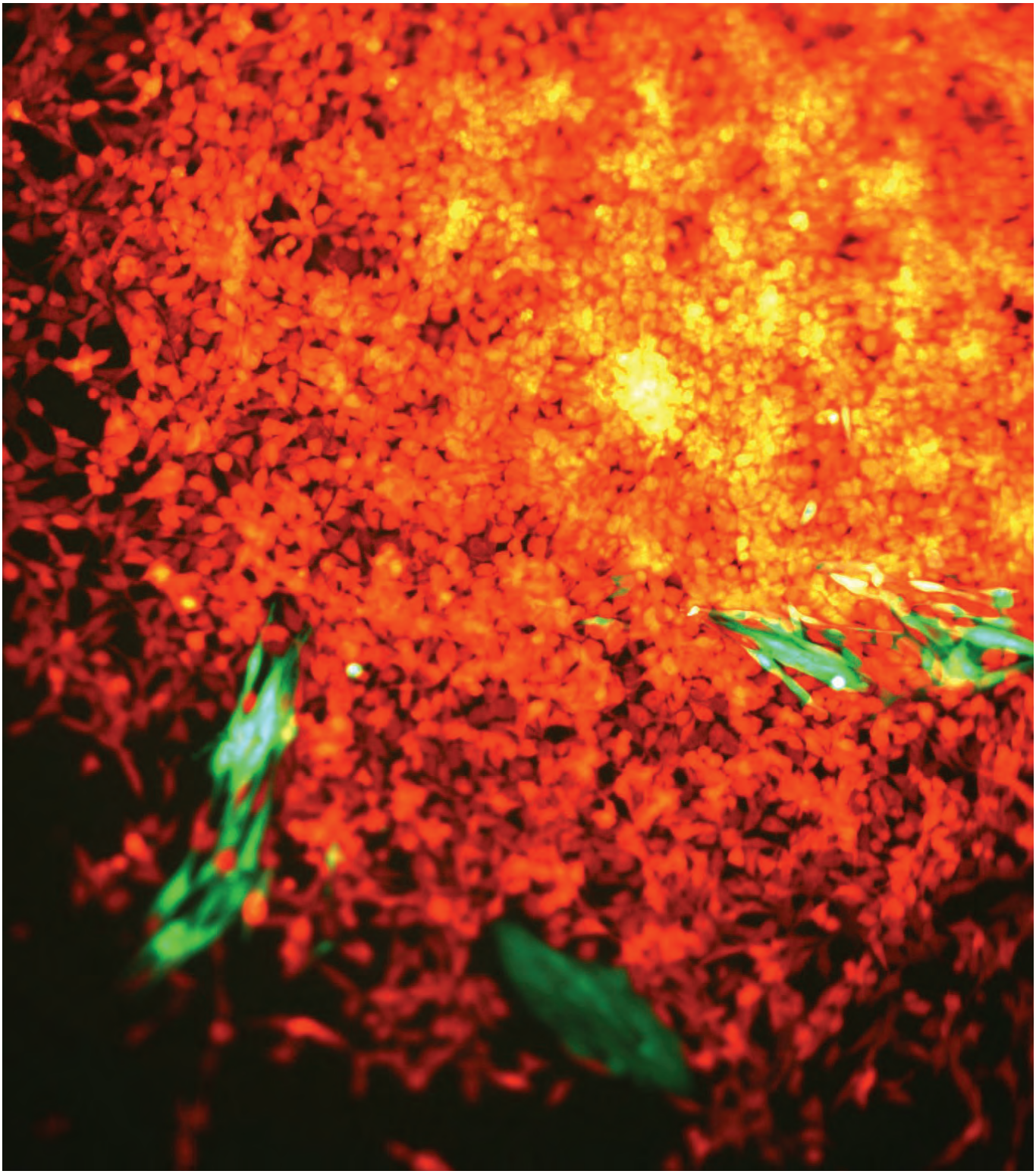
CANCER RESEARCH UK | Manchester Institute

SCIENTIFIC REPORT 2024



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COVER IMAGE

Immunofluorescent image of an A375 mCherry spheroid co-cultured with MeWo GFP.

Image supplied by Vanessa Parietti (Skin Cancer and Ageing)

SCIENTIFIC REPORT 2024

MANCHESTER INSTITUTE

MANCHESTER 1824
The University of Manchester

CANCER RESEARCH UK | Manchester Institute

CONTENTS

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

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

DIRECTOR'S INTRODUCTION

Professor Caroline Dive

Director of the Cancer Research UK Manchester Institute

Welcome to the 2024 scientific report of the Cancer Research UK Manchester Institute. This year saw the Institute fully settled and positioned to maximise the potential of being based on the site of the Christie NHS Foundation Trust with a wealth of opportunities to collaborate and drive transformational cancer research.

We celebrated the formal opening of the Paterson Building in July with colleagues from the Christie and the University of Manchester's Division of Cancer Sciences, with guest of honour Professor Sir Paul Nurse, Nobel Laureate and Director of the Francis Crick Institute, declaring the building officially open. It was a momentous occasion, with guest speakers Andy Burnham Mayor of Greater Manchester, former Christie patient Adele Adams, Dame Nancy Rothwell (the then President and Vice Chancellor of The University of Manchester), Roger Spencer (Chief Executive Officer of the Christie NHS Foundation Trust) and Dr Iain Foulkes (Executive Director Research & Innovation at Cancer Research UK). Everyone had a wonderful time and later in this report we share highlights from the event.

The Institute also had cause to celebrate another important event in the calendar, our annual colloquium. This year, we were finally able to hold the colloquium at a venue outside our workplace again. Having together faced and overcome significant challenges over several years – from the fire at the Institute and resulting relocations, to the pandemic and the following budget cuts, and the emotional impact these events have had on everyone – we were eager to get away together again and reconnect. We relaunched the event as the first joint CRUK Manchester Institute and CRUK National Biomarker Centre Colloquium and held it at the grand Palace Hotel in Buxton. The two-day event included plenary talks – from Jos Jonkers (NKI) and Margaret Frame (University of Edinburgh) – 2nd year talks from our PhD Students, presentations from our research groups and core facilities, and two wonderfully lively poster sessions alongside social events. We further bonded during a group hike up to local beauty spot Grin Low Tower where we enjoyed glorious views of the Peak District. We also welcomed to the colloquium Sylvain Delaunay from the German Cancer Research Center (DKFZ) in Heidelberg, who will be joining us in January 2025 as a new Junior Group Leader. He gave an excellent talk on the epitranscriptome driving tumour cell state transition, showing how palmitic acid is an inducer of motile transition in a breast cancer xenotransplantation model that sparked many questions. We look forward to welcoming Sylvain in the New Year. Overall, I was delighted to see the collective feeling of belonging and togetherness at the colloquium, which was highlighted in the feedback from our external speakers.

Reflecting the success of this year's consolidatory period, external reviews of our operations (by CRUK), in vivo facility (by the Animals in Science Regulation Unit) and core facilities (by an external panel) were very successful, and we received positive feedback. You can read further details about these reviews in the following pages.

Our staff are thriving in our new building, and it has been another productive year. As always, it is my immense pleasure to spotlight their accomplishments here.

External funding augments the breadth of our research and helps support the development of our researchers. First, I would like to congratulate Junior Group Leader Evangelos Giampazolias on receiving a prestigious ERC Starting Grant. This significant award will allow him to pursue how nutrient-host-microbiome interactions define immunity to cancer. This is a fantastic opportunity for Evangelos to expand his flourishing research group, Cancer Immunosurveillance, which he only established last year.

Congratulations to Deputy Director Claus Jørgensen and collaborators who have been awarded an inaugural Interdisciplinary Treatment Grant from Pancreatic Cancer UK. These awards aim to fund bold, pioneering collaborative projects that improve our understanding of how to effectively treat pancreatic cancer with a more integrated and holistic approach. Claus and his team will explore whether tumour cells develop a similar scar tissue in primary and metastatic PDAC and how this influences therapeutic response.

We got everyone together for a photo to celebrate our inaugural joint CRUK Manchester Institute-National Biomarker Centre Colloquium, taken outside the Palace Hotel in Buxton.

I would also like to acknowledge the particularly pleasing success of Senior Group Leader Santiago Zelenay and colleagues from the CRUK National Biomarker Centre, and the Manchester University NHS Trust in attracting a CRUK Biomarker Project Award investigating pro-tumourigenic inflammation as a predictor of relapse post-surgery in early-stage non-small cell lung cancer. This study translates Santiago's fundamental discovery research into a clinic ready biomarker, really maximising the synergy of the Mancunian cancer research ecosystem.

Another significant achievement this year was the launch of a new platform to understand immunotherapy response and side effects in cancer. I am delighted that the National Biomarker Centre and Manchester Institute are part of a national team of academic institutions and major NHS trusts contributing to this important new initiative developing solutions to the current challenges in immunotherapy. Funded by MRC and the Office for Life Sciences, supplemented with matched funding from industry partners, MANIFEST (Multiomic ANalysis of Immunotherapy Features Evidencing Success and Toxicity) aims to build a robust platform of standardised biomarkers that will help predict response, resistance and toxicity to optimise the use of current and future immunotherapies. I also enjoyed a moment of fame sitting on the red sofa in the BBC Breakfast studio talking about the importance of understanding patients' response to immunotherapy and our vision and ambitions for the programme.

We continue to publish an impressive collection of scientific discoveries, some of which are presented in our research highlights section. Among those featured is research published in *Science* by Evangelos Giampazolias based on the serendipitous finding that vitamin D regulates the gut microbiome to promote cancer immunity. I am also pleased to report a first author publication by Clinical Research Fellow Mathew Sheridan, who completed his PhD with Georges Lacaud. Published in the *Journal of Hematology & Oncology*, they identified a new small compound that effectively targets acute myeloid leukaemia with epigenetic regulator KAT6A translocations, which holds therapeutic promise for patients harbouring these mutations.

Mathew also gave an excellent overview of this research for his pre-PhD viva presentation and passed with flying colours. Mat was in good company as we had 12 other PhD students who successfully passed their vivas this year. Further in this report you can read more details about these talented students and their theses.

As an Institute, we know from experience how connected communities are critical for the advancement of science. Taking part in conferences enables researchers to share findings, exchange ideas, and to build networks for collaboration and career development. This is especially important for early career researchers

at the vanguard of cancer research, so I am pleased that many of our students attended the International PhD Student Cancer Conference this year and gave presentations. Next year, our students will be hosting the conference, which they are very excited about! You can find out more about the conference in the Education section in the following pages.

At this year's European Association for Cancer Research (EACR) conference in Rotterdam I was delighted to be the EMBO keynote speaker, where I presented my research on small cell lung cancer metastasis. I was joined by Claus Jørgensen who spoke on the role of the tumour microenvironment in pancreatic cancer. It was also great to see several researchers from the CRUK Manchester Institute and CRUK National Biomarker Centre, including Florent Mouliere, Victoria Fife, Amaya Virós, Louis Roussel and Yitao Chen, who presented their research findings at the conference.

We also had notable successes from our early career researchers who have presented their research at meetings. Lucy Barton, a PhD student in the Translational Oncogenomics group, won Best Poster Award at the Pan Prostate Cancer Group meeting in Copenhagen. Lucy is working on chromosome 8q gains and prostate cancer aggression and she was commended for thinking out of the box for alternative explanations for 8q and aggression behind c-Myc.

PhD student Charlotte Russell was awarded the best presentation prize at this year's UK Cancer Metabolism Network Meeting. Charlotte, who is based in the Skin Cancer and Ageing group, was awarded the prize for her talk on how brain lipids promote melanoma brain metastasis. As her first time presenting at a conference, receiving this award is an outstanding achievement.

Our Biological Resources Unit have also been recognised at meetings. Lisa Doar and Jo Roberts won first prize for their poster on improving animal welfare at the Institute of Animal Technology meeting. They showcased their refinement project setting out how they designed and 3D printed an X-ray jig that enables the preferential use of inhalation anaesthesia for tumour targeted X-ray work, rather than an injectable anaesthetic. This method is much less invasive for the mice with quicker recovery time post procedure, and it is easier to adjust the anaesthetic dose for more sensitive strains of mice. This award is a measure of our BRU's commitment to improving animal welfare alongside their technical expertise and collaborative approach.

Our early career researchers continue to enjoy connecting with members of public in a range of engagement activities with great enthusiasm. Helping to inspire the next generation of cancer researchers is important for securing ongoing scientific research in the UK and I would like to thank all who took part. You can read more about those activities further on in the report.

Lastly, now we are settled in our new home, I am looking forward to seeing the rewards from newfound partnerships and stronger collaborations across the Manchester Cancer Research Centre and beyond that integrates our basic discovery, translational and clinical research towards improved patient outcomes.

Professor Caroline Dive, CBE., FMedSci.
Interim Director, Cancer Research UK Manchester Institute

RESEARCH HIGHLIGHTS

In this section we highlight some research publications from 2024 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.

Ali A, Elumalai T, Venkatesulu B, Hekman L, Mistry H, Sachdeva A, Oliveira P, Clarke N, Baena E, Choudhury A, Bristow RG. (2024)
Tale of two zones: investigating the clinical outcomes and research gaps in peripheral and transition zone prostate cancer through a systematic review and meta-analysis.
BMJ Oncol. 3(1):e000193.

Localised prostate cancer shows great clinical, genetic and environmental heterogeneity; however, prostate cancer treatment is currently guided solely by clinical staging, serum PSA levels and histology. Increasingly, the roles of differential genomics, multifocality and spatial distribution in tumorigenesis are being considered to further personalise treatment. The human prostate is divided into three zones based on its histological features: the peripheral zone (PZ), the transition zone (TZ) and the central zone (CZ). Each zone's tumour may have different biology, prostate cancer incidence, prognosis and outcomes. These potential variations in clinical outcomes lacked a comprehensive understanding of the underlying differences between zonal cancers. Indeed, previous studies had indicated differences in biochemical relapse-free survival (bRFS) and clinical features between PZ and TZ tumours, raising the need for a systematic investigation.

This systematic review and meta-analysis by Amin Ali, former clinical fellow in Rob Bristow's lab, contributes significantly to the understanding of PZ and TZ prostate cancer in the context of patients treated with surgery in the pre-MRI era.

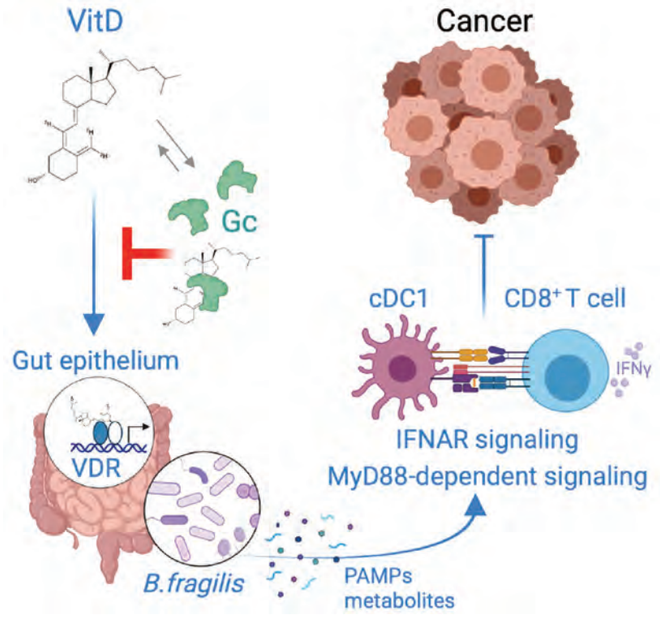
The study demonstrated that patients with TZ tumours exhibit notably better bRFS and subsequent distant metastases-free outcomes than those with PZ tumours. Furthermore, their study revealed that PZ tumours are associated with higher Gleason group and T staging, while TZ tumours are linked to higher prostate specific antigen levels at diagnosis.

These findings provide a comprehensive insight into the distinct characteristics and clinical outcomes associated with PZ and TZ prostate cancer.

Clinically, the findings suggest the potential importance of considering the specific zone of origin when assessing prostate cancer prognosis and planning treatment strategies, especially for patients treated with surgery. Moreover, it highlights the need for further research to delve into the underlying differences and refine clinical practice, potentially leading to more personalised and effective management of prostate cancer.

Giampazolias E, Pereira da Costa M, Lam KC, Lim KHJ, Cardoso A, Piot C, Chakravarty P, Blasche S, Patel S, Biram A, Castro-Dopico T, Buck MD, Rodrigues RR, Poulsen GJ, Palma-Duran SA, Rogers NC, Koufaki MA, Minutti CM, Wang P, Vdovin A, Frederico B, Childs E, Lee S, Simpson B, Iseppon A, Omenetti S, Kelly G, Goldstone R, Nye E, Suárez-Bonnet A, Priestnall SL, MacRae JI, Zelenay S, Patil KR, Litchfield K, Lee JC, Jess T, Goldszmid RS, Reis E Sousa C. (2024)
Vitamin D regulates microbiome-dependent cancer immunity.
Science 384(6694):428-437.

Despite unprecedented clinical success, T cell-based immunotherapies present significant heterogeneity in response rates, often attributed to dampened activation and limited tumour infiltration of $CD8^+$ T cells. Studies in mice and humans have shown that gut commensals can modulate anti-cancer immune responses dictating the efficacy of immunotherapy but have failed to identify species that are consistently associated with improved patient prognosis. These discrepancies convolute our understanding of how microbiome modulates cancer immunity.



Schematic displaying how vitamin D regulates the gut microbiome to promote cancer immunity. Vitamin D acts on the intestinal epithelium, via the Vitamin D receptor (VDR), favouring the gut commensal B. fragilis to confer systemic cancer immunity and improving immunotherapy success. Reused from Giampazolias et al. Science 384,428-437(2024) DOI: 10.1126/science.adh7954.

The Cancer Immunosurveillance group recently made a breakthrough in their efforts to understand the host determinants that define microbiome-dependent cancer immunity. They discovered that a single micronutrient, vitamin D (vitD), enhances the ability of the gut microbiome to induce potent T cell-mediated immunity to cancer, dictating immunotherapy success in preclinical models. VitD alters the microbiota and promotes cancer resistance by acting on the intestinal nuclear receptor VDR.

Although vitD doesn't introduce dramatic changes in the microbiota composition, it favours a small expansion of the gram-negative bacterium *Bacteroides fragilis*. Oral administration of *B.fragilis* promotes cancer resistance specifically in vitD-sufficient mice but not in vitD-deprived hosts, highlighting the importance of vitD in the modulation of the anti-tumour activity of intestinal commensals. Similarly, faecal transplants from vitD^{High} donors enhance T cell-mediated tumour control and response to immunotherapy in wild-type animals with intact microbiome, despite any competition with the existing microbiota. In humans, higher vitD levels correlate with lower cancer risk, enhanced response to immunotherapy and increased patient survival. Currently, they are trying to understand how vitD defines a 'good' microbiome and how the latter promotes immunity to cancer by studying the bidirectional interactions between commensal species and host cells.

The group's latest findings provide an unmatched opportunity to understand how the gut microbiome instructs immunity to cancer and identify microbiome-immune checkpoints that can be targeted to overcome immunotherapy resistance.

Sheridan M, Maqbool MA, Largeot A, Clayfield L, Xu J, Moncaut N, Sellers R, Whittle J, Paggetti J, Iqbal M, Aucagne R, Delva L, Baker SM, Lie-A-Ling M, Kouskoff V, Lacaud G. (2024)
The small inhibitor WM-1119 effectively targets KAT6A-rearranged AML, but not KMT2A-rearranged AML, despite shared KAT6 genetic dependency.
J Hematol Oncol. 17(1):91.

In this study, the Stem Cell Biology group investigated the therapeutic potential of targeting the epigenetic regulator KAT6A in acute myeloid leukaemia (AML), focusing on aggressive subtypes characterised by rearrangements involving KAT6A/MOZ (KAT6Ar) and KMT2A/MLL (KMT2Ar). While MOZ-rearranged AMLs are relatively rare, MLL rearrangements (MLLr) are more common and represent over 70% of infantile leukaemia and up to 10% of adult leukaemia. Infants with MLLr typically face very poor survival outcomes, whereas adults show only slightly better prognoses.

Researchers tested WM-1119, a first-in-class KAT6A inhibitor, across various experimental models, including murine systems and human AML cell lines. The findings demonstrated that WM-1119 effectively inhibited the proliferation and clonogenic potential of KAT6Ar AML cells. This treatment not only completely halted cell growth but also significantly increased myeloid differentiation markers and suppressed leukaemia-associated gene expression. These results suggest that targeting KAT6A's catalytic activity could overcome the differentiation block seen in AML, offering a promising therapeutic strategy for KAT6Ar AML.

In contrast, the effects of KAT6A inhibition on KMT2Ar AML were less pronounced. Genetic and pharmacological experiments showed that while KAT6A's catalytic activity plays a limited role in KMT2Ar leukaemogenesis, complete deletion of the protein – affecting both catalytic and non-catalytic functions – was necessary to disrupt leukaemia growth in KMT2A::MLLT3 (MLL-AF9) models. This suggests that targeting the entire KAT6A protein could be a more effective strategy than inhibiting its enzymatic function alone.

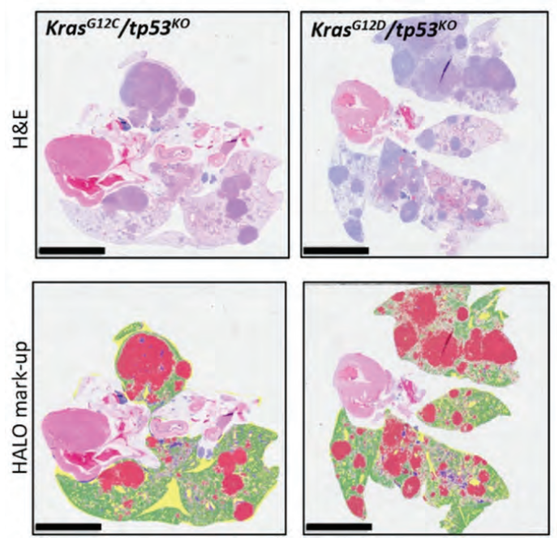
The study highlights WM-1119's therapeutic promise for KAT6Ar AML and proposes that targeted degradation of KAT6A could offer a more effective approach for treating KMT2Ar AML, paving the way for more refined, subtype-specific therapies.

McDaid WJ, Wilson L, Adderley H, Martinez-Lopez A, Baker MJ, Searle J, Ginn L, Budden T, Aldea M, Marinello A, Aredo JV, Viros A, Besse B, Wakelee HA, Blackhall F, Castillo-Lluva S, Lindsay CR, Malliri A. (2024)
The PI3K-AKT-mTOR axis persists as a therapeutic dependency in KRASG12D-driven non-small cell lung cancer.
Mol Cancer. 23(1):253.

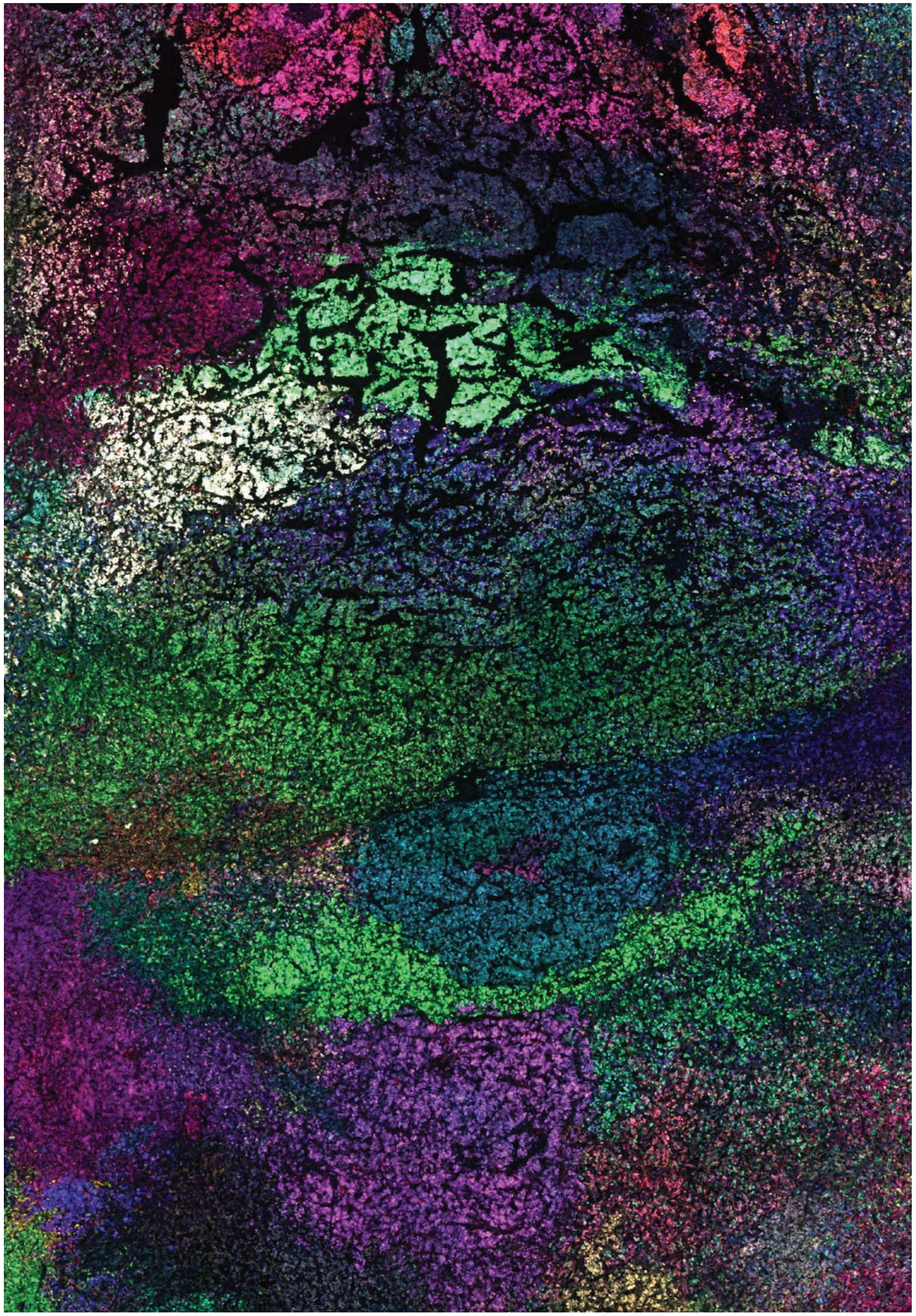
KRAS is a GTPase that functions as a molecular switch, regulating proliferation and survival pathways within cells including the mitogen-activated protein kinase pathway (MAPK) and PI3K-AKT-mTOR pathway. It is also the most commonly mutated oncogenic driver in cancer, resulting in hyperactivation of these pathways to drive tumorigenesis. KRAS was once regarded as undruggable however direct inhibitors of mutant KRAS now exist, targeting variants such as KRAS^{G12C} and KRAS^{G12D}. These inhibitors represent a major translational breakthrough for non-small cell lung cancer (NSCLC) and cancer in general with FDA approval granted to two KRAS^{G12C} inhibitors. However, resistance to these small molecules has highlighted the need for rational combination partners necessitating a critical understanding of signalling downstream of KRAS mutant isoforms.

