Paterson
Institute for Cancer Research

Paterson Institute

newsletter

The Newsletter for the Paterson Institute for Cancer Research

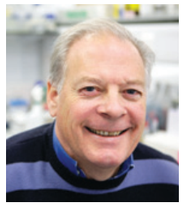
Cell Division Success

Issue 27 - June 2013

MANCHESTER 1824
The University of Manchester

CANCER RESEARCH UK

Director's Introduction



Peter Stern

In July, Peter Stern will retire after twenty-four years as a Senior Group Leader in the Institute. During this time he has made many valuable contributions to the field of cancer immunology, in particular with his work in harnessing the immune system to attack the 5T4 protein which is highly expressed in many carcinomas.

His pioneering discoveries have led to therapeutic approaches involving 5T4 progressing to late phase clinical trials. He is not stepping away from research completely as he will remain actively involved through an honorary position with the University's Institute of Cancer Sciences and, in particular, will continue his fruitful collaboration with Vaskar Saha to study 5T4 and its association with acute lymphoblastic leukaemia. I would like to take this opportunity to thank Peter for his contributions to the Institute over the years and to wish him all the best for the future.

It is always a pleasure to report on various notable achievements by members of the Institute. The work of Iain Hagan, and his Cell Division Group, was recently reviewed by an international panel of cell cycle experts who rated his research very highly. Iain is extremely well regarded in his field, not only for his research output but also for his wider contributions through organising meetings and courses, sitting on grant committees and providing novel reagents to the cell cycle community. This level of contribution is mirrored by his activities in the Institute which include his role as the inaugural chair of the Education Committee which plays a very important role in supporting our students. In 2011, he took on a pivotal responsibility as part of the Institute's Senior Management Team during the directorial transition. I would like to congratulate Iain on his recent success and thank him for all of his hard work and contributions to the Institute over the last few years. I look forward to further exciting discoveries by the Cell Division team through their work in unravelling the complexities of mitotic commitment and exit.

Giacomo de Piccoli and Dragana Ahel have both been awarded Career Development Fellowships from Cancer Research UK to start their own research groups studying the regulation of genome stability. Giacomo, a post-doctoral research fellow in the Cell Cycle Group will move to the University of Warwick where he shall continue his work on the S phase checkpoint. Dragana will study the role of SNF2 type ATPases at the University of Oxford. Bill Harris, who recently completed his PhD in the Leukaemia Biology Group, is the recipient of the Paterson Institute Dexter Award for Young Scientists 2012 as well as being judged the Institute of Cancer Sciences/Paterson Institute for Cancer Research Postgraduate Student of the Year. I would like to extend my warmest congratulations to all for these prestigious awards and wish them all the best as they embark on the next stage of their careers.

Finally, I would like to congratulate everyone who took part in the recent gruelling 40 mile Keswick to Barrow walk raising vital funds and awareness for Cancer Research UK and to thank everyone who gave their time to support our recent annual Schools' Day.

Engaging with our supporters, whose generosity allows us to carry out our research is extremely important and for the last six years, our local Senior Research Engagement Manager, James Dunphy, has enthusiastically and effectively coordinated these events. James has done a superb job in developing links with our local fundraisers and providing opportunities for researchers to meet our supporters. Furthermore, he has also played a wider role in Paterson life in his capacity as goalkeeper for the Institute football team and as a member of the editorial group that compiles this newsletter. James will be taking on the new challenge of leading local engagement for CR-UK researchers across the northern half of England as well as Scotland. Happily, this new position will ensure that we will still see him around the Institute from time to time, and I would to take this opportunity to wish him all the best in his new role and thank him for all his hard work at the Paterson Institute over the last six years.

Richard Marais
Director

Front cover:
Members of the Cell Division Group: Front (L-R): Ben Hodgson, María-José Villalobos Quesada (joint with the Applied Computational Biology and Bioinformatics Group), Iain Hagan, Ye Dee Tay. Back (L-R): Agnes Grallert, Kuan Yoow Chan.

Fundraising

Sporting Legends go Head to Head in Celebrity Sports Quiz

Manchester United legend Roy Keane alongside Professor Nic Jones, Director of the MCRC, Chief Scientist of Cancer Research UK and ardent Manchester United fan

Sporting legends recently went head to head at the Bobby Moore Fund Celebrity Sports Quiz in aid of the "More Tomorrows" fundraising campaign for the new Manchester Cancer Research Centre (MCRC) research building. Hosted by Dan Walker, Colin Murray, Mark Chapman and Kelly Cates, the event raised £60,000.

The interactive quiz, with questions set by ITV's 'Voice of Football' Clive Tyldesley, was held at The Point at Lancashire County Cricket Club. It attracted a host of sporting celebrities including John Barnes MBE, Roy Keane, Ricky Hatton MBE, Gareth Southgate, Pat Nevin and Kevin Sheedy. John Barnes wowed guests with a surprise live rendition of his 'World in Motion' rap, the memorable hit by New Order produced for the England football team's 1990 FIFA World Cup campaign.

The Bobby Moore Fund was established by Stephanie Moore MBE in partnership with Cancer Research UK in 1993. The fund was set up in memory of her husband, World Cup hero, Bobby Moore OBE, who died from bowel cancer. Stephanie Moore said: "When we decided to roll out our flagship London fundraising event, the Celebrity Sports Quiz, in a new city in the UK, Manchester seemed the obvious choice.

"Vibrant, dynamic and arguably the sporting capital of the North, Manchester has also historically played a crucial role at the forefront of cancer research. For more than a century, scientists and doctors in Manchester have been pivotal in the advancement of cancer research and care around the world. With more pioneering research, Manchester can become a world leader in the fight against cancer, creating more tomorrows for more people."

For more information about More Tomorrows, please visit **www.moretomorrows.org**

Researchers of the Future Visit the Paterson Institute

The Paterson Institute recently welcomed 32 local sixth form students. They all took part in practical scientific research as part of the Institute's annual schools' day. The aim of the day is to engage with local schools, giving students a practical 'hands on' insight into a potential career in cancer research, whilst also highlighting the impact of our work.

This is the ninth year the event has taken place, having initially been established by the late Dr Les Fairbairn. The programme was developed in line with the A-Level syllabus but also expanded to highlight the work that happens beyond the students' current learning.

Throughout the day, the students had the opportunity to visit three areas of work for 90 minute sessions. The Paterson had representatives from three groups (Drug Discovery, Cell Signalling, and the Molecular Biology Core Facility) to help organise the activities.

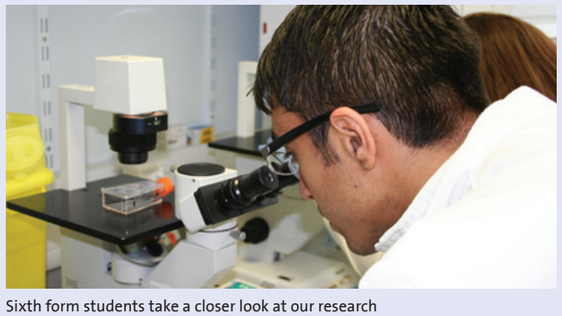
The feedback from the students was excellent, with all stating that they found it interesting, informative, easy to understand and relevant to their studies, with a high percentage of them indicating they would consider a career in cancer research. When asked what they enjoyed most about the day three students replied:

"Cell signalling /Molecular Biology – very relevant topics to my A-Level studies, therefore gained a deeper and more rounded insight in cells, particularly DNA."

"The Practical aspects in all 3 sessions as it gave the opportunity to use real lab equipment, which isn't available in school."

"Drug discovery was the most enjoyable as I enjoy chemistry and want to do pharmacology in the future."

Thanks to all the groups involved in organising, setting up and delivering this fantastic event.



Sixth form students take a closer look at our research

The Keswick to Barrow Walkers' Challenge

By Gill Campbell and Darren Roberts

Happy that it's all over

After signing up in January to what was termed "a Walk in the Park", and following several months intense training, three teams from the Paterson Institute took part in the 47th Keswick to Barrow walk on Saturday 11th May. Teams of between six and twelve people walked the 40 mile route through the Lake District in a single day to raise funds for charity.

