



CANCER
RESEARCH
UK

Manchester
Institute

MANCHESTER
1824

The University of Manchester

Newsletter

FEATURE - MOVE TO THE NEW PATERSON BUILDING

Welcome new Group
Leader Evangelos Giampazolias
Grants Awards and Meetings
QQR success
Publications



Autumn 2023



Some images in this publication have been reprinted under the terms of the Creative Commons Attribution (CC BY) license. Scan here for more information



Director's Introduction



It is my pleasure to welcome you to this edition of the Cancer Research UK Manchester Institute newsletter. Inside, we feature our latest research news, activities and events so that readers can learn more about our community here at the Institute.

First and foremost, I am so excited to announce that we have finally moved into our new research building on the original site next to the Christie NHS Foundation Trust. It is more than six years since the devastating fire that resulted in our Institute relocating to Alderley Park in Cheshire. While our temporary home there allowed us to continue our research, it is really great to be back and reunited with our colleagues at the Christie and in the Oglesby Cancer Research Building just across the street. The modern ten-storey bespoke designed building is a fantastic place to work, and we are all integrating well within our new environment.

Importantly, I would like to recognise that we would not be back in our new home if it wasn't for the remarkable resilience, patience and enormous efforts of many individuals across the Institute, together with the determination and hard work of the Paterson Redevelopment Project partners – The Christie, Cancer Research UK and The University of Manchester – and of course the support of the many generous donors to the project. I am very proud of all our staff at the Institute who have excelled in all aspects of Institute life, despite the fire, the relocation, the pandemic and the move back to Withington and I would like to thank everyone who helped facilitate our return to the 'Withington Cancer Campus'. It has been a long journey, but now we can start to reap the benefits that the synergies in discovery and translational research empower through colocation of researchers, clinicians, and allied healthcare professionals. In these pages we share with you our journey and celebrate our return as we deliver our cancer research ambitions in Manchester. As always, our high-quality research continues, and it is my great pleasure to highlight our

accomplishments. Congratulations go to Claus Jørgensen and his Systems Oncology group who underwent a highly successful quinquennial review of their research programme earlier this year. I am delighted that the calibre of their past research and future plans has been recognised with this impressive result. The team and their work are highlighted further on in the newsletter.

This year we also welcomed Claus as our Deputy Director of the CRUK Manchester Institute, taking over from Iain Hagan who has been stellar in supporting me and the Institute over the past three years. I would like to thank Iain for all his hard work and generosity with his time – he made the demanding and challenging period as we organised our return to the Paterson Building so much easier. As we move into a new phase re-establishing ourselves in Withington, I look forward to working with Claus and greatly value his strategic insights on important institutional decisions.

I am delighted to welcome Evangelos Giampazolias, who joined us at the start of this year from the Francis Crick Institute as a Junior Group Leader. Evangelos is establishing his new Cancer Immun-surveillance group here at the Institute, exploring how the immune system recognises and responds to cancer through the integration of cues released by dying cells and commensal microbes. You can find out more about the team and their research in the following pages.

Securing external funding is critical to augmenting the breadth of our research and ensuring our ongoing success, so it is with great pleasure that I congratulate Institute Fellow Amaya Virós, who was awarded a prestigious CRUK Advanced Clinical Scientist Fellowship this year. This is a fantastic achievement and enables Amaya and her group to continue their critical research exploring the role lipids play in melanoma metastasis, tropism and immunotherapy response at different sites in the body. We look on with anticipation as Amaya further develops her important research programme.

I would also like to congratulate Sara Valpione, consultant oncologist at The Christie and honorary senior lecturer at The University of Manchester. Sara also holds an honorary contract with CRUK MI having worked in our Institute as a clinical scientist for several years. She was recently awarded a substantial grant to research new therapies for hard-to-treat oesophageal cancer. This is excellent news for Sara, and I wish her all the best in delivering her vital programme of research.



Photo credit Nick Caville BDP

As we know first-hand, connected communities are critical for the advancement of science. Taking part in conferences enables researchers to share findings, exchange ideas, and to network for collaboration and career development. This is especially important for our early career researchers who are the future of cancer research, so I am thrilled that many of our students attended the International PhD Student Science Conference this year. This conference, organised by students for students, was a great success and saw PhD students Bradley Revell and Parsa Pirhady win first and second place prizes for their posters. Bradley, from the Leukaemia Biology group, was recognised for his work on the molecular mechanisms of transcription factors IRX3 and FOXC1. Parsa is from the Translational Oncogenomics group and focuses on the DNA damage repair pathway in prostate cancer. Great work, Bradley and Parsa. Congratulations also to Federica Spaggiari from the Small Cell Lung Cancer Biology group who won a poster prize at the North West Cancer Research Scientific Symposium.

Our early career researchers also presented their research at the Division of Cancer Sciences Postgraduate Research Showcase at the Oglesby Cancer Research Building. Congratulations to the Cancer Inflammation and Immunity group on their resounding success. Two PhD students in the group won prizes – Maria Koufaki won first prize for her poster and Charles Earnshaw won an award for his oral presentation.

Now a regular feature, the selection of highlighted publications showcasing the Institute's research has been written by some of our early career researchers. You can read more about our recent progress in leukaemia, the use of diabetes drugs to treat cancer, and how developing open-source platforms can support researchers and patient care.

Our early career researchers continue to enjoy connecting with members of the local community. It was great to see such enthusiasm and dedication behind the creation of a well-designed and inspiring outreach experience, 'The Biomarker Lab', that they took to several schools in the area during British Science Week. Helping to inspire the next generation of cancer researchers is an important engagement activity and I would like to thank our young researchers who took part.

Lastly, I hope you all had wonderful summer and managed to enjoy some restorative breaks. I am looking forward to bringing in the new year with everyone, strengthening existing partnerships and forging new collaborations as we drive forwards in our new facility with our exciting and impactful research.

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

CRUK MANCHESTER INSTITUTE MOVES TO THE NEW PATERSON BUILDING

CRUK Manchester Institute moves to the new Paterson Building

By Andrew Porter

This spring saw the completion of our long-awaited move to the new Paterson Building. Since the fire in 2017 that forced the relocation of the Institute, we have been eagerly looking forward to a return to our Withington site next to the Christie Hospital. Thanks to the tireless efforts of many Institute members and partners over the years, we were able to relocate to our brand-new home, with all the Institute housed by late June.

Covering over 25,000 square metres, the new Paterson Building has been constructed in partnership between the Christie NHS Foundation Trust, The University of Manchester and Cancer Research UK. It replaces the old Paterson Building which

was badly damaged by fire and subsequently demolished. This ten-storey building is now full of researchers, clinicians, support and administrative staff from the Manchester Institute who are working together to find new ways to detect and treat cancer.

The completion of the Institute relocation was cause for great celebration, and a tribute to the many people who have worked to design and deliver this fantastic research centre. From the careful demolition of the old building (from which much of the building materials were recycled), the digging of fresh foundations down to the Withington bedrock and up to the installation of floor-to-ceiling windows – weighing up to 600 kg! – work progressed

on the build despite challenges from the COVID-19 pandemic and disruptions to supply chains.

Stuart Pepper, Chief Laboratory Officer, has been one of the people overseeing progress on the build since the fire. Complex planning decisions were made at many points, and we had to draw on the experience of a wide range of professionals. "The whole project has been an amazing experience. Working in huge teams of builders, designers and engineers, and learning to understand how such a large building contract is managed has been fascinating."

Acknowledging the important role for good communication when working in inter-disciplinary



Watch our Institute members moving into the Paterson Building

Looking onto the Oglesby Cancer Research Building from the Paterson. Three of our research groups are based in the OCB.



Working with a view: write-up spaces along the front of the building on each floor.



Gary Spencer performs the first experiment!



Gill Campbell and Karen Lee unpacking the Scientific Operations area on Floor 5.

teams, he added “It has been a pleasure to work with experts in many different roles and forge numerous positive working relationships along the way.”

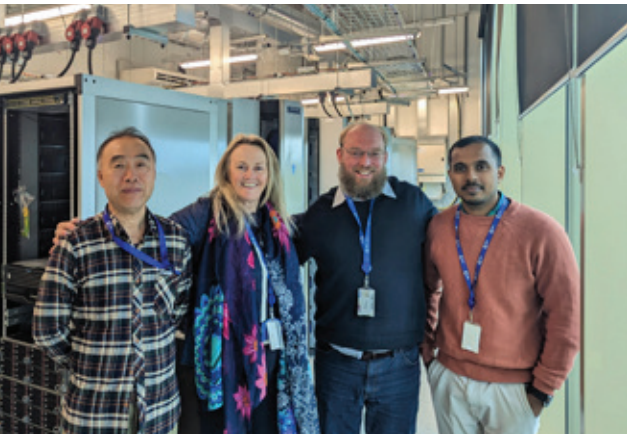
The relocation moved in stages with lots of behind-the-scenes activity. Thanks to the incredible efforts of our IT and Scientific Computing Team (SciCom), all the hardware from the Alderley Park data centre was relocated to the new Paterson data centre within a single day. This involved an astonishing amount of coordination to transport and install huge amounts of computer hardware and cabling, including 46 servers, 25 storage enclosures, 19 switches, one large tape library and hundreds of cables and tapes. The new storage system includes three petabyte of data storage systems – imagine how much data 750,000 DVDs can hold and you get close!

This computing infrastructure is essential for processing the huge amounts of data extracted from lab and patient samples, including DNA sequencing of tumour samples, high-content imaging and mass spectrometry experiments. CRUK MI's new High Performance Compute (HPC) cluster, Griffin, has been handed over to users.

Most of the research groups moved in steadily over a 6-week period, preceded by plenty of tidying, sorting and boxing of equipment and experiments. Exceptionally careful planning was undertaken by teams of ‘Move Champions’ and a team working on how best to use the space in the shared laboratory blocks who had worked out everything from new locations for fridges and freezers to the order in which experiments were paused and restarted.

The first groups to move were Leukaemia Biology, led by clinician scientist Tim Somerville, and Leukaemia Immunology and Transplantation, headed by Institute Fellow Mark Williams. Notably, Gary Spencer, long-time member of the Leukaemia Biology lab, was photographed on 27 April performing the very first experiment in the new building.

Both groups are looking forward to the opportunities for collaboration that will be possible by being co-located with researchers from the University's Division of Cancer Sciences (DCS), as well as clinicians and clinical trials staff from the Christie Hospital. Joining them on the fifth floor is Georges Lacaud's Stem Cell Biology group, who have a long-standing interest in the early events of blood development in the context



Caroline Dive with Scientific Computing. L-R: ZhiCheng Wang, Caroline Dive, Marek Dynowski and Anoop Sanalkumar. Sci Com and IT worked hard preparing the computing infrastructure that helps our researchers handle the vast amounts of scientific data and perform complex cancer bioinformatics analysis.

of blood cancers, such as leukaemia. Physically locating these groups together allows a space for sharing ideas and developing new collaborations.

Mark Williams said, “having different groups all around us – who tackle different parts of immune-oncology and different aspects of the biology of blood cancer – really is essential for our work.”

BDP Principal Architect for the Paterson Building project **Ged Couser** said “We are so proud to have worked on the new Christie Paterson and to be witnessing these moments as the building becomes occupied. It shows that great design can create flexible spaces which centre on diagnoses, patient care, and vital, world-leading research in a truly collaborative environment; about which, we are so excited.” He added that the scheme was a “prime example of what can be achieved with the right planning, funding and design to create effective, beautiful, highly specialised places that impact positively on communities, businesses and local people.”

