University of BRISTOL

University of Bristol Cancer Research Fund (UCRF)

2022/23 Report

Introduction

I would like to start by sincerely thanking the supporters of the University Cancer Research Fund (UCRF). The UCRF is an endowment fund which supports a wide range of cancer research from across the University. It comes entirely from donations from the public, ranging from individual donations to charity fundraising events, for which we are extremely grateful.

The UCRF seed corn annual funding call is intended to help researchers with pump-priming grants or to buy small items of equipment for cancer research projects. The scheme is open to all academic staff from all faculties at the University of Bristol who conduct cancer research. We particularly encourage applications from early career researchers and researchers working in, or collaborating with, people outside the traditional medical faculties. The purpose is to support truly innovative ideas and generate pilot data to support future external funding applications from charities and/or research councils. Projects are awarded a maximum of £5,000 and up to ten projects are supported annually, depending on funds available.

This year the UCRF supported a wide range of interesting, novel projects (summarised in this report), all working towards the prevention and treatment of cancer. The UCRF funded 7 projects selected by the University of Bristol Cancer Research Network steering group, supporting ideas that have promise to develop into high impact research, ranging from ‘developing tools for a more targeted approach to treat ovarian cancer’ to ‘improving the efficacy of immunotherapy’. The research described in this report is just a small sample of the breadth and depth of the Cancer Research being carried out at Bristol University, supported by the University Cancer Research Fund. The total investment in for the UCRF seed corn funding call this year was £33,722.20.

On a personal note, having acted as Chair of the UCRF for the last six years, it is time for me to handover to my successor, Professor Athene Lane. It has been a huge privilege to work with the UCRF over the years, witnessing the power of these small pilot grants to seed the growth of important breakthroughs in cancer research. I am pleased to leave the fund in the capable hands of Athene and wish it every future success.

The UCRF fund continues to be hugely influential in supporting early career researchers and large grant applications and I would like to thank you once again, for your generosity in supporting Cancer Research at Bristol.

Professor Ann Williams
Chair for UCRF

JAMES ARMSTRONG
Study: Patient-Derived Organoids for Ovarian Cancer Drug Screening
Award: £5000

Ovarian cancer is a major healthcare challenge, with around 7500 people diagnosed every year in the UK and <27% surviving past five years. While there are many drugs available to clinicians the treatments that are chosen are typically “one-size-fits-all.” This broad approach is out-of-step with our modern understanding of how ovarian cancer survives and spreads in the body. For example, we know that different tumours have different genetics, which means that some tumours are resistant to certain types of drugs and using these drugs will not eradicate that cancer. This is reflected in the wide range of clinical outcomes observed between patients.

The Armstrong Group is taking a *personalized medicine* approach that aims to guide clinicians in selecting the drug candidates that are best matched to the genetics of the patient tumour. Specifically, our aim is to take biopsies from ovarian cancer patients and use these to grow lots of “mini tumours” in the laboratory. These are known as “cancer organoids” which have been shown by others to have very similar genetics and structure to the original tumour. Ovarian cancer organoids can be used to test panels of anticancer drugs and these results have been shown to match how well patients respond to certain chemotherapy treatments.

While this is an exciting prospect, the high cost and impracticality of isolating, growing, and testing organoids for each individual patient means that this is unlikely to ever be a valid route for a national healthcare service. *We are taking a new angle on this problem*: using artificial intelligence to link the organoid drug testing results to the genetic makeup of the tumour. We hope that this will allow a new medical approach in which a clinician takes a tumour biopsy, finds out its genetic sequence, and then uses our machine learning tool to identify the drug combination that is most likely to work for that particular cancer.

The UCRF has provided us with the funding to set up the early stages of this research project. We have obtained ethical approval to work with tumour biopsies provided by clinicians at St Michael’s Hospital. We collect these biopsies and use them to grow ovarian cancer organoids in our laboratories at the University. We have been using a method previously reported by others, but in our hands, found that we needed to tweak the conditions that were needed to encourage the organoids to grow. In parallel, we have set up workflows for imaging and analysing how ovarian cancer cells respond to different doses of anticancer drugs: the next step for us is to use these methods on our ovarian cancer organoids.

