Loughrey MB, Dunne PD, Tsantoulis P, Huels DJ, Tejpar S, Sansom OJ, Leedham SJ. Dynamic and adaptive cancer stem cell population admixture in colorectal neoplasia. *Cell Stem Cell.* 2022 Aug 4;29(8):1213-1228

3. Koppens MAJ, Davis H, Valbuena GN, Mulholland EJ, Nasreddin N, Colombe M, Antanaviciute A, Biswas S, Friedrich M, Lee L; Oxford IBD Cohort Investigators, Wang LM, Koelzer VH, East JE, Simmons A, Winton DJ, Leedham SJ. Bone Morphogenetic Protein pathway antagonism by Grem1 Regulates Epithelial Cell Fate in Intestinal Regeneration. *Gastroenterology*. 2021 Apr 2:S0016-5085(21)00579-5. doi: 10.1053

4. Davis H, Irshad S, Bansal M, Rafferty H, Boitsova T, Bardella C, Jaeger E, Lewis A, Freeman-Mills L, Giner FC, Rodenas-Cuadrado P, Mallappa S, Clark S, Thomas H, Jeffery R, Poulsom R, Rodriguez-Justo M, Novelli M, Chetty R, Silver A, Sansom OJ, Greten FR, Wang LM, East JE, Tomlinson I, Leedham SJ. Aberrant epithelial *GREM1* expression initiates colonic tumorigenesis from cells outside the stem cell niche. *Nature Medicine* 2015; 21(1):62-70.

5. England, FJ, Lin, M, Sigal, M & Leedham, SJ Defining the mucosal ecosystem: epithelial-mesenchymal interdependence in gastrointestinal health and disease. Nat Rev Gastroenterol Hepatol 22, 741-754 (2025).

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1.4 Overcoming T Cell Dysfunction to Enhance Cancer Immunotherapy

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Prof. David Church *david.church@well.ox.ac.uk*

PROJECT OVERVIEW

Background:

The immune system can recognise and kill cancer cells but its function is suppressed within tumours preventing rejection of disease. Releasing T cells from immune suppression by targeting immune checkpoints such as CTLA-4 and PD-L1 results in strikingly effective clinical responses in some patients with cancer. However, **only a minority of patients with a subset of cancers durably respond to existing immunotherapies**. There is a need to identify and therapeutically target distinct mechanisms of immunosuppression.

Our recent work identified **a novel inhibitory pathway** that limits T cell immunity to cancer metastasis (Yang J et al., *Nature* 2025). We demonstrated that the arachidonic acid metabolite thromboxane A_2 (TXA_2) acts via the Rho guanine exchange factor ARHGEF1 to suppress T cell effector function. Importantly, we found that limiting TXA_2 availability *in vivo* using **aspirin** augments anti-metastatic immunity by preventing activation of the ARHGEF1 pathway in T cells (Yang J et al., *Nature* 2025). These findings provide a mechanistic immunological explanation for longstanding observations linking aspirin to improved cancer outcomes. This project will determine whether targeting the TXA_2 pathway can enhance anti-tumour immunity and improve responses to immunotherapy in colorectal cancer.

Research plan:

Aim 1. Determine how targeting the TXA_2 pathway affects tumour progression and anti-tumour T cell immunity. Using orthotopically implanted organoid models and newly developed conditional genetic tools, we will determine how inhibition of the TXA_2 pathway affects tumour growth, metastatic burden and anti-tumour T cell responses in colorectal cancer. High-dimensional spectral flow cytometry and RNA sequencing will be used to define the functional and transcriptional states, clonal diversity and differentiation of tumour-reactive T cells.

Aim 2. Determine whether targeting the TXA_2 pathway synergises with immune checkpoint blockade. We will test whether genetic or pharmacological perturbation of the TXA_2 pathway improves responses to immune checkpoint blockade in colorectal cancer models. We will assess tumour growth, metastatic burden and anti-tumour T cell responses to

determine whether disrupting TXA_2-mediated immunosuppression enhances therapeutic efficacy.

Aim 3. Determine whether the TXA_2 pathway regulates anti-tumour T cell responses in human colorectal cancer. In collaboration with Professor David Church, we will investigate the role of TXA_2 signalling in human T cells and its relationship with T cell functional states in colorectal cancer. Using patient-derived samples, we will determine whether TXA_2 signalling is associated with T cell dysfunction and whether perturbing this pathway can enhance T cell function.

DISEASE RELVEANCE

Colorectal cancer is the third most common cancer worldwide and a leading cause of cancer death, with metastatic disease accounting for most mortality. This project has strong translational relevance to cancer immunotherapy. Our recent work identified the TXA_2 pathway as a previously unrecognised mechanism by which TXA_2 suppresses anti-tumour T cell immunity (Yang et al., *Nature* 2025). Because TXA_2 production can be inhibited by widely available drugs such as aspirin, this pathway represents an attractive target for therapeutic intervention.

The research is particularly timely given growing clinical interest in aspirin for cancer prevention and recurrence, including ongoing prospective trials such as Add-Aspirin. By linking mechanistic studies in preclinical models with analysis of T cells from patients, the project will help bridge the gap between experimental immunology and clinical application. Given the low cost, safety profile and global availability of aspirin, successful translation of these findings could ultimately improve access to effective immunotherapy strategies worldwide.

KEY TECHNOLOGY

This project combines i*n vivo* cancer modelling, high-dimensional single-cell immunology and human translational immunology.

1) *In vivo* cancer models: orthotopically implanted organoid models of colorectal cancer.
2) High-dimensional spectral flow cytometry: marker panels established within the laboratory for Cytek Aurora, resolving the activation, differentiation and exhaustion states of tumour-reactive T cells at high resolution.
3) RNA sequencing: dissecting polyclonal T cell responses to define transcriptional programmes, clonal diversity and differentiation trajectories.

4) Computational analysis: bioinformatic analysis for integrating transcriptomic, clonal and functional datasets.

5) Human translational immunology: T cells isolated from patients with colorectal cancer, analysed using functional immune and signalling assays established in the laboratory.

TRAINING OPPORTUNITIES

This project will provide multidisciplinary training for a student passionate about cancer immunology and immunotherapy, whether from a fundamental science or clinical background. You will gain expertise in primary and metastatic mouse cancer models and advanced cellular and molecular immunology, including high-dimensional spectral flow cytometry, RNA-seq and CRISPR-based genetic approaches, together with the bioinformatics skills to integrate transcriptomic, clonal and functional datasets. The project also provides training in translational, patient-focused research: working with primary human samples and applying clinical assays of pathway and immune activity.

Our laboratory is based in the Department of Oncology and also embedded within the NDM Centre for Immuno-Oncology (CIO). This dual setting offers exceptional breadth of expertise spanning fundamental immunology, cancer biology and clinical translation, with strong support for seminar/conference presentations and high-impact publications. You will also receive training in experimental design, data analysis, scientific communication and manuscript preparation, preparing you for careers in academia or clinical research.

We are looking for a motivated student with passion, talent and determination. You will have the chance to work on grand challenges in immune regulation and tumour immunity, taking ownership of your research - identifying the most important questions, designing and performing experiments, and publishing your findings.

KEY PUBLICATIONS

1. **Aspirin prevents metastasis by limiting platelet TXA2 suppression of T cell immunity.**
   Yang J[#], Kanemaru YY, Morris BI, Contursi A, Trajkovski D, Xu J, Patrascan I, Benson J, Evan AC, Conti AG, Deka AA, Dahmani L, Belltheus A, Zhang B, Okkenhaug H, Whiteside SK, Imianowski, CJ, Wesolowski AJ, Webb LV, Puccio S, Mitra S, Tacconelli S, Bruno A, Berardino SD, Michele, AD, Welch H, Yu IS, Lin SW, Mitra S, Lugli E, Weyden L, Okkenhaug K, Parsy KS, Patrignani P, Adams DJ, Roychoudhuri R[#].
   Nature (2025). Apr;640(8060):1052-1061. PMID: 40044852.

- [#]Co-corresponding author
- Altmetric: **2348** and Academic reach: **272k** article accesses
- Featured by **774** news stories**,** including BBC News: https://www.bbc.co.uk/news/articles/c1d4n119xr7o

2. **Tumor-derived antioxidants suppress immunity by depriving T cells of reactive oxygen species.**
   Wesolowski AJ, Pillay AM, Vardaka P, Nasrallah R, Greaves R, Li H, Loffreda I, Jenkin C, James AM, Nübling A, Ward CJ, von Linde T, Conti AG, Tzeng SF, Dahmani L, Evans AC, Whiteside SK, Yamashita-Kanemaru Y, Imianowski CJ, Yang J, Gonzalez IM, Chapman J, Al-Deka A, Okkenhaug K, Murphy MP, Swiatczak B, Guittard G, Lugli E, Flatz L, Ho PC, Eil RL, Roychoudhuri R
   Science (2026). 393 (6815): 1036-1044. PMID: 42691162.

3. **BACH2 drives quiescence and maintenance of resting Treg cells to promote homeostasis and cancer immunosuppression.**
   Grant FM[*], Yang J[*#], Nasrallah R, Clarke J, Sadiyah F, Whiteside SK, Imianowski CJ, Kuo P, Vardaka P, Todorov T, Zandhuis N, Patrascan I, Tough DF, Kometani K, Eil R, Kurosaki T, Okkenhaug K, Roychoudhuri R.
   Journal of Experimental Medicine (2020) Sep 7;217(9):e20190711.
   [*]Co-first and [#]Co-corresponding author

4. **IL-7–dependent maintenance of ILC3s is required for normal entry of lymphocytes into lymph nodes.**
   Yang J, Cornelissen F, Papazian N, Reijmers PM, Llorian M, Cupedo T, Coles M, Seddon
   Journal of Experimental Medicine (2018) Apr 2;215(4):1069-1077.

5. **A distal enhancer at risk locus 11q13.5 promotes suppression of colitis by Treg cells.**

6. Nasrallah R, Imianowski CJ, Bossini-Castillo L, Grant FM, Dogan M, Placek L, Kozhaya L, Kuo P, Sadiyah F, Whiteside SK, Mumbach MR, Vardaka P, Whyte CE, Lozano T, Fujita T, Fujii H, Liston A, Andrews S, Cozzani A, Yang J, Mitra S, Lugli E, Chang HY, Unutmaz D, Trynka G, Roychoudhuri R.
   Nature (2020) Jul;583(7816):447-452. PMID: 32499651.

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1.5 Rewiring T Cell Signalling to Enhance Immunity

Dr. Jie Yang *jie.yang@oncology.ox.ac.uk*
Prof. David Withers *david.withers@immonc.ox.ac.uk*

PROJECT OVERVIEW

Background:

T lymphocytes are central mediators of adaptive immunity. By recognising antigen through the T-cell receptor (TCR) and differentiating into effector cells, they clear infected and damaged cells and help maintain immune homeostasis. The strength of TCR signalling determines the outcome of this response, governing activation, proliferation and differentiation. Insufficient signalling leaves the host unable to respond effectively to challenge, while excessive or inappropriate activation can damage healthy tissue. The threshold at which T cells activate is therefore tightly tuned by signals from the extracellular environment. Although much is known about how the TCR signalling network transmits activating signals, far less is understood about how physiological lipid mediators modulate this threshold.

Our recent work identified a previously unrecognised inhibitory pathway that regulates T cell response in cancer (Yang et al., *Nature*, 2025). We discovered that the arachidonic-acid metabolite thromboxane A_2 (TXA_2), best known for its role in platelet activation and haemostasis, acts through the Rho guanine nucleotide exchange factor ARHGEF1 in T cells to restrain T cell function. Specifically, the TXA_2 signalling inhibits TCR-driven activation of the kinase pathway, which is critical for T-cell activation and differentiation. The precise molecular nodes through which this pathway acts remain unknown.

Research plan:

Aim 1. Identify the TCR signalling events regulated by TXA_2. Using primary T cells from healthy human blood and mouse lymphoid tissue, we will perform time-course studies to track phosphorylation of key signalling molecules. Phospho-flow cytometry and western blotting will identify which steps are most sensitive to TXA_2-dependent regulation. Functional consequences will be assessed by measuring T cell activation and proliferation in acute assays and the acquisition of exhaustion-associated phenotypes under chronic stimulation.

Aim 2. Define the signalling architecture of TXA_2 regulation. Mass spectrometry-based experiments will map the TXA_2-responsive signalling network in primary T cells. Pharmacological inhibition and CRISPR-based editing of selected components will test pathway specificity and establish which nodes are required for TXA_2-dependent regulation.

Aim 3. Determine how TXA_2-dependent signalling shapes T cell function in cancer. We will determine how quantitative changes in signal strength map to functional output, and test whether the nodes identified in Aims 1 and 2 are engaged in T cells responding to tumours and in T cells from patients with cancer. Together, these studies will define how a physiological lipid mediator sets the responsiveness of T cells, and establish whether this restraint can be modulated selectively for therapeutic benefit.

DISEASE RELVEANCE

This project has broad relevance to diseases in which T cell responsiveness is dysregulated. TCR signalling must be tightly controlled: insufficient signalling can limit protective immunity to infection and cancer, whereas excessive activation can contribute to inflammatory tissue damage. Understanding the mechanisms that set this threshold could therefore reveal new opportunities to therapeutically tune T cell responses.

Our recent work identified the TXA_2 signalling as a previously unrecognised mechanism that suppresses T cell function and anti-tumour immunity (Yang et al., *Nature*, 2025). Relieving this restraint by limiting TXA_2 production with aspirin augments anti-tumour immunity, demonstrating that the pathway is therapeutically tractable. By identifying the specific molecular nodes through which TXA_2 regulates TCR signalling, this project could reveal more selective approaches to modulate T cell responsiveness beyond aspirin. Such strategies could enhance T cell function in cancer and other settings of inadequate immunity.

KEY TECHNOLOGY

This project combines quantitative signalling biology with functional immunology in primary cells.

1) Primary T cells: isolation and culture of primary human T cells from healthy donor blood and mouse T cells from lymphoid tissue, with defined TCR stimulation assays and pharmacological manipulation.
2) High-dimensional spectral flow cytometry: marker panels established within the laboratory for Cytek Aurora, resolving the activation, differentiation and exhaustion states of tumour-reactive T cells at high resolution.
3) Mass spectrometry: unbiased mapping of the signalling network in primary T cells.

4) CRISPR-Cas9 gene editing of primary human and mouse T cells: targeted disruption of candidate pathway components to establish requirement and specificity.

5) Computational and statistical analysis: quantitative modelling of signalling time-course data.

TRAINING OPPORTUNITIES

This project will provide multidisciplinary training for a student passionate about cancer immunology and T cell signalling, whether from a fundamental science or clinical background. You will gain expertise in primary T cell handling, TCR stimulation assays, flow cytometry, western blotting, CRISPR-based gene editing and mass spectrometry-based assays, together with the quantitative and computational skills needed to analyse signalling time-course and multi-omics data. The project deliberately combines molecular perturbation with functional immunology, training you to link mechanism to phenotype in a physiologically relevant system.

Our laboratory is based in the Department of Oncology and also embedded within the NDM Centre for Immuno-Oncology (CIO). This dual setting offers exceptional breadth of expertise spanning fundamental immunology, cancer biology and clinical translation, with strong support for seminar/conference presentations and high-impact publications. You will also receive training in experimental design, data analysis, scientific communication and manuscript preparation, preparing you for careers in academia or clinical research.

We are looking for a motivated student with passion, talent and determination. You will have the chance to work on grand challenges in immune regulation and tumour immunity, taking ownership of your research - identifying the most important questions, designing and performing experiments, and publishing your findings.

KEY PUBLICATIONS

1. **Aspirin prevents metastasis by limiting platelet TXA_2 suppression of T cell immunity.**
   Yang J[#], Kanemaru YY, Morris BI, Contursi A, Trajkovski D, Xu J, Patrascan I, Benson J, Evan AC, Conti AG, Deka AA, Dahmani L, Belltheus A, Zhang B, Okkenhaug H, Whiteside SK, Imianowski, CJ, Wesolowski AJ, Webb LV, Puccio S, Mitra S, Tacconelli S, Bruno A, Berardino SD, Michele, AD, Welch H, Yu IS, Lin SW, Mitra S, Lugli E, Weyden L, Okkenhaug K, Parsy KS, Patrignani P, Adams DJ, Roychoudhuri R.
   Nature (2025). Apr;640(8060):1052-1061. PMID: 40044852.

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2. **Tumor-derived antioxidants suppress immunity by depriving T cells of reactive oxygen species.**
   Wesolowski AJ, Pillay AM, Vardaka P, Nasrallah R, Greaves R, Li H, Loffreda I, Jenkin C, James AM, Nübling A, Ward CJ, von Linde T, Conti AG, Tzeng SF, Dahmani L, Evans AC, Whiteside SK, Yamashita-Kanemaru Y, Imianowski CJ, Yang J, Gonzalez IM, Chapman J, Al-Deka A, Okkenhaug K, Murphy MP, Swiatczak B, Guittard G, Lugli E, Flatz L, Ho PC, Eil RL, Roychoudhuri R
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3. **BACH2 drives quiescence and maintenance of resting Treg cells to promote homeostasis and cancer immunosuppression.**
   Grant FM*, Yang J*#, Nasrallah R, Clarke J, Sadiyah F, Whiteside SK, Imianowski CJ, Kuo P, Vardaka P, Todorov T, Zandhuis N, Patrascan I, Tough DF, Kometani K, Eil R, Kurosaki T, Okkenhaug K, Roychoudhuri R.
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4. **IL-7–dependent maintenance of ILC3s is required for normal entry of lymphocytes into lymph nodes.**
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   Journal of Experimental Medicine (2018) Apr 2;215(4):1069-1077.

5. **A distal enhancer at risk locus 11q13.5 promotes suppression of colitis by Treg cells.**
   Nasrallah R, Imianowski CJ, Bossini-Castillo L, Grant FM, Dogan M, Placek L, Kozhaya L, Kuo P, Sadiyah F, Whiteside SK, Mumbach MR, Vardaka P, Whyte CE, Lozano T, Fujita T, Fujii H, Liston A, Andrews S, Cozzani A, Yang J, Mitra S, Lugli E, Chang HY, Unutmaz D, Trynka G, Roychoudhuri R.
   Nature (2020) Jul;583(7816):447-452. PMID: 32499651.

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1.6 Exploring RNA Pseudouridylation as a Biomarker in Liquid Biopsy for Early Cancer Detection

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PROJECT OVERVIEW

Human body fluids contain cell-free nucleic acids, including DNA (cfDNA) and RNA (cfRNA), released from various cells, including cancer cells. These nucleic acids carry diverse chemical modifications that reflect their cellular origins and disease states, offering great potential for early cancer detection. While cfDNA epigenetic modifications such as DNA methylation have been extensively studied and applied to cancer diagnostics, the use of epitranscriptomic modifications in cfRNA remains largely unexplored due to technical challenges. Detecting epitranscriptomic changes in cfRNA could provide new information and expand the possibilities of early cancer detection.

Our lab develops cutting-edge sequencing methods for nucleic acid modifications. Previously, we developed a DNA methylation sequencing method, TAPS, and demonstrated its application in cfDNA sequencing for early cancer detection with commercial success (*Nat. Biotechnol.* 2019, *37*, 424, *Sci. Adv.* 2021, *7*, eabh0534). Recently, we developed BACS, a novel sequencing method for the most abundant RNA modification pseudouridine (Ψ) (*Nat. Methods* 2024, *21*, 2024).

Ψ is the most abundant RNA modification, particularly abundant in non-coding RNAs (ncRNAs), including ribosomal RNA (rRNA) and transfer RNA (tRNA). Ψ is installed by a group of pseudouridine synthases or PUS enzymes and more recently, we identified the substrates of each of the human PUS enzymes in a comprehensive Ψ map (*Nat. Cell Biol.* 2025, *27*, 2186.). Ψ plays important roles in RNA stability, splicing, and translation, and dysregulation or mutation of PUS enzymes is implicated in multiple diseases, including cancer.

This project aims to apply BACS to characterise Ψ in cfRNA from human plasma, exploring its potential as a novel biomarker for early cancer detection. cfRNA comprises a wide range of extracellular transcripts, including both coding (mRNAs) and ncRNAs. Current cfRNA assays primarily focuses on mRNAs. However, mRNAs are highly susceptible to degradation and only account for a small fraction (~2%) of the cfRNA repertoire. In contrast, the majority of cfRNAs are derived from ncRNAs, which are more structured and resistant to nuclease-mediated degradation than mRNA. Despite their stability and abundance, ncRNAs are typically discarded from current cfRNA analyses as non-informative. By leveraging BACS to detect Ψ in cfRNA, particularly in

ncRNA species, we aim to uncover new biomarkers for cancer. This approach could transform underutilised ncRNA data into a rich source of diagnostic information, advancing the power of cfRNA for early cancer detection.

DISEASE RELVEANCE

Early cancer detection not only greatly improves patient survival but also costs considerably less. Therefore, a noninvasive, low cost and reliable cancer diagnostic assay could greatly benefit cancer patients and the public. Recent studies have increasingly highlighted the emerging role of Ψ in cancer. This project offers an unprecedented opportunity to explore the clinical potential of Ψ as a biomarker in liquid biopsy for early detection across five major cancer types, including hepatocellular carcinoma (HCC), colorectal cancer, pancreatic cancer, oesophageal cancer, and lung cancer, representing diverse tissues of origin and significant global health burdens.

KEY TECHNOLOGY

1) 2-Bromoacrylamide-Assisted Cyclization Sequencing (BACS) and mBACS
2) *Nat. Methods* 2024, *21*, 2024.
3) *Nat. Cell Biol.* 2025, *27*, 2186.
4) *bioRxiv* 2026, 2026.09.05.749584.

TRAINING OPPORTUNITIES

1) Basic and advanced chemical biology, biochemistry, and molecular biology techniques
2) Knowledge in nucleic acid modifications/epigenetics/epitranscriptomics and clinical diagnostics
3) Cutting-edge sequencing technilogies
4) Cell-free RNA sequencing (liquid biopsy)
5) Bioinformatics and data analysis skills, including the use of machine learning and AI.

KEY PUBLICATIONS

1. Xu H, Kong L, Chen J, Moussawi Al K, Chen X, Iqbal A, Wing PAC, Harris JM, Tsukuda S, Embarc-Buh A, Wei G, Castello A, Kriaucionis S, McKeating JA, Lu X, Song CX. (2024). Absolute quantitative and base-resolution sequencing reveals comprehensive landscape of pseudouridine across the human transcriptome. ***Nat. Methods*** 21, 2024-2033.

2. Xu H, Kong L, Li M, Pisignano G, Cheng J, Feng F, Mehdipour P, Song CX. (2025). A comprehensive tRNA pseudouridine map uncovers targets dependent on human stand-alone pseudouridine synthases. ***Nat. Cell Biol.*** 27, 2186–2197.

3. Feng F, Pisignano G, Kong L, Grimes T, Brennan PE, Song CX. (2026). mBACS enhances pseudouridine profiling through efficient and robust chemical conversion. ***bioRxiv*** 2026.09.05.749584; doi: https://doi.org/10.64898/2026.09.05.749584

4. Liu Y, Siejka-Zielinska P, Velikova G, Bi Y, Yuan F, Tomkova M, Bai C, Chen L, Schuster-Bockler B, Song CX. (2019). Bisulfite-free direct detection of 5-methylcytosine and 5-hydroxymethylcytosine at base resolution. ***Nat. Biotechnol.*** 37, 424-429.

5. Siejka-Zielińska P, Cheng J, Jackson, F, Liu Y, Soonawalla Z, Reddy S, Silva M, Puta L, McCain MV, Culver EL, Bekkali N, Schuster-Böckler B, Palamara PF, Mann D, Reeves H, Barnes E, Sivakumar S, Song CX. (2021). Cell-free DNA TAPS provides multimodal information for early cancer detection. ***Sci. Adv.*** 7, eabh0534.

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1.7 CD1c Pathway in Malignancy and Development of Novel Therapeutics

Dr. Yi-Ling Chen *yi-ling.chen@ndm.ox.ac.uk*
Prof. Graham Ogg *graham.ogg@ndm.ox.ac.uk*

PROJECT OVERVIEW

Acute leukaemia, including acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL), is characterised by the uncontrolled expansion of immature haematopoietic cells within the bone marrow, peripheral blood, and extramedullary tissues. Despite significant advances in chemotherapy, targeted therapies, and immunotherapy, relapse remains a major clinical challenge and is frequently associated with poor outcomes and limited therapeutic options. Although current treaments have delivered considerable clinical benefit, treatment-related toxicities, antigen escape and drug resistance necessitate the development of safer and more selective therapeutic approaches.

CD1c is a non-polymorphic lipid antigen-presenting molecule that is highly expressed on professional antigen-presenting cells, but absent from haematopoietic stem and progenitor cells. Emerging evidence indicates that CD1c is selectively expressed in subsets of acute leukaemia, and remains detectable in relapsed disease, making it an attractive therapeutic target.

Previous studies have demonstrated that engineered T cells expressing CD1c-restricted T-cell receptors can recognise and kill CD1c-expressing leukaemia cells. However, cellular therapies are often expensive, time-consuming to manufacture, and difficult to scale for widespread clinical use. This project aims to develop novel CD1c-targeting therapeutics for the treatment of CD1c-positive acute leukaemias.

The student will characterise CD1c expression acute leukaemia subtypes, evaluate the efficacy and selectivity of CD1c-targeting reagents, and define mechanisms of anti-tumour activity in vivo. Together, these studies will establish the feasibility of CD1c-directed immunotherapy and provide a foundation for the development of safer, more effective treatments for patients with acute leukaemia.

DISEASE RELVEANCE

Acute leukaemia, including acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL), is characterised by the uncontrolled proliferation of immature haematopoietic cells within the bone marrow, peripheral blood, and extramedullary tissues. Despite substantial advances in chemotherapy, targeted

therapies, and immunotherapy, relapse remains a major clinical challenge and is frequently associated with poor prognosis and limited treatment options.

Although immunotherapeutic approaches have transformed outcomes for selected patient groups, treatment-related toxicities, antigen escape, and therapeutic resistance continue to limit long-term efficacy. Current therapeutic targets are often expressed on normal haematopoietic cells, resulting in prolonged cytopenias, immune suppression, and other off-target effects. Furthermore, therapeutic options for relapsed disease and certain leukaemia subtypes remain limited.

KEY TECHNOLOGY

This project will combine advanced immunology, molecular profiling, and preclinical cancer modelling approaches to evaluate CD1c as a therapeutic target in acute leukaemia.

1) Primary AML and ALL samples may be used to characterise CD1c expression across disease subtypes and assess the activity of CD1c-targeting reagents in clinically relevant settings.
2) Multiparameter flow cytometric immune phenotyping, cytotoxicity assays, and cytokine profiling will be employed to evaluate target expression, immune activation, and anti-leukaemic activity.
3) High-resolution LC-MS/MS lipidomics may be utilised to identify tumour-associated and tumour-specific lipid antigens.
4) Preclinical in vivo xenograft leukaemia models will be used to evaluate the safety, efficacy, pharmacodynamics, and anti-tumour activity of CD1c-targeting therapeutics, enabling assessment of leukaemic burden, treatment response, and potential off-target effects in a physiologically relevant setting.
5) Single-cell and Spatial multiomics may be applied to investigate the organisation of malignant and immune cells within the tumour microenvironment and identify cellular networks associated with therapeutic efficacy.

TRAINING OPPORTUNITIES

This DPhil project will provide multidisciplinary training in human immunology, including primary immune cell isolation and differentiation, functional immune assays, and multiparameter flow cytometry, lipid biology, preclinical in vivo models, and advanced multi-omics technologies and bioinformatic analysis.

The project will further develop skills in experimental design, statistical analysis, and data integration to studying human disease. Working jointly between the Ogg and Chen groups, the student will gain interdisciplinary experience with regular interaction with clinicians, researchers, and patient cohorts with translational discoveries. The translational nature of the project is enhanced through the joint supervisory arrangement, benefiting from both fundamental scientific and clinical expertise.

The student will participate in laboratory meetings, journal clubs, and University-wide seminar programmes, providing opportunities for scientific discussion, networking, and collaboration. In addition, the student will have access to the Medical Sciences Division Skills Training Programme and a wide range of courses in genomics, statistics, manuscript preparation, presentation, leadership, public engagement, and responsible conduct of research, preparing them for future careers in academia, biotechnology, or clinical research.

KEY PUBLICATIONS

1. Consonni, M. et al. Human T cells engineered with a leukemia lipid-specific TCR enables donor-unrestricted recognition of CD1c-expressing leukemia. Nat Commun 12, 4844 (2021).
2. Wu, Y. et al. Immunotherapies of acute myeloid leukemia: Rationale, clinical evidence and perspective. Biomed Pharmacother 171, 116132 (2024).
3. Cao, T.P. et al. Sideways lipid presentation by the antigen-presenting molecule CD1c. Nat Commun 17, 998 (2025).
4. Huang, S. et al. CD1 lipidomes reveal lipid-binding motifs and size-based antigen-display mechanisms. Cell 186, 4583-4596 e4513 (2023).
5. Chen, Y.L. et al. Group A Streptococcus induces CD1a-autoreactive T cells and promotes psoriatic inflammation. Sci Immunol 8, eadd9232 (2023).

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1.8 Functional Analysis of Endometrial Cancer Drivers

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PROJECT OVERVIEW

Endometrial cancer is the most common gynaecological malignancy in the developed world, but until recently has been relatively poorly studied compared to other cancer types. We have recently completed the first analysis of the whole genome landscape of endometrial cancer (https://doi.org/10.64898/2026.06.15.730391), in which we have identified novel tumour subgroups, drivers and therapeutic targets. The results hold promise to refine stratification and improve treatment and prevention of endometrial cancer, however futher validation and functional characterisation is required to realise this potential. This project will address this by detailed analysis of human endometrial cancers and precancers and through the generation and analysis of functional disease models. Analyses will include:

- Further focused analysis of priority driver mutations in the Genomics England 100KGP endometrial cancer cohort and additional human tumour series available to our group
- Integrated multimodal analysis to understand the interplay beteween epithelial drivers and the tumour microenvironment, with focus on the immune response
- Development and characterisation of established (eg https://doi.org/10.15252/emmm.202217094) and novel functional models of endometrial drivers to test their effect on cellular and tissue phenotype and on therapeutic sensitivity
- Investigation of the basis of mutation cooperativity and antagonism using in selected cases using the above systems

Supervision will be available for all aspects of the project by experienced postdoctoral wet lab scientists and bioinformaticians from the Church lab and LynchVax groups (lead Church). There will be opportunity to travel to collaborating institutes (Leiden, Groningen, Basel) during the DPhil if desired.

DISEASE RELVEANCE

Endometrial cancer is the most common gynaecological malignancy in the developed world and is increasing in incidence. Understanding the mechanisms

by which it develops and spreads will help improve risk stratification and treatment.

KEY TECHNOLOGY

Existing whole-genome sequencing and transcriptome sequencing (RNAseq) of human tumours and existing functional models is currently being extended with novel models and additional ‘omics including spatial transriptomics. The project will therefore leverage a multimodal dataset representing the current state-of-the-art beyond that available in previous studies.

TRAINING OPPORTUNITIES

The student will join a well-supported and highly collaborative research program, and benefit from teaching on all skills required including formal taught courses on computational biology. Bioinformatic analyses will be done under the supervision of the Church group, and the endometrial cancer GeCIP team, and experimental work supported by dedicated postdoctoral scientist and research assistants in the Church laboratory.

KEY PUBLICATIONS

1. https://doi.org/10.15252/emmm.202217094
2. https://doi.org/10.64898/2026.06.15.730391
3. doi: 10.1158/2326-6066.CIR-20-0149

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1.9 Tumour-Immune Evolution in Lynch Syndrome Carcinogenesis

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PROJECT OVERVIEW

Lynch syndrome (LS) affects 1 in 350 individuals worldwide and causes lifetime cancer risk of up to 80%. LS is mostly caused by a germline pathogenic variant in one of four DNA mismatch repair (MMR) genes MLH1, PMS2, MSH6 and MSH2, and rarely by EPCAM deletions. During adult life, loss of the wild-type allele causes loss of MMR, a mutator phenotype, and somatic mutations which, over repeated cell divisions, cause precancer and cancer in multiple organs including colon and endometrium. Such somatic mutations often occur at repetitive DNA microsatellites, causing microsatellite instability (MSI), and when located in coding regions, frameshifts causing novel open reading frames (ORFs). These can be recognised as non-self by cytotoxic T cells, creating a strong selective pressure for immune evasion. Thus, vaccination against frameshift mutation-derived neo-peptides before the acquisition of immune evasion is a rational strategy for LS cancer prevention, and one that we are actively pursuing. While the last decade has witnessed substantial advances in our understanding of the mechanisms of LS carcinogenesis, much remains unknown. Key questions include:

- What are the molecular and immunological alterations in aberrant crypt foci – the earliest detectable pre-neoplastic lesion in the LS colon?
- Do all precancerous polyps in LS show MMR loss and frameshift mutations?
- What are the critical steps in progression of LS precancer to cancer?
- How does the immune response against LS tumours vary from ACF to polyp to cancer?

In the last two years in the LynchVax group, we have generated a very substantial dataset of LS precancers and cancers with multimodal data (WGS, RNAseq, immunopeptidomics) which we are currently extending with spatial and functional analyses. We have also created several novel mouse lines to determine the consequences of MMR loss in vivo. This project will leverage these resources to address these questions. In doing so it will increase our understanding of LS oncogenesis and identify novel targets for precision therapy and prevention.

DISEASE RELVEANCE

Lynch syndrome is the most common hereditary cause of cancer and affects one in 350 individuals, translating to over one million people in the US alone. Understanding the mechanisms by which malignant disease develops and progresses in LS is critical to inform planed efforts aimed at cancer interception

in this population. Thus, results from this project will have near-term clinical impact to a patient group of substantial unmet need.

KEY TECHNOLOGY

Existing whole-genome sequencing, transcriptome sequencing (RNAseq) and immunopeptidomics is currently being extended with spatial and functional analyses. Single cell methods are planned in a subset of samples. The project will therefore leverage a multimodal dataset representing the current state-of-the-art beyond that available in previous studies.

TRAINING OPPORTUNITIES

The student will join a well-supported and highly collaborative research program, and benefit from teaching on all skills required including formal taught courses on computational biology. Bioinformatic analyses will be done under the supervision of the Church group, and LynchVax team, and experimental work supported by dedicated postdoctoral scientist and research assistants in the Church laboratory.

KEY PUBLICATIONS

1. Resquens-Rueda M/Gneo L… **Church DN/**de Bruyn M. CD4+ T cell-licensed CD8+ T cells drive immunotherapy response in MHC-I negative DNA mismatch repair deficient cancer (submitted)
2. Cornish AJ… Quirke P/**Church DN**/Tomlinson IPM/Sottoriva A/Graham TA/Wedge DC/Houlston RS. Whole genome sequencing of 2,023 colorectal cancers reveals mutational landscapes, new driver genes and immune interactions. *Nature.* 2024 **633:**127-136 (PMID: 39112709)
3. Nowak M… Koelzer VH/**Church DN**. Single cell AI-based detection of DNA mismatch repair deficiency in 1,988 colorectal cancers reveals prognostic and predictive value in the SCOT trial. *Cell Rep Med.* 2024 **5:**101727 (PMID: 39293403)
4. Frei AL… **Church DN**/Koelzer VH Multiparameter immunoprofiling reveals combined prognostic value of intraepithelial CD8 and intrastromal FoxP3 infiltrate in stage II/III colorectal cancer: analysis of 3,409 cases from the SCOT and QUASAR2 trials. *Lancet Oncol* **25:**198-211 (2024)
5. Glaire MA… **Church DN**. Discordant prognosis of mismatch repair deficiency in colorectal and endometrial cancer reflects variation in antitumour immune response and immune escape. *J Pathol.* **257:**340-351 (2022). PMID: 35262923

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1.10 Engineering cDC1-Directed Costimulatory Agonists for Cancer Immunotherapy

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PROJECT OVERVIEW

Background. Conventional type 1 dendritic cells (cDC1) cross-present tumour antigen and are the cells principally responsible for priming naive tumour-specific $CD8^+$ T cells. Their abundance in human tumours is associated with response to checkpoint blockade. Within tumours, however, cDC1 frequently present antigen without delivering adequate costimulation, so priming is weak and short-lived.

Rationale. Costimulatory agonists were developed to correct this deficit, but systemic 4-1BB agonism causes dose-limiting hepatotoxicity, while antibodies engineered for weaker Fc-dependent crosslinking lack efficacy. The window is narrow because agonism is delivered wherever the receptor is expressed rather than where it is needed. Conditional bispecific agonists address this by requiring crosslinking on a second antigen, but existing molecules anchor to tumour cells or stroma. We propose to anchor them instead to the cell that performs cross-priming.

Hypothesis. Targeting 4-1BB and/or CD2 costimulation to the cDC1-mediated cross-priming immune synapse enhances anti-tumour T-cell responses while minimising the systemic toxicity of conventional costimulatory immunotherapy. CD2 is included because it lowers the TCR triggering threshold, acts across a short intermembrane distance intrinsically restricted to the contact interface, and its ligand CD58 is frequently lost in immunotherapy resistance.

Aim 1: Engineer and optimise cDC1-directed bispecific agonists. Targeting arms against XCR1, CLEC9A and PD-L1 will be paired with agonistic 4-1BB and CD2 modules across several formats, varying valency, epitope and geometry, on Fc-silenced backbones so that agonism depends strictly on cDC1 engagement. Molecules will be produced in CHO cells and characterised biophysically, advancing on the ratio of on-target to off-target agonism.

Aim 2: Define how targeted costimulation regulates the cross-priming synapse. Using primary and immortalised human cDC1, engineered T cells and NY-ESO-1 cross-presentation reporters, combined with lattice light-sheet microscopy and supported lipid bilayers with Professor Michael Dustin, we will determine how localised 4-1BB and CD2 engagement reorganises the synapse and alters cross-presentation and T-cell priming.

Aim 3: Evaluate efficacy in preclinical cancer models. Lead molecules will be tested in transplantable mouse tumour models with the Withers and Gálvez laboratories, measuring $CD8^+$ T-cell priming, tumour control, immunological memory and toxicity, benchmarked against a systemic 4-1BB agonist dosed to equivalent efficacy, with formal confirmation of cDC1 dependence.

Aim 4: Anchor the strategy in human disease. Target and cDC1 distribution will be mapped across human tumours by multiplex imaging and single-cell analysis, lead molecules tested on patient-derived tumour material ex vivo, and a candidate biomarker set defined for patient selection.

The student will be supervised jointly by Professor Melero at the Oxford Centre for Immuno-Oncology and Dr Fernandes at the CAMS Oxford Institute. The project is supported by the Cancer Research UK Discovery Programme COSTIMTHER.

