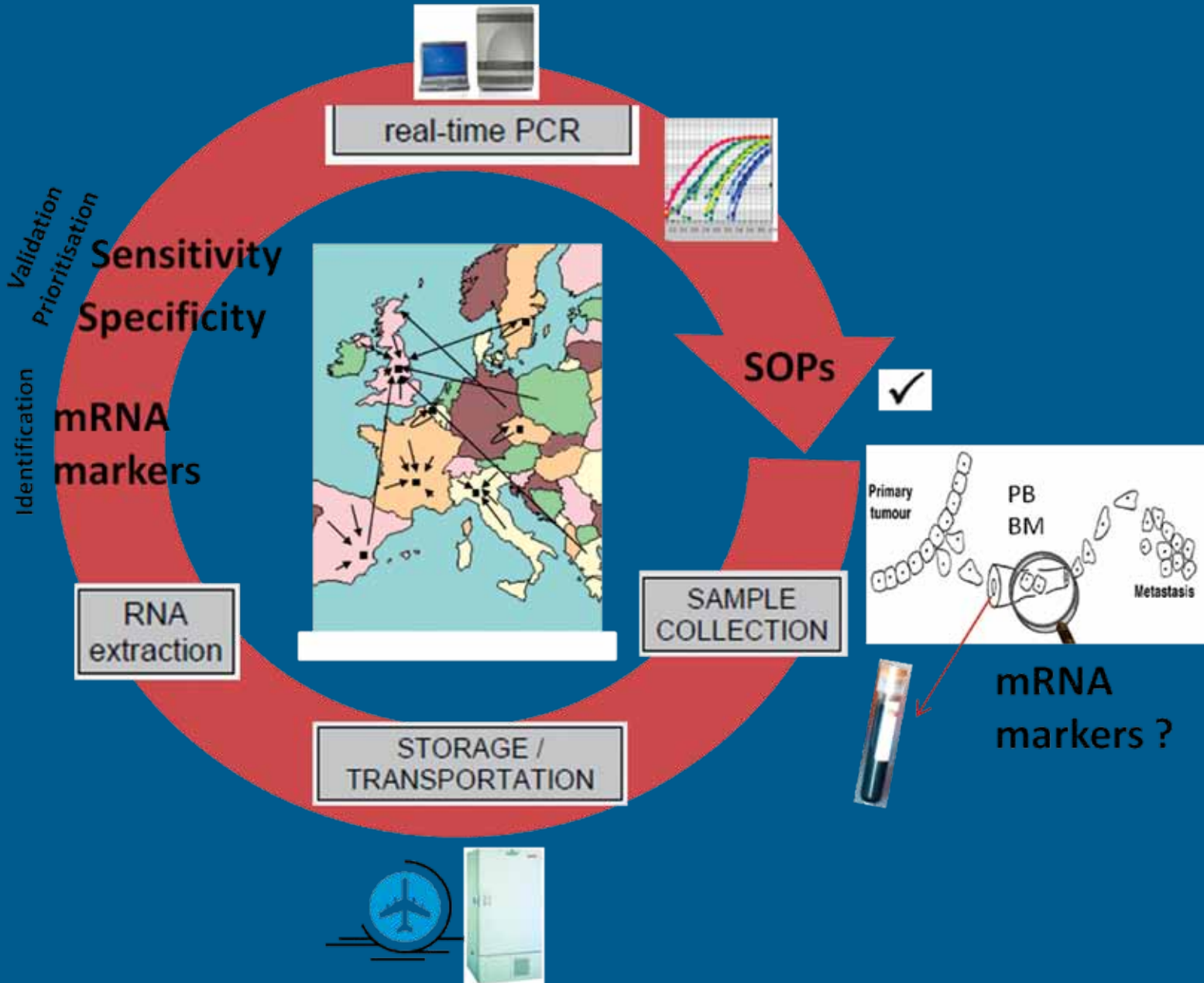


News

• British • Association • for • Cancer • Research •





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Front Cover

Standardisation of operating procedures (SOPs) for collection, storage, transport and analysis of clinical samples are important to reduce inter-laboratory assay variability and improve the power of biomarker studies. SOPs to ensure the quality of mRNA studies in peripheral blood (PB) and bone marrow (BM) across multiple centres have been established (Viprey et al, Eur J Cancer 2007; 43: 341-350); RNA species from PB and BM are preserved in PAXgene™ Blood RNA tubes for up to 48 hours at room temperature or >5 years when frozen at -80°C. mRNA markers are identified and validated prior to evaluation by real-time polymerase chain reaction (PCR) in prospective clinical trials (Viprey et al, J Pathol 2008; 216: 245-252).

Europe Map adapted from LyndseyMacCollam 1998



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Joint British
Association for
Cancer Research
Gray Institute
One-Day Meeting

**DNA Damage Repair:
Translating scientific landmarks
into new treatments for cancer**

14th March 2012

St Catherine's College, University of Oxford

This meeting will address DNA damage repair in order to identify the potential of DNA repair proteins as targets and biomarkers for cancer therapy

Confirmed speakers include:

Anthony Chalmers (Glasgow) **Nicola Curtin** (Newcastle)
Thomas Helleday (Oxford) **Steve Jackson** (Cambridge)
Sonia Lain (Stockholm) **Peter McHugh** (Oxford)
Mark Meuth (Sheffield)

We will be offering poster prizes to students and opportunities to postdocs and students to do oral presentations of their research

Further information:

www.rob.ox.ac.uk/BACR-meeting-2012



Organising committee:

Ricky Sharma (Oxford)
Elaine Willmore (Newcastle)
Sarah Norman (Oxford)





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Letter from the Chairman



Dear Colleagues
Welcome
to the autumn
2011 Newsletter
of the BACR

2011 has been a relatively quiet year for the BACR, with only one small meeting plus the NCRI conference.

You will be pleased to hear that for 2012 the executive committee is planning three exciting conferences in addition to the NCRI 2012.

The BACR "Cancer epigenetics" one-day meeting in May 2011 at the RSM in London was a great success, with 100 delegates. At its July committee meeting the executive committee selected the 2011 BACR award winners. As in recent years, the standard of the applications has been very impressive. The winners of the BACR/Astra Zeneca Frank Rose Award and the BACR Translational Award are Dr Dmitry Pshezhetskiy and Dr James Flanagan (both from Imperial College London) respectively. Both will present synopses of their work during the forthcoming 2011 NCRI meeting in Liverpool at the beginning of November. At that very meeting the BACR will sponsor Prof Mike Stratton (Wellcome Trust Sanger Institute, Cambridge) as the BACR Tom Connors Lecturer. The BACR will also organise, in time-honoured fashion, two early bird workshops. The Monday morning workshop will be on "The endothelial cytoskeleton: a dynamic target for cancer therapy", organised by Dr Chryso Kanthou, and the Tuesday morning workshop on "Unlocking the development and progression of childhood cancers" organised by Professor Sue Burchill. The Executive Committee looks forward to seeing lots of you there!

For 2012 we plan a one-day meeting on "DNA damage repair" in March, a two-day conference on "Chasing cancer stem-like cells" in September, and a one-day event on "Progress in cancer models" in November. Watch this place for confirmation and more information.

The Executive committee welcomes 4 newly appointed members: Dr Helen Reeves (University of Newcastle), Dr Jacqui Shaw (University of Leicester), Dr Paul Loadman (University of Bradford, co-opted) and Ms Lucy Shaw (University of Leeds), co-opted student member). They replace Dr Anne Thomas, Klaus Pors and Victoria Forster whose terms of office are coming to an end. We thank the outgoing committee members profoundly for their enthusiasm and engagement in running the BACR.

