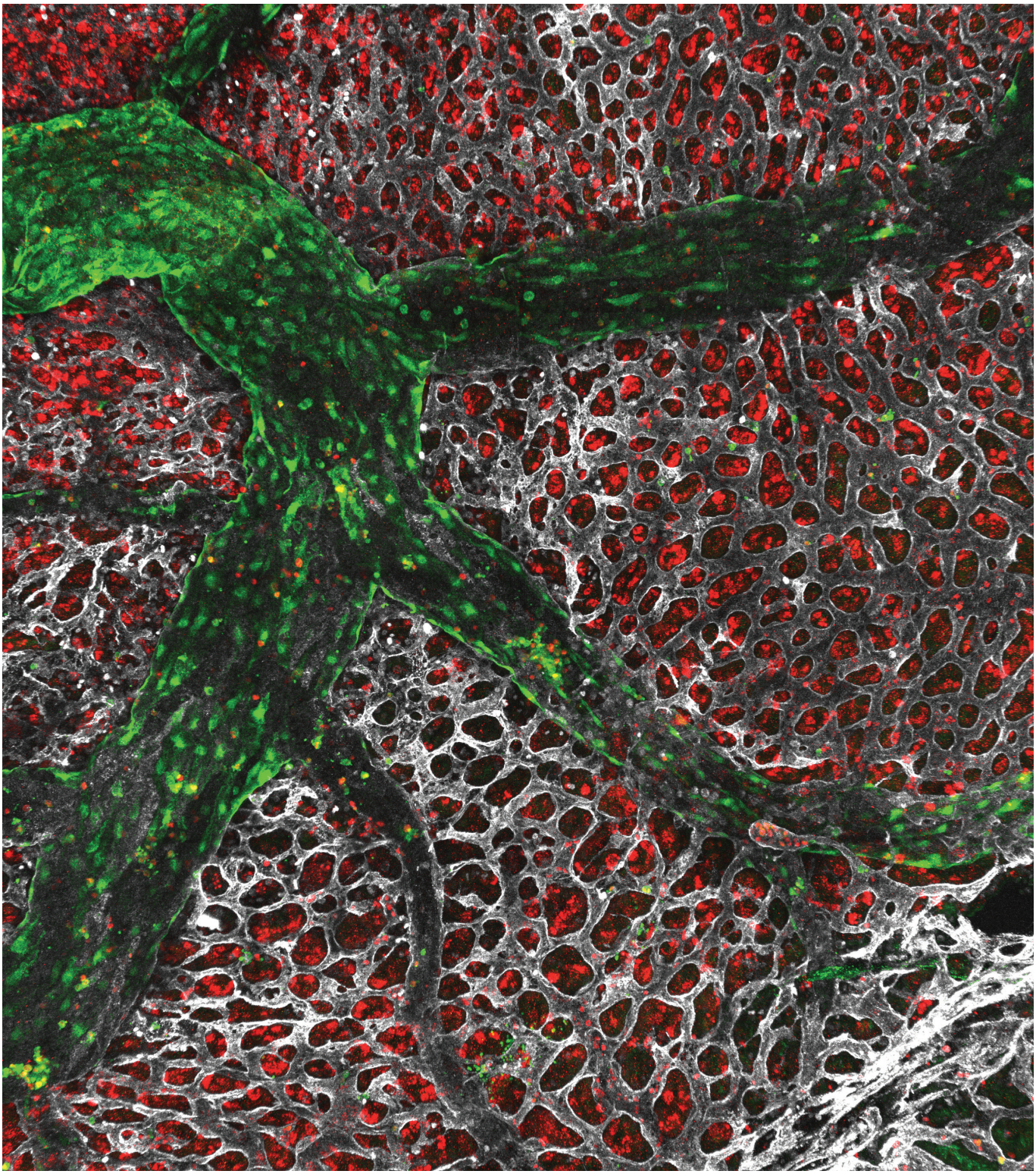
CANCER RESEARCH UK | Manchester Institute

SCIENTIFIC REPORT 2025



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COVER IMAGE

Confocal whole-mount immunofluorescence of an E10.5 mouse yolk sac shows arterial vessels (VWF, green), endothelial plexus (LYVE1, white), and hemogenic/hematopoietic cells (RUNX1, red). Rare VWF–RUNX1 and LYVE1–RUNX1 double-positive cells mark spatially distinct HE populations that give rise to lympho-myeloid and erythro-myeloid progenitors, respectively.

Image supplied by Georges Lacaud, Stem Cell Biology

SCIENTIFIC REPORT 2025

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The Cancer Research UK Manchester Institute moved to the new Paterson Building in Withington in spring 2023.



Several research groups are based in the Oglesby Cancer Research Building.

DIRECTOR'S INTRODUCTION



Professor Samra Turajlić

Director of the Cancer Research UK Manchester Institute

It is my pleasure to welcome readers to the 2025 Scientific Report for the Cancer Research UK Manchester Institute for the first time as Director. What drew me to the Institute was its scientific prestige and the opportunity to build on these strong foundations within Manchester's uniquely connected cancer research ecosystem. By bringing together fundamental biology, translational research and clinical insight, we can create a truly interdisciplinary environment focused on improving outcomes for patients with cancer. I have already been struck by the openness, curiosity and shared commitment of this community, and I am delighted to work alongside such talented researchers, clinicians and professional colleagues.

As I take on this role, I want to recognise the exceptional leadership of Professor Caroline Dive. Under her direction, the Institute navigated significant challenges while continuing to deliver world-leading research and impact. I am grateful for her continued partnership, particularly through the Cancer Research UK National Biomarker Centre, as we advance biomarker-led research and precision oncology.

My first experience of Institute culture was at the annual colloquium, a key event that reinforces the strength of our community. Held in Buxton, Derbyshire, it provided the perfect platform for me to introduce myself and get to know the researchers and their work. It was encouraging to see such energy and engagement, and to observe first-hand the strength and breadth of the science and the genuine appetite for collaboration. I was honoured to award the poster prizes to some of our early career researchers. Kirsten Tinsley won the Lizzie Hitchman Best Student Poster award; Massimo Russo won both Best Elevator Pitch and Best Poster from a Postdoc; and Griselda Awanis also won Best Poster from a Postdoc. Congratulations to all the winners for their outstanding contributions.

As part of our strategy to grow the Institute, we welcomed three new research groups in 2025. Sylvain Delaunay joined us as a Group Leader in January from the German Cancer Research Center (DKFZ), where he had been a postdoc with Prof Michaela Frye. He has established the RNA Dynamics in Cancer group, investigating how diet and RNA modifications influence plasticity in cancer cell states, particularly motility and metastasis. Within eight months, Sylvain secured Royal Society funding to explore how tRNA modifications affect cancer cell behaviour. This is an excellent start, and you can read more about his progress in the following pages.

Towards the end of the year, we appointed two Institute Fellows. William Hill joined us in October from the Francis Crick Institute, where he worked as a postdoc with Professor Charles Swanton. Will is now setting up his first independent group, Cancer Origins, where he will be focusing on how environmental exposures, such as air pollutants, shape the tissue microenvironment to support the expansion of latent oncogenic cells and promote lung cancer.

Justin Loke joined us in November from Harvard Medical School and the Dana-Farber Cancer Institute in Boston, where worked under the auspices of an AACR/CRUK Transatlantic Fellowship with Professor Ben Ebert. Funded by the Amit Patel Leukaemia Research Fellowship, established in memory of Professor Amit Patel, Justin is setting up the Myeloid Cancer Biology group. He will focus on myeloid blood cancers, including acute myeloid leukaemia, studying how different mutations interact during cancer evolution and shape disease behaviour, while continuing his clinical practice at The Christie NHS Foundation Trust.

Both have made a fantastic start, and we look forward to hearing more about their progress in the next report. My own research group, the Cancer Dynamics Lab, will be co-located between the Francis Crick Institute and Manchester, and next year we will report on their research developments.

We are also actively developing our scientific and operational strategy for the years ahead. This will include recruiting new Group Leaders and a Communications Manager, and augmenting our faculty through affiliate appointments drawn from the wider Manchester ecosystem, including The Christie and The University of Manchester. These appointments will deepen connections across disciplines and institutions, helping us translate the region's collective strengths into greater impact.



Staff and students on the last day at the joint CRUK Manchester Institute – CRUK National Biomarker Colloquium.

The past year has been another productive and successful period for the Institute, with achievements across our research community. Our researchers continue to publish influential discoveries, secure highly competitive funding and receive international recognition, and it is my pleasure to spotlight some of those accomplishments here. On a personal note, I was deeply honoured to be elected to the European Academy of Cancer Sciences, further strengthening our connections with the wider European cancer research community.

This year, we published an impressive collection of scientific discoveries, some of which are featured in our research highlights section. Among those is research published in *Cancer Cell* by Institute Fellow Amaya Virós, who leads the Skin Cancer and Ageing group. Amaya and her team demonstrated that ageing skin alters the fats available to melanoma cells, influencing how fast and where the cancer spreads. This helps explain why melanoma can behave more aggressively in older people and points to new ways to predict risk and tailor treatment according to age.

We also congratulate Georges Lacaud and his group in Stem Cell Biology, along with contributions from our core facilities, for showing that the haemogenic endothelium in different parts of the embryo follows three distinct routes to make blood cells, and that the pathway producing lifelong blood stem cells has a unique pattern of RNA isoforms that is essential for stem cell formation. These findings could help scientists generate fully functional blood stem cells in the lab for regenerative treatments for diseases such as leukaemia, aplastic anaemia and immune disorders.

In another example of the transformative science we strive for – uncovering the deep biology of cancer and turning that knowledge into hope for patients – early career researcher Charles Earnshaw, together with Senior Group Leader Santiago Zelenay, investigated whether topical therapies could overcome immunotherapy resistance in melanoma and revealed targetable mechanisms that restore anti-tumour immunity. Published in *Cancer Discovery*, these findings open new possibilities for the 50% of patients who do not respond to immunotherapy. This work reflects the collaborative, patient-focused science that defines the Cancer Research UK Manchester Institute powered by close partnerships between clinicians, researchers and our core facilities.

The power of partnership takes me to MANIFEST, a pioneering consortium and platform which I lead, bringing together 16 research organisations nationally, including CRUK MI, alongside the NHS and industry. Our publication in *Cancer Discovery* sets out how the platform will help answer fundamental questions about the immune system and cancer, and could lead to new diagnostics, treatments, better management of side effects, and novel targets to inform design of next-generation therapies. This year we have also launched prospective MANIFEST recruitment, sponsored by The Christie, and recruiting nationally with a goal of recruiting 3,000 patients receiving immunotherapy for breast, bladder, kidney or skin cancer.

Beyond personal prestige, scientific accolades are important because they promote visibility,

validate transformative discoveries and help attract research funding, while creating role models and increasing public awareness. It is therefore a pleasure to congratulate Evangelos Giampazolias, who leads the Cancer Immunosurveillance group, on receiving this year's BACR/AstraZeneca Young Scientist Frank Rose Award. His work has contributed to our understanding of the mechanisms underlying immune defence against cancer following host sensing of dying cells and signals from commensal microbes. This recognition is richly deserved, and we are excited to follow his scientific journey in the coming years.

I am also delighted to report that the Cancer Research UK Manchester Institute received an Openness Award from Understanding Animal Research for our clear communication around animal research, highlighting our innovative use of video in a recruitment campaign. This is a commendable achievement, and I congratulate everyone who has championed openness in animal research over the years, including members of the AWERB and animal facility teams. Our website is an exemplar of the kind of transparency around animal research that is so important.

External funding augments the breadth of our research and helps support the development of our researchers. Huge congratulations to Georges Lacaud on winning a BBSRC project grant to characterise the regulation of endothelial to haematopoietic cell transition in blood formation with a view to generating blood cells for therapy from human pluripotent stem cells.

In recognition of pivotal work challenging assumptions about the mechanism of transplantation, Mark Williams – who leads the Leukaemia Immunology & Transplantation group – along with Robert Wynn, Consultant Paediatric Haematologist and Director of Paediatric Bone Marrow Transplant Programme at Manchester University NHS Foundation Trust, secured major funding from Blood Cancer UK to establish a clinical trial aiming to cure untreatable leukaemia in young adults with a new type of stem cell transplant. We will follow its progress with great interest.

I am also pleased to celebrate Luciano Nicosia's achievement in obtaining a 3-year Early Career Advancement Fellowship from Blood Cancer UK. This is a fantastic opportunity for Luciano – a postdoc in Tim Somervaille's Leukaemia Biology group – and a crucial milestone in his career. His research centres on a drug called Inobrodib (or CCS1477), which has shown promise in early studies treating patients with myeloma and leukaemia. This funding will enable Luciano to develop innovative therapeutic strategies and to ultimately deepen our understanding of the molecular and epigenetic mechanisms driving blood cancer progression.

Connected communities are essential to scientific progress, and conferences give researchers the opportunity to share findings, exchange ideas and build collaborations. This is especially valuable for early career researchers. This year, our PhD students hosted the 18th International PhD Student Science Conference at The University of Manchester. I was delighted to be invited to open the conference as plenary speaker, before I knew I was to become the Director of the CRUK Manchester Institute. It was a great success, and the students deserve congratulations for organising it so well. You can read more in the Education section.

All these achievements are a testament to the collective effort of everyone who contributes to the Institute — researchers, clinicians, professional services staff, students, and our wider network of collaborators and partners. Progress in cancer research is never the result of individual effort alone; it depends on teamwork, shared purpose and sustained commitment. I would like to thank all colleagues for their dedication, creativity and resilience.

Looking forward, I am confident that the coming year will be one of continued progress, collaboration and innovation. By strengthening integration across discovery and clinical research, investing in our people and infrastructure, and expanding our partnerships locally, nationally and internationally, we will continue to push the boundaries of cancer research and deliver meaningful impact for patients.

I am excited about what we can achieve together, and I look forward to working with colleagues across the Institute and our partner organisations to shape the next chapter of the Cancer Research UK Manchester Institute.

Professor Samra Turajlić
Director, Cancer Research UK Manchester Institute

RESEARCH HIGHLIGHTS

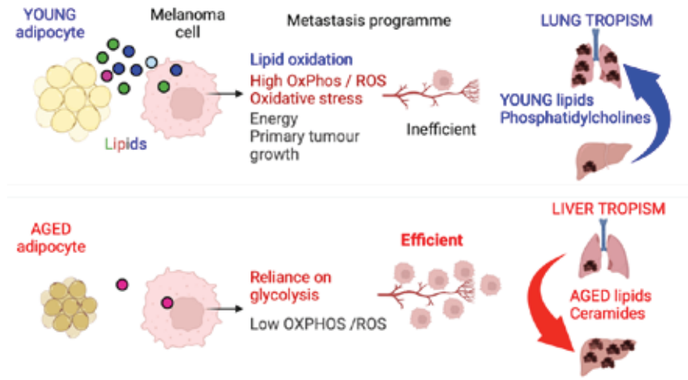
In this section we highlight some research publications from 2025 which report significant advances in specific areas. The selected papers demonstrate the breadth and the quality of the research being undertaken by the groups at the Cancer Research UK Manchester Institute.

Gurung S, Budden T, Mallela K, Jenkins B, von Kriegsheim A, Manrique E, Millán-Esteban D, Romero-Camarero I, Amaral F, Craig S, Durao P, Pozniak J, Stennett L, Smith D, Ashton G, Baker A, Zeng K, Fruhwirth G, Sanz-Moreno V, Marques J, Koulman A, Marine JC, Somervaille TCP, Motta L, Gaudy-Marqueste C, Nagore E, Virós A. (2025)
Stromal lipid species dictate melanoma metastasis and tropism.
Cancer Cell 43(6):1108-1124.e11.

Melanoma risk, progression, and metastatic patterns are strongly age-dependent, yet age is rarely treated as a biological variable in mechanistic studies. The Skin Cancer & Ageing group asked whether the age of the skin microenvironment, specifically stromal lipid availability, shapes melanoma metabolism and thereby influences the rate and destination of metastasis. Rather than focusing solely on tumour-intrinsic drivers, they wanted to understand how nutrients supplied by the surrounding tissue instruct cancer cell behaviour and metastatic tropism.

The team discovered that adipocytes in younger skin, which are the main lipid cutaneous donors, contain and secrete substantially more lipids than aged adipocytes, and melanoma cells adapt their metabolism accordingly. Lipid-rich young skin transfers lipids, driving high oxidative phosphorylation (OxPhos) in melanoma cells, slowing metastatic progression due to oxidative stress during haematogenous spread, and favouring lung seeding. In contrast, lipid-poor aged skin transfers fewer lipids, induces a moderate OxPhos state that accelerates metastasis and strongly biases dissemination to the liver. Importantly, these metabolic states are not passive but actively determine metastatic pace and organ tropism. Furthermore, age-specific lipid species activate distinct signalling pathways within melanoma cells. In young skin, phosphatidylcholines promote PI3K–AKT signalling and reinforce OxPhos programmes. In aged skin, ceramides activate a ceramide–S1P–IL6 axis that drives liver tropism and aggressive dissemination. This study links stromal lipid composition directly to cancer–immune signalling and metastatic behaviour.

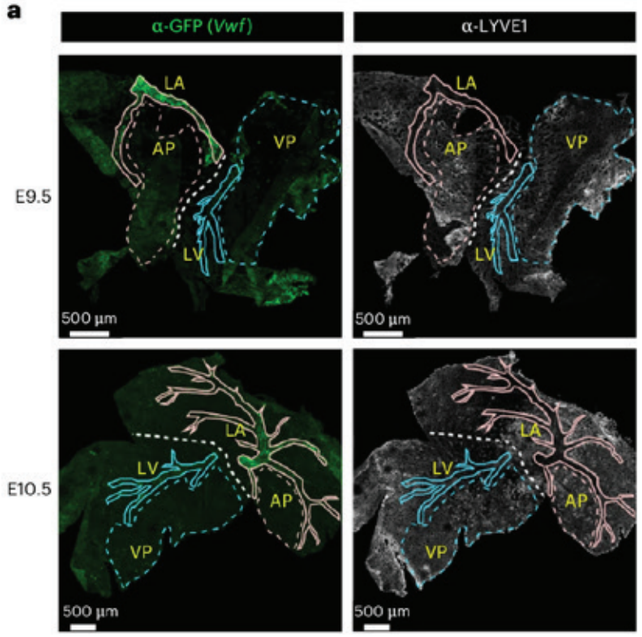
These findings are clinically relevant because melanoma metastases are not random, and liver metastases—particularly devastating and common in older patients—often arise rapidly. Their analysis of human metastases shows age-specific, non-random organ progression patterns, with significantly shorter time to liver involvement in the elderly. Ultimately, this work provides a mechanistic explanation for these observations and suggests that metabolic and lipid-dependent pathways are actionable vulnerabilities, particularly in age-defined patient groups.



Schematic showing the impact the age of the adipocyte has on metastatic tropism in melanoma.

Neo WH, Fadlullah MZH, Bhatnagar H, Barone C, Quattrini G, Timóteo-Ferreira F, Carrelha J, Sala G, Sellers R, Weightman J, Breitwieser W, Moncaut N, Thambyrajah R, Jacobsen SEW, Iqbal M, Baker SM, Azzoni E, Lie-A-Ling M, Lacaud G. (2025)
Single-cell profiling reveals three endothelial-to-hematopoietic transitions with divergent isoform expression landscapes.
Nature Cardiovascular Research 4(12):1642-1661.

All blood cells – from red blood cells to immune cells – ultimately trace their origins back to a remarkable process that occurs during embryonic development, in which a specialised



Confocal whole-mount immunofluorescence (WM IF) analysis of E9.5 (top) and E10.5 (bottom) *Vwfe*^{GFP} YS. Images show maximum intensity three-dimensional (3D) projections. Representative areas where fluorescence has been quantified are delimited by lines. Pink solid line, large artery (LA); turquoise solid line, large vein (LV); pink dashed line, arterial plexus (AP); turquoise dashed line, vein plexus (VP). Scale bars, 500 µm. Image reused from Neo et al, *Nat Cardiovasc Res* (2025) PMID: 41219569, under the Creative Commons Attribution 4.0 International License https://creativecommons.org/licenses/by/4.0/

blood vessel lining called the haemogenic endothelium (HE) transforms directly into blood-forming cells through a process known as the endothelial-to-haematopoietic transition (EHT). A longstanding mystery in blood biology is why HE cells in different locations in the embryo give rise to different types of blood cells. The yolk sac – the embryo's early nutritional structure – produces short-lived blood progenitor cells, while HE deep within the embryo, in a region called the aorta-gonad-mesonephros (AGM), produces true haematopoietic stem cells (HSCs), the long-lived, self-renewing cells that sustain the blood system throughout life.

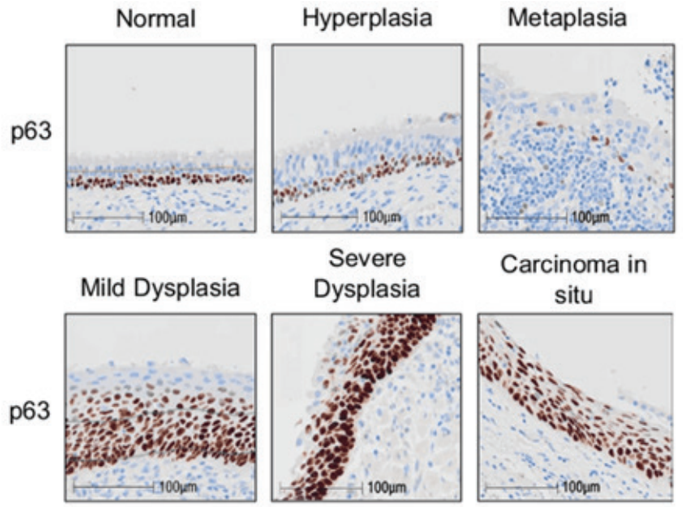
To resolve this, researchers in the Stem Cell Biology group used single-cell RNA sequencing, combined with functional experiments and whole-tissue imaging, to map HE populations in the mouse embryo at unprecedented resolution, identifying three distinct EHT trajectories/populations giving rise to: (1) erythro-myeloid progenitors in the yolk sac plexus, (2) lympho-myeloid progenitors in large yolk sac arteries, and (3) HSCs in the AGM. While all three HE populations share a core molecular signature, including transcription factors GFI1, MYCN and RUNX1, the AGM HE is uniquely enriched for chromatin-modifying enzymes and RNA-splicing machinery. Consequently, AGM-HE expresses different versions (alternative isoforms) of multiple genes, resulting in a dramatically more complex isoform expression landscape. Experimentally deleting one key RUNX1 isoform enriched within AGM-HE impaired HSC formation, suggesting that gene regulation at the isoform level impacts blood stem cell production.

These findings have significant implications for regenerative medicine. Understanding the unique molecular programmes of AGM-HE, particularly its isoform landscape, could inform new induced pluripotent stem cell-based strategies to generate functional patient-specific HSCs in the laboratory for treating diseases such as leukaemia, aplastic anaemia and immune deficiencies.

Ogden J, Sellers R, Sahoo S, Oojageer A, Chaturvedi A, Dive C, Lopez-Garcia C. (2025)
A human model to deconvolve genotype-phenotype causations in lung squamous cell carcinoma.
Nature Communications 16(1):3215.

Scientists in the former research group, Translational Lung Cancer Biology led by Carlos Lopez-Garcia, created a new model of lung squamous cell carcinoma (LUSC), a common type of lung cancer, to study the development, activity, and vulnerabilities of the disease. This new model could be the missing piece of the puzzle needed to advance research into the treatment of this type of lung cancer. In the UK, around 80 to 85% of lung cancers are non-small cell lung cancer, of which squamous cell carcinoma is one of the main types. Almost one in three lung cancer patients have LUSC. Despite this, the disease remains poorly understood and treatment options are limited. Just one in five (21%) of lung cancer patients in England survive their disease for five years or more.

Researchers in the group propose that the new cell-based model could be used to develop more effective treatments. It also has the potential to improve early detection of LUSC as it accurately reproduces the early stages of the disease. New models can also help to bridge the gap between animal testing and clinical trials, a gap which makes it harder to take drugs from the lab to the bedside. While mouse models play a critical role in cancer research, tests are not always reproducible in humans. Importantly, this new LUSC model will both offer an alternative to animal testing and allow faster, cheaper, and larger experiments to be conducted. To build their comprehensive LUSC model, the group took healthy lung cells from three donors and used sophisticated techniques, including CRISPR gene editing, to make the cells cancerous. This step-by-step process enabled the team to unravel the mutations needed to turn healthy cells into cancer cells, which was replicable across all three donors.



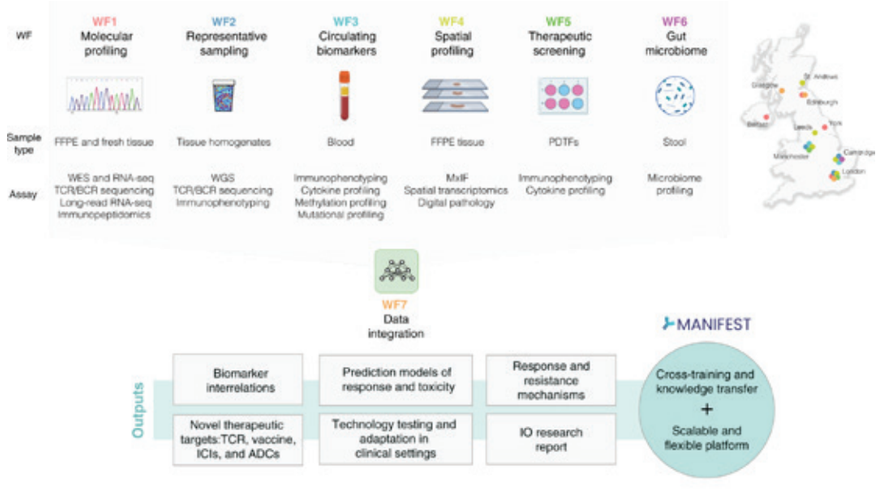
Representative haematoxylin and eosin staining of LUSC developmental stages obtained from clinical samples. This analysis was repeated in the three donors. Image reused from Ogden et al. *Nat Commun* 16, 3215 (2025).

With this new strategy to model lung squamous cell carcinoma, the authors conclude they are in a much better position to understand how this disease progresses. Developments like these accelerate research on new therapies and improve existing ones, powering us through clinical advancements for years to come.

Lim KHJ, Tippu Z, Corrie PG, Hubank M, Larkin J, Lawley TD, Stares M, Stewart GD, Strange A, Symeonides SN, Szabados B, Turner NC, Waddell T, Zelenay S, Salto-Tellez M, Dive C, Turajlic S; MANIFEST consortium. (2025)
MANIFEST: Multiomic Platform for Cancer Immunotherapy.
Cancer Discovery 15(5):878-883.

This study, led by Samra Turajlic, introduces a UK-wide, tumour agnostic research infrastructure designed to address a central challenge in modern immuno oncology: the inability to reliably predict which patients will benefit from immunotherapy and which will experience severe toxicity. Although in the last ten years huge progress has been made in the treatment of cancer with immunotherapy, many patients experience treatment failure or significant side effects. Almost no biomarkers today can effectively distinguish responders from nonresponders, predict toxicity, or guide treatment choices. So, in response to this unmet clinical need, the authors established MANIFEST: Multiomic ANalysis of Immunotherapy Features Evidencing Success and Toxicity, funded by the Medical Research Council and the Office for Life Sciences, with matched funds from industry partners. MANIFEST addresses the critical challenge in cancer treatment: predicting how patients will respond to immunotherapy. By integrating multiomic data and innovative methodologies, this platform aims to enhance treatment precision and effectiveness. The consortium is a collaborative network comprising a diverse mix of stakeholders from academia, healthcare, and industry, all united with the goal of advancing cancer immunotherapy.

This longitudinal study will test 3000 patients who have already completed their treatment and then a further 3000 who are starting treatment across the UK for breast, bladder, kidney and skin cancer, with plans to include additional cancer types as the programme expands. Over four years, data will be collected from these patients using blood tests, stool samples and tissue biopsies. The team will analyse different aspects of cancerous tumours, including their genetic makeup, where they are in relation to immune cells, and what chemical signals they are producing. They will also generate a profile of immune cells in each patient's bloodstream and analyse their gut microbiome. Industry partners in the consortium bring expertise in novel technologies and immunotherapies and will



Overview of the MANIFEST platform and respective workflows. ADC, antibody–drug conjugate; FFPE, formalin-fixed paraffin-embedded; ICI, immune checkpoint inhibitor; WES, whole-exome sequencing; WF, workflow; WGS, whole-genome sequencing.

support the implementation of these discoveries in the clinic.

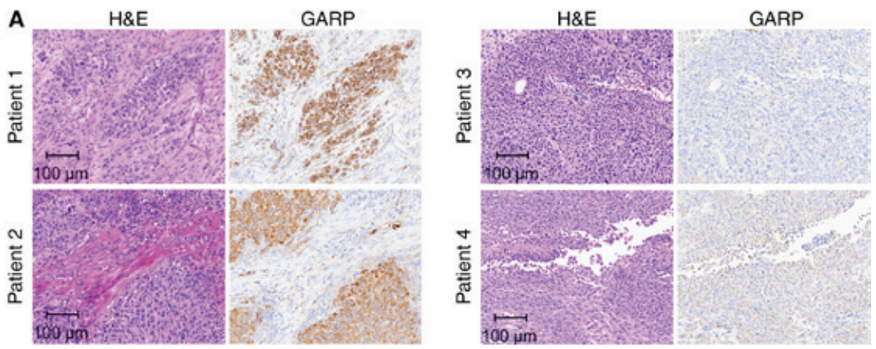
Research on this scale can bring us closer to better tests in the clinic as well as fuelling more discoveries regarding cancer immunology and new therapies. Ultimately, this consortium aims to speed up the delivery of personalised medicine for a disease that affects huge numbers of people across the UK every year.

Earnshaw CH, Dunn P, Chiang SC, Moeini A, Koufaki MA, Bonavita E, Russo M, Nebot-Bral L, Hockenhull K, Richardson E, Pidoux A, Bell CR, Baker AR, Reeves R, Sellers R, Sahoo S, Fife V, Roberts MG, Bigirumurame T, Dive C, Newton-Bishop J, Nsengimana J, Griffiths CEM, Zelenay S.
Glucocorticoids Unleash Immune-dependent Melanoma Control through Inhibition of the GARP/TGF β Axis.
Cancer Discovery [published online 14 October 2025]

First author Charles Earnshaw and the Cancer Inflammation and Immunity team investigated whether topical therapies, commonly used in non-melanoma skin cancers, could elicit anti-tumour activity in immunotherapy-resistant melanoma. Unexpectedly, glucocorticoids (GCs) were the only treatment to induce rapid and profound tumour shrinkage, even in large established tumours. This effect was entirely dependent on adaptive immunity and specifically on CD8⁺ T cells and was lost in immunodeficient mice or following CD8+ T cell depletion, despite the well-established immunosuppressive properties of GCs.

