Mechanisms regulating blood stem cell self-renewal and differentiation
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The Wilkinson research group focuses on the biology and translational applications of blood-forming haematopoietic stem cells (HSCs). Self-renewing multipotent HSCs are a rare but incredibly important cell type. Just ~100,000 HSCs generate all the cells of the blood and immune systems, which constitute ~90% of the cells within our bodies. As a long-lived stem cell population, HSCs gradually accumulate genetic mutations and are therefore thought to be a cell-of-origin for several haematological malignancies, particularly myelodysplastic syndrome and myeloid leukaemias.

HSCs are also therapeutically significant with HSC transplantation being the mainstay treatment for the most severe disorders of haematopoiesis ranging from immunodeficiencies to myeloid and lymphoid malignancies. Allogeneic HSC transplantation currently represents the only curative treatment option for a number of haematological malignancies. However, the availability of suitable donor HSCs is a major bottleneck in the use of this therapeutic option. The advent of CRISPR/Cas9 has also led to a renewed interest in HSC gene therapies using autologous HSC transplantation for various genetic diseases.

We have recently developed novel polymer-based culture systems that stably expand HSCs ex vivo, as well as methods to perform efficient genetic manipulation in these cultures. We are now applying these technologies to better understand the biology of healthy and malignant HSCs in order to facilitate the development of new haematological disease treatments.

The PhD project will aim to address biological questions related the mechanisms regulating healthy and malignant HSC activity, and/or aim to develop novel HSC-based therapies. This could include:

1. Characterising novel regulators of HSC self-renewal and differentiation;
2. Interrogating pre-malignant HSCs and leukaemic transformation;
3. Developing novel HSC-based cell and gene therapies.

Main techniques:

- Primary mouse and/or human haematopoietic stem cell (HSC) isolation and ex vivo culture (expansion, differentiation)
- HSC gene editing (to generate gene knockouts and knockins) and viral transduction
- Multicolour flow cytometry and fluorescence-activated cell sorting
- Clonal barcoding studies
- Omic assays (RNA-seq, ChIP-seq, ATAC-seq)
- Molecular cloning

Key references:

1. Meaker et al., Blood 2025. https://ashpublications.org/blood/article-abstract/doi/10.1182/blood.2025029115/547297/A-genome-wide-screen-identifies-Runx2-as-a-novel
2. Igarashi et al., Blood Advances 2022. https://pubmed.ncbi.nlm.nih.gov/36809781/
3. Wilkinson et al., Nature 2019. https://pubmed.ncbi.nlm.nih.gov/31142833/
4. Wilkinson et al., Nat Commun 2021. https://pubmed.ncbi.nlm.nih.gov/33514718/
5. Sakurai et al., Nature 2023. https://pubmed.ncbi.nlm.nih.gov/36813966/