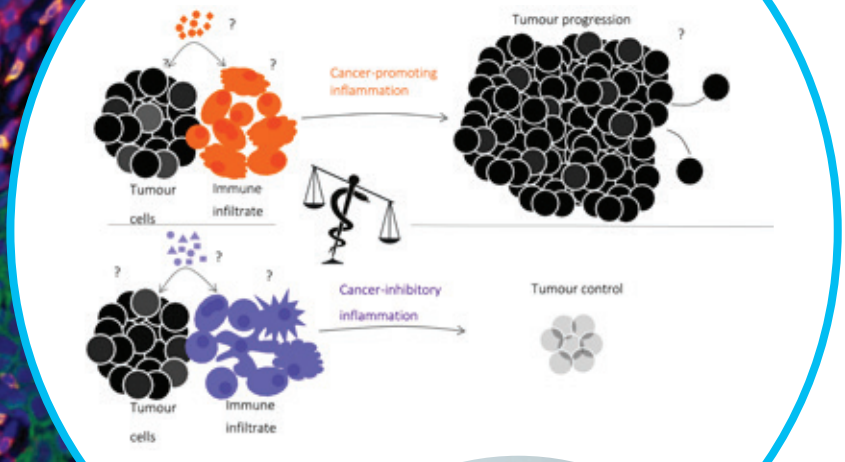
CANCER RESEARCH UK | MANCHESTER INSTITUTE

MANCHESTER 1824
The University of Manchester

Newsletter

Summer 2022



Director's Introduction

It is a pleasure to welcome you all to this latest edition of the Cancer Research UK Manchester Institute newsletter. Here, we aim to provide some 'behind the scenes' insights into the people that make up our thriving research community and I hope you enjoy discovering more about our work and successes.

First of all, I am delighted to announce that Santiago Zelenay was promoted recently to Senior Group Leader following an excellent performance during his review. He has been a Junior Group Leader at the Institute since 2015 and during this time, he has made some important discoveries that have advanced the field of cancer immunology, including taking his discovery science through to biomarker informed clinical trials with his clinical collaborators. The reviewing panel of international experts were all impressed with Santiago's past research and future plans. I would like to congratulate Santiago on his promotion; we are all looking forward to seeing more exciting research emerge from his group. Further details about his team and programme of research can be found in this newsletter.

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 Mark Williams on winning a highly competitive Clinician Scientist Fellowship from the Medical Research Council. With this funding, Mark is setting up his own research group as an Institute Fellow, focusing on leukaemia immunology and transplantation. We are delighted to welcome Mark to the Institute's Faculty and wish him all the best as he establishes his independent research programme.

Congratulations also go to Caroline Springer and Iain Hagan, who together have won a grant from the charity, Target Ovarian Cancer. Caroline, who is Director of the Drug Discovery Unit, and Iain who leads the Cell Division group, will combine their complementary expertise to discover novel therapies for ovarian cancer patients.

Institute Fellow Amaya Virós was awarded a grant from the Harry J. Lloyd Charitable Trust. One of four recipients in the final funding round of this US-based foundation, it is notable that she was the only candidate outside the US to be selected. This success is on the back of several key publications last year and having also secured funding from Wellcome and joint funding from the Melanoma Research Association and the Rosetrees Trust. Congratulations Amaya.

I also wish to congratulate Tim Budden, a postdoc in Amaya's group, who has won this year's BACR Chris Marshall Prize for Cell Signalling. This well-deserved prize recognises two significant first-author publications from Tim as well as receiving our own Institute Award, The Edith Paterson Prize for the best young scientist of 2021. It is a great time for the Skin Cancer and Ageing group and we look forward seeing the group flourish in the coming years.

Our early career researchers are an integral part of the community at the Institute. I am proud that in this newsletter, we can celebrate their passion for science, their appreciation of the broader impact that their research has on patients, families and communities – here in the UK and across the globe – and their enthusiasm to reach out and engage with those communities.

They are the driving force behind much of our important research engagement activities, as demonstrated by their recent involvement in British Science Week when a team of our early career researchers visited three local primary schools. In the following pages, you can read about how they both educated and entertained the young students.

Now a regular feature, the selection of highlighted publications showcasing the Institute's research has been written by some of our early career researchers. This is a great opportunity for them to develop their writing skills and I am impressed by the quality of their contributions.

Cover Image: In this edition we celebrate the promotion of Santiago Zelenay to Senior Group Leader. Here we showcase his research in cancer immunology. Top image shows triple-negative breast cancer with nuclei labelled in blue; cancer cells labelled in green with a pan-cytokeratin antibody. CD45, expressed by all immune cells is in red, and CD3, expressed only by T cells is in yellow *(supplied by former PhD student, Christian Bromley)*. The graphic illustrates how cellular and molecular mediators regulate the balance between the tumour-promoting and tumour-inhibitory properties of the immune system.

Conferences are critical to scientific enterprise, enabling researchers to share findings, exchange ideas, and to network for collaboration and career development. This is especially important for our young researchers, so I am thrilled that the International PhD Student Science Conference was held in person for the first time since the pandemic. This conference – organised by students for students – was a great success and saw PhD student Bianca Blochl from Cell Plasticity & Epigenetics win a prize for best poster with her work on the interplay of non-genetic mechanisms and oncogene-induced transformation. Great work, Bianca.

In my final days as President of the EACR, I recently chaired the EACR annual congress in Seville where Claus Jørgensen and Dominic Rothwell gave oral presentations. Melissa Frizziero and Julia Ogden from the Cancer Biomarker Centre, alongside Ryan Guilbert from the Cell Signalling group, were all awarded travel bursaries to attend the meeting. Being back in person, listening to a feast of science was such a tonic, and the first CRUK MI conference dinner since the pandemic was also most enjoyable!

There have been some changes recently in our Flow Cytometry core facility. We said goodbye to manager Jeff Barry, who retired earlier this year, and welcomed to the role Toni Banyard, who has worked tirelessly in the facility for many years. We look forward to working with Toni as she reshapes the facility. But we are not losing Jeff completely to retirement – he has returned to the Institute one day a week as our new Wellbeing Advisor. Read more about their new roles in the following pages.

Finally, I cannot close this introduction without remarking on reaching the significant milestone that is the fifth anniversary of the Paterson Building fire. In these pages we mark the occasion by looking back and remembering that day and our gratitude to all those who helped salvage precious samples and equipment.

We are also grateful to Andy Lloyd and Mark Craven for their ongoing hard work and commitment to managing the storage of the many items rescued from the Paterson Building. Mark gives his account of the enormous task that they have both taken on over the last five years. I am sure they are delighted that we will be moving back to the old site next year.

Looking ahead, I too am excited about returning to our home at the Christie NHS Foundation Trust site.

I would like to express my enormous thanks for the crucial support of donors and funders around the world; it really is making a difference.

I wish you all a wonderful summer.

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

Have you seen...

Our latest annual Scientific Report is available to view, detailing the latest activities of each research group, the core facilities and operations department for the year.

Manchester researchers visit local schools during British Science Week

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

Institute scientists amazed children at The Barlow RC High School. Left to Right: Scientific Officer Joanna Kelly, PhD student Alexandru Suvac, Head of Biological Mass Spectrometry facility Duncan Smith, and PhD student Mihaela Ficu.

A team of scientists from the CRUK Manchester Institute (CRUK MI) and The University of Manchester's Division of Cancer Sciences (DCS) left children 'feeling inspired and excited' about cancer research after visiting local schools during British Science Week.

Earlier this year, a group of scientists from CRUK MI and DCS, who form part of our Research Engagement Group, set about reaching out to local schools in the Withington and Didsbury area.

The aim was to host fun and interactive sessions for school children during British Science Week, giving them an insight into the work conducted here and enthusing them about research and jobs in science.

The team were successful in arranging in-person events with three schools. St Paul's Primary School, Ladybarn Primary School and The Barlow RC High School welcomed our team, where they interacted with around 550 to 600 children across the three days.

Visits began with a short presentation, introducing the children to key scientific concepts such as how does cancer arise, what are the treatment options available and how are CRUK helping to fight cancer. Our researchers then shared personal stories of how they became interested in science and why they pursued a career in the STEM academic disciplines. The final part of the visit was by far the most fun as children were able to carry out their own experiments, extracting DNA from strawberries!

A lot of planning and organisation went into these visits and we provided the schools with a personalised video to play to their students before the team's arrival. This gave the children an insight into the day-to-day life of one of our scientists, Adesewa Adebisi – a Scientific Officer in the CRUK MI Cancer Biomarker Centre. The video allowed the children to see inside our labs and showed them some of the equipment we use to carry out experiments.

Overall, we received overwhelming positive feedback from the schools, with one describing it as a *"great day inspiring scientific interest in students (and staff)."*

The primary schools in particular thought the students *"enjoyed the 'What is Cancer?' presentation as a clear effort was* [made] *to pitch it appropriately to their age/levels of understanding"* and they appreciated that the children were *"talked to and not talked at"*.

They also said, *"pupils could relate to their* [the researchers'] *learning paths and it made it seem a realistic achievement"*. All schools agreed that students *"loved the practical activity"* with one adding that they *"would love to be involved in any future visits!"*

It is the ambition of the Research Engagement Group to continue to engage and establish relationships with schools in the local community. They aim to keep hosting school visits in the future but also hope to welcome students to our own facilities – at the Oglesby Cancer Research Building and the new Paterson Building when it opens next year.

CRUK MI Postdoc Bettina Wingelhofer from Leukaemia Biology shows Ladybarn Primary School pupils how to extract DNA from strawberries.

Ana Vitlic, Research Associate in the Targeted Therapy Group, DCS, describes to students from Ladybarn Primary School her personal journey into science and her motivation to research cancer.

The team of scientists engaging pupils at Ladybarn Primary School. Left to right: Bradley Revell, PhD student in Leukaemia Biology, Bettina Wingelhofer, and Ana Vitlic.

Meeting the CRUK supporters

On the 22nd March, Cancer Research UK welcomed supporters to an in-person event at the Science and Industry Museum in Manchester.

This was a wonderful opportunity to meet the people who have supported our work for many years – including through the difficult times of the pandemic – and to hear about their experiences.

The Institute was represented by PhD student Kirsty Tinsely, who is based in the Cell Signalling group led by Angeliki Malliri. She works on understanding how cellular functions of specific proteins influence lung cancer progression. Kirsty ran interactive demonstrations at the event, explaining some of the science behind our research and showing a timeline of treatment developments.

Andrew Porter, our Research Integrity and Training Adviser, shared recent scientific achievements from the Institute, as well as the exciting plans for the new Paterson Building. We also heard from a remarkable young CRUK Ambassador, Patrick Savage, about his cancer diagnosis, treatment and recovery. He explained how his experience inspired him to support CRUK by undertaking an amazing fundraising walk in support of the new cancer research centre in Manchester.

Patrick was diagnosed with Hodgkin's lymphoma – a type of blood cancer – a day before his 19th birthday. Incredibly, just one year after starting his treatment, he walked 240 miles from London to the Christie to raise funds for the Christie Charity and CRUK. Patrick raised over £70,000 for the two charities.

And finally, there was an opportunity for the supporters to tour the Cancer Revolution: Science, Innovation and Hope exhibition at the museum, which features research from the CRUK Manchester Institute and other CRUK groups, alongside moving contributions from cancer patients and their families and loved ones.

The exhibition is now at the Science Museum, London until January 2023.

CRUK Crewe and Nantwich Fundraising Committee Annual General Meeting

Cancer is a disease of uncontrolled cell division and here Caroline is showing the Crewe and Nantwich Committee statistics about how many cells our own body will have been made in the past minute.

The Institute's Chief Operating Officer, Caroline Wilkinson, visited the CRUK Crewe and Nantwich Fundraising Committee recently to provide updates on the Institute's progress. Caroline has been attending the committee's annual general meeting for several years now and was delighted to be able to meet the group again in person this year.

She gave a presentation explaining the science behind cancer along with some of the Institute's latest developments in areas such as immunotherapy, as well as an update on the progress of the new research facility on the site of the old Paterson Building. She also explained the impact of COVID-19 on the work of the Institute and the introduction of various modifications to working practices.

Caroline said, "it is always a pleasure to visit the Crewe and Nantwich Committee. They carry out an extraordinary amount of work each year and have raised a huge amount of money for cancer research over many years.

"I am always highly impressed by the imaginative and innovative activities that they organise and thoroughly enjoy meeting and talking to the committee members. They really are an amazing group of people".

Margaret Grindrod, Secretary of Crewe & Nantwich Local Committee, who organised the event said, "it was fantastic to host Dr Caroline Wilkinson once again. Her presentation was very informative, especially for those having treatment at present or who have never heard about immunotherapy.

"We always learn something new at Caroline's events and it spurs us on to do even better, to achieve more for all the work that is being done for the cause."

SCAN ME

STAy World Cancer Day Event

By Catherine Felton
PhD student, Systems Oncology

The 4th of February is World Cancer Day and the Institute's STAy (Science Takeaway) group – comprising Postdoctoral Fellows, PhD students and Scientific Officers – commemorated the occasion by hosting "Research with a Global Outlook".

At this event, we not only heard from fellow cancer researchers about their work, but we also considered how global inequalities impact cancer research, specifically who has access to diagnostics and treatments, and who is not included in trial and sequencing data.

