Paterson
Institute for Cancer Research

Paterson Institute
newsletter

The Newsletter for the Paterson Institute for Cancer Research

Paterson Welcomes New Director

Issue 24 - May 2012

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MANCHESTER 1824
The University of Manchester

CANCER RESEARCH UK

Director's Introduction

Welcome to the spring edition of the Paterson Institute Newsletter. I am delighted to have been appointed Director of the Paterson and look forward to leading the next chapter of its development. For those of you who don't know me, I have moved here from London where I have spent the last 19 years at the Institute of Cancer Research in London, first as a Post-doc, then a Group Leader, and finally as Head of Division. My own research focuses on signalling through the RAS/RAF pathway and the role that this plays in the development and progression of melanoma, the most deadly form of skin cancer and during the course of the next year I shall be building up my research group at the Paterson. Fortunately, I will not be starting from scratch, because six of my existing post-doctoral fellows will be joining me from London over the summer. New appointments will build the rest of the lab throughout the year, including a new student who will start in the autumn. Siana Peters, my EA who has worked with me for the last year in London will keep me organised and I am really delighted that she took the decision to join me here.

I would like to take this opportunity to thank Caroline Dive and Iain Hagan, not only for their roles in managing the Institute during the previous year but also for helping me enormously in the last few months as I made the transition to Manchester. During this time, I have held discussions with CR-UK on our proposed budget for 2012-2013. This process allows us to review progress made by the Institute against its stated objectives for the previous twelve months and to agree on our objectives for the year ahead. The tough financial climate in which we find ourselves will present significant challenges over the next few years. However, we need to adopt a strategy that allows us to build our way out of these difficulties to ensure that we grow and recruit new Group Leaders to expand our research activities. We plan to recruit two to three new Group Leaders over the next 18 months to strengthen the Institute's portfolio in translational research and to advance the personalised medicine agenda. I will also be appointing a scientific advisory board to undertake a review of the Institute's research portfolio and to advise on its continuous development and research strategy. It is important to ensure that our aims are aligned with the overall strategy for cancer at both the Christie hospital and the University so I look forward to engaging with colleagues across the city to ensure that we share a joint strategic vision for cancer research across Manchester.

We have made a successful start to 2012 with publications from the Institute's scientists in high profile journals such as Cancer Cell, Molecular Cell, the Journal of Clinical Oncology, EMBO Journal and Development. I look forward to us building on this success over the coming months. This year promises to be especially busy, because several Senior Group Leaders will have their Quinquennial Reviews. These reviews offer an excellent opportunity to assess past achievements whilst prioritising research strategies for the future. We shall also be reviewing all of the core research services to ensure that these facilities continue to meet the evolving technological needs of the Institute.

I look forward to getting to know you all over the coming weeks and months and working together to ensure the continued growth and success of the Institute.

Richard Marais
Director

Cancer Research UK Research Travel Awards

Could your research benefit from a short stay in another lab? If you are a post-doctoral researcher whose funding comes from CR-UK, the Research Travel Award will allow you to visit groups elsewhere in the UK, or overseas, to carry out a specific piece of work. CR-UK are looking for proposals that will allow you to introduce new skills or techniques to your current research group and to establish or develop collaborations. They also welcome proposals that allow researchers to develop their own independent careers. The awards cover travel, accommodation and research expenses to visit another group for a period between two weeks and three months. Applications should be made by the post-doctoral researchers themselves and details of how to apply can be found here: www.cancerresearchuk.org/research-travel-award

These awards are competitive. Criteria considered by the selection panel include the quality of the proposed research and the benefits to both the applicant and their research group. The deadline for the next round of awards is July 27th 2012 followed by December 7th 2012. Further information can be obtained from Dr Matthew Kaiser: Matthew.Kaiser@cancer.org.uk.

Two of our current post-doctoral fellows are recent recipients of these awards. Later on this year, Giacomo de Piccoli from the Cell Cycle Group, will travel to Japan to pick up some new techniques that will enable him to study replication forks dynamics during replication while Radek Polanski, from the Clinical and Experimental Pharmacology Group, visited a group in Boston towards the end of last year. He describes here how this experience is helping his research.

I was recently awarded a CR-UK travel award to visit Tony Letai's lab at the Dana-Farber Cancer Institute at Harvard University in Boston. The objective of the visit was to adapt the BH3 profiling assay so that it could be used in small cell lung cancer (SCLC) circulating tumour cells (CTCs).