RACHEL BARKER
Study: Is amyloid-β a friend, foe, or both for breast cancers?
Award: £4061.75

Breast cancer and Alzheimer's disease are major causes of death globally. Ageing is an important risk factor for both and whilst the two diseases share other similar features, recent reports have shown an inverse relationship between the two conditions, whereby having one reduces your risk of having the other. The reason for this inverse relationship is unclear. A key hallmark of Alzheimer's disease is deposits of a protein called amyloid-β (Aβ) in the brain, which is toxic to neurons. Aβ is produced when another protein, amyloid precursor protein (APP) is cut by specific enzymes called β-secretases (e.g. BACE-1). The APP protein may also be cut by α-secretases (e.g. TACE) which prevents Aβ from being produced. Interestingly, APP and the secretase enzymes are all present in breast cancer cells and tissue, and APP has previously been shown to promote breast cancer cell proliferation and migration. In contrast, the Aβ peptide has been reported to be detrimental to cancer cells and adding it to cultured breast cancer cells reduces their growth.

In our experiments we found that expression of the genes encoding APP and the secretase enzymes was upregulated in breast cancer compared to a normal breast cell line. When we treated breast cancer cells with substances that induce proliferation, for example estradiol and insulin-like growth factor-I (IGF-I), levels of APP and TACE were increased but there was no change in BACE-1. Dosing cells with substances that reduce their proliferation or kill them, for example anti-estrogens and chemotherapy, caused reduced APP and TACE levels and led to an increase in BACE abundance. When we added Aβ to the cells, proliferation was reduced, and some cell death occurred.

Our results indicate that APP processing may be regulated in breast cancer. Many drugs have been developed which target the APP pathway so if we can better understand the role of APP in cancer, there may be opportunities for drug repurposing for breast cancer therapy in the future.

This UCRF funding enabled us to gather important preliminary data and submit a grant proposal to Breast Cancer Now for funding to further explore this exciting area of research.

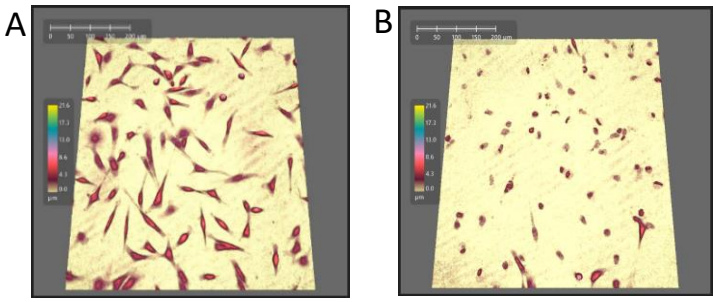
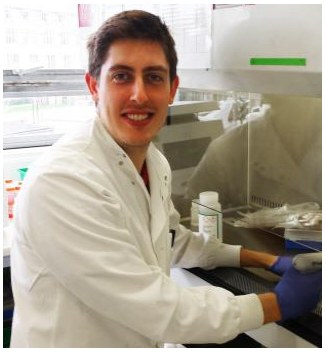


Figure 1: Live-cell imaging of MDA-MB231 breast cancer cells. (A) Control, untreated cells and (B) cells treated with 0.1μM Aβ for 48 hours. Aβ caused the cells to appear stressed, reduced their proliferation and caused some cell death.

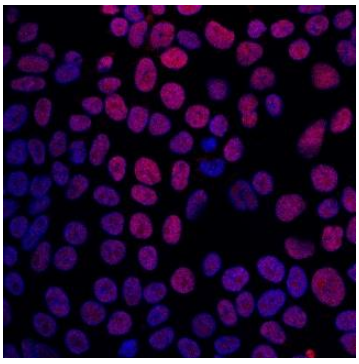


ADAM CHAMBER
Study: Defining BCL-3/NF-kB signalling in colorectal cancers following radiation
Award: £4814.22

Colorectal cancer (CRC) is one of the most common cancers worldwide. We have shown that the incidence of advanced, distal colorectal cancer is rising in young adults (<50 years old). These patients often require preoperative (neoadjuvant) therapy (short-course radiotherapy or long-course chemoradiotherapy). Unfortunately, how patients respond to treatment is highly variable but, importantly, is closely correlated with survival outcomes from this type of cancer (if they respond well to therapy before surgery, they do better overall). Therefore, there is an urgent need to identify the driving factors that lead to variation in response to preoperative therapy, and it is hoped that a better understanding of this will help more precise and individualised treatment to be given in the future.

