



CANCER
RESEARCH
UK

MANCHESTER
INSTITUTE

MANCHESTER
1824

The University of Manchester

Newsletter

Summer 2021

FEATURE - PUBLICATIONS

Meet the New Students
Reflections One Year on from Covid
Collaborations Between our Core Facilities
Paterson Building Project Update
Awards, Prizes and Events



Director's Introduction

It is a real pleasure to introduce my first edition of the newsletter as Interim Director of the Institute. It is a great privilege to lead CRUK MI and I am really excited to work with everyone to continue to take the Institute forward.

Although we are still facing the challenges of the SARS-CoV-2 pandemic, I am proud of the way everyone has united and worked hard with such resilience to continue to carry out our great research. The contents of this newsletter are a testament to everyone's efforts.

Here, we highlight some publications that showcase the breadth and quality of science that is being undertaken by our researchers at the Institute. These highlights have been written by some of our early career researchers, an opportunity for them to gain first-hand experience of scientific writing and to develop those all-important communication skills.

We review an impressive raft of scientific papers, but it is especially pleasing to see the culmination of four years' work developing a new research programme flourish. So, I would like to congratulate Institute Fellow Dr Amaya Viros on her volley of exciting publications and success in securing funding from the Wellcome and the Melanoma Research Association.

Teamwork and forming new alliances are critical to driving the ongoing success of our research and opening up new avenues of funding opportunities. In this regard, I was thrilled with the news that the collaboration between the Drug Discovery Unit and Systems Oncology resulted in a substantial grant from the Lustgarten Foundation to develop new inhibitors against pancreatic cancer. Many congratulations to Caroline Springer and Claus Jorgensen.

To identify potential synergies with our colleagues in the wider University of Manchester network, we held our first cross-pollinating discovery cancer research virtual away-day. With researchers from the

Institute, Division of Cancer Sciences, the Division of Molecular & Cellular Function, and the Division of Infection, Immunity & Respiratory Medicine speaking about their research, we spent the day exploring areas of mutual interest and alignment, seeking new avenues for collaborations and joint funding opportunities. This was a great success and further away-days are planned that we hope will spark new research partnerships.

Keeping with the theme of collaboration, it is great to see how our core facilities, which are integral to the Institute's success, are working together to bring new technological advances and truly innovate our research platform capabilities. You can read more about their latest work in the following pages. Given the challenges of the 'virtual workplace', we recently 'matched' each core facility with a CRUK MI Group Leader(s), to increase scientific and operational discussions and continue to ensure that our facilities and research needs of all groups continue to be completely integrated.

Also hugely important to the smooth running of the Institute is the work of operations teams including health and safety, logistics and laboratory services. It's great to see Colin Gleeson, Andy Lloyd and Mark Craven featured and recognised for their hard work that they carry on behind the scenes. They have played an absolutely pivotal role in helping to keep the Institute adapt to the new working practices necessitated by the pandemic.

Other recognised achievements include those made by an outstanding student, post-doc or scientific officer and each year our Institute awards its own prize. Named after a former Institute Director, the 2020 Dexter Award was presented to Wendy Trotter from the Cell Division group for her influential contributions to the cell cycle field.

I would like to welcome all new starters and our new students. Even though many of us have not physically met each other, it has been enjoyable to meet many of you virtually, not least in the new virtual 'coffee club' sessions we have initiated this year. I am especially grateful to the STAY Committee for organising a variety of entertaining online social events.

As we all become (to varying degrees) digital experts – even I am adapting to online platforms – the virtual meeting rooms not only connect us but have allowed us to explore new ways of working. Last year's colloquium was a great example of that ingenuity as we enjoyed a different programme, including the thoughts of several CRUK MI alumni who have taken a variety of career paths since leaving the Institute and it was great to welcome

them back on zoom! I for one am looking forward to this year's event in September.

Another exciting event to look forward to is the Royal Society Summer Science Exhibition this July, where a team of researchers from the Institute will be presenting a digital bonanza of activities to help explain the complexity of cancer. This is a prestigious annual event and I am proud that the Institute is being represented there by our enterprising young scientists.

Whilst we await the easing from pandemic restrictions and a return to the 'new normal', there are exciting times ahead for the Institute with a planned relocation to the new Paterson building in the spring of 2023. I hope you all share my excitement as we view the regular videos showing the rapid build of our new home at the Christie NHS Foundation Trust site, juxtaposed to the Oglesby Building. It is incredible to see the building grow, now up to five floors, and with it our vision to create one of the top cancer research centres in the world here in Manchester becoming a reality, where basic curiosity-driven, translational and clinical researchers working side by side will drive forward synergies and accelerate our cancer research to improve patient outcomes. Progress of the Paterson Redevelopment Project is reported in the following pages.

And finally, it is wonderful to see that the restrictions of the pandemic haven't dampened the spirits of our fundraisers. I am fascinated by the many inventive ways members of the public and our own colleagues continue to raise money and engage with others. Further on you can read what they have been getting up to in the name of cancer research. We are incredibly grateful for their continued efforts.

I can honestly say that the first six months as Interim Director have certainly been a challenge but have also been enjoyable. I am particularly grateful for the wonderful support of my Deputy Director Iain Hagan, to all the senior management team, and to Richard Marais for his helpful advice. The resilience of the Institute through first the fire and soon after the pandemic has been and continues to be tremendous and it is a pleasure to work with everyone at the Institute towards our goals of evolving and expanding our research to advance scientific progress and ultimately improve outcomes for people affected by cancer around the world.

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



COMING SOON

Our latest annual Scientific Report will be available soon, detailing the latest activities of each research group, publications and research projects for the year.

Histological image showing the cutaneous papilloma from a female mouse following exposure to the carcinogen DMBA/TPA. Image – supplied by Amaya Viros and Tim Budden – featured on this month's front cover of journal *Clinical Cancer Research*. Find out more in the Publications section of this newsletter.



Amazing efforts by our little big heroes

Little big heroes who inspire and support our work

By Belen Conti Vyas

The last year has been challenging in many ways, but it has also been very inspiring in many others. We were pleasantly surprised to hear some incredible fundraising stories from young CRUK supporters, who walked incredibly long distances or organised online sales to show their support to cancer research.

Receiving news of their amazing accomplishments has been a huge morale boost for all the CRUK Manchester Institute staff and has also been a very timely reminder of why we do the work we do.

One of the first stories to inspire us was 10-year-old James Leah. Despite lockdowns and restrictions, James completed an epic challenge walking 500 miles over the summer in 2020, raising over £1,560 for CRUK in the process (<https://www.justgiving.com/fundraising/james-jo>).

With his mum by his side, James visited iconic Manchester locations during his walks but also went further afield to visit places such as Scarborough and Cornwall.

His fundraiser to "help other people and kick cancer's butt" was so remarkable

that it earned him a Blue Peter Sports Badge! He also received an Appreciation Certificate from the CRUK Manchester Institute and some of our scientists got together to send him a "Thank you" video message.

We were also pleasantly surprised in early 2021, when we heard about a group of entrepreneurial Year 6 students at St. Gabriel's Catholic Primary School. The class of Ms Melanie Dickenson chose CRUK as one of the charities to support on their Christmas business project.

The team Super Santaz, who were fundraising for cancer research, created beautiful woollen mini hats and painted rocks, which they were going to sell at their Christmas markets. Unfortunately, the pandemic didn't allow this to happen, but they quickly moved to selling their creations online.

The class managed to raise a fantastic £250, which they distributed equally between all chosen charities and sent us letters to let us know about their project and why they had opted to support us. These letters were so heart-warming that they inspired our scientists to record a video with a thank you message that we shared with the class.

And the surprises kept coming! Just recently we heard of 14-year-old Kadi Boughey, who has set herself an incredible challenge of walking 100 miles in one day on 27 August 2021.

Kadi and her dad Anthony are planning to walk all the way from Trentham to Blackpool and their fundraiser has already gone over £1,600. "Having various family members suffering, I decided to try and make a small difference by raising money to help the vital research to get rid of cancer," says this inspirational teenager on her fundraising page (<https://bit.ly/3vm6WdD>).

We were delighted to share some videos about the work that goes on in the CRUK Manchester Institute with her and we are looking forward to hearing how this challenge goes.

For us Kadi, James and all the Year 6 students at St. Gabriel's school are heroes and once again we want to thank them for their amazing efforts to support Cancer Research UK!



Tim Hudson

We say goodbye to our Research Engagement Manager

We are sad to say goodbye to Tim Hudson, Cancer Research UK's Research Engagement Manager in Manchester, who is moving on to a new role this summer.

Tim joined the Institute in June 2017, one month after the fire. Despite the disruption and displacement of staff, Tim quickly and enthusiastically began working with our research groups, as well as other scientists and clinicians funded by CRUK in the area, to drive supporter and public engagement with the research taking place.

Tim has been a wonderful colleague over the past four years and we wish him well in the next phase of his career.

We are currently recruiting for his replacement and hope to introduce our new CRUK Research Engagement Manager in the next edition of the newsletter.

Relay For Lifers

Cancer Research UK's Relay For Life celebrates the power of community fundraising in the fight to beat cancer.

Teams of family and friends fundraise for life-saving cancer research then unite as a community to honour everyone affected by cancer and celebrate the progress made in research.

The Relay For Life Stockport Scientists Team have long been fundraising champions at the Institute. This is largely down to 'Captain' Steve Lyons, who has been organising and motivating an Institute team every year for several years now.

The team has members from across the Institute and the Division of Cancer Sciences at

The University of Manchester. The current roster is Steve and John Castle, Natalia Moncaut (and her daughter Lucia and son Manuel), Kim Acton, Denis Alferrez, Jack Ashton, Michelle Greenhalgh and Sam Littler. They have been supporting their local Stockport Relay for many years now.

Under Steve's expert stewardship, the team can be regularly seen deploying innovative approaches to raising money. And this year is no exception, despite the restrictions of the pandemic the Relay For Life Team continue to raise vital funds for cancer research.



'We Lay' For Life!

Ever the innovator, Steve recruited another team to get the money rolling in. These feathery fundraisers are five chickens from his own garden, who have been laying eggs for the cause.

'Yokes' aside, the team are always looking for new members to join them so if you are interested, please get in touch with Steve.

Although last year's Relay For Life event was cancelled, all the teams enrolled for 2020 were automatically re-entered for the 2021 event. However, plucky Stockport RLF Team are the only team of scientists taking part in a Relay this year, and quite rightly the Stockport Relay committee are very proud of them. We agree that they are an amazing bunch of dedicated scientists.

So, why not join RFL Stockport on Saturday 17 July at their picnic in Woodbank Park. They also hope to carry out a reduced Relay event at the

Harriers Track in Woodbank Park on Saturday 25 September 2021.

Since last year, our team have raised a huge £2112.88 for cancer research. They are looking forward to being able to carry on with more fundraising once restrictions due to Covid are eased.

Well done team on all your hard work!



'We Lay' for Life team members

Euro 2020: Relay For Life Prize Draw

The team recently organised a 'Euro 2020' Prize Draw, where for £3, staff had the opportunity to take one of the 24 countries competing. There will be multiple pots, with various prizes:

The remainder of funds will go towards Cancer Research UK.



Tournament Winners
£30 Amazon Voucher



Runner's up
A piece of fruit of your choice



Worst Team
A free hot drink in the new Paterson Building Café*

*sometime in early 2023

They have already sold out two pots of countries and raised a total of £144, of which £80 has been sent to CRUK, with the rest held back for the prizes. There may be a little extra depending on how much they spend on fruit!

Institute leukaemia survivor appeals for people to sign up for special Race for Life

One of our scientists, who is being treated for leukaemia, last year urged people to take part in a special Race for Life weekend.

The charity expected a £160 million drop in income this year, having already made a £44 million cut to life-saving research funding.

To help tackle the loss, women and men raised funds by completing their own Race for Life 5K in their nearest green space on 26 September 2020. They planned to take part outdoors alone or in small, socially distanced groups on the same day.



Wolfig set for Race for Life

The Tatton Park Race for Life 2020 was among 400 mass participation events that organisers Cancer Research UK cancelled following the coronavirus outbreak.

Dr Wolfgang Breitwieser is the head of our Molecular Biology and Computational Biology Support core facility at the Cancer Research UK Manchester Institute.

He was diagnosed with chronic lymphocytic leukaemia in 2010 after a routine blood test showed unusual changes to his red and white blood cells. Some weeks later he also noticed swelling in lymph nodes around his body.

Wolfgang was referred to the Christie NHS Foundation Trust, where he continues to receive outpatient treatment today.

He said: "As a cancer scientist and someone who has cancer, I know how important new discoveries are to help people survive the disease."

"It's thanks to advances in treatment that I have lived with this disease for 10 years and am able to continue with my work and hobbies."

"I feel remarkably well most of the time and enjoy lots of active pastimes such as cycling and running. However, I am concerned about vital research that has been delayed as a result of the pandemic and what this might mean for future generations."

"Even though the Race for Life will look different in 2020 it's important we continue raising money for Cancer Research UK to help beat cancer."

Anna Taylor, Cancer Research UK spokesman in the North West said: "We are incredibly grateful to Wolfgang for sharing his story and supporting the new Race for Life challenge this September. He is living proof how research into cancer can make a real difference."

Reported by Knutsford Guardian on 1 September 2020



Ali Raof shows of his World Cancer Day unity band

Institute scientist urges people to unite for World Cancer Day

A scientist from the Cancer Research UK Manchester Institute backed Cancer Research UK's 2021 campaign for World Cancer Day and urged everyone to join him.

Dr Ali Raof is a lead medicinal chemist in the Drug Discovery Unit at the Institute, where he helps to develop new drugs to treat cancer patients.

Ali, who grew up in Rochdale, encouraged local people to donate or wear one of Cancer Research UK's Unity Bands with pride on Thursday 4 February.

