Cancer Network Newsletter

2022: Issue 3

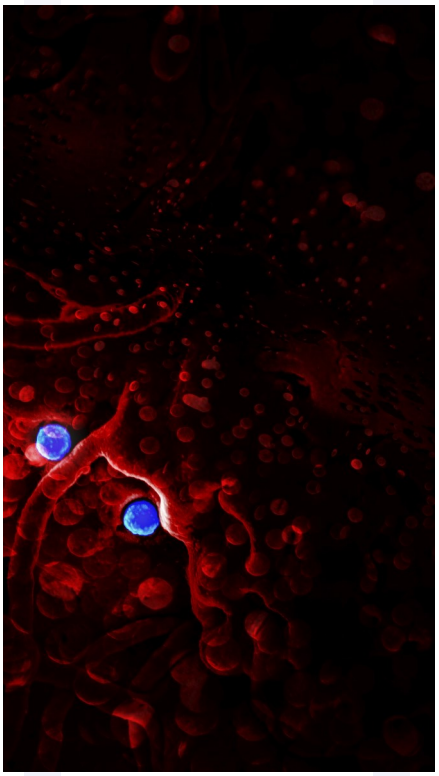
Bristol Cancer Research Network

Genes and pre-leukaemia risk

The discovery of 14 inherited genetic changes which significantly increase the risk of a person developing a symptomless blood disorder associated with the onset of some types of cancer and heart disease.

The finding, made in one of the largest studies of its kind through genetic data analysis on 421,738 people, could pave the way for potential new approaches for the prevention and early detection of cancers including leukaemia.

Led by scientists from the Universities of Bristol and Cambridge, Wellcome Sanger Institute, Health Research Institute of Asturias in Spain, and AstraZeneca, the study reveals that specific inherited genetic changes affect the likelihood of developing 'clonal haematopoiesis', a common condition characterised by the development of expanding clones of multiplying blood cells in the body, driven by mutations in their DNA. Although symptomless, the disorder becomes ubiquitous with age and is a risk factor for developing blood cancer and other age-related diseases. Its onset is a result of genetic changes in our blood-making cells.



All human cells acquire genetic changes in their DNA throughout life (somatic mutations), with a specific subset of somatic mutations driving cells to multiply. This is particularly common in blood stem cells, and results in the growth of populations of cells with identical mutations known as 'clones'.

Using data from the UK Biobank, the team were able to show how these genetic changes relate not only to blood cancers but also to tumours that develop elsewhere in the body such as lung, prostate and ovarian cancer.

Kar SP *et al*. (2022). Genome-wide analyses of 200,453 individuals yield new insights into the causes and consequences of clonal hematopoiesis. *Nature Genetics.*

Image by rawpixel.com

Inside this issue:

@BristolCancer

cancer-research@bristol.ac.uk

bristol.ac.uk/cancer

+44 117 455 6360

University of BRISTOL

Elizabeth Blackwell Institute for Health Research

EVENTS

The experience of the LGBTQ+ community in cancer research
29 September 2022, 12.00 - 13.30, online

Polygenic risk scores and Our Future Health
29 September 2022, 12.00 - 13.00, Professor David Hunter (Chief Science Advisor to Our Future Health), OS6 in Oakfield House and online

UK CLL Forum Clinical Sciences Day
4 October 2022, 9.30 - 16.45, Hybrid Event from the Hallam Conference Centre, 44 Hallam Street, London W1W 6JJ

Bristol Health Partners annual conference
4 October 2022, 12.00 - 16.00, M Shed, Wapping Road, Bristol BS1 4RN

Genomic Equity
5 October 2022, 12.00 - 13.00, Sasha Henriques (Sanger Institute), online

Objective measures of statistical evidence
5 October 2022, 12.00 - 13.00, Frank Dudbridge (Professor of Statistical Genetics, University of Leicester), OS6 Oakfield House and online

Predicting response to neoadjuvant therapy in breast cancer using multi-omics and machine learning
6 October 2022, 13.00 - 14.00, Carlos Caldas (Professor of Cancer Medicine, University of Cambridge), online

2nd North BMT Training Day
7 October 2022, 9.00 - 17.15, ETC Venues, 11 Portland Street, Manchester M1 3HU

Open Presentation from MRC's Chief Science Officer
7 October 2022, 9.30 - 10.40, Dr Rob Buckle (Chief Science Officer), Dr Mariana Delfino-Machín (Programme Manager), Laura Dickens (Associate Director of Industry Partnerships) and Tamsyn Derrick (Programme Manager), central campus

The PhD Viva Workshop
8 October 2022, 9.00 - 16.00, online

Black in Cancer conference: Empowering the next generation
10 - 11 October 2022, Science Museum, Exhibition Road, London SW7 2DD

Mendelian randomisation in many flavours
10 October 2022, 12.00 - 13.00, Zoltán Kutalik (University of Lausanne), OS6 Oakfield House and online

NEWS

Cancer Early Career Researchers' symposium

The University of Bristol's Cancer Research Network, supported by the Elizabeth Blackwell Institute, hosted its first symposium dedicated to early career researchers (ECRs) on 24 June 2022. Jointly hosted with the National Institute for Health and Care Research (NIHR) Clinical Research Network (CRN) West of England, the event showcased the extraordinary and diverse research being conducted by postgraduate students, postdoctoral researchers, clinical fellows and trainees. Over 75 people registered to take part in a programme that offered a series of oral and poster presentations from ECRs based on abstract submissions, and comprised 8 oral and 13 poster presentations delivered by our up and coming research stars.

