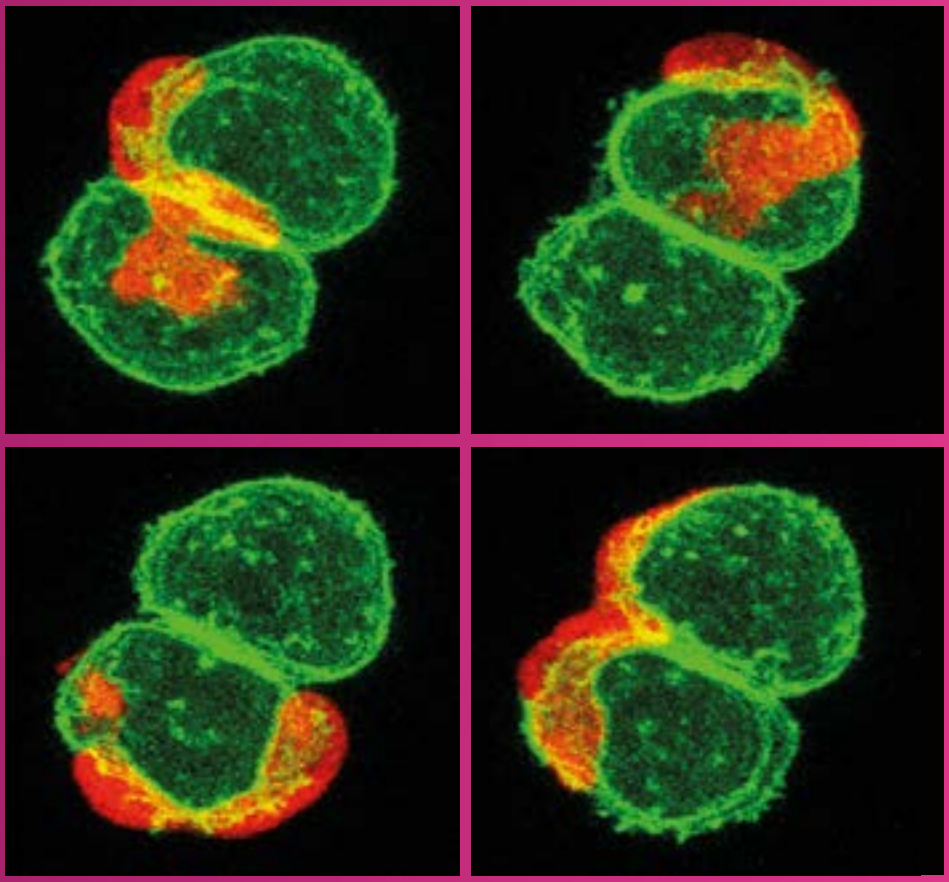
University of BRISTOL

BRISTOL CANCER

a multidisciplinary research community dedicated to finding new breakthroughs against cancer



Cancer research at Bristol received over £19 million in funding from UK Research Councils and other funders in 2020-2021, supporting exploratory work in the prevention, early detection, and treatment of this deadly disease. Our research spans across areas of expertise including cancer biology, epidemiology, engineering, physics and clinical work. This interdisciplinarity has made Bristol Cancer an international leader in the field – an achievement we are justifiably proud of and continue to support through our University Cancer Research Fund. Between 2018-2022 this fund has supported 31 early- stage projects by Bristol researchers. These exploratory studies are critical to attracting additional funding for larger and more ambitious projects that contribute to our ground-breaking understanding of how cancer works, and how we can best support those who suffer from it. Bristol Cancer continues to grow and thrive.

Philip Taylor

CEng, FHEA, FIET, SMIEEE
Pro Vice-Chancellor Research and Enterprise

Front cover image: T-lymphocytes, or T-cells, are a subtype of white blood cell that play a central role in cell immunity by hunting down and destroying cells that are infected with germs or that have become cancerous

Contents:

Introduction

Bristol cancer researchers are a vibrant cross-disciplinary community combining expertise from scientists at the University of Bristol and clinical researchers at University Hospitals Bristol and Weston NHS Foundation Trust (UHBW) and North Bristol NHS Trust (NBT). Together, they build on the long tradition of significant contribution to medical science in Bristol, from Sir Michael Epstein, the discoverer of the Epstein-Barr virus, the first described cancer virus in humans, to the Avon Longitudinal Study of Parents and Children (ALSPAC), collecting data on 14,500 families to further health research, and enrolling over 400,000 men in the CAP / ProtecT trials of prostate cancer screening and treatment.

We have the infrastructure to deliver world-leading research across cancer and a number of clinical areas, such as the National Institute for Health and Care Research (NIHR) Bristol Biomedical Research Centre (BRC) conducting innovative translational medical science research to drive through improvements in health and healthcare; the Bristol Centre for Surgical Research evaluating novel surgical approaches and surgical trials in cancer; the NIHR Applied Research Collaboration West (ARC West) applying health research and implementing research evidence to improve health and healthcare across the West of England; the NIHR Bristol Clinical Research Facility (CRF) which brings together early phase translational and experimental medicine research studies with a focus on cancer and immunity-based treatments; and the NIHR Academic Health Science Centre, a regional partnership bringing together expertise from universities and NHS organisations to improve health and care services by translating early scientific research and discoveries into benefits for patients.

There have been many advances in our understanding of cancer biology, with a concurrent expansion of drugs that might target abnormalities in cancer cells. The Clinical Trials Unit based at Bristol Haematology and Oncology Centre recruits cancer patients to over 100 trials across different tumour types; they aim to double this number over the next 5 -10 years to enable access for our patients to the most promising drugs. The Cancer Research UK Integrative Cancer Epidemiology Programme (ICEP) combines cutting-edge genomic technologies and large-scale bioinformatic platforms to establish causally relevant cancer risk-factors and identify novel molecular, predictive biomarkers and chemoprevention agents.

