Clinical PhD Project 2024

Understanding the evolutionary dynamics of myelodysplastic syndrome and factors that drive or impede progression to acute myeloid leukaemia.

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Principal supervisor's CRUK CC theme: Early Cancer Institute

Department for student registration: Department of Oncology
Department or institute where research will take place: Early Cancer Institute

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Postgraduate scheme: **Clinical Research Training Fellow (3-year PhD)**

PhD project outline:

Acute myeloid leukaemia (AML) is an aggressive blood cancer which claims the lives of 70-80% of patients within 5 years of diagnosis. Like many cancers, AML typically develops via serial acquisition of 'driver' mutations; a process that starts many years, or even decades, before diagnosis. This raises the prospect that early detection of pre-leukaemic mutations could identify individuals who will develop AML, in whom early intervention might be able to halt the disease before it fully develops. One of the difficulties with AML early detection is that clonally expanded mutations in leukaemia-associated genes are also found in the blood of healthy individuals ('clonal haematopoiesis') and so a key challenge is the ability to reliably identify which individuals will progress. In some individuals, clonal haematopoiesis can evolve to myelodysplastic syndrome (MDS) and if MDS progresses to AML the prognosis is particularly poor, with median survival ~7 months. Approximately 30% of individuals with MDS will progress to AML and so, not only is a better understanding of MDS important, but its high rate of transformation, compared to clonal haematopoiesis, makes MDS a model system in which to better understand factors that drive clonal evolution towards or away from AML. Whilst high-risk features have been identified, how and why some individuals evolve from MDS to AML is poorly understood.

AIMS/ OBJECTIVES:

The overall aim of the PhD project is to harness the power of longitudinal blood samples (collected before diagnosis of MDS+/-AML) to gain a better understanding of how and why MDS progresses to AML and how cell-extrinsic factors, such as inflammation, might affect pre-leukaemic clonal dynamics.

The project aims to answer the following questions:

1) How does clonal evolution differ in individuals who subsequently develop MDS and then do/ do not progress further to AML?

2) At what age do MDS +/- AML driver mutations occur?

3) How early can we identify individuals who will develop MDS that will progress to AML? Can we identify who will progress to AML even before they develop MDS?

4) How do inflammatory changes (commonly seen in MDS) correlate with clonal evolution?

Understanding the evolutionary processes that precede MDS+/-AML and what factors drive or halt its progression will be invaluable for developing early detection tools and preventative therapeutic interventions. Pre-cancerous clonal evolution is also not unique to blood and is pervasive throughout bodily tissues with increasing age. Disentangling the factors that determine haematopoietic clonal evolution therefore has additional broader implications and is also relevant to our understanding of cancer evolution in other tissues.

PhD experimental plan:

This project will use longitudinal blood samples that have already been collected as part of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), which recruited ~200,000 women aged 50-74 between 2001 and 2005. Approximately 50,000 of these women had annual blood sampling for up to 11 years and, since the trial started, ~100 of these women have been diagnosed with MDS, of whom ~20 also developed AML. With an average of 7 timepoint samples per person, this unique set of longitudinal samples provides an unparalleled opportunity to watch MDS+/-AML evolution unfold.

The experimental plan, using these samples, is as follows:
1) Whole genome sequencing (WGS) of the samples closest to the time of MDS+/-AML diagnosis (to assess mutational burden, mutational signatures and germline variants).
2) The WGS results will inform the design of a custom targeted DNA sequencing approach on the earlier timepoint samples, using a method which allows simultaneous detection of gene mutations, mosaic chromosomal alterations and chromosomal translocations in a single workflow. Incorporating duplex error-correction methods will allow the reliable detection of mutations when they are at very low frequency in the blood.
3) Clonal trajectories in the years pre-MDS+/-AML diagnosis will be used to infer phylogenies, evolution patterns, age at acquisition of mutations and mutation growth rates (and how these growth rates are affected by acquisition of further mutations).
4) Proteomic analysis of the longitudinal samples, focusing on assessing how inflammatory changes interplay with clonal evolution – is inflammation a cause or consequence of clonal evolution?

Main techniques:

- DNA sequencing (Whole genome sequencing, Duplex error-corrected sequencing)
- Proteomic analysis
- Bioinformatic analysis of DNA sequencing and proteomic data
- Analysis of large genomic/ proteomic datasets
- Quantitative longitudinal data analysis, using evolutionary-biology based computational models of clonal evolution

Key references:

Watson, C.J., Papula, A.L., Poon, G.Y.P., Wong, W.H., Young, A.L., Druley, T.E., Fisher, D.S, Blundell, J.R. The evolutionary dynamics and fitness landscape of clonal hematopoiesis. Science

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