This is my last letter as chairman, as Prof Caroline Dive (Paterson Inst., Manchester) will take over as BACR chairperson in November. It has been an honour and real pleasure to serve as your chairman during the past 3 years, supported by my wonderful fellow officers including our warm and charming secretary Janet, and by a bright and inspirational committee.

Best wishes

Andy Gescher
Chairman

BACR Special Conference

Cancer Epigenetics

Royal Society of Medicine – Thursday 19th May 2011

Jane Borley and Natalie Shenker, Imperial College London



*Dr James Flanagan
Imperial College London*

Thursday, 19th May
2011 saw the
UK's first BACR
Cancer Epigenetics
meeting take place
at the Royal Society
of Medicine in
central London

Dr James Flanagan (Imperial College London) who was the coorganiser of the event welcomed delegates and chaired the first session of the day, entitled "Cancer initiation and risk".

Professor Christophe Plass (German Cancer Research Center) started the session with an overview of epigenetics and its role in tumourigenesis, followed by examples of his own group's work on the epigenetic alterations that related to chronic lymphocytic leukaemia. Studies on the gene ID4 (inhibitor of DNA binding protein 4) have demonstrated aberrant methylation patterns that correlated with decreased gene expression and patient survival. The ID4 knockout mouse model of CLL has also shown aberrant methylation occurs as an early event in cancer development.

The second presentation of the session came from Professor Zdenko Herceg (International Agency for Research on Cancer) who gave an insightful talk summarising the data that shows how environmental factors and stressors affect the epigenome, and how these are tissue- and tumour-specific. Professor Herceg is coordinating the large European-wide EPIC study, which has enabled detailed analysis of the role of dietary factors in cancer

development and has demonstrated that folate and methionine levels are associated with hypermethylated and hypomethylated states, respectively, in tumour suppressor genes. He presented microarray studies that have shown that epigenetic signatures differ depending on aetiological factors; this was highlighted by investigations on hepatocellular carcinoma, which are caused by viral hepatitis infection and alcohol and the effect of smoking on microRNA in lung tissue. Aberrant methylation of the hepatitis B virus genome has been found to determine pathological outcome and may cause the virus to escape the host immune response.

The last presentation of the session was by Dr James Flanagan, who highlighted his group's work on the search for epigenetic biomarkers that predicted breast cancer risk through prospective cohort studies. These have validated previous work which described how the increased methylation of a particular locus in the ATM gene was associated with a 1.7-fold increased relative risk of breast cancer. The challenges of current and future work in the field of epigenetics was discussed, including understanding the stability of the epigenome with age and determining the biological meaning of small methylation changes.



Dr Adele Murrell
University of Cambridge

Following the coffee-break the second session of the morning, “Novel Epigenetic Approaches”, was chaired by the co-organiser of the meeting Dr Adele Murrell (University of Cambridge). Steven Catchpole (King’s College London) and Dawn Farrar (University of Essex) were invited from the abstracts submitted to the poster competition to present their respective work. Steven Catchpole is working on the function of JARID1B, a protein with demethylase characteristics. He is using a mouse model that expresses the JARID1B protein with an absent functional ARID domain. The Δ ARID mouse demonstrates delayed mammary tree development which is dependent on ER α signalling, delayed growth of spontaneous mammary tumours and decreased expression of downstream targets of ER α signalling. Dawn Farrar discussed two innovative models that their group had developed on the regulation of CTCF, a multifunctional transcription factor that is important for maintaining the chromatin structure. They have demonstrated that PARP-1 (a poly(ADP-ribosyl)ation enzyme) may be important for the regulation of CTCF function by forming complexes. The last presentation before lunch was from Professor Bryan Turner (University of Birmingham Medical School)

whose group focuses on histone modification and acetylation in tumour development. He gave an entertaining overview of the history of epigenetics and the investigations on DNA methylation and histone modifications, which left us hungry for more discussion (and lunch).

Lunch was then served and delegates were given the opportunity to meet each other while viewing the 25 posters displayed in the atrium on a wide range of fields related to epigenetics from the UK and European groups. Following lunch, the third session focused on “Epigenetic Targets and Therapies”. Professor Eamonn Maher (University of Birmingham) outlined the work carried out on renal cell carcinoma, where the majority of tumours are thought to arise from the aberrant methylation of tumour suppressor genes. Professor Steve Clifford (University of Newcastle) highlighted the challenges surrounding paediatric brain tumours where morbidity and mortality is extremely high. Interestingly, subgroups of the histopathological classification of medulloblastoma tumours have been discovered to be determined by their epigenome, which may help to categorise patients according to the most appropriate treatment arm they should receive. This is now being developed into a SIOP clinical trial where treatment modalities will be determined by the epigenetic profile of the tumour. Professor Nicholas La Thangue (University of Oxford) discussed histone deacetylase (HDAC) inhibitors. His group have demonstrated that the decreased expression of the *HR23B* gene is related to resistance of HDAC inhibitors and tumour relapse. This gene may serve as

a useful biomarker to assess the likely response of the tumour prior to initial treatment.

After the afternoon break, and the prize for the best poster was awarded to Ana Luisa Silva (University of Cambridge) for her work on the progressive hypermethylation of Wnt signalling antagonists throughout colorectal cancer development. Finally, Professor Stephen Beck delivered the keynote lecture entitled, “The Human Epigenome and Cancer Epigenome Projects”. He gave an overview of the key projects and consortia that had been established worldwide over the last 10 years since the completion of the human genome project. These have been highly productive in constructing comprehensive maps of the epigenome. The insights he gave into the technological developments that have made this feasible and the future goals of epigenetic tools in the diagnosis and treatment of cancer, were truly memorable. He predicted that whole body scanning for epigenetic biomarkers for the detection and treatment assessment of cancer will be possible within the next 5 years, which closed the meeting on an inspirational note.

In summary, this was a very enjoyable and stimulating meeting, which provided an excellent platform for discussion, debate and interaction in the combined fields of cancer and epigenetics. There was no doubt of the usefulness of bringing together experts from a wide range of fields and countries working on epigenetics mechanisms and treatments for cancer, and this is sure to be the benchmark for future UK based Cancer Epigenetic conferences.

BACR Special Conference

Cancer Epigenetics Poster Prize Winner

Ana Luisa Silva

Molecular Histopathology Division, Department of Pathology, University of Cambridge



Ana Luisa Silva
University of Cambridge

Firstly, I would like to thank the BACR for sponsoring the 1st Cancer Epigenetics meeting in the UK which was an amazing one-day event

The organization of the day, as well as the choice of outstanding quality speakers at the forefront of the epigenetics field, was excellent. A variety of engaging topics in epigenetics were covered from genome-wide DNA methylation changes in chronic lymphocytic leukaemia by Prof. Christoph Plass, to the consequences of HDAC inhibitors in cells and their involvement in cancer therapy by Prof. Bryan Turner and Prof. Nick La Thangue. The keynote speaker, Prof. Stefan Beck, closed the day with an excellent overview of the extraordinary advances achieved in the “Epigenome Project” over the past years due to the development of new technologies. He also introduced the “Epigenesys” website, a new resource for the epigenetic research community.

My work entitled “Wnt signalling antagonists are progressively hypermethylated during colorectal neoplastic progression” was awarded with the poster prize which strengthened my determination to continue my PhD research in DNA methylation and the Wnt signalling pathway during colorectal cancer progression. The entire poster session was of high quality and it was a good opportunity to discuss my work and ideas with senior scientists in my field.

