TRANSGENIC MODELS OF CANCER

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Our lab strives to recapitulate human cancer in preclinical mouse models to interrogate all aspects of disease progression within a biological context, applying model systems to study early disease through to metastasis and recurrence. For the ultimate aim of identifying novel therapeutic approaches for patient benefit, we use physiologically relevant models to validate *in vitro* discoveries. This involves state-of-the art genetic and refined transplantation models, often in combination with *in vivo* imaging modalities, to study how oncogenic pathways, altered metabolism and the tumour microenvironment contribute to cancer, and how these can be exploited for earlier detection of cancer and for therapeutic gain.

Modelling cancer *in vivo*

The Beatson Institute is internationally renowned for its scientific excellence using preclinical mouse models to study cancer in a physiologically relevant way to understand these complex human diseases. This is fundamentally important when we consider that tumour cells exist in a highly dynamic microenvironment which involves an intricate crosstalk between tumour cells and their neighbouring tissue compartments. Cancers spontaneously grow at their site of origin, invade surrounding tissue and colonise distant organs which occurs through a complex array of processes, and which can be distinct between different tumour types. Studying this multifaceted behaviour in a plastic dish has obvious limitations and requires advanced models in which tumours arise and mature in their natural environment. In this way, tumour cells directly and spatially co-evolve with stromal fibroblasts, immune cells and the endothelium, recapitulating a more accurate tumour microenvironment; are exposed to metabolic limiting conditions; and have to negotiate biological barriers in order to metastasise. Furthermore, many anti-cancer drugs fail in the clinic because, although they are effective in simplified tissue culture models, the nuances of taking these drugs into the whole animal setting cannot be ignored. The Transgenic Models lab utilises genetically engineered mouse models sympathetic to the same genetic alterations in human cancers such as breast, colorectal, pancreatic and prostate cancer, and which share the same pathology and metastatic spread seen in human patients. We also have expertise in orthotopic xenograft models, and in syngeneic allograft models permitting interrogation of immune interactions with primary and metastatic tumour cells. Monopolising these state-of-the-art preclinical models, in combination with *in vivo* imaging, our lab collaborates with colleagues at the Beatson Institute and the University of Glasgow to translate *in vitro* discoveries.

Research Collaborations

It is exciting to be involved in many diverse projects and the lab enjoys the stimulating collaborations with colleagues across all the strategic themes of the Institute probing metabolism as a cancer vulnerability, studying the interplay within the tumour microenvironment that drives metastasis and recurrence, as well as modelling early disease.

Using our expertise in prostate cancer models, we have had the pleasure of contributing to various projects with David Bryant and his lab. Building on the exciting observations in 2D and 3D assays demonstrating that the ARF3 GTPase interacts with N-cadherin to control invasion of prostate cancer cells, we showed that ARF3 was instrumental in driving prostate cancer metastasis *in vivo* (Sandilands *et al., J Cell Biol.* 2023). Similarly, PODXL found to be upregulated in patients with metastatic prostate cancer, was shown to be a key mediator of cancer invasion in both *in vitro* and *in vivo* models (Roman-Fernandez *et al, Sci Adv.* 2023). By incorporating ultrasound and sensitive fluorescence imaging in orthotopic transplant models we were able to refine these models to garner subtle information on metastatic spread of tumours at an earlier clinical endpoint by imaging the organs *ex vivo* (Figure 1). Longitudinal non-invasive imaging

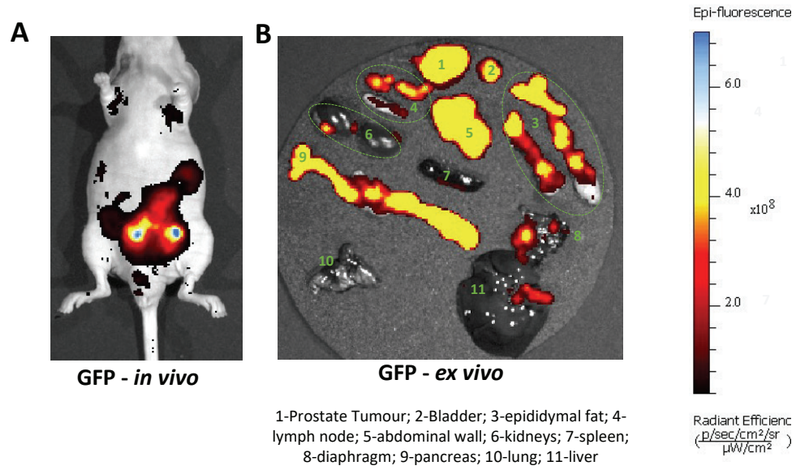

Figure 1
Fluorescence imaging reveals metastatic cells in a model of prostate cancer
A shows an *in vivo* image of a male mouse, 8 weeks post intra-prostatic injection, with human prostate cancer cell line PC3 cells (tagged with fluorescent markers). **B** Using *ex vivo* imaging from all the organs with the IVIS Spectrum, it is possible to identify fluorescent signal in the primary prostate tumour, but also identify the sites of metastasis in projects carried out in collaboration with David Bryant.

using a novel reporter mouse developed with Tim Humpton and Karen Vousden (Frances Crick Institute) also allowed us to delineate the activity of the Trp53 protein during normal development and liver injury (Humpton *et al., Sci Signal.* 2022).

Targeting cancer cell metabolism presents an important opportunity for novel therapeutic means. Continuing a long-standing collaboration with Oliver Maddocks (University of Glasgow) exploring amino acid restriction, we showed that tumour cells could be sensitised to radiotherapy by reducing serine and glycine levels (Falcone *et al, British J Cancer* 2022). Metabolic rewiring can also be a key modulator within the tumour microenvironment. Applying *in vivo* breast cancer models, we collaborated with Sara Zanivan and her team exploring how elevated PYCR1 expression in cancer associated fibroblasts (CAFs) drives proline synthesis to regulate the extracellular matrix within the tumour microenvironment, to promote breast cancer progression (Kay *et al, Nat Metab* 2022).

We have also collaborated with Stephen Tait's group to show how specific members of the BCL2 family are important in the pathogenesis of glioblastoma and offer an avenue for therapeutic intervention (Koessinger *et al., Cell Death Differ.* 2022), and with Iain McNeish's lab on how simultaneous inhibition of epigenetic regulators G9A and EZH2 can reduce tumour growth in a model of ovarian cancer (Spiliopoulou *et al., Mol Cancer Ther.* 2022).

Resources & News

Our lab is responsible for curating and training scientists in key equipment used for preclinical modelling such as the IVIS fluorescence/bioluminescence system, the PEARL near-infrared fluorescence detector, ultrasound imaging, and the IDEXX ProCyte Dx haematology analyser. As a lab, we continue to focus on innovative technologies to refine and improve cancer models for the benefit of the Institute providing expertise in surgical procedures such as orthotopic prostate delivery and mammary intraductal delivery. In all our approaches we continually promote the 3Rs.

We were delighted to welcome Louise Mitchell to the lab this year. Louise brings a wealth of experience and as Lead *In Vivo* Scientist will drive the collaborative projects and offer advice on project design and researcher compliance. Other big news is that the lab are very excited to be part of the MRC National Mouse Genetic Network, leading the Cancer Cluster (https://nmgn.mrc.ukri.org/clusters/cancer/) where, working with the MRC Mary Lyon Centre at Harwell, we will develop and improve mouse models of cancer as accurate predictors of patient response to novel therapies.

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