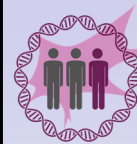# Cancer Network Newsletter
## 2023: Issue 1

Bristol Cancer Research Network

Patient-specific cancer tumours in 3D

Bowel cancer patients could in future benefit from 3D bioprinting technology which would use their own cells to replicate the complex cellular environment of solid tumours in 3D models. The University of Bristol-led advance would allow clinicians to treat the models, known as spheroids, with chemotherapy drugs and radiation to help them understand an individual patient's resistance to therapies.

Bowel cancer is the third-most prevalent cancer worldwide, a major cause of cancer-related deaths and is becoming more prevalent globally each year. While current therapies aim to shrink tumours through a combination of surgery, chemotherapy and/or radiotherapy, the heterogenous nature of bowel tumours mean that chemotherapy drugs have variable effects between patients.

Researchers have developed a new 3D bioprinting platform with high content light microscopy imaging and processing. Using a mixture of bioinks and colorectal cancer cells, the team show they were able to replicate tumours in 3D spheroids.
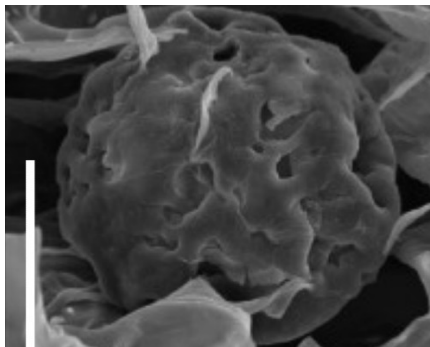
"We anticipate that this new platform technology could have significant impact in human disease modelling for evaluation of oncology drug-response in 3D. This is a big step towards personalised medicine and helping to understand why certain patients respond to chemotherapy."

Adam Perriman, founder of Cytoseek, and lead author

To investigate how the tumours might respond to drugs, dose-response profiles were generated from the spheroids which had been treated separately with chemotherapy drugs oxaliplatin (OX), fluorouracil (5FU), and radiotherapy. The spheroids were then imaged over time.

Results from their experiment showed oxaliplatin was significantly less effective against tumour spheroids than in current 2D monolayer culture structures, when compared to fluorouracil.

Perriman AW *et al*. (2022). A rapid high throughput bioprinted colorectal cancer spheroid platform for in vitro drug- and radiation-response. *Biofabrication*.

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Elizabeth Blackwell Institute for Health Research

EVENTS

BNSSG ICB Research Showcase seminar
28 March 2023, 11.00 - 12.00, Dr Anna Bibby and Dr Charlotte Archer, online

South West Integrated Clinical and Practitioner Academic Programme Promotion Event
28 March 2023, 14.00 - 15.00, online

From plants to prostates through randomised controlled trials
28 March 2023, 18.15 - 19.15, Prof Athene Lane (Bristol Medical School) inaugural lecture, Reception Room, Wills Memorial Building, Queen's Road, Bristol BS8 1RJ

Proteogenomic analyses with link to human metabolic diseases and cancer outcomes
29 March 2023, 10.30 - 11.30, Mine Koprulu (Cambridge) and Karl Smith-Bryne (Oxford), online

Translating research ideas into innovations for better NHS Outcomes
30 March 2023, 12.00 - 13.30, online

Cancer Early Career Researchers' Symposium
28 June 2023, Life Sciences Building
CALL FOR ABSTRACTS closes 16 May 2023
Further Information and to Register
ALL WELCOME

An introduction to Cancer Research UK with chief executive Michelle Mitchell
30 March 2023, 13.00 - 14.00, Michelle Mitchell OBE (Chief Executive, Cancer Research UK), online

From studying quarks to beating cancer, an upbeat story about death and destruction
14 April 2023, 16.00 - 19.00, Professor Jaap Velthuis (School of Physics, University of Bristol) inaugural lecture, Room G42, Powell Lecture Theatre, School of Physics, Tyndall Avenue, BS8 1TL

University Hospitals Bristol and Weston NHS Foundation Trust Research Showcase: Being Collaborative and Inclusive
20 April 2023, 10.00 - 16.00, Education and Research Centre, Upper Maudlin St, Bristol

RAEng/CRUK collaboration building to detect cancer earlier
24 April 2023, 10.00 - 17.00, London

The Royal Society Scientific Meeting: Tissue resilience in health and disease
26 - 27 April 2023, INNSiDE Manchester, 1 First Street, Manchester, M15 4RP

Understanding the developmental origins of cancers
26 April 2023, 16.00 - 17.30, online
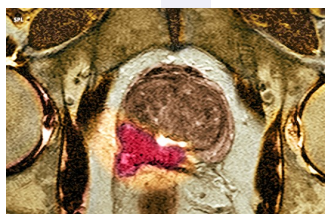
27th London Lymphoma Forum – WM and IgM-related diseases
3 May 2023, 18.00 - 21.45, Cavendish Conference Centre, 22 Duchess Mews, London W1G 9DT

SEE ALL EVENTS ON THE CANCER RESEARCH NETWORK WEBSITE

NEWS

Effects of delaying prostate cancer treatment

Active monitoring of prostate cancer has the same high survival rates after 15 years as radiotherapy or surgery, reports the largest study of its kind.

