



Paterson
Institute for Cancer Research

Paterson Institute

newsletter

The Newsletter for the Paterson Institute for Cancer Research

Paterson invests £500,000 in new Mass Spec equipment



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The University of Manchester

CANCER RESEARCH UK



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Director's Introduction



We have recently concluded our discussions with CR-UK on the proposed budget for 2008/2009. This is an important process since the CR-UK core budget provides approximately 80% of our overall budget. During the process we assess our success over the last annual funding period compared to our stated objectives and agree our objectives for the coming period. It's a very constructive and robust exercise and the final settlement was extremely satisfactory, especially given the very challenging fundraising climate that major charities like CR-UK face. The uncertain economic situation presents significantly greater challenges than normal.

An annual staff meeting is held to widely communicate the results and discuss our future plans. This meeting took place in early June and below is a brief summary of the most salient points.

The most important research objectives for 2007/2008 were to increase our contingent of Group Leaders and to invest further in our research services to ensure that they remain at the cutting edge. There was significant achievement in both areas. 3 new group leaders were recruited enhancing our expertise and activity in stem cell biology, cell signalling and the tumour microenvironment. Research services were enhanced by further recruitment and purchase of state-of-the-art equipment. For example, a new Head of the FACS Service was recruited and the facility improved by a complete refurbishment and by purchase of a new analyser. Similarly, the capacity of the mass spec service was significantly enhanced by the purchase of a new Orbitrap machine. However, all the services were improved – they are very important to the success of the Institute and keeping at the cutting edge is essential.

Our Estates department were busy overseeing the refurbishment and upgrade of quite a few of the research support areas plus a new conference room and new offices.

The Operational Services achieved all of their objectives and the Careers Club for postdocs and students has gone from strength to strength, which is culminating in a one day course entitled 'Introduction to Research Management'.

The objectives for 2008 / 2009 include the recruitment of 2 new group leaders and the Head of Drug Discovery, the development of a drug discovery programme and the enhancement of the quality of the Institute's research portfolio which will be demonstrated by successful site visits of CEP in November 2008 and of the Institute in July 2009. As you will see on the facing page, the first group leader appointment has been made.

As you can see we face a challenging year but I am confident that with everyone's help, we will achieve our goals!

Nic Jones
Director

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Paterson Postdoc wins prestigious EMBO fellowship

by Iain Hagan

Marisa Madrid arrived in the Institute in January from the University of Murcia, having completed a very productive analysis of the stress responsive signalling MAP kinase cascades in fission yeast in her graduate studies.

Marisa had been studying a MAP kinase signalling pathway that is known as the Cell Integrity Pathway (CIP). Marisa discovered that this pathway responded to a much wider range of stresses than had been previously appreciated, before establishing that CIP signalling was intimately entwined with that of a second MAP kinase signalling pathway that is known as the stress response pathway (SRP). It is the SRP that the Cell Regulation and Cell Division groups have been studying for many years because all major stresses impact upon signalling through this

pathway in some way to alter transcriptional control through a transcription factor called *atf1*. Marisa established that SRP signalling activated several protein phosphatases to turn off CIP signalling. These are important observations for the field as these two pathways can no longer be considered to be autonomous signalling modules.

Marisa was keen to expand upon this solid foundation in fission yeast cell biology/genetics by joining the Cell Division group here in the Paterson Institute to understand how the environmental signalling pathways, that she studied so extensively in her graduate programme, regulate the time at which cells divide. This is a key area to understand because it is vital that cells do not divide when they have just been damaged by environmental insult. If they were to do so then any damage to the genome that has been inflicted by the insult would be fixed and propagated to all subsequent generations. Understanding this link will identify how the physiology of cancer cells differs from those in the surrounding tissue because cancer cells are growing in the wrong place and are invariably highly stressed. Such distinctions between transformed and non-transformed tissues offer novel avenues for therapeutic intervention.

In order to support her time in the Paterson Institute Marisa applied for a prestigious EMBO fellowship. After making it through a tough selection round Marisa was interviewed in Helsinki and recently heard that her application was successful. Success in obtaining such internationally competitive independent fellowship support is a major achievement that will stand Marisa in great stead in fulfilling her ambition for an independent career. It also reflects well on the Institute in bringing the recognition of the Paterson and its facilities as a centre for world class science. We therefore wish Marisa all the best in her studies here and hope that future applications to independently support work in the Institute will be as successful.