After catching the "Happy Bus" from Barrow at 4:00am, we arrived at Keswick to slightly damp conditions with some snow lingering on the surrounding fells. The event began at 5:30am with the elite runners racing off whilst we followed on behind through the muddy fields and track that marked the start of the walk. The route led us along the picturesque west shore line of Thirlmere with the rain setting in before the lake end had been reached. Trudging headlong into horizontal rain over Dunmail Raise down to the first checkpoint at Grasmere, it became apparent this was going to be a very soggy day indeed, so we were all grateful to see our first support car manned by Crispin Miller, despite having only completed one quarter of the course.

Following the welcome respite, walkers were immediately challenged with the steepest climb of the route (a 25% incline!) over the notorious Red Bank before descending into Elterwater, a charming village at the foot of the Langdales that were, naturally, obscured in mist. We climbed once again to join the road to Coniston and endured miserable conditions as persistent heavy rain was aggravated by chilly winds. At the northern end of Coniston we were even more grateful to see the friendly faces in the second support car. Spirits were raised after donning a fresh pair of socks and we headed down the peaceful east side of Coniston Water to reach the halfway mark and a hot lunch. After some vital nourishment we continued our journey along Coniston Water and were compensated with a miraculous change in weather; brilliant sunshine, blue skies and a tremendous view of the Lakeland fells behind us.

Spurred on, we met with our final support car having walked the distance of a marathon, though were still to face the daunting, progressive climb up onto the wilds of Kirby Moor and another 14 miles to the finish. After a brief hail storm (why not!), the sun returned as the climb continued and we were rewarded with stunning views and our first glimpse of the sea. As we descended through the villages of Marton and Dalton, we were encouraged by locals lining the streets offering drinks and sweets. The final excruciating mile along Abbey Road to the finish in Barrow was undoubtedly the longest but all of us did fantastically well and made it to the end in some excellent times despite the walk being labelled one of the wettest in recent memory. Matthew Martin was the fastest Paterson participant in a superb time of eight hours and two minutes.

All the walkers would like to express gratitude to those who sustained us on the day, either as part of the support team or locals who cheered us on, which gave us that crucial extra boost to keep going. We would also like to thank those who sponsored us and helped raise over £6000 which will be divided between Cancer Research UK and The Christie. Next year's walk will be on the 10th May 2014; several of this year's walkers claimed they were keen to participate (but only in more clement conditions).

Walker	Time	Position
Matthew Martin	08:02:53	234
Kiran Batta	08:34:30	321
Koorosh Korfi	09:50:51	637
Zuzana Koledova	10:08:21	742
Ricardo Gândara	10:19:58	809
Bruno Simões	10:20:02	811
Kelly Brooks	10:30:17	875
Andrew Renehan	10:53:45	1035
Danish Memon	11:05:08	1105
Eamonn Morrison	11:18:51	1194
Romina Girotti	11:18:57	1195
Kate Hogan	11:19:04	1197
Darren Roberts	11:33:08	1280
Colin Hutton	11:33:28	1283
Julie Brazzatti	12:04:58	1492
Fran Shaw	12:05:00	1493
Gareth Hughes	12:05:01	1495
Clare McManus	12:23:12	1617
Andy George	12:32:35	1681
Siana Peters	12:32:39	1682
Yaoyong Li	12:40:45	1704
Gillian Campbell	12:41:06	1705
Keren Millea	12:42:54	1723
Eleanor French	13:26:56	1894
Paul French	13:27:00	1895
Ling Yu	13:56:28	1958
Hui Sun Leong	14:23:57	1991
Janet Taylor	14:24:05	1992

Finishing times for all the Paterson Participants.

Kiran Batta who finished the course in an impressive 8hrs 34mins

Jan Taylor and Hui Sun Leong wrapped up well

Danish Memon after 10 miles

Relay for Life 2013 – Team Members Wanted!

We have once again entered a team in this year's Stockport Relay for Life. This is a 24 hour event organised by volunteers, which raises around £30,000 for Cancer Research UK and this year will take place at Bramhall Rugby Club on Saturday 29th June. The event is a fantastic opportunity for us to show the fundraisers that we appreciate their efforts and to be involved in it is great fun.

About Relay for Life

Throughout the year, teams of 8 to 15 people get together and fundraise in their local communities to support the work of Cancer Research UK. Then everyone comes together in an inspiring overnight celebration and commemoration that unites the whole community.

On the day of Relay for Life Stockport, you can expect a celebratory mix of music, games, entertainment, food, fundraising and perhaps a few surprises! Whilst the event is in full swing, members of each team will take turns to walk around the track for the duration of the Relay. All events are overnight as this marks the fact that cancer never sleeps.

Relay for Life Stockport will begin with the inspiring Survivors' Lap of Honour. Cancer survivors will walk the first lap of the course, cheered and supported by the community. Together we celebrate life and the efforts we are all making to help beat cancer.

Some of the Paterson Scientists' team at last year's Relay for Life event

At the end of Relay for Life Stockport, everyone joins together for a final lap to celebrate their fundraising achievements and look back on an unforgettable experience.

Please contact Steve Lyons and Roshana Thambyrajah if you would like more information.

Breaking the Commitment

How the Cell Division Group is using the power of yeast genetics to identify novel anti-mitotic therapeutic strategies

By Iain Hagan

Iain Hagan

We exploit the simplicity of fission yeast to identify core principles of cell division and growth that are conserved from yeast to man. With 4000 genes, no alternative splicing and limited isoforms of each conserved component, we can move with a speed and precision that is currently unattainable in humans.

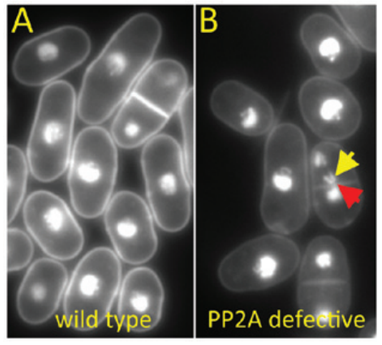
Cancer arises when the balance between quiescence, proliferation and death is adversely tipped in favour of proliferation, leading to considerable interest in looking to the cell division cycle for novel therapeutic targets. The success of anti-microtubule agents in the clinic has fuelled a particular focus on mitosis.

The spindle assembly checkpoint (SAC) delays further mitotic progression when chromosomes fail to attach appropriately to the mitotic spindle. SAC activation severely attenuates the destruction of the pro-mitotic factor Cyclin B to extend the period during which chromosomes can be captured by the spindle. While a SAC imposed delay is advantageous, indefinite arrest within mitosis would sustain a cell that is clearly having problems with genome integrity – a veritable time bomb. The duration of the SAC imposed arrest is therefore limited and cells eventually progress to one of two alternative fates even though chromosome attachment defects persist. These fates are death or mitotic slippage. Slippage is an unstructured departure from mitosis that occurs when Cyclin B levels dip below the threshold required to maintain the mitotic state. Slippage returns cells to G1 where the abnormal karyotype is detected and death is triggered. Taxol is believed to work so well in the clinic because it stabilises microtubules to perturb chromosome attachment, thereby extending checkpoint activation in all cells into the phase that triggers suicide. However, Taxol stabilises microtubules throughout the cell cycle leading to significant neuropathy prompting the question "Can we exploit our knowledge of mitosis to generate more specific agents that exceed the potency of Taxol but lack the side effects arising from microtubule stabilisation throughout the cell cycle?" We address two aspects of this activity; mitotic commitment and mitotic exit.

The rationale for therapeutic intervention in mitotic exit is clear. Blocking exit prevents slippage thereby directing cells towards the only available alternative fate: suicide. Both protein phosphatase 1 (PP1) and protein phosphatase 2A (PP2A) have been linked to the promotion of mitotic exit. We recently uncovered a direct molecular linkage between these phosphatases that drives exit. Collaboration with Jon Pines' CR-UK funded group in the Gurdon Institute has established that these controls are conserved to man. We believe that this molecular link applies beyond cell cycle controls and so will impact heavily on signal transduction research where PP2A is a major tumour suppressor.