We are delighted to have awarded a number of **oral prizes**: 1st Adam Chambers: *Novel NF-κB signalling clusters predict DFS and OS following neoadjuvant therapy in rectal cancer;* 2nd Hanin Alamir: *T-cell immunoglobulin and mucin domain 3 suppresses cytotoxic T lymphocyte anti-tumour function in a three-dimensional tumour spheroid model;* 3rd Dowan Kwon: *Procalcitonin- a new approach to tailoring antibiotic treatment in cancer patients*; and **poster prizes**: 1st Karen Neish *Cytotoxic T lymphocytes and their role in tumour immunity*; 2nd Ashley Hoskin & Kat Belfield,: *Is 5-aminosalicylic acid (5-ASA) the new aspirin?*; 3rd Bryony Hayes: *Orienting causal relationships between sleep and adiposity traits using Mendelian randomisation*. **Read more**

Society awards

Ann Williams FRSB (School of Cellular and Molecular Medicine), Professor of Experimental Oncology, has been elected as a Fellow of the Royal Society of Biology (RSB). Fellows have achieved distinction in the fields of biological research, teaching or the application of biology, and is the most prestigious grade of RSB membership.

The Society of Spanish Researchers in the United Kingdom (SRUK/CERU) announced that Carmen Galán, Professor Organic and Biological Chemistry (School of Chemistry) is the winner of their Merit Award 2022 for her prolific and outstanding scientific career both in Spain and in the UK. This award aims to recognise the career of an internationally renowned senior Spanish researcher based in the UK who has been instrumental to the advance of science, research, and innovation. Carmen is one of the co-investigators on a Cancer Research UK project looking to develop a blood test that could identify brain tumours earlier in the diagnostic pathway.

University Cancer Research Fund successes

The University Cancer Research Fund (UCRF) runs an annual scheme which supports innovative ideas in cancer research. It selects projects and ideas in their early stages that have the promise to develop into high impact research. Up to ten awards of £5,000 are made every year to University of Bristol staff to promote exciting and potentially important discoveries in cancer. The 2022 round saw the following people and projects awarded funds:

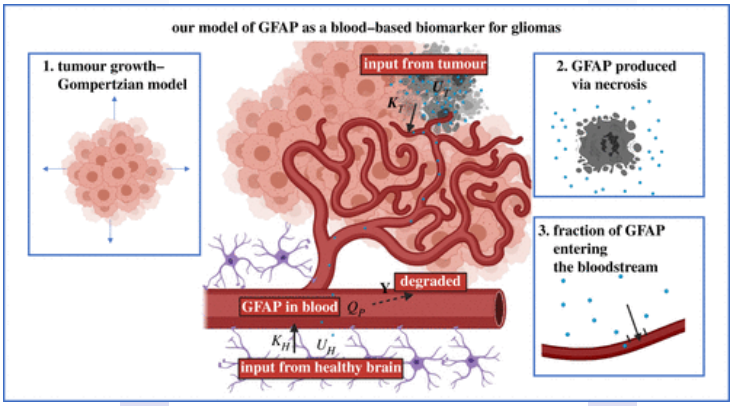
- James Armstrong (Bristol Medical School): *Patient-Derived Organoids for Ovarian Cancer Drug Screening*, £5,000
- Rachel Barker (Bristol Medical School): *Is amyloid-β a friend, foe, or both for breast cancers?*, £4,061.75
- Adam Chambers (Cellular and Molecular Medicine): *Defining BCL-3/NF-kB signalling in colorectal cancers following radiation*, £4,814.22
- Siang Koh (Cellular and Molecular Medicine): *Role of PALB2 and aldehydes in breast cancer predisposition*, £5,000
- Danny Legge (Bristol Medical School): *Investigating the metabolic perturbations in type 2 diabetes that support colorectal cancer development*, £4,970
- Bethan Lloyd-Lewis (Cellular and Molecular Medicine): *Investigating the impact of tissue mechanics on breast epithelial cell fate and cancer risk*, £4,970
- Emily Milodowski (Bristol Veterinary School): *Investigating the role of regulatory T cells in tumour escape from checkpoint blockade*, £4,906

Mathematical modelling to test for brain tumours

The development of a simple blood test for glioblastomas (GBMs) could mean earlier diagnosis and more effective and personalised treatment options.

Bristol-led research involved the development of mathematical models to assess the current use of biomarkers in the detection of GBMs and how such biomarker-based strategies can be improved.

This research is part of a wider University of Bristol-led CRUK project to develop an affordable, point of care blood test to diagnose brain tumours. This cross-disciplinary project combines biomarker discovery, development of fluorescent nanoparticle and new testing techniques with computational modelling.



The findings provide the basis for further clinical data on the impact of lowering the current detection threshold for the known biomarker, GFAP, to allow earlier detection of GBMs using blood tests. With further experimental data, it may also be possible to quantify tumour and patient heterogeneities and incorporate errors into our models and predictions for blood levels for different tumours.

Blee, J *et al*. (2022). Liquid biopsies for early diagnosis of brain tumours: in-silico mathematical biomarker modelling. *The Royal Society Interface*.

Engagement activities

Three Minute Thesis (3MT) challenges doctoral students to present a compelling spoken presentation on their research topic and its significance in a mere 180 seconds and with one static slide. It was a competition developed by the University of Queensland, whose success has led to the establishment of local and national competitions in several countries, including the UK. This year's Bristol event took place in June, when eleven semi-finalists took to the stage. Congratulations are extended to Emma Hazelwood (Bristol Medical School) who came runner up. Emma presented on her thesis entitled, *How do genetic changes cause cancer?* in front of a live in-person audience and judging panel. The winner, Sophie Johnson in the Department of History of Art, will represent Bristol at the national semi-finals over the summer. Further details about the 3MT competition, including videos of the event, can be found here.

The local **Cancer Research UK** Thornbury fundraising committee has raised an amazing 1 million pounds for cancer research since their inception in 1977. Colin Campbell (Intelligent Systems Laboratory, Faculty of Engineering) attended their celebratory afternoon tea on 13 June 2022 at the Ship Inn in Thornbury. After thanking them for all their efforts, he gave a short talk on using bioinformatics to predict single nucleotide variants driving unregulated cell proliferation (the FATHMM-MKL method used at the COSMIC cancer database in Cambridge) and bioinformatics insights in prostate cancer research.

