Bristol Cancer

a multidisciplinary research community dedicated to finding new breakthroughs against cancer
Cancer research and its treatment is a growing area of strength in Bristol and represents one of the key areas of focus for the faculties of Health and Life sciences. We are proud of our excellent researchers who as internationally acknowledged experts benefit from the collegial atmosphere and huge interdisciplinary opportunities that our University offers. Cancer research is growing in Bristol. Watch this space

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Introduction

Bristol cancer researchers are a vibrant cross-disciplinary community; they combine expertise from scientists at the University of Bristol and clinical researchers at University Hospitals Bristol NHS Foundation Trust and North Bristol NHS Trust. 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 Research (NIHR) Biomedical Research Centre (BRC) conducting innovative translational medical science research to drive through improvements in health and healthcare; the Surgical Trials Unit evaluating novel surgical approaches and surgical trials in cancer; and the NIHR Collaboration for Leadership in Applied Health Research and Care West (CLAHRC West) applying health research and implementing research evidence, to improve health and healthcare across the West of England.

There have been many advances in our understanding of cancer biology, with a concurrent expansion of drugs that might target abnormalities in cancer cells. Our Oncology Clinical Trials Unit recruits cancer patients to over 100 trials across different tumour types, aiming to double this number over the next 5 -10 years to enable access for our patients to the most promising drugs.

With the help of University Hospitals Bristol’s charity Above & Beyond 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 the strength in population health sciences, clinical trials, cancer cell biology, surgical and health-technology innovation, and health services research. In addition to recruiting and developing top cancer researchers, we have ambitions to become a Cancer Research UK (CRUK) Cancer Centre; develop an NIHR Clinical Research Facility (CRF) to expand clinical trials research; renew the CLAHRC; and to become an NIHR Academic Health Science Centre (AHSC), a partnership between universities and healthcare providers focusing on research, clinical services, education and training.

A significant strength of Bristol is the coherent cancer community, with a leadership group made up of senior researchers from a number of fields who interact to cross-fertilise research ideas and develop novel insights. We are using strategies that combine unbiased big data approaches to generate new leads for hypothesis-driven laboratory science and bringing the insight from the laboratory back to the big data sets for cross-validation. By including the non-traditional cancer fields of engineering, physics and mathematics, we hope to achieve breakthroughs that might not come within a single field of research.

These are exciting times for cancer research, with both the University and the 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 below.

Dr Axel Walther, MA PhD FRCP
Consultant Medical Oncologist; Director for Research, Bristol Cancer Research; Co-Lead Bristol Cancer Network

Prof Paul Martin, PhD FMedSci
Professor of Cell Biology, University of Bristol
Co-Lead Bristol Cancer Network
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 5-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 biomarkers for cancer risk prediction. They particularly focus on the common cancers: bowel, prostate, breast, and lung, as well as kidney, ovarian, 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 the University of Manchester. 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.

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

The CAP and ProtecT trials

The CAP (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.

The Office for National Statistics (ONS) Research Excellence Award recognises excellence by a team or individual in undertaking innovative high-quality research that provides an evidence base for sound decisions supporting the formulation of effective government policies, the management of public service delivery, and the direction of economic and commercial activities. The focus is on outstanding and ground-breaking use, analysis and presentation of data, rather than just doing the job well. The panel, on behalf of the ONS, highlighted the impact CAP has already had; the diverse dissemination of these results; collaborative working practices; and the innovative methodology developed.
Bowel cancer (also known as colorectal cancer) remains the second highest cause of cancer mortality in the UK. Research in Bristol focuses on understanding molecular pathways that are important for driving colorectal cancer progression with the aim of reducing the incidence of, and improving the outcome for, patients diagnosed with bowel cancer. Research from the team in Bristol has focused on cancer prevention for a number of years, contributing to institutions such as the NHS, the National Institute for Health Research (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 Ann Williams, Professor of Experimental Oncology, continues to participate in international clinical prevention trials assessing the use of aspirin in people at increased risk of developing bowel cancer (CAPP3). The CTB group are investigating signalling pathways (normally involved in inflammation) that are permanently switched on in a subset of cancer cells, driving stem cell plasticity and tumour cell survival. In addition, they are looking to see whether (if used in conjunction with conventional therapy) non-steroidal anti-inflammatory drugs such as aspirin can improve the response of these resistant tumours to treatment. 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 NHS Foundation Trust. This research aims to understand the mechanisms that drive early tumorigenesis and how they impact on the response of colorectal cancers to conventional therapies.

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


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: Professor Ann Williams. Right: members of the Colorectal Tumour Biology group.
The immune system and cancer

Cells of the immune system can both kill and nurture newly born cancer cells, but how do they find and interact with pre-cancer cells in the first place? And how do they help to make cancers spread?

Paul Martin, Professor of Cell Biology, works with various early cancer models in translucent zebrafish larvae. By direct visualisation of the interaction of the larval immune system with (pre-)cancer cells, his group have identified some of the first signals that attract immune or inflammatory cells to early cancer cells. The immune cells can engulf and kill pre-cancer cells; however, if the pre-cancer cells do not interact with immune cells, they grow at a much slower rate, suggesting that the immune cells can deliver growth signals as well. In zebrafish larvae this growth promotion also happens after simulated surgery, with inflammatory cells tasked with wound healing actually supporting cancer cell growth; which, if true for humans, would have implications for the surgical excision of cancers.