The former Cell Signalling group (now in the Division of Cancer Sciences, University of Manchester) compared tumour development between *Kras^{G12C}* and *Kras^{G12D}* genetically engineered mouse models (GEMMs). KRAS^{G12D} exhibited higher potency *in vivo*, manifesting as more rapid lung tumour formation and reduced survival of KRAS^{G12D} GEMMs compared to KRAS^{G12C}. To corroborate findings and contrast KRAS mutant variant-specific signalling, isogenic models of *Kras^{G12C}* and *Kras^{G12D}* initiation were generated. This increased potency associated with KRAS^{G12D} was recapitulated in the isogenic initiation model and was associated with enhanced PI3K-AKT-mTOR signalling. They also employed cell line models of established KRAS mutant NSCLC and observed that KRAS^{G12C} oncogenicity and downstream pathway activation were comparable with KRAS^{G12D} at later stages of tumorigenesis *in vitro* and *in vivo*, consistent with similar clinical outcomes in patients. Despite this, through pharmacological inhibition, the group saw that established KRAS^{G12D} NSCLC models depended more on the PI3K-AKT-mTOR pathway, while KRAS^{G12C} models depended on the MAPK pathway. Specifically, KRAS^{G12D} inhibition was enhanced by AKT inhibition *in vitro* and *in vivo* and induced a synergistic tumouricidal effect.

Their data highlight a unique combination treatment vulnerability and suggest that patient selection strategies for combination approaches using direct KRAS inhibitors should be i) contextualised to individual KRAS mutants, and ii) tailored to their downstream signalling.



KRASG12D is more potent than KRASG12C in driving NSCLC initiation in vivo. (Top left) Representative H&E images, (Bottom left) HALO mark-up and (Right) HALO quantification of tumour area and number comparing KrasG12C/tp53KO and KrasG12D/tp53KO mice from survival study (n = 5 mice per genotype); scale bar = 5 mm. Mean ± s.e.m and statistical analysis carried out using unpaired Student's t-test. ****P < 0.0001, ***P < 0.001, **P < 0.01, ns > 0.05. Reused from McDaid et al. Mol Cancer. 2024 Nov 12;23(1):253. doi: 10.1186/s12943-024-02157-x.



RESEARCH GROUPS

CDX cells can be transduced with LeGO vectors to express red, green and blue fluorescence which generates multi-coloured fluorescent cells that enable tracking of different populations through tumour evolution in vivo. The different colours represent a different clonal population of CDX cells growing in the tumour.

Image supplied by Griselda Awanis (Small Cell Lung Cancer Biology)

www.cruk.manchester.ac.uk/research-group/cancer-immunosurveillance

CANCER IMMUNOSURVEILLANCE

Group Leader
Evangelos Giampazolias

Postdoctoral Fellows
Alexander Vdovin
Thomas Elliot[1,2]

Senior Scientific Officer
Pengbo Wang

Graduate Students
Swara Patel
Emma West[1]

[1]Joined in 2024
[2]Left in 2024

The immune system serves as the body's innate defence against pernicious threats. While traditionally studied in the context of infectious diseases, it is now well-established that the immune system can also prevent cancer formation by identifying and eliminating malignant cells. T cells, a component of adaptive immunity, often play a leading role in anti-cancer immunity. Immune checkpoint blockade (ICB) therapy, which reinvigorates T cell immunity against cancer cells, stands as a pinnacle of success in treating patients with advanced cancers. Despite remarkable success in clinical care, only a fraction of patients undergoing ICB therapy achieve lasting responses. Resistance to this therapy often stems from a lack of pre-existing anti-tumour T cell responses. What initiates T cell immunity against cancer? When does it fail to initiate? Can we predict and restore T cell-mediated cancer immunity? Unravelling the origins of T cell-mediated cancer immunity is crucial to overcoming immunotherapy resistance.

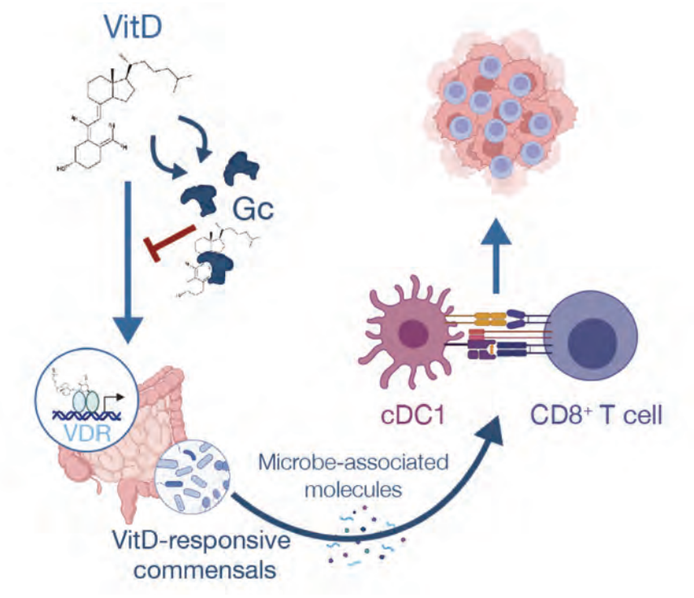
Our previous work has resulted in significant progress in our understanding of the determinants of T cell-mediated immunity and how these can be targeted to overcome immunotherapy resistance. We have shown that detection of dying tumour cells by antigen-presenting dendritic cells can elicit T cell-mediated cancer immunity and we uncovered the mechanisms that couple recognition of dead-cell-associated signals to $CD8^+$ T cell responses. Furthermore, we identified host molecules that act as natural barriers to cell death sensing, inhibiting anti-cancer immunity. Genetic deletion of these molecules partially restored anti-tumour T cell responses and significantly enhanced the efficacy of ICB therapy in pre-clinical models (Giampazolias *et al. Nature Cell Biology*, 2017; Giampazolias *et al. Cell Cycle*, 2018; Giampazolias *et al. Cell*, 2021, Lim KHJ *et al. JITC*, 2022). Our latest work identifies a role for environmental factors in the regulation of anti-cancer immunity with a focus on diet and host-microbiome interactions.

Host-microbiome interactions in cancer immunity

Studies in mice and humans have shown that gut commensals can modulate anti-cancer immune responses dictating the efficacy of ICB therapy. This suggests that detection of dying cancer cells by the immune system is necessary but not sufficient to elicit cancer immunity and that immunologically permissive environments dictated by the gut microbiome are also required. Probiotics and faecal transplantation from ICB-responders are now tested in phase 1 clinical trials in efforts to overcome immunotherapy resistance in non-responders. However, the therapeutic benefit of these attempts is uncertain. Revealing the mechanisms by which the microbiota causally promotes immunity to cancer is therefore of paramount importance in the field of cancer immunology. A confounding factor in these trials has been a general lack of consensus across studies with regards to the specific commensal species identified as conferring protective immunity to cancer. This is suggestive both of functional diversity within microbial strains across different hosts but also of redundancy across different strains that might acquire a common function if exposed to a particular environment. We showed for the first time that the ability of microbiota to instruct immune responses to cancer depends on the host availability of a single micronutrient, vitamin D (vitD), and is not an inherited property of the commensal species' origin (Giampazolias* *et al. Science*, 2024 *co-corresponding author).

The tissue availability of vitD is controlled in part by vitamin D binding protein, formally known as

Figure 1. Vitamin D regulates microbiome-dependent cancer immunity. Summary of research findings.



"group-specific component" (Gc) protein. In plasma, Gc binds to approximately 90% of vitD metabolites leaving 10% free to become bioavailable in tissues and exert their biological activity. We found that mice with increased vitD availability ($vitD^{High}$), either by genetic ablation of Gc or by feeding with high vitD diet, display increased resistance to transplantable tumours. The tumour control in $vitD^{High}$ mice is attributable to changes in the gut microbiome that trigger T cell-mediated cancer immunity. Importantly, this tumour resistance can be transferred in a dominant fashion to wild-type (WT) animals with intact microbiome [specific pathogen-free (SPF)] by coprophagy or faecal transplantation (FT) despite any competition with the existing microbiota communities across multiple animal units. FT from $vitD^{High}$ mice increased T cell-mediated tumour control and augmented the effectiveness of ICB therapy, leading to enhanced incidence of tumour rejection. We further showed that host sensing of vitD through intestinal epithelial vitamin D receptor (VDR) dictates the composition and behaviour of the gut microbiome. Combined meta-analysis revealed a slight increase in the abundance of *Bacteroides fragilis* in the $vitD^{High}$ group. We found that similarly to $vitD^{High}$ FT, oral administration of *B. fragilis* promoted tumour resistance only to mice supplemented with vitD but not to vitD-deprived hosts. In humans, higher vitD levels correlate with lower cancer risk, enhanced response to immunotherapy and increased patient survival. Overall, our findings highlight the availability of the micronutrient vitD as a host determinant that dictates the ability of the gut microbiome to establish T cell-mediated cancer immunity (Figure 1) (Giampazolias* *et al. Science,* 2024 *co-corresponding author).

In the Cancer Immunosurveillance group, we combine genetically modified mouse models, transplantable microbiome and diets to disentangle complex nutrient-host-microbiome interactions that define immunity to cancer. Our recent discoveries have uncovered a unique opportunity to exploit the complex relationship between diet, gut microbiota, immunity and cancer. We study this axis in a multifactorial manner by dissecting the mechanisms by which nutrients transform the gut microbiome, to then assess how these changes are sensed by the host to shape immunity to cancer and determine their impact on cancer onset and progression. Our ultimate vision being to identify microbiome-immune checkpoints that can be predictive of immunotherapy response and targeted to overcome immunotherapy resistance.

Publications listed on page 50

www.cruk.manchester.ac.uk/research-group/cancer-inflammation-and-immunity

CANCER INFLAMMATION AND IMMUNITY

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Clinical Fellow
Kimberley Hockenhull

Academic Clinical Lecturer
Charles Earnshaw[1,3]

[1]Left in 2024
[2]Joined in 2024
[3]Honorary position

Cancer-promoting inflammation is a well-recognised hallmark of cancer associated with malignant tumour growth, poor clinical outcomes, and resistance to therapy. The remarkable success of immune checkpoint blockade treatments across various cancer types has uncovered a distinct type of intratumoural inflammatory profile that exhibits strong cancer-suppressive properties. Unlike the more common types of inflammation found in established cancers, this cancer-restraining inflammatory response is characterised by increased infiltration of specific immune cells, notably cytotoxic T lymphocytes and conventional dendritic cells. With the overarching aim of enhancing natural immunity against cancer and improving the response to immunotherapy, our group at the Cancer Research UK Manchester Institute investigates the signals and pathways that drive or restrain the development of pro- or anti-tumourigenic microenvironments.

We integrate pre-clinical cancer models with the analysis of patient-derived samples to identify the cellular and molecular factors that contribute to successful immunotherapy outcomes. In doing so, we have uncovered pharmacologically targetable inflammatory signalling pathways associated with immune evasive tumour microenvironments and worse patient outcomes across various malignancies. In close collaboration with the Cancer Research UK National Biomarker Centre, we are assessing the value of monitoring these pathways in patient samples as potential prognostic and predictive biomarkers of treatment response. Together with oncologists from the Christie NHS Foundation Trust, we are also conducting clinical trials to evaluate the benefit of targeting pro-tumourigenic inflammation to boost responses to standard-of-care immunotherapy.

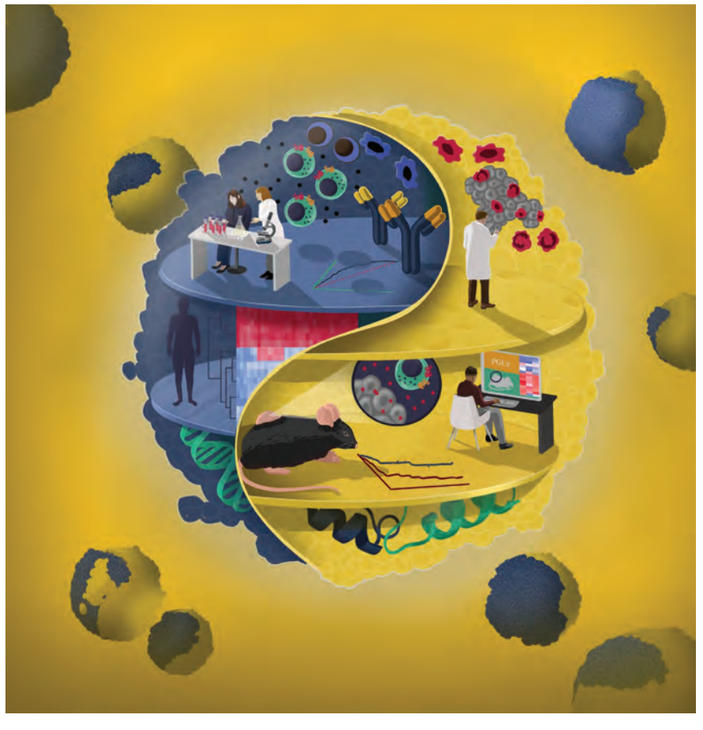
Our research has focused on how different types of inflammation found locally at tumour sites influence the effectiveness of immune responses and cancer therapies. While much attention has been given to T cell-driven inflammation, key to the effectiveness of immune checkpoint blockade (ICB), our work highlighted that inflammation is not a binary 'hot' or 'cold' phenomenon. Instead, tumours exhibit diverse inflammatory profiles, most of which potently fuel malignant tumour behaviour by limiting the anti-tumour immune responses.

Within this conceptual framework, a central focus of our research programme is cyclooxygenase-2 (COX-2)/prostaglandin E2 (PGE2) signalling, a key regulator of the inflammatory landscape within tumours. Using genetically engineered models, we have explored the direct cellular targets of PGE2 activity revealing major, non-redundant effects of PGE2 in multiple immune cell types from both the adaptive and innate immune system, reinforcing its central role in orchestrating immunosuppressive networks in cancer.

Parallel to these efforts, our recent studies have expanded into understanding how this pathway contributes to metastatic dissemination. Our findings suggest that the COX-2/PGE2 axis plays a distinct and context-dependent role in promoting metastasis, with mechanisms that diverge qualitatively from those observed in primary tumours. This line of work deepens our understanding of the immunological challenges in treating advanced-stage disease and highlights the potential of targeting inflammatory pathways across different stages of the cancer continuum.

We have also dedicated significant effort to pharmacologically reprogramming the local inflammatory milieu to enhance the efficacy of immunotherapy. A cornerstone of this work has been the development and use of a novel orthotopic tumour model that, despite robust infiltration by cytotoxic T lymphocytes, remains strikingly resistant to ICB. This finding is particularly noteworthy because the same therapeutic regimen results in complete tumour regression in related models. Intriguingly, comparative analyses of these models show no obvious differences in the abundance or spatial distribution of intratumoural T cells, highlighting how factors beyond T cell presence and location dictate therapeutic outcomes.

Figure 1: Inflammation can fuel or limit cancer growth and the response to therapy. Our group have revealed an intimate link between the COX-2/PGE2 pathway, NK cells and cytotoxic immunity that defines the intratumoral inflammatory composition and anticipates tumour fate. This illustration depicts the complex Yin and Yang interaction between pro- (yellow) and anti-tumorigenic (blue) inflammatory responses within a tumour. By in-depth profiling of murine cancer models and bioinformatics analysis of cancer patient datasets, we devised a gene-expression signature that predicts overall patient survival and response to immunotherapy across multiple cancer types (in the background) with varying degrees of opposing inflammatory milieus. *Illustration by Sam Falconer.*



Using this ICB-refractory model, we conducted a screen of repurposed, clinically approved drugs with known immunomodulatory or anti-inflammatory effects. Unexpectedly, we identified a tumour-suppressive role for glucocorticoids, which are commonly prescribed to cancer patients, including to manage immune-related adverse events from immunotherapy. Although previous work from our group demonstrates that glucocorticoids can enhance ICB responsiveness under certain conditions (Pelly & Moeini et al., 2021), our new data show they can also promote rapid tumour control in ICB-resistant models. We are actively studying the mechanism underlying this tumour-restraining effect of glucocorticoids, which so far is seemingly independent of their inhibitory effect on COX-2 expression and activity.

In our efforts to map the cellular orchestrators of tumour-suppressive microenvironments, we have generated new genetically engineered mouse models that allow the selective identification and functional manipulation of distinct conventional dendritic cell subsets. These models were developed using an intersectional genetic strategy informed by high-resolution single-cell RNA sequencing of tumour-infiltrating leukocytes, allowing us to trace and perturb key immune populations with precision.

The translational impact of our preclinical research has been greatly strengthened through parallel studies in patient samples and clinical datasets. We have made significant progress in validating a COX-2-associated inflammatory gene signature as a potential biomarker of overall survival and immunotherapy responsiveness. In collaboration with the CRUK National Biomarker Centre, and supported by a CRUK Biomarker Award, we have developed a clinically compatible assay to determine the inflammatory molecular profiles within tumour specimens. This assay is now undergoing validation under Good Clinical Practice (GCP) standards, with the aim of qualifying it for use in prospective clinical trials to guide personalised treatment selection. We also anticipate this assay could inform adjuvant treatment de-escalation strategies following surgical resection in patients treated with curative intent.

Building on this translational foundation, we are also working closely with the Translational Immunology Team at the CRUK National Biomarker Centre to establish a Patient-Derived Tumour Fragment (PDTF) platform, inspired by the pioneering work of our collaborators at the Netherlands Cancer Institute (Voabil et al., *Nature Medicine*, 2021; Roelofsen et al., *STAR Protocols*, 2023). PDTFs are generated and processed from freshly resected tumours in a manner that preserves the original tumour architecture and local microenvironment. Notably, the *ex vivo* immune response measured in these PDTFs following PD-1 blockade *ex vivo* is highly concordant with the clinical response of the donor patient to ICB. Our goal is to develop this platform into a powerful *ex vivo* avatar system for testing rational therapeutic combinations and forecasting clinical efficacy on a per-patient basis.

A key milestone this year has been the launch of the LION (Lifting Immune Checkpoints with NSAIDs) trial, a multicentre basket trial targeting patients with advanced-stage cancers including triple-negative breast cancer, non-small cell lung cancer, and renal cell carcinoma. The trial builds directly on our preclinical findings and tests the hypothesis that inhibiting the COX-2/PGE2 pathway, using a drug commonly prescribed for inflammatory conditions like rheumatoid arthritis, can improve responses to standard-of-care immunotherapy. LION represents a significant step toward translating our mechanistic insights into clinically actionable strategies that can be tested across multiple cancer types.

Publications listed on page 50

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CELL DIVISION

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[1]Left in 2024
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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, 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.

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 reliant upon these checkpoints than their normal neighbours, to make 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. We want to guide and refine the use of PKMYT1 inhibitors in the clinic by finding more about the basic biology of the molecule. We want to know how, when, and why PKMYT1 is used to regulate mitotic commitment.

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^{Cdc13} 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 Cdc14^{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. Thus, 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 Cdc14^{Flp1} engagement in these networks and the function of similar centrosomal scaffolds in human cells.

Alexandra (Ola) Hendry successfully defended her PhD thesis in June and we wish her all the best in the next phase of her career.

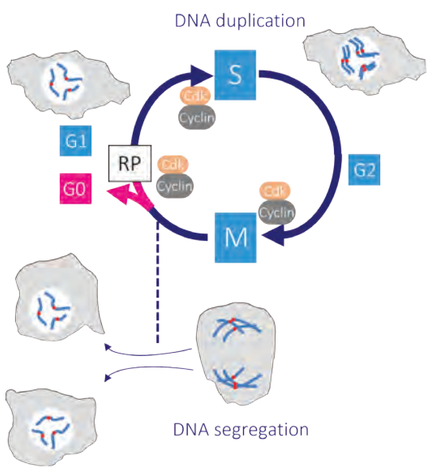


Figure 1: The human cell cycle with Cdk1-Cyclin B control of the G2/M transition. Passage through the restriction point (RP) in G1 phase commits a cell to passage through the cell division cycle. DNA replication in S phase is separated from mitosis by a gap phase, G2. Transition through the major rate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

Figure 2: PKMYT1 in 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.

Figure 3: Studying the PKMYT1 role within mitosis using metaphase synchronisation. hTERT RPE-1 cells were arrested at 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.

Figure 2

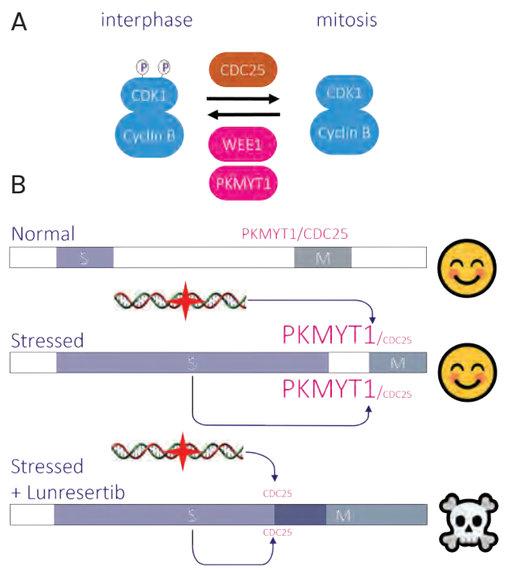
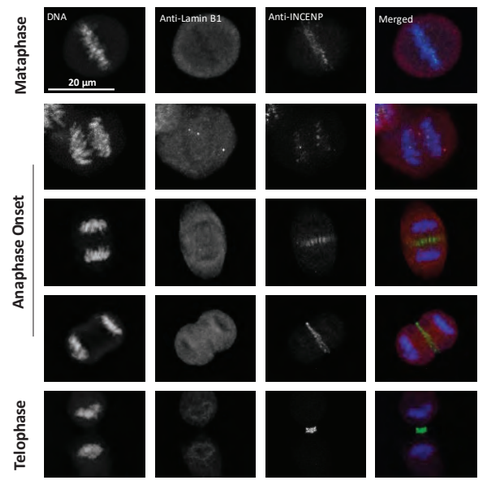


Figure 3



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[1]Left in 2024
[2]Based in Melbourne in 2024 as part of international exchange programme

In 2024, our laboratory's focus on translating mechanistic insight into candidate therapies for patients with blood cancer continued to deliver impact. Two key epigenetic regulators that have been central to our work over the past decade – the histone demethylase LSD1 and histone acetyltransferases EP300/CBP – are now the focus of active clinical development.

We previously identified LSD1 as a regulator of myeloid differentiation through its interaction with SNAG domain transcription factors GFI1 and GFI1B, and more recently reported that pharmacological inhibition of EP300/CBP bromodomains induces cell cycle arrest and differentiation across a range of preclinical models of haematological malignancy. These foundational findings underpin the current clinical evaluation of iadademstat and bomedemstat (targeting LSD1) and inobrodib (targeting EP300/CBP) in early and late phase trials internationally. Our continued engagement in both mechanistic and translational science exemplifies the bench-to-bedside ethos of our group.

Targeting blood cancer with LSD1 inhibitors – from mouse model to phase 3 clinical trial

Lysine-specific demethylase 1 (LSD1) has been a key focus of our laboratory's mechanistic and translational efforts for over a decade. Our discovery in 2012 that LSD1 regulates the differentiation block and sustains the oncogenicity of MLL-translocated leukaemia stem cells laid the foundation for subsequent preclinical and clinical development of LSD1 inhibitors. Beyond its role as a histone demethylase, we showed that LSD1 acts as a critical scaffold for SNAG domain transcriptional repressors such as GFI1 and GFI1B, and that pharmacological inhibitors can disrupt both enzymatic and scaffolding functions. In particular, dissociation of the LSD1:GFI1 complex is required for induction of leukaemia cell differentiation. These insights informed the design of early clinical trials of LSD1 inhibitors in myeloid malignancies.

Building on our preclinical findings, we collaborated with Oryzon Genomics to develop the first-in-class LSD1 inhibitor iadademstat. In a phase 1 trial in relapsed/refractory AML, iadademstat monotherapy was well tolerated and induced molecular and morphological differentiation responses, particularly in patients with MLL translocations. In the subsequent phase 2 ALICE study (published in 2024; Salomero et al., *Lancet Haematology*), we assessed iadademstat in combination with the hypomethylating agent azacitidine in newly diagnosed AML patients unfit for intensive chemotherapy and observed objective responses in 82% of evaluable patients, with manageable toxicity. These results support further clinical development of the combination, and iadademstat is also under evaluation in combination with gilteritinib in FLT3-mutant relapsed AML.

Parallel efforts have included collaboration with Imago Biosciences on bomedemstat, another tranylcypromine-derivative LSD1 inhibitor. Bomedemstat has shown activity in AML and in chronic myeloid disorders such as myelofibrosis and essential thrombocythaemia (ET). In myelofibrosis, it induces spleen and symptom responses in patients intolerant or refractory to JAK2 inhibitors. In ET, it promotes platelet count normalisation in patients unsuitable for hydroxycarbamide. Our contributions have played a significant role in shaping the global development landscape for LSD1 inhibitors, including Merck's 2022 acquisition of Imago Biosciences and bomedemstat. LSD1 inhibitors are now in clinical trials for diverse indications including sarcoma, small cell lung cancer, prostate cancer and other solid tumours, alone or in combination with standard-of-care agents including immunotherapies.

Bromodomain targeting of EP300/CBP for therapeutic benefit

A major recent focus of our group has been the preclinical and clinical evaluation of CCS1477 (inobrodib), a potent and selective first-in-class inhibitor of the bromodomains of the histone acetyltransferases EP300 and CBP. These paralogous transcriptional coactivators play critical roles in the regulation of gene expression through their acetyltransferase activity and extensive protein–protein interaction networks. They occupy key enhancer elements and acetylate diverse targets including histones, transcription factors and chromatin-remodelling complexes. Their biological importance is underscored by their role in promoting cellular growth and cell cycle progression, as well as by their involvement in recurrent chromosomal translocations in AML (e.g. MLL-EP300, MOZ-CBP) and frequent inactivating mutations in lymphoid malignancies. These mutations often enhance dependency on residual EP300/CBP activity, rendering cells particularly sensitive to bromodomain inhibition.

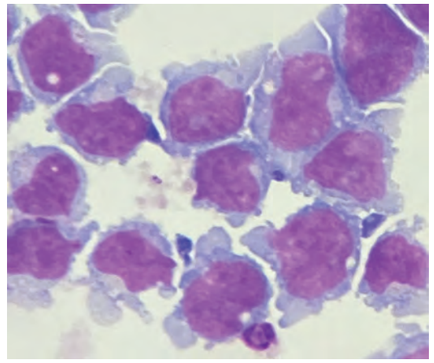

Figure 1. Leukaemia blast cells from a patient presenting with acute myeloid leukaemia.

In collaboration with CellCentric, we reported in 2023 the mechanistic and therapeutic effects of inobrodib in haematological malignancies. In AML (Figure 1) and multiple myeloma models, CCS1477 induces cell cycle arrest and differentiation through eviction of EP300/CBP from oncogenic enhancer networks and redistribution to transcriptional programmes promoting maturation. These observations served as the foundation for early-phase clinical studies of inobrodib in relapsed/refractory haematological cancers. In monotherapy trials, responses included AML differentiation and durable clinical responses in multiple myeloma and T-cell lymphoma.

Our clinical trial evaluation has continued and expanded following the early success. In relapsed/refractory multiple myeloma we have evaluated inobrodib in combination with pomalidomide and dexamethasone, and presented the results as an oral abstract at the American Society for Hematology (Searle et al., 2024; Blood). These patients had a median of six prior lines of therapy; 81% were triple-class refractory and 65% were pomalidomide-refractory. The triplet regimen, given on a 28-day cycle, was well tolerated. No additive toxicity was observed, and the discontinuation rate was low. Objective responses were seen across dose levels, with the highest dose cohort achieving a 75% overall response rate. Responses often emerged early and deepened over time. Notably, responses were seen even in pomalidomide-refractory patients, including those for whom pom-containing regimens had failed most recently, providing clinical validation of prior preclinical synergy data. Among pom-naïve patients, complete remissions and MRD negativity were also observed. Based on these and other findings, inobrodib has been granted Fast Track and Orphan Drug designations by the US FDA, and CellCentric has received strategic investment from Pfizer to support its continued development.

Although results to date are encouraging, we remain focused on understanding the molecular basis of both sensitivity and resistance to EP300/CBP bromodomain inhibition. Our ongoing work seeks to identify biomarkers of response, optimise rational drug combinations and address the mechanisms underlying primary and acquired resistance, to inform future trial design and precision targeting of this novel therapeutic strategy.