Physical activity to reduce breast cancer risk

Observational studies show that physical inactivity and sedentary behaviour are linked to higher breast cancer risk, but proving they cause breast cancer is another matter.

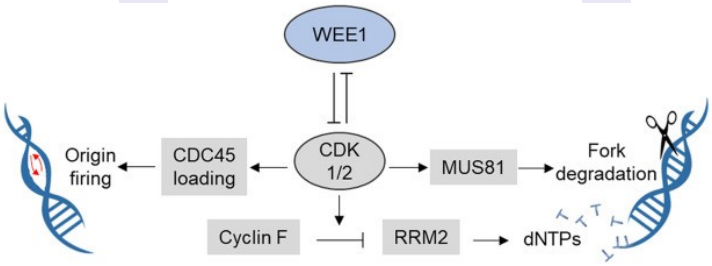
Mendelian randomisation analysis of data from over 130,000 women showed that a higher overall level of genetically predicted physical activity was associated with a 41% lower risk of invasive breast cancer, and this was largely irrespective of menopausal status, tumour type, stage, or grade. Similarly, genetically predicted vigorous physical activity on three or more days of the week was associated with a 38% lower risk of breast cancer, compared with no self-reported vigorous activity. These findings were consistent across most of the case groups.

Finally, a greater level of genetically predicted sitting time was associated with a 104% higher risk of triple negative breast cancer. These findings were consistent across hormone-negative tumour types. The findings were unchanged after factoring in the production by a single gene of two or more apparently unrelated effects (pleiotropy), such as smoking and being overweight, for example. The findings provide "strong evidence" that more overall physical activity and less sitting time are likely to reduce breast cancer risk

Lynch BM et al. (2022). Physical activity, sedentary time and breast cancer risk: a Mendelian randomisation study. *British Journal of Sports Medicine.*

The expanding role of WEE1

Upon DNA damage, complex transduction cascades are unleashed to locate, recognise and repair affected lesions. The process triggers a pause in the cell cycle until the damage is resolved. Even under physiologic conditions, this deliberate interruption of cell division is essential to ensure orderly DNA replication and chromosomal segregation. WEE1 is an established regulatory protein in this vast fidelity-monitoring machinery. Its involvement in the DNA damage response and cell cycle has been a subject of study for decades. Emerging studies have also implicated WEE1 directly and indirectly in other cellular functions, including chromatin remodelling and immune response. The expanding role of WEE1 in pathophysiology is matched by the keen surge of interest in developing WEE1-targeted therapeutic agents. This review summarises WEE1 involvement in the cell cycle checkpoints, epigenetic modification and immune signalling, as well as the current state of WEE1 inhibitors in cancer therapeutics.



Koh S-B (2022). The expanding role of WEE1. *Cellular Signalling*.

Adhering to new behaviours following prostate surgery

Interventions designed to improve men's diet and physical activity (PA) have been recommended as methods of cancer prevention. However, little is known about specific factors that support men's adherence to these health behaviour changes, which could inform theory-led diet and PA interventions. We aimed to explore these factors in men following prostatectomy for prostate cancer (PCa).

A qualitative study used semi-structured interviews with men, who made changes to their diet and/or PA as part of a factorial randomised controlled trial conducted at a single hospital in South West England. Results showed that men were ambivalent about the relationship of nutrition and PA with PCa risk. They believed their diet and level of PA were reasonable before being randomised to their interventions. Men identified several barriers and facilitators to performing these new behaviours. Barriers included tolerance to dietary changes, PA limitations and external obstacles. Facilitators included partner involvement in diet, habit formation and brisk walking as an individual activity. Men discussed positive effects associated with brisk walking, such as feeling healthier, but not with nutrition interventions.

The facilitators to behaviour change suggest that adherence to trial interventions can be supported using well-established behaviour change models. Future studies may benefit from theory-based interventions to support adherence to diet and PA behaviour changes in men diagnosed with PCa.

Robles LA *et al*. (2022). Attitudes and adherence to changes in nutrition and physical activity following surgery for prostate cancer: a qualitative study. *BMJ Open*.

Awards successes

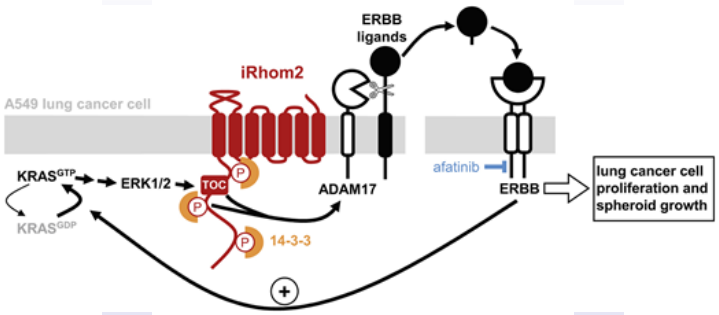
Dr Anna Chambers (School of Biochemistry) received £3,800 from **Wellcome** for *Roles of the Irc5/HELLS subfamily of chromatin remodelling enzymes in maintenance of genome stability*; the project will start in January 2023 and complete within three months.

Dr Paul Yousefi (Bristol Medical School: Population Health Sciences) was awarded £30,000 from **Wellcome** for *Predicting pleural malignancy using DNA methylation biomarkers*, which started in July 2022 and is expected to complete in one year.

KRAS-driven tumour growth of lung cancer cells

Dysregulation of the ERBB/Epidermal growth factor receptor (EGFR) signalling pathway causes multiple types of cancer. Accordingly, ADAM17, the primary shedding enzyme that releases and activates ERBB ligands, is tightly regulated. It has recently become clear that iRhoms, inactive members of the rhomboid-like superfamily, are regulatory cofactors for ADAM17.