SCLC is the most aggressive type of lung cancer which typically responds well to chemotherapy, but then relapses within a few months as a chemoresistant disease. It is not clear what causes this chemoresistance and there is currently no cure for recurrent SCLC. Our hypothesis is that an apoptotic block causes drug resistance in recurrent SCLC and we intend to use BH3 profiling to prosecute this hypothesis. BH3 profiling is based on the ability of short peptides derived from the BH3 domains of BCL2 proteins to initiate mitochondrial outer membrane permeabilisation (MOMP), a key event during intrinsic apoptosis. The more readily BH3 peptides induce MOMP, the greater the propensity of a cell to undergo apoptosis equating to a greater sensitivity to apoptosis-inducing agents. Conventional BH3 profiling requires large numbers of cells, however as SCLC is not resected, the primary source of tumour cells for our research are CTCs from patient blood which are relatively sparse. Therefore, we aim to adapt conventional BH3 profiling to allow microscopy-based analysis on rare cells. Thanks to the CR-UK travel award, I visited the Letai lab (the inventors of BH3 profiling) and spent four weeks developing the microscopy BH3 profiling assay with Jeremy Ryan, a senior technician in the group. During this time we developed a basic protocol allowing the quantitation of MOMP in single cells in response to various BH3 peptides. This was validated on cell lines with known BH3 profiles and applied to SCLC cell lines. We also conducted the assay on admixed EpCAM positive and negative cells which were stained for EpCAM expression prior to profiling, a technique which will be essential for identifying CTCs amongst contaminating leukocytes in patient samples. The data generated in Boston suggest that BH3 profiling in single cells is realistic and represents the start of what should be a fruitful collaboration with the Letai lab.

I am very grateful to Cancer Research UK for sponsoring my trip to the USA and giving me the opportunity to advance the project and experience the vibrant scientific environment of the Dana-Farber Cancer Institute.

Core Facilities Update

The Institute core facilities and services provide state-of-the-art technology to be applied to the research endeavours of our scientists. As with every year, the last twelve months has seen some major developments in equipment, the introduction of enhanced and novel techniques, and an increase in the control mechanisms for the standardisation of sample preparation and data collection.

Advanced Imaging

Microscopes are used in the study of oncology to provide visual clues and record localised information about functional properties of tissues and cells, and to investigate the spatial and temporal relationships between structures and biochemical interactions within the cell. The facility visualises biological samples from the whole tissue down to the limit of optical resolution where interactions between proteins can be imaged. Over the last year the range of techniques on offer has increased drastically, two such techniques include improvements to whole slide histological scanning and macro-confocal imaging.

The new histological scanning techniques allow for a whole slide to be rendered into data automatically so to permit analysis of localised or tissue wide effects, such as the location of indicators of specific cancers via mathematical modeling of the biological material.

A macro-confocal has been introduced into the laboratory, which permits the imaging of primary tissue from patients into a volume of 3D data. One of the main advantages of such a system is for imaging tissue that would be too large to fit under a standard microscope lens. It is hoped that over the coming year time lapse imaging will be developed so that tissue wide responses over time can be examined.

Flow Cytometry

Flow cytometry uses fluorescence imaging as a means of measuring the physical and chemical characteristics of cells using markers. We can assess cell phenotype by looking for expression of cell surface, cytoplasmic or nuclear proteins, cellular DNA or RNA content, cell cycle analysis, fluorescent protein expression, functional aspects of the cell such as enzyme activity, apoptotic status or mitochondrial membrane potential. Any population identified on a flow cytometer can be retrieved by using a cell sorter that has the ability to physically separate cells of interest from a biologically complex population.

This year we were fortunate to be the first in the world to acquire the new and so far unreleased BD FACS Jazz sorter as a direct replacement for the BD FACS Vantage that has been in service for over 18 years. The new system removes the complexity found in modern day high-end sorters and to provide a very basic but pure system capable of being operated by all. The Jazz is a dual laser two-way sorter capable of measuring six specific markers and is a welcome addition to the laboratory. The stability and simplicity of this system has allowed us to implement this system as our fluorescent protein sorter freeing much needed time on the high-end sorters for our more complex procedures.

Histology

Histology is used for studying and understanding the three dimensional organisational structure, development and functionality of tissues/cells which ultimately provides a valuable insight into the understanding of disease processes at the cellular level.

The continued shift towards high-throughput, standardised data has resulted in the unit playing a pivotal role in the strengthening of existing research and the expansion of the study of indicators of cancer (biomarkers) within the Institute. Over the last year many changes have taken place, the recent introduction of the Leica Bondmax immunohistochemistry system together with the existing platforms ensure throughput and data quality.

Work focusing on novel methods includes nucleic acid extraction from tissue coupled with morphological interpretation ensuring maximum use of primary tissue samples and utilisation of proximal ligand assays allowing for precise detection and quantification of proteins, and their interactions and modifications.