Collaborative research

Scientific collaboration remains central to our group's mission. Over the past 12 months, our laboratory has actively supported multiple studies, contributing specialist expertise in chromatin profiling, transcriptional analysis and disease modelling. In a study of triple-negative breast cancer (TNBC; Ramachandran et al., 2024; *iScience*), we collaborated to dissect the mechanistic role of the Forkhead transcription factor FOXC1, which is aberrantly expressed in a subset of TNBC and associated with aggressive disease. Despite variability in FOXC1 function across TNBC cell lines, we helped define a core set of FOXC1-regulated enhancers and revealed that FOXC1 cooperates with the druggable nuclear receptor NR2F2. These findings shed light on transcriptional circuitry relevant to both ER-negative and ER-positive breast cancers.

We also contributed to two studies exploring the mechanistic aspects of a rare leukaemia called chronic myelomonocytic leukaemia (CMML). Profiling of the epigenetic landscape of sorted monocyte populations from patients with CMML revealed extensive enhancer reprogramming, suppression of NF-κB targets and a shift toward an M2-like macrophage state, with potential implications for immune evasion and therapeutic targeting (Addinsell et al., 2025; *Leukemia*). In a comprehensive analysis of blast phase CMML, a chemo-refractory disease for which effective treatments remain elusive, we integrated transcriptomic, clinical and immunophenotypic data to identify five molecular subtypes that predict drug sensitivity (Gurashi et al., 2025; *Cell Reports Medicine*).

Publications listed on page 50

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LEUKAEMIA IMMUNOLOGY & TRANSPLANTATION

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Project Manager
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[1]Joined in 2024

For most patients with acute myeloid leukaemia (AML) allogeneic haematopoietic stem cell transplantation represents the only prospect of cure. The therapeutic effect of transplant depends on the ability of donor T cells to eliminate residual disease, but despite >50 years of clinical experience, we still don't understand why some patients relapse and others do not. 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

The cardinal pathologic feature of AML is a block to differentiation that prevents immature leukaemic blasts from forming mature blood cells. New treatments for AML often target this block, leading to monocyte/macrophage differentiation. Many of the resulting cells 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 (Figure 1). The advantage of this approach is the potential 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 unacceptable toxicity.

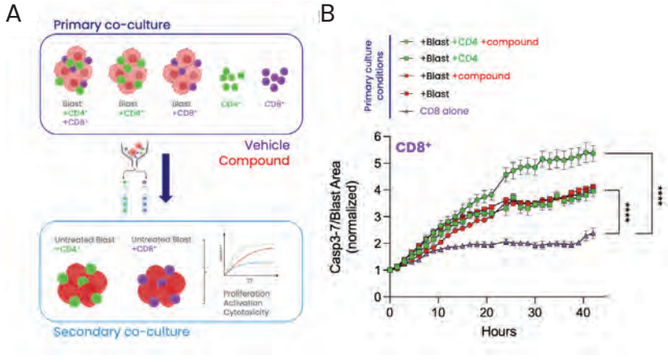

Figure 1: (A) Schematic depicting the experimental design. Leukaemia cells (blasts) were treated with compound or vehicle and cultured with CD4+ and/or CD8+ T cells, which were then removed and plated in a secondary co-culture where their ability to kill undifferentiated leukaemia cells was measured. (B) The results of the secondary co-culture cytotoxicity assay where killing was quantified using a fluorogenic caspase substrate to detect apoptosis.

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. After quality control, the AML bone marrow samples yielded >4M T cells for analysis, enabling identification of rare AML-associated populations constituting <0.1% of total T cells. Whilst analysis of this dataset is ongoing, several findings have proven robust and reproducible across different analytic approaches:

- There are numerous phenotypically distinct T-cell populations that are either highly leukaemia-associated or unique to AML (not found in normal bone marrow)

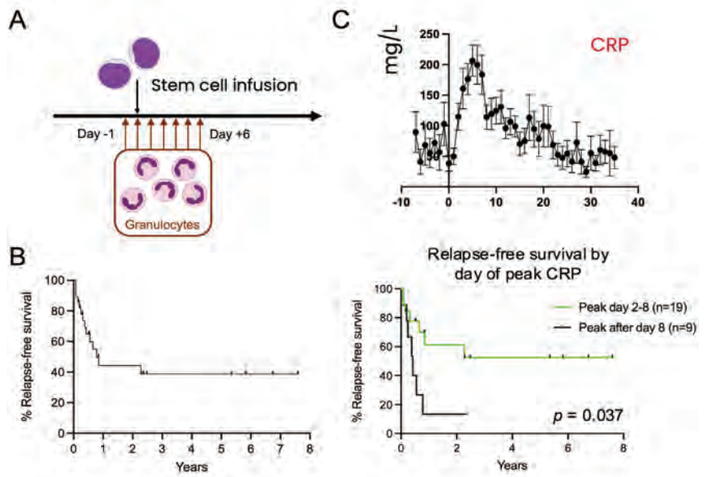

Figure 2: (A) Schematic depicting peri-transplant administration of third-party granulocytes. (B) Relapse-free survival for 28 children, many referred from palliative care pathways, who received granulocyte-augmented cord blood transplants. 24 achieved molecular remission and 14 remain alive and disease free after a median follow-up of 19 months. (C) The majority of patients experienced a putative cytokine release syndrome (CRS), with high fever and elevated inflammatory markers (CRP) in the days following stem cell infusion. This was accompanied by a transient, early lymphocyte expansion and was closely correlated with disease response. 3 children who did not experience CRS did not remit, whilst an early CRP rise, CRP peak >200 and lymphocyte peak >1.0 appeared to be associated with relapse-free survival.

- Most of these populations exhibit evidence of activation, exhaustion or senescence, suggesting anti-leukaemic T-cell responses in most patients
- Not every population is present in every patient, instead they occur in patterns suggestive of different types of immune response, with either prominent activation, exhaustion or senescence. Few samples contained no AML-associated T-cell populations.

This year we welcomed Jia Jhing Sia to the group. Her PhD will focus on the isolation and functional characterisation of these leukaemia-associated populations. This will involve isolation of rare populations using fresh patient bone marrow, the application of T-cell receptor sequencing to determine clonality, co-culture with autologous leukaemia to establish reactivity and cytotoxic potential, and the use of tissue sections to study spatial localisation and physical association with leukaemia. The aim is to determine whether antigen-driven T-cell responses are common in AML. Results will inform future studies to identify drivers of T-cell dysfunction and therapeutic strategies to promote anti-leukaemic immune responses.

Predicting transplant complications

Our laboratory is also interested in developing biomarkers that predict the onset of graft-versus-host disease (GvHD), a devastating transplant complication and common cause of death for recipients. To this end, we have a clinical study called Precision Medicine for Stem Cell Transplantation that is collecting peripheral blood samples at 8 timepoints from transplant recipients. The study opened in June 2023 and has now recruited 160 patients. Healson Ihuoma, a clinical haematology trainee, has been awarded a CRUK-MCRC Clinical Research Training Fellowship and will be joining the group later next year.

Several tissue leakage proteins can be found in plasma following transplantation, reflecting sub-clinical organ damage that may occur weeks before the onset of clinically apparent GvHD. Healson will be applying mass spectrometry- and affinity-based proteomic methods to longitudinal blood samples to discover novel biomarkers that predict GvHD onset. He will also be exploring the utility of cell free DNA methylation to detect sub-clinical inflammation and identify the tissue of origin. Our ultimate ambition is to combine our studies of relapse and GvHD, developing multi-modal signatures and algorithms capable of predicting multiple transplant outcomes.

Granulocyte-augmented cord blood transplantation

We have been working closely with Professor Rob Wynn from the Royal Manchester Children's Hospital, who has developed a highly innovative treatment that involves administering peri-transplant granulocyte infusions to cord blood transplant recipients (Figure 2A). This produced excellent results in children with relapsed/refractory leukaemia, inducing durable remissions in patients referred from palliative care pathways (Figure 2B). Together with collaborators from King's College Hospital, we have secured a ~£1m Transformational Research Award from Blood Cancer UK to deliver a multi-centre clinical trial that aims to demonstrate the safety and effectiveness of this approach in a larger cohort of young adults with very poor-risk AML. If successful, this would transform the management of these patients, offering a realistic chance of cure.

Professor Wynn has administered peri-transplant granulocytes to 28 children and observed that the majority experience a putative cytokine release syndrome (CRS), with high fever and CRP in the days following stem cell infusion. CRS was accompanied by a transient, early lymphocyte expansion and was closely correlated with disease response. Three children who did not experience CRS did not remit, whilst an early CRP rise, CRP peak >200 and lymphocyte peak >1.0 appeared to be associated with relapse-free survival (Figure 2C). A key aim of our study is to determine the safety and tolerability of this approach in adult patients whilst ensuring that we reliably induce CRS, which appears to be a critical component of the therapeutic mechanism. Granulocytes are a complex product, and their effect was an incidental discovery. There is huge potential to further improve the approach by understanding how it works and refining what already promises to be a transformational therapy. We have therefore devised a programme of translational research to accompany the trial that is aimed at elucidating the mechanism of action.

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SKIN CANCER AND AGEING

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[1]Joined in 2024
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The Skin Cancer and Ageing lab focuses on understanding how ageing influences melanoma metastasis to solid organs and therapy response. Melanoma and most cancer metastases are more prevalent in older populations, prompting our lab to investigate age-specific host factors.

Ageing and cancer share several hallmarks, such as genomic instability, genetic damage, epigenetic changes, chronic inflammation, and multiple alterations in critical signalling pathways. This overlap reflects common underlying mechanisms. Ageing also significantly impacts the immune and metabolic systems, affecting cancer incidence and progression.

In older patients, skin cancer presents unique clinical, pathological, and epidemiological hallmarks, including a higher likelihood of head and neck melanomas, solid organ metastases and increased mortality compared to younger patients at similar disease stages. Some studies suggest that aged patients respond better to immunotherapy with checkpoint inhibitors. Our lab aims to uncover why melanoma is more metastatic in aged patients, why it targets visceral organs, and how therapy responses differ between young and aged patients. We are particularly interested in age-related factors that instruct melanoma cells to colonise specific organs, noting that liver metastases are more common in older patients, while brain metastases are more frequent in younger patients.

Melanoma and the tumour microenvironment

The incidence and mortality rates in melanoma continue to rise, as does the proportion of the population who is over 60 years old in the UK. Older patients with melanoma are also at higher risk of other cancers and specifically at very high risk of developing other skin cancers, which complicates their plan of care and prognosis. Most skin cancer deaths and skin cancer complications affect the elderly, and mortality due to skin cancer is specifically increasing in this group of the population.

This trend underscores the need for targeted prevention, early detection, and tailored treatment strategies for the elderly.

We investigated how subcutaneous lipids, which support normal skin function, impact melanoma metastasis and tropism. We first show that as we age, there is a total loss of adipocyte numbers in the skin, and a loss of lipid production and secretion. Lipid abundance in the skin, which varies by age, has profound effects on melanoma metastasis and tropism. In young skin, high lipid availability makes melanoma cells oxidise lipids as an energy source, which leads to oxidative phosphorylation (OXPHOS) and oxidative stress. High levels of oxidative stress limit metastasis in blood, as cells cannot withstand additional stress. In contrast, the aged skin has fewer lipids, so melanoma cells do not rely on lipid oxidation for energy, have lower OXPHOS and oxidative stress, and are highly metastatic. Lower OXPHOS, imposed by lipid cues in the cutaneous microenvironment, drives liver metastasis. Furthermore, lipids taken up by melanoma cells are signalling molecules that drive cancer pathways. Thus, we found that melanoma cells co-opt lipids from the skin, which vary in availability by age, and use them as nutrients to fuel growth, and the metabolic adaptation to nutrient availability dictates metastasis and tropism. This work has been accepted for publication (Gurung et al), and we are now expanding our work to look at systemic age factors in different organs that will also impact the rate, site of metastasis and therapy response.

We are now studying tissue specific metabolites at metastatic sites in the brain, lung, liver and blood that we know vary by age in patients, impact melanoma cell colonisation at distant sites and have the ability to respond to therapy. Our preliminary work in brain tissue was selected for a talk at the Brain Cancer UK annual conference, and Charlotte Russell won the best presentation award at the UK Cancer Metabolism Network Meeting 2024 that took place in Birmingham.

Melanoma and diet

With ancillary funding from the Rosetrees Trust and the Melanoma Research Alliance, we are expanding the focus of our stroma research to study how obesity in humans affects the response to immunotherapy. We have new

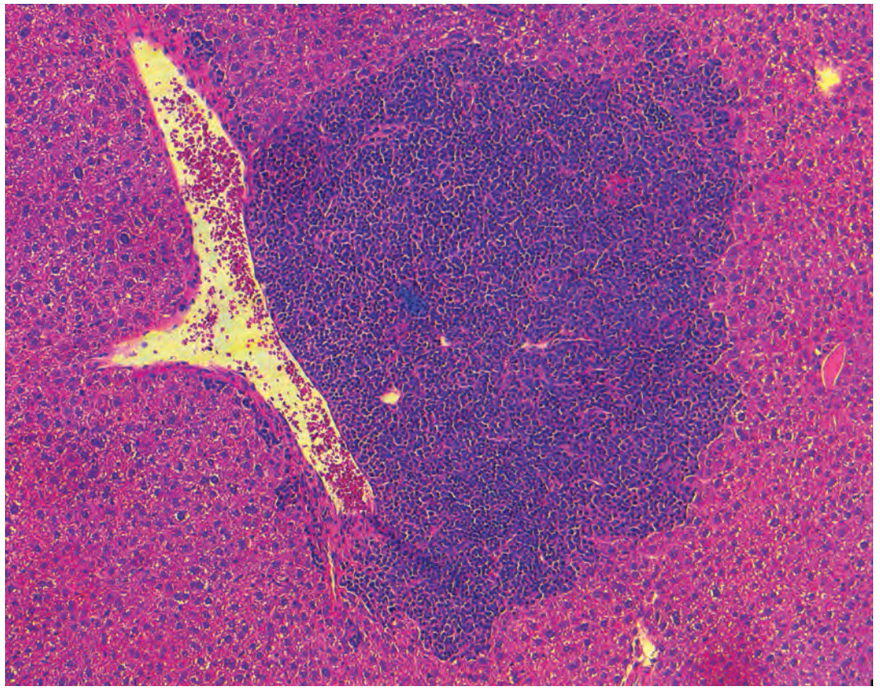

Figure 1: Melanoma liver metastasis. Image showing murine liver colonised by melanoma cells following injection with cells from the melanoma cell line 5555. Using H&E staining, dark purple areas indicate metastases, while the pink areas represent normal tissue.

Image supplied by Vanessa Parietti (Skin Cancer and Ageing)

preclinical melanoma models indicating that dietary factors and medication can synergise and enhance immunotherapy response in overweight animals. We are currently looking at how we can implement dietary interventions in humans in clinical practice to improve the response to therapy.

Epithelial cancer invasion and the tumour microenvironment

Our lab has been contributing to the CRUK Early Detection initiative by studying the tissue microenvironment factors that are in human epithelia and impact cancer initiation and invasion. Epithelial tissues are critical in physiology, as they are the primary interface between the internal and external environments, lining the surfaces of organs and cavities in the body. Their main role is to form a protective barrier against external injury. Squamous cell carcinomas (SCC) are tumours that arise from epithelia, and they have distinct clinical courses depending on the epithelium of origin. SCCs of the skin often affect aged patients in multiplicity and are the second most common human cancer. Although they are extremely common, they have a low rate of mortality (2%). In contrast, SCCs that arise from lung, head and neck, and the oesophagus have a very high rate of mortality. Our lab has found that there are differences in epithelia by anatomic site that underpin a different disease progression from in situ disease to invasive, deadly carcinoma.

UV light and melanoma immunotherapy

Melanoma incidence is strongly associated with ultraviolet (UV) light exposure, and excessive UV is linked to higher melanoma incidence. Both UV-driven inflammation and DNA damage to melanocytes have been linked to melanoma initiation. In our lab we have a research programme looking at how UV radiation can impact melanoma survival and the response to immunotherapy in cancer patients. This year, our new postdoctoral fellow Dr Isabella Mataloni has been investigating the local and systemic effects of UV radiation on immunity.

In September 2024, a new PhD student joined our lab. Lutong An is working on systemic age factors and metastasis.

Publications listed on page 51

SMALL CELL LUNG CANCER BIOLOGY

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Small cell lung cancer (SCLC) is an aggressive neuroendocrine malignancy that accounts for ~15% of lung cancers worldwide. Predominantly associated with tobacco use, SCLC is typically diagnosed at advanced, non-curative stages. High circulating tumour cell (CTC) burden drives early and widespread oligometastasis. Treatment remains a significant challenge because most patients rapidly develop resistance to platinum-based chemotherapy. Whilst immunotherapy provides limited benefit for a minority of patients, reliable predictive biomarkers are still lacking, highlighting the need for new therapeutic strategies.

At the molecular level, SCLC is defined by TP53 and RB1 inactivation, along with a complex mutation profile and expression of neurogenic transcription factors. Layered onto this, phenotypic plasticity is increasingly recognised as a source for intra-tumoural heterogeneity, drug resistance and metastasis. Our group has significantly advanced SCLC research by developing preclinical models from patients' CTCs termed CTC Derived eXplants (CDX) models, an approach now used worldwide. We have a biobank of >65 CDX models that reflect the extensive molecular heterogeneity of SCLC, and enables the study of molecular mechanisms driving metastasis and chemoresistance (Figure 1).

Understanding metastatic patterns in SCLC

SCLC is one of the most metastatic cancers, with ~80% of patients presenting with metastases at diagnosis. A major barrier to understanding SCLC metastasis has been the lack of robust and reliable metastatic preclinical and/or patient-derived models, and a paucity of biopsies from metastatic sites. Our CDX models addresses this gap by recapitulating the metastatic behaviours seen in patients. Using our *in vivo* resection protocol, we demonstrated that resected subcutaneous CDX tumours consistently metastasize to multiple organs including liver and brain; key sites linked to poor outcome.

We previously identified a rare but highly aggressive subtype of SCLC, driven by the ATOH1 transcription factor (Simpson et al. 2020, Nature Cancer). More recently, we demonstrated that ATOH1 promotes cell survival and supports CTC dissemination to the liver (Catozzi et al. 2025, Cell Reports). We also leverage our models to investigate the molecular mechanisms driving brain colonisation. To explore the metastatic cascade, we apply luciferase labelling of CDX cells prior to implantation for live animal imaging combined with single cell RNA sequencing of CTCs, early and late timepoints in the liver and brain. In collaboration with the CRUK Cambridge Institute, we are integrating WILD-seq (Wholistic Interrogation of Lineage Dynamics by sequencing), a barcoding-based lineage tracing approach, to study transcriptomic evolution during metastatic colonisation.

Deciphering vasculogenic mimicry in SCLC

SCLC cells display remarkable cellular plasticity with neuroendocrine (NE) cells (the major phenotype) transitioning to non-neuroendocrine (non-NE) states via NOTCH signalling in several CDX models. This plasticity is linked to acquired chemoresistance, metastasis and immune evasion. We previously reported that NE cells that transition to the non-NE phenotype can undergo vasculogenic mimicry (VM), a process where tumour cells develop endothelial-like properties and form vessel-like structures independent of angiogenesis and is associated with poor prognosis (Williamson et al. 2016, Nature Communications; Pearsall et al. 2023, Journal of Thoracic Oncology). VM represents the first example of functional plasticity, identified in SCLC and is observed in several CDX models where VM vessels co-localise with the non-NE marker REST. On Matrigel, only non-NE formed hollow tubules, an established surrogate of VM capability. NOTCH signalling is essential for tubule formation and our in vivo studies confirmed that VM vessels are perfused, validating their functionality.

We have recently initiated a light sheet microscopy approach to visualise 3D vessel architecture in perfused tumours *in vivo* to understand how vessels connect and localise *in situ*. Preliminary data indicates that VM vessels connect with endothelial vessels, forming distinct vascular networks (Figure 2).

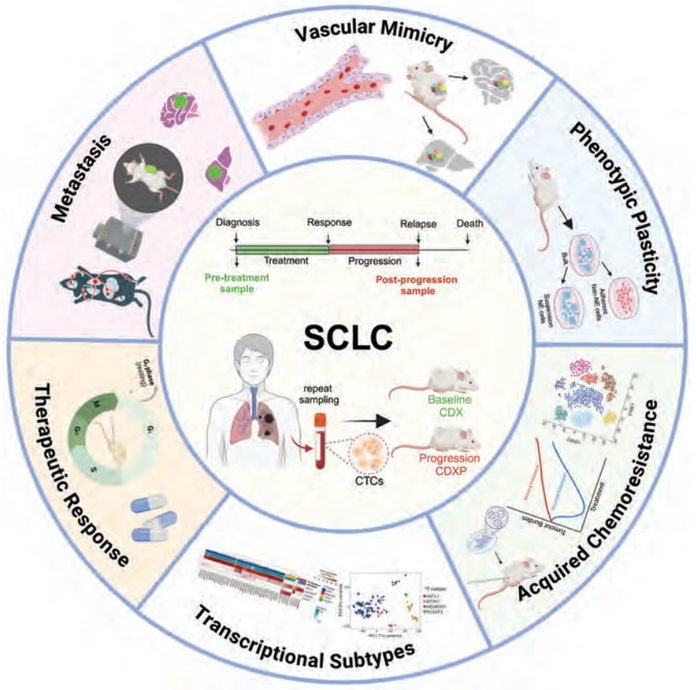

Figure 1: CDX models as comprehensive tools for investigating SCLC biology. CDX models recapitulate the molecular and phenotypic complexity of SCLC, enabling studies of neuroendocrine plasticity, vasculogenic mimicry, organ-specific metastasis, and mechanisms of chemoresistance development. These models enable longitudinal tracking of tumour evolution and therapeutic response, providing insights into mechanisms driving disease progression and potential treatments.

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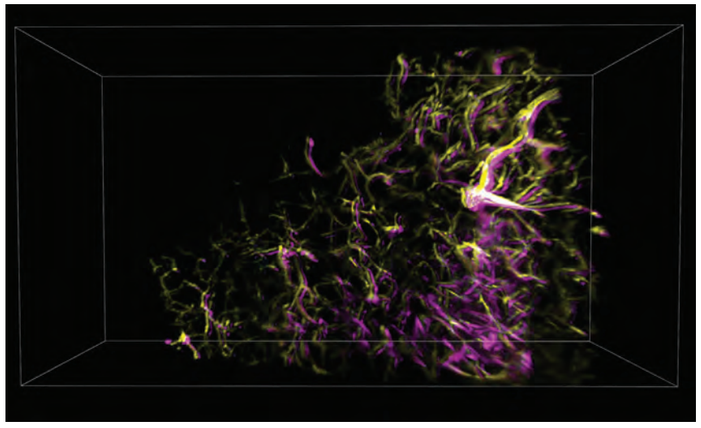

Figure 2: Exploring the functional relationship between endothelial vessels and VM vessels in CDX tumours. 3D reconstruction of CDX31 tumour slice labelled intravenously by injection with fluorescence conjugated tomato lectin (magenta, VM vessels) and CD31 antibody staining (yellow, endothelial vessels) following tissue clearing and light sheet microscopy.

Hypoxia, a known driver of cancer cell plasticity, survival, drug resistance and metastasis, is implicated in VM induction. Interestingly, non-NE cells exhibit 'pseudo-hypoxic' traits with elevated HIF1 levels, even under normoxia. We observed an inverse correlation between hypoxia and VM vessel density in large CDX tumours suggesting VM may be activated to overcome limiting oxygen levels. We hypothesize that VM in non-NE cells, stimulated by hypoxia, allows tumours alternative access to oxygen and nutrients for continued growth. We are tracking NE to non-NE transition *in vivo* using LeGO vectors (RGB colour marking). Viral integration of combinations of these primary colours in NE cells results in up to 96 distinct hues that can be imaged. We aim to determine whether cells undergoing VM and those that metastasize originate from the non-NE transition of dominant NE clone(s) and identify the specific regions of subcutaneous tumours from which they arise. Earlier studies in genetically engineered mouse models suggested that NE/non-NE cooperation is necessary for metastasis and we are now testing whether VM plays a role in this. Ongoing spatial transcriptomics in CDX models will complement these studies.

Addressing chemoresistance in SCLC

The standard-of-care for SCLC is platinum/etoposide combination chemotherapy, which initially elicits a response, however relapse typically occurs within 3-18 months. Our research focuses on understanding the molecular basis of this nearly universal pattern of initial sensitivity followed by rapid resistance. Most of our CDX models effectively capture the characteristics of the donor's tumour and reflect their initial chemosensitivity or intrinsic resistance. We have developed models of acquired resistance from initially chemosensitive baseline CDX through repeated treatment with cisplatin/etoposide *in vivo*. In select CDX models, *ex vivo* culture enables the generation of resistant lines through sequential *in vitro* treatment. For mechanistic studies, we have generated paired models from longitudinal blood samples collected from the same patient at diagnosis and relapse. We hypothesize that resistant clones recolonise the tumour with increasing diversity from a common ancestor. We are also investigating phenotypic plasticity as a contributor to chemoresistance, particularly since non-NE cells exhibit increased resistance to platinum/etoposide treatment compared to their NE precursors *ex vivo*. Using WILD-seq barcoding we are tracking subclonal dynamics and integrating RNA-seq to profile gene expression and cell state changes during resistance. These approaches aim to pinpoint resistance, monitor NE to non-NE cell transitions, identify early biomarkers of relapse and identify new therapeutic vulnerabilities.

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

STEM CELL BIOLOGY

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Acute Myeloid Leukaemia (AML) remains a devastating blood cancer characterised by high morbidity, significant genetic heterogeneity, and a dismal five-year survival rate of approximately 20%. Despite advancements in cancer therapies, cytotoxic chemotherapy remains the cornerstone of treatment for AML, but its efficacy is often hindered by resistance mechanisms and a limited therapeutic window.

The Stem Cell Biology group focuses on developing novel therapeutic strategies targeting specific molecular mechanisms driving leukaemia initiation and maintenance. Additionally, the group is dedicated to enhancing the understanding of normal haematopoietic development, with the goal of refining protocols for *in vitro* production of clinical-grade blood cells, particularly for cell-based cancer immunotherapies.

MOZ/KAT6A as a potential therapeutic target in haematological and solid cancers

Acute myeloid leukaemia (AML) is a clonal haematological malignancy that arises from mutations in haematopoietic stem cells (HSCs). These mutations result in the formation of leukaemic stem cells (LSCs), which give rise to immature blast cells incapable of differentiating. This uncontrolled proliferation leads to bone marrow failure, rendering the production of healthy blood cells impossible and resulting in high mortality rates.

One long-term interest of our laboratory is MOZ (also known as KAT6A or MYST3), a highly conserved member of the MYST family of lysine acetyltransferases (KATs). MOZ plays a crucial role in both the development and maintenance of HSCs.

MOZ/KAT6A has emerged as a significant therapeutic target in acute myeloid leukaemia research, particularly in cases involving MLL rearrangements (MLLr/KMT2Ar). This evidence underscores the potential of targeting MOZ as a therapeutic strategy in these aggressive forms of leukaemia. Beyond its role in haematologic malignancies, MOZ overexpression has been implicated in a range of solid tumours. Elevated levels of MOZ have been observed in cancers such as breast, prostate, ovarian, cervical, lung, colon, and rectal adenocarcinomas, as well as in medulloblastomas. These findings suggest that MOZ's oncogenic potential extends across diverse cancer types, making it an attractive therapeutic target not only in AML but also in solid tumours.