Ali said: "Every year, around 41,000 people are diagnosed with cancer in the North West of England so by donating or wearing a Unity Band, people can show their support for those affected.

"As a cancer scientist, I know first-hand the devastating impact the disease has on individuals and families. I also lost my own grandmother to stomach cancer, which really affected us all as a family.

"That's why I'm inviting everyone to be part of a movement that can help make a real difference to so many people's lives.

"Charities like Cancer Research UK have been hit hard by Covid-19, but we can all play a part in helping to protect people with cancer from the fallout of the pandemic."

A Unity Band is a wristband which symbolises solidarity with people affected by cancer.

Available in three different colours – pink, navy and blue – it can be worn in

memory of a loved one, to celebrate people who've overcome cancer or in support of those going through treatment.

Money raised by World Cancer Day donations or Unity Bands will help fund crucial cancer research, like the work being carried out by Ali.

He joined the Cancer Research UK Manchester Institute in 2010 and is part of a team of scientists working to develop new therapies for cancer patients. He has a first-class undergraduate degree in Chemistry and a PhD in Organic Chemistry, both from The University of Manchester.

He said: "Research is vital to help more people survive cancer in the future and it's so important that it continues. As a medicinal chemist, I work with a variety of chemical compounds and molecules in the lab to develop new drugs for specific cancers which don't currently have many treatment options.

"I have worked on a range of challenging cancer projects in the areas of lung cancers and rare leukaemias to name a few – and every mini-breakthrough in the drug design process has provided more and more insight into how to combat these and other cancers in patients.

"Many of our discoveries in Manchester have already contributed to the development of various cancer medicines which are now being used to treat patients, which is incredible to see."

But life-saving research such as this is now under threat. Due to the impact of the pandemic, Cancer Research UK

expects to see its fundraising income decline by a staggering £300m over the next three years.

Marked on 4 February, World Cancer Day is an international initiative, which unites people around the world to beat the disease. Right now, it's never been more important to help save more lives. In the UK, survival has doubled in the last 40 years and Cancer Research UK's work has been at the heart of that progress. But the charity needs more support to continue its mission.

Before the pandemic, Cancer Research UK was able to spend over £33 million in the North West of England last year on some of the UK's leading scientific and clinical research.

Anna Taylor, Cancer Research UK spokesperson for the North West of England, said: "One in two people will get cancer in their lifetime, which is why we're absolutely determined to continue to create better cancer treatments for tomorrow."

"World Cancer Day is a great opportunity for people in the North West to unite and show solidarity with everyone whose life has been touched by the disease.

"Thanks to the work of dedicated scientists like Ali, our research has played a role in developing 8 of the world's top 10 cancer drugs and we're working every day to find new ways to prevent, diagnose and treat the disease. But we can't do it alone.

"That's why we hope people across the region will donate or wear a Unity Band with pride, knowing they are helping to save lives. Together we will beat cancer."

Reported by Rochdale Online news on 24 January 2021

WORLD
CANCER
DAY



CRUK Manchester Institute marks World Cancer Day

Act of unity

Cath Felton

On 4 February this year, the staff at the CRUK Manchester Institute marked World Cancer Day on social media through a series of tweets promoting the unity bands and remembering those affected by cancer.

Cath Felton is a PhD student in the Systems Oncology group at the Institute. She shared her story on World Cancer Day:

"Today is World Cancer Day and I just wanted to say a little bit about what today means to me... I was first affected by Cancer when I was 5 years old, my dad was diagnosed with stage 4 metastatic melanoma. He died just 5 months after diagnosis.

His death has affected my whole life and as I grew up, I became increasingly curious about the disease that killed my dad and why at the time (2002) there was nothing the doctors could do to extend his life.

This curiosity led me to study at his old university, The University of Manchester, where Cancer is one of their beacons of research. And I got taught by some of the world's leading cancer experts.

It drove me all the way across the world to Seattle, to undertake a summer internship at the Fred Hutchinson Cancer Research Center, where I got my first taste of what it might be like to be a cancer researcher.

And all these learning experiences inspired me to take on a PhD at the CRUK MI, where I am continuing my journey to help further scientific knowledge and understanding around how cancers work and how we can better treat them.

Currently 1 in 2 of us will get cancer, but thanks to the work of all the researchers who have gone before me, more people than ever survive. I hope that one day my own work and passion will contribute to this global endeavour."

Remembering

This World Cancer Day 2021, our thoughts are with those who have died from cancer, and with their families and friends left behind; with our colleagues, neighbours and loved ones living with cancer today; and with all who are working together to beat cancer.

#IAmAndIWill

Melanie Galvin proudly displays her unity band for World Cancer Day



Videos that make our science more accessible

Scientific papers can appear a bit daunting for people with no science background. But sometimes all it takes is for someone to explain it in simple terms for them to realise that it wasn't that intimidating at all.

With that in mind, the CRUK Manchester Institute launched a new series of videos with our scientists, in which they explain in plain language what their recently published research is about.

From understanding how prolonged sun exposure can affect melanoma invasion or how common anti-inflammatory drugs can help boost cancer immunotherapies, researchers have been helping us understand their science.

This has been an especially useful way to connect with our supporters, as due to the pandemic our usual engagement activities – such as lab tours – had to be suspended.

With many more research papers to come, you can keep an eye on the videos already published on this link <https://bit.ly/3q0RiDf> and you can subscribe to the YouTube channel to get an update any time a new one is published.

We want to say a special thank you to the researchers who take part of this series, as well as Belen Conti Vyas (interviews, filming and editing), Andrew Porter (interviews), and Yannick von Grabowiecki (filming).

PUBLICATIONS

New method allows more accurate investigation of the cell cycle

By Amelia Jones

Researchers in the Cell Division group at CRUK Manchester Institute have developed a new method for synchronising cells, which causes less DNA damage and allows more accurate understanding of the cell cycle.

The cell cycle is the process of events that causes a cell to divide into two new cells. This process is made up of four stages that are each highly regulated and if problems arise in the regulatory machinery, cells may begin dividing uncontrollably. Uncontrolled cell proliferation is a hallmark of cancer, and so a full understanding of the cell cycle and its regulation is important in understanding cancer progression.

Investigating the cell cycle is challenging because in a population of cells each cell is progressing through the cell cycle independently. This means that at any given time every cell is at a different point in the cell cycle and so we cannot ask questions about a specific cell cycle stage. Cell cycle synchronisation is a process that brings all the cells in a given population to the

same point in the cell cycle. It allows scientists to ask targeted questions about the cell cycle at a population-wide level.

A major difficulty with synchronisation is the stress that it puts on cells. The most popular method of inducing synchrony often leads to DNA damage and chromosomal rearrangements. This means that the results we get from these experiments may be inaccurate due to the damage caused by synchronisation.

The Cell Division team turned to a drug called Palbociclib as a possible new method for synchronisation. Palbociclib is used in the clinic to treat breast cancer and belongs to a class of drugs called 'CDK inhibitors'. These drugs inhibit CDK proteins, which promote cell division, in order to slow cancer growth. Palbociclib inhibits CDK 4 and 6, which are involved in determining whether the cell begins another round of division. Other methods of synchronisation tend to pause the cell in the middle of a cell cycle, when all

the machinery is already in motion. In contrast, Palbociclib pauses the cell before it begins a new cell cycle, meaning less disruption to cell cycle machinery.

The group showed that DNA damage in cell populations synchronised with Palbociclib was markedly reduced compared to the most popular synchronisation method. This means the results from Palbociclib synchronised cells will better reflect a 'normal' cell, allowing us to reach more accurate conclusions about how the cell cycle works. This information will help us better understand the link between cell cycle regulation and cancer progression, and ultimately help us develop better treatments for fighting cancer.

Trotter EW, Hagan IM. Release from cell cycle arrest with Cdk4/6 inhibitors generates highly synchronized cell cycle progression in human cell culture. *Open Biol.* 2020 Oct;10(10):200200. PMID: 33052073.

Institute researchers discover that tumours can have different 'flavours' of inflammation

By Eduardo Bonavita

Immunotherapy has emerged as an alternative anti-cancer therapy, which has revolutionised the field of cancer research and treatment. Unprecedented outcomes continue to be observed in multiple cancer types, including malignancies where conventional therapies such as chemotherapy, radiotherapy or targeted therapy have failed.

Nevertheless, the immunotherapy excitement has been rapidly tempered by clinical data showing that only a minority of cancer patients achieve complete and long-lasting responses. This has underscored the need for extensive preclinical research to understand the basis of these remarkable but still rare outcomes.

Inflammation can fuel or inhibit cancer progression and the response to therapy. In this study, the Cancer Inflammation and Immunity group investigated the signals and pathways that regulate the establishment of tumour inflammatory microenvironments that support or restrain cancer progression. Combining the use of genetically engineered mouse cancer models with the analysis of samples from cancer patients, the group identified Natural Killer (NK) cells as key drivers of cancer-inhibitory inflammation.

In cancer models rendered immunogenic by genetic ablation of the cyclooxygenase (COX)-2 pathway, NK cells were essential for initiating an inflammatory response that preceded and stimulated cytotoxic T cell-



The illustration depicts the complex Yin and Yang interaction between pro- (red) and anti-tumorigenic (green) inflammatory responses within a tumour. Illustration by Sam Falconer.

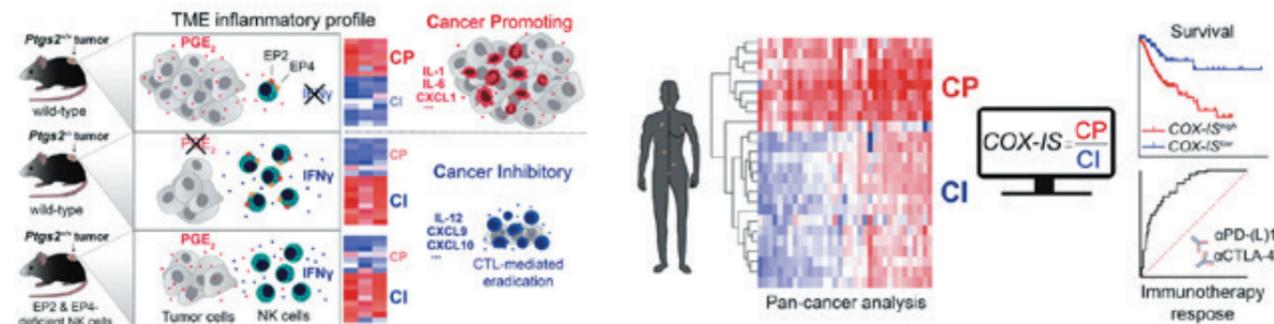
dependent tumour growth control. The analysis of patient datasets suggested the COX-2 pathway regulates equally the cellular and molecular inflammatory profile across multiple human cancer types.

Furthermore, the researchers developed an approach that by combining tumour-promoting and anti-tumour mediators improves our ability to predict overall patient survival and the response to immunotherapy in a wide range of human cancers. Collectively, these findings established the COX-2 pathway and NK cells as critical orchestrators of T cell-mediated

cancer immunity and demonstrate the value of integrating pro- and anti-tumorigenic inflammation to predict patient outcome.

Bonavita E, Bromley CP, Jonsson G, Pelly VS, Sahoo S, Walwyn-Brown K, Mensurado S, Moeini A, Flanagan E, Bell CR, Chiang SC, Chikkanna-Gowda CP, Rogers N, Silva-Santos B, Jaillon S, Mantovani A, Reis e Sousa C, Guerra N, Davis DM, Zelenay S.

Antagonistic Inflammatory Phenotypes Dictate Tumor Fate and Response to Immune Checkpoint Blockade. *Immunity*. 2020 Dec 15;53(6):1215-1229.e8. PMID: 33220234



The female immune system protects against developing aggressive skin cancer

By Hannah Frost

New research has found that differences in the biological sexes extends to how their bodies respond to cancer. Researchers here found that the immune system was more active in biological females with skin cancer, and better equipped to tackle the development of the tumour than in biological males.

Biologically, the sexes differ in more ways than you think, surprisingly this includes how likely they are to develop different diseases, such as cancer. The increased risk of developing cancer is often linked to the types of jobs males are more likely to do which would expose them to cancer causing substances in the environment – known as carcinogens. However, it is not clear whether the differences we see between the sexes is due to this exposure to carcinogens or to biological differences in sex. The Skin Cancer and Ageing team are interested in understanding more about these differences between the sexes specifically within skin cancer and what this means for patients and their treatment.

As mice are genetically and physically very similar to humans, the Skin Cancer and Ageing team started out by looking at the differences in male

and female mice that had a type of skin cancer called cutaneous squamous cell carcinoma (cSCC). They found that male mice were more likely to have an aggressive form of cSCC and only male mice developed metastasis, which is when the tumour spreads to other places in the body. Moving closer to home, the team looked at human skin samples taken from next to cSCC tumours, this way they can study changes early on in the developing cancer. Looking more closely at the cells in these skin samples revealed that in males there was a higher level of a genetic marker that causes increased cancer growth. In contrast females' skin samples showed the immune system was more active, preventing tumour growth.

The team also found that females with compromised immune systems were diagnosed younger and had more aggressive disease than females with a healthy immune system. This finding led the authors to conclude that females had less aggressive disease due to stronger immune responses. Overall, this study is important as it shows evidence that in females with cSCC the immune system responds early and defends against tumour growth, which might be responsible for the development of a less aggressive



The striking histological image of a cutaneous papilloma from a female mouse following exposure to the carcinogen DMBA/TPA – generated from this research – was featured on the front cover of the June 2021 edition of the *Clinical Cancer Research* journal. To celebrate this wonderful accolade, we have also used this image on our cover of this edition of the newsletter.

cancer. Importantly, in the future this could justify tailoring patient's treatment based upon sex as well as cancer type.

