DPhil in Cancer Science

University of Oxford

Paediatric Project Booklet

2024 Intake

CANCER RESEARCH UK | OXFORD CENTRE

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BLACK ACADEMIC FUTURES

DPhil in Cancer Science
2024 Paediatric Intake Project Book

Introduction

This handbook provides an overview for prospective students looking to study for a DPhil in Cancer Science starting in 2024 at Oxford University. The Programme provides research based doctoral training for cancer researchers from clinical, biological, engineering, mathematics, and statistics background. 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

For this admissions round, we are open to applications from two tracks in the programme, as described below, meaning that non-clinicians are eligible to apply for the fully funded (at home rate) studentships.

Application Track 3 – 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.

Application Track 4 – 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 engineering, mathematical/data, ***or*** physical 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 stipend, University/College fees, and a research consumables budget of ~£13k p.a.
Stipend provisions are summarised below:

- **Application Tracks 3 :** 4 years of stipend at the flat rate of £21,000 per annum.
- **Application Tracks 4 :** 4 years of stipend at the flat rate of £21,000 per annum.

International applicants are eligible; however, funding is limited to the Home level for this programme and therefore international applicants would need to either source further funding or support themselves financially for the remaining fees.

How to Apply

A detailed summary on how to apply can be found here. In brief, prospective students apply with a prioritised list of three projects selected from this Paediatric booklet and/or our non-clinical DPhil project booklet by **Friday 19th April 2024.** Shortlisted students will be invited to interview in May. If successful, students will be allocated a project on the basis of their ranking during the review process. It is strongly suggested that students contact supervisors of projects they are interested in applying for prior to application.

Projects

Projects are listed below in the following structure "Title [Eligible Application Tracks] – Primary Supervisor Page number."
Clicking on the project title below will take you to the project page.

1. Comprehensive Understanding the mechanisms by which molecular and phenotypic heterogeneity of MLL-Rearranged Infant ALL affects clinical outcome[3] – Anindita Roy

Primary Supervisor: Anindita Roy
Additional Supervisors: Philip Ancliff and Jack Bartram
Eligibility: Track 3 students are eligible to apply for this project.

Abstract of the project

Although there has been much progress in treating acute lymphoblastic leukaemia (ALL) in children, there is still a subset of ALLs that have a very poor prognosis. This is particularly true for infants (i.e., children <1 year of age). Infant ALL (iALL) is frequently driven by translocations of the *Mixed Lineage Leukaemia* (*MLL* aka *KMT2A*) gene, which occur in ~80% of the cases, and represents a very aggressive type of leukaemia that is characterised by chemotherapy resistance and high relapse rates leading to a very poor prognosis[1]. The major challenge is that while iALL is aggressive, necessitating high-intensity treatment strategies, infants are extremely vulnerable to toxicity from chemotherapy and stem cell transplantation. Recent studies have shown the benefit of upfront CD19 directed therapy in iALL[2, 3]. As there is no ongoing UK clinical trial for iALL treatment, the UK NCRI Leukaemia sub-group have designed an innovative treatment guideline to replace some of the most intensive and toxic chemotherapy blocks used in past protocols, as well as carefully tailoring treatment to the biological features of each patient's leukaemia. Extensive work is underway to better understand infant ALL and this includes generating complex datasets such as single cell RNA-seq, genomics, other multiomic datasets and flow cytometry. Together, these orthogonal datasets could be correlated with real-world longitudinal clinical data to predict disease outcomes and design better personalised treatments. We have formed a consortium of expert clinicians, scientists and parent advocates to deliver this.

