# University of Bristol Cancer Research Fund

## 2015/2016 Report

Professor 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 £19,794. The projects reflect the range of groundbreaking research taking place at the University. This includes investigating the cellular changes that cause cancer to start, understanding how it spreads, and identifying new drug targets to improving 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.

## Projects

### Re-activation of embryonic processes is an early event during cancer progression

**Dr. Abdelkader Essafi**

Normal cells continuously adjust to their surroundings. When under stress caused by mutations and/or external stimuli including tissue injury most cells respond by activating embryonic processes such as programmed cell death or cellular senescence. However, in a small number of cells other embryonic processes are hijacked instead leading to tumour development. Our understanding of the early stages of tumourigenesis remain poor and its exploration will lead to potential preventive therapies or early diagnostic approaches.

My main interest focuses on understanding how an embryonic regulator called Wt1 regulates development in the embryo and how these processes are repurposed when Wt1 is abnormally expressed in a many solid tumors including those of the breast, the pancreas and mesothelium. In each of those cancers, Wt1-based immunotherapy has shown very promising results but further understanding of how Wt1 can cause cancer is needed.

The UCRF award has been instrumental in acquiring normal human mammary cells that can be induced to become immortalized and in time malignant allowing analysis of progression

from normal to tumour cell in a tractable cell system. Our analysis has surprisingly revealed that Wt1 is abnormally reactivated much earlier than we expected. In fact, Wt1 is already activated in immortalized mammary cells, which means that the re-activation of Wt1 occurs during or prior to the immortalization step, considered the first step in the path for a normal cell to become malignantly transformed.

This finding has been instrumental in a successful application for a Wellcome Trust Seed Award in order to delineate the mechanisms that drive Wt1 and similar embryonic regulators to early reactivation during tumourigenesis.

## An analysis of the PPAR transcription factors as prognostic and predictive biomarkers in human high grade Gliomas

**Dr Kathreena Kurian**

Primary glioblastoma is an aggressive brain tumour that occurs in 4/100,000 per year and have a 3% five year overall survival. A surgical cure is rarely possible and there is an urgent need for improved therapies.

A recent study revealed that patients treated with drugs already in routine clinical use for type 2 diabetes and lipid control called PPARγ agonists (such as pioglitazone) had a lower incidence of high grade brain tumours including glioblastoma.

Our initial research carried out by Dr Harry Haynes (PhD student) supported by the UCRF fund has established that both PPARγ and PPARα are significantly overexpressed in primary glioblastoma brain tumour samples compared to healthy living brain tissue. Moreover, we have shown that mixed patterns of PPARγ and PPARα expression in 100 patients' samples are correlated with a significant increase in overall clinical survival. This finding has been validated in over 500 cases from the other researchers' studies in publically available databases.

We have shown that the PPARα agonist drug fenofibrate in particular inhibits the growth of PPARα-expressing glioblastoma tumour-initiating cells. We have also shown that commercial glioblastoma cell lines can be inhibited in the lab using the PPAR drugs pioglitazone and fenofibrate.

Currently we are developing a PPARα receptor knock down glioblastoma stem cell model in mice which will allow us to study the effects of the PPARα agonist fenofibrate in detail as a potential new treatment for glioblastoma. We have published a review article to let other researchers know about the potential uses of PPARγ in glioblastoma.

# The role of the cytoskeletal regulator FMNL3 in angiogenesis

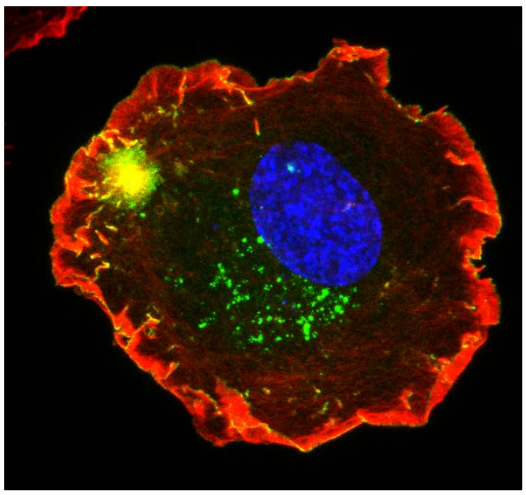
**Professor Harry Mellor**

In order to grow, solid tumours need to connect to the body's blood supply. They do this by stimulating a process called angiogenesis. Cancer cells secrete a growth factor called VEGF that tricks the body into producing new blood vessels. These grow towards the tumour, bringing it a supply of blood. The same tumour-associated blood vessels also provide a route for cancer cells to spread through the body. Drugs targeting angiogenesis can prevent these new blood vessels from forming, starving the tumour and causing it to shrink. Currently, the most widely used drug is Avastin. Avastin has been shown to be effective in shrinking some tumours, but can also exhibit side effects, including unwanted effects on normal blood vessels.

