

Newsletter

Featuring news from around the Paterson Building



CANCER
RESEARCH
UK

MANCHESTER
INSTITUTE

Winter 2013

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MANCHESTER
1824

The University of Manchester

Director's Introduction



Welcome to the new look newsletter which has been updated to coincide with the Institute's recent change of name. The rebranding of the Institute acknowledges the core funding we receive from Cancer Research UK and also recognises the generosity of our supporters. The concomitant renaming of the building to *The Paterson Building* ensures that we continue to celebrate the legacy of Edith and Ralston Paterson and the impact that they had on cancer research and treatment in Manchester.

There have been several very exciting developments over the last few months. I am delighted to announce that in September, Caroline Dive took on the role of Deputy Director of the Institute and I am sure that everyone will join me on congratulating her on this appointment. The Drug Discovery Unit performed very well at their Quinquennial review during the summer, with the result that Donald Ogilvie and his team have secured funding for their programme for the next five years. Following a successful tenure review, Tim Somerville has been promoted to Senior Group Leader and will now continue to build on the platform of basic and translational research into acute myeloid leukaemia that he has established over the last six years. We welcome Wei Xing, who joined us over the summer to head up the new department of Scientific Computing, which will provide a High Performance Computing and data management service allowing us to fully exploit the complex datasets that we obtain from the technological platforms that are now available in our core research facilities.



Caroline Dive, CRUK MI Deputy Director and Head of the Clinical and Experimental Pharmacology Group.



BRAF V600E mutant cake by Steve Lyons from the Cell Regulation Group.

The most recent success to announce is the renewal of funding from Cancer Research UK for the Manchester Cancer Research Centre. This partnership between the University of Manchester, Cancer Research UK and The Christie NHS Foundation Trust provides infrastructure and training support that facilitates interactions between scientists and clinicians with the aim of promoting better treatments for cancer patients. The next five years of funding will really help to drive the personalised cancer medicine agenda in Manchester and the North West. I would like to offer my congratulations to all involved in the renewal bid, especially MCRC Director, and CRUK MI Group leader, Nic Jones.

At the end of September, we said goodbye to two of our Group Leaders. Karim Labib has joined the MRC Protein Phosphorylation and Ubiquitylation Unit in Dundee, as well as becoming Professor of Genome Integrity at the College of Life Sciences at the University of Dundee. Ivan Ahel has moved to the William Dunn School of Pathology at the University of Oxford. His achievements over his time here were recently rewarded by CRUK with their Future Leaders' Prize which was presented to him at the NCRI conference in Liverpool. I wish them both every success in their future endeavours.

The development of the core research facilities of the Institute continues at some speed and now includes some exciting additions to the Advanced Imaging and Flow Cytometry service including installation of the super resolution gSTED microscope. These exciting technology platforms have required a good deal of enabling work to create the right environment in which they need to be housed. This has been efficiently coordinated by our Estates' team whose work is featured in this issue, along with some of the other unsung heroes from our operational staff who help to keep the building running smoothly. We are grateful to them all for their hard work.

Eve Hart joined us during the summer as our new research engagement manager and got off to a flying start with the organisation of some highly successful events, including our annual open day and several public engagement events during the Manchester Science Festival. Eve also coordinated our participation in the Great Science Bake off in which CRUK MI bakers made a very strong representation. I would have expected nothing less having observed the culinary talents of the Institute's staff over the last couple of years. There were some excellent entries but of course, I have to give a special mention to Steve Lyons for his cake depicting the BRAF mutation.

Finally as we head towards the end of the year, I would like to thank everyone for their hard work during 2013 and to take this opportunity to wish everyone a Happy Christmas and a very successful 2014.

Richard Marais
Director

Cover Image: MDCK cells forming cysts and other 3D structures in collagen, stained with β -Catenin (a basal marker, green), GP135 (an apical marker, red) and actin (blue). Image taken by Andrew Porter from the Cell Signalling group on the Institute's new 2-photon microscopy system.

Fundraising Events and Activities

By Eve Hart Keswick to Barrow

The 2013 team have just about dried off from their 40 mile walk, just in time to sign up to take part again in 2014 when registrations open after Christmas! The 2014 walk will take part on 10th May. Details of how to join the Institute's team will be announced soon.

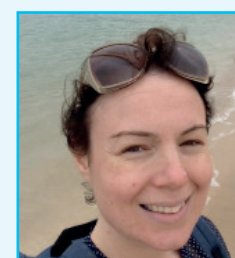
The 2013 team have presented CRUK with a cheque for £2500 for the charity. An identical amount has also been donated to The Christie Charity.

Manchester Science Festival

In October, the Institute took part in Manchester Science Festival for the first time. More than 150 people attended events in the building, including a screening of the CRUK supported documentary 'The Enemy Within'. The film looks at the last fifty years in the fight against cancer, and features Professor

Richard Marais, who chaired a discussion panel after the Institute screening on 'the next fifty years', along with Drug Discovery's Allan Jordan and CRUK's Lead Research Nurse for Manchester, Clare Dickinson. The following week, more than 60 keen science fans signed up to go 'Behind the Scenes with Cancer Research UK'. Their visit included hands on science activities, lab tours, citizen science demos and some special wow moments. These activities were part of a pilot to test whether research engagement can be used to attract new supporters to the charity, as well as to reward those who are already supporting us. Science Festival attendees were asked whether we could share news and future events with them, and more than 90 agreed.

Scientists including Rebecca Foulger from the Inositide Laboratory and Kate Smith from Drug Discovery also took part in The University of Manchester's Science Spectacular, an event aiming to share local research with families. More than 300 children and their parents extracted DNA from strawberries and learnt about targeted therapy through fun hands-on activities, far more than was anticipated as the team ran out of lysis buffer an hour before the end of the event! Kate also took part in M-cubed, the Manchester Minute Microlectures, which challenge scientists to explain their work to a lay audience in an interesting way in 60 seconds or less.



Research Engagement Manager – Meet Eve!

Eve Hart joined the Institute in May, replacing James Dunphy as CRUK's Research Engagement Manager.

James is still with the charity and is now Senior Manager, looking after the team in the North of England and Scotland. Eve is an ex-journalist and producer for the BBC, where she

managed large outreach campaigns for programmes including Stargazing LIVE and Blue Peter, and came to CRUK from the National Trust.

Eve's office, shared with the More Tomorrows fundraising team, is the last door on the left on the corridor that leads to the basement staircase to Imaging, and if you're keen to get involved in upcoming fundraising activities, on or off site, please pop in for a chat! Eve has lots of activity ideas, props to help demonstrate our science in an accessible way, and a large supply of CRUK branded T-shirts and labcoats should you be representing the Institute. Eve will be having a break from the charity in the new year to have her third baby, and her maternity leave replacement will be announced soon.

Left to Right: Super scientist certificates for young people taking part in Manchester University's Science Spectacular as part of Manchester Science Festival 2013; Dr Kate Smith showing two young scientists how to extract DNA from strawberries; the 'targeted therapy' game, in which children treated cancerous cells with bouncy ball 'medicine'; the Institute's stall at the event





Images Left to right: Live address from London from Harpal Kumar as part of the Patient Engagement event; Explaining CEP's work on CTCs with 'fluffy cells' at our Open Day; DNA replication with faulty proteins (oven gloves) at the Open Day

Research Engagement Events

It's been a busy few months at the Institute, with more than 500 fundraisers and supporters visiting to find out more about our work, and being inspired to continue supporting us. Highlights include:

- The Institute's annual Open Day. Almost 160 supporters joined us! Nine labs shared their work, along with the MCRC visitor centre. There were also talks and games, hands-on science activities, a citizen science lab and a film screening.
- A pilot event for more than 40 representatives from local companies considering making CRUK their charity of the year. The group enjoyed lab tours, including CEP, and investigating their own cheek cells under a USB microscope.
- A day-long conference, live linked with simultaneous events around the UK, in which 30 cancer patients helped inform a new CRUK strategy for including patients in its work.
- Two visits from young people from The Challenge Network, a charity working with teenagers from less affluent areas, who were inspired by the enthusiastic team from our Drug Discovery Unit.