Mass Spectrometry

Mass Spectrometry is able to detect the presence of a particular protein, as well as determining how it can be modified as a consequence of an experimental or biological variable. The study of protein components that regulate cellular behaviour is key as they represent many of the targets of current and future cancer therapies.

In the area of quantitation, we have enabled researchers to utilise a metabolic labelling technology (SILAC) in a manner that allows the comparison of three samples simultaneously and this enhances the applicability of this technology so that more biological observations can be made within a single experiment. In addition a new chemical labelling strategy (Dimethyl labelling) has been rolled out that now allows the cost effective analysis of larger amounts of biological material required to analyse very low abundance molecules within the cell.

In the area of modification analysis, we have begun the effective analysis of five new types of protein modification. A highlight is the development of a totally unique methodology which has enabled the mapping of sites of a modification called SUMOylation on target molecules of interest. This approach has enabled scientists at the Institute to interrogate the SUMOylation status of their biological system in a way that is currently unique to the Paterson Institute.

In the field of separation we have developed a unique approach to use a graphite material to effectively fractionate peptides in a way that allows the biologist to profile a much larger proportion of the protein components of their biological system (Griffiths JR *et al*., J Chromatogr A, 2012, Jan 13).

Molecular Biology Core Facility

The original project to sequence a human genome was an international collaboration that took twenty years and cost an estimated $1 billion. The latest generation of sequencing machines makes it possible to sequence genomes in a few weeks, and the cost is rapidly approaching $1000 per genome. For this purpose the core facility has an Applied Biosystems 5500xl sequencer that is being used to support a variety of projects sequencing both DNA and RNA samples.

A recent project in the model organism S.pombe detailed the discovery of ARTs, (Antisense Regulatory Transcripts), some of which were found to regulate the amount of protein expressed by their corresponding protein coding gene (see page 8). Publications such as this are revealing that our knowledge of the mechanisms by which gene expression is regulated is not yet complete; raising the possibility of, as yet, undiscovered therapeutic targets.

The use of Next Generation Sequencers to discover new transcripts leads to a need for suitable validation platforms. The core facility offers traditional quantitative PCR, an excellent technique for looking at very small numbers of transcripts, but cumbersome to use for more than a few targets. This year we are running pilot studies on the Quantigene platform, which offers a multiplexing capability and should facilitate projects looking at gene signatures of up to 35 genes.

The Cancer Research UK microarray service based at PICR is experiencing continued high demand and has recently added miRNA expression profiling to the list of services to complement Next Generation sequencing projects.

Farewell to Morgan

After five years managing the Flow Cytometry Service Morgan Blaylock will be leaving the Institute to take up a role with a leading manufacturer of flow cytometers. In his time here Morgan has done an outstanding job of developing our flow cytometry services to a very high level. Although it will be sad to see him go, we wish Morgan all the best in the next phase of his career.

Lizzy Hitchman

15 October 1981 - 30 November 2011

Elizabeth Sweeney or 'Lizzy' as she was known arrived in the Clinical and Experimental Pharmacology (CEP) group on November 6th 2006. She was employed as a joint CEP/ AstraZeneca scientific officer, to develop methodologies for multi-staining immunohisotchemistry using Q-Dot technology. Whilst most of her time was spent at the Paterson, once a week she would devote herself to a separate project at AZ. She fitted into the group immediately and worked hard and conscientiously on her projects.

Lizzy was a wonderful, gifted individual who had a love of all things. She was incredibly vivacious, and almost every day a bouncy enthusiastic girl would come to work. Her smile was well known, and she would light up the lab by her very presence. Lizzy soon became *Maitre d' of the labs*, and made new people feel part of the group the instant they arrived. She was one of those people who made it fun to come into work, and daily held court in the tea room. Here the real Lizzy shone. She would comment on everyone, and everything, often grumbling and opinionated, but always in a kind and often very humorous way. It was here that we heard the endless tales of her exploits and adventures with 'Rich' her boyfriend, soon to become fiancé and later husband. She idolised him, and told numerous tales of being pitched out of a dingy on Bala Lake, or hiking up hills and across dales on various weekends away. The banter was always entertaining, even if you were the subject matter! Lizzy loved to wear pink, and had the largest collection of shoes known to womankind. She was piqued when Rich suggested a one out, one in policy, and instead looked for alternative storage options (Rich's side of the wardrobe!)

