

IN VIVO CANCER BIOLOGY



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Our lab uses preclinical models to study cancer, interrogating the role of cancer-related pathways within a biological context. By validating *in vitro* discoveries in physiologically relevant models, we hope to expedite novel therapeutic approaches to the clinic. Specific projects in the lab focus on how the RUNX/CBFB transcriptional complex and the BCL-2 family of apoptotic regulators contribute to tumour progression, metastasis and recurrence in breast, prostate, pancreatic and other cancers. The group also co-leads the MRC NMGN *Cancer Cluster* using complex state-of-the-art mouse models to improve the understanding and treatment of cancer.

Deciphering the role of the RUNX/CBFB transcriptional complex in breast cancer.

Mutation of the genes *RUNX1* and *CBFB* are common driver events in breast cancer. As transcription factors, the RUNX/CBFB complex is involved in the regulation of many cellular and developmental pathways, and we are using genetically engineered mouse models to help unravel the elaborate and dichotomous role of the *RUNX/CBFB* genes in breast cancer. Amy Lawlor, Dale Watt and Dylan Fowler have been investigating the impact of RUNX/CBFB complex alterations on mammary tumours and their tumour microenvironment. Amy is using her background in immunology to understand how RUNX/CBFB activity within the mammary tumour epithelium orchestrates the immune microenvironment. In parallel with Amy's work studying regulation of tumour epithelium/immune interactions, Dale Watt, Laura Galbraith and masters student Dylan Fowler, have been probing the role of this complex in cancer associated fibroblasts, another important component of the breast tumour microenvironment. Together these studies aim to deconvolute the interlaced role of the RUNX/CBFB complex throughout the breast cancer ecosystem.

Investigating the role of aberrant apoptosis in tumour development and targeting the BCL-2 family as an approach to reinstate apoptosis and improve cancer therapy.

Evasion of cell death is a hallmark of cancer that can enable tumour initiation, growth, metastasis and resistance to therapy. The most frequently altered cell death pathway in tumour development is intrinsic/mitochondrial apoptosis where elevation in pro-survival BCL-2 family proteins is a common event. Kirsteen Campbell leads several projects focussed on

the BCL-2 family in solid cancers. Triple negative breast cancer is a particularly aggressive subtype of breast cancer that currently lacks targeted treatment options. Utilising our newly developed genetically engineered mouse models of triple negative breast cancer (Figure 1), Matthew Winder and Louis O'Sullivan have been investigating the role of aberrant apoptosis throughout the tumorigenic process and have uncovered important roles for distinct BCL-2 family proteins at different stages. Using these novel models, and strongly supported by expertise in the Transgenic Models of Cancer Lab, they are testing the impact of specific targeting of pro-survival BCL-2 family proteins in breast cancer prevention and treatment.

In Prostate Cancer Research-funded work, Laura Martínez-Escardo and masters student Julia Chong have been investigating the dependence of prostate cancer on pro-survival BCL-2 family members MCL-1 and BCL-XL. Together with Hing Leung and John Le Quesne's team, they are using multiplex immunocytochemistry to characterise BCL-2 family protein expression in a prostate cancer tissue microarray (Figure 2). Through a combination of *in vivo* and *in vitro* approaches they have identified vulnerabilities in the BCL-2 family that have the potential to be harnessed to improve prostate cancer treatment outcomes. Laura was recently awarded an innovation and research award from The Urology Foundation/The John Black Charitable Foundation which will allow her to further investigate how these findings can be translated into new treatment approaches.

Pancreatic cancer is a difficult to treat cancer with devastatingly poor prognosis and we have identified that pancreatic cancers with high

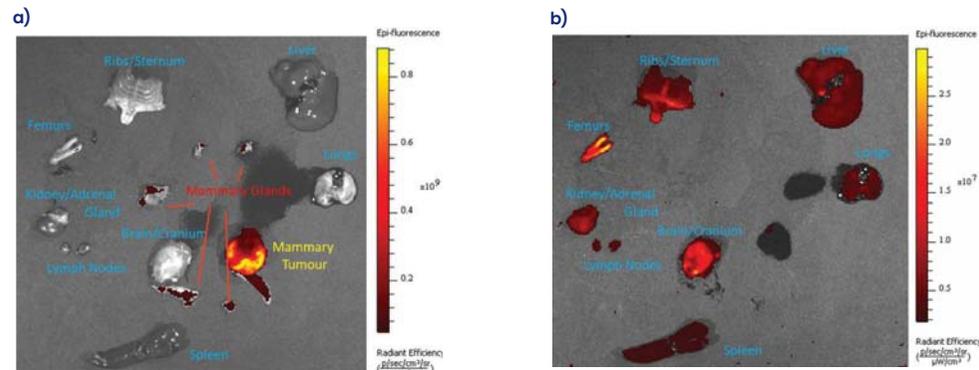


Figure 1. New genetic mouse models of breast cancer to study tumour growth and metastasis Incorporation of a fluorescent reporter gene into a novel mouse model that mimics common genetic events in breast cancer allows visualisation of tumour growth in (A) primary mammary tumour and (B) bone metastases, observed through increased signal when tissues are imaged *ex vivo* using an IVIS Spectrum Imaging System.

levels of MCL-1 and BCL-XL have worst outcomes. Yasmin Hunter has therefore been targeting the BCL-2 family in pancreatic cancer patient-derived cell lines to identify patient sub-groups that might respond to novel therapeutic treatments, including combinations with radiotherapy. Unifying our interests in targeting the BCL-2 family for therapeutic gain in breast, prostate and pancreatic cancer, Nimrit Kaur, together with Mark Jackson in Anthony Chalmer's team, has been investigating radiosensitisation through targeting the BCL-2 family across a large panel of cancer cell lines. This has extended our interests to glioblastoma and lung cancer. Through correlating radiosensitisation with genomic, transcriptomic and proteomic data they aim to identify patient sub-groups who will benefit from these new treatment combinations.

Harwell, Dale Watt is developing novel mouse models which will mirror tumour evolution more accurately, and through robust patient-relevant mouse models, assess responses to novel therapies with improved predictability. The Network is also proactive in training of the next generation of *in vivo* scientists and in November, Amy from the lab joined early career researchers from across the NMGN in Harwell for a residential training course in multiple aspects of mouse genetics.

[Publications listed on page 116](#)

Figure 2. Multiplex immunocytochemistry to investigate expression patterns of BCL-2 family proteins in prostate cancer samples. Prostate cancer tissue microarrays analysed using multiplex immunocytochemistry against multiple BCL-2 family proteins to characterise the cellular and spatial relationships of BCL-2 family proteins.

MRC National Mouse Genetic Network (NMGN) Cancer Cluster

The lab co-leads the *Cancer Cluster* as part of the MRC National Mouse Genetic Network (NMGN) (<https://nmgm.mrc.ukri.org/clusters/cancer/>). With colleagues in Glasgow, Belfast, London and Oxford we are using state-of-the-art technologies such as spatial phenotyping to study cancer-host interactions and position mouse models that recapitulate the human disease. Working with the Mary Lyon Centre at