Given MOZ's potential role in leukaemogenesis, and solid tumours, inhibiting its catalytic activity has become a promising therapeutic approach. The most notable developments in this area are WM-1119, a first-in-class inhibitor of the MYST family of acetyltransferases, and the more recent second-generation inhibitor CTX648. This promising new small-molecule inhibitor has progressed to Phase 1 clinical trials (NCT04606446) for the treatment of various solid tumours, including breast, lung, and prostate cancers.

Consequently, ongoing research is focused on exploring the broader applicability of MOZ inhibitors, with the potential to develop novel treatment strategies for both haematologic and solid malignancies. In this context, we were particularly interested in evaluating further WM1119 in MOZ and MLL rearranged AMLs.

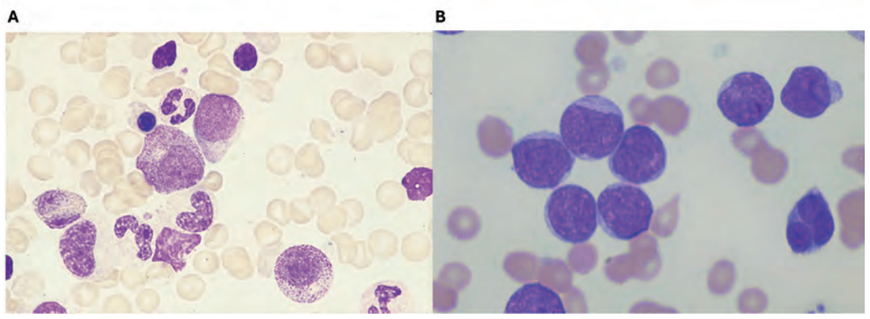

Figure 1: Morphology of bone marrow cells (A) In normal bone marrow, blast cells constitute less than 5% of the total cell population. (B) Bone marrow from AML patients showing an increased frequency of blast cells.

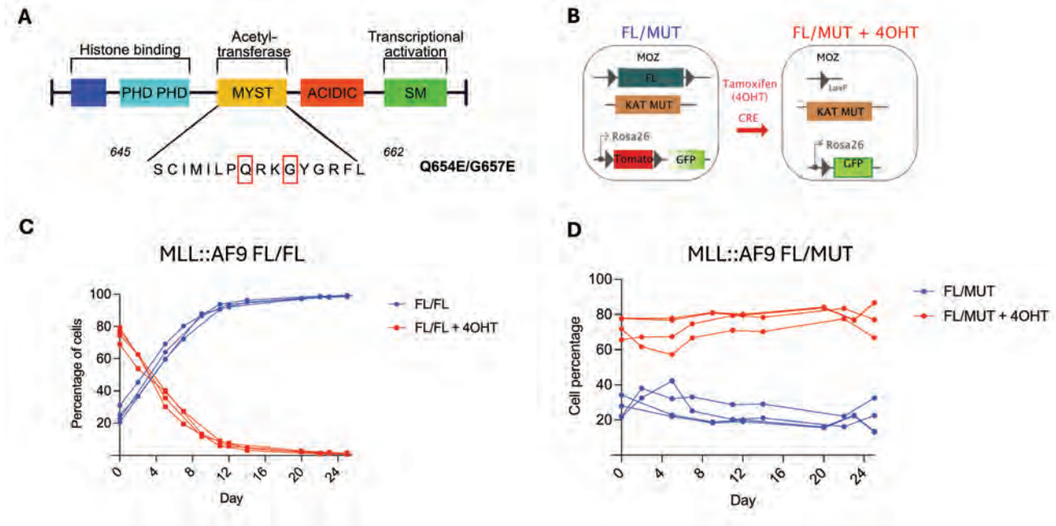

Figure 2: The KAT activity of full-length MOZ is NOT required for the leukaemogenic potential of MLL::AF9 AML cells (A) Mutation of the KAT domain in MOZ. (B) Induction of CRE activity leads to the deletion of the functional KAT6A allele, leaving the KAT mutant allele and GFP expression. (C) KAT6A-deleted cells are counter-selected while (D) KAT mutant KAT6A-deleted cells are not eliminated.

MOZ/KAT6A targeting in MOZr AMLs

AML cases involving MOZ translocations (MOZr/Kat6Ar) have particularly poor prognoses. Patients with MOZr AMLs face dismal five-year relapse-free survival rates of just 7%. Even in cases where patients undergo allogeneic stem cell transplantation during their first complete remission, the relapse-free survival rate increases only modestly to 26%. These statistics underscore the need for more effective therapies to improve outcomes in this high-risk population.

To investigate the therapeutic potential of targeting MOZ in these aggressive AMLs, we conducted studies using WM-1119 in a murine model of MOZ AML, specifically targeting the MT2 cell line (which harbours the MOZ::TIF2/KAT6A::NCOA2 fusion). The results were very promising as WM-1119 treatment completely suppressed the proliferation and clonogenic potential of MT2 cells *in vitro*. Transcriptomic analyses revealed that the treatment led to decreased expression of stemness-associated genes and disrupted critical leukaemia-associated pathways. These effects were attributed to the loss of MOZ::TIF2 fusion protein binding at key regulatory regions of the genome.

MOZ/KAT6A targeting in MLLr AMLs

To explore the broader therapeutic implications of targeting MOZ, we developed murine models of AML in which the catalytic activity or entire MOZ protein could be conditionally deleted. Our results indicated that MOZ knockout induced more significant differentiation of leukaemic cells generated by different MML rearrangements than treatment with WM-1119 or genetically inhibiting its KAT activity. These experimental findings, along with validation in human AML cell lines, suggest that targeting the full MOZ protein may offer a more effective therapeutic approach than inhibiting its catalytic activity alone. Specifically, developing targeted degraders based on the WM-1119 ligand could offer a more effective approach by simultaneously disrupting both the catalytic and non-catalytic functions of MOZ. This dual-targeting strategy could pave the way for more durable therapeutic responses in patients with aggressive forms of AML.

Cellular immunotherapies: advancing cancer treatment

In addition to studying leukaemogenesis, our group also focuses on developing novel cell-based immunotherapies. Autologous chimeric antigen receptor T-cell (CAR-T) therapies have revolutionised the treatment of haematological malignancies, receiving regulatory approvals for leukaemia, lymphoma, and multiple myeloma. However, these therapies face significant challenges in terms of costs, complexity, and scalability to profit larger patient populations.

An alternative approach involves using allogeneic cell products, which are derived from healthy donors and can be administered off the shelf. Stem cell-derived immune cells present a potential solution to generate large numbers of these cells. This approach has the potential to generate various immune cell types, including conventional αβ T cells, unconventional T cells (iNKT and γδ T cells), Natural Killer (NK) and myeloid cells.
A deeper understanding of the developmental pathways governing the generation of these immune cells will be critical for establishing scalable and effective off-the-shelf immunotherapy platforms. We are exploring new approaches to develop scalable production of immune cells. These advances could lead to more accessible and cost-effective treatment options for patients with haematological malignancies.

Publications listed on page 51

SYSTEMS ONCOLOGY

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Solid tumours are complex ecosystems where cancer cells are embedded within an intricate microenvironment comprising multiple infiltrating cell types and pathological changes to the extracellular matrix. The aim of the Systems Oncology laboratory is to determine and define how tumour cells conscribe host cells to support tumour development and develop resistance to therapies. 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 (PDA) is a dismal disease with an average five-year survival rate of 12%. Most patients are still diagnosed with inoperable or overt metastatic disease and are typically only offered chemotherapy with limited effect. Consequently, although PDA is the 11th most common cancer in the UK it is the 4th largest contributor to cancer related deaths and is projected to be the 2nd largest contributor to cancer related deaths by 2030.

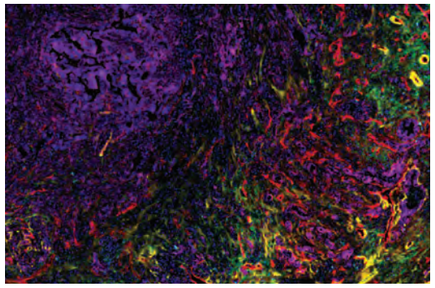
A characteristic feature of PDA is an extensive desmoplastic reaction, which makes up 85% of the tumour volume on average. Here, an abundant and pathological remodelled extracellular matrix increases tissue stiffness and interstitial pressure, which results in decreased therapeutic efficiency. Moreover,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

Mapping the tumour microenvironment of PDA

Due to the abundant tumour microenvironment much emphasis has been given to 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 recently used single cell mass cytometry to annotate the microenvironmental composition in a commonly used murine model of PDA (pdx-1 Cre; $KRas^{LSL-G12D/Wt}$; $p53^{LSL-R172H/Wt}$; KPC). The advantage of an antibody-based approach is that individual cell populations of interest can subsequently be purified and analysed functionally. We observed that PDA tumours contain two separate populations of cancer-associated fibroblasts (CAFs) distinguished by the expression of CD105 (Endoglin).

Isolation and characterisation of both $CD105^{pos}$ and $CD105^{neg}$ pancreatic fibroblasts revealed that the two stromal subsets express CD105 in a non-interchangeable manner and respond differentially to most exogeneous signals tested. This suggests that the 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. Both $CD105^{pos}$ and $CD105^{neg}$ fibroblasts are observed in the normal and tumour-bearing pancreas. Furthermore, both fibroblast populations can be identified and isolated from all murine organs tested thus far as well as in all tumour models tested (melanoma, colorectal, lung, breast and pancreatic) and human tumour tissue. Yet the abundance of other markers commonly used to denote fibroblast function appears to be restricted dependent on the tumour origin. Together, these data suggests that CD105 can be used to denote two ubiquitous fibroblast populations. Pancreatic $CD105^{pos}$ and $CD105^{neg}$ fibroblasts co-exist throughout PDA development and exhibit tumour permissive and restrictive roles respectively.



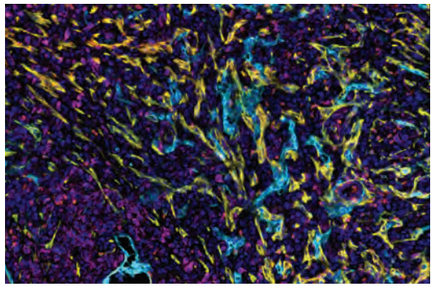


Figure 1: The tumour microenvironment.
Left. Multiplexed IF of a tumour generated by orthotopic implantation of pancreatic ductal cells harbouring CRISPR-induced genetic mutations (KRasG12D; p53null) into a *Col1a2-CreERT2;Engflx/wt* mouse to recapitulate the major mutations identified in human PDA in an environment where the CD105 expression of fibroblasts has been partially attenuated. Nuclear marker = DAPI; Cyan = CD105 (Endoglin), primarily showing vascular endothelial cells here; Yellow = aSMA+ myofibroblasts; Orange = Podoplanin+ cells (mainly co-expressed in fibroblasts here); Magenta = CK19+ tumour cells.
Right. mIF of a tumour generated by the same cell line as in 1A but implanted into a wild-type mouse. DAPI: Cyan = CD4+ T cells; Green = F4/80+ macrophages; Yellow = aSMA+ myofibroblasts; Red = CD105; Magenta = CK19+ tumour cells.
Tissues shown are fixed-frozen sections and staining was performed manually, including use of the TrueBlack Lipofuscin Autofluorescence Quencher (Biotium) and FlexAble2.0 CL750 fluorescent labelling kit (Proteintech) to facilitate direct CK19 staining. Images were captured using the Olympus VS200 Slide Scanner with Kromnigon SpectraSplit 7 filter set.

Further, such populations are broadly present across tissues and tumours, but whether the tumour-promoting and tumour-restrictive roles are conserved more broadly remains to be seen.

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. 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 in their ability 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 and the immune system and provide molecular insights into the signals that govern tumour development.

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 PDA 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 scaffold, 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. Ongoing work in the laboratory is seeking to fully explore the application of these models to interrogate tumour cell dependencies.

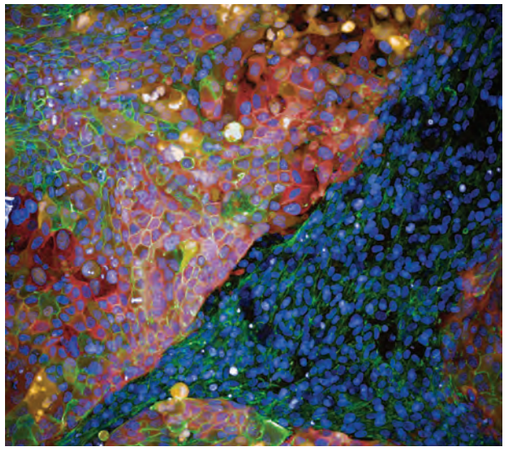


Figure 2: Tumour and host co-cultures. Patient-derived pancreatic tumour organoids (orange/red) cultured with fibroblasts (green) and immune cells (green) in a three-dimensional synthetic PEG hydrogel..

TRANSLATIONAL LUNG CANCER BIOLOGY

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[1]Left in 2024

Lung squamous cell carcinoma (LUSC) is an aggressive type of lung cancer that originates in bronchial basal cells with limited therapeutic options. Apart from chemotherapy, only immunotherapies result in marginal improvement in survival for LUSC patients. Furthermore, targetable genetic alterations are infrequent in LUSC, which results in a lack of targeted treatments that can only be overcome by unravelling new dependencies in this disease.

Barriers to progression in LUSC medicine

Early detection is currently the most effective tool to prevent deaths by LUSC. Screening programmes by CT-scanning in high-risk populations have overwhelmingly confirmed this benefit. However, 40% of patients diagnosed with early-stage disease still die within five years. High grade precancerous lesions show high risk of malignant progression but can be easily removed with minimally invasive procedures. Detection of these lesions however is rare as scalable methods to detect them during screening programmes have not been developed. Hence, preventing deaths by LUSC in patients requires improving therapeutic modalities and early detection. These improvements depend heavily on more ambitious, innovative, and patient-relevant preclinical models that recapitulate the intra-tumour and inter-patient heterogeneities so frequently observed in this disease, and the developmental stages of LUSC progression. However, existing LUSC models do not recapitulate those complexities, and this is a barrier to reversing the dismal landscape of LUSC.

Modelling the complexity of lung LUSC

Mouse models of LUSC are not sufficiently developed, arguably due to comparatively less research focus than other lung cancer types. The identification of *SOX2* (frequently amplified in LUSC and a component of the squamous differentiation pathways) as the most important LUSC driver and its incorporation in LUSC modelling strategies has made LUSC models more patient relevant.

However, multiplatform characterisation of large patient cohorts has revealed a complex landscape of molecular subtypes, with and without SOX2 amplification, with obscure biological origins and unknown vulnerabilities that are not represented by any existing experimental models.

Moreover, observation of the genomic landscape of LUSC has shown that there is no single targetable pathway that dominates this landscape. Instead, the most frequently altered pathways in LUSC are PI3K/Akt pathway (47%), squamous differentiation pathway (44%) and oxidative stress response (34%) (Figure 1). Furthermore, analysis of LUSC genomes has not shown co-occurrence or mutual exclusivity in these dysregulated pathways, although alterations that dysregulate the three pathways seem to co-occur in certain molecular subtypes.

This suggests that none of the pathways are indispensable in driving LUSC, but also that they can cooperate. Deciphering the biology of this complex inter-patient diversity requires individual interrogation using appropriate models to address several key questions:

- Can these pathways drive LUSC tumourigenesis per-se or there is an obligate cooperation between them?
- Are LUSC cells addicted to these pathways?
- Are these pathways mutually dependent?
- Are these pathways relevant in all LUSC molecular subtypes and if not, what processes drive LUSC in those subtypes?

Answering these key questions requires intensive research programmes that involve the manipulation of multiple loci. Approaches to avoid a large cost in mouse lives and distress is a responsibility of the scientific community, especially in the field of LUSC, where the new availability of more relevant mouse models will increase the number of projects involving animal research. Genetic manipulation of human bronchial epithelial cells (HBECs) is an alternative to mouse models that can facilitate the modelling of LUSC heterogeneity and developmental stages. However, a proof of principle for this alternative LUSC modelling strategy is required.

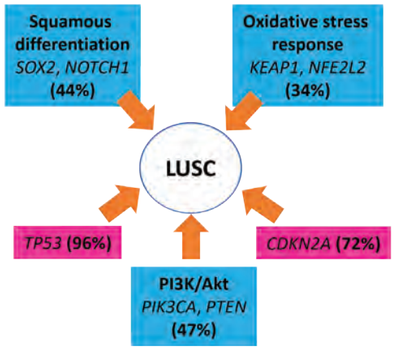

Figure 1. Summary of the most relevant tumour suppressors (pink boxes) and pathways (blue boxes) involved in LUSC development, with examples of pathway components altered in LUSC and the percentage of cases with at least one alteration targeting the pathway.

Current methodologies permit efficient expansion of HBECs, genome editing and development of organoids mimicking bronchial morphology. Using these methodologies, we can disentangle how driver alterations induce epithelial perturbations indicative of LUSC initiation and progression. Additionally, HBECs reflect human diversity better than mouse models, constitute a more adequate system to investigate the effect of exposures, mainly smoking, and predisposition.

Genetic manipulation of HBECs

In the Translational Lung Cancer Biology group, we have designed, implemented and characterised a genome engineering strategy whereby we intend to establish a proof-of-principle for the use of HBECs to model LUSC. To do this, we have generated increasingly complex mutant HBECs bearing inactivating mutations in the tumour suppressors *TP53* and *CDKN2A* (which are ubiquitous alterations in LUSC) and combinations of alterations in components of the squamous differentiation, PI3K/Akt and oxidative stress response pathways, namely, SOX2 overexpression, *PTEN* truncation and *KEAP1* truncation respectively. With this strategy we intend to capture what are the essential components of LUSC development. Analysis of air-liquid interface (ALI) organotypic cultures showed that *SOX2* overexpression induces epithelial morphologies indicative of the transition from normal to low-grade premalignant stages characterised by a prominent squamous differentiation. Addition of *PTEN* and *KEAP1* mutations results in complete loss of epithelial polarity and expansion of p63-positive cells consistent with transition to high grade preinvasive stages. Importantly, invasion assays revealed that the dysregulation of the three pathways was necessary for acquisition of invasiveness. Our observations have enabled us to define a genetic roadmap that describes the LUSC developmental stages, from a normal bronchial epithelium to premalignant and invasive stages and confirm that activation of the three pathways was necessary for complete transformation of HBECs into invasive LUSC cells. These obligate requirements were consistent with the classical LUSC subtype, in which there is a co-occurrence of alterations in the three pathways.

We also detected that simultaneous *SOX2* overexpression and PTEN truncation led to negative selection of SOX2-overexpressing cells in organotypic cultures. However, this negative selection was not observed in mutants with *SOX2* overexpression, *PTEN* truncation and *KEAP1* truncation. These results explain the reason concomitant activation of the three pathways occurs in the classical subtype and indicates that therapies currently in clinical trials to inhibit the oxidative stress response in LUSC should be targeted in classical LUSC patients.

SOX2 overexpression and the oxidative stress response pathway

Our approach to model LUSC also enabled us to explore the effect of pathway dysregulation in the transcriptome of mutant HBECs and the overall downstream processes relevant for LUSC progression perturbed by such pathways. SOX2 overexpression resulted in the expected dysregulation of biological processes related to epithelial maintenance, particularly squamous differentiation and ciliation. However, these analyses revealed that SOX2 also regulates EGFR ligands and immune pathways, including downregulation of MHC class II subunits and the upregulation of extracellular serin protease inhibitors that counteract the tumour suppressive effect of neutrophil elastases. On the other hand, the oxidative stress response downregulated interferon-α and -γ responses, together with the expected upregulation of redox- and xenobiotic detoxifying enzymes, amino acid transporters and pentose-phosphate pathway enzymes.

Mutant HBECs in vivo

To compare the behaviour of mutant HBEC-based models in vivo and in vitro and identify new biological data missing from our in vitro approach, we implanted the same genotypes subcutaneously in immunocompromised mice and carried out a comparative in vitro vs in vivo analysis. Although we did not observe major differences between the information from organotypic cultures and xenografts regarding the evolutionary trajectory, we did observe a major difference in the $TP53^{-/-}/CDKN2A^{-/-}/PTEN^{-/-}$ (TC+P) mutants. This genotype, which showed widespread mucociliary differentiation in vitro (although with evidence of hyperplasia), revealed subclonal squamous morphology in vivo.

Whole-exome sequencing of these mutants identified mutations in *NOTCH1*, a gene significantly mutated in LUSC, and with a trend of mutual exclusivity with SOX2 amplification. Furthermore, *NOTCH1* truncations in hBECs revealed a phenotype akin to SOX2-overexpression. We hypothesise that *NOTCH1* and possibly *NOTCH2* inactivating mutations replace SOX2 amplifications and mediate an alternative LUSC developmental pathway in a subset of non-classical LUSC patients.

www.cruk.manchester.ac.uk/research-group/translational-oncogenomics

TRANSLATIONAL ONCOGENOMICS

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[1]Joined in 2024
[2]Left in 2024

Our lab is focussed on understanding the aggressive biology of localised prostate and penile cancers and the discovery of new biology-based therapies to increase cure and prevent metastatic disease.

Prostate cancer accounts for one in every 14 cancers diagnosed globally, translating into 85,000 new cases and 18,000 deaths in the UK annually by 2035. Localised prostate cancers can be aggressive with a 20-fold increase in prostate cancer–specific mortality (PCSM). These cancers are treated intensively, typically with combinations of surgery, radiotherapy and androgen deprivation or androgen receptor signalling inhibition (ADT or AR-SI), to eradicate all tumour clonogens and prevent evolution of metastatic hormone(castrate)-resistant prostate cancer (mCRPC). Once patients fail these therapies, there are no curative options remaining. Therefore, preventing failure after initial local and ADT treatment provides the best opportunity to block the evolution of lethal disease. We are developing new prognostic sub-classification approaches for aggression using information on intraductal carcinoma/cribiform architecture, the presence of genomic instability in the setting of altered TP53, RB, PTEN or c-MYC status and the level of hypoxia within the tumour microenvironment (TME). By understanding the molecular landscape of high-risk disease, we hope to better understand what drives disease progression in some patients and improve personalised treatment options.

Familial predisposition to high-risk prostate cancer

Accumulating evidence implicates hereditary DDR prostate cancer genes playing a role in 10-15% of localised tumours and driving aggression, including BRCA1/2, ATM and CHK2 kinases, the mismatch repair machinery and the tumour suppressor, TP53. The relatively poor outcome observed in germline BRCA2- and ATM-driven prostate cancer reflects resistance to androgen deprivation therapies and rapid progression to distant bone metastasis. To study the evolution of hereditary prostate cancer and understand treatment resistance, we have developed robust protocols for establishing in vitro cultures of primary prostate epithelial cells (PrECs) a translational pipeline to acquire normal and tumour tissues derived from DDR gene mutated patients attending a special DDR Urology Clinic within the Christie NHS Foundation Trust. Subsequently, we have succeeded in immortalising these basal prostate epithelial cell (PrEC) cultures through expression of the human TERT (telomerase) gene. By employing high depth whole-genome sequencing, we have confirmed these immortalised PrECs possess a largely unaltered genome – a major advance over the alternative prostate tumour cell lines currently available which harbour extensive genomic aberrations.

Functional validation of our BRCA2-mutated PrEC cells shows decreased IR-induced RAD51 nuclear foci formation, decreased HR activity based on DR-GFP reconstitution, and increased PARPi (Olaparib) and RT sensitivity. Three clones have increased copy number alterations including acquisition of 8q gains found in localised prostate cancers. In ATM-mutated PrECs, we observed the classic radiosensitivity phenotype. Preliminary WGS data supports emergence of ATM-mutated clones with both heterogeneous CNAs and differential transcriptomic profiles reflecting increased chromosomal stability. Work is ongoing using in vitro and in vivo approaches to derive AR-responsive luminal cell models from these basal cell models. By combining these approaches, along with analysis of clinical samples, we aim to provide best care for patients with hereditary predisposition to prostate cancer.

Investigating the hypoxic tumour microenvironment

Tumour hypoxia represents a key component of the TME that can both vary within tumours or between patients and leads to resistance to radiotherapy, epithelial-to-mesenchymal transition and interactions with the immune system. In whole genome sequencing (WGS) studies of more than 500 patients, we have been able to associate the highest hypoxia scores with DNA mutations including CNAs, SVs and SNVs. Importantly, we are also able to associate hypoxia with aggressive evolutionary trajectories (evotypes), mutation or copy number alterations in cancer driver genes (SPOP, TP53, MYC, RB, PTEN and BRCA2) and pathway analytics supporting aberrant signalling in mitotic control, the G2 checkpoint, DNA repair, MYC targets, E2F targets, the EMT and angiogenesis. These data support the concept that hypoxia can be a co-driver of evolution of prostate cancers in collaboration with DDR defects and somatic mutations in the c-MYC, RB, PTEN and TP53 genes.

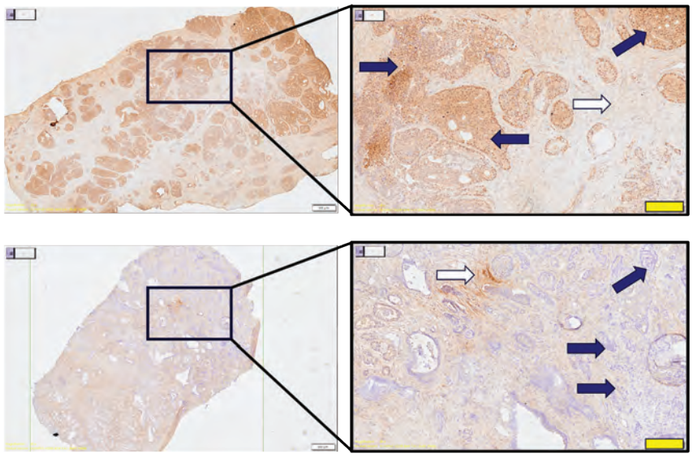


Figure 1: Immunohistochemical detection of Pimonidazole adduct formation in frozen radical prostatectomy specimens obtained during the HYPROGEN trial. Case A (upper panel) exemplifies intense staining across all tumour regions including areas with a cribriform growth pattern, whilst staining of stromal tissue is relatively weak. Conversely, the tumour cells from Case B (lower panel) are largely free of pimonidazole staining with significant staining observed in stromal cells. Of note, both cases are assigned Gleason 4+3 scores by our pathology team despite this evidence of differential hypoxic metabolism. Thus, it will be important to ascertain whether pimonidazole adduct formation is correlated with features of high risk such as genome instability, mutations in key oncogenic drivers (e.g. PTEN, MYC, BRCA2), EMT (Epithelial to Mesenchymal Transition) as well as pathological changes such as perineural invasion. Blue arrows indicate tumour regions; white arrows show stroma. Yellow scale bar = 200um.

To validate these sequencing data, we employ primary tissue specimens derived from the HYPROGEN trial in which intratumoural hypoxia is assessed by means of the tracer molecule, pimonidazole, which is administered 24 hours before paired primary-metastatic biopsies are taken in men with metastatic disease or prior to curative radical surgery in men without metastases. In-depth spatial Visium 10X and GeoMx analyses are married to inferCNV bioinformatic algorithms to cross-correlate tumour cell signalling, genetic instability and hypoxia in situ. Analyses of differentially expressed genes (DEGs) and signalling pathways across hypoxic gradients shows upregulated HIF1α and glycolysis targets and MYC target gene engagement, suggesting that some tumours have adapted to low oxygen conditions and continue to proliferate in the presence of high hypoxia. Initial immune cell studies showed upregulation of CD68 and CD74 genes within peri-necrotic areas, which may be an innate immune response to hypoxic stress. We are aligning functional MRI clinical imaging of hypoxia to our post-operative specimens that have undergone transcriptomic sequencing. The MRI protocols and images are being validated against pimonidazole, GLUT1-stained prostatectomy sections and hypoxia-based mRNA signatures in situ. These data will identify men using non-invasive imaging who might benefit from hypoxia-modification or treatment intensification.

