



Paterson
Institute for Cancer Research

Paterson Institute

newsletter

The Newsletter for the Paterson Institute for Cancer Research

Success for ACBB Group



Issue 26 - December 2012

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MANCHESTER
1824

The University of Manchester



Director's Introduction



I am delighted to report that cancer research in Manchester got an enormous boost in November with the announcement of our successful bid to the UK Research Partnership Investment Fund. I am extremely grateful to all those at the University, the Manchester Cancer Research Centre (MCRC), and the Paterson Institute who worked tirelessly to tight deadlines to get our bid submitted.

We were extremely pleased to have been awarded £12.8m towards the new MCRC building, currently being built across the road from the Paterson Institute. The funds provide £4.1m towards completion of the building itself and £8.7m towards the specialised instruments to provide the platform technologies needed to allow us to implement personalised medicine for cancer patients in the North West. The new equipment will help us to progress the basic and translational research that are pivotal to the development of further novel anti-cancer treatments and to accelerate the development of approaches that will lead to improved outcomes for patients. Notably, these technologies produce large volumes of data that can only be analysed by highly trained experts. Fortunately our team of bioinformaticians at the Institute, led by Crispin Miller, will help to develop the approaches needed to navigate our way through the complex data sets and I am very happy that earlier this year, a committee of international experts were very complementary about Crispin's research and confirmed that he produces high quality work that has an international impact. I wish to congratulate Crispin for his contributions to the field and thank him for his contributions to the Institute and to the wider bioinformatics community. I am looking forward to working with Crispin and following his research over the next few years.

More good news came recently when Caroline Dive, head of the Clinical and Experimental Pharmacology team, was presented with one of the world's leading scientific awards, the Pasteur-Weizmann/Servier Prize. This well-deserved honour is in recognition of the fantastic work by Caroline and her group in developing minimally-invasive biomarker tests for a range of cancers and treatments and I wish to congratulate both Caroline and her team.

It was a real pleasure to get my first taste of two annual Institute events. First the Institute Colloquium was a highly enjoyable scientific and sociable occasion and a great opportunity for me to learn more about what is going on at the Institute. I was particularly impressed by the quality of the student talks and was delighted to present the poster prizes to our two well deserved winners, Timurs Maculins and Janet Taylor. The event was a great introduction to life at the Institute for members of my group who have recently moved to Manchester from London. They have been joined by several new colleagues over recent weeks so the Molecular Oncology Group is now well established.

During the annual Institute Open Day, we were visited by three very special guests. Dr Elspeth Russell, a recently retired GP, is the daughter of Edith and Ralston Paterson, two pioneering doctors, after whom the Institute takes its name. Dr Russell attended the open day along with her daughter Celia and grand-daughter Phoebe. It was their first visit to the Institute and a real privilege for me to meet them. The open day is an excellent opportunity for us to communicate our progress and gratitude to our supporters so it was great to see so many of our supporters at the event. Thank you to all those members of the Institute who gave up their Saturday to guide people around the laboratories and show them what we do.

The coming year promises to be very exciting with the introduction of innovative technologies and the strengthening of our research portfolio through the recruitment of several new Group Leaders, and I would like to take this opportunity to wish you all a very happy Christmas and look forward with you to a successful and enjoyable 2013.

Richard Marais
Director

Front cover:
Members of the Applied Computational Biology and Bioinformatics Group:
Front (L-R): Maria José Villalobos (joint with the Cell Division Group), Elli Marinopoulou (joint with the Stem Cell Biology Group), Hui Sun Leong, Sharmin Naaz (joint with the Stem Cell Haematopoiesis Group), Crispin Miller, Janet Taylor, Chris Wirth. Back (L-R): Phil Chapman, Yaoyong Li, Tim Yates, Danish Memon. Also in the group: Keren Dawson.

New Students



Alekh Thapa

Hello, my name is Alekh. I grew up in Sheffield, just across the Pennines, and then moved to Manchester in 2009 to study for my BSc in Pharmacology and Physiology at The University of Manchester. During my time as an undergraduate, I discovered my interest in the molecular events governing our cells and how the disruption of these systems can cause, or be a result of, the cancer phenotype. This motivated me to join the Cell Regulation Group, led by Nic Jones. I am currently investigating the molecular mechanisms that determine MAP kinase kinase 4 mediated metastasis suppression in certain forms of cancer. I have lived in Manchester for the past three years and I enjoy many of its offerings including the diverse music scene, great places to eat out and proximity to the Peak District, where I like to go on occasional walks and bike rides.



Ewelina Testoni

Hi, I am Ewelina and I am from Poland. I began a Medical Biotechnology course at Silesian Medical Academy in Poland; however, I chose to break my studies and work in the UK in order to learn English. After two years of adventure in England, I resumed my education at the University of Manchester, from which I have recently graduated with a BSc in Molecular Biology with Industrial Experience. During my placement year at AstraZeneca in Alderley Park, I researched miRNAs and their potential use as biomarkers in the treatment of colorectal cancer. I am now continuing in the field of cancer research, which fascinates me, by beginning a PhD within the Signalling Networks in Cancer Group, led by John Brognard, where I will be investigating novel mutational drivers in lung carcinoma. The Paterson Institute offers a highly stimulating environment and I am very excited to work amongst so many talented scientists.



Anna Woroniuk

Hi, I'm Anna and I'm from Preston. I completed my degree at the University of Cambridge where I read Natural Sciences, studying Pharmacology in my final year. My interest in cell signalling pathways in cancer stemmed from a summer project I undertook at the Babraham Institute, looking at acquired resistance to MEK inhibitors in tumour cells. I've joined the Cell Signalling laboratory, led by Angeliki Malliri, and my PhD project will be looking at the role of the Rac activator STEF (Tiam2) in tumourigenesis. I am really enjoying living in Manchester city centre, particularly the great atmosphere, shopping and culture. I also enjoy swimming in my spare time and am a keen skier, so I can't wait to check out the Chill Factore in Manchester! I am excited to get started on my project and benefit from the great facilities and expertise at the Paterson.



Kate Hogan

Hi, I'm Kate and I'm from Liverpool. I did my undergraduate degree at York University, where I studied Biochemistry. During my degree, I completed the industrial component at MedImmune in Cambridge, where I spent one year in the Histology Team within the Oncology Department, developing immunohistochemistry protocols for a variety of in-house projects. I have started my PhD in the Molecular Oncology group led by Richard Marais, where I will be using transgenic models to study gene-gene and gene-environment interactions in melanoma. I have just moved to Didsbury and I am enjoying exploring the huge variety of restaurants and bars in Manchester. I am also looking forward to seeing some fantastic live music and visiting the Peak District. I have really enjoyed my time at the Paterson so far, everyone is incredibly friendly plus it is great fun living in a big city.

