CSC-COI SCHOLARSHIP DPHIL PROJECT PROPOSALS

Enrolment Year: 2026

1 Program Available

- ☑ MSD Program: 1 Program

46 Projects Available

- ☑ Cancer Biology, Immunology & Immunotherapy: 14 Projects
- ☑ Infection Immunology & Disease: 11 Projects
- ☑ Inflammation & Autoimmune Disease: 3 Projects
- ☑ Genomic Medicine & Data Science: 4 Projects
- ☑ Neuroscience: 3 Projects
- ☑ Population & Public Health: 4 Projects
- ☑ Target Discovery: 2 Projects
- ☑ Other Themes: 5 Projects

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Program 1. MSD Program

Genomic Medicine and Statistics DPhil Programme

Prof. Julian Knight (Director)

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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 2025	CSC/COI/NDM begin advertising for applications.
15th Nov 2025	Deadline for candidates to submit their CV, cover letter, list of three projects, references and other required documents to CSC
2nd Dec 2025	Deadline for candidates to apply directly to the University of Oxford for admission.
Early Jan 2026	The University will shortlist candidates for the Programme.
Mid Jan 2026	Interviews by Oxford University for the Genomic Medicine and Statistics course.
Late Feb 2026	Interviews by CSC.
Mid-Late Mar 2026	Successful candidates will be notified.

Disease Relevance

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:

- Genomic and -omic technologies (including method development, single cell genomics, imaging, model systems, CRISPR screens, genome engineering, proteomics, metabolomics, high throughput screening)
- Functional genomics (gene regulation and epigenetics)
- Genome biology (genetic variation, recombination, human history, evolution, palaeogenomics, pathogen genomes)
- Genomics of disease (Mendelian, multifactorial traits, cancer)
- Genomic analysis (bioinformatics and statistical genetics)
- From genes to clinical proof of concept (integrated drug development pipeline spanning genetic-led target discovery, structural biology, medicinal chemistry)
- 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, Immunology & Immunotherapy

1.1 Structural Mechanisms of T Cell Receptor Recognition of Peptide Antigen via pMHC Complexes

Prof. Peijun Zhang & **Dr. Ricardo A. Fernandes**

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Project Overview

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

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

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

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

Disease Relevance

- Virus infections
- Cancer
- Autoimmune diseases

Key Technology

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

Training Opportunities

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

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

Key Publications

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

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1.2 Detecting epitranscriptomic signatures in circulating cell-free RNA for early cancer detection

Prof. Chunxiao Song & **Prof. Benjamin Schuster-Böckler**

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Project Overview

Although recent advances in cancer research offer new ways to treat cancer, early detection still represents the best opportunity for curing cancer. Early stage treatment 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. In this regard, circulating nucleic acids hold tremendous potential to develop such a diagnostic assay. Human body fluids contain cell-free nucleic acids which originated from different cells of origin in the body including cancer cells in cancer individuals. Cell-free DNA (cfDNA) and cell-free RNA (cfRNA) in circulation can be extracted for analysis and has potential use for diagnostics and prognostics of cancer. On the other hand, there are widespread chemical modifications in both DNA and RNA, which are terms epigenetic modifications and epitranscriptomic modifications, respectively. The presence of tumours can alter the epigenetic and epitranscriptomic landscape at both tumour sites including cancer cells and microenvironment as well as distant cells such as cells of the immune system. While epigenetic modifications can be readily detected in cfDNA and extensively used for cancer detection, epitranscriptomic modifications in cfRNA have not been explored due to technological difficulties.

Our research aims to decode epigenetic and epitranscriptomic modifications of our genome and transcriptome to learn about the basis of human health and disease, and to facilitate translation of this information into diagnostic and therapeutic opportunities that ultimately benefit patients. With our unique expertise in chemical biology and genome technology, we have developed cutting-edge technologies in epigenetics and epitranscriptomics. Previously, we developed a DNA epigenetic modification sequencing method, and demonstrated its application in cfDNA sequencing for early cancer detection (*Nat. Biotechnol*. 2019, *37*, 424, *Sci. Adv.* 2021, *7*, eabh0534).

Recently, we developed a novel sequencing method, called BACS, for the most abundant RNA epitranscriptomic modification pseudouridine (*Nat. Methods* 2024, *21*, 2024). Pseudouridine is the most common post-transcriptional RNA modification linked to various diseases, including cancer. Our previous work has shown that the BACS method significantly outperforms older techniques in detecting pseudouridine, demonstrating its ability to identify this modification accurately and sensitively at a single-base resolution.

We plan to explore the potential clinical application of pseudouridine in cfRNA for early cancer detection using BACS. cfRNA encompass a diverse array of extracellular transcripts, including both coding and non-coding RNAs (ncRNAs) in the bloodstream. These cfRNAs originate from processes such as cell death and active secretion via extracellular vesicles, positioning them as promising biomarkers for liquid biopsy. Current detection methods for cfRNA in plasma largely focus on coding RNAs, or messenger RNAs (mRNAs), which represent only a small fraction (~2%) of the cfRNA repertoire, while the vast amount of ncRNAs are overlooked. By focusing on the highly abundant pseudouridine in ncRNAs in cfRNA, this research has the potential to transform cancer detection by providing a non-invasive, accurate, and cost-effective method for identifying new cancer biomarkers in patient blood samples.

Disease Relevance

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 pseudouridine in cancer. Analysis of public pan-cancer RNA-seq data reveals the global dysregulation of PUS genes in a wide range of cancer types. These findings suggest that the dysregulation of pseudouridine and PUS enzymes is corrected with tumorigenesis and the potential of using pseudouridine in the circulating cell-free RNA for non-invasive cancer diagnostics.

Key Technology

2-Bromoacrylamide-Assisted Cyclization Sequencing (BACS), (Nat. Methods 2024, 21, 2024).

Training Opportunities

- Basic and advanced chemical biology, biochemistry, and molecular biology techniques;
- Knowledge in nucleic acid modifications/epigenetics/epitranscriptomics and clinical diagnostics;
- Cutting-edge sequencing technilogies;
- Cell-free RNA sequencing (liquid biopsy);
- 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) 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.
3) 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.
4) Liu Y, Hu Z, Cheng J, Siejka-Zielinska P, Chen J, Inoue M, Ahmed AA, Song CX. (2021). Subtraction-free and bisulfite-free specific sequencing of 5-methylcytosine and its oxidized derivatives at base resolution. ***Nat. Commun.*** 12, 618.
5) Xu H, Chen J, Cheng J, Kong L, Chen X, Inoue M, Liu Y, Kriaucionis S, Zhao M, Song CX. (2023). Modular oxidation of cytosine modifications and their application in direct and quantitative sequencing of 5-hydroxymethylcytosine. ***J. Am. Chem. Soc.*** 145, 7095-7100.

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1.3 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 Relevance

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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1.4 Mechanisms and consequences of HLA-II expression in colorectal and endometrial cancer

Dr. David Church & **Prof. Tim Elliott**

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Project Overview

Research plan

The project aligns with a recent Cancer Research UK Senior Cancer Research Fellowship (PI: Church), and will benefit from the samples and data currently under generation in the Oxford LynchVax (PI: Church) and GO-PRECISE CRC-VAX (co-PI: Church) projects.

Correlates and candidate mechanisms: In collaboration with the Koelzer group (University of Basel), we have recently used AI-based image analysis to analyse MHC-II in nearly 3,500 colorectal and 1,500 endometrial cancers and a small number of LynchVax colonic precancers. Preliminary analysis reveals epithelial MHC-II expression coincides with the onset of dysplasia and is found in 20–50% of cancers; current work will define the clinical and molecular correlates of such expression along with its prognostic value. The student will have the opportunity to contribute to these analyses, and will lead the detailed study of MHC-II expression and its correlates in the large cohort of colonic precancers we are generating under the LynchVax and GO-PRECISE CRC-Vax industry collaborations. This work will leverage the exceptional multimodal data we will have for these samples including whole genome and transcriptome sequencing, immunopeptidomics and state-of-the-art spatial analyses of transcripts (Xenium 5k) and protein (phenocycler). This work will benefit from the multidisciplinary collaboration across the LynchVax and CRC-Vax groups. **Selected outputs** from this work will include:

- Timing and frequency of MHC-II expression in colon and endometrial cancer
- Discovery and validation of genomic and transcriptomic features associated with MHC-II dysregulation (IFNg pathway activation, alterations in MHC-II pathway etc)
- Relationship between MHC-II expression and immune infiltrate, focusing on localisation and activation/exhaustion status of CD4, CD8 and other key cell types

Parallel work will investigate the functional role of MHC-II in cancer. This work aligns with the aim of a recently-awarded Senior Fellowship to the supervisor, and will benefit from the model systems to be generated under this work. As part of this work, the student will assist with the generation and characterisation of mice carrying conditional alleles of the MHC-II master regulator CIITA together in combination with other alleles we have shown induce MHC-II expressing tumours (e.g. Pole). Deep phenotyping will include analysis of precancers and cancers to define the consequences of MHC-II dysregulation on tumour development, immune infiltrate and depending on results, immunopeptidomics on primary tumours or tumour-derived organoids. Complementary human analyses will include generation of ex-vivo organoids, induction of MHC-II by eg IFNg, and detailed phenotyping including immunopeptidomics and potentially, co-culture with HLA-matched CD8 and CD4 T cells.

Disease Relevance

The widespread use of immune checkpoint blockade (ICB) for colorectal and endometrial cancers and the proven importance of antigen presentation in sensitivity to such agents provides immediate translational relevance. We will aim to rapidly transfer the findings of this work into the clinic through our network.

Key Technology

The project will leverage available genome and transcriptome sequencing generated for precancers and cancers. Mouse models are under generation. Planned multiparameter spatial analyses will be analysed by AI under a longstanding collaboration with Viktor Koelzer (University of Basel).

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 and training to obtain accreditation for work on preclinical models. Bioinformatic analyses will be done under the supervision of the Church group, LynchVax and GSK teams, 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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1.5 Development of a Lymph-Based Diagnostic Platform to Predict Metastasis and Immunotherapy Response in Patients with Melanoma

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Project Overview

Accurate prediction of metastatic risk in early-stage melanoma remains a major unmet clinical need. Current staging systems are largely based on histopathological criteria and fail to detect a subset of sentinel lymph node (SLN)–negative patients who nonetheless relapse, while overtreating others with adjuvant immunotherapy they do not require. Circulating tumour cells (CTCs) and tumour-educated immune cells represent promising predictive biomarkers, however blood-based liquid biopsies often miss the earliest stages of metastasis — particularly in cancers like melanoma, which initially spread through the lymphatic system.

Lymph fluid, which drains directly from the tumour to regional lymph nodes, carries both tumour-derived and immune cell populations, as well as soluble mediators of tumour–immune interactions. It is the first biological compartment encountered by migrating tumour cells and drains lymph nodes, which are the sites of critical immune priming or suppression events. Despite its unique relevance, lymph has been almost entirely unexplored in oncology due to difficulties in accessing it.

Our group has developed and piloted a novel surgical technique for intraoperative collection of tumour-draining lymph fluid during routine melanoma lymph node surgery. In proof-of-principle work, we have recovered viable melanoma cells from lymph fluid that share transcriptional features with lymph node metastases, alongside diverse immune subsets. These findings establish lymph as a rich, untapped source of early metastatic and immunological signals.

The proposed DPhil project will focus on developing and analytically validating a lymph-based liquid biopsy (LLB) platform for early melanoma risk stratification. The student will build a robust, clinically deployable assay by optimising pre-analytical workflows, selecting and refining biomarker panels and assessing analytical performance.

<u>Objectives</u>

1) Optimise the workflow for lymph fluid collection, preservation and processing, and compare fresh, stabilised and cryopreserved samples for cell recovery, viability, RNA integrity and protein marker stability.
2) Develop a targeted biomarker panel for L-CTCs and key immune subsets, informed by existing high-dimensional single-cell and proteomic data from our pilot studies.
3) Validate analytical performance through reproducibility testing, spike-in sensitivity experiments for rare cell detection and cross-platform concordance analysis against gold-standard multi-omic datasets.
4) Generate preliminary performance metrics by piloting clinical application in an independent cohort of melanoma patients, correlating LLB profiles with recurrence outcomes.

Methods and Training

The student will receive training in liquid biopsy assay development, rare cell enrichment technologies, flow cytometry, targeted transcriptomics and computational analysis for multi-omic biomarker integration. They will be embedded in a multidisciplinary team spanning translational immunology, surgery, oncology, molecular diagnostics and bioinformatics.

Impact

This project will generate the first analytically validated lymph liquid biopsy platform for melanoma, providing a reproducible method for detecting early metastatic competence and immune dysfunction.

By focusing on assay optimisation and validation, the work will directly address the translational bottleneck between biological discovery and clinical implementation. The outputs will position the platform for prospective multi-centre trials, with the potential to change risk-stratification paradigms in melanoma and other lymphatically disseminating cancers.

Disease Relevance

Melanoma is the fastest rising cancer in the UK and had doubled in incidence over the past two decades. While early-stage disease can be cured with surgery, around 20–30% of patients with SLN–negative stage II melanoma will relapse. Current prognostic tools rely on histopathology and fail to identify many high-risk patients, while overtreating others with unnecessary adjuvant immunotherapy, which carries substantial toxicity and cost.

A key clinical challenge is the lack of reliable biomarkers to distinguish which patients are genuinely at risk of progression. This results in missed opportunities for early intervention and unnecessary treatment in those who may never relapse. As melanoma increasingly affects younger adults, inaccurate risk stratification carries lifelong personal and socioeconomic consequences, alongside significant pressure on health services. Immunotherapy has transformed outcomes, but is currently used without precise predictors of benefit, highlighting an urgent need for biologically informed diagnostics. By interrogating lymph — the first conduit for tumour spread and a site of critical immune regulation — this project will generate insights into early dissemination and immune escape that could refine prognostication and support more rational use of immunotherapy.

By developing and validating a LLB platform, this project addresses a critical gap in oncology, with potential impact across other lymphatically disseminating cancers.

Key Technology

This project integrates established liquid biopsy technologies with a novel lymph fluid–based approach to detect early metastatic risk in melanoma. The central innovation is the intraoperative collection of tumour-draining lymph fluid during routine sentinel lymph node biopsy (SLNB) — a technique recently developed and validated by our group. This enables matched sampling of lymph fluid, primary tumour tissue, lymph nodes and blood from the same patient, allowing direct biological comparisons between compartments.

To interrogate tumour-derived signals, the student will:

- Enrich and enumerate circulating tumour cells (CTCs) from lymph using immunomagnetic capture and label-free microfluidics.
- Define phenotypic and molecular markers of metastatic competence (e.g. epithelial–mesenchymal transition states, proliferation, immune evasion) and compare these to tumour cells isolated from matched primary and lymph node tissue.
- Profile circulating tumour cell DNA (ctcDNA) from lymph and compare with tissue to assess concordance of mutation and copy number profiles.

For immune-derived signals, the focus will be on tumour-educated immune cells present in lymph and their tissue counterparts, including:

- Functional states of $CD8^+$ T cells (activation, exhaustion, checkpoint receptor expression) in lymph vs intratumoural and nodal contexts.
- Regulatory T cell abundance and suppressive phenotype.
- Antigen-presenting cell subsets and their co-stimulatory/co-inhibitory profiles.
- T-cell receptor (TCR) clonotypes shared between lymph, tumour and node, providing insight into trafficking and immune engagement.

High-dimensional sequencing approaches (scRNA-seq, CITE-seq, TCR-seq) will be used to resolve these rare cell populations and their interactions, enabling the discovery of multi-marker signatures not detectable with single-parameter assays.

Training Opportunities

This project offers outstanding training for the DPhil candidate, combining direct involvement in clinical sample acquisition with state-of-the-art translational research methods.

The student will gain fundamental research skills in experimental design, hypothesis testing, quality control, data analysis and scientific writing, alongside experience in multidisciplinary collaboration between surgery, immunology, oncology and pathology.

They will receive hands-on training in established and advanced liquid biopsy workflows, including pre-analytical optimisation, CTC enrichment, phenotypic characterisation and circulating tumour DNA analysis. They will have the opportunity to be trained in high-dimensional molecular profiling (single-cell RNA-seq, CITE-seq, TCR sequencing) and in the integration of multiomic datasets.
Furthermore, they will develop skills in biostatistical analysis and multi-omic data integration.

Within the Nuffield Department of Surgical Sciences, the candidate will be embedded in the Translational Immunology Group (TRIG lab), participating in weekly lab meetings, research skills sessions and formal seminars and journal clubs. They will also engage with oncology-focused seminars and networking events arranged by Oxford Cancer and with clinically oriented student-led activities in the Oxford Plastic Surgery Society and Oxford Surgical Society.

The student will have the opportunity to present work at national and international conferences, contribute to peer-reviewed publications and participate in patient and public involvement activities via advocacy groups such as Melanoma Focus.

For the post-doctoral co-supervisor, this project provides a valuable platform to develop mentoring and leadership skills.

The departments involved will benefit from enhanced collaboration between surgical oncology and translational immunology, fostering knowledge exchange and methodological innovation in liquid biopsy and melanoma research.

Key Publications

1) Tumor-Infiltrating Lymphocyte Scoring Improves Progression Risk Prediction in Stage II Melanoma: A Retrospective Cohort Study. March 2025. Journal of the American Academy of Dermatology 93(10336). DOI:10.1016/j.jaad.2025.03.046
2) Global Applicability of a Risk Prediction Tool for Sentinel Node Positivity in Patients With Primary Cutaneous Melanoma. S. Lo….G.Adigbli et al. April 2025. JAMA Dermatology 161(24) DOI:10.1001/jamadermatol.2025.0318
3) Letter to the Editor: Complex Lymphatic Drainage in Head and Neck Cutaneous Melanoma and SLNB Outcomes. G. Adigbli, L. Woolley and F. Issa. JAMA Otolaryngol Head Neck Surg 2023 Vol. 149 Issue 9 Pages 853-854
4) Regulatory T cell therapy is associated with distinct immune regulatory lymphocytic infiltrates in kidney transplants. Med. 2025 May 9;6(5):100561. doi: 10.1016/j.medj.2024.11.014.Epub 2024 Dec 27.
5) The Role of Liquid Biopsy as a Catalyst for Sustained Progress in Precision Oncology – Perspective of The Young Committee of The International Society of Liquid Biopsy. May 2024. The Journal of Liquid Biopsy 5(9):100156. DOI:10.1016/j.jlb.2024.100156

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1.6 Cellular response signatures to assess colorectal cancer treatments

Prof. Simon Leeham & **Prof. Helen Byrne**

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Project Overview

Background. Cancer chemotherapeutic and radiation clinical trial outcomes rely on cross-sectional imaging detection of a reduction in tumour volume to define therapeutic success (RECIST criteria). This can lead to de-prioritisation of agents that fail to impact macroscopic tumour characteristics. However, some successful treatments may significantly alter key pathological cell interactions without immediately reducing tumour volume, e.g immunotherapies restore T-cell recognition, causing an influx of cancer-engaging immune cells. Consequently, there is an urgent need to redefine the measurement of therapeutic impact. In colorectal cancer, advancing mouse cancer models alongside human endoscopic tissue accessibility, coupled with the shifting emphasis towards neoadjuvant treatment and the desire for organ preservation in rectal/dMMR cancers, provides a unique clinical landscape to undertake temporally spaced, on-treatment tissue sampling. This creates an opportunity for quantitative assessment of cellular dynamics in response to therapeutic selective pressures.

Hypothesis and multidisciplinary aims - We hypothesise that we can couple spatial biology discovery tools, such as Xenium spatial transcriptomics with advanced multiscale mathematical analysis (MuSpAn platform) on valuable temporally spaced mouse and human samples to:
1. Identify and quantify therapeutically responsive shifts in cell interactions and molecular phenotype;
2. Distil this granular, but low-throughput, discovery biology to identify discriminatory cellular response signatures (CRS);
3. Develop and validate appropriate high-throughput companion diagnostics.

We will establish this methodology using existing tissue from mouse models of colorectal and pancreatic cancer before extending it to precious human clinical trial samples in the CRC-STARS strategic program.

Project plan - MAPK signalling is almost ubiquitously disrupted in pancreatic and colorectal cancers via multiple acquired driver gene mutations (e.g *KRAS, BRAF*). New therapeutic approaches including drugs to target mutant *KRAS* and *BRAF* are in development and entering clinical trials. Our previous work indicates a promising shift in the epithelial stem cell molecular phenotype in response to MAPK manipulating therapy, but the concomitant impact on stromal and immune compartments is unknown. We will undertake spatial transcriptomic assessment of temporally spaced “with and without” treatment samples in mouse and human tissue and take an unsupervised approach to identify key cell interactions that change with treatment across all tissue compartments. We have established workflows for integrating Xenium ST with MuSpAn. We aim to uncover discriminatory spatial reorganisation in mouse samples following therapeutic intervention by leveraging MuSpAn’s multiscale information inheritance framework. Spatial transcriptomics provides a powerful tool for discovery biology but is impractical as a clinical tool since it is low-throughput, expensive and the datasets are extremely large. This proposal also aims to distil discovery biology from ST datasets to identify the most discriminatory therapy-induced cellular dynamics, and then to develop and optimise small, multiplex IHC companion diagnostic panels for high-throughput use.

Disease Relevance

This project will demonstrate that application of spatial biology analysis to temporally-spaced samples can generate cellular response signatures for emerging drug combinations in colorectal cancer. We will develop methodologies that distil highly granular, low-throughput discovery biology from ST to drug-discriminatory response signatures for subsequent assessment with high-throughput, affordable companion diagnostics (e.g small multiplex IHC panels comprising 5-7 biomarkers).

If successful we hope this work will

1) Catalyse a shift towards measuring drug outcome at a cellular level, to enable titration of therapies through quantitatively-assessed patient response in those cancers where on-treatment tissue sampling is safe and patient-acceptable.
2) Change the paradigm for measuring therapeutic impact in clinical trials, to prevent unnecessary deprioritisation of potentially beneficial novel agents

Key Technology

1) Xenium spatial transcriptomics platform on temporally spaced mouse and human cancer samples .
2) MuSpAn spatial analysis platform (www.muspan.co.uk). This Python toolbox enables seamless construction of spatial analysis pipelines that combine established and cutting-edge mathematical tools for quantitative spatial analysis of biomedical images. MuSpAn's architecture is designed to traverse and link multiple spatial scales through spatial object (dis)aggregation and an information inheritance framework. The range of orthogonal tools enables description and quantification of cell interactions across length scales and is robust to the architectural complexity of mammalian tissues. MuSpAn acts downstream of pre-processed spatial data, ensuring applicability to any imaging modality. Critically, as the mathematical descriptors are agnostic to spatial scale, MuSpAn provides a platform for integrating multi-modal metadata with multiscale spatial analyses.

Training Opportunities

The student will have the opportunity to work with state-of-the-art mouse models and precious human clinical trial samples. They will learn how to interpret and analyse Xenium spatial transcriptomics datasets using our spatial analysis toolbox MuSpAn. The project would suit someone with a biological interest in colorectal cancer, the impact of therapeutic selective pressures and the evolution of drug resistance. Working knowledge of bioinformatics and Python software would be useful but is not obligatory as training is available

Key Publications

1) Bull, J. A., Moore, J. W., Mulholland, E. J., Leedham, S. J., & Byrne, H. M. (2025, February 10). *MuSpAn: A toolbox for multiscale spatial analysis* [Preprint]. *bioRxiv*. https://doi.org/10.1101/2024.12.06.627195
2) Bull, J. A., Mulholland, E. J., Moore, J. W., Bosque, J. J., Stolz, B. J., Boen, J., Eggington, H. R., Belnoue-Davis, H. L., Jones, H., Gatenbee, C. D., … Byrne, H. M. (2024, June 3). *Integrating diverse statistical methods to analyse stage-discriminatory cell interactions in colorectal neoplasia* [Preprint]. *bioRxiv*. https://doi.org/10.1101/2024.06.02.597010
3) Vasquez, E. G., Nasreddin, N., Valbuena, G. N., Mulholland, E. J., Belnoue-Davis, H. L., Eggington, H. R., Schenck, R. O., Wouters, V. M., Wirapati, P., Gilroy, K., Lannagan, T. R. M., Flanagan, D. J., Najumudeen, A. K., Omwenga, S., McCorry, A. M. B., Easton, A., Koelzer, V. H., East, J. E., Morton, D., … Leedham, S. J. (2022). Dynamic and adaptive cancer stem cell population admixture in colorectal neoplasia. *Cell Stem Cell, 29*(8), 1213–1228.e1218. https://doi.org/10.1016/j.stem.2022.07.008
4) Cañellas-Socias, A., Cortina, C., Hernando-Momblona, X., Palomo-Ponce, S., Mulholland, E. J., Turon, G., Mateo, L., Conti, S., Roman, O., Sevillano, M., Slebe, F., Stork, D., Caballé-Mestres, A., Berenguer-Llergo, A., Álvarez-Varela, A., Fenderico, N., Novellasdemunt, L., Jiménez-Gracia, L., Sipka, T., Bardia, L., Leedham S … Batlle, E. (2022). Metastatic recurrence in colorectal cancer arises from residual EMP1+ cells. *Nature, 611*(7936), 603–613. https://doi.org/10.1038/s41586-022-05402-9

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1.7 Integrins as building blocks of supramolecular attack particles

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Project Overview

Supramolecular attack particles (SMAPs) are core-shell nanoparticles released into the immunological synapse between cytotoxic T lymphocytes (CTL) or nature killer (NK) cells with their taget cells. They have a core of proteoglycan (SRGN), cytotoxic proteins (GZMB and PRF1), cytokines (IFNG) and chemokines (XCL1 and CCL5). The shell is composed in part of thrombospondins (TSP-1 and 4). In addition to TSPs, the alpha subunit of the integrin LFA-1 (ITGAL) is also prominently detected in SMAPs from T cells and NK cells and are candidate building blocks of the shell. ITGAL is a member of a sub family of integrins in which ligand binding is fully encoded in the alpha subunit through the inserted domain within the Calcium ion binding beta-propeller domain, which may account for the ability of SMAPs to bind the LFA-1 ligand, ICAM-1 and contribute to target cell killing. Integrin expression in effector T cells is important for tissue residence and function. Highly active CTLs express integrins with ligand binding alpha subunits: collagen binding ITGA1 and ITGA2 and the E-cadherin binding ITGAE. We will determine if ITGA1, ITGA2 and ITGAE are incorporated into SMAPs from effector CTL and NK cells expressing these integrins. Another important aspect of the project will be to understand how ITGAL protein can exist in SMAPs without the beta subunit ITGB2. In Leukocyte Adhesion Deficiency type I (LAD1), a primary immunodeficiency in which ITGB2 is absent, there is no surface expression of ITGAL or the other ITGB2 associated alpha subunits, ITGAM, ITGAX and ITGAD. Are ITGAL, and potentially other integrins, made as a conventional transmembrane heterodimers and then processed to a form that can be incorporated into SMAPs. Alternatively, is there a pathway for certain integrin alpha subunits to be co-opted into SMAP precursors in the endoplasmic reticulum directly without having paired with a beta subunit. These questions will be addressed with a combination of classical biochemistry and mass spectrometry. There will also be in interest to understand how TSPs and integrin subunits are integrated. Both TSPs and integrin alpha subunits have multiple divalent cation binding sites, including regulatory sites that bind Calcium ions. There will be an interest in understanding how Calcium ion binding to TSPs and integrins stabilizes and preserves the functional activity of SMAPs. These Calcium ion clusters may make these elements more visible in electron tomography, including analysis in liquid cells. Functional analysis will include assays in vitro and in situ. For example, collagen binding by SMAPs may lead to SMAP deposition in extracelluar matrix which may be detected in tumours and sites of inflammation. Integrin engineered SMAPs will be tested on ovarian cancer organoids with without immune cells. The project will address fundamental mechanisms involved in the immune response to cancer and intracellular infections, in addition to regulatory processes that prevent autoimmunity. Specific applications in applicability to treatment of ovarian cancer will be explored.

Disease Relevance

- SMAPs have autonomous cytotoxic activity and innate targeting, which this project will seek to understand. The project will enable partnering with GranzaBio, a start-up company focused on using protein based particles for *in vivo* cargo delivery.
- Applications of such cargo delivery included cancer immunotherapy, treatment of autoimmunity and regenerative medicine.
- Specific applications to treatment of ovarian cancer will be tested with co-supervisor Ahmed Ahmed.