Determining the role of HPV and somatic mutations in aggressive penile cancer

Penile squamous cell carcinomas (PSCC) are a rare, but aggressive and debilitating cancer with just less than 1000 cases diagnosed a year in the UK. The Christie NHS Foundation Trust is a European leader for the treatment of penile cancer using surgery. The disease is currently classified as HPV-associated and HPV-independent by the World Health Organisation (WHO) classification using p16 immunostaining, a surrogate marker of HPV. As the pathogenesis of HPV infection is thought to involve the hijacking of the p53 and Rb pathways, we are determining the effect of differential HPV genotypes and viral integration in PSCC against aggressive tumour cell signalling pathways using spatial transcriptomes, mutation analyses and immunophenotyping. Identifying patterns in these and related markers could promote alternative strategies for tailored management of this aggressive disease.

Publications listed on page 51

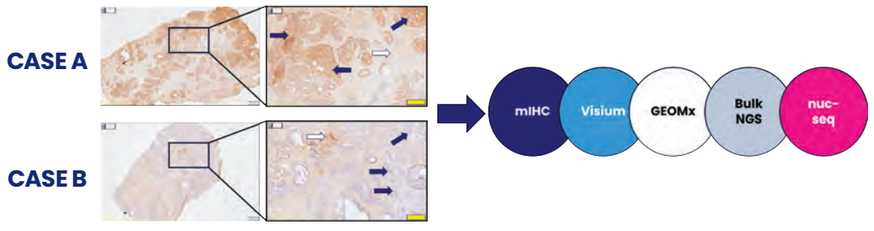
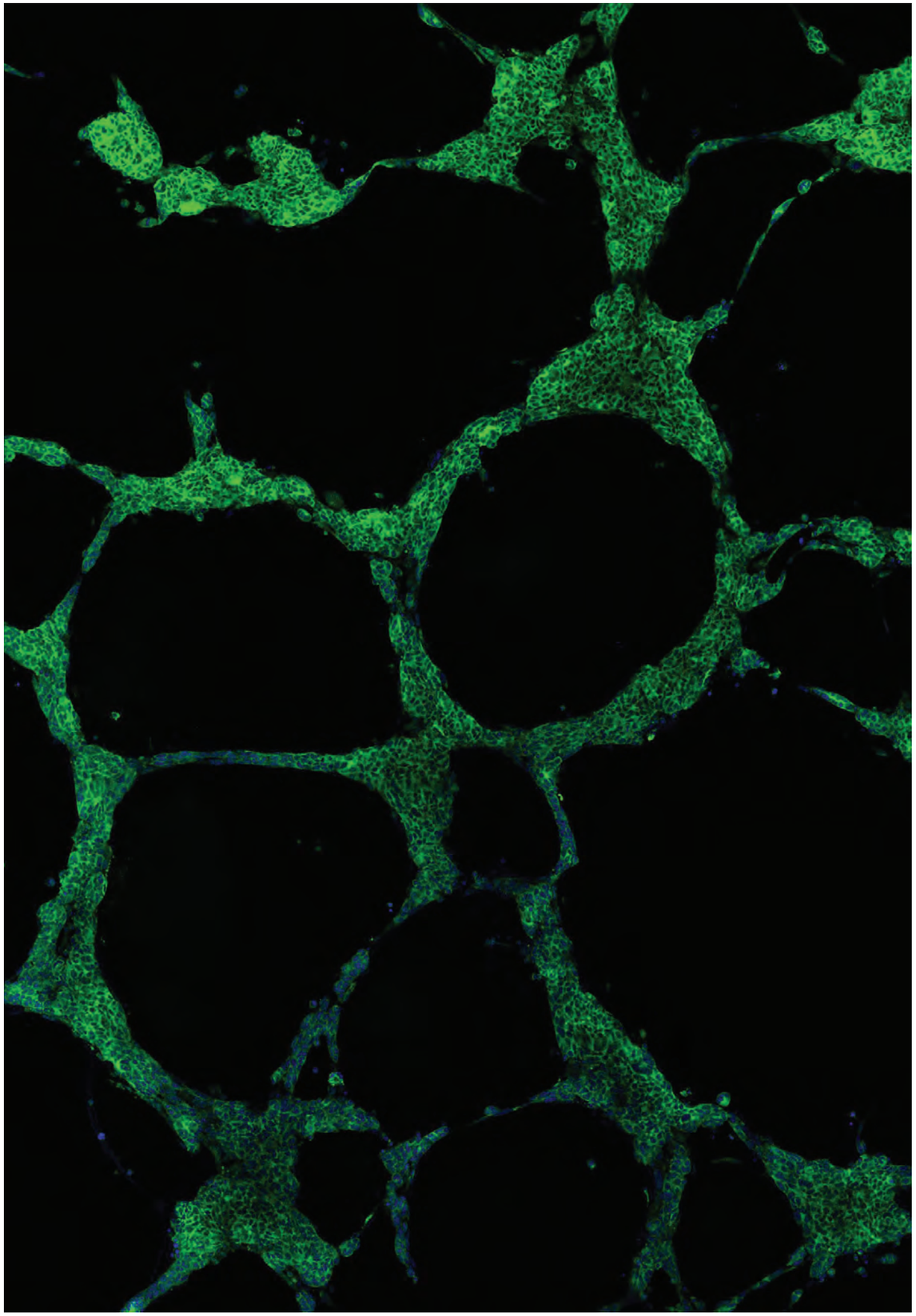


Figure 2: Schematic depicting ongoing analysis of HYPROGEN samples. Spatial transcriptomic analysis will be used to identify transcriptional programmes active in different tissue compartments. Gene expression signatures will be useful in confirming the hypoxic status of Pimonidazole-stained regions and probing the tumour microenvironment in detail. This analysis will be complimented by use of single-cell sequencing (nuc-seq) which will allow the identification of specific cell populations and their subsequent mapping to spatial features.



RESEARCH SERVICES

CDX models can be cultured ex vivo to enable phenotypic characterisation of SCLC heterogeneity and plasticity. Non-Neuroendocrine CDX cells cultured on Matrigel form tubules indicative of Vasculogenic Mimicry competence and can be visualised with an immunofluorescence antibody against human mitochondria (green).

Image supplied by Griselda Awanis (Small Cell Lung Cancer Biology)

RESEARCH SERVICES

Chief Laboratory Officer
Stuart Pepper

Last year the core facility teams were preoccupied with managing the complexities of relocating to our new building, whilst ensuring that there was minimal disruption to services, and this was achieved highly effectively. Having settled into the new building, 2024 has been an opportunity to take stock of how our facilities operate and consider how they can develop in the future. Towards the end of the year, we held a review of the core facilities conducted by an external panel. I was delighted that the feedback from the panel was very positive and that they were impressed with the range and quality of services provided.

Chief Laboratory Officer
Stuart Pepper

Over the last two years we have benefited from significant investment in equipment. Our Mass and Flow Facility has been able to add a Sony ID7000 and a Novacyte to complement the Bigfoot cell sorter that was bought last year. This facility has undergone a significant transition over the last two years with new staff contributing to the development of a truly world leading facility, as detailed in the paragraphs below. Elsewhere, we have updated our imaging platform in the BRU and funded an electroporation system to support new workflows in our GEMM team. Towards the end of the year, we placed an order for a new Astral mass spectrometer which promises to deliver some major improvements in the depth of proteomic analysis that can be obtained.

The new Paterson Building was designed to facilitate close collaborations between the core facilities. By placing the core facilities in adjacent lab and office areas there has been more potential for teams to work together, and develop workflows that bridge the more traditional technology-based silos that core facilities sometimes operate in. This has been important in supporting spatial genomic workflows and has facilitated the computational team in developing a wider portfolio of pipelines to support core facilities, beyond next-generation sequencing and proteomics.

Training is a key element of the value that core facilities deliver. With new equipment and new workflows there is a constant need to offer training so that our researchers gain important skills. This has been particularly apparent in the *in vivo* teams and Flow Cytometry, where training is always a significant part of the workload; this year Computational Biology Support and Scientific Computing have also focused on delivering training to ensure that there is a broad understanding of how to make best use of the data processing and analysis capabilities available at the Institute.

As is detailed in the sections below, every core facility has continued to evolve and adapt, with new workflows and ways of working. Working together has made our first full year in the new building highly successful as we continue to develop an ever-expanding range of support for the research groups at CRUK MI.

Biological Mass Spectrometry

Duncan Smith, Yvonne Connolly, Robert Faulkner, Adam Flinders[1]

[1]Joint with Computational Biology Support

The Mass Spectrometry facility is dedicated to supporting state-of-the-art proteomics applications for our cancer researchers, enabling them to advance their scientific discoveries. We utilise high end LCMS technologies, namely an Orbitrap Lumos coupled to nano UHPLC system to drive high-quality, impactful proteomics research.

We use a combination of established and constantly evolving workflows, along with both biochemical and software-driven solutions to further enhance our services that help to address the growing complexity of analytical biological challenges in cancer research at the Institute.

This year has seen an exciting development in rare cell proteome profiling in a collaboration with the Cancer Inflammation & Immunity group and the Flow Cytometry facility. We successfully developed a sample preparation workflow and analysis pipeline that enabled comprehensive profiling of rare flow sorted dendritic cell populations that was previously beyond our capability. We are now able to address how these cell's proteome enables their biological behaviour.

We have also demonstrated a massively enhanced ability to detect and quantitate phosphopeptides in global phosphoproteomics experiments by implementing a Data Independent Acquisition (DIA) methodology specifically for phosphoproteomics in collaboration with the Systems Oncology group. Remarkably, this approach increased the number of phosphopeptides detected by 5-fold over the conventional approach. There is a continued effort to optimise phosphosite assignment accuracy in this method to fully exploit its benefits.

In collaboration with Scientific Computing and the Computational Biology Support facility, we have successfully migrated our main DIA software pipeline from a virtualised Windows environment to the Griffin high performance computing cluster. Exploiting the wonderful environment (both hardware and staff expertise) here at the Institute has facilitated the lifting of a major data processing bottleneck that is currently inhibiting the whole field of proteomics research globally. We are now in the fantastic position where we run analyses on a scale that has not been possible before.

2025 will see the delivery of a new phenomenal Mass Spectrometry system that will boost sensitivity, speed, selectivity and robustness of all our key application areas by enabling narrow window DIA (nDIA) for the very first time. This will have a fundamental impact on the questions we can ask and answer, taking our researchers' proteomics capabilities to the next level.

Biological Resources Unit
Experimental Services

Team Leader: **Lisa Doar**
Lisa Dique, Jo Roberts, Laura Dean, Rachel Walker, Eirini Symeon[1], Tom Bosley[1], Lewis Woolley, Diane Beeston, Lisa Flynn, Jessica Walker, Wesley Moore[2], Nadia Bell[2], Gary Cooke, Kimberley Kirkham, Oliver Lesser

[1]Left in 2024
[2]Joined in 2024

2024 has been the first 'business as usual' year for us in a long time now that we have settled back into the new facility. We have been able to return to helping introduce new models and advising on improvements and refinements to deliver our animal research in an efficient manner and to maintain our high standards. Several new University of Manchester's Division of Cancer Sciences groups are now based on our site, so we have been working closely with them to help them with their animal requirements. We have also been carrying out a lot of training with new researchers and students. We have put a great amount of work into our training programme over the last couple of years to make sure it is as efficient as possible and ensuring researchers and technicians feel confident and competent when carrying out the various techniques as they set up their experiments.

We have helped establish and train technicians and researchers in several new procedures this year. These include intra-cranial injections, a procedure that was previously only undertaken by one group but now three groups are using this technique. Intra-oviduct surgery has been established for a new group working on ovarian cancer, and image guided intra-cardiac injections have been used by another group as a more reliable way of carrying out the procedure. Tear and cerebral spinal fluid collections are two other new methods of collecting a sample, which can then be used to look for key biomarkers. We have also fully rolled out the use of our inhalation irradiation jig that we developed last year, so that we now no longer need to use injectable anaesthetic for any of our X-ray work. This move to inhalation irradiation has made a huge refinement to the welfare of our mice as inhalation anaesthetic is much better tolerated and it is easier to adjust the dose. We also purchased and installed a new optical imaging system, the AMI HTX and have run several training sessions for our research staff in how to use it. So far, the feedback has been very positive, and the higher sensitivity of this instrument is allowing detection of smaller tumours, improving both the quality of the data and providing a 3Rs benefit.

There have been a few more key events and highlights over the year, starting off with a Home Office Inspection earlier in the year. The Home Office regulates animal research work, and they will visit facilities and carry out detailed audits, including a review of the facility itself, and the systems we have in place to ensure legal compliance and high-quality animal welfare. The inspection went extremely well, and we were really pleased with the positive outcome and response from the inspectors, especially when considering we had only relocated to the new animal facility a few months earlier.

A big change we made to the running of the facility was a reduction in the need to wear face masks, following on from some animal allergen testing we had carried out in April. Having systems in place to keep animal allergen levels as low as physically possible is vital to prevent the development of allergies, which is an occupational hazard when working with

animals. The results were as positive as we could have had hoped – almost undetectable levels in most of the facility, meaning we now only need to wear face masks in a couple of rooms. This makes for a much more pleasant environment for staff working in the facility.

As well as the day-to-day work, we have managed to carry out some additional activities to promote our work. We generated a poster about our inhalation anaesthetic jig we had designed to refine our X-ray irradiation work, and this won both our internal 3Rs event, and the Institute of Animal Technology Northwest Hub 3Rs competition. One of our team, Jo Roberts, was invited to talk at a multi-modal imaging workshop about the work we carry out using image guided injection on our ultrasound imaging platform. This was well received and led to the setup of a user network. Lisa Flynn and I gave a careers talk to science students at Manchester College in October, which was also very well received. Five of the students visited the Institute and had a tour of the animal research facility, which they really enjoyed. We are taking on a one-day-a-week placement student in 2025 to expose them to all areas of animal research – the hope is that by raising awareness of the role of animal technician as a potential career option it might encourage more young people into the industry.

Transgenic Breeding

Team Leader: Lauren Street[1], Natalia Moncaut[1], Jennifer Hughes[2], Daniel Bennett, Tim Bloor, Martin Vincent, Carl Conway[3], Wesley Moore[3] and Irana Bakhtiari-Cunado[3]

[1]Leave cover
[2]On leave
[3]Left in 2024

The Transgenic Breeding Team at CRUK MI specialises in breeding mice to support the research initiatives at the Institute. Maintaining a high health status is paramount, necessitating stringent protocols for introducing new transgenic lines from external sources. New mouse lines are typically transferred into the facility as embryos or sperm by the Genome Editing and Mouse Models team and undergo thorough health screening to ensure that resultant offspring are specific-pathogen-free.

Following the relocation of most breeding colonies to the Paterson Building animal unit, the service has been streamlined and optimised. With more researchers joining the Institute in 2024, we increased the number of mouse strains by 40%, while keeping the total number of cages relatively stable. This was achieved by immediate closure of some lines (already safely archived) and maintaining close colony management oversight.

Furthermore, researchers enjoy direct access to the mouse stocks, allowing them to conduct tissue sampling and experiments without having to wait for an acclimatisation period. Animal technicians also benefit from easier access to research talks and seminars. This year we launched the first Transgenic Breeding Workshop, designed for new students and postdocs. The workshop covers key topics such as mouse reproductive biology, breeding strategies, basic genetics, and interpreting genotyping results.

Computational Biology Support

Sudhakar Sahoo, Robert Sellers, Richard Reeves, Adam Flinders[1]

[1]Joint with Biological Mass Spectrometry

The Computational Biology Support (CBS) core facility provides high-quality computational biology and bioinformatics analysis solutions for researchers at the CRUK Manchester Institute. The main goal of CBS is to develop computational analysis infrastructures that enable the application of advanced bioinformatics and statistical analysis to the Institute's cutting-edge scientific research.

Our work primarily involves developing and applying computational methods 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 consists of highly experienced members with diverse expertise in analysing and interpreting datasets across various fields, including genomics, epigenomics, transcriptomics, proteomics, metabolomics, and metagenomics. 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.

Notably, there is a high-throughput image analysis workflow available to all Institute members. This automated image analysis pipeline was developed in collaboration with the Systems Oncology group. It can analyse various tissue images generated by ultra-plex imaging platforms such as CODEX, mIF, mIHC, MIBI, cyCIF, and Hyperon. Additionally, recent highlights of our efforts include a metagenomics workflow designed to support the research of the Cancer Immunosurveillance group, as well as a metabolomics workflow developed in partnership with the Skin Cancer and Ageing group. Figure 1 illustrates the metagenomics classification analysis conducted at all taxonomic levels using our workflow on data sets from Cancer Immunosurveillance.

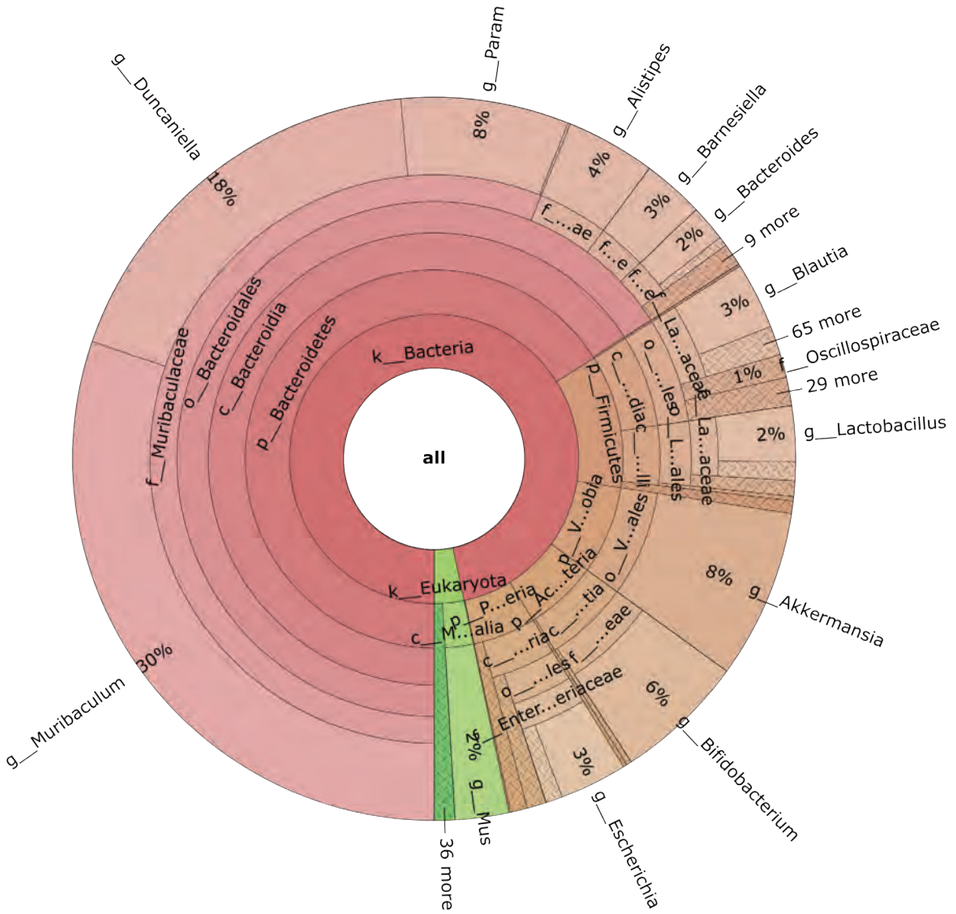


Figure 1: The metagenomics classification analysis conducted at all taxonomic levels using CBS workflow on data sets provided by the Cancer Immunosurveillance group.

(Credit Evangelos Giampazolias and Emma West).

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 high-quality data. In collaboration with the IT and Scientific Computing 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 for single-cell, spatial transcriptomics, and proteomics platforms. A recent highlight is the pipeline for the STomics platform, a spatially resolved transcriptomics platform capable of achieving subcellular resolution and profiling the whole transcriptome from a tissue. The workflow includes pre-processing, quality control, and image processing. All the optimised workflows are automated and routinely used by Core facilities to ensure the generation of high-quality, accurate data and quality control reports for the Institute's users. 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 bulk RNA-Seq data analysis. 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

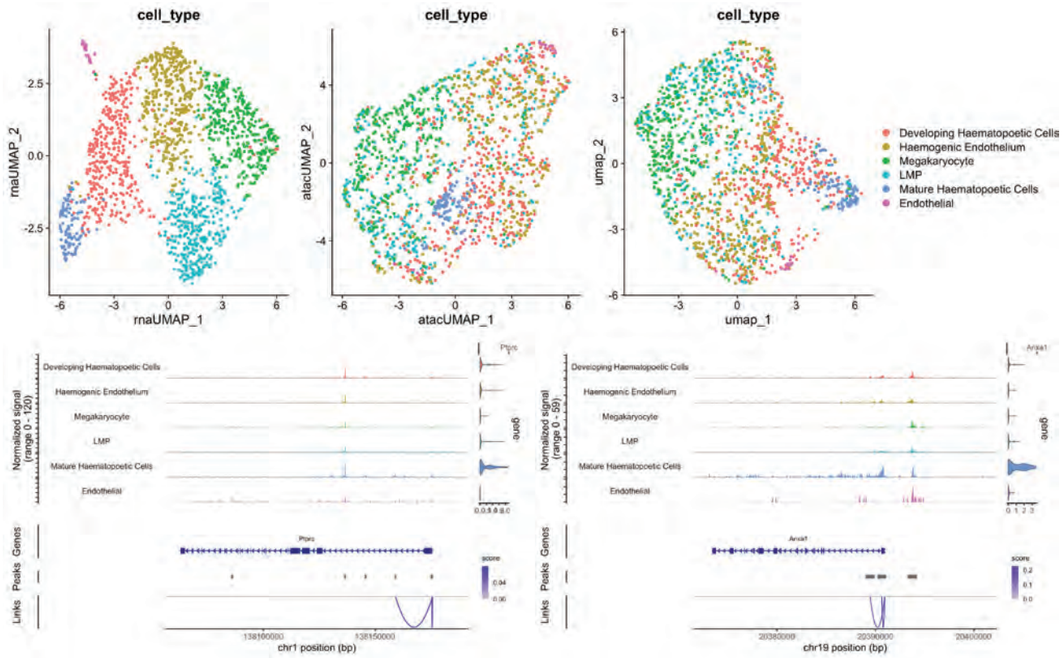


Figure 2: 10X multiome analysis using data from Ali Al-Anbaki and Georges Lacaud in the Stem Cell Biology group.

now manages these steps, allowing the MBC core facility to provide users with downstream-ready expression matrices.

Other automated pipelines implemented include those for single-cell analysis (10X Chromium/3′ and 5′ TCR sequencing, ParSE-Seq), 10X Multiome pipeline (see Figure 2) and spatial transcriptomics (10X Visium, CytAssist, Stereo-Seq), which produces quality-controlled expression matrices and spatial coordinates. Furthermore, the Dorado base caller is optimised for the PS2 Nanopore Sequencing platform to produce quality-controlled outputs and base modification sites. We also have workflows in place for Whole Genome Sequencing (WGS), Whole Exome Sequencing (WES), ChiP-Seq and ATAC-Seq that generate BAM files, which can be directly used for variant calling and epigenomic analysis, respectively.

The CBS team has been at the forefront of supporting Institute facilities 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. For advanced analysts or bioinformaticians, CBS hosted a monthly seminar series focused on best practices in bioinformatics data analysis, which has recently attracted significant attention. 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 well-informed and adhere to best-practice guidelines.

Genome Editing and Mouse Models

Natalia Moncaut, Athina Papaemmanouil, Lauren Street

The Genome Editing and Mouse Models (GEMM) facility is a core service dedicated to generating novel genetically modified mice. Using cutting-edge technologies such as CRISPR-Cas9 and other targeted genetic modification tools, our team assists in generating advanced animal models to study cancer that closely replicate the biological processes of disease initiation, progression and metastasis. We collaborate closely with researchers to develop tailored targeting strategies based on their specific needs, offering fully customisable support to help achieve their experimental goals. Through this collaborative approach, we ensure the development of optimal cancer mouse models, driving forward our understanding of the disease.

This year we introduced the use of embryo electroporation and adeno-associated virus to deliver CRISPR-Cas components to generate genetically engineered mouse models. These methods offer a highly efficient way to target large and complex genetic modifications. By using this method, we successfully generated new mouse lines carrying degron tags, point mutations and complex conditional cassettes integrating the expression of fluorescent proteins and diphtheria toxin receptors. Replacing the time-consuming, expensive and technically demanding embryo microinjection and ES-cell targeting approaches with this simpler, more efficient and potentially high-throughput method undoubtedly decreases the turnround time for generating new mouse models.

Additionally, this year we hosted the inaugural Genetically Altered Mouse Models Workshop as part of the MRC National Mouse Genetics Network. Held at the Paterson Building, this event brought together facility heads from across the UK for two days of in-depth discussions on advancing mouse model development.

Furthermore, in collaboration with the BRU Transgenic Breeding Team, we launched the First Workshop on Transgenic Breeding and Colony Management, providing foundational training for students and postdocs new to the transgenic field. This initiative will now be held annually to ensure continued education and support for early-career researchers.

Histology

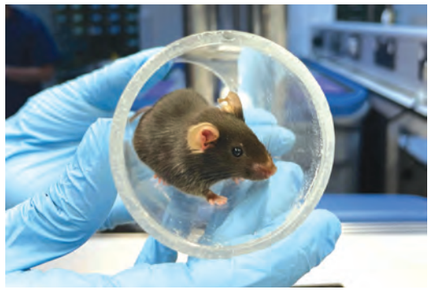
Garry Ashton, Caron Abbey, Amy Lawrence, Peter Magee, David Millard, Nicola Tonge

The Histology facility continues to be an integral service, accessed by both basic and translational research groups within the CRUK MI – underpinning their research, and allowing for the adoption and development of tissue-based experimental approaches. The unit offers a full range of both routine and advanced histological services for oncology research. Following a successful review, which validated the need for more resource, the unit will be recruiting a new post to ensure we continue to provide an exceptional service across all areas. Focus will remain on the training and continued professional development of staff, ensuring the unit continues to be at the forefront of technological development whilst offering a comprehensive and flexible service that is relevant across all research themes.
The high throughput, routine immunohistochemistry service, troubleshooting and antibody validation services continue to see exceptional demand. With the recent increase in imaging capability, the unit continues to develop higher plex immunofluorescence, allowing for 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 in demand.

In routine practice, both human and mouse tissue, in addition to organotypic assays, spheroids, agar plugs and cell pellets, continue to be evaluated together with fresh vibratome tissue sections (50–250µm) for ex vivo cultures of tumours, to evaluate and develop three dimensional studies. Requests for special stains have included Masson Trichrome, Picro Sirius Red, Alcian Blue, Cresyl Violet and PAS. Demand for cryosectioning resulted in the delivery of a second cryostat.

Tissue microarrays allow for high sample number throughput and analysis. In line with the development of spatial technology assays, many new macro- and microarrays have been constructed in addition to various formats of composite blocks. The Grandmaster TMA platform allows for accurate core sampling by incorporating a digitised H&E overlay. Many TMA projects involve the use of biobank material processed through the facility. A dedicated scientific officer is responsible for ensuring the unit is compliant with current human tissue legislation. Both laser capture microdissection and the extraction of nucleic acids have proved extremely popular. Downstream the samples are sequenced or used as a quality control step prior to spatial transcriptomic analysis.

The unit continues to focus on the development of advanced spatial technologies. In collaboration with the Molecular Biology Core, both 10X Visium and GeoMX spatial transcriptomic assays are routinely offered. In collaboration with the Visualisation, Irradiation & Analysis facility, spatial proteomics - evaluating 100+ markers - is offered.



