DPhil in Cancer Science

University of Oxford

GSK Studentships

2026 Intake Project Booklet

OXFORD CANCER

UNIVERSITY OF OXFORD

NHS
Oxford University Hospitals
NHS Foundation Trust

GO-PRECISE Studentship Project Booklet

Introduction

This handbook provides an overview for prospective students looking to apply for a GO-PRECISE DPhil as part of the GSK funded studentships.

Global biopharma company GSK is investing up to £50 million in a collaboration with Oxford to advance the understanding of how cancer develops, which could inform future development of vaccines to prevent cancer. The agreement establishes the GSK-Oxford Cancer Immuno-Prevention Programme, aimed at exploring the potential of cancer prevention through vaccination.

The programme leverages the complementary expertise of GSK and Oxford in the science of the immune system, vaccine development and cancer biology. It is hoped that the insights generated through the programme into how cancer develops could inform new approaches to vaccination for cancer prevention, offering fresh hope in the fight against the disease.

Students will receive a world-leading research training experience that integrates an education initiative spanning cancer patient care, tumour biology and research impact; on- and post-programme mentorship; and a specialised, fundamental, subject-specific training tailored to individual research needs. Students participating in the scheme will be offered:

- a choice of interdisciplinary cutting-edge cancer research projects.
- the ability to gain a working in-depth knowledge of the fundamentals of cancer biology and cancer patient care through advanced level seminars.
- a world-renowned research environment that encourages the student's originality and creativity in their research.
- opportunities to develop skills in making and testing hypotheses, in developing new theories, and in planning and conducting experiments.
- an environment in which to develop skills in written work, oral presentation and publishing the results of their research in high-profile scientific journals, through constructive feedback of written work and oral presentations.

At the end of their DPhil course, students should:

- have a thorough knowledge of the basic principles of cancer research including the relevant literature and a comprehensive understanding of scientific methods and techniques applicable to their research.
- be able to demonstrate originality in the application of knowledge, together with a practical understanding of how research and enquiry are used to create and interpret knowledge in their field.

- have developed the ability to critically evaluate current research and research techniques and methodologies.
- be able to act autonomously in the planning and implementation of research.
- have the grounding for becoming an influential cancer researcher of the future.

Selection Criteria & Eligibility

Successful applicants will enrol on a four-year programme with the first year consisting of two six-month rotations within the selected project labs. This provides students with a broad base of experience and the opportunity to explore different aspects of research. All students are admitted directly to work under the supervision of a Principle Investigator (PI).

Eligibility – Non-Clinical/Fundamental Scientist. Science graduates that hold (or be predicted to achieve) the equivalent of a first-class or strong upper second-class undergraduate degree with honours in biological, medical, or chemical science, as appropriate for the projects offered.

All applicants will be judged on the following:

- commitment and passion to a career in cancer research
- evidence of motivation for and understanding of the proposed area of study
- commitment to the subject, beyond the requirements of the degree course
- preliminary knowledge of relevant research techniques
- capacity for sustained and intense work
- reasoning ability and academic curiosity.

Funding

All offered places are fully funded at the home rate. This includes salary/stipend, University/College fees, and a research consumables budget.
Salary and stipend provisions are summarised below:

- Four years of stipend at the flat rate of £ 22,113 per annum.

How to Apply

Prospective students must apply with a **prioritised list of three projects selected from the GSK booklet by midday on Tuesday 2nd December.**

Apply through the University of Oxford Graduate Admissions website for the relevant track.

- Track 3 (Non-Clinical/Fundamental Scientist - Biological background)

On the application form, in the section headed **'Departmental Studentship Applications'**, you must indicate that you are applying for the GSK studentship and enter the reference code for this studentship **"GSK25"**

Shortlisted students will be invited to interview in January. If successful, students will then begin their first year with two lab rotations. It is strongly suggested that students contact supervisors of projects they are interested in applying for prior to application.

Can I also apply to projects in the other project booklets?

The GSK funded Studentships come with their own dedicated funding, so applicants must choose from the set list of 5 eligible projects—these are all included in this GSK project booklet. The two rotations which take place in the first year need to be taken across the GSK project offering, so rotations cannot be mixed with those listed in the other project booklets. This ensures the funding is used in line with the partnership's goals, which focus on particular areas of research.

However, it's important to know that GSK funded students are part of the wider Cancer Science DPhil programme. You'll attend the same seminars, training sessions, and events, and be part of the same research community as all other Cancer Science students. The only difference is how your project is funded.