Mechanistically, the study revealed that GCs acted directly on tumour cells, rather than immune cells, via the glucocorticoid receptor. This signalling downregulates expression of GARP, a key activator of latent TGF-β. By downregulating GARP in cancer cells, GCs diminished TGF-β signalling, thereby relieving suppression of tumour-infiltrating CD8β T cells and enabling tumour cell killing. Across multiple melanoma, breast and colorectal cancer models, GC-induced tumour control was observed only in tumours that were also sensitive to pharmacological inhibition of TGF-β signalling, demonstrating a strict dependence on this pathway. Loss and gain of function approaches confirmed that tumour cell-intrinsic GARP expression is essential for this immune-evasive mechanism. Analysis of human datasets supported these findings. In both TCGA and an independent melanoma cohort from collaborators at the University of Leeds, high glucocorticoid receptor expression and GC signalling were associated with improved overall survival, particularly in tumours with high CD8⁺ T cell infiltration. Conversely, in an in-house cohort of 40 melanoma biopsies, high tumour cell GARP expression correlated with poorer survival and diminished CD8⁺ T cell activation.

Overall, the study identifies the GARP-TGF-β axis as a tumour cell-intrinsic immune-evasive pathway that can be therapeutically targeted. It further demonstrates that glucocorticoids can, counterintuitively, promote anti-tumour immunity in a specific context, providing a rationale for patient stratification and for the development of therapies targeting this pathway.



GARP expression in melanoma cells correlates with worse outcomes in patients and associates with a dampened CD8+ T-cell activation phenotype. A, Representative hematoxylin and eosin (H&E, left) and GARP (right) staining of patients with high GARP expression (patients 1 and 2) and low GARP expression (patients 3 and 4).

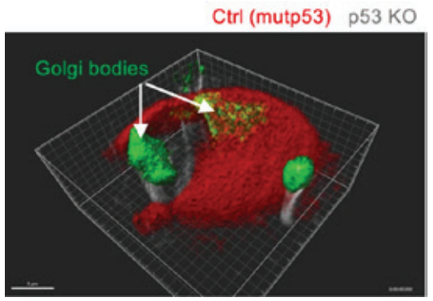
Dolma L, Patterson MI, Banyard A, Hall C, Bell S, Breitwieser W, Sahoo S, Weightman J, Gil MP, Ashton G, Behan C, Fullard N, Williams LD, Muller PA. (2025)
Mutant p53 induces SH3BGRL expression to promote cell engulfment.
Cell Death Discovery 11(1):288.

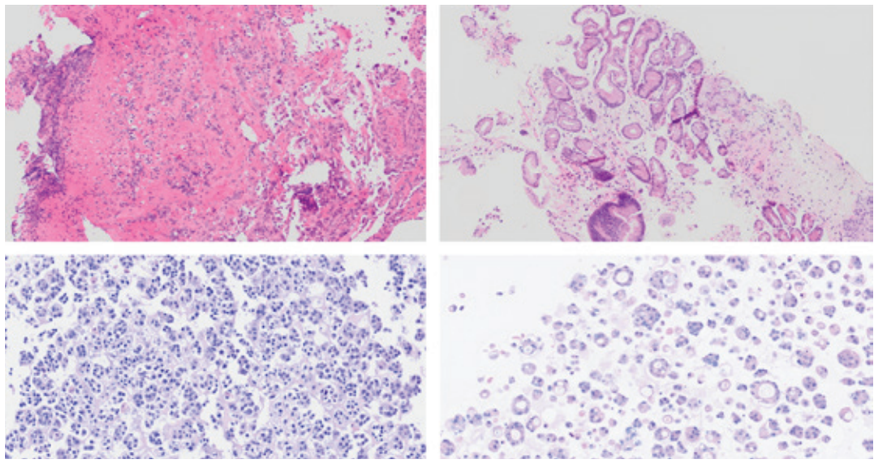
Research undertaken by former group Tumour Suppressors, led by Patricia Muller revealed a new mechanism by which mutant p53 endows cancer cells with pro-tumorigenic advantages. Mutations in *TP53* are among the most common genetic alterations in human cancers and are well known for conferring gain of function (GOF) phenotypes associated with poor prognosis. One emerging GOF phenotype is the formation of cell-in-cell (CIC) structures, a process in which a host cell with often crescent shaped nucleus, carries an internal viable cell.

In previous work, the group showed that mutant p53 drives entotic engulfment, increasing genomic instability and accelerating tumour progression in xenograft models (Mackay *et al.*, 2018). In this new study, former PhD student Lobsang Dolma and team dissect the mechanism with far greater resolution. They demonstrated that mutant p53 promotes a host driven engulfment programme, characterised by directional migration of the mutant p53 expressing "host" cell towards neighbouring "target" cells in an active capture process that enhances tumour cell competitiveness. This is distinct to other types of CIC formation like entosis wherein the internal cell invades into a host cell. Importantly, they showed that cells undergoing CIC formation display an increased etoposide resistance, which suggests CIC formation to be a stress adaptive, and a survival enhancing phenotype. Moreover, through next generation sequencing, the group identified *SH3BGRL* as a previously unrecognised transcriptional target of mutant p53 that is essential for CIC formation. SH3BGRL expression enables increased etoposide resistance in mutant p53 cells and alone promotes anchorage independent growth even in the absence of p53 mutation.

Together, these findings establish both CIC formation and SH3BGRL upregulation as mechanistic drivers of mutant p53 mediated tumour evolution. This work expands the repertoire of mutant p53 GOF phenotypes and highlights new avenues for targeting mutant p53 driven cancer cell competitiveness and therapy resistance.

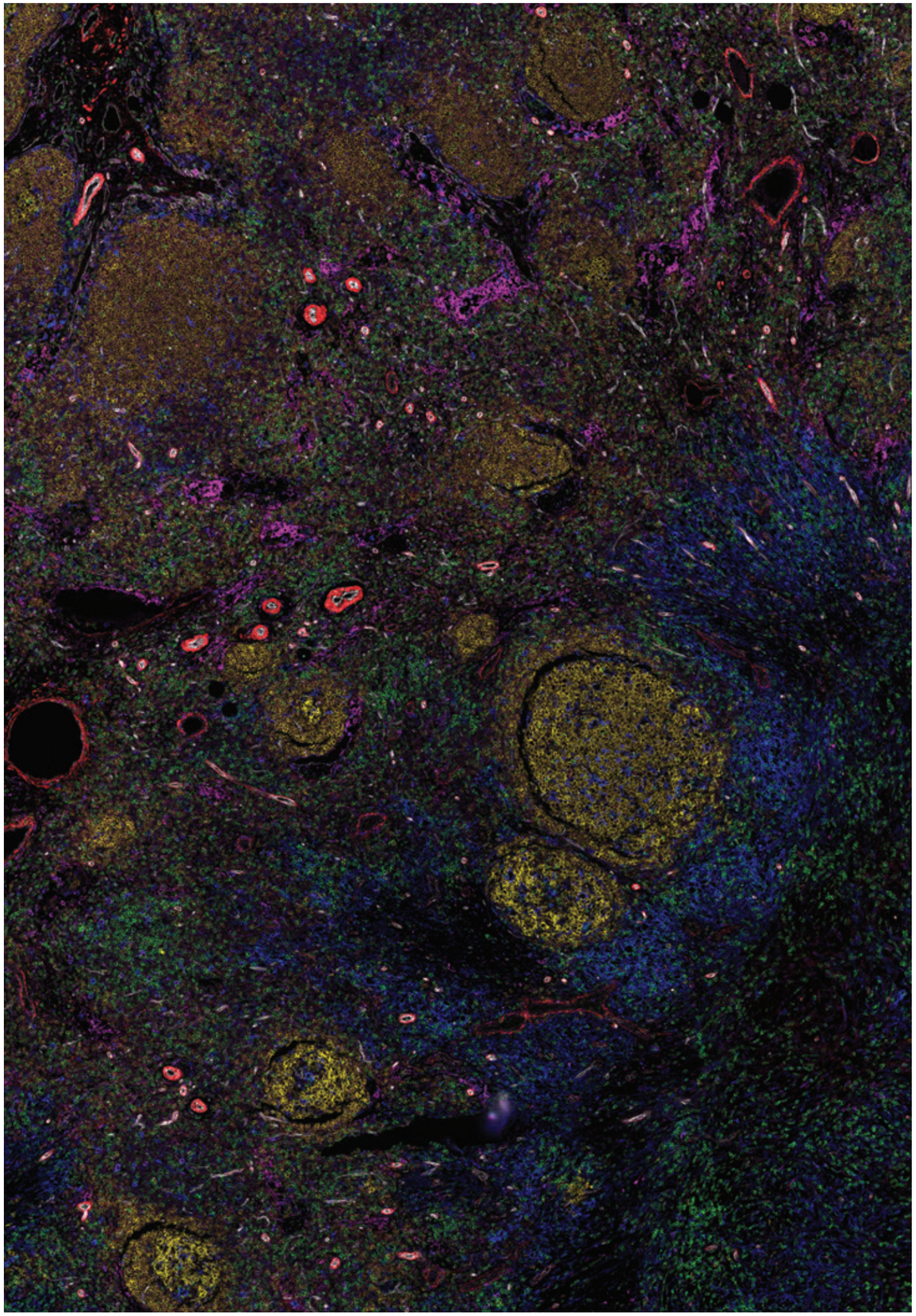
Mutant p53 status drives cell engulfment.
A431 mCherry Ctrl (mutp53) cells (red) were co-cultured with non-fluorescent p53 KO cells (grey), exposed to live Golgi-tracker dye (green) and live time-series imaging was done. A z-stack (46.08 µm in 193 planes) of the live cells was taken on the Andor spinning disk microscope (scale bar =8 µm) and 3D image generated using Imaris image analysis software (version 9.2) (Oxford instruments).





Oesophageal cancer organoids recapitulating the morphology (top) of their corresponding diagnostic biopsies (below).

Image supplied by Oliver Bartley (National Biomarker Centre, with credit to the Manchester Institute core facility, Histology)



RESEARCH GROUPS

Tumour-draining lymph nodes (tdLNs) shape responses to immune checkpoint inhibitors but can be co-opted by tumours for immune evasion. Image shows i) B-cell–rich follicles (yellow) with variable germinal centre (Ki67+) activation; ii) expanded sinusoidal regions enriched for immunosuppressive programmes linked to extracellular matrix remodelling; and iii) immune-restrictive transcriptional states associated with high mutation burden and tumour–macrophage (CD206+) interactions. CD20 (yellow), CD11c (blue), aSMA (red), Calveolin (gray), CD206 (magenta), CD8 (green).

Image supplied by Enric Ariza Ortiz (Cancer Dynamics)

CANCER IMMUNOSURVEILLANCE



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Cancer immunotherapies that enhance T cell-mediated tumour killing have transformed cancer treatment, particularly for melanoma. However, many tumour types remain resistant to current therapies, largely due to poorly understood mechanisms of resistance. Recent studies in mice and humans have highlighted a major role for the gut microbiome in regulating anti-cancer immunity and responses to immunotherapy. Despite this, the mechanisms through which microbiota promote tumour immunity remain unclear. Our work tries to address critical open-ended questions in the field of microbiome-immune interactions in cancer: (1) *How do we define a "good" microbiota that promotes immunity to cancer?* (2) *How do commensal species interact with host cells to promote cancer immunity?* (3) *Can we harness microbiome-immune interactions to prevent cancer and predict therapy response?* Our work diverges from a species-centric view of the microbiome and sets a foundation for understanding how host-microbiome interactions define T cell-mediated immunity to cancer and immunotherapy success.

Host-microbiome interactions in cancer immunity

Our research focuses on understanding how environmental factors shape anti-cancer immunity, with particular emphasis on the interaction between diet, the gut microbiome and immune responses to cancer. Building on our previous work defining the mechanisms of T cell-mediated cancer immunity, we have continued to investigate how host and microbial factors influence responses to immune checkpoint blockade (ICB) therapy.

Earlier studies from our group demonstrated that detection of dying tumour cells by antigen-presenting dendritic cells is essential for the induction of anti-tumour $CD8^+$ T cell responses. We identified molecular pathways linking cell death sensing to adaptive immunity and uncovered host-derived suppressive mechanisms that limit these responses (Giampazolias *et al Nature Cell Biology*, 2017; Giampazolias *et al Cell Cycle*, 2018; Giampazolias *et al Cell*, 2021; Lim KHJ *et al JITC*, 2022). Targeting these inhibitory pathways restored anti-tumour immunity and improved the efficacy of immunotherapy in preclinical models. These studies established a framework for understanding how immune responses to cancer are initiated and regulated.

More recently, our work has shifted towards understanding how external environmental signals influence these immune mechanisms. Increasing evidence from both mouse and human studies suggests that the gut microbiota plays a central role in determining the efficacy of cancer immunotherapy. Several commensal bacterial species have been associated with improved anti-tumour immunity and enhanced responses to ICB therapy. These observations have prompted clinical efforts using probiotics and faecal microbiota transplantation (FMT) from immunotherapy responders to overcome resistance in cancer patients. However, although promising, the benefit of these approaches remains inconsistent, largely because studies have identified different microbial species associated with therapeutic responses across patient cohorts.

Our recent work provides a mechanistic explanation for this variability by demonstrating that the anti-tumour activity of the microbiome is determined by host nutrient availability rather than by intrinsic properties of specific bacterial

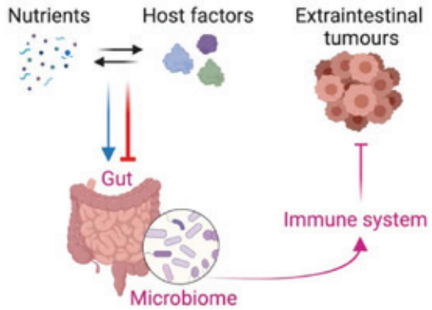


Figure 1: Nutrient-host-microbiome interactions in cancer immunity. Summary of research findings.

strains. In particular, we identified vitamin D (vitD) availability as a critical host determinant regulating microbiome-dependent cancer immunity (Giampazolias* *et al Science*, 2024, *co-corresponding author).

Using genetically modified mouse models and dietary interventions, we showed that increased tissue availability of vitD enhances resistance to transplantable tumours. This effect is mediated through alterations in the gut microbiome that promote T cell-dependent anti-cancer immunity. Importantly, the tumour-protective phenotype could be transferred to wild-type recipient mice through faecal transplantation, even in animals harbouring an intact resident microbiome, without antibiotic pre-treatment that compromises immune function. This enables, for the first time, direct dissection of microbiota-driven immunity independently of pleiotropic dietary influences on host physiology. Mice receiving vitD-conditioned microbiota displayed enhanced tumour control and improved responses to immune checkpoint blockade therapy, including increased tumour rejection rates.

Mechanistically, we found that intestinal epithelial sensing of vitD through the vitamin D receptor (VDR) regulates the functional behaviour of the microbiome. Rather than inducing major changes in microbial composition, vitD availability appeared to alter the copy numbers of genes present in several commensal bacteria, including the Gram-negative bacterium *Bacteroides fragilis*. Oral administration of *Bacteroides fragilis* promoted tumour resistance only in vitD-supplemented hosts, demonstrating that microbial anti-tumour activity is critically dependent on the nutritional environment of the host.

Our findings shift the current paradigm in immune-microbiome research away from focusing exclusively on individual microbial species and toward understanding nutrient-dependent host-microbiome interactions in the context of cancer immunity. These results may suggest that multiple bacterial species may acquire shared immune-promoting functions when exposed to permissive host environments, potentially explaining the lack of consensus across previous microbiome studies.

In parallel with our experimental work in mice, we investigated the clinical relevance of vitD-associated pathways in human cancer. Analysis of a cohort comprising nearly 1.5 million individuals revealed an inverse correlation between serum vitD levels and cancer incidence. Furthermore, examination of cancer patient datasets (TCGA) demonstrated that elevated vitD-associated transcriptional activity correlated with improved responses to immunotherapy and increased overall survival across multiple cancer types. These observations support the translational relevance of our preclinical findings and suggest that vitD-dependent microbiome-immune interactions may influence therapeutic responses in cancer patients.

Our ongoing research aims to define the molecular and cellular mechanisms underlying this axis. Specifically, we focus on characterising how vitD regulates microbiome's anti-tumour function, identifying the microbiota-derived pathways and molecules regulated by vitD that boost anti-tumour immunity as well as the host sensing pathways linking microbiota-derived signals to systemic immune activation. We are also characterising how vitD-conditioned microbiota shapes the tumour immune microenvironment and influences cancer immune surveillance during tumour initiation and progression.

To address these questions, the Cancer Immunosurveillance group combines genetically engineered mouse models, dietary interventions, transplantable microbiota systems, immunological profiling, and translational analysis of human cancer datasets. By integrating these approaches, we seek to disentangle the complex interactions between nutrients, host physiology, the microbiome and anti-cancer immunity.

Our long-term objective is to identify microbiome-immune checkpoints that can predict responsiveness to immunotherapy and provide new therapeutic strategies to overcome treatment resistance. These studies establish nutrient availability as a central regulator of microbiome function in cancer immunity and provide a framework for developing microbiome-based interventions guided by host metabolic and nutritional status.

Publications listed on page 52

CANCER INFLAMMATION AND IMMUNITY



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Cancer promoting inflammation remains a defining hallmark of cancer, associated with malignant tumour growth, poor clinical outcomes and resistance to therapy. At the same time, the success of immune checkpoint blockade therapy has highlighted the existence of distinct inflammatory states within tumours that can support potent anti-tumour immunity. Our research programme focuses on understanding how these divergent inflammatory programmes arise, how they shape tumour evolution and how they can be therapeutically manipulated to improve patient outcomes. By integrating mechanistic studies in pre-clinical models with analyses of patient-derived samples, we aim to identify actionable pathways that govern immune evasion or immune-mediated tumour control. In addition, we are increasingly leveraging emerging spatial profiling technologies to resolve how distinct inflammatory niches coexist within individual tumours and how their spatial organisation influences immune function and therapeutic response.

Over the past year, we have made significant progress in dissecting tumour-intrinsic mechanisms that suppress anti-tumour immunity. A major advance from our group, published in *Cancer Discovery* (Earnshaw et al.), uncovered a previously unrecognised immune-evasive pathway centred on the GARP-TGF-β axis. Using an immunotherapy-resistant melanoma model, we demonstrated that glucocorticoids, counterintuitively, can induce rapid and profound tumour regression in a $CD8^+$ T cell-dependent manner. Mechanistically, glucocorticoids act directly on tumour cells to suppress expression of GARP, thereby limiting activation of TGF-β and releasing cytotoxic T lymphocytes from immunosuppressive signalling. Importantly, this effect was restricted to tumours dependent on TGF-β-mediated immune evasion and was supported by analyses of human melanoma datasets, where glucocorticoid receptor signalling correlated with improved survival, while high GARP expression associated with poorer outcomes and reduced T cell activation. These findings establish the GARP-TGF-β axis as a tumour cell-intrinsic immune checkpoint and provide a strong rationale for patient stratification and therapeutic targeting of this pathway. Building on these observations, we are now investigating how glucocorticoid treatment influences responses to immune checkpoint blockade, with the aim of defining the contexts in which these widely used drugs may enhance or impair immunotherapy efficacy.

In parallel, we have continued to refine our understanding of how inflammatory signalling networks shape tumour progression and therapeutic response. Our work on the COX-2/PGE2 pathway has further reinforced its role as a central regulator of immunosuppressive tumour microenvironments and a driver of resistance to immunotherapy. We have extended our prior work to define how inflammatory pathways operate across different stages of disease, including metastatic dissemination. In addition, we are investigating the role of this pathway in pancreatic cancer using orthotopic implantation models of pancreatic cancer cell lines and organoids, in collaboration with the Systems Oncology group. These studies aim to determine how tumour-intrinsic inflammatory programmes interact with tissue-specific microenvironments to shape disease progression and therapeutic vulnerability.

To support these mechanistic studies, we have developed and applied new genetically engineered mouse models that enable the precise imaging, isolation and acute depletion of defined activated $CCR7^+$ dendritic cells. Using these new models, we have uncovered key lineage- and state-dependent functions within this intriguing dendritic cell population, which represents a convergent activation state shared by both type I and type II conventional dendritic cells. These findings reveal previously unappreciated functional specialisation within dendritic cell populations and provide new insight into how antigen presentation and T cell priming and effector activity are regulated during the immune response to cancer (Koufaki et al., 2025). Our ongoing work is further leveraging these new models to dissect the differential contribution of dendritic cells to $CD8^+$ and $CD4^+$ T cell priming in lymphoid organs and at the tumour site, providing a more integrated understanding of how systemic and local immune responses are coordinated during anti-tumour immunity.

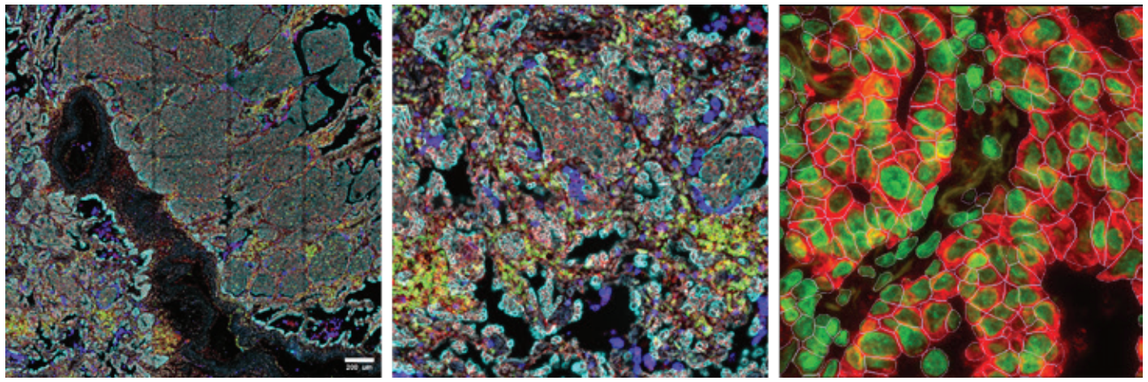


Figure 1: Establishing Spatial Whole-Transcriptome Profiling in Early-Stage Lung Cancer. Representative images of tumour sections from an FFPE early-stage lung cancer specimen, shown at increasing magnifications. Spatial whole-transcriptome analysis was performed at subcellular resolution, enabling high-resolution mapping of gene expression patterns within the tumour microenvironment.

Our translational research efforts have also advanced substantially. In close collaboration with the CRUK National Biomarker Centre, the patient-derived tumour fragment (PDTF) platform is now fully established within the CRUK Manchester Institute and has become a central component of our experimental pipeline. As part of the MANIFEST consortium, we are using this platform to assess patient-specific immune responses ex vivo while preserving tumour architecture and microenvironmental context. This system enables the functional evaluation of therapeutic strategies, including immune checkpoint blockade and rational drug combinations, and provides a powerful framework to link mechanistic insights with clinical response. Additionally, we are incorporating spatial profiling approaches within this platform to map the distribution and functional states of immune and tumour cells (Figure 1), enabling us to directly interrogate how spatially distinct inflammatory niches influence treatment responsiveness.

We continue, in close collaboration with the CRUK National Biomarker Centre, to develop and validate biomarkers of tumour inflammation and immune evasion to support the translation of our pre-clinical discoveries into clinically actionable tools. Extending on our prior work, we are focusing on identifying patients most likely to benefit from therapies targeting inflammatory and immunosuppressive pathways, including the COX-2/PGE2 axis. As part of these efforts, together with oncologists from The Christie NHS Foundation Trust, we are designing a clinical trial to prospectively validate one of our most promising biomarkers for its ability to predict relapse after surgery in patients with early-stage non-small cell lung cancer. Together, these approaches aim to enable improved patient stratification and guide the rational deployment of immunotherapy and combination treatments.

Altogether, these advances highlight substantial progress in our understanding of how tumour-intrinsic and microenvironmental factors converge to regulate anti-tumour immunity. By combining mechanistic discovery with translational and clinical approaches, our programme continues to define new strategies to overcome immune evasion and enhance the effectiveness of cancer immunotherapy.

Publications listed on page 52

CELL DIVISION



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The inappropriate proliferation of cancer cells can arise from unchecked cell division, a failure to engage cell death pathways, or simultaneous changes in both. Understanding how the diverse cues are integrated to co-ordinate cell division and death is therefore key to understanding the biology of cancer. We study cell cycle controls that determine when a cell commits to the physical process of genome segregation, mitosis. Because the regulatory networks that control cell division are highly conserved, we use both unicellular fission yeast and human cells in our investigations as the yeast work identifies core principles to frame the questions to ask of the more complex context of human cell division.

Our yeast work addresses how signals from the broad range of pathways are integrated by regulatory relays on neighbouring scaffolds on the centrosome to generate a single signal to trigger division when the time is right. Complementary studies are asking whether similar controls operate in human cells and characterise one of the key cell cycle checkpoint molecules that determines when mitosis begins, PKMYT1.

In a typical cell division cycle the G1 gap phase precedes DNA replication in S phase, before a second gap phase, G2, separates S from genome segregation with the mitotic spindle in Mitosis (M phase) (Figure 1). Growth, and developmental and environmental cues, determine whether and when a cell leaves the non-cycling G0 state to enter the cell cycle by passing through a decision point of no return in G1 phase called the "Restriction Point" (denoted by RP in Figure 1). Successive waves of CDK-cyclin activities then drive different events as cells transit the cycle. Defects in DNA integrity activate cell cycle checkpoints that block progression through key cell cycle transitions until the damage/deficiency is restored. As the mutations that enable cancer cells to bypass normal growth controls lead to the accumulation of DNA damage and change chromosome number, cancer cells become more reliant upon these checkpoints than their normal neighbours. Consequently, agents that enhance DNA damage are widely used in the clinic as they increase the level of damage in the already stressed cancer cells to a point where checkpoint defenses are unable to prevent catastrophic division. By contrast, their normal neighbours simply extend their cell cycle times to accommodate the elevated level of damage. We are therefore asking how these checkpoints operate to find ways to manipulate checkpoint controls in a manner that will selectively eliminate cancer cells.

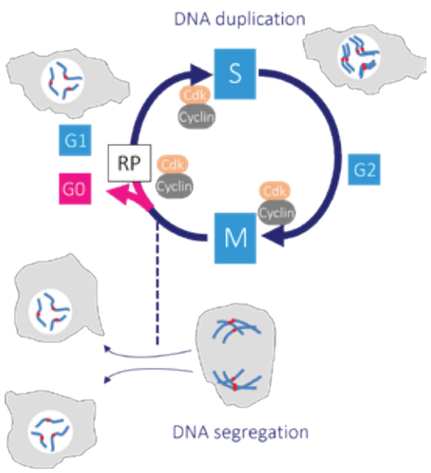


Figure 1: The human cell cycle with Cdk1-Cyclin B control of the G2/M transition. Passage through the restriction point (RP) in G1 phase commits a cell to passage through the cell division cycle. DNA replication in S phase is separated from mitosis by a gap phase, G2. Transition through the major rate limiting commitment steps into the cycle, DNA replication (S) and genome segregation (M) is driven by CDK-Cyclin activities.

The transition from G2 phase into mitosis is driven by activation of the CDK1-Cyclin B protein kinase. CDK1-Cyclin B activity is restrained through inhibitory phosphorylation by the WEE1 family kinases WEE1 and PKMYT1. When the time is right, the inhibitory phosphate is removed by CDC25 phosphatases and cells enter mitosis (Figure 2A). The checkpoint pathways that block mitotic commitment when DNA is damaged, or replication is incomplete, do so by boosting the activity of WEE1 family kinases and repressing CDC25 (Figure 2B). As cancer cells harbour more damage than normal tissue, they are more

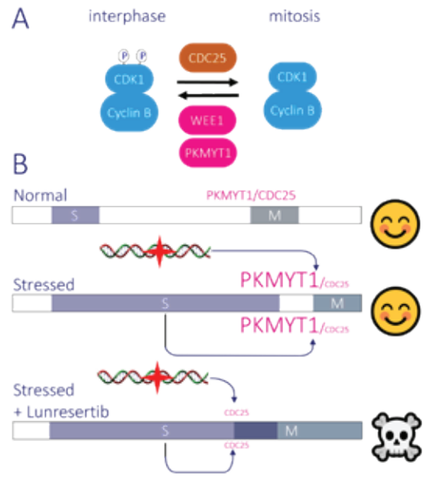


Figure 2: PKMYT1in Cdk1-Cyclin B regulation in checkpoint control. A) CDK1-Cyclin B activity is held in check in interphase as a consequence of phosphorylation of CDK1 by WEE1 family kinases. CDC25 removes the inhibitory phosphate to trigger mitosis. B) DNA damage or incomplete DNA replication trigger checkpoint pathways that boost inhibitory phosphorylation of CDK1 and reduce counteracting CDC25 activity. Lunresertib inhibition of PKMYT1 abolishes this restraint to initiate division before DNA integrity is restored, leading to death.

reliant upon these checkpoints than their normal neighbours, making targeting the checkpoint pathways a major focus in drug discovery at present (Figure 2B). WEE1 control of the CDK2-Cyclin Complexes that control the timing and execution of DNA replication alongside its inhibition of CDK1-Cyclin B means that clinical application of WEE1 inhibitors is proving problematical. In contrast, because PKMYT1 only regulates CDK1-Cyclin B, and PKMYT1 can be completely removed from untransformed cells without affecting viability, the PKMYT1 inhibitor Lunresertib is generating great excitement as its excellent pre-clinical efficacy is being matched by performance with minimal toxicity in early clinical trials.

While WEE1 has an established role in regulating Cdk2 during S-phase, the full scope of PKMYT1's roles in the cell cycle is surprisingly unexplored. The Cell Division group has revealed a novel mitotic function for PKMYT1, showing that its activity increases during anaphase and coincides with chromosome segregation. Chemical inhibition of PKMYT1 induces premature anaphase, leading to chromosome segregation errors. These errors, including chromatin bridges and micronuclei, consequently activate the cGAS-STING pathway. Our research also demonstrated that PKMYT1 is crucial for maintaining spindle assembly checkpoint integrity, as its inhibition promotes mitotic slippage in the presence of anti-microtubule drugs. Our group established a novel mitotic function for PKMYT1, which is distinct from its family member WEE1.

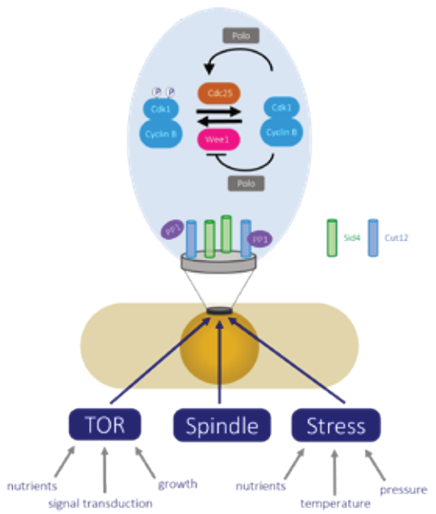


Figure 3: Studying the PKMYT1 role within mitosis using metaphase synchronisation. hTERT RPE-1 metaphase using APC/C inhibitors and then released into a fresh medium containing Lunresertib, a PKMYT1 inhibitor. This allowed specific examination of PKMYT1 function during mitotic exit by monitoring nuclear envelope reformation (Lamin B1 marker) and chromosome passenger complex dynamics (INCENP marker) via immunofluorescence microscopy.