Colorectal cancer (CRC) is the third most common type of cancer and the Wnt signalling pathway plays an important role in initiation and progression of CRC. In the work presented, I showed the promoter methylation changes of selected Wnt antagonists in a set of synchronous normal, hyperplastic or adenomatous polyps and adenocarcinoma tissue samples. Using Pyrosequencing assays we profiled the methylation status of CpG islands associated with Wnt signalling regulators and assessed the levels of expression of some of these regulators by qPCR. There is a significant stepwise increase in methylation during CRC progression, specifically targeted to the Wnt pathway antagonists, that was correlated with loss of gene expression. Other regulators of the pathway, apart from the APC gene, showed consistently normal levels of methylation throughout CRC progression. In conclusion, we have shown that Wnt antagonists are progressively hypermethylated during CRC development. We propose that CpG island hypermethylation of Wnt antagonists could be used as biomarkers for the early detection of CRC and in cancer therapeutics. I look forward to the next meeting.

Reports of Sponsored Meetings

“New concepts in cancer metastasis”

25th – 28th June Lisbon, Portugal

Tumor metastasis remains the prime cause of death for cancer patients, and therefore it is imperative that we properly understand the process of metastasis so that suitable strategies can be designed for improved diagnosis, prognostic evaluation and therapeutic intervention

In recent years a number of seminal observations have been made that have challenged prevailing paradigms about the process of metastasis. These observations have opened up new areas of research that hold the promise of uncovering the secrets of metastasis. In turn, this will pave the way to much improved management of metastatic disease. The aim of the conference “New concepts in cancer metastasis” was to bring together key researchers from across the world working in a number of these recently emerging areas in metastasis research, including the role of cancer stem cells, the metastatic niche and regulation of metastasis through the microenvironment, as well as mechanisms of tumor cell dissemination, EMT, and organ-specific metastasis. Reflecting its far-reaching ambitions, the conference was a joint

Venture between TuMIC, the Metastasis Research Society and the Champalimaud Foundation.

The conference was initiated by the TuMIC consortium (<http://www.ma.uni-heidelberg.de/inst/cbtm/mbio/tumic/>), a European Union-funded metastasis research initiative that aims to investigate and integrate newly emerging principles and ideas with the different hypotheses that have until now tried to explain the process of metastasis. A generous grant from the European Union as part of this initiative provided a

significant proportion of the funding for the meeting. The Metastasis Research Society (<http://www.metastasis-research.org/>), an international organization dedicated to understanding the process of tumor metastasis and to applying this knowledge in the clinical arena, also provided financial support. Members of the society were able to attend the conference at reduced registration rates. The Association for International Cancer Research (AICR), the British Association for Cancer Research (BACR) and the European Association for Cancer Research (EACR) also generously supported the conference by each funding an invited speaker.

The Champalimaud Foundation (<http://www.fchampalimaud.org/>) provided further financial support as well as a truly outstanding and awe-inspiring venue, namely the Champalimaud Centre for the Unknown, an award-winning complex of clinics and laboratories designed by the architect Charles Correa. This complex houses the Champalimaud Cancer Centre, a comprehensive facility dedicated to research, prevention and treatment of metastatic disease that was inaugurated in October 2010. The Champalimaud Cancer Centre aims to bring thirty research groups focused on metastasis together with clinicians treating metastatic disease in a venture that holds great promise for major a major international impact.

The TuMIC coordinator Jonathan Sleeman, the newly appointed Clinical Director at the Champalimaud Centre for the Unknown, António Parreira, and the current president of the MRS Rik Thompson opened the conference by welcoming all participants to Lisbon. Thereafter followed more than three days of an intense and fully-packed programme in which recent and unpublished data of the highest quality were presented and discussed. In addition to invited speakers, many abstracts were chosen for oral presentation, providing a great opportunity and experience for many younger scientists at the PhD student and postdoc levels. Two lively poster sessions provided further opportunities for the energetic exchange of data and ideas, fostered by the excellent standard of the research presented in the posters. The conference discussion also gave the opportunity to stand back and assess how the field is developing, and it was particularly exciting to see that several research areas are coming together to give clearer picture of how metastasis works.

The BACR-funded speaker Fiona Watt made a particularly important contribution to the meeting. She described recent work in her group using novel transgenic mouse models that allow the role of intercellular communication in wound-induced tumor formation to be investigated. Wounding of transgenic mice expressing a

constitutively active form of MEK1 in the suprabasal epidermal layers of the skin results in a much higher frequency of squamous cell carcinomas than in control mice. This is due to epidermal release of IL1-a that attracts inflammatory cells, as demonstrated by suppression of tumor formation by the IL1R antagonist Kinaret. CD26 (dipeptidyl peptidase-4), an enzyme involved in T-cell activation, is also upregulated in stromal fibroblasts from the MEK1 mice, and also plays a role in enhanced tumor growth in these mice as demonstrated by treatment of the mice with the CD26 inhibitor Sitagliptin. The data clearly illustrate the importance of the interplay between epidermal cells, fibroblasts, T-cells and macrophages in the genesis and growth of squamous cell carcinomas. This interplay was a recurring theme in other talks at the conference, also in the context of metastasis. The relevance to human disease of Prof. Watt's findings is underlined by the observation that diabetic patients treated with Melformin, another CD26 inhibitor, have a reduced incidence of some types of cancer. The organisers of the "New concepts in cancer metastasis" conference are very grateful to the BACR for their financial support that allowed Prof. Watt to make this important contribution to the meeting.



*Prof Fiona Watt
King's College London*

BACR Mid-Career Fellowship

Dr Olivier E. Pardo
Team Leader, Lecturer
Imperial College London

Identification of metabolomic changes associated with acquisition of lung cancer resistance to EGFR inhibitors

Introduction

Lung cancer is the principal cancer killer worldwide. Resistance to therapy is one of the main reasons for failing to cure patients suffering from this malignancy. This is particularly true of non-small cell lung carcinoma (NSCLC), the main form of the disease that responds poorly to conventional chemotherapy. Gene mutations leading to constitutive activation of oncogenes or receptor tyrosine kinases (RTKs) have been shown to drive development of NSCLC. Amongst RTKs, activating mutations in the epidermal growth factor receptor (EGFR) can be found in about 10% of European and up to 30% of Asian NSCLC patients. Treatment of these patients with EGFR kinase inhibitors such as Erlotinib and Gefetinib has been shown to be effective in decreasing the tumour burden and extending survival {Li, 2009 #925}. However, tumours become resistant to these compounds through mechanisms that are not yet fully understood but often involve a T790M mutation in the receptor {Li, 2009 #925}. Changes in cellular metabolism have been shown to accompany tumorigenesis and the development of classical chemotherapeutic drug resistance {Weinberg, 2009 #4317;Fritz, 2010 #4319;Jones, 2009 #4321}. Metabolic profiling has emerged as a new tool to understand – and develop novel therapeutics for – cancer {Boros,

2002 #4323;Serkova, 2007 #4325}. The aim of the 1-month work performed at the Chinese Academy of Sciences (CAS), Wuhan, China, was to analyse the metabolomic changes that correlate with the onset of resistance to the Erlotinib.

Methodology

We used four cell lines that differed in their sensitivity to Erlotinib: two (PC9 and H3255) were sensitive to the drug while the other two (PC9ER and H1975) were resistant, owing to a T790M point mutation in their EGFR. PC9ER were obtained following chronic treatment of PC9 cells with Erlotinib, providing us with a closely genetically matched cell pair, while H3255 and H1975 were derived from two distinct patients' tumours.

