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Cancer Newsletter

February / March 2015

Web Email

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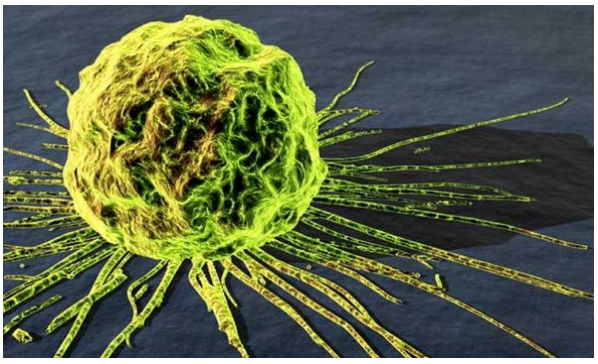
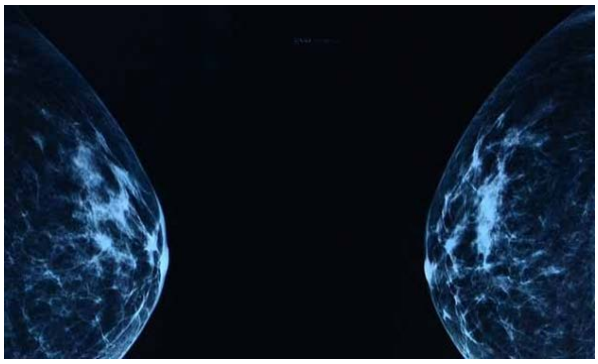


Cancer research at Bristol is a vibrant cross-disciplinary community which focuses on core strengths in cancer cell biology, genetic and lifecourse epidemiology and health services research. In partnership with Bristol NHS Trusts and the University of West of England, we aim to accelerate the identification and translation of research into clinical practice for the early detection and treatment of cancer.

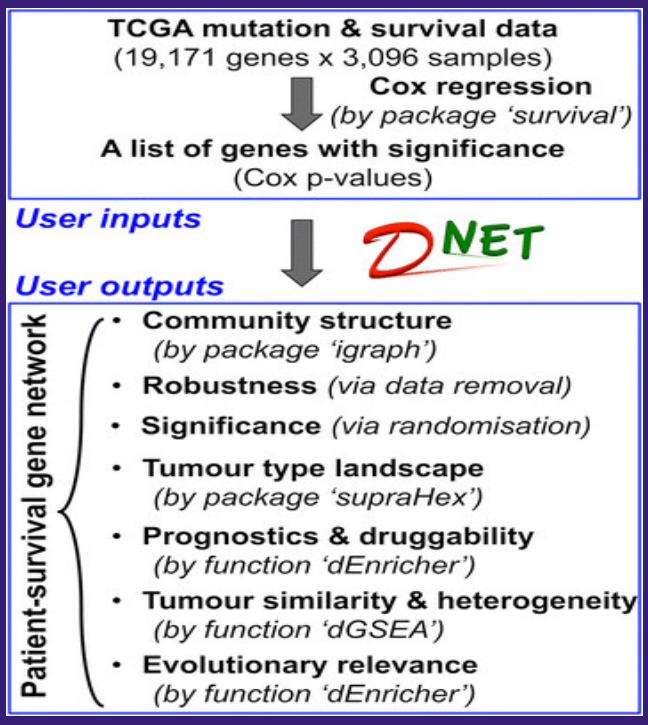


Cancer is a leading cause of death and morbidity worldwide, and with the ageing of the population and changes in lifestyle such as increasing obesity, its incidence is likely to continue to rise. Research in Bristol, lead by internationally recognised experts in the field, is looking to enhance early diagnostics, screening and prevention of a variety of cancers.

THIS MONTH'S SHOWCASED ARTICLE

The 'dnet' approach promotes emerging research on cancer patient survival

Fang, H. & Gough, J. (2014). *Genome Medicine.* 6(64). doi:10.1186/s13073-014-0064-8



Schematic workflow of dnet *in discovering and interpreting the patient-survival gene network:*

Julian Gough is Professor of Bioinformatics in the Department of Computer Science. This paper from his lab based in the new Life Sciences Building offers completely model insights and, to any cancer aficionado, some of the highlighted genes leap as key players. Others may indeed offer new drugs and targets as the authors propose. - Paul Martin, Theme Lead

We propose that patient survivalness can be addressed at cross-tumour levels. Like the cancer hallmarks, there might exist common molecular programs (likely acting as gene networks) controlling cancer patient survivalness, irrespective of tumour type, age and gender. Patient survivalness is probably not merely a statistical product of correlation with survival time, but also is a cumulative outcome of mutated genes that are rooted in their evolutionary history. Any attempts to address these questions will reshape our clinical practice in cancer prognosis, diagnostics and even therapy.

