

Leukaemia Research Group

Honours Projects

Cloning novel Mixed Lineage Leukaemia (MLL) fusions and functional characterisation and resistance studies.

Recent advances in genomic profiling have defined Acute Lymphoblastic Leukaemia (ALL) as a heterogeneous disease with multiple subgroups characterised by distinct genetic alterations. The presence of chromosomal rearrangements of the MLL gene in ALL patients is associated with extremely poor prognosis. Using transcriptomic analysis we have identified a number of poorly characterised MLL fusions in patients with ALL. This project aims to clone full-length MLL fusions from patient material into mammalian expression plasmids. This will allow future in vitro characterisation and therapeutic responses. This project will involve a range of molecular biology and cloning techniques including primer design, PCR Sanger sequencing, bacterial work and tissue culture.

Generation of resistance to combinations of the new anti-leukaemic agent ABL001 and imatinib or dasatinib using BCR-ABL1+ cell-lines.

Phase I clinical trials for the treatment of CML are currently underway using ABL001, an allosteric inhibitor, alone and in combination with ATP-competitive tyrosine kinase inhibitors (TKIs: imatinib, nilotinib or dasatinib), to inhibit the constitutively active tyrosine kinase Bcr-Abl. Generation of resistant cell lines in the laboratory setting provides a useful tool for predicting and studying patient responses in vivo.

In this project, BCR-ABL1+ cell lines will be exposed long term to gradually increasing concentrations of ABL001 in combination with dasatinib or imatinib. Mechanisms of resistance will be interrogated during resistance development and once overt resistance is observed.

PhD projects

Using in vivo modelling to reverse/prevent disease resistance in patients with high-risk ALL treated with targeted therapies.

Relapsed Acute Lymphoblastic Leukaemia (ALL) is a significant medical problem in children and adults. Recent advances in genomic profiling techniques highlighted the genetic heterogeneity of the disease; subgroups of patients harbouring a diverse range of genetic abnormalities exist. The incorporation of clinically available drugs, with known safety profiles, into current therapeutic regimens will transform outcomes for patients with high-risk subtypes of ALL. However, resistance to such targeted therapies will likely occur in a percentage of patients and in vivo modelling of resistant disease and investigations of new therapeutic strategies (combination therapy, novel drugs as they become available) is critical to proactively avoid resistance in children. This project will use patient derived xenograft (PDX) mouse models to aid the development of novel therapeutic approaches, which will likely yield superior clinical management of patients with the highest risk disease.

Project Aims

- 1) To establish in vivo models of resistance using primary cells from patients with high risk ALL
- 2) To determine baseline patient sensitivity to anti-leukemic agents in vitro
- 3) To determine the efficacy of therapeutic approaches in mouse models developed in Aim 1

Determining the prerequisites for the achievement of treatment-free remission in Chronic Myeloid Leukaemia (CML) to aid the development of new therapeutic approaches.

Tyrosine kinase inhibitors (TKIs) are used in the treatment of CML. Many patients will eventually achieve a stable complete molecular response (CMR) and approximately 40% of these patients can cease TKI therapy and remain in CMR, or treatment-free remission (TFR) long-term. Why the remaining 60% of patients relapse rapidly when TKI therapy is ceased remain undetermined, but likely hold the key to understanding and maximising TFR, one of the biggest challenges for CML clinicians today. The aims of this project are 1. to determine any difference in the quantity or quality of residual leukaemic cells in patients with stable CMR who relapse when they cease TKI therapy compared to patients who achieve TFR. 2. Whether these patients have different immune responses 3. Whether CMR and subsequent TFR are associated with specific genomic features.

Immunotherapy and Graft-versus-leukaemia (GVL)

Honours &/or PhD Projects

Evaluation of Natural Killer Cell phenotype and immune effector function in Chronic Myeloid Leukaemia.