Key Technology

- The student will have access to the nanoparticle characterization facilities of the IDRM, the Oxford-Zeiss Centre of Excellence for Biomedical Imaging at the KIR and IDRM, the Human Tissue Hub at COI, the mass spectrometry facilities of the TDI and collaboration with groups developing state of the art electron microscopy at the Rosaslind Franklin Institute.
- The student will learn how to work with human ovarian cancer organoids without and with patient immune cells.

Training Opportunities

- The project will provide training in protein purification, fluorescent labelling, flow cytometry (nano and spectral), advanced fluorescence microscopy (confocal, single molecule TIRFM, dSTORM, lattice light sheet, cryoelectron and X-ray tomography), biochemistry (gel electrophoresis, mass spectrometry analysis and 2D analysis is supported lipid bilayers), cellular immunology and molecular biology.
- The student will be trained in human tissue processing for generation of ovarian cancer organoids.

Key Publications

1) Balint S, Muller S, Fischer R, Kessler BM, Harkiolaki M, Valitutti S, Dustin ML. Supramolecular attack particles are autonomous killing entities released from cytotoxic T cells. Science. 2020;368(6493):897-901. Epub 20200507. doi: 10.1126/science.aay9207. PubMed PMID: 32381591; PMCID: PMC7116847.
2) Chang HF, Schirra C, Ninov M, Hahn U, Ravichandran K, Krause E, Becherer U, Balint S, Harkiolaki M, Urlaub H, Valitutti S, Baldari CT, Dustin ML, Jahn R, Rettig J. Identification of distinct cytotoxic granules as the origin of supramolecular attack particles in T lymphocytes. Nat Commun. 2022;13(1):1029. Epub 20220224. doi: 10.1038/s41467-022-28596-y. PubMed PMID: 35210420; PMCID: PMC8873490.
3) Hamid M, Cespedes PF, Jin C, Chen JL, Gileadi U, Antoun E, Liang Z, Gao F, Teague R, Manoharan N, Maldonado-Perez D, Khalid-Alham N, Cerundolo L, Ciaoca R, Hester SS, Pinto-Fernandez A, Draganov SD, Vendrell I, Liu G, Yao X, Kvalvaag A, Dominey-Foy DCC, Nanayakkara C, Kanellakis N, Chen YL, Waugh C, Clark SA, Clark K, Sopp P, Rahman NM, Verrill C, Kessler BM, Ogg G, Fernandes RA, Fisher R, Peng Y, Dustin ML, Dong T. Unconventional human CD61 pairing with CD103 promotes TCR signaling and antigen-specific T cell cytotoxicity. Nat Immunol. 2024;25(5):834-46. Epub 20240401. doi: 10.1038/s41590-024-01802-3. PubMed PMID: 38561495; PMCID: PMC11065694.
4) Demetriou P, Abu-Shah E, Valvo S, McCuaig S, Mayya V, Kvalvaag A, Starkey T, Korobchevskaya K, Lee LYW, Friedrich M, Mann E, Kutuzov MA, Morotti M, Wietek N, Rada H, Yusuf S, Afrose J, Siokis A, Oxford IBDCI, Meyer-Hermann M, Ahmed AA, Depoil D, Dustin ML. A dynamic CD2-rich compartment at the outer edge of the immunological synapse boosts and integrates signals. Nat Immunol. 2020;21(10):1232-43. Epub 20200914. doi: 10.1038/s41590-020-0770-x. PubMed PMID: 32929275; PMCID: PMC7611174.
5) Morotti M, Albukhari A, Alsaadi A, Artibani M, Brenton JD, Curbishley SM, Dong T, Dustin ML, Hu Z, McGranahan N, Miller ML, Santana-Gonzalez L, Seymour LW, Shi T, Van Loo P, Yau C, White H, Wietek N, Church DN, Wedge DC, Ahmed AA. Promises and challenges of adoptive T-cell therapies for solid tumours. Br J Cancer. 2021;124(11):1759-76. Epub 20210329. doi: 10.1038/s41416-021-01353-6. PubMed PMID: 33782566; PMCID: PMC8144577.

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1.8 Modulating inhibitory receptor signalling to potentiate T cell function in cancer

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Project Overview

Background and Rationale

T cell activity is controlled by a balance between activating and inhibitory receptors (IRs). IRs counteract positive signals through cytoplasmic inhibitory motifs, dampening T cell responses and contributing to tolerance. Antibody-based checkpoint blockade therapies that prevent IR–ligand interactions (e.g. PD-1/PD-L1 or CTLA-4/CD80-CD86) have transformed cancer immunotherapy. However, only a minority of patients achieve durable responses, and the molecular mechanisms by which different IRs attenuate signalling remain poorly understood. Importantly, no systematic comparison of the relative potency, mediators, and targets of clinically relevant IRs has yet been undertaken.

To overcome the limitations of antibody blockade, we developed a novel approach called Receptor Inhibition by Phosphatase Recruitment (RIPR). In this strategy, a bispecific molecule recruits the tyrosine phosphatase CD45 in cis to the cytoplasmic tail of PD-1. By directly dephosphorylating inhibitory motifs, RIPR disrupts sustained intracellular signalling and restores T cell activity. This intracellular rewiring concept has strong potential to extend beyond PD-1 to other checkpoint receptors.

Research objectives and expected outcomes

Regulation of T cell signalling by immune checkpoints such as PD-1 and CTLA-4 has been at the centre of recent breakthroughs in cancer immunotherapy. Signalling by PD-1 and CTLA-4 reduces T cell activity and contributes to an “exhausted” phenotype, severely compromising antitumor responses. In the case of PD-1, binding to PD-L1/2 triggers the tyrosine phosphorylation of signalling motifs and results in the recruitment of cytosolic phosphatases such as SHP1/2, which in turn reduces TCR and CD28 signalling. Strikingly, signalling by several immune receptors relies on the Tyr phosphorylation of signalling motifs. We hypothesise that tonic receptor phosphorylation and sustained signalling by ‘ligand-experienced’ receptors impact T cell function and resist classic antibody blockade. To address this issue, we engineered a bi-specific molecule to recruit CD45, an abundant and promiscuous receptor tyrosine phosphatase, within close proximity of PD-1 (Fig. 1). In this approach, named Receptor Inhibition by Phosphatase Recruitment (RIPR), the phosphatase domain of CD45 acts intracellularly, in *cis,* on the p-Tyr residues of the PD-1 signalling motif, thus inhibiting sustained signalling.

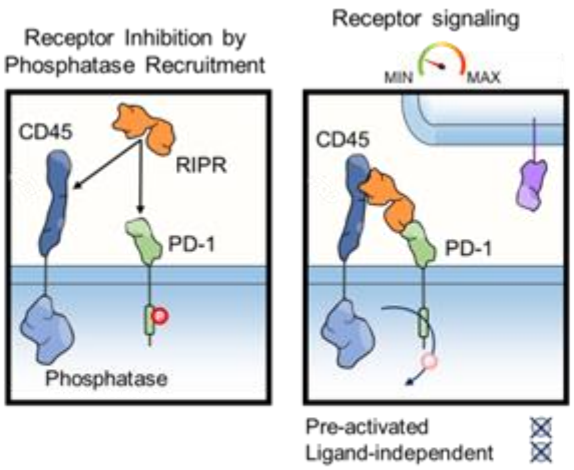

Fig. 1 | Receptor Inhibition by Phosphatase Recruitment. RIPR combines checkpoint blockade with CD45 recruitment. CD45 recruitment dephosphorylates receptors such as PD-1.

Aim 1: Determine the relative signalling potency of IRs in T cells
IRs have a distinct organisation of inhibitory motifs in their cytoplasmic domain, ranging from non-conventional single tyrosine (Tyr) motifs to a combination of two or more "classic" inhibitory motifs like ITIMs. We will perform systematic screens to determine the ability to suppress T cell function by various IRs, including PD-1, TIGIT, BTLA, TIM-3, CTLA-4, LAIR-1, ILT-2 and ILT-4. In addition, we will compare IR signalling potencies in the presence and absence of IR-ligand binding using surrogate receptor-ligand pairs.

Aim 2: Development of RIPR-based molecules to inhibit inhibitory receptors
Bispecific diabodies that recruit CD45 phosphatase to IRs, such as PD-1 and CTLA-4, were found to potentiate T cell responses. We aim to extend this concept to target additional IRs, including BTLA, TIGIT and TIM-3, which have been implicated in suppressing antitumour responses. Moreover, we will systematically test the potency of newly generated RIPR proteins using various anti-CD45 nanobodies. This information will be used to guide the design of future antagonists of checkpoint receptor signalling with strong potential for therapeutic applications.

In summary, we anticipate this project will provide: a comprehensive map of the relative potency and molecular mechanisms of major inhibitory receptors in T cells; validation of RIPR as a generalisable platform for intracellular checkpoint blockade; and, proof-of-concept for a new class of biologics that potentiate T cell responses by rewiring signalling, complementing or surpassing existing antibody therapies.
This work will deepen our understanding of inhibitory signalling in T cells, establish innovative approaches to overcome checkpoint-mediated suppression, and provide a foundation for translational strategies to improve cancer immunotherapy.

Disease Relevance

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

Key Technology

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

Training Opportunities

The candidate will receive training in molecular biology, protein design and expression, biophysical characterisation of protein interactions and various cellular assays. Moreover, the candidate will be trained in protein engineering, library design and selection using yeast display. T cell signalling assays will be used to determine the activity of newly generated RIPR molecules, providing an opportunity for training in flow cytometry and MS, among others. This training will allow the candidate to drive fundamental and applied research in academia and industry. The candidate will have full access to the facilities and resources available within the Department and the broader community at the University of Oxford.

Key Publications

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

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1.9 Discovery of potent agonist peptides for tumour-reactive T cells

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Project Overview

Abstract

T cells survey their environment through the T cell receptor (TCR), recognising peptides presented by the major histocompatibility complex (MHC). The strength and nature of the T cell response are shaped by both the TCR and co-receptors, including activating (e.g. CD28) and inhibitory checkpoint receptors (e.g. PD-1, CTLA-4). While single-cell sequencing has enabled identification of clonally expanded TCRs from tumour-infiltrating lymphocytes (TILs), discovering their cognate agonist peptides remains a critical bottleneck. This project aims to establish a robust framework for identifying potent agonist peptides recognised by effector and regulatory T cells, with a particular focus on TCRs derived from tumour-reactive TILs.

Project Overview

Identifying antigens recognised by the TCR is challenging given the extreme diversity of the three individual components involved: peptide antigens, TCR and MHC. We aim to identify peptides, neoantigens and mimotopes, recognised by the TCR of clonally expanded CD8+ effector T cells in tumour settings (Fig. 1). To this end, we will engineer large (> 10^9) peptide-MHC libraries to be displayed at the surface of yeast cells, after which we will use an affinity-based screen to identify peptides recognised by TCRs of interest. This affinity-based approach will be complemented by a functional screen using an engineered system in mammalian cells. In this recently developed approach, the peptide-MHC library is fused to a CAR-like signalling module and displayed in T cells. This functional-based selection hijacks the unique sensitivity and specificity of the CD28/CD3 signalling modules to report on a productive TCR/pMHC interaction. Sorting of cells based on the upregulation of activation markers such as CD69 and CD25 will be used to isolate agonist peptides of different potency.

The combination of affinity- and activity-based selections will guide the identification of potent agonist mimotopes, self-peptides or neoantigens using custom-built algorithms to rank closely related wild-type peptides. The identification of peptides recognised by tumour-reactive T cells will facilitate their expansion and detection using peptide-MHC molecules. Moreover, following isolation or activation with agonist peptides, tumour-reactive T cells will be characterised using single-cell transcriptomics and proteomics, for example. Agonist peptide identification combined with single-cell sequencing and quantitative proteomic analysis of relevant T cells will expand our current understanding of the role of diverse T cell subsets during an anti-tumour immune response. Furthermore, the discovery of disease-related agonist peptides opens the possibility to modulate T cell responses by peptide immunisation, an essential first step towards achieving in vivo expansion and activation of tumour-specific T cells. This research plan thus aims to contribute towards the development of relevant immunotherapies in cancer settings and a better understanding of T cell function.

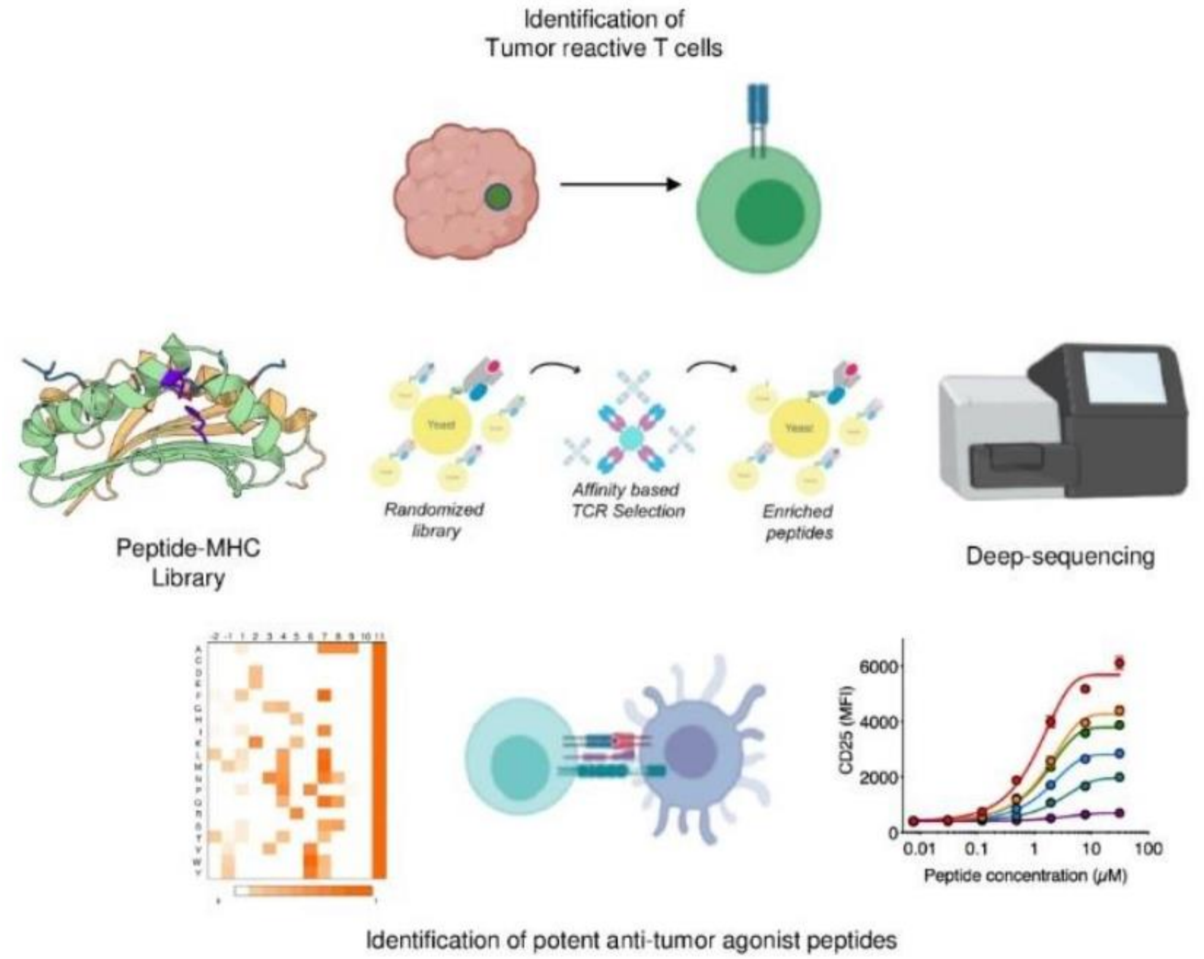

Figure 1. General overview of the experimental approach to discover peptide antigens to elicit robust anti-tumor T cell responses.

The discovery of agonist peptides is notoriously challenging and has limited the possibility of expanding tumour-reactive T cells *in vivo*. We expect that the described approach will establish a rapid and facile method to discover peptide antigens for tumour-reactive T cells. Checkpoint inhibition blockade using antibodies against PD-1 and CTLA-4 to enhance T cell activity has shown great promise in the clinic, but in most patients, this approach fails to produce durable responses. We anticipate the next stage of immunotherapy development to involve a combination of checkpoint blockade - eliciting broad but unspecific potentiation of T cell responses - with antigen-specific stimulation of tumour-reactive T cells. The identification of peptide antigens for T cells involved in anti-tumour responses is expected to guide the selection of TCRs for adoptive cell transfer and the development of high-affinity TCRs and peptide vaccines for immunotherapy.

Disease Relevance

The discovery of agonist peptides is notoriously challenging and has limited the possibility of expanding tumour-reactive T cells in vivo. We expect that the described approach will establish a rapid and facile method to discover peptide antigens for tumour-reactive T cells. Checkpoint inhibition blockade using antibodies against PD-1 and CTLA-4 to enhance T cell activity has shown great promise in the clinic, but in most patients, this approach fails to produce durable responses. We anticipate the next stage of immunotherapy development to involve a combination of checkpoint blockade - eliciting broad but unspecific potentiation of T cell responses - with antigen-specific stimulation of tumour-reactive T cells. The identification of peptide antigens for T cells involved in anti-tumour responses is expected to guide the selection of TCRs for adoptive cell transfer and the development of high-affinity TCRs and peptide vaccines for immunotherapy.

Key Technology

Protein engineering; yeast display; antigen discovery; biophysical analysis of protein-protein interactions (including SPR); flow cytometry; deep-sequencing (NGS); T cell functional assays using cell lines and primary cells; cell engineering, TCR-T

Training Opportunities

The student will receive training in molecular biology, protein design, expression, purification and biophysical characterisation and various cellular assays. Moreover, the student will be trained in protein engineering, library design and selection using yeast- and mammalian-display. T cell signalling assays will be used to validate candidate antigens, which will provide an opportunity for training in flow cytometry and RNA-seq. This training will allow the candidate to drive fundamental and applied research in academia and industry. At the end of this project, the candidate will be in a great position to lead the development of new protein drugs from conceptual design to implementation and thorough validation in an area of great interest in T cell biology and immunotherapy. The student will have full access to the facilities and resources available within the Department and across the broader community at the University of Oxford.

Key Publications

1) Gee MH, Han A, Lofgren SM, Beausang JF, Mendoza JL, Birnbaum ME, Bethune MT, Fisher S, Yang X, Bingham DB, Sibener LV, Fernandes RA, Velasco A, Baltimore, D, Schumacher TN, Khatri P, Quake SR, Davis MM, Garcia KC. Antigen identification for orphan T cell receptors expressed on tumor-infiltrating lymphocytes. (2018) Cell. Jan 25;172(3):549-563.e16.
2) Sibener LV, Fernandes RA, Kolawole EM, Carbone CB, Liu F, McAffee D, Yang D, Su DF, Yu D, Dong S, Gee MG, Jude KM, Birnbaum ME, Goddard WA, Davis MM, Groves JT, Heath JR, Evavold BD, Vale RD, Garcia KC. Isolation of a structural trigger required for TCR signaling from analysis of non-stimulatory peptide-MHC ligands. (2018) Cell. Jul; 174 (3), 672-687. e27.
3) Fernandes RA*, Li C*, Wang G, Yang X, Savvides CS, Glassman CR, Dong S, Luxemberg E, Sibener LV, Birnbaum ME, Benoist C, Mathis D, Garcia KC. Discovery of surrogate agonists for visceral fat Treg cells that modulate metabolic indices in vivo. (2020) eLife. Aug; 9:e58463
4) Sušac L, Vuong MT, Thomas C, von Bülow S, O'Brien-Ball C, Santos AM, Fernandes RA, Hummer G, Tampé R, Davis SJ. Structure of a fully assembled tumor-specific T cell receptor ligated by pMHC. Cell. 2022 Aug 18;185(17):3201-3213.e19.
5) Yang X, Garner LI, Zvyagin IV, Paley MA, Komech EA, Jude KM, Zhao X, Fernandes RA, Hassman LM, Paley GL, Savvides CS, Brackenridge S, Quastel MN, Chudakov DM, Bowness P, Yokoyama WM, McMichael AJ, Gillespie GM, Garcia KC. Autoimmunity-associated T cell receptors recognize HLA-B*27-bound peptides. Nature. 2022 Dec;612(7941):771-777.

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1.10 Unlocking antibody-dependent cellular phagocytosis to treat hepatocellular carcinoma

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Project Overview

Background. Hepatocellular carcinoma (HCC) is the fourth most common cancer worldwide and one of the fastest growing in the UK. The HCC leukocyte tumour microenvironment (TME) is rich in phagocytes, including Tissue-Resident Kupffer cells, monocyte-derived macrophages (MDM), monocytes, neutrophils, and dendritic cells. How we can best engage these phagocytes to kill tumour cells or other components of the tumour microenvironment and thus control or even clear HCC needs to be addressed. Depleting monoclonal antibodies (mAbs) are usually thought to work via antibody-dependent cellular cytotoxicity (ADCC), but they also trigger antibody-dependent cellular phagocytosis (ADCP), where Fcγ receptor–expressing phagocytes engulf antibody-opsonised targets. However, the cells that drive ADCP and the mechanisms that restrict this process in HCC, are not fully understood, hindering therapeutic exploitation. Our recent work in brain tumours showed that a unique and highly phagocytic population of FcγR-expressing MDMs was essential for the activity of depleting mAbs. Importantly, their tumoricidal phagocytic activity was strengthened following Treg depletion, suggesting that a Treg-MDM crosstalk regulates ADCP. Here, you will build upon this insight to explore how to utilise ADCP within the complex environment of the liver where an array of different phagocytic cells resides. A better understanding of ADCP and its effector cells within the TME has the potential for devising novel depleting antibody combinations that unleash the phagocytic potential of the myeloid compartment in HCC to clear tumours.

This proposal addresses three critical questions:

1) Which FcγR-expressing cells are the most phagocytic and what is their origin?
2) Which cells mediate ADCP, and how are they regulated?
3) How can ADCP be best exploited therapeutically in HCC?

Aims.

1) Assess the FcγR landscape in HCC and characterise the phenotype, dynamics and transcriptome of FcγR-expressing leukocytes;
2) Interrogate which cells mediate ADCP in vivo and how this mechanism is regulated; and
3) evaluate novel immunotherapy agents and rational combinations to treat HCC.

Methods. Mouse models of multifocal HCC and human HCC samples. Single-cell technologies will reveal transcriptional profiles and phagocytic receptors in human and murine myeloid cells of HCC. Novel multispecific mAbs targeting tumour cells, alongside combinatorial approaches, will be evaluated using mouse models and human tissue samples.

How the results of this research will be used: This work will identify regulatory mechanisms and actionable targets that enhance ADCP in HCC, enabling rational depleting-mAb combinations that unleash the phagocytic potential of the liver myeloid compartment to control or clear tumours.

Disease Relevance

ADCP is a fundamental mechanism governing the action of mAbs. Immunotherapy for HCC currently benefits only a subset of patients, and resistance often arises. Thus, this treatment approach needs to be refined. Myeloid cells are highly abundant and intrinsically phagocytic within solid tumours, particularly in HCC; harnessing this capacity offers a promising route to new mAb-based therapeutics that could synergise with T-cell–targeted agents (anti-PD-1/L1, anti-CTLA-4). However, the effector subsets and regulatory pathways governing ADCP in HCC remain poorly defined. This Fellowship will delineate the cellular and molecular control of ADCP in HCC and use these insights to develop and preclinically test ADCP-enhancing therapeutics with a clear path towards future clinical translation.

Key Technology

This project will involve the use of mouse models and single cell technologies to understand the phagocytic landscape of HCC. This implies the use of flow cytometry, single cell RNA sequencing and spatial transcriptomics.

Training Opportunities

The Galvez-Cancino Lab is a newly established group at the NDM Centre for Immuno-Oncology, University of Oxford. We combine fundamental and translational immunology to understand and therapeutically harness antibody-dependent cellular phagocytosis (ADCP). Our current focus is hepatocellular carcinoma (HCC): we seek to chart the tumour phagocytic landscape and design ADCP-driven interventions that improve patient outcomes.

Training and environment. We tailor training to the aims of each PhD. Opportunities include hands-on work with mouse models of cancer, bioinformatics training, and frequent interactions with clinicians and basic scientists across Oxford, equipping trainees with a deep, practical understanding of translational research.

Key Publications

1) Gálvez-Cancino F., Navarrete M., Beattie G., Puccio S., Conde-Gallastegi E., Foster K., Morris Y., Sahwangarrom T., Karagianni D., Liu J., Lee A.J.X., Garyfallos D.A., et al. Regulatory T cell depletion promotes myeloid cell activation and glioblastoma response to anti-PD1 and tumor-targeting antibodies. Immunity. 2025; 58(5).
2) Gálvez-Cancino F.*, Simpson A.P.*, Costoya C., Matos I., Qian D., Peggs K.S., Litchfield K., Quezada S.A. Fcγ receptors and immunomodulatory antibodies in cancer. Nature Reviews Cancer. 2024; 24(1):51–71. *Co-first authors*
3) 16. Reading J.L.*, Gálvez-Cancino F.*, Swanton C., Lladser A., Peggs K.S., Quezada S.A. (1st Author). The function and dysfunction of memory $CD8^+$ T cells in tumor immunity. Immunological Reviews. 2018; 283(1):194–212. *Co-first authors*
4) Menares E.*, Gálvez-Cancino F.*, Cáceres-Morgado P., Ghorani E., López E., Díaz X., Saavedra-Almarza J., Figueroa D.A., Roa E., Quezada S.A., Lladser A. Tissue-resident memory $CD8^+$ T cells amplify anti-tumor immunity by triggering antigen spreading. Nature Communications. 2019; 10(1):4401. *Co-first authors*
5) Gálvez-Cancino F.*, López E., Menares E.*, Díaz X., Flores C., Cáceres P., Hidalgo S., Chovar O., Alcántara-Hernández M., Borgna V., Varas-Godoy M., Salazar-Onfray F., Idoyaga J., Lladser A. Vaccination-induced skin-resident memory $CD8^+$ T cells mediate strong protection against cutaneous melanoma. Oncoimmunology. 2018; 7(7):e1442163. *Co-first authors*

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1.11 Mapping the spatial landscape and immune interactome of phagocytes in hepatocellular carcinoma

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Project Overview

Background. Hepatocellular carcinoma (HCC) is a leading cause of cancer mortality worldwide and one of the fastest-rising cancers in the UK. The HCC tumour microenvironment (TME) is rich in phagocytes, including tissue-resident Kupffer cells, monocyte-derived macrophages (MDMs), monocytes, neutrophils and dendritic cells. How best to engage these phagocytes to kill tumour cells, or other components of the TME, and thereby control or clear HCC remains an open question. Depleting monoclonal antibodies (mAbs) are usually thought to work via antibody-dependent cellular cytotoxicity (ADCC), but they also trigger antibody-dependent cellular phagocytosis (ADCP), in which Fcγ receptor (FcγR)–expressing phagocytes engulf antibody-opsonised targets. However, the phagocyte subsets that drive ADCP in HCC, and the host pathways regulating this process, are not fully understood, providing a road-block to therapeutic exploitation. Our recent work in brain tumours showed that a unique, highly phagocytic population of FcγR-expressing MDMs was essential for the activity of depleting mAbs. Importantly, their tumouricidal phagocytic activity was strengthened following regulatory T-cell (Treg) depletion, suggesting a Treg–MDM crosstalk that regulates ADCP. Building on these insights, this project will map the spatial organisation of phagocytes in HCC TME to define their immune interactome and to identify regulatory mechanisms controlling ADCP. We are seeking a dry-lab bioinformatics student, or a candidate who wishes to combine bioinformatics with se wet-lab experiments.

This project addresses two critical questions:
1) Which FcγR-expressing cells are present within the HCC TME and what is their spatial distribution?
2) Which immune interactions regulate the phagocytic capacity of FcγR-expressing cells within the liver TME?

Aims.
1) Use single-cell RNA sequencing and spatial tissue-based transcriptomics to define the FcγR landscape in HCC and characterise the phenotype of FcγR-expressing leukocytes;
2) interrogate the key immune interactions that regulate the phagocytic capacity of myeloid cells using cell–cell communication algorithms.

Methods. We will use mouse models of multifocal HCC and human HCC samples. Single-cell and spatial technologies will reveal transcriptional profiles and phagocytic receptors in human and murine myeloid cells in HCC. This is primarily a bioinformatics (dry-lab) position with the option to incorporate targeted wet-lab work.