To promote hypothesis-driven research on survivalness, we present an integrative approach called '*dnet*'. This method supervises both mutation and survival data, in the context of prior knowledge of the network, to search for a core gene network controlling cross-tumour cancer patient survival. This survival network is robust to data removal and is statistically significant as estimated under data randomisation. On evaluating performance on survival gene identifications, our method is superior to existing network-based methods (although most of them are not designed for this purpose). Via integrating with ontology and evolution knowledge, *dnet* is also able to clarify the survival network

with relevance to: prognostic and druggable power, tumour heterogeneity and commonality, and evolutionary origins. The '*dnet*' approach thus represents a significant advance in emerging research on cancer patient survivalness, especially in an ever-maturing era of personalised medical genomics.

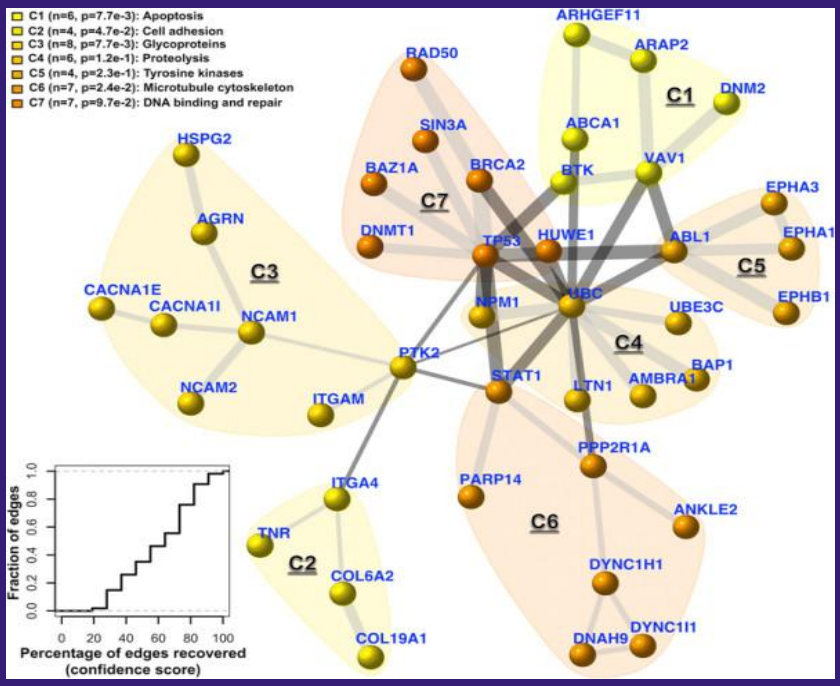


Image caption: A core patient-survival gene network, and its community structure and robustness. This network contains 42 genes, most of which, upon mutation, are significantly correlated with patient survival

Applying *dnet* to analyse all of the 'TCGA' mutation and clinical data of >3,000 patients covering multiple tumour types, we uncovered a network of genes (see figure above) for which most mutations are significantly correlated with patient survival. This survival network has community structure responsible for distinct aspects of tumour hallmarks. It is insensitive to the removal of single tumour types, is not an artifact of data characteristics, can be used for characterising relationships between tumour types and is generally informative for characterising survivalness for individual tumour types as well. The kind of survival network would not be identified via other commonly used methods or indeed attempted. Genes in this core network seem to be far more informative for prognosis when used in combination than when used individually, and are potentially druggable in the clinic; we also show this druggability is universal for cancer-specific survival networks even though their gene members differ greatly.

EVENTS

RED Medical lunchtime surgery series - How best to respond to reviewers comments
26 March 2015, 13:00, Medical Sciences Building, room C4

Abigail Smith: Resolving conflicts between replication and transcription / Asha Bayliss: Trafficking of Vascular Endothelial Growth Factor Receptor 2
27 March 2015, 13:00, Medical Sciences Building C42

BioDynamics Workshop
15 April 2015, John McIntyre Conference Centre, The University of Edinburgh

One Health Bristol Conference
25 April 2105, Langford

Prof. Sherif El-Khamisy, University of Sheffield
29 April 2015

Festival of Postgraduate Research
30 April, 14:30, Anson Rooms, Richmond Building

David Church: title tbc Project title: *Mechanistic and biomarker evaluation of POLE proofreading mutations in cancers.*
19 May 2015, 13:00 (Clinical Science Fellow, Health Foundation, University of Oxford)

Show and Tell
To note: the next Show and Tell session being organised by Population Health will take place in May / June time. Details will be confirmed closer to the time.

