University of Bristol

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Cancer Research Fund

2018/2019 Report

UCRF

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Introduction

The University of Bristol Cancer Research Fund supports early stage research at the University across a broad range of cancers. These first steps are critical to any research journey as without the evidence gathered at this early stage it is impossible to attract support for larger studies. Importantly this fund helps start innovative projects and exciting new collaborations across a number of different disciplines at the University of Bristol, all working towards the prevention and treatment of cancer. Funding comes entirely from donations from the public, ranging from individual donations to charity fundraising events.

This report details five research projects funded by your generous donations to the University of Bristol Cancer Research Fund, with a total investment of £22,070. The projects reflect the range of ground-breaking research taking place at the University and include investigations into fundamental cellular processes important for tumour growth (breast cancer) and metastases, the influence of the gut microbiome on bowel cancer, drug discovery for brain tumours and developing markers for drug response in ovarian cancer.

Once again it has been a very productive year; your generosity has supported projects during their earliest stages, which is critical for securing additional research funding for larger and more ambitious studies. This fund continues to be hugely influential in supporting early career researchers and large grant applications. Thank you, once again, for your generosity in supporting Cancer Research at Bristol.

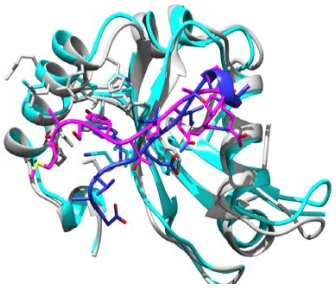
Prof Ann Williams: Chair for the UCRF

Autophagy-transcriptional crosstalk in tumourigenesis: the LMX1A/LMX1B paradigm

Dr Jon Lane

Autophagy is an important cellular stress response that enables cells to adapt and survive during extended periods of environmental challenge. Autophagy protects against cellular transformation, but an active autophagy pathway is also needed in tumour cells for efficient growth and metastasis. This highlights the complex roles played by autophagy in cancer and emphasises the need to fully understand its regulation and influence. We have found that the LIM homeodomain transcription factors, LMX1A and LMX1B—which have emerging roles in cervical, ovarian and gastric cancers—control autophagy gene expression. Interestingly, the product of one group of these autophagy genes, called the ATG8 family, binds to LMX1B in the nucleus to regulate its role as a transcription factor. This establishes a regulatory loop which could have important consequences in cancer. UCRF funding has enabled us to characterise the binding between LMX1B and ATG8 proteins (Fig. 1A), and how this alters LMX1B activity, and to carry out proteomics to determine which other proteins interact with LMX1A/B in cells (Fig. 1B). Proteomics studies suggest that LMX1A/B interact with proteins in the Catenin pathway, particularly important in colorectal cancer. Over the next few months we will be studying this potential interaction in detail using relevant cancer cell-line models with a view to obtaining future grant funding to continue this work.

A.



B.

		Binding strength	
Description	Peptides	LMX1A	LMX1B
Cadherin 2	11	2.255	37.013
Girdin	123	1.754	32.648
Catenin beta-1	18	2.112	25.477
Catenin alpha-1	21	1.702	25.141
Catenin alpha-2	27	1.972	16.256
LIM binding protein 1	6	11.04	14.954

Fig. 1A: Model of the LMX1B interaction with ATG8 proteins. LMX1B is shown in magenta; the protein shown in dark blue is a known binding partner for ATG8. Fig. 1B: Selected interactors of LMX1B.

Establishing CARM1/PRMT4 as a novel drug target in high-risk neuroblastoma

Dr. Karim Malik

Neuroblastoma (NB) is a biologically and clinically heterogeneous pediatric malignancy that includes a very high-risk subset (approximately 40% of total cases) for which new therapeutic agents are urgently required. Children in this disease subset often do not survive.

Our previous work has shown that histone methyltransferases are essential for NB cell survival, particularly PRMT5, which we demonstrated methylated and stabilizes the oncoprotein MYCN [Park et al, Mol. Oncology 2015]. This led to an ongoing CR-UK drug discovery grant evaluating small molecule inhibitors of PRMT5. We also observed effects of CARM1 and EZH2 depletion. Whilst the

role of EZH2 is NB is established, little is known about CARM1 involvement. Our preliminary investigations confirmed the inhibitory effects of CARM1 knockdown in another NB line. Importantly, we also found that CARM1 protein interacts with MYCN, the latter being a proven cancer-causing protein in NB as well as in other cancers.