The transport of equipment, furniture and experimental resources was facilitated by relocation specialists Harrow Green, whose teams ran daily shuttle trips up the A34 – the main artery between the two sites – managing the transport of delicate machinery and research materials from Alderley Park where the Institute has been based for the past five years.

The third floor houses the Cancer Biomarker Centre headed by Caroline Dive, who moved to their custom-built facilities during week four of the relocation. The eight teams in CBC will benefit from these enhanced spaces for their biomarker discovery and assay development, with regulated laboratory space for conducting clinical trial biomarker analysis, and easy interaction with the

core facilities in the pre-clinical laboratory on the fourth floor.

Our world-class core facilities are also located on the fourth floor of the Paterson Building, with offices for the team leads, write-up areas for all staff, and outstanding laboratory space packed full of cutting-edge equipment. The Histology team are glad to be back together on one site, having had their facilities split between the OCB in Withington and their main lab at Alderley Park.

The proximity to the Christie Hospital – a bridge links our building directly – will also aid the collection and processing of samples from patients receiving cancer care. These samples – which include blood and tissue – are processed by the Histology facility and by the Molecular Biology Core Facility, who can analyse the genetic sequences from patients, and Flow Cytometry, who can find and analyse unique populations of cancer cells. The Visualisation, Imaging and Analysis team have set up their microscopes and high-content screening platforms in a specially designed Dark Room, which is tightly temperature controlled to ensure the best environment for these high-resolution microscopes to image everything from whole tissues right down to the components inside individual cells.

Offices for the Biological Resource Unit (BRU), Animal Breeding teams and Genome Editing and Mouse Models team are also located on the fourth floor, so while all animal research is conducted in the specially-constructed animal facility in the basement of the Paterson Building, the team leads are still able to interact with the other facility heads – and all the core facility teams have space for informal meetings in the breakout space there.

Creating the animal facility was one of the most complex aspects of the Paterson build. The new facility provides exceptional resources for animal research, designed specifically for the use of mice in cancer research experiments. The environment is geared to the highest animal welfare standards, with all mouse cages having their own filtered air supply and automatic water dispenser, highly transparent plastic for greater visibility of the mice for welfare checks and enriched with structures for nesting and other normal mouse behaviours. The facility also provides a high-class environment for those working there, with daylight bulbs producing a bright and airy environment (that can also be switched to red light to simulate darkness for experiments involving differences in animal body clocks) and spaces custom-made for distinct aspects of research. The team designing the space drew on their collective experiences of working in multiple locations following the fire and selected the most desirable features to incorporate into this new facility.

Griffin, our new supercomputing infrastructure, is a heterogenous Linux cluster consisting of:

- » **100 standard compute nodes** each with 2x Intel CPUs, 24x cores per CPU, 256GB RAM per node
- » **2 high memory nodes**, each with 4 x Intel CPUs, 24x cores per CPU and 4096GB RAM per node
- » An **NVIDIA Redstone GPU** (graphic processing unit) system with 4 x A100 GPUs, 2x AMD CPUs, 24 x cores per CPU, 512GB RAM per node
- » Storage and HPC nodes are connected via a high-speed InfiniBand **100Gb/s connection**, allowing high-speed data transfer between the components
- » Accessing the system is much faster than before, as the network bandwidth has been upgraded from 10GbE to **25GbE**
- » The new **RStudio server** that can be used to allow web-based access to Griffin has been significantly upgraded in response to growing demand

Griffin is five times faster than the Phoenix system it replaces and uses the modern and popular SLURM batch system for effective job management. With its massive computing power, it is a crucial component of SciCom's High Throughput Data Analysis platform. Griffin is tightly integrated with our secure central storage system, the High-Performance virtualisation platform, bare metal servers and cloud services.

The platform can cover the entire data analysis lifecycle from data generation, processing and analysis to publication and archiving. It allows the secure processing and analysis of sensitive high-throughput data. In addition, we offer application and software development support to enable our scientists to use the latest Bioinformatics methods and technologies for their research. Special thanks go to OCF – the company who designed and installed the system with ZhiCheng Wang and Anoop Sanalkumar from SciCom.

The breakout space on the fourth floor also allows informal social gatherings. During relocation we organised regular coffee breaks to help staff connect with each other and share reflections on the move and new home. Staff received regular Relocation Updates covering the latest information about the move and schedules for each department. These emails also detailed the myriad of information necessary for such a complex process, such as including how to activate access badges, timings for induction sessions and IT shutdowns, and critically reminders to update the address for any new deliveries.

Relocation also took place in the Oglesby Cancer Research Building (OCRB), just over the Wilmslow Road from the Paterson, with three other CRUK MI groups in that space. Rob Bristow's Translational Oncogenomics group moved from the first floor down to the ground floor to join newly arrived Skin Cancer and Ageing group (led by Amaya Virós) and the Cell Division group (led by Iain Hagan) who both relocated from Alderley Park. Our presence in the OCRB alongside DCS colleagues, together with the Paterson and the Christie facilities form an impressive 'Cancer Campus' in Withington, with the different spaces and resources complementing each other bringing clinicians, researchers, technicians, and clinical trials staff together to address complex problems in cancer.

On the sixth floor of the Paterson Building, the final research groups to arrive were Cancer Inflammation and Immunity, headed by Santiago Zelenay - bringing their expertise in cancer immunity; the Systems Oncology group led by Claus Jørgensen who study the complex ecosystems of solid tumours - which include immune cells, fibroblasts and endothelial cells; Angeliki Malliri's Cell Signalling lab who are studying the cellular effects of key mutations found in lung cancer to identify new therapeutic targets; and the newest Institute group leader Evangelos Giampazolias and his Cancer Immunosurveillance group who study the interaction between tumours and the host immune system - you can read more about his group and research later in the newsletter (page 11).

All the lab spaces across the building from the basement to the sixth floor are accessible by dedicated lab lifts, so researchers can move between laboratories without needing to pass through office spaces. This facilitates the transfer of experimental materials and makes the lab environment more cohesive, again feeding into the collaborative nature of the building.

Breakout spaces on each floor encourage informal gatherings, while meeting rooms incorporate the latest technology for hybrid meetings with



Staff and students enjoy reconnecting with each other in the new building Floor 4 breakout space.



Steve Bagley and Alex Baker happily move their microscope into the dedicated, temperature-controlled dark room.

research colleagues from across the world. Meeting pods - great for quiet working or small one-to-one meetings - have also sprung up around the building.

Towards the end of the move, Operations, Scientific Administration, Finance and HR teams moved to their open-plan office space on the fifth floor. This area allows greater interaction between the different teams to help coordinate the work of the Institute and the wellbeing of staff, while individual pods provide a quiet space for video calls or one-to-one discussions.

Caroline Wilkinson, Chief Operating Officer for the Institute, has been heavily involved in the planning and coordination of the building and the relocation for the last 6 years. "I am incredibly proud of everyone who helped make this happen but in particular would like to mention those in the CRUK MI Operations team that contributed to the design, the relocation from Alderley Park and to setting up in the new building."

Like Stuart, she reflected on the team effort that the reconstruction and move represents, and on the benefits of good communication for coordinating across the teams and partnerships involved. "Completing this build and relocation has been a huge team effort with a collaborative approach across the partner organisations (Cancer Research UK, University of Manchester and the Christie NHS

Foundation Trust) and has benefited from excellent working relationships with those directly involved in the design and construction of the building."

Most normal Institute activities have resumed, with regular lab meetings, lectures and training activities taking place in the different spaces across the campus. Institute members - many of whom are new to the Withington site - are enjoying exploring local cafes, parkland, and other facilities in the area. It's great to see the building filling up and people enjoying bumping into colleagues in the breakout spaces or enjoying the fantastic views of Manchester and the Peak District from the higher floors.

We are incredibly grateful to the organisations in the locations where we have been based during the six years since the fire. We would also like to thank the many generous supporters who have donated to the 'Re-Write Cancer' campaign, a £20 million joint fundraising appeal from The University of Manchester, Cancer Research UK and The Christie Charitable Fund that helped meet the £150 million cost of our building. We're grateful to the foundations and local philanthropists who gave substantial funds to this campaign, and to the 1100 plus individuals who together raised an amazing £126,368!

Caroline Wilkinson reflected on the benefits that come from bringing the Institute back together after being spread across Manchester for the last few years. "It is fantastic to be in the new building and to have everyone back together on the same

site. The building is an amazing place to work and already it is clear that its design is helping to promote interactions which was something we all very much hoped would happen."

After only a few months we are already seeing these benefits of being back together. Training activities are more accessible to all Institute members and there are great opportunities for social interaction that are building the wider research community, such as presentations from core facilities managers and informal gatherings after seminars. Our visiting speakers now give their talks in the well-appointed Oglesby Cancer Research Building (OCRB) lecture theatre.

Coming to the end of such a large project which has occupied so much of their working lives over the last 6 years, we asked Caroline and Stuart for their final reflections on what the new building means to them.

Caroline said "The relocation to the new Paterson Building feels like a new phase starting in the Institute's life after a tough few years following the fire in the original Paterson Building and then the pandemic.

Stuart added "For me the focus was always on the end point - having everyone back in a functioning building and out of Alderley Park by the end of June. Completing the relocation on time and under budget is something I am proud of."

Paterson Building key facts



This building will be occupied by the largest collection of scientists, doctors and nurses in Europe



20% cement replacement material was used, resulting in significant CO₂ savings



16,000 cubic metres of materials have been recycled from the basement evacuation

The building height from the basement to the rooftop is 54.2 metres; equivalent to 12 double decker buses



10,000 m³ of concrete has been used; enough to fill four Olympic sized swimming pools





Photo credit Nick Caville BDP

Interview with Stuart Keen, Director of Capital, The Christie NHS Foundation Trust

By Gillian Campbell

Before I even sit down in our private meeting pod, Stuart is already showing me how to adjust the lighting and ventilation for maximum comfort and explains with visible delight how the ventilation system works – he spent three years after all helping to select the right solution to complement open space working. I think he got it right.

It is clear Stuart was the right person to take on this enormous and complex redevelopment project. Passionate, ambitious and with a background as a Chartered Building Surveyor, he has delivered many build projects in the public health sector, including the Ralph Lauren Centre for Breast Cancer Research at The Royal Marsden NHS Foundation Trust and The Proton Beam Therapy Centre at University College London Hospitals NHS Foundation Trust.

Launched at the deep end and right in his comfort zone, Stuart's first task after joining The Christie NHS Foundation Trust was to complete the negotiation between the 3 partners – The Christie, CRUK and The University of Manchester – for the contract and development of the new Paterson

Building. Over the next four years, he helped manage and deliver the build.

When asked his thoughts on the project, he quickly responds, "I am immensely proud. It's a fantastic achievement and I am delighted to have been involved, despite it being challenging at times."

And what were those challenges? "I didn't realise that I was going to have to deliver the project during the biggest challenge the world had faced – the COVID-19 pandemic", says Stuart.

He added, "working during the pandemic brought challenges with labour and materials, but there was also the added challenge of Brexit and latterly the commercial impact of the war in Ukraine."

Although he counters, "the strength of the partnership allowed difficult conversations to be had from different perspectives at key times that meant we could keep moving forwards with the support of the board."

The facility has moved into a new phase as it becomes operational. For Stuart, his favourite feature is

the striking entrance that looks up through three storeys. "It gives a real presence and arrival at the building", he claims.