With the help of Bristol and Weston Hospitals Charity and North Bristol Trust's Southmead Hospital Charity, we are aiming to fund the next generation of clinical cancer researchers to build on this success.

The cancer community is determined to further expand and develop cancer research in Bristol, leveraging our strengths in population health science, clinical trials, cancer cell biology, surgical and health technology innovation, and health services research. In addition to recruiting and developing top cancer researchers including clinical academic trainees, we will address healthcare inequalities, continue to build interactions with cancer patient networks to develop research priorities, and grow our cross-cutting research across fields of expertise including chemistry, physics, engineering and health data science with a view to achieving breakthroughs that might not come within a single field of research.

A significant strength of Bristol is the coherent cancer community, with a leadership group made up of researchers at different career stages and from a broad range of expertise who interact to cross-fertilise research ideas and develop novel insights.

These are exciting times for cancer research, with both the University of Bristol and NHS partners supporting this ambitious vision for increasing cross-disciplinary research and partnership. We are proud of the achievements of the Bristol Cancer community so far and look forward to further ground-breaking work by our colleagues, some of whom we introduce within this publication.

Prof Anne Ridley FMedSci FRS
Professor
University of Bristol
Co-Lead Bristol Cancer Network

Prof Richard Martin
Professor of Clinical Epidemiology
University of Bristol
Co-Lead Bristol Cancer Network

Dr Helen Winter
Consultant Medical Oncologist
Bristol Cancer Institute UHBW;
Clinical Director, Somerset, Wiltshire, Avon and Gloucestershire Cancer Alliance

Reducing the burden of cancer through prevention and early diagnosis

Previous work by Richard Martin, Professor of Clinical Epidemiology, and Caroline Relton, Professor of Epigenetic Epidemiology, has shown that lifestyle changes and modification of certain risk factors can have dramatic effects on cancer prevention. Their research distinguishes between risk factors that are possible targets for therapeutic or behavioural interventions (including lifestyle and metabolic factors) and biomarkers that can predict who may be at risk of developing the disease.

They now lead the Integrative Cancer Epidemiology Programme (ICEP), a major 10-year programme funded by Cancer Research UK, to identify modifiable risk factors for developing cancer and gene targets that could be exploited for drug prevention; categorise the interaction between genes and environmental factors in the development of cancer; and isolate blood-based 'omic biomarkers for cancer risk prediction. They particularly focus on the common cancers: bowel, brain, prostate, breast, and lung, as well as kidney, ovarian, endometrial and head and neck cancers, accounting for well over half of all new cancer cases annually.

ICEP is hosted by the University of Bristol, in collaboration with the International Agency for Research on Cancer (IARC, Lyon, France) and McGill University (Montreal, Canada). Other international links include the Nord-Trøndelag Health Study, one of the largest longitudinal population health studies ever performed, based in Norway.

Building on the success of the CAP and ProtecT trials led by Professors Martin and Donovan (see next page), Professors Martin and Relton are also developing new early cancer detection tools to address cancer mortality by finding cancer at a stage when it is still easily curable.

https://www.bristol.ac.uk/integrative-epidemiology/programmes/icep/

- Morales-Berstein F *et al*. (2022). Assessing the causal role of epigenetic clocks in the development of multiple cancers: a Mendelian randomization study. *eLife*.
- Yarmolinsky J *et al*. (2022). Genetically-proxied therapeutic inhibition of antihypertensive drug targets and risk of common cancers: a Mendelian randomization analysis. *PLOS Medicine*.
- Gormley M *et al*. (2022). Investigating the effect of sexual behaviour on oropharyngeal cancer risk: a methodological assessment of Mendelian randomization. *BMC Medicine*.

Profs Caroline Relton (left) and Richard Martin (right)

The CAP and ProtecT trials

The CAP trial (Cluster randomised triAl of PSA testing for Prostate cancer) is the largest trial of prostate cancer screening ever, addressing the controversial question as to whether a routine single PSA (prostate specific antigen) test can reduce deaths from prostate cancer.

Almost 409,000 men without known prostate cancer were either invited for a single PSA blood test or nothing, referred to as NHS standard care. Forty percent of the men invited to the blood test had this done, of whom around 4,700 had or later developed a cancer, compared to approximately 3,400 in the control group who developed prostate cancer over the 10-year follow-up period. During this period, there was no difference in the rate of men who died from prostate cancer, but longer studies are ongoing to see whether differences emerge as the treatment of prostate cancer has also become more effective over this timeframe.

Embedded within the CAP trial was the ProtecT (Prostate Testing for Cancer and Treatment) trial, looking at the best treatment for those prostate cancers detected within the CAP trial, enrolling over 3,000 men with early prostate cancer into the three treatment arms: surgery, radiotherapy, and surveillance (with further treatment if required), showing that surveillance is as effective as surgery or radiotherapy in preventing prostate cancer deaths, potentially saving thousands of men from life-changing treatment consequences.

Office for National Statistics

Winner
ONS Research Excellence Awards 2018

Prostate cancer places a significant burden on public health globally, causing an estimated 6 million years of life lost in 2016, a figure that is forecast to rise to 12 million by 2040. Amongst UK males, prostate cancer is the most commonly diagnosed cancer, affecting 1 in 8 men, and is the second commonest cause of cancer death. The CAP trial provided the first and only robust evidence comparing a low-intensity PSA-based screening strategy (a single screen) for prostate cancer with no additional screening, minimal contamination, and was designed to reduce over-detection and overtreatment while seeking a mortality benefit. It showed that while PSA-based screening increases the detection of low-risk prostate cancers, it does not save lives.

Beating bowel cancer

Bowel cancer [also known as colorectal cancer (CRC)] remains the second highest cause of cancer mortality in the UK. Research in Bristol focuses on understanding the early biology of CRC with the aim of identifying novel approaches for both the prevention and treatment of colorectal cancer.

