University of BRISTOL

University of Bristol Cancer Research Fund

2015 Report

Professor Stefan Roberts

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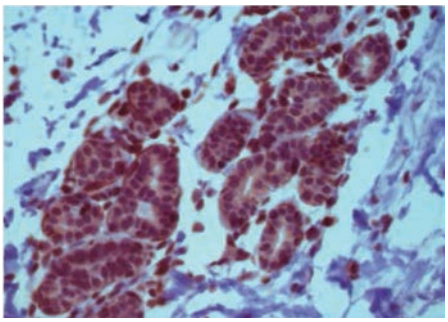
This report gives an account of three research projects funded over the last year by your generous donations to the University of Bristol Cancer Research Fund, with a total investment of £14, 951.
The projects reflect the broad range of groundbreaking research taking place at the University, from identifying new drug targets to finding new markers that can help select the right treatment, and also highlight Bristol's dedication in bringing together researchers from a variety of specialities to foster cross-disciplinary research.
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.

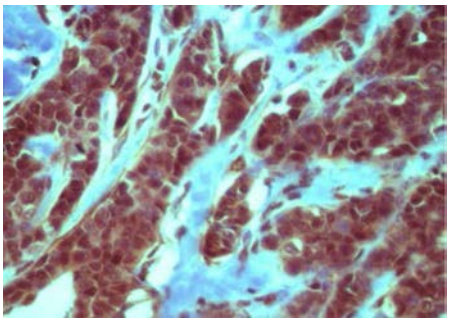
Characterisation of novel monoclonal antibodies as potential cancer biomarkers.

Dr Kevin Gaston

In a process known as metastasis cancer cells enter the bloodstream and travel to distant sites in the body where some of them form secondary tumours. These tumours are responsible for the majority of cancer-related deaths. The aim of this project was to characterise new monoclonal antibodies that may be able to identify cancers that are likely to metastasise. These biomarkers would help us to predict which cancers will progress rapidly and which will remain harmless. This would enable us to tailor treatment plans for individual patients. Such markers could also be useful for earlier cancer diagnosis.
The grant enabled us to examine healthy tissue and cancerous tissue using a technique called immunohistochemistry. We used this technique to examine how our potential biomarkers stain cells from normal breast, prostate and liver and from breast, prostate and liver cancer. As shown in the figure below we observe differences in how these antibodies stain normal tissue and cancerous tissue. We are currently working with larger numbers of samples to determine whether they can predict if tumours will spread. We have used data from this project in a recent application to the Medical Research Council that seeks funding to carry out a major international study of cancer of the bile duct.



Normal breast tissue



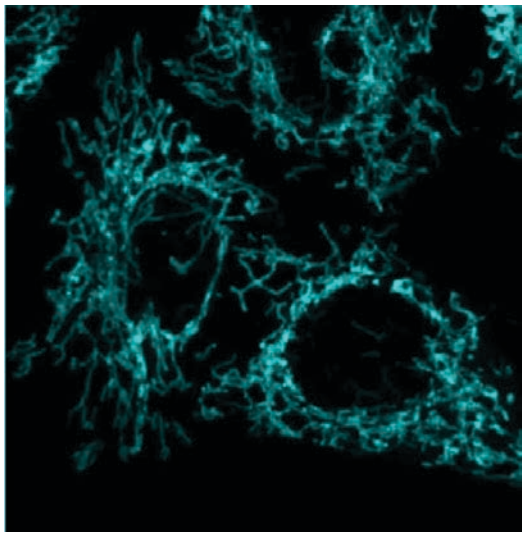
Breast cancer tissue

Mitochondrial substrates for the autophagic ATG4D peptidase amplified in ovarian and uterine cancers

Dr Jon Lane

Autophagy is an important cellular defence process that removes damaged proteins and invading pathogens. Failures in the autophagy pathway contribute to numerous human diseases, but it is not understood well in cancer. We are studying a protein that controls autophagy (ATG4D) that relocates into mitochondria (the cellular energy sources) in diseased cells. Altered mitochondrial activity is strongly linked to cancer onset and progression, meaning that understanding the roles that mitochondria play in cancer cells is a high priority. Importantly, the gene encoding ATG4D is linked to human breast, ovarian and uterine cancers.