All four cell lines were subjected to the following treatments:

1. No treatment: this condition enabled us to compare the metabolic profile of sensitive and resistant cells in normal growing conditions.
2. Erlotinib treatment: the cells were treated for 6h with twice their corresponding IC_{50} for this drug. This condition should highlight whether all effects of the drug are inhibited by the EGFR mutation and therefore inform on the metabolic on- and off-target effects of the compound. The 6h time-point was chosen so as to reflect early changes following drug exposure rather than long-term cell death-related effects.

3. DMSO control: as Erlotinib was diluted in DMSO and this solvent has been documented to affect oxidative reaction in mitochondria, we used this condition to normalise the results obtained in (2) and focus on changes linked to the activity of drug treatment *per se*.

All cell lines were grown in RPMI complemented with 5% Foetal Calf Serum and antibiotics at 37°C/5% CO₂. The cells were collected by trypsinisation and the samples processed as indicated in Figure 1. Because of time constraints, only the spectra for the cell extracts were obtained during the visit leaving the culture medium samples to be analysed at a later date by members of the team at the CAS. Ten replicates were performed per condition. The samples were analysed by ¹H NMR spectroscopy using a 600MHz Bruker Ultrashield 600Plus instrument.

Results

At this point in time, only the 1-dimensional spectra obtained for PC9 and PC9ER cells have been fully analysed. A representative spectrum for PC9 cells with integration range between 0.5-9.5ppm is shown in Figure 2. The spectra for the following conditions were compared:

- PC9 vs PC9ER
- PC9 + Erlotinib vs PC9ER + Erlotinib
- PC9+DMSO vs PC9+Erlotinib

- PC9ER+DMSO vs PC9ER+Erlotinib
- PC9 vs PC9+DMSO
- PC9-ER vs PC9-ER+DMSO

The results of the comparison for PC9 vs PC9ER and PC9 vs PC9+Erlotinib are shown in Figure 3 as we found the information provided by this analysis most compelling. Indeed, the Principal Component Analysis (PCA) and the Orthogonal Projections to Latent Structures Discriminant Analysis (OPLS-DA) show that PC9 and PC9ER are completely distinct from a metabolic point of view as demonstrated by the total separation between the two cell populations (Figure 3A). In particular, the differential analysis of the spectra, suggest that the occurrence of Erlotinib resistance is accompanied by a decrease in the reducing capability of the cells (as demonstrated by the drop in cellular glutathione levels in PC9ER) and a switch to a more glycolytic mode of energy production (responsible for the large increase in lactate in PC9ER samples). These changes are likely a consequence of exposure to Erlotinib as these effects were reproduced in PC9 cells upon Erlotinib treatment (Figure 3). In addition to these changes, PC9ER cells showed a major change in cell membrane structure as compared to PC9 cells. This was revealed by the major increase in glycerophosphocholine

(GPC) and phosphatidyl choline (PC) in PC9ER cells. The increase in GPC may to a certain extent be a compensatory mechanism for the decreased reducing capability of PC9ER as GPCs have been shown to scavenge oxygen radicals.

The data obtained so far suggest that (1) metabolic profiling may be capable of differentiating tumours that are sensitive or resistant to EGFR inhibitors and could be used as a diagnostic tool and (2) that we may be able to exploit the observed metabolic changes for therapeutic intervention. Indeed, it is predicted that the PC9ER may be more sensitive to oxidative stress than PC9 cells, a possibility we are currently investigating. Also, the changes in lipid membrane bi-layer may enable the specific targeting of compounds to Erlotinib-resistant cells and/or modulate the presentation of specific receptors on the cell surface that could be used for therapeutic intervention.

Current follow-up work

We are now pursuing this work as part of a collaborative project between the CAS and my laboratory. First, additional cell lines resistant and sensitive to EGFR inhibitors will have their metabolic profile analysed in order to confirm that the changes observed occur widely as a consequence of the onset of drug resistance. Also, various genetic mechanisms underlying resistance will be investigated. Indeed the two resistant cells analysed so far,

PC9ER and H1795, both acquired resistance as a consequence of a T790M mutation in their EGFR. However, other EGFR mutations are known to occur in lung cancer that result in Erlotinib resistance. We intend to compare the metabolic profile obtained in these various backgrounds to assess whether our data can be validated across genetic backgrounds or if common modifications can be identified.

Preliminary data seem to indicate that the decrease in reducing potential seen in PC9ER cells is reproduced in H1795 cells (data not shown). Hence, we intend to focus on identifying the underlying molecular mechanisms responsible for the drop in glutathione levels.

Only a handful of metabolic enzymes are known to regulate cellular levels of this metabolite. We now propose to use biochemical techniques including enzymatic assays and Western blotting and physical methods such as mass-spectrometry (in collaboration with the lab of Prof Guo Lin at Wuhan University-see BACR travel fellowship 2010) to study changes in the level or activity of these regulatory enzymes linked to Erlotinib-resistance. A PhD student from the Chinese Academy of Sciences is now joining our lab as a visitor to perform this follow-up work in collaboration with Prof Yulan Wang in whose lab the NMR work was performed.

The results obtained following this validation process should be the basis of joint future grant applications between our two institutions.

I would like to thank the BACR for giving me the opportunity to initiate this line of work and am grateful for the support the association has provided me along the years.

