TRANSGENIC MODELS OF CANCER

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Our lab strives to recapitulate human cancer in preclinical mouse models and interrogate all aspects of disease progression within a biological context. With 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, which allow us to study how oncogenic pathways, altered metabolism and the tumour microenvironment contribute to cancer, and how these can be exploited for earlier detection and therapeutic gain.

Modelling cancer *in vivo*

The Institute is internationally renowned for scientific excellence using mouse models of cancer in a physiologically relevant way to gain insights on complex human diseases. This is important considering 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 that are distinct between different tumour types. Studying this multifaceted behaviour in a dish has 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, while being exposed to metabolic limiting conditions, and must negotiate biological barriers in order to metastasise. Many anti-cancer drugs, although effective in simplified tissue culture models, fail in the clinic because the nuances of taking these drugs into the whole animal setting cannot be ignored. Our lab utilises genetically engineered mouse models (GEMMs) with the same genetic alterations present in human cancers and share the same pathology and metastatic spread seen in patients. We have expertise in orthotopic xenograft and syngeneic models permitting the interrogation of tumour cell/immune interactions. Monopolising these preclinical models, in combination with *in vivo* imaging, our lab collaborates with colleagues to translate *in vitro* discoveries.

Research Collaborations

The lab is involved in diverse projects across all strategic themes of the Institute, from probing metabolism as a cancer vulnerability to studying the interplay within the tumour microenvironment, as well as modelling early disease. Targeting cancer cell metabolism offers an exciting therapeutic potential. A highlight this year was a collaboration with Saverio Tardito's lab (Ackermann *et al.*, 2024, *EMBO Mol Med*) showing that selenocysteine production promotes lung metastasis in a model of triple-negative breast cancer (TNBC). TNBC cells evade ferroptosis, a lipid peroxidation-driven cell death, by secreting monounsaturated fatty acids. Inhibiting selenoprotein synthesis, reinstated ferroptosis and reduced lung metastasis *in vivo* (Figure 1). With Payam Gammage and his team, mutations in mitochondrial DNA were similarly shown to change the metabolic landscape, impacting the tumour immune microenvironment and revealing enhanced sensitivity to checkpoint blockade therapy in mouse models of melanoma (Mahmood *et al.*, 2024, *Nat Cancer*). Also, in long-standing collaborations with Jim Norman's lab, neutrophil-specific uridine phosphorylase 1 (UPP1) and metabolic rewiring in breast cancer micrometastases reshaped the tumour microenvironment by influencing immune suppression, as well as extracellular vesicle production, and invasive microenvironments (Whyte *et al*, 2024, *bioRxiv*; Gounis *et al.*, 2024, *bioRxiv*).

We have also been exploring the role of cancer-associated fibroblasts (CAFs) to drive metastasis in collaboration with Sara Zanivan's group. One such study showed that CAF-derived extracellular vesicles (EVs) deliver proteins to endothelial cells, modulating cancer, stromal, and immune cell interactions to influence tumour pathology (Santi *et al.*, 2024, *Sci Signal*). In conjunction with Gareth Inman's lab, a novel TGF-β target gene, *C1orf106* (*INAVA*) was shown to drive tumour-promoting activities in breast cancer, enhancing migration, invasion, and tumour initiation (Strathearn *et al.*, 2024, *Cells*). Collaborations with institute alumni also continue to yield fruitful results. With Mike Olson it was found that caspase-resistant ROCK1 prolongs survival in a B-cell lymphoma mouse model by creating a proliferation-suppressive bone marrow environment (Mardilovich *et al.*, 2024, *Dis Model Mech*); while Karen Vousden's lab have shown how TIGAR modulates ROS dynamics to affect tumour behaviour and stromal interactions in pancreatic cancer (Cheung *et al.*, 2024, *PNAS*).

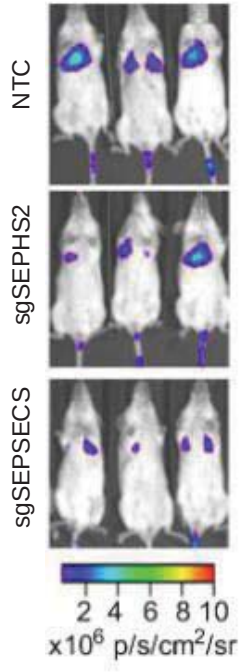

Figure 1. Representative IVIS images showing lung metastasis burden of MDA-MB-468 breast cancer cells post-intravenous transplant. Experimental groups include non-targeting control (NTC), sgSEPHS2 (targeting Selenophosphate Synthetase 2), and sgSEPSECS (targeting O-phosphoseryl-tRNA^Sec selenium transferase). Note the reduced tumour burden in the lungs of the targeted groups compared to the control group. Taken from Ackermann *et al.*, *EMBO Mol Med* (2024): 16:2749-2774.

In a national collaboration with colleagues at Glasgow, Oxford, London and Belfast we co-lead the MRC's National Mouse Genetic Network (NMGN) Cancer Cluster (https://nmgn.mrc.ukri.org/clusters/cancer/), working closely with the Mary Lyon Centre at Harwell to develop and improve mouse models of human cancer. It is exciting to work within the multi-disciplinary network and capitalise on state-of-the-art expertise in Degron Technology, Home Cage Monitoring, and the microbiome to better understand diseases such as colorectal cancer, and to contribute to network-led initiatives training early career researchers and promoting responsible animal research (Sansom *et al.*, 2024, *Cell Genom*).

Resources & News

Our lab is deeply committed to promoting Equity, Diversity, and Inclusion (EDI) and fostering a strong sense of community. This year, members of the team, led by Louise Mitchell (along with the School of Cancer Sciences VOICE Committee) have been actively involved in organising EDI activities, such as Ramadan Awareness, Neurodiversity in the Workplace, and a Diwali celebration. Jayanthi and Nimrit from the lab cooked up a storm, preparing gulab jamun for 100 people at our Diwali event! We were extremely proud of Louise being nominated for an EDI award and being asked to present these initiatives at a University of Glasgow EDI conference. The lab also hosted a masters student, Alifasya Baltimora, who undertook a 12-week research project investigating the role of CBFβ in breast cancer progression, working with Louise and PhD student Amy Lawlor.

This year, we invested in a VEVO Injection Mount, which will enhance our existing ultrasound system. This injection mount enables precise, minimally invasive delivery of cells/solutions to specific locations in murine models, eliminating the need for surgery. By providing high-resolution ultrasound guidance, the system improves cell transplantation accuracy, reduces animal stress, and shortens recovery times, supporting our commitment to the 3Rs (Replacement, Reduction, Refinement) and advancing the quality of our research.