University of BRISTOL

University of Bristol Cancer Research Fund (UCRF)

2023/24 Report

September 2024

CONTENTS

Introduction from Professor Athene Lane, UCRF Chair

I start by sincerely thanking all supporters of the University Cancer Research Fund (UCRF) which enables a wide range of exciting cancer research across Bristol University. UCRF is supported entirely by donations from individuals and charity fundraising events and we are extremely grateful.

The **UCRF seed corn annual funding scheme** helps researchers with “pump-priming” grants and small items of equipment to enable cancer research. Up to 10 projects are awarded annually up to £5,000. This funding aims to encourage truly innovative ideas and generate pilot data for applications for larger research grants and definitive evaluations from charities and UK Research Councils.

There are several notable successes from previous years awardees. The **Bristol UCRF webpage** has previous reports of the wide range of funded cancer research; https://www.bristol.ac.uk/cancer/ucrf/. We have a particular focus on encouraging early career researchers and those working in or with people outside medical faculties to develop new cancer researchers and novel collaborations.

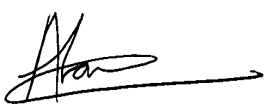
The UCRF **seed corn scheme funded 8 novel projects** working towards the prevention and treatment of cancer (total of £28,747). Projects that show promise to develop into high impact research are selected by the University of Bristol Cancer Research Network steering group of clinical and research experts. These projects are a just small sample of the breadth and depth of Bristol University cancer research supported by the UCRF.

I am excited to report on a new UCRF scheme that enables early career researchers to take their cancer research forward and helps them transition to research leaders through gaining funding for their novel ideas. Applicants to the **Investing in early/mid-career cancer researchers scheme** are also assessed by the Bristol Cancer Research Network steering group. Dr Adam Chambers, who features in this report, applied to this scheme and we wish him every success in his future career. The UCRF fund continues to be hugely influential for early career researchers developing cancer research towards larger programmes, I thank you for your generosity in making this happen.

On a personal note, I have taken over from Professor Ann Williams who led the UCRF very effectively over the last six years. My research involves designing and conducting randomised controlled trials with clinicians for the NHS and patient benefit. I have focused on prostate cancer, including the NIHR ProtecT trial of treatments for localised prostate cancer and the CRUK CAP trial of prostate cancer screening. It is a huge pleasure to Chair the UCRF, with its demonstrated power to initiate potentially important breakthroughs in cancer research.

If you would like to learn more about the UCRF, please contact the Philanthropy Office at alumni@bristol.ac.uk, or the UCRF website https://www.bristol.ac.uk/cancer/ucrf/ or by contacting myself at: uob-crf@bristol.ac.uk.

Thank you,



Professor Athene Lane
Chair for UCRF

ANGELA ATWOOD
Study: Establishing smoking cessation support within NHS Targeted Lung Health Checks
Award: £4,110

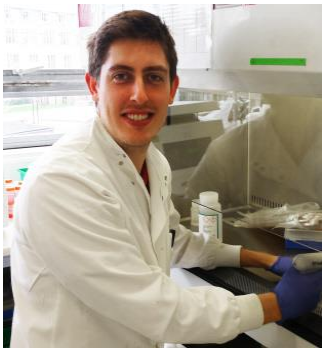
The primary aim of this project is to investigate how to best implement smoking cessation provision within Targeted Lung Health Checks (TLHCs: national NHS-based programme of lung cancer screening in current and ex-smokers aged 50 and over). TLHCs are considered a “teachable moment” to reach smokers who do not present to smoking cessation services. However, gold standard smoking cessation support, while showing promise in randomised controlled trials, fails to account for resource limitations in services. They also do not support individuals not ready to quit.