Projects

Clicking on a project title below will take you to the relevant project page. The 6-month rotational project can be found at the end of each project page.

Contents

1. Discovering and targeting 'dark antigens' in cancers and precancers – Sarah Blagden

Primary Supervisor: Sarah Blagden
Additional Supervisors: Ellie Barnes

Abstract of the project
Approximately 1:400 women carry BRCA1 and BRCA2 mutations and have a 20-50% and 40-85% lifetime risk of ovarian and breast cancer respectively as well as other cancers including pancreatic and prostate cancer. The current standard-of-care cancer preventive treatment for BRCA carriers is risk-reducing removal of breasts (mastectomy) at 30 years, and of ovaries and fallopian tubes (salpingo-oophorectomy) at 40 years of age. Surgery, particularly the removal of ovaries, can lead to significant physical and psychological morbidity and, hence, many BRCA carriers decline it. We now know that breast and ovarian cancer do not develop quickly but arise over 4-6 years as cells transition from normal to invasive cancer. This latent stage is called "precancer". In BRCA carriers, ovarian precancers are called "serous tubal intraepithelial carcinomas" (STICs) and arise as microscopic collections of abnormal cells in the fallopian tubes that spread to the ovaries and peritoneal cavity once they have transitioned to invasive cancer. Similarly, breast cancer starts as a precancer called ductal carcinoma in situ (DCIS).

It is likely that the vast majority of precancers are recognised by the body's immune cells, particularly CD8+ T cells which identify abnormal peptides (neoantigens) displayed on their cell surface by MHC class I molecules whereupon they engulf and destroy them. However, precancers that escape immune recognition can transition to invasive cancer, a process termed 'immune escape'. We hypothesise that a vaccine that specifically activates T cells to recognise the neoantigens presented by precancers could prevent them from escaping surveillance. In Oxford, we have used immunopeptidomics to sequence MHC-presented neoantigens correlated with RNA sequencing to identify the transcripts coding for these peptides, and then applied AI algorithms to predict their expression by different HLA alleles. From this we have found that BRCA-associated cancers are enriched for "non-canonical" or dark antigens (DAs), proteins encoded by normally silenced or lowly expressed regions of the genome, like transposable elements, endogenous retroviruses, or other non-coding regions. This is likely because BRCA1 and BRCA2, which are crucial for homologous recombination repair (HRR) of DNA double-strand breaks, when mutated, cause genomic instability contributing to the reactivation of normally silenced genomic elements. The aims of this project are three-fold.

The overarching purpose of this proposal is to develop and test a series of mRNA vaccines encoding these novel neoepitopes. These findings will inform the selection of a neoepitope-based vaccine that will be taken forward into a clinical trial in BRCA carriers.

Research objectives and proposed outcomes
The project will comprise of three **work packages (WPs).**

Work Package 1: Functional Characterisation of Dark Antigens identified previously

Objective: To validate the expression and immunogenicity of identified dark antigens in cancer models.

1. **Validation of Dark Antigen Expression:** Use quantitative PCR and western blotting to confirm the expression of identified dark antigens at the RNA and protein levels in cell lines and tumour tissues. Utilise LRS to validate the presence of alternative transcripts contributing to dark antigen expression.

2. **Functional Assays:** Conduct T-cell activation assays using isolated T cells from healthy donors or patients to test the immunogenicity of the identified dark antigens. Assess whether dark antigens elicit a measurable immune response, including cytokine production and T-cell proliferation.

3. **Bioinformatics Analysis:** Analyse expression data to correlate dark antigen expression levels with patient clinical outcomes and treatment responses. Explore potential associations between specific dark antigens and immune evasion mechanisms.

Work Package 3: PreClinical Validation: Validate the relevance of identified biomarkers using established mouse cancer models.

Work Package 4: Vaccine Design and Pre-Clinical Testing

Objective:

To design an mRNA-based cancer vaccine incorporating validated antigens, and to assess its immunogenicity and efficacy through *in vitro* and *in vivo* pre-clinical testing.

4.1 Vaccine Construct Design

- Incorporate identified antigens with strong immunogenic potential into an mRNA vaccine platform.
- Explore and optimise various antigen orientations and linker strategies to enhance expression and presentation.