Budden T, Gaudy-Marqueste C, Craig S, Hu Y, Earnshaw CH, Gurung S, Ra A, Akhras V, Shenjere P, Green R, Jamieson L, Lear J, Motta L, Caulin C, Oudit D, Furney SJ, Virós A. Female Immunity Protects from Cutaneous Squamous Cell Carcinoma. *Clin Cancer Res*. 2021 Jun 1;27(11):3215-3223. PMID: 33795258

Ultraviolet radiation causes rare type of eye cancer

By CRUK Press Team

Ultraviolet radiation can cause a rare type of eye cancer, conjunctival melanoma, according to research by the Molecular Oncology group and published in *Nature Communications*.

UV radiation is known to be the key environmental cause of melanoma of the skin, but its role in the development of rarer forms of melanoma in the eye was not known.

This new study has revealed strikingly similar genetic changes in conjunctival melanoma to that of cutaneous (skin) melanoma caused by ultraviolet (UV) radiation.

The team behind these findings suggest that treatments used for skin melanoma may also benefit people with this rare form of eye cancer.

The researchers, led by Professor Richard Marais at the Cancer Research UK Manchester Institute, used whole genome sequencing to examine the genetic makeup of melanomas that develop on the conjunctiva, the specialised membrane that covers the front of the eye, to better understand what causes this particular melanoma subtype.

Surprisingly, the researchers found similar genetic changes in tissue samples from people with conjunctival melanoma to the genetic changes that occur in melanoma of the skin attributed to UV radiation.

They showed that people with conjunctival melanoma driven by UV radiation have mutations in the BRAF and RAS genes, which are often seen in skin melanoma. These findings complement a similar study showing that another type of rare type of melanoma of the eye called uveal melanoma, which develops in the iris, can also be caused by UV radiation. These two studies suggest that people with particular forms of eye cancer could benefit from treatments that are currently used for skin melanoma, including those which target BRAF mutations, but not yet approved for

melanoma of the eye. Those drugs could, if proven to benefit these patients, be given based on the genetics of the tumour, rather than their location in the body.

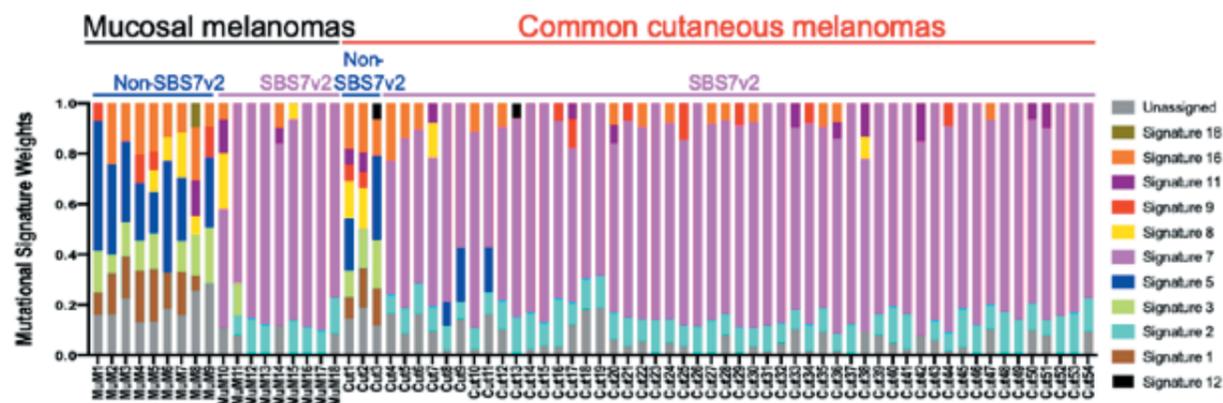
Professor Richard Marais, lead author of the study said: "Our work shows the importance of delving into the underlying biology in rare cancers,

which could identify new tailored treatment avenues for people. In this case we have identified mutations in a rare type of eye cancer that could be targeted by drugs used to treat skin cancer."

Now, ongoing work will need to explore if BRAF-targeted therapies, or other immunotherapies used for skin melanoma, could benefit people with conjunctival melanoma.

Professor Marais said: "By showing that UV radiation can cause conjunctival melanoma, we have added to our understanding of the known dangers of the sun for our eyes. It reminds us of the importance of protecting not just your skin, but also your eyes from UV light, be it in everyday life, or where the UV radiation is particularly high and causes the most damage such as on the beach, on a boat, on a mountain."

Mundra PA, Dhomen N, Rodrigues M, Mikkelsen LH, Cassoux N, Brooks K, Valpione S, Reis-Filho JS, Heegaard S, Stern MH, Roman-Roman S, Marais R. Ultraviolet radiation drives mutations in a subset of mucosal melanomas. *Nat Commun.* 2021 Jan 11;12(1):259. PMID: 33431815



Mutation spectra in mucosal and common cutaneous melanomas.

The discovery of a non-coding RNA potentially provides a new therapeutic strategy for the treatment of KRAS-mutated cancer

By Julia Morris

In 2011, two scientists named Hanahan and Weinberg published a paper that outlined the ten "hallmarks of cancer". These hallmarks are the artillery that cancer cells need to ensure their growth and survival. One of these hallmarks is "sustaining proliferative signalling", which means that the cancer cell puts measures in place to keep itself dividing. KRAS is a GTPase, meaning, when it is bound to the nucleotide guanosine triphosphate

(GTP), it possesses the ability to break proteins down.

Multiple signalling pathways within the cell are activated in response to the action of KRAS, including the RAF-MEK-ERK (MAPK) pathway. Therefore, when KRAS is mutated or amplified, cells grow and have enhanced survival capabilities. Mutated KRAS is found in several cancer types, including non-small cell lung cancer (NSCLC).

Researchers from Manchester have contributed to the finding that wild-type KRAS can also drive cancer development when too much of it is produced. The expression of mutant KRAS and the overexpression of wild-type KRAS are both indicative of poor survival.

DNA is a wondrous molecule that contains the genetic blueprint of a cell that resides in the nucleus. For the

information DNA holds to be shared with the rest of the cell, it is copied into a similar but distinct and more mobile molecule, RNA. Coding-RNA travels out of the nucleus where it is then translated into a new language to produce protein. These proteins go around the cell and perform the actions that DNA instructed them to do. A large proportion of RNA is not translated into protein but performs essential functions around the cell. This is known as non-coding RNA.

The study was led by Dr Michela Garofalo and her team. This group recognises that there is a need for a deeper understanding of the mechanisms which drive KRAS-mutated lung cancer. Additionally, they recognise that there is a vast amount of unmined knowledge in non-coding RNA. This research is a beautiful blend of both as the long non-coding RNA *KIMAT1*, has been found to play a key role in regulating the downstream

cancer-driving effects of KRAS overexpression in lung cancer.

KIMAT1 stands for KRAS-induced metastasis-associated-transcript 1. It was identified by RNA sequencing (RNA-seq) analysis in genetically modified non-small cell lung cancer cell lines that expressed either wild-type KRAS or mutated KRAS (KRAS^{G12D}). They subsequently performed a series of experiments which revealed that the transcription of *KIMAT1* from DNA is activated by MYC – a master transcriptional regulator. The knockdown of *KIMAT1* leads to reduced cell survival, growth, and invasion, all of which are needed for cancer to persist.

Additionally, the team uncovered the mechanism in which *KIMAT1* specifically drives tumour growth and progression in lung cancer. They successfully discovered that *KIMAT1* interacts directly with RNA-binding

proteins which regulate the processing of oncogenic microRNA (miRNAs), ultimately driving KRAS signalling.

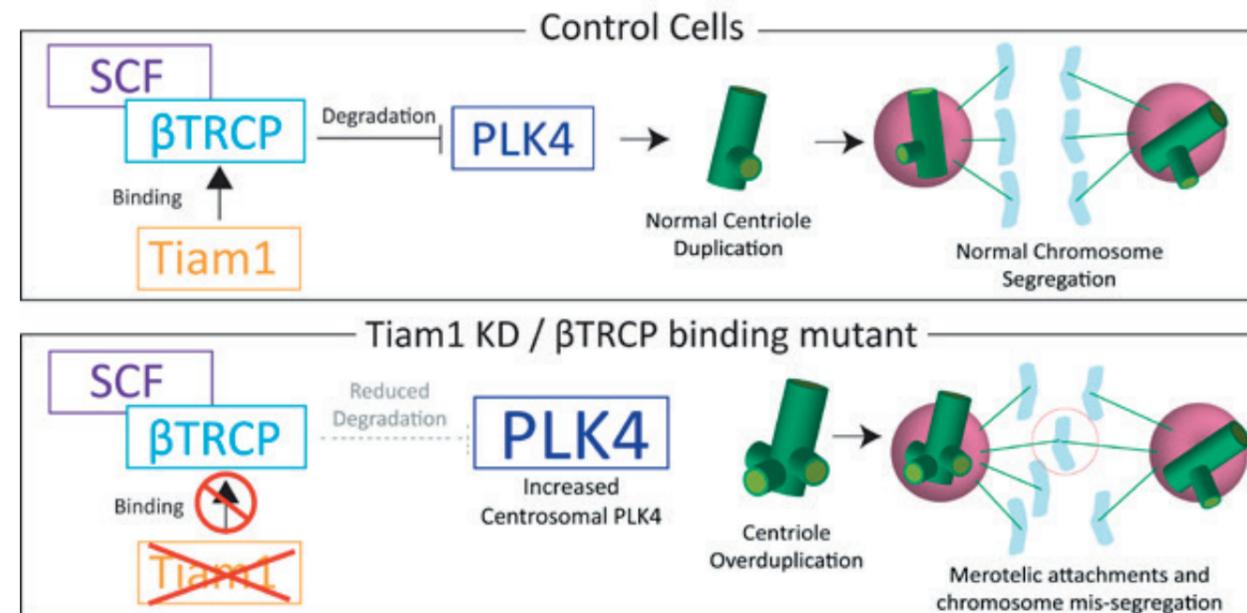
The results outlined in this study are potentially ground-breaking. The discovery of *KIMAT1* opens new avenues for the treatment of KRAS-mutated or amplified cancers. These new findings may help to aid new and more efficient ways to disrupt the KRAS signalling pathway and thus treat the now difficult to treat KRAS mutant and overexpressing cancers.

Shi L, Magee P, Fassan M, Sahoo S, Leong HS, Lee D, Sellers R, Brullé-Soumaré L, Cairo S, Monteverde T, Volinia S, Smith DD, Di Leva G, Galuppini F, Paliouras AR, Zeng K, O'Keefe R, Garofalo M.

A KRAS-responsive long non-coding RNA controls microRNA processing. *Nat Commun.* 2021 Apr 1;12(1):2038. PMID: 33795683

New role of protein uncovered in regulating cell division

By Molly Glenister-Doyle



Did you know that the majority of the cells in our body divide in order to replace dead or damaged cells and to enable us to grow? And did you know that when this division goes wrong it

can lead to the growth and spread of cancers? Well, this is why scientists at Cancer Research UK in Manchester have been closely studying the cell division process. Their recent work has

uncovered a new and important role of a protein which is able to regulate the cell division process in order to prevent cancer.

This protein – Tiam1 – has been shown by the Cell Signalling team to control cell division by regulating the number of barrel shaped structures in cells, known as centrioles. Centrioles are made up of hollow tubes which not only help give the cell shape, but more importantly, act to separate genetic material when a cell divides.

Through a series of experiments, the scientists determined that Tiam1 is able to regulate the number of centrioles in cells by depleting a protein called PLK4. They showed that Tiam1 is able to do this by binding β TCRP, which in previous studies has been shown to degrade PLK4. PLK4 is well known for its role in centriole synthesis and is often referred to as the ‘master regulator of centriole duplication’. In depleting PLK4, the team have shown

that Tiam1 acts to prevent too many centrioles from being synthesised in the cell.

The team also demonstrated that cells require Tiam1 to divide correctly and when this protein is removed, cells are often unable to properly separate their genetic material. This highlights Tiam1’s important role in facilitating correct cell division and hence its role in preventing cancer progression.

Overall, the researchers in this study showed that Tiam1 is able to suppress excess centrioles by decreasing PLK4 via its interaction with β TCRP. They also demonstrated the importance of this protein in ensuring cells divide correctly, and hence ability to prevent cancer progression.

Interestingly, previous animal studies have demonstrated that Tiam1 depletion has both tumour promoting and tumour inhibitory effects. This paper highlights the need to know more about how Tiam1 functions in order to separate these opposing features, allowing for the development of effective therapeutics.

Porter AP, Reed H, White GRM, Ogg EL, Whalley HJ, Malliri A. The RAC1 activator Tiam1 regulates centriole duplication through controlling PLK4 levels. *J Cell Sci.* 2021 Apr 1;134(7):jcs252502. PMID: 33758078

A novel dual kinase inhibitor to knock out cancer cells with a one-two punch

By Jack Ashton

Why do cancer patients relapse on otherwise promising therapies? Perhaps we are not blocking all avenues of escape from treatment and need a more comprehensive strategy.

Cancer is more complex than the single term suggests. A disease primarily of uncontrolled cell growth, it takes many sub-forms. Each person diagnosed with cancer must be comprehensively assessed to understand the biology driving their disease and the best course of action for treatment. We now live in an era of personalised medicine where therapies must be tailored to cancer cell vulnerabilities which are unique to the patient.

Researchers in Manchester are looking at particular mutated genes which cause dysregulated cell growth. A number of oncogenes – a mutated form of a gene involved in normal cell growth – are frequently found in patients with different cancer types. One such gene is *KRAS*. In its mutated form *KRAS* over-activates the protein and causes cancer cells to grow and spread in the body. Treating cancers

with mutant *KRAS* is especially difficult as there are limited options available to block the overactive *KRAS* protein. It is possible to inhibit targets downstream of mutant *KRAS*, but cancer cells often adapt to bypass these roadblocks using alternate signalling pathways. It is therefore necessary to hit these cancer cells with two different roadblocks in parallel to prevent their escape from therapy, a complicated approach requiring collaboration from multiple research teams.