DISEASE RELVEANCE

Checkpoint blockade benefits only a minority of patients, and the limiting step is frequently the failure to generate new tumour-specific $CD8^+$ T-cell responses rather than the reinvigoration of existing ones. cDC1 density in human tumours is associated with checkpoint inhibitor response across multiple cancer types, identifying cross-priming as a tractable point of intervention.

Costimulatory agonists could supply the missing signal, but their clinical development has stalled on toxicity: systemic 4-1BB agonism produced dose-limiting hepatitis, and safer variants proved insufficiently active. Restricting agonism to the cross-priming synapse addresses the cause of that toxicity rather than trading efficacy against it.

The project delivers candidate therapeutics together with a biomarker framework, cDC1 density, target receptor expression and CD58 status, for identifying the patients most likely to benefit. The approach is not restricted to one tumour type, and the human tissue component is designed to be extendable to cancers of high incidence in China, including gastric, oesophageal, hepatocellular and nasopharyngeal carcinoma.

KEY TECHNOLOGY

1) **Protein and antibody engineering:** design and assembly of bispecifics from single-domain antibody, scFv and Fab modules; systematic variation of valency, epitope, geometry and linker length; Fc-silenced backbones making agonism conditional on target engagement.

2) **Recombinant protein production:** CHO transient expression, affinity and size-exclusion purification, quality control by SEC-MALS, differential scanning fluorimetry and mass spectrometry.

3) **Receptor biophysics:** surface plasmon resonance and bio-layer interferometry for affinity ranking, epitope binning and simultaneous dual-target engagement.

4) **Cell-based agonism reporters:** 4-1BB and CD2 reporter lines with and without target-expressing cells, quantifying conditional agonism as the primary selection criterion.

5) **Human dendritic cell systems:** primary $CD141^{+}CLEC9A^{+}$ cDC1, immortalised human cDC1 lines and $CD34^{+}$/Flt3L-driven differentiation; Flt3L bone-marrow culture for mouse cDC1.

6) **Antigen cross-presentation:** NY-ESO-1 reporter systems with protein, long-peptide and dying-cell cargo; lentiviral transfer of TCRs and reporters into primary human T cells.

7) **Advanced imaging:** lattice light-sheet microscopy of live cDC1–T-cell conjugates and supported lipid bilayers reconstituting pMHC, ICAM-1 and bispecific-captured costimulatory ligands.

8) **In vivo immunology:** transplantable mouse tumour models, transgenic TCR systems, cDC1-deficient and cDC1-depletion models, tumour rechallenge, and high-dimensional spectral flow cytometry.

9) **Human tissue analysis:** multiplex immunofluorescence of tumour sections, ex vivo assays on dissociated tumour cells and tumour fragments, and analysis of single-cell and spatial transcriptomic datasets in R or Python.

TRAINING OPPORTUNITIES

– **Experimental training:** recombinant protein and bispecific antibody engineering; CHO-based production and purification; receptor biophysics by SPR and BLI; primary mouse and human dendritic cell biology; immortalised cDC1 systems; lentiviral gene transfer; antigen cross-presentation assays; lattice light-sheet immune synapse imaging; high-dimensional spectral flow cytometry; mouse models of cancer immunotherapy; multiplex imaging of human tumour tissue; and analysis of single-cell and spatial datasets in R or Python. Training will be delivered by Professor Melero and Dr Fernandes together with Professor Dustin, Dr Withers and Dr Gálvez in their respective areas, including a placement in a collaborating laboratory during the in vivo phase.

- **CAMS Oxford Institute training:** full membership of the COI graduate cohort, with COI seminars, work-in-progress sessions and the annual retreat; the first-year laboratory training course and bioinformatics courses run by Medical Sciences Skills Training; theme-based lectures by clinical scientists and heads of department; weekly grand-round seminars; and the opportunity for clinical observation within Oxford University Hospitals NHS Foundation Trust, which connects directly to the human tissue component of this project.
- **General graduate training:** NDM and Medical Sciences Division graduate programmes; departmental seminars and journal clubs; Centre for Immuno-Oncology scientific meetings; advanced microscopy and imaging courses; statistics and data analysis workshops; scientific writing, presentation and career development courses; and national and international conferences in cancer immunology and immunotherapy.
- Working across two laboratories, the student will have day-to-day supervision in each and will acquire a skill set, antibody engineering, advanced imaging, high-dimensional immune profiling and translational tumour analysis, that transfers directly to an independent research career.

KEY PUBLICATIONS

1. Gomis G et al. Antibody-Drug Conjugates Synergize with Agonist Anti-CD137 Monoclonal Antibodies in Solid Tumors. **Cancer Research** 2026. DOI: 10.1158/0008-5472.CAN-25-5849
2. López-Janeiro A et al. Conventional type-1 DC density is associated with checkpoint inhibitor response across multiple types of cancer. **Journal of Clinical Investigation** 2026. DOI: 10.1172/JCI200987
3. Luri-Rey C et al. Cross-priming in cancer immunology and immunotherapy. **Nature Reviews Cancer** 2025. DOI: 10.1038/s41568-024-00785-5
4. Melero I et al. CD137 (4-1BB)-Based Cancer Immunotherapy on Its 25th Anniversary. **Cancer Discovery** 2023. DOI: 10.1158/2159-8290.CD-22-1029
5. Teijeira A et al. Depletion of Conventional Type-1 Dendritic Cells in Established Tumors Suppresses Immunotherapy Efficacy. **Cancer Research** 2022. DOI: 10.1158/0008-5472.CAN-22-1046

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1.11 Turning Tumour Immune Escape into Co-Stimulation: Engineering Anchor-Conditional Agonists to Restore T Cell 'Go' Signals

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Prof. Ignacio Melero *ignacio.melero@immonc.ox.ac.uk*

PROJECT OVERVIEW

Background and rationale. Full T cell activation requires two signals: antigen recognition through the T cell receptor, and co-stimulation. Checkpoint-blockade antibodies release inhibitory brakes and have transformed oncology, yet most patients do not respond durably. An under-exploited reason is that tumours do not only apply brakes, they also remove the accelerator. Across tumour types, cancer cells lose or downregulate the ligands that deliver co-stimulation, including CD58 (the ligand for the CD2 co-receptor), HLA molecules, CD80/CD86 and TNF superfamily members, while retaining or over-expressing proteins that are inert or actively suppressive, such as HER2, PD-L1, mutant EGFR and cytokine receptors signalling through the JAK/STAT axis. Blocking an inhibitory receptor cannot restore a signal that is no longer delivered.

Hypothesis. Escape mechanisms are simultaneously liabilities and opportunities. The proteins a tumour retains or over-expresses are tumour-restricted anchors; the ligands it loses define which signals must be given back. Molecules that exploit the escape mechanisms to deliver “go” signals should convert escape into co-stimulation, conditional on the tumour being present.

Aim 1. Define tumour-restricted anchors and the co-stimulatory deficit. Using published genome-wide screens, transcriptomic and proteomic datasets, cell-surface interactome data from our group, and primary tumour material accessible through the co-supervisor, the student will build a paired map across selected tumours of (i) surface proteins retained or over-expressed on cancer cells but largely absent from healthy tissue, and (ii) co-stimulatory ligands lost from those same tumours.

Aim 2. Engineer anchor-conditional co-stimulation. The student will design and produce bispecific and multispecific proteins that bind a tumour-restricted anchor with one arm and deliver co-stimulation to T cells with the other. Three strategies will be compared: reconstituting a lost co-receptor interaction; agonism of TNF receptor superfamily members (4-1BB, OX40, CD27, GITR), where clustering geometry rather than ligand blockade is the active principle; and intracellular rewiring, in which our proximity-engineering platform recruits kinases to, or displaces JAK-dependent suppressive signalling from, a receptor

so that a tumour-supporting receptor behaves as a co-stimulatory one. Epitope, affinity, avidity, valency and intermembrane geometry will be varied systematically, supported by surface plasmon resonance, structural modelling and yeast-display selection.

Aim 3. Establish the design rules and test the molecules in physiological settings. Molecules will be assessed in primary human T cell assays using antigen-specific T cell receptor systems, with isogenic ligand-knockout target lines to demonstrate that the engineered molecule restores the specific signal that was lost. Read-outs include activation markers, cytokine secretion, proliferation, cytotoxicity and RNA sequencing. Selectivity will be tested by measuring anchor-independent activity. Leads will be benchmarked against approved checkpoint inhibitors and evaluated in antigen-low settings relevant to CAR-T and T cell engager escape, using in vivo and patient-derived models provided by the co-supervisor, including a recently developed multifocal hepatocellular carcinoma hydrodynamic model, where multiple genetically defined lesions arise autochthonously that allow for testing of immunotherapies in a complex cancer model.

Expected outcomes. The project will deliver a map linking tumour escape to the co-stimulatory signals it removes; quantitative design rules describing how geometry, valency and affinity govern anchor-conditional co-stimulation; and first-in-class molecules that restore T cell function selectively at the tumour, applicable where checkpoint blockade fails.

DISEASE RELVEANCE

This project addresses resistance to cancer immunotherapy, the central unmet need in clinical oncology. Checkpoint inhibitors benefit only a minority of patients, and loss of co-stimulatory ligands is an established, recurrent route of escape: CD58 loss ranks among the top mechanisms in genome-wide screens, is found in a substantial fraction of patients treated with CAR-T cells, and is associated with markedly shorter progression-free survival. Loss of HLA and of other co-stimulatory ligands similarly limits responses to checkpoint blockade, T cell engagers and adoptive cell therapies.

Because the strategy proposed here restores a missing signal rather than removing a brake, it is expected to be effective precisely in the tumours that resist current agents, and to be compatible with, rather than duplicative of, existing standard of care. The anchors under consideration (for example HER2, PD-L1 and mutant EGFR) are broadly distributed across solid and haematological malignancies, so successful molecules would be applicable well beyond a single indication. The project will also generate biomarker information that could support patient selection in future clinical development.

KEY TECHNOLOGY

The project combines protein engineering with quantitative cellular immunology. Core technologies include: rational and structure-guided design of bispecific and multispecific proteins; recombinant expression in mammalian and insect systems; yeast surface display for library design, affinity maturation and epitope selection; surface plasmon resonance and thermostability analysis for biophysical characterisation; X-ray crystallography and computational structure prediction to define epitopes and molecular geometry; CRISPR editing to generate isogenic ligand-knockout target cell lines; primary human T cell culture with antigen-specific T cell receptor systems; multiparameter flow cytometry, live-cell imaging and cytotoxicity assays; cytokine profiling; and bulk RNA sequencing with downstream computational analysis.

The group's proximity-engineering platform, which uses bispecific molecules to control which enzymes act on the cytoplasmic tail of a receptor, provides the basis for the intracellular rewiring strand of Aim 2. In vivo and ex vivo patient-derived tumour models are accessed through the co-supervisor. The student will therefore work across the full arc from computational target selection, through molecule design and production, to functional testing in physiologically relevant human systems.

TRAINING OPPORTUNITIES

The student will be trained in broad set of complementary skills spanning discovery and translation. Technical training will include molecular biology and cloning, protein design, expression and purification, biophysical characterisation of protein interactions by surface plasmon resonance and thermostability analysis, structural biology and computational structure prediction, protein engineering by yeast display library design and selection, CRISPR-based cell line engineering, primary human T cell assays, multiparameter flow cytometry, and the analysis of transcriptomic datasets.

Alongside laboratory skills, the student will be trained in experimental design, the use of appropriate controls and statistics, critical reading of the literature, scientific writing and presentation. They will present regularly at group meetings, at the CAMS Oxford Institute and Centre for Immuno-Oncology seminar series, and at national and international conferences, and will be supported in preparing first-author publications.

The project is deliberately translational, and the student will gain exposure to how academic discovery moves towards the clinic: target and molecule selection criteria, intellectual property, and the requirements of preclinical

development. Co-supervision provides direct access to clinically oriented immuno-oncology and to patient-derived material. The student will have full access to the facilities and resources of the Nuffield Department of Medicine and the wider University of Oxford, including core facilities for flow cytometry, imaging, structural biology and sequencing, and to the University's extensive graduate training programme.

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. Wojtowicz WM, Vielmetter J, Fernandes RA, Siepe DH, Eastman CL, Chisholm GB, Cox S, Klock H, Anderson PW, Rue SM, Miller JJ, Glaser SM, Bragstad ML, Vance J, Lam AW, Lesley SA, Zinn K, Garcia KC. A human IgSF cell-surface interactome reveals a complex network of protein-protein interactions. (2020) Cell 182:1027-1043
3. 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 SJ, 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
4. Chang VT*, Fernandes RA*, Ganzinger KA*, Lee SF*, Siebold C, McColl J, Jonsson 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
5. Ochoa MC, Sanchez-Gregorio S, de Andrea CE, Garasa S, Alvarez M, Olivera I, Glez-Vaz J, Luri-Rey C, Etxeberria I, Cirella A, Azpilikueta A, Berraondo P, Argemi J, Sangro B, Teijeira A, Melero I. Synergistic effects of combined immunotherapy strategies in a model of multifocal hepatocellular carcinoma. Cell Rep Med. 2023 Apr 18;4(4):101009.

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1.12 Characterising Tumour-Reactive T Cells in Lung Cancer Patients Undergoing Immune Checkpoint Inhibitor Therapy

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Dr. Yanchun Peng yanchun.peng@ndm.ox.ac.uk

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 RELVEANCE

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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THEME 2: CARDIOVASCULAR DISEASES

2.1 Extracellular Vesicle Signalling as a Driver of Inflammation and Fibrosis in Hypertrophic Cardiomyopathy

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PROJECT OVERVIEW

Hypertrophic cardiomyopathy (HCM) is a common inherited cardiac disorder characterised by cardiomyocyte hypertrophy, hypercontractility, inflammation, microvascular dysfunction and progressive myocardial fibrosis. Although cardiac myosin inhibitors can directly target sarcomere hypercontractility, the mechanisms by which genetically abnormal cardiomyocytes communicate with surrounding cells to drive adverse tissue remodelling remain poorly understood. Our recent work identifies extracellular vesicles (EVs) as a previously unrecognised signalling axis in HCM and provides the foundation for this DPhil project.

Using human induced pluripotent stem cell-derived left ventricular cardiomyocytes (iPSC-LV-CMs) harbouring pathogenic variants, we have demonstrated pathological hypertrophy, hypercontractility and increased energetic demand alongside profound changes in EV biology. HCM cardiomyocytes release fewer EVs, while transcriptomic and proteomic analyses identify coordinated suppression of EV-biogenesis pathways. Importantly, the EVs that are released exhibit disease-associated cargo remodelling, including extracellular-matrix and inflammatory signatures. Functionally, HCM-derived EVs selectively induce inflammatory expression in human left-ventricular fibroblasts, establishing a cardiomyocyte-to-fibroblast inflammatory signalling pathway.

This project will determine how HCM reprogrammes EV biogenesis and how disease-associated EVs drive fibro-inflammatory remodelling. First, we will define the molecular pathways responsible for impaired EV generation and altered cargo selection using complementary genetic, molecular, imaging and multi-omic approaches in iPSC-cardiomyocyte models. Second, candidate EV cargo and signalling pathways will be functionally interrogated in cardiac fibroblasts and multicellular cardiovascular models to distinguish association from causal signalling. Third, we will determine whether these mechanisms extend across genetically distinct forms of HCM and translate to human disease.

A major strength will be the opportunity to connect mechanistic Oxford models with CAMS/Fuwai clinical and translational cardiovascular expertise, including prospective access to cardiomyopathy and cardiac-transplantation material. Human tissue and/or biofluid studies, subject to sample availability and appropriate approvals, will enable candidate EV pathways identified experimentally to be evaluated directly in advanced human cardiac disease.

By moving from genetically controlled human models to mechanism, multicellular signalling and human validation, this DPhil will establish whether pathological EV communication represents a conserved driver of HCM progression. Ultimately, the project aims to identify EV-based biomarkers and therapeutically tractable signalling pathways that complement sarcomere-directed therapy and target the inflammatory and fibrotic consequences of HCM.

DISEASE RELVEANCE

Hypertrophic cardiomyopathy (HCM) is a common inherited cardiac disease characterised by pathological hypertrophy, diastolic dysfunction, microvascular abnormalities and progressive myocardial fibrosis. While sarcomere-directed therapies such as cardiac myosin inhibitors address hypercontractility, the mechanisms responsible for the inflammatory and fibrotic remodelling that ultimately contributes to disease progression remain incompletely understood.

Our preliminary studies identify extracellular vesicle (EV) signalling as a previously unrecognised component of HCM pathobiology. HCM cardiomyocytes exhibit suppressed EV biogenesis and release EVs with altered protein cargo enriched for extracellular-matrix and inflammatory pathways. These EVs selectively induce IL-6 in cardiac fibroblasts, directly linking the diseased cardiomyocyte to a recipient cell central to myocardial remodelling. Importantly, cardiac myosin inhibition improves the abnormal metabolic phenotype without restoring EV secretion, indicating that EV dysregulation persists despite correction of sarcomere-associated dysfunction.

Defining this pathway could reveal biomarkers of disease activity and new therapeutic targets for inflammation and fibrosis that complement existing sarcomere-directed treatments, with the ultimate aim of preventing progressive myocardial remodelling in HCM.

KEY TECHNOLOGY

This project will integrate human induced pluripotent stem cell (iPSC) disease modelling, extracellular vesicle (EV) analysis, advanced imaging and multi-omics

to define mechanisms of pathological intercellular communication in hypertrophic cardiomyopathy (HCM).

Genetically defined, iPSC-derived left ventricular cardiomyocytes will provide a human experimental platform in which EV phenotypes can be attributed directly to HCM-causing variants. EVs will be isolated using established size-exclusion and differential centrifugation approaches and characterised according to MISEV2023 guidelines using complementary technologies including nanoparticle tracking analysis, single-particle antibody-based profiling, electron microscopy and molecular assays. Our preliminary studies demonstrate the feasibility of these approaches and identify substantial genotype-dependent changes in EV abundance and composition.

Live-cell fluorescence imaging will be developed to investigate EV biogenesis, intracellular trafficking and release with temporal resolution, moving beyond conventional endpoint EV measurements. Quantitative image-analysis workflows will enable disease-associated alterations in vesicle dynamics to be linked to cellular phenotype.

Transcriptomics and quantitative mass-spectrometry proteomics will identify regulatory pathways controlling EV production and disease-specific cargo selection. EV proteomics will be integrated with cardiomyocyte molecular profiles to prioritise candidate mediators for functional validation. Candidate EV pathways will subsequently be manipulated genetically and pharmacologically and tested in human cardiac fibroblasts and multicellular cardiovascular models.

Finally, single-particle molecular profiling, including Raman-based approaches, provides an opportunity to translate mechanistic signatures into human HCM samples. Together, these technologies provide a multiscale platform linking genetic disease, EV biogenesis and cargo, intercellular signalling and clinically relevant human phenotypes.

TRAINING OPPORTUNITIES

This multidisciplinary DPhil will provide comprehensive training spanning human cardiovascular disease modelling, extracellular vesicle (EV) biology, advanced imaging, multi-omics and translational cardiovascular science.

The student will receive hands-on training in human iPSC culture and differentiation into cardiovascular cell types, including left ventricular cardiomyocytes, together with phenotypic and functional characterisation of genetically defined HCM models. Training in EV biology will encompass conditioned-media collection, differential centrifugation and size-exclusion

chromatography, nanoparticle tracking analysis, single-particle EV characterisation, molecular profiling and application of current MISEV guidelines. These approaches build directly upon established expertise and technologies within the supervisory environment.

A major component will be training in quantitative fluorescence and live-cell microscopy, developing approaches to visualise EV trafficking and release in real time. The student will acquire quantitative image-analysis skills using established and computational workflows. Training in transcriptomics, proteomics and bioinformatics will enable integration of cellular and EV datasets to identify mechanisms controlling vesicle biogenesis, cargo selection and recipient-cell responses.

Functional studies will provide experience in cardiac fibroblast and endothelial cell biology, genetic and pharmacological perturbation, and multicellular cardiovascular models. The student will therefore progress from mechanistic discovery through target validation to translational investigation.

The Oxford–CAMS collaborative environment will provide additional exposure to human cardiovascular disease and opportunities for collaborative studies using clinically relevant cardiomyopathy material. The student will also develop transferable skills in experimental design, statistics, scientific writing, presentation, research integrity and reproducible research, with opportunities to present findings at national and international cardiovascular and EV meetings.

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5. Akbar N, Digby JE, Cahill TJ, et al. Endothelium-derived extracellular vesicles promote splenic monocyte mobilization in myocardial infarction. JCI Insight. 2017;2(17):e93344. doi:10.1172/jci.insight.93344.

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2.2 Imaging in Preventive Cardiology Research

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PROJECT OVERVIEW

The Preventive Cardiology Research Group aims to improve how we identify and prevent heart disease in young people.

There is a particular interest in links between pregnancy complications such as preeclampsia and later cardiovascular disease in both the mother and child. The group uses multi-organ imaging and sample collection, in combination with new methodologies, including machine learning, to understand mechanism and disease progression. Data is collected within observational studies and randomised trials undertaken by the group both within the UK and internationally. Therefore projects in the research group are appropriate to clinical trainees as well as physiology graduates and computational scientists with an interest in clinical research.

The group works in three areas:

1) *Novel markers of early disease* - Using imaging and laboratory studies to identify early cardiac and vascular changes in young people at risk of cardiovascular disease. In particular, those predisposed to hypertension, such as families with a history of preeclampsia or preterm birth.
2) *Young adult cardiovascular prevention trials* - Running trials to understand how novel approaches to lifestyle and clinical management may be able to modify these early risk cardiovascular phenotypes to prevent the development of later disease.
3) *Artificial intelligence* - Pioneering the application of artificial intelligence to large research imaging datasets to improve the clinical tools already available to identify those at risk, such as stress echocardiography, and to identify next generation imaging and management approaches.

DISEASE RELVEANCE

The research aims to improve how we identify and prevent heart disease in young people, and much of the research is focused on applications in hypertensive pregnancy. Hypertensive pregnancy affects 1 in 10 women, is a leading global cause of maternal morbidity and mortality. Women who develop blood pressure problems during pregnancy are more likely to have high blood pressure in later life as well as heart attacks or strokes. Within 10 years, up to

one-third of affected women require treatment for hypertension, yet current care largely monitors these young women until conventional risk factors or established disease emerge. There is therefore a major need to intervene decades earlier, when cardiovascular damage may still be reversible.

KEY TECHNOLOGY

The research combines several technologies, including AI-enabled cardiovascular imaging, particularly machine-learning analysis of echocardiography, combined with multimodal imaging and digital-twin/computational models for early disease detection and prediction:

AI / machine learning for echocardiography: Applying artificial intelligence to cardiac ultrasound images to improve the clinical tools already available and better detect patterns associated with coronary disease and other cardiovascular abnormalities.

Multimodal cardiovascular imaging: echocardiography plus cardiac/brain MRI and microvascular imaging, used to identify early changes in the heart, blood vessels and brain.

Computational modelling / digital twins: using machine learning on multi-organ datasets to model how cardiovascular disease develops and progresses.

TRAINING OPPORTUNITIES

This project will provide training in imaging, cardiovascular disease development and human physiology using a range of techniques appropriate to the project. These methods include echocardiography, vascular ultrasound, cardiovascular magnetic resonance, measures of macro- and microvascular structure and function (endothelial function, microscopy, laser Doppler flowmetry, venous occlusion plethysmography) and cardiopulmonary exercise testing. Where appropriate training in image processing and analysis is available, including computational modelling and application of machine learning. The student would learn about regulatory issues surrounding clinical studies and randomised trials such as ethics, hospital R&D and GCP and attend relevant courses. The type of projects available in the research group are appropriate to both clinical trainees and physiology graduates with an interest in clinical research. As there are close links with laboratory studies on clinical samples there are also opportunities for interested, and appropriately experienced, individuals to combine clinical data collection with laboratory research.

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2.3 Multimodal Mapping of Myocardial Fibrosis in Dilated Cardiomyopathy

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PROJECT OVERVIEW

Dilated cardiomyopathy (DCM) is a leading cause of heart failure, transplantation and sudden cardiac death. Cardiac magnetic resonance (CMR) with late gadolinium imaging identifies mid-wall replacement fibrosis in the interventricular septum in around a third of patients, predicting ventricular arrhythmia and adverse outcome. The cellular mechanisms generating this fibrosis, and its stereotyped mid-wall distribution, remain unknown.

Our group combines deep clinical phenotyping, CMR, histology and spatial transcriptomics in DCM. Through UK heart transplant centre networks we have unusual access to explanted left ventricular tissue with matched pre-transplant in vivo CMR, allowing molecular readouts to be anchored to imaging-defined fibrosis in the same heart. The immediate priority is a reproducible analysis pipeline applied to existing pilot data and banked samples.

Aim 1 will establish a multimodal analysis pipeline. The student will register digitised histology and spatial transcriptomic data to CMR fibrosis maps, and extend custom in-house algorithms for membrane-based segmentation of cardiomyocytes, cell-state annotation and niche detection in myocardium, where conventional nuclear segmentation performs poorly. Quality control, benchmarking and documentation will be tested on existing pilot datasets before extension to further UK samples.

Aim 2 will define the cellular environments of mid-wall fibrosis. CMR and histology will direct sampling of fibrotic and preserved myocardium from the same heart. CosMx 18,000-plex near-whole-transcriptome imaging will resolve cardiomyocyte, fibroblast, immune and vascular states at subcellular resolution with positions retained. The student will map how these populations are organised across the fibrotic border zone and infer ligand-receptor signalling driving fibroblast activation, prioritising candidate antifibrotic targets.

Aim 3 will test a small number of prioritised pathways in established iPSC-derived cardiac organoids, using targeted perturbation rather than broad screening, to ask whether candidate mechanisms and antifibrotic effects observed in patient tissue are reproducible in a controlled human model.

As the UK dataset grows, the pipeline will be prepared for larger cohorts. Collaboration will be sought with a major Chinese cardiovascular centre with

well-characterised DCM patients, CMR and suitable myocardium. Subject to funding and approvals, a focused Chinese dataset may test reproducibility of selected UK findings in a second clinical setting.

The project builds on pilot spatial data, transplant-network tissue access, cardiac imaging expertise and an established in-house analysis pipeline. Because fibroblast activation programmes are convergent across organs, mechanisms defined here may inform fibrosis in the kidney, lung and liver, and the identification of antifibrotic candidates of broader relevance.

DISEASE RELVEANCE

1) DCM is an important cause of heart failure, transplantation and sudden cardiac death, particularly in younger adults. Mid-wall fibrosis detected by CMR is associated with ventricular arrhythmia, disease progression and mortality. However, imaging shows where fibrosis is present without identifying the cells and molecular processes involved. Current treatment primarily addresses the underlying cardiac condition and its clinical consequences, while therapies that directly target myocardial fibrosis remain an area of active investigation.
2) Combining clinical information, CMR, histology and spatial transcriptomics may provide a clearer account of the biological changes represented by the imaging findings. Establishing a reliable analysis pipeline is an essential step towards studying larger patient cohorts and determining which cellular features are consistently associated with fibrosis.
3) The initial work will focus on existing UK patients and biobank tissue, providing a practical basis for the student's research. In the longer term, applying the same methods to data and tissue collected through a Chinese cardiovascular centre could test whether selected findings are reproducible in another clinical setting. Any observed differences would be considered in relation to disease stage, treatment, sample collection and other cohort characteristics. The project will therefore address an important clinical problem while building the foundation for future collaborative studies.

KEY TECHNOLOGY

The project will develop a reproducible pipeline for integrating clinical data, CMR, histology and spatial transcriptomics. The student will begin with existing UK pilot datasets, allowing the analytical methods and quality-control procedures to be established before the study is extended to additional samples.

- **Spatial transcriptomics.** CosMx whole-transcriptome spatial imaging will provide molecular measurements from intact formalin-fixed, paraffin-embedded myocardial sections. The assay measures approximately 18,000 protein-coding genes at subcellular resolution. In contrast to dissociated single-cell methods, it retains information about the position of each cell within the tissue. This makes it possible to examine the cellular composition of fibrotic regions and their surrounding myocardium.
- **Cardiac cell segmentation.** Cardiac cell segmentation is technically challenging because cardiomyocytes are large, densely arranged and irregularly shaped. The project will build on the group's existing workflow, combining membrane staining, high-resolution imaging and deep learning-based segmentation. Cell identities will be assigned using recognised molecular markers and appropriate cardiac reference datasets, with histology used to support quality control.
- **Cardiac magnetic resonance.** Image-registration methods will align CMR-defined anatomy, serial histological sections and spatial measurements where matched data are available. The analytical pipeline will include cell-state annotation, spatial neighbourhood analysis and assessment of potential cell-cell communication. Candidate interactions will be considered alongside the physical proximity of the relevant cell populations.
- **iPSC-derived cardiac organoids** Selected observations will be examined using established iPSC-derived cardiac models. The pipeline will be designed with clear documentation, version-controlled code and standard quality-control criteria so that it can be applied consistently to larger UK datasets and, where feasible, to future samples from a collaborating centre in China.

TRAINING OPPORTUNITIES

The student will receive multidisciplinary training in cardiovascular imaging, human tissue research, spatial transcriptomics and computational analysis. The programme can be adapted for a student from a clinical, biomedical or quantitative background.

- **Year 1** During the first year, the student will develop an understanding of DCM, myocardial fibrosis, research ethics and human tissue governance. They will receive training in CMR interpretation, cardiac histology and reproducible analysis using Python or R. Working with the group's existing pilot datasets will allow the student to gain practical experience while the analysis pipeline is being established and further samples are prepared.
- **Year 2** In the second year, the student will develop expertise in spatial-transcriptomic analysis. Training will include image quality control, cardiac

cell segmentation, cell-state annotation, spatial statistics and integration with clinical and imaging data. The student will learn how to document analytical decisions, manage technical variation and produce a pipeline that can be used reliably across multiple experiments.

- **Years 3** The third year will focus on applying the pipeline to an expanded UK dataset and investigating the cellular environments associated with fibrosis. The student will also gain experience in iPSC-derived cardiac microtissues or organoids through focused experiments based on findings from the patient samples. If an appropriate Chinese collaboration and the necessary resources are in place, the student may contribute to a pilot cross-cohort analysis using harmonised methods.
- **Years 4** The final year will concentrate on validation, publication and thesis preparation. Throughout the project, the student will take part in regular supervisory meetings, laboratory and computational group meetings, journal clubs and departmental seminars. They will be encouraged to present their work at national and international conferences and will be supported in preparing at least one first-author manuscript. The project will provide a strong foundation in multimodal cardiovascular research and the practical skills required to contribute to larger clinical and international studies.

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2.4 Understanding Heterogeneity in Hypertrophic Cardiomyopathy: A Joint Oxford-Fuwai DPhil Programme

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PROJECT OVERVIEW

Hypertrophic cardiomyopathy (HCM) has highly variable clinical trajectories, even among patients with similar degrees of hypertrophy, for reasons that remain poorly understood. A joint DPhil programme would combine Oxford's advanced imaging, longitudinal phenotyping and international HCM cohorts with Fuwai's large clinical and surgical populations, longitudinal follow-up and access to myocardial tissue. The programme would focus primarily on two closely related clinical questions: how different therapies modify disease trajectory, and how we can identify patients at risk of progression. The successful student would undertake one clearly defined project within this framework, tailored to their interests and expertise.

1. How do different HCM therapies alter myocardial remodelling and disease trajectory, and can we predict treatment response?

A lead project would establish a prospective mechanistic imaging study examining myocardial remodelling following cardiac myosin inhibition and septal myectomy. Harmonised Oxford CMR approaches applied before and after treatment would determine whether medical and surgical relief of obstruction produce distinct patterns of myocardial recovery, including changes in hypertrophy, ventricular geometry, fibrosis, function, microstructure, perfusion and myocardial oxygenation. Oxford myosin inhibitor cohorts and Fuwai's high-volume myectomy programme provide complementary populations in which to address this question. Longer-term follow-up would determine the durability and clinical significance of these changes. Anatomical features including hypertrophy distribution, cavity size, midventricular obstruction and papillary muscle abnormalities could be evaluated alongside imaging and clinical characteristics to identify differential treatment response. This could ultimately inform more personalised selection between cardiac myosin inhibition, septal myectomy and alternative treatment strategies.

2. Can novel imaging and AI-derived markers predict HCM progression and long-term clinical risk?

Oxford and Fuwai have complementary, deeply phenotyped HCM populations that provide a powerful platform for joint discovery and validation of markers of disease progression. Oxford's international HCMR Registry provides long-term outcome data and established quantitative imaging phenotypes, while Fuwai provides a large independent HCM population with longitudinal clinical and

imaging follow-up. Measures of cardiac shape, strain, fibrosis, tissue characteristics and AI-derived imaging and ECG phenotypes could be evaluated across both populations, enabling markers identified in either cohort to be independently tested in the other. Serial echocardiography and CMR would determine whether baseline phenotypes or early changes identify patients at risk of progressive remodelling, fibrosis or ventricular dysfunction. Integration with ECG and clinical data could enable development and cross-validation of multimodal models predicting heart failure, arrhythmia and progression to advanced disease or septal reduction therapy.

Complementary mechanistic studies

For students with a particular interest in genetics or myocardial biology, these clinical projects could be complemented by Fuwai's genomic and myectomy tissue resources. Genetic susceptibility, including sarcomeric variants and polygenic risk, could be related to imaging-defined disease phenotypes, while spatial molecular profiling of myocardium could investigate the biological pathways underlying specific patterns of remodelling, progression or treatment response. Linking pre-operative imaging to myocardial tissue from the same patients would provide a particularly distinctive opportunity to investigate the biological basis of novel imaging phenotypes and identify potential biomarkers or therapeutic pathways.

Together, the programme would address two immediate challenges in contemporary HCM care: how treatment modifies the underlying disease, and how we identify patients at greatest risk of progression. By combining Oxford's advanced imaging, longitudinal cohorts and analytical expertise with Fuwai's clinical scale, surgical programme and myocardial tissue resources, the programme would provide a platform for developing more personalised approaches to the treatment and surveillance of HCM.

DISEASE RELVEANCE

Hypertrophic cardiomyopathy is one of the most common inherited cardiac conditions, affecting approximately 1 in 500 people world-wide, and is an important cause of heart failure, arrhythmia and sudden cardiac death. Its clinical course is highly heterogeneous: while many patients remain stable for decades, others develop progressive fibrosis, ventricular dysfunction, arrhythmias or severe obstruction requiring intervention. Our ability to predict these divergent trajectories remain limited. This unmet need is increasingly important as the therapeutic landscape for HCM changes rapidly. Cardiac myosin inhibitors have introduced a new pharmacological approach to obstructive HCM, while septal myectomy and other established interventions remain highly effective in selected patients. Gene-based and other targeted therapies are also entering clinical development. As therapeutic options expand, the key clinical challenge is shifting from whether HCM can be treated to which treatment should be given to which patient, and at what stage of disease. There

is therefore an urgent need to understand the biological basis of disease heterogeneity and develop biomarkers that predict progression and treatment response. By integrating genetics, advanced imaging, circulating biomarkers, human myocardial tissue and longitudinal outcomes, this programme aims to provide the mechanistic framework needed to enable precision treatment of HCM.

KEY TECHNOLOGY

The project will combine advanced cardiovascular imaging, longitudinal phenotyping and quantitative analysis to determine how the HCM phenotype changes naturally and in response to treatment. Oxford has developed CMR approaches including diffusion tensor CMR (DT-CMR), which assesses myocardial microstructure and cardiomyocyte organisation, and oxygen-sensitive CMR (OS-CMR), which assesses myocardial oxygenation. Together with measures of cardiac morphology, function, perfusion and fibrosis, these approaches enable detailed characterisation of myocardial phenotype and remodelling. A major focus will be harmonised imaging before and after cardiac myosin inhibition and septal myectomy to determine whether medical and surgical treatment produce distinct patterns of myocardial recovery. Serial imaging and longer-term follow-up across Oxford and Fuwai cohorts will place these changes within the broader trajectory of HCM, identifying features associated with reverse remodelling or progressive disease. Quantitative image analysis and artificial intelligence will enable these longitudinal phenotypes to be integrated at scale. Deeply phenotyped Oxford and Fuwai datasets will support discovery and cross-validation of imaging and multimodal biomarkers, including cardiac shape, strain, tissue characteristics and AI-derived imaging and ECG phenotypes. Serial data will enable models to capture trajectories of myocardial remodelling and identify patients at risk of heart failure, arrhythmia or advanced disease. Selected imaging phenotypes could additionally be interrogated mechanistically using Fuwai's myectomy tissue and genomic resources. Linking pre-operative imaging to spatial molecular profiling and histopathology of resected myocardium would allow imaging abnormalities to be mapped to their cellular and molecular substrates, while genetic data could investigate whether inherited susceptibility contributes to myocardial phenotype, progression or treatment response. These technologies provide an integrated platform for understanding myocardial remodelling, predicting progression and treatment response, and enabling more personalised HCM care.

TRAINING OPPORTUNITIES

1) Advanced cardiovascular imaging: Training in state-of-the-art CMR acquisition and analysis, including quantitative tissue characterisation, perfusion, DT-CMR, OS-CMR, magnetic resonance spectroscopy, cardiac

shape and strain analysis, with opportunities to apply harmonised approaches across Oxford and Fuwai.

2) Longitudinal phenotyping and treatment-response studies: Training in the design and analysis of prospective longitudinal studies, including serial imaging before and after cardiac myosin inhibition and septal myectomy, to characterise myocardial remodelling, disease progression and differential treatment response.

3) Artificial intelligence and quantitative data science: Training in quantitative image analysis, machine learning and longitudinal modelling, including integration of imaging, ECG and clinical data to identify disease trajectories and develop predictive models that can be cross-validated between Oxford and Fuwai.

4) Clinical and translational HCM research: Exposure to large, deeply phenotyped HCM cohorts, specialist clinical services, cardiac myosin inhibitor programmes and Fuwai's high-volume septal myectomy programme, providing experience in prospective study design, longitudinal phenotyping, mechanistic studies and clinical trials.

5) Human myocardial tissue and spatial biology: Opportunities to link pre-operative imaging with myectomy tissue through histopathology and spatial molecular profiling, enabling selected imaging phenotypes to be related directly to their cellular and molecular substrates.

6) Genomics and multimodal phenotyping: Opportunities to integrate sarcomeric and polygenic genetic data with imaging, tissue and clinical phenotypes to investigate whether genetic susceptibility contributes to differences in myocardial phenotype, disease progression and treatment response.

7) International collaborative research: Joint supervision and research experience across Oxford and Fuwai will provide training in multicentre study design, imaging and data harmonisation, cross-population validation and delivery of international translational research.

Note: Sharing of data between institutions will require an amendment into relevant existing ethics.