The potential of manipulating mitotic commitment for therapeutic gain stems from the DNA integrity checkpoints. These checkpoints block mitotic commitment when DNA is damaged or replication is incomplete. The "oncogenic stress" arising from the instability of tumour karyotypes places unnecessary strain/reliance on integrity checkpoints in tumour cells, leading to the belief that normal cells will tolerate greater manipulation of mitotic commitment controls than tumour cells.

Mitotic commitment is driven by Cdk1-CyclinB. Cdk1 phosphorylation by Wee1 kinase restrains activity until Cdc25 removes this phosphate to promote mitotic commitment (a relationship defined in CR-UK funded work with fission yeast and frogs by Paul Nurse and Tim Hunt). Encouragingly, Wee1 inhibition is proving highly effective in pre-clinical models as either a single agent or in combination with DNA damage. Clinical trials are eagerly awaited.



Chromatin and cell wall staining of wild type (A) and PP2A defective (B) cells that reveals chromosome segregation errors (yellow arrow) and cytokinesis through chromatin (red arrow) when PP2A function is compromised.

We find that Cdk1-CyclinB activation is critically sensitive to events on the centrosome. More specifically, recruitment of PP1 to a scaffold molecule, Cut12, on the fission yeast centrosome dictates the timing of mitotic commitment. Removing the PP1 docking site from Cut12 abolishes the requirement for Cdc25. The interplay between Cut12 and PP1 influences the activity of another Cut12 partner, the protein kinase polo. Polo activity is enhanced when PP1 cannot bind Cut12 yet depressed if PP1 docking is promoted. Consistently, polo activation on the centrosome and nowhere else in the cell triggers mitotic commitment. We are therefore seeking further Cut12 partners, human equivalents, and using proteomic approaches to map the polo kinase phospho-proteome. Polo was identified by David Glover's Cancer Research Campaign funded work on fruit flies in the 1980s and Polo inhibitors are now in phase 3 clinical trials.

Polo Triggers Take Off

This study uses the fission yeast *Schizosaccharomyces pombe* to uncover the mechanisms that influence the timing of cell division, a process that has implications in cancer growth and is therefore a potential therapeutic target. In their second publication in *Nature Cell Biology* within six months, the Cell Division Group describe the interaction between key components that determine when cells undergo mitosis. Since it is recognised that cancer is caused by defects in cell cycle control, the processes central to cell cycle progression can be exploited for developing cancer therapies. The onset of mitosis is therefore an important target.

Before a cell can divide it must grow (G1 phase), duplicate its chromosomes (S phase), check that duplication is completed (G2 phase) and then separate its chromosomes (M phase) for exact distribution between the two daughter cells. These different processes are coordinated exquisitely in the cell cycle. Key players are the protein kinases that drive the cell through the cell cycle by reversible phosphorylation of other proteins.

It is known that commitment to mitosis is regulated by a feedback loop that balances Wee1 kinase and Cdc25 phosphatase activities towards the mitosis promoting factor (MPF). The MPF is comprised of a cell division cycle (Cdc2) kinase and an activating cyclin. A crucial component of the feedback loop is the Polo kinase Plo1, which modulates the activity of the spindle pole component Cut12, suggesting that commitment to mitosis is promoted by events on the spindle pole bodies (SPBs).

In this paper, several elegant approaches have been adopted to examine the SPB components to elucidate how their activities influence cellular functions driving mitotic commitment. The method employed cleverly takes advantage of the similarity in the ATP binding domains of protein kinases. Generating analogue-sensitive kinases, which contain mutated ATP-binding sites, allows the kinase of interest to be selectively inhibited without blocking the activity of endogenous kinases. The analogues are then removed to restore the function of the kinase in question to determine the impact on mitotic commitment. In this study, a series of experiments were undertaken to assess the consequences of blocking or mimicking phosphorylation on Cut12 and of targeting active Cdc2 or Plo1 to different locations in the cell.

Significantly, these experiments demonstrate that feedback activity appears on SPBs long before it finally drives global mitotic commitment. They indicated that MPF activity is essential for Plo1 recruitment to the SPB in late G2 phase and that Plo1 activity at this site dictates mitotic commitment. In turn, this activity was found to immediately trigger a morphogenetic switch called NETO (new end take off), which initiates the growth at the cell tip that was created by cytokinesis in the previous cell cycle.

Overall, the Cell Division group have illustrated that the SPB, and by implication the centrosome, behaves as a stage where the integration and coordination of signals from various signalling pathways are directed to control cell-cycle progression. It is established that in human cells active MPF appears first on centrosomes, highlighting that links between the equivalent components in humans and cancer can enable such findings to be translated into the more complex controls of human cell division.

Ref: Grallert A, Patel A, Tallada VA, Chan KY, Bagley S, Krapp A, Simanis V, Hagan IM. (2013) Centrosomal MPF triggers the mitotic and morphogenetic switches of fission yeast. *Nature Cell Biology*, **15(1)**:88-95.

Latest Developments in the Core Facilities

By Stuart Pepper

Yvonne Hey of the MBCF operating the Hi-Seq

Following the successful bid to the UK Research Partnership Investment Fund that was announced in November 2012, the Paterson received £8.7m towards the purchase of specialised instruments to provide the platform technologies necessary to implement personalised medicine for cancer patients in the North West. One of the first purchases was a pair of Next Generation Sequencing (NGS) machines, an Illumina HiSeq 2500 and MiSeq, which were delivered to the Molecular Biology Core Facility (MBCF) between Christmas and New Year, ensuring that we benefited from an end of year discount.

Acquisition of these two platforms allows a significant step up in the capability of the MBCF to support a variety of workflows. The two most common applications for NGS instruments are sequencing entire genomes, or selectively sequencing areas of the genome that code for proteins (the exome). Alongside these applications we also want to sequence transcriptomes from cancer samples; using NGS it is possible to sequence either the whole transcriptome, selectively sequence protein-coding messenger RNA, or select short RNA molecules for microRNA profiling. The final application area that we are supporting will be Chromatin Immunoprecipitation (ChIP) protocols. Since the instruments were installed in early January, we have produced several data sets including budding yeast genomes, human exomes, ChIP samples and transcriptomes.

The throughput of the HiSeq is impressive; an eleven day run on the instrument can generate three billion sequence reads of 200 bases – enough to generate 50-fold coverage of four complete human genomes in under two weeks. The version that we have bought also has a rapid mode that allows the generation of 120Gb of data in just over a day and has the potential to generate entire human genome sequences within a week of receiving samples.

The MiSeq is a lower throughput instrument that provides rapid turnaround sequencing services using a high level multiplexing approach. Custom-designed panels for specific cancer genes can be sequenced within one week, allowing potentially thousands of patients a year to be screened. This platform is perfectly suited to the development of human diagnostic services and can be used to inform real time clinical decisions to improve cancer patient care.

Staff News

Andrew Porter with new arrival George and his other son Benjamin, who is three

Baby Boy for Andrew Porter

Andrew Porter (Cell Signalling) and his wife Aliya celebrated the birth of their baby boy in March – George Samuel Porter was born on the 21st March 2013, weighing 4.5kg. George is doing very well and has already enjoyed meeting the lab and had a trip to the Red Lion Pub!

Andrew also won the poster prize at the 2012 Actin Meeting in Bristol, in December. The poster illustrated the work that went into the publication "β2-syntrophin and Par-3 promote an apicobasal Rac activity gradient at cell–cell junctions by differentially regulating Tiam1 activity", for which Natalie Mack, a former PhD student and post-doc at the institute, was the first author.

Special Guests Visit the Paterson

The Institute recently hosted some special visitors, the footballer Michael Carrick of Manchester United and England, along with Stephanie Moore - widow of the late Booby Moore who famously captained the England side to victory in the 1966 world cup. They came to the Institute on behalf of the England Footballers' Foundation to promote the Bobby Moore Fund, which was set up by Stephanie Moore and Cancer Research UK to raise awareness and funds for research into bowel cancer - the disease from which Bobby died twenty years ago. The visit was a great success with demonstrations by Alison McGonagle in the Drug Discovery Lab and Steve Bagley in the Advanced Imaging Facility. A big thank you to everyone who had to work around the film crew and journalists; the visit resulted in a story in the Daily Mail providing excellent publicity and exposure for both the fund as well as the Institute.