With the kind contribution of the UCRF, we have extended this work to establish that new CARM1-inhibiting drugs can alter the molecular functions of MYCN. Specifically, we conducted next-generation sequencing and established that these novel drugs can inhibit the gene regulatory activity of MYCN. The UCRF work has thereby enabled us to apply for a further, larger grant from Children with Cancer UK to follow up this work. This would lead to establishing a novel therapeutic agent for life-threatening cancers such as neuroblastoma.

Markers of response to Bevacizumab in ovarian cancer.

Professor Harry Mellor

The project sought to identify serum markers of response to the tumour angiogenesis inhibitor bevacizumab in patients with ovarian cancer. This was a collaborative project with Dr Gemma Cass, a senior registrar in Obstetrics and Gynaecology and clinical research fellow. Gemma has been working with a cohort of patients in the South West to determine criteria for the effective use of bevacizumab in treatment regimes.

With the funding we received, we were able to obtain deep serum proteomes from 10 patients in the cohort. These comprised 5 patients who received bevacizumab and chemotherapy, and 5 who received chemotherapy alone. We were also able to compare serum proteomes for each patient before and after treatment.

The results are very interesting, and bioinformatic analysis of this large dataset has identified strong candidates for markers of bevacizumab response. Gemma is now validating these in a larger cohort by ELISA. The cohort data for these patients includes histology of tumour biopsies, surrogate markers of angiogenesis (skin capillary density), as well as data on progression and survival. Taken together, we are now able to link serum markers to outcomes of bevacizumab treatment in ovarian cancer.

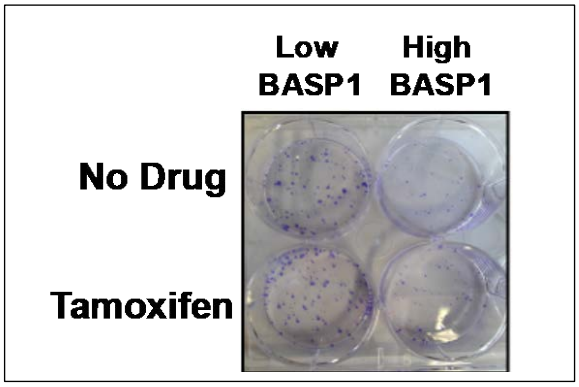
Bevacizumab is an expensive drug, and this has been an issue in its use in ovarian cancer. Serum markers that would help select patients more likely to respond to the drug are important, as are serum markers that would report on the effectiveness of the treatment. As a result of UCF funding, we now have the pilot data for an application to NIHR EME for a study to run alongside the MRC-funded ICON8 ovarian cancer trial.

The role of BASP1 in the response of cancer cells to tamoxifen

Professor Stefan Roberts

Worldwide, almost 2 million new breast cancer cases are reported each year. The drug tamoxifen is used to treat and control breast cancer. Most patients will receive tamoxifen for up to ten years post diagnosis and it has proven to be very effective in reducing the reoccurrence of breast cancer. Although tamoxifen exerts a significant therapeutic prevention of further breast cancer, it can also cause an elevated risk of developing endometrial cancer.