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2.5 Spatial Multi-Omics Mapping of Macrophage-Centred Fibro-Inflammatory Remodelling in Human Atrial Fibrillation

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PROJECT OVERVIEW

Background: Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is a major cause of stroke, heart failure and premature mortality. Progression of AF is associated with structural remodelling of the atrial myocardium, including inflammation, fibrosis and cardiomyocyte dysfunction. However, the cellular mechanisms driving these changes remain incompletely understood because conventional transcriptomic and proteomic approaches lack spatial information and cannot resolve interactions between individual cell populations within the tissue microenvironment.

Pilot data: our preliminary human spatial proteomic studies in patients with persistent AF identified marked remodelling of the right atrial myocardium characterised by expansion of M2-like macrophages, activated fibroblast populations and stress-associated cardiomyocyte phenotypes. Importantly, spatial analyses suggest that these cell types form organised fibro-inflammatory niches, with increased proximity between macrophages, fibroblasts and cardiomyocytes in AF atria, suggesting that macrophage-centred cellular interactions may drive AF-associated atrial remodelling.

Hypothesis: macrophage-centred fibro-inflammatory niches are important regulators of atrial remodelling in persistent AF and that these interactions are enriched in atrial tissue compared with left ventricular myocardium.

To test this hypothesis, the student will recruit ~30-40 patients undergoing cardiac surgery, including 15 patients with persistent AF and 15 control patients in sinus rhythm. Right and left atrial appendage tissue will be paired with left ventricular samples. Clinical phenotyping will include demographics, co-morbidities, ECG and echocardiography, medications, AF duration and sub-types, post-surgical history and post-operative outcomes.

Project objectives:

1) Validate macrophage-centred fibro-inflammatory remodelling in an independent human cohort. Multiplex immunofluorescence, quantitative histology and molecular profiling will be used to determine whether persistent AF is consistently associated with expansion of CD68+CD163+ macrophages, activated fibroblasts (αSMA+, PI16+, POSTN+) and stress-

associated cardiomyocyte populations. Fibrosis burden will be quantified using histological approaches and correlated with cellular phenotypes.

2) Determine the spatial organisation of cellular interaction networks in persistent AF. Advanced image-analysis pipelines will be used to quantify macrophage-fibroblast and macrophage-cardiomyocyte proximity, cellular neighbourhood composition and chamber-specific differences between atrial and ventricular tissue.

3) Define molecular pathways underlying fibro-inflammatory niches using spatial multi-omics. A carefully selected subset of samples will undergo Imaging Mass Cytometry and spatial transcriptomic profiling through established collaborations within Oxford. These analyses will identify signalling pathways and ligand-receptor networks associated with macrophage-fibroblast-cardiomyocyte interactions.

4) Explore effects of patient-derived macrophages on human atrial and left evntricular myocytes and fibroblasts. Using co-culture and conditioned-media experiments, the student will assess acute and chronic paracrine effects of macrophages on fibroblast activation, inflammatory signalling and cardiomyocyte stress responses, thereby validating candidate macrophage-centred pathways identified in human atrial tissue.

Project outcomes: This project will generate the first comprehensive assessment of macrophage-centred fibro-inflammatory remodelling across cardiac chambers in human AF and will improve understanding of the mechanisms driving AF-associated structural remodelling. It may also identify novel therapeutic targets to prevent disease progression and improve patient outcomes.

DISEASE RELVEANCE

Atrial fibrillation affects more than 40 million people worldwide and remains a major cause of stroke, heart failure, hospitalisation and mortality. Current therapies largely target electrical abnormalities but do not effectively reverse the structural remodelling that underpins disease progression and recurrence.

Accumulating evidence suggests that immune activation, fibrosis and cardiomyocyte stress contribute to the substrate that maintains AF. However, the spatial organisation of these processes within human cardiac tissue is largely unknown. Understanding how inflammatory and fibrotic microenvironments develop and interact with cardiomyocytes is essential for identifying new therapeutic strategies.

This project will provide a comprehensive spatial map of cellular interactions in human AF and determine why remodelling is primarily confined to the atria despite exposure of the entire heart to common systemic risk factors. Identification of disease-associated cellular niches and signalling pathways may reveal novel therapeutic targets aimed at preventing fibrosis, limiting adverse remodelling and improving long-term AF outcomes.

KEY TECHNOLOGY

- Work in clinical settings along-side cardiac surgeons and patients: i.e. patient recruitment, consenting, sample collection. The project will exploit unique access to paired human cardiac tissue and blood specimens, enabling comparison of right atrial, left atrial and ventricular remodelling within the same patient.
- Multiplex immunofluorescence (mIF) for simultaneous visualisation of immune, stromal and cardiomyocyte populations within human cardiac tissue.
- Quantitative digital pathology and image analysis to assess cellular composition, fibrosis burden and spatial relationships between cell types.
- Histological assessment of fibrosis using Masson's trichrome and Picrosirius Red staining.
- Molecular profiling using RNA extraction, quantitative PCR and protein profiling (Western blot, ELISA, proteomics where necessary) to assess inflammatory, fibrotic and stress-response pathways.
- Imaging Mass Cytometry (IMC) for high-dimensional spatial proteomic profiling of selected patient samples.
- Spatial transcriptomics to define chamber-specific gene expression programmes while preserving tissue architecture.
- Single-cell segmentation and phenotypic classification.
- Cellular neighbourhood analysis and spatial interaction mapping.
- Multi-omic data integration combining transcriptomic and proteomic datasets.
- Computational approaches in collaboration with local bioinformatics support.

TRAINING OPPORTUNITIES

The student will receive multidisciplinary training spanning clinical activities within the cardiothoracic surgery unit, cardiovascular biology, translational medicine, spatial biology, digital pathology and computational bioinformatics.

Working within an established cardiovascular research programme, the student will gain experience in recruitment and phenotyping of patients undergoing cardiac surgery, human tissue and blood collection, biobanking, and analysis of human cardiac samples. Training will include ethical conduct of human research, clinical data management and translational study design.

The student will also receive training in primary human cell culture, isolation of peripheral blood mononuclear cells, monocyte-to-macrophage differentiation, cell-cell co-culture systems, conditioned-media experiments and functional assays of fibroblast activation and cardiomyocyte stress responses. These studies will provide experience in translating observations from human tissue analyses into mechanistic cellular experiments.

Experimental training will include:

- Human cardiac tissue and blood collection and biobanking
- Multiplex immunofluorescence and immunohistochemistry
- Histological assessment of fibrosis (Masson's trichrome and Picrosirius Red staining)
- Quantitative digital pathology and image analysis
- RNA extraction, quantitative PCR, ELISA and Western blotting
- Imaging Mass Cytometry (spatial proteomics)
- Spatial transcriptomics
- Single-cell and spatial omics data analysis
- Multi-omics data integration and systems immunology approaches
- Experimental design, statistics and reproducible research practices

The student will gain experience handling high-dimensional spatial datasets and integrating molecular, imaging and clinical data to address clinically relevant cardiovascular questions.

The project will be undertaken within a collaborative environment involving cardiovascular scientists, surgeons, clinician scientists, immunologists,

pathologists and bioinformaticians. Opportunities will be provided to present findings at national and international meetings, participate in Oxford doctoral training programmes, prepare manuscripts for publication and develop skills in grant writing, scientific communication and research leadership.

Overall, this project will provide an integrated training experience in human cardiovascular research, spatial biology and translational medicine, equipping the student with skills highly relevant to careers in academia, biotechnology and the pharmaceutical industry.

KEY PUBLICATIONS

1. Leblanc FJA, Yiu CHK, Moreira LM, Johnston AM, Mehta N, Kourliouros A, Sayeed R, Nattel S, Reilly S*, Lettre G*. Single-nucleus multi-omics implicates androgen receptor signaling in cardiomyocytes and NR4A1 regulation in fibroblasts during atrial fibrillation. Nature Cardiovascular Research. 2025. PMID: 40133651. *, senior/corresponding authors.
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5. Goncalves I, Pan M, Singh P, Wang W, Zhao J, Dib L, … Monaco C, Jørgensen HF, Sun J, Edsfeldt A. Spatial transcriptomics reveals a key role of fibroblast-like vascular smooth muscle cells in human atherosclerotic cell crosstalk and stability. Eur Heart J. 2026 Jul 21;47(28):3711-3732. doi: 10.1093/eurheartj/ehaf1091. PMID: 41685669; PMCID: PMC13384730.

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2.6 Machine Learning for Dissecting Heart Failure Trajectories for Personalised Risk Assessment and Management

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PROJECT OVERVIEW

Heart failure (HF) is a major global health challenge, imposing substantial mortality, hospitalisation, and healthcare burden. HF is highly heterogeneous in its aetiology, clinical presentation, and disease course which poses challenges in diagnosis and treatment. Existing prediction models are rarely evaluated systematically or at scale within established diagnostic pathways, limiting their ability to inform referral decisions, prognosis and critical care and treatment. UK Biobank (UKB) offers linked longitudinal health records and CMR at scale, but lacks robust HF phenotypes which require temporal integration of diagnoses and imaging; its CMR protocol also lacks routine LGE, limiting direct scar assessment.

Aims:

Our project will first derive high-confidence HF phenotypes for UKB, characterise longitudinal multimorbidity trajectories leading to HFrEF and HFpEF. We will then develop tiered multimodal AI models tailored to data availability across clinical settings. Additionally, we will enhance UKB CMR imaging with virtual native enhancement (VNE), and validate the HF AI models on Fuwai's CMR scans and the ChinaHEART population cohort.

Approaches:

First, this project will integrate UKB disease labels with cardiac MRI-derived LVEF and structural measures, to derive the HF subtypes, taking temporal alignment into consideration. This inevitably contains misclassification and missing data, but serves as seed labels for refinement.

Second, we will develop a semi-supervised clustering machine learning approach, combining seed labels with CMR image phenotypes to refine HF subtypes, and risk stratification based on shared cardiac remodelling pathways [1]. Current UKB materials do not contain myocardial fibrosis (scar) imaging – the most important image marker for cardiovascular disease. To address this gap, we are supplementing UKB with VNE [2-4] – AI-based myocardial fibrosis imaging. This will enhance and refine HF phenotyping based on shared fibrosis patterns and burden.

Third, we will develop tiered multimodal AI models, including a scalable screening model, and an imaging-enhanced model. The model will be validated on Fuwai CMR scans, including patients with various HF trajectories. HF expertise and cohorts will be supported by the Fuwai co-supervisor, Professor Jiangping Song.

Additionally, we will explore variables shared between UKB and ChinaHEART, and use them to develop lower-cost proxy signatures for imaging-informed risk phenotypes and to test population-level transportability across cohorts. The approaches for HF may be further generalised to common cardiometabolic disease to study the multimorbidity of cardiovascular disease. This work is in collaboration with Professor Xi Li.

References:

[1] Kway et al., EHJ (2026), doi.org/10.1093/eurheartj/ehag702

[2] Zhang et al., Circulation (2021) 144:589-99

[3] Zhang et al., Circulation (2022) 146: 1492-503

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DISEASE RELVEANCE

Heart Failure

The project will improve phenotyping and understanding of HF by integrating longitudinal clinical and CMR information. It will characterise HFrEF and HFpEF trajectories, identify patients at risk of decompensation or progression to advanced HF, and support risk stratification relevant to medical therapy, mechanical circulatory support and heart transplantation.

Cardiovascular disease:
The project addresses a broad spectrum of common cardiovascular conditions in population studies, including myocardial infarction, ischaemic heart disease, atrial fibrillation and heart failure. It will investigate how imaging-derived cardiac phenotypes, myocardial pathology and cardiac remodelling relate to cardiovascular disease risk and outcomes.

Cardiometabolic disease:
Recognising the multimorbid and multi-organ nature of cardiovascular disease and heart failure, the project will also investigate cardiometabolic risk and related conditions, such as type 2 diabetes and chronic kidney disease. By integrating large-scale imaging, body-composition measures and population-health data, the project aims to characterise shared and distinct cardiometabolic phenotypes and identify patterns associated with cardiovascular risk.

KEY TECHNOLOGY

- **Cardiovascular magnetic resonance (CMR) imaging:**
  Analysis or interpretation of cardiac structure, function, tissue characteristics and remodelling using population-scale cardiovascular imaging resources.
- **Virtual Native Enhancement (VNE):**
  Application of AI-based, contrast-free MRI methods to generate virtual

myocardial scar/fibrosis images and phenotypes, enabling population-scale investigation of myocardial fibrosis and pathologies.

- **Big-data phenotyping:**
  Analysis of large, complex and heterogeneous population-health datasets to derive reproducible cardiovascular and multi-organ phenotypes, including discovery of cost-effective and scalable risk prediction markers or signatures.
- **Multimodal and cross-cohort analysis:**
  Integration of imaging-derived phenotypes with clinical, exposure and cardiometabolic data, followed by validation across independent population and clinical cohorts to assess robustness and generalisability.
- **High-performance computing:**
  Use of secure large-scale storage and GPU computing through Oxford's Biomedical Research Computing (BMRC) infrastructure for computationally intensive image processing, model development and population-scale analyses.

TRAINING OPPORTUNITIES

The student will be jointly hosted at the Big Data Institute (BDI) within the Oxford Nuffield Department of Population Health (NDPH), and the Division of Cardiovascular Medicine (CVM), providing interdisciplinary training across data science, population health and cardiovascular imaging.

At BDI, the student will work in an interdisciplinary environment focused on the analysis of large, complex and heterogeneous health datasets. Training will include large-scale data management, statistical and machine-learning analysis, reproducible research and the use of advanced computing infrastructure. The student will have access to office space, software licences, library resources and the Biomedical Research Computing (BMRC) facility, providing secure large-scale storage and high-performance GPU computing.

CVM will provide complementary expertise in cardiovascular imaging and clinically oriented research, with links to research programmes including HCMR, OxAMI and ORFAN studies and to the NIHR Oxford Biomedical Research Centre. The student will gain exposure to clinical cohort resources, translational research questions and specialist cardiovascular imaging expertise.

Through seminars, research meetings and networking activities across both departments, the student will develop skills in deep learning, multimodal phenotyping, cross-cohort validation, scientific communication and interdisciplinary collaboration. The joint supervisory environment will support training at the interface of AI, cardiovascular imaging and population health and provide opportunities to develop methods that are both technically rigorous and clinically relevant.

KEY PUBLICATIONS

1 Yeshe Manuel Kway, Zahra Raisi-Estabragh, Georgios Vavilis, Charalambos Antoniades, Steffen E Petersen, Thomas E Nichols, Betty Raman, Qiang Zhang, Stefan Neubauer, Mapping organ fat distribution and body composition: towards precision profiling of cardiometabolic disease risk, **European Heart Journal,** 2026;, ehag702, https://doi.org/10.1093/eurheartj/ehag702

2 Zhang, Q., D. Zhou, P. Thompson, G. Vavillis, T. Anderton, R. Ahmed, R. A. Gonzales, H. Zhang, W. Y. R. Fok, D. Atkinson, K. E. Thomas, A. Lewis, O. Rider, K. M. Channon, S. Neubauer, S. Plein, M. Lu, P. P. Swoboda, S. K. Piechnik and V. M. Ferreira (2026). "Myocardial Scar Assessment Using Artificial Intelligence-Powered Contrast-Free MRI." **JACC** 88(7): 717-735. https://doi.org/10.1016/j.jacc.2026.05.029

3 Zhang, Q., M. K. Burrage, M. Shanmuganathan, R. A. Gonzales, E. Lukaschuk, K. E. Thomas, R. Mills, J. L. Pelado, C. Nikolaidou, I. A. Popescu, Y. P. Lee, X. Zhang, R. Dharmakumar, S. G. Myerson, O. Rider, K. M. Channon, S. Neubauer, S. K. Piechnik and V. M. Ferreira (2022). "Artificial Intelligence for Contrast-Free MRI: Scar Assessment in Myocardial Infarction Using Deep Learning–Based Virtual Native Enhancement." **Circulation** 146(20): 1492-1503. https://doi.org/10.1161/CIRCULATIONAHA.122.060137

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THEME 3: GENOMIC MEDICINE & DATA SCIENCE

3.1 Evaluating Infectious Disease Interventions Using Electronic Health Records and Causal Inference Including Target Trial Emulation

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PROJECT OVERVIEW

This DPhil will use electronic healthcare records from an existing electronic research database, the Infections in Oxfordshire Research Database (IORD) (https://oxfordbrc.nihr.ac.uk/research-themes/modernising-medical-microbiology-and-big-infection-diagnostics/iord-about/), to investigate how antibiotics can be used safely and efficiently in adults admitted to hospital with suspected sepsis. The DPhil student will first develop their understanding of causal epidemiological methods and target trial emulation through courses, self-directed learning and practical examples. They will go on to use electronic healthcare data to answer three practical questions about treatment of patients with suspected sepsis presenting to hospital, specifically: Which IV antibiotics should be started? When is it safe to switch from IV to oral antibiotics? and When is it safe to stop antibiotics?

Interventions in each of these areas, namely, selecting narrower rather than broader spectrum treatments for initial treatment, early iv-to-oral switching and early stopping are all likely to reduce antimicrobial resistance (AMR) and are emphasised in national guidelines and the UK's National Action Plan to reduce the threat of AMR. However, they have primarily been assessed in terms of how much they reduce antibiotic use, because this is straightforward to measure. The safety of antimicrobial stewardship (AMS) interventions is much harder to measure well, but is paramount when these interventions are applied to serious infections, such as those resulting in sepsis where the 30-day mortality associated with bloodstream infection is 15-23% across common pathogens. Because serious infection is also common (245,000 sepsis cases annually), even small additional risks from AMS interventions could still potentially lead to hundreds of avoidable deaths nationally each year.

To determine an optimal antibiotic policy, local, regional and national guidelines must balance individual treatment outcomes against future AMR risks. Achieving this balance is only possible when both are well understood – this is the goal of this project.

Specific project aims

Research Questions

To test in patients with suspected sepsis the safety (assessed by 30-day mortality and other outcomes) of three different antimicrobial stewardship interventions

through target trial emulation using linked electronic patient and laboratory secondary care data, specifically:

- Narrow vs broader spectrum empirical treatment
- Early iv-to-oral switching
- Short total treatment durations

DISEASE RELVEANCE

Increasingly available large-scale electronic health record data have the potential to answer a number of questions about infection management that are challenging to address using randomised controlled trials (RCTs). Where possible, RCTs remain the optimal way to test which medical interventions are more effective, but not every question can be answered this way. Sometimes it can be difficult to recruit or consent patients quickly enough, or so many participants are needed a trial becomes too time consuming or expensive to run. As an alternative, target trial emulation is an approach to causal inference that uses observational data, like healthcare records, to estimate the effects of interventions by designing the analysis around the RCT that would ideally answer the research question. The hypothetical “target trial” specifies key elements including eligibility criteria, treatment strategies, start of follow-up, outcomes, and the causal effect of interest, which are then emulated as closely as possible using routinely collected data. By explicitly aligning these elements, target trial emulation aims to reduce common sources of bias in observational research and improve the interpretation of estimated treatment effects. It provides a useful framework for generating real-world evidence when randomised trials are impractical, unethical, or unavailable across multiple disease areas.

KEY TECHNOLOGY

Methodology uses causal statistical analysis approaches as applied to target trial emulation – building on the foundation of the seminal paper Hernán MA, Robins JM. “Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available.” American Journal of Epidemiology. 2016;183(8):758–764. The student will explore traditional causal epidemiological methods based on inverse probability weighting, and newer doubly robust approaches such as targeted maximum likelihood estimation (TMLE), including with machine learning methods such as the SuperLearner. The student will join an active group of DPhil students and researchers working with electronic healthcare records including clinicians and analysts, who will help ensure their work is grounded in real-world clinical experience.

TRAINING OPPORTUNITIES

Specific training in epidemiology, statistics, bioinformatics, programming and use of AI/machine learning will be provided. The student will be encouraged to attend formal causal inference training courses (eg UCL, Bristol, Harvard) and also use self-directed learning, including using LLMs for coding support and development. Both supervisors will contribute directly to this, and support will also be available from other post-docs and DPhil students in the group. The student will be based jointly in the John Radcliffe hospital and the Big Data Institute within the Modernising Medical Microbiology Unit, a broad infection research consortium of around 40 DPhil students and post-docs with expertise in infectious diseases, biostatistics, epidemiology, AI/machine learning, bioinformatics, microbiology, and molecular biology. The group runs a weekly internal seminar program, but the student will also be able to attend seminars run across the university, and access all the university's training courses, including in transferable skills.

This DPhil would suit a candidate with quantitative skills and interest, who is interested in the application of methods to answer relevant clinical questions using messy and complicated real-world data. It will be solely desk and coding based. Pre-existing experience using causal methods is not essential, but enthusiasm and potential to learn is important.

KEY PUBLICATIONS

1. Wei J, Walker AS, Eyre DW. No evidence of difference in mortality with amoxicillin versus co-amoxiclav for hospital treatment of community-acquired pneumonia. J Infect 2024 Jun;88(6):106161. doi: 10.1016/j.jinf.2024.106161
2. Wei J, Walker AS, Eyre DW. Addition of macrolide antibiotics for hospital treatment of community-acquired pneumonia. J Infect Dis 2025 Apr 15;231(4):e713-e722. doi: 10.1093/infdis/jiae639
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4. Walker AS, Ford D, … Babiker AG. Daily co-trimoxazole prophylaxis in severely immunosuppressed HIV-infected adults in Africa started on combination antiretroviral therapy: an observational analysis of the DART cohort. Lancet 2010 Apr 10;375(9722):1278-86. doi: 10.1016/S0140-6736(10)60057-8
5. Pritchard E, Vihta KD, Lipworth S, Pouwels KB, Stoesser N, Hope R, Muller-Pebody B, Quan TP, Cregan J, Brown C, Hopkins S, Eyre DW, Walker AS. An electronic health record-wide association study to identify populations at increased risk of E. coli bacteraemia. J Infect. 2025 Oct;91(4):106612. doi: 10.1016/j.jinf.2025.106612

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3.2 Decoding HLA-Restricted Human T-cell Immunity Through a Population-Scale HLA–TCR Atlas

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Dr. Hannah Kockelbergh *hannah.kockelbergh@kennedy.ox.ac.uk*

PROJECT OVERVIEW

T cells are central to adaptive immunity, recognising antigenic peptides presented by highly polymorphic human leukocyte antigen (HLA) molecules through diverse T-cell receptors (TCRs). Variation in HLA genes is the strongest genetic risk factor for many immune-mediated diseases, including inflammatory bowel disease, ankylosing spondylitis, infectious diseases and cancer, yet the mechanisms by which HLA polymorphism shapes T-cell repertoire selection and immune responses remain poorly understood. Although recent advances in single-cell sequencing now enable simultaneous profiling of immune cell states and paired TCR repertoires, the vast majority of existing datasets lack HLA genotype information, preventing direct investigation of the relationship between antigen presentation, T-cell selection and immune function.

This project will use SARS-CoV-2 as an initial test case to establish and validate computational approaches for identifying functional and clinically relevant HLA–TCR interactions before extending these analyses to a broader range of immune-mediated diseases, including autoimmune and infectious diseases. Building on our recently developed method which accurately infers classical HLA genotypes directly from single-cell RNA sequencing data, the student will develop a population-scale HLA–TCR atlas at single-cell resolution by integrating HLA genotype, paired TCR repertoires and immune cell phenotypes across large existing datasets.

The successful candidate will receive interdisciplinary training spanning computational biology, statistical genetics, immunogenetics and single-cell multiomics, while working closely with collaborators and co-supervisors in immunology and clinical medicine. The project will integrate computational analyses with contemporary understanding of HLA biology and antigen presentation to uncover the mechanisms by which HLA variation shapes T-cell repertoire selection and adaptive immune responses across health and disease.

DISEASE RELVEANCE

Many common inflammatory and autoimmune conditions show striking genetic associations with the HLA region, but these discoveries have rarely translated into an understanding of why disease develops or why immune responses differ between individuals. This limits our ability to move from genetic risk factors towards clinically useful markers or therapeutic strategies.

A major opportunity lies in understanding the interaction between an individual's inherited immune variation and the T cells that respond to infection, inflammation

and self-antigens. By linking these two components across large collections of single-cell data, this project will help identify immune responses associated with susceptibility, protection and disease progression.

The resulting framework could be applied across diseases with a strong HLA component, from inflammatory bowel disease and ankylosing spondylitis to viral infection and cancer. In the longer term, defining disease-relevant HLA–T-cell relationships could improve patient stratification, reveal previously unrecognised disease mechanisms, and highlight immune responses that could be exploited for diagnostic, prognostic or therapeutic purposes.

KEY TECHNOLOGY

This project will combine single-cell genomics, immunogenetics and computational approaches to investigate how HLA variation shapes human T-cell repertoires and immune responses.

Single-cell multiomics: Large-scale single-cell RNA-sequencing datasets with paired TCR sequencing will provide simultaneous measurements of T-cell transcriptional states and receptor sequences. These data will enable individual T-cell clonotypes to be linked to cell type, activation state and other functional phenotypes across individuals and disease settings.

HLA inference and immunogenetics: Our recently developed computational method (scTAPAS) will be used to infer classical HLA alleles directly from single-cell RNA-sequencing data, enabling HLA information to be recovered from datasets without matched genetic data. The method will be further validated and optimised across sequencing platforms, populations and disease cohorts.

TCR repertoire analysis: Computational approaches will characterise TCR diversity, clonal expansion and sequence similarity. Statistical models will identify TCR sequences and motifs associated with specific HLA alleles and test whether these relationships differ between immune cell states, populations or disease groups. Known antigen-specific HLA–TCR interactions will provide benchmarks for validation.

Population-scale HLA–TCR integration: HLA genotypes, paired TCR sequences and single-cell phenotypes will be integrated across multiple cohorts to construct a population-scale HLA–TCR atlas. This framework will enable systematic investigation of HLA-restricted T-cell responses and provide a transferable resource for studying infectious, autoimmune and other immune-mediated diseases.

TRAINING OPPORTUNITIES

This project is well suited to a student with a background in statistical genetics, or a background in statistical modelling or machine learning who is interested in developing applied knowledge in the biological sciences. The successful candidate will be benefit from supervision by a team of scientists with key expertise in statistical genetics, immunology, and single cell genomics.

You will be based in the Kennedy Institute of Rheumatology, world-leading centres in genomics and inflammatory biology. Training will be provided in data science techniques including statistical data analysis and visualisation with R and Python, the writing of computational pipelines with Python/NextFlow, and the use of high-performance compute clusters. The student will gain expertise in analysing cutting-edge sequencing datasets including single-cell transcriptomics and immune repertoire analysis; statistical genetics and HLA immunogenetics; machine learning and multi-omic integration.

The Kennedy Institute is a world-renowned research centre and has a vibrant PhD program with weekly journal club, seminars, student symposia, weekly internal institute presentations and training. A core curriculum of lectures will provide a solid foundation of a broad range of subjects including data analysis, statistical methods, and immunology summer school. In additional to institutional support, the successful applicant will benefit from being part of the University of Oxford college system. Students will also have the opportunity to work closely with both computational, experimental and clinical scientists.

KEY PUBLICATIONS

1. Ng ES, et al. Defining the genetic determinants of CD8+ T cell receptor repertoire in the context of immune checkpoint blockade. Science Advances. 2025.
2. Mentzer AJ, et al. Human leukocyte antigen alleles associate with COVID-19 vaccine immunogenicity and risk of breakthrough infection. Nature. 2023.
3. Ahern DJ, et al. A blood atlas of COVID-19 defines hallmarks of disease severity and specificity. Cell. 2022.
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3.3 Exploiting Urine Genomics to Improve Identification of Causal Pathogens and Association with Symptoms and Their Recovery

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PROJECT OVERVIEW

This DPhil will provide access to clinical and genomic data from two large urinary tract infection (UTI) trials in order to study the pathogenesis and diagnosis of UTI. The first trial, CONDUCT (https://doi.org/10.3399/BJGP.2021.0359), tested 2 different urine collection devices vs standard of care in women experiencing a UTI, showing that these devices were not better than standard practice. The second trial, MERIT (https://doi.org/10.1001/jamainternmed.2024.0264) compared d-mannose vs placebo for UTI prevention in women who had previously had recurrent UTIs, finding no advantage in d-mannose. Both trials collected a large amount of clinical data (including demographics, symptoms, known risk factors, antibiotic history, and symptom recovery) as well as culture results and genome sequence data.

Urinary tract infection (UTI) is a substantial public health problem but diagnosis of UTI can be problematic, and the causation of recurrent infection is incompletely understood.

These datasets will be made available to the student to answer the following questions:

- What is the pattern of organisms causing infection and colonization among women in primary care with acute UTI? What are the genomics of these organisms and determinants of AMR?
- What metagenomic thresholds should be used to define UTI?
- How do genomics relate to symptoms, to recovery time, and how do organisms in long and short term carriage relate to the organisms causing symptomatic infection or to recurrent infection?

DISEASE RELVEANCE

Urinary tract infection (UTI) is a substantial public health problem: e.g. the urinary tract was the most frequent source of *Escherichia coli* bacteraemia in England in

2024–25 (46.3%), and in turn *E. coli* accounted for 70.5% of antibiotic-resistant bloodstream infections in 2024. However, diagnosis of UTI can be problematic. Conventional culture is frequently contaminated with commensal bacteria, may fail to detect fastidious or partially treated organisms, or may fail to resolve organisms below species level. Molecular sequencing can detect microbial genetic material directly from urine without requiring prior culture or targeting specific pathogens, enabling broader pathogen identification and definition beyond species level, even when contaminants are present.

Around 18% of all women who have UTIs have recurrent UTI, experiencing three episodes per year or two in 6 months. Recurrent infections might arise from new ascending infections by gut or perineal bacteria, or from intracellular reservoirs in the bladder wall. By sequencing isolates when these women are symptomatic and asymptomatic, we can look at how closely related the strains are at asymptomatic and symptomatic timepoints to determine the relative likelihood of these different causes of recurrence.

KEY TECHNOLOGY

Methodology will apply bioinformatic and statistical methods. The student will join an active group of DPhil students and researchers working with genetic and clinical data including bioinformaticians, statisticians and clinicians, who will help ensure their work is grounded in real-world clinical experience.

The student will be supported by supervisors with expertise in genomics, in the clinical data and epidemiology, and with specific expertise in the clinical trials that the datasets are drawn from.

TRAINING OPPORTUNITIES

Specific training in bioinformatics, statistics, epidemiology, programming and use of AI/machine learning will be provided. The student will be encouraged to attend formal training courses (eg on statistics and bioinformatics offered by the University of Oxford) and also use self-directed learning, including using LLMs for coding support and development. Supervisors will contribute directly to this, and support will also be available from other post-docs and DPhil students in the group. The student will be based jointly in the John Radcliffe hospital and the Big Data Institute within the Modernising Medical Microbiology Unit, a broad infection research consortium of around 40 DPhil students and post-docs with expertise in infectious diseases, biostatistics, epidemiology, AI/machine learning, bioinformatics, microbiology, and molecular biology. The group runs a weekly internal seminar program, but the student will also be able to attend

seminars run across the university, and access all the university's training courses, including in transferable skills.

The student will also have strong links to the Nuffield Department of Primary Care Health Sciences and the Infection, Respiratory and Acute Care Research group located there which is co-led by Professor Hayward. They will be encouraged to develop a patient and public involvement group and to discuss their research with this group, working with them to produce lay summaries and infographics describing their research findings.

This DPhil would suit a candidate with quantitative skills and interest, who is attracted by the opportunity to learn applied bioinformatics and statistical skills, and apply them to answer important clinical questions using real-world data. It will be solely desk and coding based.

KEY PUBLICATIONS

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3.4 Multi-Omic Dissection of Genetic and Environmental Drivers of Osteoarthritis

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PROJECT OVERVIEW

Osteoarthritis (OA) is a heterogeneous disease involving multiple joint tissues and both local and systemic biological processes. Its development and progression are influenced by a combination of genetic susceptibility and environmental, lifestyle and metabolic exposures, including obesity, physical activity, diet and smoking. Genome-wide association studies (GWAS) have identified numerous genetic loci associated with OA, but translating these signals into the genes, proteins, tissues and pathways that drive disease remains challenging. Similarly, the molecular mechanisms through which modifiable exposome factors influence OA are poorly understood. Integrating genetic, exposome and molecular data provides an opportunity to identify the biological pathways through which inherited and environmental factors contribute to OA.

Proteins are key functional mediators of biological processes and major targets for therapeutic intervention. Advances in high-throughput proteomics, including Olink and SomaLogic, now enable thousands of proteins to be measured simultaneously. Combined with genome-wide genetic data, these measurements can identify protein quantitative trait loci (pQTLs), linking inherited genetic variation to protein abundance. Large plasma-based studies have revealed extensive genetic regulation of the circulating proteome, with many pQTLs overlapping disease-associated loci. However, protein abundance is also shaped by environmental exposures, and molecular regulation can be highly tissue and context specific. Circulating proteins may therefore only partially capture the molecular processes occurring within the joint.

This DPhil will investigate how genetic variation and exposome factors shape the multi-omic architecture of OA, with a particular focus on comparing molecular profiles in synovial fluid with those observed in circulation. We will use newly generated data from the *Synovial fluid To detect Endotypes by Unbiased Proteomics in OA* (STEpUP OA) consortium, which has profiled more than 7,000 proteins in synovial fluid samples and paired plasma samples from 1361 individuals with OA. These data will be integrated with large plasma proteomic resources, including UK Biobank and Fenland, together with OA GWAS, gene expression, molecular QTL and exposome data.

DISEASE RELVEANCE

Osteoarthritis (OA) is the most common form of arthritis, affecting millions worldwide. This degenerative joint disease primarily impacts cartilage, the tissue that cushions the ends of bones within joints. According to the World Health Organization, 10%-15% of adults over 60 are affected by OA. Once regarded as an unavoidable consequence of "wear and tear," OA is now understood as a dynamic molecular response to mechanical stress, aggravated by factors such as aging, obesity, and genetics.

This project takes advantage of newly generated datasets from the STEpUP OA initiative (led by Professor Vincent), the largest molecular and clinical dataset of its kind. Following the completion of its primary analysis, the resource enables comprehensive protein quantitative trait locus (pQTL) mapping in OA, offering valuable insights into the genetic architecture of the OA proteome. These findings could help unravel the biological mechanisms underlying proteo-genomic discoveries and accelerate the development of OA biomarkers, predictive models, and novel therapeutics.

KEY TECHNOLOGY

This project will combine large-scale genomic, proteomic, exposomic and clinical data using computational and statistical approaches to investigate the molecular mechanisms underlying OA.

- **High-throughput proteomics:** Proteomic profiling will form a central component of the project. Synovial fluid proteomics from STEpUP OA will provide measurements of more than 7,000 proteins from the local joint environment. These data will be complemented by large-scale plasma proteomic datasets, including UK Biobank and Fenland, generated using affinity-based platforms such as Olink and SomaLogic. Cross-compartment analyses will identify protein signatures and regulatory effects that are shared between circulation and the joint or are specific to the local OA environment.

- **Statistical and population genomics:** Genome-wide genotype data will be used to map protein quantitative trait loci (pQTLs) and identify genetic variants regulating protein abundance. Statistical fine-mapping, conditional analysis and colocalisation will be used to resolve association signals and integrate pQTLs with OA GWAS and tissue-specific expression QTLs. Mendelian randomisation and related causal inference approaches will assess genetically supported relationships between proteins and OA.

- **Exposome analysis:** Large-scale lifestyle, environmental and metabolic data will be used to identify modifiable exposures associated with OA and molecular phenotypes. Approaches for high-dimensional exposure analysis and mediation modelling will investigate how exposures such as adiposity, physical activity, diet and smoking influence the proteome and whether their effects on OA are mediated through specific molecular pathways.

- **Multi-omic integration:** Computational approaches will integrate genomic, transcriptomic, proteomic, exposomic and clinical data across population and disease-specific cohorts. Network and pathway analyses will identify convergent molecular mechanisms, while cross-tissue analyses will distinguish systemic signals from those specific to the joint. Together, these technologies will establish mechanistic links from genetic variation and environmental exposures through molecular changes to OA onset and progression.

TRAINING OPPORTUNITIES

The successful candidate will benefit from interdisciplinary supervision spanning statistical genetics, computational biology, osteoarthritis and translational medicine. Based at the Kennedy Institute of Rheumatology, a world-leading centre for inflammation and musculoskeletal research, the student will work within a highly collaborative environment bringing together computational, experimental and clinical scientists.

The project will provide comprehensive training in statistical genetics and multi-omic data science, including genome-wide association and molecular QTL analysis and integration of genomic, exposomic, transcriptomic and proteomic data. The student will develop practical skills in statistical analysis and analysis of biobank-scale datasets using cloud-base computing.

Through STEpUP OA and collaborating cohorts, the student will gain experience working with cutting-edge proteomic technologies and translating computational findings into disease biology. Opportunities to collaborate with experimental and clinical researchers will provide training in interpretation and validation of multi-omic findings.

In addition to institutional support, the successful applicant will benefit from the University of Oxford's college system. Students will also have the opportunity to collaborate closely with both computational, experimental and clinical scientists.

KEY PUBLICATIONS

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2. Ng, E.S., Nanjala, R., Jostins-Dean, L., Barrett, J.C., Todd, J.A. and Luo, Y. (2025) 'Improving population-scale disease prediction through multi-omics integration', medRxiv. doi: 10.1101/2025.11.24.25340920.
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5. Zhu et al. Variants in ALDH1A2 reveal an anti-inflammatory role for retinoic acid and a new class of disease-modifying drugs in osteoarthritis. Science Translational Medicine (2022)

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3.5 Multiparameter Tissue Landscapes: Shaping Neutrophil Functional States

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PROJECT OVERVIEW

Neutrophils represent a major arm of the innate immune defence system, with a long- held view of them being transcriptionally inactive, fast responders, mobilised in response to microbial and tissue insults. Recent developments in the field have changed this perception and firmly positioned neutrophils as transcriptionally active cells with the ability to adapt their transcriptional program. Our recent findings demonstrate that, despite limited residence times in tissues, neutrophils can tailor their properties to support organ homeostasis and mount tissue specific and transcriptionally regulated inflammatory response[1]. Importantly, in inflammation neutrophils are presented as functionally, morphologically and behaviourally heterogeneous cells in circulation and tissue[2]. Our central research question is: **How do distinct tissue niches shape neutrophil functional states, and can this be leveraged to ameliorate immunopathology?**

This project aims to uncover how distinct tissue environments shape neutrophil gene expression programs and functional states, with a particular focus on immunopathology. Building on our recently generated single-cell RNA sequencing (scRNA-seq) datasets from inflamed joint and colon tissues (unpublished), we will define common and tissue-specific neutrophil signatures and identify the transcriptional networks underlying their adaptation to regional niches. By integrating these datasets with spatial transcriptomic and high-resolution imaging data, both in mouse models and human tissue biopsies, we will explore how the geography of inflammation, including the spatial distribution of neutrophils and their interactions with tissue-resident immune and stromal cells[3], orchestrates neutrophil functional heterogeneity.