A match made at the Paterson

Hadir Marei and Tim Maculins

Tim Maculins and Hadir Marei met here at the Paterson Institute. Tim was a second year student in the Cell Cycle lab when Hadir, a new Cell Signalling student, caught his eye, and from that moment onwards love was in the air...

After a fantastic proposal in Cairo, Tim and Hadir decided to take a leap and tie the knot on 12-12-12 at the Mena House Oberoi, Cairo, Egypt.

Helen Bond and Andy Whittle

Helen Bond Wedding

Yorkshire-born Helen Bond (Cancer Research UK Senior Fundraiser, More Tomorrows Campaign) and Andy Whittle got married on the 6th April at an intimate candlelit ceremony in the wine cellar of The Angel at Hetton in the Yorkshire Dales. What better place to say your vows than in front of St Vincent, the patron saint of wine growers! Reception (party!) followed at Cracoe Village Hall where guests enjoyed a glorious afternoon of wining and dining before hitting the dance floor to the groom's carefully crafted DJ set. The new Mr and Mrs Whittle then jetted off to Antigua for some serious R&R!

Meet The Molecular Oncology Group

Developing Personalised Medicine for Melanoma Patients

By Richard Marais

Our group aims to develop new therapeutic strategies for cancer based on improved understanding of cancer biology. In particular, we focus on melanoma, and use a range of approaches including biochemistry, cell biology, molecular biology, mass spectrometry and next generation sequencing. We also make extensive use of model systems and tumour samples to understand the biology of each tumour so that we can begin to develop tailored treatments for individual patients. This approach is called "personalised medicine" because treatment is tailored to each patient's tumour, rather than using a one size fits all approach. Thus, our aim is to implement a personalised medicine approach for melanoma to improve treatment outcomes for patients and we anticipate that the lessons we learn in melanoma will be applicable to other cancer types.

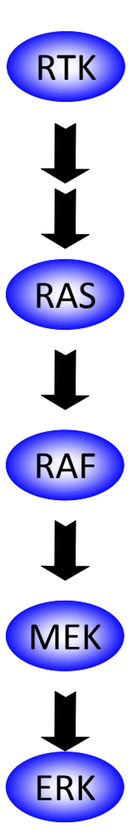


Figure 1
The RAS-RAF-MEK-ERK pathway is depicted. NRAS is activated downstream of receptor tyrosine kinases (RTK) and it activates BRAF, which in turn activates MEK and MEK activates ERK, driving cell growth and survival.

Melanoma is a potentially deadly form of skin cancer. In the UK, melanoma affects over 12,000 new patients and kills over 2,000 people each year. Work over the last decade has demonstrated that the RAS-RAF-MEK-ERK signalling pathway plays a critical role in this disease. RAS is a small G-protein that is activated downstream of receptor tyrosine kinases and RAF, MEK and ERK are cytosolic protein kinases that control cell growth and survival (Figure 1). There are three *RAS (HRAS, KRAS, NRAS)* and three *RAF (ARAF, BRAF, CRAF)* genes in humans. Notably, *NRAS* is mutated in about 20% of melanomas, and *BRAF* is mutated in a further 45% of cases.

We have found that the different genetic forms of melanoma display different biochemical properties. For example, the anti-diabetic drug metformin drives the growth of melanoma in which BRAF is mutated, but inhibits the growth of melanoma in which NRAS is mutated. This is because metformin increases the production of vascular endothelial growth factor (VEGF) in BRAF mutant, but not in NRAS mutant melanoma cells. Critically, VEGF encourages the development of new blood vessels into the growing tumours, increasing the flow of oxygen and nutrients and allowing the tumours to grow more rapidly. Agents that target VEGF overcome this effect and cooperate with metformin to suppress the growth of the BRAF tumours. These data highlight the importance of understanding the biology of each tumour if effective therapies are to be developed for individual patients.

Melanoma develops from specialised cells in the skin called melanocytes. These cells provide skin and hair tone, but more importantly, they protect us from the damaging effects of ultraviolet (UV) light radiation. UV light is present in sunlight and is produced by tanning devices, and it is the only known environmental risk factor for melanoma. The most common form of melanoma occurs on hair bearing skin that is intermittently exposed to UV light (recreational sun exposure) and we have developed transgenic models for melanoma that allow us to investigate gene-gene and gene-environment interactions that drive melanoma development. We are currently using these models to identify the genes that interact with BRAF and NRAS to drive melanoma development and to examine the role of UV light.

As an alternative approach to improving our knowledge of melanoma, we are also using next generation sequencing to reveal the landscape of mutations that occur in individual human melanoma samples. Over the last year, we have focussed on acral melanoma in particular, a rare form of melanoma that develops on the non-hair bearing skin of the hands and feet. These sites were thought to be protected from the damaging effects of UV light, but our sequencing revealed that some acral melanomas present a UV light DNA-damage "signature". This suggests that UV light also appears to play a role in the aetiology of some acral melanomas. We are also expanding our studies to examine the genetics of other rare forms of melanoma to allow us to gain further insight into melanoma biology so that we can develop new therapeutic strategies for the treatment of all forms of this disease.

A major breakthrough in melanoma treatment occurred with the development of drugs that inhibit BRAF. These drugs inhibit the RAS-RAF-MEK-ERK pathway in cells in which BRAF is mutated. Importantly, these drugs can achieve impressive clinical responses in patients whose tumours express the mutant forms of BRAF, but are ineffective in patients whose tumours express wild-type BRAF. Curiously, one of the unexpected side-effects of BRAF drugs is that they activate rather than inhibit the RAS-RAF-MEK-ERK pathway when RAS is mutated. This effect occurs because RAF drugs stabilise the formation of complexes between ARAF, BRAF and CRAF in the presence of active RAS. The complexes contain drug-bound, and drug-free RAF molecules and the drug-bound partners hyper-activate the drug-free partners, thereby hyper-activating the signalling pathway and stimulating the growth of the cells (Figure 2). Thus, while BRAF drugs inhibit the signalling pathway in cells in which BRAF is mutated, they activate the pathway in cells when NRAS is mutated and this effect is called the "*RAF-inhibitor paradox*".

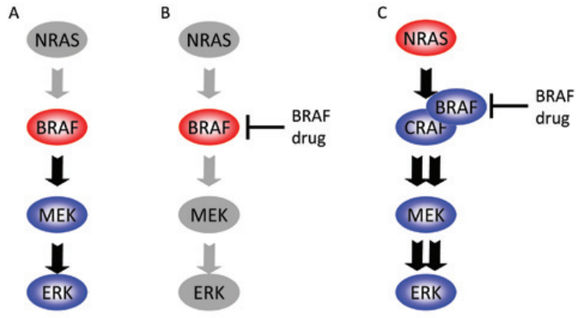
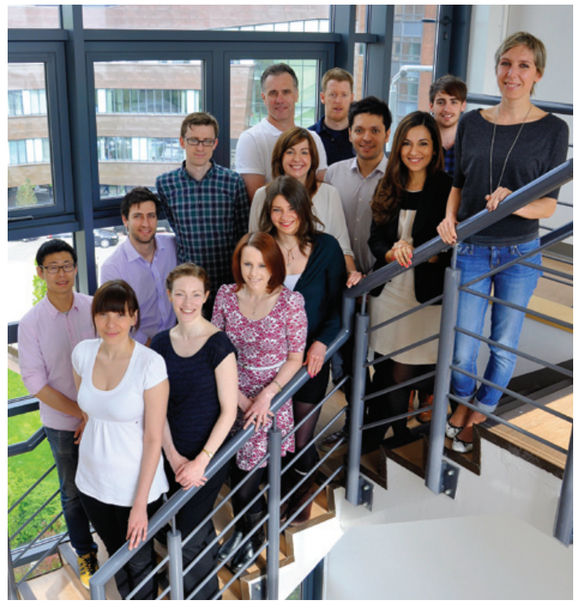


Figure 2
The RAF paradox. (A) In the presence of mutated BRAF, the MEK/ERK pathway is hyper-activated even though RAS is not active. (B) In BRAF mutant cells, BRAF drugs block BRAF activity and inhibit the activity of MEK and ERK. (C) When cells in which NRAS is mutated are treated with BRAF drugs, although BRAF is inhibited, it is driven into a complex with CRAF and hyper-activates CRAF, thereby driving paradoxical hyper-activation of MEK and ERK.