Cath Felton, a member of the STAy committee and the event organiser, began by discussing her undergraduate participation in the "SPOT on CML" project, which aimed to improve patient access to diagnosis and treatment of chronic myeloid leukaemia in low and middle-income countries (LIMCs). One of the key takeaways was that technological advances in cancer diagnosis and treatment in high-income countries cannot be transferred directly to LIMCs. In response to the unique needs of LIMCs, unique solutions must be developed in collaboration with the expertise of local researchers.

Prof David Wedge, our keynote speaker, maintained this emphasis on the significance of collaboration. David Wedge is a Professor of Cancer Genomics and Data Science at The University of Manchester.

Beginning his scientific journey as a chemist, David subsequently worked in software development and mathematics before settling at the junction of biology and big data. Much of his work is founded on an ethos of collaboration with principal investigators from under-represented groups, both as scientists and in the data we collect.

Prof Wedge described his work analysing genomic data of breast cancer in Nigerian women and comparing their genetic signatures to African American women and white women of European descent (Ansari-Pour N, Zheng Y, Yoshimatsu TF, et al. Whole-genome analysis of Nigerian patients with breast cancer reveals ethnic-driven somatic evolution and distinct genomic subtypes. *Nat Commun*. 2021;12(1):6946).

David discussed the identification of previously unknown genetic signatures that appeared to be unique to women in Nigeria, which he suggested may explain the increased presentation of more aggressive forms of breast cancer in this population.

He emphasised that findings of this nature highlight the importance of seeking to improve representation in our sequencing data. We are unable to recognise and, more importantly, address differences in presentation, progression, and overall biology of cancer in these groups due to the lack of whole-genome sequencing of the 'global majority'.

David also pointed out that we should be mindful of the vast diversity of the African genome, noting that the genomes of men from southern Africa and eastern Africa are more similar to European genomes than they are to each other.

As is the case with cancer diagnosis and treatment technologies, the research carried out by David Wedge and collaborators demonstrates that we cannot simply transfer our knowledge of breast cancer – or any cancer – from the white context in which it is researched, to the global majority. For example, one study found precision-oncology trial participants in USA to be over 80% white (Aldrighetti CM, Niemierko A, Van Allen E, Willers H, Kamran SC. Racial and Ethnic Disparities Among Participants in Precision Oncology Clinical Studies. *JAMA Netw Open*. 2021;4(11):e2133205).

Within the discussion groups that followed the talk, we considered ways in which science is inherently a collaborative process. Still, certain populations are excluded when we only collaborate with laboratories in the USA and Europe.

Helping to establish formal research partnerships with institutions and individuals across LIMCs, The University of Manchester is beginning to change this narrative. However, this raises the question of what we as researchers at the CRUK Manchester Institute can do in response.

At STAy, we hope to continue discussing cancer as an increasingly unequally distributed global burden while research resources continue to be concentrated in predominantly white and westernised institutions.

Additionally, we wish to create a space for researchers within the CRUK MI community who have expertise in research with LIMCs to share their experience in this area – with the ultimate hope of inspiring ourselves and other Early Career Researchers to build their scientific careers with these inequalities in mind and incorporating them in research design.

SCAN ME

Image left: Professor David Wedge BA, PGCE, MSc, PhD. The focus of his research at The University of Manchester is cancer evolution and heterogeneity.

Gifts in Wills for Cancer Research UK

Pledge to leave a gift in your Will

Gifts in Wills are a vital source of revenue for Cancer Research UK. These Legacy Gifts fund a third of CRUK's life-saving research, enabling long-term research projects that lead to new treatments and cures.

By pledging to leave a gift in your will, you can help the charity achieve breakthroughs beyond current knowledge and technological capabilities, and continue to save lives for generations to come.

We are delighted to report here that some of our researchers have taken part in the North West campaigns to raise awareness about Legacy Gifts.

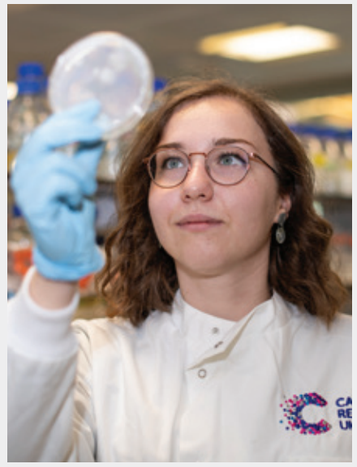
Ali Raoof, Lead Chemist in the Drug Discovery Unit at the Cancer Research UK Manchester Institute, featured in bus stop campaigns promoting leaving Gifts in Wills. He appeared at a stop in Didsbury Village – aptly on the bus route to the NHS Christie Foundation Trust – alongside Legacy Pledger, Barry from Wigan with the message, "Every pledge today helps secure life-saving research for tomorrow."

Ali hopes the visibility of these important images will send a powerful message to those considering fundraising for cancer research.

Alexandra Hendry – Ola to her friends and colleagues – is a PhD student in the Cell Division group at the Institute. She has appeared in the CRUK's promotional material online, explaining the significance of wills and the impact leaving a legacy gift to CRUK has on cancer treatment.

Ola is thankful for the Legacy Gifts, which help to fund her research. She says, "without this funding I wouldn't be able to do the work I do. I feel motivated to work harder knowing that my work could actually help someone."

Ali promotes the 'I Pledge' campaign.



Ola explains the importance of legacy gifts in funding her research.

Chemist Ali features in bus stop campaign in the North West.

12,337* People in the North West have played their part and left a gift in their Will to Cancer Research UK.

*This figure relates to all Gifts in Wills from this area up to 2019/20.

Multicellular Oncostatin M signalling drives pancreatic cancer growth

By **Mia Nuckhir**, PhD student, Breast Biology Group. Division of Cancer Sciences at The University of Manchester

SCAN ME

Manchester scientists have identified an important multicellular signalling pathway involving Oncostatin M (OSM) and Oncostatin M Receptor (OSMR) in pancreatic ductal adenocarcinoma (PDA) growth and metastasis.

PDA is the most common cancer of the pancreas. Patients with PDA have poor five-year survival rates of less than 10%. This is because the cancer is often diagnosed late, as symptoms do not present until it has progressed and metastasised to a distant organ.

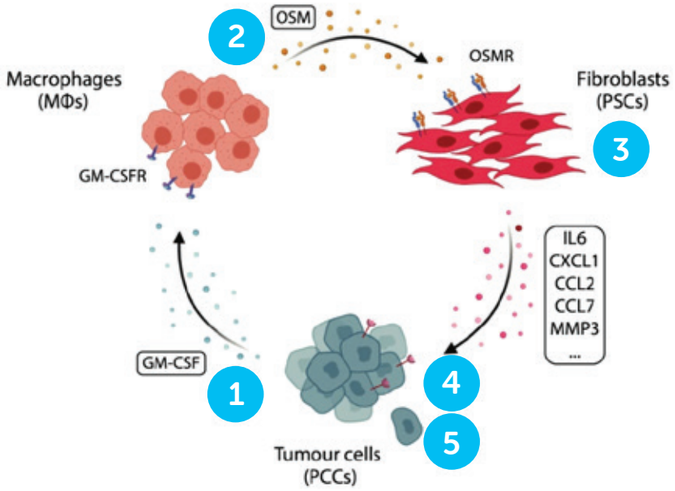
PDA is categorised by an extensive fibrous tumour microenvironment (TME). Cancer associated fibroblasts (CAFs) are a type of cell that form a major cellular component of the TME, and distinct CAF populations such as inflammatory CAFs (iCAFs) have been identified.

Until now, it has been unknown exactly how CAFs interact with other cells in the TME to promote tumour growth. Here, Manchester scientists describe the interactions between CAFs, pancreatic cancer cells and immune cells called macrophages in the TME.

The researchers first used publicly available data to investigate gene expression. They found that a group of genes, including OSMR, were more highly expressed in iCAFs, and that this expression was associated with worse overall survival in patients.

OSMR is the receptor for OSM, a secreted protein that is part of the Interleukin 6 family of cytokines. It is known that OSM is involved in mediating immunity and inflammation, and they showed that macrophages in PDA express OSM, suggesting that these cells might act on the OSMR expressing fibroblasts.

To understand how these cells signal with one another via OSM, the scientists performed further experiments using media that was conditioned by the cells grown either together (in co-culture) or separately.



Key:

1. Tumour cell-derived GM-CSF secretion
2. Macrophage secretion of OSM
3. Reprogramming of inflammatory fibroblast phenotype through:
   - OSM-OSMR engagement
   - Secretion of inflammatory factors
   - Expression of immunomodulatory receptors
4. Engagement of tumour cell survival, migration, motility and EMT pathways (e.g. JAK/STAT, ERK1/2, AKT)
5. Increased tumour growth & metastatic potential

Model outlining heterocellular OSM–OSMR signalling between pancreatic cancer cells, fibroblasts and macrophages. Pancreatic cancer cell secretion of GM-CSF induces macrophage secretion of OSM, which reprograms fibroblasts to an inflammatory phenotype, in turn accentuating tumour growth and metastasis. Lee et al. *Nat Commun* 12, 7336 (2021). https://doi.org/10.1038/s41467-021-27607-8. Shared under Creative Commons license.

The team were able to unravel a complex signalling pathway whereby pancreatic cancer cells release a cytokine called GM-CSF into the TME, which stimulates the macrophages to release OSM. The OSM then acts on fibroblasts that express its receptor (OSMR), changing them to the iCAF subtype, which causes the TME to become more inflammatory and tumour promoting.

The scientists then used a mouse model with mice that lacked *Osm* to understand whether targeting it would be a viable option for patients with PDA. They found that these mice had a more anti-tumorigenic TME and reduced primary tumour growth compared to mice that expressed *Osm*. The mice also failed to develop liver metastases.

These findings are important as they identify the OSM-OSMR signalling pathway as a therapeutic target in PDA. The next step is to investigate whether other stromal cells or direct effects of OSM on the pancreatic cancer cells may also be important in PDA.

Lee BY, Hogg EKJ, Below CR, Kononov A, Blanco-Gomez A, Heider F, Xu J, Hutton C, Zhang X, Scheidt T, Beattie K, Lamarca A, McNamara M, Valle JW, Jørgensen C. (2021) Heterocellular OSM-OSMR signalling reprograms fibroblasts to promote pancreatic cancer growth and metastasis. *Nature Communications 12(1):7336.*

Manchester scientists unravel molecular drivers of haematopoietic stem cells

By **Muhammad Fadlullah Wilmot**, PhD student, Stem Cell Biology, CRUK MI

Researchers in the Stem Cell Biology group have established a unique and comprehensive atlas of the initial molecular events that give rise to haematopoietic stem cells.

Haematopoietic stem cells (HSCs) sit at the apex of the blood system and – in the form of bone marrow transplants – are powerful treatment modalities for cancer and blood malignancies.

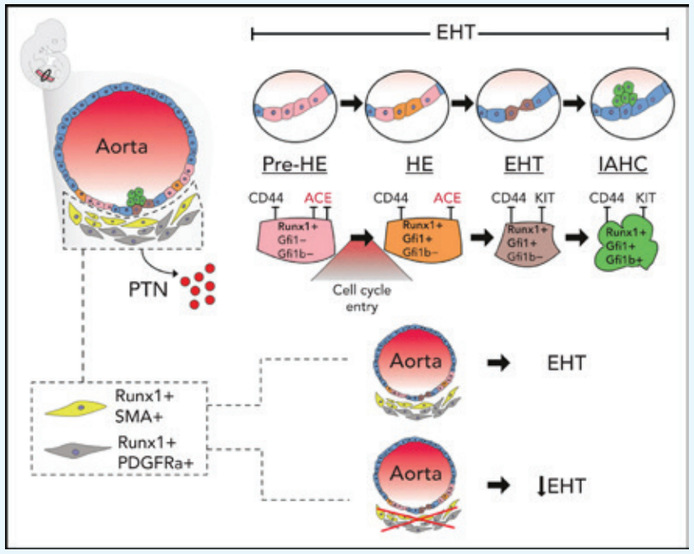
The limited availability of bone marrow for transplants has made the efficient generation of HSCs in vitro an essential goal of regenerative medicine. Understanding the intrinsic and extrinsic cues that drive HSC generation is critical for developing efficient in vitro HSC production protocols.

HSCs arise in the mid-gestation embryo from rare specialised endothelial cells called haemogenic endothelium (HE). These cells become blood cells through an endothelial to haematopoietic transition (EHT). Although HE cells exist at multiple embryonic sites, they generate HSCs mainly in the dorsal aorta (DA).

The rarity of HE cells and the limited options for isolating these cells significantly impede the study of these processes. As such, the earliest molecular events driving the commitment from HE to HSCs remain poorly characterised.

Using transgenic HE murine reporter models, the researchers took advantage of new advances in single-cell technology to explore the canonical EHT differentiation continuum within the DA and the subaortic niche cells.