A key component of the project is to map the temporal and spatial dynamics of neutrophil recruitment and adaptation in tissue. We will apply advanced mathematical and spatial modelling to analyse multiparameter tissue landscapes and infer how spatially constrained signals influence transcriptional regulatory networks using the recently developed Multiscale Spatial Analysis toolbox (MuSpAn: https://www.muspan.co.uk/). Lattice Light Sheet (LLS) microscopy will be used to visualise neutrophil morphology and behaviour in

three dimensions, enabling the integration of morphological features with transcriptomic identity using machine learning and topological data analysis[4]. This multimodal approach will allow us to identify spatially restricted transcriptional states and how these relate to disease-driving or resolving neutrophil phenotypes.

This work will capitalise on our extensive transcriptomic and imaging datasets, as well as unique genetic models[2]. The results will enhance our understanding of the spatial and transcriptional logic of neutrophil plasticity and contribute to identifying new therapeutic strategies targeting pathogenic neutrophil states in tissue-specific inflammatory diseases[5].

DISEASE RELVEANCE

Our proposed research focuses on the rapidly developing new field of neutrophil function in tissue, which has the potential to bring about a new class of therapeutics that target immune-pathogenic neutrophil states without the devastating effects of total neutrophil depletion. This is particularly relevant to diseases in which neutrophil presence correlates with heightened clinical disease activity, such as of the gut-joint axis. A new Biopsy Investigation of Oxford Synovial Cohort (**BIOPSICO**) for ultrasound-guided synovial biopsies of people with all forms of arthritis, as well as synovial and colonic biopsies of IBD patients with arthritis, just before the start of their standard of care treatment and then 3 and 6 months, has already allowed us to categorise forms of arthritis, where myeloid cells dominate vs those with a lymphpid pathotype. As a part of this project, we will capture diversity and cellular heterogeneity of these arthritis patients and examine our hypothesis that patients presented with co-morbidities, such as inflammatory bowel disease, may be characterised by a distinct inflammatory neutrophil signature.

KEY TECHNOLOGY

- Single cell and spatial transcriptomics using the most advanced platforms.
- Computational analysis of scRNA-seq/scATAC-seq and combined multimodal data.
- Methods from spatial statistics, topology and network science to describe spatial structure and phenotypic heterogeneity in health and disease

TRAINING OPPORTUNITIES

The Kennedy Institute is a world-renowned research centre and is housed in a state-of-the-art research facility. Training will be provided in a wide range of functional genomics approaches, cutting edge single cell platforms and computational pipelines. A core curriculum of lectures will be taken in the first term to provide a strong foundation across a broad range of subjects, including musculoskeletal biology, inflammation, epigenetics, translational immunology and data analysis. The student will attend weekly seminars within the department and those relevant in the wider University. They will present their research regularly to the department and the Genomics of Inflammation group, and at the Computational Genomics Forum. They will also attend external conferences at which they will present their research to a global audience. The student will also have the opportunity to work closely with members of the Wolfson Centre for Mathematical Biology at the Mathematical Institute, University of Oxford, and to further broaden their theoretical knowledge by attending lecture courses in mathematical biology, statistics and related subjects.

KEY PUBLICATIONS

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3.6 Mapping Cancer Genetics via Systems of Intelligent Agents

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PROJECT OVERVIEW

We now live in a world where large language model (LLM) agents like Claude, Gemini and GPT are pervasive. Recent papers and numerous tech blogs suggest that these agents are not only very capable scientists, but that they will soon be central to nearly all scientific progress. Here we will evaluate the merit of these claims in the context of cancer genomic biology, seeking to establish an integrated computational/experimental agentic system for understanding the effects of DNA mutations on development of cancer. Starting with a comprehensive set of somatic and germline mutations that have been linked to melanoma cancers, the DPhil student will work collaboratively with other lab members to design a system of agents which: (1) Proposes competing hypotheses for the molecular mechanisms by which each mutation causes or promotes cancer; (2) Designs a parsimonious series of experimental assays to test hypotheses and distinguish among them; (3) Conducts some assays via bioinformatic data mining in online data repositories; (4) Conducts other tests using the standard arsenal of assays available in a standard functional genomics lab. To the degree these tasks can be reliably demonstrated, there is also interest in integrating this system with closed-loop laboratory automation equipment present in the Oxford Center for Human Genetics and the Ludwig Cancer Institute. This project will be carried out in partnership with Richard White's lab at the Ludwig.

DISEASE RELVEANCE

Melanoma development is driven by somatic and germline genetic alterations, yet the functional mechanisms through which many associated mutations promote tumorigenesis remain poorly understood. This project will address this gap by integrating LLM-based agentic systems with bioinformatic analyses and functional genomics assays to systematically investigate melanoma-associated mutations. By generating and experimentally testing competing mechanistic hypotheses, the study aims to establish causal links between specific genetic variants and cancer-promoting molecular processes. This approach could provide new insights into melanoma pathogenesis, prioritise functionally relevant mutations, and identify molecular mechanisms with potential therapeutic relevance.

KEY TECHNOLOGY

This project will integrate large language model (LLM) agents with computational and functional genomics to investigate melanoma-associated mutations. A multi agent system will generate mechanistic hypotheses, design experiments, and analyse genomic datasets to evaluate mutation function. Selected hypotheses will be validated using established functional genomics assays. Where feasible, the system will be integrated with closed-loop laboratory automation, enabling iterative hypothesis generation, experimental testing and refinement. This approach combines AI-driven scientific reasoning, bioinformatics, experimental genomics and automation to systematically determine the functional consequences of cancer-associated mutations.

TRAINING OPPORTUNITIES

This project offers interdisciplinary training at the interface of artificial intelligence, cancer genomics and experimental biology. The student will develop expertise in LLM-based agentic systems, bioinformatics, computational genomics and functional genomics assays. Training will include hypothesis generation, experimental design, genomic data analysis and validation of cancer-associated mutations. The project will also provide experience in laboratory automation and closed-loop experimental systems, alongside opportunities for collaborative research across computational and experimental teams.

KEY PUBLICATIONS

1. Hu M et al. Evaluation of large language models for discovery of gene set function. Nat Methods. 2025 10.1038/s41592-024-02525-x.
2. Fong SH et al. A multilineage screen identifies actionable synthetic lethal interactions in human cancers. Nature Genetics. 2024 Nov 18. doi: 10.1038/s41588-024-01971-9.
3. Baron M, Tagore M, et al. Desmosome mutations impact the tumor microenvironment to promote melanoma proliferation. Nat Genet. 2025 May;57(5):1179-1188. doi: 10.1038/s41588-025-02163-9.

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3.7 Digital Human Cells as Models of Viral Infection and Drug Resistance

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PROJECT OVERVIEW

Description: The Ideker laboratory is engaged in the UltraCell project, an international effort to construct digital cell models of human conditions including infectious disease, neuropsychiatric disorders and cancer. We have accumulated significant whole-cell data across multiple proteomic modalities in U2OS human cells, providing a basis from which to expand to viral infection and other applications. Thus far, analysis of these data has delineated a hierarchy of 175 distinct subcellular protein assemblies, several dozen of which appear to be under significant mutational pressure in cancer or in evolution of drug resistance. While this map provides a foundation for structural cell biology and precision medicine, it also presents clear opportunities to advance virtual cell models along several key directions. Working together with the Division of Structural Biology, we will seek to match protein assemblies in our map to three-dimensional subcellular objects resolved by cryo-electron tomography imaging (cryo-ET). Working with the Centre for Medicines Discovery, we will prioritise druggable components identified in the structural map and link them to functional changes in cell state via perturbation mRNA sequencing (peturb-seq) in response to CRISPR gene edits and small molecule drugs. Interested DPhil students will have the opportunity to engage in both structural and functional aspects of ultracell mapping and to work collaboratively among the various laboratories and research units

DISEASE RELVEANCE

The UltraCell project aims to develop digital models of human cells to improve understanding of diseases including cancer, infectious disease and neuropsychiatric disorders. By identifying protein assemblies affected by cancer-associated mutations and drug resistance, this project will help define how structural changes within cells contribute to disease. Linking these assemblies to functional cellular responses may reveal disease mechanisms and identify potential therapeutic targets.

KEY TECHNOLOGY

This project integrates multi-modal proteomics, cryo-electron tomography (cryo-ET), Perturb-seq and CRISPR-based gene editing to construct structural and functional maps of human cells. Cryo-ET will link protein assemblies to three-dimensional subcellular structures, while Perturb-seq following genetic and small-molecule perturbations will determine their effects on cellular state. These approaches will support the development of data-driven virtual cell models.

TRAINING OPPORTUNITIES

The project provides interdisciplinary training in computational biology, proteomics, structural biology and functional genomics. The student will gain experience in cryo-ET, CRISPR perturbation, Perturb-seq, multi-omics data analysis and virtual cell modelling. Collaborative work across structural biology and medicines discovery groups will also provide training in integrating computational and experimental approaches for disease biology and drug discovery.

KEY PUBLICATIONS

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2. Stuart, D. I., Oksanen, H. M., & Abrescia, N. G. (2024). Integrative approaches to study virus structures. Structure and Physics of Viruses: An Integrated Guide, 247-297.
3. Zheng F, Kelly MR et al. Interpretation of cancer mutations using a multiscale map of protein systems. Science. 2021 Oct;374(6563):eabf3067. doi: 10.1126/science.abf3067.
4. Ma J et al. Using deep learning to model the hierarchical structure and function of a cell. Nat Methods. 2018 Mar 5. doi: 10.1038/nmeth.4627.
5. De Cesco, S. TargetDB: a target information aggregation tool and tractability predictor. PloS one 15.9 (2020): e0232644.

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3.8 From Retrotransposon Silencing to Immune Regulation: Investigating the Expanding Functions of Tudor Protein TDRD9

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PROJECT OVERVIEW

Sepsis is a life-threatening condition caused by a dysregulated host response to infection that causes organ dysfunction and high mortality worldwide. Neutrophils form the first line of defence against infection and represent the most abundant white blood cells. They play a role in pathogen clearance through phagocytosis, production of reactive oxygen species (ROS), and release of neutrophil extracellular traps (NETs). However, in sepsis, neutrophil development and function become profoundly altered, contributing to tissue damage, immunosuppression, and poor outcomes. Despite their central role in sepsis, the underlying metabolic mechanisms that govern neutrophil dysfunction remain poorly understood.

Transcriptomic studies have identified distinct sepsis response signatures (SRS), including SRS1, which is characterised by a relative immunosuppression and an increased mortality compared with the more immunocompetent SRS2 endotype (Cano-Gamez *et al.,* 2022; Davenport *et al.,* 2016). Neutrophils and the expansion of progenitor forms such as IL1R2+ cells, which are a hallmark of emergency granulopoiesis, were found to drive the immune suppression and the extreme response endotype SRS1 during sepsis (Kwok *et al.,* 2023).

The gene *TDRD9* is strongly upregulated in SRS1 and appears to be a key driver of the SRS separation. However, its function in immune cells is unknown. *TDRD9* is characterised in the germline, where its Tudor domain interacts with *PIWIL4*, a PIWI protein that contributes to the recruitment of epigenetic silencing machinery to target transposable elements that could otherwise compromise genomic integrity during spermatogenesis (Mann *et al.,* 2023). Intriguingly, several independent studies framed *TDRD9* gene expression as a key biomarker for a wide range of inflammatory disease, and recently, *TDRD9* knock down has been shown to reduce bacterial growth, apoptosis, and inflammation in human lung organoids (Zhang *et al.,* 2026). These observations raise the possibility that *TDRD9* may possess a previously unrecognised function during inflammation.

This project hypothesises that *TDRD9* is functionally repurposed during severe inflammation and contributes to altered neutrophil development and function in health and disease. First, *TDRD9* will be immunoprecipitated from blood cells of

patients with severe sepsis, followed by proteomic identification of interacting proteins, to determine whether its protein-interaction network reveals immune-specific functions distinct from its canonical germline role. Second, existing *TDRD9*-knockout and overexpression human iPSC models will be complemented by domain-specific perturbations. These lines will be differentiated towards the neutrophil lineage under basal and inflammation-mimicking conditions to determine whether *TDRD9* and its individual functional domains are required for neutrophil development or inflammatory responses. Transcriptomic profiling across differentiation stages and genotypes will identify *TDRD9*-dependent pathways and define when these effects emerge.

This work aims to establish whether *TDRD9* has a causal role in inflammatory neutrophil reprogramming, define its underlying molecular mechanism, and assess whether this protein network represents a potential therapeutic target in severe sepsis.

DISEASE RELVEANCE

Although *TDRD9* is canonically associated with germline biology, its dysregulation has repeatedly emerged as a biomarker across a wide range of clinically distinct diseases. Up-regulation of *TDRD9* expression in whole blood has been reported in sepsis, severe influenza, pneumonia and Kawasaki disease, as well as several cancers and metabolic disorders. This raises the hypothesis that circulating *TDRD9* may represent a conserved feature of inflammation-associated emergency myelopoiesis rather than a collection of disease-specific responses. That could explain why *TDRD9* has emerged as a key biomarker in multiple acute inflammatory conditions characterised by substantial perturbations of the myeloid compartment. However, it is unknown whether *TDRD9* actively regulates myeloid development and function. Distinguishing between these possibilities is essential for interpreting its growing clinical association and determining whether *TDRD9* represents a biomarker of emergency myelopoiesis, as well as a relevant therapeutic target.

KEY TECHNOLOGY

This project will establish a genetically tractable human induced pluripotent stem cell (iPSC) platform to investigate neutrophil development and function across defined stages of maturation. Isogenic iPSC lines comprising wild-type (WT), TDRD9 knockout (KO) and TDRD9 overexpression (OE) models will be differentiated along the neutrophil lineage, enabling the consequences of perturbations (different stresses, KO, etc) to be resolved throughout granulopoiesis rather than exclusively in terminally differentiated cells.

The platform will combine staged neutrophil differentiation with inflammatory conditions designed to model aspects of infection-associated emergency myelopoiesis. Transcriptomic profiling at defined differentiation stages will enable direct comparison of WT, KO and OE cells, identifying when TDRD9-dependent phenotypes emerge and the molecular pathways affected. Domain-specific TDRD9 mutants targeting the Tudor and DExD/H-box helicase domains will further enable structure–function analysis, distinguishing canonical TDRD9 activities from potential immune-specific functions.

Importantly, the WT differentiation system will constitute a valuable technology independently of TDRD9. Primary human neutrophils are short-lived, terminally differentiated and difficult to genetically manipulate, limiting mechanistic investigation of human granulopoiesis. A reproducible iPSC-derived system provides a renewable and genetically accessible model in which neutrophil development can be experimentally perturbed and followed longitudinally. The resulting platform, differentiation protocols and stage-resolved transcriptomic reference data could therefore be used by the wider research community to investigate additional genes implicated in neutrophil maturation, emergency myelopoiesis and inflammatory disease. The project will generate both a mechanistic system for determining the function of TDRD9 and a broader experimental resource for studying human neutrophil biology.

TRAINING OPPORTUNITIES

In this project, the student will be developing a complementary wet- and dry-laboratory skill set, with training across experimental stem-cell biology, molecular biology and computational genomics. Experimental training will include human iPSC culture, genome-engineered cell-line characterisation and differentiation towards the neutrophil lineage. The student will gain expertise in monitoring and phenotyping neutrophil maturation and in designing inflammation-mimicking experimental conditions. Training in molecular and biochemical approaches will include co-immunoprecipitation and downstream proteomic analysis to characterise *TDRD9* protein-interaction networks. Working with wild-type, knockout, overexpression and domain-specific TDRD9 models will additionally provide experience in experimental design. Computational training will include analysis of bulk and single-cell RNA sequencing as well as proteomic datasets. The student will develop proficiency in R, Python and Bash, and be trained to construct reproducible data processing pipelines, statistical analysis, visualisation and bioinformatic workflow development. Training in protein structure prediction and molecular modelling will complement experimental investigation of *TDRD9* domains and

protein interactions. Integration of transcriptomic, proteomic and structural data will provide experience in multi-modal approaches to mechanistic biology.

The student will also develop broader research competencies including scientific writing, presentation and data management.

KEY PUBLICATIONS

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5. Mann, J. M., Wei, C., & Chen, C. (2023). How genetic defects in piRNA trimming contribute to male infertility. Andrology, 11(5), 911–917. https://doi.org/10.1111/andr.13324

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3.9 Genome Architecture and Genome Editing

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PROJECT OVERVIEW

Our laboratory is interested in understanding how the genome is interpreted by cells and how this can be harnessed to identify new genes and pathways that cause human disease. We address these fundamental questions by combining developing cutting edge genomics techniqes, combined with advanced genome editing and computational biology.

In higher eukaryotes, the three-dimensional organisation of the genome plays a critical role in regulating gene expression. Many genes are controlled by regulatory DNA elements known as enhancers, which can be located hundreds of thousands of base pairs away from their target genes. These enhancers contain short DNA sequences that bind transcription factors and regulate gene expression through physical interactions with gene promoters.

We have developed a suite of methods (Micro Capture-C) which can define genome architecture in unprecedented detail. Using these approach, we investigate the fundamental mechanisms of gene regulation and determine how genetic variation influences genome organisation and contributes to human disease. These datasets present substantial computational challenges, and our lab develops novel analytical approaches, including machine learning methods, to interpret and predict patterns of genome organisation and gene regulation.

The laboratory also has extensive expertise in genome editing technologies. As a haematologist with a specialist interest in bone marrow transplantation and cellular therapy, I am particularly interested in developing novel therapeutic genome editing approaches. We have previously licensed a genome editing strategy for the treatment of β-thalassaemia and sickle cell disease to BEAM Therapeutics.

We specialise in combining wet lab approaches with computational biology and we have a number of exciting projects available at present. We are happy to tailor projects to the individual students' interests and skills. This can range from purely experimental to fully computational projects and the projects often combine a mixture of both. Potential areas include utilising Micro Capture-C to interrogate the fundamental mechanisms controlling transcription, combining functional genomics with high-throughput CRISPR screens to investigate new disease mechanisms, or designing and evaluating novel genome editing strategies.

DISEASE RELVEANCE

- The laboratory has a particular focus on the haematopoietic and immune systems, which provide experimentally tractable models for understanding gene regulation and are implicated in a wide range of human diseases.
- Our work has direct relevance to haematological malignancies and immune-mediated disease, as well as to understanding the role of immune cells in cancer and other disease contexts.
- The genome editing work aims to develop new therapeutic strategies for inherited disorders of the blood and immune systems, including haemoglobinopathies and inherited immunodeficiencies.

KEY TECHNOLOGY

- Advanced chromsome conformation capture (3C) methods (Micro Capture-C) and other functional genomics assays.
- Genome editing including base editing, prime editing and epigenome editing.
- Computational biology.

TRAINING OPPORTUNITIES

- Full training provided in molecular techniques including 3C, ChIP-seq, RNA-seq
- Training provided in genome engineering and CRISPR based genome editing
- Training in computational biology including coding in python and R
- Training scientific methodologies
- Training in preparation of material for publication and presentation skills

KEY PUBLICATIONS

1. Li H, Dalgleish JLT., Lister G, Maristany MJ, Huertas J, Dopico-Fernandez AN, Hamley JC, Denny N, Bloye G, Zhang W, Hentges L, Doll R, Wei Y, Maresca M, Dimitrova E, Pytowski L, Tunnacliffe EAJ, Kassouf M, Higgs D, de Wit E, Klose RJ, Schermelleh L, Collepardo-Guevara R, Milne TA and **Davies JO**, 'Mapping chromatin structure at base-pair resolution unveils a unified model of cis-regulatory element interactions', **Cell 2025** (188) 7175-7193

2. Hamley JC, Zhang W, Sharlandjieva V, Chen LY, Willmott D, Li H, Denny N, Agarwal G, Henteges L, Ozcan B, Doll RM, Riva S, Venkatesh S, Arachi M, Agarwal D, Akkuratov E, Baxter M, Sauka-Spengler T, Dendrou CA, Milne TA, Hughes JR and **Davies JO** 'Single-allele nanoscale mapping of regulatory variant function', *Accepted* **Nature Genetics**, Pre-print, Zenodo: doi.org/10.5281/zenodo.16990047

3. Badat M, Ejaz A, Hua P, Rice S, Zhang W, Hentges LD, Fisher CA, Denny N, Schwessinger R, Yasara N, Roy NBA, Issa F, Roy A, Telfer P, Hughes J, Mettananda S, Higgs DR and **Davies JO** 'Direct correction of haemoglobin E β-thalassaemia using base editors' **Nature Communications 2023** 14, 2238

4. Hua P, Badat M, Hanssen LLP, Hentges LD, Crump N, Downes DJ, Jeziorska DM, Oudelaar AM, Schwessinger R, Taylor S, Milne TA, Hughes JR, Higgs DR and **Davies JO** 'Defining genome architecture at base pair resolution' **Nature 2021**; 595(7865):125-129

5. Downes DJ, Cross AR, Hua P, Roberts N, Schwessinger R, Cutler AJ, Munis AM, Brown J, Mielczarek O, de Andrea CE, COMBAT Consortium, Gill DR, Hyde SC, Knight JC, Todd JA, Sansom SN, Issa F, **Davies JO*** and Hughes JR* 'Identification of LZTFL1 as the likely effector gene at a severe COVID-19 risk locus.' **Nature Genetics 2021** 53:1606–1615 (* joint corresponding)

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THEME 4: INFECTION IMMUNLOGY & DISEASE

4.1 From HLA Immunogenetics to Vaccine Response: Functional Validation and Rational Optimisation of Peptide Presentation

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PROJECT OVERVIEW

Individuals vary substantially in the magnitude and durability of antibody responses following vaccination. Our recent work across clinical trials and observational cohorts has identified human leukocyte antigen (HLA) variation as an important determinant of vaccine immunogenicity and effectiveness. However, conventional HLA association studies identify genetic markers rather than the immunological mechanisms responsible for these differences.

We have developed an *in silico* framework that transforms an individual's HLA genotype into a predicted antigen-specific peptide-presentation landscape. Rather than considering HLA alleles independently, this approach identifies groups of peptides that are preferentially presented by different HLA backgrounds and associates these "presentation programmes" with subsequent antibody responses. Using data from multiple vaccines and populations, we have identified and replicated candidate peptide programmes associated with both enhanced and impaired vaccine immunogenicity. These findings now require functional validation.

This PhD will determine how HLA-defined peptide presentation influences cellular immune responses to vaccination and whether poor-response presentation programmes can be experimentally overcome.

The project will have three linked objectives.

1. Functionally validate HLA-dependent peptide-presentation programmes. Candidate peptides identified from existing clinical trial and cohort datasets will be studied in participants selected according to HLA genotype and predicted presentation phenotype. Peptide-specific CD4 T-cell responses will be quantified using activation-induced marker assays, ELISpot and multiparameter flow cytometry. Cell sorting, T-cell receptor repertoire sequencing and targeted functional assays will determine whether computationally predicted differences in peptide presentation correspond to distinct antigen-specific T-cell populations and helper responses.

2. Identify peptide combinations predicted to overcome HLA-defined deficiencies. The student will analyse existing multiplex serological datasets alongside high-resolution HLA genotypes and peptide-presentation predictions. New computational pipelines will identify antigen regions associated with favourable or poor antibody responses and determine whether alternative peptide sequences could broaden effective HLA coverage. The aim will be to identify minimal combinations of helper epitopes predicted to compensate for presentation gaps in poorly responding HLA backgrounds.

3. Experimentally test candidate rescue strategies. Prioritised peptides and peptide combinations will be evaluated in genotype-selected human immune cells. Experiments will test whether alternative peptide presentation enhances antigen-specific CD4 T-cell activation and downstream T–B-cell interactions, providing proof-of-principle that genetically determined differences in vaccine response can be rationally modified.

The project will therefore connect population immunogenetics directly to cellular mechanism and establish a foundation for designing vaccines that remain immunogenic across human HLA diversity.

DISEASE RELVEANCE

Vaccination is among the most effective interventions in medicine, yet vaccine responses vary markedly between individuals and populations. Some recipients generate weak or rapidly waning antibody responses despite receiving identical vaccines, contributing to breakthrough infection and incomplete protection.

HLA molecules are central to adaptive immunity because they determine which pathogen-derived peptides are presented to T cells. Our studies indicate that inherited differences in HLA can substantially influence antibody responses to several vaccines, suggesting that current vaccine antigens may provide highly effective T-cell help in some individuals but less effective presentation in others.

Understanding this mechanism has broad relevance across infectious diseases rather than being restricted to a single pathogen. The project will use established vaccine systems for which we already have strong genetic and serological evidence, while developing approaches that can subsequently be applied to emerging infections and next-generation vaccines.

Ultimately, identifying HLA-defined gaps in antigen presentation could enable vaccines to be designed to provide effective immune stimulation across a wider range of human genetic backgrounds. This could improve the consistency of vaccine responses both within and between populations and contribute to more equitable global vaccine effectiveness.

KEY TECHNOLOGY

The project uniquely combines computational immunogenetics with experimental human immunology.

A major component will involve *in silico* analysis of multiplex serology and HLA data. The student will analyse antibody responses measured against multiple vaccine and infectious-disease antigens in clinical trials and population cohorts. High-resolution HLA genotype data will be integrated with computational peptide–HLA binding predictions to generate individual-level peptide-presentation landscapes. The student will develop and apply pipelines for HLA association testing, peptide-level association, dimensional reduction and identification of biologically coherent presentation programmes associated with antibody phenotypes.

These analyses will nominate specific peptides and HLA backgrounds for experimental investigation and will subsequently be extended to identify alternative peptide combinations predicted to provide broader HLA coverage.

The experimental programme will use complementary techniques to characterise antigen-specific cellular immunity. These will include **ELISpot**, activation-induced marker (**AIM**) assays, multiparameter **flow cytometry**, antigen- and phenotype-directed **cell sorting**, and functional peptide-stimulation assays. Where appropriate, sorted antigen-responsive populations will undergo **T-cell receptor repertoire sequencing** to characterise clonotypic responses associated with specific peptide–HLA combinations.

The student will therefore move iteratively between computational prediction and experimental validation: population-level datasets will identify candidate mechanisms, immunological experiments will test those mechanisms, and the resulting biological information will refine subsequent computational models and peptide-selection strategies.

TRAINING OPPORTUNITIES

The project provides interdisciplinary training spanning computational biology, human immunogenetics and experimental immunology.

The student will receive training in analysis of large-scale clinical and cohort datasets, including multiplex serological measurements, high-resolution HLA genotype data and vaccine-response phenotypes. They will develop skills in statistical genetics, HLA association analysis, peptide–HLA prediction, dimensional reduction, predictive modelling and reproducible computational pipeline development. This will include opportunities to work with collaborators specialising in quantitative and statistical methodology.

In parallel, the student will develop substantial experimental expertise in human cellular immunology. Training will include PBMC processing and culture, peptide-stimulation experiments, ELISpot, multiparameter flow cytometry, activation-induced marker assays, antigen-specific cell sorting and T-cell receptor repertoire analysis. They will learn experimental design for genotype-stratified human studies and how to integrate molecular and cellular measurements with computational predictions.

The project sits within the highly collaborative Oxford immunology and vaccinology environment, providing opportunities to interact with investigators working in HLA biology, cellular immunology, vaccine development, clinical trials and infectious disease. Through the Chinese Academy of Medical Sciences Oxford Institute and the wider CSC-COI programme, the student will also participate in seminars, research meetings and cross-disciplinary training activities spanning fundamental and translational immunology.

A central training objective will be the ability to work across disciplinary boundaries: beginning with human population data, generating mechanistic hypotheses computationally, testing these experimentally, and using the resulting biology to guide rational vaccine design.

KEY PUBLICATIONS

1. Human leukocyte antigen alleles associate with COVID-19 vaccine immunogenicity and risk of breakthrough infection - PubMed
2. High-resolution African HLA resource uncovers HLA-DRB1 expression effects underlying vaccine response - PubMed
3. Targeting hepatitis B vaccine escape using immunogenetics in Bangladeshi infants | medRxiv
4. A common NFKB1 variant detected through antibody analysis in UK Biobank predicts risk of infection and allergy - PubMed
5. Identification of host-pathogen-disease relationships using a scalable multiplex serology platform in UK Biobank - PubMed

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4.2 Immunomodulatory Treatments Targeting Neutrophil Inflammation in Severe Bacterial Pneumonia

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PROJECT OVERVIEW

Pneumonia is a common acute respiratory infection and remains one of the leading causes of death worldwide. Bacteria and viruses are the most common microbiological causes of pneumonia with bacterial aetiologies tending to result in more severe disease. Around 40% of individuals with bacterial pneumonia require hospital admission, and approximately 20% of those hospitalised will need intensive care. The incidence of severe bacterial pneumonia has been increasing due to an ageing population, antibiotic misuse and resistance, and the rising prevalence of chronic diseases. Effective treatments for bacterial pneumonia beyond antibiotics and adjuvant therapy are not available. Therefore, a better understanding of the biology of the disease is crucial.

Neutrophils are the most abundant immune cells and the primary responders to bacterial pneumonia. Yet, the neutrophil subsets and functional states in bacterial pneumonia remain elusive. Defining the molecular programmes that determine neutrophil activity will be critical for the development of effective neutrophil-targeted therapeutic strategies.

Overall aim

This project aims to characterise the immune landscape of bacterial pneumonia and elucidate the cellular programmes which drive maladaptive inflammation.

Objectives

- Map immune cells and functional states in blood and bronchoalveolar lavage (BAL)
- Identify molecular pathways which contribute to resolution or maladatpive inflammation
- Validate actionable therapeutic targets to enable the development of neutrophil-targeted therapies

Research plan

Paired samples of blood and BAL and clinical data will be prospectively collected from patients with confirmed bacterial pneumonia (n=15) at Oxford University Hospitals NHS Trust. Single cell RNA sequencing will be performed to determine the immune cell populations and their state. Neutrophil related

proteins will be measured in the blood and lung fluid to assess neutrophil degranulation (Neutrophil Elastase, Myeloperoxidase, Cathepsin G, S100A8/9, Azurocidin 1) and NETosis (ELANE-DNA complexes). Targeted mass spectrometry will be applied to neutrophils to characterise their metabolic activity. The single-cell RNA-sequencing data will be integrated with neutrophil activity and metabolic profiles, alongside clinical data, to define how neutrophil states and activity vary across disease severity.

Expected outcomes

- Define the immune landscape of bacterial pneumonia
- Identify molecular pathways associated with maladaptive neutrophil responses and impaired resolution of inflammation
- Identify candidate neutrophil pathways and targets that may inform studies of neutrophil targeted therapies

DISEASE RELVEANCE

Bacterial pneumonia remains a major cause of morbidity and mortality worldwide, particularly among older adults, young children, and individuals with chronic health conditions. Effective treatments beyond antibiotics and supportive care are limited. There is evidence that clinical outcomes are determined not only by the infecting pathogen but also by the nature and magnitude of the host immune response. Dysregulated inflammation can cause severe lung tissue damage, while inadequate immune activation can impair bacterial clearance. The cellular and molecular mechanisms that distinguish protective from pathological immune responses remain incompletely understood.

This project will apply single-cell RNA sequencing to define the immune landscape of bacterial pneumonia. We aim to identify mechanisms that distinguish protective antimicrobial immunity from maladaptive inflammation and immunosuppression. We will discover disease-associated immune cell states, transcriptional programmes, and intercellular signalling networks. These will be integrated with clinically relevant disease phenotypes to identify candidate pathways for therapeutic intervention and biomarkers for patient stratification. Our aim is to develop neutrophil-targeted immunomodulatory therapies that limit immune-mediated lung injury while preserving bacterial clearance.

KEY TECHNOLOGY

- Access to fresh paired BAL and blood samples from patients with pneumonia
- CITE-seq, enabling simultaneous single-cell transcriptomic (sc RNA Sequencing) and cell-surface protein profiling
- High troughput protein measurement methods including unlabelled mass spectrometry

TRAINING OPPORTUNITIES

The student will be embedded within the CAMS Oxford Institute and the Radcliffe Department of Medicine in a translational research environment with access to expertise in infection and immunology. The student will participate in weekly laboratory meetings and monthly journal clubs, providing opportunities to present and critically discuss research findings, and develop scientific communication skills.

We will provide training in experimental and computational aspects which are needed for the successful delivery of the project. The student will get training in CITE-seq, mass spectrometry, core cellular and immunological techniques, including primary cell culture, multiparameter flow cytometry, and functional immune assays.

KEY PUBLICATIONS

1. **ERS/ESICM/ESCMID/ALAT guidelines for the management of severe community-acquired pneumonia**, Ignacio Martin-Loeches, Antoni Torres, Blin Nagavci, Stefano Aliberti, Massimo Antonelli, Matteo Bassetti, Lieuwe Bos, **James D. Chalmers**, Lennie Derde, Jan de Waele, Jose Garnacho-Montero, Marin Kollef, Carlos Luna, Rosario Menendez, Michael Niederman, Dmitry Ponomarev, Marcos Restrepo, David Rigau, Marcus J. Schultz, Emmanuel Weiss, Tobias Welte, and Richard Wunderink, ***European Respiratory Journal 2023 61(4): 2200735***
2. **Pleural fluid neutrophil extracellular traps are associated with disease severity and risk of 1-year mortality in pleural infection: an observational, international, multicohort study (TORPIDS-3),** Julia Y. Chu, Samuel Hollins, Alguili Elsheikh, Stephen Gerry, Nikita Manoharan, Tryfon Zarganes-Tzitzikas, Yinzhou Feng, Elie Antoun, Eihab O. Bedawi, John P. Corcoran, Amy Gilmour, Federico Mei, Federica Monaco, Marco Tomasetti, Argyrios Tzouvelekis, Electra Koulousousa, Fotios Sampsonas, Malvika

Bhatnagar, Ellice Z. Chen, Paul E. Brennan, Tao Dong, Ian D. Pavord, Yuanlin Song, **James D. Chalmers**, Julian C. Knight, Najib M. Rahman, and **Nikolaos I. Kanellakis**, ***European Respiratory Journal 2026 68(2): 2600113***

3. **Pleural fluid proteomics from patients with pleural infection shows signatures of diverse neutrophilic responses: The Oxford Pleural Infection Endotyping Study (TORPIDS-2) Nikolaos I. Kanellakis,** Elie Antoun, Kiki Cano-Gamez, Julia Chu, Nikita Manoharan, Georgina Berridge, Iolanda Vendrell, Zheqing Zhang, John P. Corcoran, Alguili Elsheikh, Tao Dong, Roman Fischer, Justin P. Whalley, Julian C. Knight,and Najib M. Rahman, ***European Respiratory Journal 2025 66(1): 2500010***
4. **A pan-immune panorama of bacterial pneumonia revealed by a large-scale single-cell transcriptome atlas,** Kun Xiao, Yan Cao, Zhihai Han, Yuxiang Zhang, Laurence Don Wai Luu, Liang Chen, Peng Yan, Wei Chen, Jiaxing Wang, Ying Liang, Xin Shi, Xiuli Wang, Fan Wang, Ye Hu, Zhengjun Wen, Yong Chen, Yuwei Yang, Haotian Yu, Lixin Xie, and Yi Wang ***Signal Transduction and Targeted Therapy volume 10, 5 (2025)***
5. **Targeting neutrophil serine proteases in bronchiectasis, James D. Chalmers** Marcus A. Mall, Sanjay H. Chotirmall, Anne E. O'Donnell, Patrick A. Flume, Naoki Hasegawa, Felix C. Ringshausen, Henrik Watz, Jin-Fu Xu, Michal Shteinberg, and Pamela J. McShane ***European Respiratory Journal 2025 65(1): 2401050***

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4.3 CD1c-Mediated Immune Dysfunction under Immunosuppression

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PROJECT OVERVIEW

Immune homeostasis requires a delicate balance between infection defence and self-tolerance. This balance is particularly challenged in individuals receiving immunosuppressive therapy. One such group are organ transplant recipients, who require lifelong immunosuppression to prevent transplant rejection, but consequently experience increased susceptibility to infection and malignancy. The elevated incidence of these post-transplant complications is compounded by poorer stage-matched outcomes, resulting in substantial morbidity and mortality.

A major barrier to improving outcomes in this cohort is the lack of integrated, mechanistic understanding of the effect of post-transplant immunosuppression upon tissue immunity. While the effects of immunosuppression on conventional peptide-specific T-cell immunity are relatively well understood, their impact on lipid-mediated immune pathways remains largely unexplored. Our previous work indicates that immunosuppression may alter both lipid handling and antigen presentation in peripheral tissue.

CD1c is a non-polymorphic antigen-presenting molecule that samples a diverse repertoire of self and microbial lipids, and presents them to specialised T cells. Emerging evidence suggests that CD1c-mediated immunity plays an important role in both host defence and immune tolerance. In immunosuppressed individuals, persistent or recurrent infections may reshape host lipid metabolism, generating neo-lipid antigens that drive aberrant CD1c-mediated immune responses. This project aims to define the molecular mechanisms linking infection-induced lipid remodelling, CD1c-mediated presentation, and immune dysregulation under immunosuppression.

Patient-derived samples taken before and after kidney transplant will be utilised for integrated lipidomics, single-cell and spatial transcriptomics, and T-cell immune profiling. This will identify host- and microbe-derived neo-lipid antigens arising in immunosuppressed patients and determine how they are recognised by CD1c-restricted T cells.

By integrating these datasets, the study will generate cellular and spatial maps of lipid antigen presentation pathways active in health and under immunosuppression, providing novel mechanistic insight into infection susceptibility and immune dysfunction in immunosuppressed individuals.

DISEASE RELVEANCE

Kidney transplant recipients require lifelong immunosuppressive therapy to prevent allograft rejection, but consequently experience a substantially increased burden of infectious complications, malignancy, and immune-mediated disorders. Infections remain a major cause of morbidity and mortality following transplantation, yet the mechanisms underlying impaired immune surveillance and dysregulated host responses remain incompletely understood.