Natural Killer (NK) Cells represent a specialized subset of immune effector cells that play an important role in innate immune defence against tumour and virus infected cells. As with many cancers, the proportion of NK cells is decreased in Chronic Myeloid Leukaemia (CML) and the immunosurveillance typically afforded by NK cells is impaired, allowing for cancer progression. Recent studies suggest that low NK cell numbers and poor cytokine secretion may predict CML relapse following tyrosine kinase inhibitor (TKI) discontinuation. We will study NK cell phenotype by undertaking extensive immune-profiling of NK cell maturation/activation status and expression of cell surface receptors critical to NK cell function. In addition, NK cell cytotoxicity will be determined in newly diagnosed CML patients and following administration of TKI and/or allogeneic stem cell transplantation. We aim to investigate the prognostic significance of NK cell immune effector phenotype and function in the context of TKI discontinuation, in order to improve patient outcomes.

Chimeric Antigen Receptor T Cell Therapy in Myeloid Leukaemia.

We are developing human T cells genetically engineered to express Chimeric Antigen Receptors (CAR) that will allow them to target and kill tumour cells in the treatment of Acute Myeloid Leukaemia (AML) and CML. We will synthesize CAR constructs with specificity against target molecules such as CD123 and IL-1RAP, which are over-expressed in leukemic stem cells (LSCs), and incorporate a selection of costimulatory molecules for functional efficacy. The pre-clinical study will lead to a Phase I clinical study in patients with relapsed/refractory AML and blast crisis of CML, which have very limited treatment options, express candidate target molecules that are central to their aggressive biology and have significant unmet clinical need.

Prostate Cancer

Honours/PhD Projects

Novel biomarkers of heat shock protein 90 inhibition in prostate cancer.

The translation of promising cancer therapeutics, such as heat shock protein 90 (Hsp90) inhibitors, into clinical practice is hampered by the inability of standard laboratory models to accurately predict clinical efficacy and identify robust biomarkers of response. In our recent publications in *Clinical Cancer Research*, *Nature Communications* and *Oncogene*, we demonstrated that culturing human prostate tumours as explants can provide important new information about the efficacy and molecular targets of Hsp90 inhibitors and other agents in a whole tissue context that was not previously achieved using cell lines or animal models. Using this unique *ex vivo* technology, coupled with quantitative mass spectrometry and an investigator-initiated clinical trial, this project will identify and validate a protein signature that can accurately and reliably monitor prostate cancer patient responses to treatment with the Hsp90 inhibitor, AUY922. This signature will assist in accelerating the translation of this new agent into clinical practice.

Effects of lipids on prostate tumour cell behaviour and response to therapy.

Cancer cells have different metabolic requirements compared to normal cells, as they need to survive in an altered microenvironment characterised by hypoxia and limited nutrient supply, and are highly proliferative. They have a particular need for lipids, which are required for membrane production, energy storage and intracellular signalling. While cancer cells can upregulate synthesis of lipids, other important sources are lipids in the bloodstream, and local adipocytes in the tumour microenvironment, each of which is markedly enhanced in obesity. In this project, the effect of increased lipids on hormonal signalling in the tumour cells and their response to current prostate cancer therapies will be assessed. A better understanding of the contribution of obesity to prostate cancer progression and drug response will ultimately facilitate targeted patient interventions to improve responses to new therapies.

Mass spectrometry imaging of lipid moieties in prostate tumours.

Our research has identified a range of specific lipid moieties that are altered in prostate tumours in response to therapy. The goal of this project is to use state-of-the-art Matrix Assisted Laser Desorption Ionisation (MALDI) Mass Spectrometry Imaging (MSI) on frozen tissue sections to validate the alterations in each individual lipid, and to determine the spatial location of these specific lipid species throughout the tumour. This will provide the first data indicating which cell types from the tumour are displaying the lipid changes, and has the potential to be developed into a clinical test for newly-diagnosed prostate cancer to predict disease aggressiveness and responsiveness to therapy.