The authors show that oncogenic KRAS mutants target the cytoplasmic domain of iRhom2 to induce ADAM17-dependent shedding and the release of ERBB ligands. Activation of ERK1/2 by oncogenic KRAS induces the phosphorylation of iRhom2, recruitment of the phospho-binding 14-3-3 proteins, and consequent ADAM17-dependent shedding of ERBB ligands.

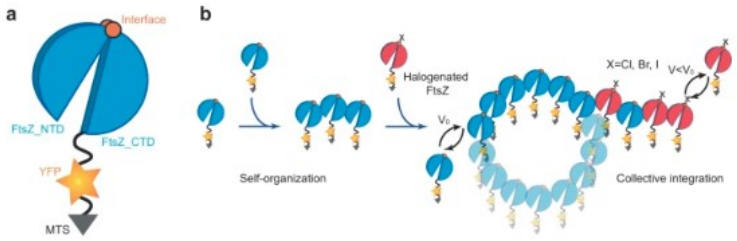


In addition, cancer-associated mutations in iRhom2 act as sensitisers in this pathway by further increasing KRAS-induced shedding of ERBB ligands. This mechanism is conserved in lung cancer cells, where iRhom activity is required for tumour xenograft growth. In this context, the activity of oncogenic KRAS is modulated by the iRhom2-dependent release of ERBB ligands, thus placing the cytoplasmic domain of iRhom2 as a central component of a positive feedback loop in lung cancer cells.

Sieber B *et al*. (2022). iRhom2 regulates ERBB signalling to promote KRAS-driven tumour growth of lung cancer cells. *Journal of Cell Science*.

Protein damage contributes to ageing and disease

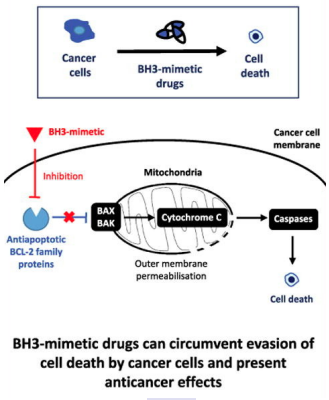
Protein halogenation is a common non-enzymatic post-translational modification contributing to aging, oxidative stress-related diseases and cancer. Here, we report a genetically encodable halogenation of tyrosine residues in a reconstituted prokaryotic filamentous cell-division protein (FtsZ) as a platform to elucidate the implications of halogenation that can be extrapolated to living systems of much higher complexity. We show how single halogenations can fine-tune protein structures and dynamics of FtsZ with subtle perturbations collectively amplified by the process of FtsZ self-organization. Based on experiments and theories, we have gained valuable insights into the mechanism of halogen influence. The bending of FtsZ structures occurs by affecting surface charges and internal domain distances and is reflected in the decline of GTPase activities by reducing GTP binding energy during polymerization. Our results point to a better understanding of the physiological and pathological effects of protein halogenation and may contribute to the development of potential diagnostic tools.



Sun H, Jia H *et al*. (2022). Halogenation of tyrosine perturbs large-scale protein self-organization. *Nature Communications*.

An overview of anticancer effects of mimetic drugs

This review sought to summarise available literature concerning the anticancer effects of both putative and validated BH3-mimetics in head and neck squamous cell carcinomas. A total of 40 studies were included, including one phase-II clinical trial assessing gossypol (combined with docetaxel) and 39 preclinical studies investigating cell lines and/or xenograft models involving the use of six validated BH3-mimetics (A-1210477, A-1331852, ABT-737, navitoclax, S63845, venetoclax) and six putative BH3-mimetics (ApoG2, gossypol, obatoclax, sabutoclax, TW-37, and YC137). In preclinical settings, most validated BH3-mimetics were capable of inducing apoptosis (*in-vitro*) and tumour growth inhibition (*in-vivo*). The majority of putative BH3-mimetics were also capable of inducing cell death, although important off-target effects, such as autophagy induction, were also described. Combinations with conventional anticancer drugs, ionising radiation, or multiple BH3-mimetics generally resulted in enhanced anticancer effects, such as increased sensitivity to apoptotic stimuli, especially considering some cell lines that showed resistance to either treatment alone. In conclusion, although clinical data are still insufficient to evaluate the anticancer effects, promising results in preclinical settings were observed concerning induction of cell death and inhibition of tumour growth.



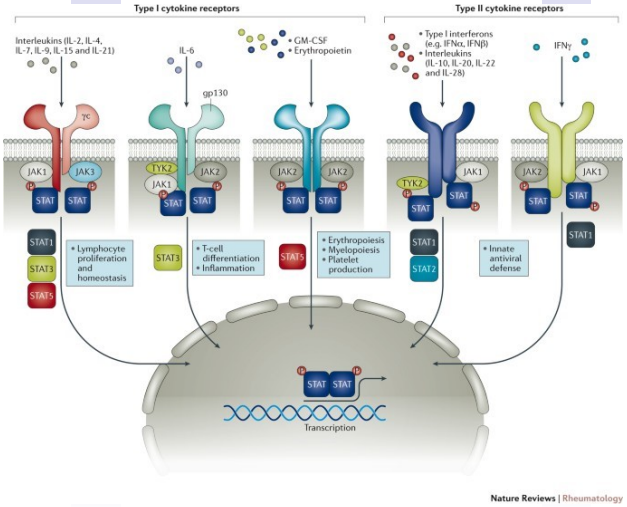
BH3-mimetic drugs can circumvent evasion of cell death by cancer cells and present anticancer effects

Melo *et al*. (2022). Anticancer effects of putative and validated BH3-mimetic drugs in head and neck squamous cell carcinomas: An overview of current knowledge. *Oral Oncology*.