New Group Leader Appointed

Dr Ivan Ahel from the CR-UK London Research Institute, where he is currently a postdoctoral fellow in the laboratory of Steve West, has accepted a Group Leader position in the Paterson Institute.

This laboratory is one of the very top laboratories in the world working on DNA replication and repair. Ivan received his PhD from the University of Zagreb, Croatia, having carried out much of his thesis work in the laboratory of Dieter Soll at Yale University. His future research will focus on DNA repair functions regulated by poly(ADP-ribosyl)ation and particularly on proteins that have a novel binding motif that recognises poly(ADP-ribose). We are delighted that Ivan will be joining us.

Paterson invests £500,000 in new Mass Spec equipment

by Duncan Smith

The history of the MBCF Mass Spec service is short and very eventful. The service was born in April 2004, when the Institute purchased of two mass spectrometers jointly with Tony Whetton's academic group. Shortly after, an LC-MSMS protein identification service was opened to all scientists on the Paterson site.

Since then, the service portfolio has grown rapidly to provide numerous applications including phosphorylation mapping, quantitative phosphorylation analysis, iTRAQ quantitation, SILAC quantitation and directed proteome mining (to name a few). This massive expansion in applications has been driven from extremely fruitful collaborations with groups from the Institute designed to implement workflows that push the boundaries of LCMS technology to cancer research. This model of Paterson driven applications development directly feeding world-class service provision is a key strength that differentiates our facility from the crowd.

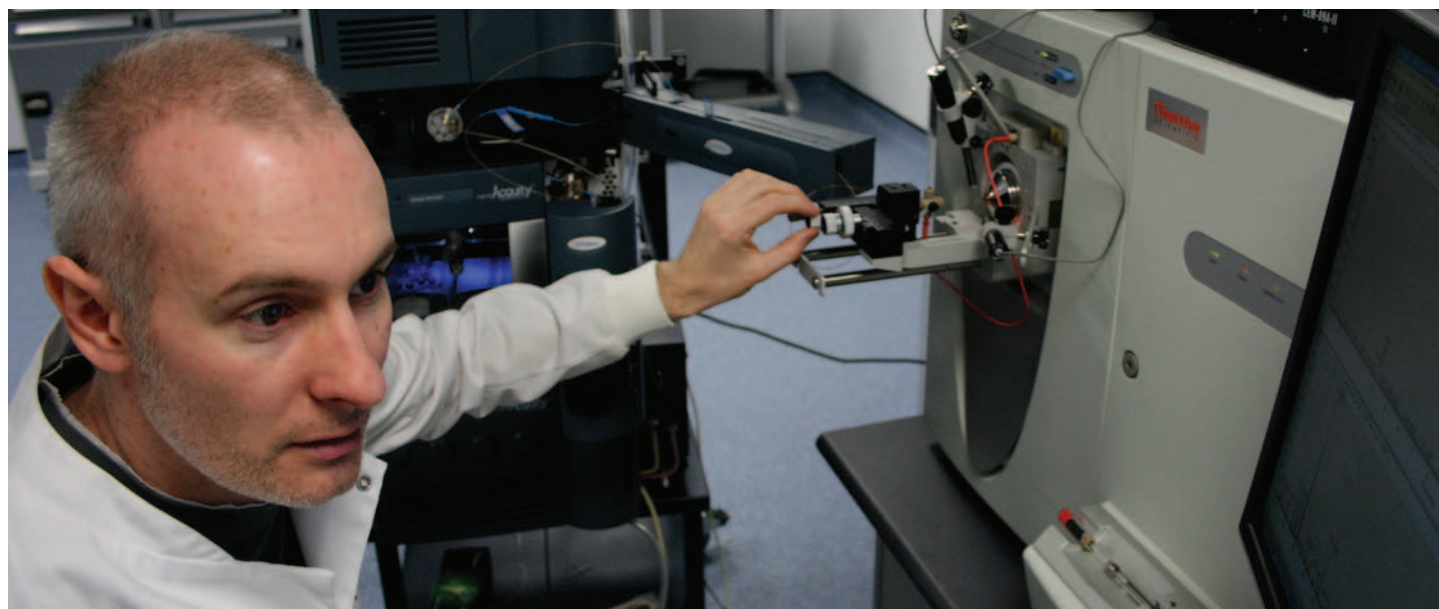
The MBCF MS service was extremely fortunate to secure £0.5 million pounds of CR-UK funding for a new LCMS platform for the 07-08 financial year. As part of this process, the Mass Spec lab has undergone a full refurbishment to provide an appropriate environment for these cutting-edge instruments. In March 08, we installed our new LCMSMS platform designed to provide an unrivalled protein identification service. This new platform consists of the nano Acquity Ultra High performance LC system and the LTQ-Orbitrap XL mass spectrometer. The new