Meet the ACBB Group

By Crispin Miller



Crispin Miller

We are interested in the way genes control how tumours grow and develop, and how their activity is disrupted in cancer. We believe that a detailed understanding of the cancer genome will ultimately lead to the development of better treatments for cancer.

While the majority of human genes encode proteins (the fundamental building blocks from which all cells are made), recent studies have revealed thousands more that appear to perform a different role. Although these genes express RNA (broadly, the precursor molecules produced by active parts of the genome), it is never translated into protein. Since they have been discovered only recently, the vast majority of these non-coding genes have yet to be assigned a function, and it is still possible that some may simply be background 'chatter' associated with the process of gene expression. However, where scientists have been able to study specific non-coding genes, their research has revealed a wide variety of different functions, and has shown that non-coding RNAs can interact with DNA, with proteins, and with other RNA molecules, to modulate and control their activity. Since they constitute nearly 40% of all human genes, non-coding RNAs have the potential to create a profound impact on our understanding of basic cell biology.

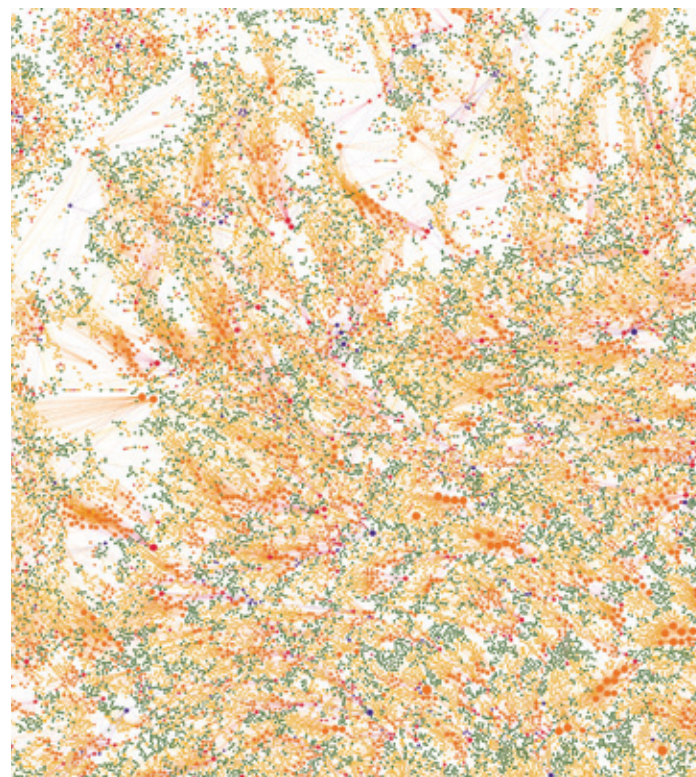
Discovering non-coding oncogenes and tumour suppressors

The main focus of our research is directed at developing a better understanding of the roles played by non-coding RNAs and how these are altered in tumours.

We are doing this by making use of the huge advances in genome sequencing technology that have occurred since the publication of the draft human genome in 2001. These allow us not only to sequence tumour DNA in order to identify mutations that disrupt the behaviour of key genes, but also to generate a global snapshot of gene-activity by measuring individual RNA levels in order to explore how they change under different conditions. At its core, the task is one of pattern recognition. Since there

are tens of thousands of genes, each capable of interacting with many others, this task is reliant on significant amounts of computing power and statistics to analyse the billions of potential relationships that need to be considered.

The Applied Computational Biology and Bioinformatics (ACBB) group is a highly interdisciplinary team that combines biology, statistics and computer science to exploit the power of these new technologies. Predictions arising from the data are then taken back to the bench for further validation and experimental study. For example, using these approaches we have recently identified new ways in which genes that sit next to each other in the genome can regulate one another to coordinate critical processes in cells as they differentiate. In the same study, we also identified other regulatory events that are dependent on antisense non-coding RNAs expressed from the complementary DNA strand to that of a protein-coding gene. Both these processes depend on the machinery that cells use to manipulate non-coding RNAs. We performed this work, in collaboration with the Cell Division Group, in fission yeast, which is a particularly useful model organism for studying non-coding genes because many of the proteins that handle these RNAs are evolutionarily conserved with their human equivalents.



Underpinning much of our work are genome annotation databases that link genes to the RNA and protein molecules they encode. The figure shows just a tiny subset of the millions of relationships we need to record. Each circle represents a different feature in the database, such as a gene (pink), or an RNA molecule (orange), and each line, a relationship between them. We use computer software to help us interpret these networks.

Supporting computational biology in the era of next generation sequencing

ACBB is highly collaborative: we work with many of the other researchers within the Institute, and the wider Manchester Cancer Research Centre (MCRC), to analyse and interpret their data. For example, this may include analysis to identify sets of genes that can help predict the behaviour of different tumours. The power of high throughput genomics to help advance our understanding of tumour cells has led computational biology to take an increasingly central role in the research programmes of many groups on site, not only to validate existing predictions, but also as a hypothesis generation tool in its own right. The rapid pace of the field also means that many of the biological questions we wish to address are equally dependent on the parallel development of appropriate methods for data processing and statistical analysis – meaning that close integration of the numerical and the biological sciences is critical. This is hard to address through a pure 'data-analysis-as-service' approach. We have instead developed a collaborative model in which support is provided by post doctorate-level scientists for more extended periods of time within a given research group. This allows them to become immersed within the group's research programme, resulting in a greater understanding of the context of the research and enabling a much deeper contribution and a more satisfactory collaboration overall.



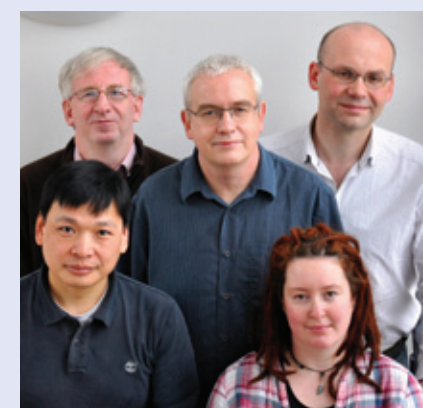
Yaoyong Li

Yaoyong Li

This type of working is exemplified by Yaoyong Li, who recently moved from a post doctoral position in ACBB to a new analyst support role, where he successfully applies his research background in Artificial Intelligence and Computer Science. Yaoyong has been a real trailblazer

for the approach, bringing his cutting edge informatics skills to many of the research programmes within the Institute and frequently developing entirely new algorithms and research methods to support the work of our collaborators. As demand for computational biology increases on site, we will be expanding this team – Yaoyong has shown how well this can work. Alongside Yaoyong, I am also proud to work with the incredibly talented scientists that comprise my group and I look forward to seeing their own projects flourish over the next few years. As we start to contemplate expansion into the new MCRC building, and with the significant award from HEFCE to fund new technology and genomics, it is an exciting time for cancer research in Manchester.