Outside the Institute, our scientists have been out to speak to many more supporter groups, or deliver hands-on science workshops for schools and families. We even set up our own temporary art gallery in Manchester! Highlights include:

- Rachel, Denis, Angelika, Bruno and Kath from the Breast Biology group who visited CRUK supporter

and Deputy Headmaster Stephen Hill at his school in Shaw, Oldham. The group told a whole school assembly about their work before running two hour-long lessons for years 5 and 6 in which the students learnt more about cells and DNA.

- Our 'Research Gallery' at Manchester's Buy Art Fair, in which images from the Institute were curated alongside contemporary art and craft to raise awareness of our work. Thousands of visitors were exposed to our science, and many said that they'd like to put some of Steve Bagley's images on their walls!
- Caroline Wilkinson presented local buskers 'Loose Change' with a prestigious CRUK Flame of Hope award to mark their momentous fundraising efforts. In less than three years the group from Trafford have raised almost £100,000 for the charity through street performances and special concerts.

And of course staff throughout the Institute have also been working hard to raise funds for the charity. Highlights include:

- The Color Run, a new addition to the Manchester sports calendar for 2013. The event, which took part at Eastlands, was a 5K run in which participants were covered in coloured cornflour, Holi style, at each kilometer mark. An Institute team took part to raise money for the charity.
- Stand up to Cancer. A 'stand better' yoga session at the Institute, and a shoe amnesty, raised almost £200 for this year's appeal.

- The Great Science Cake Off. Some of the Institute's top bakers took to the kitchen to represent their work in sugar and jam as part of a competition between CRUK Institutes and Centres around the UK to make the best science cake. The event, which gained coverage in the US media after it was picked up on Twitter, was won in Manchester by Jonathan Tugwood whose Western Blot cake was delicious as well as having fantastic attention to detail. Anna Woroniuk was runner up with her Mitosis cake! Science cakes will be back for 2014!

Relay for Life

Congratulations to the Institute's brilliant Relay for Life team who took part in this summer's Stockport event, walking in turn alongside survivors and other local supporters for a full 24 hours straight to raise money for research.

Although other Relays around the country have CRUK scientists taking part, the Stockport event is the only one to feature a team entirely made of scientists, and the organisers are rightly very proud of this fact! Steve from the team spoke at the start of the event to tell participants and friends and family exactly where their hard-raised funds are being spent, and the team shared our science with people who'd gone along to watch, from an Institute stall. The Relay as a whole raised more than £50,000 for CRUK, a fantastic total, and the date for the 2014 event has been set as 7-8th June 2014. Please speak to Steve Lyons if you'd like to join the Institute's team.

Coming in 2014!

- 'Manchester's Cancer Research History'. Walking tours as part of Manchester Histories Festival
- Schools' Day
- Open Day 2014
- Lab tours and more!



Top: Anna Woroniuk's mitosis cake, the Science Cakes runner up!; **Middle:** Jonathan Tugwood's winning western blot cake; **Bottom:** The Relay for Life Team



Left to Right: children working with scientists to make sweetie blood soup; the Breast Biology team ready to teach St Joseph's, Shaw, all about cells; the Cancer Research UK gallery at Buy Art Fair in Manchester; Steve Bagley shares the gated STED microscope with a visiting group;

Education News

There are five students starting their PhDs in the building this autumn. Let's meet them!



Daniel Mould

I'm Dan from Manchester, although I have recently - somewhat counter-intuitively - moved across the Pennines to Huddersfield, where I live with my fiancée and kittens Alfie and George. I studied Chemistry with Industrial Experience at the University of Manchester, spending my third year undertaking research in the Drug Discovery Unit here at the Institute, synthesising novel inhibitors for our in-house projects. As the top industrial

experience student, I received a prestigious Society of Chemical Industry award. In June I re-joined the DDU, to develop small-molecule inhibitors of the epigenetic target lysine specific demethylase 1, building upon existing research conducted within DDU and the Leukaemia Biology Group. While a chemist by training, I am looking forward to learning about the fundamental biological research taking place at the Institute, however apologies in advance if I look baffled by your western blots!



Emma Williams

I'm Emma from Manchester. This summer I graduated from the University of Manchester, where I studied Medical Biochemistry. As part of my degree, I spent a placement year here at the Institute with Geoff Margison, investigating the resistance of melanoma to conventional chemotherapy in the context of DNA damage repair. I loved my time at the Institute so much that I am back here for another 4 years! This time I will be

in the Leukaemia Biology Group with Big Tim (a.k.a Tim Somervaille – a necessary nickname in L.B to distinguish between our multiple Tims). I am very excited about my PhD project, which is entitled, 'Epigenetic therapies of myeloid malignancies'. I have always had huge passion for cancer research, so I am thrilled to be studying for my PhD in a leading cancer research institute with so many talented and friendly scientists!



Kirsten Garner

Hello, my name is Kirsten and I am originally from Staffordshire. I completed my undergraduate degree in Biochemistry at the University of Manchester and went on to achieve a Biochemistry MSc where I developed a keen interest in cancer biology. I have recently begun a 3 year PhD here in the Paterson Building working with Dr Federica Sotgia in the Cancer Biology Group. I will be investigating the role of inflammation and lactation

in protection against breast cancer as part of the Breakthrough Breast Cancer unit. I feel very lucky to be part of such a successful, motivated and prestigious research group, with access to state-of-the-art facilities and world-famous academics. The University of Manchester offers great opportunities to get involved in a plethora of extra-curricular activities, and the city itself is vibrant and diverse. I am thoroughly looking forward to the next three years.



Aida Sarmiento Castro

My name is Aida, and I am from a very beautiful city called León in the north of Spain where I completed my undergraduate studies in Biological sciences. Afterwards, I came to England to improve my language skills and to work in the School of Life Sciences at the University of Warwick. My interest in cancer studies led me to join the MSc course in Molecular Pathology and Toxicology at the University of Leicester. During my master's project, I conducted research into the investigation of the chemo-preventive properties of curcumin in combination with budesonide on lung cancer stem-like cells. Subsequently, I was employed by

the same University as a research assistant further investigating the chemo-preventive properties of a synthetic flavonol known as TMFol, but on prostate cancer. Wanting to further my career I applied for, and accepted, a PhD in the Breast Biology Group led by Robert Clarke, where I will be studying breast cancer stem-like cells which are resistant to endocrine therapy, by looking at single cell gene expression. I am very happy with all the support that I have received from my new colleagues. In my free time I enjoy travelling and as I am new to the city I look forward to the prospect of exploring Manchester and seeing what the city has to offer.



Genny Filiciotto

Hi, I'm Genny and I'm from Italy. I did my undergraduate degree in Biotechnology at the University of Messina, my hometown, before moving to Torino for my MSc in Molecular Biotechnology. During my master's degree, I took part in the summer internship program at the DKFZ (the German Cancer Research Centre), where I had a chance to investigate the role of Wnt signalling in mesenchymal stem cells. That

experience sparked my interest in stem cell biology and cancer, which I am pursuing by joining the Stem Cell Haematopoiesis Group led by Valerie Kouskoff. The aim of my project will be to derive induced pluripotent stem cells from leukaemia cell lines in order to model this disease both in vitro and in vivo. Out of lab hours I will do my best to go to as many live gigs as I possibly can and to enjoy all the opportunities that a city like Manchester has to offer.



7th International PhD Student Cancer Conference

By Alekh Thapa

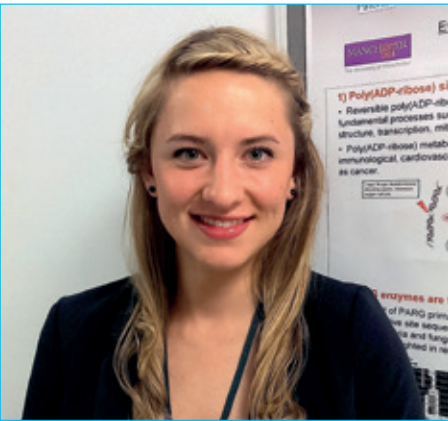
During the summer, students from the Cancer Research UK London Research Institute organised the 7th International PhD Student Cancer Conference which was held at UCL and the CRUK London Research Institute.

