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TRANSGENIC MODELS OF CANCER

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Our group strives to recapitulate human cancer in preclinical mouse models to interrogate all aspects of disease progression within a biological context (from early disease through to metastasis and recurrence). 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, to study how oncogenic pathways, altered metabolism and the tumour microenvironment contribute to cancer; and how these might be exploited for earlier detection of cancer and for therapeutic gain.

Modelling cancer *in vivo*

The Beatson Institute is renowned for its application of *in vivo* modelling to address key cancer questions. At the core of this is the Transgenic Models Lab, which facilitates collaborative science with many of our colleagues at the Beatson Institute and the University of Glasgow, as well as external research groups. 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. So interrogating aspects of this multifaceted behaviour in a plastic dish has obvious limitations. It is important therefore to use physiologically relevant 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. Our lab utilises genetically engineered mouse models sympathetic to the same genetic alterations in human cancers such as breast, colorectal, pancreatic and prostate cancer. We also have expertise in orthotopic xenograft models, and in syngeneic allograft models permitting interrogation of immune interactions with primary and metastatic tumour cells.

Research Collaborations

As for so many, this year has been challenging and unique, forcing us to adapt to working at home and putting some of our research on hold. Yet it is with immense pride that we can say this has not deterred stimulating Zoom conversations around ongoing and future research collaborations, nor our dedicated team in managing to conduct essential research when access to the lab was permitted. It has been gratifying to collaborate with David Bryant and his group on a variety of projects. For example, using orthotopic models of prostate cancer, we have been interrogating the role of the ARF GTPase Exchange Factor, IQSEC1 in cancer cell invasion and its ability to drive metastasis *in vivo*. We have also been trying to refine these models, and by combining bioluminescence and ultrasound imaging we can derive more subtle information about the metastatic growth of these prostate tumours that would ordinarily be missed (Figure 1).

Targeting cancer cell metabolism presents an important opportunity for novel therapeutic means, and to this end we have continued our long-standing collaboration with Oliver Maddocks at the University of Glasgow. In particular we have been exploring amino acid vulnerabilities such as the polyamine pathway and associated cysteine dependencies in tumour cells (Zhang *et al.*, *Nature Metabolism*, 2020), as well as the role of tryptophan metabolism in providing nutrient sources for pancreatic cancers. It is critical that we can translate the findings in the laboratory to the whole animal and confirm that tumours *in situ* adapt to the same pressures of metabolic rewiring. Using metabolic tracing *in vivo* and dietary intervention, we can probe these adaptations, as well as how we might be able to circumvent them. Increased formate is one such way that cancer cells can adjust to the increased energy demands, as we showed with Alexei Vazquez (Meiser *et al.*, *Nat Commun* 2018; Oizel *et al.*, *Cell Death Dis* 2020).

In other studies, we demonstrated with Michael Olson the relevance of pliable cancer cells towards increased tumourigencitiy (Rudzka *et al.*, *Small GTPases*, 2020); how the MSP-RON axis stimulates cancer cell growth in breast cancer models with Seth Coffelt (Millar *et al.*, *Mol Oncol.*, 2020); and we continue to collaborate with Gareth Inman's group studying the potential utility of targeting TGFβ-signalling in metastatic cutaneous squamous cell carcinoma (Dayal *et al.*, *Br J Dermatol*, 2020). Projects are also ongoing with Sara Zanivan and Seth Coffelt on models of breast and ovarian cancer interrogating the role of the tumour microenvironment, and in particular the interactions with the immune system and cancer-associated fibroblasts. This has involved applying advanced imaging techniques in exciting collaborations with Leo Carlin's group to study the dynamics of metastatic seeding of breast cancer cells and the interactions with the tumour microenvironment.

Resources and Innovations

In addition to our exciting collaborative projects briefly discussed above, our lab trains and supervises researchers at the Institute in the many complex cancer models (e.g. breast cancer, pancreatic cancer, lung cancer, prostate cancer). Our Senior Scientific Officers are responsible for curating and training our scientists in key equipment used for preclinical modelling such as the IVIS Spectrum fluorescence/ bioluminescence system, the PEARL near-infrared fluorescence detector, ultrasound imaging, and the IDEXX ProCyte Dx haematology analyser. As a group, we continue to focus on innovative technologies to refine and improve cancer models for the benefit of the Institute. In particular, our lab provides expertise in surgical procedures such as renal capsule delivery, orthotopic prostate delivery, mammary intraductal delivery and primary tumour removal. In all our approaches we continually promote the 3Rs, refining our models and exploring replacement models such as mammary organoids.