Latest Developments in the Core Facilities



Members of the AIF/Flow Cytometry team:
Back (L-R): Mike Hughes, Jeff Barry, Steve Bagley.
Front (L-R): Kang Zeng and Abi Johnson.

Over the last year, the management of the Advanced Imaging and Flow Cytometry Facilities has been merged. The AIF deals with visualising and analysing adherent cells or tissues in high detail whereas Flow Cytometry sorts and analyses thousands of non-adherent cells quickly; this merger

provides a seamless array of tools for the Institute's researchers. Within the facility there have been a range of new developments and tools that have been introduced and developed in order to provide more rapid methods of translating analogue systems (the cell) to digital data.

Two members of staff have been recently appointed so samples can be processed quicker which also allows for more people to be trained in equipment use and data processing. Abi Johnson comes from a forensic science laboratory where equipment was maintained to strict standards, she joins the flow cytometry team and is responsible for aiding in the calibration of equipment and helping to run samples. She is a mad roller derby player and likes to bake.

Kang Zeng is a past employee of the Institute that couldn't stay away! He was in Elmar Schiebel's laboratory where he developed his microscopy skills and then moved to Liverpool and then Oxford in Urlike Gruneberg's group. His role at the Institute is the day to day running of the imaging suite, teaching new users, calibrating the equipment to Good Laboratory Practice (GLP) standards and troubleshooting any problems that microscopy users may have with the equipment or image analysis.

In January another new member will start at the Institute whose role is to quality control the histology scanners, help users run their slides through the systems and aid in image analysis in order to mathematically model tissue.

Featured Publications

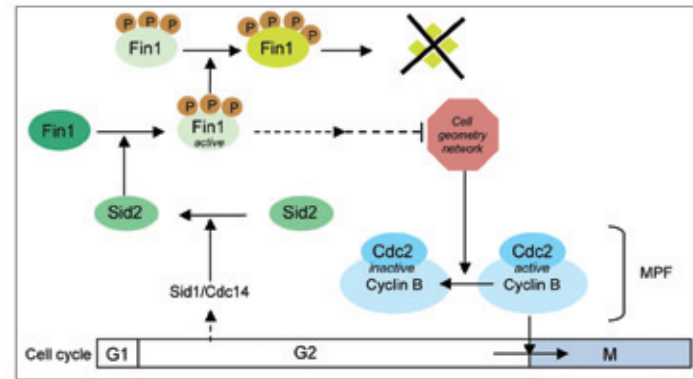
Controlling Mitotic Entry

The fission yeast *Schizosaccharomyces pombe* is a unicellular, rod-shaped organism that grows by elongation at its tips and divides by formation of a centrally placed division septum. The simplicity of its mode of division, and the ease with which it can be manipulated in the laboratory, make it an ideal model organism to study the mechanisms that control the cell cycle. These mechanisms are conserved from yeast to humans. Investigating cell cycle regulation in *S. pombe* can reveal how all stages are carried out in the correct sequence, how one stage is completed before the onset of the next stage, and how damaged cells do not continue to proliferate unchecked. This knowledge can then be applied to mammalian cells to improve understanding of cancer cell proliferation and ultimately help identify potential therapeutic targets.

In a recent paper published in Nature Cell Biology, Iain Hagan and Agnes Grallert of the Cell Division Group identify key components in the cell cycle that control when cells begin to divide in *S. pombe*. Mitosis is an important therapeutic target in cancer treatment. Many chemotherapy agents target the spindle and disrupt microtubule dynamics. Investigating the cellular processes in other stages in mitosis can lead to the identification of alternative targets for drug development and new strategies for chemotherapy. This paper focuses on mitotic entry.

The M phase promoting factor (MPF) is involved in the signal to initiate the onset of mitosis. The MPF is comprised of a cell division cycle (CDC) kinase and its activating cyclin. Understanding the function of these protein kinases requires knowledge about their direct phosphorylation targets and the effects caused by inactivation of the kinase.

In this paper, a series of exciting methods have been devised to identify the cellular functions and phosphorylation targets of selected enzymes central to the onset of mitosis in *S. pombe*. Analogue-sensitive kinases, which contain mutated ATP-binding sites that allow the kinase to be selectively inhibited without blocking the activity of non-mutant protein kinases, are used to inhibit the activity of particular kinases in *S. pombe*. The first set of experiments inhibits the kinase at the G2 phase of the cell cycle to assess whether mitotic commitment has been delayed or increased. Secondly, the kinase is inhibited during various stages of the cell cycle for a limited period of time. The analogues are then washed out to restore the function of the kinase in question to determine the impact on mitotic entry.



A schematic depicting how Sid2/Fin1 controls the transition from G2 to mitosis (M). P = phosphorylation. A dashed line indicates that the exact mechanism remains to be determined. Fin1 is activated in G2 by phosphorylation by Sid2, promoting mitotic commitment through the modulation of the geometry network. Activated Fin1 promotes its own destruction, temporarily limiting its activity.

In this experiment, if inhibition of the kinase delays the cell cycle and following reactivation of the kinase the cells burst into mitosis, the kinase has induced mitotic commitment and therefore plays a significant role in controlling mitosis.

In *S. pombe*, the Septum Initiation Network (SIN) signalling pathway is known to control events at the end of mitosis. This pathway is carefully regulated so that cytokinesis and mitotic exit are only initiated when chromosomes have properly segregated. SIN plays a role in delaying these events in response to defects in late mitosis. Sid2 is the terminal kinase in the SIN pathway. Its activity is regulated by its regulatory subunit, Mob1. When activated, the Sid2-Mob1 complex phosphorylates Fin1, a NIMA-related kinase, which in turn regulates the G2 to mitosis transition.