Although men on active monitoring – which involves regular tests to check on the cancer – were more likely to see it progress or spread than those receiving radiotherapy or surgery, this didn't reduce their likelihood of survival. The trial also found that the negative impacts of radiotherapy and surgery on urinary and sexual function persist much longer than previously thought – for up to 12 years.

The findings show that treatment decisions following diagnosis for low and intermediate risk localised prostate cancer do not need to be rushed. The trial was conducted in nine UK centres and is the longest running study of its kind. It is the first to fully evaluate three major treatment options: active monitoring, surgery (radical prostatectomy) and radiotherapy with hormones for men with localised prostate cancer.

They found that around 97% of the men diagnosed with prostate cancer survived 15 years after diagnosis, irrespective of which treatment they received. Around a quarter of the men on active monitoring had still not had any invasive treatment for their cancer after 15 years.

Hamdy F *et al*. (2023). 15-year outcomes after monitoring... *New England Journal of Medicine*.

Donovan J *et al*. (2023). Patient-reported outcomes 12 years after...*New England Journal of Medicine*.

Fighting off melanoma

A new way of reprogramming our immune cells to shrink or kill off cancer cells has been shown to work in the otherwise hard to treat and devastating skin cancer, melanoma. The University of Bristol-led discovery demonstrates a new way to clear early stage precancerous and even late-stage tumour cells.

Using miniature artificial capsules called protocells designed to deploy reprogramming cargoes that are taken up by inflammatory cells (white blood cells), the scientists show they were able to transform these cells into a state that makes them more effective at slowing down the growth and killing of melanoma cells. They showed that this was possible for both animal and human immune cells.

The study is the first to test the capacity of a protocell to deliver cargoes for reprogramming immune cells and offers a promising novel target for the development of cancer immunotherapies.

Martin P *et al*. (2022). Macrophage reprogramming with anti-miR223-loaded artificial protocells enhances in vivo cancer therapeutic potential. *Advanced Science.*

Developing a physical activity intervention

A project being overseen by the Bristol Biomedical Research Centre (BRC) will develop a physical activity intervention for South-Asian men with prostate cancer, with the help of patient and public contributors as well as relevant stakeholders. The team will use existing guidelines, evidence from previous research and the results of studies on physical activity in prostate cancer.

Researchers at the BRC will work with colleagues from the Bradford Institute of Health Research to identify South-

Asian men diagnosed with prostate cancer to take part in this study. During the study men will be asked to take part in a focus group which they will do either in person or virtually.

The focus group session will explore:
- Men's experiences of increasing their physical activity
- Their feedback on existing physical activity interventions (including brisk walking)

- What stands in the way or helps them to take part in interventions
- What motivates them (including the use of wearable activity monitors)
- How we can measure outcomes from the study

The focus group data will be used to create a model of behaviour change including the components we need for our intervention. Findings will also be used to design additional trials and apply for external funding.

Read more

Support for clinical trials

The Bristol Haematology and Oncology Centre (BHOC) Clinical Trials Unit (CTU) at University Hospitals Bristol and Weston NHS Foundation Trust has been awarded funds to support clinical trials in haematology and stem cell transplantation over the next three years. The funding, equivalent to one and half team members, will support bone marrow transplant and haematology clinical trials for emerging lymphoma, myeloma, leukaemia, and other blood cancer treatments.

The funds were awarded by the IMPACT (Partnership for Accelerated Clinical Trials) and TAP (Trials Acceleration Programme) schemes.

BHOC delivers treatment, including stem cell transplantations, for cancer patients from a regional catchment population of over 5 million. The CTU aims to offer patients the option to receive a research treatment as part of their NHS treatment choice. There are around 100 trials open and recruiting at any one time, with many more

studies being set up to open over the coming months.

As the Southwest regional centre, BHOC is the largest haematology and BMT recruiter to clinical trials in the South West and one of the UK's leading centres for trials of CAR-T cell therapy (a type of cancer treatment using cells from the patient's own immune system to fight the disease). The CTU's 40-strong team includes 10 specialist Research Nurses, of which Peter Robertson is our nominated IMPACT nurse, treating patients receiving stem cell transplants and other cellular therapy treatments within clinical trials.

Medication-related osteonecrosis of the jaw

The role of a drug holiday in the management of medication-related osteonecrosis (loss of blood flow to the bone) of the jaw (MRONJ) remains controversial. Current UK guidance does not recommend this practice given the lack of conclusive evidence, and potential risk of skeletal-related events or cancer metastasis.

MRONJ patients were given a drug holiday following diagnosis. A range of exposures data was collected; the primary outcome was complete healing. Analysis of the data evaluated the association between exposures and primary MRONJ outcome.

