IN VIVO CANCER BIOLOGY

Group Leader
Karen Blyth

Associate Scientist
Kirsteen Campbell

Research Scientist
Laura Martinez Escardo[1]

Graduate Students
Adiba Khan
Kerri Sweeney[2]
Matthew Winder

[1]Prostate Cancer Research
[2]Breast Cancer Now

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/CBFβ transcriptional complex and pro-survival factor MCL-1, contribute to tumour progression and metastasis.

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

Our lab has a long-standing interest in the RUNX/CBFβ transcriptional complex, an essential regulator of mammalian development - often found dysregulated in cancer. Indeed, in around 13% of breast cancer cases, we find genetic aberrations of the *RUNX1* and *CBFβ* 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 the enigmatic role of the RUNX/CBFβ complex using *in vitro* and *in vivo* models of breast cancer.

Adiba has shown that loss of *Cbfβ* in the mammary gland did not overtly alter the normal development of the tissue, but when combined with oncogenic WNT signalling dramatically accelerated onset of mammary tumours in a mouse model of breast cancer, providing *in vivo* evidence that CBFβ has a tumour suppressor role. RNA sequencing analysis of tumours deficient in CBFβ showed enhanced Wnt pathway activation, indicating a role for CBFβ in regulation of Wnt signalling. Interestingly, loss of *Cbfβ* in the *MMTV-PyMT* model did not accentuate tumour development, and indeed acute loss of CBFβ in cell lines derived from these tumours resulted in decreased cell proliferation. CBFβ therefore, plays a context-dependent role in different models of mammary cancer, a conundrum similar to that observed in patients.

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 *Runx2* was also deleted. An increased stem-like transcriptional signature was observed at early stages of tumourigenesis 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/CBFβ deleted mammary tumours is underway to unravel the mechanism/vulnerabilities of RUNX pathway alteration in cancer. Notably however, the functional loss of the RUNX/CBFβ 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 cancers of the blood, but we have found a key role for MCL-1 in breast cancer. In Campbell *et al*., 2018, *Cell Death Disease*, we have shown that MCL-1 is required for both tumour development and maintenance of established tumours in the breast (Figure 1A). Our preliminary data suggested that MCL-1 also has a role in prostate cancer where it can act as a barrier to tumour cell elimination by prostate cancer therapies. New therapeutic options are urgently required in both cancers as together they account for over 23,000 deaths each year in the UK. Due to its importance in cancers of the blood, inhibitors of MCL-1, so-called "BH3 mimetics", have been developed and are in clinical trials for treatment of haematopoietic malignancies. Whilst high levels of MCL-1 prevent tumour cell death, BH3 mimetics can inhibit MCL-1 and help eliminate cancer cells (Figure 1B). By characterising the role of MCL-1 in breast and prostate cancer we aim to prove MCL-1 a valid target and expedite the use of MCL-1 inhibitors in these cancer types.

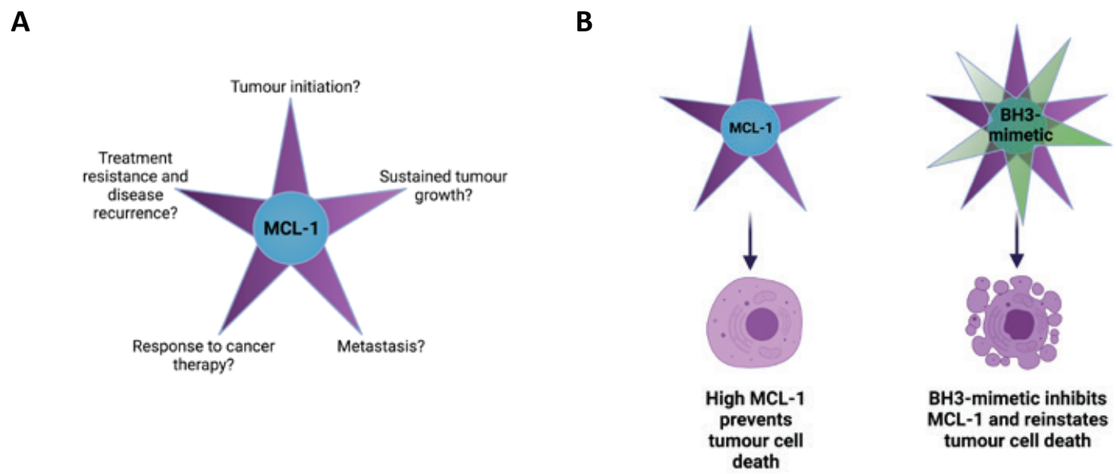

Figure 1
MCL-1 is an important mediator of cancer processes and a credible therapeutic target
A. We have shown that MCL-1 is required for tumour initiation and sustained growth in breast cancer. We are also investigating the role of MCL-1 in metastasis, response to cancer therapy and treatment resistance and recurrence. **B.** High levels of MCL-1 are found in breast and prostate cancer where MCL-1 facilitates tumour 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.

Figures created with BioRender.com

Together with Prof Stephen Tait, we have found that the anti-apoptotic function of MCL-1 is key in breast cancer (Campbell *et al*, 2021, *Cell Death Differentiation*). This is important as the anti-apoptotic function of MCL-1 is inhibited by the BH3 mimetic drugs currently in clinical trials and therefore provides 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 diagnosis. 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-Escardo 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.

Publications listed on page 101