This year, students from research institutes around Europe came together in London to exchange ideas and discuss work. Students gave talks and presented posters on topics ranging from DNA damage and stem cell biology to signalling pathways in cancer. Our very own Eva Barkauskaite, from the DNA Damage Response Group, took home the first prize for her charismatic talk on solving the structure of PARG, what this can tell us about PARG function and how this is aiding drug development targeting PARG in cancer. Rebecca Foulger, from the Inositide Group, also gave an excellent talk presenting evidence for PtdIns5P in oxidative stress regulated AKT activity. In addition to the students, keynote speakers Lewis Wolpert and Cédric Blanpain gave fascinating talks about developmental pattern formations and stem cells in the skin.

A very interactive discussion session on the topic of open access was held with a panel including the editor in chief of Nature Cancer Reviews, a representative from The Wellcome Trust and an advocate for open access publishing. Two breakout sessions were held at the LRI Lincoln's Inn Fields site, where students could either meet former PhD students who had moved into non-academic careers or obtain information and advice from postdocs about choosing the right postdoc position after completing a PhD. The LRI students organised two evenings of events, beginning with dinner by a canal with team games on the first evening, followed by food and drinks on a boat restaurant the second evening where we were blessed with a beautiful sunset (pictured). The German Cancer Research Center in Heidelberg will be hosting the 8th annual conference in summer 2014 followed by our own students hosting the 9th in the series in 2015.

Student Success

Our students have been making a mark up and down the country, and beyond, in the past few months and this has been recognised with a number of awards.



Eva Barkauskaite presented her research to the Committee at the *British Federation of Women Graduates*, and was awarded a Second Ruth Bowden Scholarship worth £2000.

At the Faculty of Medical and Human Sciences Postgraduate Showcase at the University of Manchester, where two prizes for presentations were awarded, one academic and one peer reviewed, **Hadir Marei** walked away with the 1st Prize in both categories for her work on *Selection of Rac1 Interactors by Guanine Nucleotide Exchange Factors*.

In the meantime, **Elli Marinopoulou** won the *Young Investigator Award* at the EMBO Workshop, RUNX Transcription Factors in Disease and Development, in Germany. Elli was awarded a travel grant from the organisers of the EMBO Workshop.

Well done to all the winners!

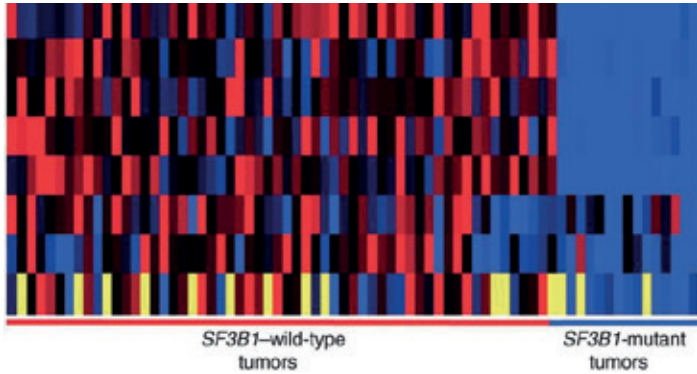
Featured Publications

Understanding the genetics of melanoma of the eye

The Molecular Oncology group, led by Richard Marais, has performed the first whole genome sequencing of uveal melanoma, a disease that affects the iris and other pigmented parts of the eye. The primary disease can be cured by radiotherapy or surgery, but its metastatic form is resistant to treatment. In a paper published in *Cancer Discovery*, they show that certain genetic mutations are associated with a better prognosis. Their findings also suggest that the DNA damage that led to the cancer is unlikely to have been caused by UV rays.

Uveal melanoma is the most common eye malignancy and has a poor outcome, with 50% of patients dying from the disease. Previous genetic studies have identified mutations in GNAQ and GNA11, which are principal driver oncogenes in this disease, and in the tumour suppressor BAP1. More recent sequencing has found mutations in SF3B1, which encodes part of the spliceosome, and such mutations are also present in haematological, pancreatic and breast cancers.

Simon Furney and the team in Molecular Oncology carried out SNP array analysis, whole genome sequencing and RNA sequencing on a set of frozen primary tumour samples. They demonstrate that uveal melanoma is a relatively simple genetic disease, with much lower frequency of structural variation when compared with cutaneous or acral melanoma. The study confirmed previous sequencing findings regarding GNAQ/GNA11 and BAP1, and showed that SF3B1 mutations are associated with alternative splicing, resulting in intron retention, alternative



Eight differentially spliced genes (rows) from 74 individual uveal melanoma samples (columns). The blue colour indicates altered splicing; red indicates normal splicing and yellow is used to represent unexpressed genes.

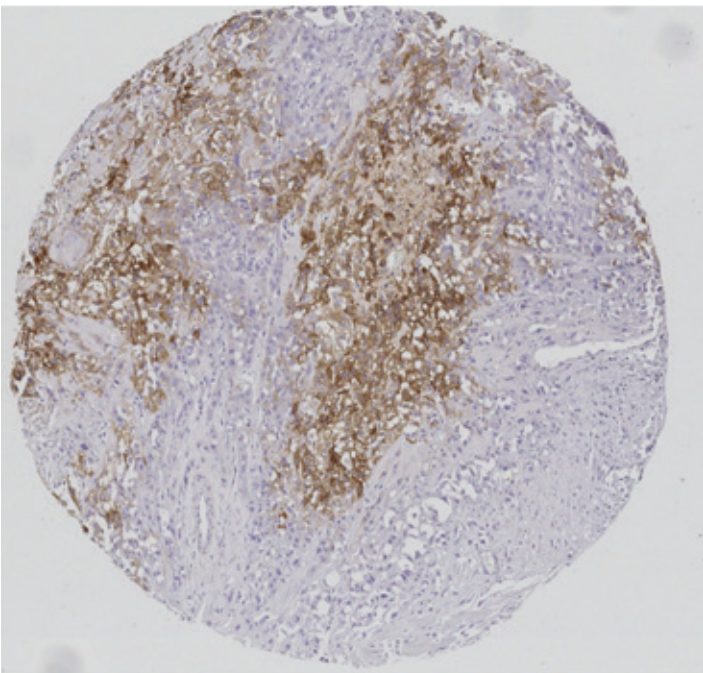
terminal exon usage and cryptic splicing. Interestingly, in contrast to chronic lymphocytic leukemia, these mutations are linked to better patient prognosis. Finally, changes characteristic of UV-induced DNA damage accounted for only ~35% of the lesions, and so they conclude that UV-induced DNA damage does not appear to play a role in the development of uveal melanoma.

Furney SJ, Pedersen M, Gentien D, Dumont AG, Rapinat A, Desjardins L, Turajlic S, Piperno-Neumann S, de la Grange P, Roman-Roman S, Stern MH, Marais R. (2013) SF3B1 Mutations Are Associated with Alternative Splicing in Uveal Melanoma. *Cancer Discovery*, Oct;3(10):1122-9. doi: 10.1158/2159-8290.CD-13-0330.

A Beneficial Signature

Research on a gene signature that could be used to personalise radiotherapy treatment has recently been published by the Translational Radiobiology group – one of the University of Manchester's Institute of Cancer Sciences groups based in the Paterson Building. Hypoxia has long been known to cause resistance to both radiotherapy and chemotherapy in tumours and the group has previously identified a 26-gene signature which can be used on clinical samples to measure the relative amount of hypoxia in tumours. Recent work, funded by Cancer Research UK amongst others, has shown that this signature was able to predict which laryngeal cancer patients would benefit from hypoxia modifying therapy in combination with radiotherapy but not those patients with bladder cancer. These results are being taken forward into a prospective clinical trial to allow the use of the gene signature in the management of patients with laryngeal cancer and modified gene signatures are being developed for those patients with bladder cancer.

