University of Bristol Cancer Research Fund

2017/2018 Report

Professors Ann Williams
and Stefan Roberts

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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. Funding comes entirely from donations from the public, ranging from individual donations to charity fundraising events.

This report details four research projects funded by your generous donations to the University of Bristol Cancer Research Fund, with a total investment of £20,000. The projects reflect the range of ground-breaking research taking place at the University to investigate prostate, breast and pancreatic cancers. This includes the cellular changes that cause cancer to start, understanding how it spreads, and identifying new combinations of drug targets to improve the quality of life of cancer patients and their families.

Most importantly, your generosity has supported projects during their earliest stages, which is critical for securing additional research funding for larger and more ambitious studies. Thank you, once again, for your generosity in supporting cancer research at Bristol.

New Chair for the UCRF: Prof Ann Williams

I have recently taken over as Chair of the committee that is responsible for deciding which research proposals will be funded by the University of Bristol's Cancer Research Fund.

As way of a brief introduction, I am a professor of Experimental Oncology and lead the University of Bristol's Colorectal Tumour Biology (CTB) Group in the School of Cellular and Molecular Medicine. Colorectal (bowel) cancer remains the second most common cause of cancer deaths in the UK. Although survival rates for bowel cancer have been improving over the past 20 years thanks to increased early screening and advances in research, there is still much to do. Our research uses cross-comparison of data from unique human tumour models (a specialism for which the group is renowned worldwide) and state-of-the-art population-based studies to understand the mechanisms that drive early tumorigenesis which will help us improve both prevention and treatment for bowel cancer.

It is a huge pleasure for me to be able to work with the University Cancer Research Fund; this fund has been hugely influential in supporting early career researchers and large grant applications. I look forward to making sure that the money you kindly donate continues to support the success of cancer research at Bristol.

Projects

Examining the feasibility of a physical activity and metformin intervention for patients with prostate cancer

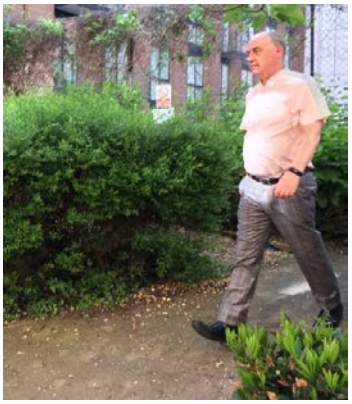
Dr Lucy Hackshaw-McGeagh
Dr Athene Lane
Professor Richard Martin



Prostate cancer is the second most common cancer in men worldwide. Although survival rates are high, one in three men undergoing treatment for early stage prostate cancer experience biochemical recurrence. Therefore, many men could potentially benefit from a low-toxicity intervention as an adjunct to their primary treatment. A growing body of evidence suggests that physical activity and metformin (a drug commonly used for type II diabetes) may have positive effects on the metabolic signals associated with the proliferation of cancer. Pre-EMpT (Prostate cancer – Exercise and Metformin Trial) is a feasibility randomised control to explore the use of these interventions in men with prostate cancer.

Men with prostate cancer average only six minutes of moderate to vigorous activity per day, with up to ten hours sedentary time, and evidence shows that the physical activity of cancer survivors decreases significantly during treatment and often does not return to pre-diagnosis levels.

Wearable technology is being increasingly used in health research and provides an opportunity to stimulate physical activity in patient groups. The grant from the University Cancer Research Fund has enabled us to purchase wrist-worn activity monitors for the trial. These will allow the study to explore the feasibility of using technology to motivate participants' activity and to record the activity taken in greater detail than using a standard pedometer. The outcomes from this trial will provide the evidence we need to apply for funding for larger studies in this area.



Can aspirin and metformin be used to improve prostate cancer outcome?

Dr Claire Perks & Hannah Carr

Prostate cancer is a slow-developing cancer that can allow some men to live for decades without displaying any symptoms or requiring treatment; however, it is not known which indolent tumours will progress to a fatal clinical disease. Aspirin (a non-steroidal anti-inflammatory drug) and metformin (medication for type II diabetes) are two commonly prescribed drugs, which have been in use for centuries. Both epidemiological and in vitro studies have shown that these drugs possess anticancer effects. Metformin has been shown to have anti-tumorigenic effects in prostate cancer cell lines;

however, little is known about the actions of aspirin alone or its combination with metformin. Using a range of prostate cancer cell lines, we have determined that the greatest effect on reducing cell growth, and blocking the cells' ability to transform into cells that have the capacity to move to other sites of the body, was observed when the drugs were used in combination. These results have been confirmed in prostate cancer cells grown in 2D cell culture which aids in understanding how the drugs work, and in 3D cell culture, a model which better mimics the way the cells grow and interact in the body (Fig. 1). We are currently performing these experiments in in vivo models and are eagerly awaiting the results. This work may provide the rationale to design future clinical trials.

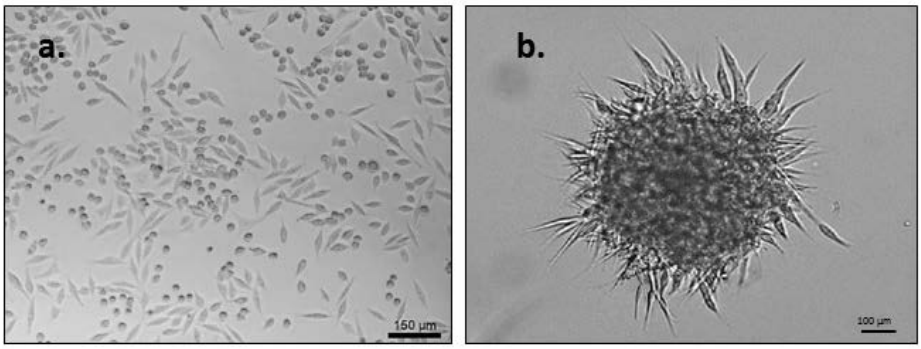


Figure 1: Prostate cancer cells grown in either 2D (a) or 3D (b).