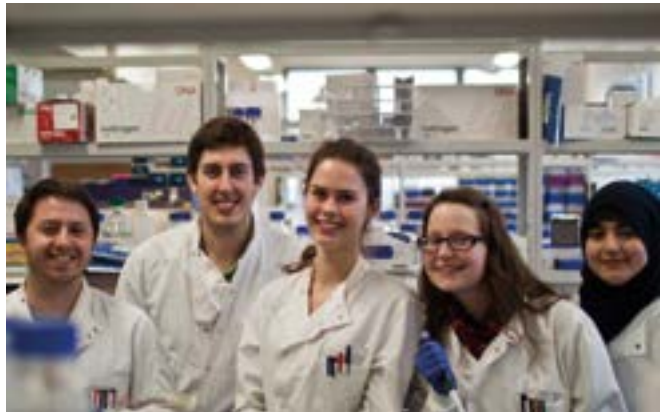
The team in Bristol have focused on cancer prevention for a number of years contributing to institutions such as the National Health Service (NHS), the National Institutes of Health (USA) and the Mayo Clinic (USA) encouraging people to eat a high fibre diet to reduce the risk of bowel cancer. The University of Bristol's Colorectal Tumour Biology (CTB) group, led by Professor Ann Williams, continues to participate in international clinical prevention trials assessing the use of aspirin in people at increased risk of developing bowel cancer (CAPP3).

Currently the CTB group is focused on two areas of research: in collaboration with Mr Adam Chambers (see page 8) they are investigating the role of BCL-3/NF-kB signalling on stem cell plasticity and therapeutic resistance; in collaboration with Dr Emma Vincent (see page 21), they are studying the effect of non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin and 5-ASA on cancer metabolism, identifying novel metabolic vulnerabilities that can be exploited both for the prevention and treatment of CRC.

The CTB group's research uses unique human colorectal model systems to derive new insights that are then validated in patient-based clinical trials through partnership with the University Hospitals Bristol and Weston NHS Foundation Trust. By combining cell and molecular biology, population health research and clinical studies, we aim to deliver an integrated programme of research to improve both the prevention and treatment of colorectal cancer.

http://www.bristol.ac.uk/cellmolmed/research/cancer/cruk-ctb.html

- Holt AK *et al*. (preprint). Aspirin reprogrammes colorectal cancer cell metabolism and sensitises to glutaminase inhibition. *bioRxiv*.
- Nounu A *et al*. (2021). A combined proteomics and Mendelian randomization approach to investigate the effects of aspirin targeted proteins on colorectal cancer. *Cancer Epidemiology, Biomarkers and Prevention*.
- Dixon SW *et al*. (2021). 5-aminosalicylic acid inhibits stem cell function in human adenoma derived cells: implications for chemoprophylaxis in colorectal tumorigenesis. *British Journal of Cancer.*



Top Left: *Beta-catenin expression (green) in intestinal epithelial cells (the nuclei of the individual cells are shown in blue). Beta-catenin signalling is critical for maintenance of the normal tissue; deregulation of this pathway represents the earliest stage of tumour development.* **Bottom left:** *Prof Ann Williams.* **Right:** *Members of the Colorectal Tumour Biology group.*

Understanding mechanisms of therapeutic resistance in colorectal cancer

Colon and rectal cancers (the two types of bowel cancer) are often treated with anti-cancer therapies designed to shrink the tumour and reduce the risk of recurrence after surgery. There is considerable variation in how tumours respond to these therapies. Therapy response can often dictate further management of the cancer, including how a tumour might be managed surgically. Therefore, understanding the biology underlying therapy response/resistance is critical in improving survival/cancer outcomes and management options for patients.

The research carried out by Mr Adam Chambers focuses on how inflammatory signalling pathways such as BCL-3 and NF-kB contribute to therapy resistance in colorectal cancer. As a colorectal surgeon, Mr Chambers has set-up a study (SectR) to collect blood and tissue samples for analysis in the lab; these laboratory findings can then be translated across to clinical samples. Several novel techniques have been introduced to the wider Colorectal Tumour Biology (CTB) group (see page 7) such as ultra-low pass whole genome sequencing (a DNA-sequencing technology used to detect genetic variation within the genome), ATAC-See and ATAC-Seq, which enable the analysis of small pieces of DNA that are released into a person's blood by tumour cells as they die (known as circulating free DNA or ctDNA). The use of ctDNA focuses on the measurement therapeutic response, but the techniques also help to determine how changes to chromatin compaction alter therapy response in rectal cancer samples. These data support other findings from the group showing that the mechanism of action of BCL-3 may be through driving changes to chromatin state leading to the downstream effects observed in transcriptional regulation and the DNA damage response.

Through collaboration with clinicians at University Hospitals Bristol and Weston NHS Foundation Trust, the group has published data regarding the changing incidence of early-onset colorectal cancer. This work will also make use of the novel assays on ctDNA to elucidate differences in biology between early and late onset sporadic colorectal cancers.

https://www.bristol.ac.uk/people/person/Adam%20C-Chambers-62e0c87e-d883-423f-9c64-a1cacf1677e0/

- Chambers AC *et al*. (2022). BCL-3 loss sensitises colorectal cancer cells to DNA damage by targeting homologous recombination. *DNA Repair.*
- Chambers AC *et al*. (submitted). BCL-3 is a critical mediator of colorectal cancer apoptosis through repressing BIM expression.
- Chambers AC *et al*. (2020). Demographic trends in the incidence of young-onset colorectal cancer: a population-based study. *British Journal of Surgery.*

Left: *Mr Adam Chambers.* **Right:** *Taking blood samples for laboratory analysis helps us understand what therapies are working.* **p9:** *Brandon Hill in Bristol.*

In-silico calculations of DNA damage for a better understanding of the radiobiological effectiveness of radiotherapy treatments

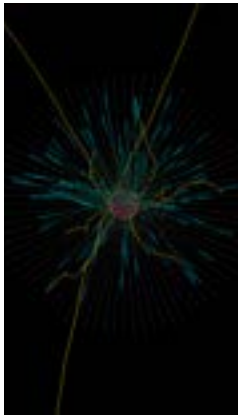
Around half of all cancer patients have some form of radiotherapy included in their treatment management. A significant challenge with external beam radiotherapy is that the beam deposits doses in all traversed tissue and thus damages healthy tissue as well. Damage to normal tissues can lead to unwanted side effects which negatively impact patients' quality of life. In brachytherapy and radionuclide therapy, radiation sources are placed directly inside the body such that the radiation dose is deposited locally, inside the tumour, and does less damage to the healthy tissue.