44% of patients stopped their medication for > 36 months. Over half of all MRONJ cases presented in the posterior mandible and dental extraction was the most common precipitating factor (76%). Almost three-quarters (72%) of patients achieved complete healing. MRONJ recurrence (new site) was reported at 30%, mainly in those with incomplete healing of the initial area. There was a lack of evidence for an association between all recorded exposures and the primary MRONJ outcome. Similarly, there was no evidence for an association between drug holiday duration and MRONJ outcome.

Results support published guidelines, which do not recommend the discontinuation of bone modifying drugs for the prevention of MRONJ, or as part of treatment for established MRONJ.

Hamid A *et al*. (2023). A case series of Medication-related Osteonecrosis of the Jaw... *Oral and Maxillofacial Surgery*.

Funding successes: Part 1

Dr Bethan Lloyd-Lewis (Cellular and Molecular Medicine) received £13,128 from the **Academy of Medical Sciences** for Deciphering the contribution of development and age to breast cancer aetiology, starting July 2023 for 5 months.

Dr Jules Lavalou (Cellular and Molecular Medicine) was awarded £51,418 from the **European Molecular Biology Organisation** for Unmasking the competitive loser status of epithelial tumours with ribosomal mutations, Feb 2023-January 2024.

The **University Cancer Research Fund** ran a large (up to £30k) early to mid-career scheme in 2022 which was awarded to Mr Adam Chambers, Clinical Lecturer in the School of Cellular and Molecular Medicine. The project, *Determining the regulation of chromatin compaction by BCL-3 following DNA damage in colorectal cancer*, aims to improve understanding of how tumours respond to anticancer therapy given to patients before surgery in rectal cancer. A protein called BCL-3 is important in this process and Adam seeks a better understanding of how this protein leads to poorer outcomes in this cancer. The research will contribute to personalisation of a patient's therapy and even give the option to avoid surgery altogether if the tumour is treated completely with chemotherapy and radiotherapy. This will have major benefits for patient outcomes both through improving survival but also by reducing the risks associated with having surgery. The project started in January 2023 and will complete within two years.

World Cancer Day 2023

An interview with Prof Richard Martin (Bristol Medical School, pictured) originally published by *PLOS ONE* on 3 February 2023.

World Cancer Day, held every 4 February, is a global initiative led by the Union for International Cancer Control (UICC) to raise awareness, improve education and catalyse action. This year's theme was 'Close the Care Gap: Uniting our voices and taking action'.

Each year, the journal *PLOS*

ONE publishes more than 1000 cancer-related research articles from authors across the globe. In celebration of

this year's theme, they interviewed *PLOS ONE* author Richard Martin, Professor of Clinical Epidemiology at the University of Bristol and co-lead

researcher of the Integrative Cancer Epidemiology Programme. They asked how Open Science can contribute to interdisciplinary cancer research and how engagement with patient communities has increased the impact of their research.

Read a summary of the interview on the Bristol Biomedical Research Centre news page

Read the full blog on the PLOS site

Risk prediction model for head and neck cancers

Head and neck cancer is often diagnosed late and prognosis for most head and neck cancer patients remains poor. To aid early detection, an international collaboration, including researchers at Bristol, developed a risk prediction model based on demographic and lifestyle risk factors, human papillomavirus (HPV) serological markers and genetic markers.

A total of 10 126 head and neck cancer cases and 5254 controls from five North American and European studies were included. HPV serostatus was determined by antibodies for HPV16 early oncoproteins (E6, E7) and regulatory early
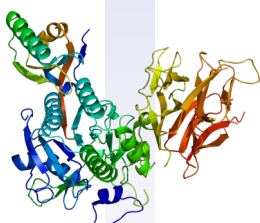
proteins (E1, E2, E4). The data were split into a training set (70%) for model development and a hold-out testing set (30%) for model performance evaluation, including discriminative ability and calibration. The risk models including demographic, lifestyle risk factors and polygenic risk score showed a reasonable predictive accuracy for head and neck cancer overall. A risk model that also included HPV serology showed substantially improved predictive accuracy for oropharyngeal cancer. The 5-year absolute risk estimates showed distinct trajectories by risk factor profiles. Based on the UK Biobank cohort, the risks of developing oropharyn-

geal cancer among 60 years old and HPV16 seropositive in the next 5 years ranged from 5.8% to 14.9%. Absolute risk was generally higher among individuals with heavy smoking, heavy drinking, HPV seropositivity and those with higher polygenic risk score. These risk models may be helpful for identifying people at high risk of developing head and neck cancer.

Budhathoki S *et al*. (2023). A risk prediction model for head and neck cancers incorporating lifestyle factors, HPV serology and genetic markers. *International Journal of Cancer*.

PCSK9 inhibition and prostate cancer risk

Prostate cancer (PrCa) is the second most prevalent malignancy in men worldwide. Observational studies have linked the use of low-density lipoprotein cholesterol (LDL-c) lowering therapies with reduced risk of PrCa, which may potentially be attributable to confounding factors. In this study, researchers from Bristol alongside members of the PRACTICAL consortium performed a drug target Mendelian randomisation analysis to evaluate the association of genetically proxied inhibition of LDL-c-lowering drug targets on risk of PrCa.