The observation that active CDK1-Cyclin B appears on human centrosomes before propagating throughout the cell has been consolidated by other data to suggest that the centrosome provides a specific microenvironment for the activation of CDK1-Cyclin B to trigger the G2/M transition. Our studies of the fission yeast centrosome equivalent, the spindle pole body (SPB), provide molecular insight into how this switch may operate. Simply blocking the recruitment of protein phosphatase 1 (PP1) to the SPB scaffold Cut12 enables cells to live without Cdc25. Furthermore, PP1 eviction from Cut12 is the only essential function for Cdk1-CyclinB Cdcl3 in driving cells into division. The means by which the Cut12/ PP1 switch regulates mitotic commitment appears to involve the mitotic kinase Polo, as Polo activity and recruitment to the SPB shows a direct, inverse correlation with PP1 recruitment to the SPB, and artificial elevation of Polo activity at the SPB drives cells into division. As Polo kinase activity is regulated by nutritional status and stress responses, Polo kinase engagement in this switch couples division timing to the specific demands of any given environmental context (Figure 3).

The threshold for Cut12 signalling that must be passed before the cell enters division is set by a signalling relay on a neighbouring scaffold molecule, Sid4. This relay regulates the SPB residence of a Cdk1-Cyclin B counteracting phosphatase called Cdcl4 Flp1. Thus, it is the dialogue between Cut12 and Sid4 that determines when division will be initiated. Sid4 also anchors the cytokinesis regulating Septum Initiation Network to the SPB. This anchorage is essential to ensure the SIN signalling can drive the events of mitotic exit and cytokinesis. Therefore, signalling from these two neighbouring SPB signalling platforms acts like the central processing unit of a computer. Converging signals from multiple pathways are integrated to generate a coherent signal that sets the flux through outgoing signalling cascades that tell the cell when to enter and exit mitosis. We are currently seeking the mechanistic basis for Polo and Cdcl4 Flp1 engagement in these networks and the function of similar centrosomal scaffolds in human cells.

LEUKAEMIA BIOLOGY



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In 2025, our laboratory continued to deliver translational impact through clinical and preclinical evaluation of novel epigenetic therapies for blood cancer. Clinical development of inobrodib (CCS1477), the first-in-class EP300/CBP bromodomain inhibitor, which we have studied extensively, advanced significantly with the presentation of positive phase 2 dose optimisation data in relapsed/refractory multiple myeloma and the opening of new combination cohorts with bispecific antibodies. In parallel, Dr Luciano Nicosia commenced a Blood Cancer UK Early Career Advancement Fellowship to deepen understanding of the mechanism of action of inobrodib. A significant new programme of work was also established in collaboration with Dark Blue Therapeutics to evaluate a first-in-class targeted protein degrader of MLLT1/3 in acute myeloid leukaemia, with early results demonstrating promising preclinical activity compared with menin inhibitors across primary patient samples.

Continued clinical and translational development of inobrodib (CCS1477)

Inobrodib (CCS1477) is a potent and selective first-in-class inhibitor of the bromodomains of the histone acetyltransferases EP300 and CBP. As reported in previous years, our mechanistic and translational studies have been central to its clinical development. In 2023, we published the foundational preclinical and early-phase clinical data demonstrating that inobrodib induces cell cycle arrest and differentiation in haematological malignancy models by inducing eviction of EP300/CBP from oncogenic enhancer networks (Nicosia et al., *Cancer Cell*, 2023). In 2024, we presented the first clinical data showing a 75% overall response rate for the all-oral triplet of inobrodib with pomalidomide and dexamethasone (InoPd) in heavily pretreated relapsed/refractory multiple myeloma (RRMM), including responses in pomalidomide-refractory and BCMA/T-cell engager (TCE) exposed patients (Searle et al., *Blood*, 2024).

In 2025, the clinical programme continued to mature. At the 67th American Society of Hematology Annual Meeting, we presented results from a randomised phase 2 dose optimisation study of InoPd (Joseph et al., *Blood*, 2025). Patients were randomised to three dose levels of inobrodib (20 mg, 30 mg, 40 mg) on an intermittent schedule with standard pomalidomide and dexamethasone. Among evaluable patients with a median of five prior lines of therapy, the emerging overall response rate was 69% at the 20 mg dose. Notably, in pomalidomide-refractory patients who had previously failed BCMA-targeted or TCE therapy, response rates of 60–75% were observed, representing at least a two-fold increase over currently available options in this setting. The safety profile remained manageable, with no additive toxicity beyond that expected from pomalidomide and dexamethasone alone.

Building on preclinical data demonstrating synergy between inobrodib and BCMA-targeted TCEs in a syngeneic myeloma model, we also opened new cohorts within our phase I/IIa study (CCS1477-02) evaluating inobrodib in combination with the approved TCEs elranatamab and teclistamab in RRMM (Searle et al., *Blood*, 2025). These cohorts are recruiting across approximately eight sites in the UK and US and will characterise the safety, tolerability and preliminary efficacy of these novel combinations. CellCentric secured $120 million in Series C funding in 2025 to support initiation of pivotal registration studies, and following recent discussions with the US FDA, a registrational phase II/III programme is planned for 2026/7.

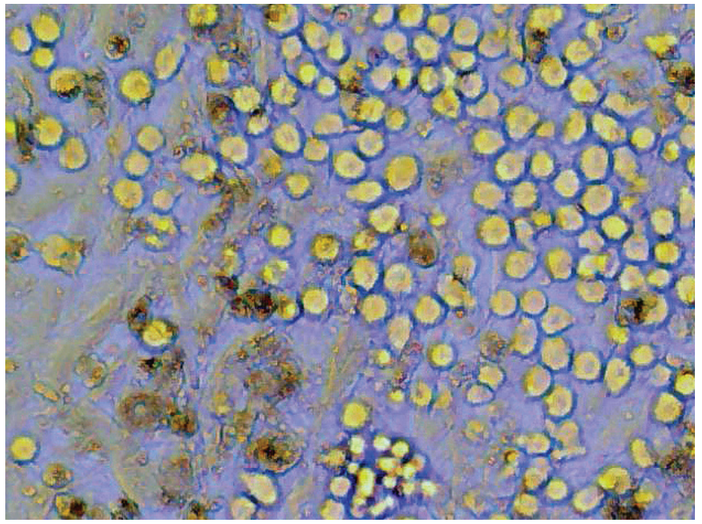


Figure 1: Primary patient AML cells growing in an in vitro stromal co-culture system.

In the group, Dr Luciano Nicosia commenced a Blood Cancer UK Early Career Advancement Fellowship in April 2025 to investigate the mechanism of action of inobrodib in greater depth. Through mass spectrometry-based proteomic analyses in AML and multiple myeloma models, he has identified a core set of proteins displaced from EP300 following CCS1477 treatment, including chromatin-associated factors involved in enhancer activation. These findings provide mechanistic insight into how bromodomain inhibition impacts EP300 activity and may inform the development of biomarker strategies to predict clinical response. Cross-linking mass spectrometry experiments with recombinant proteins suggest that CCS1477 induces conformational changes in EP300, potentially providing structural evidence for allosteric signalling between the bromodomain and key protein interaction domains. An initial compound library screen has also identified promising synergistic interactions between CCS1477 and glucocorticoid steroids, which are being validated across additional models.

Targeting the Super Elongation Complex through MLLT1/3 degradation

Menin inhibitors such as revumenib represent an important recent advance in the treatment of acute myeloid leukaemia. Menin tethers the KMT2A (MLL) protein to chromatin, facilitating aberrant transcriptional activation of HOX and MEIS1 oncogenes; pharmacological disruption of this interaction has demonstrated clinical efficacy in patients with KMT2A-rearranged (KMT2Ar) and NPM1-mutant AML. However, a key limitation of menin inhibitor monotherapy is the rapid emergence of resistance, with mutations in MEN1 appearing within months of treatment initiation, leading to disease progression and short-lived responses. This highlights a significant unmet need for novel agents capable of targeting these leukaemias more durably, including in patients who have become refractory to menin inhibition.

The Super Elongation Complex (SEC) is a multi-protein transcriptional regulator that is frequently hijacked in acute leukaemia, where it is recruited to the transcription start sites of major oncogenes including HOXA9, MEIS1 and MYC via the histone reader and scaffolding proteins MLLT1 (ENL) and MLLT3 (AF9). Critically, whereas menin acts in only a subset of SECs by stabilising KMT2A fusion proteins at specific loci, MLLT1 and MLLT3 are constitutive components of all SECs. Targeted degradation of MLLT1/3 therefore has the potential for broader anti-leukaemic activity, including against disease that is intrinsically insensitive or has acquired resistance to menin inhibition.

In February 2025 we established a collaboration with Dark Blue Therapeutics, a UK-based biotechnology company, to evaluate the preclinical potential of a first-in-class targeted protein degrader of MLLT1 and MLLT3 (MLLT-TPD).

The study is being led by Dr Ryan Robinson, a clinical research fellow in the group, and makes use of the patient biobank available at The Christie NHS Foundation Trust. A particular strength of this work is our ability to obtain freshly collected AML samples directly from the clinic, including from patients enrolled in menin inhibitor clinical trials led by Dr Emma Searle (Consultant Haematologist at the Christie Hospital), who have become refractory to treatment. In stromal co-culture experiments with primary patient cells (Figure 1), the Dark Blue compound shows potent growth inhibition across a range of AML subtypes at nanomolar concentrations, even while the menin inhibitor revumenib showed limited or no activity.

Furthermore, activity was observed in samples from patients with clinically confirmed menin inhibitor resistance. RNA sequencing of treated primary cells demonstrates downregulation of canonical SEC targets including HOXA9 and MEIS1, suppression of a leukaemia stem cell maintenance signature, and enrichment of myeloid differentiation programmes — consistent with disruption of a core leukaemia-sustaining mechanism.

These findings, presented as an oral abstract at the 67th American Society of Hematology Annual Meeting (Maloney et al., *Blood*, 2025), provide compelling early evidence that MLLT1/3 degradation offers broader and more potent preclinical activity than menin inhibition. Ongoing work will expand the panel of primary patient samples, establish patient-derived xenograft models and perform detailed mechanistic analyses to inform the design of future clinical evaluation.

Publications listed on page 52

www.cruk.manchester.ac.uk/research-group/leukaemia-immunology-transplantation

LEUKAEMIA IMMUNOLOGY & TRANSPLANTATION



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Allogeneic haematopoietic stem cell transplantation represents the only prospect of cure for most patients with acute myeloid leukaemia (AML). Success depends on the ability of donor T cells to eliminate residual disease, but this often fails resulting in disease recurrence.

Despite >50 years of clinical experience, we still do not understand why some patients relapse and others do not. Donor T-cells can also damage healthy recipient tissue, a common and potential life-threatening complication termed graft-versus-host disease (GvHD). Our group aims to better understand the immunology of AML and devise novel therapeutic strategies to improve transplant outcomes.

Inducing leukaemic differentiation to augment donor T-cell responses

AML exhibits a block to differentiation that prevents leukaemic cells from forming mature blood cells. New treatments for AML often target this block, leading to monocyte/macrophage differentiation. Many of the resulting cells, which we term leukaemia-derived antigen presenting cells (LD-APCs), are capable of antigen presentation and we are studying their ability to promote anti-leukaemia T-cell responses. CD8+ cytotoxic T cells that interact with these leukaemia-derived antigen presenting cells in the presence of CD4+ T helper cells are much more effective at killing undifferentiated leukaemia. The potential advantage of this approach is to enhance antigen presentation at sites of disease without causing widespread T-cell activation. This is particularly important in the context of stem cell transplantation where treatments that promote generalised donor immune cell activation generally cause GvHD.

During 2025, we have been developing a mouse model to help us determine the ability of LD-APCs to prime an effective immune response against leukaemia. We have also been exploring novel drug combinations and have discovered a strategy that elicits potent LD-APC differentiation. We have identified a transcriptional programme that is highly associated with antigen presentation in AML, which is frequently lost at post-transplant relapse and strongly activated by our drug treatments.

Identifying leukaemia-reactive T-cell populations

Advances in cancer immunotherapy have yet to benefit patients with AML. The basis of contemporary immunotherapy is that tumours elicit T-cell responses which they must then evade. Restoring or enhancing these responses is therefore a key therapeutic goal that is best exemplified by the success of immune checkpoint inhibitors. However, these approaches have not improved outcomes in AML, despite successful allogeneic stem cell transplantation demonstrating the curative potential of leukaemia-reactive T cells. It also remains unclear whether AML reliably elicits autologous T-cell responses or whether it is simply not an immunogenic disease, a question that must be answered if effective immunotherapies are to be devised.

To address this problem, we developed a T cell-focused mass cytometry panel and analysed >300 million cells from the bone marrow of 112 AML patients, along with 12 matched peripheral blood samples and 10 normal bone marrows. This approach revealed numerous phenotypically distinct T-cell populations that are either highly leukaemia-associated or unique to AML (not found in normal bone marrow). In 2025, we began working to confirm whether these populations are genuinely leukaemia-reactive, by testing their ability to recognise leukaemia cells from the same patient. These experiments are complicated by the high number of developing or resting T cells in normal bone marrow, and the difficulty eliciting measurable responses from exhausted T-cells – one of the populations most likely to harbour leukaemia reactivity. Figure 1 shows our strategy for determining the reactivity of the various leukaemia-associated T-cell populations. These approaches are designed to be complimentary, avoid bias, and identify bona fide reactive populations with high confidence. Results will inform future studies to identify drivers of T-cell dysfunction and develop novel therapeutic strategies to promote anti-leukaemic immune responses.

Predicting transplant complications

Our laboratory is also interested in developing biomarkers that predict the onset of GvHD, a devastating transplant complication and common cause of death. We therefore established a clinical study, called Precision Medicine for Stem Cell Transplantation (PM-SCT), which completed recruitment in December 2025, having enrolled 226 transplant recipients and collected thousands of aliquots of plasma and cryopreserved cells from blood and bone marrow. In August 2025, we were joined by Healson Ihuoma, a Clinical Research Training Fellow who has begun his PhD studies by assessing several contemporary approaches to plasma protein biomarker discovery.

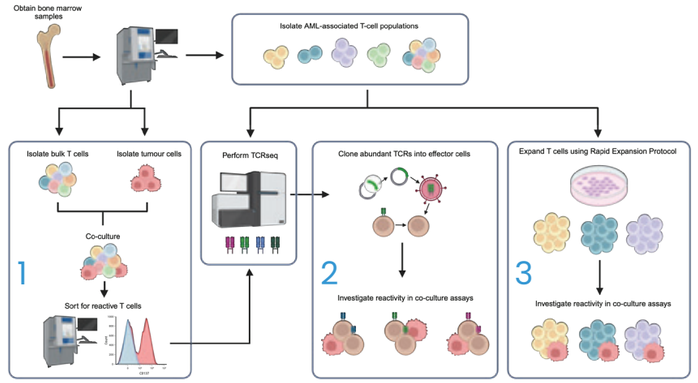
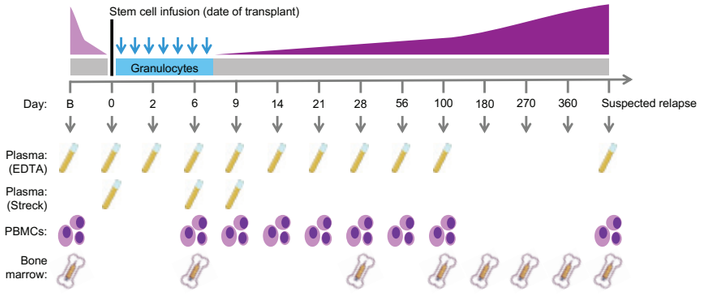


Figure 1: A strategy for determining the leukaemia reactivity of various phenotypically defined, leukaemia-associated T-cell populations. (1) Direct co-culture of T-cells with leukaemia cells isolated from patient bone marrow samples. (2) T-cell receptor (TCR) sequencing of T-cell populations of interest, followed by cloning and functional validation of selected TCRs. (3) Expansion of T-cell populations of interest followed by co-culture with autologous leukaemia cells.

Until recently, characterisation of the plasma proteome has been limited by the high cost, low coverage and long run times of traditional mass spectrometry (MS). However, recent advances in data-independent acquisition and the development of new analyser technologies permit analysis of thousands of patient samples, accurately quantifying 1,000-1,200 proteins using neat plasma and short run times. Plasma protein concentrations vary significantly between individuals but are relatively stable within individuals. Serial sampling can identify biomarkers that are obscured by interpatient variability in studies of single timepoints. So far, we have analysed ~200 plasma samples from PM-SCT, with the aim of identifying the timepoints that are optimal for GvHD prediction and determining whether high-throughput MS alone can predict GvHD. Initial results are promising, suggestive that relatively shallow, longitudinal data is actually highly informative. The next step is deep proteomic profiling of the most informative timepoints using affinity-based approaches.

Figure 2: The sample collection schedule for GRACE, a Phase I/II trial of granulocyte-augmented cord blood transplantation for very poor risk acute myeloid leukaemia.



In collaboration with the CRUK National Biomarker Centre, we are also assessing the potential of cell-free DNA methylation to predict GvHD distribution and severity. GvHD may affect multiple tissues, and the cellular origin of plasma protein biomarkers is often unclear. DNA methylation patterns are tissue/cell specific, and DNA released from affected tissues reflects both the site and severity of inflammation. The plasma concentration of cell-free DNA (cfDNA) is elevated in patients with acute GvHD, both at and before diagnosis, and the abundance of tissue-specific methylation markers is likely to mirror organ involvement and severity. These experiments will also provide orthogonal (non-protein) validation of the proteomic analysis.

Granulocyte-augmented cord blood transplantation

Working with Professor Rob Wynn from Royal Manchester Children's Hospital, and collaborators at King's College Hospital, we have established GRACE, a multi-centre Phase I/II trial of granulocyte-augmented cord blood transplantation for young adults with very poor risk acute myeloid leukaemia. This trial is assessing the safety and efficacy of an innovative transplant protocol based on the incidental finding that giving peri-transplant granulocyte infusions to cord blood transplant recipients induced durable remissions in children with highly resistant leukaemia. The study will open to recruitment in early 2026 and involves collection of a significant number of research samples (Figure 2) to support its translational aims.

Granulocytes are a complex product, and their effect was an incidental discovery. There is huge potential to further improve the approach by understanding the mechanism and refining what already promises to be a transformational therapy. The scientific research associated with the study will attempt to describe the action of peri-transplant granulocyte administration, identify key features of successful transplantation and investigate whether responders can be identified to allow targeted application of this approach. Specifically, the research will aim to address the following questions:

1. Does disease response require priming of donor T-cells against HLA mismatches shared by the recipient and the granulocyte product?
2. Does granulocyte-induced inflammation induce leukaemic differentiation?
3. Does pre-treatment sensitivity of leukaemia to interferon-gamma identify responders?
4. Can plasma proteomics identify novel biomarkers of treatment response?
5. Can immune clearance of residual disease be detected using cell-free DNA methylation analysis?

Publications listed on page 53

www.cruk.manchester.ac.uk/research-group/rna-dynamics-in-cancer/

RNA DYNAMICS IN CANCER



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Diet represents a significant factor in cancer predisposition, with certain dietary habits known to increase the risk of specific cancers. For example, consuming high amounts of red and processed meat is associated with a 15-30% increased risk of colon cancer. Similarly, diets high in sugar and refined carbohydrates are linked to an elevated risk of endometrial cancer. While much research has focused on the role of diet in cancer initiation, we know far less about how dietary factors influence the progression of the disease.

Tumour cells must constantly adapt to fluctuating nutrient availability within their microenvironment. These adaptations extend beyond metabolic rewiring and involve profound changes in gene expression regulation. It is becoming increasingly clear that the RNA layer in this regulation – including RNA synthesis, processing, chemical modification, stability, localisation and translation – acts as a dynamic interface between environmental cues and cellular behaviour. Translational control allows tumour cells to rapidly remodel their proteome without altering genomic information, enabling adaptation to stress, therapy, and metabolic constraint.

Since its inception in January 2025, the RNA Dynamics in Cancer laboratory has been dedicated to understanding how dietary and metabolic signals reshape the RNA life cycle and protein synthesis in cancer. By integrating dietary interventions, RNA biochemistry, metabolic profiling and functional genomics, our goal is to uncover how tumours exploit RNA-based regulatory mechanisms to support progression and therapeutic resistance.

RNA modifications affecting cancer cell state transition

Cancer progression is fundamentally driven by the ability of tumour cells to transition between cellular states, enabling processes such as metastasis and therapy resistance. Our research has demonstrated that RNA modifications (chemical alterations to RNA molecules) play a pivotal role in these transitions by rewiring the proteome to meet the evolving demands of cancer cells. For example, we previously showed that the mitochondrial tRNA m^5C modification is essential for mitochondrial protein synthesis, providing the energy required for cell transitioning to a metastasis-initiating state to disseminate from primary tumours (Delaunay et al., *Nature*, 2022). These findings highlight how RNA modifications act as molecular switches, enabling cancer cells to adapt their proteome in response to stress or metabolic cues.

Building on this foundation, our lab is now exploring how diet shapes the epitranscriptome to influence cancer cell states. Dietary compounds, such as fatty acids, are known to alter cancer metabolism, but their impact on RNA modifications, and consequently, proteomic adaptation, remains poorly understood. By identifying the specific RNA modifications and regulatory proteins that sustain cancer cell state transition, we aim to uncover new therapeutic targets and biomarkers for early intervention to prevent tumour adaptation.

The direct influence of diet on the epitranscriptome

Dietary nutrients can play a dual role in cancer biology, serving as essential substrates for metabolism, but they can also be used as critical substrates for tRNA modifications that fine-tune translation. These modifications enhance the accuracy and efficiency of codon-anticodon pairing, enabling cancer cells to rapidly adapt their proteome in response to metabolic stress, a hallmark of tumour progression and metastasis.

Our laboratory has uncovered compelling evidence that tRNA modifications are not merely passive byproducts of metabolism but active drivers of cancer progression. To further explore this connection, we are investigating how dietary nutrients directly influence the deposition on tRNAs, thereby reshaping translation to promote cancer progression. This research holds significant promise for translating fundamental discoveries into clinical applications. By identifying how specific dietary components influence RNA modifications, we aim to develop targeted interventions, such as dietary modulation or pharmacological inhibition of RNA-modifying enzymes, to disrupt cancer progression and improve patient outcomes.

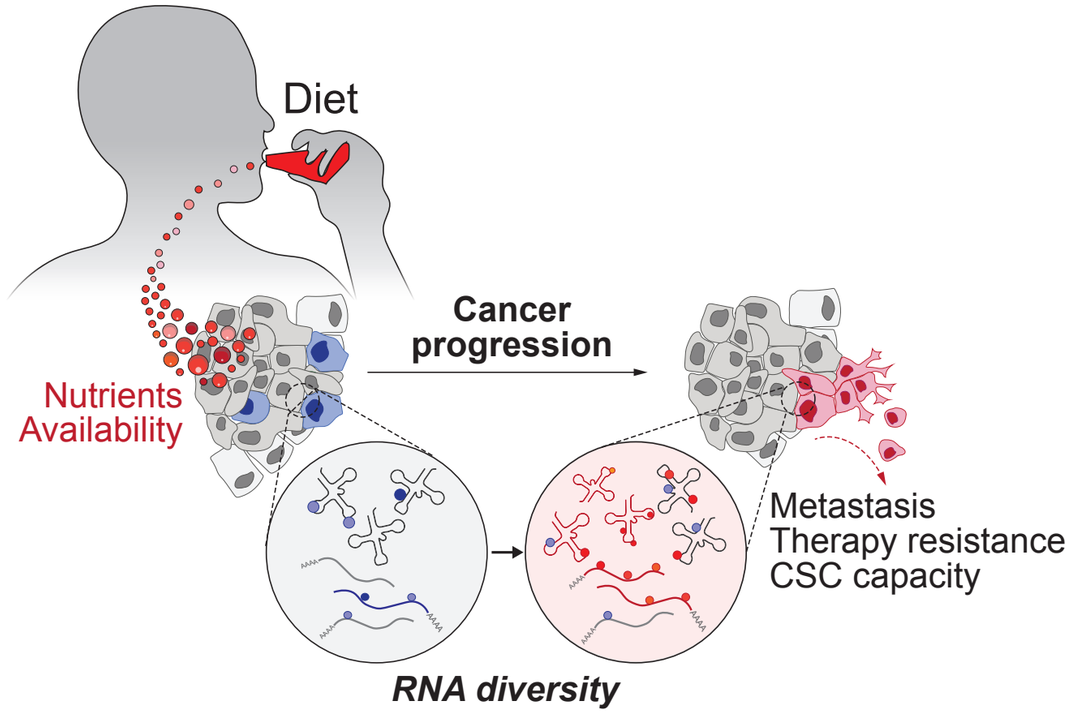


Figure 1: Nutrient availability represents a major driver of cancer progression. Our group studies how diet influences the diversity in RNA in cancer cells, using it as a bottleneck to prevent cancer progression, such as tumour growth, metastasis or resistance to therapy. To this end, we address the changes in the RNA life cycle upon dietary modulation, the consequences on the tumour behaviour and patient outcome.

Targeting RNA modifications to sensitise leukaemia cells to treatment

In 2025, we contributed to the publication of a study identifying disruption of mitochondrial tRNA modification mediated by TRMT5 as a metabolic vulnerability in acute myeloid leukaemia (Pauli et al., *Blood*, 2025). This work demonstrated that TRMT5 is essential for sustaining mitochondrial translation and respiratory chain activity. In therapy-resistant leukaemia cells, mitochondrial protein synthesis supports ATP production required to survive treatment with agents such as venetoclax and cytarabine. Genetic or functional impairment of TRMT5 reduced oxidative phosphorylation capacity, compromised energy production, and sensitised malignant cells to therapy.

SKIN CANCER AND AGEING



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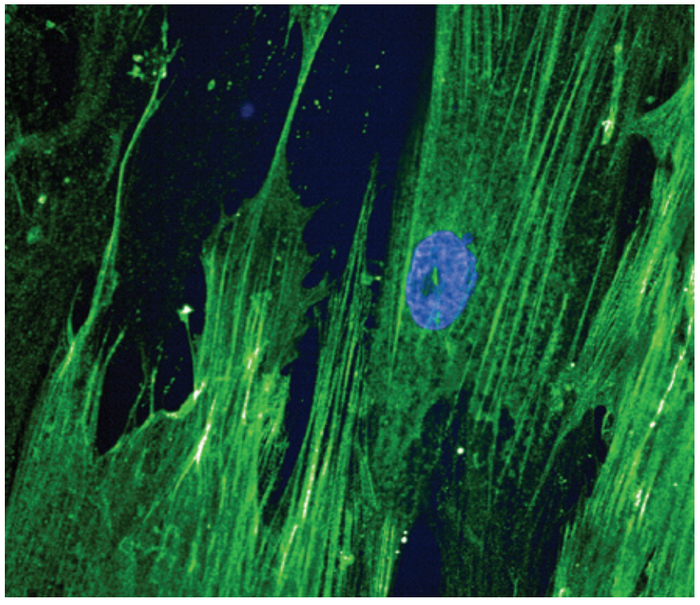
[1]Left in 2025
[2]Undertaking an MRC DTP PhD studentship with Rob Clarke, Division of Cancer Sciences, University of Manchester

Cancer, and skin cancer in particular, is increasingly a disease of the ageing population. In the UK, both incidence and mortality continue to rise, with the greatest burden falling on patients over 60 years of age. Older patients not only develop melanoma more frequently but also present with more aggressive disease and a higher incidence of additional malignancies, particularly other skin cancers, complicating treatment and long-term outcomes.

Melanoma and the tumour microenvironment

A major determinant of mortality is metastatic spread, which increases with age and shows clear organ-specific patterns. Our work focuses on understanding how age-dependent changes in the tissue microenvironment shape metastatic behaviour and therapeutic response. Two of our PhD students, Vanessa and Lutong, are characterising how ageing alters the liver and lung microenvironments, respectively, and how these changes influence melanoma progression.

In contrast, melanoma metastasis to the brain is more frequently observed in younger patients. Our MB PhD student Charlotte is investigating how age-related differences in brain metabolism and immune function influence the ability of melanoma cells to colonise this organ.



Together, these studies aim to define how organ-specific and systemic ageing processes determine metastatic patterns and patient outcome.

UV light and immune responses to melanoma

Melanoma incidence is strongly associated with ultraviolet (UV) exposure, which contributes to tumour initiation through DNA damage and inflammation. However, the systemic effects of UV exposure on cancer progression and therapy response remain less well understood. We investigated whether chronic UV exposure influences immunotherapy outcomes and found that it reduces response to immunotherapy in pre-clinical models of melanoma and colorectal cancer. Mechanistically, this effect is mediated through expansion of regulatory T cells (Tregs), which suppress anti-tumour immune responses. Chronic UV exposure increased Treg abundance both systemically and within tumours, impairing immune-mediated tumour clearance. Importantly, depletion of Tregs restored immunotherapy efficacy, highlighting a potential therapeutic strategy. This work was published in *Journal for ImmunoTherapy of Cancer* (Durao et al. 2025, 13(10):e012527).

Despite these inhibitory effects, UV exposure may also have other context-dependent effects

Figure 1: When fibroblasts interact with cancer cells, they can be rewired to promote cancer growth, becoming cancer-associated fibroblasts. Alpha-smooth muscle actin (αSMA) fibre formation is often seen in activated fibroblasts and cancer-associated fibroblasts. In this immunofluorescence image, we see fibres of αSMA (green) in lung fibroblast cells that have been co-cultured with lung squamous cell carcinoma (SCC), suggesting that these lung fibroblasts have been rewired/activated, potentially in a way that supports the SCC. Fibroblast nuclei are stained in blue (DAPI).

(Image supplied by Noah Palombo, Skin Cancer and Ageing)

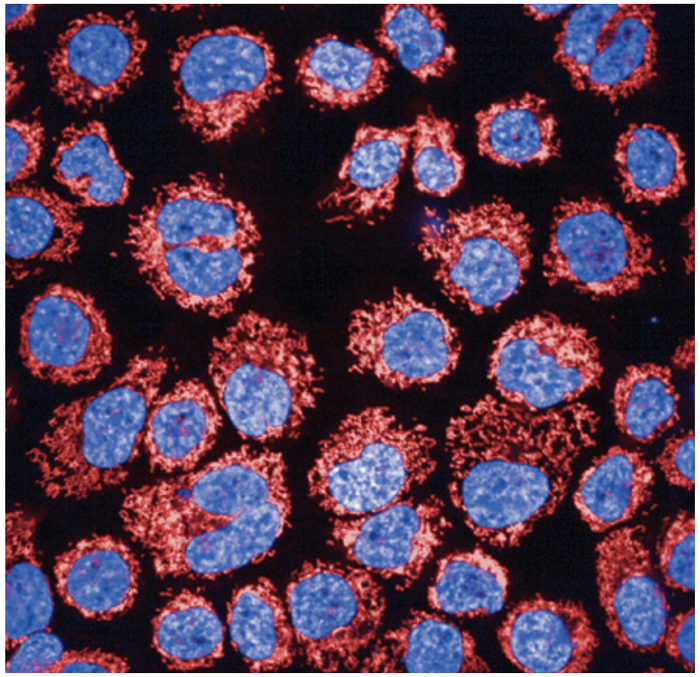


Figure 2: Immunofluorescence image of oral squamous cell carcinoma cells treated with secretome from oral fibroblasts; their mitochondria are stained in red (MitoView 633) and their nuclei are stained blue (DAPI). Stronger red staining suggests greater metabolic activity in the mitochondria.