4.2 *In Vitro* Characterisation of Vaccine Expression

- Transfect relevant cell types (e.g., antigen-presenting cells, myocytes, fibroblasts, epithelial cells) with vaccine constructs. Evaluate expression and turnover of vaccine-encoded polypeptides using techniques such as Western blotting, immunofluorescence, and qPCR.

4.3 Immunisation Protocol Optimization

- Design and test various immunisation schedules and dosing regimens in pre-clinical models. Select optimal schedule and dose based on immune response and tolerability.

4.4 Immunogenicity Assessment:

Quantify antigen-specific immune responses using

- ELISpot assays
- Cytokine release profiling (e.g., Luminex multiplex assays)
- Intracellular cytokine staining and flow cytometry
- Characterise the immunophenotype of responding T cells and other immune subsets
- Assess the cytotoxic function of effector cells (e.g., CD8+ T cells) using standard assays (e.g., granzyme B & perforin release, real-time cell killing assays)

4.5 In Vivo Efficacy Evaluation

- Test vaccine efficacy in appropriate animal tumour models.
- Monitor tumour progression, survival, and immune infiltration**.**

Translational potential

The earlier detection and prevention of cancer are central objectives of the University of Oxford and CRUK. If successful, the student will generate a data-driven pipeline to identify tumour-specific, non-canonical antigens for immunotherapy and vaccine development.

Training opportunities

This is an interdisciplinary project between the labs of Prof Sarah Blagden (cancer biology and clinical trials), Prof Ellie Barnes (immuno-oncology and vaccine design) and with bioinformatics support from Andy Blake (dataset integration). Alongside basic wet lab techniques, the student will learn bioinformatic methods, culminating in multi-omics integration to generate a comprehensive DA database.

Student Background

Good understanding of tumour biology. Ideally some lab experience.

Return to Projects list

2. Characterising and tracking vaccine specific T Cells in the periphery and in tumour sites, following the administration of novel cancer vaccines in humans – Ellie Barnes

Primary Supervisor: Ellie Barnes
Additional Supervisors: Tim Elliott

Abstract of the project
We have used state of the art approaches to characterise the magnitude, phenotype and function of vaccine generated T cells in the blood, after vaccination with ChAdOx1 and mRNA vaccine platforms. These approaches used stimulation of peripheral blood cells with vaccine antigen [1], and more recently cells sorting (using Flow Cytometry) of activated T cells after antigen stimulation (using the AIM assays) for T cell quantification, followed by sc-RNA sequencing of AIM+ T cells for in depth characterisation of T cell phenotype, cell interactions, and TCR repertoire characterisation [manuscripts in preparation/submission]. In this DPhil project you will; (i) apply similar sc-RNA seq approaches to assess in vivo human T cell responses to novel cancer vaccines, (ii) additionally track TCR clonotypes detected in the periphery in response to vaccination, to tissue sites of cancer/pre-cancer and iii) characterise in detail, the immune landscape in patients at high risk of cancer, using multiparametric flow cytometry and correlate this with subsequent vaccine responsiveness (e.g. heavy smokers/lung cancer patients vs healthy controls receiving lung cancer vaccines). This is an exciting opportunity to apply state of the art immune technologies to the development of novel cancer vaccines in humans.

Research objectives and proposed outcomes
Recent advances in cancer vaccines, such as mRNA neoantigen platforms demonstrate the capacity to induce durable, functional CD8+ T cell responses that correlate with prolonged recurrence-free survival in malignancies like pancreatic ductal adenocarcinoma. However, challenges persist in understanding the spatial distribution, clonal persistence, and tissue-specific adaptation of vaccine-induced T cells. Current methodologies combine antigen-specific T cell enrichment (e.g., AIM assays), single-cell RNA sequencing (scRNA-seq) for phenotypic profiling, and TCR clonotype tracking (e.g., CloneTrack) to decode differentiation states and longevity. Despite progress, gaps remain in linking peripheral immunity to intratumoural activity and identifying pre-vaccination immune landscapes that predict clinical efficacy. This project will bridge these gaps using cutting-edge multimodal technologies.

Work Package 1: High-resolution profiling of vaccine-induced T cell responses

Objective: Systematically map the phenotype, transcriptional programs, and clonal dynamics of vaccine-specific T cells in blood using longitudinal scRNA-seq with paired TCR analysis.
Methodology: Enrich antigen-specific CD8+ T cells via AIM assays and flow cytometry; Perform scRNA-seq with integrated TCR sequencing (10x Genomics) to resolve clonotype-specific differentiation trajectories; Apply PhenoTrack

Work Package 2: Spatial mapping of vaccine-specific T cell clonotypes

To link peripheral clonal persistence to intratumoural activity, revealing mechanisms of immune escape or clonal pruning.
Objective: Track peripheral TCR clones to pre-malignant/tumour sites and assess their functional impact on tumour evolution.