How the results will be used. This work will identify regulatory mechanisms and actionable targets that enhance ADCP in HCC, enabling the rational design of novel immunotherapies that unleash the phagocytic potential of the liver myeloid compartment to control or clear tumours.

Disease Relevance

ADCP is a fundamental mechanism governing the action of mAbs. Immunotherapy for HCC currently benefits only a subset of patients, and resistance often arises. Thus, this treatment approach needs to be refined. Myeloid cells are highly abundant and intrinsically phagocytic within solid tumours, particularly in HCC; harnessing this capacity offers a promising route to new mAb-based therapeutics that could synergise with T-cell–targeted agents (anti-PD-1/L1, anti-CTLA-4). This studentship will delineate the cellular and molecular control of ADCP in HCC and use these insights to develop and preclinically test ADCP-enhancing therapeutics with a clear path towards future clinical translation.

Key Technology

- This project involves the use of single cell technologies and spatial transcriptomics to understand the phagocytic landscape of HCC.
- This project is suitable for a person who wants to learn bioinformatic analysis of single cell and spatial omics data sets.

Training Opportunities

The student will join a dynamic and lively team of biologists in the Galvez-Cancino and McKeating laboratories that bring complementary expertise in macrophage biology and spatial transcriptomics. The Galvez-Cancino Lab in the NDM Centre for Immuno-Oncology combines fundamental and translational immunology to understand and therapeutically harness antibody-dependent cellular phagocytosis. The McKeating lab in the Target Discovery Institute studies hepatitis viruses and uses single cell spatial transcriptional analyses of infected liver tissue to understand viral driven pathogenic and oncogenic processes.

Training and environment. We tailor training to the aims of each PhD. Opportunities include hands-on work with mouse models of cancer, bioinformatics training, and frequent interactions with clinicians and basic scientists across Oxford, equipping trainees with a deep, practical understanding of translational research.

Key Publications

1) Gálvez-Cancino F., Navarrete M., Beattie G., Puccio S., Conde-Gallastegi E., Foster K., Morris Y., Sahwangarrom T., Karagianni D., Liu J., Lee A.J.X., Garyfallos D.A., et al. Regulatory T cell depletion promotes myeloid cell activation and glioblastoma response to anti-PD1 and tumor-targeting antibodies. Immunity. 2025; 58(5).
2) Gálvez-Cancino F.*, Simpson A.P.*, Costoya C., Matos I., Qian D., Peggs K.S., Litchfield K., Quezada S.A. Fcγ receptors and immunomodulatory antibodies in cancer. Nature Reviews Cancer. 2024; 24(1):51–71. *Co-first authors*
3) Menares E.*, Gálvez-Cancino F.*, Cáceres-Morgado P., Ghorani E., López E., Díaz X., Saavedra-Almarza J., Figueroa D.A., Roa E., Quezada S.A., Lladser A. Tissue-resident memory $CD8^+$ T cells amplify anti-tumor immunity by triggering antigen spreading. Nature Communications. 2019; 10(1):4401. *Co-first authors*
4) Mapping episomal and integrated hepatitis B virus transcriptomes uncovers heterogeneous gene expression and endogenous drug resistance. Harris JM, Lok J, Wand N, Magri A, Tsukuda S, Wu Y, Ng E, Jennings D, Elshenawy B, Balfe P and McKeating JA. Nat Comms 2025, in press.
5) Characterisation of HBV and co-infection with HDV and HIV through spatial transcriptomics. Cross, A. Harris, JM. Arbe-Barnes E, Nixon, C, Dhairyawan R, Hall A, Quaglia A, Issa F, Kennedy PTF, McKeating JA, Gill US, Peppa D. eGastroenterology 2024 doi:10.1136/egastro-2024-100067.

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1.12 Dissecting the role of tumor-draining lymph nodes in modulating tumor-specific T cell immunity in metastatic cancer patients

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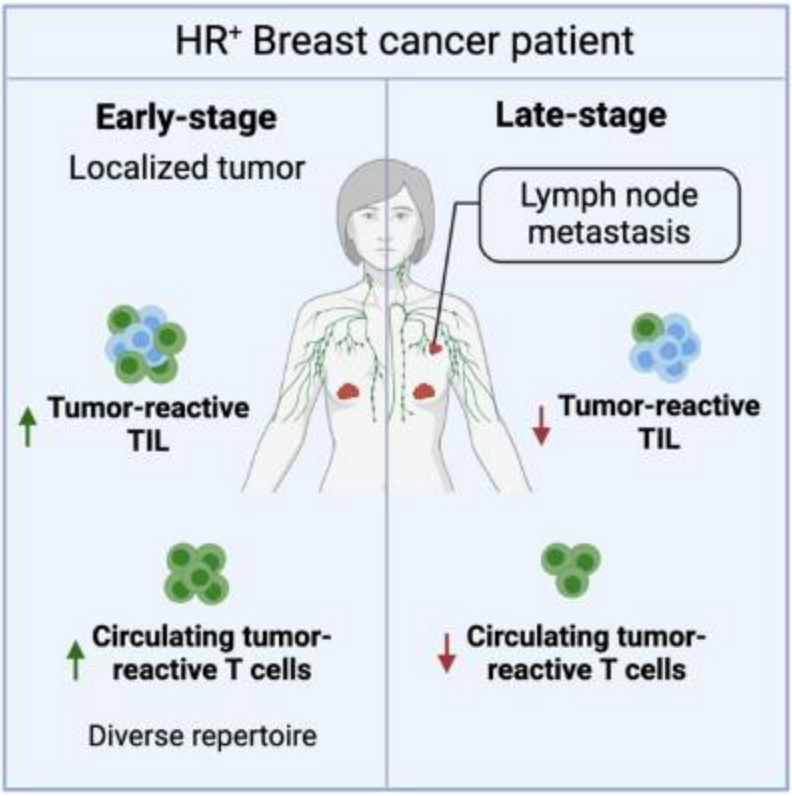
Project Overview

Tumor-specific T cell immunity is central to cancer control, yet our recent work showed that, in hormone-receptor–positive (HR+) breast cancer, it appears compromised in patients with lymph node involvement. We have showed that patients with lymph node metastasis exhibit an impaired antitumor CD8+ T-cell response, in contrast to early-stage patients who retain a more diverse, potentially exploitable repertoire (Figure 1). This observation suggest that nodal dissemination coincides with, or drives, systemic defects in tumor-specific T-cell generation, trafficking, or persistence.



Tumor-draining lymph nodes (TDLNs) are the principal sites where tumor antigens are transported and presented, priming tumor-specific T cells, but they are also frequent routes of metastatic spread. We could not determine, in our previous study, if there was any causal relation between the presence of lymph node metastasis and the impaired tumor immunity. Tumor-invaded lymph nodes have been shown to have increased regulatory T cells (Treg), which could potentially impair the generation of antitumor responses in these lymph nodes, a hypothesis that hasn't been thoroughly tested.

The aim of this proposal is to study the tumor-specific T cell response within lymph nodes of patients, and how it correlates with the tumor-specific repertoire found in the tumor. By doing so, we aim to uncover whether lymph node metastasis exacerbates defects in T cell generation, trafficking, or persistence, and whether these changes contribute to the overall compromised immune surveillance seen in metastatic disease.

Disease Relevance

Cancer remains a leading cause of death worldwide. In 2022 approximately 20 million new cancer cases were diagnosed globally and nearly 9.7 million people died from the disease. These figures reflect the high disease burden, despite treatment advances. Projections indicate that by 2050, global cancer incidence could exceed 35 million new cases per year unless major preventative, diagnostic, and therapeutic gaps are addressed.

Key Technology

Single cell RNA sequencing (scRNAseq), TCR sequencing, spatial analysis of tumor tissue, flow cytometry, cell sorting (FACS), cell culture, tissue processing, bioinformatic 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) Peng Y., et al. Broad and strong memory CD4+ and CD8+ T cells induced by SARS-CoV-2 in UK convalescent individuals following COVID-19. Nat Immunol 21, 1336–1345 (2020).
4) Pinho, M.P.; Patente, T.A.; Flatow, E.A.; Sallusto, F.; Barbuto, J.A.M. Frequency determination of breast tumor-reactive CD4 and CD8 T cells in humans: unveiling the antitumor immune response. *Oncoimmunology* 8, (2019).

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1.13 Investigating Epigenetic and Epitranscriptomic regulation in Acute Myeloid Leukemia (AML)

Prof. Yang Shi & **Prof. Stefan Constantinescu**

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Project Overview

Epigenetic and epitranscriptomic changes constitute pivotal factors driving the development and progression of various human cancers, including leukemia. Recent advancements in cancer research underscore the significance of these alterations in shaping complex regulatory networks, not only contributing to the initiation and progression of leukemia but also developing resistance to therapy.

In 2004, our laboratory identified the first histone demethylase, LSD1, whose role was later revealed to be crucial in the initiation and development of several cancers, including leukemia. More recently, our group has unveiled novel RNA modifying enzymes with potential roles in leukemia, presenting exciting opportunities for therapeutic targeting. This D.Phil project aims to unravel the intricacies of epigenetic and epitranscriptomic changes in leukemia, identifying novel therapeutic targets to advance therapy for leukemia patients.

Disease Relevance

This project focuses on Acute Myeloid Leukemia (AML) and secondary AML, which present an unmet medical need.

Key Technology

Develop proficiency in essential techniques, including cell culture and handling primary cells, cloning, CRISPR/Cas9 genome editing, qRT-PCR, virus packaging, mammalian cell transduction, chromatin immunoprecipitation, and chromosome-conformation-capture.

Training Opportunities

The collaborative environment in our lab provides a rich learning experience, enhancing skills in state-of-the-art technologies.

This includes techniques for the analysis of gene regulation (ATAC-seq, ChIP-seq, chromosome-conformation- capture, RNA-seq), advanced molecular biology, genome editing, and computational biology, etc. Trainees participate in weekly internal seminars and monthly external seminars within our Institute, which keep students abreast of recent advancements in cancer research and related fields and provide opportunities for enhancing presentation skills.

Key Publications

1) Hosseini, A*., Dhall, A*., Ikonen, N., Sikora, N., Sylvain, N., Shen, YQ., Jurgensen Amaral, ML., Jiao, A., Wallner, F., Sergeev, P., Lim, YH., Yang, YQ., Vick, B., Kawabata, KC., Melnick, A., Vyas, P., Ren, B., Jeremias, I., Psaila, B., Heckman, CA+., Blanco, A+., and Shi, Y+. Perturbing LSD1 and GSK3 rewires transcription to induce AML differentiation. Nature, 2025. 642(8067): 508-518. Apr 16. doi: 10.1038/s41586-025-08915-1. *Equal contributions; +Co-correspondence.
2) Zee, B.M., Poels, K.E., Yao, C.H., Jacobus, W.D., Senior, E., Endress, J.E., Jambhekar, A., Lovitch, S.B., Ma, J.X., Dhall, A., Harris, I.S., Blanco, A., Skykes, D.B., Haigis, M.C., Michor, F., Licht, J.D., and Shi, Y. Combined epigenetic and metabolic treatments overcome differentiation blockade in AML. iScience, 2021. May 25;24(6):102651. doi: 10.1016/j.isci.2021.102651. eCollection 2021 Jun 25. PMID: 34151238
3) Blanco, AM*, +., Skyes, DB*., Gu, L*., Wu, MJ., Petroni, R.,Karnik, R., Wawer, M., Rico, J., Li, HT., Jacobus, WD., Jambhekar, A., Cheloufi, S., Meissner, A., Hochedlinger, K., Scadden, DT+., and Shi, Y+. Chromatin state barriers enforce an irreversible mammalian cell fate decision.
Cell Rep. 2021, Nov 9;37(6):109967. doi: 10.1016/j.celrep.2021.109967.
*Equal contributions; +Co-correspondence.

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1.14 Molecular Mechanisms of Cancer Cell Plasticity

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Project Overview

During development, the high plasticity of embryonic stem cells is demonstrated by their differentiation potential into all of the diverse cell types found in the adult body. As cells commit down specific lineages, their plasticity becomes restricted, meaning they progressively lose the ability to proliferate and to differentiate into other lineages. Cancer cells often break free of this restriction, and return to a more plastic, stem-like state. Cell plasticity underlies the ability of cancers to metastasize and to develop therapeutic resistance. Even genetically homogenous cancer cells can exhibit heterogeneous responses to a given stimulus, further highlighting the role of non-genetic mechanisms in enabling phenotypic variation.

The focus of this project is on diffuse intrinsic pontine glioma (DIPG), an incurable childhood brain tumour with a 2-year survival rate of less than 10%. Recent single cell profiling studies have revealed extensive non-genetic heterogeneity within DIPGs, as well as other gliomas.

Disease Relevance

DIPG is a deadly pediatric brain cancer with no cure, thus representing a critically unmet medical need.

Key Technology

Crispr screen, single cell seq, cell biological assays.

Training Opportunities

This project aims to dissect the mechanisms that underlie cell plasticity in DIPG. The student will test numerous cellular factors for their ability to modulate plasticity, and whether any of these factors can be therapeutically targeted. They will learn to establish assays to measure the in vitro differentiation potential of DIPGs, and to perform CRISPR screens to identify factors that modulate this potential. Molecular mechanisms of the candidate hits will be explored, with a focus on epigenetic and epitranscriptomic regulators. The student will learn a broad range of techniques including glioma cell culture, epigenome profiling, genome-wide CRISPR screening and bioinformatics.

Key Publications

1) Anastas, JN., Zee, BM., Kalin, JH., Kim, MH., Guo, R.,Alexandrescu, S., Blanco, MA., Giera, S., Gillespie, SM., Das, J., Wu, MH., Nocco, S., Bonal, D.M., Suva, M.L., Bernstein, BE., Alani, R., Golub, TR., Cole, PA., Filbin, MG+., and Shi, Y+. Re-programming chromatin with a bifunctional LSD1/HDAC inhibitor induces therapeutic differentiation in DIPG. Cancer Cell, 36: 528-544. +Co-correspondence.
2) Jiao, AL+., Sendinc E., Zee, B., Wallner, F, and Shi Y+. An E2 ubiquitin conjugating enzyme links di-ubiquitinated H2B to H3K27M oncohistone function. Proc. Natl. Acad. Sci. USA 2024, Nov 26;121(48):e2416614121. doi: 10.1073/pnas.2416614121. +Co-correspondence.
3) Alan L. Jiao1, Abolfazl Maghrouni2,12, Arantxa Gutierrez Velazquez3,12, Alva Annett2, Tingyu Wen1,#, Jonathan Chan4,5, Sylvain Nguyen1, Berna Bou Tayeh1, François Le Dily3, Claudia L. Kleinman2,6, Luciano Di Croce3,7,8,*, Nada Jabado2,9,10,11,**, Yang Shi1,13,** An oncohistone-ASCL1 axis drives plasticity and gliomagenesis. Nat. Commun. Under revision. *

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Theme 2. Infection Immunology & Disease

2.1 HIV-1 nuclear transport and host genome integration

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Project Overview

Human immunodeficiency virus type 1 (HIV-1) is the causative agent behind acquired immunodeficiency syndrome (AIDS) that currently has no cure or vaccine. While antiviral treatments are effective, the rise of drug-resistant strains has become a growing concern. HIV-1 primarily infects the immune system, targeting CD4+ T cells and macrophages and is a lentivirus known to be able to infect non-dividing cells, requiring it to exploit nuclear transport mechanisms. This process is dependent on the viral capsid. The HIV capsid is a conical structure that contains the genomic material of the virus, and protect it from host innate immunity. How does the capsid navigate through the nucleus and arrive at the site of host chromatin for integration? When and where does the capsid uncoate to release its viral genome? What triggers capsid uncoating? These are key questions to understand HIV-1 infection, in particular in the cell nucleus.

We aim to apply multi-imaging modalities to investigate uncoating and nuclear transport of HIV-1. These will include super-resolution fluorescence microscopy (including the newest MINFLUX system), Focused Ion Beam and Scanning electron microscopy (cryoFIB/SEM), cryo-electron microscopy and cryo-electron tomography (cryoEM/ET). The viral core and host factors will be fluorescently tagged using non-natural AA and click chemistry and infection will be monitored from viral attachment to nuclear import. The sample will be cryo-preserved and imaged by cryoEM/ET and cryoFIB/SEM. The combination of these imaging techniques will yield unparalleled structural information of the HIV infection process within the native cells, providing the framework for development of novel therapeutics targeting HIV infection in the future.

Disease Relevance

- HIV-1
- retrovirus infection

Key Technology

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

Training Opportunities

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

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

Key Publications

1) Hou Z, Shen Y, Fronik S, Shen J, Shi J, Xu J, Chen L, Hardenbrook N, Engelman AN, Aiken C, **Zhang P*** (2025) HIV-1 nuclear import is selective and depends on both capsid elasticity and nuclear pore adaptability. *Nat Microbiol.* 10(8):1868-1885.
2) Hou Z, Nightingale F, Zhu Y, MacGregor-Chatwin C, **Zhang P*** (2023) Structure of native chromatin fibres revealed by Cryo-ET in situ. *Nature Communications* 14 (1), 6324
3) Ni T, Zhu Y, Yang Z, Xu C, Chaban Y, Nesterova T, Ning J, Böcking T, Parker MW, Monnie C, Ahn J, Perilla JR, Zhang P* (2021) Structure of native HIV-1 cores and their interactions with IP6 and CypA. *Sci Adv* 7(47):eabj5715.
4) Ni T, Gerard S, Zhao G, Dent K, Ning J, Zhou J, Shi J, Anderson-Daniels J, Li W, Jang S, Engelman AN, Aiken C, **Zhang P*** (2020) Intrinsic curvature of HIV-1 CA hexamer underlies capsid topology and interaction with cyclophilin A. *Nat Struct Mol Biol* **27,** 855–862.
5) Zhao G., Perilla J.R., Yufenyuy E.L., Meng X., Chen B., Ning J., Ahn J., Gronenborn A.M., Schulten K.*, Aiken C.* and **Zhang P.*** (2013) Mature HIV-1 Capsid Structure by Cryo-electron Microscopy and All-atom Molecular Dynamics. *Nature* 497(7451):643-6

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2.2 Characterizing the ultrastructure of coronavirus replication complexes using in-situ cryo-Electron Tomography

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Project Overview

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

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

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

Disease Relevance

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

Key Technology

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

Training Opportunities

This project offers training opportunities in:

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

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

Key Publications

1) Georg Wolff *et al.* A molecular pore spans the double membrane of the coronavirus replication organelle. *Science* (2020).
2) Wing, P.A.C.*, et al.* Hypoxic and pharmacological activation of HIFs inhibits SARS-CoV-2 infection of lung epithelial cells. *Cell Reports* (2021).
3) Staller, E., Carrique, L., Swann, O.C. *et al.* Structures of H5N1 influenza polymerase with ANP32B reveal mechanisms of genome replication and host adaptation. *Nat Commun* **15**, 4123 (2024).
4) Huang, Y., Wang, T., Zhong, L. *et al.* Molecular architecture of coronavirus double-membrane vesicle pore complex. *Nature* **633**, 224–231 (2024).

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2.3 Next-Generation Polymeric Nanocarriers for Mucosal mRNA Vaccination

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Project Overview

Despite the milestones in vaccine development, vaccines for high-priority pathogens including respiratory syncytial virus (RSV), influenza (including pandemic strains), and tuberculosis (TB) have limited efficacy. Vaccines delivered directly to mucosal barrier sites are envisioned to confer better local protection and/or produce superior long-term protection, but only a handful of mucosal vaccines have been approved. Realizing the potential of mucosal vaccines represents a grand challenge in engineering and medicine with invaluable humanitarian and economic impacts.

The lipid nanoparticle (LNP) based mRNA vaccines for SARS-CoV-2 exhibit strong immunogenicity, but they also exhibit unwanted reactogenicity, with risk correlated to dose and efficacy. The innate immune activation triggered by mRNA-LNPs could be mitigated by polymeric RNA delivery systems, which possess more tuneable chemistries which could be leveraged to achieve more favourable in vivo degradation profiles and cellular tropisms. However, the mucosa is largely composed of negatively charged extracellular matrix and sulfonated glycosaminoglycans, leading to unpackaging of RNA from polyplexes. Furthermore, thick mucus layers trap or degrade nanoparticles, enzymes break down proteins and nucleic acids, and epithelial barriers restrict penetration. We hypothesize that hydrophobic ionizable polylipidoids derived from pABOL can be engineered as resilient mucosal mRNA vaccine delivery vehicles for mRNA.

- **Combinatorial Polylipidoid Synthesis and Chemical Characterization.** We will utilize established combinatorial chemistry to generate a library of pABOL-derivative ionizable polylipidoids with different amine head groups, alkyl chain lengths, and branching structure. Polylipidoids will be characterized via gel permeation chromatography (GPC) and nuclear magnetic resonance (NMR).
- **Multi-objective optimisation of formulation chemistry.** We will rationally screen polylipidoids for their ability to form stable polyplexes with mRNA, with or without the inclusion of traditional LNP components such as helper lipids. The resulting shape, size, surface charge, pKa of the ionizable chemical group, and encapsulation efficiency of RNA will be evaluated using small-angle X-ray scattering (SAXS), dynamic light scattering, electrophoretic mobility (zeta potential), TNS assay, and the ribogreen assay, respectively. Additionally, we will perform automated in-house assessments of LNP physicochemical properties at the single-particle level using Single Particle Automated Raman Trapping Analysis (SPARTA). To functionally screen candidates, we will utilize high-throughput methodologies such as air-liquid interface transwell assays which are state-of-the-art methods for quantifying nanoparticle transport. These data will be integrated using multi-objective optimisation strategies to identify polylipidoid chemistries and material properties which promote increased delivery through mucosal layers.
- **Preclinical Validation.** Promising formulations will be progressed to evaluation in precision human lymph node slices and pre-clinical models. They will be assessed *in vitro* through stability tests under different environmental stresses to ascertain shelf-life and ideal packaging conditions. We will demonstrate *in vivo* mRNA expression from the polylipidoids following intranasal delivery in small animals via *in vivo* bioluminescence imaging. Thereafter, animal models of influenza challenge will be performed comparing intranasal and intramuscular single dose regimens with prime-boost regimens using polylipidoids, pABOL, and conventional LNPs. We will measure antibody titers and profiling antigen-presenting cells at

the injection site and distally, via immunoassays conducted on harvested blood and tissue samples.

Disease Relevance

The route of vaccine delivery plays a crucial role in the design of vaccines targeting respiratory pathogens. Immunity in the upper respiratory tract (URT) against respiratory syncytial virus (RSV) and influenza virus has been shown to provide protection against both infection and disease. Local immune components—including tissue-resident memory T and B cells (TRM and BRM) as well as neutralizing IgA—enable rapid responses that restrict viral replication at the point of entry. While intramuscular (IM) vaccination, the standard approach for most licensed influenza vaccines and the newly approved RSV vaccines, confers protection against disease, it is generally ineffective at inducing robust mucosal immunity. Evidence from both clinical and preclinical studies demonstrates that mucosal delivery of influenza and RSV vaccines more effectively elicits mucosal immune responses, which strongly correlate with protective outcomes.

Key Technology

The Stevens group has developed advanced polyelectrolyte complex (polyplex) RNA delivery formulations based on the linear bioreducible polymer poly(1,4-aminobutanol-co-cysteamine bisacrylamide) (pABOL; Figure 3). pABOL forms polyplexes with RNA via electrostatic interactions, enabling intracellular uptake and cytoplasmic release of cargo. pABOL achieves target protein translation at levels similar to LNPs when administered intramuscularly and has been clinically tested for self-amplifying mRNA delivery in SARS-CoV-2. Due to its rapidly degradable disulfide bond backbone, pABOL results in lower systemic cytokine activation, and a reduced risk of adverse effects. Polyplexes can be formulated in aqueous buffers, easily lyophilised, and are capable of small interfering RNA (siRNA), anti-sense oligonucleotide (ASO), messenger RNA (mRNA), saRNA, and ribonucleoprotein (RNP) delivery in a wide array of cell types. This contrasts with ethanol-dependent lipid formulations which require dialysis after formulation, evaporate rapidly during handling, and have limited storage stability. As hydrophobicity is associated with increased transfection efficiency, we envision that synthetically modified derivatives of pABOL can be generated as polymer-lipid hybrid formulations (polylipidoids) which have increased hydrophobicity compared to unmodified pABOL. We will increase the hydrophobicity of pABOL-derivatives by modifying the linear pABOL backbone with alkyl tails, or via formulating ionizable pABOL-derivative structures with helper lipids found in traditional LNP formulations such as DSPC and cholesterol. This is expected to provide increased resistance to unpackaging in negatively charged mucosal layers, without increased innate immune activation. We have a large suite of techniques available for generating and benchmarking a vast library of polylipidoid formulations. These include SAXS, small angle neutron scattering (SANS), SPARTA, and DLS for characterization, in addition to automated liquid handling for polyplex formulation, high throughput cell transfection, and machine learning approaches for data analysis.

Training Opportunities

The student will benefit from a highly supportive and multidisciplinary training environment through joint supervision between the Lambe group and the Stevens group. In Professor Lambe's lab, the student will gain hands-on experience in vaccine immunology and cutting-edge RNA delivery research, with a focus on mechanistic studies of cellular uptake and antibody generation. Training will cover experimental design, data interpretation, and state-of-the-art analytical techniques, while fostering independence in developing and testing novel hypotheses. The Stevens group will provide complementary expertise in advanced biomaterials, high-throughput screening, and structure–function characterization, offering access to a diverse suite of techniques such as SAXS, SANS, SPARTA, and DLS, as well as machine learning tools for formulation benchmarking.

Both groups share a strong track record of mentoring students and cultivating collaborative, inclusive research cultures. At the outset, the student will receive comprehensive induction and tailored technical training, followed by regular one-to-one supervision meetings and opportunities to present results during lab meetings. Cross-group integration will encourage the student to draw on the complementary expertise of both teams, fostering a broader perspective on translational biomaterials research. Beyond laboratory skills, the student will participate in journal clubs, seminars, and interdisciplinary workshops, building confidence in scientific communication and critical analysis. Collectively, this dual training environment will provide the student with both the depth and breadth of expertise needed to thrive in RNA therapeutics research, while supporting their professional development through mentorship, peer learning, and engagement with a vibrant, collaborative scientific community.

Key Publications

1) C. Bissett, …, T. Lambe. Systemic prime mucosal boost significantly increases protective efficacy of bivalent RSV influenza viral vectored vaccine. NPJ Vaccines (2024). 10.1038/s41541-024-00912-1
2) S. M. Murray, …, T. Lambe,…, N.M. Provine. Dosing interval is a major factor determining the quality of T cells induced by SARS-CoV-2 mRNA and adenoviral vector vaccines. Sci. Immunol. (2025). 10.1126/sciimmunol.adu4610
3) P. Gurnani, …, M.M. Stevens, C. Alexander. An improved synthesis of poly(amidoamine)s for complexation with self-amplifying RNA and effective transfection. Polym. Chem. (2020). 10.1039/D0PY00912A
4) P.F. McKay, …, M.M. Stevens, …, R.J. Shattock. Polymer formulated self-amplifying RNA vaccine is partially protective against influenza virus infection in ferrets. Oxf Open Immunol. (2022). 10.1093/oxfimm/iqac004
5) A.K. Blackney, …, M.M. Stevens. Big Is Beautiful: Enhanced saRNA Delivery and Immunogenicity by a Higher Molecular Weight, Bioreducible, Cationic Polymer. ACS Nano (2020). https://doi.org/10.1021/acsnano.0c00326

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2.4 Understanding the impact of RNA metabolism on vaccine efficacy.

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Project Overview

Despite recent milestones in therapeutics and vaccines, there remains a need for better approaches against many endemic and epidemic prone pathogens (e.g. influenza, novel coronaviruses and RSV). However, realizing the future potential of vaccines will ultimately rely on better fundamental understanding of how vaccines work.

Recent advances have identified a critical role for host RNA metabolic pathways in particular those regulating post-transcriptional editing, such as methylation and adenylation, to impact mRNA half-life and vaccine efficacy[1]. Using primary mucosal derived cell cultures, and relevant animal models, we will treat defined cell types with Lipid nanoparticle encapsidated mRNA constructs or replication deficient viral vectors. Sequencing RNAs within single cells (scRNAseq) using recently developed long-read methods[2] will generate cell type maps of transcript usage, isoform switches in innate pathways, antigen processing modules, and translation control. Integration of these data will identify specific isoform modules (e.g., RIG I/MDA5 vs TLR7/9 engagement; STING axis; mTOR/4E BP translation control; splicing factor networks) and key pathways which drive immunogenicity. These studies will enable strategies to rationally augment vaccine immunogenicity and limit off-target effects.