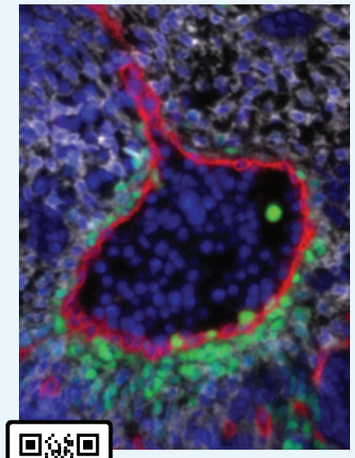
The authors conducted these analyses in the presence and absence of the key EHT regulators RUNX1 and GFI1. They uncovered a pre-HE to HE continuum marked by Angiotensin-I converting enzyme (ACE). They unravelled that HE cells begin to enter the cell cycle near the time of EHT initiation.



This study also revealed that a small subpopulation of RUNX1 expressing DA niche cells, consisting of vascular smooth muscle cells and PDGFRa+ mesenchymal cells, functionally support HSC emergence.

Overall, this novel dataset has already provided new insights into HE differentiation toward HSC and represents a unique and powerful resource to investigate these processes further.

Fadlullah MZ, Neo WH, Lie-A-Ling M, Thambyrajah R, Patel R, Mevel R, Aksoy I, Do Khoa N, Savatier P, Fontenille L, Baker SM, Rattray M, Kouskoff V, Lacaud G. (2022) Murine AGM single-cell profiling identifies a continuum of hemogenic endothelium differentiation marked by ACE. *Blood* 139(3):343-356.



SCAN ME

Immunofluorescent staining of mouse E10.5 dorsal aorta (DA). RUNX1 is green, CD31 is red, and PDGFRa is gray. RUNX1^{+} cells in the endothelial lining of the DA are hemogenic endothelial cells. Mesenchymal RUNX1+ cells, which support hematopoiesis, are abundant in the ventral subaortic region.

Both images reprinted from Fadlullah et al. Murine AGM single-cell profiling identifies a continuum of hemogenic endothelium differentiation marked by ACE. Blood 139(3):343-356. Copyright (2022), with permission from Elsevier.

Image featured on the front cover of journal Blood, Volume 139, Issue 3, 20 January 2022.

Mechanism behind Small Cell Lung Cancer Survival Revealed

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

SCAN ME

Research carried out by scientists in Manchester has revealed a mechanism behind how a specific subtype of small cell lung cancer (SCLC) – called neuroendocrine SCLC – can resist death.

Small cell lung cancer is a diverse and aggressive disease that is the sixth highest cause of cancer deaths worldwide.

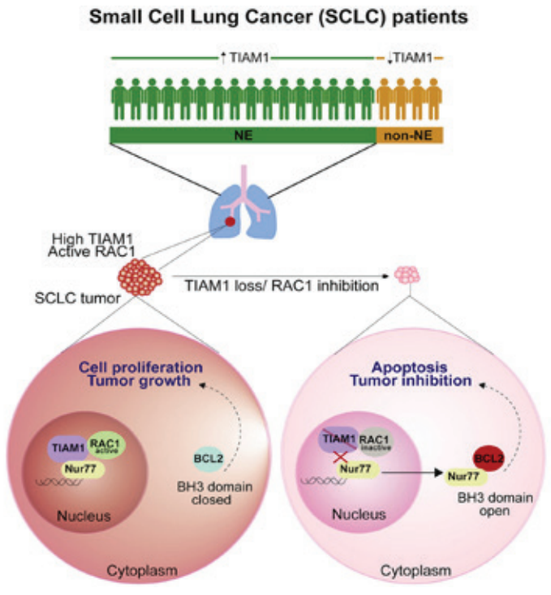
This cancer is hard to treat, particularly as most patients are diagnosed at later stages of the disease and have limited treatment options. Targeting vulnerabilities in this survival mechanism opens the door for new potential therapies for this specific type of SCLC.

Scientists from the Cancer Research UK Manchester Institute studied SCLC using three approaches – cells, tumours grown in mice and tumours from patients. They discovered TIAM1, a protein that is overexpressed in neuroendocrine SCLC, can prevent a specific type of cell death – apoptosis – from occurring. They showed that TIAM1 prevents cell death by binding to a second protein called Nur77. The binding prevents Nur77 from leaving the nucleus and stops this protein from changing the shape of another protein, BCL2.

BCL2 plays a dual role in regulating cell death and depending on its shape it can either inhibit or activate apoptosis. When Nur77 is held in the nucleus by TIAM1, it is unable to convert BCL2 from an 'apoptosis inhibiting' shape to an 'apoptosis activating' shape. This is turn allows these cells resist to death.

In further work, the researchers also demonstrated that Rac1 is involved in this process. The team were able to show that Rac1 is responsible for localising TIAM1 in the nucleus and promote TIAM1 binding to Nur77.

Overall, our scientists showed that TIAM1, which is upregulated in neuroendocrine SCLC, inhibits SCLC cell death by binding to Nur77. This prevents Nur77 from changing BCL2 from an 'apoptosis inhibiting' to an 'apoptosis activating' shape, enabling the cells to resist death. They also showed that Rac1 promotes the interaction of TIAM1 and Nur77.



Graphical Abstract from Payapilly et al. Cell Reports 2021 37DOI: (10.1016/j.celrep.2021.109979) *© 2021 The Authors.*

Although previous studies have identified the importance of Nur77 in this pathway, this is the first time that TIAM1 has been shown to play a role in localisation of Nur77. The researchers here have suggested two therapeutic targets that require further investigation. If successful, this will be an exciting step forward in the development of personalised medicine and better treatment for this diverse and aggressive disease.

Payapilly A, Guilbert R, Descamps T, White G, Magee P, Zhou C, Kerr A, Simpson KL, Blackhall F, Dive C, Malliri A. (2021) TIAM1-RAC1 promote small-cell lung cancer cell survival through antagonizing Nur77-induced BCL2 conformational change.
Cell Reports 37(6):109979.

REALISM bites

By **Mat Sheridan**, Clinical Fellow, Stem Cell Biology, CRUK MI

Institute clinician scientist Tim Somervaille was one of a dedicated team of healthcare professionals from across England and Scotland that reviewed the real-world treatments given to patients with myelofibrosis (MF), a rare and challenging blood cancer.

Patients with MF have a malignant clone and heavily scarred bone marrow that usually results in progressive bone marrow failure and early death.

The clinical presentation of this underlying pathology is variable, but it has long been recognised that MF can cause weight loss, fever, fatigue, night sweats and abdominal pain, which significantly impacts quality of life.

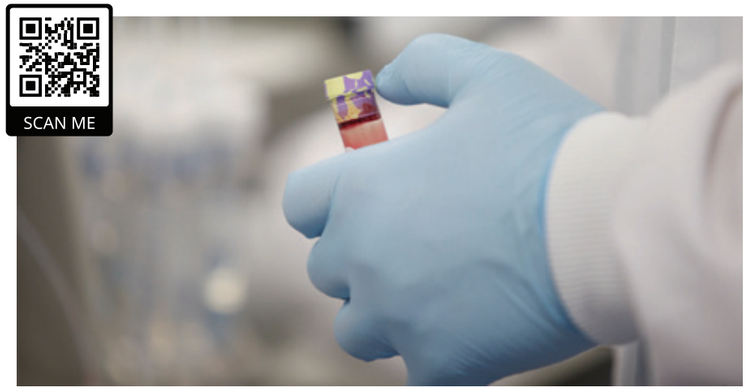
A variety of treatments from different drug classes provide symptomatic relief, though none are disease modifying. Indeed, the only option of cure for patients with MF is a bone marrow transplant, but this is associated with high mortality, particularly in older patients.

This study showed that documentation of prognostic risk and patient reported outcomes, both of which can and should inform treatment, is poorly done by healthcare professionals looking after patients with MF, whilst blood transfusions to correct the anaemia patients suffer are underutilised.

The research team confirmed that mortality is significant amongst patients because of MF and found that bone marrow transplantation is rarely used, even in younger patients. Their headline finding is that for over half the patients, the first line treatment was 'watch and wait', including for some patients deemed high risk who are more likely to have a significant symptom burden.

For those patients who are treated, there is no consistency in which drug is given first, despite some studies finding a relatively new drug, 'ruxolitinib' to be the most efficacious, although this does seem to be changing over time.

SCAN ME



Overall, this study is important as it has shown how different teams working in different hospitals across the country can pool readily available information to bring about positive change to the management of those afflicted with a rare cancer.

It also provides valuable insights into how new drugs should be developed and marketed by the drug company involved in the study and others.

Moreover, this study advocates for a more standardised approach and higher standards of documentation to ensure patients do not miss out on drugs which may improve their symptoms.

Mead AJ, Butt NM, Nagi W, Whiteway A, Kirkpatrick S, Rinaldi C, Roughley C, Ackroyd S, Ewing J, Neelakantan P, Garg M, Tucker D, Murphy J, Patel H, Bains R, Chiu G, Hickey J, Harrison C, Somervaille TCP.
A retrospective real-world study of the current treatment pathways for myelofibrosis in the United Kingdom: the REALISM UK study.
Therapeutic Advances in Hematology [Epub 28 March 2022]

Manchester scientists exploit cancer weak spot to combat therapy resistance

By **Ana Vitlic**, Research Associate, Targeted Therapy Group, Division of Cancer Sciences

SCAN ME

A team of researchers in Manchester demonstrated the role of COX-2 enzyme in cancer cells and the development of resistance to chemotherapy drugs. They showed the potential of using common nonsteroidal anti-inflammatory drugs (NSAIDs) in combination with chemo- and immunotherapy for hard-to-treat cancer models such as triple negative breast cancer.

Have you ever wondered what is the secret weapon of cancer cells responsible for treatment failure after chemotherapy?

Researchers from the Cancer Inflammation and Immunity group at the Manchester Institute have uncovered the connection between increased levels of cancer cell enzyme cyclooxygenase (COX)-2 and resistance to cytotoxic – a substance that can kill living cells, including cancer cells – chemotherapy drugs.

COX-2 is an enzyme responsible for PGE_2 synthesis, a molecule that is an important player in inflammatory processes.

In normal physiological conditions, its role includes maintaining mucosal integrity, fever, and blood vessel homeostasis. In the context of cancer however, this translates to promotion of tumour cell proliferation and survival, angiogenesis, and metastasis.

Following its close connection with inflammation, our researchers have suspected the implication of PGE_2 – produced by dying cancer cells – in driving the inflammatory environment responsible for cytotoxic therapy resistance.

The team showed that cytotoxic drugs consistently increase activation of the COX-2/PGE_2 pathway in those cancer cells with pre-existing COX-2 activity that are sensitive to chemotherapy. It is this chemotherapy driven PGE2 release that is, in turn, responsible for the inflammatory effect of the dying cancer cells.

Tumour-intrinsic inflammation is usually characterised by accumulation of neutrophils and macrophages – white blood cells that are an important part of the immune system and commonly first responders to the sites of acute inflammation. In this case however, they are often associated with immune suppression at the local tumour sites.

The team went on to show that adding celecoxib – COX-2 inhibitor and NSAIDs (such as Ibuprofen) commonly

used to treat joint pain, swelling and inflammation – to the combination of chemotherapy and immunotherapy, achieved tumour control. This new improved, anti-cancer combination therapy was able to simultaneously keep in check tumour promoting neutrophils and macrophages while boosting another type of white blood cell – T lymphocytes – by strengthening their cancer-killing activity.

Overall, the study is important as it exposes enzyme COX-2 as the weak spot of some cancer cells and demonstrates the potential of common COX-2 inhibitors in future treatment combinations.

This gives hope for those disease types that are in desperate need for novel treatment, such as triple negative breast cancer, the most notorious form of breast cancer associated with the poor prognosis.

Bell CR, Pelly VS, Moeini A, Chiang SC, Flanagan E, Bromley CP, Clark C, Earnshaw CH, Koufaki MA, Bonavita E, Zelenay S. (2022)
Chemotherapy-induced COX-2 upregulation by cancer cells defines their inflammatory properties and limits the efficacy of chemoimmunotherapy combinations.
Nature Communications 13(1):2063.

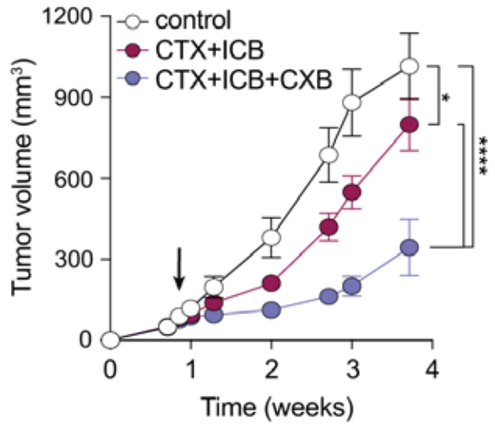


Figure shows growth profiles of tumours in mice treated with control (n=10), chemotherapy (CTX) + immune checkpoint blockade (ICB) (n=10) and CTX+ICB+CXB (n=12), pool of two independent experiments. Arrow indicates treatment start, mice received CXB or vehicle treatment bidaily. Data shows that COX-2 inhibition is essential for tumour control during chemotherapy and immunotherapy combination treatment. Bell et al. *Nat Commun* 13, 2063 (2022). https://doi.org/10.1038/s41467-022-29606-9. Shared under Creative Commons license.

Highlights from the CRUK Manchester Institute Annual Scientific Report

We are very pleased to announce that our 2021 Annual Scientific Report is now available to read online. Here, we spotlight some of the notable features in the report.

