Team SPECIFICANCER

Funded 2019-2025 by

CANCER RESEARCH UK

The Mark Foundation® for Cancer Research

The team that reshaped understanding of tissue specificity to pioneer novel combination therapies.

Challenge

Tissue specificity

CANCER GRAND CHALLENGES

Dare to think differently

Impact Report

What is Cancer Grand Challenges?

Founded by

CANCER RESEARCH UK

NIH NATIONAL CANCER INSTITUTE

"Cancer Grand Challenges funding allowed us to come together and look at scale across tumour types at different cancer drivers and tumour suppressors to solve this complex challenge."

Stephen Elledge,

SPECIFICANCER Team Lead and Gregor Mendel Professor of Genetics, Harvard Medical School and Brigham and Women's Hospital.

Cancer Grand Challenges is a global initiative that is building a pioneering, interdisciplinary community to take on and solve cancer's most complex problems.

Co-founded by the two largest funders of cancer research in the world, Cancer Research UK and the National Cancer Institute in the US, Cancer Grand Challenges aims to accelerate high-impact research and translate discoveries for public and patient benefit by transforming how team science is conducted.

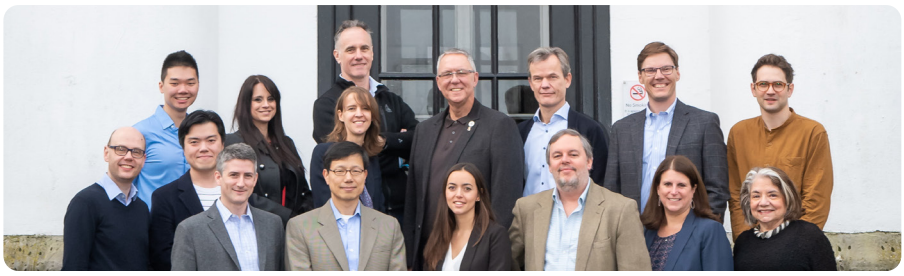
Through Cancer Research UK, Cancer Grand Challenges is building a network of like-minded partners and individual donors around the world, all of whom share our aspiration to create change. Our work wouldn't be possible without their collective support. We are especially grateful to The Mark Foundation for Cancer Research who co-funded the SPECIFICANCER team.

The challenge

In 2017, Cancer Grand Challenges set the tissue specificity challenge, to understand why, despite being expressed in a wide variety of tissues, some cancer genes contribute to tumorigenesis only in certain tissues but not in others. For example, why mutations in the BRCA1 and BRCA2 genes are only implicated in breast and ovarian cancer, when faulty genes are present in nearly all cells within the body. It was expected that solving the challenge would identify the biological mechanisms underlying tissue specificity and inform future approaches to prevent or treat cancer.

The SPECIFICANCER team hypothesised that the ground architecture of a particular tissue, its epigenetic landscape laid down during development, determines the tissue specificity of cancer driver genes. After a rigorous selection process, led by our Scientific Committee of word-leading experts, the team was chosen to tackle the tissue specificity challenge. In 2019 the team received funding from Cancer Research UK and The Mark Foundation for Cancer Research, focusing its work on some of the most potent tissue-specific oncogenes, from the RAS/MAPK, WNT/β-Catenin, and EZH2/Polycomb pathways. SPECIFICANCER investigated eight tissue types, those most commonly associated with cancer development: breast, bowel, lung, skin, kidney, liver, brain and pancreas.

Meet team SPECIFICANCER



Led by Stephen Elledge at Harvard Medical School and Brigham and Women's Hospital, this multidisciplinary team of scientists from the UK, USA and the Netherlands brought together global research leaders with expertise spanning genetics, epigenetics, bioinformatics, cell biology and clinical research.

"SPECIFICANCER systematically mapped how genes are switched on or off across tissues and how this affects the behaviour of cancer-driving and tumour-suppressing genes. The team proved that tissue specificity comes from a cell's epigenetic environment, which allows cancer drivers to signal in a way that confers an advantage."