Cellular inflammation is a critical characteristic of tumourigenesis and therapy response in bowel cancer. One signalling pathway, the nuclear factor-kappa B (NF-κB) signalling pathway, is a fundamental regulator of inflammation. A protein called BCL-3 has been identified as a co-regulatory protein of the NF-κB pathway. One feature of the preoperative therapy that patients receive is its ability to kill tumour cells through causing irreparable damage to DNA. Our published data has shown that BCL-3 promotes DNA repair in CRC cells exposed to DNA damaging therapeutics. We are also very excited about new data that shows BCL-3 expression modulates how DNA is stored in cancer cells, known as chromatin organisation. Critically, it may be that BCL-3 is functioning to cause poorer response to DNA damaging therapeutics through altering chromatin organisation.

We have used the UCRF funds to better understand the mechanism by which NF-κB and BCL-3 modulate therapy response in rectal cancer by analysing the effect of BCL-3 in chromatin organisation in greater detail. The work has been performed by Nyah Brooks, a master's student at the University. Nyah has focused on performing a technique known as ATAC-see (assay of transposase-accessible chromatin with visualisation). She has performed experiments to measure the effects of the removal of BCL-3 from colorectal cancer cells on chromatin compaction using ATAC-See (images below). Nyah still has 3 months of data collection left but early results show BCL-3 may alter chromatin compaction. These data have been taken forward to further grant applications (Academy of Medical Sciences Starter Grants for Clinical Lecturers, Bowel Research UK PhD Studentship and planned MRC Clinician Scientist award) and have led to new collaborations with researchers such as Dr Emma Vincent (University of Bristol).



Most importantly, this research aims to promote treatment stratification for patients, enabling those with potentially therapy resistant tumours to avoid unnecessary treatment, and/or developing new pre-operative treatments to improve the outcome for these patients. The overall goal is to improve survival for patients with colorectal cancer undergoing neoadjuvant therapy.

Figure 1: staining showing chromatin changes using ATAC-See in colorectal cancer cells.

BETHAN LLOYD-LEWIS
Study: Investigating the impact of tissue mechanics on breast epithelial cell fate and cancer risk
Award: £4970

Breast cancer is the most common cancer in the UK, with an estimated 4000 new cases diagnosed every month. Breast tissues are made up of connective (fibrous) tissue, glandular (epithelial) tissue and fatty tissues. Women with dense breast tissues as observed on a mammogram have more fibrous and glandular tissue compared to fatty tissue. These women have an increased risk of breast cancer, although the reason for this remains unclear.

The fibrous tissue of dense breasts is stiffer than the fibrous component in non-dense breasts. We know from laboratory models that tissue stiffness is associated with breast tumour progression. However, we still don't know how tissue stiffness affects the behaviour and properties of normal breast epithelial cells, and whether this might predispose the tissue to cancer.

The overall goal of this project is to investigate how changing tissue stiffness affects breast epithelial cell behaviours and traits. Support from the UCRF has allowed us to begin to investigate this by providing us with funds to purchase the reagents required to culture dissected mammary (breast) glands in 3D as tissue explants (**Figure 1A**) or organoids (**Figure 1B**), as well as chemical agents that change the stiffness of the surrounding microenvironment. An example of a mammary organoid treated with a chemical agent that causes stiffening of the culture matrix is shown in **Figure 1C**. We are continuing to compare the behaviours and nature of these cells in the different culture conditions. In future, our goal will be to also investigate the impact of these agents on the growth and composition of tissue explants and organoids established from the mastectomies of women with a genetic predisposition to developing breast cancer, such as women who have a family history of breast cancer and/or that carry mutated BRCA1/2 genes.

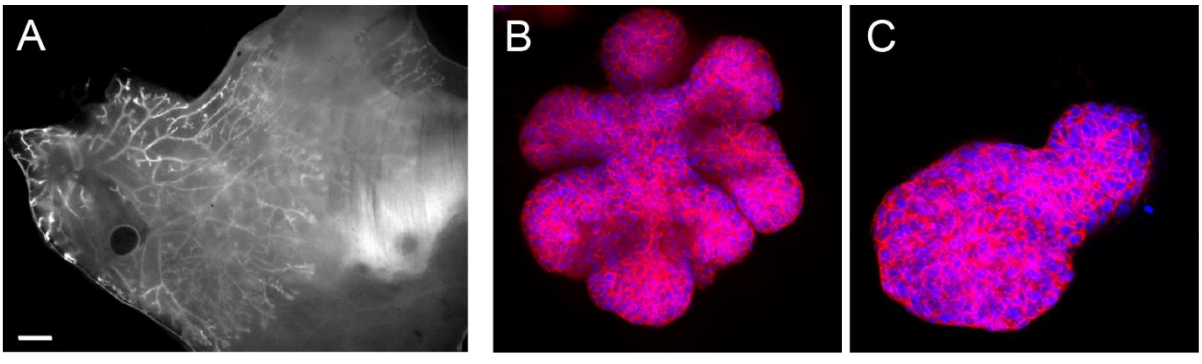
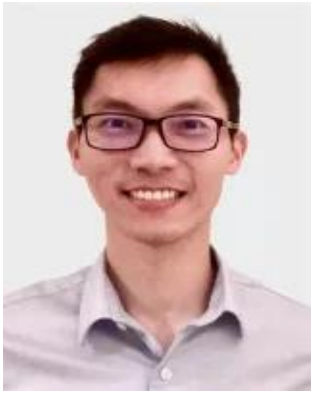