Approaches will include:

Splice/UTR control: use of CRISPRi/a or splice modulating oligos to shift isoforms; design the vaccines with optimal 5' or 3′flanking regions (Untranslated regions and polyadenylation sequences) and codon usage to improve RNA stability and target antigen expression.

Innate sensing balance: add nucleic acid or small molecule agonists of RIG I, TLR7/9, or STING to modulate vaccine uptake and immunogenicity
We will validate these results in preclinical animal models and test baseline versus optimized mRNA and viral vector formulations. Key endpoints will include the magnitude and durability of immunity; helper T cell induction, the breadth of the $CD8^+$ T cell response (polyfunctionality), and serum neutralizing antibodies. Optimized vaccine constructs will be selected for advanced preclinical studies, including influenza challenge models. This follow-on work will generate transformative vaccines.

1) Krawczyk, P. S. et al. Re-adenylation by TENT5A enhances efficacy of SARS-CoV-2 mRNA vaccines. Nature 641, 984–992 (2025). https://doi.org/10.1038/s41586-025-08842-1
2) Liu, Y. et al. High-plex protein and whole transcriptome co-mapping at cellular resolution with spatial CITE-seq. Nat Biotechnol 41, 1405–1409 (2023). https://doi.org/10.1038/s41587-023-01676-0

Disease Relevance

Despite impressive progress in vaccine technologies, significant challenges remain for pathogens that cause recurrent seasonal outbreaks or pose pandemic threats such as Influenza viruses, novel coronaviruses, and RSV. These viruses continue to evade immune responses, while other mucosal transmitted agents such as parainfluenza, metapneumovirus, and emerging zoonoses (e.g. Nipah, avian influenza) represent ongoing risks. A deeper mechanistic understanding of how vaccines engage innate sensors and shape adaptive responses is essential to build next-generation vaccines. By systematically mapping transcript isoform usage and innate pathway activation in primary mucosal cell cultures, our work will uncover determinants of immunogenicity that relevant to respiratory pathogens. This knowledge will inform strategies to elicit stronger mucosal and systemic immunity, including broader $CD8^+$ T cell repertoire and durable neutralizing antibodies.

The approaches described here are transferable to other high-priority diseases where effective vaccines remain elusive. Thus, the proposed studies have direct disease relevance across endemic respiratory infections, and pandemic-prone viruses.

Key Technology

- Primary mucosal derived cell cultures
- Relevant animal models (preclinical models, influenza challenge models)
- Single-cell RNA sequencing (scRNAseq)
- Long-read sequencing methods (e.g., spatial CITE-seq)
- CRISPRi/a (CRISPR interference/activation)
- Splice-modulating oligonucleotides
- Redesign of vaccine antigen UTRs and polyadenylation sequences
- Codon usage optimization
- Nucleic acid or small-molecule agonists targeting innate sensors (ISG-15, RIG-I, TLR7/9, STING)
- Antigen structure engineering
- Dose spacing strategies
- In vitro antigen presentation assays
- T cell priming assays

Training Opportunities

The student will join a dynamic and lively team of biologists in the Lambe and McKeating laboratories that bring complementary expertise in vaccine design and spatial transcriptomics. The Lambe Lab in the Oxford Vaccine Group combines fundamental and translational immunology to design vaccines. The McKeating lab in the Target Discovery Institute studies hepatitis viruses and uses single cell spatial transcriptional and long-read sequencing to study infected liver tissue to understand viral driven pathogenic and oncogenic processes.

1. Core scientific training:

- To learn new techniques in the areas of vaccine candidate testing and single cell transcriptomics and in vivo experimental work.The project may involve some or all of the following techniques: organoid and ALI set-up, Cellular immune assays (ELISpot, FACS & Intracellular Cytokine Staining (ICS)), Humoral immune assays (ELISA, FACS & Cultured ELISpot)
- All students will be expected to analyse, interpret and present their data internally This project will provide a broad range of skills with a unique insight into translational research.

2. Transferrable skills:

- To promote team working and leadership qualities by becoming involved in lab meetings, undergraduate supervision and teaching (not within first year), integral to their future success as an academic researcher.
- We will provide training in health and safety, research ethics and project management.
- We will endeavour to continually improve the student's communication skills (written and oral) and knowledge via regular 1-1 progress meetings, joint publications in international journals etc.

3. Career development:

- To develop a firm understanding of the expertise, reagents and critical mass of novel data required to support the development of new grants/projects.
- To gain first-hand experience in paper and grant writing.
- To encourage the student to network in the virology and immunology fields, mainly through the host labs' collaborations and attendance/presentation at conferences and workshops.

4. Knowledge transfer:

- Develop public outreach abilities through involvement in a range of activities organised by The University of Oxford, e.g. school visits and talks to the local community.

Key Publications

1) Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. M Voysey, et al., The Lancet 397 (10269), 99-111
2) Systemic prime mucosal boost significantly increases protective efficacy of bivalent RSV influenza viral vectored vaccine.Bissett C et al., NPJ Vaccines. 2024 Jun 26;9(1):118. doi: 10.1038/s41541-024-00912-1.
3) MAIT and other innate-like T cells integrate adaptive immune responses to modulate interval-dependent reactogenicity to mRNA vaccines. Amini A, et al., Sci Immunol. 2025 Aug 29;10(110):eadu3337. doi:10.1126/sciimmunol.adu3337. Epub 2025 Aug 29.
4) Multi-omics analysis reveals COVID-19 vaccine induced attenuation of inflammatory responses during breakthrough disease. Drury RE, et al., Nat Commun. 2024 Apr 22;15(1):3402. doi: 10.1038/s41467-024-47463-6. PMID: 38649734
5) Mapping episomal and integrated hepatitis B virus transcriptomes uncovers heterogeneous gene expression and endogenous drug resistance. James M. Harris, James Lok, Nadina Wand, Andrea Magri, Senko Tsukuda, Yanxia Wu, Esther Ng, Daisy Jennings, Badran Elshenawy, Peter Balfe, and Jane A. McKeating. Nat Comms 2025, *in press.*

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2.5 Using human genomics and experimental infection to explore how viral infection predisposes to bacterial pneumonia.

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Project Overview

There is marked variation in susceptibility to invasive infection, much of which is heritable. Genome-wide association studies (GWAS) have been highly successful in defining the human genetic component of thousands of human traits, including infection. However, in order to translate GWAS findings into a mechanistic understanding of disease biology, and ultimately into clinical care, GWAS require follow-up experiments defining the function of trait-associated genetic variation. GWAS loci are highly enriched for regulatory genetic variation. Expression quantitative trait locus (eQTL) studies map this regulatory variation, and their integration with GWAS results have been highly informative of human biology. A key feature of eQTL studies published to date has been that regulatory genetic variation is highly specific to biological context, and we have recently demonstrated that immune cell eQTL are specific to cell-type, activation state and infection status.

With Dr Charles Agoti's molecular virology group at the KEMRI-Wellcome Research Programme (Kilifi, Kenya), we are leveraging longitudinal infection surveillance for respiratory and blood stream infections in hospitalised children to perform large-scale GWAS of respiratory syncytial virus (RSV) bronchiolitis, pneumococcal disease and radiographic pneumonia (total 4,000 cases and 6,000 controls). Genetic association studies of invasive infection can be limited by unmeasured confounding variation, for instance differential infection incubation times, pre-hospital antibiotic treatment and pathogen strain variation. Controlled human challenge models of infection allows control of this confounding variation, potentially facilitating the discovery of host genetic determinants of pathogen control. We will therefore combine invasive infection GWAS with GWAS of intermediate infectious and immunological phenotypes in a well-established model of pneumococcal challenge, mapping the genetic determinants of pneumococcal carriage and density, bacterial shedding and nasal inflammation in challenge participants (n=581).

To understand the function of genetic loci linked to RSV/pneumococcal disease, we will leverage samples from controlled human infection experiments of sequential nasal RSV and pneumococcal infection collected as part of the RESPECCT study (Understanding how two common respiratory infections interact in the nose of healthy adults: Respiratory Syncytial Virus and *Streptococcus pneumoniae*). To map eQTL, we will quantify per-cell gene expression using single-cell RNA-sequencing in whole nasal cells, correlating expression with genome-wide genotyping data, facilitating mapping of cell-type specific genetic regulation. We will perform eQTL mapping in nasal cells following both primary and secondary infection challenge (180 samples from 90 challenge participants), allowing mapping of eQTL specific to both RSV and pneumococcal infection. In addition, the single cell nature of the data will allow us to infer which cells are infected with RSV, allowing us to distinguish genetic regulation that is driven by viral infection from changes in uninfected cells driven by respiratory tract inflammation.

Finally, we will integrate the genetic association data describing gene expression regulation, intermediate infectious and immunological phenotypes and invasive infection risk. Triangulating genetic evidence across these phenotypes will allow us to causally implicate genes in a defined cellular, infection and activation context in the pathogenesis of pneumonia. This will provide us with transformative insights into RSV and pneumococcal biology and identify biomarkers and drug targets to better-control respiratory infections.

Disease Relevance

Childhood infection led to 3 million deaths in 2019, a quarter of which were caused by pneumonia. RSV is the most common cause of hospitalised pneumonia in children, with Streptococcus pneumoniae the most common bacterial cause. Individually, both pathogens cause significant morbidity and mortality in children, however, there is a growing evidence that they interact, and co-infection may be a critical determinant of disease risk. Children frequently carry S. pneumoniae in the nasopharynx asymptomatically. While most pneumococcal carriage in children remains asympomatic, in a small number of children S. pneumoniae causes invasive disease. Progression to invasive pneumocccal disease is incompletely understood, but viral co-infection, especially with RSV, may play a key role in this process. Understanding the biological drivers of RSV and pneumococcal infections, and their interaction, will faclitate the rational design of novel pneumonia control strategies. The project will use human genetic tools, samples from children with hospitalised infection and controlled infection challange models to deliver this knowledge. The project is timely given the current rollout of new RSV vaccines and the next-generation pneumococcal vaccines. A fuller understanding of how these diseases interact will allow shaping of strategies to optimise the use of these tools to maximise their impact.

Key Technology

- Controlled human infection models
- Genome-wide genotyping
- Genome-wide association analysis
- Single cell RNA-seq
- Expression quatitative trait locus analysis
- Mendelian randomisation and genetic colocalisation analysis Training Opportunities

The project will provide excellent training in bioinformatics, statistical genetics and genomics. The student will learn to handle a range of genomic data types, using genotype and RNA-seq data to perform genome-wide association analysis, single-cell RNA-seq, eQTL analysis and approaches to integration of those data through Mendelian Randomisation and colocalization analysis. The project will allow robust training in R, alongside many bespoke genomic computational tools, e.g. SNPTEST2, IMPUTE2, BOLT-LMM, QTLtools. The student will also benefit from exposure to mucosal immunology techniques and the design and conduct of controlled human infection challenge experiments. The Oxford Vaccine Group is a collaborative and multidisciplinary environment of over 200 researchers, and the student will have exposure to full range of activities performed at OVG, including experimental medicine, vaccine design and immunology, vaccine trials and global child health research.

Key Publications

1) Gilchrist JJ, Kariuki SA, Watson JA, *et al.* BIRC6 modifies risk of invasive bacterial infection in Kenyan children. eLife 2022 Jul 22:11:e77461. doi: 10.7554/eLife.77461.
2) Gilchrist JJ, Makino S, Naranbhai V, *et al.* Natural Killer cells demonstrate distinct eQTL and transcriptome-wide disease associations, highlighting their role in autoimmunity. Nat Commun. 2022 Jul 14;13(1):4073. doi: 10.1038/s41467-022-31626-4.
3) Roestenberg M, Hoogerwerf M, Ferreira DM, *et al.* Experimental infection of human volunteers. Lancet Inf Dis. 2018. 2018 Oct;18(10):e312-e322. doi: 10.1016/S1473-3099(18)30177-4.
4) Mitsi E, Nikolaou E, Goncalves A, *et al.* RSV and rhinovirus increase pneumococcal carriage acquisition and density, whereas nasal inflammation is associated with bacterial shedding. Cell Host Microbe. 2024 Sep 11;32(9):1608-1620.e4. doi: 10.1016/j.chom.2024.07.024.
5) Brito-Mutunayagam S, Hamilton DO, Mitsi E, *et al.* Understanding the interaction of upper respiratory tract infection with respiratory syncytial virus and Streptococcus pneumoniae using a human challenge model: a multicenter, randomized controlled study protocol. PLoS One. 2025. Jul 1;20(7):e0325149. doi: 10.1371/journal.pone.0325149.

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2.6 Understanding the mucosal susceptibility to respiratory viruses

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Project Overview

Respiratory viral infections are a global cause of illness particularly in children and older adults resulting in >2 million deaths/year, however the cellular and molecular factors regulating early infection events and clinical outcome are not well understood. The nasal mucosa is the primary site for respiratory pathogens and controlling viral replication in the upper airway is essential for preventing disease and limiting transmission. Host innate responses, such as type I and III interferons (IFNs), play a role in the control of respiratory viruses. However, our knowledge of the number, location and innate-activation status of infected cells that constitute the mucosal viral reservoir is limited. This knowledge gap presents a roadblock to developing targeted anti-viral therapeutics and immune interventions. We hypothesise that defective or suppressed innate responses in the nasal mucosa promote epithelial susceptibility to viral infection.

To test this hypothesis, we will study the spatial and temporal dynamics of the nasal mucosal response to Respiratory Syncytial virus using Controlled Human Infection Models which enable deep-profiling of pathogen-host immunobiology in a time-resolved manner. Single-cell long-read sequencing and tissue-based spatial transcriptomic methodologies will uncover how the nasal microenvironment influences the trajectory of viral infection at unprecedented detail. Key observations will be explored and validated through mechanistic studies using ex vivo infection models. Together, these approaches will provide critical insights into the early determinants of host susceptibility and inform the development of effective interventions for vulnerable populations.

Key research questions:

- Are some epithelial cells hyper-permissive to infection, and why?
- Do conserved antiviral pathways exist, and can they inform new therapeutics?

Disease Relevance

Respiratory viruses, such as Respiratory Syncytial virus, Influenza A, Rhinovirus, and SARS-CoV-2 are leading causes of acute respiratory illness and pneumonia, particularly in infants, adults with chronic lung disease and the elderly. Although vaccines exist for some of these viruses, significant challenges remain due to variable vaccine uptake, viral mutations, and short-lived immune memory.

Key Technology

- Long-read RNA seq and analysis to map novel viral and host isoforms.
- Spatial transcriptomics, immune profiling, and pathological analysis of human tissue samples from donors infected with Respiratory Syncytial virus
- Spatial network analysis using pipelines to investigate cellular interactions at the micro-anatomic level.

Training Opportunities

The student will join a dynamic and lively team of biologists in the McKeating and Mitsi laboratories that bring complementary expertise in molecular virology, single cell RNA sequencing, spatial biology, mucosal immunity and human infection models. This interdisciplinary project will provide a unique training environment to gain expertise in spatial virology and human mucosal immunity. Transferable skills include oral presentations at joint lab meetings, critical review of published scientific literature by contributing to journal clubs and scientific writing by reviewing and drafting manuscripts for publication.

The student will work in Nuffield Department of Medicine Research Building and Oxford Vaccine Group and will have the opportunity to interface with a network of collaborators in Oxford, UK and internationally to translate their data to the wider biomedical community.

Key Publications

1) Mitsi E et al (2022). Streptococcus pneumoniae colonization associates with impaired adaptive immune responses against SARS-CoV-2. J Clin Invest 132. 10.1172/JCI157124.
2) Zhuang X et al (2023). Hypoxia inducible factors inhibit respiratory syncytial virus infection by modulation of nucleolin expression. iScience 27 (1): 108763.
3) Mitsi E et al (2024). RSV and rhinovirus increase pneumococcal carriage acquisition and density, whereas nasal inflammation is associated with bacterial shedding. Cell Host Microbe 32, 1608-1620 e1604.
4) Cross et al (2024). Characterisation of HBV and co-infection with HDV and HIV through spatial transcriptomics. PMID: 39149129. DOI: 10.1136/egastro-2024-100067.
5) Harris JM et al (2025). Mapping episomal and integrated hepatitis B virus transcriptomes uncovers heterogeneous gene expression and endogenous drug resistance. Nat Comms 2025, in press.

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2.7 Multi-modal spatial tissue analysis to understand hepatitis B virus persistence and disease pathogenesis

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Project Overview

Hepatocellular carcinoma (HCC), the most common form of primary liver cancer, is one of the fastest-rising causes of cancer-related deaths worldwide. Chronic viral hepatitis is the leading driver of HCC, arising from persistent liver inflammation and fibrosis that can progress to cirrhosis and malignancy. Chronic hepatitis B (CHB) remains especially widespread, with over 290 million people living with hepatitis B virus (HBV) infection. Each year, HBV causes more than 800,000 deaths, often through liver failure or cancer. Current therapies suppress viral replication but do not eliminate the virus, highlighting the urgent need for curative treatments.

HBV infects hepatocytes and promotes T cell exhaustion, enabling its persistence within the liver. The liver's architecture—composed of hexagonal lobules centred on a central vein and bordered by portal triads (portal vein, hepatic artery, bile duct)—plays a key role in shaping infection and immunity. We hypothesise that liver architecture, zonation, and immune cell distribution define the establishment and spread of HBV infection, along with the transition to chronic disease.

Recent advances in single-cell spatial transcriptomics have enabled the study of tissues in their native architecture, combining cellular transcriptomes with precise spatial context. Using the Xenium spatial transcriptomics platform, we recently profiled liver biopsies from patients chronically infected with HBV. This approach incorporated virus-specific probes and immunofluorescent staining for viral antigens and markers of non-parenchymal cells, alongside pathological examination of an adjacent tissue section. Data from three sequential biopsy sections revealed both cellular composition and spatial relationships between infected hepatocytes and immune infiltrates.

However, a single tissue section captures only a two-dimensional snapshot of the liver landscape. Reconstructing three-dimensional liver models from serial sections, integrating transcriptomic, antigen, and pathological features, provides a more complete and dynamic view of infection. Such reconstructions could reveal how immune and stromal populations interact with hepatocytes, regulate viral persistence, and contribute to tissue injury. Mathematical modelling provides a rigorous and reproducible framework to characterize the biological processes underlying complex multi-modal data. It enables the exploration of new scenarios, such as predicting how viral infection, immune responses, or therapeutic interventions dynamically interact with the liver architecture and cell populations.

This DPhil project will develop tools to integrate diverse spatial datasets into 3D liver reconstructions. These models will deepen our understanding of how tissue architecture and immune organisation influence viral infection and pathogenesis, offering insights critical for evaluating and improving therapeutic strategies.

Disease Relevance

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

- Spatial transcriptomics, immune profiling, and pathological analysis of human tissue samples from patients diagnosed with chronic hepatitis B.
- Spatial network analysis using MuSpAn pipelines to investigate cellular interactions at the micro-anatomic level.
- Development of novel mathematical modeling approaches, building on existing multi-omics integration techniques, to model three-dimensional tissue structures and cellular features.

Training Opportunities

The student will become part of a vibrant, interdisciplinary team of biologists and mathematicians in the McKeating and Byrne laboratories, which combine expertise in viral biology, spatial transcriptomics, and mathematical modelling. The project is strengthened through an established collaboration with the clinical hepatology team at King's College Hospital, London. This opportunity offers a unique training environment, providing hands-on experience in viral disease pathology alongside cutting-edge techniques in single-cell spatial transcriptomics and mathematical modelling.

The student will develop transferable skills, including delivering oral presentations at joint lab meetings, critically evaluating scientific literature through journal clubs, and contributing to scientific writing by drafting and reviewing manuscripts. The work will be based in the Nuffield Department of Medicine Research Building and the Mathematical Institute, with opportunities to engage with a network of collaborators in Oxford and internationally, facilitating the translation of research findings to the broader biomedical community.

Key Publications

1) Cross et al 2024.Characterisation of HBV and co-infection with HDV and HIV through spatial transcriptomics. PMID: 39149129. DOI: 10.1136/egastro-2024-100067
2) Mukherji et al 2024. An atlas of the human liver diurnal transcriptome and its perturbation by hepatitis C virus infection. PMID: 39209804. DOI: 10.1038/s41467-024-51698-8
3) Bull JA et al (2025). MuSpAn: a toolbox for multiscale spatial analysis. bioRxiv, 2024.12. 06.627195
4) Harris JM et al (2025). Mapping episomal and integrated hepatitis B virus transcriptomes uncovers heterogeneous gene expression and endogenous drug resistance.. Nat Comms 2025, in press.
5) Bull JA and Byrne HM (2023). Quantification of spatial and phenotypic heterogeneity in an agent-based model of tumour-macrophage interactions. PLOS Comp Biol 19(3): e1010994.

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2.8 Establishing Correlates of Protection for Enteric Fever and Invasive Non-Typhoidal Salmonella

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Project Overview

The Oxford Vaccine Group (OVG) has been working on enteric fever for more than two decades. In 2014, OVG established a typhoid controlled human infection model (CHIM), through which we demonstrated the clinical efficacy of a typhoid conjugate vaccine (TCV). These data directly supported the WHO prequalification of the first TCV in 2017. Since then, OVG has led an epidemiological study to define the global typhoid burden and conducted two large randomised controlled trials (RCTs) to evaluate TCV efficacy in endemic settings. To date, more than 60 million doses of TCV have been administered to children in low-income countries. We continue to actively follow trial participants to assess the duration of protection after a single dose and to inform updates to the WHO vaccine policy.

Two additional TCVs have since received WHO prequalification, based on non-inferiority of peak immunogenicity compared with the first licensed vaccine. Considerable work has also been undertaken to identify correlates of protection (CoPs), immune markers that can predict protection against typhoid. Anti-Vi IgG and IgA are currently being used to license new TCVs through non-inferiority trials. However, key questions remain, such as defining the antibody threshold required for protection. These data are critical for monitoring vaccine effectiveness following TCV introduction and guiding policy updates.

While TCVs are now available, no licensed vaccines exist for paratyphoid or invasive non-typhoidal salmonella (iNTS), both of which have a significant burden in low- and middle-income countries (LMICs). To accelerate vaccine development, OVG established a paratyphoid CHIM and has since started testing three vaccine candidates, with over 400 volunteers to be challenged with S.paratyphi. In addition, OVG is investigating a novel iNTS vaccine in early-phase human clinical trials alongside a CHIM model developed by UK collaborators.

Building on these efforts, we have recently been awarded two major grants (each ~£5 million) to identify and validate CoPs for paratyphoid and iNTS. This DPhil project aims to leverage data from our typhoid programme, including CHIM studies in the UK, epidemiological studies in Nepal and Bangladesh, and two large RCTs in Nepal and Bangladesh, to define the protective thresholds of anti-Vi IgG and IgA as CoPs for typhoid. The methods and knowledge gained from typhoid CoPs analysis will then be applied to accelerate the development of CoPs for paratyphoid and iNTS.

In summary, this DPhil project will apply state-of-the-art analytical approaches to identify CoPs for typhoid, paratyphoid and iNTS using contemporary cellular (flow cytometry), serological (systems serology), and molecular methods (RNA sequencing, BCR/TCR sequencing, microbiome analysis), and establish a streamlined pipeline for identifying CoPs.

Disease Relevance

Invasive Salmonella species (including S. Typhi, S. Paratyphi, S.Typhimurium and S.Enteritidis) continue to place a significant disease burden on low- and middle-income countries marked by inadequate sanitation and limited access to clean water. There are estimated to be almost 10 million cases and 200,000 deaths annually worldwide caused by these bacteria.

The escalation of antimicrobial resistance for Salmonella strains, notably underscored by the emergence of extensively drug-resistant strains in Asia and Africa, has reduced available treatment options and increased the public health threat from this disease. The World Health Organisation (WHO) has identified Salmonella species causing invasive disease as priority pathogens for research and recommended vaccines as an important tool in disease prevention and control. While the incidence of S. Typhi and S. Paratyphi peaks at school age, the non-typhoidal serovars mainly affect children in early life with a very high case-fatality rate (14%).

Key Technology

Since this project requires strong numeric skills to conduct the statistical and bioinformatic analyses. The successful candidate for this project will be expected to satisfy the following criteria:

- Demonstrated experience and ability in statistics or epidemiology
- Experience in the use of statistical software
- Excellent communication skills
- Demonstrated research interests in infectious disease and clinical trial methodology

Depending on the candidate's skills, interests and background, they may develop laboratory skills in spectral flow cytometry, functional antibody and cellular immunology assays to generate the primary data for subsequent CoP analysis.

Training Opportunities

The successful candidate will be based at the Oxford Vaccine Group (https://www.ovg.ox.ac.uk), Department of Paediatrics. OVG is a world-leading vaccine research institute with more than 200 staff. We have biweekly statistics/bioinformatics seminars and immunology lab meetings, which are accessible to all DPhil students at OVG.

Besides all the free training at OVG, the department, and the wider Oxford University, the department and OVG have separate funding schemes to support students in additional career development opportunities.

The successful candidate will also have training opportunities in the design, conduct, and analysis of RCTs and observational studies internally and externally.

Key Publications

1) Jin C, et al. Efficacy and immunogenicity of a Vi-tetanus toxoid conjugate vaccine in the prevention of typhoid fever using a controlled human infection model of Salmonella Typhi: a randomised controlled, phase 2b trial. Lancet. 2017 Dec 2;390(10111):2472-2480. doi: 10.1016/S0140-6736(17)32149-9. Epub 2017 Sep 28. PMID: 28965718; PMCID: PMC5720597.
2) Qadri F, et al. 5-year vaccine protection following a single dose of Vi-tetanus toxoid conjugate vaccine in Bangladeshi children (TyVOID): a cluster randomised trial. Lancet. 2024 Oct 12;404(10461):1419-1429. doi: 10.1016/S0140-6736(24)01494-6. PMID: 39396349.
3) McCann, Naina et al. "Efficacy, safety and immunogenicity of CVD1902, an oral live attenuated vaccine against Salmonella Paratyphi A, in the prevention of paratyphoid fever using a controlled human infection model of Salmonella Paratyphi A: a randomised controlled, phase 2 trial ." N Engl J Med. Accepted.
4) Brama Hanumunthadu et al. Safety and immunogenicity of the invasive non-typhoidal Salmonella (iNTS)-GMMA vaccine: a first-in-human, randomised, dose escalation trial. Ebiomedicine. Volume 119105903.September 2025
5) Shakya M, Voysey M, Theiss-Nyland K, et al. Efficacy of typhoid conjugate vaccine in Nepal: final results of a phase 3, randomised, controlled trial. Lancet Glob Health 2021; 9: e1561–68.

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2.9 Developing Advanced Lymphoid Organoids to Assess Safety and Immunogenicity of Vaccines against Emerging Pandemic Viruses

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Project Overview

Our aim is to develop the next generation of lymphoid organoids and lymphoid tissue precision-cut explants (hereafter referred to as explants) and establish them as essential toolkits for reducing and replacing animal models in immunology research. While we are focused on developing robust next-generation methods, we also aim to lead cutting-edge research and advance precision medicine. To achieve this, we will collaborate with partners to validate these systems in various immunological contexts. Importantly, these advances have direct real-world implications: they can accelerate vaccine development, improve safety assessments, reduce reliance on animal models, and enhance preparedness for future pandemics.

Researchers within the COI umbrella primarily focus on human immunology, providing the potential candidate with numerous opportunities to collaborate and enhance the impact of our research.

Lymphoid organoids enable the reorganization of cell suspensions into follicle-like structures that support germinal centre (GC) reactions, while lymphoid explants preserve tissue architecture and cell niches ex vivo. Both models have shown promise in uncovering novel immune mechanisms that regulate B cell activation and differentiation into antibody-secreting cells (ASCs). However, their broader adoption is limited, and a comprehensive body of evidence supporting their use across diverse immunological and translational settings is lacking.

For this project, we have outlined two work packages (WPs):

WP1: Benchmark and validate lymphoid organoids for pre-clinical profiling of current and next-generation vaccine platforms. Spleen organoids, representing mini-spleens, will support the development of immune responses and allow simultaneous profiling of multiple donors. Stimulation will use antigens modelling viral and bacterial infections. To identify correlates of protective or harmful immunity, responses in spleen organoids will be compared to tonsil- and gut-derived mucosa-associated lymphoid organoids. Outcome measures will include frequencies of plasmablasts, plasma cells, antibody-secreting cells, GC-B cells, follicular helper T cells (TFHs), GC-TFHs, and follicular regulatory T cells (TFRs). We will also analyse immunoglobulin isotypes and function, while generating single-cell RNA-sequencing, high-dimensional flow cytometry, and high-content microscopy datasets to map immune dynamics.