Methodology: Cross-reference blood TCR clonotypes with TCR sequences from tumour biopsies using single-cell or spatial transcriptomics; Deploy multiplex immunohistochemistry to spatially resolve clonally **expanded** T cells in tissue microenvironments; Analyse tumour phylogenetics to evaluate selective pressure on immunogenic neoantigens.

Work Package 3: Immune landscape stratification in high-risk cohorts

Objective: To establish immune stratification frameworks to personalize vaccine timing and combinatorial therapies by defining pre-vaccination immune signatures predictive of response in high-risk populations (e.g., smokers at risk for lung cancer).
Methodology: Use high-parameter flow cytometry (30+ markers to encompass include exhaustion markers, memory subsets, and innate lymphoid populations) to profile baseline immune states in peripheral blood and tissues. Integrate with scRNA-seq datasets from Work Package 1 to identify predictive biomarkers of vaccine responsiveness; Validate findings against reference T cell atlases

Training opportunities
This project will provide training in transcriptomics, spatial biology, and immune monitoring to advance mechanistic understanding and clinical translation of next-generation cancer vaccines.

References
[1] https://www.nature.com/articles/s41591-023-02414-4

Return to Projects list

3. Analysis of the effects of novel cancer vaccines on the phenotype and function of human dendritic cells in individuals at high risk of cancer and cancer resected patients – Tim Elliott

Primary Supervisor: Tim Elliott
Additional Supervisors: Maria Aggelakopoulou

Abstract of the project
Initiation and maintenance of T cell responses against cancer are critically regulated by dendritic cells (DCs), that present tumour- derived antigens to T cells and provide functional cues, such as costimulatory ligands and cytokines (1). Despite their pivotal role, tumour-induced alterations frequently hinder effective T cell activation, highlighting an important avenue for therapeutic intervention (1). mRNA vaccines have been shown to safely expand and diversify the repertoire of antigen-specific cytotoxic and helper T lymphocytes in various malignancies (2,3,4). Studies by our team and others support the hypothesis that mRNA-lipid nanoparticle (LNP) vaccines are taken up by specific DC subsets that are activated to drive an adaptive immune response, particularly favouring T follicular helper cell differentiation and humoral responses (5). However, our understanding about DC functions underlying the ability of cancer mRNA-LNP vaccines to induce cytotoxic T cell responses is incomplete.

This research proposal aims to: 1) shed light on DC states and functions in individuals at high risk of cancer (pre-cancer) and cancer resected patients and 2) evaluate the impact of novel mRNA-LNP vaccine formulations on DC function and cytotoxic T cell priming. To address these aims, we will employ single cell RNA sequencing, spectral cytometry, Luminex/elisa and cDC-T cell co-culture assays to profile transcriptional, phenotypic, and functional alterations in conventional DCs (cDCs), and assess their capacity to induce CD8+ T cell responses following stimulation with the vaccines. These studies will provide significant insights into DC functions that orchestrate cytotoxic T cell responses and inform the rational design of mRNA -LNP vaccines with enhanced efficacy.

Research objectives and proposed outcomes
Conventional DCs (cDCs) exert discrete functions and are characterized by distinct transcriptional identities and include two major subsets, known as type 1 cDCs (cDC1s) and type 2 cDCs (cDC2s). Cytotoxic T-cell immune responses against cancer are orchestrated by cDC1s, which have a superior ability to cross-present antigens, provide key costimulatory ligands and cytokines to prime and boost CD8+ T-cell responses. cDC2s are involved in presenting antigens on MHC class II molecules to prime diverse CD4+ T helper responses including those against tumours. The design of vaccine formulations that leverage these distinct cDC functions could be very advantageous for preventative and therapeutic cancer immunology. This project will investigate the immunomodulatory effects of various mRNA-LNP formulations on cDC1 and cDC2 subsets and identify those most conducive to eliciting strong CD8+ T cell-mediated responses.