The 26-gene signature was used as a biomarker of hypoxia in samples collected in two trials involving hypoxia modifying



A muscle invasive bladder tumour stained for the hypoxia marker CA-IX (brown)

agents - the accelerated radiotherapy with carbogen and nicotinamide (ARCON) and bladder carbogen nicotinamide (BCON) phase III randomized trials. In the ARCON trial, laryngeal cancer patients with a less hypoxic tumour were shown not to benefit from receiving carbogen and nicotinamide in addition to radiotherapy. However, those patients with more hypoxic tumours did show a benefit from receiving the additional agents. In comparison, bladder cancer patients in the BCON trial were shown to have a similar gene expression profile, but the profile could not be used to predict which patients would benefit from carbogen and nicotinamide. This work has shown that a relatively

simple assay suitable for use in a clinical laboratory could have an impact in the treatment of laryngeal cancer by targeting the use of hypoxia modifying therapies to those patients who would benefit from this addition to current radiotherapy.

Eustace, A., N. Mani, P. N. Span, J. J. Irlam, J. Taylor, G. N. J. Betts, H. Denley, C. J. Miller, J. J. Homer, A. M. Rojas, P. J. Hoskin, F. M. Buffa, A. L. Harris, J. H. A. M. Kaanders and C. M. L. West. (2013). "A 26-Gene Hypoxia Signature Predicts Benefit from Hypoxia-Modifying Therapy in Laryngeal Cancer but Not Bladder Cancer. *Clinical Cancer Research*. **19**(17):4879-88.

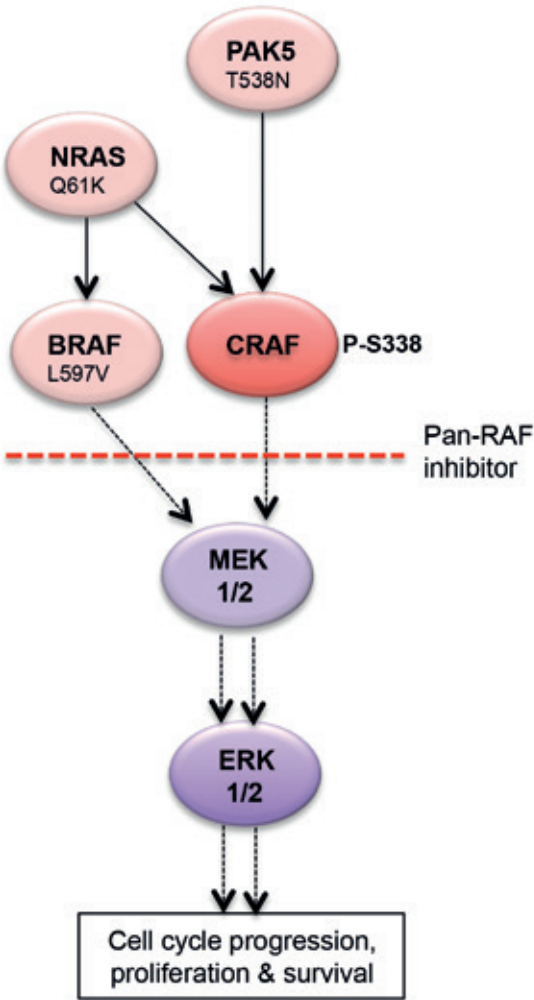
New Insights into Lung Cancer Genetics

Non-small cell lung cancer (NSCLC) is the most common and lethal cancer in the UK, with over 40,000 new cases and approximately 35,000 deaths each year. Disturbingly, Manchester experiences the highest incidence and mortality rates for lung cancer in the whole of England and Wales. An overwhelming 70% of NSCLC patients present with late-stage disease. Unfortunately, these patients have limited treatment options and the five-year survival rate is less than 10%. While survival rates for certain types of cancer have dramatically improved over the past few decades, only marginal improvements have been observed in NSCLC and it has one of the lowest survival rates. There is an urgent need to develop efficacious targeted therapies to improve overall survival. Until now, this task has presented a major challenge as the underlying genetic causes of almost half of NSCLCs remain unknown.

In a recent paper published in PNAS, Shameen Fawder and John Brognard of the Signalling Networks in Cancer Group describe a new efficient screening strategy that can identify genetic mutations in tumour cells that are potential biomarkers and possible future targets for therapeutic intervention. Protein kinases are the key regulators of signalling pathways, responsible for normal cell growth and differentiation. When kinase activity is altered by genetic mutations, they become the main drivers of tumourigenesis, causing unregulated cellular proliferation and survival.

This exciting paper explains how an innovative genetic dependency screen can identify unique mutationally activated drivers of lung cancer. In this ingenious approach, NSCLC cells containing somatically mutated genes are depleted and alterations in cell survival and proliferation are monitored in an attempt to detect mutations that are likely to be robust drivers of lung cancer. This method relies on the proposition that knockdown of a mutationally activated driver will result in a vigorous increase in cell death and inhibition of proliferation.

They identified three novel kinases with mutations in lung cancer. Significantly, targeted depletion of these kinases inhibit proliferation and result in the death of lung cancer cells, suggesting that they are potential targets for precision cancer drugs that block specific molecules in tumours. This technique



Scheme illustrating the consequence of the PAK5 mutation identified in this study. The mutated version of PAK5 has increased activity towards CRAF resulting in increased activation of the ERK pathway. Cell death can be promoted in these cells by treating with a pan-RAF inhibitor.

represents a potential important step towards the personalised treatment of lung cancer patients.

Fawdar S, Trotter EW, Li Y, Stephenson NL, Hanke F, Marusiak AA, Edwards ZC, Ientile S, Waszkowycz B, Miller CJ, Brognard J. (2013) Targeted genetic dependency screen facilitates identification of actionable mutations in FGFR4, MAP3K9, and PAK5 in lung cancer. *Proc Natl Acad Sci U S A*, **110**(30):12426-31.

“Switching” to new cancer biomarkers

The journal “Cell Death and Disease” recently featured work by the Clinical and Experimental Pharmacology (CEP) group on finding new ways of determining if anti-cancer therapies are working. The group triggered a synchronised wave of cell death in a tumour by altering a component of the cells’ own intrinsic suicide programme and measured the proteins released. They then went on to identify those proteins which could be found in a blood sample and used as specific markers of cell death following therapy. In addition, they used their model to evaluate a novel imaging probe which could be used in positron emission tomography (PET) to image tumour cell death.

The ability to determine if a therapy is successful is a critical part of clinical trials but with many cancers this is only possible either by invasive surgery, biopsies or expensive imaging techniques. As a result the ability to detect drug action in the bloodstream of the patient has been attempted on many occasions. As many cancer therapies work by inducing cell death in the tumour, CEP established a model system – the “death-switch” - by which they could control the timing and extent of cell death induced in a tumour. In order to do this, cancer cells were manipulated so that a key component of the apoptosis (a specific type of cell suicide) pathway was expressed and activated upon exposure to doxycycline. This induced wide spread and synchronous apoptosis in colorectal cancer cells in the lab and allowed the

group to use proteomic methodologies to identify proteins released from the cells undergoing apoptosis. Four of these proteins were further validated using western blotting and ELISAs before the system was tested *in vivo*. The death switch was found to induce regression of tumours with the release of the previously established biomarker cytokeratin 18 and confirmed the results observed *in vitro* with CD44 and HMGB1 being released into the bloodstream upon induction of apoptosis. To further demonstrate the utility of the death switch model, PET imaging was carried out on tumours before and after activation with the novel agent [¹⁸F] ML-10, the first imaging agent to reach phase I/II clinical trials for the imaging of cell death. This revealed that a significant increase in [¹⁸F] ML-10 occurred following induction of cell death. In summary, CEP have reported a novel model for the identification and validation of cell death biomarkers for future use in clinical trials.

Simpson KL, Cawthorne C, Zhou C, Hodgkinson CL, Walker MJ, Trapani F, Kadirvel M, Brown G, Dawson MJ, MacFarlane M, Williams KJ, Whetton AD and Dive C. (2013). A caspase-3 ‘death-switch’ in colorectal cancer cells for induced and synchronous tumor apoptosis in vitro and in vivo facilitates the development of minimally invasive cell death biomarkers. *Cell Death Dis* 4: e613.

