

# TRANSGENIC MODELS OF CANCER



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Our lab uses *in vivo* models to recapitulate human cancer and interrogate all aspects of the disease within a biological context. Validating *in vitro* discoveries in physiologically relevant models in this way will expedite novel therapeutic approaches for patient benefit. The group has expertise in modelling different cancer types but has a specific interest in breast cancer and how metabolic pathways and certain signalling nodes such as the RUNX1/CBF $\beta$  transcriptional complex and pro-survival factor MCL1 contribute to tumour progression and metastasis.

## Modelling cancer *in vivo*

The ability of cancers to spontaneously grow at the site of origin, to invade surrounding tissue, and colonise distant organs is a complex process. So interrogating aspects of this multifaceted behaviour in a monolayer setting within a dish can have limitations. It is key therefore to use physiologically relevant models in which tumours arise and mature in their natural environment *in situ*. In this way, tumour cells directly and spatially co-evolve with stromal fibroblasts, immune cells and the endothelium, recapitulating a more accurate tumour microenvironment, and have to negotiate biological barriers in order to metastasise. In addition, 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. Our group uses preclinical models such as xenograft, allograft and genetically engineered mouse models to translate and vindicate the findings from *in vitro* analyses *in vivo* for the benefit of cancer patients. The lab collaborates with many of the groups at the Institute as well as with local, national and international collaborators. For example, we have ongoing projects with Seth Coffelt (Beatson Institute) and Patricia Roxburgh (University of Glasgow), testing novel therapeutic combinations to treat breast and ovarian cancer; with Oliver Maddocks (University of Glasgow), looking for metabolic vulnerabilities *in vivo*; with Sara Zanivan (Beatson Institute), interrogating the role of the tumour microenvironment in metastasis; and with Melchiorre Cervello (CNR, Italy), assessing novel players in steatosis and hepatocellular

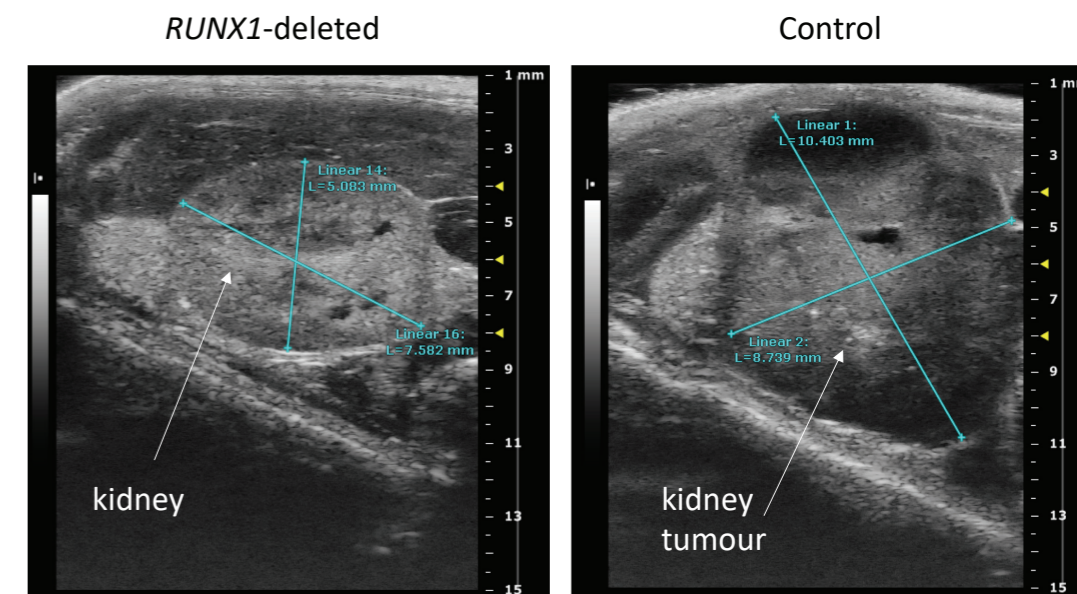
carcinoma (funded by Associazione Italiana per la Ricerca sul Cancro).

As one of the hallmarks of cancer is the adaptation to restrictive energetic sources, the cellular metabolism of tumours is often very different to the corresponding normal tissue from which that cancer emerges. Thus it is possible that such altered metabolism may provide biomarkers for disease progression and/or an Achilles heel for therapeutic intervention. Together with Jim Norman's lab and under the auspices of SEARCHBreast (<https://searchbreast.org/>), we have created a useful tissue resource from the MMTV-PyMT model of breast cancer to explore this in an *in vivo* setting. Indeed, certain metabolites (e.g. glutamate) are increased in the serum of our preclinical model during disease progression. Excitingly, these same metabolites are increased in the serum of breast cancer patients exemplifying the power of our preclinical models. Using this resource we have also collaborated with Alexei Vasquez to show that serine is increased in mammary (and intestinal) tumours. This results in increased serine catabolism to formate, with higher levels of formate in the tumour tissue and serum of disease-bearing animals, revealing a novel mechanism of how tumours can cope under the pressures of energetic restriction.

## MCL1 as a prognostic indicator and drug target in breast cancer

Breast cancer remains the most common cancer in the UK and the second biggest cause of cancer death in women. Whilst great strides have been made in treating breast cancer, there is still an ongoing need to understand the

**Figure 1**  
Ultrasound images of kidneys from an orthotopic xenograft model where renal adenocarcinoma cells (786-O) were CRISPR/CAS9 deleted for RUNX1 (left) or control (right). Increased size of the kidney effaced with tumour is indicated in the control kidney (shown by blue measurements).



disease better, and we have several projects in the lab to study this. In collaboration with Kirsteen Campbell and Stephen Tait (funded by Breast Cancer Now), we have been studying MCL1 as an exciting and novel target in breast cancer. MCL1 is renowned for its role in leukaemia, but we showed that high levels of MCL1 protein were also found in samples from breast cancer patients, and furthermore, high MCL1 correlated with significantly reduced patient survival. Using *in vivo* models, we have exciting data to prove that targeting MCL1 slows tumour growth and causes regression of pre-existing disease.

## The RUNX/CBF $\beta$ transcriptional complex in breast and other epithelial cancers

Two other understudied players in breast cancer are the RUNX1 transcription factor and its obligate DNA binding partner CBF $\beta$ . RUNX1 has an enigmatic role in breast cancer, and PhD students Alessandra Riggio and Kerri Sweeney have been using *in vitro* and *in vivo* models to probe its putative tumour suppressor and/or pro-oncogenic properties. In two independent genetic models of breast cancer, RUNX1 acts to restrain tumour onset, with data linking *Runx1* to mammary cell stemness. Nicholas Rooney in

the lab has been investigating a new role for the RUNX proteins in kidney cancer, where RUNX1 (and related family member RUNX2) is expressed in human kidney cancer patients with prognostic indication. When *RUNX1* is deleted in renal cell carcinoma (RCC) cells, growth is compromised and the cells have a reduced capacity to form tumours in an orthotopic xenograft model (Fig. 1). Furthermore, deletion of RUNX1 delays disease onset and progression in a genetic model of kidney cancer. We have been utilising RNA sequencing to understand the global gene expression changes that occur upon RUNX1 deletion.

We were delighted that Alessandra Riggio successfully defended her PhD thesis, 'The role of RUNX1 in genetic models of breast cancer', in February. Although sad to see Alessandra leave, we were delighted to welcome two new students this year; Narisa Phinichkusolchit and Adiba Khan, who have respective projects investigating the role of *Mdm2* in tumourigenesis and CBF $\beta$  in breast cancer.

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