This project comprises two studies. The first is a qualitative study to explore readiness to quit in smokers attending TLHCs. This will provide a foundation for future work to develop adjunctive interventions for smoking cessation in opportunistic settings (i.e., settings where individuals are presenting for something other than smoking cessation support) to aid smokers willing, but not ready, to quit. The second study is a quantitative pilot trial of educational materials to support a new (Swap-to-Stop) initiative that has recently been adopted in the South West TLHC which provides smokers with e-cigarettes. However, our Patient and Public Involvement (PPI) work identified that many smokers have concerns about e-cigarettes and little interest in trying them. This study investigates whether providing “myth busting” support materials alongside e-cigarettes increases the number of people willing to try them. Currently our NHS ethics approvals for both studies are nearly ready to be submitted.

The findings from these studies will aid TLHCs nationally but also inform other sites (both clinical and non-clinical such as local housing) who are implementing similar opportunistic cessation support. Funding applications are planned after this award to take both interventions to the next stage of evaluation.

This award has enabled our team to consolidate links with local TLHCs, smoking cessation services, OHID and National Centre for Smoking Cessation Training who are all involved in aspects of this project. This has been a unique opportunity to identify priority questions and design pragmatic studies that take account of local challenges and resource limitations. Unexpectedly, the research has also widened our NHS network as we have been approached by consultants from vascular surgery units who aspire to similarly embed smoking cessation support in their clinical services. These links are crucial to build, design and conduct larger pragmatic randomised controlled trials in the future.

Figure 1: Research team at Bristol TLHC clinic



ADAM CHAMBERS
Study: Determining the regulation of chromatin compaction by BCL-3 following DNA damage in colorectal cancer
Award: £29,913

The aim of this research is to improve our understanding of how tumours respond to anti-cancer therapy given to patients before surgery in rectal cancer (a specific type of bowel cancer). We have shown that a protein called BCL-3 is important in this process and now want to gain a better understanding of how this protein leads to poorer outcomes in this cancer. This research aims to aid personalisation of a patient's therapy and even give the option to avoid surgery altogether if the tumour is treated completely with chemotherapy and radiotherapy. This will have major benefits for patient outcomes both through improving survival but also by reducing the risks associated with having surgery.

The aim of this project is to better understand the role of BCL-3 in rectal cancer therapy response. Work has been completed over the past year to better understand the chromatin changes following BCL-3 after irradiation. We have been using the patient Linear Accelerator (LinAc) at Bristol Haematology and Oncology centre to enable us to do this. We study how changes in histone 3 acetylation and methylation (post-translational modifications on this protein) alter following irradiation. We have observed that BCL-3 loss perturbs the usual early fluctuations in histone 3. We believe that these changes are critical to BCL-3s role in the accumulation and repair of DNA damage. Our next set of experiments using this funding seeks to understand these changes in greater detail and in other cell lines.

In addition to the experiments performed above I have also been working to optimise the production of Tn5 protein to facilitate downstream experiments using the Assay for Transposase Accessible Chromatin (ATAC). This work has been challenging but working with a MSc student we have produced some of our own Tn5 thus facilitating downstream experiments. We have been optimising the protocol for the ATAC-see microscopy experiments ready for use with our home-made Tn5.

Significant progress has also been made towards determining the interacting partners of BCL-3 following radiotherapy. The proteomics experiment we planned has been completed. We have identified several new targets and confirmed that the experiment worked through the identification of previously known binding proteins of BCL-3. We are currently validating these results to be able to target the proteins identified in our cells and assess the response to DNA-damaging treatments. This work is very exciting and will lead onto new information regarding the function of BCL-3 in radiotherapy responses in colorectal cancer. Through collaboration with researchers in Cardiff we have access to a novel small molecule inhibitor for BCL-3 and we hope to translate the findings from this project with this collaboration.

ALEX ANDRAYAS

Study: Patient and public involvement (PPI) to inform future research on risk factors for smoking or e-cigarette use and tailoring public health policy

Award: £240

Tobacco smoking remains a critical public health challenge worldwide. Despite ongoing public health campaigns and policy interventions, many smokers find it difficult to quit due to nicotine addiction and other factors. Electronic cigarettes (e-cigarettes) or vaping devices have emerged as a safer alternative to tobacco cigarettes that can help people quit smoking by providing a less harmful means of nicotine delivery. However not all people who smoke want to, or feel able to, switch to vaping, and many people smoke alongside vaping (dual use).