TYK2 inhibition increases risk of lymphoma and lung cancer

Increased rates of lymphoma and lung cancer associated with Janus kinase (JAK) inhibitors used in the treatment of chronic inflammatory conditions have raised significant concern. A promising alternative, particularly for the treatment of plaque psoriasis, is deucravacitinib, a selective inhibitor of JAK family member TYK2.

In this paper, the authors explored possible carcinogenic effects of TYK2 inhibition by genetic proxy based on a partial loss-of-function variant in TYK2 that provides protection against psoriasis. Analyses show that genetically proxied TYK2 inhibition increases lung cancer and non-Hodgkin lymphoma risk. The findings could impact safety assessments of deucravacitinib and future novel TYK2 inhibitors.

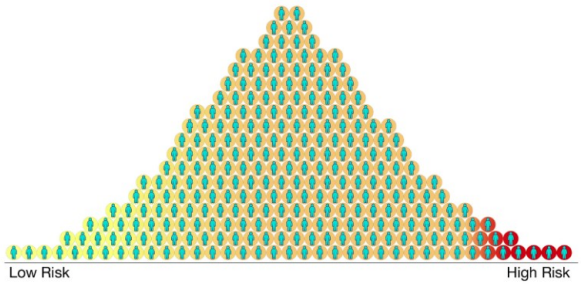


Yarmolinksy J *et al*. (2022). Association of germline TYK2 variation with lung cancer and non-Hodgkin lymphoma risk. *International Journal of Cancer*.

Polygenic scores and cancer screening

Polygenic risk influences susceptibility to cancer. Here, the authors assessed whether polygenic risk scores could be used in conjunction with other predictors of future disease status in cost-effective, risk-stratified screening for cancer.

They undertook a systematic review of papers that evaluated the cost-effectiveness of screening interventions informed by polygenic risk scores compared with more conventional screening modalities. They included papers reporting cost-effectiveness outcomes with no restriction on type of cancer or form of polygenic risk modelled. A total of 10 studies were included in the review, which investigated 3 cancers: prostate (n = 5), colorectal (n = 3), and breast (n = 2). Of the 10 papers, 9 scored highly when assessed using the quality checklist. Of the 10 studies, 8 concluded that polygenic risk-informed cancer screening was likely to be more cost-effective than alternatives.



Despite the positive conclusions of the included studies, it is unclear if polygenic risk stratification will contribute to cost-effective cancer screening given the absence of robust evidence on the costs of polygenic risk stratification, the effects of differential ancestry, potential downstream economic sequalae, and how large volumes of polygenic risk data would be collected and used.

Dixon P *et al*. (2022). Can polygenic risk scores contribute to cost-effective cancer screening? A systematic review. *Genetics in Medicine*.

Bristol Innovations

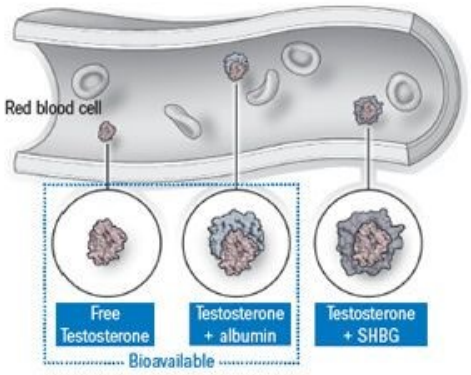
The University of Bristol has launched Bristol Innovations, a new initiative that will combine its far-reaching research expertise with the industry know-how of global partners, leading to progressive sector-wide and multidisciplinary discoveries.

Bristol Innovations is a virtual network designed to increase opportunities for University academics, researchers and entrepreneurial students to collaborate with third party stakeholders to translate research for real-world purposes. It launches at a time when the UK government has pledged to turn the UK into a global innovation hub.

Supported by the Bristol Grid – a University of Bristol digital hub for entrepreneurial activities – the network will enhance the University's efforts to apply its knowledge and expertise for the benefit of millions of people across the world. This includes working with industry partners to identify and respond to social and economic needs; exploring new spin-out and start-up opportunities; investing in more resources for business development; offering more consultancy and licencing opportunities; and working with third parties through knowledge exchange, public engagement and research commercialisation.

Free testosterone and prostate cancer

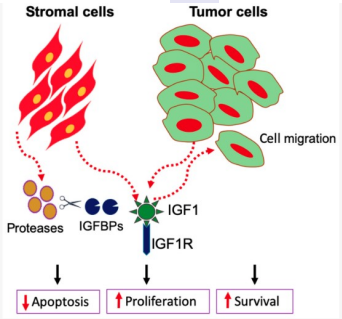
Previous studies had limited power to assess the associations of testosterone with aggressive disease as a primary endpoint. Further, the association of genetically predicted testosterone with aggressive disease is not known. The authors investigated the associations of calculated free and measured total testosterone and sex hormone-binding globulin (SHBG) with aggressive, overall and early-onset prostate cancer. Data analysis of over 80,000 cases and 95,000 controls determined that free testosterone was associated with aggressive disease in Mendelian randomisation (MR) analyses. In blood-based analyses there was no association with aggressive disease overall, but there was heterogeneity by age at blood collection. Associations for free testosterone were positive for overall prostate cancer and early-onset prostate cancer. SHBG and total testosterone were inversely associated with overall prostate cancer in blood-based analyses, with null associations in MR analysis. The results support free testosterone, rather than total testosterone, in the development of prostate cancer, including aggressive subgroups.



Watts E *et al*. (2022). Circulating free testosterone and risk of aggressive prostate cancer: Prospective and Mendelian randomisation analyses in international consortia. *International Journal of Cancer*.