Research objectives and proposed outcomes
Aim 1: Delivering a national clinical study and develop a database, to help inform the scientific and clinical agenda. **(P Ancliff/J Bartram/A Blake)**

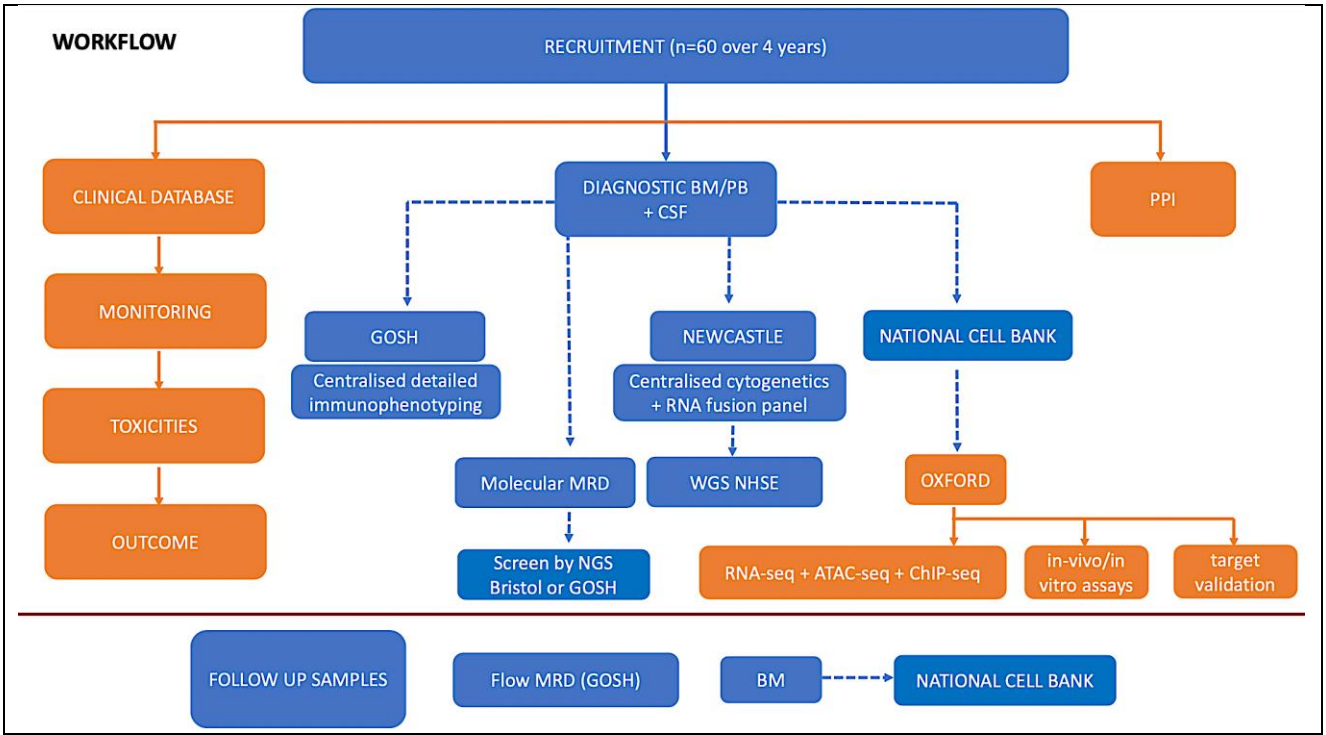

Figure 1: Schematic of project workflow. Sample collection and experimental workflow for the study. Blue boxes and arrows represent protocols that are covered by existing diagnostic pathways. Orange boxes/arrows represent research protocols (part funded by CRUK CYP Data grant). (BM: Bone marrow, PB: peripheral blood, MRD: minimal residual disease)

The national study opened in 2021. All newly diagnosed iALL patients are eligible for recruitment. There are c.12-15 cases of iALL in the UK/year. We expect to recruit >90% since all cases are presented at our National Leukaemia MDT. Expected recruitment is 60 patients over 4 years or longer, with the total recruitment period being 48 months. Recruitment to date: 33. Clinical data: A secure central database managed by Oxford Cancer will capture demographics, routine diagnostics, treatment, toxicity, and clinical outcome data. This will be via a Redcap database (including a dedicated portal) for parents.