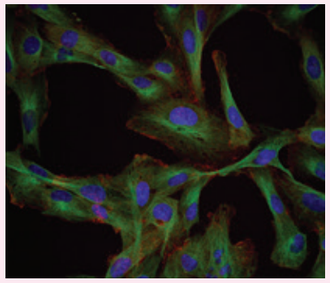
Science meets art

First, the striking image on the front cover is hard to miss. Amaya Virós and Tim Budden (from the Skin Cancer and Ageing group) supplied the image, which also made the front cover of scientific journal *Clinical Cancer Research* – June 2021 edition – that published their article 'Female Immunity Protects from Cutaneous Squamous Cell Carcinoma'. It features the cutaneous papilloma from a female mouse following exposure to the carcinogen DMBA/TPA.

SCAN ME

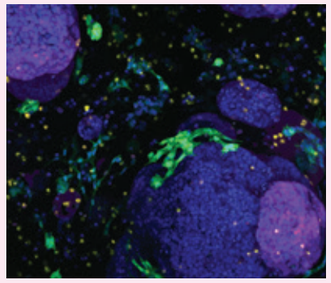
Image supplied by Amaya Virós and Tim Budden features on the front cover on our Scientific Report.

The rest of the report is also full of fascinating images contributed by our research community.



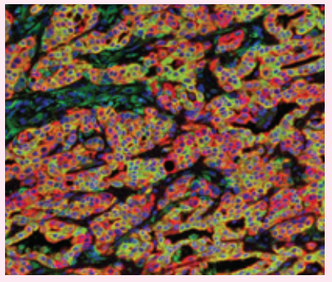
Intracellular localisation of lamellipodin (red channel) in RAS-transformed cells as evidenced by confocal microscopy. α-tubulin (green channel) is shown to delineate the cytoskeleton and 4',6-diamidino-2-phenylindole (DAPI) (blue channel) staining denotes the cellular nucleus.

Image supplied by Lisa Shlyakthina (Cell Plasticity & Epigenetics)



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

Image supplied by Joanna Kelly and Christopher Below (Systems Oncology)



Multiplex IHC images of murine prostate (pten-/-/ p53-/-) tumours stained for STING (green), CK8 (Red), and DAPI (Blue) following treatment with radiotherapy. Radiotherapy leads to an increase in STING staining. IHC staining was performed using the Bond (Rx) staining platform (CRUK MI Core Facility) and imaged using Olympus VS120 microscope (Advanced Imaging).

Image supplied by Debayan Mukherjee (Targeted Therapy, Division of Cancer Sciences, University of Manchester)

Publication highlights

Despite challenges in triplicate of the Paterson Building fire in 2017, relocation to Alderley Park, and the COVID-19 pandemic, we accomplished an impressive publication output in 2021, including the first-author papers from three PhD students:

SCAN ME

1) Max Schenk from the CRUK MI Cancer Biomarker Centre published in *Nature Communications*, where he and colleagues define a new mechanism of acquired chemoresistance in small cell lung cancer and identified a potential new therapeutic avenue for this recalcitrant tumour.

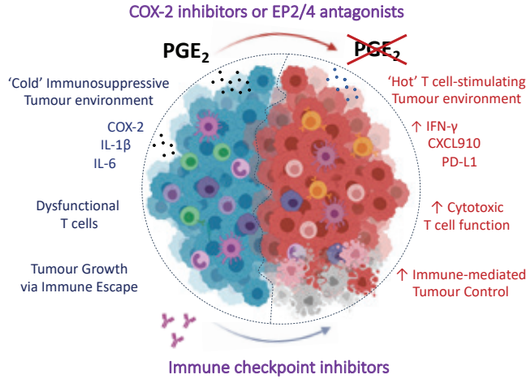
SCAN ME

2) Colin Hutton, Systems Oncology, identified two novel pancreatic fibroblast lineages with distinct tumour permissive and suppressive function that have important implications for therapeutic efficacy, published in *Cancer Cell*.

SCAN ME

3) Fabrizio Simeoni completed his PhD in the Leukaemia Biology lab. Investigating the mechanisms by which Forkhead family transcription factor gene FOXC1 blocks normal myeloid lineage differentiation in AML, he and colleagues discovered that RUNX1 – a critical regulator of myeloid differentiation – and FOXC1 interact through their respective DNA binding domains and that this protein:protein interaction could be a potential therapeutic target (published in *Cell Reports*).

We are also pleased to announce that the CRUK MI Cancer Biomarker Centre has made a significant expansion of their toolkit of immune based biomarkers, including the translation of Santiago Zelenay's COX-IS signature to clinical trials – you can find out more about Santiago's research at the Institute further on in this newsletter (page 18).

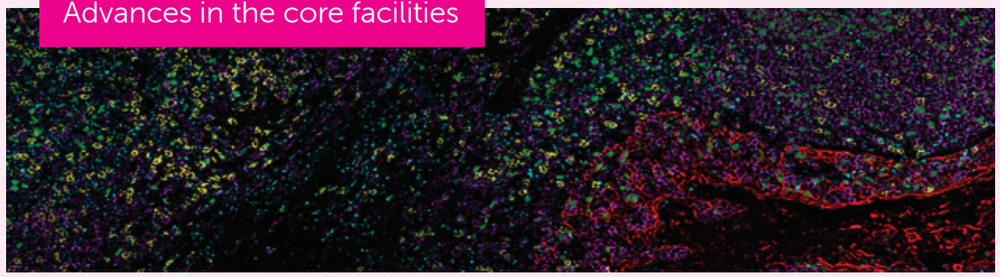


Anti-inflammatory Drugs to Turn Up the Heat of Intratumoural Inflammation. By performing in-depth inflammatory profiling of mice and human tumours, we have identified mechanisms by which anti-inflammatory drugs rapidly alter the tumour inflammatory profile, tilting the balance towards cancer inhibitory inflammation and enhancing the response to immunotherapy based on immune checkpoint inhibitors.

SCAN ME

It has also been a great pleasure to see the culmination of four years' work of Institute Fellow **Amaya Virós** result in several significant senior author papers. In further success for the group, postdoc Tim Budden was awarded the CRUK MI Edith Paterson Prize in recognition of his outstanding contributions to cancer research.

Advances in the core facilities



CODEX image demonstrating part of a 12-component panel – pancK (red) Ki67 (green), CD3e (blue), CD20 (purple), CD8 (yellow), CD107a (teal).

Our core facilities have been working together to bring new technological advances and innovation to our research platform capabilities to boost the research we undertake at the Institute.

These include CO-Detection by indexing (CODEX) – a method for single cell biology where simultaneous detection of up to 40 biomarkers in the same cell (Histology and Visualisation, Irradiation & Analysis), and the implementation of machine learning methods to analyse and understand high dimensional CyTOF output data (Scientific Computing, Flow Cytometry, VIA and the Systems Oncology research group).

Meet our new Institute Fellow

Last year we introduced Carlos Lopez-Garcia as a new Institute Fellow. He set up his new research group – Translational Lung Cancer Biology – funded by a grant from the NC3Rs to develop new human models of lung squamous cell carcinoma. We are looking forward to seeing some game-changing science from Carlos and his group in the coming years.

TRANSLATIONAL LUNG CANCER BIOLOGY

Institute Fellow
Carlos Lopez-Garcia[1]

Scientific Officer
Anthony Oojagger[1]

Graduate Student
Julia Ogden[1]

Lung squamous cell carcinoma (LUSC) is an aggressive type of lung cancer that originates in bronchial basal cells with limited therapeutic options. Apart from chemotherapy, only immunotherapies result in marginal improvement of survival in LUSC patients. Early detection is currently the most effective tool to prevent deaths by LUSC. Screening programmes by CT-scanning in high-risk populations have overwhelmingly confirmed this benefit. However, 40% of patients diagnosed with early-stage disease still die within five years, having failed to detect preinvasive lesions. These precancerous bronchial lesions show high risk of malignant progression but can be easily removed with minimally invasive procedures.

Toni enjoying the grounds at Alderley Park.

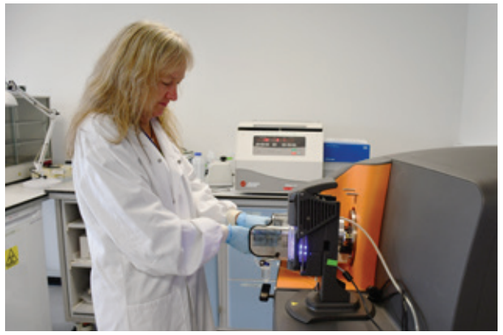
Meet the new head of Flow Cytometry

By Toni Banyard

I have 19 years' experience of being a research scientist in various organisations including the biotech sector, (Cambridge Antibody Technology aka MedImmune), pharma (Syngenta and AstraZeneca) and academia (The University of Manchester), where I completed my thesis on T cells associated with asthma.

After this, I worked at the Liverpool School of Tropical Medicine on developing their flow skills and T cell analysis in pneumonia. During that time, I was part of the successful group that won a Wellcome award for sorting instrumentation in their Category 3 facility.

I have worked for seven years now in the Cancer Research UK Manchester Institute Flow Cytometry core facility, where I have built up the analysis platform and developed the mass cytometry facility. It is a vital time for flow cytometry in the cancer field – with the increasing usage of immune therapies – and my ambition is to be leading the way in terms of cellular analysis with all our platforms.



Toni works the Helios™ CyTOF® in the lab. This technology enables deep profiling of translational and clinical research samples across a range of cell surface and intracellular markers.

Having once been a researcher, I bring that perspective to the core facility. Also knowing how industry and commercial partners will view projects allows me to facilitate both views and get the most out of the studies.

Multiplexing is the future, which is growing significantly, and I intend for this facility to maintain high standards by providing excellent comprehensive training for all staff but also providing the best equipment the market has to offer.

We have excellent scientific instruments within our facility, and we will soon be adding to these, increasing our capabilities of analysis. Using spectral analysers enables us to look at over 40 markers on single cells, which is similar to Cytometry by Time Of Flight, or CyTOF. However, I see these two platforms as quite separate and not inter-changeable – spectral analysis still uses fluorescence, which brings all the complications associated with this approach, especially when looking at this many markers, but initial comprehensive optimisation will minimise any issues downstream and the facility will cover all this training.

The following step will be to analyse these large datasets and the Flow facility is working closely with the other core facilities at the Institute to develop a pipeline that will deliver an efficient workflow. Eventually we want to extend this model to the sorting facility so analysis panels can be translated to sorting.

I intend to expand and refine all training on instrumentation and software and look forward to working with you all on future exciting studies.

On a personal note, I have lived in Manchester since 2003, in and around South Manchester, and you will get used to me talking about Molly my crazy Labrador is even the 'face' of the CyTOF lab at Alderley Park...well she is a lab after all! We like nothing better than a good walk in the Peak District with a pint after!

Molly the lab

Meet the new Wellbeing & Engagement Advisor

By Jeff Barry

As some of you will be aware, I was the Flow Cytometry core facility manager, here at the CRUK Manchester Institute, before retiring at the end of March 2022. I'd like to take the chance to thank everyone who contributed to my retirement gift; I'm now a proud owner of two Foo Dog statues and a splendid set of headphones.

But, what's this I hear, "you're retired but back to work already?" That's right, in May I returned part-time, working one day a week as the Institute's Wellbeing & Engagement Advisor. You might ask, "What does an ex-facility manager know of wellbeing?" Good question. In addition to having experience of managing and supporting my team, I was, and still am, the Unite workplace union representative. As such, I have been able to advocate on the behalf of staff. I've sat on the Health and Safety Committee, now the Health, Safety and Wellbeing Committee (HSWC) and I also lead the Union side on regular Joint Negotiation Committee meetings. Mental health and general wellbeing are beginning to be recognised as priorities within the workplace and I jumped at the chance to continue to actively promote wellbeing here at the CRUK Manchester Institute.

Stemming from this, the Institute has set up a Wellbeing Working Group whose aims are to roll out wellbeing initiatives and to monitor or benchmark the general level of wellbeing within the Institute. One aspect of my role is to help roll out health and wellbeing initiatives such as the establishment of wellbeing champions as well as supporting our network of compassionate colleagues and mental health first aiders. In general, I want to create awareness around the importance of maintaining levels of wellbeing by providing tips and guidance.

Other than encouraging and supporting staff to think about their own wellbeing, there will be a pastoral aspect to the role, as occasionally people may need help in dealing with the stresses of life. If a staff member feels the need to confide in someone, they will find me very approachable and willing to listen, total confidentiality is assured. It should be stressed that I'm not a trained counsellor or medical professional however, I will be able to direct staff to appropriate professional help and assistance.

I can be contacted in the first instance by email and if necessary, I will arrange any confidential follow-up meetings.

In addition, staff can be directed to our online self-help resources available on the Institute's intranet.

I look forward to supporting you all.

Leukaemia Immunology & Transplantation – Mark Williams

We are delighted to welcome Clinician Scientist Mark Williams as a new Institute Fellow. Until recently, he has been working here under a University of Manchester Presidential Fellowship developing his research interests.

Mark obtained his medical degree from the University of Cambridge before moving to Manchester for clinical training in Haematology. He joined the CRUK Manchester Institute in 2015, undertaking a PhD in leukaemia biology and epigenetics with Professor Tim Somervaille.