This paper demonstrates that inhibition of Sid2 or Fin1 delays mitotic commitment, indicating that Sid2Mob1 promotes mitotic commitment by activating Fin1. A remarkable feature of Fin1's activation is that it promotes its own destruction and is therefore active for a limited period during G2. Interestingly, the Cell Division Group also discovered that Sid2-Mob1 activity promotes a burst of mitosis in the absence of SIN activity, demonstrating independence from other known SIN components. This important discovery challenges whether the function of SIN components are indeed limited to their defined roles at the end of mitosis.

Ref: Agnes Grallert, Yvonne Connolly, Duncan L. Smith, Viesturs Simanis & Iain M. Hagan. (2012). The *S. pombe* cytokinesis NDR kinase Sid2 activates Fin1 NIMA kinase to control mitotic commitment through Pom1/Wee1. *Nature Cell Biology* 14(7), 738-745.

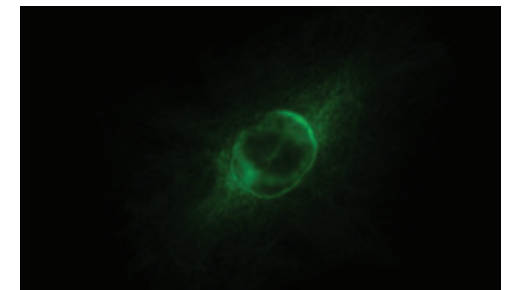
Circulating CK18 is a Biomarker of Tumour Burden in Colorectal Cancer

Blood tests that can accurately monitor the early response of a tumour to therapy would be useful in both guiding changes in the treatment of individual patients and developing new drugs (by identifying the most promising agents, suggesting the most effective administration schedules and combinations of agents).

Cytokeratin 18 is major component of the intracellular skeleton in colon cancer cells. Importantly it is not found in normal circulating blood cells. This study found evidence in a group of 171 patients with colorectal cancer that circulating cytokeratin 18 levels reflected the tumour burden.

Levels of CK18 were higher in patients with colorectal cancer than in healthy subjects, and the more advanced the cancer the higher the levels on average (although with overlap in the values). CK18 levels from veins directly draining the tumour (taken during surgery) were higher than levels in the arm supporting the suggestion that circulating CK18 comes from the tumour.

In patients treated with surgery and chemotherapy high levels prior to treatment were associated with a poor prognosis.



Cytokeratin 18, a major component of the intracellular skeleton in colon cancer cells, visualized at x40 magnification.

Following chemotherapy, levels of CK18 dropped following the first treatment. In patients whose tumours responded to therapy levels then stabilized, however in patients where the tumour grew during therapy, levels progressively increased during subsequent chemotherapy treatments. Importantly measuring CK18 gave additional information over measuring Carcino-Embryonic Antigen (CEA), a tumour marker used in clinical practice.

This paper shows that CK18 can be used both to estimate prognosis and monitor response to therapy in patients with colorectal cancer. It is now used in both academic and commercial trials of new agents in this disease.

Ref: Greystoke A, Dean E, Saunders MP, Cummings J, Hughes A, Ranson M, Dive C, Renehan AG. Multi-level evidence that circulating CK18 is a biomarker of tumour burden in colorectal cancer. (2012) *British Journal of Cancer* 107, 1518–1524.

Fixing and Copying DNA – Tying DNA Repair to Replication

Recent work by the DNA Damage Response Group published in the journal "Genes and Development" has identified a new protein which is involved the repair of damaged DNA during replication.

As cells divide, it is important that the DNA is replicated accurately so when DNA damage is detected a cell faces a choice of repairing or ignoring it. As ignoring the damage could lead to mutations or instability in the DNA, the preferred option is repair. Until now the mechanism by which these lesions are repaired when detected during the process of copying the DNA has been poorly understood. By identifying the factor, ZRANB3 (zinc finger, RAN-binding domain containing 3), and determining how it functions, the DNA Damage Response Group have started to explain this process.

ZRANB3 was found to have a unique structure-specific endonuclease activity which is coupled to ATP hydrolysis. This

activity allows ZRANB3 to cleave DNA at branched structures allowing repair and continuation of replication. Multiple mechanisms are involved in the recruitment of ZRANB3 to damaged replication forks including interactions with PCNA K63-polyubiquitin chains and branched DNA structures created when replication forks stall. Once recruited to the stalled replication fork, ZRANB3 induces a DNA strand break in the double stranded DNA whilst the replication fork regresses.

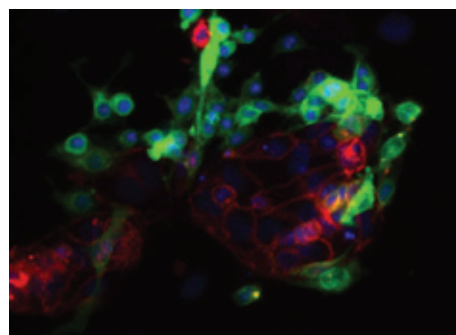
The exposed 3'-OH group is then extended by the DNA polymerase to remove the DNA lesion. The resulting 5' overhanging DNA flap is processed by FEN1 and after the sealing of the nick and reversal of the regressed replication fork DNA replication can continue. This model has been used to suggest how DNA replication and excision based repair mechanisms can be coordinated to allow the repair of DNA lesions which would otherwise block replication.

Ref: R. Weston, H. Peeters, and D. Ahel. (2012) ZRANB3 is a structure-specific ATP-dependent endonuclease involved in replication stress response. *Genes and Development* 26:1558–1572.

Regulating Cell Fate Switching Through Transcriptional Repression

Recent studies have established that most, if not all, blood cells are generated from specific types of endothelial cells with haematopoietic potential, i.e. haemogenic endothelium cells. The transcription factor RUNX1 is a frequent target of gene rearrangements and mutations in human acute myelogenous leukemia (AML) and acute lymphoblastic leukemia (ALL). Consistent with its initial implication in leukaemias, RUNX1 is critical for normal haematopoietic development and in particular for this process of endothelial to haematopoietic transition (EHT). However the precise identities and specific roles of RUNX1 downstream effector genes remain largely unknown.

In this Study, the Stem Cell Biology Group report the identification of the transcriptional repressors GFI1 and GFI1b as critical targets of RUNX1 and establish their crucial function in regulating this trans-differentiation from endothelial to blood cells. GFI1 and GFI1B are able to trigger, in the absence of RUNX1, the down-regulation of endothelial markers and the formation of round cells, a morphological change characteristic of this cell fate switch. Conversely, in *Gfi1* and *Gfi1b* deficient embryos, the first generated blood progenitors maintain the expression of endothelial and cell adhesion molecules. These cells are therefore hampered in their ability to be released in the vasculature and to be disseminated in the yolk sac and in the embryo-proper.