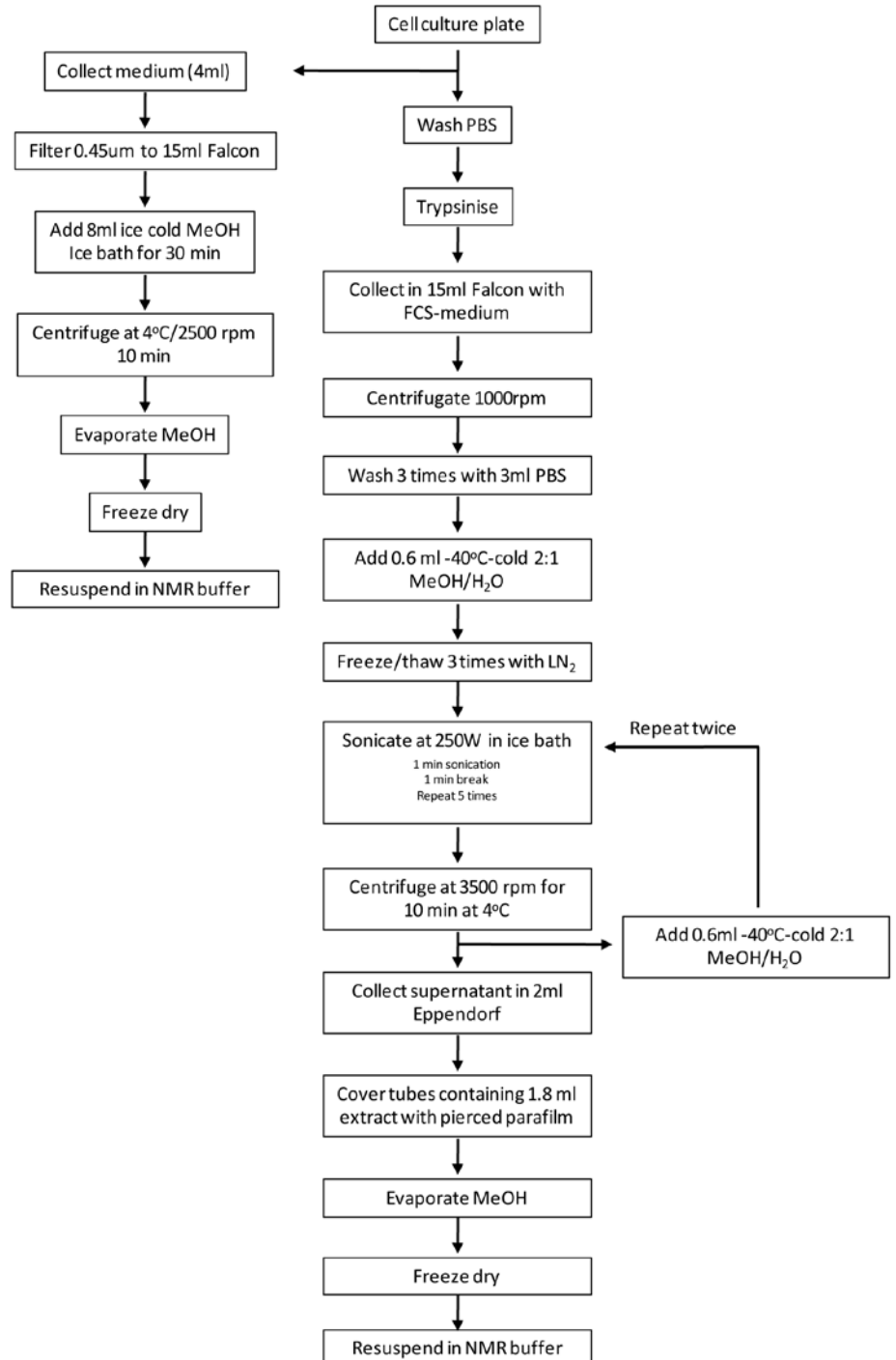


Figure 1: Protocol for isolation of metabolites from cell extracts and culture medium. Cells were grown in 10cm Petri dishes in RPMI/5%FCS at 37°C/5% CO₂ until 90% confluent. 10 dishes per condition were processed independently. Total procedure time: 3 days.

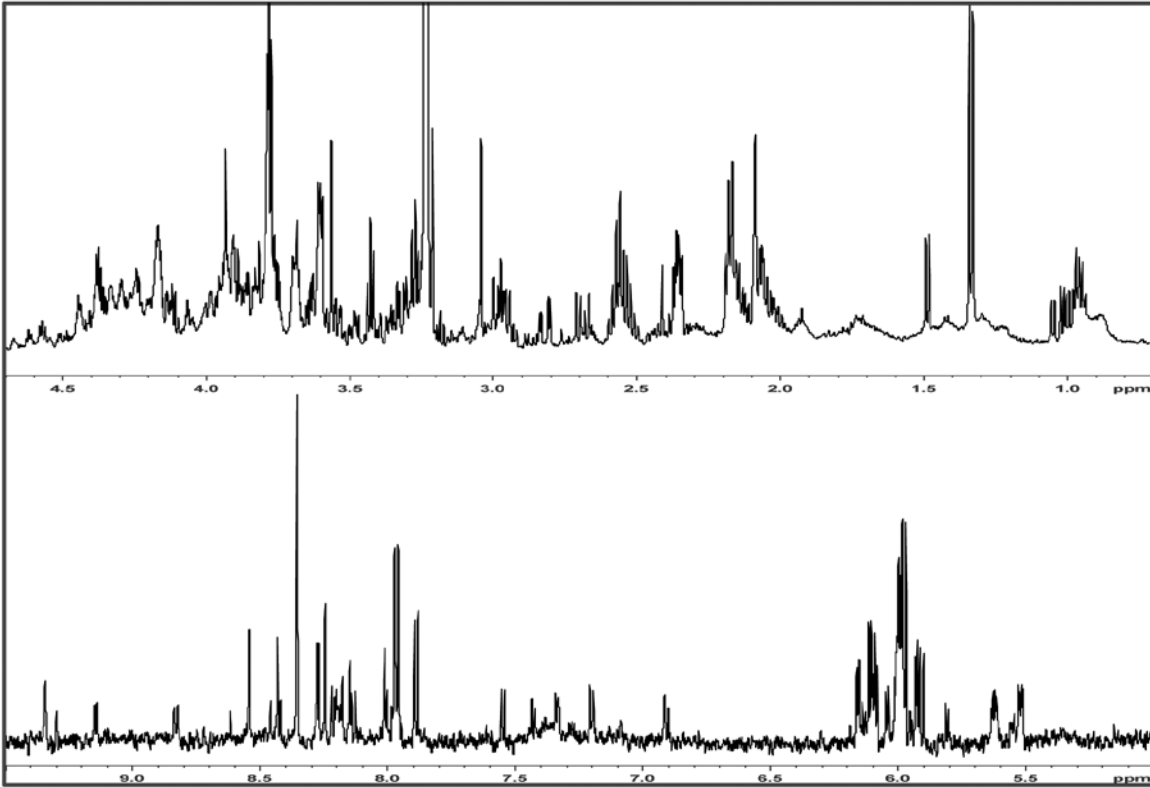


Figure 2: Representative spectra obtained for PC9 cells by 1D ^1H NMR spectroscopy using a 600MHz Bruker Ultrashield 600Plus instrument.

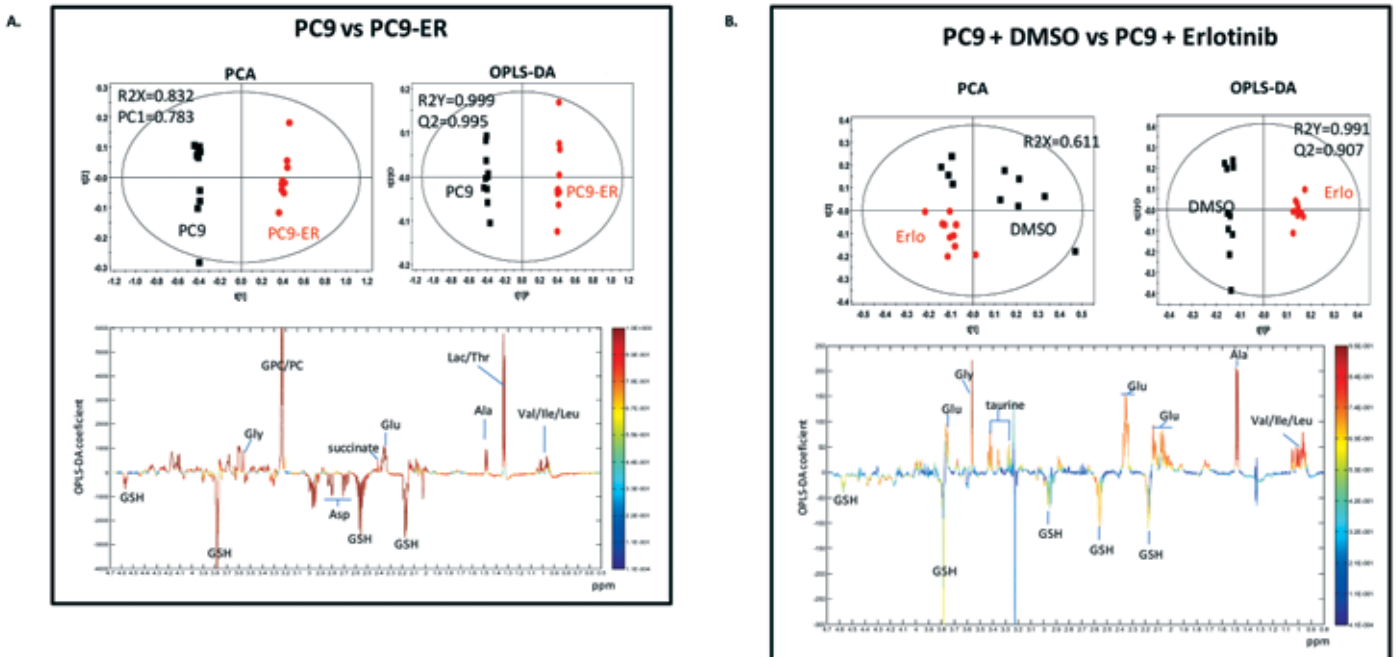


Figure 3: Metabolic profiles comparison between PC9 and PC9ER (A) or PC9+DMSO and PC9+Erlotinib (B). Differences between conditions are highlighted by PCA and OPLSDA and displayed as a heat-mapped OPLS-DA- coefficient representation.