Gemma Balmer

Head of Research, Cancer Grand Challenges

Map Key

- United States
- United Kingdom
- Netherlands

Stephen Elledge

Team lead, Harvard Medical School and Brigham and Women's Hospital, US

$24.4m
Amount of funding awarded

4
Clinical trials in development

33
Publications to date

39
Postdoctoral researchers trained

14
PhD students trained to date

9
Independent research groups established

Tackling the tissue specificity challenge

The SPECIFICANCER team uncovered important insights into tissue specificity, helping to explain what makes a tissue permissive, or not, to a specific oncogene. SPECIFICANCER highlighted the complexity of the challenge; while there may not be an overall generalisable principle, the team uncovered a variety of intricate mechanisms underlying tissue-specific cancer development.

Through a focused team effort, SPECIFICANCER pinned down the rules of one of the most prolific oncogenes, RAS, proving what was previously hypothesised based on individual studies. By systematically looking across tissues the team demonstrated an overarching requirement for Myc to tolerate a proliferative signal.

For the WNT pathway, the team has shown further levels of tissue specificity - not only in pathway dependency itself, but in the specific genes used to activate the pathway. SPECIFICANCER revealed that the oestrogen receptor is a mutator and also identified how its proliferative effects are tissue specific. Through pioneering *in vivo* screens with an intact immune system, the team revealed the role of the adaptive immune system in driving tumour suppressor inactivation.

SPECIFICANCER identified that tissues can be refractory to transformation by particular oncogenes for multiple reasons. These include a failure to activate downstream pathways, the absence of cooperating partner gene expression, or the activation of inhibitory feedback pathways that turn down signalling. Overall, the team's work showed that tissue specificity indeed comes from a cell's epigenetic environment, which allows cancer drivers to signal in a way that confers an advantage.

Paving the way for a new era of precision oncology

As well as identifying novel biological mechanisms, the team has identified tissue-specific vulnerabilities. Across tumour types, SPECIFICANCER has shown the success of a critical combination of inhibitors, epigenetic and oncogenic, which first drive differentiation to then allow execution of tissue specific developmental cell death pathways.

Based on its discovery science, the team is poised to start multiple clinical trials and is following up on additional novel therapeutic targets.

Timeline

Tackling the challenge

2017

Tissue specificity challenge set

2019

SPECIFICANCER awarded $24.4m in funding

2019

MARCH 2019

Tissue-specificity in cancer: The rule, not the exception
SCIENCE

JUNE 2019

Tissue-Specific Oncogenic Activity of KRASA146T
CANCER DISCOVERY

SEPTEMBER 2019

Proteogenomic Network Analysis of Context-Specific KRAS Signaling in Mouse-to-Human Cross-Species Translation
CELL SYSTEMS

2020

MAY 2020

A Deregulated HOX Gene Axis Confers an Epigenetic Vulnerability in KRAS-Mutant Lung Cancers
CANCER CELL

2021

MARCH 2021

The origins and genetic interactions of KRAS mutations are allele- and tissue-specific
NATURE COMMUNICATIONS

MAY 2021

MNK Inhibition Sensitizes KRAS-Mutant Colorectal Cancer to mTORC1 Inhibition by Reducing eIF4E Phosphorylation and c-MYC Expression
CANCER DISCOVERY

Tissue specificity of KRAS mutant alleles

SPECIFICANCER has identified KRAS allele and tissue-specific genetic dependencies. By comparing the common G12D with the rarer A146T, the team identified the biochemical and structural differences in how these mutant GTPases signal, exerting different downstream effects in a tissue specific manner, which reflects their mutational frequencies observed in tumours. The team went on to uncover specific roles of KRAS G12D in suppressing miRNA function and the underlying mechanisms.

In **non-small cell lung cancer** the team revealed that 50% of KRAS mutant tumours express HOXC10 due to epigenetic dysregulation caused by defects in the epigenetic regulator PRC2. The team found that these tumours are sensitive to a combination of BET and MEK inhibitors, uncovering both a therapeutic vulnerability and HOXC10 as a biomarker for response.

First author **Douglas Brubaker** is now an Assistant Professor at the Case Western Reserve University School of Medicine, US.

MYC is required for RAS permissivity

The overall rule that the team's work emphasised is that for RAS to drive transformation in a particular tissue, cells must be capable of handling a proliferative signal and therefore MYC must also be present, with RAS regulating MYC stability to allow this. The team showed in colorectal cancer how KRAS upregulates translation, both bulk and mRNA specific, via the MNK/eIF4E pathway, resulting in increased levels of MYC. This work also identified the potential for MNK inhibition to sensitise **KRAS mutant colorectal cancers** to mTORC1 inhibitors.