MI-FLS away day

The first joint Cancer Research UK Manchester Institute – Faculty of Life Sciences away day was a tremendous success.

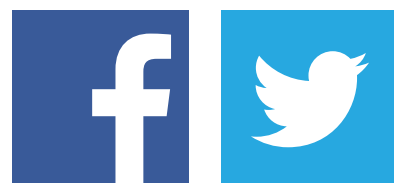
The event, held at the Manchester Conference Centre on 12 September 2013, was attended by 70 researchers from across the two sites. Group leaders, Lecturers and Post docs all enjoyed the programme of fascinating talks presented by Angeliki Malliri, Iain Hagan, Wolfgang Breitwieser, Valerie Kouskoff, Crispin Miller and John Brognard from our Institute, along with Stephen Taylor, Andy Sharrocks, Cathy Tournier, Dean Jackson, Adam Hurlstone and Claudia Wellbrock from FLS. Topics ranged from the role of mitosis and transcription factors in cancer cell death, cell signalling in pancreatic and lung cancer, melanoma biology, and the application of bioinformatics and imaging techniques to analyse cancer genetics. The day provided a great opportunity for colleagues to interact, find out more about each other’s current research interests and, importantly, to share ideas. The day ended with a sociable drink and promises to make this an annual event. Feedback was enthusiastic, with Angeliki Malliri commenting that “I thought the away day was excellent, the scientific programme, the venue, everything! We should repeat it.” Cathy Tournier also praised the event, stating that it was “An excellent away day. I hope that we can organise a similar event once a year.”

Shameem Fawder’s poster on Elucidation of novel activating drivers of lung cancer won the Poster Prize at CRUK’s Postdoctoral Career Development Day. Shameem has been awarded £1000 towards a conference of her choosing.

Social Media

Want to keep up to date with the latest news from the Cancer Research UK Manchester Institute?

Check out our recently launched facebook account and twitter feed (@CRUK_MI). You can get the latest news about research engagement events by following Eve Hart (@CRUKManchester).



Recent Awards and Events

Members of the Institute travelled to Lancaster University this September for the 20th annual Paterson Colloquium.



Dan Wiseman (L) and Romina Girotti (R) were presented with the prizes by Institute Director, Professor Richard Marais.

The event marked some changes for the Institute, and in his final Colloquium before moving to Dundee, Karim Labib opened the first session by summarising the Cell Cycle group’s research into aspects of chromosome replication. Their work in budding yeast has highlighted the role of a particular protein in the disassembly of DNA. Understanding this crucial stage of chromosome replication is important to those working on novel anti-cancer therapies, as it is a process often disrupted during the development of cancer. His fascinating presentation was followed over the three days by excellent talks from both students and group leaders, highlighting the breadth of research taking place within the Institute.

In addition to these talks, there were two poster sessions. To mark the end of the Colloquium, poster prizes were awarded, and these went to Daniel Wiseman and Romina Girotti. Romina is a post-doctoral research fellow in the Molecular Oncology group and won the prize for best poster presented by a Post-doc/Scientific Officer, for her work on new agents to overcome drug resistance in melanoma. In around 40% of melanoma cases there are mutations in the BRAF gene, and BRAF-targeting agents show great response in these tumours. However, after a short period of disease control, drug resistance is quickly developed. She found that several new drugs are active against tumours that have resistance to existing treatments, and therefore have the potential to improve survival in this disease.

Dan is a Clinical Fellow based in the Leukaemia Biology group and received the Lizzy Hitchman prize for the best poster by a student for his work investigating a potential test to predict relapse in Acute Myeloid Leukaemia (AML). Relapse is the primary obstacle to long-term survival in this disease, and identifying risk of relapse could offer the opportunity for pre-emptive therapy. Dan focused on a particular molecule that accumulates in AML cells, and found that levels of this within the plasma were linked to remission, and could be used to reliably predict early relapse. This test could therefore be used to plan more individualised treatment for patients.

International Symposium on Minimal Residual Cancer - Poster Prize

Congratulations to Ged Brady, Dominic Rothwell and Debbie Burt of the Clinical and Experimental Pharmacology Group, who received 1st prize for their poster presentation at the 9th International Symposium on Minimal Residual Cancer, held this September in Paris. Their award-winning poster showcases a protocol for transcriptional profiling of circulating tumour cells (CTCs). They describe a novel and robust methodology for the accurate amplification of RNA from a single cell. This technique will be important for CTC analysis, advancing our understanding of the biology of metastasis and potentially enabling the development of minimally-invasive biomarkers to evaluate tumour progression and response to treatment.

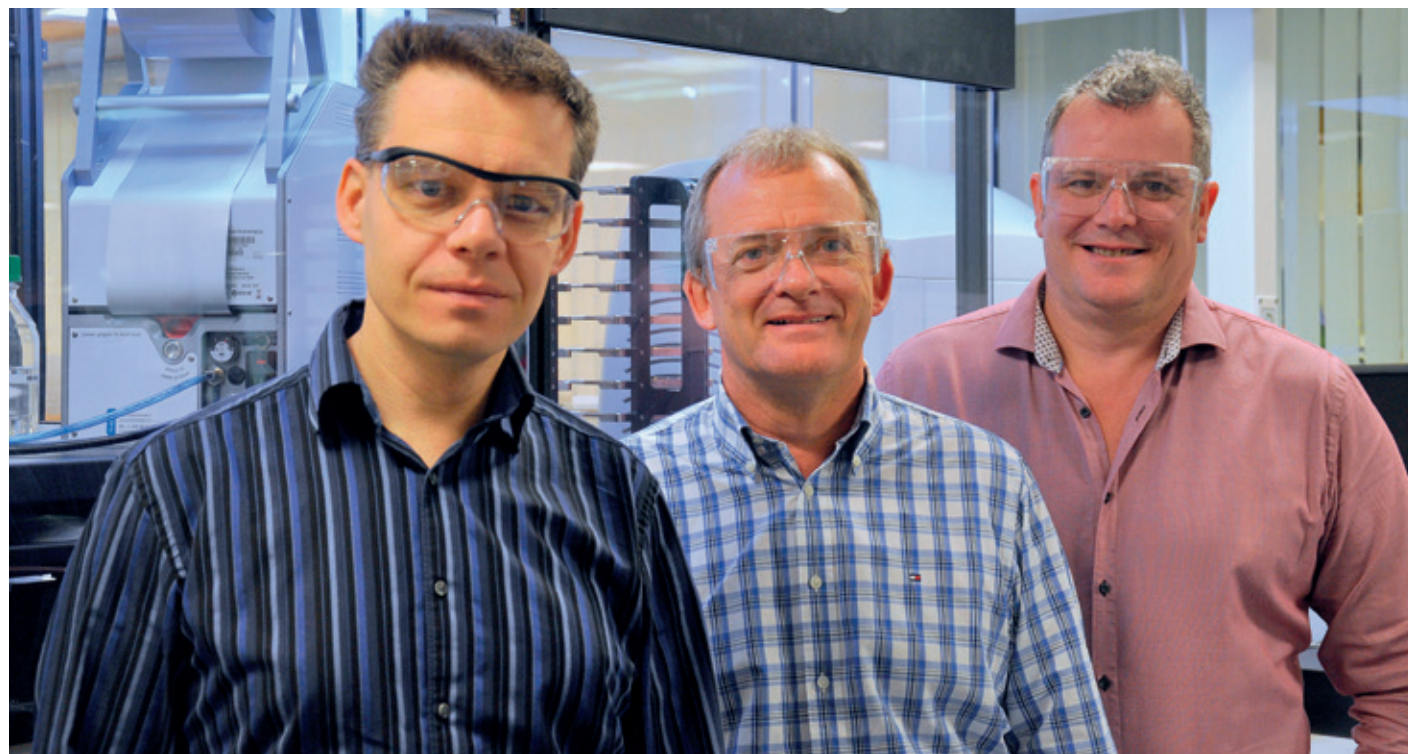
Cancer Research UK Future Leaders Prize

We are delighted to announce that Ivan Ahel was recently awarded the prestigious Cancer Research UK Future Leaders Prize at the 2013 NCRI Conference in Liverpool.