This observation supports recent studies that have shown how low-dose aspirin, an anti-inflammatory drug which might block some of the cancer growth signals, can stave off the onset of bowel and other cancers. In collaboration with Dr Tom Creed at University Hospitals Bristol NHS Trust, he has also found evidence that could point to local inflammation being one of the drivers for the formation of polyps – the precursors of most bowel cancers. His team continues to investigate the cell biology of wound healing and its associated inflammatory response using fruit fly, zebrafish and mouse models, to gain further insights into immune:cancer interaction at the site of biopsies and surgery in cancer treatment. www.bris.ac.uk/biochemistry/people/paul-b-martin/index.html


Zebrafish are invaluable in our cancer research because they are translucent, which means that it is possible to watch – live, in real-time – the interactions between cancer cells and immune cells.
Newer, better drugs to treat childhood leukaemia

Every day in the UK, ten children are diagnosed with cancer. For over a third of them the diagnosis is leukaemia. Around 20 per cent of those children are not cured and the disease returns because treatment options available today cannot completely remove the cancerous leukaemia cells in these patients.

Research undertaken by Allison Blair, Reader in Experimental Haematology, has identified leukaemia stem cells which appear to play an important role in the persistence of the disease. Her work has shown that some leukaemia stem cells are resistant to current therapies, and since these leukaemia stem cells survive treatment, and their numbers continue to grow during and after therapy, they eventually lead to clinically observable, and frequently incurable relapse.

The treatment at relapse involves even higher doses of chemotherapy, usually requiring a healthy stem cell transplant harvested from the patient when in remission. Dr Blair’s group is looking at ways in which the healthy stem cells could be expanded, thus increasing the chances of successful treatment. The same techniques could be used for treatments of non-cancerous conditions, such as sickle cell disease.

It is now also becoming possible to test new drugs designed to specifically target leukaemia cells with relative sparing of the healthy blood cells, thus avoiding one of the main side-effects of treatment: aiming to kill all – and only – leukaemia cells. Dr Blair’s group were the first to report complete elimination of leukaemia cells in vivo using the drug parthenolide. Work is ongoing to improve delivery methods of this drug, enabling its use in children.

www.bristol.ac.uk/cellmolmed/research/stem-cells/haemopoietic/

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, Reader in Brain Tumour Research, 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.

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


Left: Kathreena Kurian. Right: 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 anti-cancer 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 anti-cancer 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://research-information.bristol.ac.uk/en/person/eugenia.piddini


Right: Professor Eugenia Piddini. Left: Drosophila intestine containing early stage tumours (in green) imaged by confocal microscopy, a method which helps increase optical resolution.
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, biologists and engineers to design the nanoparticles of tomorrow. For example, Sabine Hauert, Lecturer in Engineering Mathematics, 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. Dr Hauert’s team is currently building a tumour-on-a-chip device using 3D printing to test her models using real nanoparticles under the microscope.

http://hauertlab.com


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.
Trials to improve surgical outcomes

It is difficult to trial and test surgical interventions; surgical procedures are complex with many variables, all interacting and contributing to outcomes. It can be difficult for surgeons to recruit patients because of preferences, and deciding which outcomes are relevant to patients, surgeons and the NHS is also challenging.

Jane Blazeby, Professor of Surgery, has been working over the past two decades to address these issues. She leads research to improve methods to evaluate surgery and to test its effectiveness in early and later phase studies. Her work is supported by funding from the National Institute for Health Research (NIHR) Biomedical Research Centre (for which she is the Surgical Innovation Lead), the Medical Research Council Hub for Trials Methodology Research and grants from the Royal College of Surgeons.

Professor Blazeby is currently supporting a randomised controlled surgical trial for oesophageal cancer. Funded by NIHR, the ROMIO (Randomised Oesophagectomy: Minimally Invasive or Open) study compares traditional surgery used for oesophageal cancer versus keyhole surgery to assess the impact that each approach has on survival and surgical complications. Within her team, Miss Shelley Potter is leading research to evaluate surgical breast reconstruction after mastectomy for breast cancer, aiming to develop a randomised controlled trial comparing different procedures to inform clinical practice and decision-making for women.

The team is also developing better ways to provide information for patients undergoing cancer surgery and optimising informed consent for innovative and novel procedures.

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

- McNair, AGK, MacKichan F, Donovan JL et al. (2016). What surgeons tell patients and what patients want to know before major cancer surgery: a qualitative study. BMC Cancer 16:258
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://research-information.bristol.ac.uk/en/persons/anne-j-ridley(68d1bf7e-4a1b-4bcb-abd8-316e35f5f768).html


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

Above & Beyond
aboveandbeyond.org.uk

Southmead Hospital Charity
southmeadhospitalcharity.org.uk

Elizabeth Blackwell Institute for Health Research