Mr Ramsey Cutress, Faculty of Medicine, University of Southampton
2 June 2015

MRC Integrative Epidemiology Unit: Mendelian Randomization Conference
22 June 2015, 9:00, Victoria Rooms, Bristol

Dr Peter Campbell (Head of Cancer Genetics and Genomics, Wellcome Trust Sanger Institute): title tbc
3 December 2015, 16:00, The Seminar Room, Second Floor, Oakfield House

NEWS

- Heartfelt congratulations to Richard Martin and Caroline Relton who are in receipt of a major CRUK programme grant entitled *Reducing the burden of cancer: causal risk factors, mechanistic targets and predictive biomarkers*. Along with several co-investigators across the School of Social and Community Medicine, researchers from Manchester University and the International Agency for Research in Cancer in Lyon will be involved. Expected to start June 2015 for a period of 5 years, the programme seeks to strengthen causal inference in cancer epidemiology through the application of Mendelian randomization approaches and the exploration of epigenomic and metabolomic intermediates in 6 types of cancer (lung, prostate, renal, breast, ovarian, and head and neck). The CRUK have awarded £4.1 million and recognised this as 'an ambitious programme with potential for high impact'. The team leading the programme was also recognised by the CRUK as 'being at the cutting edge of developing and deploying Mendelian randomization methodology'. The programme will be affiliated to the MRC Integrative Epidemiology Unit.

- The incidence of prostate cancer among men of Afro-Caribbean origin is higher than in white men, they are more likely to be diagnosed as emergencies and their mortality rates are higher. Until now, it has been unclear why these disappointing outcomes exist. Researchers at the Universities of Exeter, Bristol and College London studied the preferences and choice of more than 500 men who were presented with a realistic hypothetical prostate cancer investigation scenario while attending general practices in Bristol. Each man was presented with a description of a prostate cancer symptom and estimated risk of the disease. The team found that preference for investigation was lower in black men irrespective of the risk presented in the scenario. This difference was strongest in relation to the scenarios associated with the lowest risk level, with just 44 per cent of black males opting for investigation compared with 91 per cent of white males. In both groups, the most common reason for declining investigation was low risk, but significantly more black men stated that they simply did not want to know if they had cancer. The study, published on 2 March in the British Journal of General Practice (BJGP), was supported by the NIHR Collaboration for Leadership in Applied Health Research and Care South West Peninsula (PenCLAHRC). Dr Jonathan Banks, one of the study's co-authors from the Centre for Academic Primary Care, said: "The findings help us understand some of the reasons why black males have a lower preference for investigation in prostate cancer. We hope these findings may lead to new ways to help educate the black community and health professionals about symptoms and the importance of early investigation."

  Martins, T., Ukoumunne, O. C., Banks, J., Raine, R. & Hamilton, W. (2015). Ethnic differences in patients' preferences for prostate cancer investigation: a vignette-based survey in primary care. *The British Journal of General Practice.* 65, p. e161-70.
- Brain tumour tissue is removed every day by surgeons but very few patients know they can donate brain tumour tissue to research. A new national campaign launched on 24 February seeks to raise awareness for patients and healthcare professionals about donating brain tumour tissue and helping researchers find a cure for this disease. The campaign is led by leading medical researchers and the charity, brainstrust. A recent survey indicated that only 30 per cent of brain tumour patients are offered the opportunity to consent for their brain tumour tissue to be used in research. Yet a recent poll by brainstrust suggested that over 90 per cent of patients would be keen for their tissue to be used. Researchers will be able to use the donated brain tumour tissue for research into better treatments and to help find a cure for brain cancer.