As Lizzy came to the end of her project, which resulted in a first author publication, she became interested in doing a PhD. Lizzy had got the bug for research, and wanted to attain a high standard, productive career in science. She successfully competed for a CEP/ AZ Studentship in Oct 2008. Lizzy tackled her studies as she tackled life itself. She was meticulous in her paperwork and planning, and hated the sight of an untidy lab! People would often get into hot water with her for "messing up" the lab. She organised people, and processes, and threw herself into her studentship. She was a sensible girl who knew when to seek help and advice from other postdocs and her supervisors, organising regular meetings with all of them. It was during this time she married her beloved 'Rich' and became Lizzy Hitchman. Throughout this time she always kept weekends free for Rich and her family, and still managed complete her lab work by the summer of 2011, after which she set to work writing up as all students do. She wrote a great thesis that clearly showed she was a maturing, independent thinking, and hard working young scientist. Sadly she was snatched from us just a week before her viva. Her work merited a posthumous PhD which was awarded to her, and so, Dr Elizabeth Hitchman's thesis now resides alongside the many others in Caroline Dives office better known as "Big C" to Lizzy. An achievement she herself looked forward to.

She was one of the loveliest students we had the good fortune to help along her career path, and her contribution and presence during her time at both the Paterson and AstraZeneca will never be forgotten. The Institute, in recognition of Lizzy's time here, will introduce a "Lizzy Hitchman Prize", to be awarded to the student who is judged to have presented the best poster at the annual colloquium.

The Clinical and Experimental Pharmacology group.

Matt Krebs wins the Dexter award for 2011

I was so pleased to receive the Paterson Institute's Dexter Young Investigator Ward at the end of 2011.

I am indebted to my supervisors Caroline Dive, Fiona Blackhall, Malcolm Ranson and Glen Clack for the support and guidance they have given me over the last few years in transitioning me from clinician to scientist - by no means an easy feat! I was fortunate to have an exciting project in circulating tumour cells (CTCs) - cells that break off from a primary tumour, invade into the blood and are responsible for causing spread of cancer to distant organs. CTC detection and analysis will inform on important mechanisms responsible for this metastatic process. However, CTCs are very difficult to detect in the blood as they are few in number compared to the vast amount of normal red and white blood cells – comparable to searching for the proverbial needle in a haystack.

CEP has several state-of-the-art technologies to detect CTCs. My thesis specifically evaluated the ability to detect and characterise CTCs in patients with non-small-cell lung cancer. CTCs were present in a proportion of patients and were highly prognostic, in other words, the more cells present the shorter time patients survived. The potential of CTCs as a biomarker, however, extends far beyond this. By looking at the proteins and genes expressed by CTCs, not only will this inform on the process of metastasis, we may be able to select individualised treatments (predictive biomarker) and ultimately find new ways to treat cancer. In collaboration with others in CEP we have optimised methods to help achieve this endeavour. The thesis led to three first author papers (one in Journal of Clinical Oncology [JCO]), one second author paper in JCO, two review articles, two mid-author papers, a series of international presentations and even an article in the Daily Telegraph. Exciting times indeed for CTCs and work I am now continuing to pursue following successful appointment as an NIHR Clinical Lecturer. Thanks again for this award and to Cancer Research UK and AstraZeneca for funding my project.

Paterson's New Starters

Roshana Thambyrajah
Postdoctoral Scientist - Stem Cell Biology

Zahid Shah
Postdoctoral Scientist - Inositide Laboratory

Clare Hodgson
Biostatistician - CEP

Julie Brazzatti
Postdoctoral Scientist - Immunology

Emma Fairweather
Bioscientist - Drug Discovery

Samantha Fritzl
Scientific Officer - Drug Discovery

Joseph Halstead
Scientific Officer - CEP

Stephen Bramley
Scientific Officer - CEP

Featured Publications

Regulating Meiosis - It's an ART

A collaboration between the Applied Computational Biology and Bioinformatics (ACBB) Group and the Cell Division (CD) Group here at the Paterson Institute has resulted in a recent paper which describes a novel role for non-coding RNA (ncRNA).

It has been know for many years that the majority of the genome is transcribed into RNA which does not code for protein. The role of this non-coding RNA has eluded scientists with many believing it to be simply the expression of "junk" areas of the genome. To explore possible roles of ncRNA, Danny Bitton (ACBB) and Agnes Grallert (CD) used cutting edge strand-specific Next-Generation Sequencing to identify all the RNA expressed in fission yeast as they went through the meiotic life cycle. This process revealed hundreds of novel transcripts, a subset of which originated from the opposite strand to a known protein-coding gene, resulting in an antisense transcript (ART –for Antisense Regulatory Transcript). Further examination showed that these ARTs could regulate the protein levels of some of the key coordinators of sexual differentiation suggesting that they represent a major regulatory mechanism for meiosis. A significant number of these ARTs were found to arise from adjacent and overlapping pairs of protein coding genes lying head to head on opposite strands of the genome. As well as demonstrating a critical role for these transcripts in controlling meiosis, this paper demonstrates that neighbouring genes can regulate each other; a critical factor when considering the effects of knockout or knockdown studies. Scientists have long debated whether such ncRNA simply represents genome "chatter" which has persisted due to the lack of negative selective pressure against it. Bitton et al have shown that far from being junk, such ncRNA can form a dynamic and sophisticated regulatory mechanism to regulate gene expression which must be considered alongside all the other traditional modes of control.

