Project title: **"Innovative technologies for exploration of mechanisms of transcription factor function in acute myeloid leukaemia"**

Main Supervisor: **Tim Somervaille**

Research Group: **Leukaemia Biology**

Recent years have seen significant progress in the development of better therapies for people with blood cancer, with concomitant improvements in response. However, there remains a substantial unmet need for more effective, and less toxic, treatments. For example, outcomes in acute myeloid leukaemia (AML) are particularly poor in older adults and those with relapsed or refractory disease, and malignancies such as multiple myeloma are incurable for the great majority.

The overarching goal of our group at the Cancer Research UK Manchester Institute is to deliver a bench-to-bedside programme of blood cancer research and some key publications from our group in keeping with this may be found on PubMed (PMIDs: 37995682, 37539037, 34551306, 33052756, 31770110). These published studies give an idea of the scope of the research activity of our group, and the techniques and technologies in use.

Much of our effort is focussed on understanding how transcription factors and their associated chromatin cofactors sustain myeloid blood cancers such as AML. Despite substantial advances it remains the case that in 2024 we still have relatively little understanding of how transcription factors interact with other chromatin proteins to regulate gene expression. Enhanced understanding may lead to new therapeutic targets for evaluation and progression to the clinic. Many of the ongoing projects in the lab are focused around this question.

This particular PhD project will make use of a recently generated mouse model where a degron tag has been knocked into a critical leukaemia transcription factor gene of interest allowing us to deplete the protein from cells at will through addition of a small molecule. Such technology permits us to follow minute-by-minute in real time – and in vivo or in vitro - changes in transcription, enhancer occupancy and complex assembly so that novel mechanistic insights can be gleaned around the function of this essential transcription factor.

This project would be perfectly suited for an ambitious and hard-working candidate who is interested in developing skills in both laboratory and computational biology (for example, to perform and analyse ChIPseq and RNAseq techniques and datasets).