Upon induction of Gfi1 expression some flat adherent VE-cadherin⁺ haemogenic endothelium cells (red staining) upregulate CD41 (green staining) and become round loose blood cells.

This study demonstrates a critical and specific role of the GFI1 transcriptional repressors in the generation of haematopoietic progenitors from haemogenic endothelium. The results suggest that the EHT could be decoupled firstly into repression of the endothelial identity controlled by GFIs repressors and in parallel into activation of the haematopoietic cell fate programme. These new insights could result in new strategies to generate blood cells for regenerative medicine from embryonic stem cells or from induced pluripotent stem cells.

GFI1 and GFI1B control the loss of endothelial identity of hemogenic endothelium during hematopoietic commitment.

Ref: Lancrin C, Mazan M, Stefanska M, Patel R, Lichtinger M, Costa G, Vargel O, Wilson NK, Mörry T, Bonifer C, Göttgens B, Kouskoff V, Lacaud G. GFI1 and GFI1B control the loss of endothelial identity of hemogenic endothelium during hematopoietic commitment. *Blood*. 2012 Jul 12;120(2):314-22.

The Bell TOLLS for Cancer

Recently the Targeted Therapy Group have developed a novel approach for the treatment of lymphoma using radiation in combination with a TOLL-like receptor (TLR)-7 agonist.

Radiotherapy plays an important part in the local control of many lymphomas and leads to extremely high response rates even in patients that are refractory to conventional chemotherapy approaches. The cell death caused by radiation therapy has the potential to stimulate immune responses against the cancer cells. However, these immune responses tend to be weak and insufficient to improve a patient's outcome. Combining radiation therapy with a drug capable of stimulating the immune system has the potential to generate durable and effective anti-cancer immune responses capable of eradicating widespread malignant disease and reducing disease recurrence.

Using a synthetic agonist of TLR-7 which activates a systemic immune response by mimicking a viral infection, the Targeted

Therapy Group found that the anti-tumour efficacy of radiation therapy can be enhanced in pre-clinical models of lymphoma. Combination therapy but not single-agent treatment resulted in long-term clearance of tumour and enhanced survival. This response was dependent upon the activation of CD8⁺ cytotoxic T-cells, as depletion of these immune cells rendered the combination ineffective.

Moreover, the CD8⁺ T cells provided a durable response capable of protecting against disease recurrence. These data reveal that combination therapy with radiation and a TLR7 agonist is able to generate tumour-specific immunological memory. These findings demonstrate the potential for novel therapeutic combination approaches involving radiotherapy and immunotherapy for the treatment of cancer.

Ref: Dovedi SJ, Melis MH, Wilkinson RW, Adlard AL, Stratford IJ, Honeychurch J, & Illidge TM (2012) Systemic delivery of a TLR7 agonist in combination with radiation primes durable anti-tumor immune responses in mouse models of lymphoma. *Blood*, Oct 18, doi: 10.1182.

Staff News



Baby for Sarah Holt and Chris Morrow

Congratulations to Sarah Holt (DDU) and Chris Morrow (CEP) whose daughter Erin was born on 30th August. Both Sarah and Erin are doing well and the first few months have flown by.

Darren Roberts Poster Prize

Darren Roberts, postdoctoral scientist in Immunology won the poster prize at the recent 8th World Congress on Peritoneal Surface Malignancies that was held in Berlin. Darren's poster was titled "Gene expression profiling and development of a cell culture model of Pseudomyxoma peritonei".

Pseudomyxoma peritonei is a rare cancer treated only at The Christie and one other site in the UK. As a rare cancer, currently treated by specialist surgery and hyperthermic intraperitoneal chemotherapy, the biology is poorly understood with no pre-clinical models available. By using fresh surgical specimens underlying changes in gene expression were identified and cell lines developed both of which will be used in the identification and testing of additional therapies.

John Gallagher

John Gallagher, Scientific Director of Iduron in the Medical Oncology department, was recently awarded the Fell-Muir prize by the British Society of Matrix Biology. This is an annual award for research achievements in the field of Matrix Biology and for services to the Society. The group was recognised for their papers on new sequencing methods for linear polysaccharides such as heparin and heparan sulphate.

James Lynch and Emily Holmes Engagement

James Lynch (Leukaemia Biology) and Emily Holmes (Cell Regulation) got engaged in November, whilst up a mountain in the Lake District! They plan to be married in November 2013.

Football

If you would like to get involved in the Paterson football activities, we run a weekly casual football practice every Tuesday. Please contact Ricardo Gandara in Cancer Biology (rgandara@picr.man.ac.uk) to be added to the mailing list. Perhaps you can help us win our match against the Beatson Institute next year!



Basia Szul Wedding

Basia Szul, Human Tissue Coordinator in the MCRC Biobank, married Ken Hunt on 13th October at St Catherine of Sienna Roman Catholic Church in Didsbury. Their reception was at Hollin Hall Country House in Bollington and they are planning to enjoy their honeymoon skiing in the Samoens region in France.



Ricardo Gândara Wedding

Ricardo Gândara, Research Associate in Cancer Biology, married Amy Missingham, on 20th October at Santiago Church in Tavira, in the Algarve in Portugal. Their reception was in a nearby village, St. Estevão, in an old olive oil farm. Family from the UK and all over Portugal came together in the Algarve, where Ricardo and Amy lived before moving to the UK, and despite some rain everybody loved the beautiful destination.

Fundraising

Shining Through the Night

By Stuart Pepper



Around 3,000 people, many personally affected by cancer, recently took part in the Shine event which was kicked off by football legend and cancer survivor Bryan Robson at Old Trafford.

It is hoped that the 3,000 who took part will raise around half a million pounds for Cancer Research UK. Walkers set off for the mammoth walk at 8.30pm and had the choice of either a half or full marathon (either 13 or 26 miles) supporting one of 12 different areas of scientific research, including childhood cancer, breast cancer or lung cancer. Their journeys took them past landmarks including the Imperial War Museum in Salford Quays and the Paterson Institute for Cancer Research.