Figure 1. (A) Representative fluorescence image of a mammary epithelial tree cultured as a tissue explant for 9 days **(B-C)** Fluorescence images of isolated mammary epithelial cells (labelled with a red fluorescent protein) cultured as 3D organoids embedded in a matrix substance under normal conditions (B), or in the presence of a chemical that causes matrix stiffening (C). The nuclei of cells, which contain its genetic code, are shown in blue.



SIANG BOON KOH
Study: Role of PALB2 and aldehydes in breast cancer predisposition
Award: £5000

First described in 2006, PALB2 is a gene found in human cells that is important in helping cells cope with damaged DNA (which can happen under various conditions, for example from exposure to UV from sunlight). Loss of PALB2 gene in human cells has previously been found to increase the risk of getting breast, pancreatic, and ovarian cancers. Of note, in 2021, a well-validated study involving over 110,000 individuals has found that PALB2 is one of the top five genes associated with breast cancer risk.

The level of PALB2 and other related DNA-protective genes can be altered by environmental toxins. For examples, earlier studies have shown that aldehydes (a chemical commonly found in alcoholic beverages) decrease the levels of some of these DNA-protective genes in cells, leading to an unstable genome (the genetic information in the cell) that can give rise to cancer. Because alcohol consumption is strongly linked to breast cancer risk, we think that aldehydes are one of the potential cancer-inducing factors that can alter the level of PALB2 in normal cells.

To test this hypothesis, we started a project looking at how aldehydes affect normal cell properties including PALB2 levels. Using the UCRF fund, we have been able to acquire normal breast cell lines that are essential for our experiments. These breast cell lines can be cultured in the laboratory, allowing us to study their behaviours when exposed to aldehyde (Figure 1). We have also succeeded in generating “aldehyde-resistant” breast cells following long-term exposure to and selection by aldehyde in the laboratory. These cells will now serve as experimental models that can be compared with “aldehyde-sensitive” cells. By doing so, we will be able to identify the biological differences brought about by long-term aldehyde exposure. Our goal is to find biological differences that may represent early events of cancer development, enabling us to develop better ways to detect cancer in high-risk populations.
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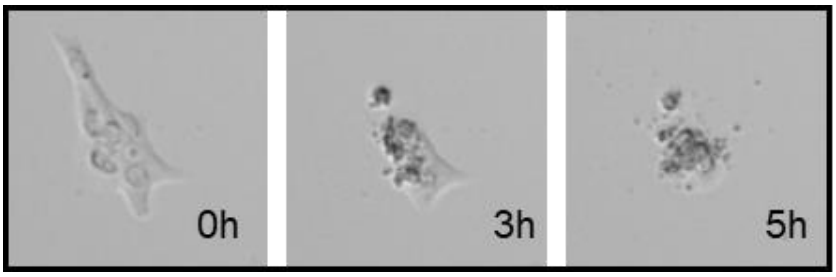

Figure 1: The fate of a normal aldehyde-sensitive human breast cell after being exposed to aldehyde for over 5 hours.

EMILY MILODOWSKI
Study: Investigating the role of regulatory T cells in tumour escape from checkpoint blockade
Award: £4906.23

Checkpoint Blockade Immunotherapy (CBI) is a new and exciting way to treat cancers by targeting our immune system. Immune cells, such as T cells, should recognise and kill cancer cells however they are effectively “switched-off” in the tumour microenvironment by the expression of receptors such as PD-1. Immunotherapies that block PD-1 have led to great advancements in the treatment of cancers such as metastatic melanoma, however many patients do not respond to the immunotherapy, and others develop severe side effects. It is increasingly important to understand how these therapies act on different cell populations within tumours to be able to optimise future combination approaches.