WP2: Collaborate with Dr Jack Tan to assess whether these models can support the pre-clinical evaluation of next-generation vaccines and the identification of new antiviral antibodies and T-cell clones. We will optimize culture conditions, growth factors, and setups to better predict both beneficial and adverse responses—two unmet needs in current models. Specifically, we will develop readouts for genotoxicity, pro-inflammatory cytokine release, abnormal antibody class switching, antibody-dependent enhancement (ADE), immune complex formation, deleterious FcγR responses, auto-reactive antibodies, and aberrant transcriptional profiles using scRNA-seq.

In summary, this project will establish next-generation lymphoid organoids as validated and versatile pre-clinical platforms. By benchmarking their ability to assess vaccine safety and efficacy, while extending their use to predict adverse effects and identify protective immune signatures, we will provide the community with powerful and scalable alternatives to animal models. Our hope is that these advances will accelerate the development of faster and safer vaccines, reduce reliance on animal experimentation, and strengthen preparedness against future pandemic threats. Beyond vaccines, this work will create a foundation for broader applications in immunotherapy and precision medicine.

Disease Relevance

- All infectious diseases.
- These 3Rs models (organoids and explants) will be tested in a variety of studies elucidating both fundamental mechanistic studies and their application to the understanding of disease pathogenesis and the discovery of novel therapeutics.
- The Cespedes group collaborates with many other groups under the COI umbrella, so the applications of these methods will not be limited to mechanistic studies and can be dynamically shaped to the working hypothesis of the project.
- Potential collaborations include: studying the effector mechanisms of T cell clones expressing different integrins and C-type lectins in cancer (Professor Tao Dong), inflammatory bowel disease (Dr Matthias Friedrich Lab), modelling tumor metastases (Dr Alex Gordon-Weeks), Vaccinology (Dr Jack Tan) and infectious diseases (Dr Peter Wing).
- Potential collaborations in other areas of molecular immunology and biophysics including the study of forces regulating T-cell activation (Professor Marco Fritzsche), Protein engineering (Dr Ricardo Fernandes), and the development of new methods to study the physical communication of cells (Professor Michael L. Dustin).
- Combined with our CRISPR/Cas9, high-dimensional and high-througput microscopy approaches, the candidate will gain substantial training in cutting-edge molecular, cellular and tissue-level immunological methods. Acquiring a future-proof skillset.

Key Technology

- Lymphoid organoids and lymphoid tissue explants.
- SpyCatcher multimerisation and Lipid Nanoparticle based vaccines.
- Recombinant vaccines harnessing glycoconjugates.
- Spectral and conventional flow cytometry.
- Live-cell imaging—widefield and confocal.
- Super-Resolution microscopy and flow cytometry.
- Dynamic Light Scattering for nanoparticle characterisation.
- Bulk deep proteome LC-MS/MS proteomics.
- Single-cell RNAseq for whole transcriptome and antigen-receptor-based clonotype identification.
- CRISPR/Cas9 knock-outs and knock-ins.

Training Opportunities

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

No prior experience is required. Candidates will receive training in cutting-edge molecular, cellular, and tissue-level immunology techniques, alongside support in mastering informatics pipelines for statistics and the analysis of complex transcriptomic and proteomic datasets. Through collaborations, they will gain exposure to intersecting fields such as biochemistry, biophysics, genetic engineering, protein engineering, virology, computational biology, and statistics.

In collaboration with Dr Jack Tan, the candidate will receive comprehensive training in next-generation vaccine and antibody development. This will include designing and producing self-assembling protein-based nanoparticle vaccines as well as mRNA vaccines, with hands-on experience in antigen engineering, expression, and formulation. In parallel, they will learn antibody discovery pipelines, from isolating monoclonal antibodies to their production, purification, and detailed functional characterization. They will also gain experience validating therapeutic antibodies in vivo, including assessments of efficacy, pharmacokinetics, and half-life in murine models.

This integrated program will equip the candidate with a versatile and future-ready skill set at the interface of vaccinology, immunology, and translational medicine, positioning them to make meaningful contributions to both academic science and biomedical innovation.

Key Publications

1) 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 (2019). https://doi.org:10.7554/eLife.47528
2) 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 (2022). https://doi.org:10.1038/s41467-022-31160-3
3) Tan, TK (2021). A COVID-19 vaccine candidate using SpyCatcher multimerization of the SARS-CoV-2 spike protein receptor-binding domain induces potent neutralising antibody responses. Nat Commun 12, Article number: 542 (2021). https://doi.org/10.1038/s41467-020-20654-7

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2.10 Comparative Analysis of TCR-Mediated Cytotoxicity Using Genome-Wide CRISPR Screens to Identify Host Factors in Natural vs. Vaccine-Induced Immunity

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Project Overview

This PhD project aims to systematically identify cellular factors that regulate T cell cytotoxicity by comparing matched TCR clones derived from natural viral infections versus vaccination responses, using genome-wide CRISPR knockout screens that the Sharma group specializes in, conducted in both target cells and directly within the T cells themselves. The research addresses a fundamental gap in our understanding of how immunological context shapes T cell programming and function. While TCRs with identical sequences can arise in different contexts, their effector functions may be influenced by distinct cellular factor networks that have not been comprehensively mapped. Through close collaboration with the Dong group, who have previously identified distinct clones of TCRs from individuals with documented natural viral infections and from vaccinated individuals with the same viral specificities, we will focus on epitopes from SARS-CoV-2. These matched TCR clones will undergo comprehensive CRISPR knockout screens targeting approximately 19,000 genes, with functional readouts measuring cytotoxicity, degranulation markers, and cytokine production to identify which cellular factors are essential for optimal T cell effector function. Parallel screens will also be conducted in target cells to identify host factors that distinguish the different clones.

This research could reveal fundamental molecular differences between naturally-acquired and vaccine-induced immunity, potentially discovering novel metabolic pathways, signaling networks, or regulatory factors that are differentially active across immunological contexts. The findings may explain why natural infection sometimes provides broader protection than vaccination, identify missing components in vaccine-induced responses that could be therapeutically targeted, and uncover previously unknown cellular factors that fine-tune cytotoxic efficiency. Downstream validation will include utilization of network-based computational tools to reconstruct pathway differences between the different modalities from different clones and reprogramming of clones using targets identified from the screen to generate novel signal transduction networks that differ between natural and vaccine-derived T cells. These insights could lead to enhanced vaccine strategies that better mimic natural immunity, improved T cell therapies through targeted manipulation of identified pathways, and development of functional biomarkers for predicting immune responses and vaccine efficacy.

Disease Relevance

Understanding the molecular mechanisms that regulate T cell cytotoxicity has direct implications in the context of infectious diseases, autoimmunity, and cancer. In this particular project, our approach of systematically mapping the cellular factors that govern cytotoxic efficiency in T cells derived from natural versus vaccine-induced immunity addresses why disease outcomes and protective breadth differ between individuals.

Key Technology

CRISPR-based genome editing, functional genomic screens, primary T cell culture, flow cytometry, computational network-based approaches.

Training Opportunities

The student will be trained in both wet and dry lab based approaches. The PhD candidate will engage in daily interactions with postdoctoral researchers and research assistants from both labs. Fortnightly lab meetings are held to discuss data and address troubleshooting issues.

Key Publications

1) Peng et al, Nature Immunology, 2020
2) Peng et al, Nature Immunology, 2022
3) Liu et al, Nature Communication, 2025
4) Sharma et al, Life Science Alliance, 2023

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2.11 Study of antibody responses against emerging pathogens toward vaccine design, therapeutics and protection

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Project Overview

Emerging pathogens can cause severe, deadly diseases when introduced into naive populations. Emerging diseases include the dengue virus, Zika virus, HIV, Ebola virus, SARS, MERS, and the most recent, COVID. They have caused severe disease outbreaks, which can turn into pandemics because we lack control tools such as diagnostic tests, therapeutics, and vaccines. COVID is a clear example of how a new pathogen emerging in Wuhan could cause a pandemic, leading to millions of deaths and affecting the global economy. It is inevitable that there will be new pathogen emergence. Therefore, it is important to prepare for new epidemic/pandemic threats.

Our lab has studied a number of emerging viruses, including dengue, Zika, SARS-CoV-2, and Ebola for more than 20 years. Our work has contributed to understanding pathogenic mechanisms, generating diagnostic and therapeutic reagents, designing vaccines, and contributing to policy development. We have published several scientific articles in high-impact journals such as Nature, Science, Cell, Nature Immunology, Nature Communications, and Immunity. For example, during the COVID pandemic, we generated reagents that were involved in establishing a protocol to measure the antibody response, which has been used to monitor the immune status in the UK population. We have generated hundreds of monoclonal antibodies from infected and vaccinated individuals. We characterized their neutralization activities, cross-reaction among the variants, and biophysical properties. In combination with crystal and cryo-EM structures, we described the antigenic distance among the variants and how new emerging variants escaped from existing ones.

The general aim of the proposed D.Phil project is to apply our expertise to study new emerging pathogens, such as Dengue virus, Sudan Ebolavirus, which caused a large outbreak in Uganda at the end of 2022, Nipah virus, enterovirus, and Monkeypox virus,which WHO declares the outbreak a public health emergency of international concern.

Disease Relevance

When a new pathogen emerges and causes severe or life-threatening disease, it has the potential to initiate a major outbreak or even evolve into a global pandemic. The impact of such an event can be catastrophic, as it not only threatens public health but also overwhelms healthcare systems, disrupts economies, and places immense pressure on governments and international organizations. This threat becomes particularly alarming when there are no vaccines or treatments readily available, leaving the population vulnerable to the spread of the disease.

This project will serve as an exercise in preparing for future emerging diseases and potential pandemic outbreaks; whether it's a new strain of influenza, a novel coronavirus, or an entirely unknown virus.

Key Technology

The student will have an opportunity to receive hand-on training in a wide range of cutting-edge technologies, including:

- Flow Cytometry and Single-Cell Sorting: Mastering the use of flow cytometers for the precise sorting and analysis of individual cells, a critical technique for immunology, medical research, and cell biology.
- Molecular Biology Techniques: Gaining expertise in fundamental molecular biology methods such as DNA/RNA extraction, PCR amplification, and gel electrophoresis, which are essential for genetic analysis and manipulation.
- Gene Editing: Learning gene-editing technologies to perform targeted modifications in genomes, allowing for functional studies of genes and their roles in disease.
- Cell Culture and Maintenance: Acquiring skills in culturing and maintaining various cell lines, which is crucial for conducting in vitro experiments, and biological research.
- Recombinant Protein Expression: Training in the expression and purification of recombinant proteins using different systems such as bacterial, yeast, and mammalian cells, which is important for structural and functional protein studies.
- Viral isolation and viral culture are essential techniques in virology and medical researches that involve extracting and growing viruses from clinical or environmental samples. Training in these methods is crucial expecially for new emerging pathogens.
- Reverse Genetics and Virus Generation: Learning reverse genetic techniques to engineer both wild-type and mutated viruses, providing insights into viral pathogenesis, replication, and vaccine development.
- Structural Biology: Exposure to methods used in structural biology for determining the three-dimensional structure of proteins and viruses, which is key for understanding molecular interactions and drug design.

This comprehensive training will equip the student with a diverse set of skills that are highly applicable across multiple disciplines in the biomedical sciences.

Training Opportunities

The student will have the opportunity to join a highly experienced team with over 20 years of expertise in virology, immunology, and molecular biology. Under the mentorship of researchers and postdoctoral fellows, the student will receive comprehensive training in a wide range of cutting-edge techniques, including flow cytometry, gene editing, reverse genetics, viral isolation, and recombinant protein expression.

The student will gain experience in generating monoclonal antibodies from single human and mouse B cells. This process is critical for advancing research in immune response and developing targeted therapies for infectious diseases. The student will learn to isolate B cells, clone antibody genes, express and purify monoclonal antibodies, and analyse their properties, which are valuable tools for diagnostic, therapeutic applications and vaccine design. Collaboration will be a key aspect of this experience. The student will work closely with our network of partners, including structural biologists based in Oxford, as well as collaborators across the UK and internationally. This interdisciplinary environment will expose the student to a broader scope of researches.

By the end of the training, the student will have acquired a well-rounded skill set, including not only laboratory techniques but also experience in collaborative research, project management, and scientific communication. This experience will prepare the student for a successful career in biomedical research, virology, immunology, or biotechnology, equipping him/her to contribute to critical areas such as vaccine development, therapeutic discovery, and pandemic preparedness.

Key Publications

1) Dejnirattisai, W. et al. The antigenic anatomy of SARS CoV-2 receptor binding domain. Cell 184, 2183-2200 e2122, doi:10.1016/j.cell.2021.02.032 (2021).
2) Dejnirattisai, W. et al. Reduced neutralisation of SARS-CoV-2 omicron B.1.1.529 variant by post-immunisation serum. Lancet 399, 234-236, doi:10.1016/S0140-6736(21)02844-0 (2022).
3) Rouvinski, A. et al. Recognition determinants of broadly neutralizing human antibodies against dengue viruses. Nature 520, 109-113, doi:10.1038/nature14130 (2015).
4) Fernandez, E. et al. Human antibodies to the dengue virus E-dimer epitope have therapeutic activity against Zika virus infection. Nat Immunol 18, 1261-1269, doi:10.1038/ni.3849 (2017).
5) Dejnirattisai, W. et al. Cross-reacting antibodies enhance dengue virus infection in humans. Science 328, 745-748, doi:10.1126/science.1185181 (2010).

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Theme 3. Inflammation & Autoimmune Disease

3.1 Discovery of new approaches to treat skin inflammation

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Project Overview

T cells are thought to contribute to many inflammatory skin diseases, yet we still know relatively little about their antigenic targets and the key pathways involved. This is an important question to solve if we are to find new treatments for patients.

The lab utilises molecular immunology technologies to discover T cell mechanisms and their relevance to disease. Specifically, the lab deploys single cell and functional T cell immunology approaches to discover nodal pathways using samples from patients before and after treatment. These human perturbation studies and functional assays are complemented by in vivo models which are important for defining in vivo biology and progressing novel therapeutic candidates. Our data have shown that a population of overlooked “unconventional” T cells makes a major contribution to skin inflammation. Such T cells recognise lipid antigens rather than the more studied peptide antigens. The T cells respond to lipid antigens when complexed with CD1a which is expressed by Langerhans cells in the skin and on other cell types. This continues to be very productive in discovery, with much interest from industry for the therapeutic applications. The project will utilise thses approaches to contribute directly to the work progressing an understanding of the role and biology of CD1a-reactive T cells in the pathogenesis and treatment of inflammatory skin disease.

Disease Relevance

It is now becoming clear the T cells which respond to lipid antigens presented by CD1a play a major role in different inflammatory skin diseases, including atopic dermatitis and psoriasis.

Key Technology

Technologies used include T cell culture and functional analyses, with the associated in vitro and in vivo techniques. As well as laboratory-based work, the lab uses single cell bioinformatic analyses for transcriptomic outputs and T cell receptor sequencing, as well as CRISPR-mediated gene editing. The lab is very “translational” with a deep and successful drive to progress the therapeutic applications, including many patents, licenses, as well as spin-outs.

Training Opportunities

The candidate will learn human tissue T cell identification, culture and functional analyses, as well as single cell analyses such as spatial transcriptomics and CITE-seq. The project will likely involve CRISPR-mediated gene editing, and use of in vivo inflammation models to define biology and progress therapeutic assets. Experience will also be gained in the patenting process and engagement with industry partners. These are skills which are transferable and valuable, which will enable a career across disciplines and therapeutic modalities.

Key Publications

1) Chen YL, Ng JSW, Ottakandathil Babu R, Woo J, Nahler J, Hardman CS, Kurupati P, Nussbaum L, Gao F, Dong T, Ladell K, Price DA, Duncan DA, Johnson D, Gileadi U, Koohy H, Ogg GS. Group A <i>Streptococcus</i> induces CD1a-autoreactive T cells and promotes psoriatic inflammation. Sci Immunol. 2023 Jun 8;8(84):eadd9232. doi: 10.1126/sciimmunol.add9232.
2) Hardman CS, Chen YL, Wegrecki M, Ng SW, Murren R, Mangat D, Silva JP, Munro R, Chan WY, O'Dowd V, Doyle C, Mori P, Popplewell A, Rossjohn J, Lightwood D, Ogg GS. CD1a promotes systemic manifestations of skin inflammation. Nat Commun. 2022 Dec 7;13(1):7535. doi: 10.1038/s41467-022-35071-1.
3) Huang S, Shahine A, Cheng TY, Chen YL, Ng SW, Balaji GR, Farquhar R, Gras S, Hardman CS, Altman JD, Tahiri N, Minnaard AJ, Ogg GS, Mayfield JA, Rossjohn J, Moody DB. CD1 lipidomes reveal lipid-binding motifs and size-based antigen-display mechanisms. Cell. 2023 Oct 12;186(21):4583-4596.e13. doi:10.1016/j.cell.2023.08.022.
4) Cotton RN, Wegrecki M, Cheng TY, Chen YL, Veerapen N, Le Nours J, Orgill DP, Pomahac B, Talbot SG, Willis R, Altman JD, de Jong A, Van Rhijn I, Clark RA, Besra GS, Ogg G, Rossjohn J, Moody DB. CD1a selectively captures endogenous cellular lipids that broadly block T cell response. J Exp Med. 2021 Jul 5;218(7):e20202699. doi: 10.1084/jem.20202699.
5) Ogg GS, Rossjohn J, Clark RA, Moody DB. CD1a and bound lipids drive T-cell responses in human skin disease. Eur J Immunol. 2023 Oct;53(10):e2250333. doi: 10.1002/eji.202250333.

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3.2 Characterisation of immune regulatory T cells responses in IBD

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Project Overview

The gastrointestinal tract in mammals houses one of the densest bacterial communities known. Here, the host and its microbial residents composed of bacteria, viruses, fungi and archaea (the microbiota) form a mutualistic ecosystem termed the 'Holobiont'1. This host microbial super-organism is essential for normal physiological processes including nutrition, immune system development and host defence. In Inflammatory Bowel Disease (IBD) encompassing Crohn's disease and Ulcerative Colitis, maladapted gene environmental interactions lead to a breakdown in healthy host microbial dialogue resulting in the development of chronic intestinal inflammation.

Intestinal homeostasis is dependent on tolerance towards health promoting bacterial symbionts alongside host protective immunity to invading pathogens. Work in the Powrie and Uhlig laboratories has identified a non-redundant role for Foxp3+ Regulatory T cells (Treg) and IL-10 in T cell mediated control of intestinal homeostasis. It is increasingly appreciated that Treg cells are not homogeneous and have distinct developmental origins, reactivities and tissue specific adaptations that drive function. Loss of function mutations in FOXP3 or IL10 (monogenic diseases) lead to intestinal inflammation in humans with evidence that microbe reactive and self - reactive Treg cells may play distinct roles in controlling chronic inflammation and autoimmunity in the intestine.

This project will adopt a multidisciplinary approach involving biology, computational biology and clinical medicine to characterise regulatory T cell populations across human tissues in health and disease. Specifically we will identify ontogenic relationships between Treg cells in distinct tissue and relate that to functional features and key cellular hubs. Through the Uhlig, Powrie and Dendrou labs the student will have access to a large well characterised single cell transcriptomic atlas of cells across tissues in health and disease (>50 million cells from >2,500 donors). In addition, there are longitudinal samples pre and post clinical intervention in IBD and samples from rare patients with monogenic forms of IBD (such as SYK gain of function, NPC1). We will address the following aims:

- Identification of Treg populations in distinct intestinal regions in health and disease. Consensus non-negative matrix factorisation will be used to identify gene expression programmmes and CellChat to identify cellular hubs associated with Treg functional features. We expect these studies to highlight key functional programmes for mechanistic analysis.
- Regulatory T cell specificity in intestinal niches. Investigation of TCR diversity, clonality and antigen-specificity inference to assess Treg and effector cell dynamics. These analyses will help to inform precursor product relationships and Treg ecology within and across intestinal niches. Investigating tissues of diseases with clear antigen – MHC association such as

coeliac disease, we will be able to study antigen specificity of effector T cells and regulatory T cells.

- Perturbation of Treg functional niches. Pathways identified in Aim 1 and 2 will be investigated using spatial transcriptomics and proteomics. Cellular and molecular apporaches will be used to probe mechanisms including CRISPR based functional assays Together these studies will provide new information on human Treg cell functional specialisation in the intestine and how that is modified in IBD. The results will provide a basis for the development of rational strategies to promote the Treg and IL-10 axis in a targeted way in IBD and other autoimmune and inflammatory diseases.

Disease Relevance

Genetic diseases and animal models confirm the key role of regulatory T cells in intestinal homeostasis. However understanding of human Treg subsets, their antigenic targets and tissue niche functions across different regions of the intestine are poorly understood. The results of these studies will provide a handle to design targeted therapeutic interventions directed at the T reg cell niche across the small and large intestine in gastrointestinal diseases such as IBD and celiacs disease. Results will inform small molecule and antibody approaches as well as Treg cell therapies.

Key Technology

- Single-cell (and spatial) multi-omics (RNA, cell-surface protein, TCR) analysis using computational pipelines/tools e.g. Panpipes, CellChat, Immunarch, Immcantation, COMPASS etc
- Machine learning approaches for population-level representation of scRNAseq data (e.g. GloScope)
- Multi-Dimensional Viewer platform for data visualisation and dissemination, including LLM capacity (chatMDV)
- Functional validation of regulatory T cell activity using complex human in vitro models that reflect organ and disease specific aspects (organ in a dish, organ on a chip).

Training Opportunities

The supervisory team provide a vibrant lab experience with expertise spanning immunology, gastroenterology and computer science. The student will receive training in cell and molecular biology approaches including organoid technologies, in vitro analysis of T cell function and in vitro CRISPR screens. They will have access to regular seminars in the KIR, group Journal Club and the KIR Genomics Forum. They will also receive regular training and mentoring with respect to computational analysis. This will involve using Python and R-based pipelines and tools for high-throughput single-cell (and spatial) multi-omics data, including transcriptomic, proteomic, and immune repertoire (TCR-seq) modalities. The student may also leverage generative machine learning approaches to better encapsulate regulatory gene network perturbations or other subtle behaviour that is not easily identifiable with standard data analyses. In addition, the student will also have the opportunity to contribute to a data visualisation platform that incorporates AI-powered language learning tools.

Key Publications

1) Gu Y, Bartolomé-Casado R, Xu C, Bertocchi A, Janney A, Heuberger C, Pearson CF, Teichmann SA, Thornton EE, Powrie F.Immune microniches shape intestinal Treg function. Nature. 2024 Apr;628(8009):854-862. doi: 10.1038/s41586-024-07251-0. Epub 2024 Apr 3.
2) Griffin H, Ceron-Gutierrez L, Gharahdaghi N, Ebrahimi S, Davies S, Loo PS, Szabo A, Williams E, Mukhopadhyay A, McLoughlin L, Irwin S, Travis S, Klenerman P, Bunn S, Cant AJ, Hambleton S, Uhlig HH, Doffinger R.NNeutralizing Autoantibodies against Interleukin-10 in Inflammatory Bowel Disease. New Engl J Med. 2024 Aug 1;391(5):434-441. doi: 10.1056/NEJMoa2312302.PMID: 39083772
3) Friedrich M, Pohin M, Jackson MA, Korsunsky I, Bullers SJ, Rue-Albrecht K, Christoforidou Z, Sathananthan D, Thomas T, Ravindran R, Tandon R, Peres RS, Sharpe H, Wei K, Watts GFM, Mann EH, Geremia A, Attar M; Oxford IBD Cohort Investigators; Roche Fibroblast Network Consortium, McCuaig S, Thomas L, Collantes E, Uhlig HH, Sansom SN, Easton A, Raychaudhuri S, Travis SP, Powrie FM. IL-1-driven stromal-neutrophil interactions define a subset of patients with inflammatory bowel disease that does not respond to therapies. Nat Med. 2021 Nov;27(11):1970-1981.
4) Thomas T, Friedrich M, Rich-Griffin C, Pohin M, Agarwal D, Pakpoor J, Lee C, Tandon R, Rendek A, Aschenbrenner D, Jainarayanan A, Voda A, Siu JHY, Sanches-Peres R, Nee E, Sathananthan D, Kotliar D, Todd P, Kiourlappou M, Gartner L, Ilott N, Issa F, Hester J, Turner J, Nayar S, Mackerodt J, Zhang F, Jonsson A, Brenner M, Raychaudhuri S, Kulicke R, Ramsdell D, Stransky N, Pagliarini R, Bielecki P, Spies N, Marsden B, Taylor S, Wagner A, Klenerman P, Walsh A, Coles M, Jostins-Dean L, Powrie FM, Filer A, Travis S, Uhlig HH, Dendrou CA, Buckley CD. A longitudinal single-cell atlas of anti-tumour necrosis factor treatment in inflammatory bowel disease. Nat Immunol. 2024 Nov;25(11):2152-2165
5) Curion et al. (2024) Panpipes: Pipelines for multimodal single-cell and spatial transcriptomic data analysis. Genome Biology, 25, 181.

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3.3 Autoimmune T cell responses in inflammatory bowel disease

Prof. Holm Uhlig & **Prof. Tao Dong**

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Project Overview

Inflammatory bowel disease (IBD) is a complex multifactorial disease caused by genetic susceptibility as well es environmental factors. The two main disease groups are Crohn's disease and Ulcerative colitis. In addition to the two polygenic disorders associated with over 300 genetic loci, there are over 100 monogenic conditions that can present with IBD-like immunopathology.

Interleukin-10 (IL-10) is a key anti-inflammatory cytokine that plays a critical role in controlling immune responses in the gut. Genetic variations that impair IL-10 signalling (either IL-10 or its receptor deficiencies) cause monogenic inflammatory bowel disease (IBD) in infants. We have discovered a novel immune mechanism that mimics this monogenic condition: neutralising autoantibodies against IL-10 (Griffin et al. NEJM 2024). These antibodies block IL-10 function and are strongly associated with poor treatment response. B-cell depletion therapy has successfully reversed this pathology in at least one paediatric patient, directly implicating autoreactive B cells and neutralizing autoantibodies in driving disease. The role of T cell responses in this condition is not clear. This project will fill that gap by characterising anti-IL-10 T cell responses in IBD patients and compare those with anti-microbial responses. We will map CD4 T cell receptor variation and functional characteristics such as cytokine production using conventional immunotyping as well as single cell transcriptomics and spatial transcriptomics. This allows to assess the impact of anti-microbial as well as autoimmune IL-10-specific T cell clonal architecture, enhancing our understanding of cytokine-targeting autoimmunity. This project aims to identify, where T cells with anti-cytokine reactivity are primed and where memory responses are maintained, and how those antigen specific T cells interact with other immune cells. This project will guide stratified medicine and inform therapeutic T cell targeting strategies.

Disease Relevance

This project addresses a novel mechanism in IBD: the presence of neutralising autoantibodies against the immunoregulatory cytokine IL-10. These antibodies mimic genetic IL-10 receptor deficiencies and may underlie treatment resistance in a subset of IBD patients. By profiling CD4 T cell populations, this study will contribute fundamentally to our understanding of disease heterogeneity in IBD. The ability to identify patients with IL-10-neutralising autoantibodies has immediate translational value, laying the groundwork for personalised immunological diagnostics. Understanding the T cell responses in this setting will be essential to understand how the immunopathology is initiated and maintained, offering to target the pathogenic mechanism that drives this subform of IBD disease.

Key Technology

Peripheral blood mononuclear cells (PBMCs) and mucosal cells from intestinal biopsies or resection material will be stained by antibodies to define lymphocyte subsets. Flow cytometry will be performed using a multicolor spectral cytometer.

To identify antigen specific T cells, we will expose lymphocytes and antigen presenting cells in a T stimulation assay and employ high-dimensional flow cytometric immunophenotyping. Antigen specific T cells will be identified by upregulation activation markers such as CD154 (CD40L) after exposure of IL10 or microbial products. Data will be analysed using FlowJo software to identify and quantify anti-microbial as well as anti-cytokine responsive T cells and their phenotypic characteristics.