Previous research has identified a plethora of risk factors that reduce the likelihood of smoking cessation, with or without e-cigarettes. Identifying key motivations such as health concerns, cost considerations, and social influences, as well as barriers like perceived safety, satisfaction, and accessibility, can help tailor public health messages and regulatory approaches. Addressing these factors, and reflecting on any differences between people who continue to smoke, switched to vaping, or dual use, is essential for enhancing their effectiveness. The complexities of these behaviours can be better understood by engaging with the public. This is crucial to translate research into effective co-produced policies and interventions that encourage people who smoke to quit or completely switch to using e-cigarettes, and discourage dual use. This in turn would reduce cancer deaths associated with smoking and is especially important given the “hardening hypothesis” where, as smoking rates fall, the remaining smoking population will be particularly resistant to existing cessation campaigns.

We plan to use focus groups to understand the reasons for using or not using e-cigarettes or dual using, any strategies used to help with switching to e-cigarettes, goals and definitions of success, and how current scientific knowledge aligns with the lived experiences of people who smoke, vape, or dual use. This will inform future research questions, and guide the design of more effective public health interventions and policies, ensuring they are relevant and grounded in real-world experiences, and promote harm reduction through vaping, ultimately contributing to a more informed and responsive approach to tobacco control.

Insights from these focus groups will provide me with a deeper understanding of the real-life challenges and motivations that people who smoke and/or vape face, help design and highlight the most appropriate, comprehensive and meaningful questions to ask for future studies. It will strengthen future grant applications by demonstrating a clear understanding of the target population and practical relevance of my research, making my proposals more compelling to external funding bodies. Conducting focus groups will deepen my expertise in research methods as a quantitative researcher, making me a more versatile and skilled member of the scientific community. This will expand my research portfolio and open new avenues for investigation, demonstrate a more thorough understanding of the research, increasing its potential impact and enable more collaborative opportunities and career advancement.

ALFIE CHAMBERS

Study: Opportunities to optimise current therapy for prostate cancer by understanding the link between amyloid precursor protein and notch signalling

Award: £5,000

Current treatments for prostate cancer, such as radiotherapy, chemotherapy or androgen deprivation therapy can be very effective. However, there can be unpleasant side effects, drug toxicity problems and for some men their prostate cancer can become resistant to therapy, impacting on overall survival rates. Therefore, new approaches to optimise current therapy, including reducing and delaying therapy resistance, slowing the rate of disease progression, as well as easing burden on patients due to side effects are all still needed.

Worldwide, prostate cancer remains the second most common type of cancer and is the fifth leading cause of cancer-related death among men. Dementia, another disease of later life is also a major cause of death globally, with 9.9 million new cases estimated each year; 60–70% of these are diagnosed as Alzheimer's disease (AD). The characteristic risk factors (e.g. advancing age and obesity) for cancer and AD are remarkably similar, yet puzzlingly, the evidence from population studies points to an unusual inverse association between these conditions (i.e. lower than expected rates of AD in cancer survivors and lower than expected rates of cancer in AD patients) that is not necessarily or readily explained by survival biases.

One protein called amyloid precursor protein (APP) has been extensively studied in the brain, particularly in relation to its role in AD. The UCRF fund has enabled us to gain preliminary data to show that APP also plays a role in prostate cancer and notably we found it is linked to a crucial and well- established pathway, Notch, that is required for cancers to progress. Although many drugs have been developed which target the Notch pathway in cancer, the trials have been disappointing. This novel link between APP and Notch may provide better, more effective ways of targeting the Notch pathway for prostate cancer therapy in the future.