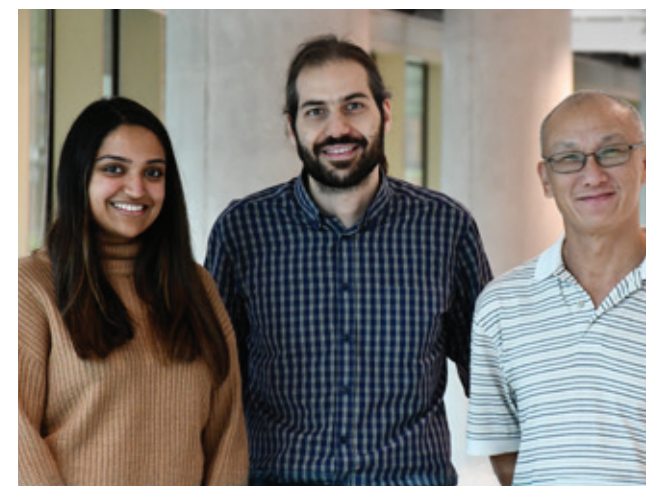
But he also must mention the wow factor as you look at the building. Have you noticed how the metal cladding shimmers and comes alive in the sunshine? Stuart exclaims, "you can see a spectacular dynamic change of colours throughout the day".



The Paterson Building will leave a remarkable legacy; "it will be a key role in the delivery of research translating to better clinical outcomes", concludes Stuart.

WELCOME OUR NEW GROUP LEADER

Meet our new Group Leader Evangelos Giampazolias



The new Cancer Immunotherapy group: (L-R) Swara, Evangelos and Pengbo.



Find out more

At the start of this year, we welcomed our newest Group Leader to the Institute, Evangelos Giampazolias. Joining us from the Francis Crick Institute in London, he has set up his first independent research group, Cancer Immunotherapy.

Evangelos has been joined by Scientific Officer Pengbo Wang, and PhD student Swara Patel. The group will grow to four when they welcome postdoctoral fellow Alexander Vdovin later this month.

The Cancer Immunotherapy group combines genetically modified mouse models and tumour engineering to disentangle complex tumour-host interactions that underpin cancer immunity. Specifically, the group focuses on understanding the mechanisms that enable the immune system to recognise and respond to cancer through the integration of cues made by dying cells and commensal microbes – microorganisms that live in harmony in our bodies. Evangelos' ultimate vision is to contribute to the basic understanding of cancer immunity and pave the way for novel therapeutic interventions.

The group has now settled into the new Paterson Building on the sixth floor alongside colleagues Santiago Zelenay, Claus Jorgensen and Angeliki Malliri. Locating these groups with similar research interests together creates opportunities for sharing ideas and developing new collaborations that strengthen their work in tackling complex questions about cancer.

Research interests and accomplishments

Cells of the adaptive immunity called CD8⁺ T cells are the spearhead of anti-cancer immunity. Immune checkpoint blockade (ICB) therapy restores T cell immunity to cancer cells and represents the pinnacle of success for treating patients with advanced cancers. Despite the substantial achievement in

clinical care, only a small fraction of patients receiving ICB therapy results in durable responses. Resistance to ICB therapy is often attributed to lack of pre-existing T cell mediated anti-cancer responses in the tumour microenvironment (TME). Therefore, the solution to overcome immunotherapy resistance is largely hidden in understanding the origin of T cell mediated cancer immunity. *What triggers T cell immunity to cancer? When does T cell mediated cancer immunity fail to be triggered? Can we predict and restore T cell mediated cancer immunity?* Evangelos has made significant progress towards addressing these questions.

Cell death elicits CD8⁺ T cell immunity by acting as a source of antigens and intracellular immunostimulatory molecule. The dominant type of cell death in the TME is mitochondrial apoptosis, which is triggered following caspase activation in response to cell-intrinsic tumour suppressor mechanisms and anti-cancer therapy. However, cells undergoing apoptosis are not always accompanied by strong anti-tumour CD8⁺ T cell responses.

Originally from Greece, Evangelos moved to Glasgow to undertake his PhD at the CRUK Beatson Institute with Professor Stephen Tait, focusing on alternative forms of cell death and characterise their impact on anti-cancer immunity. During this time, he found that triggering Caspase-Independent Cell Death (CICD) is more effective than apoptosis in promoting T cell mediated anti-cancer immune responses due to engagement of pro-inflammatory signalling within the cells undergoing CICD (Giampazolias E et al, Nature Cell Biology, 2017). These important findings earned him the Institute of Cancer Sciences Prize in 2017 and the CRUK Pontecorvo Prize for best PhD thesis in 2018.

Evangelos then joined the group of Professor Caetano Reis e Sousa at the Francis Crick Institute in London as a Postdoctoral Fellow to characterise the mechanisms that couple recognition of dead-cell-associated



Pengbo settles into the new lab space in the Paterson Building

signals to CD8⁺ T cells responses. Cross-presentation of tumour antigens by type 1 conventional dendritic cells (cDC1) is critical for generating anti-cancer CD8⁺ T cells. However, the mechanisms utilised by cDC1 to effectively couple detection of dying tumour cells to anti-tumour T cell responses remains elusive.

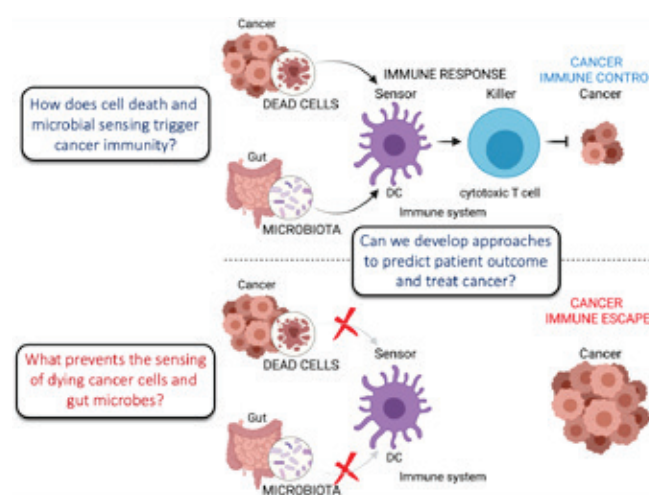
In mice and humans, cDC1 expresses DNGR-1 (a.k.a. CLEC9A), a receptor that binds to F-actin exposed by dying cells and promotes cross-presentation of antigens within the corpses. Evangelos showed that secreted gelsolin (sGSN) – an extracellular protein that circulates in plasma and is secreted by tumour cells – severs F-actin and blocks DNGR-1 ligand binding, dampening anti-cancer immunity and decreasing the efficacy of immunogenic anti-cancer therapies (Giampazolias E et al, Cell, 2021; Lim KHJ et al, Journal for Immunotherapy of Cancer, 2022). For this, he was granted an innovation patent in 2020 to explore the therapeutic potential of targeting sGSN as novel immunotherapy aiming to boost DNGR-1 mediated sensing of dying tumour cells by cDC1 and restore CD8⁺ T cell responses to cancer.

During the transition period between his postdoc and his current post, Evangelos developed an interest in the study of how host-microbiome interactions influence cancer immunity. The microorganisms that are naturally present in the body often influence the ability of our immune system to attack cancer – although it is unclear when and how the gut microbes help the immune system to fight cancer. Intriguingly, he recently found that the prevalence of a specific micronutrient and its interaction with host components tune the integration of gut-associated microbial signals to the immune system, acting as determinants of anti-cancer immunity (Giampazolias et al under revision). This work shifts the focus from

the documentation of commensal microbes with potential anti-tumour function to the identification of the host determinants that are necessary for the gut commensals to promote their anti-tumour function through the immune system.

Evangelos' group is currently characterising the cells, molecules and pathways involved in host recognition of gut commensals and study their functional consequences in cancer immunity using mouse models. Finally, in collaboration with clinicians at the Christie NHS Foundation Trust, they aim to characterise the prognostic value of their findings and set the basis of developing novel strategies to restore T cell immunity to cancer by modulating the gut microbiome.

We welcome the new group and look forward to seeing their exciting programme of research develop.



Graphical description of Cancer Immunosurveillance group scientific interest.

Success for Claus Jørgensen and Systems Oncology

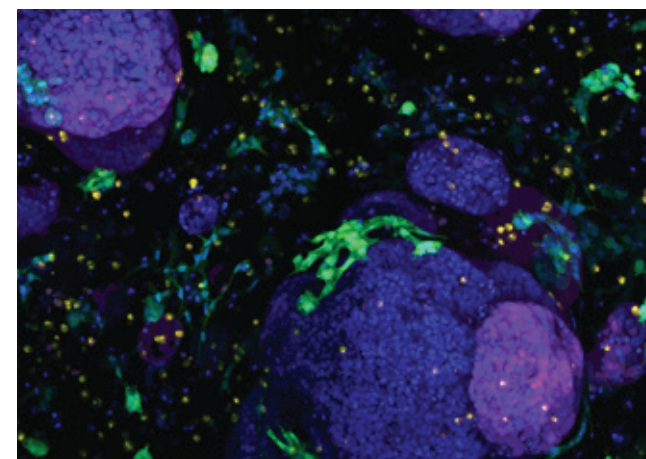


Claus Jørgensen and his research group Systems Oncology

Congratulations to Senior Group Leader Claus Jørgensen and his Systems Oncology research group for an outstanding result in their Quinquennial Review earlier this year.

Our Group Leaders are core-funded by Cancer Research UK and every five years they undergo a rigorous review by a panel of international experts to assess the quality and impact of their research programme.

Claus joined the Institute in 2014 as a Junior Group Leader to set up his independent research group, Systems Oncology. Over the past nine years he has gone from success to success, being promoted to Senior Group Leader in 2017 and then awarded Professorship by The University of Manchester in 2022.



Pancreatic cancer organoids (purple) were co-cultured with pancreatic fibroblasts (green) and bone-marrow derived macrophages (orange) in a synthetic PEG hydrogel scaffold.

Claus is also a dedicated Institute citizen who gives a lot of his time across several leadership and strategic roles. This year he took up the role Deputy Director of the CRUK Manchester Institute, taking over the reins from Iain Hagan – who had provided unwavering support to the Institute over the past three years. We look forward to working with Claus in this capacity.

Back to the science and the complexity of tumours ecosystems. We know that cancer cells are embedded within a remodelled stromal microenvironment, that comprises pathological changes to the extracellular matrix and multiple resident and infiltrating cell populations that have been conscripted by the tumour cells. The aim of the Systems Oncology laboratory is to determine how interactions between tumour cells and surrounding stroma influence disease progression and therapeutic response. Understanding how tumour cells depend on the remodelled microenvironment will enable the development of rational combination therapies, targeting both tumour cell intrinsic dependencies as well as their extrinsic dependencies on stromal reciprocal signals.

Systems Oncology focus on understanding these changes in pancreatic ductal adenocarcinoma (PDA), a notoriously lethal disease with a dismal prognosis. PDA remains an unsolved problem in cancer medicine due to late presentation, aggressive disease progression and limited treatment options. The statistics are grave. PDA is the 11th most common cancer in the UK, but with an average five-year survival rate of only 9%, this disease is the fourth largest contributor to cancer related deaths.

A hallmark of PDA is an abundant tumour microenvironment, characterised by prevalent stromal fibroblasts that have been co-opted by tumour cells – collectively known as cancer associated fibroblasts, or CAFs. CAFs cause an increase in tissue stiffness and interstitial pressure, which confers resistance to therapy. Moreover, tumour cells use CAFs and myeloid

cells to escape immune surveillance and killing by T cells.

In the Systems Oncology laboratory, they look at how tumour cells exchange information with host cells to support tumour growth and how targeting the microenvironment can be used to overcome resistance to therapies. Due to the complexity of the microenvironment and the cellular interactions, they use a combination of complex in vivo models and reductionist in vitro approaches to define the rules by which individual stromal cell populations regulate tumour cell function.

