Project title: **"Dissecting the Biology of High-Risk Leukaemia Through CRISPR Engineering"**
Main Supervisor: **Dr Justin Loke**
Co-Supervisor: **Professor Tim Somervaille**
Research Group: **Myeloid cancer biology**

Acute myeloid leukaemia (AML) is the most common aggressive leukaemia in adults. Its subtypes are defined by distinct genetic mutations. Among these, AML driven by *TP53* mutations is associated with extremely poor prognosis, as current treatments, including chemotherapy and allogeneic stem cell transplantation, are largely ineffective (PMID: 35612815). There is therefore an urgent need for improved models to better understand the biology of *TP53*-mutant AML and to provide systems in which new therapies can be tested.

In this project, we will exploit a novel transgenic mouse line that we have recently developed, which expresses a CRISPR enzyme capable of enabling bespoke edits at multiple genetic sites in murine haematopoietic stem cells (HSCs). This technology will allow you to re-capitulate the complex genetic features of *TP53*-mutant AML. Using this mouse model, we will generate and study *Trp53*-mutant leukaemias in vivo, identifying key factors upon which this disease depends for survival. This work builds upon our recent findings in myeloid neoplasms involving another commonly mutated gene (PMID: 40493884).

You will further extend this approach to human HSCs, developing a platform to engineer *TP53*-mutant leukaemias directly in human cells. This will create a platform to validate findings from the mouse studies and establish a powerful system to test new drug combinations and therapeutic approaches in a clinically relevant setting.

We are seeking a motivated, inquisitive individual with a strong interest in cancer biology and translational research. You will receive training across a broad spectrum of techniques, from molecular biology and CRISPR-based genome editing to in vivo mouse models. The project will also involve the use of primary patient samples, providing direct clinical relevance and integration into a highly translational research environment. This experience will equip you with a versatile skill set and a strong foundation to develop independent research questions in the future.