Ivan has been a Junior Group Leader at our Institute since 2009, leading a team of scientists investigating the mechanisms of DNA damage processes and their potential for cancer therapy. Throughout his career, Ivan has made many original and noteworthy contributions to his field of research. In September of this year, Ivan joined the Sir William Dunn School of Pathology at the University of Oxford, where we wish him well in his continued research.

Successful Collaboration: the Way Forward for the Drug Discovery Unit

By the Drug Discovery Unit



From Left to Right: Allan Jordan (Head of Chemistry, DDU), Donald Ogilvie (Head of the DDU) and Ian Waddell (Head of Biology, DDU).

The last twelve months have been an incredibly busy time for the Drug Discovery Unit (DDU), including a successful quinquennial review which has guaranteed our next five years of funding, the publication of eight papers in quality peer reviewed journals, the rapid progression of our portfolio, and the signing of our first two collaborative deals with potential clinical development partners.

History of the DDU

The DDU was set up in the Cancer Research UK Manchester Institute in February 2009 by Donald Ogilvie. His first task was to develop a strategy for the next five years, including recruiting a Head of Chemistry, Dr Allan Jordan, then a Head of Biology, Dr Ian Waddell, and most importantly, building a state-of-the-art, streamlined drug discovery laboratory. A fully functional laboratory was unveiled in January 2010 and the process of creating a viable drug discovery portfolio began in earnest.

Progress

Since 2010, the DDU portfolio has made excellent progress with two projects moving into the lead optimisation (LO) stage of drug discovery. One of these, a DNA repair target, is already partnered with AstraZeneca (AZ) and will be disclosed for the first time in a presentation at the American Association for Cancer Research (AACR) Annual Meeting in San Diego in April 2014. We are actively seeking partners for the other (lung based) LO project and hope to announce something in the coming year.

In addition to the two LO projects, we are vigorously pursuing three other novel targets in the early phases of drug discovery and are actively engaging in the validation of several other targets with group leaders in the Institute.

Collaboration

From its very inception, as an output of the 2009 Cancer Research UK Drug Discovery Strategy, the DDU has known that collaboration would be the cornerstone of its success. Its very placement at the hub of the Manchester Cancer Research Centre, located in the Paterson Building with access to the Christie NHS Foundation Trust (the Christie), was built on a desire to collaborate. The primary aim of the DDU is to help translate the world-leading basic oncology science carried out by principal investigators at the Cancer Research UK Manchester Institute and to develop therapeutic strategies with renowned oncologists at the Christie.

Our focus in the DDU has always been on targets with a clear clinical line of sight. In all we have looked at 116 potential oncology targets, however our strict target selection criteria means that we have only reviewed 28 in detail and narrowed those down to 15 targets. Of these, five are currently active, six have recently been closed, and the remaining four are progressing with help from external sources. As with all drug discovery efforts, one of the biggest challenges we face is fully validating the target biology. Of the six projects we have closed,

five were because we could not repeat experiments published in quality peer reviewed journals.

We have collaborated on targets generated by key Group Leaders at our Institute, including Tim Somervaille, John Brognard, Ivan Ahel, Karim Labib and most recently, Iain Hagan. We have also worked with Principal Investigators beyond the Manchester Institute including Keith Caldecott's group in Sussex, Andy Ryan at Oxford and Luca Pellegrini at Cambridge.

Technical Collaboration

It is not just at a scientific level that we collaborate. Working alongside Labcyte Ltd, we have adapted their acoustic dispensing technology and Access robotic platform to develop a fully automated assay system that allows us to run medium throughput assays of up to 20,000 compounds through a variety of biochemical and cellular assays. We are unique in the Manchester Institute in adopting an electronic lab notebook system that is backed up and fully searchable. This has been achieved through continual development of the Dotmatics system.

Industrial Partners

When we set up the group we always knew that we would need to seek partners from the pharmaceutical and biotechnology industries to help us achieve the latter stages of the drug discovery process, such as safety testing, bulk compound synthesis and pre-clinical testing. We were therefore delighted to announce our first two industrial partnerships with AstraZeneca in May this year. The first deal involves a DNA repair target of joint interest, where both partners have identified compound leads. Crucially, AZ solved the human crystal structure and has co-crystallised it with one of their compounds. In fostering a partnership, this information has been made available to the



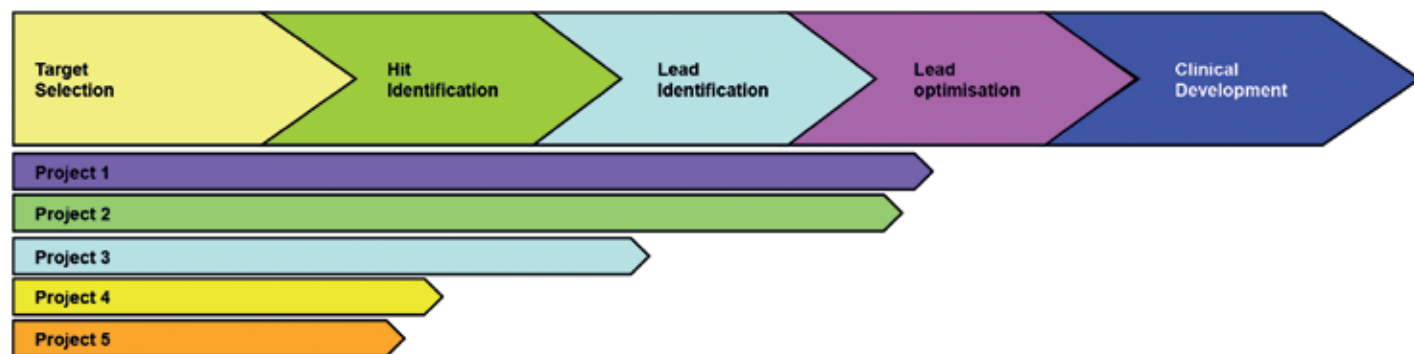
Nicola Hamilton in action using a robotic platform that allows highly accurate dispensing of compounds.

DDU, enabling our chemo-informatician, Bohdan Waszkowycz, to model potential novel interactions within the active site of the protein. Consequently, our biologists and chemists have made superb progress and this target is now one of our leading projects. The second deal involves a target initially progressed at the Manchester Institute that is of interest to AZ. In a ground-breaking deal, the DDU has been granted access to screen AZ's 1.5 million compound collection using the robotics and orthogonal assays available at Alderley Park, with the resultant hits being progressed in the DDU.

Just this month we have finally signed two more highly significant collaborative deals. The first collaboration is with GlaxoSmithKline (GSK), which again allows the DDU access to the high throughput



The Drug Discovery Unit



The current pipeline for the DDU's projects.

screening (HTS) power of large pharma on a target of mutual interest. The second deal is with HitGen, a Chinese biotech company based in Chengdu, which provides an excellent opportunity to utilise a unique hit identification technique based on DNA encoded libraries.

Publications

The Keith Caldecott collaboration for a DNA damage and repair programme led successfully to the publication of three DDU articles, one of which featured in the Journal of Medicinal Chemistry in July of this year. This article describes the discovery of novel human tyrosyl-DNA phosphodiesterase 2 (TDP2) inhibitors for the treatment of non-small-cell lung cancer (NSCLC). The TDP2 publications form part of the successful outcomes of external collaborations. Publications derived from internal collaborations have also been a feature of DDU's achievements over the past five years. In particular, interactions with Tim Somervaille and the Leukaemia Biology Group resulted in the publication of an article in Analytical Biochemistry which described the development of a novel, rapid cell-based assay that reads out enzymatic inhibition of the histone demethylase Lysine-specific demethylase 1 (LSD1) linked to human acute myeloid leukaemia.



DDU chemists in action: Kate Smith and Alison McGonagle.