During the QQR period, Systems Oncology has been made up of several postdoctoral fellows, scientific officers, PhD students and clinical fellows. Most recently, the team included Adrian Blanco-Gomez, Celia Cintas, Nasir Haider, Carol McMenemy, Xiaohong Zhang, Joanna Kelly, Catherine Felton, Felix Heider Louis Roussel, Konstantinos Georgiadis and Seung Hyun Lee. Together they all worked hard and contributed to the success of the group.

During the assessment, Claus set out the group's achievements over the past five years and his ambitions for the next five.

Claus and his group have previously described how the interactions between tumour and host cells – such as the connective tissue that produces fibroblasts in the pancreas – can regulate tumour development.

Combining expertise in tumour biology and proteomics method development, they are able to provide novel biological insights into tumour and stromal interactions.

In a landmark discovery that advances our understanding of the opposing roles of the tumour microenvironment, they identified the first fibroblast population with intrinsic tumour-suppressive functions, demonstrating that pancreatic fibroblasts are tumour-permissive and tumour-restrictive in an immune-dependent manner. Critically, they identified a mechanism linking the tumour-suppressive fibroblasts to anti-tumour immunity (Hutton et al *Cancer Cell* 2021). These studies are being validated using innovative synthetic scaffolds for 3D culture of human pancreatic organoids, enabling more physiologically relevant analysis of tumour, immune and stromal cell interactions (Below et al *Nature Materials* 2021).

The group will go on to study the function of these fibroblasts during pancreatic cancer development. Understanding how these two different populations of fibroblasts support and restrict tumour development can be used to identify approaches to re-activate tumour-restrictive properties in pancreatic cancer.

Claus and his team have also shown that interactions between stromal cell populations alter local signalling milieu to induce tumour cell migratory pathways. Ablation of these signals reduces primary tumour growth and blocks metastatic dissemination, opening new therapeutic possibilities in this hard-to-treat cancer (McCarthy et al *Cell Systems* in review; Lee et al *Nature Communications* 2021).

Over the next five years, Claus and his group will continue to examine how the microenvironment

controls tumour development. They hypothesise that understanding these mechanisms will enable the development of improved stromal targeting therapies and will work with Claus' established clinical collaborations to help translate his research into the clinic.

We look forward to more exciting discoveries from Claus and his group in the coming years. Well done!

XTABLE: a new tool to unravel the mechanisms of pre-cancerous lesions

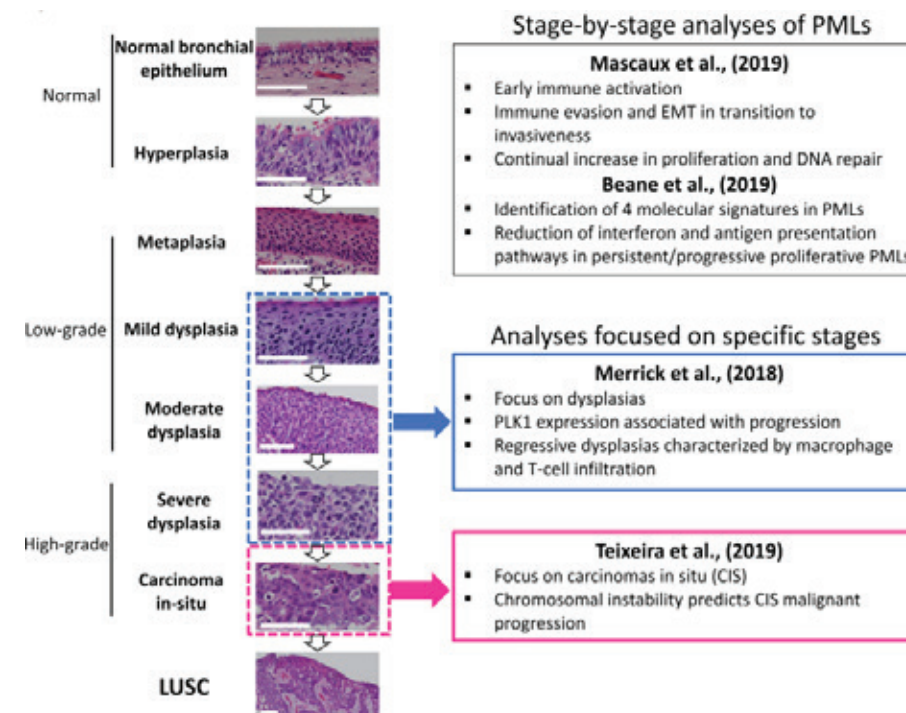
By Ariadna Fuertes Gassio, Scientific Officer, Cancer Biomarker Centre

Manchester scientists have developed an open-source platform called XTABLE (Exploring Transcriptomes of Bronchial Lesions) which can decode transcriptional datasets originating from lung squamous cell carcinoma patients.

These datasets contain information about the activity of tens of thousands of genes found in lesions often seen in the stages preceding cancer. The mechanisms behind the transition between healthy lung tissues to malignant tumours remains elusive, as cells gradually begin to form lesions that might eventually progress into tumours. Early detection of these pre-cancerous lesions could be an invaluable tool for clinicians to identify them before they become cancerous.

Lung squamous cell carcinoma (LUSC) is the second most common lung cancer and one of the leading causes of cancer-related deaths worldwide. Around half of people who are diagnosed with LUSC will be alive 5 years after diagnosis, with this figure dropping drastically once the cancer progresses and spreads to other parts of the body. This poor prognosis can be attributed to a lack of effective treatment strategies and late-stage diagnosis. Patients often do not experience any symptoms during the early stages of the disease, leading to most patients being diagnosed at a late stage when their tumour has already spread.

Researchers from the Cancer Research UK Manchester Institute have developed XTABLE, an open-source platform that compiles the most extensive databases of pre-cancerous lesions and helps other scientists to analyse them. Remarkably, the team used



Histological images depicting the developmental stages of lung squamous cell carcinoma (LUSC) and a summary of the four studies included in XTABLE. Roberts, Matthew et al. "Interrogating the precancerous evolution of pathway dysfunction in lung squamous cell carcinoma using XTABLE." *eLife* vol. 12 e77507. 9 Mar. 2023, doi:10.7554/eLife.77507. <https://doi.org/10.7554/eLife.77507>. This image has been reprinted under the terms of the Creative Commons Attribution (CC BY) license. See page 3 for more information.

XTABLE to show the point where key cellular processes of precancerous progression associated with LUSC become active. This key finding could help scientists to identify new detection biomarkers and develop future prevention strategies.

Detection biomarkers are particularly interesting in lung cancer as these biological markers could allow clinicians to detect the presence of cancer long before it presents any symptoms for the patients, improving patient prognosis. Another important feature of this platform is its accessibility, scientists will be able to validate their hypothesis using data obtained directly from patients, while also helping scientists looking at other types of

lung cancers that share a similar biology to LUSC.

Focusing our efforts on identifying these lesions before they develop into cancer may be the most efficient way of preventing lung cancer deaths at present. XTABLE could play a key role in the discovery of early detection biomarkers as well as broadening our understanding of the genetic makeup of the lesions which develop into LUSC.

Roberts, M., Ogden, J., Hossain, A. S. M., Chaturvedi, A., Kerr, A. R. W., Dive, C., Beane, J. E., & Lopez-Garcia, C. (2023). Interrogating the precancerous evolution of pathway dysfunction in lung squamous cell carcinoma using XTABLE. *eLife*, 12, e77507.

Metformin and cancer: an avenue for cancer treatment

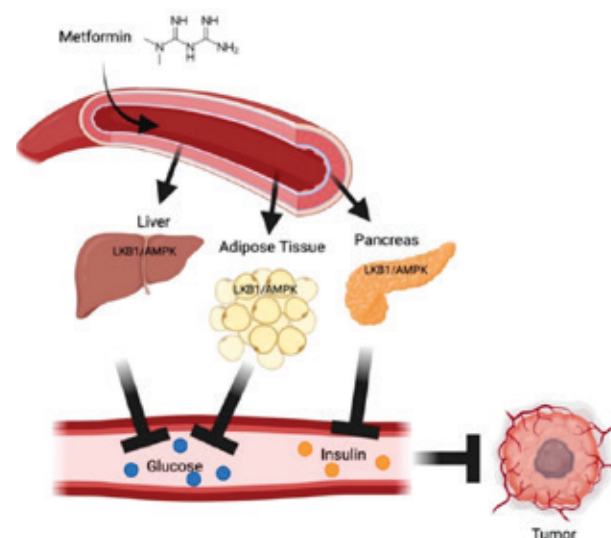
By Janhavi Rastogi, Scientific Officer, Cancer Biomarker Centre

A team of researchers from Manchester Institute, working in collaboration with Flinders University in Adelaide, have identified a novel target in colorectal cancer as a point of therapy. They show that Metformin – a commonly used oral medication for type 2 diabetes – could be used to treat cancer patients and improve patient survival rate.

Colorectal cancer (CRC) is the third most common type of cancer and one of the most prevalent causes of mortality across the world. Patients diagnosed with CRC early have a much better chance of survival than those who have been diagnosed at a later stage. The gold-standard treatments, such as surgery and chemotherapy are effective, but there are many side-effects of chemotherapy – weight and hair loss, risk of infections, nausea – that demand development of less harsh treatment options.

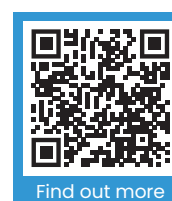
All living things need some form of food to stay alive and get energy. The fuel the body receives is tightly monitored by two proteins called adenosine monophosphate protein kinase (AMPK) and mTOR. Working in harmony, these two proteins tightly regulate cell growth. On the one hand, when a cell detects low nutrient levels, AMPK is activated to decrease cell growth but on the other, high nutrient levels activates mTOR to increase cell growth. Scientists have recently found that AMPKα1 is highly expressed in CRC patients leading to a poor survival rate and that metformin can be used to treat CRC patients.

The researchers looked to unravel the relationship between AMPKα1 activity and metformin response. By exposing different cell lines expressing high levels of AMPKα1 to metformin, the team observed increased cell death. These experiments suggest that metformin modifies the signalling pathway of the cells in such a way that it triggers cell death, displaying the anticancer property of the drug.



Overview of metformin's systemic effects on tumour growth. Metformin's activation of the LKB1/AMPK pathway in hepatocytes and adipocytes, and in the pancreas, leads to reduced blood glucose and insulin availability, respectively. Decreased glucose and insulin availability can slow tumor growth and progression. © 2022 by the authors. Skuli, S. J., Alomari, S., Gaitsch, H., Bakayoko, A., Skuli, N., & Tyler, B. M. (2022). Metformin and Cancer, an Ambiguous Relationship. *Pharmaceuticals* (Basel, Switzerland), 15(5), 626. <https://doi.org/10.3390/ph15050626> © 2022 by the authors. This image has been reprinted under the terms of the Creative Commons Attribution (CC BY) license. See page 3 for more information.

This relationship between a novel target (AMPKα1) and metformin provides new potential for treating colorectal cancer patients that show high AMPKα1 levels more effectively and improving their survival rate. The next step is to investigate the effectiveness of this diabetic drug as a monotherapy or in combination with another drug.



Find out more

Morrison, K. R., Wang, T., Chan, K. Y., Trotter, E. W., Gillespie, A., Michael, M. Z., Oakhill, J. S., Hagan, I. M., & Petersen, J. (2023).