Ref: Bitton, D. A., Grallert, A., Scutt, P. J., Yates, T., Li, Y., Bradford, J. R., Hey, Y., Pepper, S. D., Hagan, I. M., and Miller, C. J. (2012). Programmed fluctuations in sense/antisense transcript ratios drive sexual differentiation in S. pombe. Mol Syst Biol, 7:559

Stressed out Mitochondria?

Recently, the Cell Regulation Group discovered a novel mechanism by which the negative regulation of MAPK signalling is controlled.

MAP kinase (MAPK) signalling pathways mediate the response to cellular stress. They control processes such as the cell cycle and apoptosis, as well as regulating transcriptional responses, so it comes as no surprise that changes in MAPK signalling are often associated with the development and progression of cancer.

For any MAPK, it is critical that the magnitude and duration of this signalling is carefully controlled as perturbations in these parameters can have profound implications for the cell. This is achieved through the balance between positive and negative regulatory signals. The latter is achieved through the action of phosphatases which remove activating phosphate groups from the MAPK.

The Cell Regulation group have found that the fission yeast Ptc4 phosphatase, plays a critical role in down-regulating the activation of the MAPK Sty1, specifically upon oxidative stress. Ptc4 is localized exclusively in the mitochondria which created a potential dilemma, as Sty1 had previously been described as a cytoplasmic protein that shuttles into the nucleus upon activation. This was resolved by finding that Ptc4 regulates a mitochondrial pool of Sty1; but what accounts for the stress specificity of this effect? It turns out that Ptc4 is targeted to the mitochondria by a short stretch of amino acids at its amino terminus known as a mitochondrial targeting sequence (MTS). Normally, this sequence is cleaved as Ptc4 enters the mitochondria. However, upon oxidative stress, its cleavage is inhibited resulting in an accumulation of the full length phosphatase. Retention of the MTS promotes the interaction between Ptc4 and mitochondrial Sty1 resulting in down-regulation of kinase activity.

These findings raise a number of questions. Firstly, what is the role of mitochondrial Sty1? It seems likely that it phosphorylates and thereby controls the activity of mitochondrial targets. It certainly seems to make sense to have a stress-activated MAPK localised to an organelle that is the biggest source of intracellular reactive oxygen species. Do the human homologues of Sty1 also play a role within mitochondria and finally does this novel mode of regulation exist for the human homologue of Ptc4? Future work by the Cell Regulation Group will attempt to address these questions and increase our understanding of the role and regulation of these critical signalling proteins.

Ref: Di et al., EMBO J. 2011 Dec 2;31(3):563-75. H2O2 stress-specific regulation of S. pombe MAPK Sty1 by mitochondrial protein phosphatase Ptc4.

Paterson scientists get a clearer picture of biomarkers

Clinical samples are often fixed in formalin prior to staining using immunohistochemistry, a technique commonly used in both clinical and research laboratories.

In a recent paper published in the journal, Histopathology, Dr Elizabeth Hitchman and colleagues from the Clinical and Experimental Pharmacology group have demonstrated the importance of standardisation on this fixation step in tissue processing. By comparing tissue following fixation for differing lengths of times from one hour to two weeks it was demonstrated that excessive fixation (of 48 hours or longer) resulted in a decrease in the ability to detect Ki67, a commonly used indicator of tumour cell proliferation. This artifactual decrease could lead to the misclassification of a tumour or misinterpretation of results in a clinical trail or experiment. Dr Hitchman proposed that by strictly enforcing a standardised fixation protocol for tissue collected from different patients and/or hospitals would help reduce variation seen in the results of biomarker trials. This reduction in variation would lead to increased patient benefit due to easier interpretation of immunohistochemical staining in clinical trials.

Ref: Hitchman, E., Hodgkinson, C., Roberts, D., Ashton, G., Yunus, Z., Byers, R., Ward, T., Womack, C., and Dive, C. (2011). Effect of prolonged formalin fixation on immunohistochemical staining for the proliferation marker Ki67. Histopathology 59, 1261-1263.