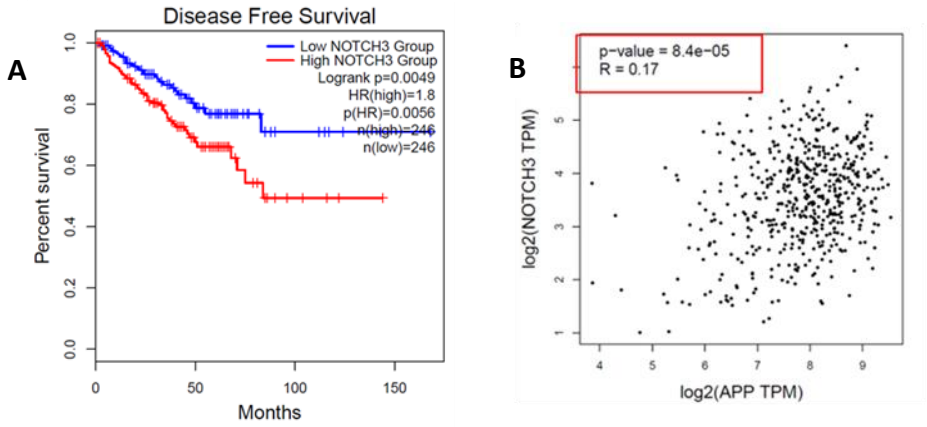


*Figure 2: Using Gene Expression Profiling Interactive Analysis (GEPIA), high NOTCH3 gene expression was associated with **significantly lower** disease-free survival in the Prostate Adenocarcinoma (PRAD) dataset and **[A]** there was a **significant positive correlation** between APP and NOTCH3 expression **[B].***

The results from the UCRF funding have been used as pilot data to support a recent grant to the Worldwide Cancer Research Fund to interrogate the link between APP and Notch in the treatment and progression of prostate cancer.



TRACEY COLLARD and ANN WILLIAMS

Study: The impact of Aspirin and 5-aminosalicylic Acid (5-ASA) on Cell Signalling and Metabolism

Award: £5,000

Tracey Collard, Ashley Hoskin and Kat Belfield (Kinome experiments)

It has been known for many years that taking regular aspirin could help prevent bowel cancer (also known as colorectal cancer). However, the potentially serious side effects associated with regular aspirin use (increased risk of bleeding) have prevented it from being recommended for this purpose for the general population. The aim of this study is to find a safer “aspirin-like” drug that could be used to help prevent colorectal cancer in people at increased risk of developing the disease. We have carried out extensive studies to show that 5-ASA (also known as Mesalazine) may have similar anti-cancer effects to aspirin. This is exciting as 5-ASA is routinely used in the control of inflammatory bowel disease; it is well tolerated with few significant side effects.

It has been known for some time that tumour cells reprogramme their metabolism to support their continued growth. Excitingly, we have shown that both aspirin and 5-ASA can prevent this metabolic reprogramming [1,2], although until now, we have struggled to identify how they do this. Understanding the mechanism of action is important if we are to recommend taking 5-ASA for colorectal cancer prevention (it will help to inform who would most benefit and how to monitor drug efficacy for example).

The UCRF grant has allowed us to take advantage of a new technology (available on loan from Pamgene), using an array-based approach that measures kinase activity in the 5-ASA and aspirin treated tumour cells. We were able to look at 144 serine/threonine phosphosites, and because we were part of a trial, PamGene performed the analysis for us. They used an in-house software called Bio Navigator to quantify the fluorescence of each array and an algorithm to predict the kinases responsible for the peptide phosphorylation (Figure 3 on the page below).

These findings have led us to investigate the importance of ERK5 signalling in 5-ASA dependent metabolic reprogramming, opening new research avenues not only for cancer prevention but potentially (using combinations of inhibitors) for the future treatment of colorectal cancer.
This mechanistic insight is crucial for developing clinical trials and will be part of the pre-clinical data for a future NIHR grant with clinicians Tom Creed and Steve Dixon using 5-ASA to prevent polyp recurrence in high-risk individuals identified at the bowel cancer screening programme (BSCP).