RESEARCH SERVICES (CONTINUED)

Institute Research Group projects

Systems Oncology

The Histology unit has aided the Systems Oncology group in working with 3D synthetic models to study alterations to organoids dependent upon drug treatment or stiffness changes. A viable protocol for the embedding and sectioning of the model has allowed for further study of the ongoing changes within the cells through immunofluorescent staining. Since there is no light sheet microscope within the Institute at present, the group have used the vibratome, cryosectioning and laser capture for isolation of ROIs from tissue pieces for further downstream analysis. The group are also using high multiplex immunofluorescence (Phenocycler-Fusion) to construct an atlas of pancreatic cancer progression. Microtomy, validation of markers with automated chromogenic IHC and customised tissue microarrays have all been used for this piece of work.

The TranMet project studies 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 plans to perform laser capture microdissection coupled with high-resolution spatial visualisation and molecular profiling at both protein and RNA levels. By comparing the primary tumour with its metastases, the Systems Oncology group aim to understand how different organ environments influence metastatic behaviour and function.

Skin Cancer and Ageing

The Skin Cancer and Ageing group have used spatial transcriptomic analysis to compare intracranial melanoma tumours. This data has been instrumental and allowed the group to design further spatial transcriptomics experiments on human samples. The Stem Cell Biology group have also used spatial transcriptomics on a precious, unique cohort of samples which required very precise ROI selection through multiple levels across the samples.

Cancer Inflammation & Immunity

The Cancer Inflammation & Immunity group have discovered a pathway used by cancer cells to evade the immune system in mouse tumour models and aim to validate this finding in human tumour biopsies. The facility is optimising and analysing a 12-plex immunofluorescence panel to look for evidence that the pathway is playing a similar role in human disease.

University of Manchester Division of Cancer Sciences Research Group projects

Targeted Therapy Group

The Targeted Therapy Group are optimising the Nanostring GeoMx spatial transcriptomics platform to enable them to identify gene changes in CD4+ and CD8+ T cells in skin biopsies taken from patients with cutaneous T-cell lymphoma receiving Pembrolizumab and radiotherapy in the PORT study. The group are also using multiplex immunohistochemistry to determine how immune cell populations change after radiotherapy in the TIMM-RAD study.

Breast Cancer Biology Group

The Breast Cancer Biology Group are characterising a novel ex vivo model for use in breast cancer prevention, aiming to determine how human breast tissue responds to various hormonal treatments. A key component of this work is the development of a 7-plex immunofluorescence panel, which will allow an in-depth characterisation of the human breast tissue and analysis of the spatial expression of different factors. The Histology unit has been instrumental in supporting this effort by lending their expertise in immunohistochemistry, guiding the development of the panel, and ensuring its successful implementation to enhance the accuracy and depth of the analyses.

IT and Scientific Computing

Marek Dynowski, Brian Poole, Christopher McCauley, John Campion, Kevin Doyle[1], Krar Haider, Matthew Young, Stephen Kitcatt, Stephen Royle[1], ZhiCheng Wang, Bijesh Choorakkatt[2]

[1]Retired in 2024
[2]Joined in 2024

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 2024, the team experienced several staff changes. After a distinguished career, IT Manager Stephen Royle retired, marking the end of his dedicated service. Shortly thereafter, Kevin Doyle, the IT and Scientific Computing Linux Systems Administrator who had been with us since 2018, also retired. We were pleased to welcome Bijesh Choorakkatt as our new Linux Systems Administrator at the end of 2024.

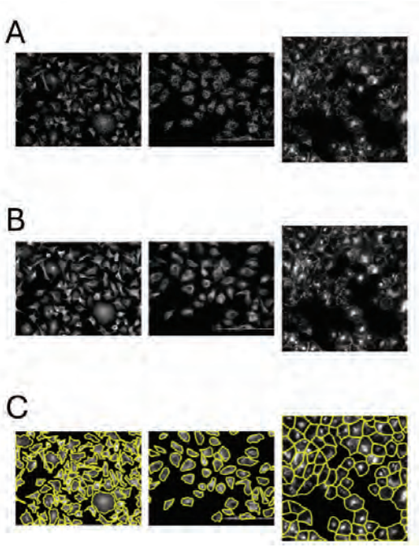


Figure 1: (A) Noisy raw image. **(B)** Imaged denoised with Cellpose in Galaxy. **(C)** Cell segmentation with Cellpose using Galaxy.

The IT team and the Scientific Computing team were merged in 2023 to create an opportunity to operate infrastructures more effectively and reduce duplication, a process that is continuing. One concrete result of the merger is that we designed a new virtualisation platform that meets IT requirements for redundancy, security, and reliability, as well as the performance and flexibility needed by Scientific Computing. This new platform, comprising CPUs and GPUs, can support business-critical services and, at the same time, provide powerful virtual desktops for interactive machine learning and artificial intelligence applications. It will replace the two separate platforms currently in operation.

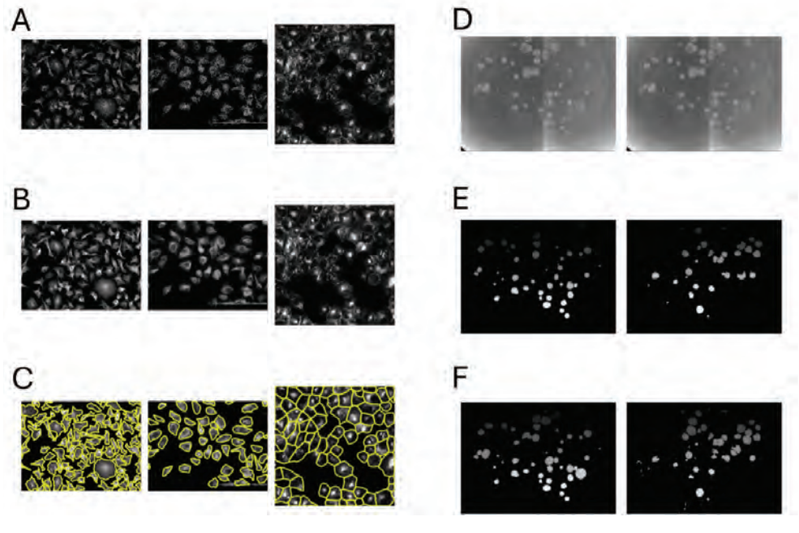


Figure 2: (A) Noisy raw image. **(B)** Imaged denoised with Cellpose in Galaxy. **(C)** Cell segmentation with Cellpose using Galaxy. **(D)** Test results of images (from Systems Oncology) segmented using Cellpose custom model, test raw image. **(E)** Predicted labels. **(F)** True labels.

The Christie IT team collaborated with the IT and Scientific Computing team to establish the CRUK Staff Wi-Fi. This network now enables members of CRUK MI and CRUK NBC to securely access the internal network and all associated services, including the Griffin HPC system. Efforts to harmonise procedures, network infrastructure, and security measures for CRUK MI workgroups in the Paterson Building and the Oglesby Lecture Theatre continued. The network protection measures already implemented in the Paterson Building were also rolled out in the Oglesby Cancer Research Building.

To facilitate collaboration with external partners and ensure that the Institute and the CRUK NBC are well-prepared to operate in a highly collaborative environment, the process for creating external user accounts has been streamlined with the HR department and the Operations team.

Together with the NBC, the IT and SciCom team has procured new Managed File Transfer (MFT) software to streamline and unify data management processes across the Institute and NBC. Significant benefits are anticipated from redesigning and automating the data transfer processes from scientific instruments to the IT and SciCom operated storage and computing systems. This automation will not only reduce the workload for users and core facility staff but also minimise errors and ensure that generated data is promptly available to researchers and bioinformaticians. Existing and future required data management processes were thoroughly examined, and their implementation started after extensive training by the software supplier.

The team also offered user training last year. It regularly provides mandatory training for new users of the Griffin High-Performance Compute (HPC) Cluster. The introduction of a training

video has enhanced this process, enabling new users to use the system most efficiently. In addition, we provide solutions to simplify the usage of the computing platforms. The Galaxy Bioinformatics Workflow portal is a powerful tool that enables users with minimal amount of training to use powerful computing resources. It is a graphical web interface designed to facilitate the ease of submission of computing jobs and comprehensive bioinformatic analysis workflows to the Institute's HPC system.

The team worked with other core facilities and researchers to develop and integrate new applications to simplify the usage especially of powerful machine learning methods.

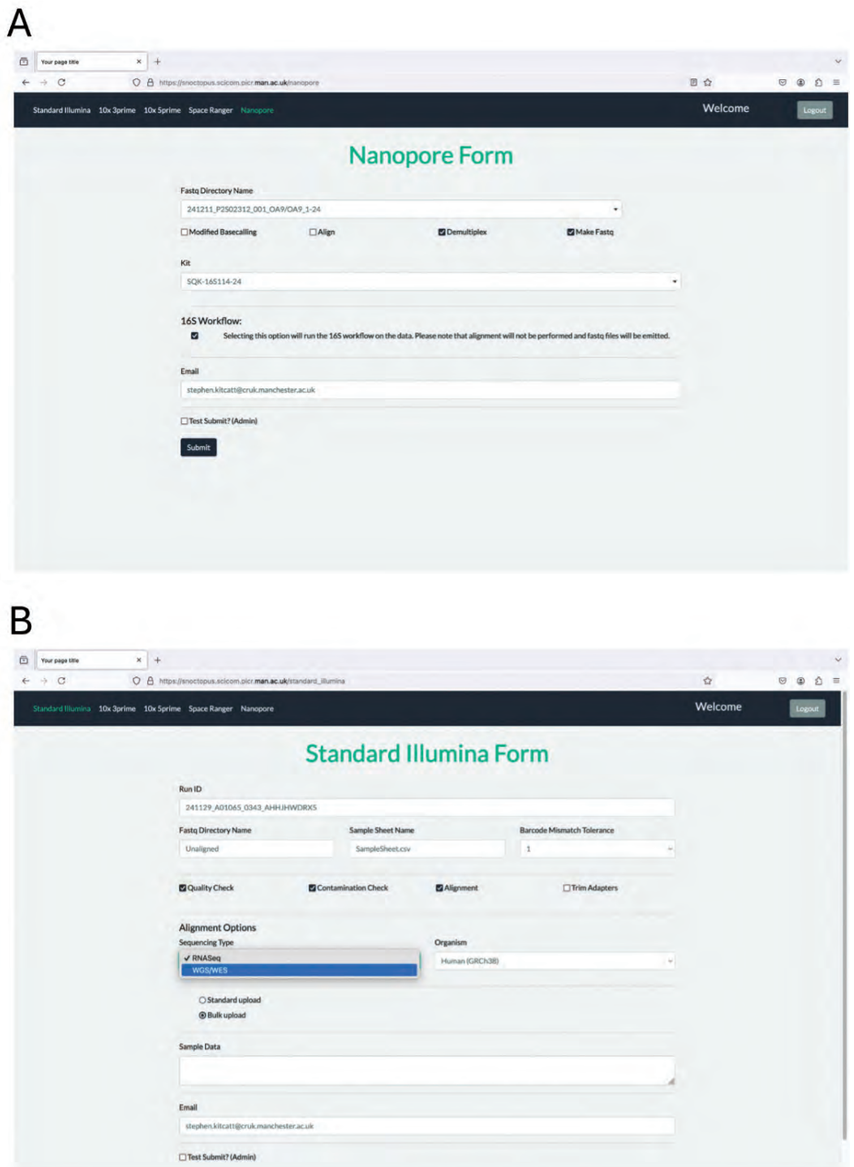


Figure 3: (A) 16S analysis workflow for data generated using Oxford Nanopore sequencers. **(B)** Whole genome/whole exome upstream analysis of data generated using Illumina sequencers.

Optimising Cellpose using Jupyter Notebooks in collaboration with the Visualisation, Irradiation and Analysis (VIA) core facility and making them available in the Galaxy portal empowers users to easily perform denoising, segmentation (see Figure 1 or Figure 2) and custom model training utilising HPC. Denoising is an important methodology for reducing the damage of irradiated fluorescent markers. Fluorescent samples can be subjected to a lower dose of laser light, which reduces photobleaching but leads to a low-quality (noisy) image. The quality of noisy images can then be enhanced using deep learning algorithms. To make this method more widely accessible we developed a Galaxy for the Care 2D and Noise 2 Void algorithms for restoring low quality images. Another Galaxy app is currently being developed by the team together with the FACS core facility to enable users to perform high-throughput analysis of their Mass Cytometry data.

In our effort to relieve Bioinformaticians from repetitive tasks, the IT and SciCom team has implemented several new automated upstream processing workflows in collaboration with Computational Biology Support (CBS) and Molecular Biology Core (MBC). The MBC laboratory staff set up sequencing experiments using the in-house Snoctopus upstream processing platform and select the type of upstream analysis to be performed once the data is generated. This approach accelerates the end-to-end generation of sequencing data, allowing Bioinformaticians to focus on more complex downstream analysis and interpretation of results. CBS and MBC designed the workflows, while the IT and SciCom teams implemented them as pipelines on the in-house Snoctopus platform. This collaboration resulted in the development of the Dorado pipeline, a high-performance base caller for Oxford Nanopore reads, a 16S pipeline for species-level bacterial identification (see Figure 3), and alignment pipelines for Whole Genome/Whole Exome data using BWA, as well as for transcriptomic data using STAR.

A replacement for the end-of-life Columbus™ Image Data Storage and Analysis system was developed in close collaboration with the VIA core facility. The new solution facilitated the decommissioning of outdated software and hardware and the archiving of legacy data while allowing users to continue conducting 2D image analysis and introduced 3D image analysis capabilities. Additionally, it enables retrieving archived legacy data for re-analysis if needed. To further enhance the Institute's capability for analysing large imaging datasets, we have implemented the open-source Napari software on a dedicated physical server.

This server is equipped with a high-speed network connection to the large-scale storage systems and the HPC managed by our team, and it can be accessed via Remote Desktop connection. Utilising Napari on this platform allows users to interactively analyse extensive 2D and 3D imaging datasets with custom plugins, under the supervision of the VIA core facility, ensuring accurate analysis.

Laboratory Services

Mark Craven, Christine Williams, Corinne Hand[1], Tony Dawson, Busola Atuegbe

[1]Left in 2024

During 2024, Lab Services continued to supply the various sites with sterilised fluids, glassware, plastics and microbiological media using our glass washers and autoclaves.

We maintain and restock communal supplies of these items for the labs based in the Paterson Building and the Oglesby Cancer Research Building (OCRB), making daily visits to remove dirty items and replace with clean ones. Our primary sites remain the Paterson Building and OCRB. During 2024, we continued to support some activities in satellite sites including the Proton Beam Therapy Centre, MCRC Biobank and Incubator buildings.

By having access to autoclaves, we can sterilise bespoke items required by labs and, in coordination with our Media Coordinator by prior agreement, we can adapt our current microbiological media and make any new alternatives requested by labs, providing greater flexibility for the labs we support.

The team also operates the lab coat laundry service across the site and provides a monthly on-site pipette clinic for our researchers. The Manager also supports the Chief Laboratory Officer in arranging statutory testing of safety cabinets and fume hoods, insurance inspections, and with the supply of first aid related items across the site.

We are contributing to the on-going sustainability initiatives and Lab Services currently holds the LEAF (Laboratory Efficiency Assessment Framework) Silver Award in recognition of the sustainability actions we have taken.

Mass and Flow Cytometry

Antonia Banyard, Emily Scanlon, Adam Milner[1]

[1]Joined in 2024

The flow and mass cytometry facility is always dynamic and has had another extremely exciting and successful year. Our instrument and technical skills portfolio continues to expand to keep pace with the explosion of new fluorophores and technologies available on the

market, ensuring our research groups can also expand and grow the ideas that lead to breakthrough results.

We have the new Sony ID7000 analyser, which has 6 lasers, 138 channels for phenotyping, coupled with incredibly powerful software and hardware to enable high throughput and high content data analysis and is a game changer for all the research groups.

We have also procured another Novocyte with full plate sampler automation to add to our platform portfolio, resulting in a total of 11 instruments within our facility.
The team has expanded to include the recruitment of Adam Milner in June 2024 who, alongside Emily Scanlon, is now part of our specialised team. The team provides bespoke training, hands-on skills and daily advice for cell sorting, cell analysis, mass cytometry and ImageStream data collection and analysis.

In terms of cell sorting, the Bigfoot Spectral Cell Sorter is now paying dividends, enabling our researchers to run longer cell sorts with greater phenotyping panels while maximising sort output in terms of cell viability, regularly using 25 parameter panels, which has never been possible until now. The CyTOF XT continues to produce robust datasets, mainly for more translational research, but from this data further studies are flourishing to determine functional abilities from patient samples.

The facility underwent a successful external review, which validated the need for an additional post to enable us to expand our expertise and ensure the acquisition and analysis of all data from our facility continues to be world leading.

Molecular Biology Core

Wolfgang Breitwieser, Leah Binnall[1], Hannah Bowden[2], Rachel Horner, Jason Rumley, Poppy Spiers[2], John Weightman

[1]Left in 2024
[2]Joined in 2024

The Molecular Biology core facility provides a comprehensive NGS service that includes sample QC, sequencing library prep and sequencing on Illumina and Oxford Nanopore instruments. The service is used by Institute research groups as well as other University of Manchester groups based in our building, with over 120 projects processed for more than 20 research teams in the last year. Closely following the latest developments in sequencing technologies, the team strives to provide the optimal solutions for the successful processing of often challenging samples. For example, in a recent project we demonstrated that minute amounts of genomic DNA derived from laser-capture microdissection can be effectively used for whole genome sequencing, thereby permitting the mutational analysis of tiny tissue samples, such as micro-biopsies, typically consisting of only a few hundred cells.

A significant and increasing proportion of NGS projects involves gene expression and chromatin (e.g. ATAC) analysis in single cells. Most projects are currently processed using an emulsion-based technology, including scRNA-Seq, immune cell profiling, multiome (scRNA & ATAC-Seq), and CRISPR screen projects (e.g. Perturb-Seq). A further frequent application is Smart-Seq for single cell transcriptome profiling of rare cell populations. For this microwell plate-based technology the service has adopted a miniaturisation and automation approach, employing the department's robotic platforms. In addition, we are currently exploring automation solutions to incorporate further single cell technologies, including combinatorial indexing, into the core service.

The Molecular Biology team collaborates with most other core facility groups on a range of services, e.g. with BRU in pathogen testing for in vivo experiments, the Mass and Flow Cytometry facility for single cell applications, the Genome Editing and Mouse Models team for molecular analysis, Histology and VIA in spatial transcriptomics workflows. In addition, Scientific Computing implements most NGS data processing workflows, data storage and transfer. A dynamic and flexible interaction with the computational teams, in particular Computational Biology Support, is essential for frequent implementation of novel methodologies, e.g. in single cell and spatial omics. Specifically, spatial transcriptomics is a service that spans multiple facilities involving Histology, VIA, Scientific Computing, and Computational Biology Support. The service is comprehensive and includes all aspects of tissue processing, imaging, region selection, followed by transcriptome capture, library prep and sequencing.

The department has made great use of the recently acquired Oxford Nanopore PromethION P2 platform. This high throughput long read sequencer is used for a variety of applications and emerges as a strong alternative to short read sequencing. Nanopore technology identifies bases and derives sequences as nucleotide strands pass through biological pores embedded in a membrane as the main component of a sequencing flow cell. The emerging sequencing reads are independent of molecule size and can produce uninterrupted contigs of many thousands of bases. In addition, the sequencing platform can be trained to identify modified nucleotides allowing for its use in e.g. methylation sequencing studies. This has recently been successfully applied to genomic DNA samples as well as cell free DNA. Therefore, long-read sequencing is emerging as a valuable tool for methylation analysis of circulating tumour DNA.

Using dedicated instrumentation, the department's compound screening service supports high-throughput, high-accuracy compound dispensing. It is predominantly used for custom drug testing experiments, e.g. dose response tests, as well screens using dedicated compound libraries, including the recently purchased library of FDA approved drugs consisting of ~2,800 compounds. In addition, the dispensing platform is integrated into some NGS applications, predominantly in single cell RNA-Seq, e.g. Smart-seq protocols, to aid cost effective sample processing by assay miniaturisation and high sample throughput.

Visualisation, Irradiation & Analysis

Steve Bagley, Alex Baker, Jianhua Tang, Henry Banks

The Visualisation, Irradiation & Analysis (VIA) facility within Cancer Research UK Manchester Institute has a large remit, including the training of researchers, operation of instruments, supply of support documentation, maintenance and quality control of hardware and outputs, and experimental design for microscopy, high content screening and tissue-based imaging.

The roles of the VIA team have been recently reorganised in response to research demands. They have supported 33.5K hours of live cell imaging, 1.5K hours of high content screening, imaged 10.5K histology slides, given over 5K hours of time supporting image processing and analysis, and provided over 170 training sessions. Support is ongoing with other facilities in the fields of spatial biology pipelines and in vivo imaging. The facility also recently underwent a successful external review to examine relevancy to research demand, communication and to assist in setting its future ambition and purpose.

Additive manufacturing using 3D printing has been a key function of the facility since 2012. This allows low-cost design and production of devices. In 2024, demand for different types of novel 3D-printed apparatus has grown across research groups, the Biological Resources Unit, and Histology.

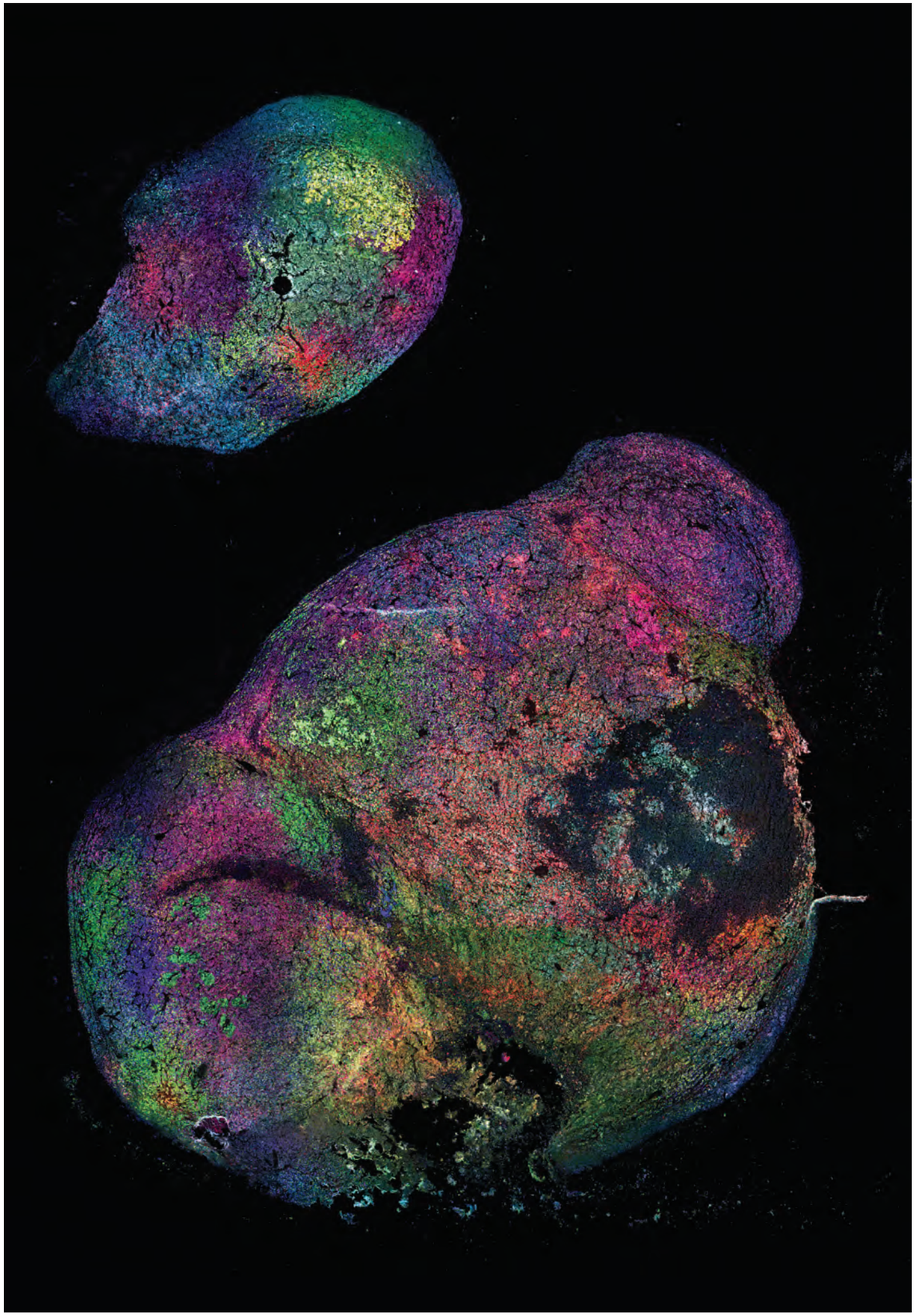
For five years the facility has been undertaking the examination of tissues by labelling with up to 50 fluorescent probes using the Akoya CODEX system, to enable the analysis of complex protein relationships across small tissue sections. Working with the National Biomarker Centre, the older Akoya CODEX system was replaced with the Akoya Phenocycler II, which permits a greater number of fluorescent labels, larger tissue sections and tissue micro arrays to be analysed.

Over the last two years the facility has been working upon the open microscopy initiative; the development and integration of instruments based on open-source software. The facility team has built one system and is planning to construct a second. The advantage of utilising open-source designs where possible is that instruments would not be limited to a single manufacturer hence the most suitable components can be integrated and permit an adaptable upgrade pathway in response to the research requirement.

A recent development is the adoption of the LEAF scheme, which contains actions that lab users can take to save plastics, water, energy and other resources. By taking part in the programme, laboratories will reduce their carbon emissions and create an environment that supports research quality. The facility has endeavoured to view this as a priority and was recently awarded the highest level of the scheme in October 2024.

The facility has also taken part in a microscopy for schools' project and has assisted over thirty lab tours. Two internal talks and one external talk on multiplex imaging and analysis were given by the facility.

Through advancements in imaging, design, and sustainability, the facility remains integral to cutting-edge cancer research, supporting diverse imaging modalities in collaboration with other research teams and facilities.



PUBLICATIONS AND OPERATIONS

CDX cells can be transduced with LeGO vectors to express red, green and blue fluorescence which generates multi-coloured fluorescent cells. The different colours represent a different clonal population of CDX cells growing in the tumour.

Image supplied by Griselda Awanis (Small Cell Lung Cancer Biology)

RESEARCH PUBLICATIONS

Cancer Immunosurveillance
(Page 12)

Evangelos Giampazolias

Refereed research publications

Giampazolias E, Pereira da Costa M, Lam KC, Lim KHJ, Cardoso A, Piot C, Chakravarty P, Blasche S, Patel S, Biram A, Castro-Dopico T, Buck MD, Rodrigues RR, Poulsen GJ, Palma-Duran SA, Rogers NC, Koufaki MA, Minutti CM, Wang P, Vdovin A, Frederico B, Childs E, Lee S, Simpson B, Iseppon A, Omenetti S, Kelly G, Goldstone R, Nye E, Suárez-Bonnet A, Priestnall SL, MacRae JI, Zelenay S, Patil KR, Litchfield K, Lee JC, Jess T, Goldszmid RS, Reis E Sousa C. (2024)
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Cancer Inflammation and Immunity (Page 14)

Santiago Zelenay

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Leukaemia Biology (Page 18)

Tim Somervaille

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(Page 22)

Amaya Virós

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Georges Lacaud

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Rob Bristow

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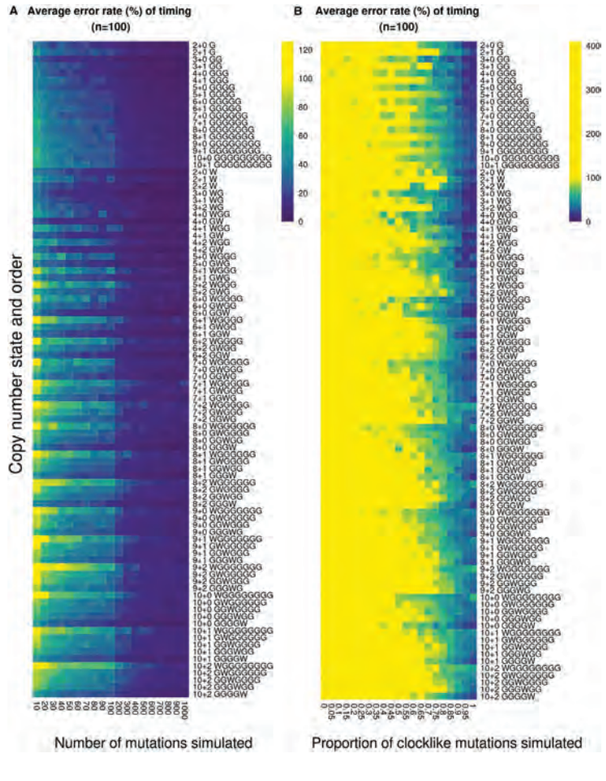

Average error rate of time points calculated from simulated data, expressed as a percentage. n = 100 randomly simulated sets of time points for each order, copy number state, and condition. Colour scales are capped at 100% error rate to allow better visualization of lower percentages. (A) Average error rate of calculated time points when varying the number of simulated mutations. (B) Average error rate of calculated time points when varying the proportion of clock-like mutations simulated. Figure reused from Jakobsdottir et al. *Bioinformatics*. 2024 Jun 3;40(6):btae281. doi: 10.1093/bioinformatics/btae281.