Investigating the Role of PDIA3 in Controlling a Pro-metastatic Secretome in Breast Cancer

Professor Jo Adams

Despite improved early detection and identification of molecular subtypes, cancer recurrence and metastasis remains the major cause of death for women who contract breast cancer. Invasive ductal carcinoma is the most common form of breast cancer and it is now recognised that pre-conditioning of the microenvironment (i.e. functional activities of secreted products released by tumour cells and surrounding normal cells) has an important role in tumour invasion and metastasis. The goal of this project is to explore how activities of the intracellular protein, protein disulphide isomerase A3 (PDIA3), which controls the correct folding of a variety of secreted proteins, modulate the phenotypes and microenvironment of breast cancer cells.

Thanks to the UCRF funding, we have established that PDIA3 is present in triple-negative invasive ductal carcinomas, which are the most difficult to treat (Fig. 2, overleaf). By applying a chemical inhibitor of PDIA3 to breast cancer cell lines from basal- or luminal-phenotype breast cancers, we identified that PDIA3 activity is necessary to support effective cell adhesion, F-actin organisation and migration; these phenotypes fundamentally support tumour invasion and metastasis in vivo. Ongoing experiments are testing whether PDIA3 inhibition can improve sensitivity of the cells to chemotherapeutic agents such as 5-fluorouracil. Treatment of breast cancer cells with media containing the secreted products of wild-type or PDIA3-gene-knockout fibroblasts has demonstrated a paracrine, PDIA3-dependent promotion of pro-metastatic phenotypes. These studies provide initial evidence that PDIA3 can act to promote a pro-metastatic environment, by direct effects in breast cancer cells and also by promotion of indirect, pro-adhesive, extracellular communication between fibroblasts and breast cancer cells. The results indicate that PDIA3 inhibition could be relevant as a future possible translational target in breast cancer.

The data will be used in external funding applications and for publication. The research activity has also provided laboratory research training to a Master's by Research postgraduate student and has defined the context for a summer undergraduate research experience project.

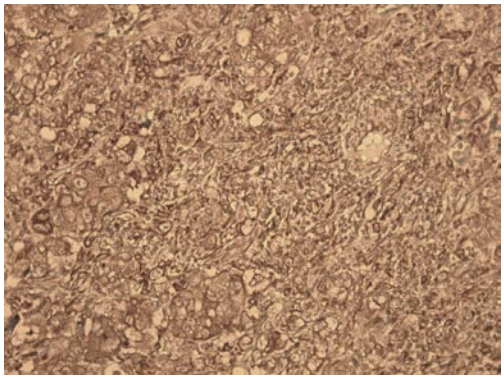


Figure 2: PDIA3 staining (dark brown) of a section from a triple-negative invasive ductal breast carcinoma. Tumour sample provided by Wales Cancer Bank.

Hybrid epithelial-mesenchymal states drive pancreatic cancer heterogeneity

Dr Abdelkader Essafi

Pancreatic cancer is a fatal cancer due to early spreading, cellular heterogeneity (i.e. different cells within a tumour have different properties), and resistance to therapy. Central among the mechanisms that underpin these processes is the epithelial mesenchymal transition (EMT). EMT and the reverse process, MET, are fundamental processes that drive cell movement and stem cell generation in the embryo and are hijacked in tumours and during wound healing.

Modelling pancreatic cancer in vivo (e.g. mouse models) or ex vivo (e.g. human organoids) has been instrumental in appreciating many mechanisms underlying obstacles to early and effective treatments. The current in vivo models are limited by the differences in physiology between humans and mice, while human organoids lack the physiological context of a functional organ. These limitations are partially solved by the implantation of human 3D culture cells in a mouse pancreas and following their progression through the multistep process of pancreatic tumorigenesis. This can be achieved by engineering vectors that permit the visualisation and genetic manipulation of human cells so processes such as EMT are dissected in vivo.

The UCRF fund has been used to create a vector: pGoldiLox (Fig. 3), which allows the tempo-spatial control of gene expression while lineage tracing in vivo.
This vector and the cell models generated in this project have been a part of an application to the Medical Research Council to investigate pancreatic cancer.

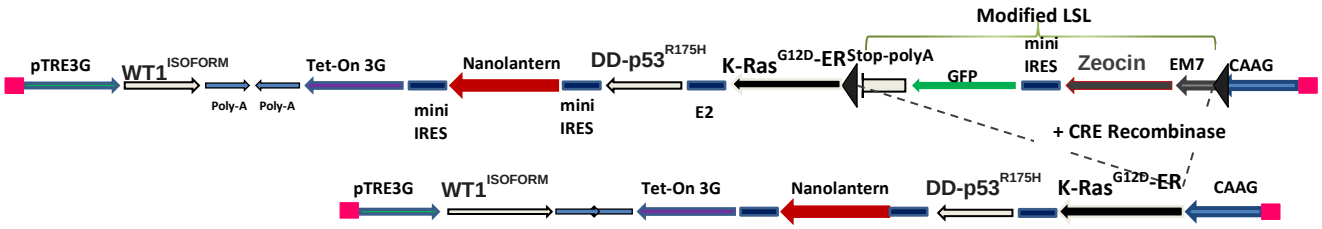


Figure 3: pGoldiLox: a versatile tool for gene expression and knockdown
pGoldiLox is a single vector to control (Dox-dependent) the tissue-specific expression of cDNAs and RNAi from safe harbour loci.