This project will address this knowledge gap using well-characterised clinical samples from kidney transplant recipients receiving immunosuppressive therapy, including peripheral blood, alongside samples from patient suffering with repeat infection and healthy controls. The findings may identify novel biomarkers of immune competence and reveal therapeutic opportunities to improve immune monitoring and infection management in transplant recipients and other immunosuppressed populations

KEY TECHNOLOGY

- **Patient-derived immune cell models:** Peripheral blood mononuclear cells will be obtained from kidney transplant recipients and healthy controls. Monocyte-derived dendritic cells (mo-DCs) will be generated ex vivo and used as a clinically relevant model to investigate the effects of immunosuppressive therapies and associated lipid remodelling on CD1c expression, lipid antigen loading, and T-cell activation using multiparameter flow cytometry.
- **Lipidomics and Antigen Discovery:** High-resolution liquid chromatography-mass spectrometry (LC-MS/MS) will be used to profile host and microbe-derived lipids in clinical samples. CD1c ligand isolation and lipid capture platforms will enable identification of candidate neo-lipid antigens generated during infection and immunosuppression.
- **Single-Cell and Spatial Multiomics:** Single-cell CITE-seq, T-cell receptor (TCR) sequencing and spatially resolved transcriptomic profiling of patient tissues will provide high-resolution characterisation of cellular states, immune networks, and CD1c-reactive T-cell repertoires in immunosuppressed individuals.
- **Clinical Translation and Systems Integration:** The project will leverage well-characterised samples from kidney transplant recipients and healthy controls. Advanced bioinformatics and systems immunology approaches will integrate high-dimensional datasets to generate molecular maps of immune dysfunction under immunosuppression.
-

TRAINING OPPORTUNITIES

This DPhil project will provide multidisciplinary training in immunology, lipid biology, transplantation research, and advanced multi-omics technologies. The student will gain expertise in human immunology using clinical samples, including primary immune cell isolation and differentiation, functional immune assays, and multiparameter flow cytometry. Training will also be provided in bioinformatic analysis, and the interpretation of complex immunological datasets.

The project will further develop skills in experimental design, statistical analysis, and data integration to studying human disease. Working jointly between the Bottomley and Chen groups, the student will gain interdisciplinary experience with regular interaction with clinicians, researchers, and patient cohorts with translational discoveries. The translational nature of the project is enhanced through the joint supervisory arrangement, benefiting from both fundamental scientific and clinical expertise.

The student will participate in laboratory meetings, journal clubs, and University-wide seminar programmes, providing opportunities for scientific discussion, networking, and collaboration. In addition, the student will have access to the Medical Sciences Division Skills Training Programme and a wide range of courses in genomics, statistics, manuscript preparation, presentation, leadership, public engagement, and responsible conduct of research, preparing them for future careers in academia, biotechnology, or clinical research.

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. Chen, Y.L. et al. Group A Streptococcus induces CD1a-autoreactive T cells and promotes psoriatic inflammation. Sci Immunol 8, eadd9232 (2023).
4. Bottomley M.J. and Harden P.N. Update on the long-term complications of renal transplantation. Br Med Bull. 106:117-34 (2013).
5. Bottomley M.J. et al.Localised signalling networks co-opt TGF-β2 to promote an immuno-exclusive mesenchymal niche within human squamous cell carcinoma (pre-print). MedRxiv (2026). doi: 10.1101/2025.05.23.25327735.

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4.4 Studying How Viral Glycan Shields Impair Innate Immune Sensing and Adaptive Immunity across Scales

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PROJECT OVERVIEW

Protein glycosylation is one of the most consequential yet least understood post-translational modifications and is highly relevant for both immunity and respiratory infection biology. Glycan structures are not static: they vary by cell type, are reorganised in the intercellular interfaces of immune cells, shift as infection progresses through different tissue compartments, and evolve under immune selection pressure. Despite their established roles in viral entry, innate immune sensing, and antibody recognition, how glycosylation patterns change over the course of a respiratory infection - and how those shifts feed back into immune responsiveness and infectivity - remains largely uncharacterised. This project addresses that gap using advance ex vivo system integrated into an integrated spatial multi-omics platform applied to primary human organoids and explants.

Enveloped respiratory viruses such as influenza A and SARS-CoV-2 acquire glycans via the host glycosylation machinery in the ER/Golgi, making shield composition cell and tissue dependent.

This provides two mechanisms to outsmart host immunity. On the innate side, the lung collectins SP-A and SP-D recognise high-mannose glycan structures on viruses and opsonise them for macrophage clearance; complex sialylated glycans instead engage inhibitory siglec receptors and evade collectin recognition. On the adaptive side, glycan density on virus glycoprotiens (often reffered to as “spikes”) masks underlying epitopes from B cell receptors and neutralising antibodies, and can act as trans ligands for Siglecs on NK cells, and T cells, thus impairing the adequate clearance of virus-infected cells. Siglec binding on B cells, on the other hand, will increase the threshold for B-cell activation by phosphatase recruitment to BCR-rich domains driving antigen capture.

Whether these two effects are driven by the same glycans or different ones is a central unresolved question. Similarly, how different glycan repertoires interfere with the communication of the innate and adaptive arms of antiviral immunity remains little studied.

The project will address this using two parallel organoid arms. In Aim 1, primary human air-liquid interface (ALI) lung organoids co-cultured with alveolar macrophages will be challenged with a panel of glycoengineered influenza spikes and/or virions spanning high-mannose and complex glycoform states, with innate readouts including SP-D binding, macrophage phagocytosis, cytokine and type I interferon secretion, and viral spreading. In Aim 2, we will study how these processes then interfere with the recruitment, activation, and effector function of human lymphocytes, including viral clearance, and the quantity and quality of germinal centre-like reactions driving the production of antiviral antibodies.

A unified spatial multi-omics platform based on mass spectrometry will provide mechanistic resolution (e.g. transcript and protein-level understanding of cellular glycosylation) with functional glycan and immunological readouts (e.g. detailed glycoconjugate structural

characterisation, and the trajectories of immune cell populations stimulated in isolated and immune-connected lung organoids, including T-cells and antibody-secreting cells).

Together, this unified approach will define not only whether the double-evasion or trade-off hypothesis holds, but the molecular mechanism by which glycan shield composition drives divergent immune trajectories.

DISEASE RELVEANCE

- Seasonal influenza causes approximately 290,000–650,000 deaths annually and relies on heavily glycosylated surface proteins - haemagglutinin and neuraminisdase - for host cell entry, and deploy glycan shielding as an evolving mechanism of immune escape.
- Current influenza vaccines produced in embryonated eggs have glycan structures that differ from those on circulating human-airway-adapted virions. Vaccine effectiveness data support a link between this glycan mismatch and reduced antibody breadth, but the contribution of egg-adaptation to innate immune recognition has not been examined, we will examine the impact of virus-glycans on the resulting immune response using spleen organoids.
- If this project identifies a trade-off between collectin opsonisation and epitope masking, this principle could directly inform glycoengineering strategies for recombinant vaccine antigens—prioritising glycoforms that are well-opsonised by lung collectins while minimally shielding neutralising epitopes. This is relevant across influenza, SARS-CoV-2, and future pandemic respiratory pathogens, with direct translational benefit to the respiratory virus vaccine development programmes that are a major public health priority in China and globally.

KEY TECHNOLOGY

- Conventional Flow Cytometry (~15+ parameters).
- Spectral Flow Cytometry (~34+ parameters).
- Ex vivo expanded, genetically engineered primary human T cells.
- TCR-Tg T cells, T-cell clones, and tumoroids.
- SIM and Airyscan Microscopy—3D reconstruction of immune synapses, tissue Immunofluorescence, and organoids
- Mass spectrometry
- **Primary human organoid biology**. Air-liquid interface (ALI) lung and spleen organoids are derived from primary human bronchial or alveolar progenitors, and primary spleen cells. While lung organoids recapitulate pseudostratified airway epithelium with ciliated cells, goblet cells, and club cells in correct proportions; spleen organoids recapitulate key aspects of systemic immunity, providing a source of influenza-specific T and B cells.

Co-culture with HLA-matched macrophages or autologous alveolar macrophages reconstitutes the innate sensing compartment of the distal lung and supports productive influenza and SARS-CoV-2 infection - replacing animal models that poorly replicate human airway glycobiology.

- **Advanced mass spectrometry.** Glycosylation changes will be studied through a unified -OMICs platform based on glycomics, proteomics and transcriptomics. The Struwe lab in the Kavli Institute for Nanoscience Discovery houses ~12 mass spectrometers dedicated to advanced analyis of cellular and structural glycoprotemics. Proteomics of organoid lysates and secreted fractions resolves the protein-level signalling contributing to glycosylation. Bulk RNA-seq transcriptomics will help identify cell populations within organoid microarchitecture and expression of glycan biosynthetic machinery. Glycomics will characterise virus glycovariants and map infection-induced remodelling of host organoid cell-surface glycans across epithelial cells, stromal cells, myeloid cells and migrating lymphocytes, therefore directly connecting virus and host glycan dynamics. Multi-omics data integration will identify correlated glycosylation molecular regulation and dynamics.

- **Virus glycoengineering**. A glycovariant panel of influenza A virions and recombiannt virus glycoprotien spikes will be produced using chemical glycosylation modulators (i.e. kifunensine to arrest high-mannose processing and swainsonine to block complex glycan processing) or relevant glycosyltrasnferase KO cells. Glycan structures and glycan processing will be confirmed by mass spectrometry.

- Single-cell RNA seq of primary cells, tissues and organoids

TRAINING OPPORTUNITIES

In all the techniques mentioned above and more, as necessary to ensure the success of your project.

My goal as a mentor is to provide opportunities for developing a future-proof skill set grounded in rigorous scientific reasoning, while encouraging creativity, independence, and focused problem-solving. I aim to strengthen each candidate's abilities by fostering a dynamic learning environment that nurtures curiosity, self-awareness, collaboration and sustained professional growth.

No prior experience in these techniques is required. Candidates will receive comprehensive training in cutting-edge molecular, cellular, and tissue-level immunology, together with support in developing proficiency in informatics pipelines for statistical analysis and the interrogation of complex transcriptomic and proteomic datasets.

Through interdisciplinary co-mentoring, as a student you will also gain exposure to complementary fields including biochemistry, glycobiology, mass spectrometry, biophysics, genetic engineering, protein engineering, virology, computational biology, and statistics.

Together, these opportunities will equip the candidate with a versatile and future-ready skill set spanning molecular and cellular immunology, tissue biology, quantitative biology, and translational medicine. The combination of mechanistic reasoning, advanced experimental

approaches, computational analysis, and interdisciplinary collaboration will prepare them to make meaningful contributions to both academic research and biomedical innovation.

KEY PUBLICATIONS

1. Saliba, D. G. et al. Composition and structure of synaptic ectosomes exporting antigen receptor linked to functional CD40 ligand from helper T cells. Elife 8, doi:10.7554/eLife.47528 (2019).
2. Cespedes, P. F., Gonzalez, P. A. & Kalergis, A. M. Human metapneumovirus keeps dendritic cells from priming antigen-specific naive T cells. Immunology 139, 366-376, doi:10.1111/imm.12083 (2013).
3. Cespedes, P. F. et al. Surface expression of the hRSV nucleoprotein impairs immunological synapse formation with T cells. Proc Natl Acad Sci U S A 111, E3214-3223, doi:10.1073/pnas.1400760111 (2014).
4. Cespedes, P. F. et al. T-cell trans-synaptic vesicles are distinct and carry greater effector content than constitutive extracellular vesicles. Nat Commun 13, 3460, doi:10.1038/s41467-022-31160-3 (2022).

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4.5 A Systems Level Interrogation of Cell Surface Proteins Regulating T-Cell Immunological Synapses. Part I: Lectins & Integrins

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PROJECT OVERVIEW

T cells are key orchestrators of adaptive immunity. Their high migratory capacity and diverse immunoreceptor repertoires enable dynamic interactions with immune and non-immune cells, creating networks of immunological connections that, when appropriately regulated, eliminates threats while preventing excessive or prolonged damage to the host. Two major $CD4^+$ T-cell subsets maintain this immunological equilibrium: helper and regulatory T cells (Th cells and Tregs, respectively). Whereas Th cells provide signals that sustain and coordinate the responses of other leukocytes, Tregs constrain immune activation to limit self-damage. $CD8^+$ T cells constitute another major functional branch, delivering cytotoxic signals that eliminate infected or malignant cells. More recently, a population of KIR-expressing $CD8^+$ T cells has been implicated in immune regulation through the elimination of self-reactive lymphocyte subsets.

$CD4^+$ and $CD8^+$ T cells execute these diverse functions through the assembly of specialised cell–cell junctions termed immunological synapses (ISs). These interfaces reorganise interacting immunoreceptors into supramolecular architectures supporting the spatially and temporally controlled exchange of information between immune cells. Mechanistically, the proximity of the engaged membranes creates confinement that promotes receptor–ligand interactions that may otherwise have weak monovalent binding affinities. Therefore, the IS works as a molecular hub promoting the integration of a plethora of signals with diverse binding affinities, from nanomolar to micromolar *KD* values, while imposing organisational principles that cannot be reproduced by conventional soluble 3D protein–protein interaction arrays using soluble proteins or oligomeric probes.

Importantly, the function of the IS extends beyond receptor organisation and T-cell activation. Synaptic signalling also drives the assembly and release of specialised extracellular particles carrying immunoreceptors and effector molecules that are transferred to interacting cells in an antigen-dependent manner. These feedforward trans-cellular signals include cytotoxic supramolecular attack particles (SMAPs) and two types of trans-synaptic vesicles (tSVs): synaptic ectosomes and exosomes, which provide a physical mechanism through which transient cell-cell contacts deliver persistent effects beyond the lifetime of single synapses.

Here, we will exploit this natural capacity of T cells to release immunoreceptors and effector molecules through tSVs and SMAPs as a functional readout to

perform the first proteome–scale interrogation of cell surface proteins that regulate IS assembly and function. We will use small yet physiological densities of ~200 recombinant lectins and integrin ligands presented on synthetic APCs to identify previously unrecognised regulators of the IS. Through parallel work packages, we will rapidly prioritise candidate molecules and determine whether, and through which molecular mechanisms, these novel regulators modulate immunoreceptor architecture, signal integration, and effector outputs. Finally, we will elucidate whether these new regulators also affect immune networks dependent on T-cell function using 3D *ex vivo* systems, including spleen organoids and explants, and tumoroids, complemented with human T-cell clones and TCR-transgenic cells. Thus, we will identify new molecular regulators of T-cell immunity across its spatial and temporal scales, from millisecond receptor–ligand interactions within individual synapses to their translation into network-level immune-cell cooperation over several days.

DISEASE RELVEANCE

Candidate prioritisation will be further informed with single-cell RNA-sequencing and proteomics atlases of health and disease, allowing us to identify the most relevant cellular contexts and select the most informative model–candidate combination for mechanistic studies.

Cancer, infections, chronic inflammatory or immune-mediated diseases

KEY TECHNOLOGY

1. Conventional Flow Cytometry (~15+ parameters).
2. Spectral Flow Cytometry (~34+ parameters).
3. Ex vivo expanded, genetically engineered primary human T cells.
4. TCR-Tg T cells, T-cell clones, and tumoroids.
5. First- and Second-Generation Lymphoid Organoids
6. Precision Cut Spleen Slices
7. Total Internal Reflection Fluorescence Microscopy—single molecule and single synapse analyses in 2D
8. SIM and Airyscan Microscopy—3D reconstruction of immune synapses, tissue immunofluorescence, and organoids
9. Single-cell RNA seq of primary cells, tissues and organoids
10. Bulk proteomics and click-chemistry enriched proteomics

TRAINING OPPORTUNITIES

In all the techniques mentioned above and more, as necessary to ensure the success of your project.

My goal as a mentor is to provide opportunities for developing a future-proof skill set grounded in rigorous scientific reasoning, while encouraging creativity, independence, and focused problem-solving. I aim to strengthen each candidate's abilities by fostering a dynamic learning environment that nurtures curiosity, self-awareness, and sustained professional growth.

No prior experience in these techniques is required. Candidates will receive comprehensive training in cutting-edge molecular, cellular, and tissue-level immunology, together with support in developing proficiency in informatics pipelines for statistical analysis and the interrogation of complex transcriptomic and proteomic datasets.

Through interdisciplinary collaborations, they will also gain exposure to complementary fields including biochemistry, biophysics, genetic engineering, protein engineering, virology, computational biology, and statistics.

Together, these opportunities will equip the candidate with a versatile and future-ready skill set spanning molecular and cellular immunology, tissue biology, quantitative biology, and translational medicine. The combination of mechanistic reasoning, advanced experimental approaches, computational analysis, and interdisciplinary collaboration will prepare them to make meaningful contributions to both academic research and biomedical innovation.

KEY PUBLICATIONS

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2. Hamid, M., Cespedes, P. F., et al. Unconventional human CD61 pairing with CD103 promotes TCR signaling and antigen-specific T cell cytotoxicity. Nat Immunol 25, 834-846, doi:10.1038/s41590-024-01802-3 (2024).
3. Cespedes, P. F. et al. T-cell trans-synaptic vesicles are distinct and carry greater effector content than constitutive extracellular vesicles. Nat Commun 13, 3460, doi:10.1038/s41467-022-31160-3 (2022).
4. Cespedes, P. F., Beckers, D., Dustin, M. L. & Sezgin, E. Model membrane systems to reconstitute immune cell signaling. FEBS J 288, 1070-1090, doi:10.1111/febs.15488 (2021).
5. Saliba, D. G., Cespedes, P. F. et al. Composition and structure of synaptic ectosomes exporting antigen receptor linked to functional CD40 ligand from helper T cells. Elife 8, doi:10.7554/eLife.47528 (2019).

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4.6 Determinants of Hepatitis B Viral Tissue Rropism and Disease

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PROJECT OVERVIEW

Background

This project will explore the cellular basis of early infection events that define virus tropism and how this knowledge translates into disease. Answering the fundamental question of 'how, when and where do viruses replicate'. Spatial transcriptomics and proteomics allows us to study individual infected cells and their neighbours within tissue at unprecedented detail and to integrate with digital pathogy records. As viruses are obligate intracellular pathogens, understanding the host pathways that define host susceptibility to infection underpin the design and evaluation of new therapies and transform our understanding of disease.

Overview

Current work in our laboratory focuses on the host pathways that regulate viral infection of the liver. Chronic hepatitis B and Delta viral infections are a major cause of liver disease and cancer, with limited curative treatments. Understanding the hepatocyte-intrinsic and extrinsic pathways that define host susceptibility to hepatitis B and D virus is the 'holy grail' of this field. We have successfully used single-cell transcriptional profiling technologies to study the spatial relationships between infected cells and their uninfected neighbours. Combining high-resolution imaging of viral RNAs in infected tissue with AI-informed digital pathologies allow us to uncover the cellular and molecular basis of pathogenesis.

Specific aims

We will address the following overall aims

- To characterise the heterogeneity of the HBV infected liver at single cell resolution and impact of infecting viral genotype.
- To map the molecular and spatial niches of viral and immune heterogeneity with pathology.

DISEASE RELVEANCE

Hepatitis B virus (HBV) is a global health challenge with over 290 million infections and major cause of liver disease and cancer. Hepatocellular carcinoma (HCC) is one of the fastest rising and most common causes of cancer-related deaths in the world and there is an urgent need for new therapies.

KEY TECHNOLOGY

Probe enriched long-read RNA sequencing of infected cells and bio-informatic analysis of complex transcriptomic data sets. Single-cell tissue transcriptomics and imaging of viral RNAs along with spatial analysis of the viral niche and relationship to local pathology.

TRAINING OPPORTUNITIES

- **Experimental training**: The student will join a dynamic and multi-disciplinary team of biologists, clinical scientists and mathematicians that provides a unique training environment to gain expertise in molecular virology, super resolution imaging techniques to visualize viral RNAs in complex tissues, digital spatial profiling and bio-informatic analysis of complex transcriptomic data sets.
  Transferable skills including oral presentations at joint lab meetings, critical reviewing of scientific literature by contributing to journal clubs and scientific writing by reviewing and drafting manuscripts for publication. Additionally, the student will have the opportunity to interface with our network of collaborators in Oxford, across the UK and internationally to translate their data to the wider biomedical context.

- **General graduate training**: Graduate students will have the opportunity to access the range of training courses available to university students as well as the student community networks at both Ludwig Cancer, NDM and DPAG.

- **Skills required in the candidate**: We are seeking an enthusiastic and proactive student with knowledge in virology, qualitative or quantitative data collection and analysis.

KEY PUBLICATIONS

1. Harris, J. M. et al. Episomal and integrated hepatitis B transcriptome mapping uncovers heterogeneity with the potential for drug-resistance. Nature Communications 16 (2025). https://doi.org/10.1038/s41467-025-63497-w
2. Russell, R. A. et al. Therapeutic vaccination strategy targeting the PreS1 region of L-HBsAg for HBV/HDV co-infection. JHEP Rep, 101997 (2026). https://doi.org/10.1016/j.jhepr.2026.101997
3. Bull J.A. et al. MuSpAn: a toolbox for multiscale spatial analysis. Nature Communications 17 (2026) https://doi.org/ 10.1038/s41467-026-75649-7
4. Ha, J. et al. Hypoxia inducible factors regulate pneumovirus replication by enhancing innate immune sensing. Proc Natl Acad Sci U S A 123 (2026). https://doi.org/10.1073/pnas.2506647123
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4.7 Defining the Human B Cell Response to a Single Dose of ChAdOx1 BDBV Vaccination – Origins, Maturation and Cross-Reactivity

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PROJECT OVERVIEW

There are multiple filoviruses that cause severe disease and mortality in the global south – ranging between 40-90%. The largest outbreak caused by Ebolavirus occurred from 2013-2016 and the second largest is ongoing in the DRC caused by Bundibugyo ebolavirus (BDBV). There are no vaccines available against BDBV, with most Ebola vaccine and immunology studies focused on Zaire ebolavirus.

This project will analyse longitudinal samples from a Phase I clinical trial of the ChAdOx1 BDBV vaccine developed at the by a team led by COI PI. We will investigate the magnitude, phenotype and clonal composition of the B cell response and determine how these features vary between individuals and over time. The central question will be how the human B-cell response to a single dose of ChAdOx1 BDBV is generated and matured, whether responding cells arise from typical memory/activated populations or circulating t-bet^{+} B-cell populations, and whether these responses produce cross-reactive immunity to Sudan virus (SUDV) and Zaire ebolavirus (EBOV). Particular emphasis will be placed on understanding differences between high and low antibody responders, and the responses after a single or booster response, also the effect of age on B cell responses, and the establishment and maintenance of B cell memory.

The project will integrate serology and multiparameter flow cytometry with bulk B cell receptor (BCR) sequencing and single-cell RNA and V(D)J sequencing. Longitudinal repertoire analysis will be used to identify vaccine-induced clonal expansion, somatic hypermutation, class switching and persistence of B cell lineages. Single-cell analysis will help to understand the phenotype and transcriptional state of responding B cells and link these features directly to paired BCR sequences. Antigen-specific phenotyping will distinguish conventional B-cell populations from circulating atypical B cells using a combination of markers such as CD21, CD27, CD11c, FcRL5 and T-bet/TBX21, recognising that these phenotypes are overlapping rather than definitive lineage markers. Selected BCRs may be expressed as recombinant monoclonal antibodies and characterised for antigen binding and functional activity. Multiplex immunoassays using BDBV and related ebolavirus antigens will further examine the specificity and breadth of vaccine-induced antibody responses. BDBV-, SUDV- and EBOV-GP reactivity will be compared to determine whether

cross-reactivity is already present in early responding clones or emerges as lineages accumulate somatic mutation over time or after booster doses.

Together, these approaches will provide a detailed molecular and cellular description of B cell immunity following BDBV vaccination and identify features associated with the magnitude, quality and durability of the antibody response.

Research aims:

1) Characterise the magnitude and phenotype of the B cell response to BDBV vaccination, including the contribution of conventional and other B-cell populations, including atypical and B-regs.
2) Define the clonal architecture and maturation of the vaccine-induced BCR repertoire and determine whether cross-reactive BDBV/SUDV/EBOV lineages are present early or develop during maturation.
3) Resolve vaccine-responsive B cell populations using single-cell analysis and link cellular phenotype to antigen specificity and clonotype.
4) Functionally characterise selected vaccine-induced antibodies for BDBV-specific and cross-reactive recognition of SUDV and EBOV.

DISEASE RELVEANCE

Bundibugyo ebolavirus (BDBV) causes Bundibugyo virus disease, a severe form of Ebola disease characterised by an acute febrile illness that progresses to gastrointestinal symptoms, organ dysfunction, haemorrhagic manifestations and death. BDBV was first identified during an outbreak in Bundibugyo District, Uganda, in 2007. The second largest Ebolavirus outbreak, caused by BDBVis ongoing in the Democratic Republic of the Congo, highlighting the continued public health need. Previous BDBV outbreaks have been associated with case-fatality ratios of approximately 30–50%, and there are currently no licensed BDBV-specific vaccines or therapeutics.

The geographic distribution of BDBV includes regions where healthcare infrastructure and access to medical countermeasures are extremely limited, paired with ongoing conflict and militia control renders effective outbreak control extremely difficult. Vaccines that induce robust and durable immunity are consequently an important component of outbreak preparedness and response.

There is only one licensed Ebola vaccine and it specifically targets Zaire ebolavirus, and immune responses to one ebolavirus species do not necessarily confer equivalent protection against another. BDBV glycoprotein is antigenically distinct from other ebolavirus glycoprotein, although conserved epitopes can support some degree of cross-reactive antibody recognition. Characterising the B cell and antibody responses induced by BDBV vaccination will therefore provide important information for evaluating BDBV-specific immunity and may

also inform the design of broader vaccine strategies targeting multiple ebolavirus species. The project will test whether cross-reactive recognition is associated with particular circulating B-cell phenotypes and whether it changes as vaccine-induced clones mature over time.

KEY TECHNOLOGY

1) Multiparameter flow cytometry and cell sorting will be used for detailed B cell immunophenotyping, identification of vaccine-responsive populations, and isolation of defined B cell subsets, including conventional memory/activated populations and circulating atypical B cells and B-regs will be defined using combinations of CD21, CD27, CD11c, FcRL5 and T-bet where technically feasible.
2) Bulk BCR sequencing will be used to characterise immunoglobulin repertoires at scale, including V(D)J usage, clonotype structure, repertoire diversity, clonal expansion, somatic hypermutation, isotype distribution, and longitudinal lineage tracking.
3) Single-cell RNA and V(D)J sequencing will provide paired transcriptomic and BCR information at cellular resolution, enabling identification of B cell states, vaccine-responsive clonotypes, transcriptional programmes, and links between cellular phenotype and BCR sequence.
4) Cell culture and recombinant antibody expression will be used to produce selected monoclonal antibodies identified from BCR sequencing datasets for downstream functional characterisation and comparison of BDBV, SUDV and EBOV reactivity.
5) Serological assays will quantify vaccine-induced antibody responses using ELISA and related binding assays, with functional antibody assays incorporated where appropriate.
6) Multiplex immunoassays will enable simultaneous assessment of antibody recognition across multiple BDBV and related ebolavirus antigens, supporting analysis of response breadth and cross-reactivity. Where sample availability and assay performance permit, differentially labelled BDBV, SUDV and EBOV GP probes will be used to identify antigen-specific and cross-reactive B cells directly in blood.

TRAINING OPPORTUNITIES

The project offers broad training at the interface of clinical vaccinology, experimental immunology and computational biology. The student will work with samples and immunological data generated within a clinical vaccine trial and gain an understanding of clinical study design, longitudinal sampling,

human biological variability and the constraints involved in translating experimental measurements into conclusions about vaccine responses.

Laboratory training will include PBMC handling, B cell immunophenotyping, flow cytometry and cell sorting, mammalian cell culture, antibody cloning and expression, ELISA and multiplex immunological assays. This will include antigen-specific phenotyping of conventional and atypical circulating B-cell populations including B-regs and assessment of BDBV/SUDV/EBOV cross-reactivity. The student will also develop expertise in bulk immune-repertoire sequencing and single-cell RNA/VDJ sequencing.

Computational training will include analysis of high-dimensional flow cytometry, BCR repertoire analysis, bulk and single-cell transcriptomics, statistical analysis of longitudinal human datasets and integration of cellular, molecular and serological measurements. Particular emphasis will be placed on reproducible analysis and appropriate statistical treatment of inter-individual variation.

The combination of experimental and computational approaches will enable the student to follow a biological observation from a clinical sample through cellular and molecular characterisation to functional validation. This provides a strong foundation for subsequent work in vaccine immunology, infectious disease, antibody biology or translational immunology.

KEY PUBLICATIONS

1. Flaxman A, Sebastian S, Appelberg S, et al. Potent immunogenicity and protective efficacy of a multi-pathogen vaccination targeting Ebola, Sudan, Marburg and Lassa viruses. PLoS Pathog 2024; 20: e1012262.
2. Sebastian S, Flaxman A, Cha KM, et al. A multi-filovirus vaccine candidate: co-expression of Ebola, Sudan, and Marburg antigens in a single vector. Vaccines (Basel) 2020; 8: 241.
3. Ewer K, Rampling T, Venkatraman N, et al. A monovalent chimpanzee adenovirus Ebola vaccine boosted with MVA. N Engl J Med 2016; 374: 1635–46.
4. Rojek A, Fieggen J, Apiyo P, et al. Ebola disease: bridging scientific discoveries and clinical application. Lancet Infect Dis 2025; 25: e165–76.
5. Bowyer G, Sharpe H, Venkatraman N, et al. Reduced Ebola vaccine responses in CMV+ young adults is associated with expansion of CD57+KLRG1+ T cells. J Exp Med 2020; 217: e20200004.

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THEME 5: INFLAMMATION & AUTOIMMUNE DISEASE

5.1 Multi-Omic Discovery of Pathways Governing Skin Immune Homeostasis in Health and Disease

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PROJECT OVERVIEW

SUMMARY:

Why do kidney transplant recipients develop skin cancer at rates up to 100-fold higher than the general population? This project will investigate how advanced kidney disease (uraemia) and the immunosuppressive drugs required after transplantation alter immune surveillance within clinically normal skin.

Using a unique longitudinal patient cohort, we will study skin and blood samples collected before and after kidney transplantation, allowing each patient to act as their own control. The project combines single-cell genomics, spatial transcriptomics, and functional immunology to understand how local tissue environments regulate skin-resident immune cells, particularly CD8+ T cells.

The ultimate goal is to identify mechanisms that impair anti-viral and anti-tumour immunity in the skin, providing insights that could inform safer immunosuppressive strategies and reduce cancer risk in transplant recipients.

OVERVIEW:

AIM 1: BUILD A CELLULAR ATLAS OF SKIN IN END-STAGE KIDNEY DISEASE

The project will begin with analysis of existing single-cell CITE-seq data from abdominal skin obtained from patients with end-stage kidney disease and healthy age-matched controls.

This work will generate a detailed cellular atlas of skin, defining how uraemia alters immune, stromal, and epithelial cell populations. Findings will be validated using multiplex immunofluorescence and used to identify signalling pathways disrupted by kidney failure. This will provide both a novel biological resource and a reference framework for subsequent analyses.

AIM 2: DEFINE HOW IMMUNOSUPPRESSION SHAPES THE SKIN IMMUNE MICROENVIRONMENT

Spatial transcriptomic profiling will be performed on abdominal skin, using the Bruker CosMx platform, housed at the CAMS Oxford Institute Gene and Spatial Profiling Hub, of which the primary supervisor is Academic Lead.

Building on Aim 1, cells will be mapped into their spatial context to identify tissue niches that support or suppress immune function. Particular focus will be placed on changes in CD8+ T cells and their interactions with neighbouring cells following initiation of immunosuppressive therapy.

These studies will reveal how immunosuppression remodels local immune networks within human skin. The role of these perturbed networks in subsequent disease development will be tested by re-analysis of existing bulk spatial multi-omic data of skin cancer excised from kidney transplant recipients and non-immunosuppressed controls.

AIM 3: TEST THE FUNCTIONAL CONSEQUENCES OF DISRUPTED IMMUNE SIGNALLING

Key discoveries from Aims 1 and 2 will be investigated experimentally. CD8+ T cells isolated from blood and skin will be stimulated using both polyclonal and clinically relevant viral antigens, including Human Papillomavirus, Varicella Zoster, and CMV.

The capacity of these cells to proliferate, produce cytokines, and mediate cytotoxic responses will be measured before and after transplantation. Where Aim 2 identifies important stromal or tissue-derived signals, patient-derived cells will be incorporated into co-culture systems to determine how local microenvironments influence CD8+ T-cell function.

Together, these experiments will move beyond description to establish the mechanisms through which uraemia and immunosuppression impair skin immune surveillance.

DISEASE RELVEANCE

Skin complaints are highly prevalent in patients with advanced kidney disease and is a major source of morbidity, yet the underlying mechanism remain poorly understood. Kidney transplantation substantially improves survival and quality of life in these patients, but the long-term immunosuppression required to prevent graft rejection increases susceptibility to infection and cancer. Consequently, skin complications are amongst the most common and burdensome consequences of transplantation. Most kidney transplant recipients develop viral warts, approximately one-third develop skin infections, and up to half will develop skin cancer during long-term follow-up.

Despite this clinical burden, little is known about how uraemia and the initiation of immunosuppressive therapy alter the cellular composition, tissue organisation and immune function of clinically normal skin. Existing studies have largely focussed on established disease, making it difficult to distinguish early alterations in tissue immune homeostasis from disease-specific responses.

The project will generate the first longitudinal spatial atlas of photo-protected skin before and after kidney transplantation. By combining spatial profiling with functional analyses, it will define how uraemia and immunosuppression reshape

skin immunosurveillance. These data will establish a critical reference framework for future studies of post-transplant skin disease and identify potentially tractable mechanisms that may contribute to infection and cancer susceptibility.

KEY TECHNOLOGY

- **Single-cell multi-omic profiling (CITE-seq)** will be used to generate a high-resolution cellular atlas of skin from patients with end-stage kidney disease. By simultaneously measuring gene and protein expression, this approach enables detailed characterisation of immune, stromal and epithelial cell populations and the signalling pathways altered by uraemia.
- **Spatial transcriptomics** using the Bruker CosMx platform will provide single-cell molecular profiling while preserving tissue architecture. This technology allows cells to be analysed within their anatomical context, enabling the identification of tissue niches, cell-cell interactions and local signalling networks that regulate immune homeostasis. The project will leverage expertise and infrastructure within the CAMS Oxford Institute Gene and Spatial Profiling Hub, where the primary supervisor serves as Academic Lead.
- **Bioinformatic integration of single-cell and spatial datasets** will enable reconstruction of tissue organisation and immune signalling networks before and after kidney transplantation. These analyses will identify candidate mechanisms linking systemic immunosuppression to altered skin immune surveillance.
- Findings will then be validated through **functional immunology experiments** using patient-derived cells. Skin- and blood-derived CD8+ T cells will undergo phenotypic and functional assessment, including antigen-specific stimulation with clinically relevant viral antigens. Co-culture systems incorporating patient-derived stromal populations will be used to directly test how local tissue microenvironments influence immune function following transplantation.

Together, these approaches provide a rare opportunity to gain experience across computational biology, single-cell genomics, spatial biology and experimental immunology within a clinically relevant human disease setting.

TRAINING OPPORTUNITIES

This project offers interdisciplinary training at the interface of clinical medicine, immunology, genomics, and computational biology. The student will develop expertise in the analysis of cutting-edge single-cell and spatial transcriptomic datasets, gaining experience with bioinformatic approaches used to

characterise cellular populations, tissue organisation, and cell-cell communication within complex human tissues.

Training will be provided in the analysis and interpretation of large-scale genomic datasets, including integration of single-cell and spatial data. The student will work closely with bioinformaticians and clinician-scientists within Oxford's translational research environment.

The project also provides extensive laboratory training. The student will gain experience in primary human tissue processing, immune cell isolation, flow cytometry and cell sorting, cell culture, functional T-cell assays, and multiplex immune phenotyping. They will participate in the design, execution, and interpretation of experiments using patient-derived samples from a unique longitudinal transplant cohort.

Exposure to the Bruker CosMx spatial transcriptomics platform through the CAMS Oxford Institute Gene and Spatial Profiling Hub will provide experience with one of the most advanced spatial biology technologies currently available.

Throughout the DPhil, the student will leverage the broader scientific ecosystem and training infrastructure offered by the University to develop skills in experimental design, critical data interpretation, scientific writing, and presentation.

The combination of computational and experimental training will equip them with a versatile skill set applicable to both academic medicine and translational biomedical research.

KEY PUBLICATIONS

1. **Clinical Equipoise and Unimproved Outcomes following Posttransplant Cutaneous Squamous Cell Carcinoma.** Crisp THJ., Peleva E., et al, (2026), Kidney International Reports, 11
2. **How Can Spatial Transcriptomic Profiling Advance Our Understanding of Skin Diseases?** Kumaran G. et al, (2025), Journal of Investigative Dermatology, 145, 522 – 535
3. **Localised signalling networks co-opt TGF-β2 to promote an immuno-exclusive mesenchymal niche within human squamous cell carcinoma.** Bottomley MJ. et al, (2025), MedRxiv, 2025.05.23.25327735
4. **Cutaneous adaptive immunity and uraemia: a narrative review**. Zibandeh N., Li Z, et al, (2024), Frontiers in Immunology, 15

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5.2 Peripheral Glial Cells in Skin Homeostasis and Disease

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PROJECT OVERVIEW

The skin is a complex barrier organ in which immune, stromal and nervous systems continuously interact to maintain tissue homeostasis and coordinate responses to injury and disease. While considerable attention has focused on immune cells and sensory neurons, the contribution of peripheral glial cells - the cells that accompany nerves throughout the skin - remains remarkably poorly understood.

Glial cells have traditionally been considered support cells of the nervous system, maintaining neuronal function and facilitating nerve repair. However, emerging evidence is challenging this view. In peripheral tissues, glial cells can sense changes in their local environment, communicate with immune and stromal cells, and contribute to inflammation and tissue repair. In the intestine, for example, glial cells have emerged as important regulators of local immune responses and tissue homeostasis.

The skin contains an extensive network of peripheral glial cells associated with sensory and autonomic nerves. These cells are ideally positioned to integrate neuronal signals with changes in the surrounding tissue environment, yet we know surprisingly little about their functions in healthy skin. There is increasing evidence that cutaneous glia respond to tissue perturbation: they contribute to wound healing and regeneration and undergo molecular changes in inflammatory skin disease and pathological scarring. PDF 2 Project Proposal.docx Together, these observations raise the possibility that glial cells are not simply supporting nerves, but form an active component of the skin tissue microenvironment.

This DPhil project will investigate the role of glial cells in skin homeostasis and disease. We will define how cutaneous glial cells are organised within healthy skin, how they interact with surrounding neuronal, immune and stromal populations, and how their molecular identity and spatial organisation change following tissue perturbation. By combining transcriptomic approaches with advanced imaging and functional experimental models, the project will determine whether changes in glial cells are simply a consequence of tissue pathology or whether glia actively shape inflammatory and repair responses.

Ultimately, this work aims to establish cutaneous glia as an integral component of the skin cellular ecosystem and uncover previously unrecognised mechanisms through which the peripheral nervous system contributes to tissue homeostasis and disease.

DISEASE RELVEANCE

Chronic inflammatory and fibroproliferative skin diseases arise from dysregulated communication between immune, stromal and nervous systems. Despite major advances in understanding immune and neuronal contributions to skin pathology, the role of peripheral glial cells within this multicellular network remains largely unexplored.