Work Package 1: Investigate the impact of different mRNA-LNP formulations on the transcriptome and phenotype of cDCs

- Apply scRNAseq analysis and high-dimensional spectral cytometry to assess the transcriptomic and phenotypic alterations in cDCs in healthy individuals, individuals at high risk of cancer (pre-cancer) and cancer resected patients.
- Assess analyte release by Luminex/elisa assays.
- Evaluate changes in cDC states and phenotypes after stimulation with different mRNA-LNP formulations.

Work Package 2: Determine optimal mRNA-LNP formulations that functionally activate cDCs to cross-prime cytotoxic T cells

cDC1s present tumour- derived antigens to T cells and provide functional cues, such as costimulatory ligands and cytokines, to prime or re-activate them.

- Human *in vitro* antigen-specific cDC1-CD8 T cell co-culture assays will be deployed to assess the cross-presentation ability of cDC1s in individuals at high risk of cancer (pre-cancer) and cancer resected patients. cDC1s will be pulsed with soluble antigens or stimulated with different mRNA-LNP formulations and then co-cultured with antigen-specific CD8 T cells. Proliferation, extracellular marker and intracellular cytokine staining and cytotoxicity assays will be performed to assess T cell proliferation, the phenotype, the function and their cytotoxic ability.

Translational potential

This project has strong translational potential in the context of cancer immunotherapy, particularly for vaccine development. The identification of mRNA-LNP formulations that preferentially activate cDC1s could lead to next-generation cancer vaccines with improved efficacy. In addition, insights into DC states in high-risk individuals may inform tailored vaccine strategies based on immune profiling and could support rational pairing of mRNA vaccines with checkpoint inhibitors or cytokine adjuvants. Finally, it could inform biomarker development for predicting vaccine responsiveness.

Training opportunities

The DPhil student will be based at the Centre for Immuno-Oncology in the Old Road Campus Research Building. The student will be supervised by the Elliott and Aggelakopoulou groups with considerable experience in DC and T cell biology. This research project is designed to foster autonomous learning, enabling the student to actively shape the scope and trajectory of their investigation. It offers extensive training in foundational and cancer immunology, incorporating a diverse array of cellular and functional immunological assays to support comprehensive skill development. The student will have access to cutting-edge technologies such as DC/CD8 co-culture systems, high-dimensional spectral and flow cytometry, Luminex and ELISpot assays and scRNAseq analysis. The project will enhance their skills in experimental design, data interpretation, literature review, and scientific writing. The student will also have multiple opportunities to present their findings at inter-departmental seminar series and national and international conferences.

Student Background

You should hold a first degree in a relevant discipline such as biology or immunology or related field. A Master's degree in Immunology/ Cancer Science will be an advantage but is not a prerequisite. Previous laboratory experience in cellular immunology (e.g. cell culture, flow cytometry) will be an advantage but is not required, as the DPhil student will be trained and will have daily supervision as required by senior lab members and collaborators. Excellent communication skills and ability to work as part of a team are essential.

References

1) Luri-Rey, C., et al., *Cross-priming in cancer immunology and immunotherapy.* Nat Rev Cancer, 2025. **25**(4): p. 249–273.
2) Cafri G, Gartner JJ, Zaks T, Hopson K, Levin N, Paria BC, Parkhurst MR, Yossef R, Lowery FJ, Jafferji MS, Prickett TD, Goff SL, McGowan CT, Seitter S, Shindorf ML, Parikh A, Chatani PD, Robbins PF, Rosenberg SA. mRNA vaccine-induced neoantigen-specific T cell immunity in patients with gastrointestinal cancer. J Clin Invest. 2020 Nov 2;130(11):5976-5988. doi: 10.1172/JCI134915. PMID: 33016924; PMCID: PMC7598064.
3) Sethna Z, Guasp P, Reiche C, Milighetti M, Ceglia N, Patterson E, Lihm J, Payne G, Lyudovyk O, Rojas LA, Pang N, Ohmoto A, Amisaki M, Zebboudj A, Odgerel Z, Bruno EM, Zhang SL, Cheng C, Elhanati Y, Derhovanessian E, Manning L, Müller F, Rhee I, Yadav M, Merghoub T, Wolchok JD, Basturk O, Gönen M, Epstein AS, Momtaz P, Park W, Sugarman R, Varghese AM, Won E, Desai A, Wei AC, D'Angelica MI,

Kingham TP, Soares KC, Jarnagin WR, Drebin J, O'Reilly EM, Mellman I, Sahin U, Türeci Ö, Greenbaum BD, Balachandran VP. RNA neoantigen vaccines prime long-lived CD8^{+} T cells in pancreatic cancer. Nature. 2025 Mar;639(8056):1042-1051. doi: 10.1038/s41586-024-08508-4. Epub 2025 Feb 19. PMID: 39972124; PMCID: PMC11946889.