Insulin-like growth factor and prostate cancer

Previous studies had limited power to assess the associations of circulating insulin-like growth factors (IGFs) and IGF-binding proteins (IGFBPs) with clinically relevant prostate cancer as a primary endpoint, and the association of genetically predicted IGF-I with aggressive prostate cancer is not known. Here, the authors aimed to investigate the associations of IGF-I, IGF-II, IGFBP-1, IGFBP-2 and IGFBP-3 concentrations with overall, aggressive and early-onset prostate cancer. In observational analyses, IGF-I was positively associated with risks of overall, aggressive and possibly early-onset disease; associations were similar in Mendelian randomisation analyses. Co-localisation also indicated a shared signal for IGF-I and prostate cancer. Men with higher IGF-II and IGFBP-3 had higher risks of overall prostate cancer, whereas higher IGFBP-1 was associated with a lower risk; these associations were attenuated following adjustment for IGF-I. These findings support the role of IGF-I in the development of prostate cancer, including for aggressive disease.



Watts E *et al*. (2022). Circulating insulin-like growth factors and risks of overall, aggressive and early-onset prostate cancer... *International Journal of Epidemiology*.

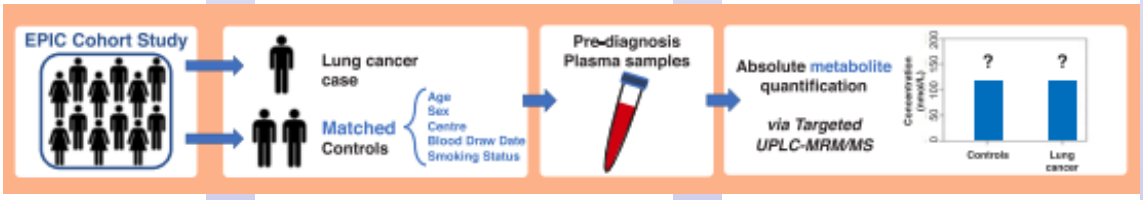
The role of metabolites in lung cancer

Tobacco exposure causes 8 of 10 lung cancers, and identifying additional risk factors is challenging due to confounding introduced by smoking in traditional observational studies. Using Mendelian randomization (MR), the research team screened 207 metabolites for their role in lung cancer predisposition using independent genome-wide association studies (GWAS) of blood metabolite levels and lung cancer risk. A nested case–control study was subsequently performed using pre-diagnostic blood samples to validate MR association with lung cancer incidence data from population-based cohorts.

An MR-based scan of 207 circulating metabolites for lung cancer risk identified that blood isovalerylcarnitine (IVC) was associated with a decreased odds of lung cancer after accounting for multiple testing. Molar measurement of IVC in pre-diagnostic blood found similar results. Results were consistent across lung cancer subtypes.

Independent lines of evidence support an inverse association of elevated circulating IVC with lung cancer risk through a novel methodologic approach that integrates genetic and traditional epidemiology to efficiently identify novel cancer biomarkers.

Smith-Byrne K *et al*. (2022). Circulating Isovalerylcarnitine and Lung Cancer Risk: Evidence from Mendelian Randomization and Prediagnostic Blood Measurements. *Cancer Epidemiology, Biomarkers and Prevention*.



Testosterone, vitamin D, and prostate cancer

Observational studies and randomised controlled trials (RCTs) have shown an association between vitamin D levels and prostate cancer progression. However, evidence of direct causality is sparse and studies have not examined biological mechanisms, which can provide information on plausibility and strengthen the evidence for causality.

The team performed a systematic review and meta-analysis to assess the evidence from both human and animal studies examining the effect of vitamin D on testosterone, and testosterone on advanced prostate cancer or prostate cancer-specific mortality. A meta-analysis of ten human RCTs showed evidence of an effect of vitamin D on total testosterone. Five human RCTs showed evidence of an effect of vitamin D on free testosterone. Three human cohort studies of testosterone on advanced prostate cancer or prostate cancer-specific mortality provided inconsistent results. There is some evidence that vitamin D increases levels of total and free testosterone, although the effect of testosterone levels within the normal range on prostate cancer progression is unclear. The role of testosterone as a mechanism between vitamin D and prostate cancer progression remains inconclusive.

Robles LA *et al*. (2022). Does testosterone mediate the relationship between vitamin D and prostate cancer progression?... *Cancer Causes and Control*.

Targeting neoantigens in immunotherapy

Neoantigens derived from somatic mutations are specific to cancer cells and are ideal targets for cancer immunotherapy. KRAS is the most frequently mutated oncogene and drives the pathogenesis of several cancers. Here, the authors show the identification and development of an affinity-enhanced T cell receptor (TCR) that recognises a peptide derived from the most common KRAS mutant, KRASG12D, presented in the context of HLA-A*11:01. The affinity of the engineered TCR is increased by over one million-fold yet fully able to distinguish KRASG12D over KRASWT. While crystal structures reveal few discernible differences in TCR interactions with KRASWT versus KRASG12D, thermodynamic analysis and molecular dynamics simulations reveal that TCR specificity is driven by differences in indirect electrostatic interactions. The affinity enhanced TCR, fused to a humanised anti-CD3 scFv, enables selective killing of cancer cells expressing KRASG12D.

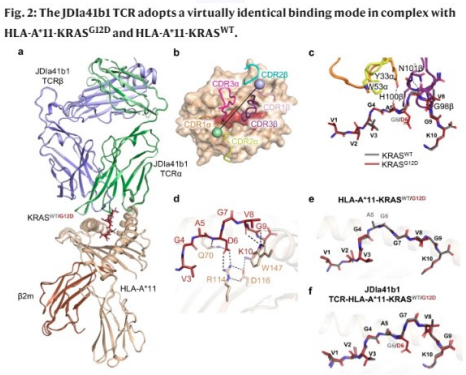


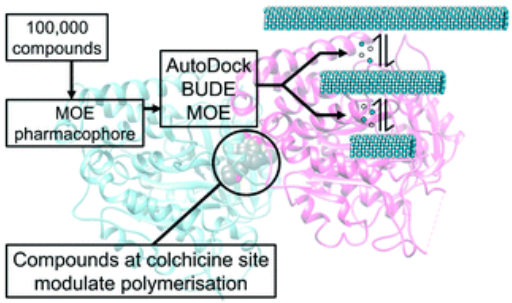
Fig. 2: The JDIa41b1 TCR adopts a virtually identical binding mode in complex with HLA-A*11-KRAS^{G12D} and HLA-A*11-KRAS^{WT}.