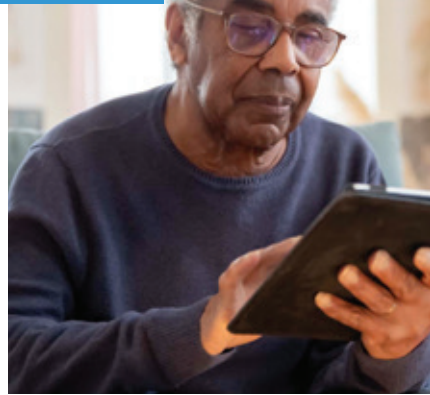
Elevated basal AMP-activated protein kinase activity sensitizes colorectal cancer cells to growth inhibition by metformin. *Open biology*, 13(4), 230021.

SNAP! Matching Patients to Clinical Trials with a New Digital Solution

By Robert Faulkner, Mass Spectrometry Core Facility



Find out more



In the UK there are over 100 clinical trials recruiting for patients with each of the common cancer types such as breast, lung or colorectal cancer. With so many options available, matching up the right patient to the right trial can be difficult.

Digital tools already exist to help the matching task, yet they are either limited in their search abilities or are not publicly and freely available. So, the team in Manchester identified the need for a user-friendly, easily accessible digital tool that would streamline the process.

The researchers produced an open-source, digital application that can extract all relevant trial information from a study record online. This information is then filtered, ranked by specific criteria and then compared to the tumour genotype of the patient. Finally, a score linking trial suitability to the patient is assigned. Oncologists can then use this score to better identify the most appropriate clinical trial currently available for the patient's individual circumstances.

So far, the team have reported several case studies where the tool has successfully matched a patient to a suitable clinical trial. As the tool is developed further, both patients and oncologists will continue to reap benefits as the matching process is made more efficient and economical. The digital tool continues to be put through its paces as it is being used to support the ongoing TARGET (Tumour characterisation to Guide Experimental Targeted therapy) National study in the UK.

O'Regan, P., Hoskins, R., Grave, C., Stevenson, J. A., Frost, H., Graham, D. M., Krebs, M. G., Freitas, A., & Landers, D. (2023). Digital ECMT Cancer Trial Matching Tool: an Open Source Research Application to Support Oncologists in the Identification of Precision Medicine Clinical Trials. *JCO clinical cancer informatics*, 7, e2200137.

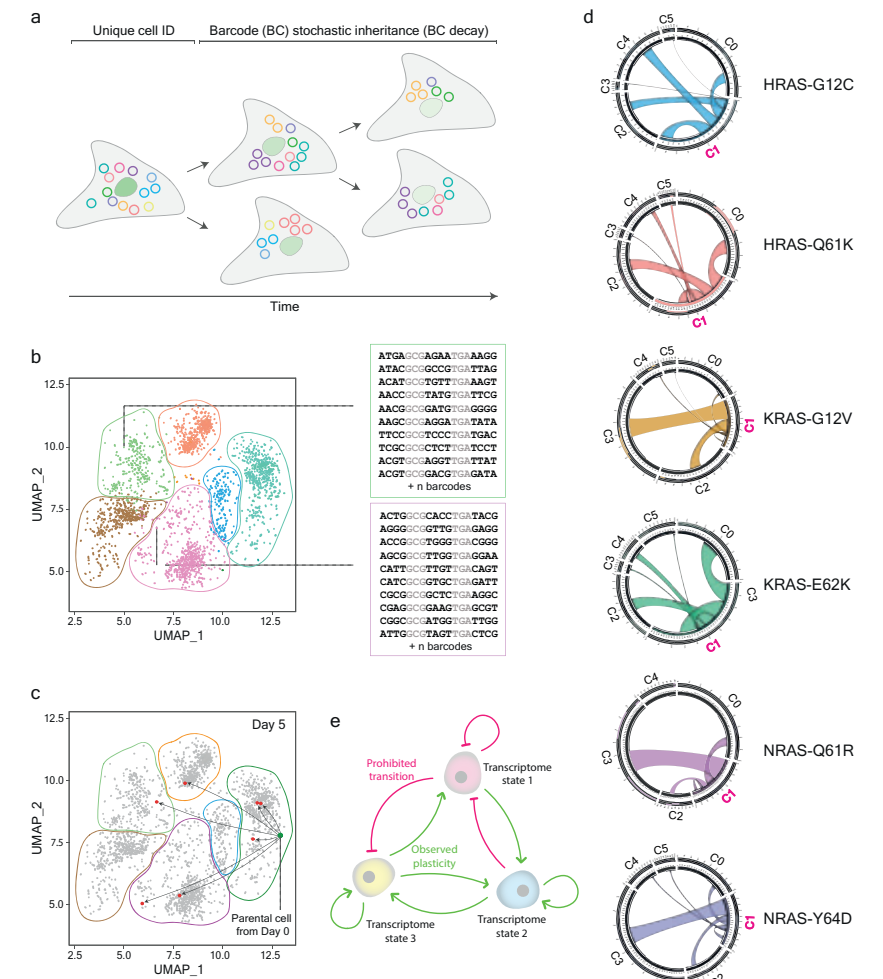
more studies are needed to confirm these observations, the findings have opened the door to a new approach to developing cancer drugs by considering the plasticity-shaping environment in which tumours grow. Furthermore, this technique could help predict which patient tumours could become resistant to certain therapies and help tailor a patient's treatment plan.



Find out more

Shlyakhtina, Y., Bloechl, B. & Portal, M.M. BdLT-Seq as a barcode decay-based method to unravel lineage-linked transcriptome plasticity. *Nat Commun* 14, 1085 (2023).

Development of Barcode decay Lineage Tracing (BdLT-Seq) to explore plasticity. Blue, pink, green, orange, purple and yellow circles represent episomes which are enclosed inside a cancer cell and give it a 'unique ID'. The cancer cell divides over time, giving rise to new cancer cells that inherit some episomes from the parent cell. This property of inheritance can be used to identify individual cells and trace them back to their roots. This forms the basis of BdLT-Seq. Source: Shlyakhtina, Bloechl & Portal, (2023).



New technology explains how cancer cells evolve and become resistant to drugs

By Naomi Torrisi, Scientific Officer, Cancer Biomarker Centre

Why is cancer so unpredictable? Why does it evade therapies? In a new study, researchers answer these questions with a novel tool exploring 'plasticity'. Plasticity – or cell switching – is a property allowing cells to switch into different cell phenotypes or alter their functions to adapt to their environment.

Cancer cells show remarkable plasticity, which lets them enter the bloodstream and circulate around the body where they can form secondary tumours. It is understood that plasticity in cancer cells can also push tumours to evolve and resist drug resistance. However, scientists do not fully understand how the cell switching process of plasticity drives cancer cells to evolve resistance.

A team led by Maximiliano Portal (now based at the CRUK Scotland Institute) developed a new type of cell tracing technology which, for the first time, allows us to trace the natural plasticity of cancer cells. The technology is called Barcode decay Lineage Tracing-Seq or 'BdLT-Seq', which works by tracing episomes – circular DNA – tagged with a unique 'barcode'. Multiple uniquely tagged episomes are introduced into a given cell, which generates a unique 'fingerprint' that allows scientists to identify any cell within a given population without affecting their genome.

By tagging episomes, the researchers can trace specific cells after they divide and look for differences in gene expression patterns. They found that the

genetic component interacts with and rewires non-genetic networks to determine the response of malignant cells to therapy and suggest that, in this context, cell plasticity could play a fundamental role in disease progression.

Moreover, the team used the tool to reveal how cancer cells use plasticity to develop drug resistance. The researchers treated cells with TRAIL, a cytokine naturally expressed by immune cells that display anti-cancer properties, and used BdLT-Seq to identify which cancer cells were susceptible or resistant to the treatment.

Overall, BdLT-Seq is a useful new method that unravels how gene-expression switching contributes to cancer progression. While

Researchers discover novel drug target to help treat prostate cancer

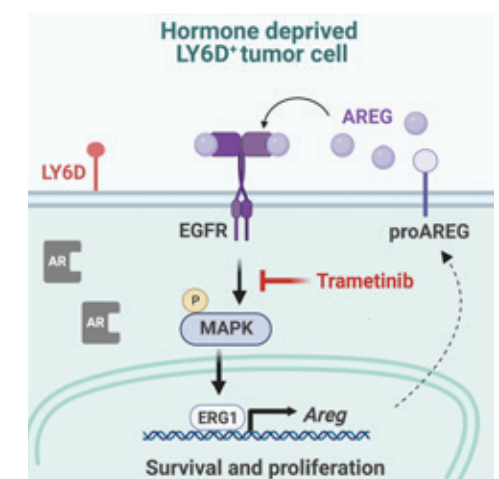
By Kirsten Tinsley, PhD student, Cell Signalling

Research from the CRUK Manchester Institute has identified a new group of proteins involved in prostate cancer resistance that could be used to improve patient survival.

Prostate cancer, or PCa, is the second most common cancer type in men and affects over one million people globally each year. When caught early enough, most patients survive for at least 10 years. Treatment usually consists of surgery followed by radiotherapy. However, if this approach does not cure the cancer, some men receive a hormone therapy known as androgen deprivation therapy (ADT). This dramatically reduces the level of male hormones such as testosterone, which can help slow tumour progression.

Sadly, some patients stop responding to this hormone treatment. In these cases, the cancer is said to have become castration resistant (CR). CR-PCa is usually incurable with a high mortality rate. Around half of patients with CR-PCa have alterations in a gene called PTEN, which is important for stopping cellular growth. This mutation turns off PTEN, allowing tumour cells to continue growing.

Recently, researchers found that a protein on the surface of cells, called LY6D, is increased in prostate tumour cells. They found that cells with increased LY6D produce more tumours in castration resistant mice.



Find out more

Graphical abstract showing conditional deletion of PTEN in mouse prostate epithelium caused an expansion of transformed LY6D+ progenitor cells without impairing stem cell properties. © 2023 The Authors.

The team then discovered that a network of interacting proteins (known as the EGFR-MAPK-ERK pathway) was increased. This pathway governs cell growth and survival and is likely responsible for the increased growth in LY6D-high tumours.

The researchers therefore treated LY6D-high cells with drugs – such as trametinib and erlotinib – that are known to inhibit this pathway. Notably, this treatment decreased the growth of the LY6D-high cells.

Overall, this important new data shows the potential for treating prostate cancer patients that have a PTEN mutation with these drugs, alongside hormone therapy. There is hope for this combination therapy to reduce the occurrence of castration resistance and improve future outcome for these patients.

Steiner, I., Flores-Tellez, T. D. N. J., Mevel, R., Ali, A., Wang, P., Schofield, P., Behan, C., Forsythe, N., Ashton, G., Taylor, C., Mills, I. G., Oliveira,

P., McDade, S. S., Zaiss, D. M., Choudhury, A., Lacaud, G., & Baena, E. (2023).

Autocrine activation of MAPK signaling mediates intrinsic tolerance to androgen deprivation in LY6D prostate cancer cells. *Cell reports*, 42(4), 112377. Advance online publication.

This image has been reprinted under the terms of the Creative Commons Attribution (CC BY) license. See page 3 for more information.



Quiet RNA may be the secret to treating leukaemia

By Michael Jones, PhD student, Leukaemia Biology



Find out more

A group of CRUK scientists reveal how targeting the 'quiet' sections of the genome may be a new way to treat aggressive blood cancer

The marrow in the centre of our bones produces all the cells found within our blood. Acute myeloid leukaemia (AML) is an aggressive type of blood cancer, where certain cell types grow and divide uncontrollably.