LC system facilitates maximum resolution peptide separations and the Orbitrap is the highest performance protein identification mass spectrometer in the world today. The procurement has already delivered on its promise of maximum performance protein identification with an effective boost in sensitivity of 100 fold over the previous generation of instruments. In addition, this platform has more than doubled our service throughput capabilities. There is now a requirement to build an informatic pipeline capable of utilising both the volume and quality of the data being produced. Our priority is now to provide such an informatic solution to efficiently translate these data into research enhancing information rapidly. The Nano Acquity-Orbitrap platform represents our major tool in terms of our protein identification, quantitation and post-translational interests into the future.

There is going to be an explosion of applications on this platform in the coming year (including workflows currently serviced on the older instruments and totally new applications). The applications developed will be driven directly from the needs of the research groups on site (so get in there quick).

I'm now proud to offer a Mass Spec service with truly world-class capabilities.

Here's to a very bright 2008 and beyond. Thanks to all involved for support and patience.



Genomic Analysis of Archival Material meeting June 08

by Stuart Pepper



Host Stuart Pepper introduces Dr Kim Linton to discuss her recent work with archival samples.

In June the Paterson Institute played host to a one day meeting examining progress in the genomic analysis of archival formalin fixed paraffin embedded samples. These samples represent an invaluable resource as there are literally millions of such samples stored in hospitals around the UK, often with several years clinical follow up.

Traditionally it has not been possible to extract DNA and RNA from these samples however in the last few years there have been improvements in methods which are now allowing exploitation of this resource.

To open the day Professor Gordon Stamp, from the Imperial College Faculty of Medicine, discussed different ways in which samples can be treated during the fixation process and how this can impact on the quality of subsequent analysis. Further talks from Dr Phil Chambers (Genomic

Variation Laboratory Service, CR-UK) and Dr Angela Jones (London Research Institute), who discussed how archival DNA could be analysed using either pyrosequencing and microarray platforms, completed the morning session.

During the day Dr Kim Linton, from the Christie Hospital, presented the results of a project that has been carried out in collaboration between the Paterson Institute, the Christie Hospital and The University of Manchester. This work has resulted in a recent publication in the British Journal of Cancer describing the acquisition of clinically relevant microarray data from archival sarcoma samples. Since writing the paper there have been further technical developments and Kim was able to present these to a mixed audience of academic scientists, clinicians and NHS staff, all of whom had an interest in this technology. Kim concluded by remarking that this had been a good example of the MCRC in action as it had required coordination of a highly multidisciplinary team to achieve the final publication.

Presentations were also given by Mahesh Iddewela (University of Cambridge) on an alternate approach to microarray profiling of archival material and Dr Gavin Kelly, who rounded the day off with an excellent presentation discussing the difficulties of working with data generated from these particularly challenging samples.



Professor Gordon Stamp from the Imperial College Faculty of Medicine opened the day

Paterson at Race for Life

by James Dunphy

On Sunday 1st June a team of a dozen representatives from the Paterson Institute lent their support to Manchester's Race for Life. This race had 6,700 women from across Manchester running the 5km course to raise money for Cancer Research UK.