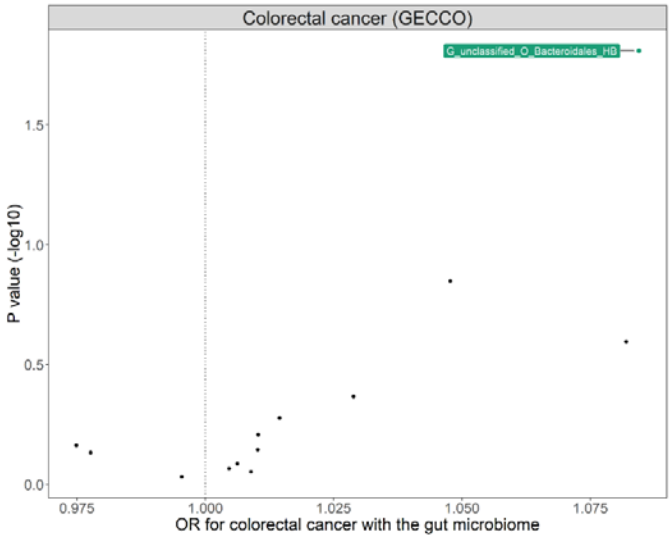
Breast cancer cells respond to tamoxifen by switching important cancer genes off. We found that the protein BASP1 enhances the therapeutic effects of tamoxifen and that breast cancers that contain BASP1 are more likely to be responsive to tamoxifen. Endometrial cancers normally contain low levels of BASP1. Our proposal was to test if BASP1 might underlie the different effects of tamoxifen on breast and endometrial cancer. Endometrial cancer cells were engineered to express greater levels of BASP1 and tested in their ability to form colonies of cells that are characteristic of cancer. The colonies are stained blue to visualise the extent of uncontrolled growth. In the normal endometrial cancer cells (with low BASP1) several large colonies form. Treatment with tamoxifen does not inhibit endometrial cancer cell growth. When the endometrial cancer cells contain high BASP1 there is a strong inhibition of cancerous cell growth. These results suggest that BASP1 can inhibit the growth of endometrial cancer cells. However, unlike in breast cancer, BASP1 does not have any effect on the response of endometrial cancer cells to tamoxifen. We next analysed the genes in endometrial cancer cells that are regulated by tamoxifen and BASP1. We found that the regulated genes are different to those found in breast cancer cells. Taken together these results provide new understanding of why tamoxifen kills breast cancers but promotes endometrial cancer. Further studies will allow us to determine the specific genes in endometrial cells that are responsible for their different response to tamoxifen.



The human gut microbiome in colorectal cancer: causal effects vs. confounded relationships.

Dr Kaitlin Wade

Whilst the human gut microbiome has been implicated in playing a role in the development and progression of various cancers, there is a concerning lack of robust evidence able to discern correlation from causation. Despite this lack of causal evidence, the gut microbiome has the potential to be a good candidate given the prevailing hypothesis around its contribution to health.



Therefore, I targeted the gut microbiome and its implications on cancer as an area that would benefit substantially from the application of causal inference methods, specifically, Mendelian randomization (MR). MR is a method that uses human genetic variation to proxy for an ideally modifiable exposure (here, the gut microbiome) to provide an unbiased causal estimate of the effect of that exposure on a particular outcome in a manner analogous to a natural randomized controlled trial

(RCT). With data available to me, coupled with my expertise in the implementation and interpretation of such causal inference methods and the University Cancer Research Fund (UCRF), I was able to apply MR to interrogate the causal impact of the human gut microbiome on colorectal cancer. For this, I combined summary-level data from the genome-wide association studies (GWASs) of the gut microbiome in the Flemish Gut Flora Project (FGFP, PI: Jeroen Raes), including ~3000 individuals, and of colorectal cancer from the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO), a collaborative effort with of over 40,000 participants.

The GWAS of 154 gut bacterial taxa (and 3 metrics of diversity) conducted by the FGFP identified evidence for a host genetic contribution to 13 of the bacterial taxa including the presence (vs. absence) and relative abundances of bacteria within the *Firmicutes* and *Bacteroidetes* phyla. Using the MR-Base platform and with thanks to the UCRF grant, I was able to test the causal relevance of variation in these 13 gut bacterial taxa measures on colorectal cancer.

Preliminary analyses conducted with this grant provided evidence that presence of an unclassified genus within the *Bacteroidales* order of bacteria increases the risk of colorectal cancer by 8% (95% CI: 2%, 15%; *P*=0.02). This result is consistent with observational studies suggesting that genera within the *Bacteroidales* order of bacteria are more present in colorectal cancer cases compared to controls and adds more evidence to suggest that this observation may be due to a causal impact of the bacteria on colorectal cancer, rather than the reverse. The outcome from this work is being presented at both the National Cancer Research Institute and American Society of Human Genetics conferences in 2019 and will contribute to ongoing efforts with a GECCO working group aiming to support or challenge the role of the human gut microbiome on colorectal cancer.