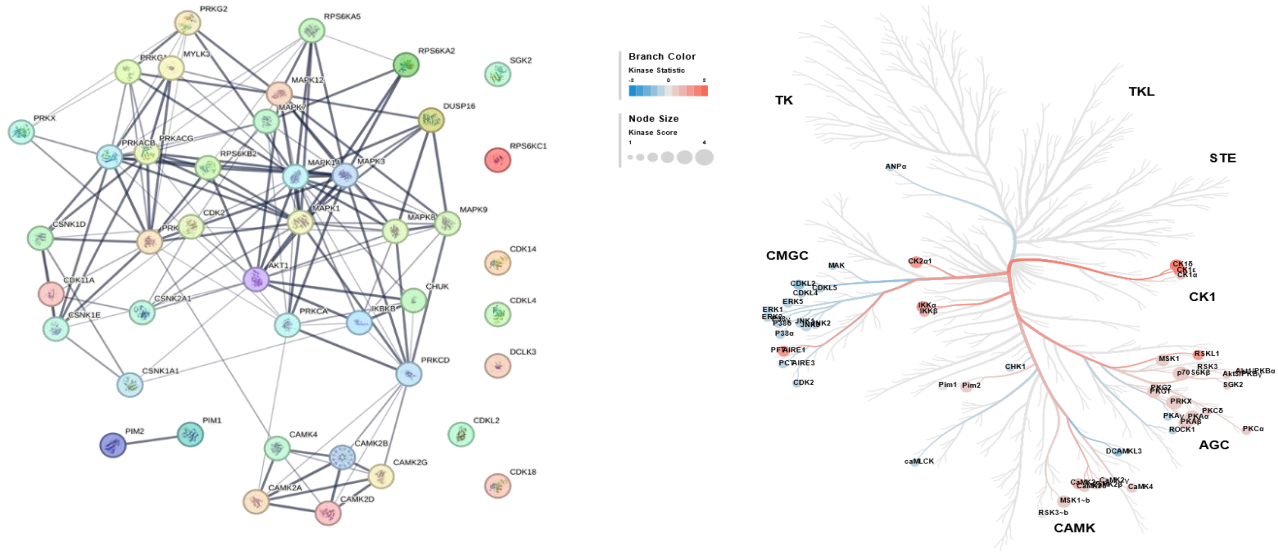
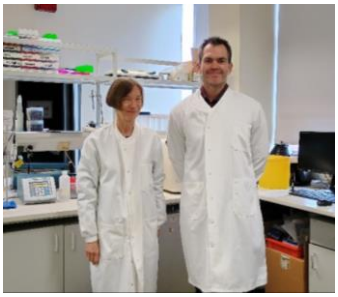


Figure 3: Data from Kinome indicates metabolic changes in 5-ASA treated cells could be regulated by ERK signalling.

UKA/STRING analysis highlighted MAPKs
UKA (upstream kinase analysis) uses publicly available databases on kinase-substrate relationships and an algorithm to predict the kinases responsible for peptide phosphorylation. STRING predicted functional associations between proteins.

References

1. Holt AK, Najumudeen AK, Collard TJ, Li H, Millett LM, Hoskin AJ, Legge DN, Mortensson EMH, Flanagan DJ, Jones N, Kollareddy M, Timms P, Hitchings MD, Cronin J, Sansom OJ, Williams AC, Vincent EE. Aspirin reprogrammes colorectal cancer cell metabolism and sensitises to glutaminase inhibition. Cancer Metab. 2023 Oct 19;11(1):18. doi: 10.1186/s40170-023-00318-y.
2. Hoskin AJ, Holt AK, Legge DN, Collard TJ, Williams AC, Vincent EE. Aspirin and the metabolic hallmark of cancer: novel therapeutic opportunities for colorectal cancer. Explor Target Antitumor Ther. 2023;4(4):600-615. doi: 10.37349/etat.2023.00155.