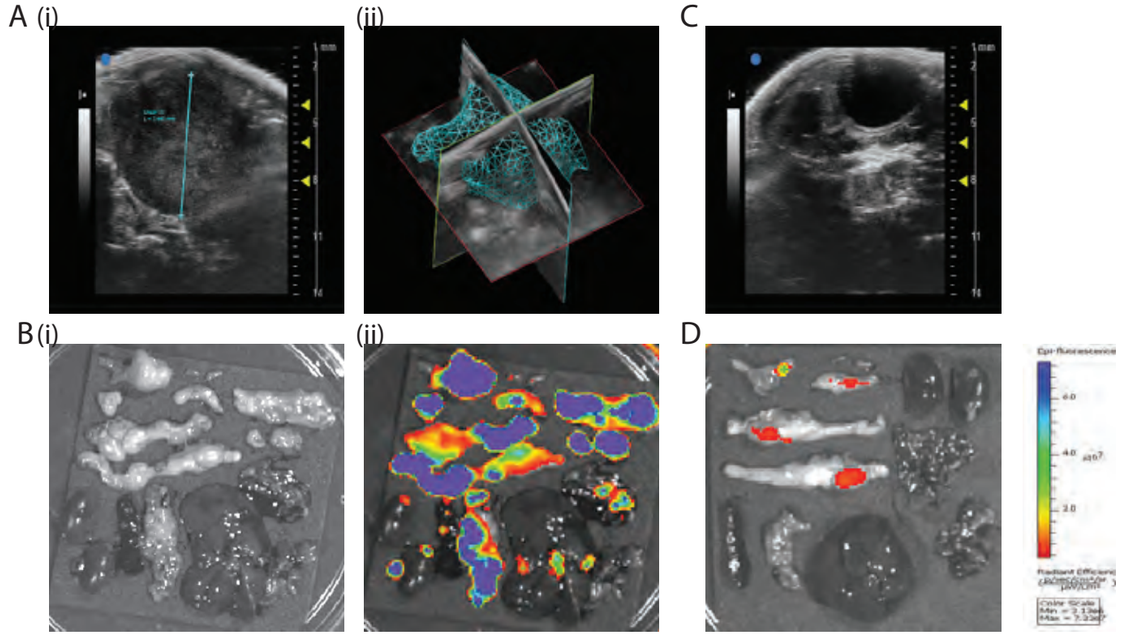

Figure 1
Multimodality imaging in a model of metastatic prostate cancer
(A)(i) An ultrasound image of a male mouse 8 weeks post intra-prostatic injection with human prostate cancer cells (PC3). The blue line denotes the diameter of the prostate tumour while (ii) shows the same tumour, this time in a 3D view re-constructed from multiple 2D cross-sections. This allows for the rendering, using Vevo-lab software, of a 3D volume as evidenced from the blue mesh shown in the image. **(B)(i)** A greyscale image of organs harvested from the same mouse depicted in **(A)**. **(ii)** The PC3 cells were tagged with fluorescent markers and using the IVIS Spectrum it is possible to detect fluorescent signal from tumour cells and identify the primary tumour in the prostate (top left), and also track and identify sites of metastasis as evidenced by fluorescent signal present. **(C)&(D)** Ultrasound and IVIS images (respectively) for a second male mouse 8 weeks post intra-prostatic injection with PC3 cells. No prostate tumour was detectable by ultrasound imaging **(C)**, however IVIS imaging **(D)** showed a weak signal in a small area of the prostate (top left). There is also a signal detected in some of the proximal organs (epididymal fat & lumbar lymph nodes) suggesting sites of metastasis. The difference is striking between **(B)&(D)** highlighting the sensitivity of the IVIS. The scale to the right of **(D)** is for radiant efficiency and applies to IVIS images presented.