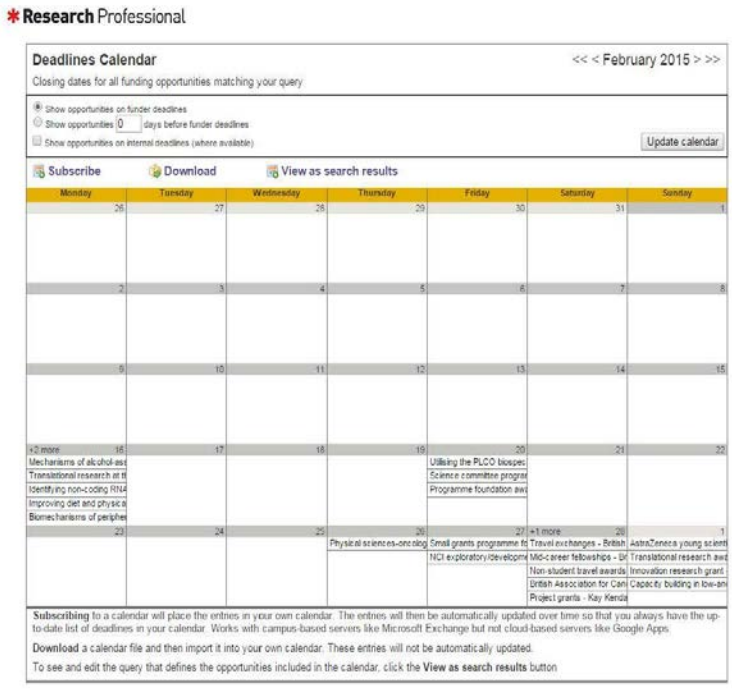
MINI MD

The UoB Mini MD programme is a new initiative to give early career basic scientist researcher with an interest in cancer an opportunity to learn about clinical issues, treatments and pathways. PhD students beginning basic science programmes related to cancer will spend several half day sessions over a two week period visiting outpatient clinics, surgical theatre sessions and teaching sessions on clinical issues to gain a better understanding of the potential relevance to patients of their current research, help them shape the science questions to be better aligned with clinical issues, and build the relationships with clinicians to drive forward translational research. The programme will be run as a pilot beginning in October 2015, with limited places but with a view to expanding it in the coming years. There are no costs associated with this programme.

Current PhD students are invited to send an application by email to Dr Axel Walther, Prof Ann Williams, or Prof Paul Martin outlining their research aims and how participation in the programme would help their research. A brief statement of support form the supervisor is required, including an indication that the PhD student will be able to spend the time in the clinic.

FUNDING OPPORTUNITIES

A **calendar** of potential **funding opportunities** for Cancer has been set up via Research Professional which details the funding opportunity according to submission deadline for the whole year. This calendar is accessible via their **website** and will be updated automatically according to the search criteria for Cancer Studies and Oncology. Other areas can be added by request- please email the theme with suggestions and/or comments.



British Medical Association

Research Grants

Aim to encourage and further medical research in a variety of subject areas, ranging from rheumatism and arthritis to cardiovascular disease, cancer and neurological disorders. The following awards are available: TP Gunton grant (£40,000) for proposals on public health relating to cancer; Strutt and Harper grant (£40,000) on improving the uptake of preventative measures.

Award Amount: £40,000 Deadline: 09-Mar-15

Department of Health

Programme Development Grants for Applied Research: Mesothelioma Themed Call

Aim to increase the rate and number of successful applications for a full programme grant by supporting the completion of the necessary preparatory work involved in a competitive stage-2 grant application. Development grants can support activities such as: evidence synthesis that might include modelling; selection or development of interventions or measures of outcome; pilot or feasibility studies to determine recruitment and participant retention rates, inform sample sizes calculations or optimise delivery of the intervention; demonstration of practical ability to undertake elements of the future programme, such as when complex data linkage is required; strengthening of existing collaborations with methodological experts necessary to deliver the proposed research programme.

Award Amount: £100,000 Deadline: 10-Mar-15

Society for Pediatric Radiology Research and Education Foundation

Pilot Award

Aims to provide a higher level of support for pediatric radiology -related projects c
can be used to fund protected time. Applications should endeavor to focus on unique aspects of
imaging or image -guided therapy/inte
imaging expertise in improving health care in children, embrace broader cross boundary impact, including public policy or translational medicine, cultivate multidisciplinary cooperation, and provide opportunities for additional funding.

Award Amount: US$50,000 Deadline: 15-Mar-15

Cancer Research UK

Multidisciplinary Project Award

Supports collaborations between cancer researchers and scientists from engineering or physical science disciplines. The research themes within remit for this award include: the direct application of physics, engineering, chemical or mathematical concepts to address the underlying physical processes of cancer, including tumour initiation, growth and metastasis; the development and translation of technologies for direct applications in, or a clear path to, a direct application in the prevention, diagnosis or treatment of cancer.