Single-nucleotide polymorphisms (SNPs) associated with LDL-c from the Global Lipids Genetics Consortium genome-wide association study and located in and around the HMGCR, NPC1L1 and PCSK9 genes were used to proxy the therapeutic inhibition of these targets. Findings support a strong association between genetically proxied inhibition of PCSK9 and a lower risk of total and early-onset PrCa, potentially through an alternative mechanism other than the on-target effect on LDL-c. Further evidence from clinical studies is needed to confirm this.

Fang S *et al*. (2023). Association between genetically proxied PCSK9 inhibition and prostate cancer risk: A Mendelian randomisation study. *PLOS Medicine*.

Funding successes: Part 2

Dr Vanessa Tan (Bristol Medical School) was awarded £190,802 from **Cancer Research UK** for the *Role of directly measured metabolic profile as an intermediate between adiposity and endometrial cancer: triangulation of evidence from independent sources*, starting May 2023 for three years.

Prof Karim Malik (Cellular and Molecular Medicine) received £209,363 from the **Children's Cancer and Leukaemia Group** for *Combined inhibition of methyltransferases and BH3 mimetics to induce neuroblastoma cell death*. During normal growth and development of the body we are continuously regenerating cells. As well as new cells being made, the number of older cells needs to decrease to maintain balanced growth. To maintain controlled growth, cells undergo programmed cell death. A crucial defining feature of cancer cells is they can resist programmed cell death and continue to survive and proliferate, in part due to a relative increase in pro-survival proteins. Drugs have been developed that can inhibit such pro-survival proteins, however, there can be side-effects and drug resistance; it is therefore crucial to limit drug dosage and devise effective drug combinations. Studies show that using a second drug (a methyltransferase inhibitor) in combination with inhibitors of pro-survival proteins leads to dramatic neuroblastoma cell death, despite using approximately 100-times lower levels of the inhibitor of pro-survival proteins. This combination may therefore (i) lead to specific and pronounced neuroblastoma cell death, (ii) limit side-effects of conventional chemotherapies, and (iii) reduce the risk of relapsing disease. This project will rationalise these of inhibitor combinations for high-risk neuroblastoma patients, for whom there remains a significant unmet need for novel targeted therapies. The project will run March 2023-Fenruary 2025.

The role of BCL-3 in colorectal cancer therapeutic response

The proto-oncogene BCL-3 is upregulated in a subset of colorectal cancers (CRC), where it has been shown to enhance tumour cell survival. However, although increased expression correlates with poor patient prognosis, the role of BCL-3 in determining therapeutic response remains largely unknown. Researchers at Bristol, Glasgow, Cardiff and Sussex investigated the function of BCL-3 in the DNA damage response.

In this paper, the team identifying a novel role for BCL-3, where inhibiting BCL-3 expression sensitises CRC cell lines to irradiation-induced cell death by reducing homologous recombination and show that
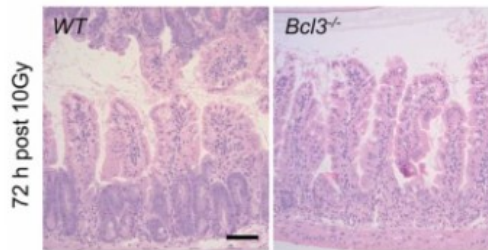
BCL-3-/- mice are sensitised to DNA damage inducing agents.

This work furthers our understanding of therapeutic resistance in CRC and offers a rationale for targeting BCL-3 as an adjuvant to convention-al therapies, particularly in the setting of neo-adjuvant therapy for locally advanced rectal cancer.

Parker C, Chambers AC *et al*. (2022). BCL-3 loss sensitises colorectal cancer cells to DNA damage by targeting homologous recombination. *DNA Repair*.

Image: Loss of Bcl3 impairs intestinal regeneration and sensitises the epithelium to DNA damage. Representative H&E staining of wild-type (WT) and Bcl3KO (Bcl3-/-) mice 72 h following whole-body irradiation (10 Gy). Scale bar, 100 μm

Adiposity and endometrial cancer risk

Increased adiposity is a known risk factor for endometrial cancer (EC). This collaborative study between the Universities of Manchester and Bristol and the QIMR Berghofer Medical Research Institute in Brisbane, Australia, aimed to disentangle the separate causal roles of child and adult adiposity on EC risk in adults, including endometrioid and non-endometrioid histological subtypes using multivariable Mendelian randomisation.

The analyses employed genetic associations derived from UK Biobank as proxies for child and adult body size in 12,906 cases and 108,979 controls that participated in the Endometrial Cancer Association Consortium. In multivariable analyses, adult body size increased overall EC and endo-

metrioid EC risk, while child body size had minimal effect.