(Image supplied by Noah Palombo, Skin Cancer and Ageing)

on immune function. Our postdoctoral fellow, Dr Isabella Mataloni, is investigating how chronic UV exposure reshapes immune responses across different systemic cell types. We are also examining how these effects intersect with ageing, given that cumulative UV exposure increases over the lifespan and may modify age-associated immune decline.

The tumour microenvironment and epithelial cancer invasion

Squamous cell carcinoma (SCC) arises in epithelial tissues across multiple organs, yet clinical outcomes vary markedly by site. For example, cutaneous SCC rarely metastasises, whereas oral and lung SCC are highly invasive and frequently fatal.

We hypothesised that these differences are driven by the tissue microenvironment rather than tumour-intrinsic factors. Using advanced 3D models, we demonstrated that the same SCC cells exhibit markedly different invasive behaviour depending on the fibroblasts present. Dermal fibroblasts suppress invasion, whereas oral and lung fibroblasts promote it, indicating that site-specific stromal cues dictate cancer behaviour.

Mechanistically, we found that fibroblasts from different tissues have distinct lipid metabolic profiles and transfer specific lipid species to cancer cells. These lipids activate signalling pathways that drive invasion and metabolic reprogramming in SCC. In contrast, dermal fibroblasts are relatively lipid-poor and do not promote invasive behaviour.

These findings establish fibroblast-derived lipid signalling as a key determinant of epithelial cancer progression and provide a mechanistic explanation for site-specific differences in clinical outcome. Our work has now been accepted for publication in *Nature Metabolism*.

Publications listed on page 53

SMALL CELL LUNG CANCER BIOLOGY



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Small cell lung cancer (SCLC) is an aggressive neuroendocrine malignancy representing ~15% of lung cancers worldwide. Predominantly associated with tobacco use, SCLC is typically diagnosed at advanced, non-curative stages, with high circulating tumour cell (CTC) burden driving early and widespread metastasis.

Whilst platinum-based chemotherapy elicits initial responses, relapse is nearly universal within months. Although current immune checkpoint inhibitors benefit only a minority, DLL3- targeted T cell engagers show promise for SCLC subtypes expressing this NOTCH ligand. At the molecular level, SCLC is defined by TP53 and RB1 inactivation, a complex mutational landscape and expression of neurogenic transcription factors. Our research is underpinned by our biobank of >65 SCLC preclinical models derived from individual patients' CTCs, termed CTC Derived eXplants (CDX) models, reflecting the molecular and subtype heterogeneity of SCLC. The biobank enables the study of mechanisms driving metastasis and chemoresistance, supports the development of novel targeted therapies and, in close collaboration with the CRUK National Biomarker Centre, drives discovery and validation of tissue and blood-based biomarkers for stratified treatments.

Dissecting the metastatic cascade

SCLC is among the most metastatic cancers, with ~80% of patients presenting with metastases at diagnosis. Our CDX models recapitulate metastatic behaviours observed in patients, consistently disseminating to the liver and brain following subcutaneous implantation and resection. We previously identified a rare but highly aggressive subtype of SCLC, driven by the ATOH1 transcription factor (Simpson et al., *Nature Cancer*, 2020). This year, we demonstrated that ATOH1 promotes cell survival and supports CTC dissemination to the liver (Catozzi et al., *Cell Reports*, 2025). To explore transcriptional dynamics underpinning SCLC metastasis, we are employing luciferase labelling of CDX cells prior to implantation for live animal imaging, combined with single cell RNA sequencing of subcutaneous tumours, CTCs, micro and macro liver metastases (Figure 1a). Early analyses have revealed distinct transcriptomic changes in micro-metastasis suggesting that early arriving tumour cells undergo active remodelling to successfully colonise the liver microenvironment. Several candidate mediators have emerged from these analyses and are currently undergoing functional validation (Figure 1b). To capture the evolutionary dynamics of metastatic progression, we are employing two complementary lineage tracing strategies. In collaboration with the Hannon laboratory at the CRUK Cambridge Institute, we are applying WILD-seq (Wholistic Interrogation of Lineage Dynamics by sequencing), a barcoding approach enabling simultaneous tracking of clonal behaviour and transcriptional state changes during metastatic progression and we have established a pipeline for generating barcoded cell populations in multiple CDX models. Complementing this, we have implemented RGB colour marking with LEGO vectors to enable visualisation of clonal diversity and phenotypic plasticity in vivo. In three CDX models, subcutaneous tumours maintain broad clonal diversity (represented by diverse and equally distributed populations of coloured cells), demonstrating the highly tumorigenic nature of SCLC cells (Figure 2a). In contrast, in two CDX models with frequent liver metastasis, SCLC cells growing in the livers showed marked clonal bottlenecking (fewer colours present), indicating strong selective pressure to colonise the liver (Figure 2b).

Phenotypic plasticity and vasculogenic mimicry

Increasingly, the dynamic behaviour of SCLC encompassing phenotypic plasticity, intra-tumoral heterogeneity and capacity to transition between neuroendocrine (NE) and non-neuroendocrine (non-NE) states, is emerging as a central driver of metastasis, immune evasion and drug resistance. Most CDX models harbour a minority non-NE population, and several models undergo spontaneous NE to non-NE transition ex vivo. A striking example of SCLC phenotypic plasticity is vasculogenic mimicry (VM), a process where tumour cells develop endothelial-like features and form vessel-like structures independent of angiogenesis. First described by our group in SCLC, VM is observed across multiple CDX models and is associated with poor prognosis (Williamson et al., *Nature Communications*, 2016; Pearsall et al., *Journal of Thoracic Oncology*, 2023). VM vessels co-localise with the non-NE marker REST in vivo and only non-NE cells form hollow tubules on Matrigel (an in vitro surrogate for VM), confirming that VM capacity is unique to the non-NE cell state. In vivo studies confirmed that VM vessels are functionally perfused. Using LEGO vectors, we are currently tracking NE to non-NE transition and the lineage dynamics underlying VM formation and function in vivo. By integrating spatial transcriptomics and LEGO-based lineage tracing, we aim to determine whether VM-capable cells arise from specific regions of NE-dominant tumours. Earlier work in genetically modified mouse models suggested that NE/non-NE cooperation is required for efficient metastasis; we are now testing whether VM represents a functional mechanism through which non-NE cells support the metastatic dissemination of NE cells.

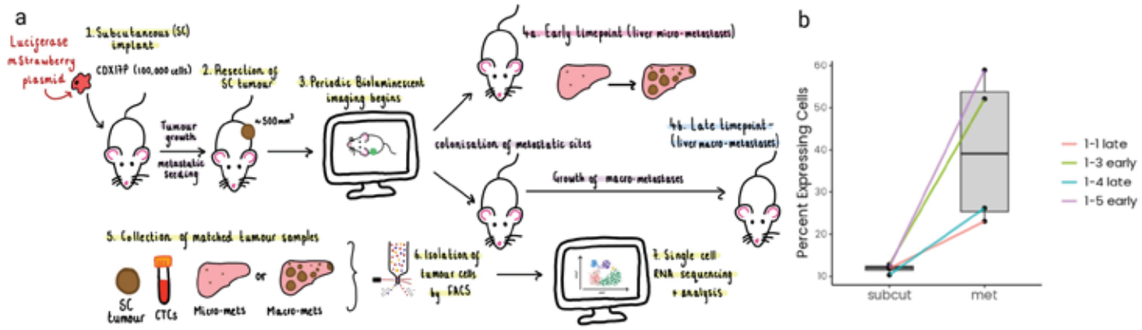


Figure 1: Single cell transcriptomic profiling across the metastatic cascade. a) Schematic overview of the experimental workflow for scRNAseq profiling of CDX17P samples spanning subcutaneous tumours, circulating tumour cells and liver metastases, b) proportion of cells expressing metastasis supporting candidate 'X' across subcutaneous tumours and liver metastasis. Lines connect individual subcutaneous tumours to their matched liver micro-metastases (early) or macro-metastases (late).

Targeting chemoresistance and cell cycle vulnerabilities

Resistance to platinum-based chemotherapy is near universal in SCLC and our CDX models faithfully recapitulate this clinical pattern. A central question is whether resistant populations emerge from pre-existing subclones selected under therapeutic pressure or arise through transcriptional reprogramming of a common ancestral population. To address this, we are employing WILD-seq barcoding integrated with transcriptional profiling to track clonal dynamics in response to chemotherapy to resolve gene expression and cell state changes that potentially drive resistance. This will enable us to identify early molecular signatures of relapse and pinpoint the vulnerabilities that emerge as resistance develops. A compelling set of such vulnerabilities lies in cell cycle regulation. The near universal loss of RB1 and TP53 function and aberrant DNA damage repair leaves SCLC cells heavily reliant on remaining checkpoint machinery for survival, thereby creating a targetable dependency. Using CDX models and in collaboration with Iain Hagan's Cell Division group, we show that inhibition of PKMYT1, a kinase regulating mitotic entry, induces DNA damage and apoptosis ex vivo across a range of CDX models. In a promising pilot study, combination treatment with standard-of-care chemotherapy demonstrated improved tumour growth control in vivo over chemotherapy alone. Ongoing work is focussed on refining biomarkers of response and assessing whether PKMYT1 inhibition can stimulate an anti-tumour immune response in what is considered an 'immune' cold tumour.

Taken together, our SCLC biology programme spanning lineage tracing, single cell transcriptomics, spatial profiling, functional modelling, and therapeutic interrogation seeks to deliver a comprehensive understanding of SCLC metastasis, plasticity and resistance, with direct translational implications for patient stratification and new therapeutic development.

Publications listed on page 53

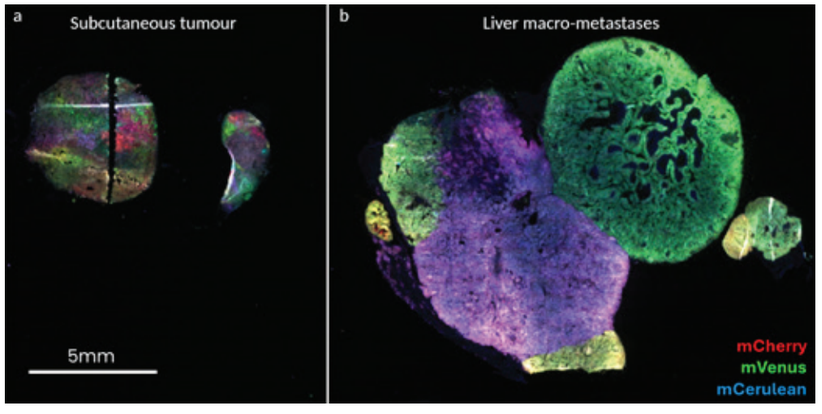


Figure 2: LEGO-based clonal tracking reveals metastatic bottlenecking. Representative immunofluorescence images of LEGO-labelled CDX17P showing a) subcutaneous tumours characterised by broad clonal diversity, with multiple colour populations distributed throughout the tumour, and b) matched liver macro-metastases showing a marked reduction in clonal diversity, with only a subset of colour populations represented.

www.cruk.manchester.ac.uk/research-group/stem-cell-biology

STEM CELL BIOLOGY



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[1]Left in 2025
[2]Joined in 2025
[3]Funded by MCRC

Acute Myeloid Leukaemia (AML) remains one of the most devastating and treatment-resistant forms of blood cancer, characterised by profound genetic heterogeneity and persistently poor clinical outcomes, with five-year survival rates of approximately 20%.

The Stem Cell Biology group, led by Georges Lacaud, is dedicated to uncovering novel therapeutic vulnerabilities in AML and deepening our understanding of normal haematopoietic development to enable next-generation immunotherapies and cell-based treatment strategies.

Our research programme integrates two complementary and mutually reinforcing lines of investigation. The first focuses on dissecting the molecular mechanisms that drive leukaemia initiation, disease maintenance, and the emergence of chemoresistance, with the ultimate goal of identifying actionable targets for clinical translation. The second programme is centred on elucidating the developmental pathways governing blood cell generation during embryogenesis, work that directly informs the rational design of cell-based therapeutic strategies, including the in vitro generation of haematopoietic stem and progenitor cells.

In 2025, the group finalised several studies spanning both programmes. A study identified the retinal determination gene network as a novel therapeutic target in AML. Another study presented the largest single-cell transcriptomic atlas of AML to date, revealing age-related gene regulatory network differences in t(8;21) AML. Finally, in another line of investigation, we identified three distinct endothelial-to-haematopoietic transition trajectories with divergent isoform landscapes, fundamentally advancing our understanding of blood cell emergence during development.

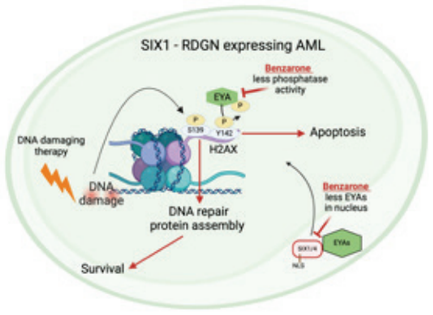


Figure 1: Working model illustrating the action of benzarone on retinal determination gene members. (1) Benzarone disrupts the interaction between EYA and SIX proteins, leading to reduced nuclear shuttling of EYA. In parallel, (2) Benzarone inhibits EYA phosphatase activity, preventing dephosphorylation of H2gX at Tyr142. This shift favours apoptotic signalling over DNA repair in response to DNA-damaging therapy.

Retinal determination gene network as a therapeutic target in AML

Our group published a study identifying the retinal determination gene network (RDGN) as a direct transcriptional target and critical dependency in MOZ- and MLL-rearranged AML (Figure 1). Using ChIP-seq of Ty1-tagged MOZ-TIF2 and complementary transcriptomic analyses, we demonstrated that the transcription factors SIX1, SIX4, and their phosphatase cofactor EYA1, are directly activated by both MOZ-TIF2 and MLL-AF9 fusion proteins. The SIX1-EYA1 complex was shown to enhance HOXA9-driven leukaemic transformation, reinforcing the differentiation block characteristic of AML and maintaining blast morphology in leukaemic cells.

Single-cell RNA sequencing of murine MOZ-TIF2 AMLs revealed that SIX1-expressing and MEIS1-expressing cells occupy mutually exclusive cellular states, a striking dichotomy that was recapitulated in human AML patient datasets and cell lines. This finding suggests that AML can be sustained by parallel transcriptional programmes, each capable of independently maintaining the leukaemic phenotype. Interestingly, the RDGN plays a significant role in the DNA damage response: EYA phosphatases dephosphorylate histone H2AX at Tyr142, shifting the cellular balance from apoptosis toward DNA repair and thereby enabling chemoresistance. Accordingly, High SIX1 expression in chemotherapy-treated patients was found to associate with significantly reduced overall survival, establishing SIX1 as both a prognostic biomarker and a candidate therapeutic target.

Using the repurposed drug Benzarone, which disrupts SIX-EYA protein-protein interactions, we demonstrated selective anti-leukaemic effects in SIX1-expressing AML cells while sparing normal haematopoietic progenitors. When combined with cytarabine, Benzarone showed synergistic efficacy both in vitro and in vivo. This work establishes RDGN targeting as a promising therapeutic approach not only for AML but potentially for other malignancies characterised by aberrant SIX1/RDGN re-expression, including breast, colorectal, and ovarian cancers.

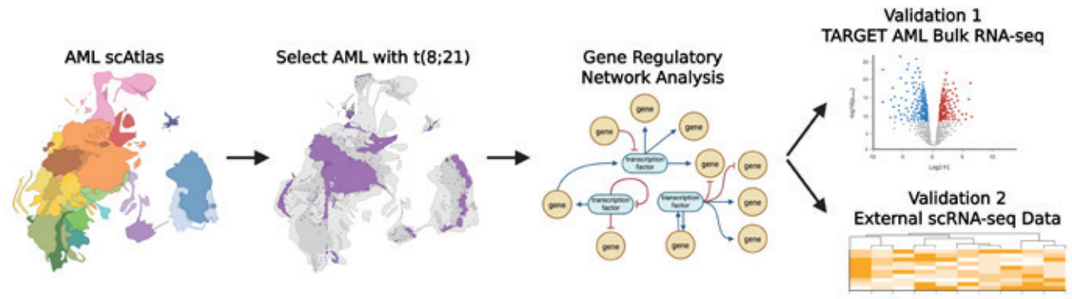


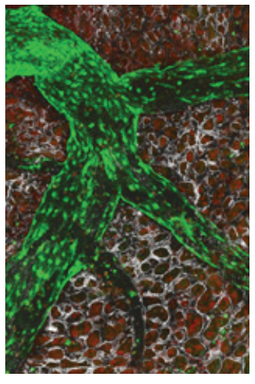
Figure 2: Depiction of the workflow to generate and validate the t(8;21) AML gene regulatory network (GRN) from AML.

Single-cell atlas of AML reveals age-related gene regulatory networks in t(8;21) AML

To overcome the inherent limitation of small sample sizes in individual single-cell RNA sequencing studies, we performed large-scale computational integration of 20 published scRNA-seq datasets to generate the AML scAtlas. This comprehensive resource comprises 748,679 cells derived from 159 AML patients and 51 healthy donors, making it, to our knowledge, one of the largest single-cell AML data resource assembled to date. The atlas is publicly available through the CELLxGENE platform, providing an invaluable tool for the wider research community (Figure 2).

We leveraged the AML scAtlas to investigate t(8;21) AML across different age groups, motivated by the hypothesis that the known prenatal origin of paediatric t(8;21) disease underlies its superior clinical prognosis compared to adult-onset disease. Applying pySCENIC gene regulatory network inference, we identified two distinct age-associated GRN signatures. The inferred-prenatal signature, enriched in paediatric and adolescent cases up to age 17, is defined by transcription factors including BCLAF1, TAL1, MYB, IKZF1, and YY1, many of which have well established roles in foetal haematopoiesis. The inferred-postnatal signature, associated with adult-onset disease, is characterised by inflammatory and metabolic regulators including IRF1, IRF7, SPI1, and HDAC2.

Figure 3: Confocal whole-mount immunofluorescence of an E10.5 mouse yolk sac shows arterial vessels (VWF, green), endothelial plexus (LYVE1, white), and haemogenic/haematopoietic cells (RUNX1, red). Rare VWF–RUNX1 and LYVE1–RUNX1 double-positive cells mark spatially distinct HE populations that give rise to lympho-myeloid and erythro-myeloid progenitors, respectively.



These signatures were validated in a larger bulk RNA-seq cohort drawn from the TARGET and BeatAML databases (n=83) and further refined using single-cell multiomic data combining scRNA-seq and scATAC-seq to reconstruct denoised enhancer-driven GRNs via SCENIC+. Inferred-prenatal samples showed enrichment for stemness-associated genes, a higher HSC/progenitor cell type composition, and predicted increased sensitivity to cytarabine, venetoclax, and daunorubicin. In silico perturbation modelling identified BCLAF1 and EP300 as high-priority therapeutic targets, with BCLAF1 representing a novel and previously unexplored vulnerability specifically in paediatric t(8;21) AML.

Three distinct endothelial-to-haematopoietic transition trajectories

By combining functional single-cell assays with full-length Smart-seq2 scRNA-seq across yolk sac (YS) and aorta-gonad-mesonephros (AGM) haemogenic endothelium (HE) populations, we identified three distinct endothelial-to-haematopoietic transition (EHT) trajectories. The first, termed HEYSP, is located in the YS endothelial plexus, marked by LYVE1 expression, dominant before embryonic day E9.5, and primed for erythromyeloid progenitor (EMP) generation. The second, HEYSA, is found in large YS arteries, marked by VWF/CD24a expression, prevalent after E9.5, and skewed toward lymphomyeloid progenitor (LMP) output (Figure 3). The third trajectory, HEAGM, displays a robust arterial endothelial identity and possesses unique haematopoietic stem cell (HSC)-generating capacity.

Comparative transcriptomic analysis of all three populations identified a universal HE signature comprising 515 genes, with Gfi1 and Mycn standing out as the only transcription factors showing truly HE-restricted expression across all anatomical sites. AGM HE was uniquely enriched for chromatin modifiers and RNA processing genes, a finding that correlated with markedly increased isoform complexity. This included differential isoform usage of stemness-associated factors such as Runx1, suggesting that post-transcriptional regulation plays a previously underappreciated role in HSC specification.

To establish functional significance, CRISPR-Cas9 deletion of Runx1 exon 6 across all transcripts was performed, which impaired long-term HSC detection in both the AGM and foetal liver, establishing a direct causal link between isoform diversity and HSC specification. This comprehensive scRNA-seq resource, capturing three complete EHT trajectories giving rise respectively to EMPs, LMPs, and HSCs, is publicly accessible at https://shiny.cruk.manchester.ac.uk/(AGMYSdatasetfinal) and represents a valuable tool for the developmental haematopoiesis community.

Publications listed on page 54

www.cruk.manchester.ac.uk/research-group/systems-oncology

SYSTEMS ONCOLOGY



Group Leader
Claus Jørgensen

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Joanna Kelly

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Translational Research Facilitator
Luke Taylor[1]

[1]Working jointly with clinicians at the Christie NHS FT, MRI FT and the MCRC Biobank

Solid tumours are complex ecosystems where cancer cells are embedded within a complex microenvironment comprising multiple host cell types and a pathological remodelled, stiff extracellular matrix. The aim of the Systems Oncology group is to determine and define how tumour cells conscribe host cells and how the evolving microenvironment, in turn, controls tumour development and therapeutic resistance. Understanding these rules will enable the development of rational combination therapies targeting both tumour cell intrinsic dependencies as well as their extrinsic dependencies on stromal reciprocal signals.

Pancreatic Ductal Adenocarcinoma

Pancreatic Ductal Adenocarcinoma (PDAC) is a dismal disease with an average five-year survival rate of ~8% (UK data). Most patients are diagnosed with inoperable or overt metastatic disease and are typically only offered combination chemotherapy with limited effect. Consequently, although PDA is the 11th most common cancer in the UK, it is currently the 4th largest contributor to cancer related deaths and is projected to be the 2nd largest contributor to cancer related deaths by 2030.

A characteristic feature of PDAC is an extensive desmoplastic reaction, which makes up 85% of the tumour volume on average. Here, an abundant and pathological remodelled extracellular matrix increases tissue stiffness and interstitial pressure, which results in decreased therapeutic efficiency. Moreover, the microenvironment contains an abundant fibroblast and myeloid cell infiltrate, which reduces immune surveillance and confers resistance to therapy.

Mapping the tumour microenvironment of PDAC

Due to the abundant tumour microenvironment, much emphasis has been given to the mapping of signalling pathways by which tumour cells conscript host cells. Pre-clinical studies have further demonstrated that these pathways can be successfully targeted to improve therapeutic response. However, in some cases, therapeutic and genetic targeting of the microenvironment has resulted in accelerated disease progression rather than retardation. Collectedly, these results suggest that interactions between tumour and host can be tumour restrictive as well as tumour promoting, yet the molecular mechanisms governing these pro- and anti-tumour effects remain poorly defined.

We previously used single cell mass cytometry to annotate the microenvironmental composition in a commonly used murine model of PDAC (pdx-1 Cre; KRasLSL-G12D/Wt; p53$^{LSL-R172H/Wt}$; KPC), revealing that PDAC tumours contain two separate populations of CAFs distinguished by the expression of CD105 (Endoglin). Subsequent analysis across normal fibroblasts and tumour tissue (breast, colorectal and lung) revealed that both CD105^{pos} and CD105^{neg} fibroblasts were present in all tissue examined so far but that the ratio between these populations varies greatly between tissue and tumours. Isolation and characterisation of CD105^{pos} and CD105^{neg} pancreatic fibroblasts revealed that CD105 is expressed in a noninterchangeable manner e.g., CD105^{neg} fibroblasts under current conditions tested do not start to express CD105, and CD105^{pos} fibroblasts, under current conditions tested, will not completely shut down CD105. Furthermore, CD105^{pos} and CD105^{neg} fibroblasts respond differentially to most exogeneous signals tested. Together, this suggests that these subsets may have distinct functional roles in the tumour microenvironment. Indeed, tumour cells co-implanted with CD105^{pos} fibroblasts grew slightly faster than tumour cells implanted in isolation, suggesting a tumour permissive role of CD105^{pos} fibroblasts. In contrast, co-implanted CD105^{neg} fibroblasts restrict tumour growth. The tumour restrictive role of CD105^{neg} fibroblasts depends on a functional immune system. As such, CD105^{neg} fibroblasts lose their tumour suppressive function when injected into immune deficient animals. The tumour restrictive role of CD105^{neg} fibroblasts depends on a functional immune system. To subsequently interrogate how CD105^{neg} fibroblasts might engage the immune system to regulate tumour growth, we aimed to identify functionally important transcriptional programmes and the upstream transcription factor(s) regulating these. To this end, we undertook a computational predictive analysis to identify regulators of differentially regulated genes from CD105^{pos} and CD105^{neg} CAFs isolated from the KPC mouse and CD105^{neg} fibroblasts co-cultured with tumour and immune cells in vitro. This identified a putative transcriptional regulator. Importantly, in contrast to the tumour suppressive effect observed from co-implanted CD105^{neg} wild-type fibroblasts, loss of this transcriptional regulator significantly blunted the ability of CD105^{neg} fibroblasts to control tumour growth. Notably, this was correlated with decreased immune cell infiltration in developing tumours. Together, these results demonstrate an intricate relationship between tumour suppressive fibroblasts, the immune system and provides molecular insights into the signals that govern tumour development. Ongoing work in the lab is further interrogating the mechanisms whereby CD105^{neg} fibroblasts control tumour growth.

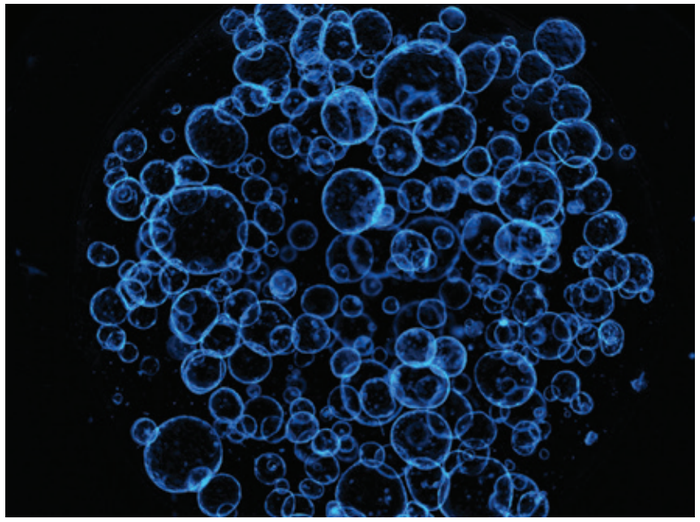


Figure 1: A mouse pancreatic organoid line grown in vitro. Credit: Luisa Ferreira, Systems Oncology.

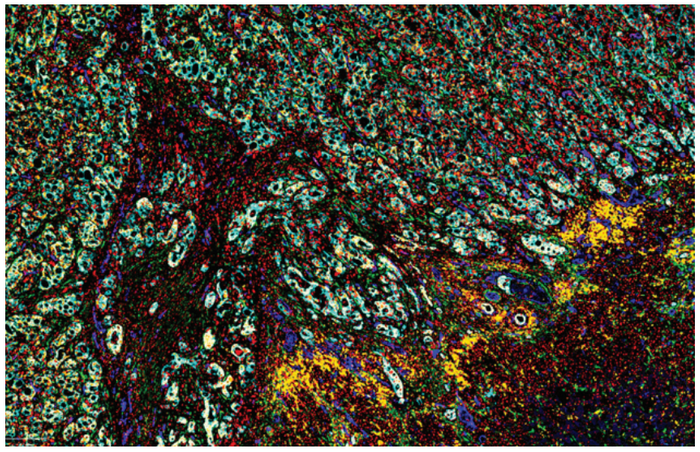


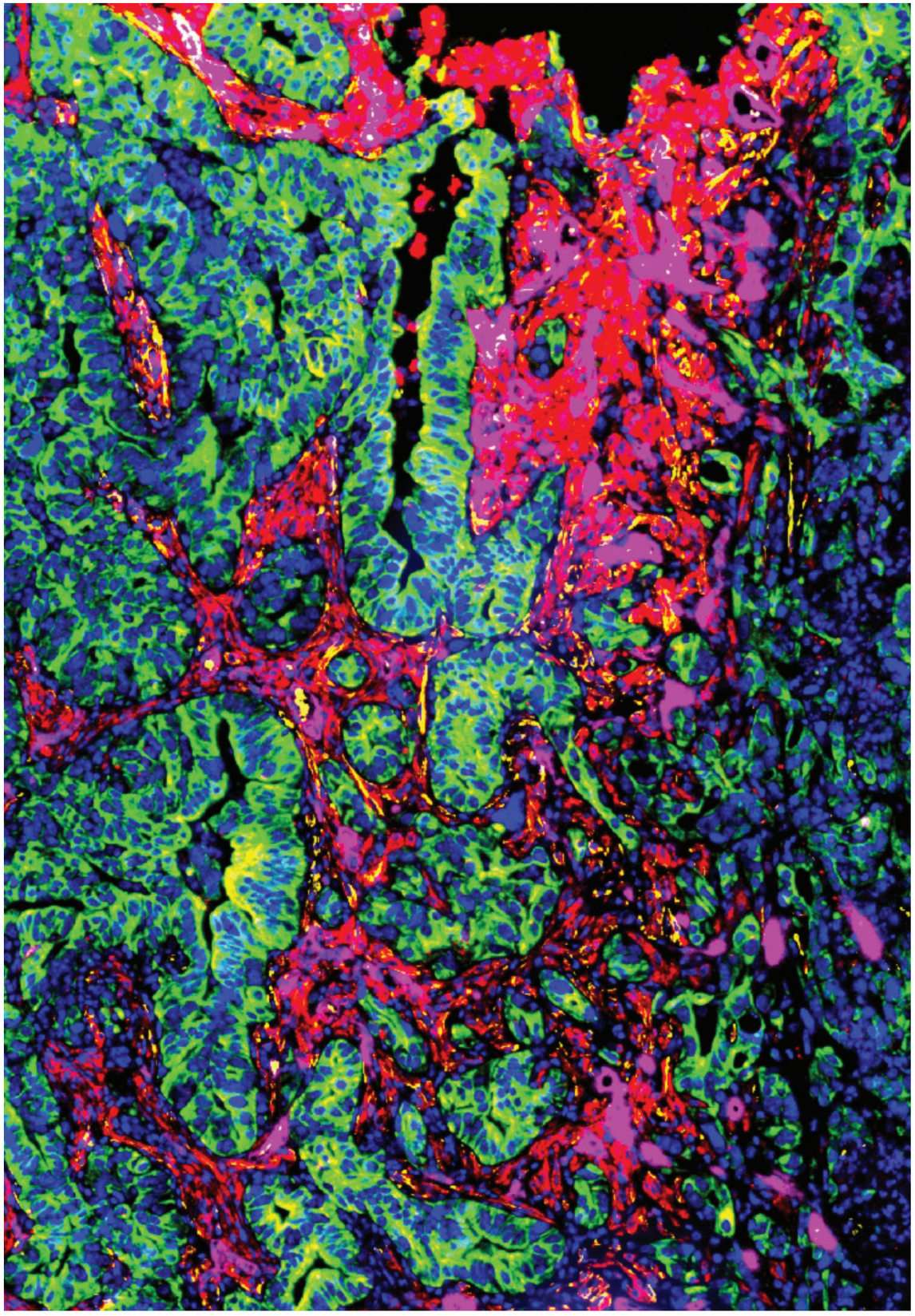
Figure 2: Multiplexed imaging of metastatic PDAC. Credit: Soren Buchholz, Systems Oncology.