The day is best described by one of the participants:

"We arrived at 10am (5 in our group, ages ranging from 9-40 years old) the rain was falling and by the time we started the race we were soaked to the skin. What a brilliant atmosphere, what a feeling when you finish, I know it's about raising money but if you were there you'd of seen it was more than that. Every person there gave a few hours of their time in the rain, soaked to the skin, crossed over the finishing line with a smile. Thank You to everyone."

Thanks to Claire, Najma, Olga, Seema, Mandy, Ting, Ahmet, Dimitrios, Gail, Aileen, Babra and Monique who helped lead the runners to the start, cheer them up the last hill, keep the crowds back(!) and provide the well deserved medals at the end. It is hoped that this race will raise over £500,000 for the Charity.



Monique Melis (Targeted Therapy)
and Najma Rachidi (Cell Division)
hand out medals



Paterson staff on duty at the finish line



Paterson staff and volunteers before the race



Paterson staff and volunteers lead the runners
to the starting line

Keswick to Barrow walk

By Sarah Lewis



All my hiking friends told me I was completely mad. 'You're going to walk through the Lake District,' they said, 'for 40 miles, by-passing all those lovely hills?' Admittedly, a 40 mile race along a flat tarmac road is not my typical hiking day out, but since it's in aid of a good cause I decided to at least give it a try.

I slightly regretted my decision when we were rudely awakened in the middle of the night to hastily get ready and sleepwalk our way down the road to the coach that was taking us from Barrow to the race start. I do remember Katalin and Martin (this year's brilliant walk organisers) telling everyone that it was an early start....but 3.30 am?! We began to realise exactly what we had taken on when the coach took a painfully long time to reach our destination, acutely aware as we were that however far the bus drove us, we had to walk that same distance back again. Without any time for second thoughts we were off, swiping our time tags at the start line. Many members of the 21-strong Paterson team sped off into the distance, but my aim was simply to finish the walk, never mind doing it quickly, so I set off at and maintained my

usual hiking pace: a slow plod. The weather was unusually nice for the Lake District, sunny but with enough cloud cover to keep the temperature cool. Even without hilltop views, I have to admit that the scenery throughout the first half of the walk was stunning. I greatly appreciated the rare opportunity to look out over the waters of Thirlmere bathed in a beautiful dawn light. Carrying enough rations for a week was perhaps not entirely necessary as the K2B is incredibly well organised, with regular checkpoints offering food, drink and first aid, and a feast of sandwiches at 20 miles. I think that everyone was, however, a little sick of orange squash and bananas by the end of the day.

After a mere thirteen and a half hours I crossed the finish line, cheered on by a small yet dedicated welcoming committee. I was reunited with my much speedier team-mates, nursing their blisters back at the B&B, and we treated ourselves to a well-deserved takeaway dinner. This year the sponsorship raised is being split equally between Christie's Hospital and Cancer Research UK, so many thanks to friends, relatives and of

course staff and students here at the Paterson Institute for your generosity, it is much appreciated.

Acknowledgements, facts and stats:

This year's total sponsorship raised is over £2,500! Thank you to all our colleagues, friends and family for the very generous contributions!

Special thanks to Denise Owen for her help with the fundraising, and to our corporate sponsors: [Scientific Lab Supplies](#), [Jencons](#), [Bioline](#), [The Danwood Group](#), [Starlab](#).

The team members would also like to give a big thank you to James Dunphy, Chris Wareing, Sandra Strassburg and Deepthy Francis for their encouragement and patience at the 30-mile mark and their support before and after the walk.

The two Paterson teams were ranked 52 and 101 from 244 teams and 19 and 38 from 54 teams outside of Cumbria. Our fastest team member was Chris Cawthorne, who finished 38 out of 2,029 starters (1,822 walkers finished)

The individual times this year were (h.min.sec.):

Chris Cawthorne: 6:32.13
John Mcburney: 7:16.04
Gavin Wilson: 7:57.58
Katalin Boros: 8:37.07

Patrycja Sroczynska: 9:13.11
Arek Welman: 9:14.16
Nimesh Joseph: 9:18.55
Lu Zhang: 9:48.03
Jian Mei Hou: 9:49.12
Cristina Martin-Fernandez: 9:52.50