In contrast, child body size but not adult body size increased non-endometrioid EC risk. As such, child adiposity has an indirect effect on endometrioid EC risk that is mediated by adult adiposity but has a direct effect on non-endometrioid EC risk that is independent of adult adiposity.

These novel findings indicate that interventions targeting adiposity during distinct periods in life have a critical role in preventing subtype-specific EC.

Kennedy OJ *et al*. (2023). Child and adult adiposity and subtype-specific endometrial cancer risk: a multivariable Mendelian randomisation study. *International Journal of Obesity*.

Coffee consumption and cancer risk

Coffee contains many bioactive chemicals and associations with cancer have been reported in observational studies.

This Mendelian randomisation (MR) study conducted by researchers at the Universities of Bristol, Cambridge and Uppsala (Sweden) and the Karolinska Institutet (Sweden) investigated the causal associations of coffee consumption with a broad range of cancers. Twelve independent genetic variants proxied coffee consumption. Genetically-predicted risk of any cancer (59,647 cases) and 22 site-specific cancers was estimated in European-descent individuals in UK Biobank. Univariable and multivariable MR analyses were conducted.

Genetically-predicted coffee consumption was not associated with risk of any cancer in the main analysis but was associated with an increased risk of digestive system cancer, driven by a strong association with oesophageal cancer.

The findings provide strong support for a causal association of coffee consumption with oesophageal cancer, but not for the majority of cancer types, and the underlying mechanisms require investigation.

Carter P *et al*. (2022). Coffee consumption and cancer risk: a Mendelian randomisation study. *Clinical Nutrition*.

Using fluorescence biomarkers to detect gliomas

Improving intraoperative accuracy of high-grade areas with glioma with a validated surgical biomarker will aid neurosurgical decision-making and sampling. This project, in collaboration with Bristol's Brain Tumour Research Centre, designed a multicentre, prospective surgical cohort study (GALA-BIDD) to validate the presence of visible fluorescence as a pragmatic intraoperative surgical biomarker of suspected high-grade disease within a tumour mass in patients undergoing 5-aminolevulinic acid (5-ALA) fluorescence-guided cytoreductive surgery. A total of 106 patients with a suspected high-grade glioma or malignant transformation of a low-grade glioma were enrolled. A total of 80 out of 81 fluorescent patients were diagnosed as high-grade gliomas on postoperative central review with 1 low-grade glioma case. Among the eight patients given 5-ALA who did not show any visible fluorescence, none were high-grade gliomas.

The findings show that in patients where there is clinical suspicion, visible 5-ALA fluorescence has clinical utility as an intraoperative surgical biomarker of high-grade gliomas and can aid surgical decision-making and sampling. Further studies assessing the use of 5-ALA to assess malignant transformation in all diffuse gliomas may be valuable.

Watts C *et al*. (2023). Refining the Intraoperative Identification of Suspected High-Grade Glioma Using a Surgical Fluorescence Biomarker: GALA BIDD Study Report. *Journal of Personalized Medicine*.
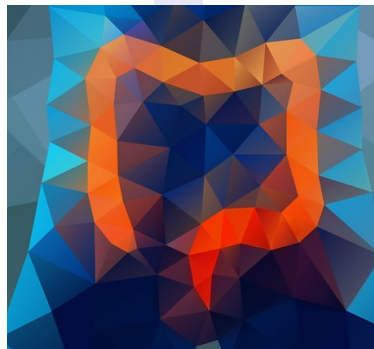
Early and later life adiposity and colorectal cancer risk

Observational studies have linked childhood obesity with elevated risk of colorectal cancer; however, it is unclear if this association is causal or independent from the effects of obesity in adulthood on colorectal cancer risk.

The study team conducted Mendelian randomization (MR) analyses to investigate potential causal relationships between self-perceived body size (thinner, plumper, or about average) in early life (age 10) and measured body mass index in adulthood (mean age 56.5) with risk of colorectal cancer.

Genetically predicted early life body size was estimated to increase odds of colorectal cancer, with stronger results for colon cancer and distal colon cancer. After accounting for adult body size, effect estimates for early life body size were attenuated towards the null for colorectal cancer and colon cancer, while the estimate for distal colon cancer was of similar magnitude but more imprecise.
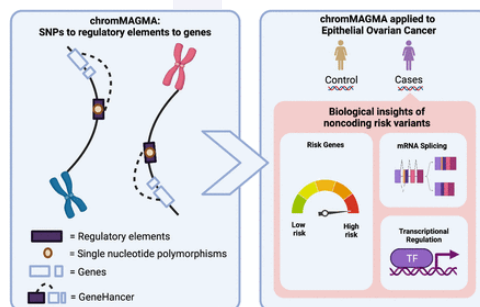
Findings suggest that the positive association between early life body size and colorectal cancer risk is likely due to large body size retainment into adulthood.

Papadimitriou N *et al.* (2023). Separating the effects of early and later life adiposity on colorectal cancer risk: a Mendelian randomization study. *BMS Medicine*.