The Next Five Years

It has been a very successful first few years for the DDU. Our ambition over the next five years is to deliver the first candidate drug whilst maintaining a viable portfolio of drug discovery targets. Given our size this is a challenging target but one that we believe is achievable through collaboration both inside and outside Cancer Research UK.



Wei Xing

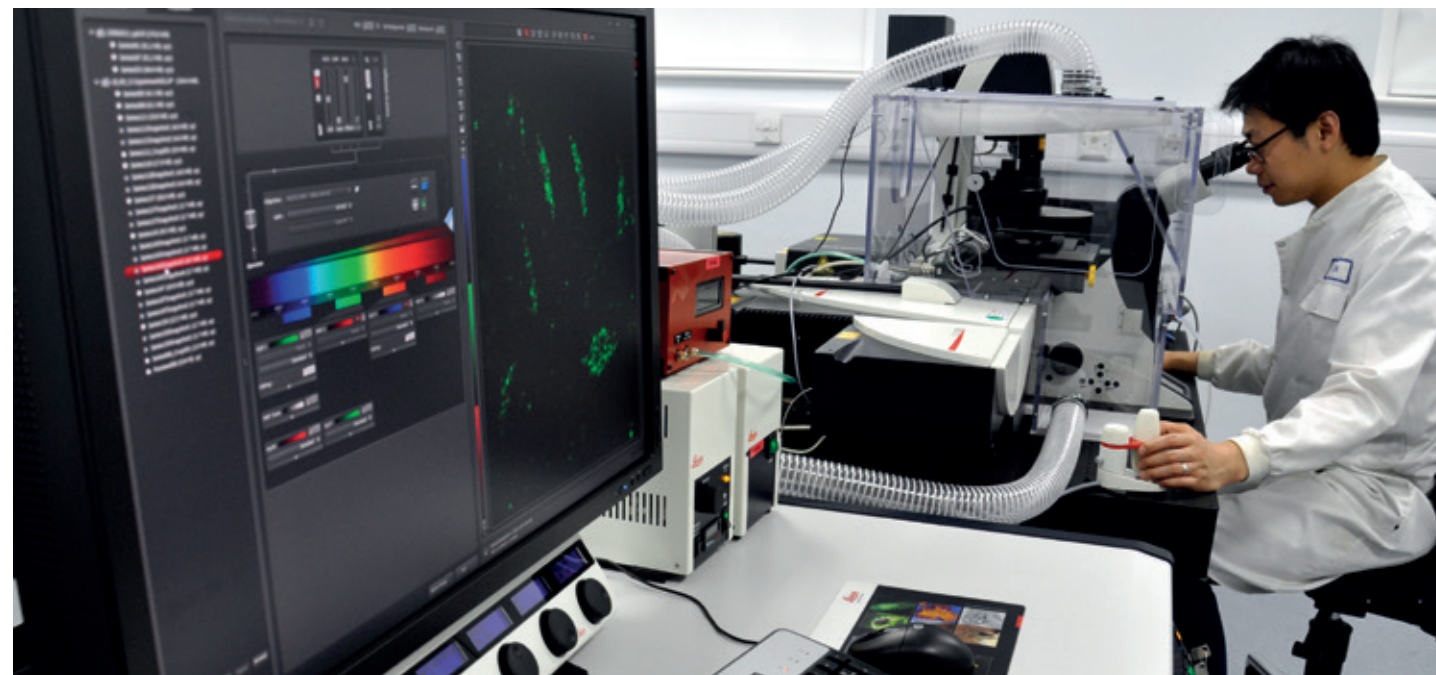
The Institute Welcomes Wei Xing

Wei joins us from the Institute of Cancer Research to become the Head of Scientific Computing. The newly created department of Scientific Computing has the specific purpose of providing a state-of-the-art HPC (high performance computing) and large-scale data management service. The CRUK Manchester Institute will benefit greatly

from the valuable expertise provided by Wei and his team in Scientific Computing that will support and advance our translational cancer research.

Wei's primary focus will be to provide the underlying infrastructure needed for large-scale cancer data integrative analysis, intelligent bio-computing platforms and integrative network biology, all of which he is eager to help develop within the Institute. Wei says that "HPC has become a pre requisite for the proper exploitation of cancer genomics data, in part, a consequence of the high volumes of data produced by recent advances in deep sequencing, imaging, and mass spectrometry. These have the potential to revolutionise translational cancer research and to offer new therapeutic strategies for personalised and stratified medicine". Zhi Cheng Wang has joined the Scientific Computing department from the Institute's IT team.

Developments in the Research Facilities



Haoran Tang from the Molecular Oncology group with the gSTED system.

From Micro to Nano-scopy

A new super-resolution microscope has arrived in the Institute, which allows nanoscale molecular imaging and has already started to generate some fascinating data.

The gated Stimulated Emission Depletion (gSTED) system consists of diffraction limited laser beam, which is centred down the middle of doughnut shaped laser (ring not jam!) The inner beam excites a label attached to the structure of interest whilst the outer beam deactivates. This on/off imaging results in a microscope resolution that previously was impossible to attain using photons, approaching a 28-35nm resolution. Considering

an antibody:antibody:fluorophore is around 40nm in size, the resolution provided by this new technology is greater than current labelling technologies and traditional imaging methods.

Already the system has proven itself capable of imaging individual molecules that make up microtubules and has been employed to explore the anatomy of adhesion complexes. It is hoped that this new technology will permit methods that will allow greater fidelity when imaging viable cells.

The equipment and development of a room that is isolated from vibration and air currents (which adversely affects the system) was generously funded by the Manchester Cancer Research Centre and the Cancer Research UK Manchester Institute.

Population to Numbers

Flow Cytometry is based upon microscopy techniques of illumination whilst combining fluidics technology to sort and analyse cells. Over the years the number of parameters that can be measured from a single cell, and the number of sub-populations that can be created have increased dramatically; however the principle technology of recording whether a label is present or not in the entirety of a cell, has remained the same for fifty years. Traditionally, microscopy offered resolution and detail whilst flow cytometry offered speed and statistically robust results.

The Amnis ImageStream has recently been introduced into the Institute. This instrument combines classical flow cytometry with high content screening techniques, allowing every cell in

a population to be analysed at a sub-cellular level of resolution. Whereas with classical flow cytometry, if two labels are present in the same cell, then a positive is recorded with the ImageStream and both labels can be assessed for co-localisation. The present installation has seven lasers which can record up to 12 channels of information and allows up to 5000 cells per second to be analysed at a range of magnifications up to x400.

The equipment, which is run to Good Clinical Practice Laboratory standards, is housed in the Clinical and Experimental Pharmacology (CEP) basement laboratory, and ensures that the system performs within acceptable levels of illumination and detection. The equipment is run by four members of staff, two from CEP and two from the Imaging and Cytometry facility, whilst day to day standardisation and trend analysis is carried out by Jeff Barry.

Staff News

New Arrivals

There have been a number of recent new arrivals for a few members of staff.



A sleepy Wilbur Gene
Amanda Williamson (Translational Radiobiology) and her husband Ross have celebrated the birth of their baby boy, Wilbur Gene.



Olivia Bobbi Jones
Laura Jones (HR Advisor) gave birth to a baby girl, Olivia Bobbi Jones at a healthy 9lbs.



Nathaniel Tugwood at 5 weeks old
Jonathan Tugwood (CEP) and his partner Val became parents to Nathaniel Joseph Tugwood. Nathaniel was initially rushed to Alder Hey hospital for emergency heart surgery, but fortunately the operation went well and baby Nathaniel is recovering at home.

Wedding Bells



Adam and Zara on their wedding day
Adam Freestone got married to Zara at Gawsworth Church in Macclesfield, with a reception at the charming Bridge Hotel in Prestbury. To round off what will undoubtedly be the most memorable year for Adam, he is due to be a father for the first time on New Year's Eve!



Steve and Kath boarding the steam train
Steve Morgan married his lovely bride Kath at Ramsbottom Civic Hall in the summer. The wedding party arrived by steam train where they enjoyed champagne and canapés, and later on Steve entertained the guests by singing while dressed up as Rod Stewart!