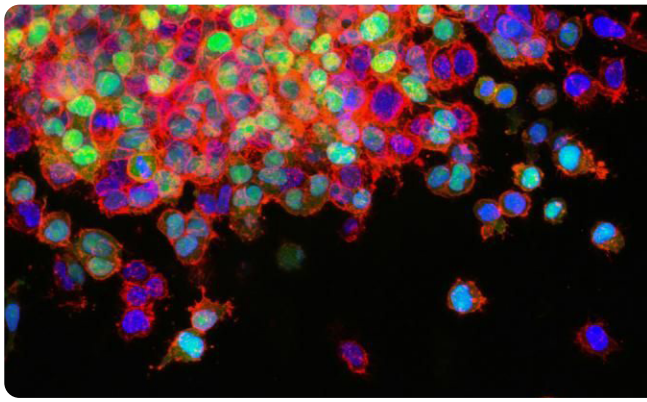


Image credit: NCI

Uncovering the bigger picture

Timeline Key:

- Tissue specificity of KRAS mutant alleles
- Tools & technologies
- Critical combinations
- Exploiting epigenetic interplay
- Tissue specificity of aneuploidy
- Unlocking WNT permissiveness

JUNE 2021

NOTUM from Apc-mutant cells biases clonal competition to initiate cancer
NATURE

Identifying targets for colorectal cancer prevention

In the **intestine,** when investigating tissue specificity of the WNT pathway, SPECIFICANCER identified that Apc-mutant stem cells secrete WNT antagonists, especially NOTUM. This suppresses WNT signalling in the surrounding wild-type stem cells, leading to their differentiation. Apc-mutant clones can then take over the intestinal crypt and drive tumourigenesis. This work uncovers NOTUM as an important target for **colorectal cancer** prevention and, together with industry partners, the Sansom lab is currently exploring NOTUM inhibitors in preclinical models.

First author **Dustin Flanagan** is now a Lab Head at Monash University, Australia.

JUNE 2021

Oncogenic BRAF, unrestrained by TGFβ-receptor signalling, drives right-sided colonic tumorigenesis
NATURE COMMUNICATIONS

Modelling intra-tissue cell-type specificity

The team explored not just tissue specificity, but cell type specificity of oncogenic mutations to drive transformation, developing a representative model of right-sided **colorectal cancer.** The team showed that for BRAF to be oncogenic in this model, TGFβ receptor signalling must be lost and YAP must be activated. Inflammation driven by the colorectal microbiome could also substitute for MAPK pathway activation to activate the transcriptional programs required for tumourigenesis.

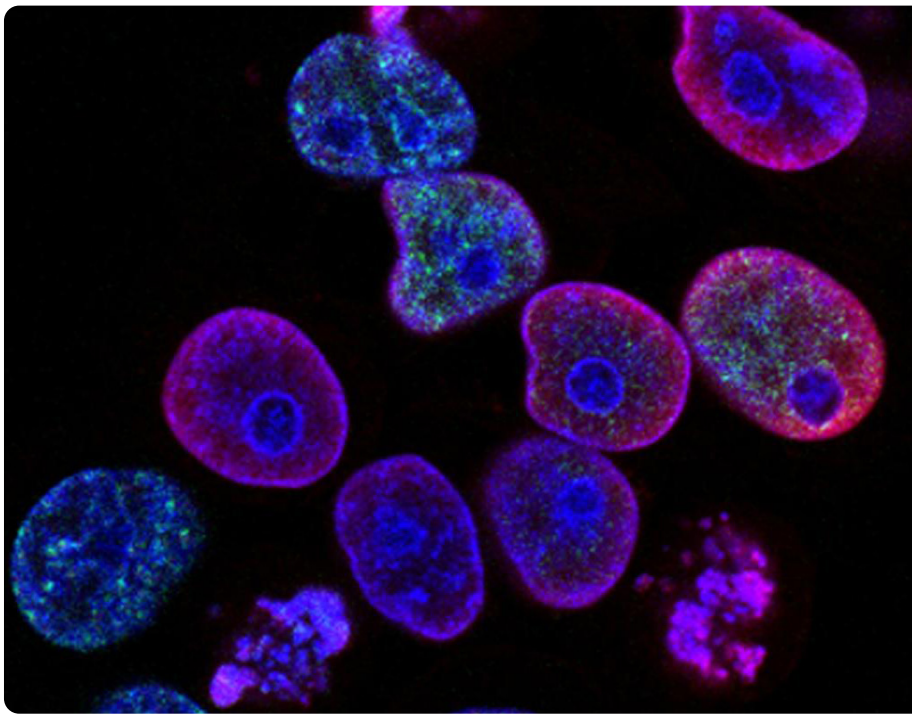


Image credit: NCI

SEPTEMBER 2021

The adaptive immune system is a major driver of selection for tumor suppressor gene inactivation
SCIENCE