In addition to flow cytometry, single-cell transcriptomics and cite-seq will identify and characterise antigen specific T cells. Single cell transcriptomics will be performed using 10x technology according to established protocols and pipelines in the lab (Bolton et al., Gastroenterology 2022; Thomas et al., Nat Immunology 2024; FitzPatrick et al., Nature Immunology 2025). Transcriptomics technology will allow per-cell resolution analysis across multiple modalities including gene expression signatures, T cell receptor profiling, and surface protein expression using CITE-seq. This approach will enable precise immunophenotyping of autoreactive and antimicrobial T cell populations in IBD patients, allow to assess their memory status, and activation profile, clonal expansion and functional analysis.
Spatial transcriptomic single cell analysis will be performed on fresh frozen or paraffin embedded tissue sections of IBD patients using 10X Xenium hybridisation technologies as well as in-house developed long-range spatial sequencing. In combination with deconvolution of the 10x transcriptomic cellular signatures, this will allow to assess cell-type organ composition, cell–cell interactions (for instance antigen specific T cell responses in colocalisation with tissue specific dendritic cells, monocytes and macrophages), heterogeneous spatial niches, tissue specific gene programs, and ligand–receptor interaction networks.

Among others, the analysis of the complex multimodal datasets will be performed in a Multi-Dimensional Viewer (MDV), software platform environment, a tool for analyzing, annotating and sharing multi-dimensional data allowing spatial clustering, network analysis and investigation of longitudinal data.

Training Opportunities

This project will provide a unique insight into translational research; from clinical aspects of patients presenting with severe forms of inflammatory bowel disease towards immunology mechanisms and will allow the DPhil student to interact with both basic researchers and clinicians.
This project applies cutting edge immunology in close collaboration with experts in T cell and mucosal immunology from Oxford and internationally. The project have close link to projects at the Centre for Human Genetics in Oxford aiming to understand genetic basis of inflammatory bowel disease in children and adults.
Laboratory techniques include generation and analysis of single cell and spatial transcriptomic and proteomic data, analysis next generation DNA sequencing data, flow cytometric assays, T cell culture and differentiation, and high-resolution microscopy. A key training opportunity is to interact with clinicians as well as bioinformaticians and computer scientists to develop models for antigen specific cell-cell interactions in inflammatory bowel disease.

The CAMS Oxford Institute as well as the Centre for Human Genetics support structured DPhil training with mentoring opportunities on technologies and personalised medicine in the field of genomics and immunology. In addition to core training opportunities, we support science communication. Data will be presented at the international and internal scientific conferences and published in a high-impact journals to maximise reach.

The successful applicant will communicate the research with patient stakeholders and the public.

Key Publications

1) Griffin et al. Neutralizing Autoantibodies Against IL-10 in Inflammatory Bowel Disease. N Engl J Med. 2024 Aug 1;391(5):434-441.
2) FitzPatrick et al. Immune-epithelial-stromal networks define the cellular ecosystem of the small intestine in celiac disease. Nat Immunol. 2025
3) Thomas et al. A longitudinal single-cell atlas of anti-tumour necrosis factor treatment in inflammatory bowel disease. Nat Immunol. 2024 Nov;25(11):2152-2165.
4) Bolton et al. An integrated taxonomy for monogenic inflammatory bowel disease. Gastroenterology. 2021 Nov 12:S0016-5085(21)03737-9.
5) Wang et al. Gain-of-function variants in SYK cause immune dysregulation and systemic inflammation in humans and mice. Nat Genet. 2021 Mar 29. doi: 10.1038/s41588-021-00803-4.

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Theme 4. Genomic Medicine & Data Science

4.1 Cell-free DNA landscape in pleural infection and its association with clinical outcomes and disease severity

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Project Overview

Pleural infection is a severe and complicated disease with increasing incidence worldwide. Pleural infection is associated with high morbidity and mortality. Patients develop pleural effusions (pleural fluid) which is the accumulation of fluid between the lungs and the chest wall and require hospitalisation and often receive invasive treatments like surgery.

Currently, there are no biomarkers to stratify patients to the most appropriate treatment. Better understanding of the underlying biology of the disease could help us develop tailored treatments which could improve clinical outcomes for patients with pleural infection.

Neutrophils are the most abundant type of white blood cell and act as the body's first line of defence against bacterial infections. They rapidly migrate to sites of injury or invasion, where they engulf and destroy pathogens through phagocytosis and the release of antimicrobial substances like antimicrobial granules and neutrophil extracellular traps (NETs).

In a recent study (TORPIDS-2, European Respiratory Journal 2025 66(1): 2500010) we showed that pleural infection patients show diverse levels of neutrophil mediated immune activity. This means that patients show different neutrophilic responses and is important because neutrophils could cause tissue damage but also be targeted with drugs.

In a follow up study (TORPIDS-3, in submission), we investigated the biological role of NETs in pleural infection. We discovered some important associations with clinical outcomes.

Cell-free DNA (cfDNA) screening and sequencing is used for non-invasive prenatal testing, oncology, and monitoring of organ transplant recipients. cfDNA fragments bear important information about the tissue pathology based on the epigenetic state and fragmentation patterns. The clinical use of cfDNA in pleural infection remains unexplored.

Our aim for the current project is to investigate the biological role of cfDNA in pleural infection and its' association with important clinical outcomes like survival, severity of the disease, response to treatment and length of hospital stay. We will apply cutting edge technologies like nanopore sequencing which have already been established (Cell Genomics 2025 Aug 7:10097). cfDNA will be isolated from pleural fluid and serum prospectively collected for the PILOT study (Eur Respir J. 2020 Nov 26;56(5):2000130.). This is the largest biobank in pleural infection worldwide. The cfDNA data will be analysed alongside detailed microbiological and clinical phenotyping together with other complementary -omic readouts of the immune response being generated as part of this study. Samples provided by our collaborators will be used to externally validate the results in a separate and independent cohort.

Disease Relevance

Pleural infection is a severe and complicated respiratory disease. For the proposed project we will use specimens prospectively collected from patients with pleural infection. Therefore, the disease relevance is very high. This project will involve phenotyping of real-world clinical samples. The generated biological data will be associated with clinical parameters and outcomes with the aim to discover biomarkers for patient stratification. This is a methodology which we have developed, applied in previous in previous projects and published.

Key Technology

This project involves the application of cutting-edge technologies like next generation sequencing and deep phenotyping of clinical samples:

- cfDNA next generation sequencing using the Nanopore platform
- Blood and pleural fluid prospectively collected from patients

Training Opportunities

The student will benefit from significant training opportunities. First, the cfDNA extraction, sequencing and state of the art analysis. The pipeline for this is already established. For this the student will receive bioinformatics training on the use of R and Python. Moreover, we will provide training for multi-omic data analysis and integration of diverse datasets.

Key Publications

1) The bacteriology of pleural infection (TORPIDS): an exploratory metagenomics analysis through next generation sequencing, Lancet Microbe. 2022 Apr;3(4):e294-e302. doi: 10.1016/S2666-5247(21)00327-X. Epub 2022 Mar 11.
2) Pleural fluid proteomics from patients with pleural infection shows signatures of diverse neutrophilic responses: The Oxford Pleural Infection Endotyping Study (TORPIDS-2), Eur Respir J. 2025 Jul 14;66(1):2500010. doi: 10.1183/13993003.00010-2025. Print 2025 Jul.
3) The circulating cell-free DNA landscape in sepsis is dominated by impaired liver clearance Cell Genom. 2025 Aug 7:100971. doi: 10.1016/j.xgen.2025.100971.
4) Epigenetics, fragmentomics, and topology of cell-free DNA in liquid biopsies, Science, 2021 Apr 9;372(6538):eaaw3616. doi: 10.1126/science.aaw3616.
5) Prospective validation of the RAPID clinical risk prediction score in adult patients with pleural infection: the PILOT study Eur Respir J 2020 Nov 26;56(5):2000130. doi: 10.1183/13993003.00130-2020. Print 2020 Nov.

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4.2 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 Relevance

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
2) Yazicioglu Y*, Marin E*, Bentkowska K, Andrew H, Johnstone J, Mitchell R, Wong Z, Zec K, Fergusson J, Borsa M, Raza IG, Attar M, Ali M, Kronsteiner B, Furlani I, MacRae J, Devine MJ, Coles M, Buckley C, Dunachie S, Clarke AJ. Asparagine availability controls germinal centre B cell homeostasis. Science Immunology. 2024. 9(102), pp. eadl4613 *Equal authorship.
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
4) Psarras A, Clarke AJ. A cellular overview of immunometabolism in systemic lupus erythematosus. Oxford Open Immunology. 2023. 4(1): iqad005
5) Müschen, M. (2019). Metabolic gatekeepers to safeguard against autoimmunity and oncogenic B cell transformation. Nat Rev Immunol, DOI: 10.1038/s41577-019-0154-3

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4.3 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. 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, 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. 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. 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.

Disease Relevance

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

1) Khoyratty T*, Ai Z*, Ballesteros I, Mathie S, … **Udalova IA**. Distinct transcription factor networks control neutrophil-driven inflammation. ***Nature Immunology***, 2021 Sep;22(9):1093-1106.
2) Wang L, Luqmani R, Udalova IA. The role of neutrophils in rheumatic disease-associated vascular inflammation. Nature Reviews Rheumatology. 2022 Mar;18(3):158-170.
3) Thomas T, Friedrich M, Rich-Griffin C, Pohin M,…. **Buckley CD.** A longitudinal single-cell atlas of anti-tumour necrosis factor treatment in inflammatory bowel disease. Nat Immunol. 2024 Nov;25(11):2152-2165.
4) O Vipond, JA Bull, PS Macklin, U Tillman, CW Pugh*, **HM Byrne***, HA Harrington* (2021). Multiparameter persistent homology landscapes identify immune cell spatial patterns in tumours. PNAS 118 (41): e2102166118.
5) **Devaprasad A**, Ai Z, Mukherjee AK,…. **Udalova IA** (2024). Zfp263 is a transcriptional checkpoint of neutrophil development. BioRxiv. 2024.08.22.609132.

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4.4 Large-scale data analytics on longitudinal electronic health records to understand the clinical trajectories and outcome of HBV infection

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Project Overview

This DPhil focuses on applying big data analytics, statistical methods, and machine learning to analyse large, multi-centre longitudinal electronic health records (EHRs) routinely collected from the UK National Health Service (NHS) secondary care services. The aim is to improve understanding of the clinical trajectories and outcomes of chronic hepatitis B virus (HBV) infection.

This is an exciting opportunity to contribute to a significant research programme addressing one of the most important challenges—and opportunities—in clinical medicine. The group leads the National Institute for Health and Care Research (NIHR) Health Informatics Collaborative (HIC) Viral Hepatitis and Liver Disease theme, a nationwide initiative collecting EHR data from patients with viral hepatitis to use in research for patient benefit. This collaboration has established a large longitudinal dataset from nine NHS trusts (with more joining) across England, comprising laboratory results, demographics, comorbidities, treatment and clinical information, imaging reports, and pathology reports. The studentship will have access to this established comprehensive dataset to address relevant research questions.

The group is at the forefront of national health informatics collaboration and uses these resources to uncover patterns in disease progression and generate actionable insights into patient outcomes. The student will gain hands-on experience in healthcare data science and have opportunities to collaborate across disciplines. With the group’s combined expertise in data science, infectious diseases, hepatology, and informatics, the student will develop statistics or machine learning-based models and validate them using these established datasets. There may also be opportunities to design and prototype clinical tools.

Specific areas that may be explored include: understanding HBV dynamics and predictive modelling for key biomarkers; investigating treatment eligibility and outcomes; understanding those individuals who do not suppress viraemia on antiviral treatment; identifying patients most at risk for severe outcomes including liver cirrhosis, decompensation, and hepatocellular carcinoma (HCC, the most common primary liver cancer).

The DPhil will benefit from an interdisciplinary supervision team. Dr Tingyan Wang is an NIHR Advanced Fellow and Senior Data Scientist with over ten years’ experience in machine learning, statistical methods, and natural language processing for healthcare research. Over the past six years, she has focused on hepatitis B, leading data-driven research on treatment responses and infection outcomes within the NIHR HIC Viral Hepatitis and Liver Disease theme, and collaborating with industry to provide evidence for clinical trials in HBV new drug development. Professor Philippa Matthews, is a clinician (Consultant) in Clinical Infection and a Clinical Group Leader at the Francis Crick Institute. Her research focuses on HBV infection, employing a range of methods to explore the interaction between host and pathogen aiming to develop improved understanding of the infection’s burden and characteristics, improve monitoring and treatment methods, and guide preventive interventions. She is also a Clinical co-Lead of the NIHR HIC

Viral Hepatitis and Liver Disease Theme. Professor Paul Klenerman is an internationally recognised clinician scientist who has made major contributions to viral immunology. His research focuses on understanding host immune responses to persistent virus infections, and liver/gut defence mechanisms.

Disease Relevance

Chronic hepatitis B (CHB) affects an estimated 254 million people worldwide and caused over 1.1 million deaths in 2022. Individuals with CHB are at increased risk of progression to severe stages including liver cirrhosis and HCC. Risk prediction is critical for guiding treatment and screening, yet current management of CHB is hindered by limited understanding of long-term disease trajectories and insufficient predictive tools.

Long-term antiviral treatment with nucleos(t)ide analogue (NA) suppresses HBV replication and reduces the long-term risk of cirrhosis and HCC, but eligibility criteria remain restrictive. Recent guidelines from the WHO (2024), EASL (2025), and China (2022) recommend broader treatment, recognising the potential benefits of relaxed and simplified treatment criteria. As an increasing number of individuals embark on NA therapy, there is a pressing need to understand therapeutic responses, and to identify and interpret the clinical significance of situations in which virologic suppression is inadequate.

By integrating epidemiological, clinical, and laboratory data, the research aims to better understand trajectories and outcomes, supporting more effective patient stratification and management. These findings will directly inform clinical guidelines and public health strategies, with the potential to improve outcomes and reduce disease burden.

Key Technology

This project will apply advanced data analytics to analyse large-scale, longitudinal electronic health records (EHRs) to generate new insights into chronic hepatitis B. We have established a diverse cohort of >24,000 patients, representing ~10% of the UK HBV population, with follow-up spanning 2 to 20 years. The dataset incorporates laboratory, clinical, and treatment information across multiple NHS secondary care centres, creating one of the largest longitudinal resources for HBV outside clinical trials. Its size and depth enable robust analysis of risk factors, therapeutic responses, and long-term outcomes across heterogeneous patient groups.

The core technologies of this project will combine statistical modelling and machine learning approaches tailored to time-series and survival analysis, with natural language processing (NLP) including large language models (LLMs) to extract insights from unstructured clinical text such as radiology and pathology reports. These methods will be developed into reproducible pipelines for analysing complex healthcare data, supporting prediction of clinical outcomes, and translation of findings into strategies for improving patient care.

By integrating rich, heterogeneous data sources including demographics, diagnoses, laboratory results, treatment, imaging and pathology reports, and long-term outcomes, the project will create a comprehensive picture of clinical trajectories in chronic hepatitis B. This multimodal dataset will also support the study of comorbidities such as obesity, steatotic liver disease, diabetes, and viral coinfections, and their impact on outcomes.

Analyses will be conducted in secure Trusted Research Environments, using cloud-based and GPU-enabled computing for scalability. Together, these technologies will transform routinely collected healthcare records into actionable insights for CHB management. The resulting models and predictive tools will inform clinical decision-making, guide public health strategies, and provide an evidence base for novel therapeutic development in HBV.

Training Opportunities

This DPhil offers outstanding training in data analytics, machine/deep learning, statistical methods, and natural language processing including large language models for healthcare data analysis. The studentship provides access to a large anonymised dataset within a secure Trusted Research Environment (TRE) for large-scale analysis and GPU-enabled computing, enabling real-world application of advanced healthcare data science methodologies.

The student will join a collaborative, interdisciplinary research environment supported by a group with broad expertise in data science, infectious diseases, hepatology, and clinical informatics. Our group works closely with other teams, including the Clinical Informatics Group leading the Thames Valley and Surrey Secure Data Environment (TVS SDE) programme, part of the NHS SDE network. We also lead collaborations with the pharmaceutical industry, generating real-world data insights to support HBV drug development. The student will gain skills to work at the interface of academia, the NHS, public health, and industry.

The studentship is affiliated with the Nuffield Department of Medicine and is based at the Peter Medawar Building for Pathogen Research (PMB), where the student can engage with renowned scientists and clinicians in infectious diseases, hepatology/gastroenterology, and related fields. The PMB houses around 150 scientists, studying immune responses to viral infection including HBV—focusing on the host, the pathogen, and genomics—providing valuable context for the DPhil research. Meanwhile, the studentship provides access to the Big Data Institute (BDI) on Oxford’s Old Road Campus, which offers a vibrant environment for data-driven research and cross-disciplinary collaboration. BDI hosts over 30 group leaders and 300 staff, where you will engage with researchers in data science and AI. It also regularly features national and international speakers. Closely linked to the NHS, BDI hosts the NIHR Oxford Biomedical Research Centre, the Academic Health Science Centre, and the EPSRC Centre for Doctoral Training in Healthcare Data Science.

Key Publications

1) Wang T, Campbell C, Stockdale AJ, .., Barnes E[#], Matthews PC[#]. 2025. Distinct virologic trajectories in chronic hepatitis B identify heterogeneity in response to nucleos(t)ide analogue therapy. *JHEP Reports*, 7(1): 101229.
2) Campbell C, Wang T, Gillespie I, Barnes E, Matthews PC[#]. 2024. Analysis of electronic health record data of hepatitis B virus (HBV) patients in primary care: hepatocellular carcinoma (HCC) risk associated with socioeconomic deprivation. *Public health,* 226: 215.
3) Gillespie IA, Barnes E, Wong IC, Matthews PC, Cooke GS, Tipple C, Elston RC, Liu Y, Smith DA, Wang T, Davies J, et al. 2023. Patient Biochemistry and Treatment Need in Chronic Hepatitis B Virus Infection Across Three Continents: Retrospective Cross-Sectional Cohort Studies. *Infectious Diseases and Therapy*, 12(11):2513-32.
4) Wang T, Smith DA, Campbell C,..., Davies J, Barnes E[#], Matthews PC. 2022. Cohort Profile: The National Institute for Health Research Health Informatics Collaborative: Hepatitis B Virus (NIHR HIC HBV) research dataset. *International Journal of Epidemiology*, 52(1): e27-e37.
5) Smith DA[†], Wang T[†], Freeman O[†], Crichton C, Salih H, Matthews PC, Davies J, …, Barnes E[#]. 2020. National Institute for Health Research Health Informatics Collaborative (NIHR HIC): development of a pipeline to collate electronic clinical data for viral hepatitis research. *BMJ Health & Care Informatics*, 27(3):e100145

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Theme 5. Neuroscience

5.1 Perfusable Lymphoid Organ-on-a-Chip: Towards Personalised Glioma Immunotherapy

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Project Overview

Background

Immunotherapy has reshaped cancer care, yet adult diffuse gliomas still resist durable control due to profound immunosuppressive myeloid populations, sparse T-cell infiltration, and cancer-associated antigen heterogeneity. Cancer vaccines are promising, but only a subset of patients mount meaningful responses, and we lack a functional, patient-specific way to predict benefit.

This DPhil project will aim to model and validate a perfusable lymphoid organ-on-a-chip (LO-chip) as a human screening platform for glioma vaccines and immune therapy combinations. Patient peripheral blood mononuclear cells (and, where available, tumour-infiltrating lymphocytes) will be embedded in a dual-channel microfluidic device that supports continuous perfusion, recirculation, and real-time sampling. We will present clinically relevant antigens (e.g., EGFRvIII, IDH1 R132H, H3K27M, PTPRZ1), autologous tumour lysates, and mRNA LNP vaccines ± immune checkpoint blockade; with subsequent resolution of antigen-specific B- and T-cell responses by multiparameter flow cytometry for activation induced markers, and single-cell RNA/VDJ sequencing.

Beyond ranking vaccine strategies, the platform enables recovery of tumour-reactive BCRs/TCRs for downstream CAR/TCR engineering and target discovery, accelerating translation to early-phase trials.

Objectives & outcomes

- Build and benchmark the LO-chip: optimise extracellular matrices, flow rates, and stimulation; demonstrate specificity and reproducibility vs 2D/3D controls.
- Functionally screen vaccine targets: quantify priming, activation, class switching, and cytotoxic programmes in patient PBMCs/TILs; prioritise patient-matched regimens.
- Create a adaptive immune receptor library to recover antigen-specific BCRs/TCRs

Methods

Microfluidic organ-on-chip (perfusion/recirculation), ECM scaffolds, mRNA LNP vaccines, autologous tumour lysates, multiparameter flow cytometry with antigen-specific probes, ELISA/multiplex cytokines, 10x Genomics scRNA-seq/VDJ, recombinant antibody engineering, CAR T development, discovery proteomics and surface plasmon resonance for target validation.

Supervision

Dr Bo Sun (Neuro-immunology), Prof Tao Dong (T-cell immunology) and Associate Prof Olaf Ansorge (Neuropathology)

Disease Relevance

Gliomas account for ~80% of adult primary brain cancers and carry poor prognoses despite maximal surgery, radiotherapy, and temozolomide. Immune checkpoint inhibitors and CAR-T therapies have underperformed in glioma compared to other tumours, largely due to an immunosuppressive microenvironment, low neoantigen visibility, and poor T-cell trafficking. Cancer vaccines are attractive because they can prime durable, tumour-specific responses; however, clinical translation has been inconsistent and heterogenous subsets of patients mount robust responses.

By providing a patient-specific functional testbed, the LO-chip can forecast which antigens and combinations (e.g., vaccine ± ICI, tumour lysate adjuvants) elicit meaningful B- and T-cell immunity. This can triage candidates for trials, match patients to the most promising strategy, and generate therapeutic leads (BCRs/TCRs) for engineered cell therapies. The platform directly addresses a critical unmet need in glioblastoma and IDH-mutant astrocytoma, with potential to improve response rates, extend survival, and reduce futile exposure to ineffective interventions.

Key Technology

- **Perfusable lymphoid organ-on-a-chip**: Dual-channel microfluidic device enabling continuous perfusion/recirculation, precise dosing, longitudinal sampling, and immune-cell migration within extracellular matrix (ECM) scaffolds.
- **Antigen delivery formats**: Messenger RNA (mRNA) lipid nanoparticle (LNP) vaccines encoding glioma antigens (and controls), autologous tumour lysates, and combinatorial regimens with immune checkpoint inhibitors (ICIs).
- **High-resolution immunophenotyping**: Multiparameter flow cytometry (B-cell differentiation, antigen-presenting cell (APC) activation, T-helper/cytotoxic function), antigen-specific B-cell probes (protein tetramers), T-cell proliferation and function assays, and multiplex cytokine/chemokine quantification (e.g., interleukin-1 beta, interleukin-6, interferon gamma, tumour necrosis factor alpha).
- **Single-cell multi-omics**: 10x Genomics single-cell RNA sequencing (scRNA-seq) for state/trajectory mapping; 10x variable/diversity/joining (VDJ) for recovery of antigen-specific B-cell receptors (BCRs) and T-cell receptors (TCRs); integrated bioinformatics (batch correction with single-cell variational inference (scVI), Leiden clustering, differential testing, receptor repertoire statistics).
- **Target discovery & biophysics**: Immunoprecipitation with recombinant monoclonal antibodies from expanded B-cell clones, followed by discovery proteomics (liquid chromatography-tandem mass spectrometry, LC-MS/MS) and binding validation (surface plasmon resonance, SPR).
- **Comparative benchmarking**: Matched conventional peripheral blood mononuclear cell (PBMC) stimulation assays to quantify added value of perfusion and three-dimensional (3D) context (relative to two-dimensional (2D) controls).

Training Opportunities

- You'll receive broad, interdisciplinary training across wet-lab, microphysiology and computational analysis:
- Experimental immunology & microfluidics: Primary human peripheral blood lymphocyte/tumour infiltrating lymphocyte handling; dual-channel chip setup (perfusion/recirculation/sampling); mRNA lipid nanoparticle vaccine preparation; antigen dosing; longitudinal readouts under flow.
- Immune profiling: Panel design and multiparameter flow; antigen-specific probes (protein/MHC tetramers); ELISA/multiplex cytokines; live-cell imaging.
- Single-cell & repertoires: 10x scRNA-seq + VDJ; analysis pipelines; Adaptive Immune Receptor Repertoire analysis.
- Target discovery & biophysics: Recombinant expression of monoclonals from expanded B-cell clones; immunoprecipitation; discovery proteomics (LC-MS/MS); surface plasmon resonance validation.
- Computation & reproducibility: R/Python, version-controlled notebooks, robust metadata handling, statistics (parametric/non-parametric tests; multiple-testing control).
- Translational skills: Research governance/ethics for patient samples; interdisciplinary collaboration; manuscript/grant writing; conference presentations.

Key Publications

1) **Sun, B.,** Fernandes, D., Soltys, J., Kienzler, A.-K., Paneva, S., Harrison, R., Ramanathan, S., Harrison, A. L., Makuch, M., Fichtner, M. L., Donat, R. F., Akdeniz, D., Bayuangga, H., Im, M. G., Williams, R., Vasconcelos, A., Thomsen, S., Fower, A., Sun, R., … Irani, S. R. (2025). Permissive central tolerance plus defective peripheral checkpoints license pathogenic memory B cells in CASPR2-antibody encephalitis. *Science Advances*, *11*(16), eadr9986. https://doi.org/10.1126/sciadv.adr9986
2) Ng, E. S., Milotay, G., Tong, O., A. Taylor, C., Sun, S., Niu, G., Watson, R., **Sun, B**., MacKay, S., Gilchrist, J. J., Little, M., Fairfax, B. P., & Luo, Y. (2025). Defining the genetic determinants of CD8+ T cell receptor repertoire in the context of immune checkpoint blockade. *Science Advances*, *11*(30), eadu3461. https://doi.org/10.1126/sciadv.adu3461
3) **Sun, B**., da Costa, K. A. S., Alrubayyi, A., Kokici, J., Fisher-Pearson, N., Hussain, N., D'Anna, S., Piermatteo, L., Salpini, R., Svicher, V., Kucykowicz, S., Ghosh, I., Burns, F., Kinloch, S., Simoes, P., Bhagani, S., Kennedy, P. T. F., Maini, M. K., Bashford-Rogers, R., … Peppa, D. (2024). HIV/HBV coinfection remodels the immune landscape and natural killer cell ADCC functional responses. *Hepatology*, *80*(3).
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5) Sivakumar, S., Jainarayanan, A., Arbe-Barnes, E., Sharma, P. K., Leathlobhair, M. N., Amin, S., Reiss, D. J., Heij, L., Hegde, S., Magen, A., Tucci, F., **Sun, B.,** et al., … Bashford-Rogers, R. (2025). Distinct immune cell infiltration patterns in pancreatic ductal adenocarcinoma (PDAC) exhibit divergent immune cell selection and immunosuppressive mechanisms. *Nature Communications*, *16*(1), 1397. https://doi.org/10.1038/s41467-024-55424-2

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5.2 Lipid nanoparticle functionalisation

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Project Overview

Roughly 1 in 17 people are estimated to suffer from a rare genetic disorder, with 95% of disorders lacking approved treatments. There are increasing efforts to develop gene therapies, but most efforts fail for similar reasons – failure to deliver enough of the gene to the target organ/tissue safely. The most popular vector for delivering gene therapies has been the adeno associated viruses (AAV). However, AAV have a very limited cargo size (~4.5Kb), and despite being relatively safe in comparison to other viral vectors, have caused numerous serious side effects and even several deaths in patients. Therefore, there is a global change in direction away from the use of AAV, with many pharmaceutical companies stopping their AAV gene therapy programs.

The use of lipid nanoparticles (LNP) for delivering DNA and RNA based treatments has gained increasing traction in enzyme replacement therapies, gene editing treatments, and more recently in mRNA vaccines. However, the biodistribution of current formulations are still mostly limited to the liver when injected systemically.

We propose to mimic our own body's strategy for reducing non-specific targeting –glycans. Almost all proteins and exosomes in circulation are glycosylated, and these serve to prevent non-specific interactions, and sometimes help to mediate specific interactions with lectins. We will test a range of glycoproteins and glycolipids to see how they change the biodistribution of lipid nanoparticles, and see if they can reduce liver targeting, and increase delivery of genes to target tissues and organs.

Successful delivery of genes into target tissues and organs of interest will lead to pilot studies for delivering gene therapies into animal models of congenital diseases such as congenital myasthenia and congenital disorders of glycosylation.

Disease Relevance

LNP are a platform technology that is used for the delivery of vaccines, gene therapies, gene editing treatments and metabolites. They have enormous potential for a huge variety of medical applications.