Working together, the Molecular Oncology and DDU groups have developed a new dual inhibitor, CCT3833 that inhibits both RAF – a protein activated by mutant *KRAS* – and SRC – a master regulator of cancer cell growth distinct from the actions of mutant *KRAS*. The researchers demonstrate that CCT3833 blocks dysregulated cell growth and induces cell death of *KRAS* mutant cancer cells. Importantly, this inhibitor also prevented tumour growth in mice implanted with *KRAS* mutant cancer cells and is now being assessed in patients. Encouragingly, CCT3833 was

able to significantly halt tumour growth in a patient with *KRAS* mutant cancer to which previous therapy had been ineffective.

Overall, this study is important as it shows that both RAF and SRC must be inhibited in combination to drive response to treatment in *KRAS*-mutant cancers. CCT3833 is therefore a leading candidate for treatment of patients with *KRAS*-mutant tumours and its evaluation in clinical trials continues with great excitement.

Saturno G, Lopes F, Niculescu-Duvaz I, Niculescu-Duvaz D, Zambon A, Davies L, Johnson L, Preece N, Lee R, Viros A, Holovanchuk D, Pedersen M, McLeary R, Lorigan P, Dhomen N, Fisher C, Banerji U, Dean E, Krebs MG, Gore M, Larkin J, Marais R, Springer C. The paradox-breaking panRAF plus SRC family kinase inhibitor, CCT3833, is effective in mutant *KRAS*-driven cancers. *Ann Oncol.* 2021 Feb;32(2):269-278. PMID: 33130216

Meet the new students

We welcomed 10 new PhD students and three clinical research fellows to the Institute in September 2020, and although their inauguration to the CRUK MI took place virtually during the Colloquium, they still enjoyed a comprehensive and interesting introduction to their new peers and colleagues.



Oliver Bartley

Hi, my name is Oliver and I recently started my PhD in the Tumour Immunology and Inflammation Monitoring laboratory within the Cancer Biomarker Centre. I originally grew up in a tiny village in North Wales called Trelawnyd – where the sheep actually outnumber the villagers five to one! I eventually moved to Manchester to undertake a BSc in Biomedical Sciences at The University of Manchester and added an extra year on the end by switching to the integrated masters’ programme, in which I spent my time studying ovarian cancer in Prof Richard Edmondson’s lab at St Mary’s Hospital. I’m thoroughly excited to have joined the Institute and my current project centres around utilising liquid biopsies to optimise immunotherapy for small cell lung cancer patients. Outside the lab, I enjoy travelling, going to festivals, and most importantly, football!



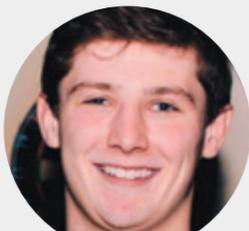
Bianca Blochl

Hi, my name is Bianca and I am from Stuttgart, in the south of Germany. I completed my degree in Molecular Medicine at the University of Tübingen, situated in a charming small town. For my masters project, I investigated the effects of a small molecule inhibitor in human in vitro models of MLL-rearranged leukaemia. During my undergraduate degree, I spent eight months at the Biochemistry Department of the University of Oxford and my internship in the X Chromosome Inactivation Lab encouraged me not only to pursue a career in research but also to return to the UK for my PhD. Now I am happy to have joined the Cell Plasticity and Epigenetics group, led by Maxi Portal. My work will focus on the underlying mechanisms of non-genetic heterogeneity and cellular plasticity in the context of cellular transformation and drug tolerance. Outside the lab, I enjoy many different sports, especially football and running. I am always up for cooking or baking new recipes as well as hiking and rock scrambling, so I am looking forward to exploring more of the surrounding countryside.



Yitao Chen

Hi, my name is Yitao and I am originally from Guangzhou, the south of China. Prior to starting here at the CRUK Manchester Institute, I completed my undergraduate degree in Biomedical Sciences at The University of Manchester in 2019. I was intrigued by the relevance of combining different disciplines, such as mathematics and computer science in biological research, and thus I decided to undertake a masters in Bioinformatics and Systems Biology. During this year, I worked on two bioinformatics projects, learning different programming languages. One of the projects applied machine learning algorithms to identify proteomic biomarkers of prostate cancer, which invoked my interest in cancer research. I am therefore really pleased to be able to join Caroline Dive’s Cancer Biomarker Centre here at the Institute. My project aims to develop bioinformatic methods that integrate multi-omics data from liquid biopsies for the early detection of non-small cell lung cancer. In my free time, I enjoy watching football and I’m a fan of Real Madrid football club. I also enjoy snowboarding and have been snowboarding annually for the past four years, which I am looking forward to resuming after the interruption due to the pandemic.



Liam Clayton

Shwmae pawb! My name is Liam and I am from Wales. I began my PhD project in September 2020 in the Stem Cell Biology group, with my research project focusing specifically on transcriptional changes in acute myeloid leukaemia.

My love and commitment for projects and working toward an end goal arose from an early age. A task was set by my year 5 teacher of Penllergaer primary school to design a Welsh landmark for St David's day. Sure enough, this was very exciting for an eager youngster. Therefore, myself alongside my father crafted a fantastic edition of the millennium stadium. This very early desire of goal setting and hard work set a great foundation for subsequent projects. Trusting an 8-year-old with a hammer and nails however may not have been the brightest idea in the world. Evidently the desire of pursuing a career in scientific research undoubtedly arose from my paternal side.

Following fantastic support from my mother through my school and college studies, I had the pleasure of carrying out my biomedical degree and masters in one of the most renowned capital cities of the world - Cardiff. This is where my true interests in cancer research and specifically leukaemia took hold, inspiring me to work with chronic myeloid leukaemia for my final year project. With a family experience of cancer and awareness of the public feeling that having a cancer diagnosis comes with an extremely dire prognosis, I felt driven to work in cancer research. That I can do this at a brilliant institution that has great potential for translational research is something I find especially rewarding. Whether it be going into battle with the colossal machine that is tissue culture, getting intimate with the microscope, or generating a greater understanding of my field through seminars... I really love what I do!



Lobsang Dolma

Hi, my name is Lobsang and I am a Tibetan born in a small town in India called Ladakh. Currently, I am a first year PhD student in Patricia Muller's Tumour Suppressor group wherein my project focuses on the role of mutant p53 (mutp53) on cell-in-cell (CIC) structure formation in cancer. Primarily, my work involves the molecular characterisation of mutp53-induced CIC events and their role in tumour cell invasion, stemness and chemoresistance. Prior to joining the CRUK Manchester Institute, I completed both my undergraduate (BSc Biology Joint Hons) and postgraduate (MRes in Biomedical Sciences) studies at the University of Brighton. My interest in cancer biology, particularly in cancer driver genetic mutations, came mainly from my experience during my undergraduate project, studying the extent of novel S100P inhibitor C72's inhibition of S100P and RAGE binding in PDAC and its influence on the cell proliferation and growth in PDAC cells *in vitro*. For my MRes degree, whilst the pandemic cut short my original project plan which was to study the potential PPAR β/δ induced directed differentiation of blood-derived endothelial progenitor cells (EPC) into alveolar type 2 epithelial cells (AEC2s) in co-culture models *in vitro*, I found it both challenging and fulfilling to be able to eventually complete a newly revised systematic review project on the comparative effects of Pioglitazone and Fenofibrate on cardiovascular disease risk in metabolic syndrome. Since having joined the Institute, I am grateful now to be in the lab and continue keeping up with experimental challenges and questions within cancer biology. When not in the lab, I enjoy talking to my family, listening to music and watching comedy shows.



Pedro Durao

I am a Portuguese PhD student who worked in Lisbon at Champalimaud, Centre for the Unknown. I worked in Eduardo Moreno's lab where I studied Cell Competition, a process by which fitter cells (winner cells) are able to sense and eliminate less-fit cells (loser cells). I used *Drosophila* as a model to understand the specific role of a gene called fu2 in Cell Competition. As you can imagine, I am now working on a very different topic, which is the role of ageing and UV irradiation in immunotherapy response to melanoma. This topic is really interesting to me since it allows me to get involved in translational research on a very hot topic. I am working in the Skin Cancer and Ageing group led by Amaya Viros.

In my free time I like to watch television series and spend time with my friends. Working here has been a very good experience so far. It is a challenging but very healthy work environment full of people from different cultures and with different perspectives. I can't wait to explore more of Manchester and meet more people, now that Covid restrictions are being eased.



Charles Earnshaw

My name is Charles, and I am a new PhD student in the Cancer Inflammation and Immunity Group at CRUK Manchester Institute led by Santiago Zelenay. I grew up in Peebles in the Scottish Borders. I studied medicine at Gonville & Caius College, Cambridge, where I developed a love for the study of both medicine and how cancer cells interact with the host immune system. After completing the Academic Foundation Programme in Liverpool, and an Academic Clinical Fellowship in Manchester, I started my specialist registrar training in Dermatology at Salford Royal NHS Foundation Trust. I decided to undertake a PhD at this point, as my long-term ambition is to combine a research career with my clinical work. My PhD aims to understand the innate immune system involvement in melanoma development, with a goal of discovering ways of transforming immunologically 'cold' unresponsive melanomas to 'hot' T cell-inflamed tumours. I will use a range of high-throughput techniques, operating at the single-cell level, to characterise the immune pathways active in several cutting-edge mouse models of melanoma, with validation in human melanoma specimens. Outside of work I love to golf, travel, and hike in the highlands of Scotland with just the occasional distillery visit.



Victoria Gernedl

Hi, my name is Victoria, and I am from a small town 40 km south of Vienna, Austria. Prior to commencing my PhD studies at the CRUK MI, I studied Molecular Biotechnology in Vienna. During my studies, I trained for a year at the Children's Cancer Institute in Sydney, Australia, where I investigated the use of nanoparticles in cancer therapy for children. Following graduation, I commenced working as a next-generation sequencing research technician for two and a half years at the Center for Molecular Medicine in Vienna. Here my work focused on the study of epigenetic changes in cancer and immune cells. My interest in studying cancer brought me to Manchester and Caroline Dive's Cancer Biomarker Centre. I am very excited about undertaking my PhD here. My research project involves the investigation of the immune landscape of early-stage non-small cell lung cancer and seeks to establish a multi-modal biomarker to predict relapse in patients. I am a passionate saxophone and flute player and have joined the Manchester University Choir and Wind Orchestra groups. On my weekends, I enjoy hiking and being in nature. I am pleased that the Peak District National Park is close to Manchester.



Maria Koufaki

Hello, my name is Maria and I come from the enchanting capital city of Greece, Athens. My keen interest in human physiology and cell biology led me to pursue my undergraduate (BSc in Biological Sciences) and postgraduate (MSc in Molecular Biomedicine) studies and graduate with honours from the University of Athens. My MSc thesis revolved around the molecular mechanisms linked to tumour-associated vascular function. I also undertook a 4-month Erasmus traineeship at the Karolinska Institute in stunning Stockholm, Sweden. Being fascinated by the cellular and molecular interplay that defines tumour complexity, I have started my PhD in Cancer Inflammation and Immunity group, led by Santiago Zelenay. I am very excited to now pursue my PhD studies in Santiago's team, where I aim to characterise intratumoural dendritic cell subsets in cancer. Outside the lab, I love baking and eating desserts, and balancing this out by running and playing volleyball.



George Morrissey

Hello, my name is George and I am originally from the Peak District, where I grew up in the delightful spa town of Buxton. I am a junior doctor that has just completed the middle section of my medical training at hospitals in Northwest London. I studied pre-clinical medicine at Magdalene College, Cambridge before completing my clinical studies at University College London. Since then, I have spent 4 years working as a doctor in Brighton, Surrey and London, including an enjoyable oncology job at Charing Cross Hospital. I have always enjoyed research and was fortunate to spend a year as a Clinical Research Fellow with the 100,000 Genomes Project at St. George's in London with the aim of bringing next generation sequencing technologies to mainstream NHS care. It was here that I became particularly interested in molecular oncology and how it had changed the management of lung cancer. I have joined Angeliki Malliri's laboratory working with Dr Lindsay at the Christie to study resistance to a new class of exciting drugs in lung adenocarcinoma. I am particularly excited by the translational nature of this project; we hope to explore whether mechanisms identified in the laboratory occur in patients and if we can develop strategies to overcome resistance to these targeted therapies.

Away from the laboratory I am excited to be back in the North West and look forward to revisiting the Peak District as well as exploring the beauty of the Lake District and North Wales. I am also excited to return to the Etihad and watch my beloved Manchester City!



Parsa Pirhady

I am Parsa Pirhady and I am originally from Iran. I completed my undergraduate degree at the University of Sheffield in Biomedical Sciences. There I fell in love with cancer research and abandoned my initial plans of attending medical school. After my undergraduate degree, I continued my studies by undertaking an MSc(Res) in Translational Oncology. I was fortunate enough to join the lab of Prof Thomas Helleday, who is a world leader in translational cancer research and one of the main individuals behind PARP inhibitors.

My main area of interest in cancer research has always been the DNA damage repair pathway (DDR). That is why I applied to be a part of Prof Rob Bristow's pioneering lab and focus on the interplay between DDR and prostate cancer.

So far, I have been extremely lucky in the early steps of my academic career to secure positions in world-leading laboratories that endeavour cutting-edge research. I am very confident that being part of the Bristow lab and CRUK MI is going to make me a stellar scientist in the years to come.

As to my hobbies and personal interests, I love everything political and controversial. My greatest talent is talking (albeit a bit too much!). So anything that would require a heated discussion, be it the geopolitical implications of the war in the Middle East or the separation of art from the artist, is what I revel in.