2022

SEPTEMBER 2022

Proteogenomic analysis of cancer aneuploidy and normal tissues reveals divergent modes of gene regulation across cellular pathways
ELIFE

2023

APRIL 2023

Combating castration-resistant prostate cancer by co-targeting the epigenetic regulators EZH2 and HDAC
PLOS BIOLOGY

APRIL 2023

KaryoCreate: A CRISPR-based technology to study chromosome-specific aneuploidy by targeting human centromeres
CELL

Immune regulation of tissue specificity

By performing CRISPR screens *in vivo*, in mouse models with an intact immune system, the SPECIFICANCER team uncovered insights into the role of the adaptive immune system in driving tumour suppressor inactivation. This inactivation occurs in a tissue specific manner and is key in allowing tumours to avoid immune detection.

First author **Tim Martin** is now an Assistant Professor at the University of Virginia, US.

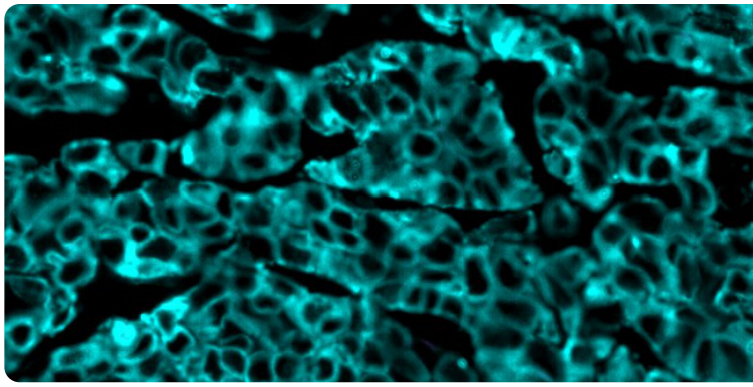


Image credit: Amy Schade

MAY 2023

ERα-associated translocations underlie oncogene amplifications in breast cancer
NATURE

JULY 2023

Oncogenic K-Ras suppresses global miRNA function
MOLECULAR CELL

AUGUST 2023

One-step generation of tumor models by base editor multiplexing in adult stem cell-derived organoids
NATURE COMMUNICATIONS

2024

FEBRUARY 2024

Accurate and sensitive mutational signature analysis with MuSiCal
NATURE GENETICS

Oestrogen drives oncogene amplification

In **breast cancer,** the team identified that oestrogen regulates focal amplification to drive oncogene expression via oestrogen receptor associated translocations, thereby uncovering that the oestrogen receptor both stimulates proliferation and acts as a mutator. The team hypothesises that tissue specificity of the oestrogen receptor to drive cancer cell proliferation is defined by oestrogen receptor binding site accessibility.

Co- first author **Doğa Gülhan** is now a Principal Investigator at Mass General Hospital Cancer Centre and an Assistant Professor at Harvard Medical School, US.

MAY 2024

Chromosome evolution screens recapitulate tissue-specific tumor aneuploidy patterns
NATURE GENETICS

SEPTEMBER 2024

KaryoTap Enables Aneuploidy Detection in Thousands of Single Human Cells
BIORXIV

Tissue specificity of aneuploidy

The SPECIFICANCER team developed whole-chromosome genetic screening methods, followed by *in vitro* evolution, to reveal tissue-specific selection for particular chromosomes, chromosome arms, and translocation patterns. Mechanistic analyses uncovered activation of Notch signalling as the pro-tumorigenic consequence of chromosome 1q gain in **breast cancer.** The team also investigated how different tumour types and normal cells compensate for aneuploidy, providing the first analysis of tissue-specific RNA- and protein-level compensation.

First author **Emma V Watson** is now a HHMI Freeman Hrabowski Scholar and Assistant Professor at the University of Massachusetts Chan Medical School, US.