In 2020, Mark won a University of Manchester Presidential Fellowship to develop a research programme that combined his doctoral experience of leukaemia biology and epigenetics with his clinical interest in haematopoietic stem cell transplantation.

This year, Mark secured a competitive Clinician Scientist Fellowship funded by the Medical Research Council, and with this grant, he has been able to set up his own group, 'Leukaemia Immunology and Transplantation'.

Mark is an Honorary Consultant in Haematology at The Christie NHS Foundation Trust, with a practice in stem cell transplantation. He aims to understand the mechanisms that allow leukaemia to evade the donor immune system leading to post-transplant relapse and to develop novel therapeutic approaches for relapse prevention and treatment. He also leads a Manchester Cancer Research Centre Town Hall project to develop novel biomarkers that predict transplant outcomes.

Acute myeloid leukaemia (AML) is a fast-growing type of blood cancer that affects myeloid blood cells. Around 3,000 people are diagnosed with AML each year and the greatest challenge in the management of acute myeloid leukaemia is disease relapse, which is due to chemoresistance of leukaemia cells with disease repopulating potential.

Allogeneic haematopoietic stem cell transplantation is the only curative therapy for many patients with acute myeloid leukaemia and other poor-risk haematological malignancies. Recipients are 'conditioned' with chemo/radiotherapy before receiving blood-forming stem cells harvested from a donor. These stem cells repopulate the bone marrow and provide a new immune system, which eliminates the cancer. However, disease relapse remains the most common cause of death and in some cases is due to the failure of donor T cells to eliminate residual leukaemia. Donor T cells are often dysfunctional at relapse and leukaemic cells frequently exhibit reduced immunogenicity.

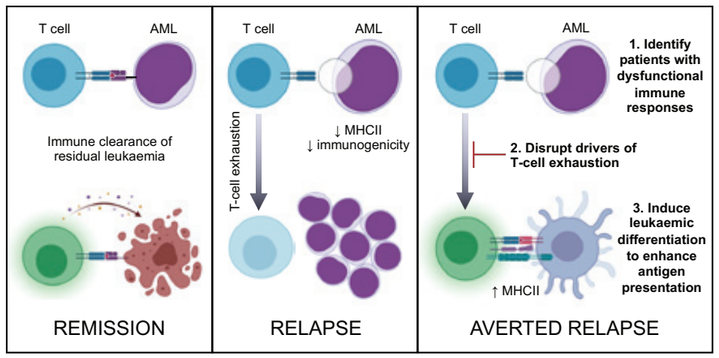
In the Leukaemia Immunology and Transplantation laboratory, Mark and his team are aiming to develop a comprehensive strategy to prevent post-transplant relapse.

To achieve this ambition, he is setting out to address three key objectives: 1) developing novel biomarkers to identify patients at risk of relapse; 2) defining the critical drivers of T-cell dysfunction; and 3) exploring the potential of pharmacological induction of leukaemic differentiation to augment donor T-cell responses.

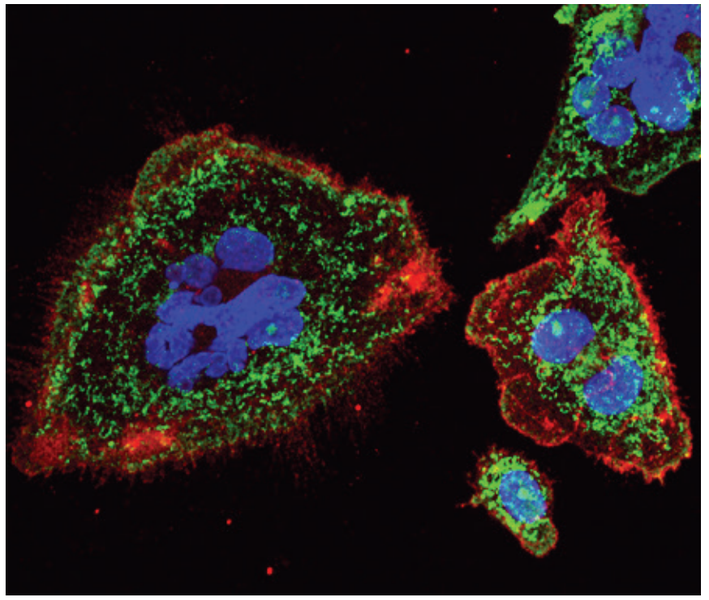
Developing biomarkers of immune dysfunction to predict post-transplant AML relapse

After treating cancer, any remaining cancer cells in the body can become active and start to multiply, causing a relapse of the disease. Early recognition and identifying at-risk patients are critical to preventing relapse. This is because established relapse compromises graft function and excludes the possibility of influencing donor immune responses. Existing methods used to determine whether a treatment was completely effective – such as minimal residual disease detection – are only useful for a minority of patients and do not give any information regarding the actual relapse mechanism. Mark hypothesises that biomarkers of immune dysfunction could predict disease recurrence in the majority of patients and guide manipulation of the donor immune response to avert relapse.

Recent studies have found that exhausted T cells (TEX) are detectable in the blood and bone marrow of patients who go on to experience relapse. Mark established a study to collect peripheral blood from transplant recipients to investigate whether detection of TEX could be a useful relapse biomarker.



A strategy for preventing post-transplant AML relapse by identifying patients with early evidence of immune dysfunction then intervening to modify both T cell- and AML-mediated mechanisms of relapse, namely T-cell exhaustion and leukaemic immune evasion through downregulation of MHC class II (MHCII).



Macrophage-like cells derived from patient AML. Stained for MHCII (green) and the co-stimulatory molecule CD86 (red).

Identifying drivers of post-transplant T-cell exhaustion

T cell exhaustion is a state of T cell dysfunction that arises during cancer. T-cell dysfunction occurs in many cancers and treatments that re-invigorate T cells have revolutionised cancer care. However, these therapies cause significant toxicity when given to transplant patients.

Because there are many potential causes of T-cell dysfunction, it is important to identify those most relevant to the T cells that fight leukaemia, to target them without causing unacceptable side effects.

To understand how donor T cells become dysfunctional, Mark and his group will study the expression of genes and the structure of DNA in thousands of individual T cells from patients with AML relapse after transplant.

This will allow them to explore in detail the changes that occur as T cells become dysfunctional and identify the major drivers of dysfunction in patients. Targeting these processes will then form the basis of novel therapeutic strategies to treat or prevent post-transplant relapse.

Inducing leukaemic differentiation to augment donor T-cell responses

AML frequently displays proteins that are involved in the activation of T cells, called MHCII. Expression is often lost at post-transplant relapse, and this reduces the ability of leukaemia to activate T cells, providing a mechanism of immune evasion. How MHCII proteins are regulated in AML is not known.

AML is a cancer of the blood-forming cells of the bone marrow. Through a process termed differentiation these cells normally give rise to the mature cells found in blood, some of which strongly express MHCII. This process becomes blocked in AML but can be re-established by a recently developed class of drugs called LSD1 inhibitors.

Using leukaemia and T cells isolated from patient samples, Mark will investigate the ability of these drugs to drive MHCII expression in AML and promote T-cell activation. LSD1 inhibitors are currently in clinical trials for AML, providing a clear pathway to clinical application, should their results support their use for post-transplant relapse.

Before novel preventative therapies can be given to patients, those at risk of relapse must be identified. Recent studies suggest that early detection of dysfunctional T cells may predict relapse. Changes in the protein content of blood have also been observed that reflect the activity of T cells against leukaemia. Mark and his group plan to analyse thousands of patient samples and identify changes in the protein content of blood and the properties of T cells that precede AML relapse, in order to develop new predictive blood tests.

As Mark establishes his group and research programme, he will make important discoveries about immune dysfunction and leukaemic immune evasion that leads to AML relapse after stem cell transplantation.

With these results, new therapeutic strategies for treating or preventing disease recurrence can be conceived. Development of new blood tests that predict AML relapse will enable therapeutic targeting of at-risk individuals and improving transplant outcomes.

We congratulate Mark on his success and wish him all the best in building his independent research programme over the coming years. Well done!

Santiago Zelenay is promoted to Senior Group Leader

We are delighted to announce that Santiago Zelenay, who leads the Cancer Inflammation and Immunity group at the Institute, has been promoted to Senior Group Leader. He gave a fantastic lecture – which was also our first large-scale talk held in person since the start of the pandemic – and impressed the interview panel with his outstanding research accomplishments and future plans.

Dr Zelenay focuses his research on boosting the immune response to cancer. Immunotherapy has been a breakthrough treatment against cancer, allowing even cancers that do not respond to more traditional therapies to be treated. Unfortunately, many patients do not have a lasting response to immunotherapy, and the problem of resistance – as well as determining which patients will most likely benefit from treatment – is a major challenge in oncology.

Santiago joined the Institute in 2015 following a highly successful postdoc position with Caetano Reis e Sousa at the Cancer Research UK (CRUK) London Research Institute and later at the Francis Crick Institute. During his time at the Crick, Santiago discovered a mechanism used by cancers to escape detection by the immune system, which has the potential to be exploited therapeutically. This work underpins the current and future research programme of Santiago's Cancer Inflammation and Immunity (CII) group.

Tumours produce a substance called PGE_2 – prostaglandin E2 – which drives a 'bad' immune response, making them more resistant to immunotherapy. PGE_2 is generated by the COX-2 enzyme, and inhibitors of COX-2 include aspirin, as well as other drugs already in clinical use. Santiago and his team are testing whether using these drugs to block COX-2, in combination with immunotherapy and chemotherapy, can significantly boost the effect of those other drugs. They have seen very promising results in mouse models of cancer, including effects in tumours that are normally resistant to immunotherapy and chemotherapy.

This pre-clinical research indicated that COX-2 inhibitors should boost the efficacy of immunotherapy treatments in patients. These inhibitors are now being tested in a clinical trial funded by Breast Cancer Now and led by the team at the Christie NHS Foundation Trust, including Dr Becki Lee and Dr Anne Armstrong.

Notably, Santiago and his team have devised a method for assessing the balance between 'good' and 'bad' immune responses in patients – what they call a COX-2 score – and another clinical trial is about to get underway to test whether this score can be used to guide the treatment of patients.

Santiago's work is widely recognised, and he has been awarded several prestigious prizes. In 2017, he received the CRUK Future Leaders in Cancer Research Prize, which acknowledges those with the potential to achieve world-leading status. In 2019, he went on to win the inaugural BIAL Prize in Biomedicine 2019, along with Caetano Reis e Sousa. The BIAL Prize recognises work published in the biomedical field that is of exceptional quality and scientific relevance. The award-winning study published in *Cell*, "Cyclooxygenase-dependent tumor growth through evasion of immunity", describes the ground-breaking discovery that cancer cells use the COX-2/PGE_2 pathway to evade the immune system.

Further success has followed over the last 18 months, with an impressive raft of achievements for Santiago and his team. The first ever postdoc to join the CII group was Dr Eduardo Bonavita in 2016. He enjoyed great success working with Santiago and recently left to set up his own research group at the Humanitas Research Hospital in Lombardy, Italy on a competitive fellowship. This move is a credit to Santiago's superb mentorship and enthusiasm, and we wish Eduardo every success as he continues his own research.

Two exceptional CII group PhD students recently passed their PhD viva examinations, having both joined the Institute in 2017. First was Christian Bromley for his thesis on "The dual role of inflammation in cancer progression and immunotherapy response". Chris won a prize as one of the top 3 poster presentations at the International PhD Student Cancer Conference (IPSCC) in 2019 for his work, and also produced much of the online content for the Institute's contribution to the prestigious Royal Society Summer Science Exhibition.

More recently, Charlotte Bell defended her thesis, demonstrating her science communication skills with a fantastic pre-viva talk on "Manipulating the dark side of chemotherapy-induced inflammation to unleash anti-cancer immunity". Charlotte helped produce and narrate video content for the Royal Society – the exhibition was held online in 2021 due to the COVID-19 pandemic – as well as securing funding from the British Immunological Society to produce a novel science engagement activity helping children create cardboard tumour models via a Zoom workshop. She was also the 2021 winner of our Lizzy Hitchman Prize for best student poster at the Institute Colloquium.

Santiago gives a fascinating talk for his promotion review.

Alumni – where are they now?

We caught up with some of Santiago's former group members to find out how they are getting on.

Former postdoc Eduardo Bonavita said, "I have been working alongside Dr Santiago Zelenay from the very beginning of his career as Group Leader at CRUK MI. At that time the Cancer Inflammation and Immunity Group was made of only three members (including the two of us). Now, after more than six years, I can testify to his outstanding skills as mentor and supervisor. The training I received in his lab allowed me to grow both as a scientist and as a man and thanks to his support I have achieved the goal of becoming an independent investigator.

"After a one-year long selection process, I have been awarded a start-up grant from the Italian Association for Cancer Research (AIRC) to establish a new research unit in Italy. From April, I have been working hard to set up the Cellular and Molecular Oncoimmunology (CMO) Lab at the Humanitas Research Hospital, which sits in the countryside of Milan. The mission of the CMO Lab will be to provide a deep understanding of the mechanisms of immune evasion in cancer, with a particular interest on the immune pathways bridging innate and adaptive immunity. The ambition of CMO Lab will be to translate the basic findings to the clinic and reduce the gap between fundamental cancer research and clinical practice.