Our observations suggest that ATG4D may have important, additional mitochondrial targets that might explain the significance of its enhanced expression in cancer. The award from the University Cancer Research Fund is allowing us to understand how ATG4D works and its potential links with cancer. To do this, we have made cancer cell-lines that contain a tagged ATG4D protein that allows us to visualise it as a green colour. Using this system we can study mutated versions of ATG4AD and also identify other proteins that it binds to. We will next apply this new knowledge and technology to breast cancer cell-lines (in which ATG4D is most frequently altered) to predict the impact of ATG4D function in cancer. It is hoped that this will lead to further funding to understand the roles of ATG4D and its related family members in human cancer.

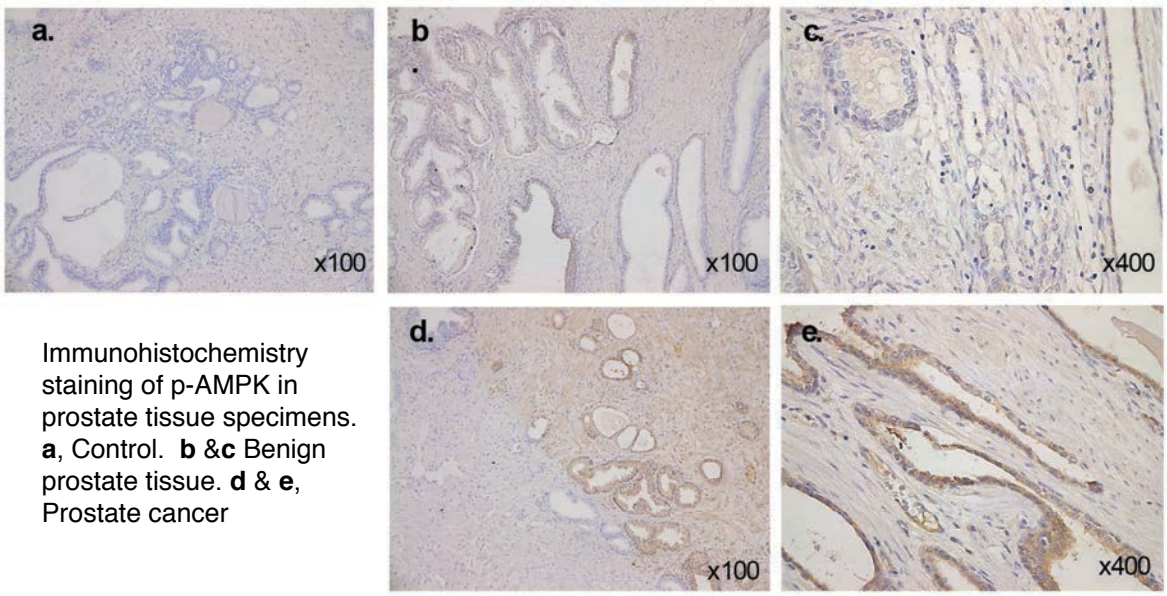


This image shows HeLa cells stably expressing ATG4D that has been tagged with a green marker. We are using these cells and others to identify novel targets of ATG4D

Examining colorectal tumour tissue to establish signalling pathways affected by patients taking metformin to determine whether administration of this drug can improve patient survival.

Miss Kathryn McCarthy
Dr Claire Perks
Professor Jeff Holly

Colorectal cancer continues to be one of the most common causes of cancer related death. It is diagnosed in around 250,000 people a year worldwide but its current treatment remains ineffective with frequent relapses and a 5-year survival rate of 11%. Metformin, an anti-diabetic drug, has been shown to possess anticancer effects, providing the rationale to design clinical studies to examine the potential benefit of metformin in cancer treatment. Despite this, further confirmation is needed. In this project, the aim was to examine tumour tissue from patients with colorectal cancer to establish which signals within the cancer cells are affected in patients taking metformin and which signals are altered according to the amount of physical activity in the patients' normal lifestyle.
We aimed to assess 60 samples and currently 30 tissue specimens have been collected with more samples in the pipeline. Standard immunohistochemistry staining will be used to examine changes in important molecules; we shall assess the localisation and expression of metabolic biomarkers related to cancer progression such as p-AMPK which increases in response to the drug metformin. So far the conditions and antibodies required for this technique have been optimised in prostate tumour samples (see figure) and we are ready to begin staining with the colorectal specimens. Completion of these studies funded by the University Cancer Research Fund will provide the crucial pilot data for a large study.



Immunohistochemistry staining of p-AMPK in prostate tissue specimens. **a**, Control. **b** &**c** Benign prostate tissue. **d** & **e**, Prostate cancer