OCTOBER 2024

AKT and EZH2 inhibitors kill TNBCs by hijacking mechanisms of involution
NATURE

Critical combinations

SPECIFICANCER found that EZH2 acts as an epigenetic insulator, with the PRC2 complex instructing tissue-specific oncogenes by cooperatively regulating cell state and reinforcing the effects of specific oncogenes in different tissues by preventing apoptosis. The team has shown in pre-clinical models that EZH2 inhibition cooperates with AKT inhibition in **triple negative breast cancer (TNBC)** and RAS pathway inhibition in **colorectal cancer,** with both cell death pathways converging on the pro-apoptotic protein BMF. This work gives hope for targeted therapies, especially important for TNBC, where, except for BRCA positive patients, none are approved.

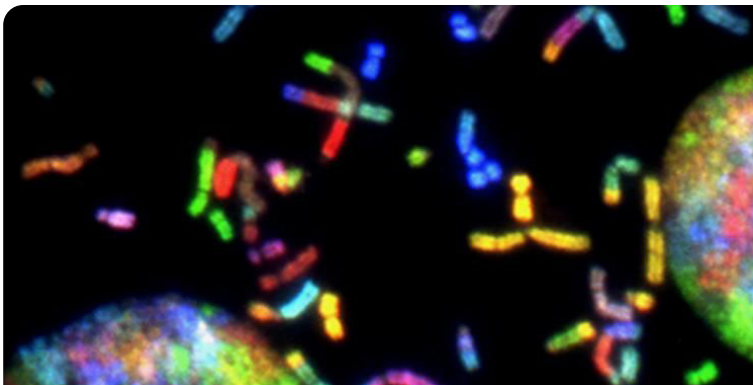
First author **Amy Schade** is now a Principal Scientist at Novartis, US.

DECEMBER 2024

Epigenetic and Oncogenic Inhibitors Cooperatively Drive Differentiation and Kill KRAS-Mutant Colorectal Cancers
CANCER DISCOVERY

First author **Patrick Loi** is now a Senior Scientist at Bayer, US.

Image credit: NCI



2025

JUNE 2025

Synergistic anti-tumor effect of combined EZH2 and DOT1L inhibition in B-cell lymphoma
BLOOD

Exploiting epigenetic interplay

SPECIFICANCER showed how EZH2 cooperates with other epigenetic programs to regulate the expression of tissue-specific genes, further demonstrating how EZH2 exerts tissue-specific effects. The team demonstrated the promise of combined EZH2 and histone deacetylase (HDAC) inhibition in **castrate-resistant prostate cancers,** an incurable form of the disease. In prostate, upregulation of ATF3, a transcription factor responsive to a wide range of cellular stresses, is critical in mediating cancer cell death.

In blood cancer, the team identified EZH2 inhibition combined with inhibition of epigenetic regulator DOT1L, as an option to treat **B-cell lymphoma.** Mechanistically, this inhibitory combination results in B cell differentiation and synergistic anti-tumour effects.

OCTOBER 2025

Integrative Proteogenomics and Forward Genetics Reveal a Novel Mitotic Vulnerability in Triple-Negative Breast Cancer
CANCER DISCOVERY

Decoding taxane sensitivity in TNBC

In **TNBC,** by integrating proteogenomics with functional genetics SPECIFICANCER identified that inactivation of the tumour suppressor PTPN12 drives chromosomal instability. The team uncovered why some TNBCs are sensitive to taxanes and microtubule targeting agents, a standard of care for TNBC, identifying options to select for those patients who will respond. Mechanistically, inactivation of PTPN12, a tyrosine phosphatase, leads to dysregulation of CDK2 and subsequently the APCFZR1 ubiquitin ligase complex, resulting in its hyperactivation. By identifying the underlying mechanism, the team has also opened the possibility of developing selective therapies.