Mathew Sheridan

Hello, my name is Mat. I was born in Birkenhead in 1986 and grew up in Wallasey, on the Wirral. I studied medicine at the University of Sheffield between 2004 and 2010 and undertook an intercalated BSc in Immunobiology at Imperial College from 2006 to 2007. After graduating from medical school, I worked as a Foundation doctor in Bristol for a year before a further year in Cheltenham. I then worked on a farm in the Elqui Valley in Chile for 3 months, before a few months of medical work in West Bengal, India and Durban, South Africa. I moved to Brighton for two years, working as a junior doctor in Eastbourne before returning to Bristol to undertake Haematology training in 2015.

The majority of my work as a haematology trainee involves haematological malignancy. We are particularly bad at treating acute myeloid leukaemia (AML) – it is clearly more than one disease, but our treatment algorithms do not recognise this. I wanted to understand more about the disease biology and undertook a Postgraduate certificate in Genomic Medicine at the University of Exeter in 2017, which gave me the confidence to apply for this PhD in Professor Lacaud's Stem Cell Biology group. I clearly wasn't confident enough as I didn't get it the first time I applied! But I'm now very lucky to be able to work on the role of the histone acetyltransferase, KAT6A, in AML.

Having not worked in a lab since 2007, this year has been a huge challenge, made all the more challenging by societal lockdowns when moving my girlfriend and our two daughters, aged three and six months the 180 miles from the South West to North West but we're now enjoying the diversity and inclusivity of Manchester and its surrounds, exploring the many parks and great food on offer.



Oliver Sinclair

My name is Oliver, and I recently started a PhD within the Leukaemia Biology lab. The aim of the project is to apply functional genomics to primary Acute Myeloid Leukaemia, to validate high confidence drivers of disease identified by the group. Currently my work involves studying CRISPR techniques and applying them to challenging settings within leukaemia. Prior to joining the Institute, I had worked with AstraZeneca in two roles. The first being a protein scientist involved in reagent production for assay development. The second role being in HIT discovery developing and running assays. More recently I worked within the Lighthouse Covid testing laboratory, helping to run the day to day of the lab and tackle some of the logistical challenges.

In my spare time I would love to try and gain some skills in mechanics, to allow me to fix the 1990s Volvo I bought two years ago. I also recently moved to Didsbury/Withington, so am keen to explore the area.

I look forward to finally meeting everyone face to face in the coming months!

Reflections one year on from Covid

– with the heads of Health and Safety, Logistics and Lab Services

Health and Safety - By Colin Gleeson

Like everyone else, I first became aware of SARS-CoV-2 (Covid-19) through news reports of the spread of the disease in Wuhan and China. It was evident that there was great concern when the Health Secretary began to make statements in the House of Commons about its spread. It was around this time that I flagged this potential problem to our Chief Laboratory Officer, Stuart Pepper. But at that early stage the information about the disease was unclear, including its basic modes of transmission, so we monitored the situation. Of course, in the fullness of time the virus reached the UK and necessitated the instruction from Government to "stay home" followed by the University's decision to implement a shutdown.

The SARS-CoV-2 pandemic and the accompanying shutdown presented enormous challenges to the Institute as it initially stopped or severely restricted normal research activity. Subsequently, it also required a re-think of the way we carried out our research activities and a concomitant re-set of all our research support systems. To meet these challenges, the Institute set up its Covid Strategy Group, which included the Director, Deputy Director, Chief Operating Officer, Chief Laboratory Officer, and heads of Human Resources, Finance, IT

and Health and Safety. We met to discuss the shutdown and would go on meeting at 9am every weekday for months. We continue to meet weekly, even now.

The Institute executed a controlled shutdown. We quickly took steps to shut down our activities safely and provide our landlord with assurance that this had been achieved. Whilst almost everyone in CRUK MI was at home, the Covid Strategy Group met online every morning and started to plan for opening up again when it was safe. It was readily apparent that this would be challenging due to social distancing and hygiene requirements and the availability of basic PPE, such as gloves and face masks.

Step by step, we developed phased plans to open up and I developed the Institute Covid Risk Assessment. Once plans were established, we held a Health and Safety Committee meeting that included University Safety Services and Faculty of Biology, Medicine and Health representation. We talked through our plans with them, and it was a relief and pleasing that they recognised a lot of hard work had been put into these plans and that they were deemed appropriate and proportionate.

Consequently, we went ahead with our plans and rolled out numerous meetings with our

research groups to discuss the practical details. As time moved on, we put in place other measures such as supervisory plans, developed a Covid Induction presentation and amended fire evacuation and first-aid plans. All these changes made for a very busy work schedule for many people, which was quite stressful but also incredibly satisfying knowing we were making a positive impact on the situation. An enormous change was taking place and that required hundreds of decisions.

The Covid Strategy Group was, in my opinion, crucial in driving, developing and implementing these changes. Richard Marais, as Director, led the Strategy Group and attended every meeting and was involved in every aspect of our response. Establishing and continuing with the daily running of the Strategy Group was hugely beneficial to our response to the pandemic. It enabled us to respond with agility to the challenges we faced. We opened up for research as early as was feasible and have continued to finesse plans to increase occupancy and hence increase the amount of research being undertaken. As we ease out of restrictions the Covid Strategy Group will continue to work together to maximise our research efforts moving forwards.

Logistics - By Andy Lloyd

The last four years in my role have changed considerably and at times have been extremely challenging. Since the Paterson Building fire in 2017, we have been in a disaster recovery phase with the temporary move of the Institute to Alderley Park. The biggest challenge at this time was adapting to my new role as facilities manager in a new environment, whilst also managing my staff across two sites to provide a consistent service, alongside being involved in the planning and discussions of the requirements for the new building.

From the middle of 2019, I was already planning for a potential no-deal scenario relating to Brexit. This involved assessing our current stores' items usage and their expiry dates while putting in place contingencies for ensuring the continuation of supply of consumables such as tissue culture plastics, media and reagents in preparedness for any delays or breaks in the supply chain. During the first six months of 2019, I examined the current demand on consumables and increased orders every month by around 30% to ensure we had approximately three months of extra supplies for post Brexit (at that time expected to occur at the end of October).

Although Brexit eventually happened at the end of January 2020, we did not see any major disruption initially, other than a rise in prices. We felt at this point in a good position to weather the initial Brexit storm but at the beginning of March I began to realise that the threat from Covid could cause an even bigger disruption than Brexit. By the middle of March, it was clear after seeing the effects of the pandemic in the rest of Europe that the situation was becoming very serious. In the week before the country went into lockdown, I looked at the contingency plan and

identified that the highest risk to my service would be the decrease in staffing due to potential illness and disruption of the liquid nitrogen/dry ice supplies. I discussed this with some of our users and one group decided to risk assess their own vapour phase tanks and move one of their tank's contents to a freezer, whilst we still had dry ice supplies and staff to assist. We raised the liquid nitrogen levels of all cells bank to give that extra resilience just in case there were disruptions to deliveries. Once the Institute went into shut down, I had to ensure that we still had staff on both our sites to receive any goods already in transit to and also maintain and monitor the liquid nitrogen supply at both sites for the groups' sample stores. This was especially difficult at Alderley Park due to the 'buddy system' for this type of working and ensuring someone else could always be on site with me when needed, sometimes at short notice.

As the instruction to shutdown was announced, we had to ensure that the lab areas were closed down correctly, ensuring hazardous and general waste had been cleared from lab areas, incubators were closed down and gasses turned off, equipment not in use was turned off and the building was left in a safe condition. During this time, we also dealt with unexpected issues such as clinical samples arriving on site for groups who were not present to receive them, so we had to communicate remotely as to what was required. We continued to have a presence on site throughout the national lockdown.

Once lockdown began easing, I had to adapt the services we offered to work in a Covid-secure way. We also had new issues with procurement regarding the additional PPE we required such as personal face masks, hand sanitiser. This was an especially challenging time as demand for PPE exceeded

capacity for many months and I had to source from new companies. Some of our procurement routes were blocked, such as NHS supplies that were understandably being prioritised for the clinical setting and Covid research labs. Luckily, I could call upon suppliers with whom I had previously built a good relationship to ensure these items could still be obtained and be ready for the planned re-opening of the Institute.

We then re-examined the pre-Covid service we had offered and streamlined it to still provide all essential services such as goods in, delivering consumable orders and providing a daily porters' van service whilst short-staffed.

Although life feels like it is returning to normal, and whilst the Covid threat is decreasing, we are still adapting due to the increase in demand for our services, as the sites become busier. Currently, I am co-project managing the triage/disposal route for the remaining equipment post-fire from the old Paterson Building, which are stored in various places around the University site, whilst supporting the senior management team by providing audits in relation to the new building. I am also starting to think further ahead to the logistics involved in the move back from Alderley Park to the new building and how operationally my team will function as they may potentially support three sites as the Institute transitions from Alderley Park to the Withington site.

Personally, I feel that I have progressed as a manager from experiencing all these disasters.

I now feel I have additional skills in how to react and adapt in my role from what I have learned about disaster recovery, contingency planning, future planning and managing staff during extreme circumstances.

Laboratory Services - By Mark Craven

The wider operations teams have had some unusual issues to work through during the last year due to the Covid-19 pandemic.

I was part of the Health and Safety Operations' team and together we needed to interact with CRUK MI, the University and Alderley Park (AP)-based processes to simultaneously and safely close the Oglesby Cancer Research Building (OCRB), whilst keeping floor two open, and to safely pause our activities at AP whilst the larger site remained open. I had to safely manage my on-site teams based in OCRB and AP during the closure, keep in touch, and support the teams during lockdown. I also kept in touch with fifteen staff members whilst we were in lockdown.

I supported our Chief Laboratory Officer, Stuart Pepper and Head of Health and Safety, Colin Gleeson by being part of the team last on site to assist the final tissue culture-based shutdown and then first on site prior to the return of the lab and support staff to make the transition as smooth as possible.

Some roles required a daily on-site presence at OCRB and AP and

could not be carried out remotely. I was, amongst others, granted Key Worker status to help perform these strategic tasks

In moving back, my teams contributed to the processes put in place to allow the safe return of Covid compliant lab work. I oversaw the cleaning team's return at OCRB and the adaptation required as part of the new cleaning regimes necessary for a safe return to work. Waste deliveries were reinstated at AP, and new Covid-related PPE was sourced, supplied and monitored in both buildings. I have coordinated Preventative Maintenance monitoring of equipment on site, such as safety cabinets at AP and autoclaves and glass washers at OCRB, acting as chaperone when necessary. Returning early, the Lab Services team was able to resupply clean glassware, fluids and microbiological media to the returning scientists for the reopening of the labs.

The logistics of supplying the essential sterile plastics to the labs became complicated by the unfortunate combination of Brexit and Covid during the early part of 2021. As an Institute, we were fortunate to have put robust Brexit

contingencies for such items in place during last year, however due to Covid, the same items we required were also essential to the ongoing Covid testing regime and inevitably shortages occurred. We all wanted the same items at the same time and the "just in time" supply model has struggled to meet this demand. Some of these issues remain as of today. For example, it is much more time consuming, and expensive, to find and buy the single use tissue culture plastics and PPE compared to last year.

As a result of these additional pressures, I have had to source alternative supplies and, where practical, minimise the price increases whilst maintaining the quality of any product substitutions.

It would seem the day job pre-Covid was considerably easier and less challenging than it is today, but things are moving forwards and we can look forward to the future. I am supporting Stuart Pepper in the planning of the new Lab Services Department and other support structures within the new building.



Collaborations between our Core Facilities

Behind the scenes the CRUK MI core facilities collaborate in defining new workflows, refining methods and introducing new instrumentation. The combined skillsets of the members of the facilities in collaboration with the research groups permit a holistic view of a research initiative. Over the last year there have been several new initiatives:

CODEX

With fluorescence microscopy there has been limit to the number of fluorescent signals that can be separated and discerned. Over the last year the Histology and Visualisation, Irradiation and Analysis teams have introduced CO-Detection by indEXing (CODEX) – a method for single cell biology where simultaneous detection of up to 40 biomarkers in the same cell (single

cells or tissues). The system utilises subsequential labelling via microfluidics to achieve high dimensionality. The Histology team are developing new tissue methods to develop the technique, such as mini-tissue microarrays, whilst the VIA team are developing the visualisation technology and methods of data visualisation and analysis.

CyTOF Machine Learning

Over the past year Scientific Computing, Flow Cytometry, VIA and Systems Oncology have been collaborating on finding and implementing machine learning (ML) methods to analyse and understand high dimensional CyTOF output data to overcome the challenges that arise from the manual analysis of data.

Mass cytometry, or CyTOF (cytometry by time-of-flight), is a development of flow cytometry analysis instrumentation in which antibodies are labelled with heavy metal ions rather than fluorochromes, and then time-of-flight mass spectrometry is used for output. Due to the high dimensionality output, ML would permit data understanding. For instance, the manual gating process is not only laborious and time consuming but is also subject to human bias as it requires a fundamental understanding of what markers define specific cell populations.

DeepCyTOF¹ was chosen to assess if ML methods can be used to analyse high dimensional CyTOF data. It is a supervised machine learning algorithm that integrates deep machine learning into automatic cell population gating. It uses a Domain Adaption, de-noising

stacked autoencoder and multiple distribution-matching residual networks (MMD-ResNet) – meaning only one sample with labelled cells is necessary to train the model – and then it can be used for the subsequent analysis.

Using the code published with the Li et al. 2017 paper (cited below) provided the team with some challenges – unfortunately version information about the Python libraries used for running the code was missing. After Stephen Kitcatt, a programmer in the Scientific Computing Core facility, solved all the issues the code was ready to be used on the GPU node in our Phoenix HPC cluster. Stephen used publicly available benchmark datasets to reproduce the results presented by Li et al. Afterwards, he assessed the performance of the DeepCyTOF algorithm by using real data provided by Toni Banyard from the FACS core facility and Adrian Blanco-Gomez from the Systems Oncology group.