"From September my Lab will welcome two PhD candidates who will work on exciting projects focusing on liver cancer, with great translational potential.

"I wish to be an inspiring supervisor for these students as Santiago has been for me and the rest of the team!

"I was very happy and proud (but not surprised!!!) to learn about Santiago's promotion and I am looking forward to hearing about the next steps in his brilliant career."

Shortly after finishing his PhD, Chris Bromley joined pharmaceutical company BenevolentAI as an Advanced Bioinformatics Data Scientist.

"I recently completed my PhD in Santiago's Cancer Inflammation and Immunity lab. During my PhD, I used bioinformatics approaches to explore the interaction of cancer-promoting and cancer-inhibitory inflammation in cancer. Using machine learning methods, network analysis, multi 'omics integration, analysis of bulk and single cell transcriptomics as well as multivariate survival analysis, we identified a conserved set of pro-tumourigenic inflammatory mediators that powerfully and consistently predicted poor survival of cancer patients and inherent resistance to immune checkpoint inhibitors. Making use of Santiago's powerful network of internal and external collaborators I was able to validate my *in silico* findings experimentally and in validation datasets. I thoroughly enjoyed my time in the lab developing a deep understanding of cancer immunology from those around me.

"I have since moved to London for a new role as an Advanced Bioinformatics Data Scientist at Benevolent AI; a cutting-edge pharmaceutical company harnessing the power of artificial intelligence to both mine literature data, as well as structured data such as that from next generation sequencing, in order to discover new targets in a disease agnostic manner. My role involves using methods for multi 'omics analysis to build data packages in support of new targets, as well as developing novel machine learning algorithms and ways of analysing data. In addition, I provide strategic input to projects collaborating closely with software engineers, AI scientists, drug discoverers and project managers."

Eimear Flanagan says,

"My five-year PhD in the Cancer Inflammation and Immunity lab was exciting and rewarding. Santiago was a fantastic supervisor – extremely supportive, enthusiastic and a fountain of knowledge. I am so grateful for the friendship and support from all CII members, past and present, as well as the opportunity to carry out cutting edge research and to attend interesting conferences, lab retreats and an immunology summer school.

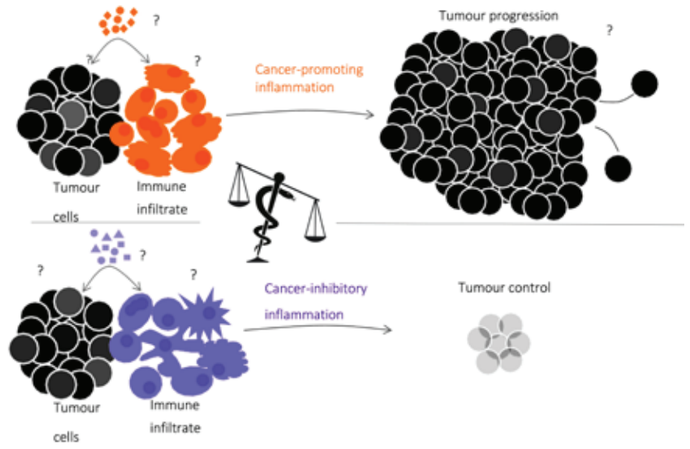
"Since finishing my PhD, I have started as a scientist at Redx Pharma here in Alderley Park. Redx is a drug discovery biotech with projects ranging from drug discovery through to phase 2 trials. My role involves analysing patient samples from a clinical trial, specifically analysing immune cells and cytokines in the blood. As well as that, I am also involved in a research and discovery project. I am thoroughly enjoying my new role."

The CII team are also developing a novel platform for testing combinations of drugs on tumour samples taken from patients undergoing surgery. The tumour tissue is then dissected into tiny fragments and grown in the lab for up to 48 hours. These fragments retain the characteristics of the original tumour, including the balance of 'good' and 'bad' cancer immune responses. Treating fragments of the tumour with different combinations of drugs allows our researchers to work out which drug combinations the tumours are responding to.

In early work looking at tumour fragments from patients who had already received treatment, the combinations of therapies which worked best to slow the growth of the tumours in the lab critically matched the treatments that worked best for patients. Santiago and his team are now taking these exciting findings forward with the aim of developing a clinical test, which can guide doctors to prescribe the most suitable treatments for their patients following surgery.

We look forward to seeing Santiago expand his team and develop his research programme further over the next six years as he realises his future plans in this important area of cancer immunology. There is no doubt that his investigations into how the tumour inflammatory environment stimulates or inhibits cancer growth and spread will change the way we treat cancer.

Eduardo Bonavita is setting up his lab Cellular and Molecular Oncoimmunology (CMO) at the Humanitas Research Hospital.



Schematic representation illustrates the main research questions of the Cancer Inflammation and Immunity group, focused on uncovering the cellular and molecular mediators that regulate the balance between the tumour-promoting and tumour-inhibitory properties of the immune system.

Marking the Paterson Building fire anniversary

Paterson Redevelopment five years on from the Paterson Building fire

Five years ago on 26 April, a fire started at the Paterson Building in Withington, Manchester – home of the Cancer Research UK Manchester Institute – that would change everything. We are grateful that no one was hurt, although our research was badly disrupted for many months.

We have turned this catastrophic event into a world changing cancer centre – and now a new home for our Institute is taking shape.

All our staff over the years have showed great resilience by adjusting to the change and continuing to produce terrific research, despite the setback and unsettling times.

We would like to thank our staff and all who have supported us over these last five years.

We are also grateful to the Greater Manchester Fire and Rescue Service who quickly tackled the blaze and stopped the fire spreading further.

You can support the redevelopment by going to manchester.ac.uk/rewrite

Photo credit
Chris Clark, BBC

Their quick response helped us rescue many valuable research materials, and recovery attempts began even while the fire blazed.

The recovery process ran for months and many colleagues across The University of Manchester helped us find temporary space to continue our research.

Then we relocated to a new, temporary home at Alderley Park where we rebuilt our core facilities and services. Our teams have since been hard at work – to prevent, diagnose and treat cancer – despite the challenges.

We are grateful to the support we received from the academic community across the country and further afield.

Damage to the Paterson Building was extensive and demolition began to make way for a new building. The Paterson Redevelopment Project is nearing completion, and a world-class research centre is taking shape.

It will be home to one of the largest concentrations of clinicians and researchers in Europe. The Paterson Building represents the next generation of cancer research across the CRUK Manchester Institute, The University of Manchester, and The Christie.

Wolfgang Breitwieser at Alderley Park

Photo credit ITV

Photo credit Manchester Evening News

Photo credit ITV

Find out more and help support the amazing discoveries that will save lives around the world

SCAN ME

The Paterson Redevelopment Project is progressing well, and we anticipate our scientists will be working in there within the next 12 months.

Institute Director Caroline Dive and Nic Jones, Director of Strategic Initiatives at MCRC, celebrate topping out on top of the new building.

The Story of the Crates from the Paterson Building

By Mark Craven, Lab Services Manager.

Andy Lloyd (our Facilities Manager) and I are delighted to have been asked to do a 'big reveal' on the seemingly never-ending saga of the Paterson Building items held in storage. I hope our story is as informative for everyone as it has been therapeutic for me to write.

Since we have recently celebrated the 5th anniversary of the fire, for those of us with memories long enough to remember, it seems a propitious time to answer all those questions we don't get asked about what happened to all those crates.

To set the scene, we worked with several specialist organisations who led the complex recovery and relocation of all the rescued items from the Paterson Building: Recom Solutions, Davis French & Associates, ISS, and Harrow Green. This process was of course assisted by our Institute staff who filled the many crates, including items that had accumulated over the past few decades of the Institute operating in the building.

Through the generosity of our colleagues at The University of Manchester, various spaces were found at the North Campus to home items that we needed to keep.

We made new friends with colleagues at the University who helped facilitate access to the site for our waste

At the start: the 50 wooden crates housing specialised equipment.

Andy and Mark dressed to clear the Barnes Wallis Building.

Mark moving a pallet of stored items.

Andy loading the dismantled wooden crates.

contractors and our teams during the lockdown period. Access cards needed updating, keys were cut, and barriers were opened for us. We were even taken under the wing of the domestic team at the Barnes Wallis Building, who kindly provided us somewhere to make a much-appreciated brew.

The 'move teams' transferred over 250 black crates filled by the former occupants of the Paterson Building to the various storage sites. We placed specialised lab equipment in 50 bespoke wooden crates. We also stored a range of unwanted IT kit: PCs, laptops, printers, peripherals, and the server racks – to be disposed of at a later date.

The infrastructure of the Biological Resources Unit (BRU) was uplifted and stored in The University of Manchester Barnes Wallis Building – a conference venue in the North Campus with over 800m^2 of exhibition space – together with 60-plus crates of Lab Services' spare glassware in the space previously known as 'Harry's Bar'.

Having now been inside Harry's Bar in both Venice and Manchester, I prefer the Venetian original as the dress code does not include full body PPE and masks – as you can see in the accompanying photographs.

Mark and Andy loading the 'Roll On, Roll Off' skip.

Looking at the featured photographs, readers can also possibly gauge how much fun Andy and I were having during this task. Here I can deploy an overused phrase by saying (at least for myself) that I was definitely not in my comfort zone whilst knee deep in a skip. Unfortunately, Andy was enjoying himself throughout, which did not help me.

We also uplifted a surprising assortment of lab and office-based items such as freezers, centrifuges, coffee cups, wall art and books. One mystery object of some age eluded identification even up to its final visit to the scrap yard.

Another important duty was to make the items safe prior to disposal. Yunis Alhassan, our resident electronics expert, showed how adept he is in removing UV light bulbs from a multitude of devices, and in recycling unwanted kit for spare parts.

Returning items to the owner or rehoming items elsewhere initiated a complex and time-consuming sequence of events.

Firstly, we opened each box and crate to identify the contents. Next, we separated the items, entered the details onto spreadsheets, followed by photographing and triaging the items. As the photos show, this was not a simple operation. Due to the limitations in space and our available time alongside our day jobs, we undertook the task in stages.

We delivered portable items of interest to the Oglesby Cancer Research Building for further assessment to determine whether items had value for re-use or to go for scrap.

Andy demonstrated meticulous record keeping skills and collated some impressive facts and figures around the process (see below).

We have spent in total under £4000 in charges to scrap, recycle, and where appropriate rehome, the entire contents of the five rooms, which for a project stretching over 18 months is a bargain.

So hopefully now no one who has read this needs to ask me or Andy, "so, where did all those crates go?"

As a result of opening and sorting by hand each crate, wooden box, cardboard box, carrier bag and bin we produced the following waste streams:

- 1.5 tonnes — I.T. waste filling two Luton vans
- 2 tonnes — Wood waste within a 20-yard roll on, roll off skip
- 7 tonnes — Non-hazardous waste collected in three 12-yard skips and 2 x 40-yard roll on, roll off skips
- 15.5 tonnes — Waste Electrical and Electronic Equipment (WEEE) and mixed scrap metal

The AACR meeting returns to New Orleans

The AACR Annual Meeting 2022 in New Orleans gets underway.

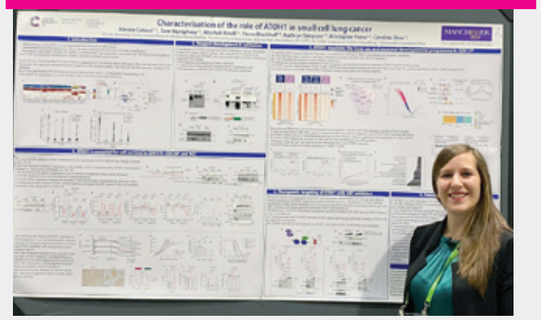
The AACR Annual Meeting is a scientific conference of great significance to the cancer research community and one that our scientists always aim to attend. Here at this prestigious event, scientists, clinicians, other health care professionals, survivors, patients, and advocates gather to share the latest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

In April this year, the meeting took place at the Ernest N. Morial Convention Center in New Orleans, Louisiana. The tag line for 2022 was "Decoding Cancer Complexity-Integrating Science-Transforming Patient Outcomes".

We are delighted that several of our researchers were able to attend in person this year. Here you can find out what some of them presented and what they enjoyed most about the face-to-face meeting.

Alessia Catozzi presents a poster

PhD student, CRUK Manchester Institute Cancer Biomarker Centre



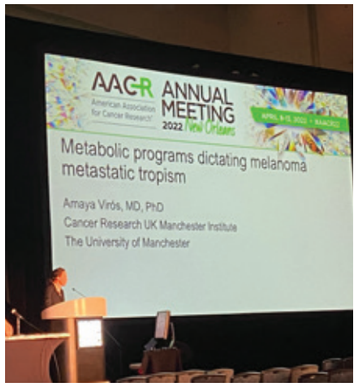
Alessia with her poster at the AACR Annual Meeting 2022 in New Orleans.

"I presented a poster around the role of a newly described transcription factor (ATOH1) expressed in an aggressive subtype of small cell lung cancer (SCLC). Within the Cancer Biomarker Centre, we have made use of patient derived CDX models to deplete ATOH1 to study its loss of function effects and found that cancer cells of this subtype of SCLC heavily rely on ATOH1 for cell survival.