Martin Brandenburg: 9:53.00
Deborah Maskell: 12:22.40
Guilherme Costa: 12:24.24
Peter Molitoris: 12:24.35
Wilawan Bunjobpol: 12:26.54
Ting Zheng: 12:47.40

Sarah Lewis: 13:28.07
Catriona Parker: 14:25.43
Lenka Zvirinska: 30 miles completed
Silvia Oliveira: 35 miles completed
Olga Tsoulaki: 20.5 miles completed

In Brief

Congratulations to Jeff Cummings, Tim Ward, Alastair Greystoke, Malcolm Ranson and Caroline Dive whose paper - biomarker Method Validation in Anticancer Drug Development - was downloaded a total of 767 times in February from the British Journal of Pharmacology, making it one of the top 3 downloaded papers in February 2008.

Staff News

Congratulations to [Ricky van Deursen](#) (Cell Cycle) and his wife Hilary on the birth of their son Matthew James van Deursen (right) Born 23rd May 2008 at 1.38am Weighing 6lb 2oz.



Welcome to.....

[Vincent Pritchard](#) - Domestic

[Helen Rushton](#) - Cell Signalling group - Postdoc

[Luke Harrison](#) - CEP - Postdoc

[Kieran Mellody](#) - Stromal Tumour Interaction - Senior Scientific Officer

[Yasushi Kojima](#) - Akira's Lab - Postdoc

[Gary Spencer](#) - Leukaemia Biology Lab - Senior Scientific Officer

[Owen McGinn](#) - Immunology group - Postdoc

[Matthew Lancashire](#) - CEP - Laboratory Aide

[Carol Walley](#) - Domestic

TRF Refurbishment

by [Jenny Varley](#)

By the time you all read this the building works on the second floor will be completed. Given the experience with the previous scheme this development has been a delight to oversee. As well as the obvious lack of frequent fire alarms (usually during heavy rain so that we all get cold and wet!), there has been minimal disruption to any activities in the Institute. The main contractors, Parkinsons, have been excellent and a pleasure to work with. The scheme has slightly over-run but only by a week or so, and by the middle of June we should have formally accepted the area.

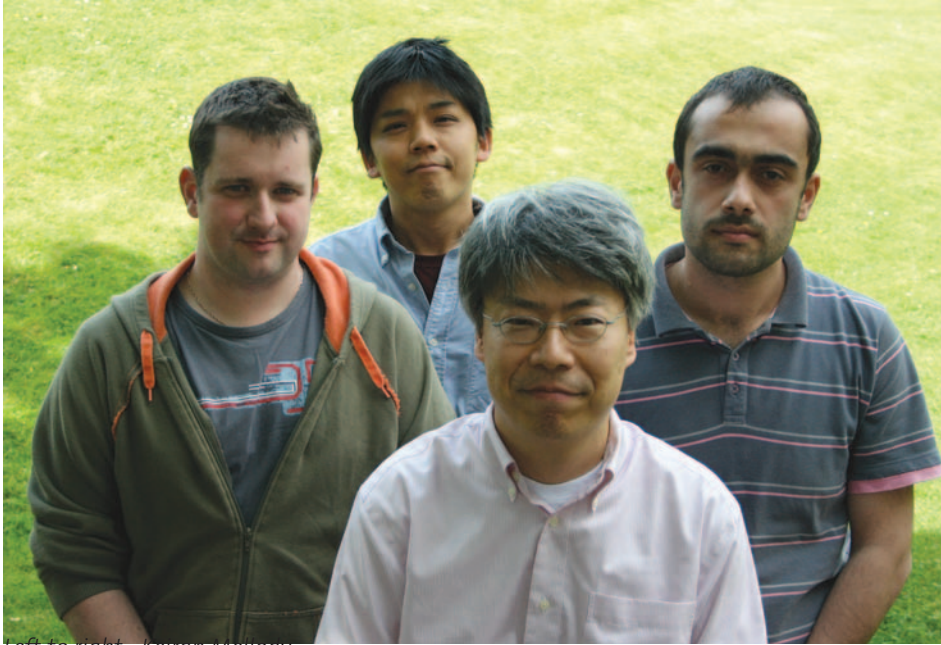
The development provides refurbished accommodation for Peter Stern's Immunology group as shown in the picture below, and new space for a facility for assays done to the standard of GCLP associated with immunotherapy trials. There is also space for a Chair in Breast Oncology plus up to two further group leaders (all to be appointed). The laboratories and offices have been designed such that the areas should be suitable for most activities, including tissue culture space and instrument rooms. There is also a large shared facility for minus 80° freezers and nitrogen storage, instrument rooms and a good-sized working cold room.