Using several Immune, full pancreas and mesenchymal pancreas datasets, the team could show that a very high rate of accordance between manually and automatically DeepCyTOF gated cells can be achieved if the number of cells in the sample used for training the network is high enough. Using a sample with 1085 cells from an immune cell dataset resulted in a prediction accuracy between 88.36

and 89.37% (Figure 1A). However, doubling the number of cells resulted in a prediction accuracy of 93.53% (Figure 1B), which is similar to the number described in the article. Furthermore, he was able to demonstrate that a model trained on one dataset can be used to gate cells from different but similar datasets.

After the effectiveness of DeepCyTOF had been established, Stephen simplified the usage of the algorithm by creating a Shiny app that allows users to train models and gate cells using a graphical user interface utilising the GPU resources on the Phoenix HPC system. Using the Shiny Proxy server to deploy the DeepCyTOF shiny app enables users to have exclusive and direct access to their data produced by the FACS core facility.

The effective collaboration between three core facilities and the scientists of the Systems Oncology group enabled the successful creation of a machine learning-based tool that can be used by CRUK MI scientists for automated high-throughput gating of large CyTOF datasets.

¹Li, Huamin and Shaham, Uri and Stanton, Kelly P. and Yao, Yi and Montgomery, Ruth and Kluger, Yuval. Gating mass cytometry data by deep learning. bioRxiv, 10.1101/054411, 2017

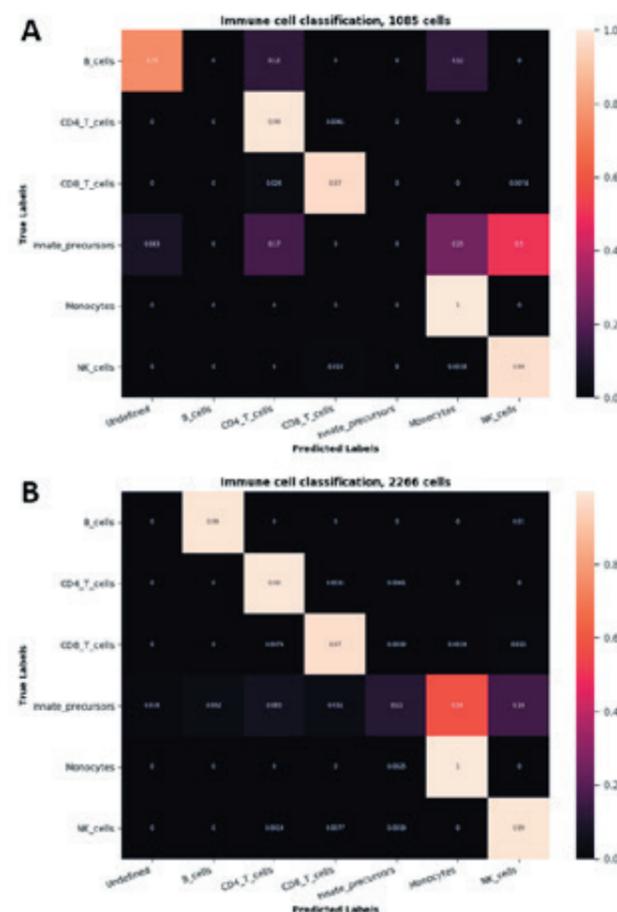
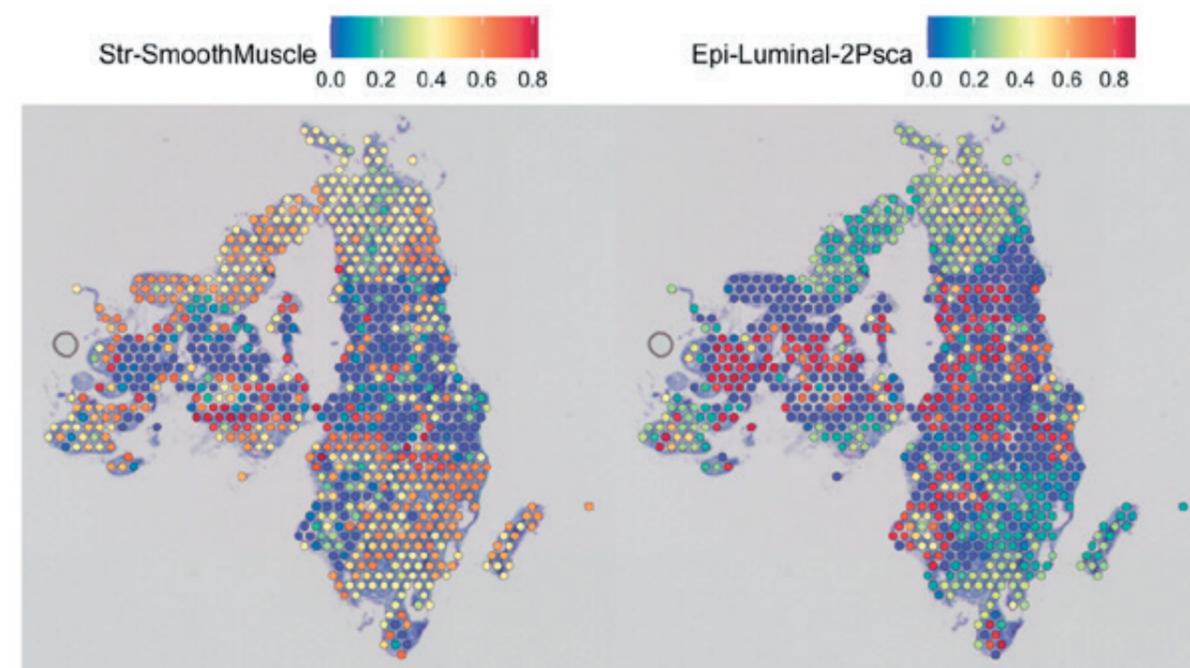


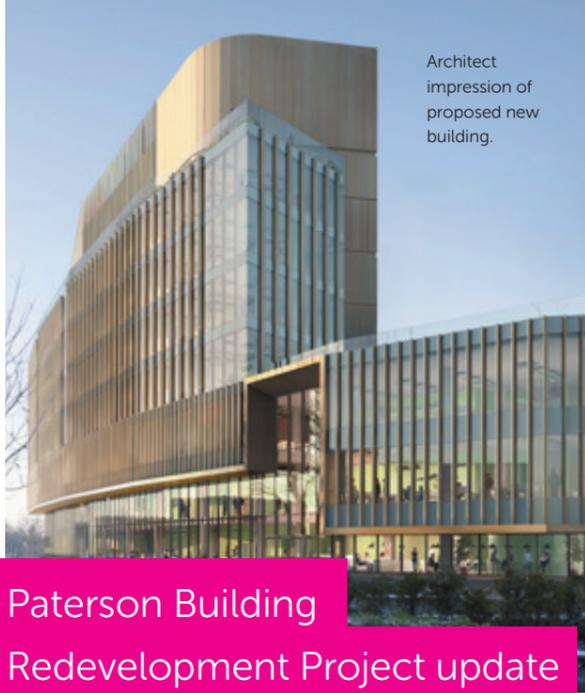
Figure 1| Confusion matrix of Immune cell classification. A. Using a model trained on 1085 cells. B. Using a model trained on 2266 cells.

Spatial Transcriptomics

Molecular Biology Core, Histology, Computational Biology Support team and VIA have been developing the 10x Genomics Visium workflow for spatial gene expression. Using a customised slide from 10x and the expertise of all four facilities localisation of gene expression can be visualised and numerated. Future development being worked upon include the use of five colour fluorescence and CODEX to work alongside spatial transcriptomics.



Validation of 10x Genomics Visium Spatial Transcriptomics



Paterson Building Redevelopment Project update

In 2017, a fire caused serious damage to the Paterson Building, leading to the displacement of over 350 scientists and research of our staff at the CRUK Manchester Institute. Whilst causing setbacks in our world-leading research activities, the fire gave rise to a new opportunity to create a brand new and globally leading cancer research facility. As construction continues, the new facility lends promise to scientific collaboration and a transformation in cancer patient outcomes.

Over the last two years a huge amount of work has been undertaken by a wide-ranging team of people, including architects, engineers and construction experts, as well representatives of The Christie NHS Foundation Trust, The University of Manchester and of course the Institute. Up until December 2020, the only visible change as a result of all this work was the demolition of the old building, and the appearance of a large hole in the ground where it used to stand.

For those who have passed the site recently it is clear that this year the project has moved from a design phase to construction, and each week the building seems to grow a little bigger.

Fascinating build facts

The scale and speed of the concrete pouring is very impressive. So far 10,000 cubic metres of concrete, weighing approximately 25 tonnes, have been poured. As part of the overall green strategy for the building, twenty percent of the material is actually 'concrete replacement', which yields significant reductions in CO₂ emissions related to actual concrete production.

Although the building is not yet at full height, the views are already impressive. From the fourth floor you can look out and see either the Etihad or Old Trafford football grounds (your choice which way you look!) or to the south you can see the Air Traffic Control tower at Manchester airport, and of course to the north the city centre skyscrapers are clearly visible as well.

What to expect in the coming months

So, what will happen over the next 18 months? The concrete structure is on target, to be finished in September this year, and the focus then switches to walls and internal structures. Fitting out of the basement has now started and already large equipment items, such as autoclaves, are being ordered for delivery later this year. There is also a rolling programme of adding detail to the design – just to give a couple of examples, currently there is a focus on the specification of such aspects as the floor coverings and blinds, as well as work on the details of how the various IT networks for UoM and The Christie will connect into and through the building.

From the start of the project there has always been an ambitious timeline as we all want to be in the new building as soon as possible. So far, despite the Covid-19 pandemic, construction has remained on-target and everyone involved is working hard to keep to the construction completion date at the end of December next year. Once construction is completed, there will be some final fit-out work to undertake and then we can look forward to saying goodbye to our neighbours (and the geese!) at Alderley Park and final moving into our new building after more than five years since being displaced by the fire.

Our legacy

This new facility is designed to support our translational approach to cancer research and care, by promoting the interaction, integration and collaboration between research and clinical staff through co-location. As a result, joint research programmes will be stimulated that tackle some of the most important challenges in cancer detection and care. The new building, with its state-of-the-art facilities and with the research it supports will also act as an important tool in attracting new talent from all over the world.

The building will be twice the size of its predecessor, bringing together the largest concentration of scientists, doctors and nurses in Europe. A further 400 staff will be supported by the facility, alongside the 350 research scientists and support staff who are currently displaced.

A big hole in the ground where the Paterson Building used to stand.



View across to central Manchester from the fourth floor of our new building.



Meet the new Research Integrity and Training Adviser

By Andrew Porter

In January the Institute appointed a dedicated Research Integrity and Training Adviser to support good research practice and coordinate training for early career researchers. Andrew Porter formerly worked in the Cell Signalling Lab as a post-doc and later as senior scientific officer.

I began this new role in January 2021, having worked in the Institute since 2011 as part of the Cell Signalling lab. I'm really excited about this opportunity to support researchers across the Institute with training and advice, building on my local knowledge, personal experiences in research and through drawing on resources from the wider research integrity community, such as webinars and conferences.

A major part of my role is to review papers before submission to journals. I support authors in meeting best practice in reporting methods and figure presentation, give feedback on consistency in the text, and I can also be an extra pair of eyes to spot errors or suggest where extra clarity might be useful. Catherine

Winchester, who has a similar role at the CRUK Beatson Institute, has given me very helpful guidance, and following her suggestion we now check papers with iThenticate software, to help avoid any issues with plagiarism.

I'm about to start running a specific Research Integrity Induction for all new staff, which will cover good research practice, introduce important regulatory frameworks, and give opportunity for discussion around research ethics and research culture. Even via Zoom I've enjoyed discussions with group leaders, facility heads and students about what research integrity means to them, and what support they would benefit from. I will be coordinating ongoing training in research practices, such as data handling, statistics and imaging, reporting animal experiments and career development.

Other things I'm involved with include promoting the work of our researchers on social media, supporting the STAy committee of early career researchers with their new plans following lockdown, and being part of a data management working group.

This is a dynamic time in research integrity. Publishers, funders, universities, and governments are all releasing plans around research culture, reproducibility and good research practice, and my aim is to help our researchers put these into practice in ways that benefit them and their research.



In memoriam: Brian Iles Lord

It is with sadness that we report the death of highly regarded former member of the Institute, Dr Brian Iles Lord, who died on 12th February 2021. Brian was a pioneer in stem cell biology and haematopoiesis, and his work included the first biological proof of the novel concept of the stem cell niche – an area of tissue around stem cells that helps support their self-renewal and differentiation.

Here we share some details of his academic life, and memories from his colleagues at the Institute.

Brian was born and schooled in Rochdale, Lancashire. He obtained his degree in Physics with Biophysics from King's College London in 1959 and was later awarded a doctorate from the Institute of Cancer Research/The Royal Marsden Hospital in Sutton in 1963, where he studied the kinetics of erythrocyte behaviour with the eminent Professor

Leonard Lamerton. Brian then went on to study in the USA on a prestigious Fulbright Scholarship at the University of Washington from 1965-1966, before returning to the UK to join the Department of Experimental Haematology at the Paterson Laboratories (the former name for the CRUK Manchester Institute). Here he worked alongside Ray Schofield, also well-known for his work on the stem cell niche.

We caught up with Ray and spoke to him about his fond memories of Brian. He said, "Brian and I shared a lab and office for almost 20 years, from when he arrived in 1966 at the Paterson Laboratories, until 1985 when I 'retired' to become a farmer in West Wales."