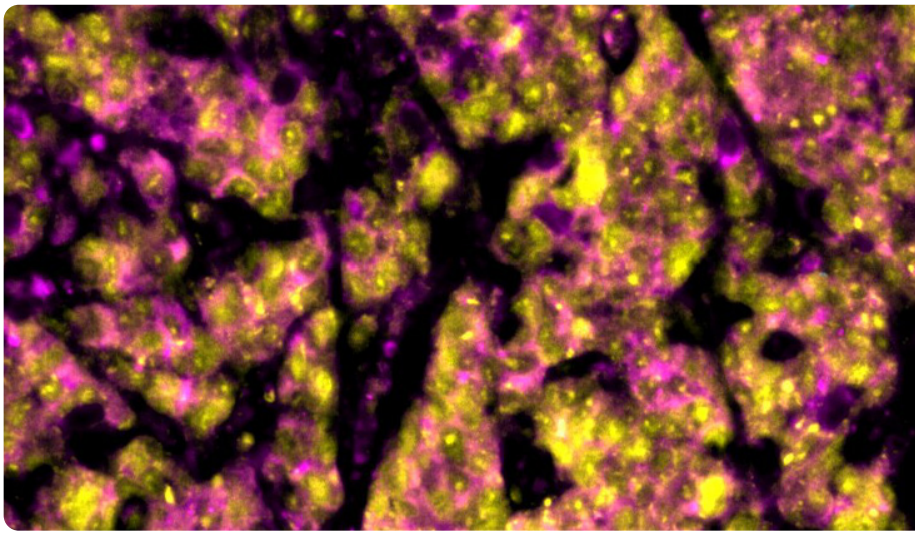


Image credit: Amy Schade

NOVEMBER 2025

Hepatic zonation determines tumourigenic potential of mutant β-catenin
NATURE

Unlocking WNT Permissiveness

In contrast to the colon, WNT signalling alone has no effect in the liver, with this tissue being non-permissive, unless MYC is also activated. Here, MYC cooperates with β-catenin mutations by driving a proliferative-translatome. The team identified zonal differences within the liver which determine the ability of Wnt to drive tumorigenesis. Wnt driven differentiation is incompatible with tumourigenesis due to downregulation of the proliferative-translatome, cells must therefore escape differentiation, which can be achieved by MAPK activation. Exploiting these mechanisms, SPECIFICANCER went on to show the potential of mTOR and IGFBP2 inhibitors to supress tumorigenesis.
The team also explained why APC loss isn't permissive in the liver, as this overactivates WNT signalling and tips the balance to differentiation, whereas Axin mutations only activate a subset of WNT target genes that are permissive for tumour formation.

First author and SPECIFICANCER future leader **Alex Raven** is now a UK Research and Innovation Future Leaders Fellow at the Cancer Research UK Scotland Institute, UK.

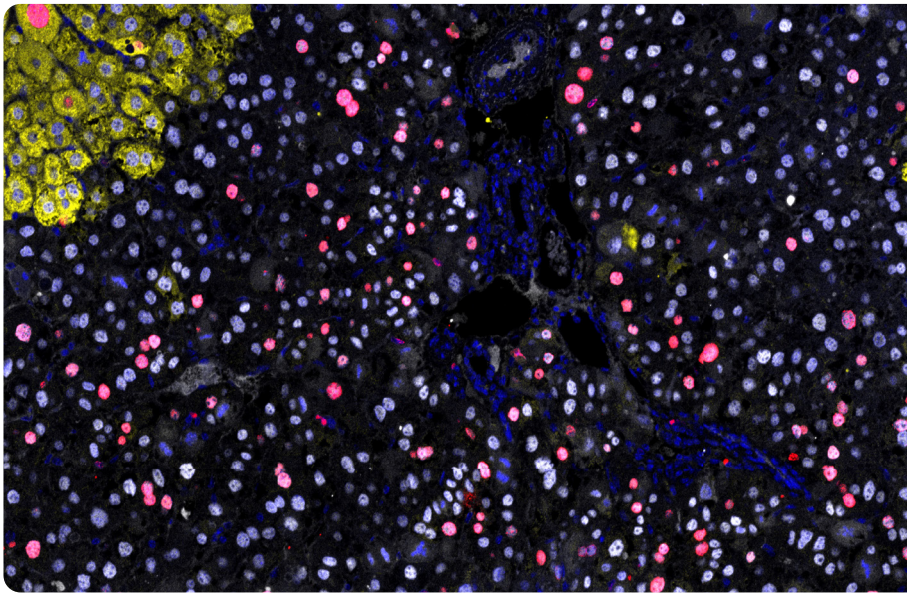
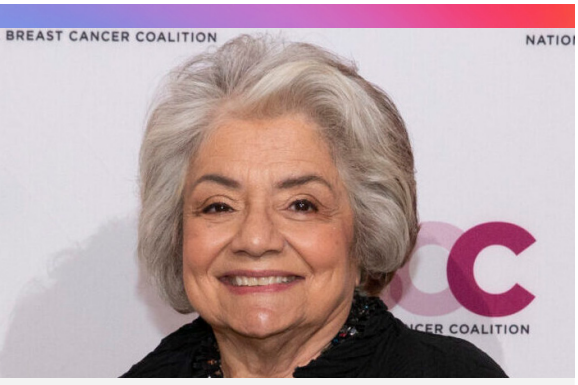