Summer Party

Earlier on this year, the Institute held its first ever Summer Party in the garden of a local pub. The event was a chance for all staff to take an evening off and enjoy the company of their colleagues away from their desks and laboratory benches.

It was a splendid summer evening with plenty of laughter, jugs of refreshing Pimms and of course factor-30 sunscreen to protect us from the beautiful Manchester sunshine!

The party was a wonderful success, during which Stuart Pepper, our Chief Laboratory Officer, was presented with his Flame of Hope Special Commendation Award in the Research Engagement category. The award, from Cancer Research UK, celebrates and recognises the exceptional contribution and achievements of dedicated CRUK ambassadors and volunteers.

Stuart Pepper was nominated for the award due to his passion and outstanding dedication to the charity. Stuart is always happy to volunteer his time and knowledge for the charity, above and beyond his role as Chief Laboratory Officer, and this award is a small token of recognition. CRUK has always depended on the outstanding dedication and commitment of its supporters who, like Stuart, are willing to go the extra mile to fundraise, educate and spread the word for cancer research.



Stuart Pepper with his award



We asked James Dunphy, CRUK Senior Research Engagement Manager why he nominated Stuart for the award, and this is what he had to say:

Stuart is a fantastically passionate communicator of our research, regularly acting as an ambassador for the charity.

He communicated at a wide variety of events over the last year, with a range of audiences and he always ensures his message is tailored appropriately. This includes hosting 12 lab demonstrations (some of which are held on evenings and weekends), for around 150 supporters, supporting the Institute open day, running a practical workshop for local sixth formers, and attending Race for Life and Shine. Feedback from those who have met him always highlights Stuart's passion and breadth of knowledge.

Stuart demonstrated fantastic flexibility and commitment to the charity above and beyond his normal role, through his support of last year's Shine event. At very short notice he deputised for a member of staff and acted as the Pit-stop Manager for the Institute. This involved working through the night, setting up the pit-stop, erecting marquees and tables, making flasks of tea, managing and motivating 20 volunteers, whilst offering kind words of encouragement to the 2000 marathon walkers who passed by. His passion and enthusiasm was appreciated by both the walkers and volunteers, ensuring they were fully energised throughout the night.

Operations News

In this section, we catch up with some of the teams who help keep the building running smoothly. First, Health and Safety Manager, Colin Gleeson, explains how “near miss” reporting can contribute to the maintenance of a safe working environment for all.



Colin Gleeson

Health and Safety

By Colin Gleeson

An accident is an undesirable event which can result in loss or damage to the building or equipment; injury; or even

death. A ‘near miss’ refers to any incident that does not have an adverse outcome. The main concern around near misses is the potential for damage or injury if the incident was to re-occur. For this reason, it is equally important to report near misses as it is to report accidents.

A near miss report will trigger an investigation of the event to determine the cause and prevent re-occurrence, and also detect any patterns between incidents so that possible weaknesses in operational procedures can be rectified. Some near misses are considered more serious than others as the potential consequences are extremely dangerous. Such incidents are reportable to the Health and Safety Executive (HSE). Unfortunately, we had such an incident recently where a pressurised liquid nitrogen vessel vented its contents causing a low oxygen atmosphere in the room. On this occasion the low oxygen alarm was activated so thankfully no one was harmed. But there have been notable incidents in other research establishments where fatalities have occurred due to similar incidents. Our investigation of this incident resulted in additional training for some and additional personal low oxygen alarms for ‘end users’ who dispense liquid nitrogen from pressurised vessels.

Estates Projects

By Steve Alcock

Numerous and varied projects have been accomplished by the Estates team over the last twelve months to provide a safe and comfortable working environment for everyone in the Paterson Building. The Estates team comprises Steve Alcock, Graham Hooley, Lewis Parkinson and Tony Woollam and have carried out tasks ranging from replacing the 250 Kilowatt chiller which supplies the basement area, to simple office refurbishments, including new lighting, ceilings, carpets and decoration.

One of the larger and more complicated projects recently undertaken was to modify office accommodation on the ground floor into laboratories. The most demanding challenge was to provide a solution to the stringent temperature parameters required by the sensitive microscopy systems to be housed in these rooms, which was achieved by installing an air-conditioned, ventilated ceiling. Close collaboration and careful discussions with all parties involved ensured the modified environment was fit for purpose.



The new cold room in Lab services

Another interesting project was to provide a new cold room facility for the Laboratory Services department. Through careful planning, the cold room has been ‘future-proofed’, should it be needed for a different purpose, by installing several power points within the room.



The Logistics Team: (L-R) Maurice Cowell, Sedia Fofana, Jonathan Lloyd, Andy Lloyd. Also in the team: Edward Fitzroy, Antony Griffin and Stephen Keane.

The Logistics Team

By Maurice Cowell

The Logistics Department provides an efficient and vital role in supporting the research carried out at the Institute. This includes the receiving, checking, booking in and distributing of goods as well as collecting and correctly disposing of waste - be it general rubbish, yellow bags or genetically-modified waste. We also manage the moving of heavy equipment or furniture, and set up various meeting rooms for numerous events.

As a department we are responsible for the ordering, delivery and changing of cylinder gases, liquid nitrogen and dry ice. Additionally, we manage the spirit stores where laboratory solvent waste is taken on a weekly basis, organised and disposed of as and when required.

Ordering and distribution of the Central Stores stock ordered via the intranet is also our responsibility and we ensure adequate stock levels are maintained at all times. This includes the media and enzymes stored in the Institute freezers. We are always looking for the best prices and often change suppliers to ensure that this is the case. We have been able to make savings by assessing our gas cylinders and cutting down on certain gas ones thus decreasing rental charges.

We work with all groups to trace and confirm delivery of goods with suppliers, and deal with missing, damaged or wrong items. We are always looking to improve the way we work to benefit the Institute.

FUN FACT

Did you know that the Institute uses up to 90,000 litres of liquid nitrogen each year to keep stocks of cells frozen at minus 196°C.

In the spotlight with Gill Campbell



Gill is the Grants Advisor for the researchers at the Cancer Research UK Manchester Institute. It is her role to support applicants throughout the whole application process, from identifying potential funding opportunities to coordinating peer reviews. The ultimate aim is to increase the number of successful applications that the Institute submits. This supplementary funding is necessary to carry out the full breadth of research that we wish to

undertake. Gill is also involved in scientific administration for the Institute, which includes writing articles for the Newsletter and our website.

1. What is your favourite part of the UK?

Wastwater in the Lake District National Park

2. What was your best ever holiday and why?

Touring Australia – swimming in the sea, exploring tropical forests, visiting vineyards and meeting the most unusual fauna on the planet

3. Which website do you always check, and why?

BBC weather – my journey to work involves a lot of walking

4. What is your favourite film?

Tough...but today I will say Pale Rider

5. What is your favourite band/singer?

Jeff Buckley had an amazing voice and wrote hauntingly beautiful lyrics – why do the good ones die young?

6. If you had to change careers tomorrow, what would you do?

I adore the outdoors so being a Nature Reserve Warden would be perfect

7. What is the most important lesson that you have learnt from life?

Worrying is a waste of life

8. Name three things you would take with you to a desert island?

My Kindle, sun cream and a box of vegetable seeds

9. What is your greatest fear?

Stepping stones! Ludicrous but true – I have an intense fear of falling off/down things

10. How would you like to be remembered?

As a caring, reliable and easy-going person

11. If you could change one thing in your past what would it be?

I am who I am because of my past, so I don't really want to change anything, although more self-confidence would have been good

12. What is your signature dish to cook?

I don't have a signature dish as I love 'creating' different dishes (mayhem), but my hot and spicy chick peas are appreciated

13. You've just won the lottery and have £5 million pounds to spend. What do you buy first?

After paying off the mortgage, a holiday home in Italy... or France...

14. What is your idea of perfect happiness?

Walking in the hills in a (dry) autumn with my (yet to be attained) hairy dog(s), with the anticipation of a roaring fire, a glass of red and a tasty meal at the end of it

15. What keeps you awake at night?

Global overpopulation

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