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 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 organisation of some highly successful events, including our annual open day and several public engagement events during the Manchester Science Festival.

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

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

Feature Article - 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 and be 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 Lyons.

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.
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.
- Lab tours and more!
- Ancient Histories Festival - ‘Manchester’s Cancer Research History’. Walking tours as part of the Manchester Histories Festival.

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.
- 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.

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

- 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.
- The 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.
- Labs tours and more!
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 chemist 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 undertaking research in the Drug Discovery Unit and the Leukaemia Biology Group with Big Tim (a.k.a Tim Somerville – 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!

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 Somerville – 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 at the Paterson Building working with Dr Federica Sorta 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 Leon 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-protective 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 Filiotti
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 DFKZ (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.

Student Success

Our students have been making a mark up and down the country, and beyond. In the past few months, 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 Rac Interactors by Guanine Nucleotide Exchange Factors.

In the meantime, Elii Marinopoulou won the Young Investigator Award at the EMBO Workshop, RUNX Transcription Factors in Disease and Development, in Germany. Elii 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 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.


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 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.


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 NSCLC’s remain unknown.

In a recent paper published in PNAS, Shamine 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 mutually 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 mutistically 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 inhibited 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 represents a potential important step towards the personalised treatment of lung cancer patients.

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 established biomarker proteins were 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 postradiation 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 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 suicide programme and established biomarker cytokeratin 18 and confirmed the results observed in vitro with CD44 and HMGBl 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 [18]F-M-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 [18]F-M-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.


**Recent Awards and Events**

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

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 Grotti. 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

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, Karm 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 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 screening of compounds.
specific demethylase 1 (LSD1) linked to human acute myeloid
leukaemia. Described the development of a novel, rapid cell-based assay
which reads out enzymatic inhibition of the histone demethylase Lysine-
desinhibitors 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
from 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.

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
from 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.

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.

From Micro to Nano-scropy

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 photos, 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 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.
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.

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.
**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 were 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.

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 new cold room in lab services

**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