A Cut Above The Rest

Dr Navin Mani from the Translational Radiobiology group has written an article which was selected as the front cover feature for the 2011 Christmas edition of the prestigious British Medical Journal. The BMJ is the UK's premier medical journal and is read by the majority of practising clinicians.

The article is an insightful analysis into the philosophy of medical diagnosis, examining the use of Occam's razor and other diagnostic paradigms. Occam's razor, which is also known as the principle of parsimony, states that entities must not be multiplied beyond necessity, or put another way 'the simplest explanation is to be preferred'. The article goes on to scrutinise how this approach intertwines with other philosophical approaches, ranging from the well established field of Bayesian statistics through to the lesser known contributions of Reginald Jones (professor of natural philosophy and MI6's principal scientific adviser during the second world war), who stated 'no set of mutually inconsistent observations can exist for which a coherent explanation cannot be conceived.' Although written from a medical diagnostic perspective the underlying philosophy is applicable throughout all areas of science and makes for interesting and thought-provoking reading.

Dr Mani is a trainee Head and Neck Surgeon, currently working as a clinical research fellow with the translational radiobiology group. His research at the Paterson involves investigation of a gene-signature biomarker of tumour hypoxia in head and neck cancer.

BMJ

BMJ 2011;343:d7769 doi: 10.1136/bmj.d7769 (Published 20 December 2011)

FEATURE

CHRISTMAS 2011: FOOD FOR THOUGHT

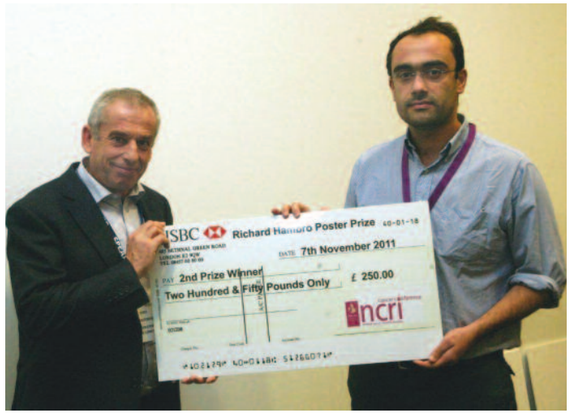
What Three Wise Men have to say about diagnosis

Navin Mani and colleagues examine Occam's razor, Hickam's dictum, and Crabtree's bludgeon

Navin Mani *specialty registrar, otolaryngology—head and neck surgery*[1], Nick Slevin *consultant, clinical oncology*[2], Andrew Hudson *specialty registrar, clinical oncology*[2]

[1]Department of Head and Neck Surgical Oncology, Christie Hospital, Manchester M20 4BX, UK; [2]Department of Head and Neck Clinical Oncology, Christie Hospital, Manchester

Prize for Paterson Student at the NCRI Meeting



We congratulate Ahmet Acar from the Stromal-Tumour Interaction Group, led by Dr Akira Orimo, who was runner up in the best student poster competition at the NCRI meeting in Liverpool in November. His work, which is a collaboration with Professor Göran Landberg in whose group Ahmet is now based, describes how Notch signalling mediates myofibroblast differentiation of human breast carcinoma-associated fibroblasts. Ahmet describes the work that led to his recent prize below.

Tumours are highly complex pieces of tissue, consisting of a variety of cell types in addition to cancerous cells. These additional cells, which are collectively known as the stroma, can also play a substantial role in tumour development. One of the most abundant cell types found within the tumour stroma is carcinoma-associated fibroblasts (CAFs). These cells have come under particular scrutiny over the last decade due to their crucial roles in various aspects of tumour growth, invasion and metastasis. Hence elucidation of the altered cellular pathways responsible for the tumour-promoting ability of these cells is one of the key steps in developing new strategies in the fight against cancer.

Previously, we developed a mouse tumour xenograft model in which human breast CAFs were experimentally generated (exp-CAFs). Using exp-CAFs, we set out to analyse the cellular pathways mediating the activated, tumour-promoting ability of these cells. We found that aberrantly activated Notch signalling in exp-CAFs is functionally important to maintain the activated status of these cells. More specifically, activation of Notch signalling in exp-CAFs is mainly stimulated by high levels of the Notch ligand Jagged1 and the receptor Notch3. Jagged1-induced activation of Notch3-mediated signalling results in the exp-CAFs being maintained in an activated state. By performing loss-of-function studies, in which various Notch components were silenced using either shRNAs or chemicals, we were able to demonstrate the functional relevance of Notch activity in exp-CAFs. Additionally, we can force normal fibroblasts to adopt a CAF-like state when they are forced to express Notch components. Collectively, our findings strongly suggest a key role for Notch signalling in mediating the active phenotypes of human breast carcinoma-associated fibroblasts. Studying the crosstalk between tumour cells and CAFs during tumour progression could help to further understand the biology underpinning various carcinomas and facilitate the development of novel stroma-targeted therapeutic approaches.

