Our lab uses in vivo models to study cancer processes, interrogating aspects of the disease and cancer-related pathways within a biological context. By validating in vitro discoveries in physiologically relevant models we hope to expedite novel therapeutic approaches. The group has expertise in modelling different cancer types but has a specific interest in breast and prostate cancer, and how certain signalling nodes such as the RUNX/CFBβ transcriptional complex and pro-survival factor MCL-1, contribute to tumour progression and metastasis.

Deciphering the role of the RUNX/CFBβ transcriptional complex in breast cancer

Our lab has a long-standing interest in the RUNX/CFBβ transcriptional complex, an essential regulator of mammalian development - often found dysregulated in cancer. Indeed, in around 13% of breast cancer cases, we find genetic alterations of the RUNX1 and CFBβ genes. Importantly, the nature of these alterations differ between subtypes where mutation and gene loss are associated with oestrogen-receptor positive (ER+) disease, while gain of RUNX gene function has been proposed to drive oestrogen-receptor negative (ER-) subtypes of breast cancer. PhD students Kerri Sweeney and Adiba Khan have been exploring relevant models we hope to expedite novel therapeutic approaches.

In collaboration with Prof Ewan Cameron (University of Glasgow) and funded in part by Breast Cancer Now, Kerri has focused on the role of RUNX1, and in particular to its effects on mammary stemness. Deletion of Runx1 in an oncogenic β-catenin setting accelerated disease onset in an in vivo model, and was further accentuated if Runx1 was also deleted. An increased stem-like transcriptional signature was observed at early stages of tumorigenesis in this model. Similarly, we found that deletion of Runx1 in 3D mammary cell culture resulted in increased mammosphere and colony forming capabilities and was accompanied by an upregulation of stem cell markers. Further transcriptional profiling of RUNX/CFBβ deleted mammary tumours is underway to unravel the mechanism/s of RUNX pathway alteration in cancer. Notably however, the functional loss of the RUNX/CFBβ complex in mammary tumours evoked changes to the immune composition of tumours that may be seminal in driving tumorigenesis, a hypothesis we are actively exploring.

Investigating the function of MCL-1 in tumour development and targeting of MCL-1 to improve cancer therapy

MCL-1 is a protein best known for its role in cell survival. We are investigating whether drugs that inhibit MCL-1 (BH3 mimetics) can reinstate tumour cell death and improve response to current anti-cancer therapies. BH3 mimetics currently in clinical trials and therefore provide further evidence for the potential anti-cancer effects in breast cancer.

Interestingly, while thought to be responsible for tumour initiation, metastasis and treatment resistance, we have found that breast cancer stem cells were particularly dependent on MCL-1 and were effectively killed by MCL-1 inhibiting drugs. A focus of PhD student Matthew Winder’s work is to further define the requirement for MCL-1 in breast cancer stem cells and, with Dr Kirsteen Campbell, aims to unravel the role of MCL-1 at the time of tumour initiation, during the metastatic process, and in mediating cancer therapy resistance and disease recurrence (Figure 1A).

Advanced prostate cancer, where the tumour has spread to distant sites around the body, is a lethal disease. Furthermore, bone metastases is a particularly painful and debilitating condition. MCL-1 seems preferentially increased in advanced prostate cancer and in bone metastases. Together with Prof Karen Blyth and Prof Hing Leung, Dr Kirsteen Campbell recently secured funding from Prostate Cancer Research for a 3-year project to investigate whether targeting of MCL-1 can improve response to hormone therapy and/or chemotherapy in advanced prostate cancer. Dr Laura Martinez-Escandor has joined our group this year and also works closely with Prof John Le Quesne and Prof Crispin Miller and their teams to pursue this research.

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