4) Lopez J, Powles T, Braiteh F, Siu LL, LoRusso P, Friedman CF, Balmanoukian AS, Gordon M, Yachnin J, Rottey S, Karydis I, Fisher GA, Schmidt M, Schuler M, Sullivan RJ, Burris HA, Galvao V, Henick BS, Dirix L, Jaeger D, Ott PA, Wong KM, Jerusalem G, Schiza A, Fong L, Steeghs N, Leidner RS, Rittmeyer A, Laurie SA, Gort E, Aljumaily R, Melero I, Sabado RL, Rhee I, Mancuso MR, Muller L, Fine GD, Yadav M, Kim L, Leveque VJP, Robert A, Darwish M, Qi T, Zhu J, Zhang J, Twomey P, Rao GK, Low DW, Petry C, Lo AA, Schartner JM, Delamarre L, Mellman I, Löwer M, Müller F, Derhovanessian E, Cortini A, Manning L, Maurus D, Brachtendorf S, Lörks V, Omokoko T, Godehardt E, Becker D, Hawner C, Wallrapp C, Albrecht C, Kröner C, Tadmor AD, Diekmann J, Vormehr M, Jork A, Paruzynski A, Lang M, Blake J, Hennig O, Kuhn AN, Sahin U, Türeci Ö, Camidge DR. Autogene cevumeran with or without atezolizumab in advanced solid tumors: a phase 1 trial. Nat Med. 2025 Jan;31(1):152-164. doi: 10.1038/s41591-024-03334-7. Epub 2025 Jan 6. PMID: 39762422; PMCID: PMC11750724.

5) Verbeke R, Hogan MJ, Loré K, Pardi N. Innate immune mechanisms of mRNA vaccines. Immunity. 2022 Nov 8;55(11):1993-2005. doi: 10.1016/j.immuni.2022.10.014. PMID: 36351374; PMCID: PMC9641982.

4. Impact of different LNP formulations on T cell immunodominance – Tim Elliott

Primary Supervisor: Tim Elliott
Additional Supervisors: Maria Aggelakopoulou

Abstract of the project
This research proposal aims to investigate the impact of mRNA and lipid nanoparticle (LNP) formulations on T cell immunodominance. Recent studies have shown that LNP-based mRNA vaccines can elicit potent T cell responses and enhance humoral immunity (1). However, the specific effects of different LNP compositions and mRNA modifications on T cell immunodominance patterns remain unclear. We hypothesize that altering LNP components, such as ionizable lipids and fusogenic helper lipids, as well as mRNA modifications, will influence antigen presentation and subsequent T cell activation, potentially shifting immunodominance hierarchies (2). By systematically evaluating various LNP-mRNA formulations in both *in vitro* and *in vivo* models, we aim to identify optimal combinations that can selectively enhance desired T cell responses against specific epitopes. This research will provide valuable insights for the rational design of more effective mRNA vaccines and could have significant implications for improving vaccine efficacy against infectious diseases and cancer.

Research objectives and proposed outcomes
Emerging evidence highlights lipid nanoparticles (LNPs) as critical platforms for mRNA vaccine delivery, with composition-dependent effects on immune activation. Recent studies demonstrate that LNP formulations containing ionizable lipids (e.g., C12-200, cKK-E12), β-sitosterol, and fusogenic helper lipids like DOPE enhance antigen presentation in dendritic cells (DCs) and drive robust T cell proliferation and cytokine production (IFN-γ, TNF-α, IL-2). Concurrently, mRNA modifications such as N4-acetylcytidine (ac4C) by NAT10 and m6A methylation have been shown to regulate translation efficiency and degradation kinetics, directly impacting T cell expansion and differentiation. Despite these advances, the interplay between LNP composition, mRNA modifications, and T cell immunodominance hierarchies—the preferential targeting of specific epitopes during immune responses—remains unexplored. This knowledge gap limits the rational design of vaccines capable of directing T cells against high-priority epitopes in infections or cancer.