Travel Exchange Fellowship

Mieke Van Hemelrijck

Cancer Epidemiology Group, Division of Cancer Studies,
King's College London



When I applied for a Travel/Exchange Fellowship from the BACR, I wanted to improve my epidemiological knowledge by studying how nutritional components and genetic changes might influence prostate cancer biology

I had never conducted a study within the discipline of nutritional epidemiology and was very keen on learning about the extremely complex set of variables that define a person's diet. I also wanted to learn about genetic epidemiology as this is a relatively new discipline that seeks to elucidate the role of genetic factors and their interaction with environmental factors in the occurrence of disease.

Therefore, I was very excited when I finally arrived in Switzerland at the end of February. For the next three months I was going to work at the Institute of Social and Preventive Medicine. Under supervision of Professor Sabine Rohrmann I focused on gene-environment interactions, more specifically on the association between heterocyclic amines and the risk of prostate cancer.

A western diet has long been considered as a potential risk factor for prostate cancer. In the context of meat consumption, evidence is weak for an association between both red and processed meat intake and PCa risk (1-2). However, the intake of grilled meat is thought to be related to PCa risk since high-temperature cooking of meat leads to formation of mutagenic heterocyclic aromatic amines (HCA), which have been shown to induce tumours in experimental animal models (3-4). Cooking at higher temperatures and for longer periods of time both

result in the formation of more HCA (3-4). To date, several studies have evaluated the association of intake of meat cooked at high temperature and PCa risk, but results are inconsistent (5-9).

The association between PCa risk and intake of the three most mass-abundant HCAs detected in cooked meat, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx), and 2-amino-3,4,8-dimethylimidazo[4,5-f]quinoxaline (DiMeIQx), was also studied in our European Prospective Investigation into Cancer and Nutrition (EPIC)-Heidelberg cohort. Even though meat consumption, cooking methods, and degree of browning of the respective food items were assessed with a detailed questionnaire, the results did not indicate that HCA intake, as consumed in a regular diet, was associated with PCa risk (10-11). However, experimental studies have shown that levels of PhIP approximating human dietary exposure stimulate cellular signalling pathways and result in increased growth and migration suggesting a link with the promotion and progression of neoplastic disease (4, 12). One of the reasons for these null-findings might be that the association between HCA intake and PCa risk is modified by different genotypes/polymorphisms in genes encoding for HCA-metabolizing enzymes.

Sharma and colleagues evaluated the modifying effects of rapid *NAT1* and slow *NAT2* acetylator genotypes in a case-control study nested within the Multiethnic Cohort based on 2,106 PCa cases and 2,063 controls, but found no evidence for an increased risk of PCa associated with consumption of well-done meat, *NAT1*, *NAT2*, or their interactions (13).

Since additional studies with more precise exposure measures are needed to test this hypothesis, I aimed to assess interactions with different polymorphisms for the association between HCA and PCa risk in a case-control study nested within the EPIC-Heidelberg cohort, a study in which my mentor Professor Rohrman is extensively involved.

The manuscript describing the findings from this study is currently under peer review and will be published soon. Briefly, our study indicated that the association between HCA intake and PCa risk is modified by polymorphisms in genes such as *GSTT1*, *GSTM1*, *CYP1A1*, and *MnSOD*; however these modifications are not necessarily concordant with the underlying biological hypotheses. Considering genetic variation is an important step in elucidating the mechanism of action between meat intake and risk of PCa. Other large studies are needed to investigate the complex interplay of

polymorphisms in gene encoding HCA-metabolizing enzymes and intake of different HCA.

This training at the Institute of Social and Preventive Medicine in Zurich was an excellent opportunity to learn new epidemiological methods and I am most grateful to the BACR for the contribution they made towards the cost of my research visit.

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Travel Bursaries

American Association for Cancer Research (AACR)

'Targeting P3K/mTOR Signaling in Cancer'

24th – 27th February **San Francisco**



*Emma Haagensen
University of Newcastle
Northern Institute
for Cancer Research*

Thanks to being awarded a travel bursary from the British Association of Cancer Research, I was able to attend an AACR Special Conference entitled *'Targeting PI3K/mTOR Signaling in Cancer'* in San Francisco from the 24th-27th February 2011

I am currently a second year PhD student at the Northern Institute for Cancer Research, Newcastle University working under the supervision of Professor Herbie Newell and Dr Ross Maxwell, and my project focuses on the identification and evaluation of non-invasive imaging biomarkers for novel PI3K and MEK inhibitor combinations.

This relatively small but very focussed conference brought together many of the prominent investigators in the rapidly growing PI3K/mTOR field to discuss their recent advances. The sessions focussed on every aspect of this area from basic research to clinical studies, and provided a unique forum to review the remarkable progress in this field. Moreover, this meeting provided an opportunity for me to present very relevant new data surrounding mTOR as a determinant of the synergistic interaction of PI3K and MEK inhibitors, and allowed me to get useful feedback before publication.

I found the whole conference extremely interesting; in particular a couple of sessions surrounding the role of sterol regulatory element binding proteins (SREBPs) and PH domain leucine-rich repeat protein phosphatase (PHLPP) were impressive, as well as many of the advances reported in the clinical trials of various PI3K/mTOR inhibitors, including a remarkable insight into the PI3K δ inhibitor, CAL101, in B cell malignancies.

I would like to thank the BACR for making it possible for me to attend such a relevant conference which allowed me to meet and discuss my work with some of the most senior investigators in the field, and thus provided me with many new ideas especially as I enter the final year of my PhD.

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Travel Bursaries

102nd Annual meeting of the American Association for Cancer Research (AACR) 2nd – 6th April Orlando, Florida



*Triantafillos Liloglou, PhD
University of Liverpool,
School of Dentistry & Biomarkers
Group Liverpool CR-UK Centre*

This year I was awarded a travel bursary by BACR to cover part of the costs for presenting my work at the 102nd annual meeting of the American Association for Cancer Research (AACR) in Orlando, FL

This is the largest cancer meeting worldwide attracting tens of thousands of researchers covering the whole spectrum of cancer research from basic biology to clinical oncology.

I presented my work on DNA methylation biomarkers in bronchial washings for lung cancer diagnosis. We demonstrated that by using 6 methylation markers in addition to cytology we can virtually double the sensitivity of detection (from 43% to 82%) at specificity of 92.5%. This is of particular importance as lung cancer is by far the highest killer cancer in the UK and a significant percentage of cases are diagnosed at late stages not allowing efficient therapeutic intervention. My work is funded by the Roy Castle Lung Cancer Foundation and CR-UK, and is part of a much wider effort to tackle lung cancer mortality in the UK, the Liverpool Lung Project. This is the largest lung cancer population study in the UK and one of the largest worldwide.

