University of Bristol Cancer Research Fund

2014 Report

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Introduction

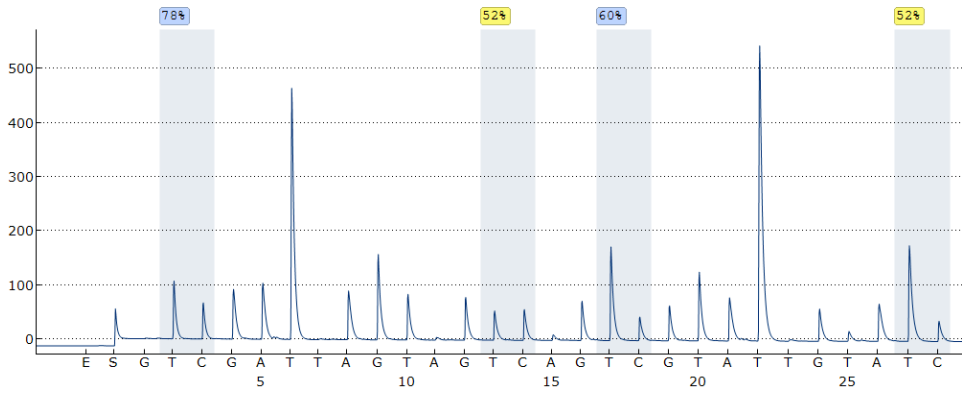
This report details the outcomes of the research projects funded from the 2013 awards. The fund was able to support 6 projects with a total investment of £20,097. These awards reflect the broad range of research activity in the University, from basic research designed to identify new drug targets, through to studies designed to improve the quality of life of cancer patients and their families. Most of the projects funded led to the bringing together of researchers with different specialities to foster cross-disciplinary research. Importantly, through these awards, we have been able to support projects at their earliest stages, funding the work needed for larger and more ambitious studies.

Dr Keith Brown and Dr Patrick Case
Prenatal aetiology of paediatric malignancies

The cause of most childhood cancers is uncertain, although it is clear that they begin before birth. We showed recently that exposure of embryonic cells to stresses that mimic what we think occurs across the placenta during pregnancy, cause DNA damage that might contribute to childhood cancer development. Apart from DNA damage, epigenetic modifications like DNA methylation can switch on or off genes and also contribute to cancer.

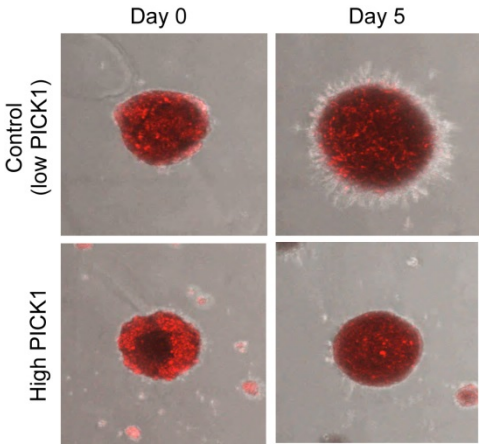
In this project we subjected embryonic cells to stresses and examined the exposed cells for changes in DNA methylation using highly sensitive methods. We found no overall change in methylation in the bulk of the DNA but we did observe small alterations in a few genes. Interestingly, these genes are known to be involved in cell fate decisions, such as whether stem cells differentiate into more specialised cells. It is thought that defects in decisions like stem cell differentiation are part of the process whereby embryonic cells give rise to childhood cancers. The small changes that we have seen mean that only a minority of cells have been altered by the stresses that they were exposed to.

Our future work will attempt to isolate these cells and to further analyse the epigenetic changes induced in them. We will do this by applying for grants that extend our studies into how stresses during pregnancy cause both genetic and epigenetic changes in embryonic cells before birth.



Pyrosequencing analysis of DNA methylation in embryonic cells

Dr Jonathan Hanley
Identification of actin-based processes regulating the invasion of primary human astrocytoma cells.
Astrocytoma is the most common form of human brain cancer. These tumours commonly reoccur when surgically removed and current chemotherapy and radiotherapy treatments are not very effective. Consequently patients with grade III and IV tumours have a dire prognosis. The more aggressive forms are characteristically invasive, with tumours often present throughout the brain and spinal cord.
Mammalian cells contain a highly changeable skeleton, made up of the protein actin, which forms filaments that shrink and grow to physically manoeuvre parts of the cell or its constituents, and is important for cell shape, movement and invasion. The invasive behaviour of astrocytoma is linked to regulation of the assembly and breaking down of actin filaments. The actin cytoskeleton is controlled by a large number of associated proteins, one of which is called PICK1, which inhibits the formation of actin filaments.



Astrocytoma tumours grown in vitro

We have discovered that lower levels of PICK1 are present in astrocytoma cells compared to normal brain tissue. The funding from the University Cancer Research Fund has allowed us to make important steps towards defining the impact of reduced PICK1 expression in astrocytoma cells. When we artificially increase PICK1 expression in cancer cells in vitro, the migration of astrocytoma cells is reduced, and the invasion of cells away from an in vitro “tumour” is also reduced.