Key Technology

Lipid and protein reconstitution to make LNP

Fluorescent microscopy will be used to look at the localisation of lipids, proteins and genes delivered by lipid nanoparticles into cells and tissues.

In vivo imaging to look at the biodistribution in live mice.

Digital droplet PCR will be used to quantify DNA delivery into different tissues and organs to assess biodistribution post-mortem.

Training Opportunities

This project offers a unique opportunity for working with all four major biological macromolecules, study their biochemistry, and how they interact with *in vitro* and *in vivo* biological systems. They will learn how to formulate these different macromolecules to make LNP, and use a variety of analytical tools to determine the biodistribution of the LNP and its cargo.

Training will also be available to obtain a personal license for working with mice, and further training will be provided to carry out restricted procedures in live animals, as well as in post-mortem tissue dissection to isolate different organs and tissues.

Key Publications

1) Cossins J, Kozma I, Canzonetta C, Hawkins A, Beeson D, Sepulveda P, Dong YY. Dose escalation pre-clinical trial of novel DOK7-AAV in mouse model of DOK7 congenital myasthenia. BrainCommunications. 2025;7(1):fcaf046.
2) Li A, Pike AC, Webster R, Maxwell S, Liu WW, Chi G, Palace J, Beeson D, Sauer DB, Dong YY. Structures of the human adult muscle-type nicotinic receptor in resting and desensitised states. Cell Reports. 2025 May 27;44(5):115581.
3) Dong YY, Wang H, Pike ACW, Cochrane SA, Hamedzadeh S, Wyszyński FJ, Bushell SR, Royer SF, Widdick DA, Sajid A, Boshoff HI, Park Y, Lucas R, Liu WM, Lee SS, Machida T, Minall L, Mehmood S, Belaya K, Liu WW, Chu A, Shrestha L, Mukhopadhyay SMM, Strain-Damerell C, Chalk R, Burgess-Brown NA, Bibb MJ, Barry CE 3rd, Robinson CV, Beeson D, Davis BG, Carpenter EP. Structures of DPAGT1 explain glycosylation disease mechanisms and advance TB antibiotic design. Cell. 2018;175(4):1045-1058.e16.
4) Dong YY, Pike ACW, Mackenzie A, McClenaghan C, Aryal P, Dong L, Quigley A, Grieben M, Goubin S, Mukhopadhyay S, Ruda GF, Clausen MV, Cao L, Brennan PE, Burgess-Brown NA, Sansom MSP, Tucker SJ, Carpenter EP. K2P channel gating mechanisms revealed by structures of TREK-2 and a complex with Prozac. Science. 2015;347(6227):1256-9.
5) Andrew Quigley*, Yin Yao Dong*, Ashley C W Pike*, Liang Dong, Leela Shrestha, Georgina Berridge, Phillip J Stansfeld, Mark S P Sansom, Aled M Edwards, Chas Bountra, Frank von Delft, Alex N Bullock, Nicola A Burgess-Brown, Elisabeth P Carpenter. The structural basis of ZMPSTE24-dependent laminopathies. Science. 2013 339(6127):1604-7 * Joint 1st authors

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5.3 Developing cortical network biomarkers in amyotrophic lateral sclerosis

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Project Overview

This is a **neuroimaging project** in **amyotrophic lateral sclerosis** (ALS), one of the most rapidly progressive neurodegenerative diseases. Pathology in ALS is increasingly understood to be at a network level in the brain. The work will suit someone interested in **developing a deep knowledge of the clinical syndrome of ALS** (and its overlap with frontotemporal dementia, FTD), keen on learning **advanced neuroimaging analysis** involving **higher-level statistics and basic coding**, alongside practical experience of working with human research participants and data.

The **Oxford ALS group** (in collaboration with the Oxford Centre for Human Brain Activity, OHBA) **has led the field** in the application of superconducting quantum interference device (SQUID)-based **magnetoencephalography (MEG)** in ALS. We have identified consistent changes in the **beta frequency bursting** patterns at rest, and **gamma activity** during activity, with the potential to serve as biomarkers of therapeutic response. Dynamic network modelling has revealed dramatic **cortical network changes prior to symptoms** in carriers of the *C9orf72* hexanucleotide expansion which accounts for 10% of all European and North American ALS.

This project will be **among the first in the world** to employ wearable optically pumped magnetometer–based magnetoencephalography (**OPM-MEG**) to investigate cortical dysfunction in ALS, including asymptomatic individuals at high genetic risk of ALS and FTD as carriers of the *C9orf72* expansion. OPM-MEG offers **increased cortical sensitivity,** flexibility, and the capacity to measure **brain activity during more naturalistic movement**. This represents a step-change in our ability to capture and characterise biomarkers of ALS-related dysfunction before as well as after the ‘clinical horizon’.

The student can **initially leverage a rich existing dataset** of SQUID-MEG recordings (with structural MRI data) in affected ALS patients, *C9orf72* expansion carriers, and healthy controls, through an ongoing Oxford-led cohort called ‘ACORN’. By integrating these data with newly collected OPM-MEG recordings, the student will explore:

1) Using OPM-MEG during naturalistic movement tasks (e.g. stand and walk).
2) Corticomuscular coherence (CMC) and cortical disinhibition in ALS and at-risk carriers as a source of novel biomarkers.
3) Cross-modality integration of OPM-MEG and SQUID-MEG, to identify convergent markers of cortical dysfunction.

DPhil basic structure:

- Year 1: Training in MEG acquisition and analysis, recruitment, piloting of tasks, and initial OPM-MEG data collection.
- Year 2: Continued data collection, interim analyses and multimodal integration
- Year 3: Analysis of gene carriers, advanced multimodal analyses, thesis write-up.

Disease Relevance

ALS is one of the most rapidly-progressive neurodegenerative diseases, characterised by progressive motor system dysfunction, leading to death within 30 months of first weakness for half of affected individuals. There is currently no highly effective disease-slowing therapy, with a uniquely high individual, carer and societal burden of disease. ALS is fundamentally a brain pathology, forming a clinicopathological and genetic spectrum with frontotemporal dementia (FTD).

A major barrier to therapeutic development in ALS-FTD is the lack of biomarkers to demonstrate therapeutic benefit of candidate drugs more sensitively than the currently used outcome measures of disability accrual or survival. Any hope for prevention strategies in the 15% of ALS cases linked to monogenetic variants, most commonly a hexanucleotide expansion in *C9orf72*, will need to capture the very earliest pathological and compensatory changes.

Key Technology

Pathogenesis in ALS-FTD involves changes at the neuronal network level that require tools sensitive to cortical neurophysiology. MEG is the leading technology for this approach and an area of rapid development, with internationally leading analysis expertise at OHBA. MEG has already shown leading biomarker promise in ALS using SQUID-based technology in the resting state and during hand grip tasks.

The core emerging technology underpinning this project is wearable OPM-MEG, a recent innovation that overcomes several limitations of conventional MEG. OPMs do not require cryogenic cooling, enabling lightweight, scalp-mounted sensors that move with the head. This improves signal-to-noise ratio, particularly for deep and frontal brain regions, and allows participants to perform naturalistic motor tasks not possible in SQUID-MEG systems.

In ALS, OPM-MEG has particular interest because it has the potential to enable the study of motor cortex-muscle synchrony (CMC) and cortical disinhibition (thought to be be underpinned by interneuronal changes), during movements such as reaching, grasping, sit-to-stand transitions and walking.

As well as training the candidate in core principles of neuroimaging analysis, this project will integrate OPM-MEG data with SQUID-MEG datasets collected in ALS, controls, and gene carriers through the ACORN study.

Such multimodal integration offers a unique opportunity to cross-validate cortical markers across techniques and modalities, strengthening their potential as clinical biomarkers. The combination of cutting-edge OPM-MEG acquisition, established imaging datasets, and advanced analysis pipelines (e.g. FSL, OHBA MEG analysis tools) places this project at the forefront of brain network analysis.

Training Opportunities

This project provides an opportunity to be among the first to generate OPM-MEG data in those affected by ALS and also asymptomatic, high-risk genetic carriers, a population of immense scientific and translational value. The findings will inform mechanistic models of ALS progression and establish novel candidate biomarkers to improve therapeutic trials in affected individuals, and ultimately establish a framework for preventive interventions.

The student will join a highly interdisciplinary team within the University of Oxford's Nuffield Department of Clinical Neurosciences (NDCN). This incorporates the world-leading Oxford Centre for Integrative Neuroimaging (OxCIN, based at the OHBA site), with expertise spanning multimodal neuroimaging across species as well as the full range of clinical neuroscience. They will receive training in:

- Neuroimaging methods: Hands-on training in OPM-MEG acquisition and analysis; integration with SQUID-MEG and MRI data.
- Formal courses: Oxford's world-leading FSL course, the MRI graduate training programme, and workshops on MEG data analysis at OHBA.
- 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 in MEG and MRI
- Collaborative environment within OHBA and, with opportunities to interact with physicists and computational neuroscientists.
- Transferable skills development, including coding (Python, MATLAB), statistical modelling, and multimodal data integration.
- Career development support, including encouragement for presentation of data at national and international conferences and manuscript preparation.

Key Publications

1) Brickwedde, M., Anders, P., Kühn, A. A., Lofredi, R., Holtkamp, M., Kaindl, A. M., ... & Uhlhaas, P. J. (2024). Applications of OPM-MEG for translational neuroscience: a perspective. **Translational Psychiatry**, 14(1), 341.
2) Trubshaw, M., Gohil, C., Yoganathan, K., Kohl, O., Edmond, E., Proudfoot, M., ... & Turner, M. R. (2024). The cortical neurophysiological signature of amyotrophic lateral sclerosis. **Brain Communications**, 6(3), fcae164.
3) Trubshaw, M., Yoganathan, K., Gohil, C., Stagg, C. J., Nobre, A. C., Talbot, K., ... & Turner, M. R. (2025). Gamma activation spread reflects disease activity in amyotrophic lateral sclerosis. **Clinical Neurophysiology**, 2110823.
4) Yoganathan, K., Trubshaw, M., Kohl, O., Gohil, C., Echeverria-Altuna, I., Dharmadasa, T., ... & Turner, M. R. (2025). Reduced beta bursting underpins loss of corticomuscular coherence in amyotrophic lateral sclerosis. **Brain Communications**, in press.
5) Trubshaw, M., Gohil C., Edmond E., Proudfoot, M., Yoganathan, K., Wuu, J., … & Turner M.R. (2025). Divergent brain network activity in asymptomatic *C9orf72* and *SOD1* variant carriers compared with established amyotrophic lateral sclerosis. **Human Brain Mapping**, in press.

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Theme 6. Population & Public Health

6.1 Chronic infection, immunity and inflammation in disease aetiology

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Project Overview

Several infectious pathogens are well-established causes of certain cancers, including for example *H. pylori* for stomach cancer, HBV/HCV for liver cancer, and HPV for cervical cancer. However, uncertainties persist on their causal relevance for other cancer types and diseases, the health effects of other chronic infections (e.g. certain types of herpesviruses), and the roles of host immunity, chronic inflammation and pathogen subtypes in the aetiology of cancers and other non-neoplastic conditions (e.g. cardiometabolic, autoimmune, and neurodegenerative diseases). Large prospective biobank studies, such as China Kadoorie Biobank (CKB: www.ckbiobank.org) and UK Biobank (UKB: www.ukbiobank.ac.uk) with heterogeneity in patterns of chronic infection, disease rates and genetic architecture can help address many evidence gaps.

CKB and UKB have measured IgG antibody levels against ~50 antigens from 20 pathogens (i.e. bacteria, parasite and virus), using a custom-designed multiplex serological panel, among about 100,000 (CKB: 40K; UKB: 60K) participants. Together with extensive demographic, lifestyle, genetic (e.g., genotyping and WGS), multi-omics (e.g., proteomics, metabolomics, blood biochemistry) and health outcome data collected, these serological data will enable comprehensive assessment of the causal roles and molecular pathways of multiple chronic pathogen infections in the aetiology of cancers and other non-neoplastic diseases.

The DPhil project will be developed according to the student's interests and aptitude, with the potential to focus on specific disease(s) or chronic infection of particular pathogen(s), or both. Some of the key research objectives may include:

1) Examining the associations of chronic infection(s) with risks of disease(s) and estimating the infection-attributable disease burden in both populations;
2) Evaluating the role of host genetics (e.g. HLA variants) in susceptibility to development of specific types of chronic infection and related disease(s);
3) Elucidating the interplay between infections, host immunity, inflammatory pathways and identify potential drug targets, by using integrative analyses of genetics and multi-omics data;
4) Assessing the predictive value of individual and co-infecting pathogens, in combination with lifestyle, environmental, and genetic factors, for estimating disease(s) risk across diverse populations.

Disease Relevance

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

Key Technology

- This project will use high-dimensional multi-omics datasets, including multiplex serolomics, whole genome sequencing, proteomics, metabolomics, combined with detailed questionnaire data, physical measurements, and electronic health records, for ~100,000 individuals from diverse populations.
- Conventional and novel analytic approaches, such as linear, Cox regression, squencing-based GWAS, Mendelian randomisation, co-localisation, genome-to-genome analysis and maching learning will be applied to address specific research questions. Analyses will explicitly account for potential sources of bias, including confounding, reverse causation, multiple testing, collider bias and pleiotropy, to ensure robust interpretation of results.
- Findings will be compared, replicated and meta-analysed across CKB and UKB, and with other studies and/or publicly available datasets.

Training Opportunities

The student will work within a multi-disciplinary research team, and will have various training opportunities and gain research experience in a range of epidemiological methods. By the end of the DPhil, the student will be competent to plan, undertake and interpret analyses of large-scale datasets, and to report research findings, including publications in peer-reviewed journals as lead author and presentations at scientific conferences.

The student will be based in NDPH. There are excellent facilities and a world-class community of population health, data science, infectious disease, and genomic medicine researchers. There will be in-house training in epidemiology, statistics, and genetics and opportunities to work with internal collaborators and external research institutes.

Key Publications

1) Yang, L., C. Kartsonaki, P. Yao, C. de Martel, M. Plummer, D. Chapman, Y. Guo, S. Clark, R. G. Walters, Y. Chen, et al. The relative and attributable risks of cardia and non-cardia gastric cancer associated with Helicobacter pylori infection in China: a case-cohort study. *Lancet Public Health.* 2021; 6(12): e888-e896.
2) Yao, P., I. Millwood, C. Kartsonaki, A. J. Mentzer, N. Allen, R. Jeske, J. Butt, Y. Guo, Y. Chen, R. Walters, J. Lv, C. Yu, M. Plummer, C. de Martel, G. Clifford, L. M. Li, T. Waterboer, L. Yang and Z. Chen. Sero-prevalence of 19 infectious pathogens and associated factors among middle-aged and elderly Chinese adults: a cross-sectional study. *BMJ Open.* 2022; 12(5): e058353.
3) Hamilton, E. M., L. Yang, N. Wright, I. Turnbull, A. J. Mentzer, P. C. Matthews, Y. Chen, H. Du, C. Kartsonaki, Y. Pang, et al. Chronic hepatitis B virus infection and risk of stroke types: a prospective cohort study of 500,000 Chinese adults. *Stroke.* 2023; 54(12): 3046-3053.
4) Kartsonaki, C., P. Yao, J. Butt, R. Jeske, C. de Martel, M. Plummer, D. Sun, S. Clark, R. G. Walters, Y. Chen, J. Lv, C. Yu, M. Hill, R. Peto, L. Li, T. Waterboer, Z. Chen, I. Y. Millwood, L. Yang. Infectious pathogens and risk of esophageal, gastric and duodenal cancers and ulcers in China: A case-cohort study. *Int J Cancer* 2024; 154(8): 1423-32.
5) Yang, L., C. Kartsonaki, J. Simon, P. Yao, Y. Guo, J. Lv, R. G. Walters, Y. Chen, H. Fry, D. Avery, et al. Prospective evaluation of the relevance of Epstein–Barr virus antibodies for early detection of nasopharyngeal carcinoma in Chinese adults. *Int J Epidemiol* 2024; 53: 1-9.

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6.2 Multi-omics approaches to inform drug target discovery

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Project Overview

Functional genetic variants modify the expression and/or activity of proteins which may represent potential drug targets. These natural experiments in human populations can improve the drug development process, such as assisting in prioritising targets based on predicted efficacy, assessing safety, identifying alternative indications and informing clinical trial designs. 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 fulfil 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, serology) in all or subsets of participants. Previous research highlights the benefits of assessing drug targets using genetic data from diverse populations (www.ckbiobank.org/achievements/drug-targets).

The DPhil project will assess the biological pathways and clinical outcomes associated with genetic variation in potential therapeutic targets, and will identify novel protein 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 objectives:

1) Identifying potential novel therapeutic targets by analysing whole-genome sequencing data from CKB, UKB and other cohorts, to associate common and aggregated rare variants with specific diseases;
2) Prioritising proteins targets through integrated proteogenomic analyses —combining pQTL mapping, Mendelian randomisation and colocalization analyses to identify genetically-supported drug targets for specific diseases;
3) Using a phenome-wide (PheWAS) approach to assess the efficacy, safety, and alternative indications (i.e. repurposing) of established and emerging drug targets at different stages of clinical development, using relevant functional genetic variants and pQTLs;
4) Exploring the biological mechanisms and pathways of potential drug targets using multi-omics biomarker datasets including proteomics, metabolomics, metagenomics and serology.
5) Using machine learning and AI tools to assess target druggability, with potential follow-up and design of laboratory studies for prioritised drug targets for specific diseases.

Disease Relevance

CKB and UKB have long-term follow-up of over 20 years each, for several 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, or renal diseases.

Key Technology

- This project will use high-dimensional multi-omics datasets, including 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, such as linear, logistic and Cox regression, whole genome-wide association studies, rare variant gene burden tests, Mendelian randomisation, co-localisation and machine learning methods.
- 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 training in genetics, epidemiology, 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 presentations 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 and genomic medicine researchers. There will be opportunities to work with external partners from industry and other research institutions.

Key Publications

1) Wang B, Pozarickij A, Mazidi M, Wright N, Yao P, Said S, Iona A, Kartsonaki C, Fry H, Lin K, Chen Y, Du H, Avery D, Schmidt-Valle D, Yu C, Sun D, Lv J, Hill M, Li L, Bennett DA, Collins R, Walters RG, Clarke R, Millwood IY, Chen Z. Comparative studies of 2168 plasma proteins measured by two affinity-based platforms in 4000 Chinese adults. *Nat Commun.* 2025; 16(1):1869. doi: 10.1038/s41467-025-56935-2.
2) Yao P, Iona A, Pozarickij A, Said S, Wright N, Lin K, Millwood I, Fry H, Kartsonaki C, Mazidi M, Chen Y, Bragg F, Liu B, Yang L, Liu J, Avery D, Schmidt D, Sun D, Pei P, Lv J, Yu C, Hill M, Bennett D, Walters R, Li L, Clarke R, Du H, Chen Z. Proteomic Analyses in Diverse Populations Improved Risk Prediction and Identified New Drug Targets for Type 2 Diabetes. *Diabetes Care.* 2024; 47(6):1012-1019.
3) Holmes MV, Kartsonaki C, Boxall R, Lin K, Reeve N, Yu C, Lv J, Bennett DA, Hill MR, Yang L, Chen Y, Du H, Turnbull I, Collins R, Clarke RJ, Tobin MD, Li L, Millwood IY, Chen Z, Walters RG. PCSK9 genetic variants and risk of vascular and non-vascular diseases in Chinese and UK populations. *Eur J Prev Cardiol.* 2024; 31(8):1015-1025.
4) Fry H, Mazidi M, Kartsonaki C, Clarke R, Walters RG, Chen Z, Millwood IY. The Role of Furin and Its Therapeutic Potential in Cardiovascular Disease Risk. *Int J Mol Sci.* 2024; 25(17): 9237.
5) Millwood IY, Bennett DA, Holmes MV, Boxall R, Guo Y, Bian Z, Yang L, Sansome S, Chen Y, Du H, Yu C, Hacker A, Reilly DF, Tan Y, Hill MR, Chen J, Peto R, Shen H, Collins R, Clarke R, Li L, Walters RG, Chen Z. Association of CETP Gene Variants With Risk for Vascular and Nonvascular Diseases Among Chinese Adults. *JAMA Cardiol.* 2018; 3(1): 34-43.

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6.3 Obesity, molecular pathways and long-term health risks

Prof. Zhengming Chen, **Dr. Andri Iona** & **Prof. Fiona Bragg**

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Project Overview

Obesity is one of the most important global public health challenges of this century, currently affecting >900 million adults with rising prevalence in China and many other countries. Despite advances in our understanding of causes and consequences of obesity, many important research questions remain inadequately investigated, including the true disease burden attributed to high adiposity and the underlying mechanisms, optimal levels of adiposity associated with lowest overall disease burden in different populations, and the reasons why many lean or normal weight people develop metabolic diseases. Large prospective biobank studies, such as China Kadoorie Biobank (CKB: www.ckbiobank.org) and UK Biobank (UKB: www.ukbiobank.ac.uk) with heterogeneity in risk exposures, mean adiposity levels, disease rates and genetic architecture can help to address the evidence gaps.

In CKB and UKB, extensive data on lifestyle behaviours (e.g., diet, smoking, alcohol drinking, physical activity), adiposity traits (e.g., BMI, WC, WHR, %BF) and health outcomes (e.g., >100,000 deaths and >4 million episodes of hospitalisation in CKB) have been collected, complemented by large-scale, and still expanding, biological assays, involving genetics (genotyping and WGS), metabolomics (e.g., >5000 metabolites), proteomics (e.g., ~10,000 proteins) and other biomarkers (e.g., blood biochemistry, gut microbiome, serology) in all or subsets of participants. Integrative analyses of these data in diverse populations offer unique opportunities for novel discovery. Previous research in CKB highlights our achievements in obesity-related fields (www.ckbiobank.org/achievements/obesity).

The DPhil project will use an integrated approach to evaluate the epidemiology of obesity and develop precision health approaches for disease prediction, stratification and prevention in diverse populations. The specific area of research will be developed according to the student's interests and aptitude, and may include some of the following key objectives:

1) To examine and compare the associations of adiposity with risks of specific diseases, disease subtypes and multi-morbidity in Chinese and UK populations;
2) To determine the causal relevance of adiposity for disease risks, using Mendelian randomisation (MR) approaches;
3) To investigate the molecular mechanisms linking adiposity with specific diseases and traits, with a focus on metabolites and proteomics;
4) To identify protein biomarkers that may causally affect levels of adiposity using pQTLs identified in GWAS, and to explore potential druggability of known (e.g., GDF15, RET, GLP1, Leptin, FABP4) and new proteins using various downstream analyses (e.g., enrichment, KO mouse models, MR-PheWAS).
5) Using machine learning and AI tools to derive "molecular adiposity" that may better characterise metabolic health and identify high-risk individuals for early lifestyle intervention.

The research will help generate an adiposity-disease association atlas, assess cause-effect associations, clarify underlying mechanisms, discover molecular signatures of adiposity, explore ancestry differences, and identify potential drug targets for treatment of obesity and its associated diseases, informing the development of precision metabolic health.

Disease Relevance

CKB and UKB have long-term follow-up of over 20 years each, for several 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-omics datasets, including genetics, proteomics, metabolomics, metagenomics and serology, combined with detailed questionnaire data, physical measurements, and electronic health records, for over 1 million participants.
- Analytic methods will include conventional and genetic epidemiology, such as linear, logistic and Cox regression, whole genome-wide association studies, rare variant gene burden tests, Mendelian randomisation, co-localisation and machine learning methods. The analyses will be run on local servers and/or through a cloud-based research analysis platform.
- 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 other colleagues and 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 training in genetics, epidemiology, 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 epidemiological, genetic, proteomic, and metabolomics data, and report research findings, including conference presentations and 3-4 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 and genomic medicine researchers. There will be opportunities to work with local collaborators and external partners from industry and other research institutions.

Key Publications

1) Bragg F, Tung K, Guo Y, Iona A, DU H, Holmes M, Bian Z, Kartsonaki C, Chen Y, Yang L, Sun Q, Dong C, Chen J, Collins R, Peto R, Li L, Chen Z. Associations of general and central adiposity with incident diabetes in Chinese men and women. *Diabetes Care* 2018; 41: 494-502
2) Chen Z, Iona A, Parish S, Chen YP, Guo Y, Bragg F, Yang L, Bian Z, Holmes MV, Lewington S, Lacey B, Gao RQ, Liu F, Zhang ZZ, Chen JS, Walters RG, Collins R, Clarke R, Peto R, Li LM. Adiposity and risk of ischaemic and haemorrhagic stroke in 0.5 million Chinese men and women: a prospective cohort study. *Lancet Global Health* 2018; 6(6): e630-e640
3) Iona A, Bragg F, Fairhurst-Hunter Z, Millwood IY, Guo Y, Wright N, Lin K, Yang L, Du HD, Chen YP, Pei P, Cheng L, Schmidt D, Avery D, Yu CQ, Lv J, Clarke R, Walters R, Li LM, Parish S, Chen Z. Conventional and genetic associations of BMI with major vascular and non-vascular disease incidence and mortality in a relatively lean Chinese population: U-shaped relationship revisited. *Int J Epidemiol* 2024; 53(5): dyae125.
4) Iona A, Yao P, Pozarickij A, Kartsonaki C, Said S, Wright N, Lin K, Millwood I, Fry H, Mazidi M, Wang BH, Chen YP, Du HD, Yang L, Avery D, Schmidt D, Sun DJY, Pei P, Lv J, Yu CQ, Hill M, Chen JS, Bragg F, Bennett D, Walters R, Li LM, Clarke R, Chen Z. Proteo-genomic analyses in relatively lean Chinese adults identify proteins and pathways that affect general and central adiposity levels. *Commun Biol* 2024; 7(1): 1327.
5) Tinworth AC, Iona A, Yao P, Millwood IY, Fry H, Clarke J, Wang BH, Mazidi M, Kartsonaki C, Walters RG, Du HD, Yu CQ, Chen YP, Sun DJY, Yang L, Schmidt DV, Lv J, Avery D, Li LM, Bennett DA, Peto R, Clarke R, Bragg F, Chen Z. GDF15 and its receptors as pathways mediating smoking related weight change. *eBioMedicine* 2025; 117: 105806.

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6.4 How do we assess disease complexity and burden of disease to drive improvements in outcomes for infants undergoing surgery

Prof. Marian Knight & **Dr. Benjamin Allin**

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Project Overview

Every year in the UK approximately 500,000 children undergo an operation, the most complex of which are undertaken in hospitals that provide specialised surgical care. The long-term health and wellbeing of children with many complex surgical conditions is affected by the need for repeated operations, functional problems, for example incontinence, and multiple admissions to hospital. There is currently little robust evidence to guide how these children are treated, and this is significantly impacting long-term health and wellbeing. Better research on treatment effectiveness is needed.

One of the key questions underpinning choice of treatment is assessment of the complexity of a child's condition, and the impact of co-morbidities on outcomes of different surgical approaches. Using data from the newly developed Children's Surgery Outcomes Reporting System, the student will undertake a programme of research that will involve:

- Comprehensive review of the literature to assess the impact of different co-morbidities and other features of disease complexity on the number of operations, infections, quality of life and survival of children with these conditions
- Using data from CSOR, and other sources where available, describe the burden of co-morbidities and features of disease complexity amongst infants undergoing surgery
- Using data from CSOR, and other sources where available, develop a model to classify the impact of co-morbidities and other features of disease complexity on the outcomes of infants, using both machine learning (artificial intelligence) and standard statistical techniques.

Disease Relevance

Improved understanding of the factors associated with outcomes of surgery for children, and therefore the value of different approaches to improving outcomes through different surgical approaches.

Key Technology

The project will entail employing a range of different epidemiological techniques. Standard literature search, appraisal and review techniques will be used. Standard statistical and machine learning techniques will be used to develop algorithms to predict outcomes in large children's surgery datasets. This will involve data cleaning, imbalanced data handling, data pre-processing, feature description and selection, development of predictive models, and model validation and interpretation.

Training Opportunities

The student will work within a multi-disciplinary team and will gain research experience in literature review, epidemiological, statistical and machine learning methodology, study design and analysis. Students have access to relevant modules from the departmental MSc courses to obtain formal training in relevant techniques. Regular research meetings and workshops will be held which the candidate will be expected to attend and to present research findings.