"My favourite part of the meeting was the poster session, as you could discuss the research with fellow scientists while having coffee and traditional New Orleans 'beignets'. In addition, the poster sessions were huge, with topics ranging from cancer immunology to nanoparticle therapeutics, and from microfluidics to clinical trials.

"Plenary sessions were also very interesting, discussing the current hot topics in oncology."

The Skin Cancer and Ageing group go to AACR



Amaya presents at AACR Annual Meeting 2022 in New Orleans.

Amaya Viros is a Clinician Scientist funded by Wellcome and leads the Skin Cancer and Ageing group at the Institute. Her lab investigates why skin cancer is more common and more deadly in elderly patients. One stream of her research programme looks at the features of the tumour microenvironment that affect melanoma outcome in the elderly population.

At the AACR, Amaya gave a talk in the major symposium, 'Aging and the Tumor Microenvironment's Impact on Minimal Residual Disease and Cancer Recurrence'. During this session, she discussed how metabolic programmes dictate the direction and distribution of distant metastases to certain organs in melanoma.

This research is significant because metastases are the principal cause of cancer death. Understanding the molecular cues that influence the route, direction and speed of metastatic spread is essential for the development of innovative therapeutic strategies and improving patient outcomes.

Shilpa at the AACR Annual Meeting 2022 in New Orleans.

Shilpa Gurung is a PhD Student in the Skin Cancer and Ageing lab. Her project focuses on how the age of adipocytes affects melanoma metastasis and tropism and she had the opportunity to share at the AACR some of her findings on how adipocyte age-dependent metabolic programming informs melanoma metastatic burden and tropism.

Shilpa said, "The biggest cancer conference – AACR – has been the highlight of my PhD. Here I had the opportunity to network with cancer researchers from all over the world and present my findings at the minisymposia, 'Age and the tumour microenvironment', where I received lots of intriguing questions and feedback. These comments helped us to review our final experiments for my PhD."

This critical contribution to Shilpa's PhD would not have been possible without the generous funding from the Doctoral Academy Conference Support Grant at The University of Manchester and CRUK.

The AACR meeting was the pinnacle for Shilpa, building on several other meetings where she presented her PhD work. She says, "My abstract was selected for international meetings at various sessions, and I finally got the opportunity to give a talk in person after two years of COVID-19 restrictions."

Shilpa won a competitive Travel Award to attend the VIB (Vlaams Instituut voor Biotechnologie) Conference series: Tumour Heterogeneity, Plasticity and Therapy, which would have taken place in Leuven in May last year. Due to the COVID-19 pandemic, the event was moved to a virtual platform.

"The Society for Melanoma Research (the 18th International Congress was held virtually on 28th -31st October 2021) helped me to share my project with the great minds of melanoma experts from different melanoma fields, who gave their thoughts and suggestions on my project that helped to better improve my study in the context of melanoma. Here, I was pleased to present my data at the session, 'Dormancy and microenvironment'.

"The Biochemical Society Conference (held in Edinburgh, 9th -10th December 2021) on the adipocyte across biological scales was a great first in person meeting that I attended after two years.

"Not only did I get the chance to meet experts in adipocytes research, but they also held many different sessions on career advice and grant applications – critical for the next step of my PhD.

"Here, I not only shared my PhD study with a focus on adipocyte biology, but my abstract was also selected for the Elevated short talks Early Career Researcher Competition and was awarded the Best Speaker Award."

Congratulations to Alessia, Amaya and Shilpa. We are all really pleased to be able to return to attending meetings and conferences in person.

International PhD Student Cancer Conference 2022

The International PhD Student Cancer Conference (IPSSC) brings together PhD students from top cancer research institutes across Europe. In June this year, the 15th annual conference was hosted by students from the DKFZ Heidelberg, Germany.

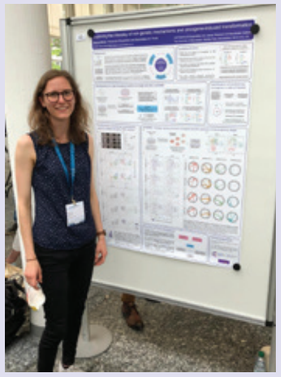
The packed three-day programme featured high-profile keynote speakers, student talks, poster sessions, career workshops and opportunities for networking.

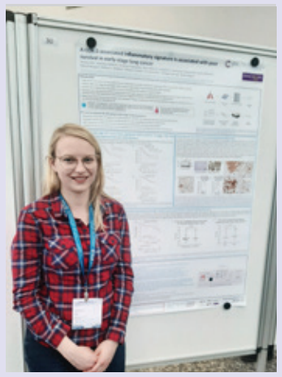

The event was rounded off with a wonderful conference dinner, which took place on a boat trip down Neckar River.

Four of our students gave talks – Katherine Moran, Felix Heider, Maria Koufaki, and Lucy Ginn – and several presented posters.

We are delighted that Bianca Blochl won a prize for best poster with her work on the interplay of non-genetic mechanisms and oncogene-induced transformation. Bianca is studying for her PhD in the Cell Plasticity & Epigenetics group at the Institute, led by Maximiliano Portal.

Congratulations Bianca!


Bianca Blochl and her award-winning poster


Victoria Fife, who liaised with the IPSSC Events Team on behalf of CRUK MI, with her poster on COX-2 associated inflammation in early stage lung cancer

MI Talks at the IPSSC 2022

Katherine Moran
Cell Plasticity & Epigenetics
Exploring non-genetic heterogeneity and plasticity in isogenic cancer models... one cell at a time

Felix Heider
Systems Oncology
Fibroblast-regulated immune clearance of pancreatic cancer cells

Maria Koufaki
Cancer Inflammation and Immunity
Characterisation of a newly identified intratumoural dendritic cell population

Lucy Ginn
Cell Signalling
Evaluation of RAC signalling as a therapeutic target in non-small cell lung cancer

PostdoCaRe Europe

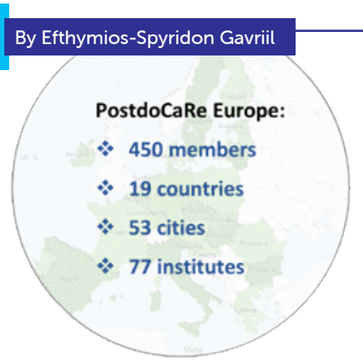
By Efthymios-Spyridon Gavriil

'PostdoCaRe Europe', the European Network for Postdocs in Cancer Research, founded in February 2021 by 'Postdocs for Postdocs', provides a platform for both scientific and personal exchange among postdocs in European cancer research institutes.

We aim to organise our own scientific and networking events, share general advice and experience, job opportunities, and invitations to cancer research meetings. So far, we have over 450 members from 19 countries, 53 cities and 77 institutes! Our goal is to include postdocs from all European countries and continue growing our network.

In October 2021, we launched a series of virtual events on cancer research related topics. We have successfully organised three 'Nanosymposia' on 'Spatial Omics', 'Tumour Microenvironment' and 'Tumour Immunology'.

We were honoured to have as our keynote speakers, Jun Hee Lee (University of Michigan), Erik Sahai (The Francis Crick Institute), Daniela Thommen (Netherlands Cancer Institute) and Johanna Joyce (University of Lausanne).



In addition, many postdocs from all over Europe presented their breakthrough research, demonstrating the amazing potential of the next generation of cancer researchers. We will continue organising such events and we hope to have an in-person conference in 2023.

So, if you are a postdoc, all you need to do to become a member of our network is to join our Slack page 'https://postdocareeurope.slack.com' using your institutional email. Final year PhD students and recent PhD graduates are also welcome.

There are no registration fees, you can get involved in our activities as much as you want to, and we are open to ideas and suggestions from everyone.

You may also follow us on LinkedIn (www.linkedin.com/company/postdocare-europe) to stay tuned about upcoming events and contact us at 'postdocare.europe@gmail.com'.

Join us now and help us build a strong network of young scientists and shape the future of cancer research.

Early Career Researcher Cancer Immunotherapy Meeting

Back by popular demand, the Proteintech events team organised their second Cancer Immunotherapy Early Career Researcher Event.

With international travel to conferences still uncertain, they aim to provide a platform to young scientists to present their work to an international audience and help boost their visibility while presenting alongside leaders in their field.

On 28th April this year, Institute scientist Santiago Zelenay featured as one of their Keynote speakers, alongside Dr Mike Chapman, from the Toxicology Unit, University of Cambridge.

Santiago is an expert in cancer immunotherapy, and his group at the CRUK MI focuses on understanding the underlying mechanisms that mediate cancer-inhibitory versus tumour-promoting inflammation in order to design new therapies for cancer patients (find out more on page 18).

He gave a rousing presentation on 'manipulating inflammation to raise cancer immunogenicity and the response to immunotherapy'. His talk was well received and provoked much interest amongst the early career researchers.

The programme also included four talks by early career researchers followed by a dynamic Q&A session.

Institute scientist one of four to receive last ever Harry J. Lloyd Charitable Trust funding

Congratulations to Institute Fellow Amaya Virós, who has been awarded one of the final research grants from US charitable trust, Harry J. Lloyd.

Since 2004, The Harry J. Lloyd Charitable Trust has granted 144 melanoma research grants, totalling $17,972,631.

The Trust has now completed its melanoma research granting solicitation process. Before it finally closed its doors earlier this year, HJL invited the board members to propose a candidate on whom to bestow their remaining funds in a "by-invitation-only last round".

Richard Marais, Institute scientist and world leading researcher in melanoma, has sat on the board since 2007 and nominated Amaya to apply.

Amaya was one of four candidates selected for funding, and the only person outside of the US.

She will use the funding to investigate why melanoma thrives in the brain - brain melanoma metastases are a leading cause of death in advanced melanoma patients and more frequently affect younger individuals.

MRC funds Clinician Scientist Fellowship at the Institute

Mark Williams has been awarded a Clinician Scientist Fellowship from the Medical Research Council.

With this funding, he is establishing his own research group as an Institute Fellow, focusing on the mechanisms that allow leukaemia to evade the donor immune system leading to post-transplant relapse and to develop novel therapeutic approaches for relapse prevention and treatment.

You can find out more about Mark's research programme earlier in the newsletter (page 16).

Save the date for the return of the in-person Institute Colloquium

We are delighted to announce that this year's Institute Colloquium is going to be held in person for the first time since the pandemic. The event will take place at the Alderley Park Conference Centre, at the slightly later date of 5th-7th October 2022.

The Colloquium is a great opportunity for our staff and PhD students to present and discuss their work and to develop collaborations with each other. It also gives the chance for our incoming students to meet their new colleagues and learn a bit more about what we do.

Over the three science-packed days, the programme will include up to the minute talks from our Group Leaders and Institute Fellows, progress talks from our second year PhD students, the popular alumni session, posters and much more.

We are also especially pleased to be able to provide some evening entertainment on 6th October at the Metropolitan pub in West Didsbury.

We are very much looking forward to finally being able to all get together in person and share our research and ideas.

Suppliers A Go-Go go to the Institute Colloquium

By David Jenkins, Purchasing Officer, CRUK MI

The Cancer Research UK Manchester Institute presents 'Suppliers A Go-Go', a creation of mine to come up with a way to bring our scientists face to face with laboratory equipment suppliers.

This is an important interaction as it helps the suppliers understand the science we undertake here at the Institute and provides the opportunity for them to assist with relevant products and inform us of the latest technology available. It has proved to be a great way of building a network with our suppliers.

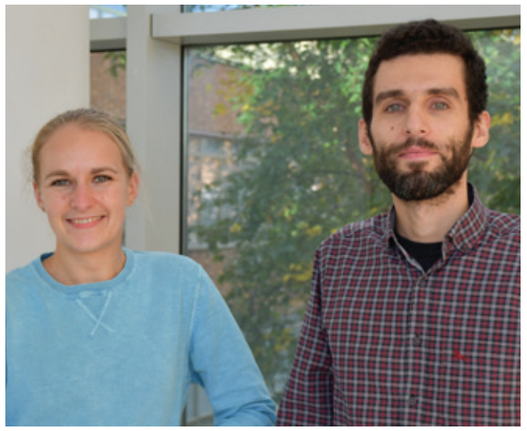
It all started back in 2018 and was an instant success. Originally, I thought of the name 'Scientist A Go-Go' (a twist on the 1981 classic song "Einstein A Go-Go" by Landslide) but soon found out there is already a Science Magazine in the USA with that name. Therefore, the obvious alternative name to give it was 'Suppliers A Go-Go'. Critically, the suppliers also pay to attend these events, which generates important funds for the Institute.

I am pleased to announce Suppliers A Go-Go will be sponsoring the annual Colloquium this year. On the 6th October, Suppliers A Go-Go will be exhibiting at the Colloquium (alongside our own poster event). In attendance will be a selection of 25 of our most popular suppliers, with plenty of freebies and prize draws. Please do make the time to visit the exhibition stands, speak with the representatives, and make new contacts, all while getting hold of some great free branded merchandise. Also, do not forget to enter the FREE prize draws.

I look forward to return of this great event and seeing you all together there.

10th Global Young Scientists Summit 2022

By Efthymios-Spyridon Gavriil, Postdoctoral Fellow, Drug Discovery Unit, CRUK MI



In our last newsletter, we featured the fantastic news that Institute postdoctoral scientists Lisa Shlyakhtina and Efthymios-Spyridon Gavriil had been selected to attend the 10th Global Young Scientist Summit, online. Here we catch up with Efthymios, who gives his account of the experience.