This work suggests that the control of PICK1 expression may be a useful therapeutic target to reduce the invasive capacity of astrocytoma.

Dr Alyson Huntley
Supportive care for men with prostate cancer

Men with prostate cancer are likely to have a long illness pathway and experience debilitating effects on their sexual and urinary function with subsequent psychological distress. Supportive care interventions may be helpful for acute and long term consequences of cancer diagnosis and treatment. The Evidence Synthesis Of Prostate cancer Supportive care (ESOPS) study was carried out in the Academic Unit of Primary Care, School of Social and Community Medicine by Drs Alyson Huntley & Maggie Evans. The mixed-method study reviewed both the experiences and views of men with prostate cancer concerning supportive care, as well as the evidence-base for approaches that have already been tested in clinical trials. This work was funded by a National Institute of Health Research – Research for Patient Benefit (NIHR-RfPB) grant and resulted in two academic papers to date describing the findings.

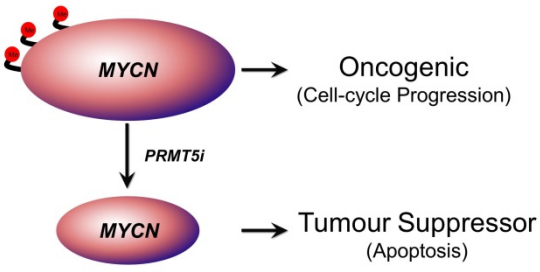
The qualitative review indicated that the most valued form of support men had experienced for their prostate cancer was one-to-one peer support and support from their partners. It also indicated that men perceive support groups to have two different roles that of information giving (health professional led), and emotional sharing (peer led). Some men following diagnosis indicated the need to be referred by health professionals to one-to-one peer support, or to local support groups.

The intervention review concluded that there a lack of high quality evidence for supportive care approaches for men with prostate cancer. Interventions around the time of treatment for prostate cancer generally included a significant proportion of information and education. Longer term trials generally involved more specfic psychological approaches and peer support. Quality of life, depression, anxiety, coping and self-efficacy of the men were the most common measures in these trials. The majority of the trials recruited Caucasian men and there were no studies on single, gay or significantly younger men. There was only one active monitoring study which recruited men in the long term, all the other studies were clustered within 18 months of primary treatment. Overall, there were few differences in outcome measures comparing supportive care to usual care alone. However there was limitied evidence of benefit for quality of life and depressive symptoms from individual trials. In conclusion, published trials on supportive care for men with prostate cancer appear to provide appropriate interventions and measure appropriate outcomes but with very little success. Better quality trials are needed that take in to account men experiences and needs, their different backgrounds and which investigate longer term support.

The University of Bristol Cancer fund supported the running of an evidence consolidation workshop at Southmead hospital in March this year. At this meeting we presented the results detailed above to an invited audience of over 25 people including patients, consultants, general practitioners, nurses, health care commissioners, researchers from the University of Bristol and other universities as well as representatives from the South West cancer network and clinical guideline development. The main aim of the workshop was help us write the research up in the most appropriate and focused way but also to discuss how to move the research forward into future projects. The workshop provided an excellent forum for both these aims, and was particularly beneficial in forging links with all the interested parties to high-light the issue of supportive care for men with prostate cancer.

Dr Karim Malik
Analysis of the methylated proteome in normal and cancer cells
Funding from the University Cancer Research Fund enabled us to explore protein modifications which might be critical in the development of neuroblastoma, a childhood tumour associated with very poor prognosis.

By using liquid chromatography - tandem mass spectrometry (LC-MS/MS) within the University of Bristol Proteomics Facility, we confirmed that a critical oncoprotein known as MYCN was modified by a partner protein known as PRMT5. This enables MYCN to have cancer-promoting properties; conversely depleting PRMT5 leads to death of cancer cells.



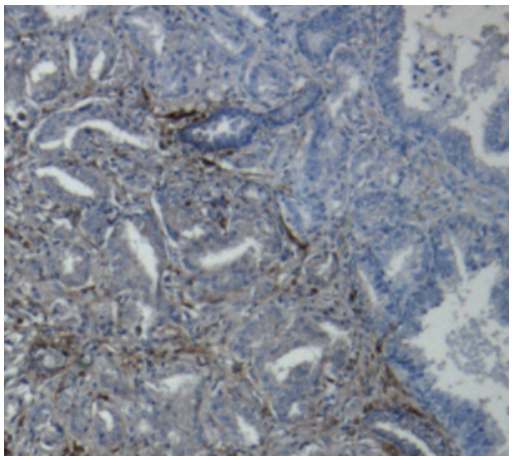
High levels of MYCN require modification by methylation (small red circles) and lead to enhanced cancer growth. Diminishing methylation leads to reduced (unmethylated) MYCN which can act oppositely, ie to trigger cell-death.