Identifying genomic risk variants

Candidate causal risk variants from genome-wide association studies reside almost exclusively in noncoding regions of the genome and innovative approaches are necessary to understand their biological function. Multimarker analysis of genomic annotation (MAGMA) is a widely used program that nominates candidate risk genes by mapping single-nucleotide polymorphism summary statistics from genome-wide association studies to gene bodies. We augmented MAGMA to create chromatin-MAGMA (chromMAGMA), a method to nominate candidate risk genes based on the presence of risk variants within noncoding regulatory elements (REs). We applied chromMAGMA to a genetic susceptibility dataset for epithelial ovarian cancer (EOC), a rare gynecologic malignancy characterized by high mortality. This identified 155 unique candidate EOC risk genes across five EOC histotypes; 83% (105/127) of high-grade serous ovarian cancer risk genes had not previously been implicated in this EOC histotype. Risk genes nominated by chromMAGMA converged on mRNA splicing and transcriptional dysregulation pathways. chromMAGMA is a pipeline that nominates candidate risk genes through a gene regulation-focused approach and helps interpret the biological mechanism of noncoding risk variants for complex diseases.

Namei R *et al.* (2022). chromMAGMA: regulatory element-centric interrogation of risk variants. *Life Science Alliance*.

Vitamin C and digestive system cancers

Vitamin C is an antioxidant with a potential role in the prevention of digestive system cancers, but there is yet no consensus whether vitamin C has a causal role in these cancers. The aim of this study was to utilize Mendelian randomization to decipher the potential causal associations of vitamin C with risk of digestive system cancers.

In this study, ten genetic variants previously found to be significantly associated with circulating vitamin C were used as instrumental variables. Effect size estimates for the genetic associations of the vitamin C-associated genetic variants with six major malignancies of digestive system were obtained from the FinnGen and UK Biobank studies. Results from the two studies were combined using meta-analysis.

Genetically predicted higher circulating vitamin C showed a suggestive association with lower risk of small intestine and colorectal cancer after accounting for multiple testing. Genetically predicted circulating vitamin C was not associated with cancers of the oesophagus, stomach, or pancreas.

Results from the study indicate that vitamin C might play a role in the prevention of small intestine and colorectal cancer.

Larsson SC *et al*. (2022). Circulating vitamin C and digestive system cancers: Mendelian randomization study. *Clinical Nutrition*.

Targeting immune cells to reduce cancer progression

Several immune cell-expressed microRNAs (miRs) are associated with altered prognostic outcome in cancer patients, suggesting that they may be potential targets for development of cancer therapies. The University of Bristol-based study team used translucent zebrafish to demonstrate that genetic knockout or knockdown of one such miR, microRNA-223 (miR223), globally or specifically in leukocytes, does indeed lead to reduced cancer progression.

As a first step toward potential translation to a clinical therapy, the team described a novel strategy for reprogramming neutrophils and macrophages utilising miniature artificial protocells (PCs) to deliver anti-miRs against the anti-inflammatory miR223. Using genetic and live imaging approaches, they showed that

phagocytic uptake of anti-miR223-loaded PCs by leukocytes in zebrafish (and by human macrophages *in vitro*) effectively prolongs their pro-inflammatory state by blocking the suppression of pro-inflammatory cytokines, which, in turn, drives altered immune cell-cancer cell interactions and ultimately leads to a reduced cancer burden by driving reduced proliferation and increased cell death of tumour cells.

This PC cargo delivery strategy for reprogramming leukocytes toward beneficial phenotypes has implications also for treating other systemic or local immune-mediated pathologies.
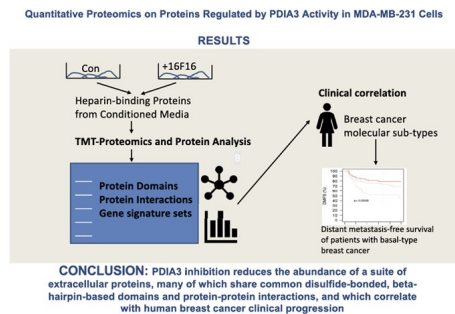
López-Cuevas P *et al*. (2022). Macrophage Reprogramming with Anti-miR223-Loaded Artificial Protocells Enhances In *Vivo* Cancer Therapeutic Potential. *Advanced Science*.

Therapeutic targets for breast cancer

Metastasis and recurrence of breast cancer remain major causes of patient mortality and there is an ongoing need to identify new therapeutic targets relevant to tumour invasion. Protein disulphide isomerase A3 (PDIA3) has been correlated with aggressive breast cancers. We show that either prior PDIA3-inhibition by the disulphide isomerase inhibitor 16F16 or depletion of heparin-binding proteins strongly reduces the activity of conditioned medium (CM) of MDA-MB-231 human breast cancer cells to support pro-migratory cell

spreading and F-actin organisation by newly adherent MDA-MB-231 cells. The predominant types of disulphide-

Quantitative Proteomics on Proteins Regulated by PDIA3 Activity in MDA-MB-231 Cells

bonded domains in the extracellular proteins contained beta-hairpin folds, with the knottin fold the most common. From human breast cancer datasets, the extracellular

proteins were found to correlate specifically with the basal subtype of breast cancer and their high expression in tumours correlated with reduced distant metastasis-free survival. These data provide new evidence that PDIA3 may be a relevant therapeutic target to alter properties of the ECM-associated microenvironment in basal breast cancer.