Attending the annual AACR meeting gave me the opportunity to communicate with colleagues with common research interests and discuss aspects of my work during my poster presentation.

Thus I received important feedback but also created new links for future collaboration, one of which is actually already on-going. In addition, this meeting provided clues for new points of focus in cancer research as well as emerging technologies that can bring science closer to the clinic, which is what I do as a translational scientist.

I am obliged to the BACR for this important financial support in attending this meeting, especially at these times where research funding is limited.



*Matt Ablet
Paterson Institute for
Cancer Research
University of Manchester*

I would like to thank the British Association for Cancer Research for providing me with funds which enabled me to attend and present my work at this incredible conference in sunny Florida

I am currently a final year PhD student at The University of Manchester working under the supervision of Dr Robert Clarke within his Breast Biology group at the Paterson Institute for Cancer Research. Briefly, my project involves optimising methods used to enrich for normal and malignant stem cells in breast cell lines and primary samples and to investigate the role of the CXCR4 signalling pathway in these enriched populations.

The American Association for Cancer Research (AACR) is an extremely large conference attracting more than 16,000 attendees with excellent oral and poster presentations throughout the 5 days. As well as these presentations there were also smaller mini-symposia and workshops where the sessions had a more intimate feel about them and made you forget the size of the conference. I particularly enjoyed the workshops and found them very helpful in gaining an insight into areas of cancer I was less familiar with. The plenary sessions were amazing, both in content and size. I have never been to a conference of this magnitude before and nothing can prepare you for the size of the lecture hall where the plenary sessions take place.

With my project centring on breast cancer, the talks by Max Wicha, Morag Park and Matthew Ellis were of particular interest for me, which focused on breast cancer signalling, the breast microenvironment and resistance of breast cancer to therapy (respectively). As well as other numerous stimulating talks (on breast cancer as well as other cancers), there were thousands of posters on display over 4 days of the conference. Careful forward planning was required to see all the talks and posters of interest to me.

I feel I have learnt a lot from this conference, both about breast cancer as well as expanding my knowledge of the cancer field in general. To be able to present my work and discuss it with other fellow students as well as professors and experts from a more clinical setting was certainly advantageous to my project. I would like to thank the BACR for giving me this opportunity to attend the AACR.

Travel Bursaries

The Biology of Cancer: Microenvironment Metastasis & Therapeutics

26th – 30th April

Cold Spring Harbor Laboratories, New York



*Thomas Cox
Institute of Cancer Research
Chester Beatty Laboratories*

First of all I would like to extend my gratitude to the British Association for Cancer Research for awarding me a travel bursary that allowed me to attend and present my work at the recent CSHL meeting in New York this Easter

This was the first meeting of a new series, which is planned to alternate annually with the CSHL meeting on 'Mechanisms & Models of Cancer'. The meeting attracted a formidable international audience of roughly 350 scientists and clinicians across multiple disciplines yet maintained a very relaxed and friendly atmosphere. Spread over 4 days, the meeting encompassed 68 talks across 10 plenary sessions in diverse yet inter-related fields including tumour genetics, cancer cell metabolism and plasticity, immunology and inflammation, xenograft and model systems through to molecular imaging of metastasis, translational and personalised medicine. Alongside an excellent lineup of speakers were several informal technical workshops and interactive panel discussions, plus poster sessions where 144 delegates were given the opportunity to showcase their work. Socially, the conference provided an excellent opportunity for networking with extended poster sessions, afternoon and evening networking events and a debut soprano recital from Jennifer Jonson Cano prior to the conference banquet.

The funding gave me the opportunity to discuss and present my current work on the critical role of lysyl oxidase in fibrosis enhanced metastasis. It also gave me exposure to a wide range of experts within the field and served as a platform for establishing some exciting collaborations.

Once again, I would like to express my thanks to the British Association for Cancer Research for funding my attendance at this conference. I would highly recommend this conference to others and look forward to attending it again.

Travel Bursaries

1st International Notch Targeting in Cancer Conference

22nd – 25th June

Mykonos



*Dr Natalie Cook
Clinical Fellow
Cambridge Research Institute*

The 1st
international
Notch targeting
in Cancer
conference took
place on the
Greek Island
of Mykonos, on the
22nd-25th June
2011

Due to the funding I received from the BACR I was able to attend this conference and I was lucky enough to be chosen to present the research I had been undertaking for the last 3 years as part of my PhD. The conference attracted a mix of scientists, clinicians and pharmaceutical companies, which made for some interesting debates. Due to it being a smaller sized conference the sessions were extremely interactive and multiple aspects of Notch targeting in cancer were openly discussed.

On the first day there were some excellent general talks about the progress we have made, both pre-clinically and clinically with Notch targeting, and an update on clinical trial results was presented. The second day had a more varied list of topics, including the role Notch plays in angiogenesis, different approaches to inhibit the Notch pathway, and a session discussing Notch in breast cancer. I gave a 30 minute presentation about my research; the role Notch plays in pancreatic cancer and the translation of this into the clinic. I received extremely useful feedback from world experts in this field, such as Lucio Miele and Adrian Harris.

The final day included sessions on neuroblastoma, lung cancer and targeting components of the gamma secretase complex, highlighting the fact that this may also play an important role in cancer. Small group workshops took place in the afternoons of the conference, which were led by experts in the field, debating Notch targeting: the good, the bad and the ugly! These debates involved pharmaceutical company representatives, scientists and clinicians so it was extremely useful to have opinions from different specialities. I found this an excellent meeting to attend, and I have made some useful contacts for future collaborations in this field.

Travel Bursaries

Gordon Research Conference *Mammary Gland Biology* 12th – 17th June 2011 Newport, Rhode Island



Holly Barker

*Department of Cancer Biology
The Institute of Cancer Research,
London*

After thoroughly enjoying the Gordon Research Conference (GRC) on Mammary Gland Biology in Italy in 2010, I travelled a bit further this year to attend the same conference at Salve Regina University on Rhode Island in the USA

I found this conference even more useful than the year before as it had a strong focus on the role of the tumour microenvironment in breast cancer progression. Metastatic progression is highly dependent on the tumour microenvironment, and ever-amassing evidence supports a role for the extracellular matrix (ECM) in regulating tumour progression. Particular attention has been focused on the role of matrix remodelling enzymes, such as the lysyl oxidase (LOX) family, in mediating metastasis. The LOX family consists of LOX and four LOX-like enzymes LOXL1-4. They are all secreted copper-dependent amine oxidases that catalyse the cross-linking of ECM proteins. During my post-doctoral training I have been studying LOXL2 and have obtained exciting results that suggest this enzyme may be an important therapeutic target for the prevention of metastatic disease. I presented these results in a poster on the first day of the conference and received helpful feedback from many conference attendees. My research is now moving in a new direction and I was able to gain useful suggestions from experts in this area.

A number of eminent scientists were present during the course of the conference. They gave general lectures, keynote addresses, led discussions, were present in small groups at lunchtimes and were generally available for informal discussions between sessions and during the social evenings. I found the content of the sessions to be highly relevant to the research we are undertaking in the Hypoxia and Metastasis team at the ICR. I would recommend this conference to anyone studying mammary gland development and breast cancer and would like to thank BACR for making my attendance at this conference possible.