Data obtained from these analyses have enabled us to attain a project grant from the Neuroblastoma Society which will fund further research in our laboratory over the next 3 years. This will focus on developing new therapies based on eliminating MYCN, and thereby killing cancer cells.

Professor Richard Martin
The role of fascin-1 as a biomarker in aggressive prostate carcinoma: pilot case-control study

Prostate cancer is the most common male cancer in the UK and the second most common cause of cause of cancer-related death. Aggressive or advanced cancers can spread quickly and warrant intensive treatment, but up to 90% of men with prostate cancer have localised disease that is slow growing (indolent) and can be treated conservatively to avoid treatment side effects. The ability to distinguish early those prostate cancers that will progress more quickly from those that will remain relatively harmless is one of the most significant clinical challenges in cancer management, and is urgently needed to improve therapeutic decision-making.

The grant from the University Cancer Research Fund has enabled clinical scientists involved directly with men who have prostate cancer to work with cell biologists at the University of Bristol in a novel collaboration to examine new biomarkers with the goal of distinguishing indolent versus aggressive prostate carcinomas early after diagnosis. The focus of this study was fascin-1, a protein that is important for the aggressive clinical course and invasion and spread (metastases) of cancer cells. With the funding from the University Cancer Research Fund, we have been able to generate new pilot data from samples from surgically removed prostate tumours, obtained from the Wales Cancer Bank. The results suggest that fascin-1 is more likely to be found in more aggressive compared with less aggressive prostate cancer. The expression of proteins known to regulate fascin-1 in other cancers was also examined. We are currently extending the findings in order to complete the work. These data will be used to support new grant funding applications allowing us to undertake a large prospective study, and to test associations of fascin-1 with clinically relevant endpoints, including metastases and death.

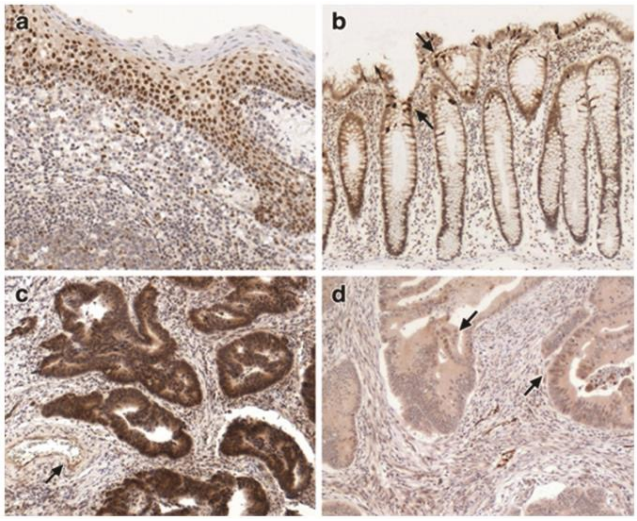


Fascin-1 positive and negative areas within a prostate tumour

Prof Ann Williams
Proteomic analysis of the Bcl-3/NFκB driven anti-tumour immune response
The purpose of the study was to identify whether expression of the Bcl-3 proto-oncogene in epithelial tumour cells can suppress anti-tumour immune responses, thus contributing to tumour growth. Although research into the function of Bcl-3 (highly expressed in a number of important epithelial tumours) is in its infancy, this factor is already proving to be important for a number of oncogenic pathways. The aim was to understand the role of BCL-3 in regulating tumour-derived growth factors that impact both on the pro and anti-tumoural functions of the Bcl-3/NF-κB transcriptional complex.

Using the well characterised Renca mouse model of tumour immunity, we have shown a highly significant increase in tumour growth with BCL-3 expression as compared to the vector or mutant transfected control cells. Analysis of the impact of BCL-3 expression on tumour immunity is currently underway. This funding has allowed us to purchase the reagents necessary for carrying out SILAC (stable isotope labelling with amino acids in culture) for the use in quantitative proteomics using the Orbitrap LC-MS/MS. We have generated light (R0K0), medium (R6K4) and heavy (R10K8) labelled cells and will adopt a

two tiered approach to identify targets of the BCL-3/NF-kB transcriptional complex important for increased tumour growth and immune modulation. In addition using co-immunoprecipitation, we will identify the BCL-3 interactome to enable novel mechanistic interactions to be identified. Although analysis of the experiments is not yet complete, data generated will be used to support a new collaboration with Dr David Morgan and we propose to submit an application for a Cancer Research UK Immunology Award later this year



IHC staining: a) Tonsil positive control for BCL-3 immunoreactivity. b) Normal colon showing moderate BCL-3 immunoreactivity in the cytoplasm, with occasional strong positive cell (arrows). c) Area of carcinoma showing strong cytoplasmic and nuclear BCL-3. The endothelium of the artery shows nuclear and cytoplasmic immunoreactivity (arrow). d) In this tumour sample the bulk of the tumour glands show weak or absent BCL-3 immunoreactivity, although foci of nuclear positivity are present (arrows).