Award Amount: £500,000 Deadline: 25-Mar-15

Cancer Research UK

Prospective Sample Collections Project Grants

Support prospective collections of samples associated with clinical trials as well as strategy enabling sample collections.

Award Amount: not specified Deadline: 25-Mar-15

Cancer Research UK

Feasibility Study Project Grants

Fund investigator-led studies testing aspects of feasibility, tolerability or efficacy.

Award Amount: £150,000 Deadline: 25-Mar-15

Cancer Research UK

Phase III Clinical Trial Grant

Support studies for cancer treatment directed at the tumour, such as chemotherapy, radiotherapy and surgery, with the principal objective of improving survival. Grants are for a maximum of 10 years.

Award Amount: £100,000 Deadline: 25-Mar-15

Bone Cancer Research Trust

Research Grants

Support novel research proposals that will lead to interventions to improve the time to diagnosis for patients with bone cancer. BCRT offers small grants worth up to £10,000, pump-priming grants of up to £30,000 and project grants of up to £75,000.

Award Amount: £75,000 Deadline: 28-Mar-15

Cancer Research Institute

Irvington Postdoctoral Fellowships

Support young scientists at leading universities and research centres around the world who wish to receive training in cancer immunology. Projects should be hypothesis driven, mechanistic studies in both immunology and tumour immunology that directly impact understanding of the immune system's role in cancer risk, tumour initiation, progression, metastasis, host response to tumours or the treatment of cancer.

Award Amount: US$164,500 Deadline: 01-Apr-15

Cancer Research UK

New Agents Committee Trial Grants

Support early phase patient trials of new cancer treatments including combinations of treatments and radiotherapy.

Award Amount: £300,000 Deadline: 03-Apr-15

Wellcome Trust

Research Career Development Fellowships in Basic Biomedical Science

Enable postdoctoral scientists to become independent research scientists and undertake research at an institution in the Republic of Ireland. Scientists must work across the remits of specific funding streams, including cellular, developmental and physiological sciences; genetic and molecular sciences; infection and immunobiology; neuroscience and mental health; population health.

Award Amount: not specified Deadline: 17-Apr-15

Worldwide Cancer Research

Project Grants

Support fundamental and translational research into the causes, mechanisms, diagnosis, treatment and prevention of cancer. Proposals that demonstrate a small clinical element as an essential part of a basic or translational research project may be permitted.

Award Amount: £250,000 Deadline: 24-Apr-15

European Society for Medical Oncology

Translational Research Fellowships

Support research in oncology through training, career development and translational research projects. Each applicant must be: full or junior ESMO member, or apply for membership; an oncologist with at least one year experience in medical, radiation or surgical oncology; be under the age of 40; be proficient in English.

Award Amount: €72,000 Deadline: 01-May-15

Cancer Research UK

Cancer Immunology Project Awards

Aim to to catalyse research and build the UK's research base in cancer immunology by funding immunologists in non-cancer fields. Proposals may address any area of immunological research including any of the following key areas: cellular and molecular immunology; inflammation, allergy, transplantation and auto immunity; the immune response to infection; the interaction of immune cells with tissues; immunity and disease susceptibility or resistance.

Award Amount: £300,000 Deadline: 18-May-15

NOTE: Paul Martin is on this CRUK panel and welcomes discussions with anyone thinking of applying to this call.

Department of Health

Research for patient benefit – including mesothelioma themed call

Supports high-quality research that will be of direct benefit to users of the NHS in England. Proposals covering a wide range of health service issues and challenges are encouraged, including:

- studies of the provision and use of NHS services;
- evaluations of the effectiveness and cost effectiveness of interventions;
- examinations of the resource utilisation of alternative means for healthcare delivery;
- scrutinising of innovations and developments;
- feasibility studies

In addition, funding is available for clinical and applied health research into mesothelioma, including prevention, earlier diagnosis, treatment and care.

Award Amount: £350,000 Deadline: 21-May-15

Medical Research Council

UK-Thailand joint health research call

The scientific remit includes studies into Cancer, particularly those outlined below which are major causes of death in Thailand: Lung cancer: basic research to understand the disease mechanisms, and research and development related to biological markers for disease detection, monitoring and treatment; Cholangiocarcinoma: basic research on early diagnostic markers, and potential new more effective therapies; Oesophageal cancer: basic research related to disease development mechanism, and biological marker for treatment.

Award Amount: £444,000 Deadline: 02-Jun-15

Cancer Research UK

Population Research Committee Project Grants

Support projects that address clinical and public health epidemiology, educational and behavioural research in areas of prevention, screening and early diagnosis, clinical trials methodologies or statistics, and secondary physical effects of treatment.