Aim 2: Detailed characterisations of each patient's leukaemia, including biomarkers to better understand disease biology and response to treatment. **(collaboration T Milne)**

2.1 At diagnosis, all patient BM samples will undergo comprehensive characterisation as part of the diagnostic workup (Figure 1), including: i) detailed immunophenotyping; ii) State of the art cytogenetics and RNA-fusion panel for detailed molecular characterization; iii) Ig/TCR rearrangement status by next generation sequencing to monitor MRD; iv) Whole genome sequencing (WGS) via the NHS Genomics Medicine Service/Genomics England. All diagnostic tests (as NHS standard of care) will be streamlined and undertaken in centres of excellence in a standardised manner (Fig 1).

2.2 To further unravel and understand the mechanisms by which molecular heterogeneity of MLL-rearranged infant ALL affects clinical outcome, we will perform comprehensive characterisation of diagnostic and relapse samples using multi-omic profiling. Samples will undergo RNA-sequencing, ATAC-sequencing and ChIP-sequencing for MLL-rearranged protein complex members, and key histone modifications such as H3K4me3, H3K27ac and H3K27me3 will be used to further define the global transcriptomic and epigenetic profile of the cells (A Roy/T Milne, Oxford).

2.3 Once specific molecular profiles/leukaemic subpopulations have been identified, including minor myeloid subclones that might cause plasticity or relapse; these will be correlated with a variety of clinical parameters and outcome to ascertain whether they are relevant prognostic biomarkers. To address the challenges of biomarker/target discovery in such a rare disease we will leverage established collaborations with the Interfant-21 trial (joint scientific committee has been set up, and additional funding secured through Fight Kids Cancer grant), and the HARMONY alliance (https://www.harmony-alliance.eu/) to validate identified biomarkers.

2.4 We will create and utilise comprehensively characterised primary patient material, in combination with state-of-the-art preclinical models[4], to provide unique insights into novel therapeutic and prognostic targets in iALL. Full molecular characterization of iALL will give us the opportunity to study these cases in unprecedented detail at a multi-omics level. This will allow us to generate gene regulatory networks to identify key molecular pathways perturbed in iALL[5, 6] and how this correlates with clinical outcome. We will combine these findings with results of ongoing funded projects using CRISPR essentiality screens and molecular and functional screens in mouse models[4]

Aim 3: Data integration and analysis **(A Blake).** All longitudinal clinical and research data will be integrated for each patient to provide a comprehensive personalised map of the disease. This can then be correlated with outcome and treatment related toxicity to understand patient heterogeneity (collaboration A Blake). Data for all iALL patients on the national study, will be collected and uploaded to the database. We will also include parent reported outcomes as this is an important measure to understand whether our improved treatment guidelines are effective. The ultimate goal will be to use machine learning approaches to map clinical and biological patterns that will predict poor treatment response in patients, allowing personalised treatments in future studies.

Translational potential of the project

Since the last international trial for treatment of infant ALL (Interfant-06) closed in July 2016, infants diagnosed with ALL in the UK have not been enrolled in any clinical trials. While we will continue to work closely with our European and international colleagues, the UK is unable to participate in the next international trial (Interfant-21) as it has no randomisation arm. This leaves a vulnerable patient population without the benefit of a structured clinical trial in one of the poorest risk leukaemia's. The current national study (2021 onwards) will ensure the implementation of risk-adapted treatment guidelines for all infants with ALL in the UK with the most comprehensive characterisation of the leukaemia and follow-up to date. We anticipate that patients will benefit immediately by the introduction of novel therapy approaches in our UK-NCRI-LSG guidelines, but it is imperative to capture real-life clinical data to learn about the efficacy and toxicity of these newer therapies compared to historic treatments. The study will allow us to monitor these treatment responses as well as investigate the biological mechanisms, which underpin its success or failure, including finding predictive biomarkers. This will lead to better stratification and a personalised medicine approach, which is a longer-term goal of this study. In addition, the phenotypic and molecular dataset generated will be an invaluable resource to clinicians and scientists treating patients or studying the biology of iALL. The most important feature of this project that will benefit

patients is the true integration of clinical and scientific strategies in order to accelerate the development of effective therapeutic options.