In the Bristol Particle Physics group, researchers are using computational algorithms known as the Monte Carlo methods, developed to calculate the deposited energy in particle detectors, to calculate the deposited energy in DNA during irradiation and how much of it is damaged during the process. These models can improve our understanding of how DNA damage occurs.

The team around Professor Jaap Velthuis is mainly focusing on the evaluation of the effectiveness of α-particle based therapies by investigating *in-silico* (experimentation performed by a computer) the distribution and complexity of radiation induced DNA damage in these treatments. The high linear energy transfer of α-particles causes more complex DNA damage which is harder for the cell to repair. As a result, the a-particles do a lot of damage to the DNA. Furthermore, α-particles have a limited range in the body and thus will only damage the cells in the tumour. This work will lead to a better understanding of novel treatments and allow the comparison of the effectiveness of different treatment modalities.

https://www.bristol.ac.uk/people/person/Jaap-Velthuis-9847498a-837b-4212-bdc0-5fe5230c9325/

- Velthuis J *et al*. (2023). Performance of a Full-Scale Upstream MAPS-Based Verification Device for Radiotherapy. *Sensors*.
- Beck L *et al*. (2020). A novel approach to contamination suppression in transmission detectors for radiotherapy. *IEEE Transactions on Radiation and Plasma Medical Sciences*.
- Pritchard JL *et al*. (2020). High-resolution MLC leaf position measurements with a large area MAPS. *IEEE Transactions on Radiation and Plasma Medical Sciences*.



Left: *Group photo from left to right: Dr Lana Beck, Ms Jinyan Duan, Ms Laura Ballisat, Prof Jaap Velthuis, Dr Chiara De Sio, Ms Katie Maclean, Ms Yuyao Shi.* **Right:** *Energy deposited in DaRT, a therapy in which metal seeds loaded with 224Ra are inserted in the tumour.*

Brain cancer research: accelerating discovery and clinical applicability

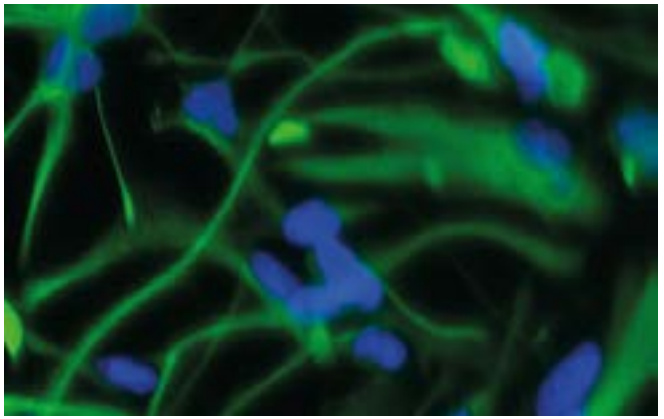
Since the early 1990s the incidence of cancers of the brain, central nervous system and intracranial tumours has increased by almost a third. Primary brain tumours are the biggest cancer killer of children and people under 40. In terms of the numbers of life years lost, it is the most fatal of all cancers.

The University of Bristol Brain Tumour Research Centre led by Kathreena Kurian, Professor of Neuropathology, works across complementary areas of research, linking Bristol's ground-breaking research in cancer epidemiology and population health with molecular biology and drug delivery. The centre aims to discover novel risk factors, biomarkers of progression, and drug targets for brain cancer using population health data; use *in vitro* models and clinical biobanks to screen and validate targets using machine learning; and translate work to *in vivo* with direct drug delivery into the brain cancer using nanoparticles and nanocarriers.

To date, pre-clinical model systems in brain cancer fail to predict efficacy and adverse effects of novel compounds when tested in clinical trials. This is compounded in the case of brain cancer by problems with drug delivery to the brain cancer, which is hidden behind the blood-brain barrier. Overall, the chance of success from target identification to the approval of a new drug is around four percent, at huge cost. Using world-leading population health expertise in Bristol to select genetically supported targets could double success at 25 percent lower costs. In collaboration with industry and other research partners, validation of targets and testing direct delivery of these to the brain could revolutionise our treatment of brain cancer.

https://www.bristol.ac.uk/translational-health-sciences/research/neurosciences/research/brain-tumour/

- Ghirardello M *et al*. (2022). Carbon dot-based fluorescent antibody nanoprobes as brain tumour glioblastoma diagnostics. *Nanoscale Advances*.
- Andrews LJ *et al*. (2022). Prevalence of BRAFV600 in glioma and use of BRAF Inhibitors in patients with BRAFV600 mutation-positive glioma: systematic review. *Neuro-Oncology*.



Right: *Prof Kathreena Kurian.* **Left:** *Attaching a fluorescent marker to affected cells will allow surgeons to identify high-grade tumour cells and remove as much cancer as possible, while leaving normal brain cells intact.*

Harnessing the power of healthy tissue to contain tumour growth

It is becoming increasingly clear that the communication between tumour cells and surrounding healthy cells plays an important role in tumour growth. Recent efforts in cancer research aim at better understanding the nature and impact of this bidirectional communication to identify novel anticancer strategies.