Award Amount: £300,000 Deadline: 19-Jun-15

Cancer and Polio Research Fund

Research Grants

Support research into cancers, with particular reference to the causes, development and treatment of these diseases, or research into polio and other crippling diseases. Grants may be used for direct costs of research and to support research symposia or lectures for the dissemination of findings.

Award Amount: not specified Deadline: 15-Oct-15

Cancer Research UK

CRUK and Bupa Foundation Cancer Prevention Fund

Supports postdoctoral researchers and healthcare professionals who conduct research into behavioural and lifestyle changes that can prevent people from getting cancer. Applications must have the potential to be translated into practice or influence policy.

Award Amount: not specified Deadline: 23-Oct-15

Leukemia and Lymphoma Research

Bennett Fellowships

Awarded to outstanding clinical and non-clinical qualified postdoctoral researchers to establish themselves as independent investigators in any aspect of haematological research relevant to the charity's mission. Fellowships are up to five years in duration together with one research assistant or postdoctoral post.

Award Amount: not specified Deadline: 01-Nov-15

Royal Society

Research Professorships

Enable world-class scientists to be relieved from teaching and administration duties in order to focus on research. Research in any of the natural and applied sciences, including medical science, engineering and interdisciplinary research, may be supported.

Award Amount: £1.1M Deadline: 03-Nov-15

Cancer Research UK

Clinician scientist fellowship

This enables scientists to develop their clinical academic research career. The fellowship provides salaries for the fellow and one research assistant, and associated running expenses for up to four years.

Award amount: Not specified Deadline: 20-Nov-15

PUBLICATIONS

Biswas, M., Ades, A. E. & Hamilton, W. T. (2015). Symptom lead times in lung and colorectal cancers: what are the benefits of symptom-based approaches to early diagnosis? *British Journal of Cancer*. 112, p. 271-277.

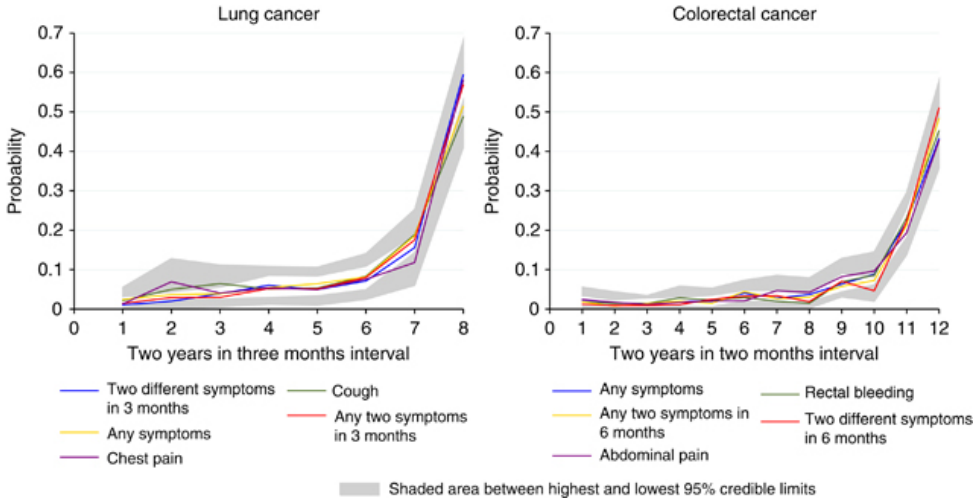


Image caption: *Symptom Lead Time distribution for five investigative criteria, lung and colorectal cancers. Shaded areas between the highest and lowest upper and lower 95% credible intervals.*

Clive, A. O., Wilson, P., Taylor, H., Morley, A. J., de Winton, E., Panakis, N., Rahman, N., Pepperell, J., Howell, T., Batchelor, T. J. P., Jordan, N., Lee, Y. C. G., Dobson, L. & Maskell, N. A. (2015). Protocol for the surgical and large bore procedures in malignant pleural mesothelioma and radiotherapy trial (SMART Trial): an RCT evaluating whether prophylactic radiotherapy reduces the incidence of procedure tract metastases. *BMJ Open*. 5(1), p. e006673.

