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Project Title **“Novel pathways and therapies in acute myeloid leukaemia”**
Group Leader Tim Somervaille
Research Group Leukaemia Biology

This 4-year PhD studentship will be based in our new world class research building next to the Christie NHS Foundation Trust, Withington, Manchester.

Acute myeloid leukaemia (AML) is defined by a block to the normal differentiation of myeloid cells resulting in accumulation of blasts in the bone marrow and failure of normal haematopoiesis (Khwaja et al., 2016, Nature Reviews Disease Primers). Despite the genetic heterogeneity the differentiation block is the cardinal feature of the disease and emerging evidence reveals that mutations cluster in particular categories of gene. Indeed, the great majority of patients with AML have one or more mutations targeting a transcription factor, chromatin modifier or regulator of DNA methylation and this emphasises the absolute centrality of epigenetic and transcription factor dysfunction to the disease. Investigation of this dysfunction holds rich promise for discovery of new therapeutic targets for development through to the clinic: AML remains a significant cause of morbidity and mortality, with poor long-term survival despite treatments including chemotherapy and bone marrow transplantation.

We are looking for a hard-working, focussed, ambitious person to join our happy, interactive and excellent team. Our laboratory makes use of the latest in vitro and in vivo techniques and technologies to interrogate questions about critical epigenetic mechanisms of myeloid lineage blood cancers with the goal of developing novel treatments for patients. We make substantial use of experimental techniques such as ChIP sequencing and single cell and bulk RNA sequencing. These technologies in turn make substantial use of bioinformatics analysis approaches. We would be particularly happy to receive applications from individuals with a strong academic track record and Masters-level and/or other laboratory research experience in leukaemia or cancer. We will also consider applications from individuals with exceptional bioinformatics skills who are looking to expand their experience and training with wet lab work.

There is significant flexibility in project choice for the successful applicant. In the lab we have ongoing projects across a range of leukaemia epigenetics topics. As an example, however, one option would be to work on the role of the IRX3 repressor protein in leukaemia. This protein is highly expressed in around 30% of cases of AML and nearly 50% of cases of T-acute lymphoblastic leukaemia and has a capacity to immortalize stem and progenitor cells, and to confer a differentiation block. The question in hand is, how does the protein do this? Building on ongoing work in the lab, we would want to make use of the latest mass spectrometry and high throughput technologies to identify the proteins which IRX3 interacts with in the cell, and to make use of CRISPR screening and cell-based assays to identify which of them is functionally important and why. An important and relevant past paper of ours pertinent to this potential project is Somerville et al. (2018) Cell Reports (<https://pubmed.ncbi.nlm.nih.gov/29346763/>).