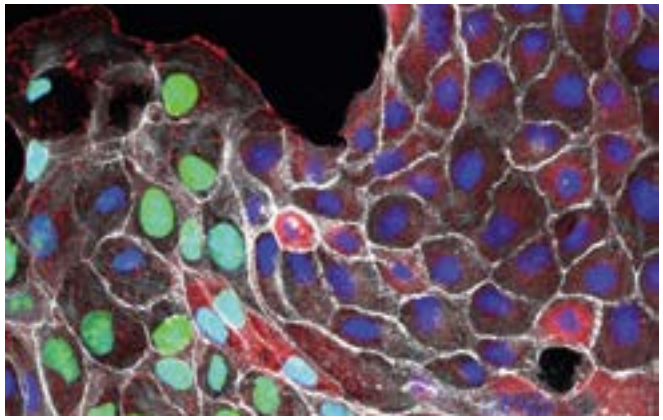
Eugenia Piddini, Professorial Research Fellow in Cell Biology, uses mammalian cell culture models and *Drosophila* intestinal tumours to model the early stages of tumorigenesis and to investigate how communication between tumours and healthy cells impacts on tumour growth.

Using the *Drosophila* fruit fly, a very powerful genetic model organism to study tumorigenesis, the Piddini group have shown that tumour cells kill surrounding normal host cells, a phenomenon known as "tumour host cell competition". Her team has further shown that this process fuels tumour growth, as it allows tumour cells to clear space that they can expand into. Indeed, the Piddini group have been able to contain growth of these intestinal tumours by protecting healthy cells from cell competition and from being killed by the tumour.

The Piddini group continues to investigate the competition between tumour and host cells to identify the molecular mechanisms that allow tumour cells and healthy cells to compete. Their aim is to identify molecular interventions that by modulating cell competition help to contain tumour growth. This could help in the design of a new class of anticancer treatments that exploit and bolster the ability of healthy cells surrounding the tumour to contain tumour growth. This would be a complementary strategy to traditional anti-cancer therapies that focus instead on killing tumour cells directly.

https://piddinilab.wordpress.com/

- Kozyrska K *et al*. (2022). p53 directs leader cell behaviour, migration and clearance during epithelial repair. *Science*.
- Baumgartner ME *et al*. (2021). Proteotoxic stress is a driver of the loser status and cell competition. *Nature Cell Biology*.
- Vishwakarma M and Piddini E (2020). Outcompeting cancer. *Nature Reviews Cancer*.



Right: *Prof Eugenia Piddini.* **Left:** *Drosophila intestine containing early stage tumours (in green) imaged by confocal microscopy, a method which helps increase optical resolution.* **p12:** *The Henrietta Lacks statue in Royal Fort Gardens, University of Bristol. Ms Lacks (1920-1951) was an African-American whose cancer cells are the source of the HeLa cell line, the first immortalised human cell line and one of the most important cell lines in medical research.*

Nanomedicine: making treatments smart

Chemotherapy often causes unwanted side effects by drugs being delivered throughout the body, rather than just targeting the cancer. Researchers at the University of Bristol are exploring how smart delivery vehicles (nanoparticles) could be used to treat a variety of cancers, from leukaemia to brain tumours, by carrying drugs directly to the cancer while avoiding the surrounding healthy cells.

The University of Bristol provides a unique cross-disciplinary environment that brings together clinical researchers, chemists bioethicists, biologists and engineers to design the nanoparticles of tomorrow. For example, Sabine Hauert is Associate Professor in Swarm Engineering; is a 'swarm engineer'; her group builds new computational models to understand the behaviour of trillions of nanoparticles in the body when their design is subtly changed.

There are many ways to design nanoparticles, some with molecules to recognise cancer cells, some using materials that react to lasers or magnetic fields to release anti-cancer drugs or heat to kill cancer cells.

Nanoparticles could potentially be made specific for different tumour types, offering new therapeutic avenues. Nanoparticles can also "light-up" in various ways, which is helpful to locate cancers in a non-invasive way, or to assess the response to treatment.

Dr Hauert's models are helping clinicians in Bristol understand which nanoparticle designs will give rise to the most effective treatments, for example, by making sure that all the cancer cells in a tumour receive the optimal drug dose. Data generated from these simulations are currently being used in conjunction with machine learning to automatically design nanoparticles for different tumour scenarios. Her team is currently building a tumour-on-a-chip device using 3D printing to test her models using real nanoparticles under the microscope. She is also working with bioethicists to understand what the first in-human clinical trials of nanoswarms for cancer treatment might look like.

http://hauertlab.com

- Swana MC, Blee J, Stillman N, Ives JCS and Hauert S (2022). Swarms: The Next Frontier for Cancer Nanomedicine. In: Balaz I & Adamatzky A (eds) *Cancer, Complexity, Computation*. Springer Nature, pp269-288.
- McCormick SC *et al*. (2021). Measuring nanoparticle penetration through bio-mimetic gels. *International Journal of Nanomedicine*.
- Stillman NR *et al*. (2021). Evolutionary computational platform for the automatic discovery of nanocarriers for cancer treatment. *NPJ Computational Materials*.