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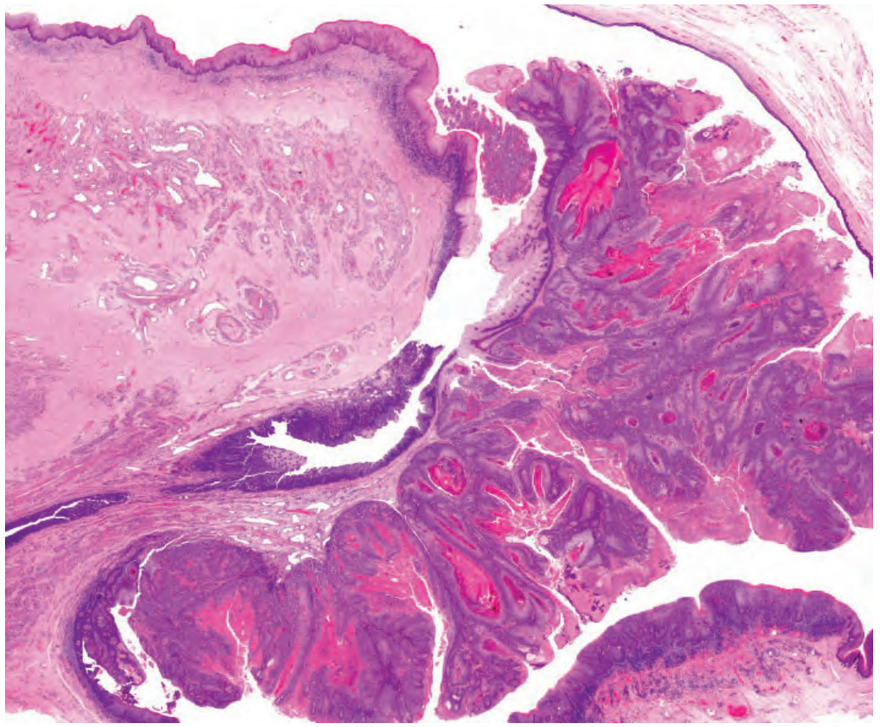
Histological image showing the whole mount penis lesion.

Image supplied by Diego F. Sanchez Martinez (Translational Oncogenomics)



EXTERNAL SEMINAR SPEAKERS 2024

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.

Jen Morton
CRUK Scotland Institute

Manuel Valiente
CNIO

Renato Ostuni
San Raffaele Scientific Institute

Thomas Mercher
INSERM

Jessica Strid
Imperial College London

Jim Hughes
University of Oxford

Alberto Mantovani
Humanitas University

Triparna Sen
Icahn School of Medicine at Mount Sinai

David Withers
University of Birmingham

Laura Wood
Johns Hopkins University

Phil Jones
Wellcome Sanger Institute

Justin Loke
Dana Farber Cancer Institute

Dinis Calado
The Francis Crick Institute

Ingo Ringshausen
University College London

David Kent
University of York

Sergio Quezada
University College London

Julie Helft
Institut Cochin

Erica Sloan
Monash University

Marina Pasca di Magliano
University of Michigan

Alexis Barr
Imperial College London

Karim Labib
University of Dundee

Karen Vousden
The Francis Crick Institute

Richard Weller
The University of Edinburgh

Eugenia Piddini
University of Bristol

James Nathan
University of Cambridge

Alejandra Bruna
Institute of Cancer Research

Ivan Ahel
University of Oxford

Doug Winton
University of Cambridge

Samra Turajlic
The Francis Crick Institute

Vivian Li
The Francis Crick Institute

Nicola Aceto
ETH Zurich

Mariano Barbacid
CNIO

Eva Perez-Guijarro
National Cancer Institute

David Bryant
University of Glasgow

Adam Hurlstone
University of Manchester

John Brognard
National Institutes of Health

Leila Akkari
Netherlands Cancer Institute

Spatial expression of glutamate decarboxylase in murine brain.

Image supplied by Charlotte Russell (Skin Cancer and Ageing)

OPERATIONS

Chief Operating Officer
Caroline Wilkinson

Chief Laboratory Officer
Stuart Pepper

Chief Finance Officer
Mike Berne

Chief Human Resources Officer
Rachel Powell

The Institute is now settled into its new location with 2024 providing an opportunity to consolidate and review our operating processes as we look to expand and maximise the potential of being back on the site of the Christie NHS Foundation Trust. The Administration and Scientific Administration teams worked together with colleagues from the Christie to organise the event marking the formal opening of the Building in July 2024. Our guest of honour Professor Sir Paul Nurse, Nobel Laureate and Director of the Francis Crick Institute, declared the Paterson Building officially open during a highly enjoyable day. Both those teams also organised our first full off-site colloquium since 2019, which was a joint event with the Cancer Research UK National Biomarker Centre (NBC) marked by two days of stimulating presentations and poster sessions. The Operations team of the Institute continues to support the activities of NBC alongside their Institute responsibilities.

Chief Operating Officer
Caroline Wilkinson

Gill Campbell and Andrew Porter from Scientific Administration continued the development of a new external website for the Institute due for launch in early 2025 with support from Ruth Cox and Minerva Cheng. Ruth moved into a new role of Operations Project Lead within the Scientific Administration team and is now also Executive Assistant to the Deputy Director.
During the summer we prepared for a detailed review of our operations by Cancer Research UK, which took place in the autumn as part of a series of reviews they were conducting across their core funded institutes. This has helped us to refine some of our processes and facilitated the sharing of best operational practices across the institutes.

In March, the Animals in Science Regulation Unit (ASRU) conducted an audit of our in vivo facility and its related governance processes as part of their regular programme of auditing establishments that conduct research under the Animals (Scientific Procedures) Act. AWERB Chair Sally Robinson and Home Office Liaison Contact Simon Poucher helped to ensure we were well prepared. This was augmented by a mini-internal audit of our governance processes conducted by Sally Robinson and Colin Gleeson prior to the visit by ASRU's Inspectors. We were very pleased with the highly successful outcome of the audit.
We have made great progress during the year towards our sustainability goals using the LEAF initiative to guide our activities. LEAF is a standard set by UCL to improve the sustainability and efficiency of laboratories. All the Institute's research groups and facilities have achieved at least bronze status. This initiative is being led by Stuart Pepper (Chief Laboratory Officer) who has established a cross-Institute working group to drive our efforts on this objective. We have also participated in the cross-CRUK Institutes working group. Six labs have achieved gold status and five have silver. This was following several visits from UoM LEAF auditors who praised how we are approaching this initiative. We now have a clear roadmap for all research groups to achieve silver by spring 2025. We have continued to work closely with Dalkia, the Facilities Maintenance contractor for the Paterson Building, over further initiatives to reduce energy consumption.

In terms of team changes, we said goodbye to Michael Alcock and Nigel Fletcher from the Logistics team, Vikki Rosheski from Finance and Andrew Haines from Human Resources and thank them all for many combined years of service to the Institute. We welcomed Minerva Cheng to the Administration team, Rebecca Grant in Human Resources, Abigail Scott in Finance, and Wilfred Seville to Logistics.

The Operations team is looking forward to the Institute's growth and development in 2025 and supporting the new Institute Director and their team, and the new teams led by Sylvain Delaunay (RNA Dynamics in Cancer) and William Hill (Cancer Origins).

Institute Administration Team
Caroline Wilkinson, Ruth Cox, Karen Lee, Minerva Cheng[1]

[1]Joined in 2024

The Institute Administration Team plays a crucial role in supporting the Senior Management Team and Faculty, ensuring the smooth operation of the Institute. Ruth Cox is now Operations Projects Lead and Executive Assistant to Claus Jorgensen in his role as Deputy Director. Karen Lee is Executive Assistant to Caroline Wilkinson, Chief Operating Officer and Stuart Pepper, Chief Laboratory Officer. We were pleased to welcome Minerva Cheng to the team as Administration Services Coordinator in 2024.

This year, the Administration Team had the enjoyable task of helping to organise the Paterson Building Open Day – the official opening and celebration of our new building, which took place in July and included guest speakers, Professor Sir Paul Nurse, Andy Burnham Mayor of Greater Manchester, and former Christie patient Adele Adams together with speeches from Dame Nancy Rothwell (the then President and Vice Chancellor of The University of Manchester), Roger Spencer (Chief Executive Officer of the Christie NHS Foundation Trust) and Dr Iain Foulkes (Executive Director Research & Innovation at Cancer Research UK). In addition, the team organise social events providing opportunities for our staff and students to meet for informal discussions and interactions.

We have also been pleased to relaunch the now joint CRUK Manchester Institute and National Biomarker Centre Colloquium at a new off-site venue. The team led on arranging the event at a new location in Buxton, which was a great success, and we plan to return next year.

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 37 external seminar speakers in 2024 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. Details can be found at cruk.manchester.ac.uk/seminars.

Human Resources
Rachel Powell, Andrew Haines[1], Rebecca Grant[2], Julie Jarratt, Laura Jones, David Stanier[3]

[1]Left in 2024
[2]Joined in 2024
[3]Joint with Scientific Administration

Over the past year, the HR Department has continued to deliver a high-quality proactive service to the Institute, Cancer Research UK 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.

During 2024, we were successful in appointing and onboarding 53 new individuals. By providing a full on-boarding service, we ensure that all new appointees are integrated smoothly into the Institute or NBC and embrace our culture. We have provided one-to-one support to each of our new appointees. We collaborated with our funders Cancer Research UK, and with their help and support have been able to make use of the endorsed funder Global Talent Route for international individuals. We have supported 5 Global Talent visas successfully; this is in addition to 7 Skilled Worker Visas. In addition, we are delighted to have recruited a new Junior Group Leader, Sylvain Delauney, who will join the Institute in January 2025. We look forward to continuing to support the growth of the Institute and NBC as it expands over the next couple of years.

We are committed to developing our staff and ensuring that Personal Development Reviews (Contribution & Development Reviews) are undertaken. The department also facilitated the successful promotion of 7 individuals this year. In addition, we have continued our commitment to joint partnership working with the Union,

which has resulted in the renewal of the workforce agreement and revision of several policies and procedures throughout the year. These include the revision of the Flexible Working Policy, Sickness Absence Policy and the creation of a new Carer Leave Policy.

Over the year, the department has had a continued drive on and commitment to wellbeing initiatives and supporting mental health within the Institute. Our aim is to ensure that all people within the Institute have a supportive environment that enables them to flourish and achieve their best through workplace initiatives and practices in a place that is conducive to supporting individuals' health and wellbeing. Members of the department sit on the Institute's Wellbeing Group, which has been established to promote general wellbeing within the Institute.

The Institute implemented its Equality, Diversity and Inclusion strategy in 2023, and the HR department has continued to support this work throughout 2024. Members of the department sit on the EDI Steering Committee, which provides leadership, drive and strategic direction. The department has strongly supported the Institute's EDI vision, which is to create a diverse and inclusive culture that develops, attracts, and maintains a positive environment for staff and students whilst achieving its aim to deliver world leading cancer research.

The department's key EDI strategic priorities for 2025 are: continuation of the EDI interim action plan; commencement of the process of Athena Swan Bronze accreditation; development of the use and implementation of support plans for staff within their roles; continuation of training and awareness in neurodiversity together with a continued focus on wellbeing initiatives.

Finance and Purchasing

Mike Berne, Denise Owen, David Jenkins, Muhammad Raja, Abigail Scott[1], Vikki Rosheski[2]

[1]Joined in 2024
[2]Left in 2024

Over the past year we have seen an increase in funding and collaboration opportunities. While inflation has begun to settle down compared to the last few years of uncertainty, the observed growth in all round costs remains a concern. We continue to foster good relations with funders and suppliers to encourage best use of money and resources to allow our scientists to undertake their programmes of research. The Finance team continues to support the Institute Director and Senior Management Team in the management of the £17m budget, which is reduced compared to last year to account for the transition of the Cancer Biomarker Centre to become the CRUK National Biomarker Centre, the finances of which are also managed by the Institute's Finance team.

The Finance team plays a critical role in assisting with costing proposals and providing advice for new research proposals and contracts for all our groups. Despite global financial pressures, the Institute's scientific community has continued to be successful in winning a number of new awards this year relating to research applications and contractual agreements.

Scientific Administration

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

[1]Joint with HR

The Scientific Administration team provides a variety of services to aid the smooth running of the Institute. A major project for 2024 was working together with the Christie NHS Foundation Trust to plan the official opening of the Paterson Building. This was held in July with the official duties conducted by guest of honour Professor Sir Paul Nurse. The Scientific Administration team produced a range of presentations which highlighted the history of research on the Paterson Building site including the work of Ralston and Edith Paterson after whom the building is named, the build phase, and current research activity. We were delighted to be joined on the day by descendants of the Patersons.

We have continued to showcase our new building through tours and research activity presentations to donors, fundraising groups, and various Cancer Research UK teams, such as Press Officers and shop managers and volunteers.

Members of the Scientific Administration team contributed to the organisation of our first off-site colloquium since 2019, which was held in Buxton and was a great success. Our postgraduate education programme continues to be overseen by Postgraduate Education Manager Julie Edwards (see the Education section of this report for further details). Julie manages PhD recruitment, admissions and administration, organises the Institute's Education Committee, and provides pastoral support to our student community.

Colin Gleeson and Chris Bamber comprise our Health and Safety team and have contributed to refining our H&S processes in the new building while working on some new sustainability initiatives. Further details can be found elsewhere in this report.

Gill Campbell is our Grants Advisor and Scientific Operations Officer who assists our scientists in sourcing external funding opportunities and contributes to the applications through helping to prepare sections such as an applicant's profile, their publications, host/environment description, data management plans, training, and research engagement. She also co-ordinates the activity of the Institute's Grants Committee who peer review applications and help applicants prepare for grant/fellowship interviews. This year there was funding success through applications to CRUK, Blood Cancer UK, Pancreatic Cancer UK, US Department of Defense and the Rosetrees Trust.

Gill also plays a vital part in the Institute's communications activities and compiles and edits this report as well as the Institute's newsletter and keeps the external website up to date. Through much of 2024, Gill led on a project to produce a new external website for the Institute together with Andrew Porter and with contributions from Ruth Cox and Minerva Cheng. The team worked with external providers who undertook the development of the site, while consulting widely across the Institute over its format and design and producing new content.

Andrew Porter is our Research Integrity and Training Adviser who supports the Institute's scientific community through a pre-submission manuscript review process and by providing training sessions and workshops for our early career researchers covering topics such as thesis writing, statistical analysis, use of generative AI and a research integrity induction for new students and staff. He is continuing with a major project to deploy an electronic lab notebook (ELN) platform across the Institute. Andrew co-wrote and secured a UKRI Metascience Research Grant with Professor Andrew Stewart, University of Manchester Institutional Lead for Open and Reproducible Research. From this we are receiving funding for more tablet computers for our in-lab testing and will access support from a post-doctoral research associate to investigate barriers and test possible solutions in support of the ELN roll-out.

Andrew continues to participate in events in the wider research integrity and culture sector. In 2024, amongst other activities, he attended the World Conference on Research Integrity in Athens where he presented a poster on research integrity inductions. He was invited to participate in the Open Science to Increase Reproducibility In Science (OSIRIS) project using the Institute's research integrity activities as an example of good practice.

Andrew is also a key part of the Institute's communications team overseeing our social media channels and research engagement facilitating many tours and filming opportunities supported by Karen Lee, Minerva Cheng and Ruth Cox.

David Stanier is the Institute's Information Governance Coordinator and Administrative Officer supporting the Institute's Information Governance Guardian, Caroline Wilkinson, with the management of information security, data protection and records management to ensure information governance disciplines are embedded within working practice across the Institute. In addition, David manages several areas which contribute to the smooth running of the Institute, such as courier services, Institute induction sessions and managing stationery supplies.

David and Caroline are part of the University of Manchester's Information Governance Guardian Network for FBMH and regularly interact with the University's Data Protection Officer and Information Governance Office over any IG queries and best practice. He chairs the meetings of the Institute's Information Governance (IG) Committee, which amongst other activities seeks to review any institutional IG requirements as well as considering the management of IG risks for the Institute's risk register.

Health and Safety

Colin Gleeson, Chris Bamber

The Health and Safety Team further consolidated our health and safety arrange-ments in the Paterson Building. This included the development of cross-organisational agreements that summarised health and safety arrangements and responsibilities between the stakeholders in the Paterson Building (The Christie NHS Foundation Trust, CRUK MI and The University of Manchester's Division of Cancer Sciences). This helps to minimise ambiguity around legal and operational responsibility and to ensure that all health and safety

arrangements are covered concomitantly reducing our organisational risk.

We also reviewed and revised many of the health and safety documents and much of the information on our intranet to make it more user friendly for staff and students. We scaled up our workplace monitoring activities including rolling out two CRUK MI and NBC-wide inspection programmes (one a self-inspection survey and the other led by the Health and Safety Team), carrying out behavioural safety surveys and regular fire safety walk arounds. We also continued to monitor compliance with Occupational Health surveillance requirements and regulated chemical and biological agents (such as explosive precursors, the controlled drugs list, schedule five of the ATCSA and animal biproducts).

We also made a significant contribution to sustainability initiatives in our laboratories. We reviewed our waste processing and were able to identify waste processing routes, which were legally compliant, and at the same time reduced the Institute's carbon footprint, thus saving energy and reducing costs.

We continue to support staff and students with pragmatic health and safety advice, review risk assessments and undertake task analysis where necessary to better understand the risk from our research work. We play an active role in the wider University community making contributions to several specialist advisory groups (e.g. The Genetic Modification and Biohazards Advisory Group and Ionizing Radiation Safety Working Group) and make significant contributions to our landlord's building and facilities management arrangements, both formally by committee meetings and more informally by direct contact with key people on site.

Logistics

Andrew Lloyd, Edward Fitzroy, Sedia Fofana, Jonathan Lloyd, Robin Sherratt, Wayne Howarth, Wilfred Seville[1], Michael Alcock[2], Nigel Fletcher[2]

[1]Joined in 2024
[2]Left in 2024

Over the past year the logistics team has successfully delivered an efficient and reactive service, providing support for the research activities carried out in the Paterson and Oglesby Buildings. The team has also supported the GEMM team based at the Incubator Building and the MCRC Biobank team located in the Kay Kendall Laboratories.

The team operates a back of house service and takes direct delivery of consumables from the couriers. Using live finance programmes, goods are then receipted and distributed accordingly. Items that cannot be delivered immediately are stored in the department at the appropriate temperature pending their delivery.

Logistics is responsible for the disposal of Institute laboratory waste. We support all recycling initiatives. Using both the University and Christie services enables us to recycle large volumes of Institute waste, reducing waste going to landfill. Across both buildings, we are currently recycling cardboard, plastic bottles, tin cans, wooden pallets, polystyrene boxes, ice/gel packs, ink toners, glass, plastic media bottles as well as waste electrical equipment (WEE).

The team looks after the Institute's liquid nitrogen reserves and monitors the liquid nitrogen levels in the cell storage tanks, topping up on a weekly basis. In 2024, the Institute had 60,000 litres delivered to site and used 17,680kg of dry ice.

They are also responsible for the changing of all gas cylinders. The manifolds are monitored daily, and cylinders are replaced as necessary. There are several standalone cylinders located around both the OCRB and Paterson Building, which the team is also responsible for changing over. We have around 150 cylinders across both sites.

Researchers can order central stores stock items via the intranet, which can be collected or distributed by the Logistics team. We currently stock over 200 stores items from tissue culture essentials to cleaning products. We add new products all the time, most recently focusing on those that support our sustainability goals. We also have available the enzymes and media stored in the Institute's freezers (Sigma, Life tech, Promega, New England Bio labs, and Qiagen). We have consignment agreements in place with suppliers and buying in bulk, producing some savings for the Institute.

In addition, the team supports the moving of heavy equipment and furniture around the Institute. This includes general disposal and the rearrangement of existing equipment to accommodate newly arrived equipment. The team has also supported the onsite electronics technician by moving equipment to provide access for maintenance purposes.

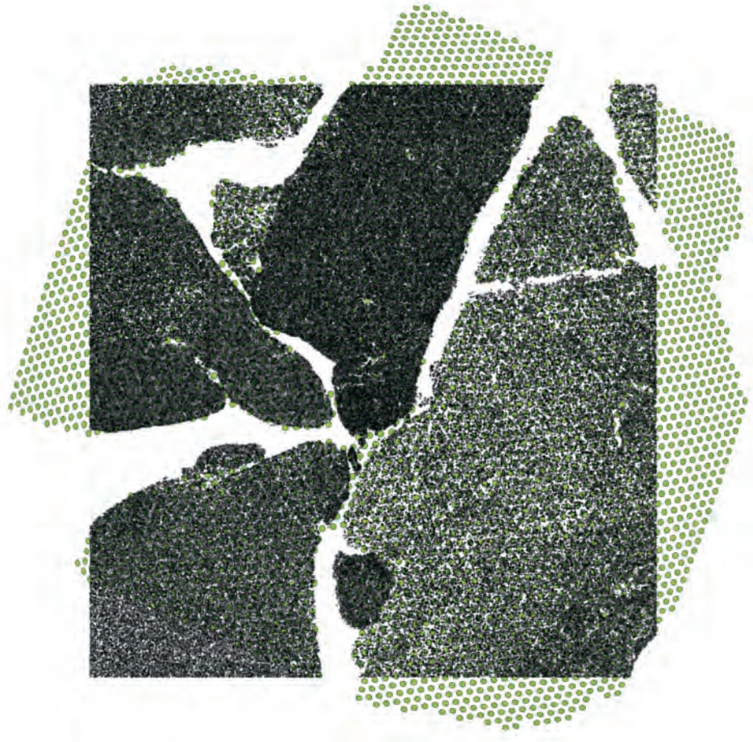


Image shows cellular centroid locations ('+' signs) on serial section A (ssA) and the registered/aligned Visium SD spot locations from serial section B (ssB). Image registration allows measurements to be taken from cells in ssA using Hyperion imaging mass cytometry (protein) and analysed alongside the transcriptome of "the same" cells [10um sections] from ssB using Visium SD. This method is extensible, meaning any feasible multiomic combination can be assayed via the use of serial sections and image registration.

Image supplied by Rob Sellers (Computational Biology Support)

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, reviewing processes, staff training, and facilities for the care and use of mice, and encourages 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 have now spent a full calendar year at the animal facility in the new Paterson Building in Withington.

We used 18,166 mice in total during 2024. Of these, 7,370 were used in the breeding programme for the production and supply of mice for CRUK MI researchers (an increase of 12.1% over 2023). We used 10,796 mice in experimental research programmes in 2024, including the generation of new genetically altered mice (an increase of 72.6% compared to 2023). The number of mice used in 2024 reflects a more normal year of use compared to the previous year when there was a period of downtime whilst we moved to our new research facility. Other than when we moved last year, the total number of mice used in 2024 was lower than any year since 2014.

The Institute continues to promptly report any unexpected events to the Animals in Science Regulation Unit (ASRU), all of which have been resolved with ASRU. ASRU conducted an audit of our animal facility in March 2024. This involved staff interviews, inspection of documentation and the facilities. We were delighted with the very positive outcome and feedback that we received.

AWERB reviewed four new project licence applications and nine 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 3Rs, poster event in January 2024; such events allow us to share best practice and generate discussion around the topic areas.

We continue to build a Culture of Care amongst staff working with mice. In 2024, there were 12 AWERB Recognition Awards given for a wide range of activities to encourage good practice across the Licensees. We have completed a survey of licensees to i) find positive examples of Culture of Care in action (relating to animals, people and science); ii) examine the emotional burden of animal work; and iii) examine the role of communication from a Culture of Care perspective. We discussed the results of the survey and formally launched our Culture of Care Pledge at an event in October 2024, which was opened by Dr Penny Hawkins of the RSPCA. In response to the survey, we have also developed an 'in vivo listening ear' role. This role will help facilitate discussions between in vivo staff on emotional matters relating to animal work.

We have introduced many significant refinements to the way we perform procedures. One example of refinement is the use of image guided injection of tumour cells into the left ventricle of anaesthetised mice to investigate cancer spread. This was previously achieved using anatomical markers and resulted in a much lower success rate for certain types of cancer cells. Another example is the development of a jig manufactured by 3D printing that allows mice to be exposed to irradiation under much shorter periods of anaesthesia delivered by inhalation rather than by injection.

We also engaged with external fora to help share and further develop best practices in animal welfare:

- Members of the Institute contributed to external activities related to animal welfare, 3Rs or AWERB tasks, for example the Royal Society for the Prevention of Cruelty to Animals (RSPCA) meeting on running an effective AWERB in June 2024, or through contributions to the Laboratory Animal Science Association
- Our poster on the scientific use, welfare and husbandry of SKH1 mice was recognised with the Andrew Blake Tribute Award, which is run by the Institute of Animal Technology (IAT)
- Our poster on the refinements of the irradiation jig to allow for gaseous anaesthesia won the Northwest IAT branch poster award
- Caroline Wilkinson and Sally Robinson are members of the national Establishment Licence Holders Forum; Sally 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 Presidents Advisory Group; Natalia Moncaut is a convenor for the genetically altered animals section of LASA; and Simon Poucher is a member of the Home Office Liaison, Training and Information Forum (HOLTIF)

Commercialisation and Innovation Support

Nathalie Dhomen, Martyn Bottomley

Cancer Research Horizons (CRH) is Cancer Research UK's innovation engine. By arrangement with The University of Manchester, CRUK owns and is responsible for the development and commercialisation of intellectual property arising from CRUK funded research at the University. Our local commercialisation support team aims to bridge the gap between cutting edge academic research and industrial development of cancer therapeutics, medical technologies, and diagnostics.

Over the past year, our Cancer Commercialisation and Innovation Lead, Nathalie Dhomen, has continued to provide a link into the commercialisation support infrastructure of both Cancer Research Horizons and The University of Manchester Innovation Factory – the University's technology transfer office. She supports researchers and clinicians in identifying new high-value IP and innovations arising from their research and can facilitate access to oncology-focused expertise in technology evaluation, patent applications and management, funding for development, commercialisation, preclinical and clinical development, drug discovery, market intelligence and spin-out formation.

This past year we've supported a dozen active translational projects and taken several new innovation disclosures from researchers across the Manchester Cancer Research Centre (MCRC). With three patents being supported through to the international application stage at the CRUK Manchester Institute and CRUK National Biomarker Centre, we've supported the translational development of these projects towards the clinic by accessing translational funding, engaging external consultants and tapping into our expert networks and alliances. We look forward to seeing the products and services that are taking shape entering the clinic and making a difference to patients and their families.