Training opportunities

The student will be embedded in the excellent scientific environment of the WIMM. He/she will be supported by experienced postdoctoral researchers in the lab, as well as collaborating labs to learn cutting edge functional/molecular techniques such as flow cytometry, in vitro and in vivo assays, RNA-sequencing, ATAC sequencing, and ChIP-sequencing. All of these techniques are already in use in our labs; and additional training opportunities will be available for computational analysis (via dedicated courses at the Centre for Computational Biology, WIMM) and with A Blake's Team at Oxford Cancer for Big Data pipelines and analysis. The student will be encouraged to take up the excellent training opportunities provided within the WIMM and the University of Oxford, to develop their research career. In addition, they will gain experience in running a national clinical study including collating all clinical outcome and toxicity data under the guidance of expert clinical trial leads at GOSH.

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2. Genetic and cellular landscape of paediatric myelodysplastic syndromes.[3] – Prof. Adam Mead

Primary Supervisor: Prof. Adam Mead
Additional Supervisors:
Eligibility: Tracks 3 students are eligible to apply for this project.

Abstract

Paediatric myelodysplastic syndromes (PMDS) are a rare group of blood cancers driven by mutation of haematopoietic stem cells (HSC) and characterised clinically by unexplained cytopenia coupled with specific blood cell morphological abnormalities. There is a wide spectrum of clinical severity varying from mild, asymptomatic cytopenia to progressive bone marrow failure and/or acute myeloid leukaemia (AML) (1, 2). Unlike adult MDS, this group of conditions are rare within the paediatric population with an estimated incidence of 1.4 cases/million (3). An additional challenge in PMDS relates to the fact that in children, germline predisposition to PMDS is frequent; at least 30% of patients develop PMDS on the background of an underlying genetic predisposition syndrome (4), such as GATA2 (5) and SAMD9 and SAMD9L (6). However, despite this, for many children with PMDS the molecular basis of the disease is unclear, with ~66% of patients screened using extended targeted next generation sequencing panels of 100+ genes, have no mutation identified (7). There is an urgent need for advances in diagnostics, development of disease biomarkers as well as new therapeutic approaches.

To meet this unmet need, we established a UK PMDS observational prospective study with full ethical approval already in place (NHS REC reference number: 15/LO/0961).

All UK tertiary paediatric haematology centres are participating and to date we have recruited over 100 participants, providing a truly unique resource of blood and bone marrow samples from children with this rare disease.

Research Objectives

In this project, the student will analyse UK PMDS study samples using a customised PMDS targeted next generation sequencing (NGS) panel in order to characterise the genetic basis of these rare conditions as well as monitor genetic evolution in serial samples pre- and post-treatments such as bone marrow transplant. Cases with well-defined phenotypic features and no mutations detected by the targeted next generation sequencing panel will be selected to have whole genome sequencing (WGS) carried out. This will provide an excellent training in cutting edge genetic techniques.

The second major focus of this work is to understand the cellular landscape of PMDS, employing a range of single cell genomics and stem cell biology techniques in which the Mead lab has extensive expertise.

Translational Potential

The most tangible impact of this work on patient outcomes is likely to come from better approaches to diagnose, monitor (biomarkers of early relapse) and treat patients with PMDS and JMML. The detailed documentation of phenotypic and genotypic data from MDS sub-groups, including response to treatment and outcomes will further inform the natural history of these syndromes and enable us to provide recommendations for diagnosis as well as disease sub-type specific management plans, timing of treatment interventions and provide evidence based risk stratification for patients, that is currently not available.

Training opportunities

The Mead laboratory leads on single-cell research at the WIMM (8-13) and the student will gain a state of the art training in this exciting field. Professor Mead has supervised 22 DPhil students/clinical fellows and examined 20 PhDs. Notably, students coming through the Mead Laboratory have been awarded a number of prizes, including the Ita Askonas Medal for best WIMM day student presentation (2017 & 2018), the RDM Graduate Prize (2018) and CRUK Oxford Centre DPhil

prize (2019 & 2023). Professor Mead was awarded the Radcliffe Department of Medicine Award for Excellent Supervision, March 2020.

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