This year there were a good number of volunteers from the Paterson Institute who offered to help run a Pit Stop in the school car park on the corner of Cotton Lane. Around nine o'clock we gathered in the dark waiting for our lorry full of provisions to arrive. Once the lorry dropped off our tents, banners and supplies we had an hour of frenetic activity while we quickly assembled an operational coffee, snack and toilet stop. Once that was done, we had a curiously calm hour waiting for the first Shine participants to arrive, one or two volunteers at this point thought that we had far too many helpers and that there wasn't enough to do..... then round the corner came the first few power walkers racing through the night, followed by a trickle, and then very quickly a flood of people as approximately 2000 participants arrived for refreshments. Helping these committed fundraisers on their way can be both uplifting and quite emotional as people often want to share a few words about their experiences. By 2.00am the last walkers were on their way leaving us to dismantle the pit stop and head home tired but very aware that many of the people we had served still had a long walk ahead of them.

For more information about the Shine series: please visit www.cruk.org/shine

Three Generations of the Paterson Family Visit the Institute

The first Director of our Institute was Professor Ralston Paterson. In the 1930's he was the leading authority in the world in the treatment of cancer by radiotherapy. Together with his wife, Dr Edith Paterson, he established a programme of basic research into cancer, particularly in the fields of radiation science, genetics and drug development. The research was initially carried out in a series of huts and converted houses adjacent to the Christie hospital. When the Patersons retired in 1962, Professor Laszlo Lajtha was appointed as the first full-time Director of the research laboratories. It was he who named the research laboratories after the Patersons.

At this year's open day we welcomed over 100 supporters and members of

the public. This included for the first time, some very special guests. They have since taken their time to write in following their visit:

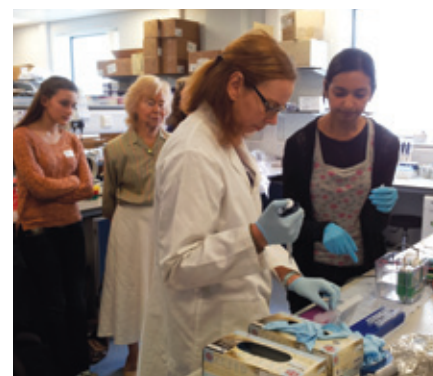
"As the daughter of Ralston and Edith Paterson, I particularly enjoyed the Open Day as did my daughter Celia and granddaughter, Phoebe who came along with me. We found the visits to the research laboratories both interesting and informative. My parents would have been very proud of the enormous strides made in research at the Institute": Elspeth Russell (nee Paterson).

The day included a talk by Professor Richard Marais and demonstrations provided by eight different lab and research facilities within the Institute. The purpose of the open day is to thank the people that support us and inspire them about the work we do. The feedback received following the event was fantastic and included the following:

"The people in the labs are inspiring. They all said thank you to us fundraisers but really the thank you should be to them: truly amazing";

"The day has motivated us to continue and increase fundraising activities";

Thank you to all the groups and guides who contributed to making the day a resounding success.



Shameem Fawdar (a Postdoctoral Fellow in the Signalling Networks in Cancer Group) demonstrates gel loading to Celia Russell, one of the grand-daughters of Drs Ralston and Edith Paterson. Watching the demonstration is Dr Elspeth Russell, the daughter of the Patersons along with one of her grand-daughters, Phoebe.

Inspirational Fundraiser Remembered



Members of the Rochdale Cancer Research UK fundraising committee recently visited the Paterson to remember their friend and colleague - Miss Rene Butterworth.

Miss Butterworth joined the British Empire Cancer Campaign Committee in November 1968. She became the assistant secretary and then continued to serve as secretary until the 1980's. She remained an active committee member for many years and although she no longer took part in the actual fundraising events, she remained interested in all of the activities of the committee and supported them financially in all their events until her death aged 90 on the 8th November 2010. Rene was well known in Rochdale, a keen golfer and bridge player. She was a great friend to all of the committee members and is much missed by those who knew her.

A plaque has been erected within the Paterson to commemorate Miss Butterworth's 50 years of fundraising which is worth hundreds of thousands of pounds. The committee were delighted to be welcomed to the Institute and the visit has inspired them to redouble their fundraising in 2013.

Relay for Life

In the last newsletter Emily Holmes wrote about the Institute's fundraising activities for CRUK's Relay for Life, which included a pop-up hair salon, football sweepstake, cake sale, raffle and a 24-hour relay in Stockport. We are delighted to announce that the total raised by Paterson scientists was £3326.22! A huge thank-you to everyone who contributed.

The total amount raised by the Stockport Relay was £46,641.

Stand up to Cancer Gala Dinner

On the 18th October, Caroline Wilkinson and Allan Jordan were invited to represent the Institute at the Stand up to Cancer Gala Dinner in London.

Held at Three Mile Studios the day before the SU2C televised event, which raised over £7M for translational cancer research, the Gala Diner brought celebrities and major donors together with scientists to highlight the achievements in bringing new treatments for cancer, but also highlighting areas where more research (and more funding) is clearly needed.

Whilst the Paterson budget did not allow for bidding in either the silent and open auctions for items such as custom Harley-Davidsons, a night on the town with Alan Carr or an OK Magazine photoshoot, the evening offered an opportunity to mingle with those who make major contributions to our research.

The event was hosted by Vernon Kay and Tania Bryer, with entertainment from impressionist Jon Culshaw, the Noisettes and soul legend Beverley Knight MBE. All the performers gave up their time largely due to their own personal or family experiences with cancer and the celebrities Allan and Caroline spoke to were clearly interested and impressed with the work at the Paterson. Indeed, Beverley Knight, who lost her father to cancer in 2010, personally asked that her thanks and encouragement be sent back to everyone, for the work conducted in the Institute and its potential future impact on the treatment of cancer.

The Paterson supported SU2C in various ways with a cake sale and raffle with "money can't buy prizes" raising over £500. The Beatson and Paterson football team also arranged their annual game (in association with Transnetyx) to coincide with Stand Up to Cancer. Once again, for the third year running, the Beatson failed to defeat the Paterson in normal time, in a hard fought 5-5 draw (goals from Matt Lancashire x 2, Tim Somerville, Mike Tallis and Dan Morris), with our Scottish friends having to rely on penalties to secure their victory.

Thanks to everyone for their amazing support of the Stand up to Cancer event.



Caroline Wilkinson and Allan Jordan from the Paterson Institute with Beverly Knight (middle).



The teams representing the Beatson and Paterson Institutes in white and red respectively.

Recent Awards and Events

Grant Success



The role of MOZ in AML

Georges Lacaud, Stem Cell Biology Group Leader, has been awarded significant funding by Leukaemia & Lymphoma Research to undertake a three-year project to identify and characterise genes

regulated by MOZ and MOZ-TIF2. MOZ (monocytic leukaemia zinc finger protein) is a transcriptional coactivator with histone acetyltransferase (HAT) activity, and plays a role in the maintenance of haematopoietic stem cells.