We have shown that the RAF-inhibitor paradox underlies the development of non-melanoma skin lesions (keratoacanthomas and squamous cell carcinomas) in about a third of patients treated with these drugs. Notably, this is not because the BRAF drugs act as tumour promoters *per se*; rather they act by accelerating the growth of pre-existing, pre-malignant tumours in susceptible patients. The drugs in effect place a growth-selective advantage on these pre-existing tumours, and this knowledge led us to discover that anti-proliferative agents such as 5-fluorouracil can be used to treat these lesions in patients for whom surgery is not an option.

Although BRAF drugs have provided a paradigm shift in the treatment of melanoma, unfortunately the responses to these drugs are generally short-lived and most patients will fail on treatment after a relatively short period of disease control. Furthermore, about 20% of patients do not respond to BRAF drugs despite the presence of a BRAF mutation. We have therefore continued to develop new BRAF drugs and are testing if these are effective in patients whose tumours are resistant to the pre-existing drugs. We are also studying how resistance develops in patients undergoing treatment.



The Molecular Oncology Group. Back row: (L to R) Haoran Tang, Mike Gavrielides, Matthew Martin, Richard Marais, Simon Furney, Eamonn Morrison
Front row: (L-R) Franziska Baenke, Clare McManus, Kelly Brooks, Kate Hogan, Berta Sanchez-Laorden, Koorosh Korfi, Romina Girotti, Grazia Saturno

Sarah Ejiama is the latest addition to the team

My Group relocated to Manchester in October 2012. We are a multi-disciplinary team that provides an excellent training environment for scientists and clinicians alike. Our philosophy is that patient care should be based on in-depth knowledge of cancer biology and we work at the basic-clinical interface to translate our basic research findings into patient benefit. At the Paterson Institute for Cancer Research we aim to continue to investigate the biology of melanoma and to use the knowledge from those studies to develop and implement a platform for personalised medicine for melanoma patients.

Education News

Where are they now?

We caught up with some of our former PhD students who have recently left the Institute to see how the next phase of their career is going. This includes Bill Harris who is the recipient of the Paterson Institute Dexter Award for Young Scientists for 2012.

Elvan Boke

I carried out my PhD studies in the Cell Division group at the Paterson Institute, before starting my current position as a post-doctoral research fellow in Tim Mitchison's group at Harvard Systems Biology. During my PhD, I worked with fission yeast and elucidated a novel mechanism of mitotic control via a phosphatase relay, and now, took on a completely different path with zebrafish and frogs to find out the mechanisms involved in germ cell determination and germ line assembly. It is actually interesting how useful my yeast genetics and biochemistry background has been for a wide variety of things.

After dealing with various pathways in detail, and placing them in the bigger picture of the cell cycle, now I can think of organismal problems in parts, which makes the design of experiments much simpler and the forward way of thinking much clearer. Also, I should confess I've already heard Iain (Hagan) in my head several times, reminding me of the proper controls for my experiments!

As for my new location, Harvard Systems Biology is a truly thrilling department to work in. We have an "open-door" lab policy here, and you can walk in and work in any lab, as long as it is associated with your problem of interest. The department is composed of a mixture of biologists, physicists and mathematicians, with very broad interests ranging from systems pharmacology for cancer treatments to mathematical modelling of cell size, and modelling antibiotic resistance in bacterial cells – so it caters to almost every taste. To compare Boston and Manchester – let's say, no matter how much I liked Manchester, I can't deny the fact that I am enjoying the (mostly) sunny Boston nowadays!

Lilly Sommer

I finished my PhD in the Inositide laboratory in June 2012. During my studies, I identified new interactors for phosphatidylinositol-5-phosphate using Surface Plasmon Resonance technology. Amongst others, I found a transcription co-factor that appears to require the binding to a lipid in order to function properly.

After completing my PhD, I worked in Science Communications, first at the Manchester Cancer Research Centre and now in Vienna at the Max F. Perutz Laboratories. My job essentially is to spread the message of what our scientists do and what is happening at the institute, both to the public and to the employees. In our team, we write press releases about the latest papers and events, prepare a monthly newsletter and the annual report, but we are also involved in event organisation, such as the recent press conference with the Austrian Federal Minister for Science and Research.

I really enjoy the job, it's very diverse in its tasks, I meet lots of different people, and it allows me to continue to stay in touch with science. My scientific background definitely makes it easier for me to understand the story that scientists want to publicise and help them make it accessible to a wider audience. Having managed a PhD project also helps to maintain focus when juggling several projects at the same time. Vienna is a great city with lots of culture and far too many delicious pastries.

Malgorzata Gozdecka (Gonia)

During my PhD in Nic Jones' group, I had a great opportunity to investigate the role of transcription factor ATF2 in cancer. Together with my colleagues, including Steve Lyons, I identified ATF2 as a critical mediator of tumour suppressive activity of JNK during liver tumour development. Furthermore, we uncovered the comprehensive set of JNK and ATF2 target genes which mediate this suppression. We have shown that the expression of these JNK-ATF2 regulated genes is frequently lost in several human tumours, which points out the need for selection against the pathway during tumour evolution.

In December 2012, I started my postdoctoral studies at the Wellcome Trust Sanger Institute in Cambridge under the supervision of George Vassiliou and Brian Huntly. My research project focuses on the understanding of the role of epigenetic regulators commonly mutated in human acute myeloid leukaemia (AML) for the development of this disease. The Sanger Institute provides a broad spectrum of cutting edge technologies, genetic mouse models, and has close collaborations with other institutes and companies. Thus, it offers a great opportunity to make substantial progress in the understanding of tumour biology and facilitating the current therapy.

Bill Harris – winner of the Dexter Award for Young Scientists 2012

Receiving the Dexter Prize at the end of my PhD capped the most productive, successful and enjoyable period in my life to date.

As is often the case with successful scientific discoveries, fortune played a part in some aspects of this project. In the first instance I feel fortunate to have completed my doctoral studies in the Leukaemia Biology group of Tim Somervaille, who helped instil such a high level of drive and focus whilst contemporaneously offering support and guidance whenever it was needed.

My project involved looking at how a loss in epigenetic regulation can be critical in maintaining leukaemia stem cells (LSCs), a compartment of cells within a given leukaemia which drive the disease. Epigenetics is a level of gene expression regulation which is catalysed by enzymatic activity and can therefore potentially be targeted pharmacologically. We identified an epigenetic regulator called LSD1 which is crucial for the propagation of LSCs and, in collaboration with the Paterson's Drug Discovery Unit (DDU), we developed inhibitors of LSD1 activity which show efficacy in primary patient leukaemia samples within a therapeutically relevant dose range. Based on this work, LSD1 inhibitors that we developed and others like them are currently being prepared for use in clinical trials. The success of this work afforded me the opportunity to speak about my work at the prestigious 2011 American Society of Hematology conference in San Diego and I was also awarded a scholarship to present the project at the 2011 European Hematology Association "Acute Myeloid Leukaemia: Molecular" conference in the south of France. In 2012 we published this work in Cancer Cell, a high impact and most respected journal in the field of cancer studies.

In keeping with the theme of fortune, the success of this work would not have been possible without two further important factors. Firstly, I was lucky to work with a group of people who epitomised the support, teamwork and collegial spirit needed to publish such a high impact paper. Secondly, scientists at the Paterson are fortunate to have such up-to-date and well-equipped core facilities within the Institute. I would particularly like to thank the Molecular Biology, Flow Cytometry and Biological Resources facilities for their roles in helping this project progress.

Following my doctoral studies I gained a place to study Medicine. Ultimately I hope to combine the skills and experience garnered from both basic research and Medicine to help reduce the gap between bench and bedside in terms of scientific discoveries and novel therapies. Maybe one day I will use the LSD1 inhibitors we developed in the clinic!