Modelling human pancreatic cancer

While much progress has been made in collecting and growing human pancreatic cancer cells in the laboratory, most available in vitro models do not replicate the biophysical and cellular microenvironment of PDAC tumours. In an ongoing collaboration with Prof Linda Griffith (MIT) and Prof Martin Humphries (UoM) we have adapted a fully synthetic scaffold to support the growth of both tumour and host cells. To develop more representative models, we comprehensively characterised the stiffness, extracellular matrix composition and tumour cell adhesive requirements. This then informed which peptide ligands were included to replicate the key adhesive signals found in the tumour microenvironment of pancreatic cancer. Tumour cells grown in these scaffolds produce their own extracellular matrix, which we found engage integrin ligands in a similar manner to what is observed in vivo. Due to the synthetic nature of these scaffolds, they can be modified to recapitulate the entire stiffness range of patient tumours and differentially engage stiffness signalling pathways. Critically, these hydrogels support the growth of human patient derived pancreatic cancer organoids as well as host cell populations, such as fibroblasts and immune cells, commonly found in the microenvironment of these tumours. In recent studies we have begun to analyse how human PDAC tumour cell organoids interact with human fibroblasts and immune cells to alter tumour cell signalling and therapeutic response. To this end we have further modified the model and are comparing the similarity between tumour cells grown under various conditions in the laboratory with tumour cells directly from patient tissue – by undertaking this comparison in an iterative manner we aim to develop miniature tumour avatars that optimally reflect the tumour biology of individual patients to better understand the biology and treatment of human PDAC.

Mapping and modelling tumour progression

Most newly diagnosed PDAC patients present with overt metastasis (~55%) while ~25% have local but inoperable tumours and only the remaining ~20% are offered surgery. PDAC commonly metastasises to liver, peritoneum and lung. While metastasis presents a significant clinical problem there is paucity in the availability of tissue and models to study this advanced disease stage. As such, most of our current understanding of the disease and our ability to develop and test new treatments is based predominantly on information from the primary tumour. To address this, we have started to collect samples from both primary and metastatic tissue to study the tissue and make the models to understand the underlying biology and test novel therapies.



RESEARCH SERVICES

Multiplexed immunofluorescence staining of mouse pancreatic ductal adenocarcinoma. Cytokeratin 19 (green), CD31 (magenta), α-smooth muscle actin (yellow), and platelet-derived growth factor receptor α/β (cyan). Nuclei were counterstained with DAPI. Staining was performed using the automated Bond RX system with tyramide signal amplification. Images were acquired with an Olympus VS200 slide scanner.

Image supplied by Luisa Ferreira (Systems Oncology, with credit to the Histology core facility)

RESEARCH SERVICES



Chief Laboratory Officer
Stuart Pepper

Over the last year the CRUK Manchester Institute core facilities have continued to develop, with the addition of new equipment and the recruitment of new staff. The following section demonstrates the sheer variety and scale of support offered to research groups at the Institute, allowing refined analysis of a wide variety of sample types. Also mentioned are some of the instances where core teams have made the most of the opportunities provided in the Paterson Building to work together and provide new workflows that cross the boundaries of traditional siloed core technologies, resulting in enhanced support for the research groups on site.

Chief Laboratory Officer
Stuart Pepper

This process of working across teams is well established with spatial technology workflows where a combination of histology, imaging, sequencing and data analysis need to combine efficiently to deliver results. With the arrival of our Bigfoot sorter, we have now been able to sort directly into chips that support single cell sequencing, opening new opportunities for genomic analysis of rare cell populations. Elsewhere, the supreme mass resolution offered by the Astral mass spectrometer is also revolutionising the depth of analysis possible, allowing deeper profiling of more limited samples. Coupling the capabilities of the flow and mass spectrometry teams expands the possibility of proteomic analysis on vanishingly rare cell populations.

With the relocation of the breeding team to the Paterson Building last year, there is now the possibility of greater interaction between breeding and experimental activities. This has improved the timeline for delivering mice to the experimental unit, allowing greater flexibility when planning studies. The GEMM team has also continued to support breeding activity through optimised cryopreservation programmes.

A good example of how the core teams can work in close collaboration with the research groups is illustrated by a project that supported the transition from using a Caesium source to X-rays for immune cell ablation. This project delivered a successful outcome that is now being considered by other sites to enable the transition to X-ray dosing whilst maintaining consistent scientific outcomes.

Working alongside the laboratory-based teams we have our IT and Scientific Computing, and Computational Biology Support teams. The close working between the 'dry' and 'wet' lab teams allows delivery of end-to-end workflows with data analysis by the CBS team delivered through automated pipelines supported by Sci Com. The reports for these two teams demonstrate the breadth of support offered, but also the pace at which new developments are happening – with AI of course having an impact in this area.

This last year has also seen the laboratory-based core teams commit to obtaining LEAF – Laboratory Efficiency Assessment Framework – certification to show progress with sustainability initiatives. It is great to see that all the facilities, including Lab Services, now have at least a Silver Award, with some already at, or working towards, the gold level.

There have been several exciting new appointments across the core facilities, and we have had one notable retirement with Yvonne Connolly leaving the Institute. Having been based in a molecular biology research group, Yvonne worked alongside myself setting up the Molecular Biology Core facility before continuing to work with Duncan providing fantastic support for the mass spectrometry facility as it developed. Yvonne retired in September after a total of 41 years working at the Institute. We all wish Yvonne well for a long and happy retirement.

Biological Mass Spectrometry
Duncan Smith, Yvonne Connolly[1], Robert Faulkner, Adam Flinders[2]

[1]Left in 2025
[2]Joint with Computational Biology Support

The Mass Spectrometry facility provides advanced proteomics technologies and expertise to support the Institute's cancer research programmes. Our role is to enable researchers to investigate the molecular complexity of cancer by generating high-quality quantitative proteomics data from diverse and often challenging biological samples. By combining state-of-the-art liquid chromatography-mass spectrometry (LC-MS) instrumentation with continually evolving experimental workflows and computational pipelines, the facility translates complex biological questions into robust and impactful proteomics research.

A major milestone this year was the installation and commissioning of a next-generation Orbitrap Astral mass spectrometer, which became operational in the first quarter of 2025. This platform represents a substantial technological advance beyond our previous flagship instrument. The system combines Orbitrap mass accuracy with the ultra-high acquisition speed of the Astral analyser, a new class of time-of-flight mass analyser specifically developed for high-performance proteomics. The addition of this instrument places the Institute at the forefront of next-generation proteomics technologies and enables experimental strategies that were previously beyond the reach of our facility.

The Astral analyser can acquire hundreds of tandem mass spectra per second (up to ~200 Hz), allowing extremely dense sampling of peptide ions during chromatographic separation. This capability enables the routine implementation of narrow-window data-independent acquisition (nDIA), where all peptides within very small mass ranges are systematically fragmented and analysed. By combining very narrow isolation windows with extremely fast MS/MS acquisition, these methods allow comprehensive and reproducible interrogation of complex proteomes while maintaining optimal chromatographic sampling. The speed and efficiency of this platform also enable advanced DIA workflows that maximise proteome depth while maintaining robust quantitative performance across large sample cohorts.

In practical terms, this translates into substantially deeper proteome coverage, improved quantitative precision and markedly improved data completeness across large experimental cohorts, reducing missing values that can otherwise limit large comparative studies. In internal benchmarking experiments, the Astral platform now enables routine quantification of approximately 7,000 - 10,000 human proteins per run, reflecting a step-change in achievable proteome depth compared with previous generation instrumentation.

The new platform has already had a significant impact on research across the Institute. We are now routinely achieving deeper proteome coverage from limited or challenging biological material, including rare cell populations and complex tissue and tumour samples, enabling researchers to explore signalling networks, tumour-immune interactions and cellular state transitions with greater molecular resolution.

Alongside these advances, the facility continues to develop new experimental workflows to address emerging biological questions. In collaboration with the Cancer Inflammation & Immunity group and the Mass & Flow Cytometry facility, we advanced approaches for profiling the proteomes of rare flow-sorted immune cell populations. Furthermore, in collaboration with the Systems Oncology group, we have demonstrated successful profiling of tiny Laser Capture Micro Dissected samples utilising a FAIMS ion mobility device in tandem with the Orbitrap Astral.

The facility also underwent a significant staffing transition during the year. After an exceptional 41 years of service, Yvonne Connolly retired in September 2025. We thank Yvonne for her enormous contribution over the last four decades and wish her a long and happy retirement.

Together, these developments position the Mass Spectrometry facility to deliver faster, deeper and more comprehensive proteomics analyses, supporting the next generation of cancer research across the Institute.

Biological Resources Unit
Experimental Services
Team Leader: **Lisa Doar**
Lisa Dique, Jo Roberts, Laura Dean[1], Rachel Walker, Lewis Woolley, Diane Beeston, Lisa Flynn, Jessica Walker, Wesley Moore[1], Nadia Bell, Melissa Hewson[2], Henry Mafe[2], Gary Cooke, Kimberley Kirkham, Oliver Lesser

[1]Left in 2025
[2]Joined in 2025

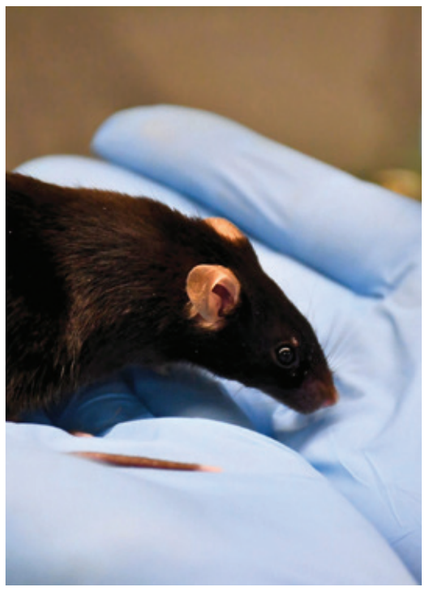
Throughout 2025, we have continued to be involved in the training of new research staff. We have assisted two research groups in establishing their animal work. The first was from the Division of Cancer Sciences, at The University of Manchester, and the second was new CRUK Manchester Institute Group Leader, Sylvain Delaunay. We have also helped establish several new procedures this year, including image guided pancreas injections (further details are described below), orthotopic tongue injections, the introduction of a new Thoraeus filter for a cell ablation model on our X-ray irradiation system, and pilot work

for a cutting-edge magnetic guidance project. Image guided injections of cells is now a key procedure that we perform in the facility, using ultrasound imaging to inject cells directly into an organ of interest without the need for surgery. We already have several routes established – bladder wall, intra-cardiac and liver injections – and this year we added pancreas injections. Image guided work is technically challenging to learn and requires substantial practice to perform well, but the benefits in terms of good scientific practice and animal welfare are enormous. The procedure is much quicker, which also makes it much more efficient. Since there is no need to make a surgical incision, post-operative complications associated with surgery can be avoided, such as wound dehiscence and swelling. There is also less risk of infection, and a much smaller dose of analgesia is administered as it is a less invasive route. Another key benefit over the traditional surgical route is that there is visual confirmation that the cells have been delivered on target, and any miss-dose is immediately visible.

Although image guided injection is not a broadly established technique, it has generated a great deal of interest. Joanne Roberts, who has led the development of this method at the Institute, has given talks on this subject in the past and we have been invited to talk at a rodent surgery conference in 2026 and asked to present a webinar on the topic. We value these fantastic opportunities to promote the procedure more widely across the industry and share the scientific and animal welfare benefits.

Another area we have worked hard on in 2025 is sustainability in the facility. The Institute is signed up for the green initiative Laboratory Efficiency Assessment Framework (LEAF), which recognises 3 levels of achievement – bronze, silver and gold. The Biological Resources Unit (BRU) reached the bronze level very quickly, but obtaining silver level has involved considerable work. Many changes that can be implemented in a standard laboratory are not easily applied in an animal research facility, where we must manage animal waste and handle drugs used in cancer treatment. Currently, there is limited guidance on sustainability for animal research facilities, so careful consideration over which measures could be implemented was required. Following discussions with our Health & Safety Officer, we determined that changes could be made to our disposal methods. For much of our waste we were able to switch from the clinical waste route to the alternative 'tiger stripe waste route' (used for non-infectious, offensive/ hygiene waste), which can be incinerated at a lower temperature. As a result, we have replaced many of the waste bags in rooms throughout the facility, providing cost savings and reducing our carbon footprint. Furthermore, we introduced paper recycling and changed our mouse cage cards from laminated to cardboard so that they can be recycled. We also reviewed our consumables and have managed to find re-usable products to replace some of our single use plastics. These changes helped us obtain our silver level, so in 2026 we will be working towards the gold level.

Focusing on staff development is critical to the continual development of the facility, and this year staff have attended conferences that centre on different areas of laboratory animal science, or rodent imaging. Several team members also attended an engagement event at Manchester Museum, where Cancer Research UK showcased work carried out at the Institute, which included our work with mice. The event was attended by the public and school children, providing a stimulating opportunity for our staff to demonstrate how animals are used in research and to raise awareness. We also submitted a nomination for the Understanding Animal Research Annual Openness Award in recognition of our contribution to the Culture of Care pledge, public engagement work, and recruitment videos that we developed and displayed publicly on LinkedIn to show our staff working in the animal facility. The Cancer Research UK Manchester Institute won the 2025 award – a fantastic achievement which highlights our commitment to openness in animal research.



Transgenic Breeding

Team Leader: Lauren Street[1], Natalia Moncaut[1], Jennifer Hughes[2], Daniel Bennett, Tim Bloor, Martin Vincent[3], Henry Mafe[4], Katie Howarth[4] Emma Mcconnell[5], Sarah Balmforth[4]

[1]Leave cover
[2]On leave
[3]Left in 2025
[4]Summer student in 2025
[5]Joined in 2025

The Transgenic Breeding Team at CRUK Manchester Institute specialises in breeding and assisting in the colony management of genetically engineered mice to support the Institute's research programmes.

The team currently operates with four members who oversee the care and management of approximately 100 strains. Responsibilities include daily husbandry, welfare monitoring, colony observations, coordination of timed matings, routine genotyping sampling to support experimental requirements, and tissue dissections. The team works closely with the Genome Editing and Mouse Models facility, which generates or imports new mouse lines. These animals undergo comprehensive health screening to ensure that resulting animals remain specific pathogen-free. Maintaining a high health status across the colonies and between teams operating within the Biological Resource Unit remains a central priority, with strict protocols in place for the introduction of new lines from external sources.

During the past year, the Transgenic Breeding Team underwent further consolidation following the relocation of all remaining mouse strains from the Incubator Building at the University of Manchester in summer 2025. As a result, the team now operates exclusively from the Paterson Building. With all animals situated on a single site, access to mice for experimental and tissue purposes has improved, while the consolidation of sites has streamlined workflows and enabled closer collaboration with the Experimental Team.

Despite the reduction in team size, the service has continued to support researchers' requirements through more effective colony observations, prioritisation of key lines, and continued effective communication with research groups. These efforts have helped ensure that breeding colonies remain productive, and that animals are available to meet experimental timelines.

Looking ahead, the team will continue to focus on maintaining high standards of colony health and welfare, optimising breeding strategies, and supporting the introduction and management of new genetically engineered mouse lines to meet the evolving needs of the Institute's research programmes.

Computational Biology Support

Sudhakar Sahoo, Robert Sellers, Richard Reeves, Adam Flinders

The Computational Biology Support (CBS) core facility provides high-quality computational biology and bioinformatics analysis solutions for researchers at the Cancer Research UK Manchester Institute. The main goal of CBS is to develop a computational analysis infrastructure that enables the application of advanced bioinformatics and statistical methods to the Institute's cutting-edge cancer research.

Our work primarily involves developing and applying computational solutions to analyse high-throughput sequencing and multiplex imaging datasets generated by advanced technological platforms. We create workflows and pipelines that integrate custom-built tools with open-source software, all of which operate on the high-performance computing facility available at the Institute.

The CBS team comprises highly experienced members with diverse expertise in analysing and interpreting datasets across genomics, epigenomics, transcriptomics, proteomics, metabolomics, metagenomics, and imaging. We work with data ranging from bulk to single-cell and spatial resolutions. Over the years, CBS has developed workflows and pipelines for high-throughput omics, multi-omics, and multimodal data analysis and integration. These resources have significantly supported researchers at the Institute in producing high-quality publications.

On the imaging modality side of research, image analysis plays a crucial role in cancer research and clinical management, serving as an essential tool for tumour cell detection. Over the years, we have tested and developed an automated image analysis pipeline in collaboration with researchers at the Institute. It can analyse various tissue images generated by ultra-plex imaging platforms such as CODEX, mIF, mIHC, MIBI, cyCIF, and Hyperion. This tool is continuously updated with improved image segmentation algorithms as they are published.

A recent highlight of our development efforts is the integration of an AI-based supervised learning model designed to analyse large-scale 3D imaging datasets—particularly relevant as the Institute is preparing to acquire Light Sheet Microscopy capabilities. Anticipating that CBS will support the analysis of these datasets, we have already installed and validated the necessary software packages using publicly available Light Sheet data. We are now eager to apply this workflow to the in-house datasets that will soon be generated. Figure 1 shows a 3D rendering of an E9.5 mouse embryo reconstructed from Light Sheet image stacks and visualised using the ParaView software package (v6.0.1).

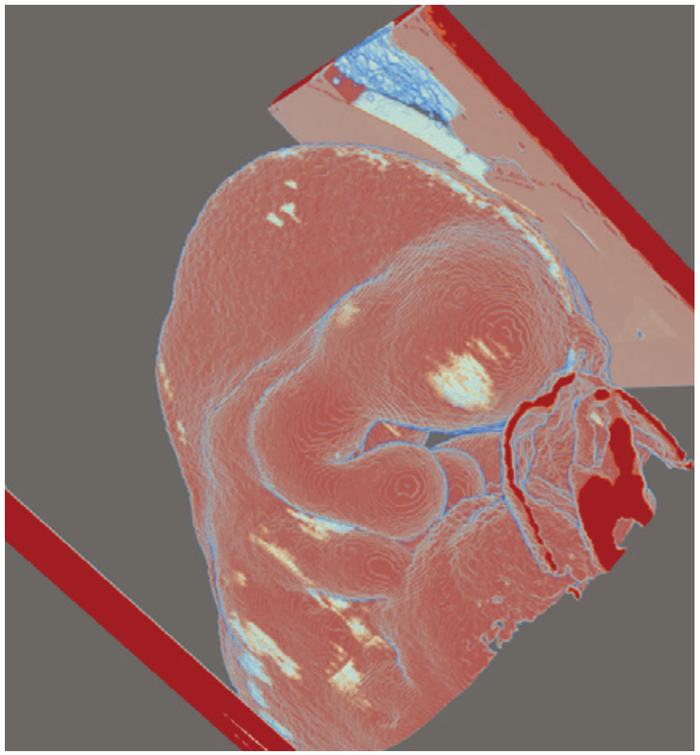


Figure 1: Light Sheet microscopy image data constructed from image stacks; Data and Scripts for Pipeline from doi: 10.1109/ACCESS.2022.3210542. Credit: CBS.

high-quality data. In collaboration with the Scientific Computing (SciCom) core facility, CBS has successfully converted numerous workflows into pipelines that are now utilised by other core facilities and researchers throughout the Institute. For instance, upstream pipelines have been developed and automated for analysis of genomics/epigenomics, transcriptomics, and proteomics at bulk, single-cell, and spatial resolutions.

This infrastructure helps researchers to analyse results more effectively, saving time by reducing the effort needed for pre-processing and quality control. Additionally, they guarantee consistent data generation across the Institute. An example of such automated pipelines is the optimised RNA-Seq workflow for analysing bulk RNA-Seq data. Typically, the sequencing output consists of FASTQ files; however, to perform downstream analysis, researchers need an expression or count matrix. Generating this matrix requires quality control of the FASTQ files, removing low-quality reads or bases, and mapping the reads to a reference genome or transcriptome using an appropriate alignment programme. The automatic RNA-Seq pipeline now manages these steps, allowing the MBC core facility to provide users with downstream-ready expression matrices (see Figure 2 showing the pictorial representation of the implementation).

CBS is also actively involved in supporting core facilities to test, validate, and ensure quality control (QC) of data produced by newly acquired instruments, platforms, or library preparation protocols. This support not only helps the core facilities calibrate their instruments but also ensures the generation of

Figure 3 shows an example of results obtained from the downstream-ready data generated by the ATAC-Seq pipeline described above.

CBS not only maintains existing workflows and pipelines but also continuously develops new ones whenever new technologies emerge or

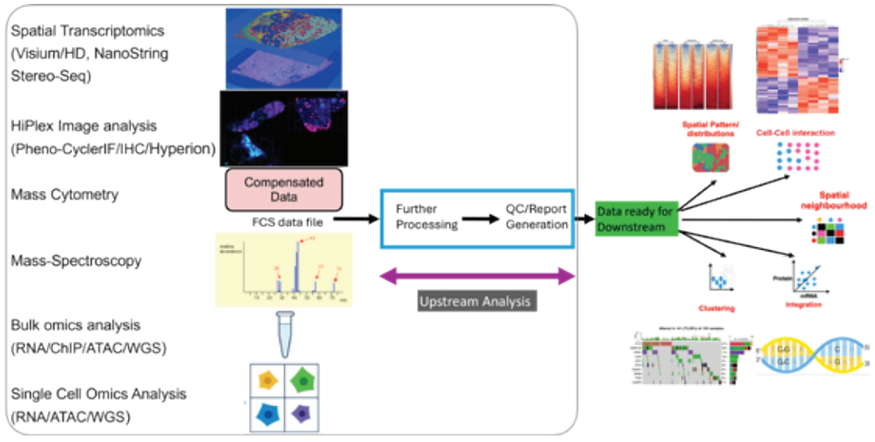


Figure 2: Automatic Pipeline Implementations (Bulk/Single Cell/Spatial Omics): CBS, SciCOM, MBC and other Core Facilities.

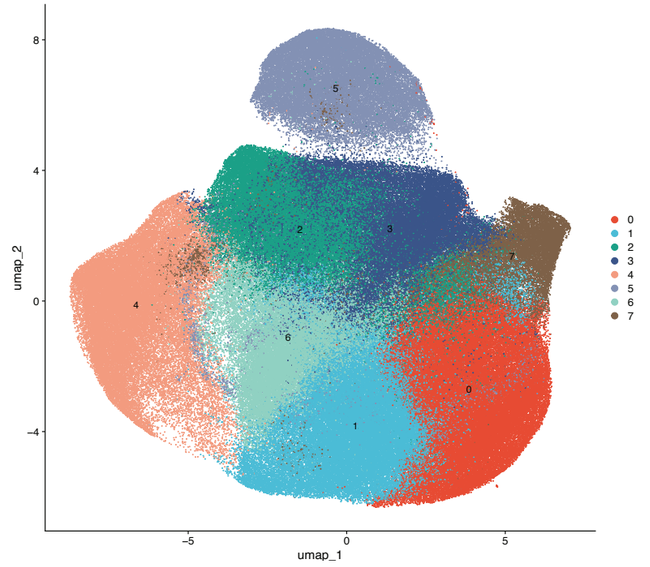


Figure 3: Illustration of single-cell RNA-based clustering approach used to group epigenetic signals. Credit: CBS and Leukaemia Biology.

improvements are needed in the current analysis infrastructure. As such, this year's highlights include the introduction of an additional method to enhance the accuracy of peptide identification for the Mass Spectrometry facility, as well as the development of a new workflow to analyse data from the Curio Trekker spatial platform. We have implemented Cascadia, an open-source deep learning method that predicts peptide sequences directly from DIA data without requiring a reference database. It complements the commercial software Spectronaut™ directDIA, currently the main tool for DIA analysis at the Institute, by enabling detection of peptides that may be missed due to sample-specific mutations, alternative splicing, or non-canonical translation. Incorporating Cascadia has increased sensitivity and broadens the detectable proteome.

As noted above, another important development is a new analysis pipeline for the Curio Trekker spatial platform, a spatial transcriptomics technology that achieves true single-cell (or single-nucleus) resolution by directly mapping cell positions, unlike array-based methods that often require complex computational deconvolution. Our workflow includes all major components – pre-processing, quality control, and image processing and is designed to scale with large datasets. Figures 4 and 5 demonstrate preliminary unannotated clustering results generated from our pipeline for seven mouse embryos.

The CBS team has had a particularly productive year this year. We have continued to serve as both analysts and consultants for potential research projects. Our role has expanded with the launch of our highly regarded Institute-wide NGS data analysis training programme, which we offer on an annual basis. This year's highlights include training in complex mass spectrometry (MS) data analysis. For advanced analysts or bioinformaticians, CBS has designed and conducted a monthly seminar series on best practices in bioinformatics data analysis. This educational lecture programme aims to incorporate emerging technologies, effectively disseminating our advancements in knowledge throughout the Institute, and ensuring that our research methodologies are informed and adhere to best-practice guidelines.

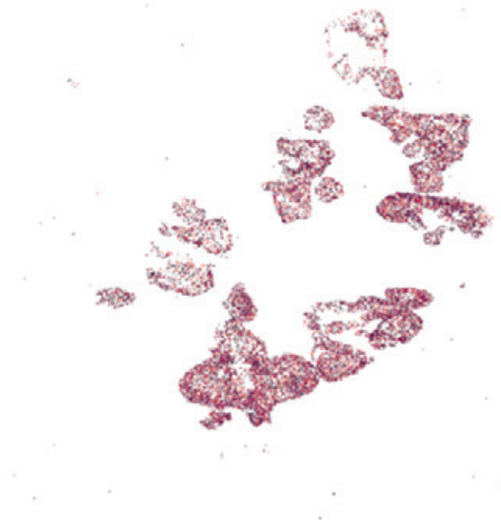


Figure 4: Image generated at single cell solution from raw coordinates obtained from the Trekker platform. Credit: MBC, CBS.

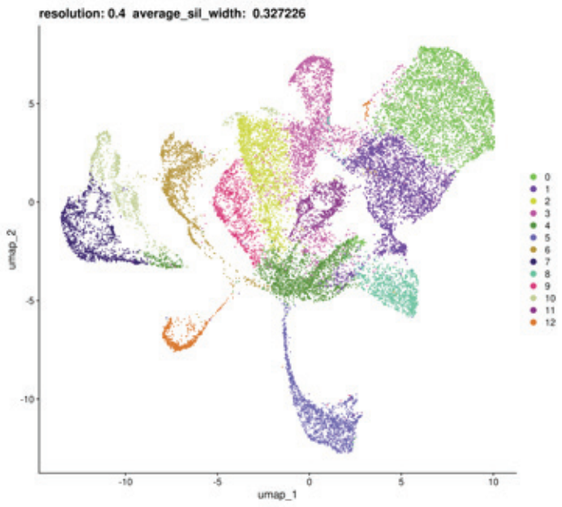


Figure 5: Grouping of cells using Leiden clustering methods. Credit: CBS.



Genome Editing and Mouse Models

Natalia Moncaut, Athina Papaemmanouil, Lauren Street

The Genome Editing and Mouse Models (GEMM) core facility provides advanced genome-engineering expertise to generate new, bespoke mouse models for cancer research. Using state-of-the-art CRISPR technologies and targeted genetic-modification approaches, our team works closely with researchers to design and deliver precise models that capture key mechanisms of tumour initiation, progression, and therapeutic response. Through this collaborative and highly tailored support, GEMM continues to enable the development of high-quality cancer mouse models that drive innovative research across CRUK Manchester Institute.

This year, GEMM made significant progress across multiple areas that strengthened our contribution to cancer research. We successfully generated several new mouse models, including a collaborative project with a research group at University College London, broadening the scientific reach of the facility. A further 32 strains were added to our cryo-archive, enhancing long-term preservation and accessibility of valuable lines. We also refined and streamlined the process for importing new mouse strains into the Institute, reducing lead times and improving overall project efficiency. Importantly, GEMM-generated models contributed to newly published research articles and supported ongoing PhD theses, reflecting the scientific impact of the facility's work across the Institute and wider research community.

In addition to model generation, GEMM continues to provide essential support to the Breeding Team through routine and complex genotyping services, as well as strategic input into planning complex breeding schemes for multi-allelic mouse models. This year, the facility also played an active role in transgenic community engagement and knowledge exchange, co-organising the 2nd UK Facilities Workshop on Genome Engineering Technologies as part of the MRC National Mouse Genetics Network. Furthermore, GEMM contributed to training and skills development across the field by delivering a three-day Colony Management workshop within the Genetically Altered Section of LASA, strengthening best practice in genetically modified mouse management.

Histology

Garry Ashton, Caron Abbey, Nicola Tonge, David Millard, Amy Lawrence, Peter Magee

By offering a full range of both routine and advanced histological services, the Histology core facility underpins oncology research across the CRUK Manchester Institute and the wider site. The facility allows for the adoption of tissue-based experimental approaches, which continue to grow in range and complexity, across a large number of both basic and translational research groups. The training and continued professional development of core facility staff has once again ensured excellent staff retention, whilst allowing the unit to offer a comprehensive and flexible service. Comprehensive training of researchers from other groups enables independent research across several key areas, supported by facility staff.

The high throughput routine immunohistochemistry, immunofluorescence, troubleshooting, and antibody validation services continue to see exceptional demand. Associated with these services is the validation of markers used for both spatial transcriptomic and proteomic profiling. With the recent increase in imaging capability, the unit continues to develop higher plex immunofluorescence, enabling extensive analysis of tissue sections. Seven plex marker studies are now offered in addition to twelve plex cyclic labelling. These techniques have both been automated to run on the BondRX platforms. Multiplexing using both mRNA in situ hybridisation and protein immunohistochemistry on single tissue sections is also available.

Over the last year, use of spatial transcriptomics and proteomics has expanded. The unit has been key in delivering data for projects incorporating the GeoMX DSP, Visium and Phenocycler Fusion assays. Composite blocks, macro-arrays and multi-formatted tissue microarrays have all been built, which together with various multi-sectioning strategies have all proved extremely popular, enabling high throughput sample analysis and a cost reduction with all platforms.

Many groups are now using human tissue in their studies. All histology samples accessed through the MCRC Biobank are prepared by the core facility. The unit works closely with the biobank and all groups using human tissue to ensure compliance with current human tissue legislation.

Over the year, laser capture microdissection followed by the downstream extraction of RNA, DNA, and protein has proved popular. In addition, special stains have been used by various groups. These include Masson Trichrome, Alcian blue PAS, Cresyl Violet, Oil Red O, and other trichrome stains. Furthermore, the unit has routinely prepared both FFPE and frozen human and mouse tissues, in addition to organotypic assays, spheroids, agar plugs, and cell pellets, which have been used for both routine and advanced analysis with an array of techniques. Groups have also used vibratome tissue sections (50–250µm) for ex vivo cultures of tumours to evaluate and develop three-dimensional studies.

In collaboration with the Visualisation, Irradiation and Analysis facility, we have also been heavily involved with the purchase of a new light sheet microscope. Over the next year, evaluation of tissue clearing and other techniques associated with this area of work will take place.