Germon A *et al*. (2022). Protein disulfide isomerase A3 activity promotes extracellular accumulation of proteins… *Cell Physiology*.

Cost-effectiveness of prostate cancer screening

Most guidelines in the UK, Europe and North America do not recommend organised population-wide screening for prostate cancer. Prostate-specific antigen-based screening can reduce prostate cancer-specific mortality, but there are concerns about overdiagnosis, overtreatment and economic value. The aim was therefore to assess the cost effectiveness of eight potential screening strategies in the UK.

The study, a collaboration between Bristol, Oxford, the Ka-

rolinska Institute (Sweden) and the Fred Hutchison Cancer Research Center in Seattle, USA, used a cost-utility analysis with an individual-based simulation model. The model was calibrated to data from the 10-year follow-up of the Cluster Randomised Trial of PSA Testing for Prostate Cancer (CAP). Treatment effects were modelled using data from the Prostate Testing for Cancer and Treatment (ProtecT) trial. The main outcome measures were projected lifetime costs and quality-adjusted life-years from a National Health Service perspective.

All screening strategies increased costs compared with no screening, with the majority also increasing quality-adjusted life-years. At willingness-to-pay thresholds of £20,000 or £30,000 per quality-adjusted life-year gained, a once-off screening at age 50 years was optimal, although this was sensitive to the utility estimates used.

Keeney E *et al*. (2022). Cost-Effectiveness Analysis of Prostate Cancer Screening in the UK: A Decision Model Analysis Based on the CAP Trial. *PharmacoEconomics*.

Identifying genetic risk of ovarian cancer

Known risk alleles for epithelial ovarian cancer (EOC) account for approximately 40% of the heritability for EOC. Copy number variants (CNVs) have not been investigated as EOC risk alleles in a large population cohort.

Single nucleotide polymorphism array data from 13 071 EOC cases and 17 306 controls of White European ancestry were used to identify CNVs associated with EOC risk using a rare admixture maximum likelihood test for gene burden and a by-probe ratio test. We performed enrichment analysis of CNVs at known EOC risk loci and functional biofeatures in ovarian cancer–related cell types.
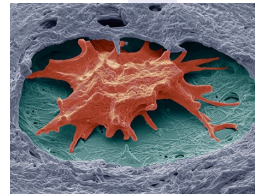
We identified statistically significant risk associations with CNVs at known EOC risk genes; BRCA1, RAD51C, and BRCA2. Four suggestive associations were identified for rare CNVs. Risk-associated CNVs were enriched at known EOC risk loci identified by genome-wide association study. Noncoding CNVs were enriched in active promoters and insulators in EOC-related cell types.

CNVs in BRCA1 have been previously reported in smaller studies, but their observed frequency in this large population-based cohort, along with the CNVs observed at BRCA2 and RAD51C gene loci in EOC cases, suggests that these CNVs are potentially pathogenic and may contribute to the spectrum of disease-causing mutations in these genes. CNVs are likely to occur in a wider set of susceptibility regions, with potential implications for clinical genetic testing and disease prevention.

DeVries AA *et al*. (2022). Copy Number Variants Are Ovarian Cancer Risk Alleles at Known and Novel Risk Loci. *Journal of the National Cancer Institute*.

Body mass index and site-specific cancer risk

Body mass index (BMI) is known to influence the risk of various site-specific cancers, however, dissecting which subcomponents of this heterogenous risk factor are predominantly responsible for driving disease effects has proven difficult to establish. We have leveraged tissue-specific gene expression to separate the effects of distinct phenotypes underlying BMI on the risk of seven site-specific cancers.

SNP-exposure estimates were weighted in a multivariable Mendelian randomisation analysis by their evidence for colocalization with subcutaneous adipose- and brain-tissue-derived gene expression using a recently developed methodology. Our results provide evidence that brain-tissue-derived BMI variants are predominantly responsible for driving the genetically predicted effect of BMI on lung cancer. Results additionally suggest that adipose-tissue-derived BMI variants may predominantly drive the effect of BMI and increased risk for endometrial cancer, highlighting a putatively important role in the aetiology of endometrial cancer.

The study provides valuable insight into the divergent underlying pathways between BMI and the risk of site-specific cancers.

Leyden GM *et al*. (2022). Disentangling the aetiological pathways between body mass index and site-specific cancer risk using tissue-partitioned Mendelian randomisation. *British Journal of Cancer*.

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**.

Swiss Cancer League
Swiss Bridge award

Closing date: 30 April 2023   Award amount: CHF 250,000

Supports high-quality cancer research projects in Europe. This year, young investigators with projects focusing on cancer therapy resistance are eligible for application.

