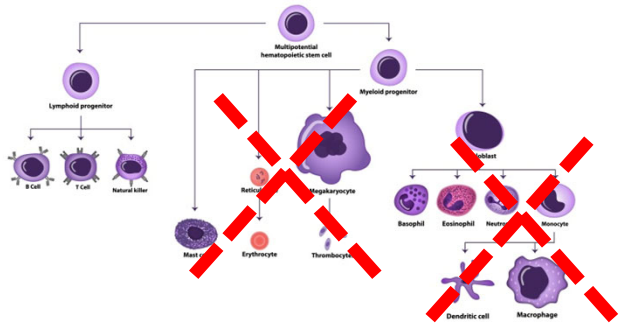
Investigating RNA splicing alterations as an unexplored causal factor of leukaemia

Molecular Mechanisms in Leukemia Laboratory

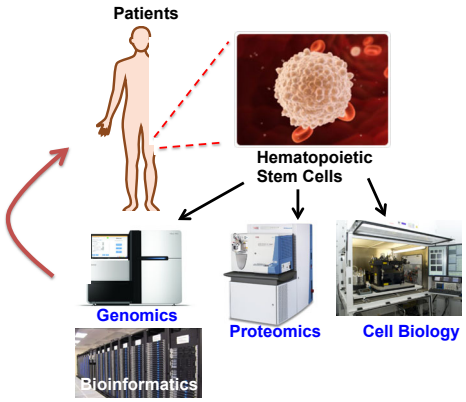
What We Study

Leukemia



- **Leukemias are amongst the common blood cancers in adults, arising from molecular defects in hematopoietic stem cells and leading to impaired blood production**
- **Acute Myeloid Leukemia (AML) is a particularly aggressive leukemia with poor survival (long term disease-free survival of <10% and a median overall survival of <12 months in patients aged over 60 years).**
- **There is a need to better understand the biology of leukemia in order to develop more effective treatments**

Translational Cancer Research



We combine cutting-edge "wet" lab techniques with advanced bioinformatics and data science to further the concept of personalized medicine in leukemia

Project 1: Targeting drug resistance pathways in Acute Myeloid Leukemia

Treatment relapse is a major clinical problem in the management of Acute Myeloid Leukemia (AML). The prognosis for patients following relapse remains poor.

The standard of care treatment for AML is induction chemotherapy, but its non-specific and cytotoxic nature is associated with significant side-effects. With the increasing advent of next-generation sequencing based genomic profiling, it has become clear that leukemic ells in patients have a range of recurrent somatic mutations. Drugs that specifically target these mutations, or target pathways specifically affected by these mutations, could potentially lead to the eradication of leukemic cells whilst sparing healthy haematopoietic stem cells.

We have recently discovered that a stress response pathway is specifically upregulated in AML patients who have the most aggressive form of the disease and who respond most poorly to treatment.

Hypothesis: We hypothesise that this stress response pathway enables leukemic cells to survive chemotherapy.

Objectives: In this "wet-lab" focused project, we will aim to dissect the mechanisms driving the upregulation of the stress response pathway in leukemic cells. Furthermore, we will investigate whether pharmacologically inhibiting this stress response pathway might sensitise leukemic cells to chemotherapy.

Project 2: Identifying mechanisms of aberrant RNA splicing in drug-resistant leukemia

Using cutting-edge bioinformatics and machine learning techniques, we have recently discovered that RNA splicing, a fundamental biological process occurring in all cells, is aberrant in leukemic cells. Our discovery adds to a growing body of literature suggesting that RNA splicing defects are widespread across a broad range of cancers.

RNA splicing as a driving mechanism of cancer has been relatively poorly studied, mainly because the technologies to enable us to do so have been lacking until very recently. However, new advancements in next-generation sequencing, including third-generation RNA-sequencing, are enabling us to answer important questions concerning RNA splicing defects.

The causes of the aberrant RNA splicing we have identified in leukemia remain unknown.

Hypothesis: We hypothesise that genetic and epigenetic mechanisms are contributing to the dysregulation of RNA splicing in leukemia.

Objective: In this project straddling bioinformatics and the "wet lab", we will use bioinformatics and "big data" approaches the interrogate the large amounts of cancer genomics data that have already been generated by a number of groups around the world. We will test our hypotheses *in silico* and validate inferences that emerge in the "wet lab"

Techniques You Will Learn

Project 1

- Stem Cell Biology techniques
- Tissue Culture
- Molecular Biology
- Biochemistry
- Gene Expression analyses
- Transcriptomics
- Epigenetics techniques
- Western Blotting
- Analyses of primary samples
- Drug discovery

Project 2

- Bioinformatics
- Programming
- Genomics & Transcriptomics
- Big data Analyses
- RNA splicing Analyses
- Genomics
- Molecular Biology
- Tissue Culture

Who We Are

We are a multi-disciplinary team of cancer research scientists, clinicians and computational bioinformaticians

Interested? Get in touch:
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