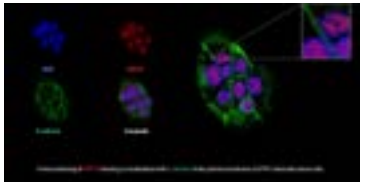
Right: *Understanding how trillions of nanoparticles move and interact in tumour tissue could prove instrumental to improving tissue penetration and cellular uptake of targeting drugs.* **Left:** *Dr Sabine Hauert.*

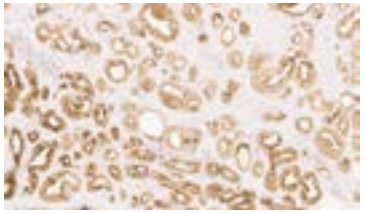
Cancer endocrinology and metabolism

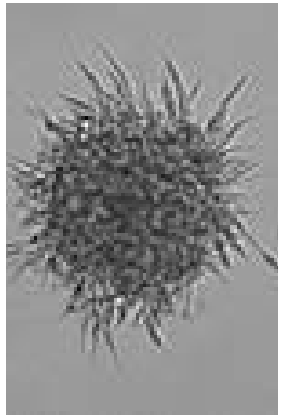
Dr Claire Perks is an Associate Professor in Tumour Cell Biology in Translational Health Sciences in Bristol Medical School. Her team is based in the Learning and Research Building at Southmead Hospital, which facilitates their collaborations with clinical colleagues that specialise in breast, urological and colorectal cancers. With the increasing prevalence of obesity, patients in Western societies are now likely to present with co-morbid conditions such as diabetes. Dr Perks' laboratory pursues collaborative multi-disciplinary research projects to delineate the impact of altered metabolic conditions on cancer, to determine ways in which risk and progression can be ameliorated and treatment optimised. They have a particular interest in insulin-like growth factors that are complex fundamental, nutritionally dependent regulators of growth and metabolism and together with insulin, have been increasingly associated with cancers linked to a Western diet and lifestyle. The team performs mechanistic studies using cell lines to understand the molecular processes underpinning a range of phenotypes important for tumour development including proliferation, survival, migration, and invasion. The team also plays an integral role in clinical studies, through analysis of human samples, including tissue and blood. Their overall aim is to identify better and more effective ways of treating patients and the work may lead to implementing interventions to prevent the cancer from developing. It is also hoped that this work will highlight the negative impact that obesity/type 2 diabetes can have on how cancers develop and respond to treatment. This may empower people to take positive approaches to tackling obesity/type 2 diabetes to benefit from the improved health that could be achieved.

https://www.bristol.ac.uk/translational-health-sciences/research/imeg/

- Fang S *et al*. (2023). Association between genetically proxied PCSK9 inhibition and prostate cancer risk: a Mendelian randomization study. *PLoS Medicine*.
- Mashat RM *et al*. (2022). A role for ER-beta in the effects of Low-Density Lipoprotein Cholesterol and 27-hydroxycholesterol on Breast Cancer Progression: involvement of the IGF signalling pathway? *Cells*.
- Kingshott G *et al*. (2021) Alteration of Metabolic Conditions Impacts the Regulation of IGF-II/H19 Imprinting Status in Prostate Cancer. *Cancers. 13(4):825*.







Top left: *Immunostaining of GRP78 and E-cadherin in colon cancer cells.* **Bottom left:** *Immunohistochemical staining of pmTOR in prostate cancer tissue.* **Middle:** *Prostate cancer cell growing in 3D.* **Right:** *Dr Claire Perks.*

Improving outcomes for women having oncoplastic and reconstructive surgery for breast cancer

Over 55,000 women every year are diagnosed with breast cancer in the UK and despite improvements in treatment, almost 40% of these will require surgery to remove the whole breast (mastectomy). Having a mastectomy can dramatically affect women's well-being and breast reconstruction is routinely offered to address this.

Decision-making for breast reconstruction, however, is complex. This is because several different procedures can be performed, and women need detailed and accurate information about the short and long-term outcomes of different operations so they can make an informed decision about surgery. Such information is currently lacking.

Over the last decade, Shelley Potter, Associate Professor of Oncoplastic Breast Surgery, has been working to establish a much-needed evidence base for reconstructive breast surgery. She leads research into the outcomes of implant-based breast reconstruction and studies to determine whether it is possible to use oncoplastic breast conserving surgery, operations that combine removing the breast cancer with plastic surgical procedures to rebuild or reshape the breast, to avoid the need for mastectomy. Her work is funded by the National Institute of Health and Care Research (NIHR), the Royal College of Surgeons, Association of Breast Surgery and the Bristol and Weston Hospitals Charity.

Miss Potter also currently leads the NIHR-funded Brighter Study which is using routinely collected hospital record data and questionnaires to investigate the long-term clinical and patient-reported outcomes of different approaches to breast reconstruction. This internationally novel work will help women make more informed decisions about breast reconstruction in the future.

https://www.bristol.ac.uk/population-health-sciences/centres/surgical-research/

- Johnson L *et al*. (2023). Impact of procedure type on revision surgery and secondary reconstruction after immediate breast reconstruction in a population-based cohort. *Cancer Research*.
- Sewart E *et al*. (2022). The impact of radiotherapy on patient-reported outcomes of immediate implant-based breast reconstruction with and without mesh. *Annals of Surgery.*
- Potter S *et al*. (2020). Therapeutic mammaplasty is a safe and effective alternative to mastectomy with or without immediate breast reconstruction. *British Journal of Surgery*.

Left: *Performing reconstructive breast surgery needs to be an informed decision.* **Right:** *Miss Shelley Potter.* **p16:** *The Clifton Suspension Bridge, one of Bristol's most recognisable structures, designed by Isambard Kingdom Brunel in 1835.*

Understanding cancer metastases to develop new treatments

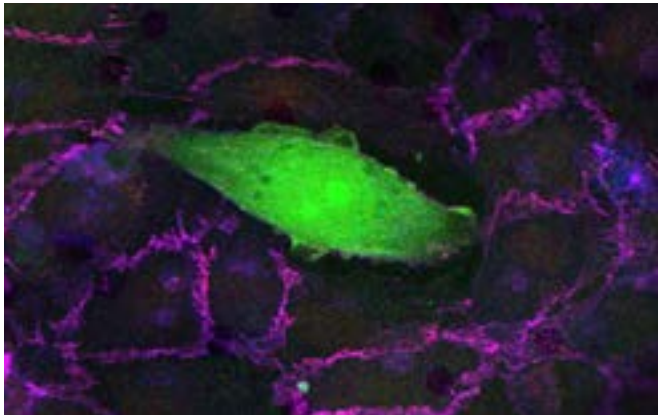
If a cancer was detected before it had spread, it could be treated more effectively, and the patient would have a much higher chance of being cured. However, if a cancer has spread from organ of origin to other parts of the body, for example bone, brain or lung, then it becomes more difficult to treat and patients are rarely cured.