The recipients of the MCRC's inaugural Springboard Award, co-funded by Cancer Research Horizons to pump prime early-stage translational projects with a strong potential for patient impact, have also made great strides in progressing their projects towards clinical implementation. Four projects, including one led by CRUK National Biomarker Centre researchers addressing the diagnostic challenges of biliary tract cancer, have been funded through the scheme, and have generated exciting translational data and novel IP. Based on the success of the first round, a second iteration of the award is due to launch in the first half of the coming year.
Looking forward, areas in which we expect to further support researchers are in enabling the sharing and wider use of large molecular or multi-omics datasets and providing access to pooled CRISPR screens that identify and validate new drug targets and approaches that will change the cancer landscape.

Cancer Research Horizons has a dedicated data team that can help researchers maximise the impact of cancer datasets, through their expertise and through such funding opportunities as the Data Innovation Awards, which provides funding and support to help researchers make these datasets more accessible and usable by third parties including commercial entities. We have seen one of these awards deployed successfully and effectively within our local ecosystem by The Christie NHS Foundation Trust's Clinical Outcomes and Data Unit (CODU) and look forward to building similar success for the innovative cancer datasets being generated across the ecosystem.

To support access to CRISPR screen technology, Cancer Research Horizons has a long-standing collaboration with AstraZeneca organised as the Functional Genomics Centre (FGC), a world-leading centre of excellence in genetic screens, cancer models, CRISPR vector design and computational approaches to big data. Its goal is to support CRUK funded researchers to identify novel targets and drug resistance mechanisms to help develop new cancer medicines, and new projects are currently under discussion with CRUK MI and NBC researchers.

We actively manage a broad portfolio of development programmes and exciting licensing opportunities originating from the Cancer Research UK Manchester Institute that continue to attract commercial partners. These projects include novel pan-cancer treatment response biomarkers from the Cancer Inflammation and Immunity group, assets from the National Biomarker Centre, novel blood production technologies from the Stem Cell Biology group, as well as unique cancer research tools, both laboratory-generated and digital. We are seeing an increasingly diverse range of research innovations being developed by CRUK funded researchers in Manchester, and we look forward to advancing their discoveries to beat cancer in the years ahead.

POSTGRADUATE EDUCATION

Postgraduate Education Manager
Julie Edwards

Postgraduate Tutor
Santiago Zelenay

Postgraduate Director and Chair of the Education Committee
Tim Somervaille

The Cancer Research UK Manchester Institute offers postgraduate degrees (PhD) for students interested in a career in cancer research. The Institute considers 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 great majority continuing in academia, industry or healthcare, and securing positions in destinations across the UK, Europe and the USA. In 2024, 100% of our graduates found positions following PhD completion: academia (54%), scientific industry (23%) and return to clinical training (23%). The Education Committee also oversees PhD students from the CRUK National Biomarker Centre and has representatives from NBC sitting on the committee.

In 2024, we welcomed nine new graduate students to our PhD programme, working in a variety of fields, including cancer immunology, leukaemia biology, cancer biomarkers, small cell lung cancer biology, and translational oncology.

It was also particularly gratifying to see that, over the past twelve months, some of our PhD students and clinical research fellows have published first author papers including in the *Journal of Hematology & Oncology* and *BMJ Oncology*.

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 most 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 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 mental health and wellbeing. A programme of in-house training events, external and internal seminars provides an invaluable opportunity in encouraging 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 and Oglesby Buildings – to connect with the wider scientific community.

Student research and activities continue to thrive in the new building, which opened in April 2023, 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.

The CRUK Manchester Institute and CRUK National Biomarker Centre annual colloquium took place at a new external venue in October 2024 at the Palace Hotel, Buxton in the Peak District. This presented a great opportunity for staff and students to reunite off-site for the first time since 2019.

The colloquium provides the chance for our new intake of students to meet other established PhD students, group leaders, postdoctoral fellows, and scientific officers, and other members of the Institute. 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.

We congratulated student Jingru Xu from the Stem Cell Biology group, who was awarded the Lizzy Hitchman Prize for the best poster presentation by a PhD student for her project on the role of immune modulator interferon regulatory factor 2 binding protein 2 (IRF2BP2) in AML.

Cancer Research UK contributes towards PhD student attendance at the annual International PhD Student Cancer Conference (IPSCC) allowing students from the top cancer research institutes across Europe to organise and 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.

The 17th International PhD Student Cancer Conference brought together 140 students in June 2024, hosted by students from the Max Delbruck Centre (MDC), Berlin.

The two-and-a-half-day programme featured high profile keynote speakers, student talks, poster sessions, career workshops and opportunities for networking and scientific discussions with plenary speakers.

POSTGRADUATE EDUCATION (CONTINUED)

CRUK Manchester Institute was represented by 23 students from years 1-4. The programme featured three excellent talks chosen from abstracts submitted by CRUK Manchester Institute students:

Liam Clayfield, Stem Cell Biology – "Investigating the role of the retinal determination gene SIX1 in acute myeloid leukaemia"

Mathew Sheridan, Stem Cell Biology – "Investigating the requirement of KAT6A and its KAT activity in AML"

Charles Earnshaw, Cancer Inflammation and Immunity – "Glucocorticoids stimulate T cell-dependent melanoma growth control"

CRUK Manchester Institute PhD students are excited to be hosting the 18th IPSCC in Manchester in June 2025. The planning and organisation are well underway, and we are looking forward to welcoming PhD students from the UK and international centres to Manchester!

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 2024 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, Donor Funding Drug Resistance Appeal, The University of Manchester, National Biomarker Centre (NBC) and the Manchester Cancer Research Centre MB-PhD Scheme.

Education Committee 2024

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.

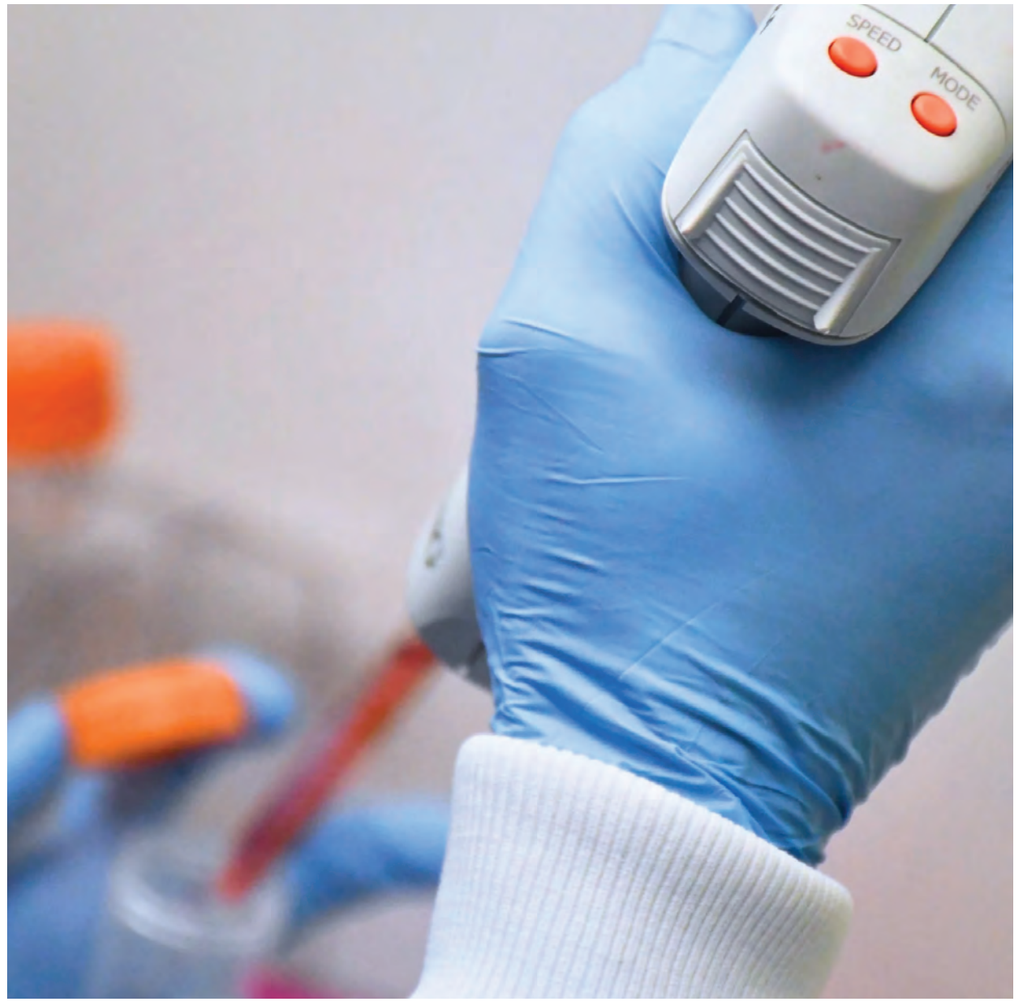
Our goal is for every student to have a project that is both achievable and intellectually stimulating and demanding. Projects and students are monitored by the Education Committee to ensure that the proposed plan for research is achievable, and that progress is made consistently throughout the duration 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
Caroline Dive, Interim Director, Ex-Officio Member
Julie Edwards, Postgraduate Manager
Santiago Zelenay, Postgraduate Tutor

Amaya Virós
Carlos Lopez Garcia[2]
Caroline Wilkinson
Claus Jørgensen
David Millrine[1]
Dominic Rothwell
Georges Lacaud
Mark Williams

Student Representatives
Sophie Richardson[2]
Florentia Moussoulou
Swara Patel[1]

[1]Joined in 2024
[2]Left in 2024



THESES

Amin Ali (CRF)
Translational Oncogenomics (formerly Prostate Oncobiology)

The Role of Prostate Zones in Cancer Progression

Catherine Cooper (nee Felton)
Systems Oncology

Exploring stimulus-driven heterogeneity in an organoid model of pancreatic ductal adenocarcinoma

Alexandra Hendry
Cell Division

Functional Dissection of the Cell Cycle Kinase PKMYT1

Julia Ogden
Translational Lung Cancer Biology

Building a novel human model to deconvolve the cancer-associated phenotypes of genetically dysregulated pathways in lung squamous cell carcinoma

Joshua Searle
Cell Signalling

The role of the E3 ubiquitin ligase HUWE1 in Non-Small Cell lung cancer

George Morrissey
Cell Signalling

Investigating acquired resistance to KRAS G12C inhibitors in KRAS mutant non-small cell lung cancer

Charles Earnshaw (CRF)
Cancer Inflammation & Immunity

Dissecting Melanoma Immunogenicity to Enhance Therapy Response

Lobsang Dolma
Tumour Suppressor

Functional Significance of mutp53 driven cell engulfment in cancer

Mathew Sheridan (CRF)
Stem Cell Biology

Investigating the requirement of KAT6A (MYST3/MOZ) and its KAT activity in AML

Oliver Bartley
Translational Immunology, CRUK National Biomarker Centre

Intrinsic Mechanisms of Immune Evasion in Small Cell Lung Cancer (SCLC)

Yitao Chen
Bioinformatics/Biostatistics, CRUK National Biomarker Centre

Identifying Predictive Biomarkers and Novel Drug Targets in Small Cell Lung Cancer via Multi-Omics Analysis

Pedro Durão
Skin Cancer & Ageing

Ultraviolet Radiation in cancer: friend or foe?

Victoria Fife (nee Gernedl)
Translational Immunology, CRUK National Biomarker Centre

COX-2 associated inflammation as a prognostic biomarker for relapse in early-stage 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. This year they continued to make the most of being in Withington and reaching out to our neighbours.

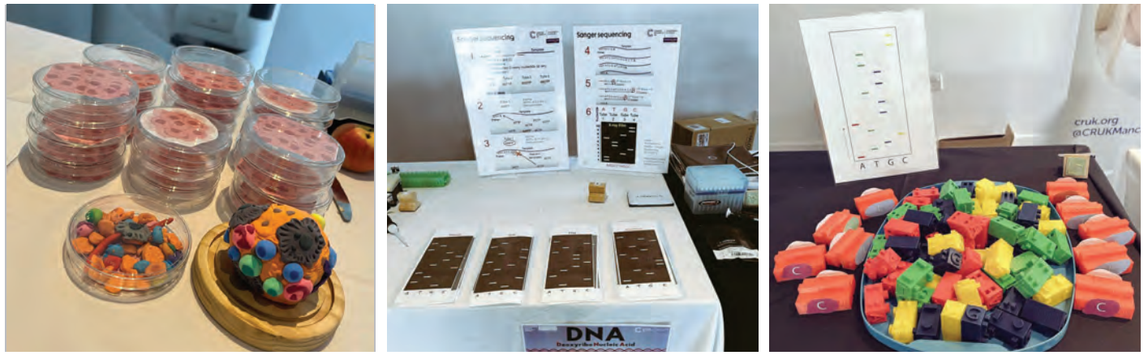
Engagement activities
Engagement activities start ramping up from World Cancer Day, held every year on 4 February. The aim is to raise worldwide awareness, improve education and catalyse action by working together to save millions of preventable cancer deaths and make access to life-saving cancer treatment and care equitable for all. It is an opportunity for our researchers to highlight the international impact of 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 again took part 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 and ran several activities demonstrating the improvements in cancer research over time, including DNA sequencing games and a real-time DNA sequencing demonstration supported by Oxford Nanopore. Over the two days, our team engaged with hundreds of school children from across the region, plus members of the public, who all enjoyed the learning experience.

Royal Society Summer Exhibition on Tour
In August, the team took part in the Royal Society Summer Exhibition on Tour, further developing their DNA-themed activities and engaging with over 1000 visitors across two days at Jodrell Bank. Our early career researchers and scientific officers also gave lectures on how we use liquid biopsies and circulating tumour DNA to detect and treat cancer.

New Scientist Live
Our scientists also participated in New Scientist Live, an educational and enlightening festival that showcases the latest breakthroughs, innovations, and discoveries in science and is accessible to anyone and everyone. Two Institute PhD students took part in the MCRC-led exhibit, which attracted over 30,000 visitors across three days, including 6,000 school children.



Some of the creative activities that our researchers brought to the Royal Society Summer Exhibition on Tour to engage budding young scientists.

Institute PhD student Parsa Pirhady from Translational Oncogenomics entertains visitors at New Scientist Live

Engagement support
Throughout the year, our researchers have supported individuals across the Institute and in partner organisations by providing presentation materials and hands-on kits for individual school visits and scout or guide group activities. Several researchers have taken part in The University of Manchester's Division of Cancer Sciences-led 'Microscopes 4 Schools' scheme, taking microscopes into local schools to support several activities as well as a 'meet the researcher' session.

The team also supported the 'I'm Still Me' art exhibition that was hosted in the OCRB and Paterson Building foyers. Our scientists helped the artists create digital content based on their portraits of patients with facial prostheses for the large art screens on the ground floor of the Paterson Building.

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.
The team have coordinated press visits, filming and photography for partners including the Christie press team when they require laboratory access. In February, the team co-ordinated a highly successful photoshoot with a CRUK professional photographer. Several images of researchers and core facilities staff have featured in digital and print campaigns throughout the year.

Fundraising for Movember 2024
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 £1,500, 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 CRUK Manchester Institute and the CRUK National Biomarker Centre for 2024 was £17.1m. The major source of this funding was awarded by Cancer Research UK (CRUK) via a core grant of £11.0m plus additional strategic funding of £0.4m. 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 supported by Research England generated income of £2.1m.

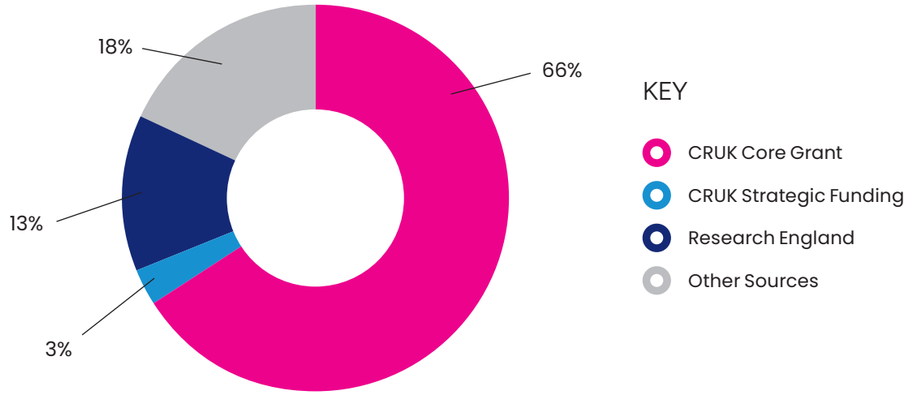
The balance of the Institute's funding is received from a number of additional sources. The research carried out through these additional projects enhances and supports the research undertaken by the core funding.

These sources are as follows:

- Blood Cancer UK
- CellCentric
- Christie NHS Foundation Trust
- European Commission
- European Research Council
- Harry J Lloyd Charitable Trust
- Imago Bioscience
- Lustgarten Foundation
- Medical Research Council
- Melanoma Research Alliance
- National Institute of Health Research
- NC3Rs
- Ono Pharmaceuticals
- Pancreatic Cancer Research Fund
- Prostate Cancer UK
- Rosetrees Trust
- Sosei Heptares
- UKINETS
- Wellcome

We are immensely grateful to all our sponsors.

CRUK MANCHESTER INSTITUTE FUNDING 2024



PATERSON BUILDING OFFICIAL OPENING CELEBRATION

Staff, funders, donors and special guests attended the official opening of the Paterson Building in July.

"Partnership is the Greater Manchester way". Those words were said by guest speaker Andy Burnham, Mayor of Greater Manchester, and perfectly described the significant milestone for the Cancer Research UK Manchester Institute.

The Paterson Building was officially opened on 17 July by guest of honour Professor Sir Paul Nurse, Nobel Laureate and Director of the Francis Crick Institute. We would like to highlight that this landmark achievement is a testament to the hard work and unwavering commitment of the Institute, alongside colleagues in the Manchester Cancer Research Centre partnership, and marks the completion of a journey that began seven years ago with a devastating fire.

The special guest of the day was Nobel-Prize winning scientist Professor Sir Paul Nurse who officially unveiled the plaque to mark the opening of the building.

After six years of development, and one year since construction finished and researchers, clinicians and administrative staff began moving in, we were finally able to celebrate and mark the next phase of our research here in Manchester.

The Paterson Building represents the embodiment of Manchester's commitment to cancer research and finding new cures for cancer. Co-locating 700 researchers, clinicians, and administrative staff, and directly connecting a research facility with The Christie, one of Europe's largest cancer hospitals, Manchester now has the facilities and expertise to be one of the world's leading comprehensive cancer centres.

We were delighted to have the opportunity to share this significant milestone with the many people who have contributed to making the Paterson Building a reality. Hosted on Floor 7 of our building, spectacular views across Manchester and the Pennines were enjoyed from the terrace and it made for a momentous occasion and a wonderful day of celebrations.

The Institute Operations teams supported the event and helped prepare the visual content displayed on big screens for the audience to enjoy. We shared the history of cancer research on the site, along with memories of the old building and contrasted these with details of the construction of the new building.

A timeline for the Paterson history brought to life the key players from the conception of the Paterson Laboratories in 1932, right up to the present day. There was much focus on the groundbreaking work of Dr Ralston Paterson and his wife, Dr Edith Paterson, which paved the way for breakthroughs that continue to save lives today and whose legacy led to the Paterson Building being named in their honour.

Images left to right: Mayor of Greater Manchester Andy Burnham addresses the audience on Manchester being the future of cancer research; The descendants of Ralston and Edith Paterson joined us for the celebrations; Showcase of the Paterson's archives.

We were pleased that the descendants of the Paterson's were able to join us and share in the celebrations. They brought with them treasured artefacts and publications for everyone to admire. It was a special day for them; many of the family members had not realised the impact their trailblazing ancestors had on cancer research in Manchester.

Following on from refreshments, the afternoon featured talks from several guest speakers, Roger Spencer (Chief Executive Officer of the Christie NHS Foundation Trust), Dr Iain Foulkes (Executive Director Research & Innovation at Cancer Research UK), and Dame Nancy Rothwell (the then President and Vice Chancellor of The University of Manchester) who all affirmed the respective commitment to cancer research in Manchester. Andy Burnham also joined to confirm Greater Manchester's commitment to research power in the north of England. However, it was former Christie patient Adele Adams' personal journey of how she navigated non-Hodgkin lymphoma that truly captured the audience. It brought home how our research is for people like Adele by offering opportunities to join clinical trials and experimental medicines that extend life and allow us to overcome cancer.

Roger Spencer, Chief Executive at The Christie
During his presentation at the official opening, Roger focused on the benefits patients will see from the new facility through additional clinical trials and novel research and chaired the event.

Adele Adams
Adele took the audience through an emotive and personal cancer journey from being diagnosed with stage 4 non-Hodgkin lymphoma to undertaking a clinical trial that has given her hope.

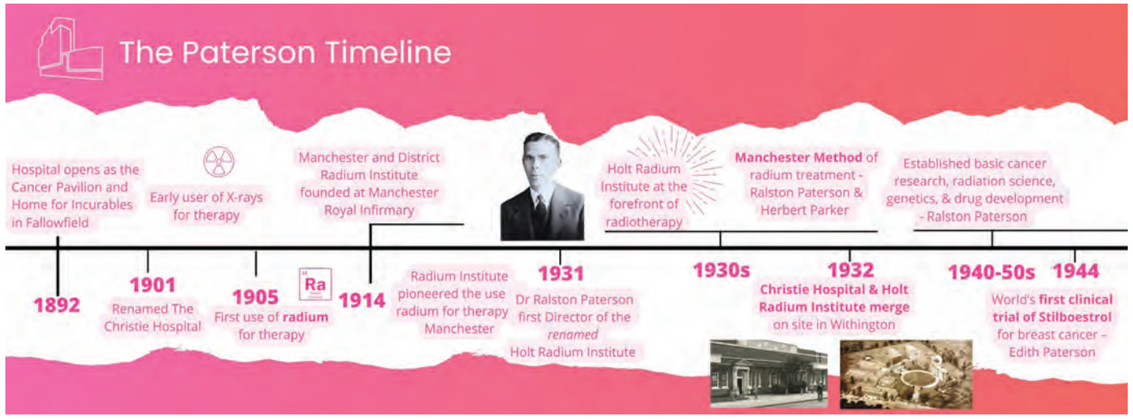
Andy Burnham, Mayor of Greater Manchester
Andy spoke about the importance of research to the Greater Manchester region and how Manchester has become a powerhouse for cancer research over the past 20 years.

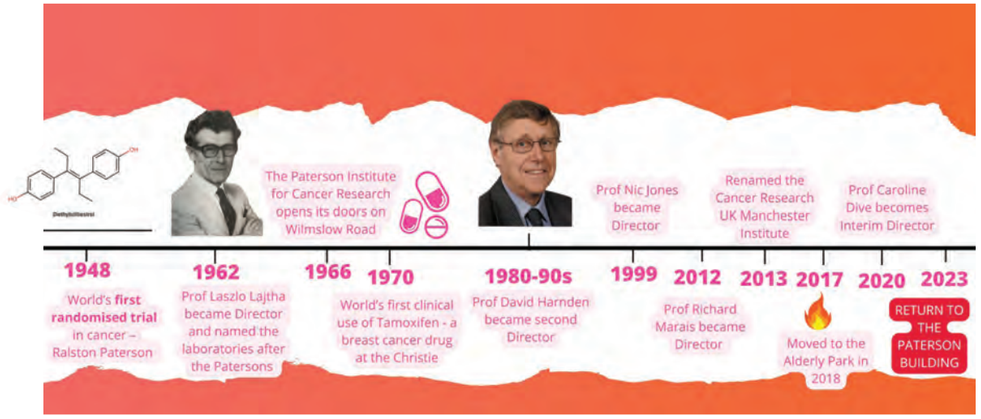
Prof Dame Nancy Rothwell, President of The University of Manchester
Nancy spoke about how cancer research is a research strength at The University of Manchester, reflective in the university's Cancer Beacon.

Dr Iain Foulkes, Executive Director of Research and Innovation at Cancer Research UK
Iain spoke about the unwavering support CRUK offered at the time of the fire and the commitment to the Institute and other CRUK research in Manchester.

Prof Sir Paul Nurse, Chief Executive of The Crick
Paul officially unveiled the plaque commemorating the official opening of the Paterson Building.

PATERSON BUILDING OFFICIAL OPENING CELEBRATION (CONTINUED)





Left to Right: Andy Burnham, Dr Iain Foulkes, Professor Dame Nancy Rothwell, Professor Sir Paul Nurse, Roger Spencer, Adele Adams, Professor Nic Jones, Professor Caroline Dive, Lord-Lieutenant of Greater Manchester Diane Hawkins, and Professor Robert Bristow at the official opening of the Paterson Building on 17 July 2024.

More than 200 people joined us to celebrate including leaders and representatives of the MCRC Partnership: The University of Manchester, Cancer Research UK and The Christie and other cancer organisations across Manchester, patients, philanthropists whose generosity helped make the building a reality, and representatives of the building contractors and designers.

MCRC Director and Institute Group Leader Prof Robert Bristow concluded, "The Paterson Building opening triggers the next phase of cancer research in Manchester. Thanks to the co-location of laboratory and clinical researchers, ideas and innovation will be free flowing that we hope will enable more research to be translated into the clinic and double the number of patients who can access a clinical trial by 2030."

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.

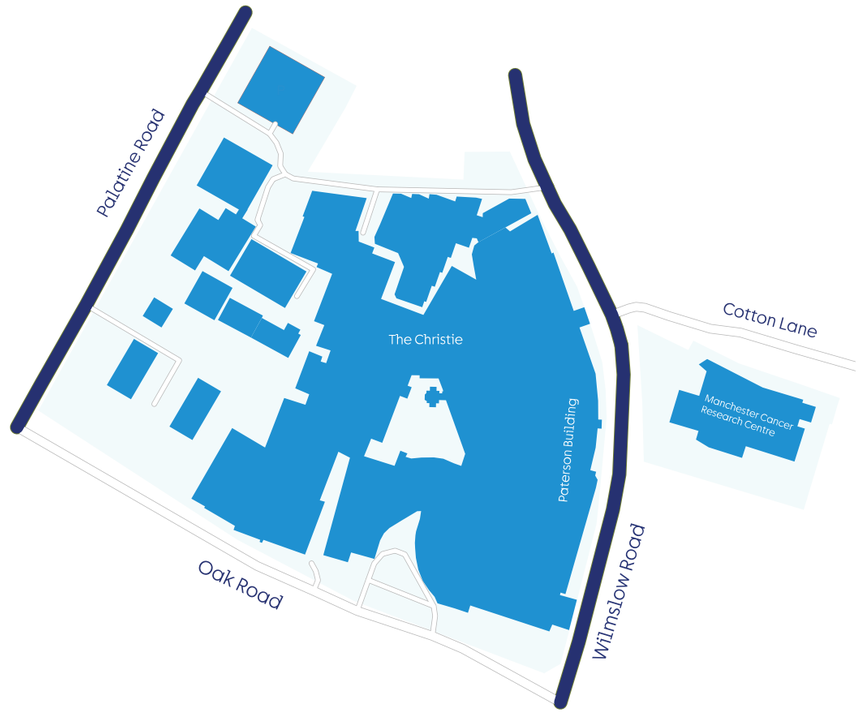
In addition to postgraduate and postdoctoral opportunities, the Institute is seeking to recruit outstanding candidates to the positions of Group Leaders. The packages provided are extremely attractive and commensurate with the experience of the applicant, with significant funding for personnel, recurrent 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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Cancer Research UK is a registered charity in England and Wales (1089464), Scotland (SC041666) and the Isle of Man (1103).
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