The 10th Global Young Scientists Summit, held online from 17th to 21st January 2022, was an amazing opportunity to interact with eminent scientists and young researchers from all over the world.

The speakers' line-up included Nobel Laureates and Fields Medallists, Millennium Technology Prize, Turing Award and IEEE Medal of Honour recipients.

It was a unique event as all these brilliant scientists delivered fantastic lectures, not just describing their latest findings, but also mainly focusing on their career pathway, the aspirations they had when they were young and the hurdles they had to overcome.

I was inspired by their passion for science and that despite all their major achievements, they never stop dreaming about the future and how scientific breakthroughs can make our world a better place.

In addition to these lectures, panel discussions were held to address the greatest challenges of research and humanity. 'Preparing for the Next Pandemic', 'Has Scientific Research Fundamentally Changed' and 'Artificial Intelligence, Ethics and Governance' were some of the discussed topics.

As a cancer researcher, I was thrilled by the lectures of Prof Thomas Cech on 'Complete Replication of Chromosome Ends', Prof Benjamin List on 'Chemical Catalysis as Enabling Science and Technology for Humankind' and Prof Ada Yonath on 'Exploiting Genetic Code Translation Principles for the Design of Next Generation Therapeutics'.

As a young scientist, I enjoyed Prof Barry Marshall's talk 'How Curiosity Driven Research Resulted in the Nobel Prize in Medicine' as he described the rejections he received in his first steps and that he was not even allowed to present his findings at a conference.

Furthermore, during his talk on 'Using Electron Microscopy to Study Ribosomes in Action', Dr Venki Ramakrishnan advised the young audience that reward and recognition might come much later in our careers, saying that 'If you think you are in the running for a Nobel Prize, you should try to be very careful and not die!'

Although all lectures were breathtaking, if I had to choose my favourite part of the conference that would be Prof Cédric Villani's talk 'On Finding Theorems, and a Career'. He gave the best description of a PhD: "A PhD is certainly the most important diploma in science ... The advisor gives you a problem that nobody knows if there is a solution ... so, you really become a researcher fighting against the unknown".

Overall, the Global Young Scientists Summit 2022 was a wonderful experience that broadened my scientific perspectives and fuelled my passion for research. I am grateful to Cancer Research UK for nominating me to attend.

Speakers online at GYSS 2022. Clockwise from top left: Ada Yonath (Nobel Prize in Chemistry, 2009), Aaron Ciechanover (Nobel Prize in Chemistry, 2004), Cedric Villani (Fields Medal, 2010), and Benjamin List (Nobel Prize in Chemistry, 2021).

Manchester researchers propose new treatment opportunity for ovarian cancer patients

We are delighted to announce that Caroline Springer and Iain Hagan have secured funding from the charity, Target Ovarian Cancer.

Research spend on ovarian cancer has dropped by one third in five years, so it is the ambition of Target Ovarian Cancer to fund life-saving research to help double survival rates.

This novel translational project for new treatments in ovarian cancer brings together the complementary disciplines of the two research leaders.

Caroline Springer, Director of the Drug Discovery Unit here at the CRUK Manchester Institute, contributes expertise in cancer therapeutics – developing potent compounds and delivering inhibitors to the clinic – with a proven pipeline within our Institute that accelerates successful compounds into clinical trials.

Iain Hagan, who leads the Cell Division group, adds basic science into the mix, with his leading expertise in cell cycle control and pharmacological perturbation. Iain is world renowned for his ground-breaking research on yeast and manipulation of this model system to elucidate the mechanisms underpinning fundamental cellular processes.

His important discoveries about the molecules that control the cell cycle have improved our understanding of cancer cell proliferation that have led to the identification of new therapeutic targets.

Only 35 per cent of women diagnosed with ovarian cancer in the UK survive for ten years or more. Survival from ovarian cancer is much worse than for many other cancers, due to late diagnosis and a lack of effective treatment options.

Our research teams will combine their scientific approaches, incorporating the active part of inhibitors designed by DDU into an exciting new technology applied by Iain.

They will target a protein with a known key role in cancer cell multiplication that is responsible for the persistence of ovarian cancer observed in a proportion of patients, limiting their treatment options.

Caroline and her team have already synthesised novel inhibitors that can prevent this protein from working. They will then rework the design of these selective inhibitors to further synthesise molecules capable of triggering cells to activate a natural mechanism of protein destruction. These 'PROTAC' inhibitors can then destroy the harmful proteins and kill the cancer cells.

What makes this project novel is the two-pronged approach of targeting this particular protein and using PROTACs to destroy the protein that causes the proliferation of ovarian cancer.

The unique combination of these drugs and PROTACs have potential as therapeutic options for this set of ovarian cancer patients who are unable to benefit from existing PARP drugs.

Congratulations Caroline and Iain. We look forward to seeing exciting results emerge from this project over the next three years.

Institute BACR Chris Marshall Prize winner

Congratulations to Tim Budden, this year's chosen winner of the BACR Chris Marshall Prize for Cell Signalling.

Tim, a postdoc in the Skin Cancer and Ageing group led by Amaya Virós, is a highly accomplished and driven researcher with expertise in melanoma and non-melanoma skin cancer. Here, he has been focusing on the role of age and sex in skin cancer.

In the three years that he has been at the Institute, he has published two key first author papers in high impact journals and a further two collaborative papers. In recognition of these ground-breaking studies, in 2021 Tim was awarded the CRUK Manchester Institute Edith Paterson prize for best young scientist.

The BACR Chris Marshall Prize recognises and rewards the achievements of a young scientist in the field of Cell Signalling.

As part of the prize, Tim will receive £1,000 and the opportunity to present an oral paper at the BACR 60th Anniversary Meeting, with all conference expenses paid.

We look forward to hearing from Tim all about this exciting opportunity.

Well done, Tim!

Animal Welfare Recognition Awards

Most of our research does not involve animals but some animal research is essential if we are to understand, prevent and cure cancer.

Our scientists only use animals where there is no alternative, and the welfare of our mice is a primary concern. The necessity, ethics and conduct of all research is critically reviewed by our Animal Welfare & Ethics Review Body (AWERB). The AWERB has a role in promoting the day-to-day implementation of the principles of the 3Rs (Replacement, Reduction and Refinement) and supporting a 'Culture of Care'.

A new AWERB Recognition Award scheme was recently set up to recognise the commitment of our animal technicians to animal welfare. So far, four awards have been presented. We wish to congratulate the following winners:

Irana Bakhtiari Cunado has been recognised for exceptional teamwork, stepping up during periods of COVID-19 related staff absences, and demonstrating commitment to the animals and the team.

Eirini Symeon has been recognised for her proactive approach to new learning and development and for putting care and welfare for animals actively into her daily work practices.

Laura Dean has been recognised for her proactive approach to the care and welfare of her mice.

Thomas Bosley has been recognised for using his analytical skills in a proactive and positive way to support the team.

All winners received an AWERB recognition voucher. We would like to thank all the winners again for their commitment to the team and animal welfare.

Origami animal competition winners

The IAT (Institute of Animal Technology) Tech Month 2022 took place in March this year to celebrate the work of Animal Technologists.

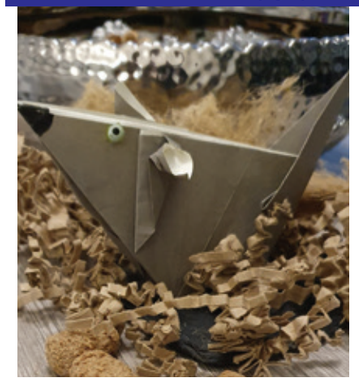
Our own animal technicians organised some fun with origami - the Japanese art of folding paper – by having an animal origami competition to mark the occasion.

There were many fabulous entries from the Biological Resources Unit, and three overall winners were selected and presented with an Amazon gift voucher.

While Laura Dean crafted a stunning pink (of course!) Flamingo.

Irana Bakhtiari-Cunado created a wonderful group of colourful animals.

Rachel Walker folded a lovely grey mouse.



Animal Farm

Karen Lee, who is providing maternity cover for the role of Executive Assistant to the Chief Operating Officer and the Chief Laboratory Officer, enjoyed cuddling a lamb at the Alderley Park Farm open day in April (her rucksack had to be searched on the way out!).

Karen clearly enjoying cuddling her lamb.

Baby boomers

The Cox family welcome baby Clover.

Ruth Cox, EA to the Director, and family are delighted to welcome baby Clover who was born at home on 16th April.

Her siblings were very surprised to wake up on Easter Sunday to an extra special delivery from the Easter Bunny!

Proud mum Mel with baby Thomas.

Melanie Galvin - Service Manager for Preclinical Pharmacology in the CRUK MI Cancer Biomarker Centre – and her husband Richard welcomed Thomas Edgar Galvin into the world.

He was born on 7 December 8.44pm, weighing in at 7lb 5oz (he has grown a little since then!).

Simon Poucher, our Regulatory Liaison & Training Officer, welcomed his first granddaughter, Emily Elizabeth Hughes, who was born on 5 May at 5.45am and weighing in at 8lb 4 oz.

Farewell to longstanding colleague

After a long and illustrious career at the former Paterson Institute and now CRUK MI (renamed in 2013), we say farewell to our wonderful colleague and friend Deepti Wilks.

Deepti joined the Experimental Radiation Oncology (ERO) group of the Paterson Institute in 1988 to work on a project led by Catharine West - Professor of Radiation Biology at The University of Manchester. From 1991 to 2001, Deepti co-authored 10 publications involving translational radiation research aimed at predicting cancer patient response to radiotherapy. Whilst working with ERO, Deepti also collaborated with the former Carcinogenesis group at the Paterson.

Always keen to improve her skill set she went on to work in several molecular biology-based departments and then in 2008 went full circle, from bench to bedside, to take up a pivotal role in the development and implementation of the Haematological Malignancy Biobank. Deepti's tenacity, drive and determination has led to the biobank having now an international reputation as it is among the most comprehensive collections of primary material for myeloid malignancy. She also had the opportunity to be involved with ground-breaking research in Leukaemia Biology (Tim Somervaille) and Epigenetics of Haematopoiesis (Dan Wiseman/ Kiran Batta).

Deepti has truly left a lasting legacy of work that the Institute can be proud of! We wish her a happy and healthy retirement. Her passion for cancer research hasn't quite ended as she is a keen volunteer for research engagement and outreach initiatives. For example, the 'In2Science' mentoring programme (recognised via CRUK Instagram) and fundraising (recently The Christie Charity Bethan Tower Run).

Currently she is facilitating the Open Lab initiative designed to connect cancer researchers working across the UK.

We wish Deepti all the best and we will miss her! Thank you, Deepti from us all.

SCAN ME

Find out more about the Cancer Research UK Open Lab Initiative

Efthymios-Spyridon Gavriil

Efthymios is a Postdoctoral Scientist in the Drug Discovery Unit at the Cancer Research UK Manchester Institute. He has a strong background in the discovery of novel inhibitors as anti-cancer agents.

His current research here involves the design, synthesis, purification and full identification of series of compounds that act as inhibitors of a kinase linked to pancreatic cancer.

Efthymios is also a very active member of the Institute, and you will find him featuring in two other articles in this edition! You can discover more about how he helps organise scientific and networking events at the Institute on behalf of the European Network for Postdocs in Cancer Research, PostdoCaRe Europe, and his impression of virtual Global Young Scientists Summit he attended in January 2022.

1. **What is your favourite part of the UK?**
Manchester.

2. **What was your best ever holiday and why?**
August 2021 in Lefkada, an island in west Greece. Good company and amazing beaches made the perfect combination for a holiday to remember.

3. **Which website do you always check, and why?**
www.aek365.com to read the latest news for my favourite football team AEK.

4. **What is your favourite film?**
The Godfather: Part II.

5. **What is your favourite band/singer?**
Lorde.

6. **If you had to change careers tomorrow, what would you do?**
Be an astrophysicist.

7. **What is the most important lesson that you have learnt from life?**
'It's all relative'.

8. **Name three things you would take with you to a desert island?**
A guitar, a guitar pick and a guitar guide for beginners.

9. **What is your greatest fear?**
'Change can be scary, but you know what's scarier? Allowing fear to stop you from growing, evolving and progressing'.

10. **How would you like to be remembered?**
As someone who contributed to improving cancer patients' outcomes.

11. **If you could change one thing in your past what would it be?**
Spend more time studying abroad.

12. **What is your signature dish to cook?**
Pasta with tomato and basil sauce (I definitely need training in how to cook...).

13. **You've just won the lottery and have £5 million pounds to spend. What do you buy first?**
Another ticket. Then, use the rest to start a scholarship foundation for underrepresented groups in higher education.

14. **What is your idea of perfect happiness?**
Spending every day surrounded by people you love and feeling excited about life.

15. **What keeps you awake at night?**
Global inequalities in many aspects of our lives (health, food, education, ...).

Editorial Team:
Steve Bagley
Gillian Campbell
Karen Lee
Andrew Porter
Caroline Wilkinson

Cancer Research UK Manchester Institute
The University of Manchester, Alderley Park, SK10 4TG
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