A time of remembering and glimpses of the Hutch in spring

A journey down memory lane and a time to wish them well …

The MRC Cancer Unit was sad to say goodbye to its Unit Manager, Maria Dasseville, who has now retired.

Maria has spent 24 years working for the MRC, initially at the Cancer Trials Unit and then for the Cancer Unit since its inception.

Maria was in fact the first member of staff recruited for the Cancer Unit. She set about recruiting, training and establishing the HR, finance and general admin teams. Maria was heavily involved in setting up key essential systems of work, organising the support team infrastructure, supporting the Director in establishing the new scientific teams of the Unit – a mammoth task which she performed with great skill and dedication. Getting the Unit operating effectively, providing first class support to the scientific teams was down to Maria and her leadership of her team.
Maria’s hard work and leadership skills came again to the fore during the highly complex and successful move of the Unit into the University in 2013 which was achieved in record time. Maria’s experience and abilities have been recognised both within the MRC and the University, when she has been seconded to help with corporate wide initiatives for both organisations. Maria continued in her role, building and evolving the team as the Unit grew, be it towards staff numbers and funding levels or towards managing risks and ensuring best practice and compliance – a feat that no doubt was key to the Units consistent high performance at audits and league tables.

Today as the time has come to say goodbye, we would just like to say thank you and that she will be greatly missed. We wish her all the very best for the future!

The x5 has a new driver!

On a theme of goodbyes, the Cancer Unit wishes every success to Matt McAusland who moves on to newer adventures at the Department of Medicine. The tradition of ever friendly advice and support for those never-ending grant applications continues in the safe hands of Andy Measor who joins the CU from his former position at the Research Operations Office. A warm welcome to Andy!

Other recent arrivals & departures

We welcome Calvin Cheah (Laboratory Informatics Developer), Callum Campbell (Research Associate), Clement Bodineau (Visiting Researcher), Richard Phillips, Daniel Fernandez and Ahmad Komber (Visiting Student). We would like to wish Kalina Hass, Emma, Kerr, Mathew Vithayathil, Jin-Soo Kim, Megha, Bhandari, Jaiwen Dong, Ben Cowley, Pahini Pandya, Georgina Jones, Sakshi Chadha, Tom Schoufour, Naseer Pasha and Edward Taylor all the best in their future careers.

Enlightened!

The lighting upgrade project is nearly complete. Thank you to Nathan, Michael and Oliver from Sotham Ltd, who have been working seamlessly through the building and for always being approachable and flexible. Also thank you to Karen, Oana and Francois for planning the work carefully for each floor. The whole building will have LED “smart” lights with forecasts to save an estimated 223,441 kWh of energy and reduce the CO2 emission by 79 tonnes per year!
Of festivals and reaching out…

On the day the clocks sprang forward, team Hutch was out there, yet again taking part in the Cambridge Science Festival. In spite of the formidable weather, this year the Festival recorded a footfall of 67000 people over the two weeks and the Biomedical Campus had over 3000 visitors in one day alone, at the event held in the CAST building! Sharing a room with the CRUK CI and the University society CATS (who had models of their own this year, thanks to the MRC CU sponsorship from last year), the Hutch activities, diverse and each brilliant in its own way, were themed around the importance of Early in Cancer. Particularly poignant, was the fact that this year we had patients who had benefitted from the research that had started out in our labs, spending the day with us to tell their story. Visitors young and old enjoyed their day, be it through hooking ducks to discover mutations, pretending to be a cancer cell navigating a blood vessel, simulating a western blot or a mass spec device or playing early detection sleuths catching rogue cancer cells. Not only did our scientists talk about the traffic light genes that stall cancers on their journey, but they also managed to punch in an inspirational element for the younger ones entitled ‘A scientist is a person just like you’. We are grateful to the Cambridge MRC community for a second edition of the MRC Cambridge Activity Book and to our CRUK CI and CCC colleagues for help with logistics.

Not always do we wait for our audience to come to us - thanks to the enthusiasm of our scientists, no matter how busy they are, we find the time to reach out to schools in our local community. An afternoon’s visit to the STEM club at Sawston Village College was an example of just this. Jamie Blundell and Rebecca Fitzgerald spent time with a handful of kids who loved Jamie’s clever game of trying to race DNA polymerase in its job of faithfully replicating DNA and marvelled at Rebecca’s demonstration of how a simple sponge down a string could mimic the function of a complicated looking endoscope. A well-received prelude to the start of a more lasting relationship with the school, planned over the next academic year.