The overall aim of PD-1 blockade is to improve the way that $CD8^+$ (killer) T cells recognise and kill cancer cells. In the RencaHA tumour model, we have shown that a population of regulatory T cells (T_{reg}), usually responsible for restraining and preventing the activation of killer T cells, can also respond to PD-1 blockade. They do this by increasing proliferation and generating a larger population of T_{reg} in the tumour, and by changing the type of receptors expressed at on their cell surface. I hypothesise that the increased presence and function of T_{reg} in tumours after PD-1 blockade reduces responsiveness of the tumour to immunotherapy and promotes disease progression.

In this project I will continue to use microscopy to further characterise how T_{reg} interact with killer T cells in the tumour, whilst also investigating how changing receptor expression may be associated with different levels of regulatory (suppressive) function. This information will help us to understand how and where we can refine current immunotherapy treatments to target specific populations of cells, improving treatment efficacy and reducing side effects.

The funding for this research has been extended until 2024.

DANNY LEGGE & EMMA VINCENT

Study: Investigating the metabolic perturbations in type 2 diabetes that support colorectal cancer development

Award: £4970

The incidence of type 2 diabetes continues to increase in the western world - there are currently more than 4.9 million sufferers in the UK alone and this figure is predicted to rise to 5.5 million in 2030. Importantly, people with type 2 diabetes are more likely to develop colorectal cancer (also known as bowel cancer) than people without diabetes although the reason for this is not fully understood. Here we proposed to investigate how type 2 diabetes, and the systemic metabolic environment associated with it, effects the intestinal epithelium itself (the lining of the bowel, from which the colorectal cancers arise). Understanding this is critical if we are to find more effective ways to screen for, to prevent and treat colorectal cancers in people with type 2 diabetes.

Metabolism is a critical process that all cells must use to stay alive. Cancer cells alter their metabolism to generate the energy and compounds required to support their growth and proliferation known as metabolic reprogramming. Metabolic reprogramming is a hallmark of cancer and essential to support the chronic proliferation of tumour cells. We hypothesised that people with type 2 diabetes might have some early signs of altered metabolism in the cells of their large intestine, changes that precede tumour development and could provide a possible explanation for the increased rate of colorectal cancer in type 2 diabetes patients.

As it is difficult to source normal human intestinal tissue, we used a mouse model of type 2 diabetes, taking samples of mouse intestine, incubating them with two key metabolites glucose and glutamine. We were able to identify metabolic changes that had arisen in the diabetic mice using a machine called a mass spectrometer, by comparing results with those from tissue from non-diabetic littermates. Early insights from our work suggest that there are changes in the metabolic processes in the cells taken from diabetic mice. With support of UCRF this work will help us understand why people with type 2 diabetes are more at risk of developing colorectal cancer, with the aim of designing more effective ways to prevent cancers associated with type 2 Diabetes.

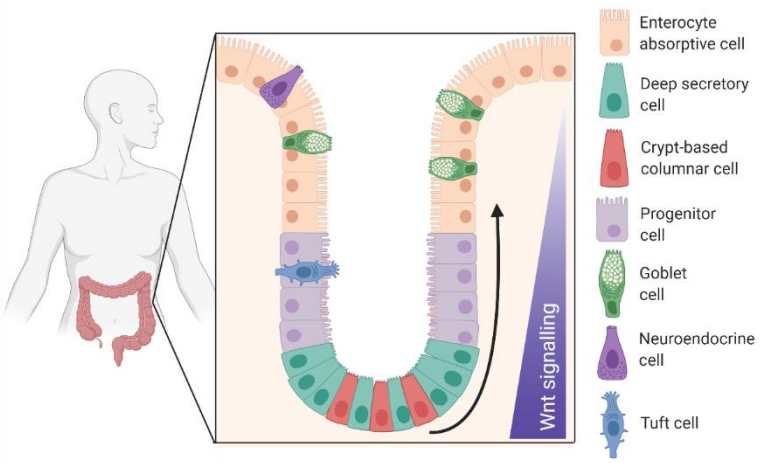

Figure 1: Intestinal epithelium, diagrammatic representation of the cells lining the colonic crypt (from Amy Holt, Investigating the effects of aspirin on colorectal cancer cell metabolism PhD Thesis 2021)

The funding for this research has been extended until 2024.

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Thank you for supporting the University of Bristol Cancer Research Fund

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