There are already indications that cutaneous glia respond strongly to disease and injury. Transcriptional alterations in Schwann cells have been reported in inflammatory skin disease and keloid scars, while experimental studies demonstrate roles for injury-activated glial cells in wound healing and tissue regeneration. Preliminary analysis underpinning this project further suggests that glial cells in human inflammatory skin acquire immune-associated transcriptional programmes.

By defining how glial cells change during skin inflammation and tissue remodelling, and determining whether these responses actively influence disease, this project could reveal an unexplored cellular mechanism underlying chronic skin pathology. More broadly, understanding glial regulation of peripheral tissues may identify therapeutic opportunities to modulate pathological inflammation and promote effective tissue repair.

KEY TECHNOLOGY

The project will combine complementary approaches to study cutaneous glial cells at molecular, spatial and functional levels:

- Single-cell/single-nucleus transcriptomics to define glial populations and identify how they change between healthy and diseased skin.
- Spatial transcriptomics and computational analysis to investigate the localisation of glial states and their interactions with immune, neuronal and stromal cells.
- 3D whole-mount imaging using our established skin clearing approach and glial reporter mice to visualise and quantify the cutaneous glial network in intact tissue.
- In vivo genetic models and in vitro cell culture/ skin organoid models to manipulate glial cells and determine their functional contribution to skin homeostasis, inflammation and repair.
- Multiplex imaging and RNAscope to validate candidate pathways and map glial responses within their tissue context.

TRAINING OPPORTUNITIES

This interdisciplinary project integrates experimental and computational approaches to uncover fundamental roles of peripheral glial cells in skin homeostasis and disease. It is particularly suitable for a candidate with a keen interest in cell biology, neuroimmune interactions and tissue biology who is passionate about discovering fundamental biological concepts with relevance to human disease.

The project will provide high-level training in cutting-edge imaging and genomic approaches, including whole-tissue visualisation and quantitative high-resolution microscopy, single-cell/single-nucleus sequencing and spatial transcriptomics. The student will also gain experience in *in vivo* functional genetics and models of tissue inflammation and repair, with opportunities to relate mechanistic discoveries to human skin disease.

Importantly, the student will learn to move between discovery and mechanism: using transcriptomic and spatial data to generate hypotheses, validating these experimentally, and testing their functional significance in vivo. The interdisciplinary research environment will provide exposure to immunology, neuroscience, imaging and computational biology, while offering an excellent opportunity to understand how fundamental biological discoveries can inform our understanding of clinically relevant disease.

This is a creative and discovery-driven project suited to a curious student who is excited by challenging biological questions and keen to develop scientific independence.

KEY PUBLICATIONS

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2. Karjalainen J, Hain S, Progatzky F. Glial-immune interactions in barrier organs. Mucosal Immunology. 2025. doi:10.1016/j.mucimm.2024.12.012.
3. Gopee NH, Winheim E, Olabi B, et al. A prenatal skin atlas reveals immune regulation of human skin morphogenesis. Nature. 2024;635:679–689. doi:10.1038/s41586-024-08002-x
4. Ye JH, Chen YL, Ogg G. CD1a and skin T cells: a pathway for therapeutic intervention. Clinical and Experimental Dermatology. 2024;49(5):450–458. doi:10.1093/ced/llad460.
5. Hardman CS, Chen Y-L, Salimi M, et al., Ogg GS. CD1a promotes systemic manifestations of skin inflammation. Nature Communications. 2022;13. doi:10.1038/s41467-022-35071-1

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5.3 Therapeutic Induction of Fibroblast Quiescence for Treatment of Inflammatory Diseases

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PROJECT OVERVIEW

Background and Rationale

Inflammatory arthritis is characterised by persistent joint inflammation, progressive tissue destruction and recurrent disease flares. Although current therapies can effectively suppress inflammation and induce clinical remission, many patients relapse following treatment reduction or cessation, suggesting that pathogenic mechanisms persist and confer an ongoing risk of disease recurrence.

We have shown that synovial fibroblasts - specialised stromal cells that form the lining of the joint, the synovial tissue - are key regulators of inflammation, tissue organisation and joint damage and contribute to the persistence and recurrence of arthritis. Fibroblasts acquire stable disease-associated phenotypes that persist even when inflammation has resolved.

We have identified transcription factors KLF4 and KLF9 as candidate regulators of a healthy immunoregulatory fibroblast state and represent key molecular switches capable of modifying fibroblast phenotype and function. Understanding whether manipulation of these pathways can reverse pathogenic fibroblast activation could identify new therapeutic strategies for achieving durable remission.

Hypothesis

Therapeutic reprogramming of synovial fibroblasts towards a quiescent state will promote resolution of inflammatory arthritis and enhance the durability of remission.

Research objectives

1) Determine the effects of gain-of-function (CRISPR activation) and loss-of-function (CRISPR deletion) of KLF4 and KLF9 on the phenotype and function of human synovial fibroblasts *in vitro*.
2) Determine the effects of fibroblast-specific conditional deletion in experimental inflammatory arthritis *in vivo*.
3) Investigate *in vivo* fibroblast-specific targeting strategies suitable for therapeutic application.

Experimental Approach

The project will combine human primary synovial fibroblast assays with complementary experimental mouse models of inflammatory arthritis. Human fibroblasts will undergo targeted gain- and loss-of-function manipulation of

KLF4/KLF9, followed by phenotypic and functional characterisation. Key findings will then be tested *in vivo* using fibroblast-specific conditional genetic models. Synovial fibroblast populations and their molecular states will be characterised using cellular, molecular and transcriptomic approaches. Disease activity and joint pathology will be assessed longitudinally to distinguish effects on disease initiation, resolution and relapse. An important feature of these studies will be using a model of arthritis flare we have developed to test resilience to repeat inflammatory challenges, modelling remission stability. This will establish whether therapeutic manipulation produces a transient reduction in inflammation or instead induces a re-calibration of the fibroblast compartment to restore tissue homeostasis.

Finally, we will translate these mechanistic findings towards therapeutic application by exploring novel strategies to modulate KLF4/KLF9 activity *in vivo*. We will investigate PROTAC-mediated targeted protein degradation and *in vivo* lipid nanoparticle (LNP)-based delivery strategies as approaches to manipulate transcription factor activity therapeutically. These studies will establish whether the molecular pathways identified in human and genetic models can be targeted pharmacologically and whether such interventions can reproduce the durable, homeostatic tissue state observed following genetic manipulation.

Together, these integrated studies will establish a mechanistic framework linking transcription factor activity in synovial fibroblasts to inflammatory disease, resolution and relapse. Importantly, they will determine whether targeting KLF4/KLF9 can shift the fibroblast compartment from a disease-promoting state towards a stable homeostatic state, providing a potential new therapeutic strategy focused on restoring tissue resilience and preventing disease recurrence.

DISEASE RELVEANCE

Current therapies predominantly target inflammatory mediators or immune-cell pathways and can effectively control disease activity, but they do not reverse the underlying alterations that persist within the site of inflammation, the synovial tissue, and predispose joints to relapse. We propose that durable disease control may require active restoration of the stromal compartment to restore tissue homeostasis.

The studies outlined in this proposal will determine whether targeting KLF4/KLF9 can shift synovial fibroblasts from a disease-promoting pathogenic state towards a stable, homeostatic phenotype, thereby enhancing resolution of inflammation and increasing tissue resilience to subsequent inflammatory challenge. This could establish a new therapeutic paradigm focused not only on suppressing inflammation, but on restoring the cellular and molecular properties required to maintain remission.

The translational potential of this approach will be explored using emerging therapeutic technologies, including PROTAC-mediated protein degradation and *in vivo* LNP-based cargo delivery to modulate KLF4/KLF9. Successful completion of this work could identify novel disease-modifying strategies that complement

existing anti-inflammatory therapies by targeting the stromal tissue compartment. Ultimately, this research aims to move beyond transient control of inflammation towards restoration of a resilient, homeostatic joint environment capable of maintaining remission and resisting disease relapse.

KEY TECHNOLOGY

The project integrates established experimental platforms with advanced genomic and emerging therapeutic technologies to define how KLF4/KLF9 regulate synovial fibroblast state and determine whether these pathways can be therapeutically manipulated to promote durable remission.

- Human primary synovial fibroblast models with targeted gain- and loss-of-function approaches to establish the cellular functions of KLF4/KLF9.
- Cellular and functional assays to assess fibroblast activation, inflammatory responses, migration and interactions with immune cells.
- Fibroblast-specific conditional mouse models to determine the causal contribution of KLF4/KLF9 to inflammatory arthritis *in vivo*.
- Longitudinal experimental arthritis models, including of disease flare, supported by joint histopathology and imaging, to distinguish effects on disease initiation, resolution, remission and relapse.
- Single-cell and bulk transcriptomic approaches to resolve fibroblast heterogeneity and identify molecular states associated with pathogenicity, resolution and tissue homeostasis.
- Integrated molecular profiling to define KLF4/KLF9-dependent transcriptional programmes and identify mechanisms regulating fibroblast state and tissue resilience.
- Innovative translational technologies, including *in vivo* PROTAC-mediated targeted protein degradation and lipid nanoparticle (LNP)-based delivery to investigate targeted manipulation of fibroblast transcriptional programmes as a novel therapeutic modality.

Together, these technologies provide a complementary pipeline from human disease-relevant cellular assays and mechanistic discovery through *in vivo* validation and therapeutic translation.

TRAINING OPPORTUNITIES

We are based at the Kennedy Institute of Rheumatology where the student will be embedded within a highly collaborative and multidisciplinary translational research environment. This setting provides an excellent opportunity to bridge fundamental discoveries in immunology and cutting-edge technologies with clinically relevant questions and, ultimately, the development of novel therapeutic strategies. The combination of mechanistic biology, advanced technologies, preclinical modelling, and close interaction between academic

and industry researchers makes this an especially exciting environment in which to develop as an independent translational scientist.

Importantly, the project presents a unique opportunity to work at the interface of clinical and translational immunology within the Centre of Excellence in Restorative Immunology, a collaborative initiative bringing together leading academic and industry laboratories across several UK universities, including the Universities of Oxford, Birmingham, Newcastle, Cambridge, Glasgow and University College London, that aims to advance progress towards stable remission in inflammatory diseases.

A major attraction of this project is the breadth of cutting-edge research approaches that the candidate will be able to develop, including extensive training in fibroblast biology, preclinical *in vitro* modelling, alongside advanced molecular and cellular techniques, including CRISPR-based gene activation and deletion in primary cell lines, and the application of preclinical disease models to investigate disease mechanisms. These approaches will be complemented by histological and imaging analyses, as well as single-cell and spatial transcriptomic technologies, enabling investigation of disease mechanisms at both cellular and tissue levels.

By the end of the DPhil, the candidate will have mastered a suite of cutting-edge experimental and analytical techniques and be well-positioned to develop as a future clinical academic scientist working in translational immunology.

KEY PUBLICATIONS

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5.4 Defining Immune Mediated Mechanisms and Therapeutic Targets in Focal Segmental Glomerulosclerosis Using Human Glomerular Models

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PROJECT OVERVIEW

Focal segmental glomerulosclerosis (FSGS) is a major cause of nephrotic syndrome and progressive kidney failure, with limited targeted treatment options. Although traditionally considered a podocyte disorder, emerging evidence suggests that immune-mediated mechanisms contribute to disease pathogenesis in a subset of patients with idiopathic FSGS (iFSGS). The rapid recurrence of disease following kidney transplantation implicates circulating pathogenic factors, while recent identification of podocyte-directed autoantibodies provides evidence for an autoimmune component in some patients. However, the immune and inflammatory pathways driving glomerular injury remain poorly understood.

Our Kidney Research UK-funded programme is investigating the molecular mechanisms of recurrent iFSGS using spatial transcriptomics and glomerular proteomics in a unique collection of longitudinal human kidney biopsies. These approaches will identify early disease-associated pathways, cellular responses and interactions within the glomerular microenvironment.

This DPhil will investigate the hypothesis that dysregulated immune and inflammatory signalling contributes to glomerular injury in iFSGS and that targeting these pathways can prevent or reverse disease-associated cellular dysfunction.

The student will undertake three interconnected research aims.

Aim 1: Identify immune and inflammatory pathways associated with human FSGS. The student will participate in analysis and integration of spatial transcriptomic and proteomic datasets from human FSGS biopsies, focusing particularly on immune signalling, inflammatory responses and interactions between glomerular cell populations. Candidate pathways will be prioritised based on their association with early disease, cellular localisation, biological relevance and therapeutic tractability.

Aim 2: Determine how candidate pathways contribute to glomerular injury. Selected targets will be investigated using human glomerular cell models, including podocyte monoculture, multicellular co-culture and

microfluidic glomerulus-on-chip systems established in our group. Genetic perturbation, including CRISPR interference (CRISPRi), and pharmacological manipulation will establish the functional consequences of altered pathway activity. Defined inflammatory stimuli and patient-derived serum/plasma will be used to investigate how candidate pathways influence susceptibility to immune-mediated injury. Quantitative readouts will include inflammatory signalling, cytoskeletal organisation, cell adhesion and survival, and glomerular filtration barrier integrity.

Aim 3: Evaluate therapeutic modulation of immune-mediated glomerular injury. Prioritised pathways will be manipulated genetically and pharmacologically to determine whether intervention prevents or reverses glomerular injury. Experimental molecular and cellular responses will be compared with human FSGS signatures to establish disease relevance and prioritise potential therapeutic targets.

By combining human disease multi-omics with mechanistic experimentation in advanced glomerular models, this project will establish whether immune and inflammatory pathways identified in human FSGS contribute causally to glomerular dysfunction and provide a platform for developing targeted therapies.

DISEASE RELVEANCE

FSGS is an important cause of nephrotic syndrome and kidney failure in children and adults. Idiopathic FSGS is particularly challenging because its underlying mechanisms are poorly understood, responses to conventional immunosuppression are variable, and disease frequently recurs following kidney transplantation.

Emerging evidence suggests that immune-mediated mechanisms contribute to disease in a subset of patients. The identification of circulating podocyte-directed autoantibodies has provided evidence for autoimmune podocyte injury, while the roles of other circulating factors, inflammatory signalling and interactions between resident glomerular cells remain incompletely understood. These findings raise the possibility that immune and inflammatory pathways could represent targets for more selective therapeutic intervention.

This project will investigate immune-associated molecular pathways identified directly from human FSGS biopsies, using genetic and pharmacological manipulation in advanced human glomerular models to establish their functional significance. By determining how inflammatory signalling influences podocyte injury, multicellular glomerular responses and filtration barrier integrity, the research aims to identify therapeutically actionable mechanisms.

Findings may inform the development of targeted treatments for FSGS and provide insights relevant to other immune-mediated and proteinuric glomerular diseases.

KEY TECHNOLOGY

This project integrates spatial and proteomic profiling of human FSGS with advanced functional models of the human glomerulus, providing a pipeline from patient tissue discovery to mechanistic and therapeutic validation.

Spatial transcriptomics: Spatial transcriptomic datasets from serial human FSGS biopsies will be generated through our existing programme using 10x Genomics Xenium or the new Atera spatial platform**.** The student will participate in analysis and integration of these datasets to define cell-specific disease states, immune and inflammatory response pathways, and altered signalling between podocytes, mesangial cells, glomerular endothelial cells and infiltrating immune populations. Comparison across disease stages will help distinguish pathways associated with early injury from secondary responses to established glomerular damage.

Glomerular proteomics: Glomeruli will be isolated from formalin fixed paraffin embedded biopsy sections by laser-capture microdissection (LCM) followed by mass-spectrometry proteomics, working with the Oxford Discovery Proteomics Facility. This approach is established within our FSGS programme. Integration of spatial transcriptomic and proteomic evidence will prioritise candidate immune/inflammatory pathways for functional investigation.

Human glomerular models: Functional validation will use human podocytes, mesangial cells and glomerular endothelial cells in established monoculture and Transwell co-culture assays, alongside microfluidic culture under flow using the Emulate Organ-Chip system**.** Our programme has already established podocyte-mesangial co-culture on-chip and is progressing towards multicellular glomerular models. The project provides scope for further bioengineering and refinement of these systems to reproduce relevant features of the human glomerular microenvironment.

Candidate pathways and assays: Pathways will be manipulated using CRISPRi and therapeutic/pharmacological approaches**.** Defined inflammatory stimuli and patient-derived FSGS serum/plasma will provide complementary disease challenges. Established assays within our group include quantitative imaging and cell tracking, cytoskeletal and differentiation markers, inflammatory readouts, cell adhesion/survival and functional assessment of albumin permeability**.**

TRAINING OPPORTUNITIES

This interdisciplinary DPhil will provide broad training at the interface of immunology, human kidney disease, advanced in-vitro modelling and therapeutic development. A personalised training programme will combine hands-on research with formal courses available through the Medical Sciences Division Graduate School, Oxford Biomedical Data Science training programmes, Centre for Human Genetics and wider University.

The student will receive practical training and supervision in human glomerular cell culture, gene editing and CRISPRi, quantitative cellular phenotyping and advanced multicellular culture. Building on established expertise within the group and collaborating teams, they will develop skills in microfluidic Organ-Chip culture, experimental bioengineering and optimisation of physiologically relevant human glomerular models. Training in computational biology will include analysis and biological interpretation of spatial transcriptomic and proteomic datasets and integration of multi-modal human disease data. This combination will enable the student to move iteratively between observations in patient tissue and experimentally testable mechanistic hypotheses.

Membership of the Oxford Academic Kidney (OAK) network will providing access to a multidisciplinary community of basic, translational and clinical kidney researchers.

Alongside formal DPhil supervision, mentoring will be provided to support scientific development, career planning and progression towards research independence.

The student will participate in group and departmental research meetings, journal clubs and seminars and will be supported to present their work at national and international scientific meetings, developing oral, written and visual science communication skills. They will also have opportunities to participate in established patient and public involvement (PPI) activities, gaining experience in communicating research with patients and incorporating patient perspectives into research design and dissemination.

KEY PUBLICATIONS

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2. **May CJ, et al. (2026).** PLCε regulates podocyte differentiation and TGF-β1 responses via alteration of SMAD2/SMAD3 ratio. *Cell Communication and Signaling*. 24:391. DOI: 10.1186/s12964-026-02867-3.
3. **Hengel FE, et al (2024).** Autoantibodies Targeting Nephrin in Podocytopathies. *New England Journal of Medicine*. 391:422–433. DOI: 10.1056/NEJMoa2314471.
4. **Barreto AD et al (2026).** Discovery of kidney disease targets using multimodal human podocyte injury models. *Stem Cell Reports*. DOI: 10.1016/j.stemcr.2026.102868.

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THEME 6: NEUROSCIENCE

6.1 Multimodal Prediction in Amyotrophic Lateral Sclerosis

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PROJECT OVERVIEW

This is a data science biomarker development project in Amyotrophic lateral sclerosis (ALS). ALS is a disease of the motor system that causes progressive weakness and is life shortening. The project would be suitable for someone interested in learning skills in proteomic and genetic analysis, multimodal data integration and statistical analysis, whilst gaining experience working with human participants.

ALS overlaps clinically, pathologically and genetically with frontotemporal dementia. Progression of ALS is highly variable; whilst the median survival is less than three years from symptom onset, around 10% of people with ALS will live beyond 10 years. Around 15% of cases of ALS occur due to underlying dominant rare gene variants, but in most cases the underlying aetiology is unclear, potentially reflecting the interaction of ageing, common genetic variation and potentially modifiable factors.

The Oxford MND Centre is internationally renowned for its highly characterised clinical cohorts, which include people affected by genetic and non-genetic forms of ALS, people at elevated genetic risk of developing ALS, healthy and disease controls. Accompanying clinical data, we have obtained high depth CSF and serum proteomics, genomic and imaging data. Alongside these cohorts, we work with large scale population datasets (UK Biobank, All Of Us) and primary care datasets develop insight into the drivers of ALS risk and disease progression.

The student will utilise these datasets to address key research questions, including:

- Can we combine genetic, biomarker and modifiable exposure data to predict the development of ALS in people at elevated genetic risk?
- Can we predict future progression of disability using fluid biomarker, imaging, clinical and genetic data

The basic structure of the DPhil will follow:

Year 1: training in biomarker, population scale and genetic data analysis, familiarising with existing datasets. Specification of overall project goals. Training in participant-facing research methods.

Year 2: Development of analytical methods, exploratory data analysis, initiate final analysis

Year 3: Replication of findings; integration of additional datasets (e.g. imaging) final analysis and thesis write up.

DISEASE RELVEANCE

ALS currently has no effective treatment and no established means to prevent onset or reduce risk in those with a genetic predisposition. Approaches to improve prediction of risk and clinical progression are essential to enable the clinical trials by improving participant stratification and development of treatment-responsive biomarkers. The project makes use of established datasets to address this gap.

KEY TECHNOLOGY

The project primarily makes use of technical developments in biomarker and genetic analysis, including mass spectrometry, proximity extension assay panel proteomics and whole genome sequencing.

TRAINING OPPORTUNITIES

The project focuses on integrative analysis in unique datasets. The student will join a highly interdisciplinary team within the Oxford MND Centre in the University of Oxford's Nuffield Department of Clinical Neurosciences (NDCN). They will receive training in:

- Proteomic and genomic analysis, multimodal data integration
- Clinical neuroscience: Exposure to ALS patient recruitment and assessment, with opportunities to learn about related neurodegenerative disorders

In addition, the student will benefit from:

- Cross-disciplinary mentorship from experts proteomics, genetics and ALS
- Collaborative environment within NDCN
- Transferable skills development, including coding (R, Python), advanced statistical methods (time-to-event, mixed effects modelling, ML / discrimintative AI) and multimodal data integration.

Career development support, including encouragement for presentation of data at national and international conferences and manuscript preparation.

KEY PUBLICATIONS

1. A proteomic signature for prognostic stratification in amyotrophic lateral sclerosis View ORCID DG Lester, P Piazza, E Dellar, P Desai, H Klimovski, CV Chalitsios, M Weinreich, E Alhathli, A Strange, D Melamed-Kadosh, T Ziv, PJ Shaw, A Admon, V Drory, A Malaspina, J Cooper-Knock, I Magen, E Hornstein, A Omole, G Nagappan, A Taylor, K Talbot, MR Turner, AG Thompson. MedRxiv (2026) doi: https://doi.org/10.64898/2026.07.20.26358511

2. Neurodegenerative disease in C9orf72 repeat expansion carriers: population risk and effect of UNC13A. J Gao, AGL Douglas, CV Chalitsios, J Scaber, K Talbot, MR Turner, AG Thompson. Brain (2025)

3. Amyotrophic Lateral Sclerosis and Frontotemporal Dementia Have Distinct Prediagnostic Blood Biochemical Profiles. CV Chalitsios, J Gao, CAC Coupland, J Hippisley-Cox, MR Turner, AG Thompson. Annals of Neurology (2025)

4. Elevated Cerebrospinal Fluid Ubiquitin Carboxyl-Terminal Hydrolase Isozyme L1 in Asymptomatic C9orf72 Hexanucleotide Repeat Expansion Carriers. ER Dellar, I Vendrell, B Amein, DG Lester, EC Edmond, K Yoganathan, T Dharmadasa, A Sogorb-Esteve, R Fischer, K Talbot, JD Rohrer, MR Turner, AG Thompson. Annals of Neurology (2024). doi: 10.1002/ana.27133.

5. Data-independent Acquisition Proteomics of Cerebrospinal Fluid Implicates Endoplasmic Reticulum and Inflammatory Mechanisms in Amyotrophic Lateral Sclerosis. E Dellar, I Vendrell, K Talbot, BM Kessler, R Fischer, MR Turner, and AG Thompson. Journal of Neurochemistry. doi: 10.1111/jnc.16030 (2023)

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6.2 Developing Antigen Specific Treatments for Myasthenia Gravis

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PROJECT OVERVIEW

Myasthenia gravis (MG) is the archetypal autoimmune disorder where 85-90% of patients produce antibodies against their own muscle type nicotinic acetylcholine receptors (AChR) at the neuromuscular junction. It affects ~1 per 10,000 people worldwide. Although the incidence of MG is greater in older populations, there is an increased risk of juvenile onset MG associated with the Chinese population.

Despite recent advances in new treatments for autoimmune disorders, with the introduction of FcRn inhibitors and complement inhibitors, all current treatments indiscriminately suppress important parts of the immune system, leading to increased risk of infectious diseases and cancer.

Our approach is to develop antigen-specific treatments for MG. We will leverage our experience in studying AChR structure, structural prediction software, gene therapies, as well as antibody engineering to produce AChR antigen specific treatments. Using AChR molecules as the targeting molecule, a range of therapeutic strategies can be explored, giving the student a lot of room for creative input, from AChR-Fc antibody drug conjugates; AChR containing viral-like particle (VLP) gene therapies; to AChR-CAR-T cells.

To begin with, a pipeline of the most exciting and tractable therapeutic strategies will be established after initial discussions with the supervision team. These will be designed using bioinformatics approaches, engineered with the help of DNA synthesis, and produced using our established recombinant protein production platforms. The yield, correct folding and stability of the treatments will be assessed using molecular biology methods like fluorescence microscopy using a battery of AChR specific probes, and biophysical methods like differential scanning fluorimetry.

Target engagement and killing by the engineered treatments will first be tested *in vitro* on isolated immune cells expressing AChR specific B-cell receptors. Target binding can be measured using fluorescent microscopy or flow cytometry and cell killing can be assessed using colorimetric viability assays.

Ultimately, the therapeutics that produce the most positive outcomes in *in vitro* testing will be applied to an AChR immunized mouse model of MG to determine their *in vivo* efficacy. The mouse disease phenotype can be assessed using strength tests to assess different types of weakness, neuromuscular signalling using electromyography, immune status using flow cytometry, and circulatory anti-AChR antibody titred using cell-based assays or radioimmunoprecipitation assays.

DISEASE RELVEANCE

- This proposal is entirely focused on the development of novel therapeutics for the autoimmune disorder myasthenia gravis.
- Data from this project will help inform efforts to produce antigen-specific immunotherapies for other antibody mediated autoimmune disorders such as neuromyelitis optica and autoimmune encephalitis.

KEY TECHNOLOGY

- **AChR structural biology and antigen design:** structural analysis of the nicotinic acetylcholine receptor (AChR) and structural prediction software to guide the design of AChR-based, antigen-specific constructs.
- **Antibody and gene therapy engineering:** antibody engineering combined with gene therapy approaches to generate AChR-Fc antibody-drug conjugates, AChR-containing viral-like particle (VLP) gene therapies, and AChR-CAR-T cells.
- **Bioinformatics-guided design and DNA synthesis:** bioinformatic approaches to design candidate constructs, engineered via DNA synthesis and produced using established recombinant protein production platforms.
- **Biophysical and cellular characterisation:** fluorescence microscopy with AChR-specific probes, differential scanning fluorimetry, and flow cytometry to assess construct yield, folding, stability, target binding and cell killing in vitro.
- **In vivo disease modelling:** an AChR-immunised mouse model of myasthenia gravis, characterised using strength testing, electromyography, flow cytometry-based immune profiling, and antibody titre assays (cell-based assays or radioimmunoprecipitation).

TRAINING OPPORTUNITIES

- **Structural biology and bioinformatics:** training in AChR structural analysis and structure-guided, bioinformatic design of antigen-specific constructs.
- **Molecular and protein engineering:** hands-on training in antibody engineering, viral-like particle (VLP) gene therapy design, DNA synthesis workflows, and recombinant protein production.
- **Cell and molecular biology techniques:** training in fluorescence microscopy, flow cytometry, differential scanning fluorimetry, and colorimetric viability assays.
- **In vitro immunology:** training in AChR-specific B-cell receptor assays, target binding assays, and cell-killing assays.
- **In vivo disease modelling:** training in mouse model work, including strength testing, electromyography, and antibody titre assays (cell-based assays or radioimmunoprecipitation).

- **Cross-disciplinary supervision:** the opportunity to work across the Dong (NDCN) and Sun (JR West Wing) research groups, with exposure to a range of therapeutic strategies including antibody-drug conjugates, gene therapy, and CAR-T approaches.

KEY PUBLICATIONS

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5. Ryan-Phillips F, Henehan L, Ramdas S, Palace J, Beeson D, Dong YY. Assessing the Utility of ColabFold and AlphaMissense in Determining Missense Variant Pathogenicity for Congenital Myasthenic Syndromes. Biomedicines. 2024 Nov 8;12(11):2549. doi: 10.3390/biomedicines12112549. PMID: 39595115; PMCID: PMC11592069.

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THEME 7: PUBLIC HEALTH AND POPULATION HEALTH

7.1 Data-Driven Approaches to Respiratory Disease Diagnosis in Primary Care

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PROJECT OVERVIEW

Respiratory symptoms such as cough, wheeze and breathlessness are common in primary care, but establishing the underlying diagnosis can be difficult. Patients may have asthma, COPD or another respiratory disease, while symptoms and individual diagnostic tests are often non-specific. Diagnostic pathways can therefore involve multiple investigations, repeated consultations and referrals, with variable access to high-quality testing.

The long-term goal of our research programme is to make respiratory diagnosis in primary care as accurate, simple, accessible and cost-effective as possible. Ideally, a single rapid, low-burden test would provide sufficient diagnostic information. Where this is not possible, we need to understand which combination and sequence of tests provides the greatest additional diagnostic value while minimising cost, complexity and burden for patients.

This DPhil will use complementary datasets being generated through an established programme of respiratory diagnostic research:

- Asthma-Dx – a prospective primary-care diagnostic platform collecting symptoms and structured clinical history, spirometry, FeNO, blood biomarkers and home monitoring alongside novel physiological and digital diagnostic technologies.
- CORMORANT – a 500-participant primary-care COPD diagnostic accuracy study providing detailed symptoms, clinical characteristics, smoking history, spirometry and independently adjudicated diagnostic outcomes.
- PUFFIN – a national multi-site respiratory diagnostic platform commencing recruitment in 2027, evaluating standard and novel diagnostic tests in 550 people presenting to primary care with suspected respiratory disease, including clinical assessment and home monitoring.
- AIRE – a collaborative programme collecting real-world respiratory consultation recordings and clinical-history data, with complementary work developing speech/acoustic features and AI-assisted respiratory assessment.

Using these resources, the DPhil will:

- Integrate diagnostic information from heterogenous sources such as symptoms, clinical history, standard tests and novel physiological/digital measurements, to develop harmonised datasets and identify complementary or redundant information.
- Evaluate whether a single test can provide sufficient diagnostic information and quantifying the incremental value of additional investigations.
- Develop methodology to combine and evaluate diagnostic data from multiple sources and tests to compare different potential diagnostic pathways.
- Evaluate and compare single-test, combined and sequential approaches to identify pathways that balance diagnostic accuracy with cost, accessibility, feasibility and patient burden.
- Assess generalisability and equity, including robustness to missing or poor-quality data and variation in performance across clinically relevant patient groups.

The project will sit within a multidisciplinary collaborative environment spanning the Asthma-Dx, CORMORANT, PUFFIN and AIRE research teams; Oxford Primary Care Clinical Trials Unit; Department of Physiology, Anatomy and Genetics; Oxford University Hospitals; NIHR HealthTech Research Centre in Community Healthcare; and academic and industry partners developing respiratory diagnostic technologies

DISEASE RELVEANCE

Respiratory disease is a major cause of morbidity and healthcare utilisation, but diagnosis in primary care remains challenging. Patients commonly present with non-specific symptoms such as cough, wheeze and breathlessness, which may be caused by different respiratory conditions or by non-respiratory disease. Diagnostic pathways can therefore involve multiple tests, repeated consultations and referrals, while access to objective respiratory testing is variable.

Improving diagnosis has the potential to enable earlier treatment, reduce inappropriate treatment and provide more efficient use of NHS resources. However, simply adding more diagnostic tests is unlikely to be the solution. Ideally, primary care would have access to a single, accurate, rapid and low-burden test that could identify the underlying respiratory condition. Where this is not possible, diagnostic pathways need to determine which tests provide additional information and in what order they should be performed.

This project will therefore address a broader question than the accuracy of any individual respiratory test: how can diagnostic information be combined and deployed to provide the most accurate, accessible and cost-effective pathway

for patients with respiratory symptoms in primary care. This project addresses the data approaches to this in the combination of different tests to maximise diagnostic accuracy across different diagnoses.

KEY TECHNOLOGY

The project will investigate data-driven and multimodal approaches to respiratory diagnosis, using statistical modelling and appropriate artificial intelligence/machine-learning methods alongside established diagnostic accuracy methodology.

The underlying data will include symptoms, clinical history, demographics, spirometry, oscillometry, home monitoring and selected novel physiological, digital and audio-derived measurements from a range of candidate respiratory technologies. Asthma-Dx and PUFFIN provide a particularly rich platform combining standard diagnostic investigations with multiple novel respiratory technologies, while CORMORANT provides a large primary-care COPD diagnostic dataset containing detailed clinical information and spirometry.

AIRE provides an additional source of multimodal information through real-world respiratory consultations, with systematic identification of clinical-history features and analysis of speech and acoustic biomarkers.

The technological focus will be on determining how different sources of diagnostic information can be combined most effectively, rather than simply developing increasingly complex prediction models. Potential approaches will include regression and prediction modelling, machine-learning classification, feature selection, multimodal data integration and rigorous model validation.

A key question will be how the minimum number of tests can combine into a coherent pathway using alternative combinations and sequences of tests, taking account of:

- diagnostic accuracy;
- cost and resource requirements;
- accessibility and availability in primary care;
- test duration and complexity;
- patient acceptability and burden;
- and the consequences of missing or poor-quality data

TRAINING OPPORTUNITIES

The DPhil will provide interdisciplinary training in diagnostic accuracy, medical statistics, data science, respiratory medicine and health technology evaluation.

The student will be supported by supervisors and collaborators with established expertise in primary care respiratory diagnosis, diagnostic accuracy, medical statistics, respiratory medicine and respiratory physiology, alongside collaborators with complementary expertise in data science and technology development.

The candidate will join a thriving D.Phil programme in the NDPCHS, with regular training offered on a wide range of research methods and skills and career support. The NIHR Healthtech Research Centre will offer the opportunity to engage with industry and to attend training related to Healthtech development, regulation and evaluation. The canaidate will present their work to the 30+ members of the infections Respiratory and Acute Care Research group and will draw on our extensive network of patient and public contributors to access tailored support for their research.

The training programme will be tailored to the candidate's background and interests and can develop towards methodological statistics, physiological signal analysis, clinical-history/audio data, multimodal prediction, or optimisation of diagnostic pathways.

Diagnostic and statistical methodology

- Diagnostic accuracy study design and analysis
- Prediction modelling and regression
- Model discrimination and calibration
- Missing-data methods
- Internal and external validation
- Comparative evaluation of diagnostic strategies

Data science and statistical methods

- Data harmonisation and database development
- Reproducible data-analysis workflows
- Feature extraction and selection
- Analysis of physiological, longitudinal and audio-derived data
- Multimodal data integration

Respiratory medicine

- Clinical assessment of respiratory symptoms
- Asthma, COPD and other respiratory diseases
- Interpretation of spirometry and oscillometry

- Respiratory physiological and digital diagnostics
- Primary care and community diagnostic pathways

Health technology and implementation

- Assessment of health technology, through integration within the NIHR HRC in Community Healthcare
- Patient acceptability and diagnostic burden
- Accessibility and equity in diagnostic pathways
- HealthTech evaluation and translation into clinical practice

KEY PUBLICATIONS

1. Oganesova Z, Panchenko S, Roberts N, Welch L, Mosgrove F, Cook C, Richards G, Salmon J, Turner PJ, Hayward GN, Wanat M, Ashdown HF. Stakeholder-informed prioritisation of HealthTech innovation across chronic respiratory disease: the HERON study. Thorax 2026 (to be published shortly).
2. Broomfield H, Talker L, Lim RH, et al. Development and evaluation of a multivariate prediction model for diagnosing asthma in patients with clinically suspected asthma using capnography. medRxiv. 2025. doi:10.1101/2025.11.25.25340952.
3. Talker L, Dogan C, Neville D, Lim RH, Broomfield H, Lambert G, Selim A, Brown T, Wiffen L, Carter J, Ashdown HF, Hayward G, Vijaykumar E, Weiss ST, Chauhan A, Patel AX. Diagnosis and Severity Assessment of COPD using a Novel Fast-Response Capnometer and Interpretable Machine Learning. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2024;21(1):2321379. doi:10.1080/15412555.2024.2321379.
4. Nicholson BD, Turner PJ, et al. Evaluation of the diagnostic accuracy of two point-of-care tests for COVID-19 when used in symptomatic patients in community settings in the UK primary care COVID diagnostic accuracy platform trial (RAPTOR-C19). PloS One. 2023; 18(7):e0288612. doi: 10.1371/journal.pone.0288612. eCollection 2023.
5. Petousi N, Talbot NP, Pavord ID, Robbins PA. Measuring lung function in airways diseases: current and emerging techniques. Thorax. 2019;74(8):797–805. doi:10.1136/thoraxjnl-2018-212441.

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7.2 From Early Detection to Timely Treatment: Evaluating Hypertension Policy Implementation and Outcomes in China

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PROJECT OVERVIEW

Hypertension exemplifies an important challenge in prevention: risk identification is only valuable if detection leads to timely treatment, sustained blood pressure control and improved health outcomes. China's Healthy China 2030 agenda and national primary care programmes have strengthened hypertension detection and management, but earlier detection does not always lead to timely treatment or sustained blood pressure control. This DPhil will examine whether earlier diagnosis leads to earlier treatment and improved long-term outcomes, and which patient, service and implementation factors contribute to delays along this pathway, and the implications of alternative implementation strategies for health care use, costs, and population health.

Step 1: Systematic review and conceptual framework

The student will conduct a systematic review of hypertension screening and early detection policies, focusing on the pathway from detection and diagnosis to treatment initiation, sustained blood pressure control and long-term cardiovascular outcomes. Where appropriate, meta-analysis will quantify associations. The review will assess where pathways may succeed or fail, how implementation and health system capacity shape progression through care, and whether effects differ across population groups. Where available, it will also consider evidence on healthcare use, costs, and inequalities. It will identify key evidence gaps and inform the conceptual framework and empirical questions for the subsequent studies.

Step 2: Mapping variation in policy implementation and data opportunities in China

The student will map how the timing, content and intensity of hypertension policy implementation vary across Chinese settings, together with the geographic and temporal coverage of candidate longitudinal datasets. On this basis, the student will identify policy contrasts for which implementation timing can be linked to individual-level longitudinal data, and determine the most appropriate data source(s) and empirical design for each subsequent study.