BEN EDE and ANN RIDLEY

Study: Novel palmitoylation pathways involved in trans endothelial cell migration of T-cell acute lymphoblastic leukaemia

Award: £4,802

Modern chemotherapies for childhood T-cell acute lymphoblastic leukaemia (T-ALL) have resulted in substantial increases in long-term survival. However, patients who do not respond well to chemotherapy still have a poor prognosis with treatment failure. For example, T-ALL cells can escape chemotherapy by crossing blood vessel walls to enter different body sites such as the brain. At this stage, T-ALL is particularly difficult to treat. Blood vessels are lined by endothelial cells, which T-ALL cells must attach to in the bloodstream before they can enter the brain. Recent research in our laboratory led to the discovery that two enzymes in endothelial cells are important for T-ALL cell attachment. We aim to work out how these enzymes contribute to T-ALL attachment and if we can inhibit these enzymes to reduce endothelial attachment. This could lead to new treatments for T-ALL patients who do not respond to chemotherapy.

We have identified 4 ZDHHC palmitoyl transferases that alter T-ALL cell adhesion to endothelial cells, using Jurkat cells as a T-ALL cell model and primary human umbilical vein endothelial cells (HUVECs). We have also optimised a proteomics methodology for detecting palmitoylated proteins from HUVECs and completed three control experiments with the Bristol Proteomics Facility and identified multiple palmitoylated proteins (Figure 4). Some of these were known to be palmitoylated by other research groups in a variety of cell types, whereas others are new potential drug targets. Having now established this method we aim to test which proteins are targeted by the 4 ZDHHC proteins, using siRNA knockdown coupled with proteomics. In addition, we have set up conditions to measure T-ALL cell trans endothelial migration. Using this knowledge and methodology, the final step will be to test whether knocking down any of the 4 selected ZDHHC proteins alters T-ALL migration through endothelial cells and whether the expression and/or localisation of palmitoylated targets of ZDHHC proteins changes in cells.

Having developed an optimised method for detecting palmitoylated proteins in endothelial cells with the UCRF funding will help tremendously in future research as previously unknown targets have been identified in our initial tests, some of which are relevant to endothelial cell-cell junctions and hence could affect T-ALL cell migration. Our goal is to continue to research endothelial cells and palmitoylation in T-ALL cell migration, publish these results to lead to a future grant application.

UCRF funding has helped Ben Ede's career by re-establishing research links on leukaemia, specifically T-ALL. T-ALL was the focus of his PhD studies, and his passion is research that could contribute towards helping T-ALL patients.

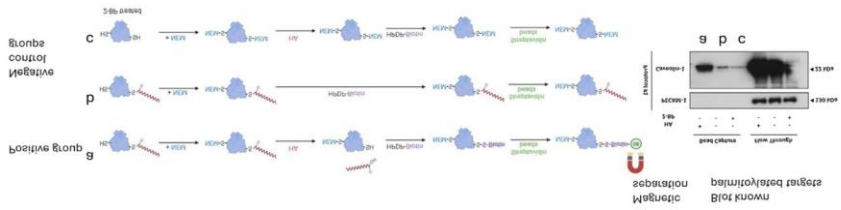


Figure 4: Methodology for detecting palmitoylated proteins and example of results.


YI LIU and ZHAOZHEN XU
Study: Assessing capability of large AI models in text mining of cancer studies
Award: £4,880

Large Artificial Intelligence (AI) models (also known as Foundational Models or Large Language Models (LLMs)) are a new exciting trend emerging in the research and application of AI and healthcare. These models e.g. OpenAI's ChatGPT are in widespread use and powering modern embedded AI services in personal computers and smartphones. These deep neural network Transformer models have been extensively trained with general as well as domain specific knowledge, and with their substantially large parameter sizes (in the billions or trillions), they are able to perform really well in various foundational tasks.

The use of large AI models is also a new paradigm in machine learning:

1. Foundational models can be adapted (via finetuning or prompt engineering) to new tasks without being trained extensively on the task data, which might make them more accessible to non-technical teams.
2. As they are substantially larger than traditional models, the top models cannot be trained or deployed on laptops or older High Performance Computers, but interfaced via online paid-for AI service platforms (e.g. OpenAI's API or Google Collab).

The extraction of cancer risk factors, clinical outcomes, statistical methods and information from published articles is a crucial step in conducting systematic reviews and evidence synthesis of cancer studies for categorising studies and assessing their quality. These steps can be automated by text mining of the papers using natural language processing and machine learning pipelines to reduce manual efforts and save time.