The TranMet project is an autopsy study driven by the Systems Oncology group and The Christie NHS Foundation Trust, investigating how different organ environments affect cancer spread in pancreatic and oesophageal cancers. Through the facility, frozen and FFPE tissue samples are processed and stained from rapid autopsies of consented donors, with laser capture microdissection performed for genomic and proteomic profiling. This is coupled with high-resolution spatial visualisation and molecular profiling at both protein and RNA levels. Currently, the group is also evaluating how molecular quality is influenced by postmortem intervals, ensuring the integrity of downstream analyses. By comparing the primary tumour with its metastases, the project aims to understand how different organ environments influence metastatic behaviour and function.

The Histology team has also worked closely with the CRUK National Biomarker Centre pre-clinical team, supporting use of the Visium HD platform for staining fixed-frozen tissues and preparing frozen and FFPE tissues as part of large in vivo studies.

Histology is widely used by groups from the Division of Cancer Sciences at The University of Manchester, supporting several projects, including study of rare paediatric low-grade glioma organoids, analysis of the gene expression response to anti-PD1 treatments, and developing laser capture dissection workflows to support large semi-spatial proteomics analysis on breast lobule response to tamoxifen.

IT and Scientific Computing

Marek Dynowski, Bijesh Choorakkatt, Brian Poole, Christopher McCauley, Joe Hughes[1], John Campion, Krar Haider, Matthew Young, Stephen Kitcatt, ZhiCheng Wang

[1]Joined in 2025

The Cancer Research UK Manchester Institute IT and Scientific Computing (IT and SciCom) team consists of experienced IT professionals, software developers, HPC system engineers, and data architects. It provides High Performance Computing, large-scale data storage, software development, and general IT services to CRUK MI and the CRUK National Biomarker Centre (NBC).

In 2025, Joe Hughes joined our team to provide second level support and got immediately involved in user support and important and complex infrastructure projects.

The installation of the new Microsoft Azure Local (AZL) Hybrid cloud infrastructure was successfully completed. This infrastructure combines the functionality of the previously separate VMware and oVirt virtualisation operated by IT team and the SciCom team into one platform. This reduces the administrative workload, and it exemplifies the strategic benefits resulting from the merging of IT & SciCom teams in 2023.

The new AZL platform consists of a cost-effective on-premises component, including GPUs for powerful virtual Linux and Windows workstations for Imaging analysis and ML/AI workloads, and a public cloud component for cloud-bursting during periods of high demand or to provide hardware that isn't available locally. The infrastructure also allows us to implement authentication methods in the future to connect external Software as a Service to the Institute's IT infrastructure, providing a seamless experience for users.

As part of the benefits arising from the merger and increased collaboration with other core facilities, the IT & SciCom team worked jointly with the CRUK National Biomarker Centre to implement a Managed File Transfer (MFT) solution GoAnywhere, to streamline and unify data management processes across the

Institute and NBC. This initiative brings significant advantages by redesigning and automating data transfer workflows from scientific instruments to IT & SciCom managed storage and computing systems. The resulting automation will reduce the workload for users and core facility staff even further, minimise errors, and ensure that generated data becomes available to researchers and bioinformaticians without delay. Existing and future data management requirements were carefully assessed, and implementation is now underway following comprehensive training provided by the software supplier.

The IT team has successfully completed the complex Windows 10 to Windows 11 migration project across the CRUK Manchester Institute and National Biomarker Centre ahead of the planned deadline of 16 October 2025. This upgrade represents a significant advancement in security, performance, and overall user experience for all staff and researchers. The transition ensures that our systems remain fully supported and aligned with the latest technology standards, enabling improved collaboration tools and streamlined workflows. As part of the project, the Helpdesk team upgraded 118 Windows 10 PCs and procured 65 new Windows 11 devices. Additionally, 121 obsolete computers were removed from the network and responsibly disposed.

Extensive development work was performed on the Institute's Snoctopus platform to further automate upstream processing workflows, in close collaboration with Computational Biology Support (CBS), the Molecular Biology Core (MBC), and the Nucleic Acid Biomarker (NAB) team at the CRUK National Biomarker Centre.

The laboratory staff use the in house Snoctopus upstream processing web platform to set up sequencing experiments and select the required upstream analysis once data is generated. This streamlined workflow accelerates end to end sequencing data generation and enables bioinformaticians to focus on more complex downstream analysis and interpretation.

IT and SciCom partnered with the NAB team to integrate Olink data analysis into Snoctopus by adding the "ngs2counts" application. This tool converts Next Generation Sequencing (NGS) output into counts files that report the number of reads for each Olink sequence, along with a run metadata file required for import into NPX™ Map or NPX™ Map CLI.

In addition, the legacy bcl2fastq application used for generating and demultiplexing Illumina fastq files was replaced with the newer bclconvert tool (Figure 1). This tool offers significantly improved performance and introduces valuable features, such as extracting UMI sequences during demultiplexing, which further enhances the robustness and efficiency of upstream data processing.

The team also completed the migration from RStudio to Posit Workbench, moving from a server based to a user based licensing model following the supplier's transition to a more complex licensing structure. As part of this upgrade, several new Integrated Development Environments (IDEs) were introduced, including Jupyter Notebook, the more advanced JupyterLab, Positron Pro (a new R and Python IDE), and Visual Studio Code, alongside the traditional RStudio Pro environment.

Figure 1: New bclconvert web application.

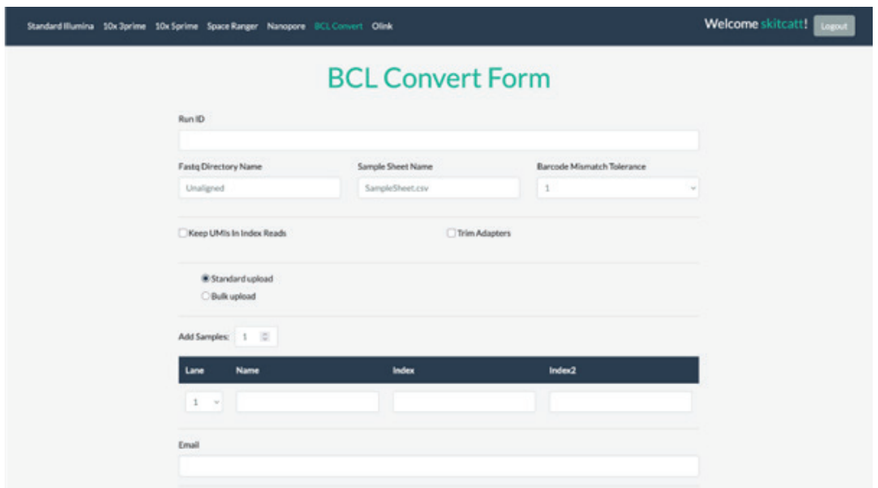
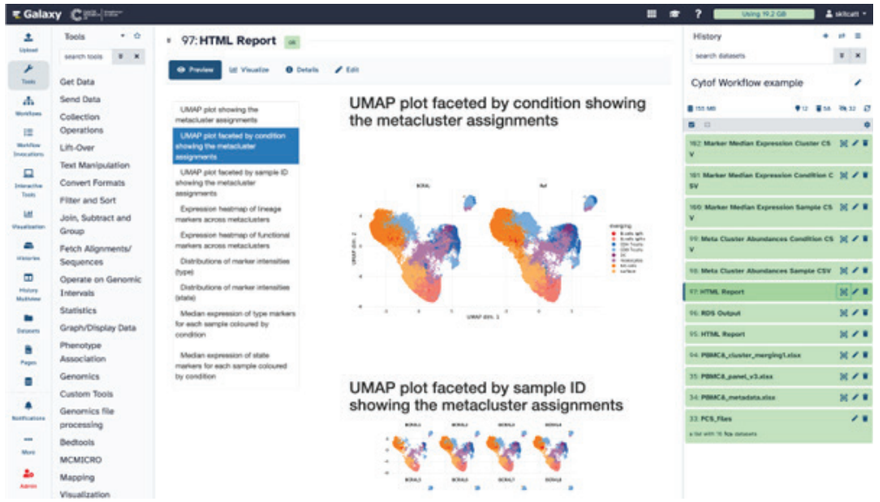


Figure 2: Screenshot of the CyTOF web app on the Institute's Galaxy Bioinformatics workflow analysis platform.



Because Posit Workbench is designed for power users and comes with a higher cost model, IT & SciCom have also implemented a cost-effective alternative for users with less demanding requirements. Specifically, we are introducing an RStudio environment within the Galaxy Bioinformatics Workflow Portal, providing an accessible and suitable option for nonpower users.

In close collaboration with Antonia Banyard, Head of the Mass and Flow Cytometry core facility, and Zoë Smith from the Leukaemia Immunology & Transplantation group, Stephen Kitcatt from IT & SciCom developed a web application (Figure 2) for the analysis and visualisation of high-dimensional single-cell cytometry data. The platform supports immune profiling, tumour microenvironment characterisation, and biomarker discovery through an integrated pipeline encompassing preprocessing, normalisation, dimensionality reduction, clustering, and interactive visualisation of differential expression values. Outputs include publication-ready figures and structured spreadsheets containing the underlying data, enabling seamless transition to downstream manual analysis.

The IT & SciCom team also supported the NAB team, in collaboration with Peter Kuhn's group at the University of Southern California, in implementing two novel AI-based algorithms that combine supervised and unsupervised approaches to identify and classify circulating tumour cells (CTCs). In addition, the team is contributing to the deployment and training of a supervised algorithm Streamlining, integrated within the existing Ocular framework. This solution is designed to significantly reduce analyst workload by minimising the number of false-positive CTCs requiring manual classification.

At the end of the year, the new version of Laboratory Information Management System (LIMS) –LabWare 8 – was ready to deploy and the team worked quickly to manually install on over 70 machines in NBC, ensuring minimal break in service for users since the previous version was no longer available as part of the database migration. All lab machines were operational with the new software by the middle of the first day of deployment and then user PCs and laptops were rolled out thereafter.

The team also undertook a complete rewrite of the Genetically Modified Organisms (GMO) submission application for tracking GMOs, extending its accessibility to members of The University of Manchester. User information is now sourced from a centralised user management system, and the application has been migrated to a standalone platform built on an updated, more secure framework leveraging Microsoft's latest technology.

In summary, it has been another productive and successful year for the IT and Scientific Computing team.

Laboratory Services

Mark Craven, Aaron Koomson, Busola Atuegbe, Tony Dawson, Christine Williams[1]

[1]Left in 2025

During 2025, Lab Services has continued to supply laboratories across the site with sterilised fluids, glassware, plastics, and microbiological media using our glass washers and autoclaves.

The team maintains and restocks communal supplies for laboratories based in the Paterson Building and the Oglesby Cancer Research Building (OCRB). Daily rounds are carried out to collect used items and replace them with clean and sterilised materials, ensuring laboratories have continuous access to essential resources. Our primary service areas remain the Paterson Building and OCRB, although we also support

some activities in satellite sites including the Proton Beam Therapy Centre and MCRC Biobank.

Through access to autoclave facilities, the department can sterilise bespoke items required by laboratories. In addition, working with the Media Coordinator we can, by prior agreement, adapt existing microbiological media or produce alternative formulations requested by research groups. This provides greater flexibility and tailored support for the laboratories we serve.

The team also operates the site-wide laboratory coat laundry service. In addition to these core services, the department provides a monthly on-site pipette clinic, allowing researchers to have pipettes checked and maintained conveniently on site.

The Lab Services Manager also supports the Chief Laboratory Officer in coordinating statutory testing of safety cabinets and fume hoods, arranging insurance inspections and overseeing the provision of first aid supplies across the site.

The team contributes to the organisation's ongoing sustainability initiatives. This year, the Laboratory Services achieved Laboratory Efficiency Assessment Framework (LEAF) Silver accreditation.

Mass and Flow Cytometry

Antonia Banyard, Emily Scanlon, Adam Milner, Sam Thompson[1]

[1]Joined in 2025

The Mass and Flow Cytometry facility provides a key service to all research groups, and both our instrument portfolio and the flow team are continuing to grow in size and complexity. We were delighted to recruit Sam Thompson in September 2025 as an experienced scientist to increase our capacity for training and work throughput. We are also delighted that Adam was awarded his PhD in May from The University of Manchester.

The Bigfoot sorter is proving to be exceptional and invaluable for a large multidisciplinary lung cancer project with the CRUK National Cancer Biomarker Preclinical team, particularly in tracking metastases. This platform enables the sorting of larger, sensitive, and rare CDX cells, such as metastases, using different nozzle configurations and gentle handling to achieve over 90% post-sort viability for downstream sequencing. The facility is working closely with the Molecular Biology Core facility to utilise the Bigfoot for direct cell sorting into 10X chips to eradicate any handling errors and maximising rare cell populations for single cell sequencing. Through this work, the Mass and Flow Cytometry facility is now a recognised site for research and development with Thermo, the manufacturer of the Bigfoot, which has also led to global collaborations using this cell sorter. The facility has been able to use new cytometers, both spectral and image enhanced, from various vendors due to the excellent reputation the facility has for innovation and experimental curiosity. This prominence led to our team being invited by Cytek to demonstrate the Imagestream using our work for a users day at The University of Manchester.

We are very pleased to host the Manchester Flow Club meetings every three months in collaboration with the Flow Facility at The University of Manchester. This creates an excellent scientific and technical discussion forum between the two sites and has already resulted in further collaboration with the researchers at the university.





This year was very successful for the Mass and Flow Cytometry facility, and we continue to improve and refine our training schemes for all cytometer platforms – including multi-parametric analysis workflows – which is invaluable in ensuring we continue to get the best from this technology.

Molecular Biology Core

Wolfgang Breitwieser, Hannah Bowden, Rachel Horner, Jason Rumley, Poppy Spiers, John Weightman

As in previous years, a major focus of the department has been on the exploration and improvement of clonal sequencing methodologies, particularly in single cell and spatial transcriptomics. In single cell sequencing, we have prioritised on expanding the range of technologies, such as sample multiplexing, as well as fixed tissue processing. Sample fixation has clear advantages, e.g. in patient biopsies or tumour explants from mouse models, as they can be stored and processed in batches at later time points. An important validation project was therefore initiated to ascertain that fixed cells retain the RNA content for high quality analysis. Another validation project centred around multiplexing samples with the aim of making the methodology more cost effective without compromising output quality. Furthermore, in collaboration with the Mass and Flow Cytometry core facility, we successfully tested methods for more efficient cell capture by direct chip loading from cell sorters, thus circumventing laborious cell washing and counting steps that often lead to significant cell loss.

Over the last year, the service also saw a significant increase in demand for more complex single cell analysis types, e.g. combined transcriptome and genome analysis (scMultiome), concomitant analysis of gene expression and immune repertoire profiling (scTCR-seq), as well as tissue marker profiling (Cite-seq), and CRISPR based screening projects (Perturb-seq).

Another major focus has been on spatial transcriptomics (ST). In this multi-facility spanning service that includes Histology, VIA, Scientific Computing and Computational Biology Support, we continued to increase the number of samples for processing a multitude of diverse projects. While current ST methodologies do not lend themselves to straightforward automation, we devised workflows for optimised throughput and efficient sample handling. We also saw a diversification of input samples, including fresh and fixed tumour and autopsy material, as well as tissue and organoid microarrays. In addition, we have started to apply panels for simultaneous, spatially resolved transcript and protein detection on tissue sections, thereby expanding modalities for analysis.

Despite the great strides made by ST technology providers towards achieving improved cellular and subcellular resolution, as well as the introduction of machine learning tools for cell segmentation and cell type annotation, there remains significant shortcomings in many spatial technologies in the sensitivity of detection. To overcome some of these limitations, we explored methodologies for spatially resolved single cell transcriptome analysis. In a series of validation projects, the use of single cell methodologies that incorporated information on the spatial origin of cells within the tissue led to superior detection

rates, thus promising a valuable improvement for spatial tissue interrogation.

Another line of investigation in clonal sequencing was improving the analysis of epigenetic modification of genomic DNA, e.g. by methylation. For this, we supported several method validation projects with the aim of overcoming some of the known weaknesses of bisulfite sequencing, which until recently has been the prevalent technique in this field. As a result, enzymatic methylation sequencing (EM-Seq) methods using TET2 and APOBEC3A enzymes have emerged as attractive and efficient alternatives. We further explored using long read sequencing on the department's Nanopore Sequencing platform, finding that native DNA sequencing supported by advanced base calling algorithms allows for the direct identification of modified bases (methyl-cytosine, hydroxymethyl-cytosine). A similar approach, through native RNASeq, has been explored to identify modifications in cellular RNAs, such as N6-methyl-adenenosine, or pseudo-uridine.

Visualisation, Irradiation & Analysis

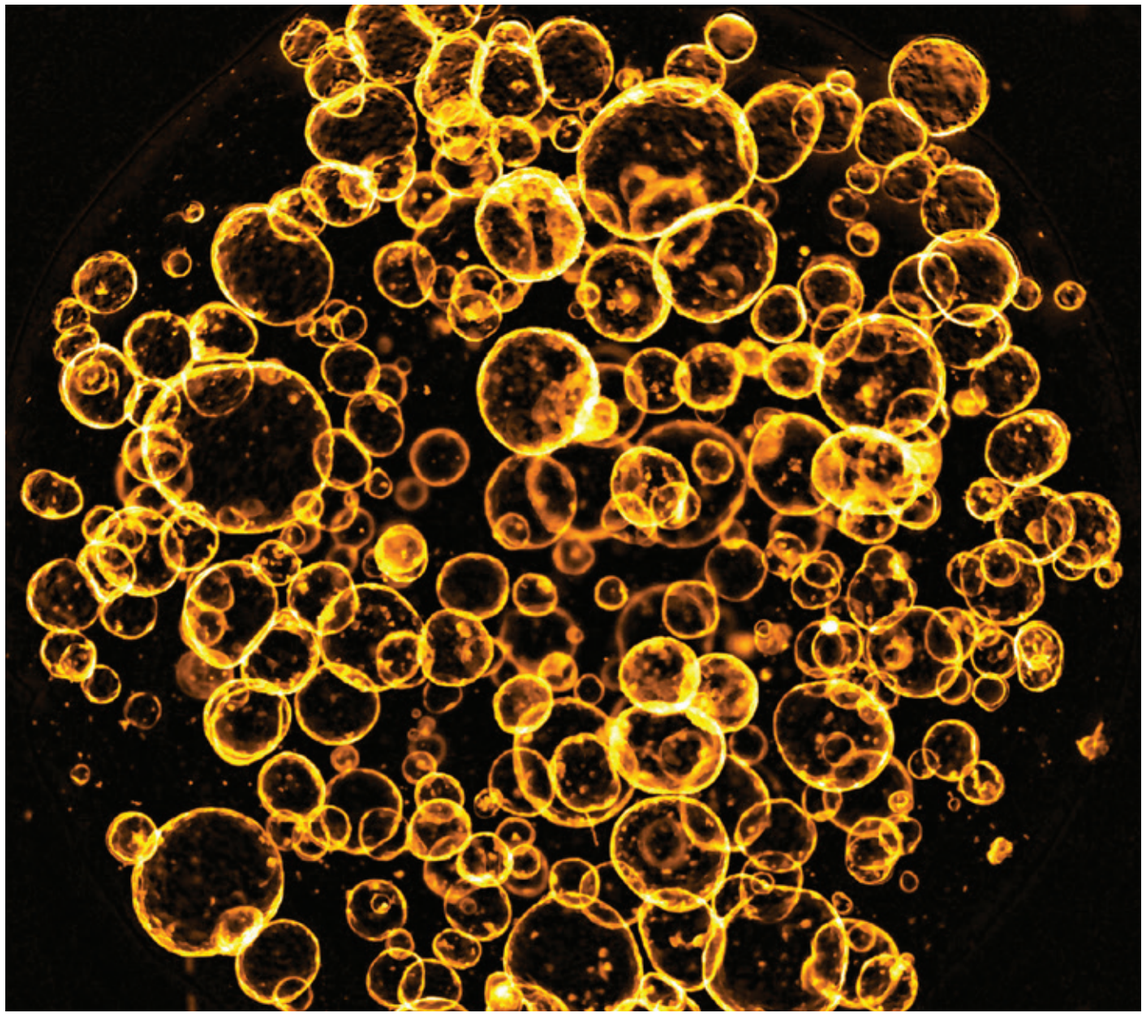
Steve Bagley, Henry Banks, Alex Baker, Jianhua Tang

The Visualisation, Irradiation & Analysis (VIA) facility operates under the remit of providing training in all forms of microscopy, instrument operation, hardware maintenance, quality control, experimental design and the design of new instruments and workflows. In 2025, the facility supported 20,000 hours of live cell imaging and 1,000 hours of high-content screening. We imaged over 12,000 histology slides, provided over 5,000 hours of support for image processing and analysis, and delivered over 140 training sessions. Ongoing support is provided in collaboration with other facilities in the fields of spatial biology pipelines and in vivo imaging.

This year has been characterised by the specification and procurement of two novel instruments, and the development of original workflows:

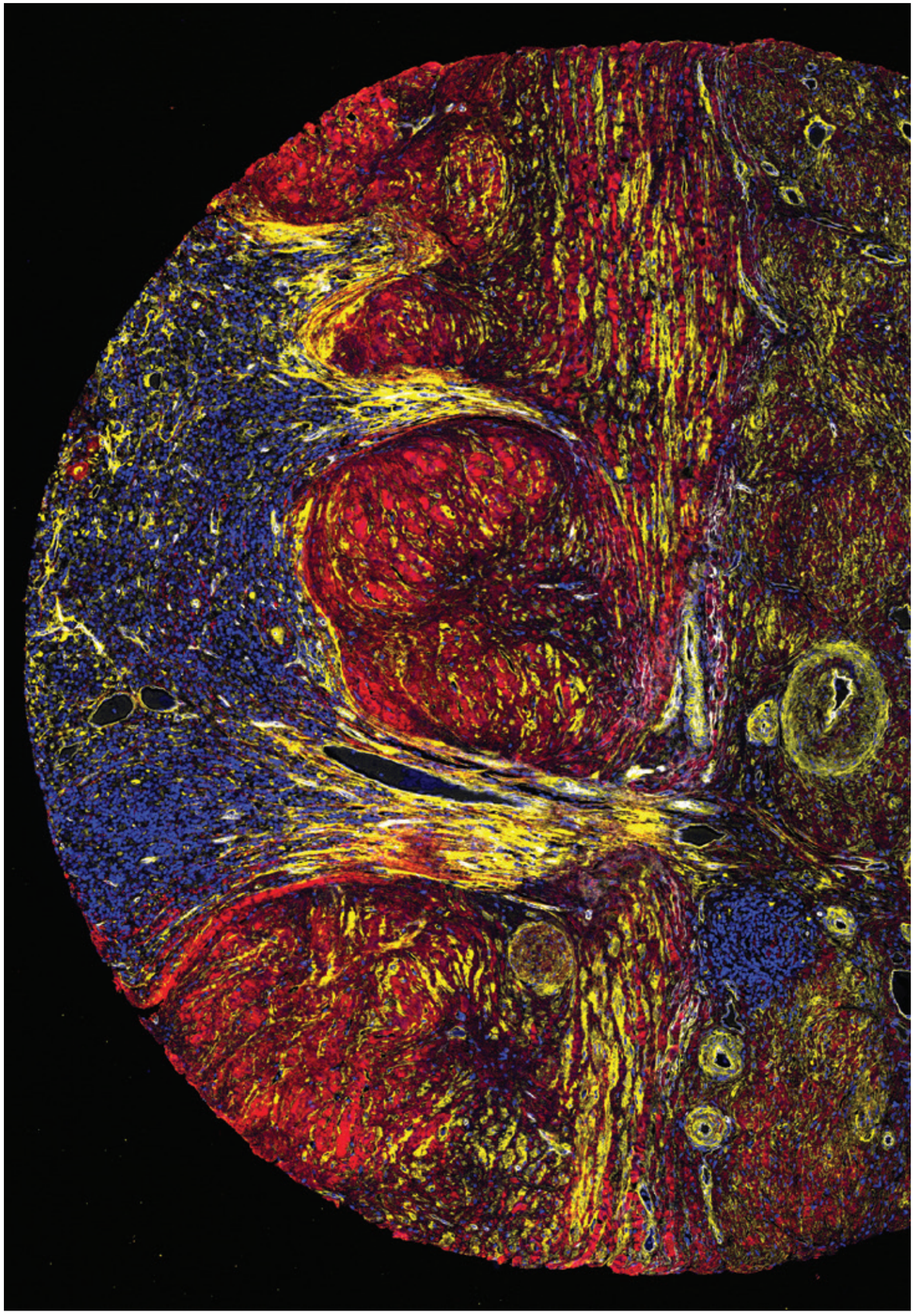
- An open-source High Content Screening System utilising an open frame and a Seven-laser Hub for confocal imaging has been constructed. This design is intended to enable high-plex 2D, 3D and 4D data collection that is both cost-effective and facilitates new forms of statistically viable imaging.
- Serial section is the predominant technique in histological studies; these samples are one cell thick and typically comprise less than 1% of the total volume of a biopsy. A new initiative within the Institute permits the assessment of up to 1cm thick tissues thus allowing three-dimensional assessment of cell communities. The procurement of the Alpenglow 3Di Hybrid Open-Top, Light-Sheet Microscope was secured in collaboration with the research groups, Histology facility, Scientific Computing and Computational Biology Support.
- The laboratory transitioned from a caesium-137 gamma source to an electronically generated X-ray source, delivering cost savings, improved environmental sustainability, and eliminating risks associated with using radioactivity. A research group recently relocated to the Institute had previously utilised gamma to deplete a murine stem cell population for the transplantation of donor stem cells. To enable this work to operate under x-rays, a new workflow has been established. In the absence of a suitable conversion factor, a methodology has been developed using a new beam hardening filter and a pilot study was undertaken to demonstrate its effectiveness. This workflow has now become an established procedure within the Institute and has generated significant interest in the field.

The coming year will see the generation of large data sets containing 3D histology, an increase in data derived from clinical-based research projects and a new initiative to increase the number of fluorescence signals that can be utilised with tissues.



KrasG12D, Tp53null mouse pancreatic ductal organoids (cells grown in 3D embedded in a basal membrane extract). EVOS imaging system, 10X. 1 – Orange-hot look-up table inverted.

Image supplied by Luisa Ferreira (Systems Oncology)



PUBLICATIONS AND OPERATIONS

Image using PhenoCycler from a patient with ccRCC showing an area with no residual tumour cells after treatment with immunotherapy. Left side shows where the tumour cells were originally but is now heavily infiltrated with immune cells, including T cells and macrophages. Middle shows packed areas of dense extracellular matrix. Right side shows renal tubules and glomeruli. Markers used: DAPI (blue), collagen IV (yellow), collagen I (red), CD34 (white).

Image supplied by Matous Elphick & Anne-Laure Cattin (Cancer Dynamics)

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Cancer Immunosurveillance
(page 14)

Evangelos Giampazolias

Refereed research publications

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Cancer Inflammation and Immunity (page 16)

Santiago Zelenay

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Leukaemia Biology
(page 20)

Tim Somervaille

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Clinical Trial.

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(Page 22)

Mark Williams

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Skin Cancer and Ageing
(Page 26)

Amaya Virós

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Stromal lipid species dictate melanoma metastasis and tropism.
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Small Cell Lung Cancer Biology
(Page 28)

Caroline Dive and Kathryn Simpson

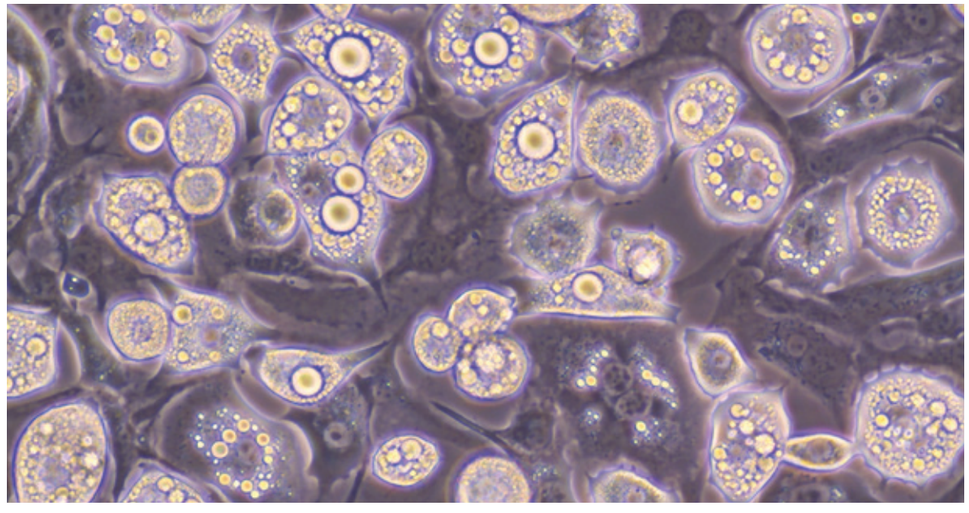
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Brightfield image of differentiated mouse adipocytes. Differentiation is marked by the development of intracellular lipids (lipid bubbles inside the cell) upon administration of differentiation media. Image supplied by the Skin Cancer and Ageing group.