This work thus reveals a molecular mechanism that drives TCR selectivity and describes a soluble bispecific molecule with therapeutic potential against cancers harbouring a common shared neoantigen.

Poole A *et al*. (2022). Therapeutic high affinity T cell receptor targeting a KRASG12D cancer neoantigen. *Nature Communications*.

Microtubule inhibitors as anticancer agents

Targeting the colchicine binding site of α/β tubulin microtubules can lead to suppression of microtubule dynamics, cell cycle arrest and apoptosis. Therefore, the development of microtubule (MT) inhibitors is considered a promising route to anticancer agents. Our approach to identify novel scaffolds as MT inhibitors depends on a 3D-structure-based pharmacophore approach and docking using three programs MOE, Autodock and BUDE (Bristol University Docking Engine) to screen a library of virtual compounds. From this work we identified the compound 7-(3-hydroxy-4-methoxy-phenyl)-3-(3-trifluoromethyl-phenyl)-6,7-dihydro-3H-imidazo[4,5-b]pyridin-5-ol (6) as a novel inhibitor scaffold. This compound inhibited several types of cancer cell proliferation at low micromolar concentrations with low toxicity. Compound 6 caused cell cycle arrest in the G2/M phase and blocked tubulin polymerization at low micromolar concentration, inducing apoptosis via activation of caspase 9, increasing the level of the pro-apoptotic protein Bax and decreasing the level of the anti-apoptotic protein Bcl2. In summary, our approach identified a lead compound with potential antimitotic and antiproliferative activity.



Elseginy SA *et al*. (2022). Identification and validation of novel microtubule suppressors with an imidazopyridine scaffold through structure-based virtual screening and docking. *RSC Medicinal Chemistry*.

Cancer prevention strategy meeting

Prof Richard Martin (Bristol Medical School: Population Health Sciences, pictured) gave a talk at the Cancer Research UK Prevention Strategy Meeting on 16 May 2022 at the Royal Society in London. His talk focused on utilising large-scale, population-based genomic data to address CRUK's new cancer prevention strategy and he presented several examples of the application of genomic methods directly relevant to the strategic themes & priorities of the strategy: improving the evidence base for precision prevention; understanding molecular mechanisms; and therapeutic innovation. He then described future potential use of population-based genomic data in prevention, inspired by CRUK's strategy, including using Mendelian randomization to identify relevant surrogate endpoints for prevention trials; Mendelian randomization of the somatic genome to identify new causes of cancer and inform risk stratification; and integration within NHS infrastructures, such as the new lung health check programme, risk stratification in rapid diagnostic centres and the NHS genomic medicine service.

FUNDING OPPORTUNITIES

Research Professional provides access to an extensive database of funding opportunities. You can set up individualised funding alerts based on keywords or areas of research . UoB staff and students have **FREE** online access to the database.

You can search for funding information by discipline, sponsor, database searches, by recent calls or by upcoming deadlines. Find out more about **Research Professional** on the RED website. Note that some calls may have an internal process; do always remember to check the major bids webpage here to see if there is an internal process.

The following listings represent a *brief selection* of available funding for the Cancer Research community. **Full listings of opportunities** are sent out via School Research Directors, and **are available on the Research Development website**.

National Cancer Institute, US

Physical sciences-oncology network – physical sciences-oncology projects (U01 clinical trial optional)

Closing date: 1 November 2022 Award amount: USD 2 million

These foster the convergence of physical sciences approaches and perspectives with cancer research to advance the understanding of cancer biology and oncology by forming transdisciplinary teams of physical scientists, cancer biologists and physician scientists. The following is supported: establishing a physical sciences perspective within the cancer research community; facilitating team science and field convergence at the intersection of physical sciences and cancer research; collectively testing physical sciences-based experimental and theoretical concepts of cancer and promoting innovative solutions to address outstanding questions in cancer research.

World Cancer Research Fund International

Regular grant programme

Closing date: 7 November 2022 Award amount: £350,000 / £60,000

This supports research on the link between diet, nutrition, body composition, physical activity, and cancer prevention and survival. Two types of grants are available: investigator initiated grants, worth a maximum of £350,000 each for up to four years; pilot and feasibility grants, worth up to £60,000 each over two years.

Cancer Research UK

Biomarker project awards

Closing date: 24 November 2022 Award amount: £300,000

These provide funding for biomarker assay development, validation and qualification where there is a clear line of sight to clinical implementation. Proposals may use invasive or imaging techniques and

cover all types of biomarkers, including predisposition, screening, diagnostic, prognostic, predictive, pharmacological and surrogate response markers. Biosamples or images can be collected as part of the application, or accessed from existing sample or data sets.

Union for International Cancer Control
Yamagiwa-Yoshida memorial international study grants

Closing date: 30 November 2022 Award amount: USD 10,000

These enable cancer investigators from any country to carry out bilateral research projects abroad that exploit complementary materials or skills and involve advanced training in experimental research methods and techniques. Basic, translational or applied cancer research is eligible.

Nuovo-Soldati Foundation for Cancer Research
Fellowships

Closing date: 1 December 2022 Award amount: €40,000

These support young doctors in pursuing a research project on cancer cells with the main aim being to support innovative techniques or novel therapeutic approaches.

Cancer Research UK
Prevention and population research project awards

Closing date: 14 December 2022 Award amount: £500,000

These provide support for focused research proposals centred on key questions in prevention and population research.