AACR 2013

By Danielle Potter

This year I was granted a BACR/CR-UK student travel award worth £1000, which assisted my attendance at the American Association for Cancer Research (AACR) annual meeting in Washington D.C. I was fortunate to be able to present a poster on my PhD project, which is aimed at investigating the rational drug combination of a PI3K inhibitor with a BH3 mimetic in colorectal cancer cell lines, to help improve therapeutic strategy for patients with more advanced and metastatic colorectal cancer.

This was my first international conference and I was a little nervous about going and presenting a poster but once I got there, and realised the enormity of the conference, it made me understand how fortunate I was to be a part of it and it all became very exciting. I received a great deal of interest in my poster and received a lot of positive feedback.

This was an awe-inspiring experience that opened my eyes to the bigger picture of cancer research. I was exposed to interesting, novel and stimulating research from leading institutes from around the world and met some pioneering scientists that left me totally inspired. It was such an honour to attend this meeting and it has left me even more motivated and content in my career choice. One day I would love to be given the opportunity to speak at such a prestigious conference as this.

Danielle taking in the sights of Washington D.C.

New Postgraduate Tutor

Ian Waddell recently took over the responsibility for students in CR-UK funded groups at the Paterson Institute in his capacity as Postgraduate Tutor. Ian is based in the MCRC Drug Discovery Unit at the Paterson Institute, which he joined in June 2011, as Head of Biology.

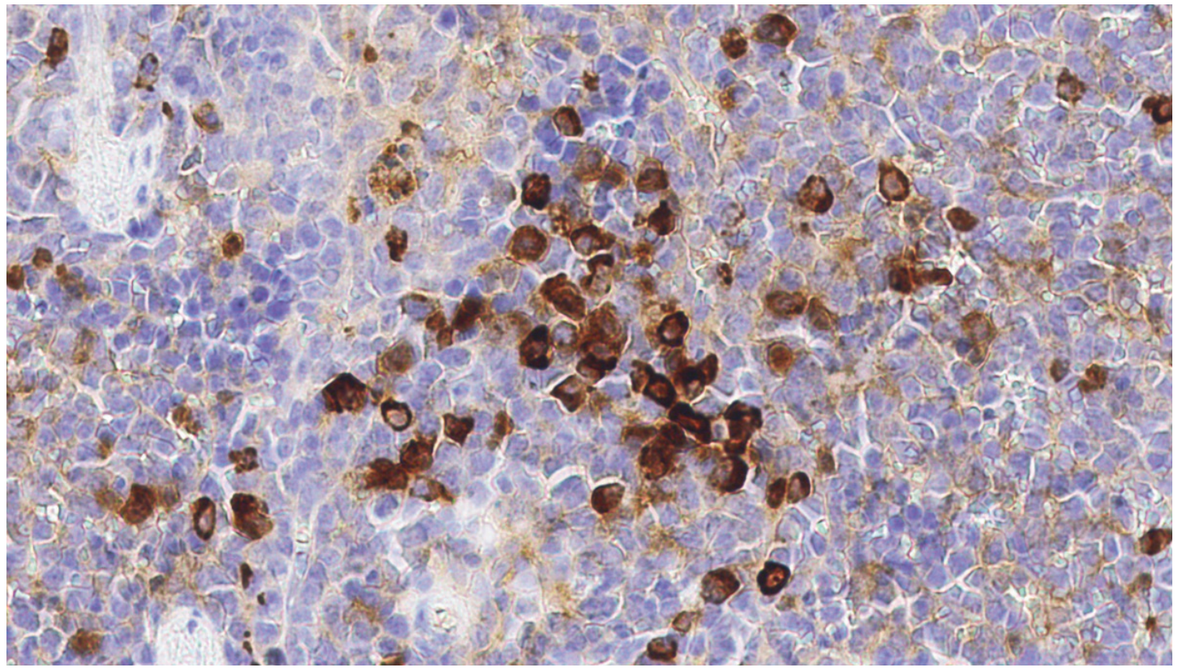
Ian gained his BSc and PhD in Biochemistry at the University of Dundee and continued there as a postdoctoral fellow and then a lecturer for five years. During this time Ian was a supervisor for PhD and MSc students, which he found to be very rewarding and a good experience for his new role as PGR tutor at the Paterson.

Ian worked for Zeneca from 1994 where his interest in Oncology began when he led the Cachexia team looking at preventing the skeletal muscle wasting associated with pancreatic cancer. Following the merger with Astra in 2000, he returned to Diabetes and Obesity as a project and line manager and was directly involved in a number of projects that have subsequently progressed to late stage clinical trials. In 2005, he moved into the Oncology group at Alderley Park as Director of Bioscience where, amongst other things, he led the high throughput screening, lead identification and lead optimisation groups (including the integrative pharmacology group). In the last three years at AZ, Ian was the Oncology Director of Discovery Medicine at Alderley Park and was responsible for the preclinical translational science aspects of all development compounds emerging from that site.

After 20 years in industry he is glad to have made the move back into a teaching environment and is excited about becoming more involved in the day-to-day life of the Paterson Institute. Ian's experience of managing large groups in industry has presented him with a wide range of different challenges over the years which he believes will serve him well in supporting students and guiding them through their PhDs.

When Ian completed his PhD (which he produced on a type writer!) he remembers that there was little, or no, support for students outside of their lab, whereas now there is a well-developed system to provide academic and pastoral support to students. It is this difference, along with obvious advances in technology, which he feels is the main benefit to completing a doctorate today.

Featured Publications



B-lymphoma cells driven by MYC oncogene undergo high rates of apoptosis (Caspase 3 staining), requiring the activities of JNK and ATF2 activities

Stress Signalling Pathways in B-Cell Lymphomas

In a recent publication in the journal "Oncogene", Jacek Walczynski, a former PhD student in the Cell Regulation Group, presented his findings about the activities of stress induced signalling pathways in some types of B-cell lymphomas.

Currently, in western countries, 1 in 5000 people is diagnosed with B-cell lymphoma, which comprises around 5% of all cancers. B-lymphoma cells are a malignant form of B-lymphocytes arrested at a specific stage of differentiation. A common feature in some B-lymphoma types, as in many other tumour types, is the aberrant activity of the gene MYC. Years of research have uncovered that MYC regulates cellular programmes for growth and is indispensable for tumours to establish why MYC is often referred to as a "Driver Oncogene". Understanding MYC-dependent activities would help in devising ways to combat tumour and lymphoma growth in particular.

It has been known that hyperactive MYC not only regulates tumour cell growth but that it also induces apoptosis, a specific form of cell death that often comes as a result of cellular stress such as DNA damage. The Cell Regulation Group has a longstanding interest in the molecular events triggered by cellular stress, in particular signalling pathways that involve JNK kinase. At the start of his investigations, Jacek found that lymphomas that have highly activated MYC also often show strongly active JNK kinase and upregulated ATF2, a stress induced transcription factor and target for JNK activation. To find out whether JNK and ATF2 activities were important in cellular processes triggered by MYC, he generated B-lymphoma cells that were highly active for MYC but were deficient in ATF2. Surprisingly, inactivation of ATF2 led to significantly reduced cell death triggered by MYC and to significantly more aggressive behaviour of lymphomas. In addition, JNK and ATF2 were shown to direct the induction of apoptosis in response to chemotherapeutic drugs but only once B-lymphocytes have progressed towards lymphoma stages by the actions of MYC. In its capacity as a transcription factor, ATF2 was shown to be at the top of a hierarchy of other transcription factors that regulate the activation of apoptotic genes. These results also imply that the evaluation of activated JNK and ATF2 in clinical samples of B-lymphoma may provide an indication of their sensitivity to chemotherapeutic agents.

Ref: Walczynski J, Lyons S, Jones N, Breitwieser W. Sensitisation of c-MYC-induced B-lymphoma cells to apoptosis by ATF2. (2013) *Oncogene* **Feb 18**. doi: 10.1038/onc.2013.28.