Key Publications

1) Rivero-Arias O, Buckell J, Knight M, Craig BM, Ramakrishnan R, Kenny S, Allin B; CSOR Collaborative Group. Defining treatment success in children with surgical conditions. Arch Dis Child. 2024 Apr 18;109(5):377-386. doi: 10.1136/archdischild-2023-326156. PMID: 38135491; PMCID: PMC11041596.
2) Allin BSR, Opondo C, Bradnock T, Kenny SE, Kurinczuk JJ, Walker G, Knight M; For and on behalf of the NETS(2HD) collaboration. Impact of rectal dissection technique on primary-school-age outcomes for a British and Irish cohort of children with Hirschsprung disease. J Pediatr Surg. 2022 Dec;57(12):902-911. doi: 10.1016/j.jpedsurg.2022.05.006. Epub 2022 May 20. PMID: 35934524.
3) Burdall O, Allin B, Ford K, Gupta A, Lakhoo K, Knight M, Hall NJ; For and on behalf of the BAPS-CASS NEC Collaboration. Association between timing of re-introduction of enteral feeding and short-term outcomes following laparotomy for necrotising enterocolitis. J Pediatr Surg. 2022 Jul;57(7):1331-1335. doi: 10.1016/j.jpedsurg.2021.09.006. Epub 2021 Sep 17. PMID: 34579967.
4) Allin BSR, Opondo C, Bradnock TJ, Kenny SE, Kurinczuk JJ, Walker GM, Knight M; NETS2HD collaboration. Outcomes at five to eight years of age for children with Hirschsprung's disease. Arch Dis Child. 2021 Apr 21;106(5):484-490. doi: 10.1136/archdischild-2020-320310. PMID: 33139346; PMCID: PMC8070639.
5) Allin B, Long AM, Gupta A, Knight M, Lakhoo K; British Association of Paediatric Surgeons Congenital Anomalies Surveillance System Necrotising Enterocolitis Collaboration. A UK wide cohort study describing management and outcomes for infants with surgical Necrotising Enterocolitis. Sci Rep. 2017 Jan 27;7:41149. doi: 10.1038/srep41149.

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Theme 7. Target Discovery

7.1 Spatial Biomarker discovery for viral-hepatocellular carcinoma

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Project Overview

Liver cancer, particularly hepatocellular carcinoma (HCC), is a major global health challenge and one of the fastest growing causes of cancer mortality. Chronic hepatitis B or D are the major drivers of HCC with over 290M cases worldwide. Co-infection with hepatitis B and D viruses (HBV/HDV) drives especially aggressive disease, with an accelerated onset of cirrhosis and HCC. Both viruses often remain undiagnosed until advanced liver damage emerges. The long, complex course of HBV-associated disease, coupled with ilimited classification systems, hampers the development of effective therapies. Current access to treatment requires patients to meet strict clinical criteria, leaving many without intervention. There is a pressing need for personalised approaches that consider disease stage, molecular and cellular changes in the liver, and co-existing pathologies.

Spatial transcriptomics offers new opportunities for diagnosis and treatment stratification by mapping gene activity within intact tissues. This approach reveals cellular interactions, tissue microenvironments, and disease-specific molecular signatures. Combining imaging, sequencing, spatial transcriptomics enables the discovery of novel biomarkers, refined disease staging, and personalised therapeutic strategies. Importantly, compatibility with routine clinical workflows such as formalin-fixed paraffin-embedded tissue processing and pathological examination, is key for translating this technology into practice. We hypothesise that transcriptional profiling, combined with pathological features, can uncover molecular pathways critical to disease progression and reveal new therapeutic targets.

To explore this, we recently applied single-cell spatial transcriptomic Xenium platform to biopsies from patients infected with HBV and those co-infected with HBV and HDV, spanning different disease stages. Adjacent biopsy sections were analysed with H&E staining to provide pathological context. Moving forward, we propose to extend this work by applying near-single-cell spatial deep sequencing to sequential sections. Integrating these datasets will allow the identification of virus-specific and stage-specific transcriptional signatures, linked to molecular pathways, and potential therapeutic targets. This project aims to bridge molecular and pathological insights, paving the way for improved disease classification and personalised treatments for HBV- and HDV-associated liver disease.

Disease Relevance

Hepatitis B and D viruses are a global health challenge 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 biomarkers to inform personalised therapies.

Key Technology

- Spatial transcriptomics, immune profiling, and pathological analysis of human tissue samples from patients diagnosed with chronic hepatitis B and D.
- Spatial network analysis using MuSpAn pipelines to investigate cellular interactions at the micro-anatomic level.
- In vitro viral replication models for mechanistic validation studies

Training Opportunities

The student will join a vibrant, interdisciplinary team of biologists and hepatologists in the McKeating, Galvez-Cancino and Melero laboratories, which combine expertise in viral biology, spatial transcriptomics, macrophage biology and liver cancer. The project is strengthened through an established collaboration with the clinical hepatology team at King's College Hospital, London. This opportunity offers a unique training environment, providing hands-on experience in viral disease pathology, HCC biology alongside cutting-edge techniques in single-cell spatial transcriptomics.

The student will develop transferable skills, including delivering oral presentations at joint lab meetings, critically evaluating scientific literature through journal clubs, and contributing to scientific writing by drafting and reviewing manuscripts. The work will be based in the Nuffield Department of Medicine (NDM) Research Building and Oxford Centre of Immuno-oncology, with opportunities to engage with a network of collaborators in Oxford and internationally, facilitating the translation of research findings to the broader biomedical community.

Key Publications

1) Cross A et al. (2024). Characterisation of HBV and co-infection with HDV and HIV through spatial transcriptomics. eGastroenterology 2024 doi:10.1136/egastro-2024-100067.
2) Mukherji *et al* (2024). An atlas of the human liver diurnal transcriptome and its perturbation by hepatitis C virus infection. Nat Comms PMID: 39209804. DOI: 10.1038/s41467-024-51698-8
3) Harris JM et al (2025). Mapping episomal and integrated hepatitis B virus transcriptomes uncovers heterogeneous gene expression and endogenous drug resistance. Nat Comms 2025, *in press.*
4) Gálvez-Cancino F et al (2025). Regulatory T cell depletion promotes myeloid cell activation and glioblastoma response to anti-PD1 and tumor-targeting antibodies. Immunity. 2025; 58(5).
5) Heras-Murillo I et al (2025). Immunotherapy with conventional type-1 dendritic cells induces immune memory and limits tumor relapse. Nat Comms 16

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7.2 Expanding deep topographic proteomics into the 3rd dimension to enable ovarian pre-cancer grading

Prof. Roman Fischer & **Dr. Sarah Blagden**

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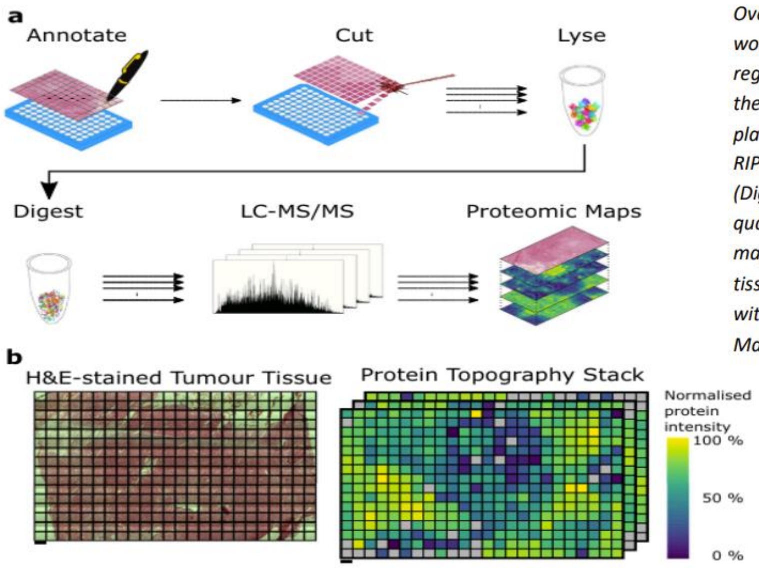
Project Overview

This PhD project aims to tackle a significant gap in understanding ovarian cancer by deciphering the biological mechanisms representing developmental stages of 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. In close collaboration with the leading expert in STICs, Professor Blagden (Dept. of Oncology, Oxford), 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 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 Relevance

Ovarian cancer is often diagnosed at an advanced stage but the most common form, high grade serous ovarian cancer (HGSOC), arises from precursor lesions called serous tubal intraepithelial carcinoma (STICs) within the fallopian tube where earlier precursors such as serous tubal intraepithelial lesions (STILs) and Secretory Cell OUTgrowths (SCOUTs) have also been identified. Unlike carcinoma in situ (CIN) in the cervix that, since 1920s, has been graded 1-3 according to risk of malignant progression, there is no grading for STICs, even though there is biological evidence that some are more aggressive. This knowledge gap has resulted in confusion around their correct clinical management, ranging from patients being given reassurance, regular surveillance, to chemotherapy! It is possible that, like CIN, early STICs require only observation whereas more advanced cases need adjuvant treatment. Additionally, there is confusion as to whether SCOUTs and STILs represent true precursors to STICs.

This project aims to define a STIC grading system at a molecular level, providing unbiased proteomic characterization for the first time. Understanding the specific pathways that lead towards invasive HGSOC would have a transformative impact on its early detection and management. Methodologies developed in this project could be applied to other precancers.

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 SCOUT/STIL/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 these 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 tumour 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 of training 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 translational research 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) Bogaerts, J.M.A., Steenbeek, M.P., van Bommel, M.H.D. et al.Recommendations for diagnosing STIC: a systematic review and meta-analysis. Virchows Arch 480, 725–737 (2022). https://doi.org/10.1007/s00428-021-03244-w
4) Vit Weinberger, Marketa Bednarikova, David Cibula & Michal Zikan (2016). Serous tubal intraepithelial carcinoma (STIC) – clinical impact and management, Expert Review of Anticancer Therapy, 16:12, 1311-1321, DOI: 10.1080/14737140.2016.1247699

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Theme 8. Other

8.1 Pathogenic mechanisms in craniofacial conditions

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Project Overview

The Oxford Clinical Genetics Group (CGG) has been studying craniofacial malformations since 1993, particularly craniosynostosis (the premature fusion of one or more of the cranial sutures separating the bones of the skull vault), with research driven by the need to provide better information for affected families. **This studentship will follow this motivation to 1) make new genetic diagnoses, and 2) increase the understanding of how craniofacial abnormalities arise.** This information is important as identification of causative variants has immediate clinical benefits - a genetic diagnosis means that families can benefit from accurate diagnosis and explanation of why the condition occurred, ending a diagnostic odyssey that may have lasted years. The family can be given estimations of recurrence risk, offered cascade testing, and prenatal or preimplantation diagnosis. In some cases, there may be specific complications to screen for, or specific management implications. Mutation identification is combined with analysis of the processes underlying development of craniofacial malformation, providing fundamental information about normal and abnormal development and potentially leading to new therapeutic approaches.

1) For the study of clinical samples, massively parallel genome sequencing has revolutionised the identification of Mendelian disease genes. Our group has identified many new human disease genes using this approach and the UK's Genomics England 100,000 Genomes project (https://www.genomicsengland.co.uk/), NHS Genomic Testing and our own genome analysis programme will provide further opportunities for discovery during the course of the studentship. This data will be scrutinised for both single nucleotide variants (SNVs) and structural variants (SVs). The student will receive training in the bioinformatic approaches needed to detect candidate causal variants. To find evidence of causality, targeted resequencing of strong candidate genes identified in the sequence datasets will be performed on probands without a genetic diagnosis. If there is sufficient suspicion candidates will be pursued with functional assays designed to the gene and variant types in question.
2) To investigate pathophysiology and in some cases confirm causality, variants of particular interest may be introduced into mice using CRISPR/Cas9 targeting. Mouse models will be phenotyped through skeletal staining and micro-CT analysis, with pathogenesis investigated through a variety of tailored assays to understand cellular and molecular mechanisms.

Disease Relevance

Craniofacial malformations are common, affecting ~3-5% of all live births, and craniosynostosis, a serious abnormality of skull development, has a frequency of ~1/2000. About 350 children each year are born with craniosynostosis in the UK, many of whom require one or more operations to correct abnormal head shape and make room for brain growth. Parents want to know what caused their child's malformation and in a quarter of these children a single fault in their DNA can be identified. Despite surgery there is increased frequency of complications affecting vision, hearing, breathing, dentition and learning, leading to multiple interventions and long-term health problems. However, there remain many affected children, likely to have a genetic alteration, in whom the cause is still unknown. The object of the proposed studentship is to screen these children for changes in their DNA that might be responsible for the development of craniosynostosis, and then analyse how these changes cause abnormal skull development. This is really important to families as a precise molecular diagnosis provides them with invaluable information on disease trajectory, treatment, options for genetic testing and risk to future children. Furthermore, the work will provide new molecular and cellular understanding of how these conditions arise.

Key Technology

- Bioinformatics. Tools used to interogate and manipulate genome sequencing data and associated outputs.
- Cell culture (including iPSCs)
- Fluorescence-activated cell sorting (FACS)
- Histology, in situ & immunohistochemistry
- Microscopy
- Single cell transcriptomics and next generation sequencing
- CRISPR/Cas9 targetting of mouse embryonic stem cells
- Basic molecular biology methodologies for analysing DNA, RNA and protein
- In vivo modelling

Training Opportunities

You will learn how to use a wide range of web resources to interpret genomic information from human, mouse and other species. For experimental work you will be exposed to a wide variety of techniques including cell culture, fluorescence-activated cell sorting (FACS), microscopy, single cell transcriptomics and next generation sequencing, as well as basic molecular biology methodologies for analysing DNA, RNA and protein, all of which are essential for functional characterisation of mutations. If working on mice you will obtain your own personal license and undergo training in husbandry and experimental analysis.

Acquisition of bioinformatics skills is central to progress in biology, whether applied to genome sequence analysis, single cell transcriptomics, or epigenomics. Full support will be available through the WIMM Centre for Computational Biology. For clearly defined projects requiring advanced bioinformatics skills there will be the opportunity for more intensive training through the in-house Computational Genomics: Analysis and Training (CGAT) programme.

Key Publications

1) Hyder Z, (22 authors), Wilkie AOM (2021). Evaluating the performance of a clinical genome sequencing program for diagnosis of rare genetic disease, seen through the lens of craniosynostosis. Genet Med 23:2360-2368.
2) Tooze RS, (21 authors), Twigg SRF, Wilkie AOM (2023). Pathogenic variants in the paired-related homeobox 1 gene (PRRX1) cause craniosynostosis with incomplete penetrance. Genet Med 25:100883.
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8.2 Novel cardiorespiratory physiological methods for endotyping and phenotyping respiratory disorders

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Project Overview

Background and Rationale. Chronic respiratory diseases—such as asthma, COPD, and bronchiectasis—are leading causes of global morbidity and mortality. A major limitation in current clinical practice is the lack of sensitive, non-invasive tools to assess lung function and disease activity, particularly in the small airways where many respiratory conditions begin. Traditional tests, such as spirometry, are crude and often fail to detect early-stage disease. As a result, patients are frequently diagnosed late, when irreversible lung damage has already occurred, and are managed with generic treatment strategies rather than targeted interventions. There is an urgent need for tools that can detect early disease, stratify patients more precisely, and monitor responses to therapy. A “treatable traits” approach—identifying specific, modifiable features of disease—has gained traction as a strategy to personalise care and develop new, disease-modifying treatments. Type-2 eosinophil inflammation is the most treatment-responsive trait in airways diseases, but other endotypes e.g. neutrophilic inflammation/infection are also present and important to recognise.

Project overview. Our research group has developed an innovative and award-winning non-invasive physiological technique: ***Computed Cardiopulmonography (CCP)***. This method uses a novel molecular flow sensor to measure gas exchange at the mouth with unprecedented precision. Coupled with computational modelling of cardiopulmonary physiology, CCP generates sensitive new indices of lung function, including metrics of ventilation inhomogeneity. We have shown that CCP-derived indices are markedly abnormal in COPD, correlate with disease control in asthma, and can detect early small-airway changes in at-risk individuals (e.g. chronic smokers) that go undetected by standard lung function tests. Furthermore, the CCP technology allows us to track cardiorespiratory responses to hypoxic or hypercapnic challenges very precisely, and further development of the technique aims to provide non-invasive estimates of cardiac output and mixed venous oxygen saturations.

The overarching aim of the research is to move away from a “fire-fighting approach” in severe irreversible respiratory diseases towards a “predict and prevent” approach, whereby we use precise phenotyping and endotyping of respiratory patients to detect disease earlier and target treatable traits.
The student will have the opportunity to combine CCP with detailed clinical, physiological (including exercise or hypoxic challenges) and biological phenotyping of patients (e.g. markers of type-2 or type-1 inflammation in blood, sputum, breath e.g. exhaled NO) and tailor their research project within the following areas:

- **Early disease detection**: Can CCP, in combination with molecular biomarkers, identify early lung disease in at-risk populations (e.g. those exposed to environmental pollution or vaping/smoking, or in those with recurrent chest infections)? Is the presence of type-2 inflammation (a treatable processs) a precursor of future airway pathology and can CCP uncover this?
- **Patient stratification:** Can CCP and deep physiological phenotyping better classify patients with unexplained breathlessness or mixed disease phenotypes?

- **Therapeutic responses:** How do novel treatments (e.g. GLP-1 receptor agonists for obesity in breathless patients or biologics for airways diseases) affect cardio-respiratory physiology as measured by CCP, exercise tests or hypoxic challenges?

Disease Relevance

Respiratory disease affects 1 in 5 people and is the third leading cause of death in the UK. Over the past seven years, hospital admissions for lung disease have increased at three times the rate of all other admissions. The most common lung conditions are airways diseases, particularly asthma and chronic obstructive pulmonary disease (COPD), which together affect 500 million people globally and over 8.5 million in the UK.

Asthma alone results in approximately 60,000 hospital admissions and 200,000 bed days annually, while COPD accounts for 1 in 8 hospital admissions across the UK.
The incidence and mortality of lung disease are disproportionately higher in disadvantaged populations and areas of social deprivation. Despite rising healthcare expenditure, there has been no significant improvement in outcomes for patients with airways diseases over the past two decades.

One major reason is that these diseases are often diagnosed too late, after irreversible lung damage has already occurred. Additionally, the heterogeneity of patient populations, with varying underlying pathobiology, makes it difficult to demonstrate the efficacy of new treatments in clinical trials. Improved patient stratification through more precise phenotyping and endotyping is therefore essential to enable more effective and targeted therapies.

Key Technology

The key technology is Computed Cardiopulmonography.This technique which was awarded the Royal Society of Chemistry Horizon Price (2022). It consists of two advances: a novel technology, the Molecular Flow Sensor (MFS), that uses laser absorption spectroscopy to measure the flow and composition of respired gases at the mouth with unprecedented precision (every 10 ms), and a new cardiopulmonary mathematical model, the parameters of which can be fitted to the MFS data to describe the particular patient's lung physiology.

A CCP assessment comprises a 12-min multi-breath washout in which a patient breathes air for 7 min before switching to pure O_2 for the remaining 5 min. CCP provides a multi-dimensional assessment of lung physiology generating novel patient-specific indices of lung function, including the parameters σlnC_L and $\sigma V_{D,}$ which represent the standard deviations for the distributions of standardised alveolar compliance and standardised anatomical deadspace across the lung volume, respectively.

An additional bespoke technology available in our laboratory in Oxford is dynamic end-tidal forcing, which can be used to exposure research participants to short periods of alveolar hypoxia, while avoiding the potentially confounding effects of changes in alveolar carbon dioxide levels. This allows precise measurement of ventilatory sensitivity to hypoxia, which holds promise as a potential 'treatable trait' in some groups of patients with respiratory disease.

In combination with this integrative physiology, our group has experience of wet-laboratory work with blood samples, nasal scrapes and induced sputum, and the use of immunobiology techniques to study cell differentials and the levels of inflammatory cytokines, e.g. using Meso-Scale Discovery multiplex assays.

Training Opportunities

The student will be embedded in an interdisciplinary team spanning clinical respiratory medicine and basic sciences: physiology, molecular biology and computational modelling. The student will acquire training and experience in:

- **Human integrative cardiorespiratory physiology,** including using the state-of-the art CCP technology, cardiopulmonary exerciuse testing, end-todfal forcing and other physiological techniques.
- **Mathematical and computational modelling,** in modeling human physiological responsies and analysing complex physiological gas-exchange data.
- **Statistical data analysis,** Including mixed-effects modelling in analysing clinical, physiological and biological data.
- **Clinical research methods,** including Good Clinical Practice training, study design and protocol development for human studies, ethics applications.
- **Wet-laboratory work,** for some aspects of the work for biomarker analysis in blood, breath, nasal and sputum samples (e.g. sputum cell processing, ELISA, flow cytometry).

This project is well suited to students with backgrounds in clinical medicine but also non-clinical students, i.e. those interested in physiology, biological sciences and translational respiratory research.

Key Publications

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8.3 Gene editing and base editing to cure severe forms of alpha thalassaemia

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Project Overview

Thalassaemia is the most common form of inherited anaemia found throughout the world and one of the most common single gene disorders. In all cases, it results from an imbalance in the production of the α-like and β-like globin chains of haemoglobin (Hb), leading to α-thalassaemia and β-thalassaemia respectively. The aim of our laboratory is to understand how the globin gene clusters are normally regulated during development and differentiation and how this is perturbed in patients with thalassaemia. By approaching these questions, we are also developing a general understanding of how mammalian genes are normally switched on and off during erythropoiesis and identifying many general principles underlying human molecular genetics.

Alpha thalassaemia is particularly common in southeast Asia, including southern China. The two most severe forms of α-thalassaemia cause HbH disease and the Hb Bart's Hydrops Fetalis Syndrome (BHFS). HbH disease is associated with a moderate or severe anaemia which may require regular blood transfusion. BHFS causes lethal neonatal anaemia and without intensive care and blood transfusion or bone marrow transplantation such infants die in the third trimester of pregnancy or shortly after birth. Our laboratory has defined most of the common mutations associated with α-thalassaemia. Whereas normal individuals have four α-genes ($\alpha\alpha/\alpha\alpha$), those with HbH disease inherit just one functional α-gene (--/-α), and those with HBFS inherit no functional α-genes (--/--).

To ameliorate or even cure these conditions we are focussed on two approaches. The first is simply to replace the missing α-genes in their normal location on human chromosome 16 using CRISPR-based site-directed genome editing. In this way the newly inserted α-genes would be activated by the α-globin superenhancer, which remains intact upstream of the deletion most commonly found in infants with BHFS: the so called southeast Asian deletion ($--^{SEA}$). Pre-clinical studies to develop this protocol will use the well-defined HUDEP2 cell line, and primary human $CD34^+$ progenitor cells, both of which can be differentiated to produce normal red blood cells.

The second approach involves reactivating the embryonic α-like gene (the zeta [ζ] gene) which remains intact but is silenced in the $--^{SEA}$ allele. Previous work has shown that embryonic Hb (HbPortland II: $\zeta_2\beta_2$) would functionally complement the missing adult Hb (HbA: $\alpha_2\beta_2$). Current work in the laboratory has identified some key pathways that silence ζ-globin expression and future work is aimed at identifying the *cis*- and *trans*-acting elements through which these pathways exert their effects. This in turn will allow us to develop CRISPR and base editing approaches to abrogate these silencing pathways and de-repress ζ-globin expression to therapeutically useful levels.

The successful applicant will join a lab of approximately 14 including students, post-docs and research assistants. The project would be suitable for a clinician-scientist or a basic scientist.

Disease Relevance

Fetuses with BHFS survive until late pregnancy because they partially reactivate the ζ-globin gene to produce small amounts of Hb Portland. More fully reactivating the embryonic ζ-globin genes in definitive erythroid cells offers a potential cure for the common, severe forms of α-thalassaemia.

Key Technology

The Higgs laboratory offers a wide range of training opportunities in cell biology, molecular biology and computational approaches to biology. We train students in all aspects of cell biology using cell lines and primary cells from a range of organisms. We use all forms of flow cytometry to isolate and characterise common and rare cell types including stem/progenitor cells and we provide full training in this technology. When required, we also train students in mouse genetics to generate specific models for our research. Molecular techniques used in the laboratory include all forms of sequence- based analysis of DNA, RNA and chromatin both in cell populations (ATAC-seq, RNA-seq, ChIP-seq, CUT&RUN etc) and in individual single cells (scRNA-seq, scATAC-seq). We also have access to the full range of proteomics, including single cell proteomics, and structural biology. The laboratory has also pioneered high resolution protocols for chromosomal conformation capture. We also routinely use genome editing, advanced forms of homology directed recombination, and synthetic biology to develop new models and approaches to understand the regulation of gene expression. An important new dimension to our research involves the use of advanced imaging, including super-resolution imaging, particularly in real time. Students interested in such projects will receive appropriate training in these techniques. We provide comprehensive training in all aspects of computational biology to analyse the resulting datasets.

Training Opportunities

Our laboratory of ~12-14 scientists, includes post-docs, students and research assistants. Students undertaking their studies in the lab have day-to-day supervision from a team of scientists who have considerable experience in all aspects of current genomics including, for example, RNA-seq, ATAC-Seq, ChIP-seq, and various forms of chromosome conformation capture. We also have considerable expertise in cell biology and imaging. A key aspect of our work in collaboration with the WIMM Centre for Computational Biology involves a full range of analytical approaches using computational biology.

Key Publications

1) Amid A, Liu S, Babbs C, Higgs DR. Hemoglobin Bart's hydrops fetalis: charting the past and envisioning the future. Blood. 2024 Aug 22;144(8):822-833. doi: 10.1182/blood.2023023692. PMID: 38457773.
2) King AJ, Songdej D, Downes DJ, Beagrie RA, Liu S, Buckley M, Hua P, Suciu MC, Marieke Oudelaar A, Hanssen LLP, Jeziorska D, Roberts N, Carpenter SJ, Francis H, Telenius J, Olijnik AA, Sharpe JA, Sloane-Stanley J, Eglinton J, Kassouf MT, Orkin SH, Pennacchio LA, Davies JOJ, Hughes JR, **Higgs DR**, Babbs C. Reactivation of a developmentally silenced embryonic globin gene. Nat Commun. 2021 Jul 21;12(1):4439. doi: 10.1038/s41467-021-24402-3. PMID: 34290235; PMCID: PMC8295333.
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8.4 Thymic involution and T cell aging

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Project Overview

A significant aspect of aging is the decline in immune response. One of the most recognized consequences of immune system aging is thymic involution. This project focus on investigating the impact of thymic involution on CD8 T aging and dysfunction. Specifically we will investigate whether thymic involution affects T cell differentiation, function, and proliferation using mouse models and cutting edging molecular biology techniques.

Disease Relevance

Aging induced T cells dysfunction reduces anti-infection and anti-tumor immune response, as well as vaccination. It is also associated with a higher prevalence of autoimmunity

Key Technology

Multiparameter flow cytometry; Single cell RNA sequencing; Adoptive cell transfer; Primary T cell culture; Mice breeding and genotyping

Training Opportunities

Students will be trained in a range of laboratory techniques including mouse experiments and primary cell culture as well as basic molecular and cell biology techniques.

Students will also have the opportunities to present his/her work at lab meetings, institute internal seminars and domestic and international conferences.

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8.5 Mechanistic study of Trip4-mediated transcriptional regulation in muscle development

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Project Overview

Transcriptional coregulators are a group of proteins that interact with DNA-binding transcription factors, regulating gene expression in response to environmental cues. Dysregulation of these coregulators has been linked to various human diseases. TRIP4, also known as ASC-1, was initially identified as a thyroid hormone-interacting factor that stimulates transcription when recruited to gene promoters in vitro. Like other coactivators, TRIP4 forms a multi-subunit complex consisting of ASCC1, ASCC2, and ASCC3. Trip4 mutations have been associated with congenital muscular dystrophy, and components of the ASCC complex are involved in various biological processes such as DNA alkylation repair and ribosome quality control. However, the precise mechanism by which Trip4 regulates transcription remains poorly understood.

The muscular dystrophy phenotype in TRIP4-deficient patients can be recapitulated by in vitro differentiation of the C2C12 myoblast cell line. Using this model, we aim to understand the mechanisms of trip4-mediated transcriptional regulation by identifying direct targets of trip4 through state-of-the-art genomic/genetic tools and advanced genetic, biochemical and mass spectrometric techniques.

Disease Relevance

Muscular dystrophy

Key Technology

Protein complex purification, mass spectrometry, genetic manipulation of cells, genomic and epigenomic analyses

Training Opportunities

Students will learn how to investigate and provide insight into a protein with unknown mechanistic function in a disease setting

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