Work Package 1: Systematic Screening of LNP Formulations on Antigen Presentation
Objective: Identify LNP components that optimize DC uptake, mRNA translation, and epitope presentation.
Methodology: Test 20+ LNP variants with variable ionizable lipids (C12-200, cKK-E12), helper lipids (DOPE vs. cholesterol/β-sitosterol ratios), and PEG content. Transfect bone marrow-derived DCs (BMDCs) with OVA- mRNA LNPs and quantify activation markers (CD40, CD86), IL-12 secretion, and MHC-I/II epitope presentation using mass spectrometry. Rank LNPs by their ability to induce cross-presentation of immunodominant vs. subdominant epitopes.

Work Package 2: mRNA Modification Engineering for Epitope-Specific Translation
Objective: Determine how chemical modifications (ac4C, m6A) alter mRNA stability and ribosomal engagement to skew immunodominance.
Methodology: Engineer OVA-mRNA with site-specific ac4C (via NAT10 co-delivery) or m6A modifications and encapsulate in top-performing LNPs from Work Package 125. Use ribosome profiling and RNA-seq in BMDCs to correlate modification patterns with epitope translation efficiency. Validate epitope hierarchy shifts using OT-I/CD8+ T cell proliferation assays and single-cell TCR sequencing37.

Work Package 3: In Vivo Immunodominance Profiling and Functional Validation
Objective: Evaluate how LNP-mRNA combinations alter epitope dominance in infection and tumour models.

Methodology: Immunize mice with top LNP-mRNA candidates and challenge with *Listeria*-OVA or E.G7-OVA tumors3. Map CD8+ T cell responses to 15 OVA-derived epitopes via tetramer staining and IFN-γ ELISpot. Deplete cDC1/cDC2 subsets to assess their roles in immunodominance using XCR1-DTR mice3.

Training opportunities

This project will elucidate how LNP-mRNA design parameters govern T cell epitope selection, enabling precision engineering of vaccines with tailored immunodominance profiles and will provide training in human primary cell culture, advanced immune profiling techniques including spectral flow cytometry, RNAseq and mass spectrometry as well as molecular and chemical biology techniques.

Student Background

You should hold a first degree in a relevant discipline such as biomedical sciences or immunology or relevant field. A Master's degree in Immunology/ Cancer Science will be an advantage but is not a prerequisite. Previous laboratory experience in molecular biology and cellular immunology (e.g. mammalian cell culture, flow cytometry) will be an advantage but is not required, as the DPhil student will be trained and will have daily supervision as required by senior lab members and collaborators. Excellent communication skills and ability to work as part of a team are essential

References

1. Alameh MG, Tombácz I, Bettini E, Lederer K, Sittplangkoon C, Wilmore JR, Gaudette BT, Soliman OY, Pine M, Hicks P, Manzoni TB, Knox JJ, Johnson JL, Laczkó D, Muramatsu H, Davis B, Meng W, Rosenfeld AM, Strohmeier S, Lin PJC, Mui BL, Tam YK, Karikó K, Jacquet A, Krammer F, Bates P, Cancro MP, Weissman D, Luning Prak ET, Allman D, Locci M, Pardi N. Lipid nanoparticles enhance the efficacy of mRNA and protein subunit vaccines by inducing robust T follicular helper cell and humoral responses. Immunity. 2021 Dec 14;54(12):2877-2892.e7. doi: 10.1016/j.immuni.2021.11.001. Epub 2021 Nov 4. Erratum in: Immunity. 2022 Jun 14;55(6):1136-1138. doi: 10.1016/j.immuni.2022.05.007. PMID: 34852217; PMCID: PMC8566475.
2. Zeng Y, Escalona-Rayo O, Knol R, Kros A, Slütter B. Lipid nanoparticle-based mRNA candidates elicit potent T cell responses. Biomater Sci. 2023 Jan 31;11(3):964-974. doi: 10.1039/d2bm01581a. PMID: 36537916.

5.Discovery and Validation of Neoantigens for Immunoprevention of Colorectal Cancer – Eoghan Mulholland

Primary Supervisor: Eoghan Mulholland
Additional Supervisors: Simon Leedham and David Church

Abstract of the project
Colorectal cancer (CRC) develops over a prolonged period (typically 5 to 17 years) through a gradual accumulation of genetic and epigenetic changes that transform normal intestinal epithelium into malignant tissue. This extended window offers a unique opportunity to study early tumorigenesis and design immunopreventive strategies, including vaccines targeting pre-cancer-specific neoantigens.