Anne Ridley FRS, Professor of Cell Biology, studies how prostate and breast cancer cells spread and form secondary tumours, known as metastases. In order to spread, cancer cells first detach from the tumour, then enter blood vessels and circulate in the blood stream. If they then attach to and migrate through the blood vessel wall in a different tissue, they may grow there to form a metastasis. Professor Ridley has shown that prostate and breast cancer cells need to change their shape to move through tissues, and to attach to blood vessels. She has also identified several molecules on the surface and inside of cancer cells that are needed for the cells to attach to blood vessel walls.

For some of these molecules, therapeutic chemicals known to reduce their activity already exist. Professor Ridley's group is currently testing some of these chemicals to see if they could be used to treat patients with prostate or breast cancer in future. This type of treatment is particularly important for patients with aggressive cancers that are likely to metastasise early and, if successful, could lead to treatments that prevent or reduce cancer metastases and thus increased cure rates for prostate, breast, and other cancers.

https://www.bristol.ac.uk/people/person/Anne-Ridley-68d1bf7e-4a1b-4bcb-abd8-316e35f5f768/

- Clayton NS and Ridley AJ (2020). Targeting Rho GTPase signalling networks in cancer. *Frontiers in Cell and Developmental Biology*.
- Kazmi N *et al*. (2022). Rho GTPase gene expression and breast cancer risk: a Mendelian randomization analysis. *Scientific Reports*.



Left: *Prof Anne Ridley.* **Right:** *Picture of prostate cancer cell (green) attached to endothelial cells (in purple; these cells line blood vessels).*

Turning cancer's quirks into its vulnerabilities

Cancer cells are biologically different from normal cells. Despite these differences, many current anti-cancer therapies are unselective, meaning they kill both cancer and normal cells equally. This lack of selectivity is the major source of treatment side effects in patients.

Dr Siang Koh's laboratory aims to address this by developing cancer-specific treatment strategies. They study cellular abnormalities found in cancer and use this knowledge to identify drugs that target them, in the hopes of discovering better and kinder treatment options that improve quality of life. The group focuses on three themes:

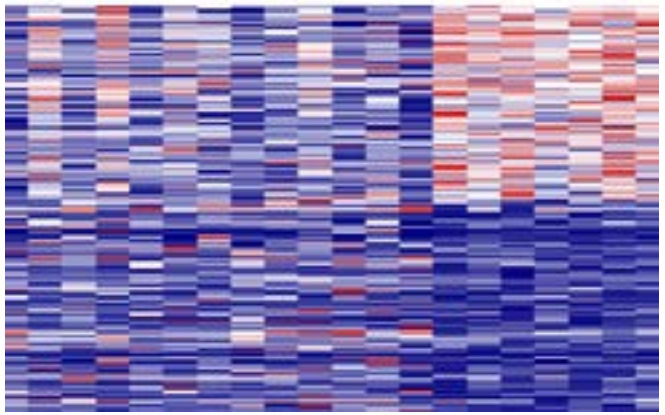
Understanding cancer initiation. Abnormalities such as BRCA1/2 gene mutations in cells and environmental toxins (like alcohol) have been known to increase cancer risk. The team studies how these mutations and toxins work together to turn normal cells into cancer cells. Insights will enable early cancer detection, allowing better disease management and preventative measures in high-risk patients.

Designing potent drug regimens. Small differences in chemotherapy doses will lead to severe toxicities. A potential solution is to use targeted drugs that attack cancer-specific abnormalities. They have identified how a class of drugs called ATR/CHK1 inhibitors amplify cellular stress in pancreatic cancer but not in normal tissues, leading to an ongoing drug combination trial for patients with advanced tumours.

Beating drug resistance. Cancer relapse occurs when a previously effective drug no longer works, and the group is searching to identify ways to prevent this. They have found how abnormalities in a RAS-related protein cause resistance to one class of drugs but sensitivity to another class of drugs. Findings will help clinicians select the right drug for the right patient at the right time.

https://www.bristol.ac.uk/people/person/Siang%20Boon-Koh-8f78afe5-7c0d-4b86-93cc-d4908d201c71/

- Koh SB (2022). The expanding role of WEE1. *Cellular Signalling*.
- Koh SB and Ellisen LW (2021). Immune activation and evolution through chemotherapy plus checkpoint blockade in triple-negative breast cancer. *Cancer Cell*.
- Koh SB *et al*. (2021). RASAL2 confers collateral MEK/EGFR dependency in chemoresistant triple-negative breast cancer. *Clinical Cancer Research.*



Right: *Dr Siang Koh.* **Left:** *Profiling the expression of each gene (row) in each patient tumour (column) will help decode cancer behaviours, paving the way to personalised medicine. Red = high expression, blue = low expression.*

Exploring the role of metabolism in cancer development

Senior Lecturer in Molecular Metabolism Dr Emma Vincent's research group is focused on the link between metabolism and cancer. They are interested in both whole body metabolism and metabolism within cells, and investigate how dysregulated metabolism influences cancer development and whether they can be targeted to prevent or treat the disease.