Image credit: Alex Raven

"The SPECIFICANCER team has uncovered mechanisms governing tissue specificity across many tumour types and identified creative ways to exploit them, with multiple clinical trials in the works. Their work is a powerful example of how international collaboration accelerates discovery from the lab to the clinic, and we are proud to support it."

Ryan Schoenfeld,

CEO, The Mark Foundation for Cancer Research, Co-funders of SPECIFICANCER



Fran Visco

Lead Patient Advocate, SPECIFICANCER

Tools and techniques

Along the way SPECIFICANCER developed many tools to help decipher the rules of tissue specificity that it has made available to the scientific community. The team has pioneered innovative screening methods and established KaryoCreate, a CRISPR-based approach to enable the study of chromosome-specific aneuploidy, KaryoTap, to allow high throughput aneuploidy; detection within tumours from single-cell sequencing data; and MuSiCal, for improved mutational signature analysis. SPECIFICANCER also developed methods to allow base editor multiplexing for the creation of organoids from adult stem cells, modelling tumours in a single step.

The team engineered permissive and non-permissive isogenic cell lines and animal models, exploring not just the situations where a mutation causes cancer, but comparing the effects of perturbations in both permissive and non-permissive tissues, changing the way tissue specificity is studied and creating open resources.

Future leaders impact

SPECIFICANCER's work was driven by exceptional early career researchers, many of whom have already been promoted or successfully moved on to top positions in academia and industry. SPECIFICANCER was a platform for launching their careers, with their experience within the team and the Cancer Grand Challenges initiative invaluable for their development. The Future Leaders Group held monthly virtual meetings, which fostered the development of further collaboration, and in some instances, inter-laboratory training. Members of the Cichowski lab visited the Sansom and Helin labs in Glasgow and London respectively, to gain expertise in colorectal cancer models and epigenetics, proving critical to the team's work.

Advocacy impact

Patient advocates are embedded into Cancer Grand Challenges teams and are important members of the teams we fund to address cancer's toughest challenges.

Fran Visco from the National Breast Cancer Coalition (NBCC) was the lead patient advocate for the SPECIFICANCER team. The advocates aimed to bring a patient viewpoint to the research, ensure findings beneficial to patients were fully realised and foster public understanding of the team's basic research. Highlights include the advocates and researchers co-developing a glossary of terms to aid public understanding of the team's work. The advocates also interviewed the researchers in a series of Advocate/Scientific Team Conversations, which led to a number of questions around the model systems the team used. This led to the team contributing towards the NBCC Models Project, with the development of various tools and educational resources.

In January 2025, Fran, who trains other patient advocates, was awarded the Presidential Citizens Medal from President Joe Biden, the second highest civilian honour in the US.

Looking ahead

The team has already uncovered the molecular mechanisms behind many tissue specific cancer drivers, with more work still to be published in further tumour types. The creative tools, technologies and resources the team has developed and made available to the scientific community will drive further discoveries in the cancer field and beyond, and ensure its legacy will continue to grow.

Beyond its pivotal discoveries which have changed the way we think about tissue specificity, SPECIFICANCER has gone on to demonstrate that manipulating cell states opens up therapeutic opportunities and revealed unexpected tissue specific synthetic lethalities. The team's work also inspired Cancer Grand Challenges to set the rewiring cancer cells challenge in 2025. The team is currently working with clinical colleagues and companies to develop multiple clinical trials, to translate its fundamental findings into better outcomes for patients.

Funded institutes:

Baylor College of Medicine
Brigham and Women's Hospital
Cancer Research UK Scotland Institute
Dana Farber Cancer Institute
Harvard Medical School
Hubrecht Institute
Institute of Cancer Research
New York University School of Medicine