The same contractors recently finished work on the ground floor, with a new conference room and improved facilities for Mass Spectrometry, Flow Cytometry, Finance and the MCRC office.



Group Spotlight - The Stromal Tumour Interaction Group

by Akira Orimo



Left to right - Keiran Menlough, Yasushi Kojima, Akira Orimo, Ahmet Acar

Tumours are highly complex tissues and the non-neoplastic cell compartment of tumours, which is often termed the “stroma”, is itself quite complex histologically.

Carcinoma cells initially recruit and/or activate these various stromal non-neoplastic cells, including fibroblasts, myofibroblasts, immune cells, endothelial cells, bone marrow-derived cells etc. The resulting stromal cells reciprocate by fostering carcinoma cell growth and survival during the course of tumour progression.

Studying the heterotypic interactions between the neoplastic cells and the

supporting stroma is believed to be essential for understanding nature of a bulk of carcinoma mass. However, such research fails to include and address another variable: that the stroma is itself altered and might co-evolve with the tumour cells during the course of tumour progression.

Indeed, numbers of these myofibroblasts are very often recruited into invasive human breast carcinomas and involved in tumour progression.

Myofibroblasts are also observed in areas of wound healing, fibrosis, and chronic inflammation. These cells produce abundant levels of extracellular matrix (ECM), cytokines and growth factors that aid in tissue repair and promote angiogenesis in sites of damaged tissues.

We previously demonstrated that a large population of myofibroblasts, designated carcinoma-associated fibroblasts (CAFs), extracted from invasive human breast carcinomas exhibited an ability to promote carcinoma growth and angiogenesis. Thus, myofibroblast-secreted stromal cell-derived factor-1 (SDF-1)/CXCL12 chemokine mediated, in part, the tumour-promoting ability of these myofibroblasts by recruiting endothelial progenitor cells (EPCs) into tumour, boosting angiogenesis (Orimo et al, Cell, 121, 335-48, 2005; Orimo and Weinberg, Cell Cycle, 5, 1597-601, 2006).

To further understand the biology of stromal myofibroblasts in tumour, we intend to study myofibroblast-tumour cell interaction in several aspects. Stroma-derived signaling likely provides a support for carcinoma cells to facilitate invasion and metastasis during tumour progression, an important biological process that remains poorly understood in spite of a decade of intensive study by many research groups. Studying about molecular insights by which these stromal cells coevolve with carcinoma cells will help understand nature of tumour-prone microenvironment. The ultimate aim would be to find out an attractive target for the development of anti-tumour therapies based on disturbing the stroma-tumour cell interactions.

Reflection on my PhD

by Claire Rooney

I started at the Paterson Institute back in 2004. The first year of my PhD consisted of three rotation projects, which was a great way to get to know the Institute and its staff.

I started out in the Cell Regulation laboratory and, being fairly new to lab work at the time, I was very grateful to everyone there for patiently helping me to get started with the various techniques. After that I moved down the corridor to Cell Signalling and finally onto Stem Cell Haematopoiesis. I really enjoyed all three projects, but I chose to go back to Cell Signalling to complete my PhD project. I have been examining the role of the Tiam1 homologue, STEF, in various aspects of tumourigenesis in my time here, which has yielded some interesting results.



Claire Rooney at work in the lab

Outside of the lab, I've been enjoying life in Manchester, it's a great city and I've also been part of some fun houseshares, which always makes moving to a new place much easier. I've been playing hockey for Wilmslow for the last three years, which has been fantastic.

Four years really does fly by, I can't believe that my time as a PhD student is coming to an end. I've learned a lot working in the Cell Signalling lab, due in no small part to the helpfulness of my labmates. I've made some great friends in my time here, and when the time comes to move on I'll be sorry to say goodbye. For now, I'm trying to finish off a few things in the lab before getting on with the thesis writing – wish me luck!