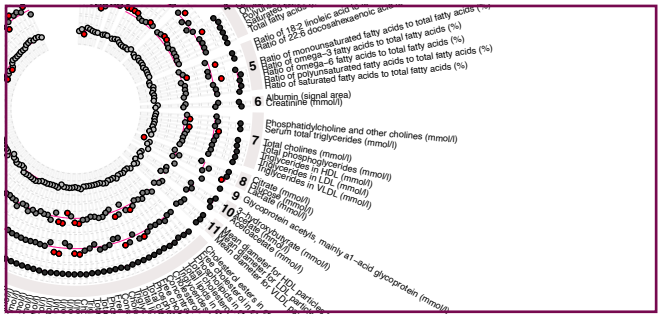
One area of interest looks at why people with metabolic diseases, like obesity and type 2 diabetes, are at an increased risk of cancer. Given the dramatically increasing prevalence of metabolic disease, the associated elevated cancer risk needs to be investigated. They mainly focus on colorectal cancer (also known as large bowel cancer) as it has been shown to be caused by obesity. They study how having a metabolic disease causes changes to the body's cells and how this might drive colorectal cancer development. The group are particularly interested in colorectal cancer prevention and whether losing weight or adhering to a particular diet might reduce colorectal cancer risk.

The group take an interdisciplinary approach to research, using techniques in epidemiology to guide and inform laboratory-based cell biology. For example, they analyse samples and data from randomised control trials of dietary intervention studies (e.g., a very low-calorie diet) to determine how losing weight changes the body's cells and tissues. They use techniques in genetic epidemiology and laboratory work to determine whether these changes might protect against colorectal cancer.

Another topic of interest is investigating and understanding how metabolism is altered in colorectal cancer cells as they develop. Cancer cells must metabolise nutrients in order to support their growth and proliferation. The group are looking to understand how they do this and how this process might be targeted for cancer prevention and treatment.

https://www.bristol.ac.uk/people/person/Emma-Vincent-712bb62c-1bde-43e5-ac46-2f3493af1997/

- Riscal R *et al*. (2021). Cholesterol Auxotrophy as a Targetable Vulnerability in Clear Cell Renal Cell Carcinoma. *Cancer Discovery.*
- Jones N *et al*. (2021). Fructose reprogrammes glutamine-dependent oxidative metabolism to support LPS-induced inflammation. *Nature Communications*.
- Bull CJ *et al*. (2020). Adiposity, metabolites, and colorectal cancer risk: Mendelian randomization study. *BMC Medicine*.



Right: *Dr Emma Vincent.* **Left:** *Visualisation of metabolomics data in a population.* **p20** *Bristol is renowned for its annual hot air balloon festival; the University of Bristol's own hot air balloon regularly takes part.*

Immunotherapy and cancer

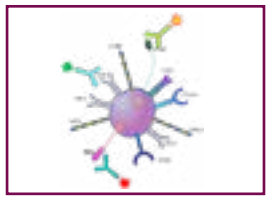
Encouraging the immune system to increase the body's anti-tumour activity, a process called immunotherapy, has transformed the management and outcomes for patients with advanced melanoma. The development of compounds that prevent tumours from growing, called checkpoint inhibitors, has achieved unprecedented results and changed the landscape for patients with many solid tumours. Accelerated approval and access to immunotherapy has led to areas of active research in improved patient selection and the identification of additional pathways for targeting. A collaboration between Consultant Medical Oncologist Dr Helen Winter and Chair in Translational Immunology Professor Linda Wooldridge in Bristol Veterinary School is exploring the role of a specific type of white blood cell, known as a T cell, in cancer and the impact of checkpoint inhibition.

The research is looking for genes and proteins (biomarkers) that can provide more information about the cancer. Identifying these allows us to predict how effective our checkpoint inhibitors are in the treatment of metastatic melanoma patients which, in turn, helps us understand the mechanisms that resist checkpoint blockades and determine alternative approaches that would make the therapy more effective. This research collaboration explores why some patients fail to respond to immunotherapy and identifies predictive biomarker and additional pathways that may be targeted to improve response and overcome resistance.

As the Bristol lead on the Microbiome Immunotherapy Toxicity and Response Evaluation (MITRE) study, Dr Winter and colleagues are also investigating the role of the microbiome with immunotherapy treatment. This is specifically looking at the gut microbiome 'signature' to see if it can predict for immune checkpoint inhibitor treatment efficacy in patients with advanced cancers.

https://www.swagcanceralliance.nhs.uk/

- Wilson TG *et al*. (2021). Treating brain metastases in melanoma: What is the optimal CNS-directed and systemic management? *Journal of Radiosurgery and SBRT*.
- Wilson T *et al*. (2021). Sequential immunotherapy in melanoma: is it a realistic alternative to dual immunotherapy? *Melanoma Research*.
- Corrie P *et al*. (2021). Identification of a microbiome signature predicting immune checkpoint inhibitor outcomes across multiple cancer types. *Journal of Clinical Oncology*.



Top left: *Dr Helen Winter.* **Bottom Left:** *Cellular analysis of receptors expressed on surface of blood derived lymphocytes using flow cytometry. Samples from patients with stage IV metastatic melanoma receiving PD-1 checkpoint blockade immunotherapy.* **Right***: Dr Helen Winter at the Lung Cancer Expert Forum 2023.* **p23:** *The mirror maze in Royal Fort Gardens, University of Bristol.*

Contact information

If you would like to find out more, or would like to help support research into the causes, prevention and treatment of cancer, please contact:

Bristol Cancer Research Network
bristol.ac.uk/cancer

University Cancer Research Fund
bristol.ac.uk/cancer/ucrf

Bristol and Weston Hospitals Charity
bwhospitalscharity.org.uk

Southmead Hospital Charity
southmeadhospitalcharity.org.uk

University of BRISTOL

Elizabeth Blackwell Institute
for Health Research

BRISTOL & WESTON HOSPITALS CHARITY

Southmead Hospital Charity

NHS University Hospitals Bristol and Weston NHS Foundation Trust

NHS North Bristol NHS Trust