In our research, we seek to discover the mechanisms that control angiogenesis. Specifically, we are trying to understand the genes that control the cell shape changes that are required to make a new blood vessel. We hope that these genes will become new drug targets for the development of cancer treatments.

Funding from the UCRF allowed us to finish a research project on a new regulator of angiogenesis called FMNL3. We showed that FMNL3 controls one of the earliest changes in blood vessel formation – the stage at which cells decide their sense of direction (polarity). We linked the role of FMNL3 to another important new gene in blood vessel formation – RhoJ. Thanks to funding from the UCRF, we have now published this work in the journal Current Biology, allowing other researchers to read our findings and hopefully to add to them. Funding also allowed us to discover a third gene involved in the FMNL3 pathway, and to use this pilot data to successfully apply for a grant from the British Heart Foundation to continue this exciting work. Funding from the UCRF this year made a significant impact to our research. We hope in turn that this work will make a contribution to the search for new drugs in cancer medicine.

A human blood vessel cell showing the first signs of polarity.



Publication:
Richards M, Hetheridge C and Mellor H (2015) The formin FMNL3 controls early apical specification in endothelial cells by regulating the polarized trafficking of podocalyxin. Current Biology 27, 2325-2331.

# To use patient-derived circulating tumour cells to develop in vivo models of prostate cancer

**Dr Claire Perks**

Prostate cancer is the most common non-cutaneous cancer diagnosed in men, with a 1 in 6 lifetime risk of developing the disease. Organ-confined disease, detected early is associated with good prognosis. However, the development of prostate cancer that has spread beyond the prostate and has become resistant to treatment leads to an end-stage lethal disease. The spread of cancer is a complex and multistage process that involves the ability of cells from the primary tumour to detach and invade blood vessels and travel around the body to establish new secondary tumours. Circulating tumour cells (CTCs) are cells released from the primary tumour and are thought to be essential for this metastatic spread.
Funds from the UCRF have enabled us to successfully extract viable CTCs from prostate cancer patients and keep them alive in culture dishes (Fig 1). We are now developing a unique model for understanding the spread of prostate cancer, whereby we are attempting to inject and grow these extracted CTCs to provide enough cells for testing drug sensitivity and for understanding drug resistance.

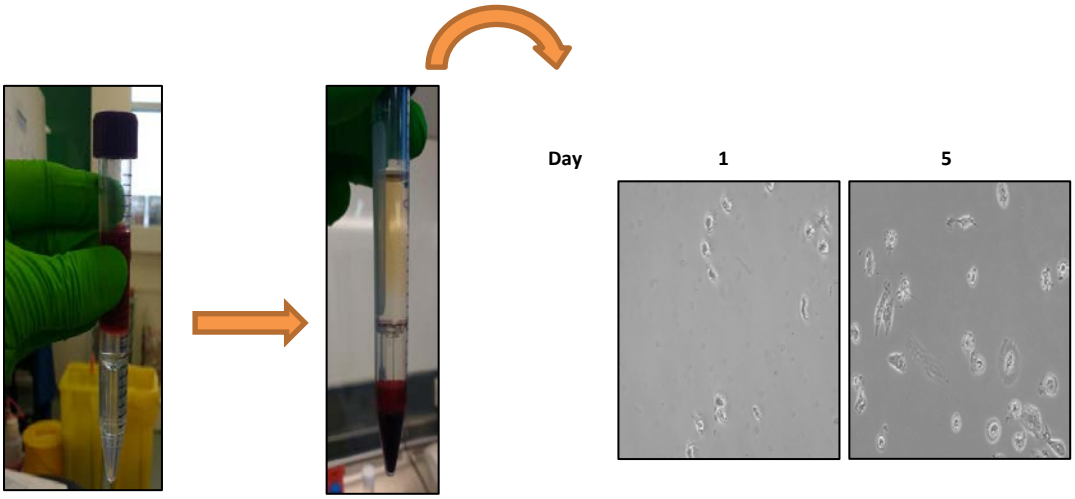



**Fig 1**: circulating tumour cells enriched from a patient with prostate cancer that has spread.