Farewell and Good Luck

We would like to say farewell and good luck to Amy Weatheritt who leaves the Institute after nearly four years, working initially in the administration team and then as an Executive Assistant to Nic Jones and the Senior Management Team.

Amy has also been a member of the Newsletter editorial team and played a major role in helping to organise many Institute events such as the Colloquium, the external seminar series and Christmas parties. We wish her all the best in her new life working for the BBC in London.

It's Our Time to Shine to Beat Cancer

Cancer never sleeps, and neither will Manchester on Saturday 8th September. Join together with family and friends to take part in Cancer Research UK's night-time walking marathon, Shine. Choose to walk a half (13miles) or full (26miles) marathon and the money you raise will bring light to the lives of those affected by cancer. You can make your fundraising even more meaningful by selecting from 12 cancers for which to SHINE.

Enter now:
www.shinewalk.org

Crowdfunding Science at The PICR

By Maria-Luisa Alonso-Nunez

A new way of raising money for research has landed at the Paterson Institute: the crowdfunding of specific research projects. Crowdfunding is a way of getting a project funded by small donations from people who get some reward from that. It's not just donating but an exchange, and it has been working for a while to get funding for music albums and films. People are willing to spend money and support different projects. So, why not scientific ones?

In November/December I took part in the 'SciFund Challenge', a worldwide experiment in which 49 scientists from different countries, disciplines and levels prepared and presented their research projects. The experiment had two main goals: one was to communicate the research that was being done in the labs and offices, and the other was to get money to fund small parts of those research projects.

Most of us made a video explaining our research and did a peer review among us to get the best out of the projects. The result of all this was fantastic. My project, "Cancer? Yeast has answers", presented the work that is undertaken in the Cell Division lab: the study of the cell division process in yeast. This project was one of the 10 successful projects of the challenge. I managed to raise $2835 for the Cell Division lab thanks to 63 contributions. It wasn't too difficult to get this. It only required a bit of time to make the video and prepare the rewards (which are goods or experiences that funders receive in exchange for participating in your project), and a bit more extra time to do some "marketing" on the social networks, different blogs and traditional mass media.

I'm really happy with the result of the initiative and the experience itself. Not only because of the money raised but also because now there are many more people who know how yeast can be used to study certain processes that happen in cancer cells. And my project got the attention of diverse people. Some contributors were people I knew but most of them were complete strangers who thought that it was worthy to fund my project. In addition it was presented as a case-study in the talk that Brian Meece (the CEO of RocketHub, the crowdfunding platform that hosted the SciFund Challenge) gave in the TEDxBrooklyn event. He mentioned only 3 projects and one of them was "Cancer? Yeast has answers", due to the rewards chosen.

As you can see, with a bit of time and effort, and loads of passion for communicating science, you can get money for your research, happy people because they fell they are part of science, and publicity for your research and the institute all around the world. I really encourage you to take part in this kind of initiatives. They are really worthy.

E-Marketplace

By Denise Owen

The Institute has been using E-Marketplace via Oracle for over 12 months now. E-Marketplace is an enhancement tool for I-Procurement which allows comparison of products across suppliers.

The catalogues within E-marketplace include up to date and accurate product and pricing details in line with agreed contracts (well, most of them do!!) The main reasons for the University implementing E-Marketplace was to improve the shopping experience for users, providing a one stop shop for large numbers of purchases, therefore decreasing the time it takes to create a requisition. Another reason was to increase the accuracy of the requisitions, which will reduce invoice holds for errors relating to incorrect pricing or product descriptions. The University are continually adding more and more suppliers to the list, which should make ordering goods and services much easier.

I think most of the staff at the Paterson who are responsible for ordering within their department have adapted extremely well to E-Marketplace, and find it much easier to order goods and services.

I would like to take this opportunity to explain briefly how E-Marketplace works once it has been created by the end users. For each requisition that you create for a supplier, it generates a Purchase order. If you create two requisitions for the same supplier on one day, it will generate two purchase orders. It is not possible for us to link the two requisitions together, so please, where possible, put all requests on one requisition, if they are for the same supplier. Please bear in mind that on average, it costs £60 to pay one invoice and each Purchase order generates an invoice. We can save money, as a University, if we plan in advance.

If anyone would like to discuss how E-Marketplace works or needs clarification on any of the above, please contact myself or David Jenkins in the Finance department.