Step 3: Evaluating the impact of policy implementation on treatment, blood pressure control and health outcomes

The empirical work will draw on longitudinal data sources, including China Kadoorie Biobank (CKB) and CHARLS. CHARLS is particularly useful for examining changes in diagnosis, treatment and blood pressure control, while CKB provides substantially larger samples and long-term follow-up for major cardiovascular outcomes. Depending on the specific research question, the student will also explore further data opportunities, including ChinaHEART, CCDFRS and Cheeloo, subject to appropriate data access and collaboration arrangements.

Using these resources, the empirical studies could examine: **(1)** whether policies promoting hypertension detection and management lead to greater or more timely treatment and, when detailed timing information is available, what factors are associated with treatment delay; **(2)** the impact of earlier diagnosis policies on blood pressure control, including whether observed effects operate through earlier treatment initiation; **(3)** the long-term consequences of differences in diagnosis, treatment timing and blood pressure control for related disease outcomes; and **(4)** the the healthcare use, costs and longer term value associated with alternative detection and treatment pathways, including, where data permit, the cost effectiveness of alternative policy or implementation strategies. Analyses may also examine how health and economic consequences vary across socioeconomic, age, sex and geographic groups, informing both equity and efficiency.

DISEASE RELVEANCE

Hypertension is a major modifiable risk factor for stroke, coronary heart disease, heart failure and premature mortality. It is usually asymptomatic, can be identified using a simple and repeatable biomarker, and usually managed effectively through lifestyle and pharmacological treatment. These features make hypertension a particularly useful setting for studying whether early detection translates into timely treatment, sustained control and meaningful prevention of later disease.

Earlier identification alone does not improve health if people with raised blood pressure are not diagnosed, do not initiate treatment, or fail to achieve sustained control. This project will therefore examine the full pathway from blood pressure detection to treatment, control and later health outcomes. By identifying where this pathway succeeds or breaks down, the research will generate evidence on how hypertension prevention can be made more effective and equitable and efficient in routine health systems.

KEY TECHNOLOGY

The project will combine systematic policy mapping, longitudinal health data and causal inference methods and health economic analysis to examine how hypertension policy implementation translates into treatment, blood pressure control and long-term health and economic outcomes.

A key methodological component will be the construction of a longitudinal implementation dataset for selected Chinese settings, capturing variation in the timing, content and intensity of hypertension policies. This will help identify policy contrasts that are suitable for evaluation and can be linked to relevant longitudinal data.

The empirical analyses will draw on complementary longitudinal resources, including CKB and CHARLS, with the choice of dataset determined by the requirements of each study. CKB offers large samples and long-term cardiovascular follow-up, while CHARLS provides repeated information on diagnosis, treatment uptake and blood pressure control. The student will also explore additional data opportunities, including Cheeloo cohort and other Chinese administrative or clinical data sources. Time to event methods will be considered to examine the effects of policy implementation on treatment delay and health outcomes. Depending on the policy setting and available data, causal effects may be estimated using interrupted time series, difference in differences, event study designs or regression discontinuity. Health economic analysis may examine healthcare resource use and longer term cost effectiveness. Sensitivity analyses and falsification tests will assess the robustness of key findings.

TRAINING OPPORTUNITIES

The student will receive training in a broad range of quantitative and applied research methods relevant to the project, including systematic reviewing and evidence synthesis, longitudinal data analysis, causal inference and policy evaluation, with opportunities to develop skills in time to event analysis and health economic evaluation where relevant to the final research plan.

The project will provide experience working with large scale longitudinal datasets and, where appropriate, linked health records. Training will cover data management, reproducible statistical programming, interpretation of complex observational data, and the principles of data governance, ethics and secure data access.

The supervisory team brings complementary expertise in epidemiology, clinical medicine, primary care, health economics, policy evaluation and Chinese population health research. The student will therefore have opportunities to

develop an interdisciplinary perspective and to work with researchers across relevant Oxford departments and research groups.

The student will also benefit from departmental and University training in research methods, academic writing, presentation and public engagement. They will network across both Nuffield Department of Primary Care Health Sciences and Nuffield Department of Population Health, accessing expertise and training cohorts covering closely related topics and methods at both departments, particularly at the Health Economics and Policy Evaluation team and China Kadoorie Biobank team, respectively. They will be encouraged to present work at seminars and conferences, engage with policy and clinical stakeholders, and develop transferable skills in collaboration, project management and communication.

KEY PUBLICATIONS

1. Bandy L, **Amies-Cull B**, et al. (2026). Estimating the Potential Impact of the 2024 UK Salt Reduction Targets on Cardiovascular Health Outcomes and Health Care Costs in Adults: A Modeling Study. Hypertension. DOI: 10.1161/HYPERTENSIONAHA.125.25159
2. Haffner SJP, Stevens RJ, **Amies-Cull B**, et al. (2026). Effect of the English National Enhanced Service on weight management referral rate: an interrupted time-series analysis. BMJ Open. DOI: 10.1136/bmjopen-2025-109943
3. Keng MJ, Tsiachristas A, **Leal J**, et al. (2019). Impact of achieving primary care targets in type 2 diabetes on health outcomes and healthcare costs. Diabetes, Obesity and Metabolism. DOI: 10.1111/dom.13821
4. Adler AI, Coleman RL, **Leal J**, et al. (2024). Post trial monitoring of a randomised controlled trial of intensive glycaemic control in type 2 diabetes extended from 10 years to 24 years (UKPDS 91). The Lancet. DOI: 10.1016/S0140-6736(24)00537-3
5. Meng X., Zhang L., **Chan KH**., et al, (2025). Association of greenness with incidence of cardiovascular disease in China: Evidence from the China Kadoorie Biobank prospective cohort study with 0.5 million adults. Eco-Environment & Health. DOI: 10.1016/j.eehl.2025.100148

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7.3 Data-Driven Measurement and Precision Targeting of Early Treatment for Acute Respiratory Infection for Efficient Evaluation of New Antiviral Drugs and Pandemic Preparedness

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PROJECT OVERVIEW

This is a proposal for a CAMS Oxford Institute DPhil Project that is mission critical to enhancing the efficiency and precision of outcome measurement in priority studies of therapeutics for acute respiratory infections (ARIs), the most likely cause of global pandemics and which account for major morbidity and numerous excess deaths each year and threaten the sustainability of healthcare systems worldwide. Effective treatments for use early on in these infections in the community has considerable potential health gain and impact, but we need to know who will benefit and who will not through rigorous pragmatic trials in the intended use populations before these often expensive treatments with the potential to drive resistance, before they are deployed at scale. ARIs, including influenza, COVID-19, respiratory syncytial virus and newly emerging viral infections, cause substantial morbidity and can result in pandemics. Enhancing the efficiency of patient-reported outcome measurement is crucial for evaluating treatments in the community, but trials often collect burdensome, partly redundant data without a clinically interpretable definition of recovery. Average effects also obscure who benefits and how benefit changes with time from illness onset.

This DPhil will develop and validate the best outcome measure to evaluate community treatment for ARI. It will use individual-participant data from PRINCIPLE (11,768 participants), PANORAMIC (26,746) and ALIC4E (3,266 across 15 European countries), with PACE data also already available for robustness and external validation. Together these randomised studies contain repeated symptom and recovery measures, treatment allocation, baseline clinical and demographic variables, healthcare use, longer-term outcomes, pathogen testing and, in PANORAMIC subsets, virological data. In particular, this project will facilitate the use of symptom diaries in clinical trials, exploring strategies for selecting appropriate outcome measures and their analytical approaches, alongside addressing the challenges of missing data.

The student will (1) Perform a systematic review of ARI outcomes and engage patients and clinicians via qualitative consensus methods to define core recovery domains and quantify Minimally Important Differences (MIDs) for outpatient populations; (2) Develop and validate streamlined outcome measures derived from daily symptom diaries, contrasting them against secondary care ordinal scales and testing performance externally using PACE data; (3) Analyse missingness patterns in self-reported longitudinal diaries and evaluate advanced

imputation techniques (e.g., Multiple Imputation by Chained Equations, Joint Modelling) to minimize bias in primary trial analyses; (4) Evaluate efficient analytical approaches (including time-to-event, ordinal longitudinal models, and landmark analyses) to capture subgroup-specific benefit and time-dependent treatment efficacy relative to symptom onset.

This research will establish an efficient, standardised measurement framework for future community ARI trials, accelerating the evaluation of critical therapeutics while reducing participant burden.

DISEASE RELVEANCE

Acute respiratory infections caused by influenza, SARS-CoV-2, respiratory syncytial virus and other established or emerging viruses are major causes of illness, healthcare use and mortality. New anti-viral drugs are emerging rapidly for treating acute viral infections: if used inappropriately, resistance will follow as short as night follows day, and the recent pandemic evidence is what can happen as a result of a mutated common virus. Rigorous trials of who to treat and who will not benefit from treatment or urgently needed and mission critical are efficient, validated patient reported outcomes to determine benefit, lack of benefit, and improved personalised treatment decision decisions. Pandemic preparedness depends on trials that can identify effective treatments quickly and reliably in community settings, where early treatment is most plausible.

Efficient, patient-centred measurement of symptoms and recovery is therefore crucial. Burdensome or poorly interpretable measures slow recruitment, increase losses to follow-up in trials, inflate sample sizes and hinder comparison across pathogens and countries. A validated parsimonious patient-reported outcome would enable faster, more inclusive therapeutic trials, including decentralised adaptive platforms. Together with robust methods for identifying who benefits and the optimal treatment window, this will improve evaluation of treatments for current infections and provide methods ready for new viral threats.

KEY TECHNOLOGY

The core technology is a reproducible pipeline for harmonising and learning from longitudinal individual-participant trial data. A common data model will map symptom items, response scales, assessment schedules, treatment timing, virology and clinical outcomes across PRINCIPLE, PANORAMIC, ALIC4E and external datasets. These data sets come from trials led by the proposed supervisors now in the Nuffield Department of Primary Health Care and will be readily available for this work.

This project will include (1) mixed methods to define outcome measures that are both clinically relevant and statistically responsive to treatment effects, such as summary measures, composite scores, and hierarchical composite scores; (2) the generation of missing data through simulations; and (3) an exploration of

efficient statistical methods to analyse the developed outcome measures using different information-borrowing strategies within a Bayesian framework.

TRAINING OPPORTUNITIES

The student will receive interdisciplinary training in clinical trial measurement and other relevant methodology, longitudinal and Bayesian statistics, psychometrics, causal inference, interpretable machine learning, reproducible programming and patient involvement. They will learn to build common data models; manage complex individual-participant datasets; address missingness; specify estimands and analysis plans; quantify uncertainty; and undertake internal-external and external validation.

The project will be supervised by Professor Chris Butler and Professor Ly-Mee Yu, with input from Dr Jane Holmes, Professor Gail Hayward and a specialist in patient-reported outcome measurement or psychometrics. Work with Oxford clinical trialists, statisticians, data scientists and CAMS investigators will provide experience of multidisciplinary collaboration, secure data governance and open research.

Outputs will include a systematic review, harmonised analysis resource, parsimonious patient-reported outcome, validated treatment-targeting models and reusable code—strong preparation for a career spanning health data science, trials and pandemic preparedness.

KEY PUBLICATIONS

1. Butler CC, Pinto AD, Harris V, et al. Oral nirmatrelvir–ritonavir for COVID-19 in higher-risk outpatients. N Engl J Med. 2026;394:1583–1594.
2. Butler CC, Hobbs FDR, Gbinigie OA, et al. Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes: PANORAMIC. Lancet. 2023;401:281–293.
3. Butler CC, van der Velden AW, Bongard E, et al. Oseltamivir plus usual care versus usual care for influenza-like illness in primary care: ALIC4E. Lancet. 2020;395:42–52.
4. Butler CC, Gillespie D, White P, et al. C-reactive protein testing to guide antibiotic prescribing for COPD exacerbations: PACE. N Engl J Med. 2019;381:111–120.

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7.4 Investigating Causes and Mechanisms of Healthy Ageing

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PROJECT OVERVIEW

One of the major achievements of the last 100 years is the extension of the human lifespan (the total life lived), through improvements in medical care, nutrition and sanitation. Globally, increases in life expectancy mean that now most people will live to old age (65 years or more); and once they reach old age, they will live longer than they used to. However, it is now becoming clear that in many countries there is a considerable and increasing gap between lifespan and healthspan (the period free from disease). Progressive physiological and physical decline are a part of normal ageing but increased age also increases the risk and occurrence of numerous debilitating diseases including heart disease, dementia and cancer.

Studies aiming to evaluate the effects of interventions on healthspan are challenging due to the need for long follow-up lengths and large sample sizes of healthy individuals to observe the outcomes of interest, large prospective biobank studies, such as China Kadoorie Biobank (CKB: www.ckbiobank.org) and UK Biobank (UKB: www.ukbiobank.ac.uk) are uniquely positioned to address these goals.

In CKB and UKB, electronic health record linkage records deaths and hospitalisation episodes for thousands of different diseases. Genome-wide genotype data are currently available for 100,000 CKB participants and all UKB participants. Whole genome sequence data are available in all participants in both CKB and UKB. Proteomic data are currently available for ~10,000 proteins in 4,000 CKB participants and for ~3,000 proteins in 54,000 UKB participants, with both datasets expected to expand considerably over the next 2–3 years. These are complemented by other blood biomarkers (e.g., clinical biochemistry, metabolomics, gut microbiome) in all or subsets of participants.

The DPhil project will assess the biological pathways and clinical outcomes associated with healthy ageing as well as identify potential opportunities for novel treatments targets for certain diseases. The specific area of research will be developed according to the student's interests and aptitude, and may include the following key research questions:

1) Leveraging longitudinal clinical records, proteomics and metabolomics to help in identifying what distinguishes healthy ageing from simply surviving longer?

2) Evaluate the importance of multi-omics, lifestyle and environmental exposures using novel machine learning approaches to determine how population-specific are mechanisms of ageing?

3) Using longitudinal multi-omics, genetics, Mendelian randomisation, disease trajectories, medications to ascertain which ageing changes are causal rather than consequences of disease?

4) Combining information from genetics, multi-omics, lifetime exposures, family structure and clinical trajectories in exceptionally healthy older adults to understand what explains exceptional resilience and healthy longevity?

5) Investigating hormones, reproductive history, multi-omics, clinical data, and lifestyle and social exposures (e.g. famine), to clarify how important are sex and gender differences in ageing trajectories?

6) Using machine learning and AI tools applied to multi-modal data such as ECG, retinal images, accelerometers combined with multi-omics can be used to determine biological age and whether organ systems age together—or independently

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DISEASE RELVEANCE

CKB and UKB have long-term follow-up of over 20 years each, for thousands of different ICD-10 coded diseases, through linkage to electronic health records and death and disease registries. The project may focus on specific disease(s) or groups of diseases of interest to the student e.g. cardiovacsular diseases, metabolic diseases, cancer, renal diseases or neurodegenerative diseases.

KEY TECHNOLOGY

- This project will use high-dimensional multi-modal data including genomewide variants, proteomics, metabolomics, wearables combined with detailed questionnaire data, physical measurements, and electronic health records, for over 1M individuals.

- Analytic methods will include classical and genetic epidemiology, such as linear, logistic and Cox regression, genome-wide-assocation studies, Mendelian randomisation, co-localisation and machine learning methods.

- Downstream invesitgations will include interrogation of biolgical and ontological databases and potentially the use of machine learning and AI tools.

TRAINING OPPORTUNITIES

The student will work within a multi-disciplinary team. There will be training in genetics, epidemiology, population health, data science, statistical analysis and attendance at relevant courses as required. By the end of the DPhil, the student will be able to plan, undertake and interpret analyses of large-scale genetic, proteomic, and epidemiological data, and report research findings, including conference presentation and publications as the lead author in peer-reviewed journals.

The project will be based within the CKB research group, part of NDPH and based in the Big Data Institute. There are excellent facilities and a world-class community of population health, data science, epidemiology and genomic medicine researchers. There will be opportunities to work with external partners from industry and other research institutions.

KEY PUBLICATIONS

1. Zenin, A et al. Identification of 12 genetic loci associated with human healthspan. Communications Biology, 2: 41 (2019)
2. Argentieri, M.A., et al. Proteomic aging clock predicts mortality and risk of common age-related diseases in diverse populations. Nature Medicine 30, 2450-2460 (2024).
3. Bennett DA et al. Proteomic organ-specific signatures, ageing traits, disease risks and genetic architecture in an East Asian population. EBiomedicine, 130 (2026).
4. Fan, J et al. Frailty index and all-cause and cause-specific mortality in Chinese adults: a prospective cohort study. Lancet Public Health, 5:12 (2019)
5. Sun, Q et al. Healthy lifestyle and life expectancy at age 30 years in the Chinese population: an observational study. Lancet Public Health, 7:12 (2022)

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7.5 Alcohol, Lifestyle Factors and Health: Causal Mechanisms across Populations

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PROJECT OVERVIEW

Unhealthy lifestyle behaviours (e.g., alcohol drinking, smoking, poor diet, low physical activity) are leading modifiable risk factors of chronic diseases. Notably, alcohol consumption is widespread globally and is an established cause of several major conditions, including certain cancers, cardiovascular disease and liver disease. However, uncertainty remains about alcohol's causal effects for many other diseases. The underlying biological mechanisms through which alcohol influences different diseases also remain incompletely understood, including whether the moderate alcohol drinking has any causal health benefits and through which pathways. Whether alcohol's health effects differ by populations and are modified by genetic (including the markedly reduced capacity to metabolise alcohol in East Asian populations with ALDH2 deficiency) and other lifestyle factors, also remains a major research gap.

Large prospective biobank studies in diverse populations, such as China Kadoorie Biobank (CKB: www.ckbiobank.org) and UK Biobank (UKB: www.ukbiobank.ac.uk) are uniquely positioned to address these research gaps. The project will involve in-depth analysis of CKB and UKB data, each comprising around 0.5 million participants with extensive lifestyle and environmental exposure data collected by baseline surveys and resurveys, comprehensive health outcomes, genomic and high-throughput multi-omics data.

The overall aim of the DPhil project is to generate novel insights into the causal health effects and biological mechanisms of alcohol consumption, with potential extension to other major lifestyle risk factors, and implications for disease prevention and treatment development. Contrasting lifestyle patterns, disease rates, and genetic architecture across populations provide opportunities to assess the consistency of findings and identify potential population differences in lifestyle-related health impact.

The specific area of research will be developed according to the student's interests and aptitude, and may include the following key objectives:

- Investigating the associations of alcohol drinking, and potentially other major lifestyle risk factors, with selected health outcomes and related intermediate traits, and assessing causality using genetic approaches (Mendelian randomisation);
- Analysing multi-omics data (e.g. proteomics, metabolomics, gut microbiome) to characterise molecular signatures related to alcohol, and potentially other lifestyle factors;

- Identifying novel candidate mediators underlying alcohol-disease relationships and assessing their downstream effects, using integrated analytical approaches (e.g. Mendelian randomisation, colocalisation, network analysis, phenome-wide association analysis, enrichment analysis, tissue expression analysis), to explore biological mechanisms and pathways;
- Comparing findings across ancestries and investigating potential effect modification by genetic and other factors;
- Using machine learning methods to develop and validate a novel biomarker score for alcohol, and potentially other selected lifestyle factors, and assessing its association with health outcomes.

DISEASE RELVEANCE

CKB and UKB have long-term follow-up of over 20 years each, for thousands of different ICD-10 coded diseases, through linkage to electronic health records and death and disease registries. The project may focus on specific disease(s) or groups of diseases of interest to the student e.g. cardiovascular diseases, metabolic diseases, cancer, or renal diseases.

KEY TECHNOLOGY

- This project will use high-dimensional multi-omics datasets, such as whole genome sequencing, proteomics, metabolomics, metagenomics and serology, combined with detailed questionnaire data, physical measurements, and electronic health records, for over 1M individuals.
- Analytic methods will include conventional and genetic epidemiology, including linear, logistic and Cox regression, whole genome-wide association studies, Mendelian randomisation, and co-localisation. Bioinformatic approaches such as enrichment and tissue expression analyses, and machine learning methods will also be included.
- Druggability assessment will include the use of machine learning and AI tools, and interrogation of in silico databases. Drug targets identified may be further assessed through collaboration with laboratory scientists, and in vitro and in vivo studies will be designed.

TRAINING OPPORTUNITIES

The student will work within a multi-disciplinary team. There will be in-house training in genetics, multi-omics, epidemiology, statistical analysis, and scientific writing, along with attendance at relevant courses where necessary. By the end of the DPhil, the student will be competent to plan, undertake and interpret analyses of large-scale high-dimensional data, and report research findings in publications as the lead author in peer-reviewed journals and presentations at national/international conferences.

The project will be based within the CKB research group, part of NDPH and based in the Big Data Institute. There are excellent facilities and a world-class community of population health, data science and genomic medicine researchers. There will be opportunities to work with external partners from industry and other research institutions.

KEY PUBLICATIONS

1. Im PK, Wright N, Yang L, Chan KH, Chen Y, Guo Y, Du H, Yang X, Avery D, Wang S, Yu C, Lv J, Clarke R, Chen J, Collins R, Walters RG, Peto R, Li L, Chen Z, Millwood IY, China Kadoorie Biobank Collaborative Group. Alcohol consumption and risks of more than 200 diseases in Chinese men. Nat Med. 2023;29(6):1476-86.doi: 10.1038/s41591-023-02383-8
2. Millwood IY, Walters RG, Mei XW, Guo Y, Yang L, Bian Z, Bennett DA, Chen Y, Dong C, Hu R, Zhou G, Yu B, Jia W, Parish S, Clarke R, Davey Smith G, Collins R, Holmes MV, Li L, Peto R, Chen Z, on behalf of the China Kadoorie Biobank Collaborative Group. Conventional and genetic evidence on alcohol and vascular disease aetiology: a prospective study of 500 000 men and women in China. Lancet. 2019;393(10183):1831-42.doi: 10.1016/S0140-6736(18)31772-0
3. Iona A, Wang B, Clarke J, Chan K, Kakkoura MG, Clarke C, Wright N, Yao P, Mazidi M, Im PK, Rahmati M, Kartsonaki C, Morris S, Fry H, Millwood IY, Walters RG, Chen Y, Du H, Yang L, Avery D, Schmidt-Valle D, Li F, Yu C, Sun D, Lv J, Hill M, Li L, Clarke R, Bennett DA, Chen Z, China Kadoorie Biobank Collaborative G. Associations of 2923 Olink proteins with demographic, lifestyle, environmental and health characteristics in middle-aged Chinese adults. European journal of epidemiology. 2025.doi: 10.1007/s10654-025-01311-z
4. Xiao S, Liu B, Argentieri MA, Belbasis L, Shovlin CL, Collister JA, Wang S, Hannon E, Liu J, Chan K, Mosaoa RM, Li L, Lv J, Yu C, Sun D, Mill J, Clarke R, Hunter DJ, Bennett D, Nevado-Holgado AJ, Chen Z, Amin N, van Duijn CM. Proteomic signatures of smoking and their associations with risk of incident diseases and mortality in diverse populations. Nature Communications. 2025;17(1):928.doi: 10.1038/s41467-025-67656-x
5. Mazidi M, Wright N, Pozarickij A, Millwood IY, Walters R, Kartsonaki C, Bennett DA, Yao P, Du H, Fry H, Yu C, Iona A, Wang B, Chen Y, Sun D, Yang L, Lv J, Im PK, Avery D, Goel A, Watkins H, Wang H, Kyriakou T, Brennan P, Peto R, Collins R, Li L, Clarke R, Chen Z, China Kadoorie Biobank Collaborative Group. Cross-Ancestry Proteogenomic Analyses Identified New Therapeutic Insights for Ischemic Heart Disease. J Am Coll Cardiol. 2026;88(10):1107-20.doi: 10.1016/j.jacc.2026.05.049

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7.6 Delineating Human Vulnerability to the Harm of Non-Optimal Temperature

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PROJECT OVERVIEW

Background

Climate change increases global average temperature, extreme temperature events, and temperature variability. While heat waves and cold spells are clearly harmful, even moderately high and low temperatures may also carry health risks, and emerging evidence suggest that temperature variability may also play an important role. There is ample evidence on the short-term (in days) effects of temperature on a range of major diseases, but there remain major knowledge gaps about the long-term health effects, what makes certain individuals more or less vulnerable to the harm of non-optimal temperature, and why.

With the increasing availability of high-resolution spatiotemporal data on temperature (and other environmental risk factors, e.g. air pollution) and large-scale proteomics and metabolomics data in population-based biobanks, there are unique opportunities to identify individual-level vulnerability or protective factors and uncover the underlying biological mechanisms.

This project will utilise existing and emerging data in the prospective China Kadoorie Biobank (CKB) and UK Biobank (UKB), totalling over 1 million adults in China and the UK. By integrating spatiotemporal ambient temperature and other environmental exposure data with the extensive baseline surveys and resurveys, comprehensive follow-up for disease development, and high-throughput assays on genomics, proteomics, and metabolomics in the biobanks, this project will uncover the impact of non-optimal temperature on individual and networks of proteins and metabolites and assess their causal relevance to major disease outcomes using a multi-omics approach, with a particular focus on identifying key vulnerability and protective factors to inform future climate change adaptation and mitigation strategies.

The precise project will be developed according to candidate's interests and aptitude, but will likely to include the following components:

- To examine and compare the long-term trends of ambient temperature and its variability across populations;
- To identify key vulnerability and protective factors to the impact of short- and long-term temperature exposure on major disease outcomes and uncover the underlying biological mechanisms using multi-omics approaches;

- To determine the causal relevance of temperature-sensitive biomarkers for disease risk and potential drug target discovery, using genetic epidemiology approaches (e.g. Mendelian randomisation and co-localisation)

DISEASE RELVEANCE

CKB and UKB have long-term follow-up of over 20 years each, for thousands of different ICD-10 coded diseases, through linkage to electronic health records and death and disease registries. The project may focus on specific disease(s) or groups of diseases of interest to the student e.g. cardiovascular disease, metabolic disease, or renal disease.

KEY TECHNOLOGY

- This project will use high-dimensional multi-omics datasets, such as whole genome sequencing, proteomics, metabolomics, combined with detailed questionnaire data, physical measurements, and electronic health records, for over 1M individuals.
- Analytic methods will include conventional, environmental, and genetic epidemiology, such as linear, logistic and Cox regression, distributed lag non-linear modelling, case time-series and case-crossover analysis, Mendelian randomisation, co-localisation and machine learning methods etc.
- Druggability assessment will include the use of machine learning and AI tools, and interrogation of in silico databases. Drug targets identified may be further assessed through collaboration with laboratory scientists, and in vitro and in vivo studies will be designed.

TRAINING OPPORTUNITIES

The student will work within a multi-disciplinary team, and will gain research experience in systematic literature review, study design and planning, data analysis and scientific writing. There will also be in-house training in environmental epidemiology, statistical programming, molecular epidemiology, and, if necessary, attendance at relevant courses. The student will be part of a Wellcome-funded research programme titled THERMOS-Epi (Temperature, Health, and Exposome Research Multi-OmicS and Epidemiological approaches), which will offer hands-on learning opportunities via collaborative research with international partners. By the end of the DPhil, the student will be competent to plan, undertake and interpret analyses of large and high dimensional datasets, and to report research findings, including publications as the lead author in peer-reviewed journals and presentation at national/international conferences.

The project will be based within the CKB research group, part of NDPH and based in the Big Data Institute. There are excellent facilities and a world-class

community of population health, data science and genomic medicine researchers. There will be opportunities to work with external partners from industry and other research institutions.

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THEME 8: OTHER

8.1 Modulating APC-Driven T-cell Immunity in a Human Splenic Organoid Platform

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PROJECT OVERVIEW

Antigen-presenting cells (APCs), particularly dendritic cells (DCs), determine the magnitude and quality of adaptive T-cell responses by integrating antigen presentation, co-stimulation and cytokine signals. Understanding how APC state controls T-cell activation, differentiation and effector function is relevant to transplantation, vaccination, infectious disease and cancer [1].

Secondary lymphoid organs (SLOs) provide the specialised environment for APC–lymphocyte interactions. Human splenic organoids offer an exciting opportunity to study these processes within an organised, multicellular human lymphoid environment [2,3]. Our group has already established splenic organoids from deceased organ donors to investigate immunoregulation of vaccine responses, with initial characterisation demonstrating germinal-centre formation. Recent work also provides proof-of-principle that alloimmune T-cell responses can be modelled in human splenic organoids [2]. This project will now build on these foundations by introducing defined immune-cell populations to create a 'reconstituted' system in which APC–T-cell interactions can be manipulated and analysed.

Transplantation provides a tractable setting in which to establish this approach. Allograft rejection results from recipient T-cell recognition of donor alloantigens, either 'directly' as intact donor MHC–peptide complexes or 'indirectly' as donor-derived antigen presented by recipient APCs [4]. Introducing allogeneic immune cells, with autologous cells as a control, will provide a defined stimulus to investigate how APC state influences human alloimmune responses.

Japanin is a naturally occurring tick-derived immunomodulatory protein that selectively reprograms human DCs [5]. It alters DC differentiation and responses to diverse activating stimuli, producing a distinct, non-canonical phenotype characterised by altered co-stimulatory/co-inhibitory molecule expression and inflammatory and T-cell-polarising cytokine production. Confidential unpublished transcriptomic analyses support structured APC reprogramming rather than global suppression. Preliminary studies also demonstrate efficacy in mouse models of neuroinflammation and allergic airway inflammation. Japanin therefore provides an unusually selective mechanistic probe with which to

perturb APC state and determine how this alters downstream T-cell responses. Responsiveness of resident human splenic APCs will be tested directly.

The project will develop a human splenic-organoid model for controlled analysis of APC–T-cell interactions, using alloimmunity as the primary experimental setting. Selectivity will be addressed by comparing effects on alloimmune responses with unrelated antigen-specific viral recall responses.

Overall Aim:

To develop a cellularly reconstituted human splenic-organoid model and exploit it to determine how APC state controls CD4 and CD8 T-cell responses, using alloimmunity as the primary experimental setting and Japanin as a mechanistic probe.

Objectives:

1) Establish and characterise cellular reconstitution of human splenic organoids using autologous immune-cell populations, defining cell infiltration and localisation, APC phenotype and function, and baseline CD4 and CD8 T-cell activation.
2) Establish a controlled alloimmune stimulus using allogeneic immune-cell populations, quantify the resulting CD4 and CD8 T-cell responses, and use defined APC/T-cell combinations to dissect direct and indirect pathways of allorecognition.
3) Determine how selective APC reprogramming by Japanin alters alloimmune responses, measuring effects on APC phenotype and function and downstream T-cell activation, proliferation and effector function.
4) Determine whether Japanin-mediated APC reprogramming produces an immune state distinct from conventional broad immunosuppression by comparing effects on alloimmune versus antigen-specific viral recall responses, and defining dose-response, persistence and reversibility.

DISEASE RELVEANCE

Solid-organ transplantation is a life-saving treatment for end-stage organ failure, but long-term graft survival remains dependent on immunosuppressive therapy. Current therapies predominantly inhibit lymphocyte activation or proliferation and are associated with important consequences of broad immune suppression, including infection, malignancy and drug toxicity.

APCs occupy a pivotal upstream position in transplant immunity because they determine how donor alloantigens are recognised and shape subsequent T-cell

responses. Selectively manipulating APC state therefore provides a means to investigate whether alloimmune responses can be modified while retaining protective immunity. Japanin provides an unusually selective experimental perturbation with which to test this principle.

Selectivity will be assessed by measuring antigen-specific viral recall responses, for example to CMV or EBV, in parallel with alloimmune responses in matched organoids. This will determine whether APC-directed reprogramming can generate a qualitatively different immune state from conventional broad immunosuppression.

The underlying biology extends beyond transplantation. Effective vaccination and antiviral immunity depend on appropriate APC-driven T-cell responses, while defective APC-dependent priming can contribute to ineffective tumour immune surveillance. The platform should therefore provide mechanistic insights relevant to vaccination, infectious disease and cancer.

KEY TECHNOLOGY

This project will build on the Oxford human splenic-organoid platform by introducing defined immune-cell populations to create a system in which APC–T-cell interactions can be experimentally manipulated and interrogated. Experimental complexity will increase progressively over the three-year DPhil.

Year 1 – Characterisation and cellular reconstitution:

The splenic-organoid system will be characterised for cellular composition, APC representation and baseline immune activity. Autologous PBMC and subsequently defined immune-cell populations will be introduced. Fluorochrome labelling, immunofluorescence/confocal imaging and multiparameter flow cytometry will determine cell survival, infiltration, spatial localisation and phenotype. Initial experiments will determine which endogenous or introduced APC populations are responsive to Japanin; subsequent studies will focus on responsive population(s) and quantify downstream CD4 and CD8 T-cell effects.

Year 2 – Modelling and dissecting alloimmunity:

Allogeneic immune cells will provide a controlled alloimmune stimulus, with autologous reconstitution defining the corresponding non-allogeneic response. Flow cytometry and functional assays will quantify CD4 and CD8 T-cell activation, proliferation and effector function. CTL function will include degranulation (CD107a), granzyme B and IFN-γ production and, where feasible, killing of labelled allogeneic targets. Defined APC and T-cell populations will distinguish direct from indirect allorecognition. Japanin will test how APC

reprogramming modifies these responses, with conventional immunosuppression providing a comparator.

Year 3 – Selectivity, mechanism and durability:

Effects on alloimmunity will be compared with antigen-specific viral recall responses, for example CMV/EBV, in matched organoids studied in parallel to assess preservation of unrelated immunity. Dose-response, timing and washout studies will define persistence and reversibility. Functional, cytokine and spatial analyses, supplemented where justified by molecular or transcriptomic approaches, will identify APC changes associated with altered downstream T-cell function.

TRAINING OPPORTUNITIES

The project will provide progressive training in human cellular immunology, transplantation biology and experimental immune modelling, while developing the student towards scientific independence.

Human organoid and cellular immunology:

The student will receive hands-on training in human splenic-organoid culture, primary immune-cell isolation and manipulation, APC/DC biology and cellular reconstitution. Fluorescent cell tracking and immunofluorescence/confocal imaging will provide training in analysing immune-cell migration, localisation and spatial interactions within a multicellular tissue environment.

T-cell immunology:

Multiparameter flow cytometry, FACS and functional assays will be used to measure CD4 and CD8 T-cell activation, proliferation and effector function, including CTL degranulation, cytokine production and cytotoxicity. Defined APC–T-cell combinations will provide practical and conceptual training in antigen presentation and direct and indirect allorecognition.

Mechanistic analysis:

Cytokine assays and quantitative analysis will relate APC phenotype to downstream immune function. Where justified by experimental findings, transcriptomic approaches and bioinformatics will provide training in mechanistic analysis of APC and T-cell states.

Supervision and research environment:

Fadi Issa and Joanna Hester will lead experimental and day-to-day scientific supervision. Jon Austyn will provide complementary expertise in DC biology and transplantation immunology, and Pat Nuttall in tick-derived therapeutics

including Japanin, with regular project discussions and review of experimental progress. The student will participate in the wider Oxford transplantation and immunology community, including the Oxford Immunology Network and internal and cross-departmental seminars, workshops and other activities. The project will also benefit from Jon Austyn's well-established academic links with Xiamen University in China, providing opportunities for wider scientific exchange.

Training will progress towards independent experimental design, hypothesis formulation and critical interpretation, providing a strong foundation for future research in transplantation and broader applications of human immune modelling.

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8.2 From Tissue Mosaicism to Diagnosis: Improving Genetic Testing in Developmental Disorders

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PROJECT OVERVIEW

Postzygotic somatic mosaicism (PZM) is an important and under-recognised cause of rare developmental disorders. In clinical practice, diagnosis can be challenging because pathogenic variants may be present in only a subset of cells and may be absent or detected at very low levels in blood, despite being enriched in clinically affected tissues. Consequently, patients with mosaic disease may receive delayed, incomplete or incorrect molecular diagnoses, limiting accurate prognosis, genetic counselling and access to appropriate clinical management.

The clinical impact of mosaicism depends not only on the pathogenic variant itself, but also on its distribution across tissues and cell types. During development, mutant and wildtype cells may differ in their survival or proliferative capacity, resulting in tissue-specific enrichment or depletion of pathogenic cells. However, these processes of developmental selection have not been systematically quantified across tissues and cell types. Understanding them is therefore essential for interpreting mosaic variants and determining which tissues are most informative for genetic testing.

This project will determine how developmental selection shapes the tissue distribution of pathogenic mutations. We will exploit complementary mouse models of genetic mosaicism and high-throughput single-cell transcriptomics to quantify mutant cell representation across tissues at single-cell resolution. We will focus on Cornelia de Lange syndrome (CdLS) and ATR-X syndrome, rare multisystem developmental disorders for which our team has established relevant mouse models and expertise.

The project has three objectives.

Objective 1: Quantify tissue-specific selection in postzygotic mosaicism. We have developed an inducible mouse model of mosaic CdLS in which Nipbl is deleted in a subset of cells during early embryogenesis. Neonatal mice will undergo whole-animal dissociation, and mutant and wildtype cells will be distinguished using a genetic reporter. Multiplexed single-cell RNA sequencing will quantify mutant cell representation across major tissues and cell types, identifying populations that selectively enrich or deplete pathogenic cells.

Objective 2: Identify shared principles of selection across different forms of genetic mosaicism. Female carriers of X-linked pathogenic variants are functional mosaics because of X chromosome inactivation (XCI). We will perform equivalent single-cell analyses in female mice carrying pathogenic Hdac8 or Atrx variants. Integrating these datasets with the PZM model will test whether common tissue- and cell-type-specific selective pressures operate across genetically distinct developmental disorders.

Objective 3: Establish an experimental system for mechanistic studies of developmental selection. Wildtype and mutant mouse embryonic stem cells will be combined and differentiated into selected lineages, including erythroid and neuronal cells. Additional lineages will be prioritised from the in vivo single-cell results. We will determine whether this system recapitulates tissue-specific selection observed in vivo, providing a scalable platform for subsequent mechanistic studies.

The project will generate a quantitative atlas of developmental selection across tissues and forms of genetic mosaicism, together with openly available single-cell datasets and analytical approaches. It will establish principles governing the distribution of pathogenic cells during development and provide an experimental framework for improving the interpretation, diagnosis and future clinical management of mosaic developmental disorders.

DISEASE RELVEANCE

Rare developmental disorders caused by postzygotic somatic mosaicism present a significant challenge in clinical genetics. Patients may have a pathogenic variant in clinically relevant tissues, while standard blood testing is negative or detects only a very low variant allele fraction. This can lead to delayed diagnosis, uncertainty about recurrence risk and prognosis, and difficulty explaining differences in clinical severity between affected individuals.

Cornelia de Lange syndrome provides a clinically relevant example. Mosaic *NIPBL* variants may be depleted from blood, meaning that a negative blood result does not reliably exclude mosaic disease. However, clinicians currently lack evidence-based guidance on which alternative samples should be prioritised, how results from different tissues should be interpreted, or whether variant levels can help explain the patient's phenotype.