Last but not the least, we had high school visitors from Hungary who had won their national competition for the Albert Szent-Gyorgi
prize, which included a visit to 'the prestigious Biomedical Campus in Cambridge!' 😊. Thanks to Karol, David S, Bryn and Alessandro, they had a chance to see how bacteria act as workhorses of molecular biology, how computer modelling can help us understand cancers and a trivia laden tour of the world of pipetting robots and microscopy. Very special thank you notes have since come our way.

MRC Cancer Unit: Research successes

A new role for the breast cancer gene BRCA2 - safeguarding genes during transcription:

Inheritance of a mutated copy of the breast cancer gene BRCA2 predisposes families to cancers of the breast, ovary, pancreas or prostate at an early age. Despite intensive effort from scientists worldwide, how faults in BRCA2 cause cancer susceptibility is not well understood. Most available information suggests that BRCA2 is involved in homologous recombination to repair double strand breaks in DNA, which occurs each time that a cell divides. This DNA repair function is lost in cells with mutant BRCA2, causing DNA mutations to accumulate across the genome, and triggering early-onset of cancer.

Now evidence has emerged that this is not the only way that mutation of BRCA2 leads to cancer. New research, recently published in the journal Cell Reports, by a research team led by Professor Ashok Venkitaraman at the Unit has unexpectedly found that BRCA2 safeguards the expression of genes located throughout the human genome, preventing their breakage during the transcription process that precedes the synthesis of new proteins essential for normal cellular function. The research team has found that BRCA2 safeguards the transcription of DNA into RNA, by coupling to the molecular machinery involved in transcription, and ensuring that it smoothly moves across genes. In cells with mutant BRCA2, the transcription machinery gets held up as its starts, the proximal pause sites, causing accumulation of RNA-DNA duplexes which in turn leads to an increase in double strand breaks and genomic instability and ultimately results in cancer.

These findings not only point to a surprising new way in which the inheritance of mutant BRCA2 may predispose to cancer, but also promises the future development of new treatments that target other proteins associated with the transcription machinery that may allow BRCA2 mutant cancer cells to survive.

New insights into how Metabolic Reprogramming underpins uncontrolled cell growth and migration in Cancer

Cancer cells reprogram their metabolism to support the high energetic demands that are a cost of uncontrolled growth. Amongst these metabolic changes, activation of glucose metabolism is chief. It is known that glucose is metabolised via glycolysis and then fully oxidised in the mitochondria, also known as the power-house of the cell. Research has now shown that mitochondria are impaired in several cancer types. However, to what extent mitochondrial dysfunction contributes to the tipping towards glycolysis remains unclear.
A new line of research led by Dr Christian Frezza at the Unit, recently published in *Molecular Cell*, capitalises on a new cell based model of mitochondrial dysfunction to address this link. Researchers, for the first time, have shown that mitochondrial defects lead to a profound metabolic rewiring of glucose metabolism and activation of glycolysis.

They further go on to show that this crosstalk between dysregulated mitochondrial metabolism and glycolysis in fact impinges on another important cellular metabolite - Glutamine. Glutamine is the most abundant amino acid in human blood and it is widely used by cancer cells for their growth. Through their study the researchers illustrate how, in situations of mitochondrial damage the breakdown of glutamine is co-opted to replenish NADH, one of the most important cellular messenger molecule for multiple energetic reactions, and how this is achieved by a pathway known as reductive carboxylation. This glutamine-dependent NADH supply is essential to drive the activation of glycolysis, which in turn can support cell migration – a defining hallmark of cancer.

This is the first time that a bridging molecule, glutamine, and a metabolic pathway has been identified that link the loss of mitochondrial function with a switch to using glucose for metabolic needs and an eventual progression to cancer. This evidence expands our understanding of the energetic reprogramming associated with uncontrolled growth and cell migration and offers new opportunities for targeting cancers.