Large AI models might further improve the automation pipelines, e.g. replacing simpler text embedding methods (such word2vec) for better accuracy and robustness, and mimicking traditional predictors (e.g. a classifier based on decision tree) to explain the predictions.

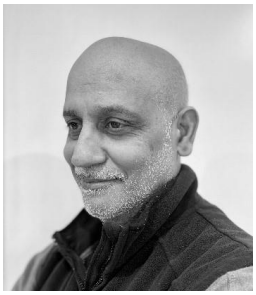
We will work on two projects:

1. Extraction of data of interest from biomedical publications and preprints as well as assessing basic quality or risks-of-bias of these published results using the extracted data.

2. to instruct large AI models to work as traditional predictors with the aim to assess their potential model hallucinations (e.g. predictions that are seemingly sensible but factually incorrect) and attempt to instruct the models to make explanations of their inferences.

Currently the projects are on-going and we are hopeful and excited about the outcomes and insights of this seed corn funding research for us and other research teams hoping to employ AI services in their future work.

The funding for this research has been extended until 2025.



KARIM MALIK and JODIE BOJKO

Study: Regulation of mRNA epitranscriptomic marks by oncogenes

Award: £4,980

It is well understood that DNA sequence alterations in genes can result in uncontrolled growth of cancer cells. Additionally, genes can be switched off (under-expressed) or inappropriately induced (over-expressed). Switching on of genes creates a copy of the gene information as messenger RNA (mRNA) molecules (transcription) which is converted to specific proteins within the cell's protein factories (translation). Gene transcription and translation changes can alter levels of growth-promoting or growth-inhibiting proteins, and the balance is fundamental to regulated cell growth.

We have tested the proposition that cancer-causing proteins regulate translation by modifying the molecular structure of mRNAs. Some modifications we have identified are likely critical in cancer development, and inhibiting these changes may lead to new therapies for cancer. Mutation of genetic material is frequently associated with disease, in particular cancer as is modifications of DNA, for example by methylation. The study of DNA and chromatin modifications, called epigenetics, has revolutionized oncology, leading to the rapid development of novel cancer therapies.

The study of modifications of RNA, or epitranscriptomics, has recently been recognized as a vital focus for cancer research. Epitranscriptomic regulation involves numerous enzymes that catalyse post-transcriptional modifications of mRNAs, lncRNAs, rRNAs and tRNAs. These modifications include methylation, pseudo uridylation and queuosinilation, and the consequence of such changes can be alterations in the cellular proteome which facilitate tumorigenesis. Therefore, the enzymes that catalyse RNA modifications represent a new class of therapeutic targets for cancer therapy, and the modified RNAs may also have utility as disease biomarkers.

As oncogenes (genetic mutations that can cause cancer) are known to co-opt cellular regulatory mechanisms such as epigenetics, we sought to examine whether they might also influence the cancer cell epitranscriptome. Using neuroblastoma cells as a model, we deployed mass spectrometry to identify modifications of mRNA that may be regulated by oncogenes involved in the development of this deadly childhood cancer. As shown in Figure 5, pharmaceutical inhibition of a protein methyltransferase that neuroblastoma is dependent on, led to numerous changes in mRNA modifications. These changes highlight epitranscriptomic enzymes that neuroblastoma is potentially reliant on further studies on one of these, PUS7, are still in progress.

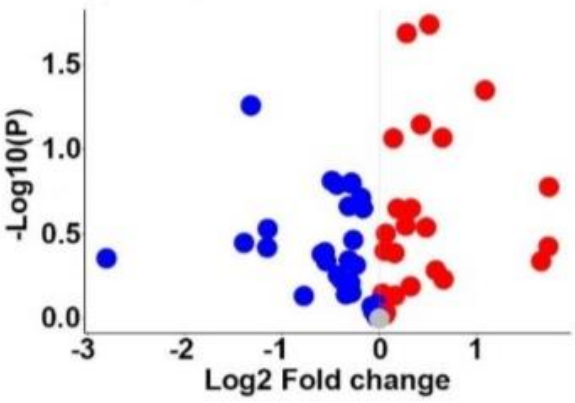
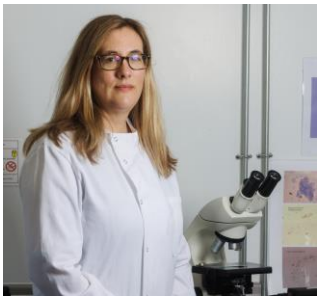