Over 3,000 new cases of AML are diagnosed in the UK every year, and 5-year survival rates are low at 13%. Understanding new ways to treat patients and increase survival is a top priority.

RNA is the messenger molecule between our DNA and proteins, instructing when and where proteins are made. Some types of RNA – known as long non-coding RNA (lncRNA) – do not carry these messages, and here we refer to them as 'quiet' regions of the genome. Though largely 'quiet' in nature – their precise role is still

unknown – lncRNAs can be quite the heavy hitters when it comes to cancer; changing how proteins are expressed to help cancer cells survive.

The team in Manchester employed a large-scale screening method to turn off thousands of lncRNAs across millions of cells at once and found one notable candidate – termed SGOL1-AS1 – to be a key player in AML.

When the team investigated further, they showed SGOL1-AS1 to be crucial in the survival of leukaemic cells, as when this lncRNA was lost, cells began to die. SGOL1-AS1 also regulates inflammation – an important process known to assist AML development. The researchers also showed patients with AML who express high amounts of SGOL1-AS1 have lower overall survival than those who do not.

Based on these findings, the team proposed a model where high

levels of SGOL1-AS1 encourages AML growth by increasing the expression of genes related to inflammation. Developing drugs to reduce the amount of SGOL1-AS1 should in turn reduce leukaemia burden, by turning off the inflammation genes, and ultimately increase patient survival.

Overall, this study uncovers the important role of lncRNAs in leukaemia. As high SGOL1-AS1 results in a negative outlook for patients with this devastating blood cancer, targeting this lncRNA may provide new treatment options in the future.

Selkirk, E., Patel, R., Hoyle, A., Lie-A-Ling, M., Smith, D., Swift, J., & Lacaud, G. (2022).

SGOL1-AS1 enhances cell survival in acute myeloid leukemia by maintaining pro-inflammatory signaling. *Heliyon*, 8(11), e11362.

Seminar speakers uncovered

The CRUK Manchester Institute runs a regular external seminar series that is vital for connecting us with world-class researchers across a broad spectrum of cancer research. It is an especially important experience for our early career researchers to be exposed to a range of internationally renowned speakers and have the opportunity to engage with them in person. So here we introduce a new section of our newsletter where some of our early career researchers have written about their take on recent seminars.



23 June 2023

Christian Frezza – The role of mitochondria in cancer

By Shilpa Gurung, PhD Student, Skin Cancer and Ageing

In a highly anticipated seminar, Professor Christian Frezza, a renowned expert in cancer metabolism, shared ground-breaking insights into the pivotal role of mitochondria in cancer development and progression. Our group has been following Prof Frezza's research closely as we delve into cancer metabolism

in our own lab. His innovative protocol for isolating functional mitochondria has been embraced worldwide, and we are using it to investigate the intricate functions of these organelles and their involvement in cancer metabolism.

Prof Frezza's quest revolves around understanding the link between

fumarate – a metabolite of the tricarboxylic acid (TCA) cycle in the mitochondria – and its association with carcinogenesis and metastasis. Notably, fumarate accumulation is observed in hereditary leiomyomatosis and predisposes to renal cell carcinoma.

In this seminar, Prof Frezza shared his team's recent work on epigenetic modifications induced by fumarate accumulation in the TCA cycle. Mechanistically, his team has unveiled how fumarate represses the demethylation of antimetastatic miRNA clusters, leading to the expression of epithelial-mesenchymal transition (EMT) in fumarate accumulated cells (Sciakovelli et al., 2016). This study highlighted the critical consequence of a defective TCA cycle and the epigenetic consequences leading to carcinogenesis and poorer clinical outcome. Furthermore, Prof. Frezza's lab also discovered how fumarate

accumulation induces changes in mitochondrial morphology, leading to the release of mitochondrial DNA into the cytosol and the subsequent activation of inflammation-driven immune markers in renal cells (Zecchini et al., 2023). These discoveries shed light on the diverse roles of metabolites in carcinogenesis and immunometabolism, offering promising avenues for targeted therapeutic strategies.

Prof Frezza's seminar provided invaluable insights and enriched our knowledge, leading to stimulating dialogues related to our ongoing investigations into the microenvironment's influence on melanoma metabolic programming. His dedication to nurturing young scientists through platforms like Twitter is inspiring to our Institute's Early Career Researchers. His engaging and honest attitude during the early career discussions fosters an open and collaborative environment

which is conducive to innovative and synergistic and research partnerships. We eagerly anticipate future publications from Prof. Frezza's ground-breaking research group and thank him for sharing his work with us.



Find out more

Sciakovelli, et al., (2016)

Fumarate is an epigenetic modifier that elicits epithelial-to-mesenchymal transition. *Nature*, 537(7621), 544–547.



Find out more

Zecchini et al., (2023). Fumarate induces vesicular release of mtDNA to drive innate immunity. *Nature*, 615(7952), 499–506.

Medicines is that they are the first that target the 'ON' form of RAS. Clinical trials of RAS 'OFF' inhibitors showed promising response rates, but response was often short lived, and resistance was inevitable. It is hoped that compounds which target the 'ON' form of RAS will lead to more durable responses. Dr Singh gave a clear account of the development and mechanism of these novel compounds. The ingenious mechanism utilises a ubiquitous cellular protein to act as a chaperone helping the compound to bind to active RAS. Dr Singh presented exciting data comparing the RAS 'ON' inhibitors to earlier RAS inhibitors demonstrating the increased potency of the RAS 'ON' inhibitors.

There are many groups at the Institute who are testing these compounds, and it was fascinating to gain direct insight into their discovery.

influencing multiple aspects of cellular behaviour. In cancer, mutations prevent RAS from being switched 'OFF' leading to increased signalling. The oncogenic role of RAS was first shown in the 1970s but until 2013 it was believed to be an undruggable target. This changed when in 2013 Ostrem et al. discovered a pocket on the 'OFF' form of RAS which was susceptible to covalent inhibition – a groundbreaking discovery.

Ten years later there is a multitude of RAS targeted therapies but what is novel and most exciting about the compounds from Revolution



27 June 2023

Mallika Singh – Directly Targeting RAS: Lessons from Tri-complex RAS-GTP Inhibitors

By George J Morrissey, Clinical Fellow, Cell Signalling

Earlier on in the summer we were fortunate to receive a lecture from Revolution Medicine's Dr Mallika Singh. Revolution Medicine are global leaders in RAS targeted therapies.

RAS is the most frequently mutated oncogene in human cancer with a prevalence often quoted at 30%. RAS is thought of as a molecular switch dependent upon its GTP binding status – when bound to GTP it is considered 'ON' whilst when bound to GDP it is considered 'OFF'. When GTP bound, RAS can interact with a wide range of downstream effectors

AWARDS, PRIZES AND EVENTS

Former Institute scientist awarded half million pounds to find new treatment for oesophageal cancer



In our last newsletter, we reported that Sara Valpione, former Institute clinical scientist, had been selected to attend a cancer sandpit workshop led by UKRI funding agency, the Medical Research Council.

The workshop brought together researchers from diverse disciplines to drive co-development of innovative technologies to understand hard-to-treat cancers.

Sara, consultant oncologist at The Christie NHS Foundation Trust and now honorary senior lecturer at The University of Manchester, formed an interdisciplinary team to put a project together that could explore pioneering technologies to treat oesophageal cancer, a rare cancer that is often diagnosed at late stage when hard-to-treat.

The oesophagus – commonly known as the food pipe – carries food from the throat to the stomach. More than 9,000 people are diagnosed with oesophageal cancers in the UK each year, and this disease is responsible for 5% of cancer related deaths.

So, we were absolutely thrilled to discover that Sara and her team

were successful and have just been awarded half a million pounds of funding to produce a new immunotherapy for oesophageal cancer patients.

This investment is part of a £2million funding package to tackle some of the hardest-to-treat cancers, recently announced by Prime Minister Rishi Sunak.

New treatments are necessary because even when the most common form of the cancer – oesophageal adenocarcinoma (OAC) – is discovered at an operable stage there is a 50% risk of it recurring after surgery and chemotherapy. Only 10–15% of patients with this cancer live beyond 5 years from diagnosis.

Immunotherapies that boost the immune system and help the body fight the cancer can prolong life for up to 20% of patients.

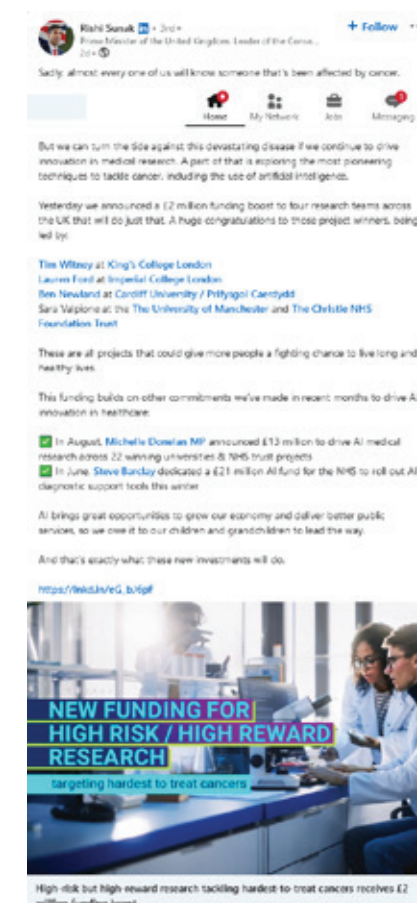
The interdisciplinary research team has learnt how, in some cases, the body's immune system shuts down its own anti-cancer defences, so they want to find a way to stop this happening.

This lab-based work involves an 'RNA therapeutic', using a technology similar to the COVID-19 mRNA vaccines. The RNA molecules that the team will study can switch immune cells on, and they will design a new strategy to focus the delivery of medicines to a specific cell. The team will then put the new RNA-based therapy inside the cancer, targeting the specific group of cells responsible for disrupting the anti-cancer immunity.

Sara said, "We are so pleased to have received the funding to enable us to test our hypothesis in the lab. If we can create a new medicine that can precisely target a specific type of cell within the

tumour, and restore anti-cancer immune responses, this will be a game-changer for oesophageal cancer patients, bringing new hope. If we discover the drug performs as we anticipate in a lab setting, we will plan to start a clinical trial and test it on patients, although this is some way off. The results of this project should be very exciting and will contribute to our understanding of immunoncology and oesophageal cancer. Not only could this be a useful weapon against OAC, but it could have wider benefit, as our theory could be applied to other forms of the disease."

Dr Megan Dowie, the Medical Research Council's head of molecular and cellular medicine adds, "we're pleased to be supporting all the interdisciplinary teams that were brought together by our activity aiming to target



technological innovation for understanding cancers of unmet need. Dr Valpione's project has a great multidisciplinary approach to address important questions for oesophageal cancer. The collaboration of life and physical sciences researchers will help achieve the changes we need to address hard-to-treat cancers with potential for translation to other types of cancer too."

Announcing the news on Linked In, the Prime Minister said, "Almost every one of us will know someone that's been affected by cancer. And cancer of the brain, lungs and oesophagus are some of the hardest to cure with the lowest survival rates. But we can turn the tide against this devastating disease if we continue to drive innovation in medical research. A part of that is exploring the most pioneering techniques to tackle cancer, including the use of artificial intelligence. We announced a £2 million funding boost to four research teams across the UK that will do just that. A huge congratulations to those project winners."

The project is a collaboration between The Christie, The University of Manchester, University College London, Imperial College London and the University of Edinburgh. Congratulations Sara!