**Understanding how supporting cells of the tumour kill the killers**

Cancers have developed numerous ways in which to prevent our defences, that is our immune system, from destroying a tumour. Many immune populations are found within a tumour, but it is the T cells that can ultimately decide tumour fate, and thus tumours frequently suppress their function.

A tumour is much more complex than a collection of cancer cells with many other cell types needed – these cells support the tumour in numerous ways and are known as the stroma. One population of supporting stromal cells, the cancer associated fibroblast, is associated with poor patient survival. T cells are often found near cancer associated fibroblasts, raising the possibility that cancer associated fibroblasts may help the tumour by interfering with our immune system.

New research by Jacqui Shields and her team, recently published in *Nature Communications* has shown that cancer associated fibroblasts are able to eat tumour cell debris and present the material to T cells entering the tumour. This presentation process would normally instruct T cells to proliferate and activate so they can destroy their targets. However, in the tumour, cancer associated fibroblasts present material along with a negative signal through molecules FASL and PDL-2, which instead tells T cells to die, and allows the tumour cells to continue growing.

The mechanisms identified show for the first time that cancer associated fibroblasts directly interact with T cells to mediate immune suppression within the tumour but also helps to explain why cancer associated fibroblasts are associated with poor survival.
Conferences & Awards

Mr Siong Liau, Consultant Hepatobiliary and Pancreatic Surgeon and a clinical Scientist at the MRC CU has been awarded one of the most prestigious surgical travelling fellowships in the British Isles, the 2018 Association of Surgeons of Great Britain and Ireland (ASGBI) Moynihan Travelling Fellowship, to travel as an ambassador of British and Irish surgery to similar world renowned centres in Seoul and Tokyo.

Dr Jacqui Shields was invited to present her groups latest work on the use of single cell sequencing to help define the stromal landscape of evolving tumours in the Recent Advances in Single Cell Technologies Session of the 2018 AACR annual meeting held in Chicago - the biggest in their history with nearly 15,000 delegates attending.

Other News

Congratulations to Jennifer Harris, PhD student in the Shields lab, for securing an MRC sponsored six months policy internship at the Department of Health and Social Care – 10 weeks in, Jennifer says she’s really enjoying the fast-paced, front-line aspect of the new role, knowing that from one day to the next, she could be talking to a patient directly about their health experiences and then briefing ministers and attending events in Parliament!

Congratulations to Ashley Ferguson, MPhil student in the Frezza lab, for donating her hair to the Little Princess Trust which provides real hair wigs, free of charge to children & young adults who have lost their own hair through cancer treatment and other illnesses. In Ashley’s own words ‘I chose to donate my hair because I wanted to give back to a community my project is invested in: those affected by cancer.’ She also raised £376 for the charity. Well done Ashley!

Upcoming events

MRC CU Open Day – 19 June 2018 – will host visitors from local high schools who will be taken on a hands-on activity and meet-the-researchers tour across the CU labs followed by a careers session.

Dr Sakari Vanharanta from the Unit is one of the lead organisers of an international PhD course on metastasis biology in Basel (12-14 September). More details and registration links can be found on: http://www.baselbc.org/events/International-PhD-course-2018/

Dr Shamith Samarajiwa and Dr Dora Bihary from the MRC CU will be teaching again at the 2018 CRUK Bioinformatics Summer School (July 23 to 27th). The course will include training on computational analysis of functional genomics data and is open to all students and researchers affiliated to the CRUK-Cambridge-Centre.
Our scientists in the limelight

Professor Rebecca Fitzgerald delivered the 2018 Croonian Lecture with a talk entitled ‘Precision Diagnosis of Oesophageal Cancer using Pill on a String’. Her talk highlighted, amongst other aspects, improved cancer outcomes arising out of the CytoSponge and associated molecular tests to identify early stage oesophageal cancer.

The Croonian Lecture, dating back to 1738, is the most prestigious Annual Lectures organised by the Royal Society and the Royal College of Physicians.

Our heartiest congratulations to Rebecca!

The lectureship was conceived by William Croone (above), one of the first Fellows of the Royal Society. Among the papers left on his death in 1684 were plans to endow two lectureships, one at the Royal Society and the other at the Royal College of Physicians. His widow later bequeathed the means to carry out the scheme. The lecture series began in 1738. (source: RSOC website)
Recent publications