This DPhil project focuses on the discovery and functional validation of neoantigens arising in pre-cancerous colorectal lesions. Our aim is to identify and characterise tumour-specific antigens from serrated, conventional, and familial adenomatous polyposis (FAP)-associated lesions using whole-genome sequencing (WGS) and long-read RNA sequencing, integrating these data with immune profiling and spatial biology. Ultimately, this work will inform the development of precision cancer vaccines for CRC prevention.

Resources available include:

- A comprehensive biobank of human pre-cancer lesions.
- Advanced human organoid and non-human in vivo models.
- Proprietary spatial statistics platform (MuSpAn).
- Expertise in organoid culture, multi-omics, and histopathology.

Research objectives and proposed outcomes
Identify CRC-specific neoantigens arising during early tumour evolution using high-resolution genomic and transcriptomic profiling. Characterise the immune landscape across distinct polyp subtypes and tissue compartments. Test antigenic drivers in vivo, evaluating their immunogenicity and therapeutic potential in mouse models of intestinal pre-cancer.

Work Package 1: Neoantigen Discovery through Multi-Omics Integration

Objective: Identify and prioritise pre-cancer-specific neoantigens in colorectal polyps.
Approach:

- Perform **whole-genome sequencing (WGS)** and **long-read RNA sequencing** on human polyp subtypes (serrated, conventional, and FAP-associated).
- Detect **somatic mutations**, **alternative splicing events**, and **fusion transcripts** to generate a comprehensive catalogue of candidate neoantigens.
- Integrate genomic and transcriptomic data using **neoantigen prediction pipelines** and correlate with immunopeptidome data from matched samples.
  Outcome: A refined list of high-confidence, lesion-specific neoantigens for downstream validation.

Work Package 2: Immune Profiling and Spatial Contextualisation

Objective: Characterise the immune landscape and spatial organisation of immune–epithelial interactions in pre-cancerous lesions.
Approach:

- Apply **spatial transcriptomics** and **multiplex proteomic imaging** to human polyp tissues.
- Quantify immune cell phenotypes, their abundance, and spatial distribution using our in-house **MuSpAn spatial analysis platform**.
- Compare immune architecture across distinct histological and mutational subtypes.
  Outcome: A spatially resolved immune atlas of early CRC lesions, revealing how neoantigen emergence correlates with immune editing and evasion.

Work Package 3: Functional Validation of targets and their context using human organoids and non-human model systems.

Objective: Validate neoantigen immunogenicity and assess how oncogenic signalling pathways influence antigen presentation and responses.
Approach:

- Modulate key pathways (**Wnt, MAPK, IFNγ**) using genetic or pharmacological tools ex vivo with human polyp organoid systems.
- Use **non-human models of intestinal polyposis** (e.g., *ApcMin*, inducible models) to test how key pathway modulation impacts in vivo systems.
- Explore **immune cell recruitment**, and **TME remodelling** over time in these models.
  Outcome: Mechanistic insights into how pathway dysregulation alters immune visibility, supporting rational design of immunoprevention strategies.

Translational potential
Each year, around 42,000 people in the UK face a life-changing diagnosis: colorectal cancer. For up to half of those who respond poorly to treatment, the disease spreads further leading to distant metastases and more aggressive outcomes. By developing our understanding of pre-cancerous lesions, we're working toward the development of preventative vaccines that could stop colorectal cancer before it starts.

Training opportunities
This interdisciplinary project is based at the Centre for Human Genetics and provides a rich array of training opportunities. The student will gain hands-on experience in genetic data analysis, tissue sample preparation for histopathological examination, and access to a collection of spatial transcriptomic datasets. In addition, they will be trained in fundamental wet lab techniques, develop a strong understanding of tumour biology, and explore key concepts in vaccine development.

Student Background
This project aims to identify and validate neoantigens arising in pre-cancerous colorectal lesions to inform the development of preventive cancer vaccines. Using whole-genome and long-read RNA sequencing, combined with immune profiling and spatial biology, it will characterise tumour-specific antigens across serrated, conventional, and FAP-associated polyps. Spatial transcriptomics and proteomics will map immune–epithelial interactions, while ex vivo models will assess neoantigen immunogenicity and the impact of oncogenic pathways on immune recognition. By integrating genomics, immunology, and spatial data, the project advances understanding of early colorectal tumorigenesis and supports the development of precision immunoprevention strategies targeting a major digestive cancer.

Return to Projects list