This news was originally published on The University of Manchester website

Fellowship funding success

Advanced Clinical Science Fellowship

Dr Amaya Viro
Cancer Research UK Manchester Institute



Congratulations to Amaya Virós who has been awarded a prestigious CRUK Advanced Clinician Scientist Fellowship.

Her Skin Cancer and Ageing group focuses on how ageing influences melanoma initiation and progression and developing rationales of adjuvant care for patients at high risk for melanoma progression. With this substantial new funding, Amaya can continue developing her exciting research and explore the role lipids play in melanoma metastasis, tropism and immunotherapy response at different sites in the body. Fantastic achievement Amaya, well done!

CRUK Manchester Institute scientists present their work in Florida

We are delighted that researchers from the Cancer Biomarker Centre represented the Institute at the American Association for Cancer Research (AACR) Annual Meeting this year.

This large scientific conference is of great significance to the cancer research community and one that some of our scientists always aim to attend. Here at this prestigious event, scientists, clinicians, other health care professionals, survivors, patients, and advocates gather to share the latest advances in cancer science and medicine.

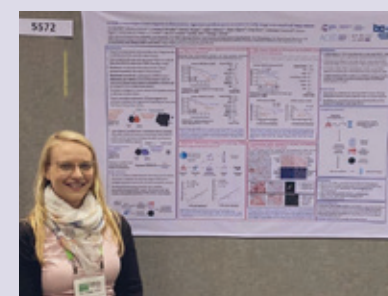
In April this year, the meeting took place at Orange County Convention Center, Orlando,

Florida. The tag line for 2023 was "Advancing the Frontiers of Cancer Science and Medicine".

One of the largest cancer conferences in the calendar, delegates were able to listen to 243 clinical trial presentations, hear from 630 invited speakers from 25 countries (49% women, 35% minority, 9% early-career) and watch paradigm-shifting plenary sessions on critical topics, such as targeting KRAS, immune ecosystems, early detection and interception, and new concepts in drug discovery and engineering.

PhD student Victoria Fife presented her poster showcasing her research project exploring tumour inflammation and the risk of

recurrence of non-small cell lung cancer after surgery. This is an outstanding piece of work from the Cancer Biomarker Centre, along with collaborators Santiago Zelenay from the Institute, Phil Crosbie from the Christie NHS Foundation Trust, and Lisa Coussens from the Knight Cancer Institute at the Oregon Health and Science University in USA.



Victoria Fife from the Cancer Biomarker Centre presents her poster at the AACR Annual Meeting 2023 in Florida.

International PhD Student Cancer Conference 2023



Our PhD students enjoying the 2023 International PhD Student Cancer Conference.

The International PhD Student Cancer Conference (IPSCC) brings together PhD students from top cancer research institutes across Europe. In June this year, the 16th annual conference was hosted by students from the Cancer Research UK Cambridge Institute.

The packed three-day programme featured high-profile keynote speakers, student talks, poster sessions, career workshops and opportunities for networking.

Bradley Revell from Leukaemia Biology did a fantastic job of giving an overview of our Institute to everyone at the conference, while Oliver Bartley from the Cancer Biomarker Centre and Lobsang Dolma from the Tumour Suppressors group gave talks on their research projects, alongside several of our students who presented posters.

We are delighted that we took two poster prizes home this year! Congratulations to Bradley Revell on winning first prize for his research poster, and to Parsa Pirhady from the Translational Oncogenomics group for winning second place.

Bradley was recognised for his work on the molecular mechanisms of transcription factors IRX3 and FOXC1, and Parsa won his award for his research on the DNA damage repair pathway in prostate cancer. Well done!



Bradley giving an expert overview of our Institute and Parsa (left) and Bradley (right) receive their poster prizes.

Success at the Division of Cancer Sciences Postgraduate Research Showcase

Congratulations to Maria Koufaki and Charles Earnshaw, PhD students in the Cancer Inflammation and Immunity group at the Institute, who both won prizes at the Division of Cancer Sciences Postgraduate Research Showcase.

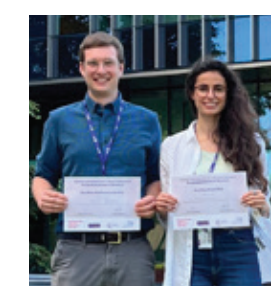
Held across the road from the Paterson Building at the Oglesby Cancer Research Building, the June event highlighted how we do cancer research differently here in Manchester, spotlighting our world class facilities and experts, how we are internationalising research, our Team Science culture, and the digital tech future for cancer research and care.

Over two days, we enjoyed an excellent demonstration of cutting-edge science from 16 speakers and 20 poster presenters from across the Division of Cancer Sciences and CRUK Manchester Institute. It was a great opportunity for clinical and non-clinical postgraduate researchers to showcase their incredible PhD work.

The postgraduates also heard from two keynote speakers. Dr Laura Greaves, from the Wellcome Centre for Mitochondrial Research at the University of Newcastle, gave a fantastic talk about her research from PhD to senior lecturer on mitochondrial dysfunction and cancer, and Dr Rebecca Lee – former PhD student at CRUK MI and now based in DCS – discussed her work on translating pre-clinical research into the clinic via the CACTUS trial.

We are proud that our students earned two prizes. Maria won first-place poster prize and says, "I was excited to discuss my work on developing new mouse models to study immune cell activation in tumours. In particular, I focus on an enigmatic dendritic cell state that is conserved across cancer types and between mouse and human, and I presented my findings unravelling its functional properties".

Charles received an award for his talk and tells us, "I presented my research on trying to find ways to turn immunotherapy-unresponsive melanomas into responsive tumours. I showed that in my experimental models, corticosteroids can paradoxically induce immune-mediated tumour growth inhibition and showed that the likely mechanism is due to steroids acting on the tumour cells directly." Excellent work, well done both!



Now that our Institute has returned to the Withington campus at the Paterson and Oglesby Buildings, events like these will be critical in helping to drive our postgraduate research community, providing our students with peer support, the opportunity to share ideas, and gain valuable insights into their research.

A clean sweep for the Cancer Inflammation and Immunity group: Charles and Maria proudly present their prize certificates standing in front of the new Paterson Building.

Championing Wellbeing and Wellbeing Champions

By Gillian Campbell



WELLBEING CHAMPIONS

[STAFF + STUDENTS]

Become a Wellbeing Champion!*

Bring your ideas, share your passion, help organise & promote wellbeing activities & events:

- Social events – coffee club, film society, book groups
- Physical activities – running, walking, step challenges, team sports
- Institute-based events – health checks, workshops

*Training will be provided (must be able to commit for at least a year)

For more information contact: Jeff Barry (Jeff.Barry@cruk.manchester.ac.uk)

Scan for wellbeing support



Wellbeing at work is everyone's responsibility, so let's start talking about wellbeing and looking out for yourself and your colleagues.

WELLBEING CHAMPIONS

- Jeff Barry
- Gillian Campbell
- Erminia Romano

When it comes to improving wellbeing at work, small things make a big difference if you practice them consistently.

If you need support for your wellbeing, there is a range of online and in person services available.

Staff can access the Employee Assistance Programme, **Health Hero** – a confidential and independent counselling and information service. Call 0800 358 5997 or +44 141 271 7555.

Qwell provides free, safe and anonymous online mental health support for students whenever you need it.



Scan to go to Health Hero



Scan to go to Qwell

of this strategy, Jeff Barry was appointed as Wellbeing & Engagement Adviser and a Wellbeing Focus Group (which reports into the Institute's Health, Safety and Wellbeing Committee) has been established to roll out wellbeing initiatives and to monitor wellbeing within the Institute.

Jeff, who we introduced in our Summer 2022 Newsletter, has been instrumental in establishing a network of Wellbeing Champions here at the Institute, as well as promoting awareness around wellbeing by providing tips and guidance.

Wellbeing Champions play an essential role in shaping and promoting an organisation's wellbeing strategy. As well as signposting key services and resources, they take the lead in organising activities that bring people together and put the spotlight on healthy living. They are also a dedicated point of contact and are ready to listen and support both staff and students.

We currently have three Wellbeing Champions at CRUK MI. We would like to grow our network of support and are reaching out for more staff and students to join up and help support wellbeing initiatives so we can hold our own events here.

If you are interested in becoming a Wellbeing Champion or have any questions, please get in touch with Jeff Barry.

Wellbeing – feeling positive and satisfied with life – is important in every area of our lives, including while we are at work. We know that when people are in a positive state of wellbeing at work, they are better able to develop their potential, be more productive and creative, build relationships with others, have better stress management, and make meaningful contributions.

That is why here at the Institute, we aim to create a safe and positive working environment by encouraging a healthy lifestyle, promoting social activities and providing support for both staff and students' mental wellbeing.

There are many factors that can affect our wellbeing, and while some factors are outside of our control, others we can influence.

Wellbeing will mean different things to different people, but we recognise a person's wellbeing encompasses physical, mental, social and financial health too. With this more holistic view, we can see our state of wellbeing as existing on a spectrum that we each have the ability to move along from day to day.

The Institute is committed to fostering a culture of wellbeing at work. A successful strategy relies on buy-in and co-operation from all levels of the Institute and building a culture of wellbeing requires a team effort. As part

Fundraising for Movember 2023

By David Jenkins

YOUR DOUGH WILL SAVE A BRO



MOVEMBER.COM
DONATE NOW

Movember themed Café Talk

On Thursday 16 November, I plan to run a 'Movember themed Café Talk' at the Espresso Lab Café in the Oglesby Building.

This event will include a talk on men's cancer and involves doctors who are part of the FASTMAN Movember Centre of Excellence for Prostate Cancer at the Christie NHS Foundation Trust. The aim is to encourage men to talk about their concerns about cancer and to provide accurate information about the research we are doing here at the CRUK Manchester Institute to help men live longer. This talk will be aimed at the general public and researchers interested in men's cancer. Anyone signing up will receive a ticket for a FREE cake and coffee at the Espresso Lab Café.

David's Lucky Dip

Thursday 23 November will see the return of 'David's Lucky Dip'. This hugely popular tombola type fundraiser has a guaranteed prize every go and is always great fun.

Please keep a look out this November for my fundraising events and you can donate to my Movember page by scanning the QR Code on my Promo "Your Dough Will Save A Bro".

Thank you!

David's Great British Bake-Off Halloween Special

After a few years break, due to the pandemic, I will be resuming my annual Movember Fundraising events this November.

I will be starting with 'David's Great British Bake-Off Halloween Special' on Tuesday 31 October, in the foyer of the Paterson Building. Everyone will be pleased to know I will be baking a selection of

my favourite and most popular bakes of cupcakes, loaf cakes, rocky road and much more. I am also creating some Halloween themed treat bags.

The Biomarker Lab takes to the road

By Molly Glenister-Doyle, Scientific Officer, CRUK MI Cancer Biomarker Centre

The Research Engagement Team at the Cancer Research UK Manchester Institute created a new and stimulating outreach experience called 'The Biomarker Lab'. This activity allows students to screen simulated patient samples for cancer by detecting a fictional biomarker called FLAVO.

The Biomarker Lab debuted at several locations, including the 1st Didsbury Guides, Queensgate Primary

School, and Manchester Museum during British Science Week 2023. The Lab was seen as an enormous success and gave students an excellent insight into work carried out at the Institute.