In the Midst of Death There is Life

Targeted Therapy -led by Tim Illidge, in collaboration with the Clinical and Experimental Pharmacology Group - have published their study describing how the immune system is required for complete tumour eradication. By introducing a gene which is fatal to cancer cells when expressed, they were able to determine the role played by the immune system in the success of cancer treatment. Traditionally, researchers have believed that the mechanism by which therapy causes tumour cells to die, known as apoptosis, does not provoke an immune response. Recently evidence has come to light that some therapies which induce apoptosis are able to provoke an immune response to the tumour cells.

By using a doxycycline inducible mutant of caspase-3, which was constitutively active, it was possible to induce widespread and coordinated apoptosis in tumours with up to 80% of the tumour undergoing apoptosis within 24 hours. This led to the release of the traditional danger signals, HMGB1 and HSP90, and tumour eradication in the presence or absence of a functional immune system. In the absence of a functioning immune system this tumour eradication was not sustained, indicating a role for the immune system in this process. Moreover, a functioning immune system provided protection upon rechallenge with tumour cells. This was also demonstrated when depletion of CD8 T cells allowed tumour regrowth following initial regression. This work has not only demonstrated that apoptotic cell death can elicit a CD8 T cell-dependent anti-tumour immune response but also that this response may be responsible for the long term eradication of the tumour and protection against rechallenge.

By taking this work forward it is hoped that increased understanding of how the immune system responds to apoptotic cell death within the tumour will lead to strategies for the generation and maintenance of an anti-tumour immune response. This may lead to the combination of conventional apoptosis-inducing anti-cancer therapies with immunotherapeutic strategies to enhance the immune response and long term tumour clearance.

Ref: Melis M, Simpson K, Dovedi S, Welman A, MacFarlane M, Dive C, Honeychurch J and Illidge T. Sustained tumour eradication after induced caspase-3 activation and synchronous tumour apoptosis requires an intact host immune response. (2013) *Cell Death Differ* **20**, 765-773.

Maintaining Integrity

All eukaryotic cells have to create a single and near perfect copy of their chromosomes in order to survive cell division. An exact replica of every chromosome is produced via DNA synthesis, a process fundamental to the understanding of cell proliferation in all organisms. The mechanics of chromosome replication are therefore especially relevant to human cancer, as the activation of oncogenes (genes that have the potential to cause cancer) is thought to cause defects in replication, which drive tumour development. Chromosome replication is an intricate process that is still relatively poorly understood. A deeper knowledge of the structure, function and regulation of the eukaryotic replisome will help optimise novel strategies that better exploit replication defects in tumour cells.

In a recent paper published in *Cell Reports*, Magdalena Foltman and Karim Labib from the Cell Cycle Group describe the replisome components in budding yeast that maintain chromatin integrity during chromosome replication.

To control gene expression in a tightly regulated manner, eukaryotic cells have evolved multifarious transcriptional machineries and chromatin states. The chromosome replication machinery is assembled in a stepwise process; the key regulated step being the assembly at origins of the essential DNA helicase known as Cdc45-MCM-GINS, which unwinds the parental DNA duplex at replication forks. The Mcm2-7 complex (the catalytic core of the helicase), having been loaded at replication origins during G1 phase, initiates chromosome replication by recruiting Cdc45 and GINS.

Chromosome replication severely disrupts the chromatin, the integrity of which is preserved by the transfer of parental histones and the deposition of new histones. The Cell Cycle group screened systematically for replisome components that bind to histone complexes released from chromatin in cell extracts of yeast. Analysis of gene expression patterns demonstrated that the Mcm2 helicase subunit and FACT (facilitates chromatin transcription) bind together to parental histone complexes that have been released from chromatin. Additional experiments suggest that FACT and Mcm2 are the most important of many factors in the replisome that are able to pick up histones. The finding that FACT is not recruited to Mcm2-7 at replication origins before initiation, but is subsequently present at DNA replication forks, indicates that FACT and Mcm2 help to retain parental histones transiently at the fork before deposition onto nascent DNA just behind the replisome.

Overall, this paper proposes that the eukaryotic replication and transcription machineries use similar histone-binding modules to process parental histones in order to preserve chromatin integrity during chromosome replication. Future studies will address how FACT associates with the replisome progression complex and how other replisome components might also contribute to the transfer of parental histones at replication forks.

Ref: Foltman M, Evrin C, De Piccoli G, Jones RC, Edmondson RD, Katou Y, Nakato R, Shirahige K, Labib K. Eukaryotic replisome components cooperate to process histones during chromosome replication. (2013) *Cell Reports*, 3(3):892-904.

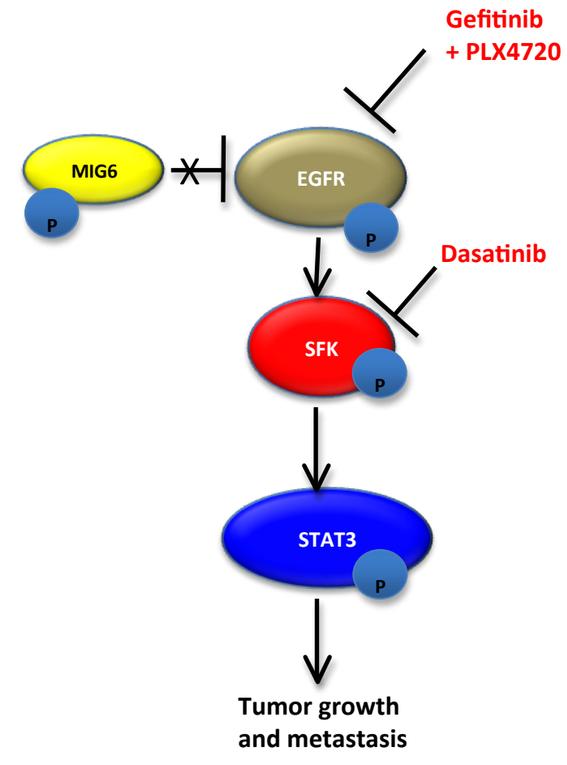
Two Drugs Are Better Than One

Melanoma patients who have tumours carrying mutations in BRAF can benefit from treatment with vemurafenib, a targeted therapy which inhibits mutated BRAF. However, after a short time they often develop resistance to this drug and, in some patients, the tumours are already resistant to this type of treatment. Work by Romina Girotti and colleagues in the Molecular Oncology Group shows that the growth of BRAF inhibitor-resistant cancer cells or tumours can be stopped by drugs which block a different biological pathway.

By developing melanoma cell lines which are resistant to vemurafenib, they were able to demonstrate the mechanism by which these cells become resistant and that by combining vemurafenib with another drug, dasatinib, they were able to overcome the observed resistance.

The resistant cell lines were developed by exposing BRAF mutant melanoma cells to increasing concentrations of the BRAF inhibitor PLX4720 over two months. After this, the phosphorylation state (an indicator of activity) of receptor tyrosine kinases in the cell lines was determined and it was discovered that EGFR phosphorylation was increased in the resistant lines. Further studies revealed that the downstream target AKT was activated and the negative regulator of EGFR, MIG6, was inactivated in the resistant cell lines providing further evidence for the role of EGFR in vemurafenib resistance. It was also noted that the drug resistant cell lines were more invasive than the sensitive ones but that invasion could also be blocked by inhibiting the EGFR pathway. This indicates that EGFR activation is not only increasing the resistance of these cell lines to BRAF inhibitors but also increasing their ability to invade and metastasise. Combining both BRAF inhibitors and SRC- related kinase inhibitors (or broad range kinase inhibitors) may help prevent the emergence of resistance in certain BRAF mutated melanoma patients. These findings highlight the need to understand the molecular mechanisms that underpin resistance to targeted therapies and the approaches that can be taken to determine which drugs might help an individual patient.

Ref: Girotti R, Pedersen M, Sanchez-Laorden B, Viros A et al. Inhibiting EGF Receptor or SRC Family Kinase Signaling Overcomes BRAF Inhibitor Resistance in Melanoma. (2013) *Cancer Discovery* **3**, 158-167.



The EGFR pathway becomes highly activated in cell lines which are resistant to BRAF inhibitors. This can be overcome by inhibition of this pathway by various drug treatments.