Education and Research Foundation for Nuclear Medicine and Molecular Imaging
The Nuclear Medicine Pilot Research Grant in Neuroendocrine Tumors (NETs)

Closing date: 1 May 2023   Award amount: USD 100,000

Designed to help a basic or clinical scientist in the early stages of his/her career conduct novel and innovative research that may be leveraged to lead to further funding from other foundations, corporations or government agencies.

Cancer Research UK
Drug development project

Closing date: 10 May 2023   Award amount: USD 100,000

Can develop new cancer treatments from preclinical development through to early phase patient trials. All technology areas are considered, including small molecule, biological and other therapeutics.

Breast Cancer Now
PhD studentships

Closing date: 10 May 2023   Award amount: £150,777

Studentships are meant for researchers in the UK and Republic of Ireland with a strong track record in their field. Applicants should indicate how their proposal meets one or more of Breast Cancer Now's key strategic objectives as outlined in our strategy:

1) Improving treatments, care and services for those affected by secondary breast cancer.
2) Improving support for the physical and mental health, and the emotional wellbeing of people affected by breast cancer.
3) Developing kinder, smarter treatments for people with breast cancer and improving access to treatments for those affected.
4) Improving detection and diagnosis of breast cancer.
5) Furthering our understanding of why breast cancer occurs and spreads and using our knowledge to help prevent breast cancer developing.

National Cancer Institute
Exploratory Grants in Cancer Epidemiology (R21 Clinical Trial Optional)

Closing date: 7 June 2023   Award amount: USD 275,000

Exploratory/developmental research grant that focus on different aspects of cancer control by modifying behaviour, screening, and understanding aetiologic factors contributing to the development of cancer, and developing ways to control cancer. The overarching goal is to provide support to promote the early and conceptual stages of research efforts on novel scientific ideas that have the potential to substantially advance population-based cancer research, such as the development of novel techniques, agents, methodologies, models, or applications that could have a major impact on a field of cancer research (e.g. epidemiologic, biomedical, behavioural, health care delivery or clinical).

Cancer Research UK
Experimental medicine award

Closing date: 8 June 2023   Award amount: £5 million

This supports investigator-led studies for translational research conducted in association with a clinical trial or clinical study, with the objective of optimising treatment and maximising patient benefit.

Cancer Research UK
Multidisciplinary project award

Closing date: 6 July 2023   Award amount: £500,000

Supports collaborations between cancer researchers and scientists from engineering and physical science disciplines. The aim is to generate creative research ideas and explore their applicability in cancer research. Proposals across all engineering and physical science disciplines including physics, engineering, mathematical and computational modelling, chemical and molecular sciences, materials science, molecular and tissue engineering and regenerative medicine are welcomed.

FEATURED PUBLICATION

Acceptability of Automated Robotic Clinical Breast Examination: A Survey

Jenkinson G, Houghton N, van Zalk N, Waller J, Bello F, Tzemanaki A (2023).
Journal of Participatory Medicine.

In the United Kingdom, women are invited to attend screening mammography from 50 to 70 years of age. However, 10% of invasive breast cancers occur in women 45 or younger. This represents an unmet need for young women. Identifying a suitable screening modality for this population is challenging; mammography is insufficiently sensitive while alternative diagnostic methods are invasive or costly. Robotic Clinical Breast Examination (R-CBE) - using soft robotic technology and machine learning for fully automated clinical breast examination - is a theoretically promising screening modality with early prototypes under development. Understanding the perspectives of potential users, and partnering with patients in the design process from the outset, is essential for ensuring patient-centred design and implementation of this technology.

This pilot study investigates the attitudes and perspectives of women towards the use of soft robotics and intelligent systems in breast cancer screening. It aims to determine whether such technology is theoretically acceptable to potential users, and to identify aspects of the technology and implementation system that are priorities for patients, allowing these to be integrated into technology design.

Results showed enthusiasm for R-CBE with 92% of respondents indicating they would definitely or probably use R-CBE. 83% would willingly be examined for up to 15 minutes. The most popular location for R-CBE was at a GP surgery, whereas the most accepted method for receiving the results was an on-screen display (with an option to print information) immediately after the examination.

Early patient participation in the design process allowed the authors to identify key development priorities for ensuring this new technology will meet the needs of users. Ongoing patient and public involvement at each stage of development will be essential.

Watch the YouTube video about project ARTEMIS: Advanced Robotic breasT ExaMination Intelligent System

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The content of this newsletter is not the intellectual property of the Network, but rather an amalgamation of information obtained through a variety of sources including our community members, research groups and University of Bristol school bulletins and press releases.

Affiliations are stated wherever possible, however please note that omissions do happen and we apologise in advance for any you may come across. All information is merely for educational and informational purposes. We cannot offer medical advice and any queries regarding treatment for a specific medical condition or participation in a clinical trial should be addressed to your healthcare provider. While the information herein has been verified to the best of our abilities, we cannot guarantee that there are no mistakes or errors.

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