Cancer Research UK
Early detection and diagnosis project award

Closing date: 15 December 2022 Award amount: £500,000

This supports research projects that drive a transformational change in how and when early cancers and pre-cancerous states are diagnosed. Projects should aim to detect and diagnose consequential pre-cancerous changes and cancer at the earliest possible point at which an intervention might be made, reducing the burden of late-stage disease.

Rising Tide Foundation
Clinical cancer research grants

Closing date: 31 December 2022 Award amount: unspecified

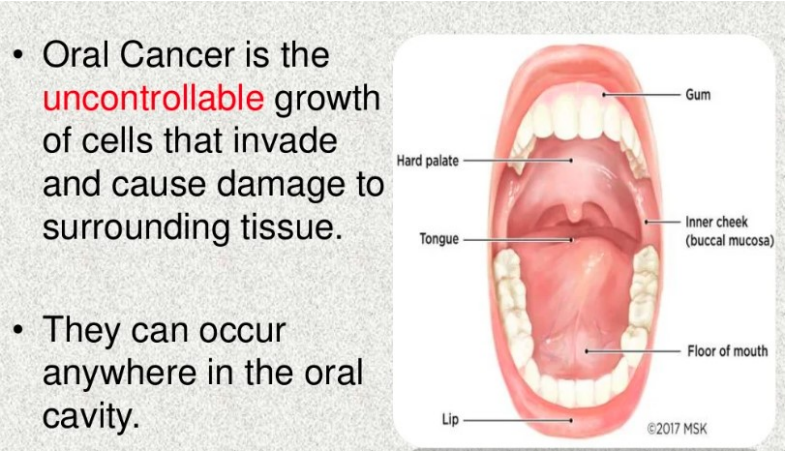
These support innovative, patient-centred clinical trials that have the potential to impact the lives of cancer patients in a timely manner. The aim is to improve treatment options and quality of life for cancer patients by funding clinical studies focused on prevention, detection, treatment and survivorship.

FEATURED PUBLICATION

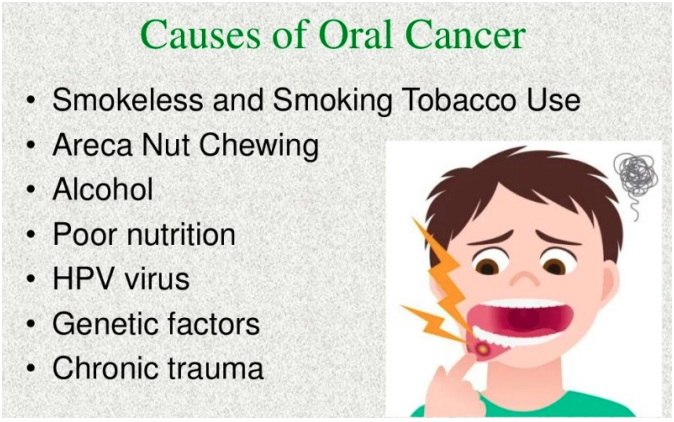
An update on oral cavity cancer: epidemiological trends, prevention strategies and novel approaches in diagnosis and prognosis

Gormley M, Gray E, Richards C, Gormley A, Richmond RC, Vincent EE, Dudding T, Ness AR and Thomas SJ (2022). *Community Dental Health*.

In the UK, the incidence of oral cavity cancer continues to rise, with an increase of around 60% over the past 10 years. Many patients still present with advanced disease, often resulting in locoregional recurrence and poor outcomes, which has not changed significantly for over four decades. Changes in aetiology may also be emerging, given the decline of smoking in developed countries. Therefore, new methods to better target prevention, improve screening and detect recurrence are needed. High-throughput 'omics' technologies appear promising for future individual-level diagnosis and prognosis. However, given this is a relatively rare cancer with significant intra-tumour heterogeneity and variation in patient response, reliable biomarkers have been difficult to elucidate.



From a public health perspective, implementing these novel technologies into current services would require substantial practical, financial and ethical considerations. This may be difficult to justify and implement at present, therefore focus remains on early detection using new patient-led follow-up strategies. This paper reviews the latest evidence on epidemiological trends in oral cavity cancer to help identify at risk groups, population-based approaches for prevention, in addition to potential cutting-edge approaches in the diagnosis and prognosis of this disease.



Cancer Network

CONTACTS

The Cancer Research Network is led by a Steering Group:

@BristolCancer

cancer-research@bristol.ac.uk

bristol.ac.uk /cancer

00 44 117 455 6360

University of BRISTOL
Elizabeth Blackwell Institute for Health Research

Bristol Cancer Research Network

Network Co-Leads:

- Anne Ridley, *Head of School of Cellular and Molecular Medicine*
- Helen Winter, *Medical Oncologist and Clinical Director, SWAG Cancer Alliance*
- Richard Martin, *Professor of Clinical Epidemiology*

Steering Group members:

- Jonathan Aning, *Consultant Urological Surgeon, Bristol Urological Institute*
- Laura Ballisat , *PhD student*
- Johanna Blee, *Research Associate*
- Anya Burton, *Senior Research* Associate
- Adam Chambers, *Clinical Lecturer*
- Grace Edmunds, *Clinical Research Fellow*
- Sabine Hauert, *Assistant Professor in Robotics*
- Kathreena Kurian, *Professor of Neuropathology and Consultant Clinical Neuropathologist*
- Sarah Stuart, *Research Development Associate for the Faculties of Health and Life Sciences*
- Matimba Swana, PhD student
- Jaap Velthuis, Professor of Physics
- Axel Walther, *Research Lead, Bristol Haematology & Oncology Centre*
- Ann Williams, *Professor of Experimental Oncology*
- Emma Vincent, *Senior Lecturer in Molecular Metabolism*
- Catherine Brown, *Network Administrator*

Sign up to the Elizabeth Blackwell Institute newsletter