Recent Awards and Events

Major Award for Paterson Director Richard Marais

Professor Richard Marais, Director of the Paterson Institute for Cancer Research and head of the Molecular Oncology Group, is a world leader in melanoma research. Malignant melanoma is a potently deadly form of skin cancer. There are over 200 new cases of melanoma each year at the Christie NHS Foundation Trust and annually this disease kills over 2,000 people in the UK. Richard has recently been granted considerable funding by the Wellcome Trust through its prestigious Senior Investigator Award scheme. This significant award will enable Richard to make substantial advances towards developing personalised medicine for malignant melanoma.

This award builds on Richard's earlier success studying BRAF, a protein kinase belonging to the RAF (Rapidly Accelerated Fibrosarcoma) family that plays an essential role in the RAS–RAF–MEK–ERK–MAP signalling pathway responsible for normal cell growth and differentiation. Point mutations in the BRAF gene causes overactive signalling via the MEK and ERK pathways, leading to excessive cell proliferation and survival.

In 2002, Richard and others discovered that oncogenic BRAF is mutated in approximately half of human melanomas, which led to the development of BRAF-targeting drugs (vemurafenib and dabrafenib). Improvements have been achieved in progression-free and overall survival in 60-80% of BRAF mutant melanoma patients. Unfortunately, the remaining patients relapse after a relatively short period of disease control.

More recently, Richard and his team in Molecular Oncology have worked together to develop models of melanoma driven by BRAF and RAS oncogenes to investigate interactions between the genes and their environments. Richard has also described key differences between BRAF and RAS signalling in melanoma. Importantly, he identified that BRAF inhibitors activated, rather than inhibited, RAF in RAS mutant melanoma cells, an unexpected paradox in RAF signalling.

Richard and his group will undertake a five year study using parallel approaches in genomics and mass spectrometry to analyse tumour samples from BRAF mutant melanoma patients undergoing treatment with BRAF or MEK inhibiters. He proposes to characterise the molecular drivers of metastatic cancer and correlate this with clinical features, tumour responses and patient outcome. These studies will help refine patient stratification and biomarker development, which will be used to predict individual patient responses and mechanisms of resistance. Ultimately, it is Richard's ambition to optimise personalised treatment for melanoma patients by drawing treatment guidelines based on the results of these studies.

Paterson Postdoctoral Prizes

James Lynch receiving his prize

The first North West Bio-Pharma Postdoctoral Symposium, held on 8 March 2013 at AstraZeneca's Alderley Park, was well attended by numerous postdoctoral scientists from AstraZeneca and the Universities of Manchester, Liverpool, Leeds and Sheffield. It is with great pleasure that we proudly announce the news of our triple success at this event.

James Lynch of the Leukaemia Biology Group won the prize for best talk for his presentation on the novel role of the TTC5 protein in preventing apoptosis of acute myeloid leukaemia stem cells by regulating the turnover of MYC. These findings have recently led to a first author publication for James in *Cell Death and Disease.*

Bruno Simões of the Breast Biology Group won the runner-up prize for his talk on breast cancer stem cells and endocrine therapy resistance. He presented data demonstrating that breast cancer stem cells are not targeted by current endocrine therapies, indicating that drugs targeting these cells are necessary for the effective treatment of estrogen receptor-positive breast cancer.

Urszula Polanska, formerly of the Stromal Tumour Interactions Group, won the prize for best poster; she presented the results of her study focusing on the role of cancer-associated fibroblasts in progressing ductal carcinoma in situ.

Each winner was awarded an Amazon voucher. This is a great result for the Paterson Institute and illustrates the high calibre of our postdocs' research and their determination to be the best in their field.

Grant Success

Investigating 5T4 in Childhood Acute Lymphoblastic Leukaemia

Owen McGinn

Vaskar Saha, Peter Stern, and Owen McGinn have recently received a grant from Leukaemia & Lymphoma Research to fund their investigations into the childhood cancer, acute lymphoblastic leukaemia (ALL). In particular, this grant will allow Owen to expand on the previous observation that sub-types of B-ALL at a high risk of relapse express 5T4, a protein which the Immunology group has shown is involved in the invasion and migration of tumour cells. Work will focus on determining if 5T4 can be used as a marker of leukaemia initiating cells, a cell type previously linked to the recurrence of the leukaemia. To do this, work will test whether 5T4 is present on cells which are more drug resistant compared to those without 5T4 and try to determine if signalling by proteins previously associated with 5T4 function can alter the level of drug resistance.

For children with precursor B-ALL that relapse on current intensive chemotherapy regimens, second line therapy is challenging. Diagnostic markers that are predictive of poor treatment response are scarce, and modern treatment protocols base risk stratification mostly on in vivo response to treatment by monitoring persistence of minimal residual disease (MRD) after induction chemotherapy. Leukaemia progression does not appear to be associated with a high degree of ongoing genetic instability in ALL but rather with clonal evolution and selection of a limited number of genetic lesions. Several reports have led to the hypothesis that ALL may be maintained from a rare subpopulation of leukaemia initiating cells (LICs). Recent data using ALL samples from patients with treatment resistant disease has provided evidence that ALL is composed of highly related, but genetically diverse, clonal subpopulations. Patient cells with very high risk for relapse (VHR) ALL appeared to have greater numbers of LICs, allowing reconstitution of disease from injection of as few as 100 cells. Other studies suggest that ALL can be propagated as dynamic multi-clonal populations of LICs. Identification of markers and mechanisms common to B-ALL which are resistant to standard therapy could allow the evolution of less toxic and more effective therapy. This work will investigate the potential of 5T4 as just such a marker.

Research Travel Awards

This award provides support for ambitious Cancer Research UK postdoctoral researchers to visit a UK or overseas lab to learn new skills, develop their research career and foster collaborations

We will provide:

- Support for up to three months
- Funding up to £6,000 for the travel, accommodation, subsistence and research expenses

We want to see proposals that:

- Develop your own research skills and career
- Will help you become an independent investigator
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We will not support:

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For more information and how to apply, please go to:
www.cancerresearchuk.org/research-travel-award

For any queries please contact:
Dr Matt Kaiser
matthew.kaiser@cancer.org.uk
020 3469 5337

NEXT APPLICATION DEADLINE THURS 5TH SEPTEMBER 2013

CANCER RESEARCH UK

In the spotlight with Helen Bradley

from the Advanced Imaging and Flow Cytometry Facility

Helen is a Scientific Officer in the Advanced Imaging Facility where she carries out Histology Image Analysis. She joined the Institute six months ago, directly after completing her PhD where she investigated glucose transporter protein localisation in skeletal muscle at the University of Birmingham. Helen spends most of her time trying to mathematically model histology and will be assisting with the new ImageStream system when it arrives in June. The system is part microscope and part flow cytometer and will allow us to image a stream of cells and put numbers to cell-cell interactions, co-localisation, cell cycle analysis and compartmentalisation studies.

1. What is your favourite part of the UK?
   The Outer Hebrides – but I was there in the sunshine!

2. What was your best ever holiday and why?
   Havana. A vibrant city – mojitos, cigars and some beautiful buildings

3. Which website do you always check, and why?
   BBC news – I like to know what's going on

4. What is your favourite film?
   The Shawshank Redemption

5. What was the last CD you bought?
   Jake Bugg's album

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

7. What is the most important lesson that you have learnt from life?
   Stand by your decisions

8. Name three things you would take with you to a desert island?
   Bikini, suncream, deckchair

9. What three things would you put in Room 101?
   The Simpsons, cyclists on the pavement, shopping centres on a Saturday

10. What is your greatest fear?
    Not sure about my greatest fear but I would never do a bungee jump

11. How would you like to be remembered?
    As a good friend

12. What relaxes you?
    A ballet class, or failing that a glass of wine

13. What is your signature dish to cook?
    My lasagne is not bad

14. You've just won the lottery and have £5 million pounds to spend. What do you buy first?
    A large house with a hot tub overlooking the sea

15. What is your idea of perfect happiness?
    Walking along the British coastline in the sun

16. What keeps you awake at night?
    A good book

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