Gilbert, R., Bonilla, C., Metcalfe, C., Lewis, S., Evans, D. M., Fraser, W. D., Kemp, J. P., Donovan, J. L., Hamdy, F. C., Neal, D. E., Lane, J. A., Smith, G. D., Lathrop, M. & Martin, R. M. (2014). Associations of vitamin D pathway genes with circulating 25-hydroxyvitamin-D, 1,25-dihydroxyvitamin-D, and prostate cancer: a nested case-control study. *Cancer Causes and Control*. Published online 9 December 2014.

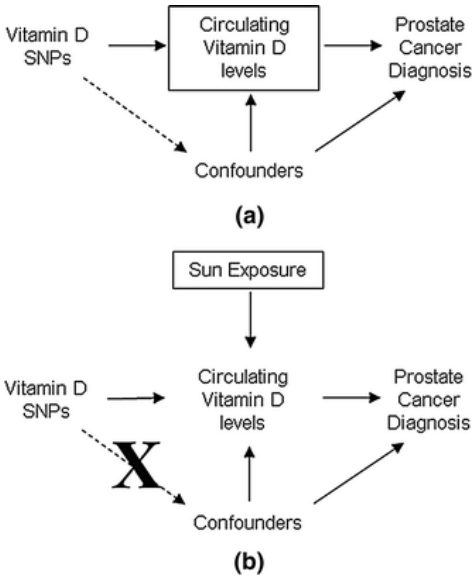


Image caption: Diagram describing collider bias. ***a*** *If we condition on circulating vitamin D levels (box), we could create on association of SNPs with confounders (dashed line).* ***b*** *If we condition on sun exposure (box), the association between SNPs and confounders is not generated because the SNPs are not associated with sun exposure (dashed line is removed)*

Vincent, E. E., Elder, D. J. E., O Flaherty, L., Pardo, O. E., Dzien, P., Phillips, L., Morgan, C., Pawade, J., May, M. T., Sohail, M., Hetzel, M. R., Seckl, M. J. & Tavaré, J. M. (2014). Glycogen synthase kinase 3 protein kinase activity is frequently elevated in human non-small cell lung carcinoma and supports tumour cell proliferation. *PloS one*. 9(12), p. e114725.

Banks, J. P., Walter, F. M., Hall, N., Mills, K., Hamilton, W. & Turner, K. M. (2014). Decision making and referral from primary care for possible lung and colorectal cancer: a qualitative study of patients' experiences. *The British Journal of General Practice : the journal of the Royal College of General Practitioners*. 629(64).

Bibby, A. C., Clive, A. O., Slade, G. C., Morley, A. J., Fallon, J., Psallidas, I., Pepperell, J. C. T., Slade, M. G., Stanton, A. E., Rahman, N. M. & Maskell, N. A. (2014). Survival in patients with malignant pleural effusions who developed pleural infection: a retrospective case review from 6 UK Centers. *Chest*. Published online 27 November 2014.

Mavrou, A., Brakspear, K., Hamdollah-Zadeh, M., Damodaran, G., Babaei-Jadidi, R., Oxley, J., Gillatt, D. A., Ladomery, M. R., Harper, S. J., Bates, D. O. & Oltean, S. (2014). Serine–arginine protein kinase 1 (SRPK1) inhibition as a potential novel targeted therapeutic strategy in prostate cancer. *Oncogene*. Published online 10 November 2014.