Stem Cell Biology

(Page 30)

Georges Lacaud

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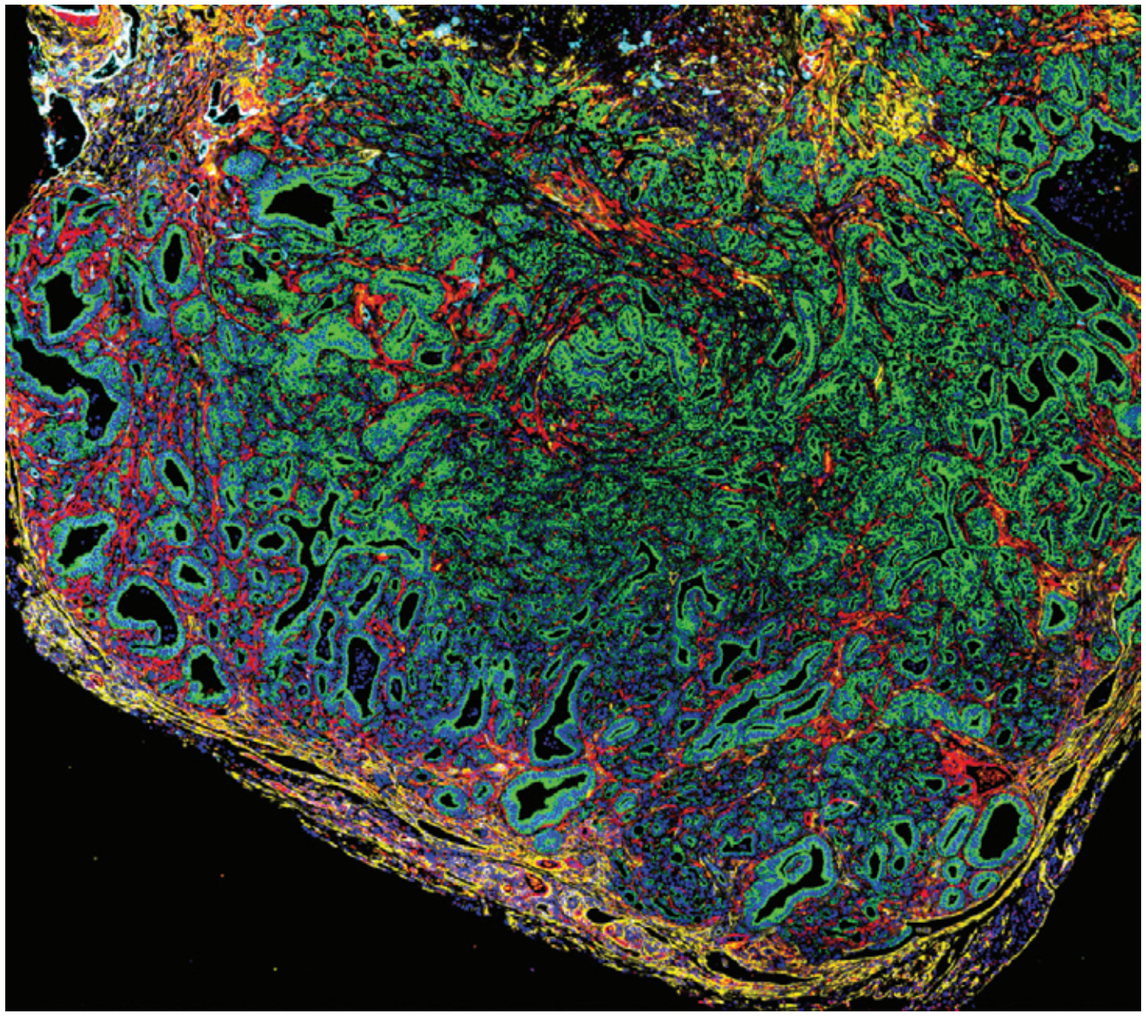
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Multiplexed immunofluorescence staining of mouse pancreatic ductal adenocarcinoma. Cytokeratin 19 (green), CD31 (magenta), α-smooth muscle actin (yellow), and platelet-derived growth factor receptor α/β (cyan). Nuclei were counterstained with DAPI. Staining was performed using the automated Bond RX system with tyramide signal amplification. Images were acquired with an Olympus VS200 slide scanner.

Image supplied by Luisa Ferreira (Systems Oncology, with credit to the Histology core facility)

EXTERNAL SEMINAR SPEAKERS 2025

The seminar series that we run is vital for the Institute, connecting world-class researchers across the broad spectrum of cancer research. Now well established in the Paterson Building, we have fully reconnected with colleagues across the Manchester Cancer Research Centre and developed solid relationships that have enabled us to invite an excellent set of internationally renowned speakers. The postdoctoral researchers and technical staff at the Institute continue to give weekly seminars, which are important in bringing our scientists together and helping to integrate the entire cancer research efforts of the Institute.

These are the external speakers who joined us this year:

Irmela Jeremias
Helmholtz Munich

Filipe Pereira
Lund University

Maria Secrier
UCL Genetic Institute

Goran Jonsson
Lund University

John Haanen
Netherlands Cancer Institute

Daniel Tennant
University of Birmingham

J.T. Poirier
NYU Grossman School of Medicine

Gioacchino Natoli
European Institute of Oncology

Laura Machesky
University of Cambridge

Trevor Graham
Institute of Cancer Research

Elisa Panada
Cell Reports Medicine

Evangelia Petsalaki
EMBL-EBI

Pierre Guermonprez
Institut Pasteur

Joan Seoane
Vall d'Hebron Institute of Oncology

Stefan Knapp
Goethe University Frankfurt & Structural Genomics Consortium

Mikaël Pittet
Ludwig Institute for Cancer Research

Murad Mamedov
University of California, San Francisco

Amir Hosseini
University of Oxford

Eliane Piaggio
Institut Curie

Pascal Meier
Institute of Cancer Research

Peter Kuhn
University of Southern California

Stefan Prekovic
Utrecht University

Berta L. Sanchez-Laorden
Universidad Miguel Hernández

Matheus Dos Santos Dias
Netherlands Cancer Institute

Sergio Quezada
University College London

Eiji Hara
Osaka University

Christoph Klein
University of Regensburg

Eleni Tomazou
St Anna Children's Cancer Research Institute

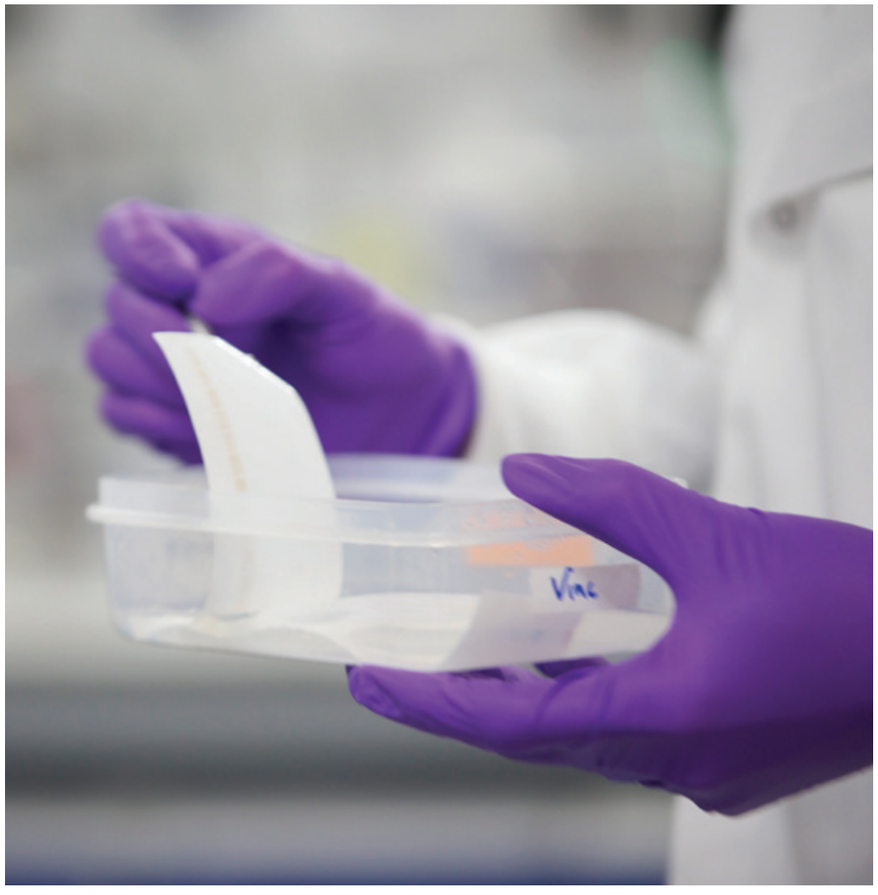
George Poulogiannis
The Institute of Cancer Research

Sohrab Salehi
Memorial Sloan Kettering Cancer Center & Columbia University

Alice Sherrard
Yale University

Riccardo Mezzadra
Memorial Sloan Kettering Cancer Center

Dieter Saur
Technical University of Munich



OPERATIONS



Chief Operating Officer
Caroline Wilkinson



Chief Laboratory Officer
Stuart Pepper



Chief Finance Officer
Mike Berne



Chief Human Resources Officer
Rachel Powell

2025 was an eventful and exciting year for the Institute, marked by the arrival of our new Director, Professor Samra Turajlić, in September. The Operations team provided support as Samra became familiar with the Institute's activities, governance and operational functions, and played a major role in supporting the new Group Leader recruitment call towards the end of the year. We also welcomed new Group Leader Sylvain Delaunay at the start of the year, and Institute Fellows Will Hill and Justin Loke in the autumn. The Operations team supported their onboarding, including laboratory set-up, risk assessments, equipment purchases, recruitment of staff and PhD students, ASPA Project Licence applications, reagent transfers and external funding applications.

During the year, the team said farewell to Ruth Cox, who left after more than a decade at the Institute to take up a new role at the University of Manchester. We thank Ruth for her many years of dedication to the Institute and wish her every success in her new role. In the autumn, we welcomed Armağan Doğan Stewart and Ros Ballinger to the team.

The administration team supported a wide range of Institute events, including the Scientific Advisory Board visit in October. Our Postgraduate Education Manager, Julie Edwards, supported the postgraduate student cohort in organising the International PhD Student Cancer Conference, which was held in Manchester for the first time since 2015 and was an enormous success. The 2025 conference welcomed 105 attendees, including CRUK Manchester Institute students and Institute administrators from thirteen cancer research institutes and centres across Europe. Students from all PhD years at CRUK MI played key roles in organising and delivering the event, contributing to its smooth execution and success. Feedback highlighted the conference as both enjoyable and professionally enriching. Alongside talks and poster sessions, the students organised careers workshops and a patient advocate session. The event also benefited from considerable support from Institute Group Leaders: Santiago Zelenay, Amaya Virós and Sylvain Delaunay contributed to a PI panel; and Claus Jørgensen and Mark Williams joined a panel on careers in academia. Samra Turajlić gave the opening keynote lecture shortly before her announcement as the new Director.

In 2025, the Operations team continued to make strong progress with the roll-out of the Electronic Laboratory Notebook (ELN), including onboarding and training research groups and core facilities in the use of eLabFTW, the Institute's chosen platform. The project is being led by Andrew Porter, Research Integrity and Training Adviser, working closely with IT, Scientific Computing and electronics engineer Yunis Al-Hassan. We have also shared our experience with the wider research community: Andrew presented at a Jisc-hosted webinar, at the University of Manchester Research Lifecycle Showcase in February, and in an online seminar for other Cancer Research UK Institutes.

Andrew also led the Institute's research engagement activities, including events designed to promote openness about how, why and when animals are used in our research. This work, together with a recruitment video featuring animal care, contributed to the Institute receiving an Openness Award from Understanding Animal Research.

We launched our new external website on World Cancer Day in February 2025 and have continued to develop its content. While an external company delivered the back-end development, all content generation, site population and some design works were undertaken by the Institute Operations team, including Gillian Campbell, Andrew Porter and Ruth Cox, helping to reduce costs while ensuring the site reflects the Institute's priorities and identity.

Our AWERB Chair, Sally Robinson, was elected as the new Chair of the Animals in Science Committee (ASC). The ASC is an independent, non-executive advisory public body that provides impartial, balanced and objective advice to the Home Office on issues relating to the Animals (Scientific Procedures) Act 1986 and its functions under the Act. The ASC is also responsible for advising, promoting and sharing good practice with and between Animal Welfare and Ethical Review Bodies (AWERBs) across the UK.

Institute Administration Team

Caroline Wilkinson, Ruth Cox[1], Karen Lee, Minerva Cheng, Ros Ballinger[2], Armağan Doğan Stewart[2]

[1]Left in 2025
[2]Joined in 2025

The Institute Administration Team plays a crucial role in supporting the Senior Management Team, Core Facilities Team, Faculty and the Director, ensuring the smooth operation of the Institute. The team has expanded this year with the addition of Armağan Doğan Stewart as Postgraduate Education Coordinator and Operations Project Lead and Ros Ballinger as Executive Assistant to the Director. Minerva Cheng took up the role of Executive Assistant to Claus Jorgensen in his capacity as Deputy Director when Ruth Cox left the Institute in June, alongside her role as Administrative Services Coordinator. Karen Lee serves as Executive Assistant to Caroline Wilkinson, Chief Operating Officer, and Stuart Pepper, Chief Laboratory Officer.

This year, the Administration Team has been preparing to support Samra Turajlić as the new Director of the Institute as Caroline Dive stepped down from her position as Interim Director. We are grateful for Caroline's exceptional leadership and dedication during the interim period, and we will continue to work closely with her in her role as Director of the National Biomarker Centre. The team has also supported high-profile visits to the Institute this year, including members of our Scientific Advisory Board, which was a great success, and potential new Group Leaders.

The team was also pleased to organise the joint CRUK Manchester Institute and National Biomarker Centre Colloquium in Buxton, providing an excellent platform for scientific exchange within the Institute. In addition, the team supported the rollout of the new Institute website and organised social events, providing opportunities for our staff and students to meet for informal discussions and interactions.
We have continued to be involved with hosting many tours of the Paterson Building for groups, fundraisers, donors and colleagues from the University and CRUK. We hosted 30 external seminar speakers in 2025 and have organised a busy programme of internal seminars, student talks and PhD viva talks alongside a range of education and engagement events for staff and students throughout the year. Our gratitude extends to all the invited speakers who generously shared their insights.

Scientific Administration

Caroline Wilkinson, Gillian Campbell, Julie Edwards, Andrew Porter, David Stanier, Colin Gleeson, Chris Bamber and Armağan Doğan Stewart[1]

[1]Joined in 2025

The Scientific Administration team provides a broad range of services that support the smooth running of the Institute. In 2025, the team helped our new Director, Professor Samra Turajlić, settle into her role and supported new Group Leaders and Institute Fellows as they established their research groups. The team also continued to support Cancer Research UK fundraising and University of Manchester philanthropic activity by showcasing the Institute's research through presentations to donors, fundraising groups, Cancer Research UK teams, press officers, shop managers and volunteers.

During 2025, we developed and recruited to the new role of Communications and Research Engagement Manager, with the successful candidate due to start in the first quarter of 2026. This role will take forward the Institute's communications and engagement activity, including development of an overarching communications strategy, further enhancement of the external website, and support for recruitment campaigns as the Institute continues to grow and develop.

David Stanier is the Institute's Information Governance Coordinator and Administrative Officer, supporting the Institute's Information Governance Guardian, Caroline Wilkinson, in the management of information security, data protection and records management. His work helps ensure that information governance disciplines are embedded in working practices across the Institute. David also manages several operational areas that contribute to the smooth running of the Institute, including courier services, induction sessions and stationery supplies. David and Caroline are part of the University of Manchester's Information Governance Guardian Network for the Faculty of Biology, Medicine and Health, and regularly engage with the University's Data Protection Officer and Information Governance Office on information governance queries and best practice.

David chairs the Institute's Information Governance Committee, which reviews institutional information governance requirements and considers the management of information governance risks for the Institute's risk register. This year, David increased his activity in raising awareness of information security risks and associated mitigations. He also completed the intermediate GDPR Practitioner training and achieved a distinction.

Gillian Campbell is the Institute's Grants Advisor and Scientific Operations Officer. She supports scientists in identifying external funding opportunities and contributes to applications by helping prepare sections such as applicant profiles, publication summaries, host and environment descriptions, data management plans, training statements and research engagement content. Gillian also coordinates the Institute's Grants Committee, which peer reviews applications and helps applicants prepare for grant and fellowship interviews. In 2025, there was a significant increase in the number of applications submitted, including many from our newest Group Leaders and Institute Fellows and from the new Director. Funding success included an application by Professor Georges Lacaud to BBSRC, a Royal Society Research Grant awarded to new Group Leader Dr Sylvain Delaunay, and a Prostate Cancer UK Fellowship awarded to early career researcher Dr Shaun Scaramuzza from the Translational Oncogenomics group.

Colin Gleeson and Chris Bamber comprise the Institute's Health and Safety team. During the year, they contributed to refining health and safety processes in the new building, developed new sustainability initiatives and responded to emerging regulatory requirements. Further details are provided elsewhere in this report.

The Institute's postgraduate education programme continues to be overseen by Postgraduate Education Manager Julie Edwards, with further details provided in the Education section of this report. Julie manages PhD recruitment, admissions and administration, organises the Institute's Education Committee, and provides pastoral support to the student community. This year, we welcomed Armağan Doğan Stewart to the Operations team as Postgraduate Education Coordinator and Operations Project Lead, supporting the postgraduate programme and assisting Group Leaders with administrative tasks and projects. Julie also provided oversight and support for the student-led International PhD Student Cancer Conference, which brought together participants from across Europe and provided an invaluable learning experience for the Institute's postgraduate community.

Andrew Porter is the Institute's Research Integrity and Training Adviser. He supports the scientific community through a pre-submission manuscript review process and by delivering training sessions and workshops for early career researchers. Topics include thesis writing, statistical analysis, the use of generative AI and research integrity induction for new students and staff.

In 2025, the number of manuscripts submitted for review increased significantly compared with the previous year. Andrew continued to refine the process, introducing additional compliance checks for BioRender, advice on generative AI declarations, and use of ImageTwin software to help identify inadvertent duplication of panels during figure construction. Andrew also provides advice throughout the year on manuscript preparation, data management and related topics, helping to support good research practice across the Institute.

Andrew has also developed a Research Engagement Team, which now has ninety members across CRUK MI and the National Biomarker Centre. The team provides a valuable resource for research engagement activity, with members using shared guides, templates, booklets and graphics throughout the year. It also provides a record of past activities and future plans, supports the coordination of volunteers for demonstrations and photography requests, and helps guide future events across the Institute.

In June 2025, the Institute hosted a stand at the Universally Manchester festival, which welcomed more than 2,000 visitors. The activities built on those developed for British Science Week 2025, demonstrating how and why mice are used in cancer research. The event provided an opportunity to engage with a wide public audience and formed part of the Institute's submission to Understanding Animal Research's Openness Award, which the Institute won in 2025.

The Electronic Laboratory Notebook project moved from testing to implementation in October 2025. ELN access is now available to all Institute researchers, making CRUK MI the first Cancer Research UK Institute to have such a system in place. Shared in-lab tablet computers provide convenient access to experiments and resources. The ELN, based on the open source eLabFTW software, provides a central platform for recording experiments, logging resources and sharing data across groups and core facilities. Andrew has worked with the Information Governance Committee to provide oversight of these data management changes.

Major milestones included launching the ELN at the Colloquium through a presentation and two posters, including a worked example from Amy Lawrence of the ELN in Histology; delivering inductions and training with most research groups and core facilities; working with IT and Scientific Computing to purchase, configure and deploy 50 in-lab tablet computers for ELN access across the Paterson Building and OCRB; supporting the Histology Core Facility to move routine sample-processing forms fully into eLabFTW and away from paper-based processes.

Finance and Purchasing

Mike Berne, Denise Owen, David Jenkins, Muhammad Raja, Abigail Scott

With the appointment of the new Director of the Institute came a notable and welcome revitalised energy, which has been reflected in the increasing numbers of grant applications submitted and the generation of several successful collaborations.

The Finance team continues to provide support to the Institute Director and the management of the Institute budgets, including those of the CRUK National Biomarker Centre and the CRUK funded centre awards within in the Manchester Cancer Research Centre. The Finance team also provides research support and continues to be critical in assisting with costing grant proposals and giving advice for new research proposals and contracts for all research groups. Despite global financial pressures, we continue to be successful in winning several new awards this year relating to research applications and contractual agreements.

The team also works closely with the Institute's HR team and Postgraduate administration teams to manage funding sources, student stipends and staff salaries. In addition, to support the smooth running of the Institute, the team crucially maintains a close working relationship with the University of Manchester's operational teams, including the contracts and legal teams, procurement, research finance and research support functions.



Health and Safety

Colin Gleason, Chris Bamber

Health and safety arrangements for the Paterson Building that were developed in 2024, including those with other stakeholders, were this year tested through several compliance visits and exercises. An inspection of our open-source radioactive work arrangements undertaken by the Environment Agency found we were compliant with the legislation. The staff involved in the development of these arrangements and those that implement them on a day-to-day basis were commended by the inspector.

We have also responded to changing expectations issued by the Health and Safety Executive, who released a bulletin highlighting that the testing of microbiological safety cabinets to the British Standard (typical of academic institutions in the UK) was not fully compliant with regulation 9 of COSHH. Following a gap analysis of our testing regime, some refinements were identified that were introduced ahead of the new regulation coming into effect to ensure we remained compliant.

Similarly, to ensure compliance with University and Institute governance requirements, we surveyed all staff who require occupational health surveillance, with particular focus on those who work in our murine animal facility to ensure that our management arrangements help to guarantee that annual health surveillance is maintained.

The Health and Safety team have continued to monitor performance of the Institute's health and safety procedures by undertaking internal inspection programmes and compliance surveys and found that the Institute performs very well in this regard. Any minor issues are communicated to the relevant individuals, and advice provided such that improvements and refinements are introduced promptly. We also continue to play active roles in the wider university community (e.g. Genetic Modification and Biohazards Advisory Group and Ionizing Radiation Safety Working Group) and contribute to our landlord's building and facilities management arrangements. We continue to support our staff and students with pragmatic health and safety advice, review risk assessments and undertake task analysis where necessary to better understand the risks from their research. This year, two new research groups were established and as we continue to grow, we anticipate that evaluating the health and safety needs of our research community will expand over the short and medium term.

The team have initiated a review of our staff induction process and how we can facilitate a smoother settling-in phase for new research groups. We anticipate completing this review in the coming months, with subsequent implementation of the updated induction process.

Human Resources

Rachel Powell, Kate Fu[1], Rebecca Grant, Julie Jarratt, Laura Jones, Irraith Maan[2], David Stanier[3]

[1]Joined in 2025
[2]Joined and left in 2025
[3]Joint with Scientific Operations

The HR department has continued to deliver a high-quality proactive service to the Institute, CRUK National Biomarker Centre (NBC) and colleagues at The University of Manchester and Cancer Research UK. The department provides advice and guidance to managers and staff on all employment-related matters such as recruitment, onboarding, policy guidance, employment legislation and best practice.

This has been an exciting year for the department and the Institute with the appointment of our new Director, Professor Samra Turajlić, who joined the Institute in September this year. During 2025, we were successful in appointing and onboarding 63 new members of staff. The department has provided a full onboarding service, ensuring that all new appointees are integrated smoothly into the Institute, NBC and its culture. We welcomed and actively supported the launch of four new groups to the Institute (Sylvain Delaunay, Samra Turajlić, William Hill and Justin Loke). The team provides personalised one-to-one support to each of our new appointees to enhance their onboarding experience. We have supported our international colleagues in the successful approval of Global Talent Visas, Skilled Worker Visas and Temporary Work – Government Authorised Exchange Visas, along with providing financial support such as visa and Immigration Health Surcharge fees (staff) and visa loans. This year CRUK launched their 2025 evidence and analysis of the impact of the UK immigration system on cancer research policy report, to which we contributed evidence on visas and recruitment, as well as a summary blog. We look forward to continuing to support the growth of the Institute and NBC over the next couple of years.

We are committed to developing our staff and ensuring that Personal Development Reviews are undertaken. This year, the department facilitated the successful promotion of several individuals. In addition, we have continued our commitment to joint partnership working with the Union, which has resulted in the renewal of several policies and procedures. Work has also been underway to review and improve processes ahead of the introduction of a new system that will combine HR and Recruitment in one place. This is intended to streamline operations and enhance the experience for both applicants and employees.

The department has maintained a strong focus on wellbeing initiatives and mental health support across the Institute and NBC, with the aim of fostering a supportive environment in which all staff can thrive and achieve their best. In 2025, we have introduced a range of wellbeing activities and provided ongoing training for the Wellbeing Champions along with the renewal of Mental Health First Aider qualifications. The wellbeing activities included book swaps, wellbeing walks, photography competitions, the launch of the Sunflower Scheme, and flu vaccinations for staff and students. In February, we held a 'Time to Talk' event, which is an initiative that encourages us all to take the time to 'check in' on each other with the aim to reduce any stigmas around mental health. This campaign also underpins some of our ongoing wellbeing work within the Institute and NBC.

We have remained committed to our Equality, Diversity and Inclusion (EDI) vision to create a diverse and inclusive culture which develops and maintains an attractive environment for staff and students whilst achieving the Institute's aim to deliver world class cancer research. We have developed a comprehensive support plan for individuals who have both registered and unregistered disabilities. We have partnered with the University's EDI team to deliver Active Bystander training for our staff. In addition, the Institute's new website includes a dedicated section highlighting our EDI aims and the ongoing work in this area at the Institute.

In 2026, we will continue to review our current EDI position by analysing existing data and conducting a comprehensive staff survey. This will help us identify barriers and perceptions that may impact inclusion. The findings will help inform our strategic direction and support our commitment to achieving an Athena Swan accreditation. The insights gained from this exercise will underpin our long-term approach to equality, diversity, and inclusion.

Logistics

Andrew Lloyd, Edward Fitzroy, Sedia Fofana, Jonathan Lloyd, Robin Sherratt, Wayne Howarth, Wilfred Seville

Over the past year, the Logistics' team has successfully delivered an efficient and responsive service that supports research activities across the Paterson and Oglesby Cancer Research Buildings.

The team's role is varied and encompasses a wide range of responsibilities. Key activities include:

- Receipting and distribution of goods
- Waste management support
- Cryogenics, dry ice delivery, and compressed gases
- Central stores
- Facilitating the movement of equipment

Receipting and distribution

The team operates a back-of-house service and accepts direct deliveries of consumables from couriers. Live finance systems are used to receipt and distribute goods accordingly. Items that cannot be delivered immediately are stored within the department at the appropriate temperature pending delivery.

Waste management support

Logistics is responsible for the disposal of Institute laboratory waste and actively supports all recycling initiatives. By working with The University of Manchester and Christie NHS Foundation Trust services, the Institute recycles large volumes of waste, reducing the amount sent to landfill. Across both buildings, the Institute currently recycles cardboard, plastic bottles, soft plastics, tin cans, wooden pallets, polystyrene boxes, ice/gel packs, ink toners, plastic media bottles, and waste electrical and electronic equipment (WEEE).

Cryogenics, dry ice delivery, and compressed gases

The team manages the Institute's liquid nitrogen reserves, monitoring cell storage tank levels and carrying out weekly top-ups. In 2025, the Institute had over 60,000 litres of liquid nitrogen delivered to site and used 18 tonnes of dry ice. The team is responsible for the supply, safe storage, and changeover of the Institute's compressed gas cylinders across the Paterson and Oglesby Buildings. Gas manifolds are monitored daily, and cylinders are replaced as required. Several standalone cylinders containing specialised gas mixtures are also maintained by the team. In total, approximately 150 cylinders are managed across both sites.

Central stores

Researchers can order central stores items via the intranet for collection or delivery by the logistics team. The team currently stocks over 200 items, ranging from tissue culture essentials to cleaning products, and the inventory continues to expand, with recent additions focused on sustainability improvements.

Enzymes and media from suppliers including Sigma, Life Technologies, Promega, New England Biolabs, and Qiagen are stored in the Institute's freezers. By consignment agreements and bulk purchasing arrangements with suppliers, we generate cost savings for the Institute.

Facilitating the movement of equipment

The team supports the movement of heavy equipment and furniture across the Institute. This includes the disposal of obsolete items, rearranging existing equipment to accommodate new installations, and supporting the on-site electronics technician by relocating equipment to provide access for maintenance and repair work.

Electronics

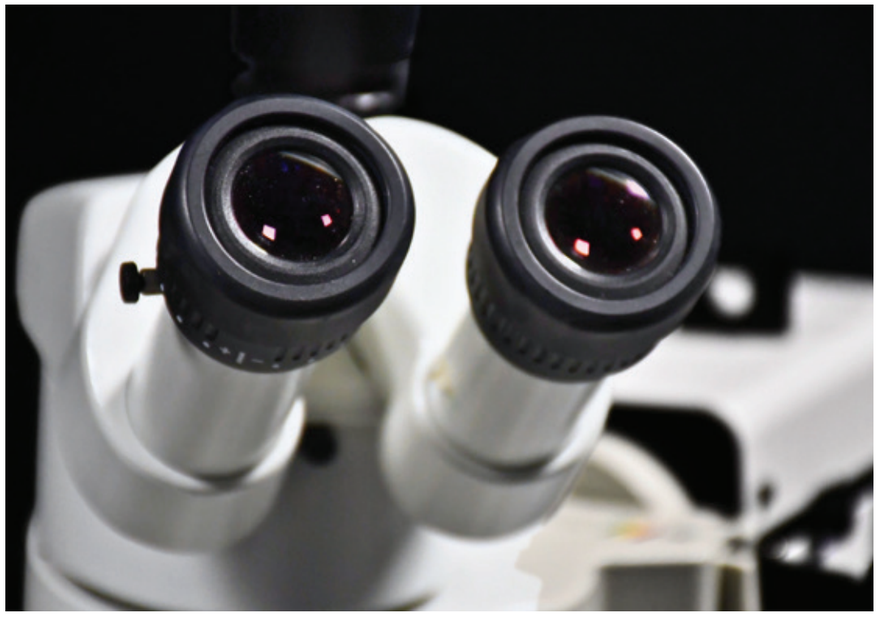
Yunis Al-hassan

The electronics engineer provides substantial support in the smooth running of the Institute in relation to maintaining the longevity of numerous items of laboratory equipment. He continues to provide the Institute with an equipment repair, maintenance, and PAT testing service, which resulted in less equipment down time and significant economic benefit to the Institute with minimisation of repair costs and avoidance of the unnecessary cost of equipment replacement. The Institute's electronics engineer also tracks equipment which is under warranty, service contract or in-house repair. This service also provides a considerable economic benefit to the Institute.

Animal Welfare

Caroline Wilkinson, Establishment Licence Holder, **Simon Poucher**, Regulatory Liaison and Training Officer, **Sally Robinson**, Animal Welfare & Ethical Review Body (AWERB) Chair, **Stuart Pepper**, Chief Laboratory Officer

The Institute upholds high standards of welfare for the laboratory mice used in our research. All animal research activities in the UK are conducted under the Animals (Scientific Procedures) Act 1986 (A(SP)A). The Institute's Animal Welfare and Ethical Review Body (AWERB) has oversight of the research involving animals at the Institute and is required to conduct several tasks under A(SP)A. The AWERB supports all staff involved with animal research by promoting a Culture of Care, providing staff training, reviewing processes and facilities for the care and use of mice, and encouraging implementation of the replacement, reduction and refinement (3Rs) of the use of mice in our research. The AWERB also reviews proposed collaborations and grant applications involving animal research.



We used 15,046 mice in total during 2025. Of these, 5,469 were used in the breeding programme for the production and supply of mice for CRUK MI researchers (a decrease of 26% over 2024). We used 9,577 mice in experimental research programmes in 2025, including generation of new genetically altered mice, (a decrease of 11% compared to 2024). We currently have 20 project licences granted by the Home Office.

The Institute continues to promptly report any unexpected events to the Animals in Science Regulation Unit (ASRU). We had 22 unexpected observations (68% were mice found dead overnight when observed as healthy at the previous check). We also reported seven potential non-compliance incidents where a procedure deviated from what was authorised. All events have been resolved with ASRU.

The AWERB reviewed three new project licence applications and twelve amendments prior to their submission to ASRU for approval. The reviews by AWERB are a required task and ensure that projects will be conducted causing least harm, using the fewest number of mice and only when non-mouse alternatives are not appropriate or available. We held a retrospective review meeting for all licensees to hear about the scientific advances made through the use of animals and how the 3Rs had been incorporated into their research programmes during the year. Such events allow us to share best practice and generate discussion around the topic areas. Additionally, we delivered a workshop for those studying brain tumours, involving scientists outside CRUK MI, to share experiences and best methods.

We continue to build a Culture of Care amongst staff working with mice. In 2025, there were six AWERB Recognition Awards given for a wide range of activities to encourage good practice across the licensees. We continue in our commitment to clearly communicate the benefits and developments in animal research with the public. This includes a new Institute website that names members of the AWERB. We participated in events at the Manchester Museum during British Science Week and at the Universally Manchester Festival, a community festival organised by the University of Manchester. At these events, we demonstrated why mice are a good model for studying certain aspects of cancer biology. We organised an interactive activity in which participants matched pairs of tumour histology images – for example, two different lung tumour samples – and then predicted which image came from a patient and which came from a CDX (a circulating tumour cell-derived xenograft grown in a mouse). This proved challenging as they are very similar in appearance, which helped illustrate the point that tumours grown in mice have very similar characteristics to those isolated from patients.