Back then, there was still much to discover about the biology of the haematopoietic stem cell. Together they explored the characteristics and properties of haemopoietic progenitor cells, early descendants of stem cells that can differentiate to form one or more kinds of cells, making many scientific breakthroughs in the field.

Demonstrating true collaborative spirit, they also worked alongside Mike Dexter – at the time a postgraduate student – who was later to become the Director of the Institute and subsequently Director of Wellcome, as well as Nydia Testa.

Brian was a pioneer of progenitor cell kinetics and responses to radiation in rodent haemopoietic tissue. He studied the effects of the stem cell niche on radiation and chemical carcinogenesis, and interventions to mitigate haemopoietic damage due to chemotherapy.

He was a key investigator in the first clinical trial of haemopoietic growth factors – substances capable of safely stimulating the proliferation and differentiation of blood-forming cells in patients that help them make more white blood cells, especially granulocytes, macrophages, and cells that become platelets. The trial, carried out at the Christie NHS Foundation Trust, helped complete the full haematopoietic picture of response with the kinetics of granulocyte development.

Over his academic lifetime, he published 130 papers and wrote a number of review articles and edited a number of books. He was appointed as an Honorary Professor in Experimental Haematology in the School of Medical Sciences, Division of Cancer Sciences, The University of Manchester in December 2020, prior to his death.

Ray added, "Of course, there was much more to Brian than work, he was a lacrosse player and Monday mornings in winter always involved a discussion of our games on the previous Saturday. He was a gardener and keen on DIY. He was also a regular contributor to the



Brian Lord at work in the Paterson Laboratories



Ray Schofield (left) and Brian Lord

Christmas shows that we staged for the lab party, which were largely satirical and aimed at the upper echelons of the Institute! He had a good, quiet sense of humour, and until a few weeks before he entered the hospice, we were swapping jokes that we had received on emails.

"He and I were quite different personalities, but he was so easy and friendly to work with that I can safely say that we never had a non-scientific dispute in the whole of our time together, even though we were always in very close contact. At any time that I needed some practical help, he was the first person I turned to, and I never had to turn to anyone else."

Ray concluded, "Brian acted as a mentor to many members of the Experimental Haematology Group over the years, not just in a scientific context but also personally. There will be former visitors to our group from around the world who will remember Brian with a great deal of gratitude.

Some people leave behind better footprints than others and I think all of those who were associated with Brian Lord will consider that their lives would have been poorer if they had not known him."

Brian is survived by his wife Margaret, daughter Rosemary, a Consultant Medical Oncologist and Deputy Medical Director at the Clatterbridge Cancer Centre, son Graham, Vice-President and Dean of the Faculty of Biology, Medicine and Health, at The University of Manchester and Honorary Consultant in Nephrology and Transplantation, Manchester NHS Foundation Trust, and six grandchildren.

We also asked other former colleagues to share their memories.



Catharine West

Prof Catharine West, Professor of Radiation Biology at the University of Manchester, who worked at the Institute with Brian said,

"He was a pioneer...I just remember him as a nice man who was interested and interesting."



Ruth Roberts

Prof Ruth Roberts, Director and Co-founder of ApconiX and Chair and Director of Drug Discovery, University of Birmingham said,

"When I was a PhD student in the Dexter lab, Brian was always ready with a kind word and wisdom to help me through difficult challenges. His door was always open to all of us and he had a genuine passion for science and research."

Awards, Prizes & Events

Events

Colloquium 2020 highlights

The CRUK Manchester Institute Colloquium usually takes place every September at Lancaster University, however last year we held the event virtually. Despite the challenge of translating a retreat-based event onto a virtual platform, the Colloquium was a great success and provided an alternative opportunity for our new intake of students to interact with other established PhD students and members of the Institute, including group leaders, postdoctoral fellows, and scientific officers.

This forum communicates up to date science in the form of oral presentations given by group leaders and second year PhD students, and we were still able to host poster presentations from a range of scientists across the Institute, covering all aspects of cancer research. Poster prizes are awarded, including the Lizzy Hitchman Prize for the best poster presented by a PhD student or clinical fellow, which this year was awarded to Eimear Flanagan from the Cancer Inflammation and Immunity group, and Best Poster Prize to a postdoc, which went to

Brian Lee, formerly of the Systems Oncology lab.

The virtual platform also opened up the opportunity to take a novel and exciting approach to the event, enabling us to invite more guests and diversify the programme. We included two external seminars and an alumni session as part of the proceedings.

We were privileged to hear talks by Professor Adele Fielding from University College London, and Professor Kostas Kostarelos from the National Graphene Institute. Prof Fielding gave a fascinating insight into UK's clinical trials programme for Acute Lymphoblastic Leukaemia and her unique opportunity to perform translational research arising from these trials, whereas Prof Kostarelos told us how his team are bridging the gap between fundamental nanomaterials engineering and pharmaceutical development towards the realisation of advanced therapeutic modalities that can be applied to cancer.

The alumni session was also hugely enjoyable, providing the occasion for some to reconnect with former colleagues and for others to discover where a PhD or postdoctoral position at the CRUK MI can lead, make new connections, and see how to balance

an academic career with family life. We would like to thank for their time and humour, Timurs Maculins and Hadir Marei, now both at Genentech in San Francisco; Marina Parry, who is based at University College London; Elvan Böke, now leading her own research group in Barcelona; and Dan Tennant, who started his own group at the University of Birmingham.

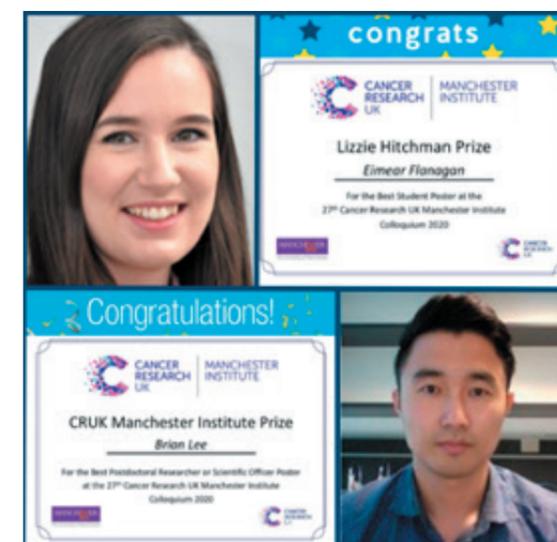
To make the online poster sessions more fun, we introduced 'elevator pitches' to precede each of the three sessions. These featured six selected posters within that session where the authors each gave a 90-second pitch on their poster. As always, the quality of the posters was outstanding, and it made hard work for the panel of judges to choose the two prize winners.

And finally, it would not be a colloquium without socialising in the evenings. So, we would like to thank the STAY committee for bringing everyone together with their inventive and family-friendly online social activities.

In September this year we hope to hold the event in person at Alderley Park, but if restrictions don't allow it, we know that we can put together an exciting virtual experience.



Image right: Eimear receives the Lizzy Hitchman student prize and Brian wins the postdoc prize.



STAY update

The Science Takeaway (STAY) committee have made the most of a different year this year with all events and activities moved online. In the spirit of keeping our research community connected across the institute, STAY ran a number of virtual social activities. These included hosting regular coffee mornings and fortnightly Quarantine Quizzes (with prizes!) throughout the lockdowns to keep us engaged with our peers whilst at home.

STAY successfully secured additional funding from the University's 'Anything but Research' fund, enabling us to run online Escape Rooms and board game evenings for our early career researcher community, away from the lab. The online Escape Rooms were a fun way to meet researchers



across different sites and come together in teams to solve various tricky challenges. These were enjoyed by all attending and helped us connect whilst in-person activities were on hold.

The STAY committee further assisted with the planning of the annual Institute Colloquium, where we fed back into design of the virtual poster sessions, coffee breaks, and importantly the Colloquium Quiz – where good humoured team rivalries were quickly established in teams mixed across different labs and career stages.

We are keenly looking forward to our upcoming in-person events (following social distancing guidelines), so watch this space if you're an ECR and want to get involved!

Cryopreservation and Assisted Reproductive Technologies in Genetically Altered Animals

By Natalia Moncaut

Every year the LASA Animal Science Transgenic Group, where Natalia Moncaut from our Genome Editing and Mouse Models core facility (previously Transgenic Production Facility) is part of the organising committee, organises highly interactive meetings with a focus on the laboratory mouse.

The Laboratory Animal Science Association (LASA) is the UK society for scientists and laboratory animal professionals with an interest in animal research, 3Rs, care and welfare, education and training, ethics and policy and regulation of animal research.

The main aim of these meetings is to provide ample opportunity for learning, building professional networks and sharing best practice with others working in the field all around the UK. In April this year, the LASA working group organised the 3rd Technical Forum about Cryopreservation and Assisted Reproductive Technologies in Genetically Altered Animals, sponsored by Charles River.

In contrast to previous forums, and for obvious worldwide reasons, this time the forum was held virtually. This situation presented some new challenges to the group but offered a unique opportunity to shift a UK-only

national meeting to an international one. Remote participation allowed the organisers not only to invite the most prominent specialists in the field, including Rob Taft from The JAX Centre for Genetics of Fertility and Reproduction, USA and Toru Takeo from the Kumamoto University, Japan, but also permitted the participation of many junior staff.

The sessions were structured to include a series of presentations by many international experts in their respective fields, followed by opportunities for attendees to present and interact with colleagues and speakers around virtual poster sessions and round tables. Across all the

sessions several topics were covered, including innovations and tips for cryopreservation in different species (mouse, rat, zebrafish, opossum, frog), alternative uses for cryopreservation and the impact of Covid-19 in breeding colonies.

The interesting programme and virtual nature of the forum attracted more than 180 participants from 21 different countries (98 Institutions) all around the globe. After receiving great feedback about the meeting, the LASA Animal Science Transgenic Group has already started to plan the next forum, considering the possibility of a hybrid meeting combining virtual and in-person options.



A great IVF lesson by Toru Takeo, Kumamoto University, Japan



Exploring Cancer Landscapes with the Royal Society

The Cancer Research UK Manchester Institute is presenting an exhibit at the prestigious Royal Society Summer Science Exhibition. The event, originally to be held at the Royal Society building in London last year, was postponed due to the pandemic.

Now this year we are going totally digital with inspiring talks, interactive workshops, virtual tours, games and more.

The Institute team are Andrew Porter, Joanna Kelly, Chris Bromley, Charlotte Bell, Steve Bagley and Gill Campbell and together they have been working hard to translate their ideas and concepts for a physical exhibition onto a digital platform. They have been supported by Yannick von Grabowiecki, Belen Conti Vyas, Marek Dynowski and his team in Sci Com, and Chris McCauley.

This is an excellent opportunity for the Institute to engage with the public and showcase our work in cancer research.

Cancer is complicated. Tumour cells are surrounded by immune cells and cells called fibroblasts, which support and hold different cells together by

making connective tissue. These and many other components make up the tumour landscape or 'microenvironment' and can change how tumours grow or respond to treatment.

Every patient's tumour is unique, and different kinds of cancer contain different mixtures of components. It is only by understanding the individual landscape of each tumour that we can provide the best treatment to help more people survive cancer.

Here at the CRUK Manchester Institute, we have teams of scientists using cutting-edge techniques to explore cancer landscapes in order to understand that complexity and expose new ways to treat cancer.

To explain more about our work, we've created a digital experience in which everyone can find out what makes up a tumour, and see how different patients might respond differently to treatment.

Find out what makes up a tumour and join us in exploring the cancer microenvironment.



Thursday, 8 July 2021
Lightning lecture 8pm – 8:15pm

Title: Mapping tumours

Synopsis: Tumours are not just solid lumps but are made up of many different cell types and components.

Join researcher Dr Joanna Kelly to find out more about these 'tumour landscapes' and why understanding the details of their composition could be the key to developing the cancer treatments of the future.

Saturday, 10 July 2021
Public workshop (adult) 10am – 11am

Title: Breaking into tumours

Synopsis: Solve puzzles and use clues to learn about the different cell types commonly found in tumours and navigate your way through one.

Public workshop (family) 3pm – 4pm

Title: Cardboard tumours

Synopsis: Learn about the different cell types commonly found inside tumours by constructing a cardboard tumour model. Can you help anti-cancer immune cells to find their way into the tumour?

Cross-pollinating discovery cancer research in Manchester

In April, the Institute hosted a virtual 'away day' with cancer scientists from across the University of Manchester. This was the first in a new series of events connecting the Institute, the Division of Cancer Sciences, the Division of Molecular & Cellular Function and the Division of Infection, Immunity & Respiratory Medicine, designed to strengthen collaborations and share the fantastic basic cancer research across the Faculty of Biology, Medicine and Health.

The event featured eight speakers in synergistic sessions including cell cycle and DNA damage repair, signalling in cancer, tumour immunology and inflammation, and tumour epigenetics, and was attended by around 50 academics via zoom.

We heard engaging talks that stimulated lively discussions and fulfilled the ambition of the event to 'cross-pollinate' knowledge and ideas



Our scientists connect at virtual away day.

with colleagues who may not have interacted with each other before and to explore new avenues for potential collaborations across the Faculty.

We are looking forward to getting together again in the coming months, virtually or in person, to further explore the exciting opportunities available.

Prizes

Wendy Trotter wins 2020 Dexter Award

We are delighted to announce that the Institute's Dexter Award for the Best Young Scientist of 2020 is awarded to Wendy Trotter from the Cell Division group.

The prize recognises the most impressive scientific achievement by a student, post-doc or scientific officer and is named after a former Institute Director, Professor Mike Dexter. The judging panel felt that Wendy has made significant and far-reaching contributions to the cell cycle field and therefore was very deserving of the award.