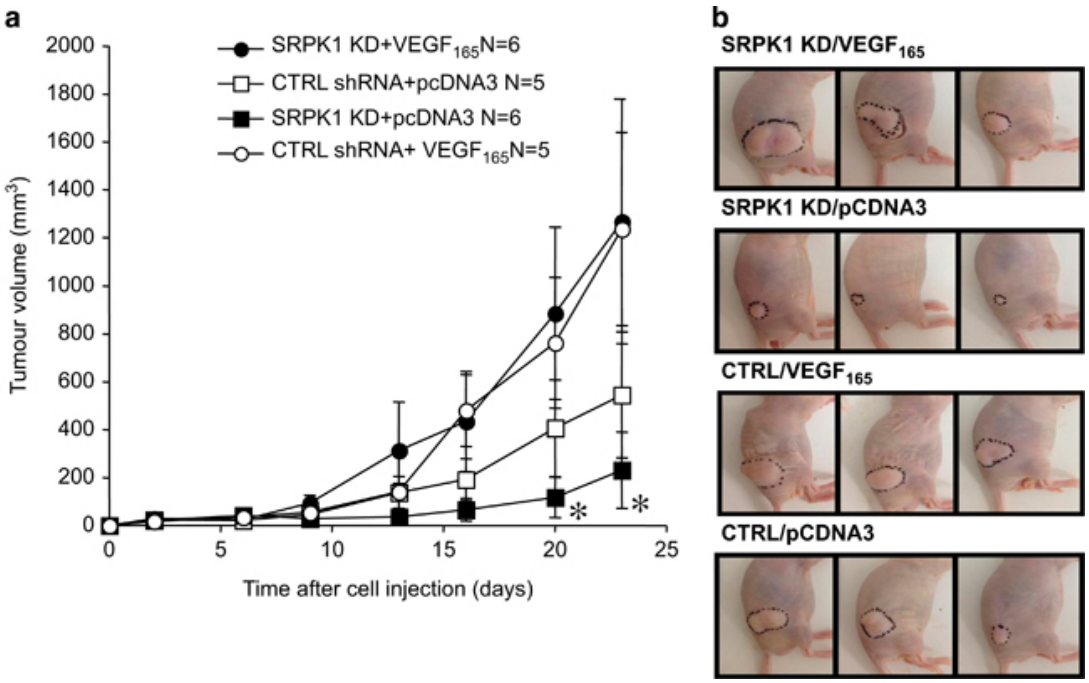


*Image caption: Exogenous expression of VEGF cDNA from a VEGF promoter rescues the effect of SRPK1-KD on tumour growth in vivo. (**a**) Tumour growth curves for four groups of mice injected subcutaneously with the following stably transfected cells: open circles, control shRNA and $VEGF_{165}$ plasmid; filled circles, SRPK1-KD and $VEGF_{165}$ plasmid; open squares, control shRNA and empty vector; filled circles, SRPK1-KD and empty vector. *P<0.05. (**b**) Examples of tumour growth in all mice groups (tumours outlined in black).*

Adams, J. C. (2014). Fascin-1 as a biomarker and prospective therapeutic target in colorectal cancer. *Expert review of molecular diagnostics*. 15(1), p. 1-8.

Ramani, P., Taylor, S., Miller, E., Sowa-Avugrah, E. & May, M. (2015). High phosphohistone H3 expression correlates with adverse clinical, biological and pathological factors in neuroblastomas. The Journal of Histochemistry and Cytochemistry. Published online 14 February 2015.

Morgan, R. G., Molnar, E., Jones, R. F., Collard, T. J., Lane, J. D., Greenhough, A., Paraskeva, C. & Williams, A. C. (2015). Nutrient stress alters the glycosylation status of LGR5 resulting in reduced protein stability and membrane localisation in colorectal tumour cells: implications for targeting cancer stem cells. *British Journal of Cancer.* 112, p. 714-719.

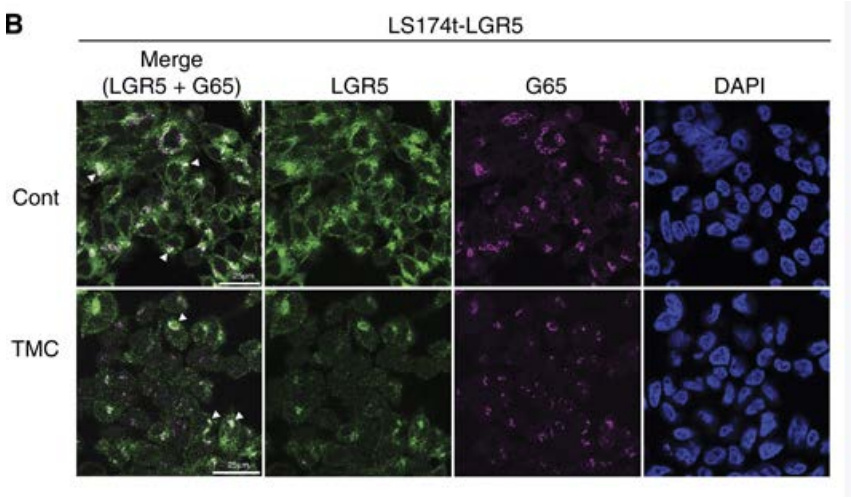


Image caption: Inhibiting LGR5 glycosylation results in reduced localisation within the cis-Golgi network. Confocal laser scanning microscopy Z-sections showing intracellular LGR5 expression in fixed and permeabilised (A) LoVo and (B) LS174t-LGR5 cells following 24 h treatment with DMSO control or 1 μg·mL⁻¹ TM.

Marchand, C. & Medford, A. R. L. (2014). A retrospective analysis of the relationship between EBUS-TBNA diagnostic utility and lung cancer stage. *Thorax*. 69(2), p. A173.