In December this year, we also won an Openness Award from the Understanding Animal Research organisation for a range of activities, including being the first organisation to use technicians caring for animals in videos as part of a national recruitment campaign.

We have introduced many significant refinements to the way we perform procedures. Examples of this include a magnetic guidance system which works in combination with the ultrasound/photo-acoustics system to allow guided sensing and drug delivery to treat pre-invasive lesions of ovarian cancer. We have also enhanced our ability in the use of ultrasound imaging. Key improvements are improved skin preparation – shaving standards, amount of gel used, correct alignment of image, full abdominal scan – to find any 'hiding' tumours and to detect any abnormalities or ascites; and the use of gaiting to give a sharper image.

We are also working to reduce our carbon footprint whilst conducting mouse studies. Actions that contributed to our achievement of a silver medal in the Laboratory Efficiency Assessment Framework include introducing tiger-striped clinical waste bags where possible, discontinuing the lamination of cage labels, and replacing disposable items used in surgery with reusable alternatives, such as scrub containers and instrument trays. We have also introduced reusable weigh boats and holding containers, reduced the use of disposable PPE following on from allergen testing, which demonstrated that mask use could be significantly reduced and restricted to specific scenarios.

Finally, we engaged in external fora to help share and further develop best practices in animal welfare. Examples are given below:

- Caroline Wilkinson is a member of the Establishment Licence Holders' Forum
- Sally Robinson is Secretary General to the Council of the Laboratory Animal Science

Association (LASA), a member of the NC3Rs Board (and other NC3Rs activities) and a member of the IAT President's Advisory Group. Sally was appointed as the new chair of the Animal Science Committee (ASC) in June 2025 and our NVS, Lucy Whitfield is also a member of the ASC. Sally was also a member of the scientific organising committee for the FELASA congress held in Athens in June 2025.

- Natalia Moncaut is a convenor for the genetically altered animals' section of LASA
- Simon Poucher is a member of the Home Office Liaison, Training and Information Forum (HOLTIF)

Commercialisation and Innovation Support

Nathalie Dhomen

Cancer Research Horizons (CRH) serves as Cancer Research UK's dedicated innovation arm. Through an established agreement with The University of Manchester, CRUK retains ownership of intellectual property generated from CRUK-funded research at the University and oversees its development and commercialisation. Our on site commercialisation support team works to close the gap between frontier academic discovery and the industrial advancement of cancer therapeutics, diagnostics, and medical technologies.

Our Cancer Commercialisation and Innovation Lead, Nathalie Dhomen, acts as the primary point of connection to the commercialisation frameworks within both Cancer Research Horizons and The University of Manchester Innovation Factory – the University's technology transfer office. Nathalie works with researchers and clinicians to uncover high value intellectual property and promising innovations, while also enabling access to a wide network of oncology focused expertise. This includes support in technology assessment, patent protection and management, translational and commercial development funding, drug discovery capabilities, market insight, and the creation of spin out companies.

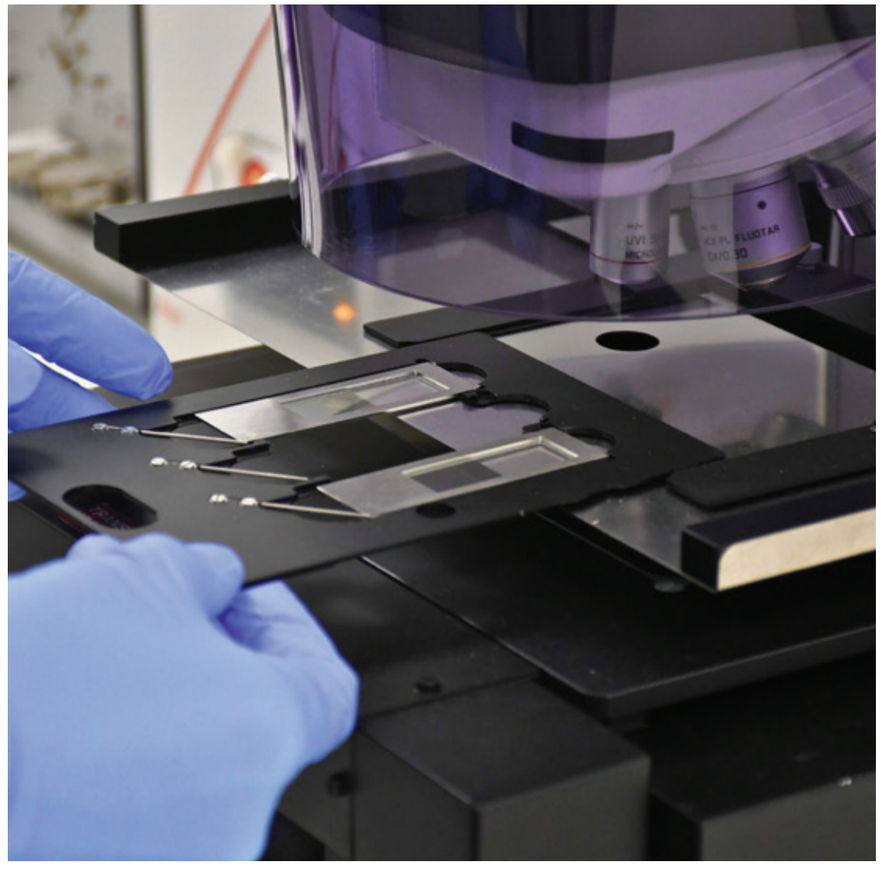
Over the past year, we continued to guide and resource nearly a dozen active translational efforts, spanning biomarker assay development, therapeutic platform technologies, and software- and data driven opportunities across the Manchester Cancer Research Centre ecosystem. CRH's Early Validation Fund has been strategically applied to advance several initiatives, including evaluating clinical testing platforms for innovation from the CRUK Manchester Institute's Cancer Inflammation and Immunity group, and producing tool compounds for exciting Systems Oncology group research.

A notable achievement was securing support from CRH's Translation Fund (https://www.cancerresearchhorizons.com/researchers/access-funding) to generate a comprehensive dataset enabling the characterisation of RAS driven cancers. This award highlights both the scientific calibre and the translational potential of data resources developed within our community and represents the third major data intensive project backed by CRH in four years. The first locally supported dataset, funded through a Cancer Research Horizons Data Catalyst Award, comprises a unique real world lung cancer dataset built by The Christie NHS Foundation Trust's Clinical Outcomes and Data Unit (CODU). With structured clinical information paired with baseline and longitudinal CT imaging, it has already attracted significant commercial interest, and its data access committee is reviewing multiple external requests. In addition, a second Data Catalyst Award was secured last year to support the curation, annotation, integration, and dissemination of an exceptional dataset generated by the CRUK Accelerator funded PMPnet Manchester team, working closely with CRUK MI facilities. The CRUK MI will play a key role in preparing this asset for responsible access and use by both academic and commercial partners.

Supporting entrepreneurial development has remained an important part of our mission. We were delighted that Professor Georges Lacaud, who leads the Stem Cell Biology group, was nominated for Entrepreneurial Group Leader of the Year at last year's Cancer Research Horizons Innovation and Entrepreneurship Awards. We were equally pleased to host Professor Sir Tony Kouzarides as he introduced PRIMED, a UK wide initiative created to inspire and equip the next generation of scientists to pursue venture creation. His visit catalysed the formation of a Manchester PRIMED cohort, including early career researchers from CRUK MI, who plan to hold their first event in February next year.

Our maturing intellectual property portfolio continues to grow, with another priority patent filing submitted in October and further filings anticipated in early 2026. For each active project, we remain focused on accelerating progress towards clinical application through targeted translational funding routes, specialist consultancy input, and engagement with our extensive networks and strategic partners. We are excited to see several technologies and services advancing towards clinical evaluation, bringing us closer to tangible impact for patients and their families.

We continue to manage a diverse and expanding pipeline of development programmes and promising licensing opportunities arising from the Cancer Research UK Manchester Institute. The breadth of innovation emerging from CRUK funded research in Manchester continues to increase year on year, and we look forward to driving these discoveries forward as part of our collective mission to beat cancer.



POSTGRADUATE EDUCATION



Postgraduate Education Manager
Julie Edwards



Postgraduate Education Coordinator
Armağan Doğan Stewart[1]



Postgraduate Tutor
Santiago Zelenay



Postgraduate Director and Chair of the Education Committee
Tim Somervaille

[1]Joined in 2025

The Cancer Research UK Manchester Institute offers postgraduate degrees (PhD) for students interested in a career in cancer research. The Institute considers the education of both research and clinician scientists to be a major investment in the future of cancer research and has an excellent track record of launching careers in basic, translational and clinical research. As part of this commitment, we have an active postgraduate programme that provides students and clinical research fellows with the potential and opportunity to study for a cancer-related PhD degree. This is achieved through a structured training programme that aims to improve effectiveness in research, provide professional and management skills, and enhance career development. Our PhD students have exceptional employment prospects following graduation, with the majority continuing in academia, industry or healthcare, and securing positions in destinations across the UK and Australia. In 2025, 100% of our graduates found positions following PhD completion: academia (73%), return to clinical training (18%), and scientific administration (9%). The Education Committee also oversees PhD students from the CRUK National Biomarker Centre and has representatives from NBC sitting on the committee.

In 2025, we welcomed twelve new graduate students to our PhD programme, working in a variety of fields and research groups, including translational immunology, systems oncology, stem cell biology, nucleic acid biomarkers, leukaemia immunology and transplantation, RNA dynamics in cancer and cancer origins.

It was also particularly gratifying to see that over the past twelve months some of our PhD students and clinical research fellows published first author papers in *Journal for Immunotherapy of Cancer*, *Cell Death Discovery*, and *Cancer Cell*. Other students contributed to publications as middle authors, including *Cancer Discovery*, the *Journal of Trends in Molecular Medicine* and *Cell Reports*.

The Cancer Research UK Manchester Graduate Programme

We aim for each student to receive high quality training in scientific research through an intellectually demanding but achievable research programme. Each project is peer-reviewed in advance of commencement and monitored with formal student assessments at key stages throughout the duration of the programme. Modes of assessment include annual written reports, oral presentations, and progress meetings, which are designed to provide formal points at which progress (of both the student and the project) can be monitored but are also beneficial in the development of presentation skills fundamental to academic careers in science and beyond. Graduate training and student welfare are monitored by the Institute's Education Committee, with members including Institute group leaders and fellows, operational managers and student representatives, providing a diverse range of experience and expertise. A main supervisor and a second or co-supervisor are nominated for each student, providing advice and support on both academic and non-academic matters. Students are assigned an advisor (like a personal tutor on an undergraduate programme) whose role is to provide impartial support and advice in a pastoral capacity.

The CRUK Manchester Institute has an established internal and external seminar series featuring talks from leading scientists in cancer research, and all our students benefit from these events. Speakers are internationally renowned scientists, and we consider it essential that our students are exposed to outstanding research from leaders in different disciplines, providing a broad understanding of many aspects of cancer research and basic biology. In addition, we hold an internal series of weekly scientific talks from postdoctoral researchers, scientific officers, and core facility managers, which is also an integral part of our students' learning. While students themselves are asked to give talks at key points during their PhD, they also have opportunities to present their work at lab meetings, student forums, and external conferences. Conferences and seminars play an essential and important role in connecting and networking with colleagues across the Institute, nationally and internationally.

Staying connected with peers and colleagues is a key component for students, not only in terms of research progress, but also mental health and wellbeing. A programme of in-house training events, external and internal seminars provide an invaluable opportunity for students from the CRUK Manchester Institute and Division of Cancer Sciences at The University of Manchester – with whom we share some of the space in the Paterson Building – to connect with the wider scientific community.

Student research and activities continue to thrive in the Paterson Building, affording access to advanced state-of-the-art equipment and excellent core facilities alongside the Oglesby Cancer Research Building and the Christie NHS Foundation Trust.

STAy (Science TakeAway) is a committee group run by postdoctoral researchers, junior scientists and students in the CRUK Manchester Institute and Division of Cancer Sciences with the aim of providing a forum for scientific discussions and idea-sharing to foster networking. STAy creates a structured and impactful programme covering career support, guidance on grant writing, peer review, lab management, event organisation and leadership development, encouraging students, scientific staff and postdocs to connect and establish a broad network of career mentors with opportunities to engage with experts who have successfully navigated their career transitions.

In October 2025, the CRUK Manchester Institute and CRUK National Biomarker Centre annual colloquium took place once again at the Palace Hotel, Buxton in the Peak District. This presented a great opportunity for staff and students to connect off-site.

The colloquium provides the chance for our new intake of students to meet other established PhD students, members of the Institute, group leaders, postdoctoral fellows, and scientific officers. This event provides a forum to communicate up to date science in the form of oral presentations given by group leaders and second year PhD students, as well as poster presentations from a range of scientists across the Institute covering all aspects of cancer research.

This year, Kirsten Tinsley, a postgraduate student from the former Cell Signalling group, was awarded the Lizzie Hitchman Prize for the best PhD student poster presentation for her project titled *"The role of cell–cell interactions in the survival and dissemination of SCLC circulating tumour cells."*



Kirsten Tinsley (R) is presented with the Lizzie Hitchman Prize for the best PhD student poster at Colloquium by Institute Director Samra Turajlić.

International PhD Student Cancer Conference organising committee members feeling happy on the opening day.



International PhD Student Cancer Conference
Cancer Research UK also contributes towards PhD student attendance at the annual International PhD Student Cancer Conference (IPSCC) allowing students (typically years 2 to 4) from the top cancer research institutes across Europe to present at their own scientific conference. The conference is organised by students for students from the core participating institutes: The Francis Crick Institute, CRUK Manchester Institute, CRUK Cambridge Institute, CRUK Scotland Institute, Netherlands Cancer Institute (NKI), European School of Molecular Medicine, Milan (SEMM, IFOM & IFEO), Max Delbruck Centre (MDC), German Cancer Research Centre (DKFZ), CRUK City of London, Institute of Cancer Research, CRUK Oxford Institute for Radiation Oncology, Cancer Research Karolinska Institute, and Institut Curie.

This year, the 18th International PhD Student Cancer Conference was held in Manchester in June and was expertly hosted by our students from the CRUK Manchester Institute. The conference took place in the Schuster Building on the main campus of the University of Manchester.

We welcomed 73 PhD students from across the UK and international centres to a two-and-a-half-day programme featuring high-profile keynote speakers, 25 student talks, poster sessions with 71 posters, career workshops, and opportunities for networking and scientific discussion with plenary speakers.

The organising committee consisted of 29 students, supported by Julie Edwards, Postgraduate Education Manager, and Alexia Strickson, a final-year PhD student from Leukaemia Biology, who served as the organising committee coordinator. Organising the conference was an enormous task, but the students took on the challenge with gusto, dividing themselves into specific working groups, including finance, logistics, publications and communications, and social activities.

The conference launched with high energy from the Keynote Speaker Samra Turajlić, who was serendipitously invited before knowing she would become our Institute Director. The first day also featured presentations from the students and concluded with a social event at the student union, providing an opportunity for informal networking.

Day two included a full schedule of PhD student talks, alongside the EMBO keynote lecture delivered by Maria Rescigno of Humanitas University. The programme also incorporated a patient advocates session and careers workshops, reflecting the conference's commitment to both scientific advancement and professional development. The day ended with a poster session and conference dinner.

Institute Director Samra Turajlic gives fascinating opening lecture at the IPSCC before taking up her appointment with us.



The final day featured keynote presentations from Caroline Dive, Santiago Zelenay, and Sylvain Delaunay of the CRUK Manchester Institute, alongside further PhD student talks and a second poster session. The conference closed with the presentation of prizes.

CRUK Manchester Institute was represented by 33 students, six of whom were selected to talk about their research projects. In addition, 17 students from our Institute presented posters to showcase and discuss their thesis projects.

Student Talks

Louis Roussel, Systems Oncology – "Developing an isogenic series of CRISPR edited organoids to deter-mine transformative dependencies of KRas-mutant alleles"

Lucy Barton, Translational Oncogenomics – "Chromosome 8q gains and prostate cancer aggression"

Kirsten Tinsley, Cell Signalling – "The role of cell-cell interactions in the survival and dissemination of small cell lung cancer circulating tumour cells"

Jingru Xu, Stem Cell Biology – "IRF2BP2/TRIM28/DNMT1 suppresses transposable elements expression to maintain AML survival"

Hannah Sheedy, Nucleic Acid Biomarkers – "Development of a single-cell methylation workflow to un-derstand the biology of circulating cells in early-stage non-small cell lung cancer"

Sophie Richardson, Nucleic Acid Biomarkers – "Cell-free DNA methylome and fragmentome analysis for disease relapse monitoring in patients with Ewing Sarcoma"

PhD studentship recruitment
PhD recruitment to our core funded studentships is highly competitive, with between 300-500 applicants competing for between four and eight places each year. CRUK core funded studentships are full time for 4 years with an approved research project to be undertaken in one of our core funded research groups. Some students are allocated joint supervisors in different groups, fostering important collaborations and providing exposure to different disciplines. Interviews are typically conducted annually over a two-day period in January/February, however, additional PhD studentships afforded by different funding routes may be advertised at various times throughout the year.

PhD studentships and clinical fellowship funding in 2025 were awarded to the CRUK Manchester Institute core funded groups via CRUK core funding to the Institute, Cancer Research UK Manchester Centre Clinical Training Fellowships, Ian Harty Charitable Fund, Roy Castle Lung Cancer Foundation, National Biomarker Centre (NBC) and the Manchester Cancer Research Centre MB-PhD Scheme.

Education Committee 2025
The Education Committee acts for postgraduate students and consists of group leaders, the Chief Operating Officer, the Postgraduate Tutor and the Postgraduate Education Manager from the CRUK Manchester Institute.

Our goal is for every student to have a project that is both achievable and intellectually stimulating and demanding. Projects and students are monitored by the Education Committee to ensure that the proposed plan for research is achievable, and that progress is made consistently throughout the duration of the studentship. Various assessments at key stages throughout a CRUK Manchester Institute PhD studentship are a vital component in ensuring successful PhD completion and graduation of our students. Such assessments are not only crucial in the development of students throughout their postgraduate programme but importantly enhance future employability and academic careers.

Education Committee Members
Tim Somervaille, Postgraduate Director & Chair
Julie Edwards, Postgraduate Manager
Armağan Doğan Stewart, Postgraduate Education Coordinator[1]
Santiago Zelenay, Postgraduate Tutor

Amaya Virós
Caroline Wilkinson
Claus Jørgensen
David Millrine
Dominic Rothwell
Georges Lacaud
Mark Williams

Student Representatives
Anna Pidoux[1]
Florentia Moussoulou
Swara Patel

[1]Joined in 2025

THESES



Bianca Blöchl
Cell Plasticity and Epigenetics

Dissecting the contribution of RAS mutants found in cancer to evolutionary



Liam Clayfield
Stem Cell Biology

Investigating the role of the retinal determination gene network in acute myeloid leukaemia



Maria Koufaki
Cancer Inflammation & Immunity

Characterisation of intratumoural conventional dendritic cells in Cancer



Parsa Pirhady
Translational Oncogenomics

Mismatched: The Lynch Syndrome Puzzle in localised prostate cancer



Alexia Strickson
Leukaemia Biology

Investigation of transcription factor driven changes in mesenchymal stromal cells during myelofibrosis



Sophie Richardson
Nucleic Acid Biomarkers, NBC

Liquid biopsies for the management of Ewing sarcoma cancer



Louis Roussel
Systems Oncology

Transformative dependencies of Kras-mutant alleles in PDAC



Michael Jones
Leukaemia Biology

The role of TLE3 in acute myeloid leukaemia



Seung Hyun Lee (CRF)
Systems Oncology

A digital pathology atlas for pancreatic precancer lesions



Oliver Sinclair
Leukaemia Biology

Bromodomain targeting therapeutics in haematological malignances



Kirsten Tinsley
Cell Signalling

The role of cell-cell interactions in the progression of small cell lung cancer

CANCER RESEARCH UK MANCHESTER INSTITUTE'S RESEARCH ENGAGEMENT

Research engagement forms an integral part of the culture at the Institute, with our early career researchers being the driving force behind the organisation of many activities. In this section, we celebrate their passion and enthusiasm for communicating science and reaching out to engage with local communities.

Engagement activities
Engagement activities start ramping up from World Cancer Day, held every year on 4 February. The aim is to raise worldwide awareness, improve education and catalyse action by working together to save millions of preventable cancer deaths and make access to life-saving cancer treatment and care equitable for all. It is an opportunity for our researchers to highlight the international impact or the important work they do, via social media channels.

Helping to inspire the next generation of cancer researchers is an important part of engaging with young people. National events can facilitate this interaction, and our researchers are always keen to get involved. British Science Week is an annual celebration of science, technology, engineering and maths that supports thousands of activities across the UK.

British Science Week
The Cancer Research UK Manchester Institute team of Research Engagement volunteers – which includes over 80 members - took part once again in British Science Week activities at Manchester Museum, in collaboration with the Museum of Medicine and Health at The University of Manchester. Our enthusiastic volunteers designed a series of three activities focusing on animals in research, with a range of hands-on activities looking at models of cancer:

- demonstrating why we use mice in our research, including an activity of matching images of primary tumour samples to CDX samples (for instance, tumours grown in mice derived from patient samples, especially useful where the original patient material is in limited supply) to demonstrate how similar they are and matching the organs of humans to organs of mice
- showing how we care for the mice we use – bringing cages, feed and enrichment for attendees to handle - and playing an extended video of mice in our animal unit, including tumour-bearing mice
- illustrating our commitment to the 3Rs principles (replacement, reduction, and refinement) by highlighting emerging models for studying cancer, including organoids with multiple cell types, and an in vivo lung cancer series developed from healthy primary human lung cells



Research engagement activities at the Universally Manchester Festival 2025



David proudly displays his bags of lucky dips! Another of his initiatives to raise money for men's cancers.

Universally Manchester Festival
This year the Research Engagement team also took part in the Universally Manchester festival which, since 2017, has been a welcoming and inclusive space for visitors of all ages to enjoy a free, fun, and interactive experience. Every year, thousands from the local neighbourhoods and beyond come together to explore research, engage with arts and cultural institutions, and connect with staff, students, and community partners.

This year the event attracted over 2000 visitors, and our team shared the set of activities that they prepared for British Science Week to a new and different audience. Everyone who visited our stand enjoyed informative conversations with our researchers along with the hands-on activities.

These activities contributed to the Institute receiving the Openness Award from Understanding Animal Research, which was awarded in December 2025.

Engagement support
Throughout the year the team has supported individuals across the Institute and in partner organisations by providing hands-on kits for individual visits to schools and Scouts and Guides groups, including materials for DNA extraction from strawberries, which is always very popular, and microscopes for science activities

We supported the Christie-led art exhibition of paintings by patients and staff, which was hosted in the Oglesby Cancer Research Building, and created digital content from the paintings displayed on art screens in the Paterson Building.

Presentations supporting CRUK teams
Our Research Integrity and Training Adviser, Andrew Porter gave three well-received talks to CRUK non-research teams covering the research of the Manchester Institute and National Biomarker Centre, presenting to the MFE Regional Team meeting, the LFRM Cohort North Division and the A&R Digital team.

Two of our early career researchers – Charles Earnshaw and Victoria Fife – took part in filming for the Cancer Research UK World Cancer Day Future Leaders Film, contributing half a day each to filming in the Paterson Building, with associated preparation time and operational support

Paterson Tours and Activities
This year, the Institute's Operations team have run or supported over 40 visits to the Paterson Building, ranging from individual visits by potential donors to large scale tours for CRUK teams and supporters.

Often these tours include an overview of our research and the building from Stuart Pepper, Caroline Wilkinson and Andrew Porter.

Throughout the year, the team have coordinated press visits, filming and photography for partners, including the Christie press team when they require laboratory access.

Fundraising for Movember 2025
Institute Finance Purchase Officer David Jenkins has been fundraising for men's health for over ten years. The Movember Foundation is the only global charity focused solely on men's health and this Movember David worked exceptionally hard to raise funds to tackle some of the biggest health issues faced by men: prostate cancer, testicular cancer, and poor mental health.

David has been fundraising for the charity since 2009 and this year he managed to raise over £2,067 from his bake sale, reaching a jaw-dropping milestone of £10,000 since he started. The Movember Foundation highlighted David's contributions and named him in the top 3 Workplace Ambassadors.

This is an incredible achievement, and we are proud of David's commitment to the cause and for his imagination in fundraising campaigns. We would also like to thank everyone at the Institute for their generosity.

ACKNOWLEDGEMENT FOR FUNDING OF THE CANCER RESEARCH UK MANCHESTER INSTITUTE

The total funding of the Cancer Research UK Manchester Institute for 2025 was £24.0m. The major source of this funding was awarded by Cancer Research UK via a core grant of £14.7m plus additional strategic funding of £2.9m. This funding enables the various scientific groups and service units within the Institute to carry out their research.

The infrastructure of the CRUK Manchester Institute is partially funded by Research England generated income at a cost of £2.1m.

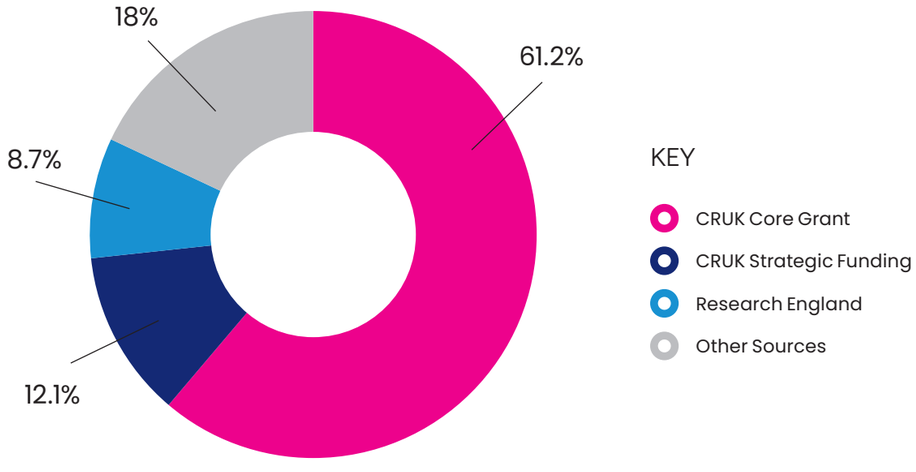
The balance of the Institute's funding is received from a number of additional sources. The research carried out through these additional projects enhances and supports the research undertaken by the core funding.

These sources are as follows:

- BBSRC
- Blood Cancer UK
- CellCentric
- Christie Hospital NHS Foundation Trust
- Dark Blue Therapeutics
- European Commission
- European Research Council
- Imago Bioscience
- Lustgarten Foundation
- Medical Research Council
- Melanoma Research Alliance
- National Institute of Health Research
- NC3Rs
- Ono Pharmaceuticals
- Pancreatic Cancer Research Fund
- Pancreatic Cancer UK
- Prostate Cancer UK
- Rosetrees Trust
- Royal Society
- Sosei Heptares
- UKINETS
- Wellcome

We are immensely grateful to all our sponsors.

CRUK MANCHESTER INSTITUTE FUNDING 2025



CAREER OPPORTUNITIES AT THE CANCER RESEARCH UK MANCHESTER INSTITUTE

The Cancer Research UK Manchester Institute has a strong programme of basic and translational research. There are close links with clinical and translational research groups throughout the Christie Hospital site.

The Institute offers excellent laboratory facilities and outstanding core facilities, including molecular biology services, next generation sequencing, real-time PCR, mass spectrometry, flow cytometry, histology, advanced imaging, and a biological resources unit. Details of all groups and facilities are given in this report and can guide interested parties to the appropriate contacts.

Opportunities exist at a number of levels in the Institute. We have a well-established programme of degrees by research which is described in the section on Postgraduate Education. We encourage applications from suitably qualified graduates to apply to join either the PhD or MD programmes. Graduates with a first or 2.1 honours degree in a biological science can apply each year to train for a four-year PhD in one of our research laboratories. The University of Manchester offers a wide range of training for new and existing students which provides opportunities to acquire skills that will complement the research programme and help achieve personal and career development goals. At the Institute, we also ensure that postgraduate students are provided with high quality, relevant and appropriate training alongside development opportunities. The Institute also has a well-developed process for ensuring excellent pastoral care and mentoring for all students.

Postdoctoral applicants of high calibre are regularly sought. Although Postdoctoral Fellows will be encouraged to apply for their own fellowships, funded positions are available for outstanding candidates. Interested applicants should contact the Group Leaders directly, with details of their research interests and recent experience.

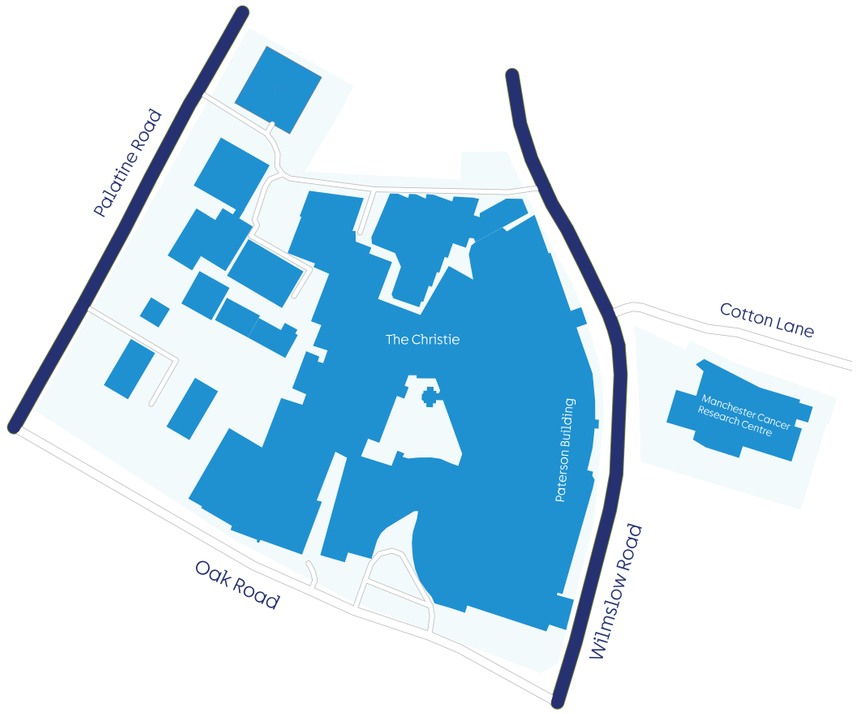
In addition to postgraduate and postdoctoral opportunities, the Institute is seeking to recruit outstanding candidates to the positions of Group Leaders and Senior Group Leaders. The packages provided are extremely attractive and commensurate with the experience of the applicant, with significant funding for personnel, recurrent expenditure and equipment.

Specific vacancies can be found on our web pages:

www.cruk.manchester.ac.uk/careers

But suitably qualified and enthusiastic individuals should contact the Institute at any time to enquire about career possibilities.

CONTACT DETAILS



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