Before Wendy joined the Cell Division group, Iain Hagan had no experience of conducting research in human cells and so Wendy established all of this work and translated the group's ideas into highly successful experiments. Due to logistical reasons, Wendy has been unable to join the rest of the lab

in Alderley Park. Instead, she works independently in a lab in the OCRB where she has set up, managed and driven everything independently. Her work has had an international impact in three areas.

Currently, the most prominent is the application, development and boundary testing of a scheme for synchronisation of cell cycle progression with CDK4/6 inhibitors. This appeared as a two-author article in Open Biology in October last year and has been featured by CRUK. This is a complex study in which Wendy tested and stretched a number of parameters to define the application and limitation of this technology.

Senior Scientific Officer Wendy has pushed further boundaries with the application of CRISPR resulting in high success rates for this technology (80% heterozygotes, 10 - 20%



homozygotes) and is continuing to drive innovation with an approach to confer rapid destruction kinetics through the development of a combination degron method. The Cell Division group have shared their methods and reagents with prominent cell cycle groups all over the world, demonstrating the far-reaching impact of Wendy's achievements. As well as sharing the protocols and reagents, she continues to provide technical expertise and guidance.

Wendy is a tremendous ambassador for the Cell Division lab and the Institute and a deserving recipient of the Dexter Award.



PhD student Amelia Jones is helping widen access to higher education

Millie Jones gives back with the Brilliant Club

Congratulations to Amelia Jones who was invited to work with The Brilliant Club, an award-winning charity that aims to widen access to higher education. In pursuit of their mission, the charity recruits PhD and postdoctoral researchers to deliver a range of university-style tutorials to high-achieving pupils from underrepresented backgrounds, with the goal of boosting their chances of getting accepted into top universities.

Amelia is a PhD student in the Cell Division group at the Institute, where she is working on the function of a subunit of a specific protein in cell cycle control. She will be taking part in The Scholars Programme, where she will design and deliver a course based on her own research. The aim of this approach is to challenge pupils beyond the scope of the standard curriculum, providing them with key skills and confidence to help them secure a place at a highly selective university.

Supporting The Brilliant Club in this way is a great opportunity for Amelia to gain teaching and public engagement experience important for her own career, as well as the chance to give back to the local community.

Amelia was given training in February before getting started the tutorials with her pupils. She has given her first four tutorials so far and it is going really well. The students are 14-15 years old and just in the middle of their GCSEs. She has been focusing the first few tutorials on the maths-based part of the Chemistry GCSE, and she has really enjoyed seeing them become more confident with the 'mole calculations' over the past few weeks.

Amelia says, "There are definitely challenges with running the tutorials over the internet rather than in person, but the students have all been really engaged and have clearly learned to adapt over the last year.

"It's quite a lot of work to put together the lesson plans each week, especially with some of the content that I've not re-capped since I was doing GCSEs myself, but overall I'm really enjoying it. I'm looking forward to seeing how the rest of the term goes!"

As to why she wanted to volunteer with this scheme, she says, "I'm really interested in science communication in general, so this felt like a good way to get some experience communicating with a younger audience. Also, most PhD students get the opportunity to gain teaching experience in undergraduate labs, but due to our location at AP that's a bit more difficult. This was a good chance to get a similar experience.

"I also really care about the attainment gap in schools. Covid has most severely impacted the pupils who were already at a disadvantage, so it's likely that this gap is only going to get wider. I'd like to do what I can to help, even if it's just with a small group!"

Caroline Dive receives Distinguished Service Award

Congratulations to our Interim Director Caroline Dive, who has been recognised with a Distinguished Service Award by the International Association for the Study of Lung Cancer (IASLC).

Each year, the IASLC honours professionals who have made major contributions to the field of thoracic cancers with its Distinguished Service Awards.

Professor Dive received the Mary J. Matthews Pathology/Translational Research Award for 2020. This award recognises an IASLC scientist for a lifetime achievement in pathology and translational research of thoracic malignancies.

Caroline is the Director of the CRUK MI Cancer Biomarker Centre and is currently President of the European Association for Cancer Research. Her research interests span tumour biology, biomarker discovery, preclinical pharmacology, and biomarker assay validation and qualification.

Internationally recognised for her contributions to cancer research, Caroline has received numerous accolades over the years.

She was awarded the Pasteur-Weizmann/Servier International Prize in 2012 for her biomarker research, the AstraZeneca Prize for Women in Pharmacology in 2016 and the 2019 Heine H. Hansen Lectureship Award by the IASLC. She was also awarded Commander of the Order of the British Empire (CBE) for her services to cancer research.

The award is presented in honour of Dr Mary Matthews, who served as a senior investigator and pathologist at the National Cancer Institute's Medical Oncology Branch. She was pioneer in the foundation of the histologic subtypes of lung cancer and the relationship between those subtypes and the clinical course of lung cancer. Geno Saccomanno, MD, PhD, a physician and cancer researcher who dedicated his life to developing a pioneering technique to assist in the early detection of lung cancer was the first to receive the award in 1994.

Double funding success for Institute Fellow

We are proud to announce that Amaya Viros, a talented Clinician Scientist at the Institute, has been granted funding from the Melanoma Research Alliance, the largest non-profit funder of melanoma research in the world.

Dr Viros set up her first independent research group at the Institute just over four years ago to study skin cancer and ageing, with a particular emphasis on melanoma.

She was one of 14 researchers this year to have been awarded a prestigious MRA Young Investigator Award.

These awards, issued near the start of Melanoma Awareness Month in May, provide critical funding to address urgent unmet needs in melanoma. Amaya will use this three years' funding to investigate the interplay between melanoma and adipocytes in the skin, and how these interactions may change during aging. Adipocytes, also known as lipocytes and fat cells, are the cells that primarily compose adipose tissue and are emerging as important determinants of healthy lifespan and contributors to cancer biology and treatment.

In more great news, Amaya secured further funding from the charity



Wellcome. Since 2016, she has been funded on an esteemed Wellcome Trust Intermediate Clinical Fellowship to develop an ambitious programme of research looking into why elderly people are more prone to developing melanoma and why they are less likely to survive if they develop the disease. She has recently been awarded a fully costed extension to her fellowship for a further 12 months, which will allow her to expand her research to investigating the characteristics of aged skin and tumour growth and how that

drives immunotherapy response in the elderly.

Underpinning this funding success is Amaya and her team's exciting research that has been recently published. They have demonstrated how prolonged sun exposure can affect melanoma invasion and that female immunity might protect against some skin cancers.

Congratulations Amaya.

Institute success in national Oncology Development Programme



We wish to offer our congratulations to Professor Caroline Springer and Professor Richard Marais on getting their entrepreneurial projects through to the development phase of the Alderley Park Oncology Development Programme.

The Oncology Development Programme at Alderley Park, led by Bruntwood SciTech and funded by Innovate UK and Cancer Research UK, was launched last year to develop and nurture an entrepreneurial culture

amongst cancer researchers in the UK and help accelerate the translation of emerging cancer research into patient benefits. The goal of the national programme is to bring forward viable oncology projects much more quickly in order to significantly increase their likelihood of commercial success, and ultimately, to meet patients' needs.

Caroline Springer, Director of the CRUK Manchester Institute DDU and Richard Marais, Molecular Oncology Group Leader have been working

together on two tumour inhibitor projects.

Structured in four parts, the programme kicked off with a Pre-Development Workshop for 32 projects. Caroline and Richard were selected to attend with their two projects. Following the workshop, eight projects were then chosen, so their success is particularly impressive as both projects were selected to receive grant funding to take them to the next stage. During the Development Phase 1 of the programme, Caroline and Richard will learn about business start-up methodologies and tools to help them form their own commercial companies.

Following the 11-week intensive Phase 1 Programme, a final 6 projects will be invited to join Phase 2 of the Development Programme.

This is really exciting news, and we are all looking forwards to see what comes next. Well done!

Drug Discovery and Pancreatic Cancer collaboration wins grant

Two multidisciplinary groups working together at the Institute have secured funding to explore treatment opportunities for pancreatic cancer.

Director of Drug Discovery, Caroline Springer and Claus Jorgensen, who leads the Systems Oncology group, were recently awarded a competitive grant from the Lustgarten Foundation.

Pancreatic Ductal Adenocarcinoma (PDA) is a dismal disease and is currently the fourth largest contributor to cancer-related deaths in the UK. It is an extremely difficult cancer to treat as the cells that surround the tumour – the microenvironment – diminish the

immune response and confer resistance to therapy. Understanding the role that the microenvironment has in shaping the therapeutic response is critical to developing the right therapies.

Having successfully completed two stages of applications for the Therapeutics Focused Research Program, the team will now work to identify targetable pathways in the tumour microenvironment to develop drug compounds against this disease.

We look forward to hearing more as this exciting project develops.

Staff News

Teaching at the University of Manchester

Ali Raoof, from our Drug Discovery Unit, took part in several teaching activities at The University of Manchester. In October and November 2020, he successfully delivered a medicinal chemistry lecture course via Zoom, including written exam questions. This was followed up by tutoring sessions with some undergraduate students in the course to go over pass paper questions and revision techniques. This was so successful that he ended up doing another follow up session a few weeks later!

Ali also gave an annual Master of Research lecture, entitled *Introduction to Drug Discovery* to intercalating medical students in January 2021.

Our very own "TV star"



Noel and his wife were the lower scorers throughout the programme

On 19 January 2021, one of our own made his debut appearance on the national TV programme *Pointless!* Noel Kelso, from the Cancer Biomarker Centre, and his wife showed off their obscure knowledge on pop music, tennis and presidential signatures. Not only did they give two pointless answers on the tennis round, but they also found the all-important final pointless answer. When asked about Nobel Prize winners, Sir Paul Nurse was the reply that brought the jackpot home. Congratulations!

A virtual Xmas party that reached Twitter's culinary royalty



Nigella was delighted with David's cake

In December 2020 we could not get together to celebrate Christmas with the usual party and festive cheer. But that didn't stop us from having a fun online day.

We recruited plenty of volunteers to teach workshops during the day. We learnt to cook a delicious cheesecake with Richard Marais; Ruth Cox taught us how to create our own stockings; Yannick von Grabowiecki showed us Photoshop tricks to create funny Christmas cards; Andrew Porter directed our online Xmas Band; we had an online boardgames break hosted by our STAy Committee; and David Jenkins taught us to bake and decorate the most amazing peanut chocolate cake, inspired in a recipe by Nigella Lawson. David's creation looked so amazing that even Nigella herself congratulated him on Twitter!

This day full of events was followed by an evening Quiz and Scavenger Hunt, in which several prizes were handed out to people who participated on the day workshops' but also those who showed the most festive spirit in categories that included best background, best Christmas pet, most festive jumper and silliest headwear.

It was a fantastic celebration and we want to thank to everyone who was involved in the organisation of this event.

Christmas carols at The Christie

Joanne Roberts (from our BRU facility) dressed up as Rudolph and, with a group of fellow musicians, played Christmas carols in front of The Christie Hospital, bringing joy to patients, family, NHS workers and many others!



Some neighbours also walked by to listen and enjoy the festive spirit

It's pets' time!

During the different lockdowns and restrictions, pets have always been a source of happiness for many. We asked our staff to share some of their favourite pics and this is the very cute result:



David Stanier adopted Betty last September. She was a rescue from RSPCA Stockport, but now is an Instagram star (@bettywiththegoodfur)!



This is Arno, the scientist. Jackie Mitchell's cat has learnt a lot about science attending several Molecular Oncology Lab meetings and other seminars and talks!



Moo enjoying the Manchester sun! Thanks to Tim Somerville for sharing this very lovely pic!

In the Spotlight



Colin Gleeson

Colin has been the Health and Safety Manager at the CRUK Manchester Institute for over 17 years and during that time he has supported the Institute through many changes.

Alongside his regular duties of providing advice on all aspects of health and safety, which include managing the Institute's disposal of hazardous chemicals and biological agents, as well as developing policy and guidance documentation and providing training, his biggest career challenges without a doubt have been managing the aftermath of the Paterson Building fire and Covid pandemic! Colin's particular expertise in biological safety proved to be especially useful during the pandemic.

He has also made significant contributions to the design and delivery of the Oglesby Cancer Research Building and following the fire, the Paterson Building Redevelopment as well as numerous refurbishment projects.

Colin is a pleasure to work with, always looking to balance compliance and safety standards with a pragmatism to keep our research moving ahead.

- 1 **What is your favourite part of the UK?**
The Lake District.
- 2 **What was your best ever holiday and why?**
Disneyland Florida.....the kids didn't moan or complain once for two whole weeks!
- 3 **Which website do you always check, and why?**
A bit boring....but the BBC. I'm interested in news and current affairs, so I check this every day.
- 4 **What is your favourite film?**
Difficult one...it changes on a regular basis. Going back in time ... probably Spartacus. More recently, it would be Gravity with Sandra Bullock and George Clooney.
- 5 **What is your favourite band/singer?**
David Bowie.
- 6 **If you had to change careers tomorrow, what would you do?**
A hill walking or mountain guide.
- 7 **What is the most important lesson that you have learnt from life?**
To take time over things which are important and don't worry too much about the rest.
- 8 **Name three things you would take with you to a desert island?**
A knife, a flint and steel to start fires with and sun cream.
- 9 **What is your greatest fear?**
In the sea with a shark!
- 10 **How would you like to be remembered?**
As "that bloke who won millions on the lottery!"
- 11 **If you could change one thing in your past what would it be?**
Not that I'm obsessed but I'd win big on the lottery!
- 12 **What is your signature dish to cook?**
Sweet and Sour Chicken.
- 13 **You've just won the lottery and have £5 million pounds to spend. What do you buy first?**
This again!Errr.....A new house.
- 14 **What is your idea of perfect happiness?**
A day with nothing to worry about!
- 15 **What keeps you awake at night?**
Our dog and/or cat.

Editorial Team:

Steve Bagley
Gillian Campbell
Belen Conti
Ruth Cox
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