Members of the Research Engagement Group at CRUK Manchester Institute (CRUK MI) were keen to create something new to follow on from the success of their outreach activities during British Science Week

2022, when they ran the Strawberry DNA Extraction activity (see page 4 of the Summer 2022 newsletter). When developing the new activity, the team focused on keeping it as visual and interactive as possible, leading to the creation of 'The Biomarker Lab'. The idea behind The Biomarker Lab was to replicate an 'ELISA experiment' in a way school children could easily understand. An ELISA – short for enzyme-linked immunosorbent assay – is a common method of detecting if a biomarker is present in a sample. A biomarker is a biological substance that is a sign of normal or abnormal processes in the body. For example, cancer biomarkers can be extracted from blood samples. If the biomarker is present, a colour change will occur; the more intense the change, the greater the concentration of biomarker.

In the Biomarker Lab, students detect if a fictional biomarker – FLAVO – is present in test 'samples' by pipetting them into a pre-made 24-well plate. If the indicator in the wells changes colour, this tells the student that FLAVO is present, and the test 'patient' is likely to have cancer. Students are then provided with follow up 'samples', allowing them to assess a patient's response to treatment. Overall, the students got a comprehensive overview of how ELISAs work and

their importance in cancer screening and treatment monitoring, all while getting hands-on with pipettes, samples and plates.

The activity was brought to life through a fantastic team effort. To highlight a few individuals for their contributions, Bradley Revell and Joanna Kelly sourced appropriate pH indicators, Andrew Porter developed the logistical requirements – such as the volume of solutions required for each experiment – and Molly Glenister-Doyle helped to source equipment such as pipettes.

Sophie Richardson and Catherine Felton designed a detailed and engaging activity sheet to go with the experiment, which contained background information about our fictional protein biomarker, a protocol for students to follow, a space to record results and questions to answer whilst carrying out the experiment.

Finally, no activity would be complete without some in-house testing, and several scientists were happy to lend a hand, including Andrew, Mollie Anne Halford, Erminia Romano and Ana Vitlic.

Alderley Park

At the Bruntwood Schools' day at Alderley Park, Catherine, Joanna, Sophie and Tim Budden took the opportunity to showcase the Biomarker Lab.

The event was aimed at young people who were exploring careers in science and saw year 10 students from across local schools in Cheshire take a hands-on approach with cancer research. The students loved the activity, with a Bruntwood representative commenting, "the cancer research activity came up several times as a highlight of the day!"



Catherine and Tim showcase the Biomarker Lab at the Bruntwood Schools' day at Alderley Park.

Future

The hope is that this activity can easily be recreated and adapted for use at future events and by other Cancer Research UK Institutes.

The team plan to continue engaging and building relationships with local communities through participating in similar future events, especially now we have moved to the new Paterson Building and the team are back together at the heart of the cancer campus in Manchester.

Executive Assistant turns Event Assistant at the weekends

By Gillian Campbell



Naomi and fellow event assistant at the Shine Night Walk.

Event assistants act as ambassadors for Cancer Research UK, supporting the delivery of their events season. They take on highly responsible roles and gain experience in areas such as course obstacles and volunteer management.

Naomi Samuels is the Executive Assistant to the Director of the CRUK Manchester Institute Cancer Biomarker Centre and interim Director of CRUK MI, Caroline Dive. She has a passion for the charity sector and at the weekends you can find her working as a CRUK Event Assistant.

During events season, Naomi works on the Race for Life, Shine

Night Walk and Pretty Muddy events in the northwest. Despite the brutal early starts – she has to wake up at 4am to get on the site for 5am to help set up the courses – and endure what is often freezing cold and wet weather, she absolutely loves it. She enjoys interacting with the competitors and hearing their stories as to why they are raising money for CRUK in these physically challenging events. It can be emotional but hugely rewarding and she always has a laugh with the other event assistants.

Naomi started the role in August 2021 and her first event was a Race for Life in Oldham's Alexandra Park. Hundreds of people unite at this event with one purpose – to raise valuable funds for life-saving research. The Race for Life is for everyone of all ages, backgrounds and abilities to come together and beat cancer. So, people can choose to take part in a 3K or 5K race and Naomi helps to set up both courses. During the pre-race inspirational speech from a cancer survivor, it really hit Naomi as to

why she was there and saw that it is the personal stories that give the role real meaning.

Since Naomi became an Event Assistant two years ago, she is noticeably stronger! It is very physical work, but the team have great fun while delivering inspiring events which bring together communities, survivors and those who have been touched by cancer.

Cancer Research UK is always looking for more volunteers and marshals at these events. So, if you are interested in helping out, speak to Naomi!

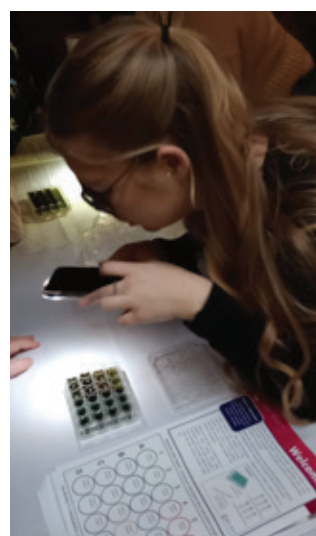


Naomi and team at a Race for Life event.

Manchester Museum

A team of nine scientists from the Institute – Andrew Porter, Deepti Wilks, Duncan Smith, Erminia Romano (from the Division of Cancer Sciences, based in the Paterson Building), Hannah Sheedy, Maria Peiris Pages, Mollie Anne Halford, Molly Glenister-Doyle and Mukkarram Hossain – attended the Inspiring Futures event at the recently reopened Manchester Museum.

This event aimed to promote future study in healthcare and showcased diverse careers within the NHS. Cancer Research UK staff teamed up with Stephanie Seville from the Museum of Medicine and Health, and Ellie Chambers from the Manchester Cancer Research Centre to provide a collection of stalls focusing on cancer research and treatment. With a total of 1137 students attending across two days, the Biomarker Lab got great exposure, with students enjoying the interactive experiments and talking to the researchers.

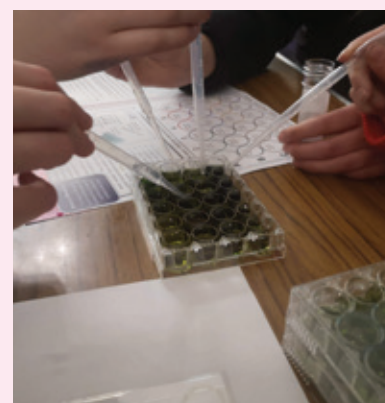


Institute scientists take the Biomarker Lab to more than 1000 students at the Inspiring Futures event at the Manchester Museum.

British Science Week

The activity was carried out at several locations by members of the team over British Science Week 2023, captivating the interests of young people from across Greater Manchester.

Sophie took the Biomarker Lab to her guide group in Didsbury, whilst Kathryn Simpson visited a local school, carrying out the activity with around 30 children.



Guide group in Didsbury take part in the Biomarker Lab and learn all about ELISAs with Sophie.

Squash success for Matthew Roberts



Matthew Roberts might be known to us as a mathematics biologist, but we didn't know about his secret passion for squash. Originally from South Africa, he came to England 7 years ago to pursue a career as a professional squash player while he completed his master's in mathematics. Sadly, that didn't work out for him, but he still manages to play the game at a high level – he regularly plays against a World Top 150 player!

After building up his fitness during the pandemic, he started to win tournaments. Now, despite a few injuries, he is still doing well. Here he shares some of his good news and would like to reach out to any other squash players in the Institute – who knows, maybe we can set up our very own squash league!



Ranked in the Top 10 in Lancashire 2022/2023



Represented Lancashire Men's Team for round 1 of inter-counties



Successfully defended his Ian Stewart Memorial Trophy – the Club Championships title held at The Northern (Lawn Tennis Club) where they do squash too! – after first winning it last year.

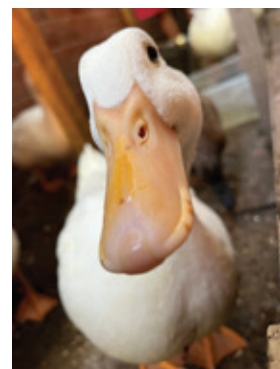
Welcome new baby



Congratulations to Hannah Frost from the digital Experimental Cancer Medicine Team – part of the Manchester Institute Cancer Biomarker Centre – who welcomed to the world a baby girl in March this year. Edith Moira Hamer-Frost, was born on 17th March, weighing 7lb 11oz.

Cute Pets!

Meet this lovely curious duck. She is called Potato – because she was the chubbiest of the ducklings! Potato and her siblings live with Dave Lee, formerly based in Computational Biology Support.



Noel Kelso is Puzzling!

Quiz Meister Noel Kelso, QA Officer for CBC, features in a new television quiz show on Channel 5 called 'Puzzling', which began broadcasting on Thursday 22 June. He appeared on screen on 3 August. If you want to see how he got on, you can find it on the Channel 5 catch up service.

IN THE SPOTLIGHT



Nasir Haider

Nasir is a PCUK Career Foundation Fellow in the Systems Oncology group at the CRUK Manchester Institute – you can discover more about the group and their research earlier in the Newsletter (page 12).

Nasir is originally from Canada and completed his undergraduate degree and PhD at the University of Toronto, before moving to the UK to start his postdoctoral position here in 2019. He is a highly motivated researcher who has dedicated his career to understanding the signalling mechanisms that drive oncogenesis and therapeutic response.

Over the past four years Nasir has achieved much, including securing his own fellowship funding from Pancreatic Cancer UK to uncover and target mutant KRAS – the major genetic driver in pancreatic cancer – to determine response to drug treatments and utilise this information to design novel therapeutic combinations.

- 1 **What is your favourite part of the UK?**
Wales, I love the landscapes.
- 2 **What was your best ever holiday and why?**
My best holiday was a family trip to Hawaii when I was in university. One day, I spent the morning on the beach, the afternoon in a rainforest, and the evening above the clouds at the Mauna Kea Observatory seeing the most stars I have seen in my entire life.
- 3 **Which website do you always check, and why?**
I check CBC News to see what is happening in my home country of Canada.
- 4 **What is your favourite film?**
Recently, Dune, but Blade Runner is a classic.
- 5 **What is your favourite band/singer?**
Jay-Z.
- 6 **If you had to change careers tomorrow, what would you do?**
I would either want to be a nature photographer, or a chef.
- 7 **What is the most important lesson that you have learnt from life?**
"You miss 100% of the shots you don't take".
- 8 **Name three things you would take with you to a desert island?**
My library of unread/half read books, a telescope and a boat.
- 9 **What is your greatest fear?**
The Deep Ocean.
- 10 **How would you like to be remembered?**
I would like to be remembered as someone having made a significant impact on the wellbeing of others. Whether that be through my research, my friendship or my actions.
- 11 **If you could change one thing in your past what would it be?**
Looking back, I wish I were more ambitious when I was younger.
- 12 **What is your signature dish to cook?**
My signature dish is tacos.
- 13 **You've just won the lottery and have £5 million pounds to spend. What do you buy first?**
Given the market, probably a house in the countryside with a large yard for my son to run around and play.
- 14 **What is your idea of perfect happiness?**
Perfect happiness to me is time with my family out in nature.
- 15 **What keeps you awake at night?**
The inequalities I see present in healthcare, both within the UK and internationally.



Photo credit Nick Caville BDP

Editorial Team:

Steve Bagley
Gillian Campbell
Karen Lee
Andrew Porter
Caroline Wilkinson

**Cancer Research UK Manchester
Institute**

The University of Manchester
Wilmslow Road
M20 4BX

e: enquiries@cruk.manchester.ac.uk
www.cruk.manchester.ac.uk
twitter.com/CRUK_MI

Design and Layout:

cornerstone design & marketing
www.cornerstonedm.co.uk

The University of Manchester
Royal Charter Number: RC000797