Science Communication Roadshow

Twenty researchers at the were the first to take part in the Science Communication Roadshow, aimed at boosting their skills and confidence in communicating their work to the CR-UK supporters.

In the words of Professor Nic Jones, who spoke at the start of the day, "our research is funded overwhelmingly by the generosity of the general public, and we have a duty to explain clearly what we do with their donations."

The Roadshow was set up to support LEAD (formerly Project Local), to empower scientists to interact with supporters in their local community. The topics covered included "Who are our

supporters", "Mind your language", "Powerpoint pitfalls", "Lab tours and open days" and "The media".

The Pilot workshop was a great success, with most attendees rating the day five out of five and saying it had increased their motivation to interact with our supporters. Comments included "a good mix of interactive activities and presentations" and "highly interactive without being embarrassing!"

Depending on the final results of the formal evaluation of the pilot, the Roadshow will be rolled out to the other CR-UK Institutes, and possibly other sites in future.

Researchers of the future visit the Paterson Institute

by James Dunphy



The Paterson Institute invited 48 of the best scientific sixth form students from across the northwest to come and spend a day getting 'hands on' research experience.

This is the 4th year that the event has taken place and it is growing in popularity with all the available places being taken up by the 8 schools involved. The event was originally developed by Dr Lez Fairbairn but has recently been run by Stuart Pepper, who is the Head of Molecular Biology Core Facility, and he stated:

"The main aims are to inspire them into following research careers and help raise awareness of the research Cancer Research UK funds."

The programme has been developed in line with the A-Level syllabus but also expanded to highlight the work that happens

beyond the students current learning. During the day the students had the opportunity to visit 3 areas of work for 90 minute sessions. The Institute had representatives from 6 groups (Bioinformatics, Advanced Imaging, Cell Division, Immunology, Clinical Experimental Pharmacology, Molecular Biology Core Facility) to help facilitate the activities. The students were given the opportunity to run PCR's, read DNA sequences, perform cell culture and use advanced imaging systems.

Their feedback from the event was excellent, with all stating that they enjoyed the activities and found them relevant with many stating they would like to learn even more. One student said:

"It was great to see some real life labs; we would never get to see some of this amazing equipment back at school"

Andrea Welsby, who is the Head of Biology teacher at Loretto Grammar School and who has been instrumental in helping to develop the day, stated:

"I think it is fantastic for the students to have the opportunity to visit such an Institute and over the last four years I have seen some change their career aspirations and direction due to their experience here."

The day was a huge success both in terms of student experience and the support provided by the Paterson Institute, with all of the groups taking time to plan meticulous interactive, enjoyable sessions.



The Institute opens its doors to fundraisers

by James Dunphy

On the 7th June the Institute hosted its biggest ever Open Day. We had more visitors and more demonstrations than ever before. The 90 visitors came from a variety of places, including volunteers from Cancer Research UK shops, members of cancer support groups, fundraising teams, even our local MP John Leech made an appearance.

The morning began with an update from the local fundraisers about forthcoming activities and recent successes. This was followed by a talk from Professor Hawkins about his current work in the CR-UK department of Medical Oncology.

A quick lunch break and the visitors were split into 12 groups to begin the "best part of the day". Each group was expertly guided around the Institute, where they had the opportunity to visit 4 different labs for some excellent interactive demonstrations during their two hour tour.

The feedback from the day was extremely positive, a treasurer from a fundraising group stated it was:

"An excellent and informative day. I'm now spurred on to raise more money!"

A volunteer from a Cancer Research UK shop was equally happy, saying:

"Excellent day, it brings to life the wonderful research being done!"

Thanks to all involved in this day as it was clearly a resounding success enjoyed by all.



Caron Abbey and Garry Ashton give a demonstration in the Histology department



Geoff Margison demonstrates DNA 'spooling' to local fundraisers in the Carcinogenesis lab



A cheque for over £10,000 was handed over to Mr Peter Whalley of CR-UK by the Moon and Stars group



Local fundraisers gather in the coffee room prior to the start of the tours