Dates for Your Diary – 2012

Date	Event	Further Information	Other Details
Sunday 20th May	Great Manchester Run	www.greatrun.org/	To volunteer on the day and support the Drug Discovery team contact James Dunphy
Sunday 27th May	Stockport Race for Life	www.raceforlife.org.uk	
Saturday 23rd June	Tatton Park Race for Life	www.raceforlife.org.uk	
Sunday 24th June	Tatton Park Race for Life	www.raceforlife.org.uk	
Saturday 30th June	Stockport Relay for Life	www.cancerresearchuk.org/relay	To join the Paterson team contact James Dunphy
Sunday 1st July	Bolton Race for Life	www.raceforlife.org.uk	
Sunday 22nd July	Manchester Race for Life	www.raceforlife.org.uk	To volunteer at this event, contact James Dunphy
Sunday 2nd September	Tatton Park Race for Life 10k	www.raceforlife.org.uk	
Saturday 8th September	Cancer Research UK's Shine	http://shine.cancerresearchuk.org/	To volunteer at this event, contact James Dunphy
24th – 26th September	Paterson Colloquium		For more information contact Caroline Wilkinson
4th – 7th November	NCRI Cancer Conference	www.ncri.org.uk/	

Relay for Life – entries now open

It is tradition for the Paterson to enter a team into this fantastic community organised event.

Stockport Relay for Life is a 24 hour team event that takes place in Bramhall on Saturday 30th June

In the words of Steve Lyons:
"Relay for Life fundraising events are unique because they are organised entirely by volunteers from the local community. The Stockport Relay for Life is always great fun and provides an opportunity to inform people about the important work of CR-UK in a festival-like atmosphere. It is vital that we lend our support to our hardworking fundraisers in Manchester by having a team from the Paterson participate in the Stockport Relay for Life. On the day of the relay, all the teams gather together to take part in a 24 hr walk. This actually great fun, with each team displaying a stall of some kind (the Paterson team usually demonstrates DNA extraction to the public), there is food, drink, music and other entertainment."

If you are interested in taking part please email :jdunphy@picr.man.ac.uk

Staff News

Roberta Ellis has been invited to meet with the University Registrar Will Spinks as she has worked for the University for 25 Years.

New Position for Andrzej Rutowski

Congratulations to Andrzej Rutkowski (PhD student) who has a secured a post-doc at the University of Cambridge. The job will involve analysis of the kinetics of RNA synthesis and decay in herpesvirus infections. He will be working in the newly established group of Dr. Lars Dölken, who has been developing a novel method for labelling newly synthesised RNA and analysing only the nascent molecules. This method will be combined with other high-throughput platforms, such as RIP-Chip, SILAC and next-generation sequencing. The project will be focused on herpesvirus infections, but this new methodology could have huge implication in other fields of research, including cancer.

Stargazing Live

Claire Hart, an SSO in the Genito Urinary Cancer Group is a member of the Charlie Bates Solar Astronomy Club which is part of NASA Nightsky Network which works to bring astronomy and science to the general public and allow space education to be accessible and fun. On Monday 16th January, Claire arranged for staff and patients to view hydrogen alpha emission of the Sun through a specialised solar telescope in connection with the BBC's Stargazing Live. Through this telescope (Coronado PST) people were able to view the Sun's chromosphere and were able to see a couple of sunspots, dark filaments across the surface and a couple of prominences lifting off the solar surface into space. Over the summer months Claire hopes to come to The Christie regularly with the telescope and through the Christie Volunteer services will allow patients to view the Sun as an activity available for them to enjoy whilst waiting for treatment and brighten up their stay at the hospital.

In the Spotlight

In this edition, we feature Iain Hagan, head of the Cell Division Group.

1. **What is your favourite part of the UK?**
   Ross and Cromarty

2. **Which website do you always check, and why?**
   None because I am a Luddite at heart

3. **What is your favourite film?**
   Tampopo

4. **If you had to change careers tomorrow, what would you do?**
   No idea

5. **What is the most important lesson that you have learnt from life?**
   Everyone is different

6. **Name three things you would take with you to a desert island?**
   Walking boots, Solar powered ipod charger, ipod

7. **What is your greatest fear?**
   City winning the title this year

8. **How would you like to be remembered?**
   Someone who was unexpectedly calm when City won the title in 2012.

9. **If you could change one thing in your past what would it be?**
   My futile attempt to learn Japanese Kanji

10. **What is your signature dish to cook?**
    Mackerel in Ginger Miso

11. **You've just won the lottery and have £5 million pounds to spend. What do you buy first?**
    The trip of a lifetime for the family

12. **What is your idea of perfect happiness?**
    A trip of a lifetime for the family

13. **What keeps you awake at night?**
    The continued conflict between my organisational skills and deadlines

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