Specifically, MOZ is involved in the chromosome translocations associated with acute myeloid leukaemia (AML). Chromosomal translocations resulting in the fusion of MOZ-TIF2 (transcriptional intermediary factor 2) have been identified in patients with AML. Patients with these translocations often exhibit rapid progression and poor response to therapy. MOZ is found translocated to three other proteins, all of which have, or are associated with, HAT activity. Aberrant acetylation of MOZ targets by MOZ leukaemic fusion proteins may participate in the process of leukaemogenesis. Georges' group has already demonstrated that mice lacking HAT activity of MOZ have strong defects in the proliferation of haematopoietic stem and precursor cells.

This grant will allow them to characterise the cellular events modulated by HAT activity of MOZ and to identify genome-wide MOZ binding sites and their epigenetic signature. They also aim to investigate the extent to which MOZ-TIF2 affects the expression of some of the genes found at MOZ binding sites. Understanding these molecular mechanisms altered following translocations could lead to the development of new strategies for the treatment of leukaemia.

Circulating Tumour Cells in Pancreatic Cancer

Caroline Dive, Ged Brady and Kyaw Aung from the Clinical and Experimental Pharmacology Group (CEP), together with



Caroline Dive

Pancreatic Specialist Oncologists at the Christie Hospital, Juan Valle and Richard Hubner, have recently been awarded substantial financial support by the Pancreatic Cancer Research Fund. This will enable them to undertake a two-year project to study the development of

blood-borne biomarkers to work towards improving treatment selection for pancreatic cancer patients.

Improving survival for patients diagnosed with advanced pancreatic cancer remains a major challenge. Chemotherapy can control the disease and improve quality of life but offers only modest survival improvement. Cancers develop through a number of genetic mutations most likely starting within the developing pancreas with increasing mutations arising in the tumour itself. These mutations may be detected by detailed analysis of repeated biopsies over time, which is impractical in patients. Previously, CEP and the clinical team at The Christie established that genetic mutations can be tested from cell-free DNA (cfDNA) in 34% of patients with advanced pancreatic cancers.

Circulating tumour cells (CTCs) in the pancreas can be isolated from a blood sample of patients allowing single cell analysis. This enables cfDNA and CTCs to be used to monitor tumours in real time without having to perform a tumour biopsy. This new grant will enable them to perform mutational profiling of cfDNA using next generation sequencing. It will also allow them to undertake DNA analysis of CTCs to obtain information regarding additional mutations (due to tumour evolution) that may impact on the development of drug resistance. RNA analysis of CTCs will be performed to identify relevant expressed therapeutic targets, which can be used to guide treatment selection in each individual patient. Ultimately, they aim to pave the way for profiling molecular characteristics of pancreatic tumours from a single blood test.

Paterson Colloquium 2012



Poster prize winners Janet Taylor and Timurs Maculins with Institute Director Richard Marais (centre).

More than a hundred members of the Institute attended this year's Colloquium, which was held for the second year running at Lancaster University, during the final week of September.

The event was particularly memorable as it marked the first Colloquium since Richard Marais took over as Director and fittingly, he got things underway with the first presentation. He described his lab's work on BRAF signalling in melanoma, and how drugs directed towards cells expressing a mutant form of BRAF can result in a dramatic clinical response. Unfortunately, patients often relapse after a fairly short period. Work by the Molecular Oncology Group has identified some of the ways in which cells get round the block to cell signalling provided by these drugs. Some of this work was presented on posters by members of Richard's group who joined us in Lancaster just before moving to Manchester to join Richard at the Institute.

There were a record number of posters this year which led to highly vibrant and successful poster sessions. The poster judging

panel had a very difficult job but after much deliberation, the prizes went to Janet Taylor and Timurs Maculins. Janet is a joint post-doc between the Applied Computational Biology and Bioinformatics and Translational Radiobiology Groups. She won the prize for best poster presented by a Post-doc/Scientific Officer, for the work that she carried out alongside John Hall describing how the expression of a particular microRNA helps to classify tumour samples that have been fixed and stored. Previously, it has not been possible to re-visit these old samples and classify them by analysing mRNA as the material has degraded over time. However, by studying a smaller type of RNA, they were able to distinguish between various types of cervical and bladder cancers using these FFPE (formalin-fixed paraffin-embedded) samples. This technique will allow much more information to be gained from archived tissue samples that are often associated with long-term clinical data.

Tim's award for the best student poster was especially poignant as the prize was renamed this year as the Hitchman Poster prize in memory of Lizzy Hitchman, a student in the Clinical and Experimental Pharmacology Group, who tragically passed away last year, just days before sitting her PhD viva. Tim, a member of the Cell Cycle Group, has identified a protein which helps to disassemble the replisome, which is a complex molecular machine responsible for carrying out DNA replication. Very little is known about how the replisome is disassembled following DNA replication but during his PhD, Tim has discovered that a protein called Dia2 plays a critical role in this process. It has been a very exciting few months for Tim who successfully defended his PhD thesis in November and is now looking forward to his wedding in December when he will marry fellow PhD student, Hadir Marei. We wish them all the best!

The 2012 Pasteur-Weizmann/Servier International Prize

Professor Caroline Dive, Lead of the Clinical and Experimental Pharmacology Group (CEP), has been awarded the 2012 Pasteur-Weizmann/Servier International Prize in recognition of her pioneering studies in the identification of new serum based biomarkers and for the development of non-invasive procedures in the early diagnosis and management of cancer.

The Pasteur-Weizmann/Servier International Prize is one of the world's leading scientific awards and includes a prize of €150,000. It is awarded every three years to an internationally renowned scientist and their team for making a significant contribution to biomedical discoveries that lead to therapeutic development. This year, the award recognises scientific and medical advances in the field of cancer research.

Caroline's group focuses on circulating tumour cells (CTCs) and the evaluation of their clinical utility as a source of biomarkers to aid patient treatment. These markers can be used to screen

and diagnose patients and importantly to monitor response to treatment in a non-invasive manner without having to perform a tumour biopsy. The overall aim of the group is to work towards developing a personalised approach to medicine where patients get the treatment tailored to their specific cancer characteristics. Caroline was formally announced as the laureate of this Prize at the prestigious Singer-Polignac Foundation in Paris on 28 November 2012. When receiving the award, Caroline said: "I am truly honoured to receive the 2012 Pasteur-Weizmann/Servier Prize. The award will support our translational cancer research into specific markers of circulating cancer cells and also the group's work in clinical trials to monitor disease and response to novel drugs." Caroline further stated: "The equipment required to analyse CTCs and understand their biology calls for huge investment. The Prize will be a very welcome boost to our funds."