This project will address these practical gaps by mapping the distribution of pathogenic cells across tissues and cell types in relevant disease models. The findings will support more informed decisions about diagnostic sampling, interpretation of low-level or tissue-restricted variants, and counselling of patients and families. Comparison with X-linked mosaicism will further explore

why some mutant cell populations are retained or lost during development and how this may contribute to variable disease expression.

By linking developmental biology with real-world diagnostic questions, the project aims to generate evidence that can be translated into improved testing strategies for patients with suspected mosaic developmental disorders. It will also provide a stronger framework for discussing diagnostic uncertainty, phenotype variability and the limitations of relying on blood-based testing alone.

KEY TECHNOLOGY

The key enabling technology is multiplexed single-cell RNA sequencing (scRNA-seq) and deep Next-Generation sequencing coupled to genetically defined mouse models of mosaic disease**.** This combination allows developmental selection to be quantified across tissues and cell types at a resolution that has previously been difficult to achieve.

In our inducible model of postzygotic mosaic Cornelia de Lange syndrome, *Nipbl* is deleted in a subset of cells during early embryogenesis and mutant cells can be distinguished from wildtype cells using a genetic reporter. Whole-animal dissociation followed by flow sorting and multiplexed scRNA-seq will therefore allow the relative representation of mutant and wildtype cells to be quantified simultaneously across major neonatal tissues and individual cell populations.

Equivalent single-cell profiling of female mice heterozygous pathogenic *Hdac8* and *Atrx* variants will extend this approach to functional mosaicism generated through X chromosome inactivation. Integrating these datasets provides a powerful comparative framework for distinguishing gene-specific effects from more general principles of developmental cell selection.

Importantly, scRNA-seq provides information beyond mutant cell abundance. Transcriptomic profiles will identify molecular pathways associated with selective advantage or disadvantage and reveal transcriptional consequences in both mutant cells and neighbouring wildtype populations.

Quantitative analyses will compare observed and expected mutant cell proportions using mixed-effects regression, with appropriate correction for multiple testing. Potential biases arising from differential recovery of cell types during tissue dissociation will be controlled by comparing mutant and wildtype populations obtained from the same animals.

Together, these technologies transform tissue-specific mosaicism from a largely descriptive phenomenon into a quantitatively and mechanistically tractable problem.

TRAINING OPPORTUNITIES

This interdisciplinary project will provide the student with uniqueTRAINING OPPORTUNITIES in state-of-the-art technologies spanning rare disease biology, genetics, single-cell genomics, Next-Generation sequencing, genetic counselling, ethics and quantitative data analysis. A central training objective will be to develop the ability to integrate experimental and computational approaches to address clinically relevant questions in human genetics.

The student will gain practical experience in genetically engineered mouse models, experimental analysis of developmental mosaicism, tissue dissociation, flow cytometry and cell isolation. They will develop expertise in the design and application of multiplexed single-cell RNA sequencing experiments, including experimental design, quality control and interpretation of complex cellular datasets.

A major component of the project will be quantitative and computational training. The student will learn reproducible analysis of single-cell transcriptomic data, integration of datasets across genotypes and experimental models, statistical modelling of mutant cell representation, and appropriate approaches to multiple testing and data visualisation. These skills will enable the student to move beyond descriptive single-cell analysis towards quantitative testing of biological hypotheses.

The complementary in vivo and embryonic stem-cell components will also provide training in experimental model development and in translating observations from complex tissues into tractable mechanistic systems.

The resulting training programme will equip the student to work across experimental genetics, genomics and quantitative biology, while maintaining a clear focus on clinically important questions in rare developmental disease.

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8.3 Mapping Human Regulatory B Cell Function across the Lymphoid System to Identify Novel Therapeutic Targets in Immune-Mediated Disease

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PROJECT OVERVIEW

Regulatory B cells (Bregs) are increasingly recognised as important mediators of immunological tolerance, with therapeutic potential in immune-mediated diseases. However, their heterogeneity, tissue distribution and immunoregulatory mechanisms in humans remain poorly defined. This limits the development of therapies to enhance Breg function and prevent inflammatory damage in autoimmunity or transplantation, or to inhibit Breg function where immune responses need to be reactivated in infection or cancer.

Human Breg expansion

- We have developed novel techniques to expand human Bregs (expBregs) ex vivo from peripheral blood and spleen
- Demonstrated for the first time, in vivo function of human expBregs, in a humanised mouse model of skin transplantation
- These techniques provide a robust platform to investigate human Breg biology and therapeutic potential

Single-cell multi-omic analysis

- We have conducted integrated single-cell transcriptomics, BCR sequencing and CITE-seq of human expBregs derived from spleen and peripheral blood
- Identified potential novel immunoregulatory signatures associated with Breg function
- Interrogation of these pathways could identify novel therapeutic targets to:
  - Enhance Breg function in autoimmune disease and transplantation
  - Inhibit Breg-mediated immunosuppression in infectious disease and cancer

Spatial Whole-Transcriptomic Analysis of Human Lymphoid Tissue

- Breg phenotype and function are likely shaped by the local tissue microenvironment.
- The extent to which Breg immunoregulatory programmes are conserved or tissue-specific remains unknown.

- We have developed a unique pipeline to access multiple tissues from deceased human organ donors.
- This enables unprecedented comparison of Bregs across multiple lymphoid and mucosal tissues within the same individual.
- We are performing whole-transcriptome spatial analysis of Bregs and B cells from:
  - Blood
  - Tonsil
  - Spleen
  - Systemic and mucosal lymph nodes
  - Nasal and intestinal mucosa
  - Bone marrow

We propose to map the molecular and cellular programmes regulating human Breg function across the lymphoid system and to identify novel drug targets to improve outcomes in immune-mediated disease.

In Aim 1, we will define immunoregulatory B-cell signatures across human lymphoid tissues. Using spatial transcriptomic analysis, we will compare tissue-resident Bregs and non-regulatory B cells across multiple tissues from the same individuals. We will integrate our transcriptomic, proteomic and BCR sequencing data as well as publicly available datasets of health and disease to identify conserved and tissue-specific human Breg signatures, differentiation states and intracellular signalling pathways associated with regulatory function.

In Aim 2, we will identify intracellular signalling pathways critical to tissue-resident Breg function. Pathways identified in Aim 1 will be interrogated using a high-throughput, arrayed CRISPR/Cas9 RNA library to identify pathways that modulate the differentiation/function of tissue-resident Bregs. The 20 candidates demonstrating the greatest phenotypic changes will undergo functional validation using in vitro suppression assays. Findings from functional assays will inform Aim 3 by providing intracellular targets by which to improve the function of patient-derived Bregs.

In Aim 3, we will validate therapeutic targets in patient-derived and disease-relevant systems. We will use novel splenic organoids established in our group, to investigate whether Breg-critical drug targets identified in Aim 2, can be modulated to dampen Breg function and boost immune responses to SARS-CoV2 vaccines within a physiologically relevant human immune microenvironment. Targets will also be evaluated in in vitro suppression assays using patient-derived samples, including from kidney transplant recipients (KTRs). We will ask whether the suppressive function of patient-derived

expBregs from KTRs with poor clinical outcomes can be improved ex vivo (CRISPR, small molecule inhibitors, mAbs).

DISEASE RELVEANCE

The importance of regulatory B cells (Bregs) in maintaining immune homeostasis is increasingly recognised. Functionally deficient Bregs are associated with poor outcomes in autoimmune diseases including systemic lupus erythematosus, rheumatoid arthritis and multiple sclerosis, while animal studies support Breg-based therapy as a potential treatment. In transplantation, Breg signatures are associated with operational tolerance in kidney transplant recipients (KTRs), and Breg frequency may predict acute rejection and graft function.

Conversely, Bregs can negatively regulate protective immunity. Breg-mediated immunoregulation has been associated with impaired responses to repeated influenza vaccination, greater disease severity during SARS-CoV-2 infection, and tumour progression. Bregs within the tumour microenvironment of a spectrum of solid organ cancers are associated with poor outcomes, highlighting their potential as therapeutic targets.

Despite this potential, clinical translation of Breg therapy remains limited by their rarity in peripheral blood, the absence of unique human Breg markers, and differences between human and murine Bregs. Furthermore, it remains unclear whether human Breg programmes are conserved, inducible, or tissue- and lineage-specific.

We will harness our unique access to paired human lymphoid tissues from deceased human organ donors, together with spatial whole-transcriptomic analysis, high-throughput CRISPR screening, innovative human splenic organoids and patient-derived suppression assays, to define the molecular regulation of human Bregs and identify novel therapeutic targets. This integrated approach will unlock the translational potential of Bregs for targeted modulation of immune responses in transplantation, autoimmunity, infection and cancer.

KEY TECHNOLOGY

Human Splenic Organoids: Single-cell suspensions from spleens (n=50 donors) will be plated into transwells alongside antigens of interest, including multiple iterations of SARS-CoV-2 vaccines, and in the presence or absence of therapeutic target modulators or genetically edited Bregs.

CRISPR/Cas9 library screening: Gene knockouts of critical Breg transcription factors and pathways within splenic cell pools prior to SARS-CoV-2 vaccine stimulation, or within KTR-derived Bregs (n=20 donors) prior to suppression assay co-cultures, will define mechanisms involved in Breg-mediated

immunoregulation. A CRISPR/Cas9 arrayed multi-guide RNA library (Synthego libraries, Lonza Nucleofector 96-well unit) of 200-300 gene targets will enable high throughput screening of candidate gene targets.

Single-cell RNASeq & BCR sequencing analysis of our existing datasets: Comparisons of human B cells of different activation states and immunoregulatory capability from peripheral blood vs. spleen, will permit the distinction of regulatory vs. activation signatures and identify potential developmental relationships by using single cell RNA sequencing (10X Genomics), BCR and RNA velocity analysis and Cite-Seq.

Single-cell spatial whole-transcriptome analysis of our existing datasets: Novel 10X Genomics Atera technology will permit whole-transcriptome mapping of tissue-resident Breg and B cell distributions, changes in GC organisation, intracellular signalling pathways and cellular interactions at a single cell level, across multiple lymphoid tissues in the human body.

Fluorescence-activated cell sorting: Isolation of tissue-resident Bregs will enable the functional evaluation of Breg-critical intracellular signalling pathways using CRISPR/Cas9 library screening, splenic organoids and *in vitro* suppression assays.

Flow Cytometry & Spectral flow: To assess baseline and emerging Breg phenotypes as part of the readout for CRISPR library screening and functional assays.

TRAINING OPPORTUNITIES

Cell culture: The Translational Research & Immunology Group (TRIG), where this project will be based, has extensive experience in primary human cell culture, *in vitro* suppression assays and splenic organoids. There is ample access to large tissue culture facilities. A team of PIs and post-doctoral researchers will provide hands-on training to support the student.

Gene editing: Multiple gene editing technologies and their application in primary human lymphocytes, including guide RNA design, CRISPR/Cas9 and nucleofection, are well-established within TRIG. Dedicated post-doctoral researchers and PIs will provide training and supervision.

Single cell spatial transcriptomics*:* TRIG has extensive experience in single cell sequencing and spatial transcriptomics. TRIG has ready access to 10x Genomics platforms, including the Atera, Xenium and Visium HD, within the department. Dedicated post-doctoral researchers will provide training and supervision.

Bioinformatics: Alongside post-doctoral-led training in the analysis of large transcriptomic datasets within TRIG, the DPhil candidate will be encouraged to apply to the Oxford Biomedical Data Science Training Programme. This 6-week

course provides foundation training in R for data science, genomics, single cell RNA sequencing analysis and the Linux command line.

Flow Cytometry & FACS sorting: TRIG has multiple flow cytometers and cell sorters to support this project. The DPhil candidate will receive detailed training by post-doctoral researchers and project supervisors regarding flow cytometry principles as well as practical supervision. TRIG has close links with the Experimental Medicine Division Flow Cytometry Facility, which regularly provides tutorials, including to TRIG-based researchers.

Presentation skills & critical appraisal: TRIG hosts weekly laboratory meetings and journal clubs, where researchers present and critically appraise their work as well as other advances in the literature.

Weekly supervisions: The DPhil candidate will meet with project supervisors on a minimum weekly basis, to discuss data, progress and challenges. These meetings are designed to ensure professional and pastoral support for the student.

KEY PUBLICATIONS

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3. Mauri C et al. Human regulatory B cells in health and disease: therapeutic potential. J Clin Invest. 2017 Mar 1;127(3):772-779. doi: 10.1172/JCI85113. Epub 2017 Mar 1. PMID: 28248202; PMCID: PMC5330739.
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8.4 How Does Metabolism Program B Cell Immunity?

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PROJECT OVERVIEW

The systems and pathways of cellular metabolism, modified either by the microbiome or cell-intrinsic programs, are critical to almost all aspects of the immune response. An essential function of metabolism is to dynamically respond to the needs of the cell, typically as it encounters a new microenvironment, or is required to rapidly divide, secrete cytokines, or produce antibodies.

One of the most important outstanding questions in the field is how immune cell metabolism actually operates within tissues in life, and how this is altered in disease.

The germinal centre reaction is a tightly choreographed process occurring in secondary lymphoid tissue, as B cells refine their antigen specificity through interaction with T follicular helper cells. The GC reaction is essential for the production of high affinity antibodies and humoral immunity.

GC B cells have the highest proliferation rate of any cell in the body, and yet which metabolic programs are activated and are essential for this process is poorly understood. Importantly, events occurring in the GC reaction lead to the majority of non-Hodgkin's lymphomas, and are dysfunctional in autoimmune disease. This project aims to identify and understand metabolic programs active in GC B cells, to modify them experimentally using conditional knockout approaches in mouse models, and to target them therapeutically in pre-clinical models.

In this project, you will study the metabolic pathways activated during the germinal centre (GC) reaction in health and in autoimmune disease, using cutting edge technologies and methods which allow measurement of metabolism with high *in vivo* fidelity. You will have the opportunity to attend the outstanding educational programme provided at the KIR, and to also regularly present your own data in group meetings, seminars, and at international conferences.

DISEASE RELVEANCE

B cells drive lupus, multiple sclerosis, rheumatoid arthritis, and many other often severe autoimmune diseases. B cells are also the origin cell of most lymphoma. Equally important is the role of B cells in normal protective immunity, for example following vaccination, and they are increasingly recognised as key players in the response to cancers, through the formation of tertiary lymphoid structures.

KEY TECHNOLOGY

- Mouse models and patient-derived samples.
- High-dimensional platforms such as single cell RNA sequencing, spatial molecular profiling, and spectral flow cytometry.
- Metabolomics and stable isotope tracing.
- Advanced imaging modalities.

TRAINING OPPORTUNITIES

This project provides a broad training in immunology, with comprehensive coverage of standard and advanced techniques including disease models, advanced flow cytometry, confocal imaging, and single cell RNA sequencing. For study of metabolism, you will develop expertise in stable isotope resolved metabolomics, and extracellular flux measurement using the Seahorse platform, and the bioinformatic analysis of these data. Computational biology training will be provided, both within the group and in formal courses.

KEY PUBLICATIONS

1. Johnstone J, Yazicioglu Y, **Clarke AJ**. Fuelling B cells: dynamic regulation of B cell metabolism. *Current Opinion in Immunology. 2024, 91, 102484*
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3. Yazicioglu Y, Marin E, , Sandhu C, Galiani S, Raza I, Ali M, Kronsteiner B, Compeer E, Attar M, Dunachie S, Dustin ML, **Clarke AJ**. Dynamic mitochondrial transcription and translation in B cells control germinal center entry and lymphomagenesis. *Nature Immunology.* 2023. 24(6):991-1006
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8.5 Targeting deISGylating Enzymes to Fine-Tune Innate Immunity

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PROJECT OVERVIEW

Type I interferons (IFN-I) are central regulators of antiviral defense, inflammation, and tumor immune surveillance. However, their therapeutic exploitation is challenging because insufficient IFN-I activity can permit infection and immune escape, whereas excessive or prolonged signaling can drive tissue damage and inflammatory disease. There is therefore a major opportunity to identify druggable molecular regulators that can fine-tune, rather than indiscriminately activate, innate immunity.

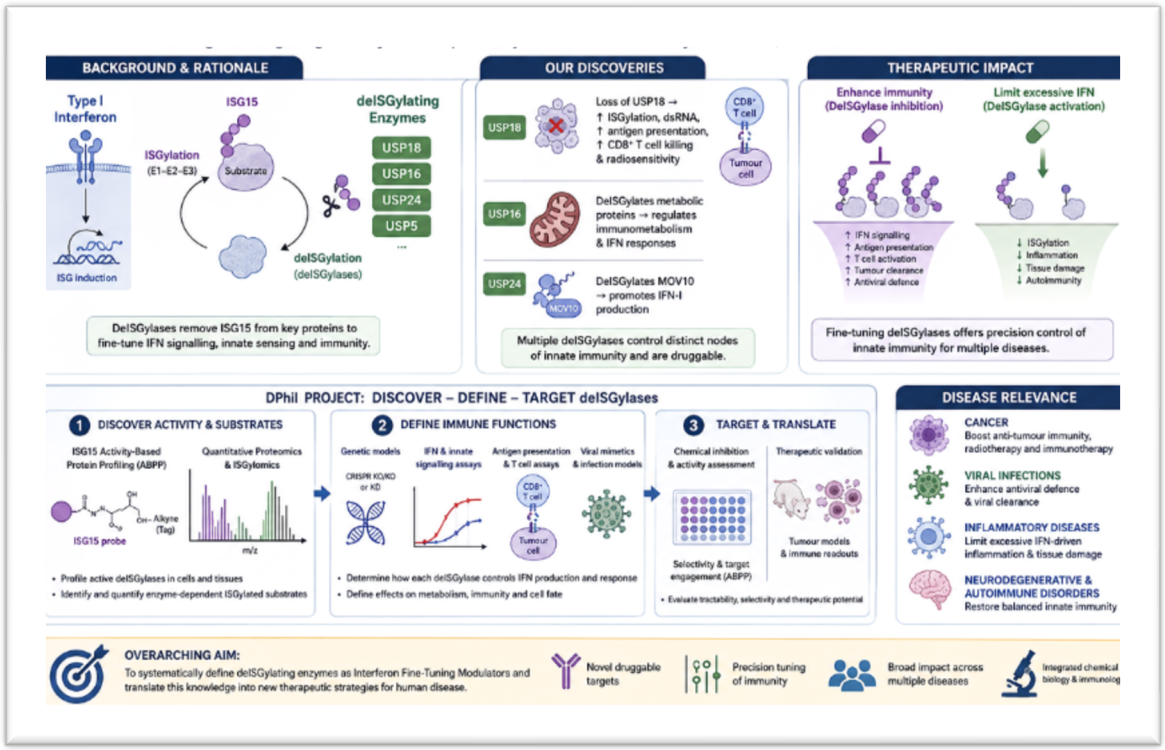
Our laboratory studies a class of such regulators that we define as **Interferon Fine-Tuning Modulators (InFiNeMods)**. This DPhil project will focus specifically on **deISGylating enzymes**, proteases that remove the IFN-induced ubiquitin-like modifier ISG15 from cellular proteins. ISGylation is strongly induced following IFN stimulation and regulates protein activity, interactions, localization, and stability across pathways involved in antiviral defense, immune signaling, metabolism, and cellular stress. Although USP18 is the predominant human deISGylase, recent work demonstrates that additional ubiquitin-specific proteases possess physiologically relevant deISGylating activities, suggesting that cells use a network of enzymes to control distinct components of the ISGylome.

Our previous studies established USP18 as an important regulator of cancer immunity. Loss of USP18 increases protein ISGylation, promotes accumulation of innate immune ligands, enhances antigen-presentation pathways, and increases cytotoxic T-cell recognition and tumor-cell radiosensitivity. Building on this work, we identified USP16 as an ISG15-cross-reactive protease controlling a subset of metabolic ISGylated proteins, and USP24 as a deISGylase that regulates IFN-I production through deISGylation of the RNA helicase MOV10. These discoveries indicate that individual deISGylases regulate different biological nodes within innate immunity and may therefore offer distinct therapeutic opportunities.

The student will systematically define the **activity, substrates, immune functions, and therapeutic tractability of human deISGylating enzymes**, initially prioritizing USP18, USP16, USP24, and other ISG15-reactive USPs identified through activity-based profiling. The project will integrate three complementary objectives: **(1)** map deISGylase activity and substrate specificity

using ISG15 activity-based probes and quantitative proteomics; **(2)** determine how individual enzymes regulate IFN production, IFN responsiveness, antiviral defense, and immune-cell recognition using genetic and cellular models; and **(3)** evaluate selected deISGylases as therapeutic targets using chemical and genetic perturbation approaches.

The overarching aim is to establish whether selective modulation of individual deISGylases can provide a means of precisely tuning innate immune responses. This work could uncover a new class of druggable immune regulators for cancer, infectious disease, and inflammatory disorders.



Graphical abstract: *Targeting deISGylating Enzymes to Fine-Tune Innate Immunity*

DISEASE RELVEANCE

Dysregulated IFN-I signaling contributes to a wide spectrum of human disease. Insufficient innate immune activation facilitates viral persistence and tumor immune escape, whereas excessive or chronic IFN activity contributes to inflammatory and autoimmune pathology. Therapeutic strategies capable of adjusting the magnitude or duration of IFN responses are therefore potentially applicable across multiple disease settings.

The ISG15/deISGylation system represents a particularly attractive intervention point because it operates directly downstream of interferon and regulates multiple components of innate immunity. Dysregulated ISGylation has been implicated in infection, cancer, inflammatory disease, and neurodegeneration. Our previous work demonstrated that USP18 loss enhances tumor antigenicity, cytotoxic T-cell recognition, and radiosensitivity, establishing proof-of-concept that a deISGylase can be therapeutically exploited to augment antitumor immunity. More recently, USP16 and USP24 have emerged as deISGylases controlling immunometabolic pathways and antiviral IFN production, respectively.

By defining how individual deISGylases regulate distinct immune pathways, this project aims to identify therapeutic nodes that enhance protective immunity while minimizing the consequences of indiscriminate IFN activation.

KEY TECHNOLOGY

The project will combine **activity-based protein profiling, quantitative mass spectrometry, functional genomics, and immune phenotyping** to connect deISGylase enzymatic activity with molecular substrates and immune function.

A central technology will be **ISG15 activity-based protein profiling (ISG15-ABPP)**. Electrophilic ISG15 probes covalently label catalytically active deISGylating enzymes, allowing their activity to be measured directly in complex biological samples rather than inferred from protein abundance. Our laboratory has established both gel-based and mass-spectrometry-based ISG15-ABPP workflows, including approaches suitable for inhibitor profiling and medium- to high-throughput analysis. These methods have already contributed to identification of cellular ISG15-cross-reactive enzymes including USP16 and USP24.

Quantitative **proteomics and ISGylomics** will then be used to identify enzyme-dependent substrates and signaling networks following genetic or pharmacological perturbation. Targeted biochemical experiments will validate candidate enzyme-substrate relationships and determine how deISGylation changes protein function or complex formation.

CRISPR/Cas9 gene editing, RNA interference, and complementary genetic approaches will generate enzyme-deficient or catalytically impaired cellular models. These will be combined with IFN stimulation, viral mimetics, and disease-relevant perturbations to measure IFN production and responsiveness, ISG expression, innate immune sensing, cell viability, and inflammatory

phenotypes. Where appropriate, tumor models will be coupled to antigen-presentation and immune-cell killing assays.

Finally, chemical biology and inhibitor profiling will be used to test the tractability and selectivity of prioritized deISGylases, providing a direct bridge between mechanistic discovery and therapeutic development.

TRAINING OPPORTUNITIES

The student will receive multidisciplinary training at the interface of **innate immunity, ubiquitin/UBL biology, chemical biology, mass spectrometry, and therapeutic discovery**.

A major component will be advanced mass-spectrometry-based proteomics. The student will learn sample preparation, quantitative proteomics, ISG15 enrichment strategies, activity-based protein profiling, and associated computational analysis. Particular emphasis will be placed on ISG15-ABPP, a platform developed and implemented within our collaborative environment for profiling endogenous deISGylase activity and assessing inhibitor potency and selectivity. The laboratory also provides access to complementary proteomic approaches including ubiquitomics, immunopeptidomics, and interaction proteomics.

The student will gain extensive training in molecular and cellular biology, including CRISPR/Cas9 genome editing, gene silencing, cloning, protein biochemistry, interferon signaling assays, and functional characterization of innate immune pathways. Depending on the direction of the project, training will also include tumor immunology, antigen-presentation assays, cytotoxic immune-cell cocultures, and viral-mimicry models.

An important feature of the studentship will be learning to integrate **mechanistic biology with therapeutic target validation**. The student will use activity-based probes and small molecules to assess target engagement, selectivity, and functional consequences and will learn how orthogonal genetic, biochemical, proteomic, and pharmacological evidence can be combined to evaluate a therapeutic hypothesis.

This extends the multidisciplinary training environment described in the previous proposal, which already combines ubiquitomics, ABPP, proteomics, chemical biology, cell biology, immunology, and exposure to translational collaborations. The student will additionally benefit from the broader Oxford/CAMS Oxford Institute and Centre for Medicines Discovery environment and from interactions with academic and industrial collaborators.

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3. Mukhopadhyay R, Draganov SD, Oosenbrug T, Akkermans JJLL, Kikkert M, Knobeloch KP, Fritz G, Guzmán M, Zuñiga S, Kim RQ, van der Veen AG, **Kessler BM**, **Pinto-Fernández A**, Geurink PP, Sapmaz A. USP24 is a cross-reactive DUB targeting MOV10 to regulate IFN-I production. Nat Commun. 2026 Jun 19;17(1):7741. doi: 10.1038/s41467-026-74490-2. PMID: 42321163; PMCID: PMC13433998.

4. Gan J, **Pinto-Fernández A**, Flierman D, Akkermans JJLL, O'Brien DP, Greenwood H, Scott HC, Fritz G, Knobeloch KP, Neefjes J, van Dam H, Ovaa H, Ploegh HL, **Kessler BM**, Geurink PP, Sapmaz A. USP16 is an ISG15 cross-reactive deubiquitinase that targets pro-ISG15 and ISGylated proteins involved in metabolism. Proc Natl Acad Sci U S A. 2023 Dec 12;120(50):e2315163120. doi: 10.1073/pnas.2315163120. Epub 2023 Dec 6. PMID: 38055744; PMCID: PMC10722975.

5. Hannah B. L. Jones, Simeon D. Draganov, Sofia Schönbauer Huamán, Peter A. C. Wing, Chuong Nguyen, Zhu Liang, Julia Dörner, Jasper Lithgow, Emma Murphy, Alice Beard, Andrea Pierangelini, Jack W. Houghton, Mackenzie E. Robert, Sarah Flannery, Anthony Tumber, Iolanda Vendrell, Edward W. Tate, Paul R. Elliot, Graham M. West, Darragh P. O'Brien, Eidarus Salah, Andrew P. Turnbull, Christopher J. Schofield, **Benedikt M. Kessler**, Lennart Brewitz, **Adán Pinto-Fernández**. Activity-Based Proteomics Discovery of Deubiquitinating Enzyme Inhibitors with Immunomodulatory Activity, 13 April 2026, PREPRINT (Version 1) available at Research Square [https://doi.org/10.21203/rs.3.rs-9106698/v1]

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8.6 Role of the Natural Ubiquitin Mutant UBB+1 in Cellular Protein Turnover, Neuronal and Immune Ageing

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PROJECT OVERVIEW

Introduction:

The goal of this project is to understand how an abnormal form of a protein, called UBB, affects brain cells as we age [1]. UBB is not a normal protein, but is produced by a copying mistake in cells. Unlike the healthy version of this protein, it cannot perform its usual role in clearing damaged proteins and instead builds up inside cells, especially in long-lived brain cells that do not divide. As neurons age, they gradually lose their ability to maintain protein balance and respond to cellular stress. In Alzheimer's disease, these age-related vulnerabilities are amplified, leading to the accumulation of damaged proteins and progressive neuronal dysfunction [2]. This disruption may push neurons into a senescent-like state- a condition in which cells remain alive but lose normal function. It is important to emphasize that it is unclear whether neurons can truly undergo senescence and, if so, how this contributes to disease progression. This DPhil project will be undertaken in the framework of a collaborative project between the Oxford and Technion teams.

Experimental approach: This integrated strategy combines advanced quantitative proteomics, chemoproteomics, genetic manipulation, and functional neuronal phenotyping, leveraging our validated 3D human neuronal ageing model as well as in immune cells [3]. The holistic approach enables mechanistic dissection of UBB processing pathways while directly assessing their impact on neuronal health and ageing trajectories. In particular, 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. We shall explore the application and subsequent optimisation of the UbSite approach [4,5] and also extend this beyond Ubiquitin to ISG15, critical for interferon signalling pathway regulation.

Expected outcomes: Ageing is the strongest risk factor for Alzheimer's disease and other neurodegenerative conditions, yet the underlying molecular processes are not fully understood. Advanced proteomic tools developed by the Oxford team will enable us to delve into high-resolution biochemical changes over time to define the ageing process. Chemical probes designed by the Oxford team will profile and discover potential UBB+1 processing enzymes that will be characterized by the Oxford team in immune cells and by the Technion team in neuronal cultures. Collectively, our work will include novel molecular insights

underlying neuron proteostasis and provide the framework for developing therapeutics to promote healthy neuron ageing.

DISEASE RELVEANCE

Our established 3D human neuronal system is uniquely positioned to serve a dual purpose: it faithfully models UBB-driven AD-like pathology while also providing a controlled platform to investigate mechanisms of healthy neuronal ageing. This integrated framework allows us to distinguish fundamental ageing-associated changes from those that drive pathological decline. Moreover, the platform offers a scalable and mechanistically informed setting for screening candidate modulators of ubiquitin signalling and proteostasis, enabling identification of compounds or molecular interventions that ameliorate UBB-induced dysfunction. Together, this follow-up project advances our original vision from foundational discovery toward comprehensive mechanistic resolution of UBB biology in both healthy and pathological brain ageing.

KEY TECHNOLOGY

- Mass spectrometry (MS)-based methodologies including advanced proteomic techniques to identify ubiquitin modifications on amino acids such as Lysine, but also Serine, Threonine, Tyrosine and Cysteine as well as protein N-termini.
- Cellular health assays
- Cell viability (MTT, LDH release)
- Mitochondrial membrane potential (JC-1, TMRM)
- Proteostasis markers (ubiquitin-protein conjugates, autophagy flux)
- Reactive oxygen species (ROS) and oxidative stress markers
- Structural and functional imaging
- Confocal microscopy for dendritic morphology and synapse density
- Calcium imaging to assess neuronal excitability and activity patterns
- Analysis of neuronal-specific metabolites
- These integrated readouts will allow us to correlate proteostasis defects with neuronal connectivity, plasticity, and functional resilience during ageing.

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
- Potential visits between the Oxford and Technion sites

KEY PUBLICATIONS

1. van Leeuwen FW, de Kleijn DP, van den Hurk HH, Neubauer A, Sonnemans MA, Sluijs JA, Köycü S, Ramdjielal RD, Salehi A, Martens GJ, Grosveld FG, Peter J, Burbach H, Hol EM. Frameshift mutants of beta amyloid precursor protein and ubiquitin-B in Alzheimer's and Down patients. Science. 1998 Jan 9;279(5348):242-7. doi: 10.1126/science.279.5348.242. PMID: 9422699.
2. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: An expanding universe. Cell. 2023 Jan 19;186(2):243-278. doi: 10.1016/j.cell.2022.11.001. Epub 2023 Jan 3. PMID: 36599349.
3. 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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5. 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.

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8.7 Harnessing RAS Neoantigen-Specific T Cells and Reversing Post-Transplant Exhaustion to Prevent Relapse in Juvenile Myelomonocytic Leukaemia

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Dr. Eleni Louka eleni.louka@ndcls.ox.ac.uk

PROJECT OVERVIEW

Background and central hypothesis.
Juvenile myelomonocytic leukaemia (JMML) is a rare, RAS-pathway-driven childhood myeloid cancer in which allogeneic haematopoietic stem-cell transplantation (HSCT) is the principal curative treatment, yet relapse remains common. Strikingly different outcomes can occur despite similar driver mutations. We hypothesise that differences in RAS-mutant neoantigen recognition and the durability of donor T-cell function help determine whether residual JMML stem cells are eliminated or escape immune surveillance. This DPhil builds directly on the national paediatric MDS/JMML cohort, serial biobank and pilot immune multi-omic data, including preliminary evidence of T-cell exhaustion in relapsing patients.

Aim 1 - Identify functional RAS neoantigen-specific T-cell responses.
We will select genetically and clinically annotated JMML cases with recurrent NRAS/KRAS mutations, including indolent disease and divergent outcomes after HSCT. Combining mutation and HLA typing with patient-specific peptide prediction, we will screen blood and marrow T cells for responses to mutant versus wild-type RAS epitopes. Activation-induced marker assays, cytokine readouts, peptide-MHC multimers where feasible and paired single-cell transcriptome/T-cell receptor (TCR) sequencing will identify candidate antigen-reactive clonotypes. High-priority TCRs will be reconstructed and tested for HLA-restricted recognition and killing of RAS-mutant JMML cells, including stem/progenitor-enriched fractions. Demonstrating recognition of endogenously processed antigen, rather than peptide-pulsed targets alone, will be essential.

Aim 2 - Define and reverse post-HSCT T-cell dysfunction.
Using longitudinal diagnosis, early post-HSCT remission and relapse/long-term remission samples, we will compare donor-derived T-cell phenotypes, clonal expansion and functional competence in patients who relapse versus those who remain disease-free. Integrated single-cell RNA/protein/TCR profiling and multiparameter flow cytometry will map exhaustion-associated states, their temporal evolution and inhibitory interactions with JMML stem and myelomonocytic cells. Functional restimulation and leukaemia co-cultures will

distinguish true loss of anti-leukaemic function from transient activation. Candidate mechanisms, including inhibitory receptor pathways and suppressive cytokine circuits, will be tested by selective blockade or other ex-vivo perturbations to assess recovery of cytotoxicity without excessive alloreactivity.

Integration, feasibility and outputs.
The two aims converge by asking whether RAS-reactive clones are absent, suppressed or recoverable after HSCT. Analyses will account for HLA restriction, donor chimerism, treatment exposures and inter-patient heterogeneity. If a particular RAS epitope is not immunogenic in a given HLA context, we will prioritise other recurrent mutations/alleles and broader relapse-associated TCR populations. The project will deliver validated candidate neoantigens and TCRs, cellular biomarkers of relapse risk, and mechanistically supported strategies for restoring graft-versus-leukaemia activity, laying the groundwork for safer, targeted immunotherapies.

DISEASE RELVEANCE

JMML is an aggressive childhood leukaemia initiated by activating RAS-pathway mutations, often within the haematopoietic stem-cell compartment. Its clinical behaviour is exceptionally variable: some children experience indolent disease whereas others relapse despite allogeneic HSCT. The existing Children with Cancer proposal estimates post-transplant relapse at approximately 35-40%, emphasising the need for approaches that prevent immune escape rather than merely intensifying cytotoxic treatment.

This project tackles two related unmet needs: defining whether common somatic RAS mutations can be recognised as tumour-specific neoantigens, and understanding why donor immune cells sometimes fail to sustain graft-versus-leukaemia activity. Comparing longitudinal samples from children with different outcomes should reveal whether effective mutation-directed T-cell responses are associated with durable disease control, and whether T-cell dysfunction precedes clinical relapse.

The intended impact is a foundation for immune-based relapse prediction and rational interventions that restore anti-JMML activity while minimising graft-versus-host disease. Because RAS mutations also occur in other paediatric and adult malignancies, the insights may extend beyond JMML; any clinical application would require further preclinical safety and efficacy evaluation.

KEY TECHNOLOGY

Clinical cohort and molecular stratification. Serial banked blood and marrow samples from the UK Paediatric MDS/JMML study will be linked to mutation, treatment, chimerism and clinical outcome data. Targeted sequencing, high-sensitivity single-cell genotyping and HLA typing will define patient-specific mutant clones and candidate HLA-restricted epitopes.

Neoantigen-specific immunology. HLA-binding/processing prediction will guide synthesis of mutant and matched wild-type RAS peptides. Peptide stimulation, activation-induced marker assays, intracellular cytokine staining, ELISpot and peptide-MHC multimer staining (where appropriate) will quantify specific CD4/CD8 responses. Single-cell 5-prime RNA sequencing with surface-protein profiling and paired TCR sequencing will connect antigen specificity, clonality and cellular state. Candidate TCRs will be cloned into reporter or primary T cells and evaluated against peptide-pulsed and naturally RAS-mutant targets, with HLA blockade, wild-type controls and cytotoxicity readouts.

Transplant immune ecosystems and perturbation. Longitudinal single-cell multi-omics, spectral/multiparameter flow cytometry and computational donor-recipient demultiplexing will distinguish expansion, activation and exhaustion of donor T cells. Intercellular ligand-receptor analysis, supported by spatial profiling of available trephines, will prioritise suppressive niches. Ex-vivo JMML/T-cell co-cultures and focused antibody or pathway perturbations will test reversibility of dysfunction; restoration of target-cell killing, cytokine production and proliferative capacity will be measured alongside alloreactivity controls.

Analysis and quality. Case-matched longitudinal comparisons will adjust for time after HSCT and major clinical confounders; findings will be validated across independent specimens where material permits. Scarce samples and HLA diversity will be addressed through prioritisation of informative patient/allele groups and orthogonal assays.

TRAINING OPPORTUNITIES

This interdisciplinary DPhil will provide integrated training in paediatric leukaemia biology, translational immunology and quantitative single-cell analysis across the Mead, Dong and Louka research programmes at Oxford. The student will gain hands-on experience of clinical sample processing, flow cytometric sorting, targeted mutation detection, HLA-informed neoantigen discovery, antigen-specific T-cell assays, TCR repertoire analysis and functional leukaemia/T-cell co-culture systems.

Professor Mead and Dr Louka will supervise the JMML clinical and disease-biology components, including access to the UK paediatric MDS/JMML research infrastructure, malignant stem-cell biology and longitudinal multi-omics. Professor Dong's group will lead training in antigen-specific human T-cell biology, peptide screening, functional cytotoxic T-cell assessment and TCR-based approaches. Together, the supervisors offer complementary expertise spanning biological discovery to therapeutic validation.

The student will develop reproducible computational workflows for single-cell RNA/protein/TCR integration, donor-recipient assignment, longitudinal statistics and ligand-receptor analysis, with support from established WIMM facilities. Training will include rigorous experimental design, handling of limited paediatric material, research ethics and patient-data governance, critical interpretation of translational endpoints, presentation and manuscript writing. Regular cross-group meetings and opportunities to engage with the JMML clinical network will help the student become an independent scientist equipped to develop biomarker-led immune therapies.

KEY PUBLICATIONS

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