Figure 5: Volcano plot showing changes in mRNA modifications in a neuroblastoma cell line treated with a protein methyltransferase inhibitor.

This data will help in future grant applications. In addition, Dr Bojko, a recent PhD graduate, has attained valuable experience in taking an idea forward by attaining and managing the UCRF funding. This will benefit her progression towards becoming a future independent researcher.



LINDA WOOLRIDGE and JESSICA BELL

Study: T-cell receptor (TCR) profiling in melanoma patients undergoing treatment with checkpoint inhibitor blockade and its potential use as a predictive biomarker

Award: £4,980

There have been some major advances in the use of immunotherapy for the treatment of cancer over the last couple of decades. In cancer immunotherapy, one of the aims is to harness the ability of immune cells, called T-cells, to recognize and destroy cancer cells in the patient. One of the most significant breakthroughs has been the development of monoclonal antibodies, called checkpoint inhibitors. These drugs block inhibitory checkpoint pathways, such as the programmed cell death (PD-1/PD-L1) pathway, within the tumour thereby allowing T-cells to activate and eliminate tumour cells. These drugs have yielded impressive clinical benefits such as tumour regression and improved survival.

However, ~60% of patients may not respond to these treatments and furthermore, up to 60% of patients can develop side effects that can cause significant morbidity and sometimes mortality. Therefore, it is important that we conduct research to understand why some patients do not respond to checkpoint inhibitors and why some develop side effects.

We have been working with Dr Helen Winter at the Bristol Haematology and Oncology Centre (BHOC). We have been collecting blood samples from patients before and after treatment with checkpoint inhibitors, and subsequently tracking how the patients respond to treatment. Within these samples, a population of T-cells that proliferates in response to checkpoint blockade can be observed within 3 weeks of starting treatment.

T-cells recognize ‘antigens’ that are expressed at the cancer cell surface (Figure 6). Antigen recognition is mediated by the T-cell receptor (TCR). The funding provided by the UCRF will allow us to further characterise this population of proliferating T-cells to determine the pattern of TCRs expressed by the T-cells. We will then be able to look for correlations between changes in the pattern of TCR expression and clinical response to treatment with checkpoint inhibitors.

The UCRF funding will also be supporting the career development of Dr Jessica Ball, a clinical fellow who will be working on this project and intends to pursue a career in clinical academia with a focus on cancer immunotherapy.

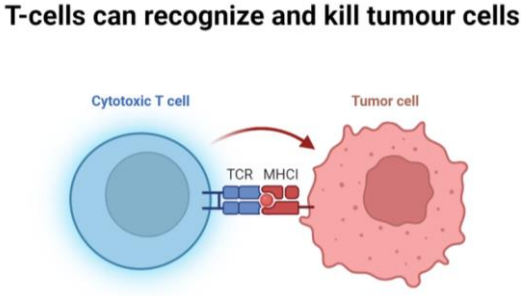


Figure 6: Cytotoxic action of T-cells on cancer tumour cells through T-cell receptors. Overall, the aim of this project is to try and identify biomarkers that can more accurately predict which patients would benefit from these expensive drugs and pinpoint those that are more likely to suffer side effects. Defining the mechanisms that underlie a lack of response to checkpoint inhibitors may also allow future development of more effective immunotherapies.

University of BRISTOL

Thank you for supporting the University of Bristol Cancer Research Fund

Philanthropy Office
University of Bristol
31 Great George Street
Bristol, BS1 5QD

alumni@bristol.ac.uk
bristol.ac.uk/alumni
+44 (0)117 394 1046