The prize money will fund cutting-edge equipment for the purification of CTCs, increasing the number of trials the team can conduct and helping them to identify and characterise new molecular markers.

MCRC Updates

Autumn Marks the Start of Construction Work on New Cancer Research Building

Construction work on the new Manchester Cancer Research Centre (MCRC) building has now started, marking a new phase for cancer research in Manchester.

Following approval of building plans by Manchester City Council’s Planning Committee in March 2012, enabling work on site began in the spring as scheduled. Scientists in the new building will be focused entirely on early cancer research that aims to understand how cancer starts, develops and progresses. They will translate this information into improved tests and treatments for cancer patients with the overarching aim of improving patient survival. “The new MCRC research building complements existing facilities on the site and has been designed to facilitate collaboration between researchers to speed up the translation of laboratory discoveries into clinical trials and ultimately patient benefit,” said Professor Nic Jones, MCRC Director.

Manchester has recently received a £12.8 million funding boost following a successful bid by The University of Manchester to the UK Research Partnership Investment Fund (UKRPIF). The funds – announced by the Higher Education Funding Council for England (HEFCE) – have been awarded to the University to part fund the construction of the building. They will also provide a range of specialist research equipment that will be central to future partnerships with industry and research charities for the benefit of cancer patients.

The new £28.5 million laboratory research building will accommodate 250 staff, with scope to colocate some of the cancer research groups from The University of Manchester’s main campus. Overall, the new building provides space for an additional 150 scientists on the site and over 6,000m² for expansion of research activity. Working alongside these researchers, The Christie will re-locate around 100 staff from its clinical trials coordination unit to the top floor of the building. With the project now well underway, a fly-through of the MCRC research building has been developed to provide a glimpse of the first-class facilities that are essential for the expansion of cancer research in Manchester. The new facility is due to be completed in summer 2014.



View of the new MCRC building from Wilmslow Road



View of the new MCRC building from Wilmslow Road



Well-equipped research laboratory



Space to work and think outside of the laboratory



Breakout zone to facilitate collaboration and networking

Timeline

- | | |
|---------------|---|
| March 2012 | Planning approval obtained |
| May 2012 | Enabling works on site started |
| November 2012 | Breaking the ground event marks start of construction |
| Summer 2014 | Building completed and ready for use |

Cancer Survivors Break the Ground

On Thursday 8 November 2012, inspirational cancer survivors took the first step in starting construction of the new Manchester Cancer Research Centre research building.

Stan Parker, aged 73, from Salford, together with nine-year-old Amber Irvine, from Ashton-Under-Lyne, began the excavation of the new site. They dug the first piece of ground that will be the foundations of one of the largest cancer research centres in Europe.

Amber Irvine was diagnosed with acute lymphoblastic leukaemia in 2009. Following two-and-a-half years of chemotherapy, Amber has made a good recovery and has been in remission from cancer for 12 months. Mum Samantha Irvine said: “We have faced some very tough times over the past few years, but Amber has remained brave throughout. It is fantastic to know Amber is playing a small part in helping to create a building which is going to save future generations affected by cancer – a disease which has had such an impact on our lives.”

Stan Parker was diagnosed with oesophageal cancer in 2004 and had surgery to remove most of his oesophagus. The following year his cancer spread to his liver and he underwent intensive chemotherapy at The Christie. In 2006, Stan joined a clinical trial

of a new drug, tremelimumab, and six years later he is still on the same trial.

“I have received the most fantastic cancer treatment here in Manchester. It makes me incredibly proud to know that Manchester Cancer Research Centre researchers will be on my doorstep and are going to make such a difference for people like me diagnosed with the disease in the future. Without the vitally important research into cancer which has happened in this city, I would not be alive today.”



Cancer survivors Amber Irvine and Stan Parker break the ground with Professor Nic Jones

More Tomorrows Fundraising Campaign

To fund the construction of the new Manchester Cancer Research Centre building, Cancer Research UK, The University of Manchester and The Christie have launched a fundraising campaign – More Tomorrows.

The new cancer research building will cost £28.5 million and the partners have already raised over 40% of these funds. The More Tomorrows campaign will raise the remaining £16 million for the capital costs of the building. With funds already received from HEFCE to the University, and a £1 million donation to Cancer Research UK from the PACCAR Foundation, we are well on our way.

For more information about the More Tomorrows campaign, visit our website www.mcrc.manchester.ac.uk/moretomorrows or follow us on Twitter @More_Tomorrows.

MORE
TOMORROWS
MANCHESTER
REVOLUTIONISING CANCER TREATMENT

The Christie
NHS Foundation Trust

MANCHESTER
1824
The University of Manchester

CANCER
RESEARCH
UK

In the Spotlight With Kiran Batta

From the Stem Cell Biology Group



Kiran has been at the Institute as a Post-doctoral Fellow for a year having joined us directly from Penn State University, USA.

His research focuses on reprogramming skin cells to blood cells. When he is not at bench, he either runs or reads.

1. What is your favourite part of the UK?

Lake District

2. What was your best ever holiday and why?

New York, Strangely I felt home even though New York isn't my home.

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

Ted.com, You get to listen to expert speakers from all walks of life

4. What is your favourite film?

CRASH

5. What is your favourite band/singer?

John Mayer

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

Detective

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

Do not find a reason to be Happy

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

My Wife, Solar Power Panels and a Caravan?

9. What three pieces of music would you like to take to the desert island?

Bollywood music, Beatles and Buddhist Chants

10. What is your greatest fear?

Idea of quitting Science

11. How would you like to be remembered?

With a smile

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

I am happy with my past

13. What is your signature dish to cook?

Tamarind Rice

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

Build a home for old people and a nice house for myself

15. What is your idea of perfect happiness?

Being with loved ones

16. What keeps you awake at night?

Failed experiments

November

A group of fearless Paterson staff grew and groomed their moustaches during November as part of the 'Movember' fundraising campaign.

The aim of Movember is to raise vital funds and awareness for men's health, specifically prostate cancer and testicular cancer. We all enjoyed following the progression of their Mos from scruffy stubble to triumphant tashes as you can see from the photo below!

Their current fundraising total is £1313.



Mo Bros from L to R: Ricardo Gândara, David Jenkins, Steve Alcock, Denis Alferez with Ian Waddell behind.

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