Irena Babina
Department of Surgery
RCSI ERC Beaumont Hospital

A BACR travel fellowship enabled me to attend the 2011 Gordon Research Conference in Mammary Gland Biology in Newport, Rhode Island

This small and focused conference is aimed at stimulating an interactive environment between young researchers and established scientists in the field. In addition to morning and evening lecture sessions, poster sessions in the afternoon and communal meals, “Meet the expert” lunch sessions were organised, where select speakers offered scientific and career advice to graduate students and post-doctorate fellows, thus providing ample time to meet and network not only with the senior scientists, but also junior researchers. The relaxed and informal atmosphere throughout the conference (maintained by chairs Pepper Schedin and Matt Smalley) further facilitated discussions among the attendees.

As a second-year PhD student, this conference was my first opportunity to attend and present my work in an international arena, and I found it enormously beneficial for my personal and professional development. My project is concerned with exploring the regulation of breast cancer cell migration by lipid rafts, given the key contribution of cell migration to breast cancer metastasis. I had the privilege to give both oral and poster presentations of my findings that sub-membranous trafficking of the cell migratory protein CD44 can differentially control breast cancer cell motility. Both presentations initiated exciting prolonged discussions, and I gained a lot of interesting insights into my work, which gave rise to some new ideas.

A particularly enjoyable aspect of the conference was that the vast majority of the work presented

by keynote speakers and early-career investigators was novel and unpublished. This in turn resulted in stimulating discussions, which often extended through to social events. I was thrilled to have one of those discussions with Dr. Russ Hovey, who spoke about effects of dietary fat intake on the mammary gland, which directly relates to my current PhD project and is something I studied closely as an undergraduate. Furthermore, it was fascinating to hear Prof. Zena Werb talk about her research and give her insights into scientific careers, which is what every PhD student needs to know about.

As a result of active participation in this Gordon conference, I was invited to be a discussion leader at the 2012 Mammary Gland Biology Gordon Research Seminar, which will be held prior to the commencement of the 2012 conference. It will permit graduate and post-doctorate researchers to present and discuss their unpublished work in the area of breast cancer research, and will provide a wonderful opportunity for me to interact with the next generation of leading cancer researchers.

I am very grateful to the BACR for supporting me to attend this landmark conference. It enabled me to discuss my work in breast cancer with many of the leading experts in the field, encouraged networking and potential collaborations, as well as providing a high-quality educational environment. I would highly recommend this conference to others as it was a thoroughly enjoyable and inspiring experience for a young cancer biologist.

PREDECT: a powerful new European Consortium addressing novel laboratory models for cancer target validation

PREDECT is a European consortium of 26 principle investigators, managed by Servier, AstraZeneca and the University of Helsinki, which brings together academic laboratories, biotechs and the pharmaceutical industry. This research network aims to develop innovative models and technologies for the preclinical evaluation of cancer therapy targets. The program of work should eventually improve the clinical success of therapies designed for the treatment of cancer.

There has been an explosion, in the last decade, of the knowledge regarding the genetic changes that are associated with cancer. This knowledge provides great opportunities for improved, selective treatments through the design of new drugs and antibodies that are targeted specifically to those changes in tumour cells responsible for the survival, proliferation and spread of the cancer. A challenge for drug discovery is to establish which of the many molecular changes associated with a particular cancer type, in a particular patient subgroup, are responsible for the pathology and which are associated “bystanders” playing a minimal or no role. Accumulating information suggests that an alarmingly high proportion of new drugs, targeted to recently-identified molecular changes in cancer, lack efficacy when tried in patients. One reason for this lack of efficacy may reflect the use of over-simplified laboratory models of cancer that do not represent the complexity and heterogeneity of tumours. In these “reductionist” models promising drug targets may not work as they would in a cancer patient and consequently drug inhibition has only a modest or no effect clinically.

PREDECT sets out to provide new laboratory models of human cancer that better reflect the complexity and heterogeneity of cancers. Working in teams investigating breast, prostate and lung cancers, PREDECT will use advanced mouse models of cancer, some of which will be genetically engineered and matched to particular groups of patients with these cancers, to progressively “deconstruct” the complex tumours into simpler forms for use on the laboratory bench. Examples are thin slices of tumour tissue and tumour cells growing in three-dimensions together with supporting cells, rather than the simple, conventional two-dimensional models. At each stage of the reduction of complexity, the tumour cells will be profiled to establish how closely they represent the tumour of origin, growing *in vivo*, and thus how closely they represent a human tumour. Novel complex models with the appropriate profiles can eventually be used to validate that a new, potential target for cancer treatment is worth pursuing.



The PREDECT project will provide robust technologies permitting the biotechnology and pharmaceutical industry to take early decisions on whether or not to invest in and pursue an intensive drug discovery programme on a new target, reducing wasted effort. If the technologies suggest the target is valid, these PREDECT platforms will also permit early validation of biomarkers indicating which cohorts of patients would be suggested to benefit from the drug, increasing the likelihood of success for the patient in clinical trial, and decreasing trial duration and expense. Additionally, laboratory models that better represent cancer pathologies will permit academic researchers to perform investigations of tumour biology with greater fidelity.

Professor John Hickman, Coordinator for Servier of the PREDECT consortium comments: *"The Innovative Medicines Initiative has allowed cancer researchers in Industry to come together to determine which are the bottlenecks in the drug discovery process that limit the emergence of more effective cancer therapies. We believe that inadequate laboratory models to investigate and validate potential targets have contributed to the failure of recent clinical trials where the drugs lacked efficacy. To create innovative technologies and platforms, more representative of the complexities associated with human tumours, we need top-flight academic expertise in cancer cell biology, bioinformatics and systems biology to complement our efforts in drug discovery. Having experienced in my own career both academic and industrial cultures, it has been exciting to create a programme which demonstrates to partners that the cultural differences between us are minimal and that we are united in trying to fulfil the urgent medical need for better cancer treatments."*

Dr Emmy Verschuren, academic coordinator and representative of the IMI funding Managing Entity at the Institute for Molecular Medicine Finland, University of Helsinki, weighs in: *"PREDECT is very timely. It is absolutely essential to comprehensively re-factor our model systems now, but it is also a significant task that requires academia and industry to pull together. We are bringing experts in key cancer biology areas together with young group leaders and industry partners as never before. Even with so many hands, this is not light work, but a job that has to be done urgently."*

Dr Steve Wedge, Deputy Coordinator from AstraZeneca adds: *"A large collaborative effort is required to systematically interrogate the behaviour of cancer targets across preclinical models of increasing complexity. This is the power of PREDECT, which brings together researchers with diverse expertise to work in true partnership, one example being that many of the supporting postdoctoral fellows within the consortium are to be co-supervised by both an academic and an industrial partner."*

The five-year PREDECT project, providing new tools for target validation to improve drug efficacy, integrates a group of pharmaceutical companies composed of Hoffmann-La Roche, Bayer Schering Pharma, AstraZeneca, Boehringer Ingelheim International, Orion Pharma, Sigma-Tau and Servier whose total in-kind contributions to the project are matched by funding from the IMI Joint Undertaking, resulting in a total of 17.2 Million Euros.





The academic and biotechnology company expertise essential to the programme is provided by The University of Helsinki, Biomedicum Genomics Ltd and VTT Turku (Finland), University of Tartu (Estonia) Radboud University Nijmegen and Erasmus University Rotterdam (Netherlands), Institute of Cancer Research (UK), Oncotest GmbH and the Margarete Fischer-Bosch Institute (Germany), Ecole Polytechnique Fédérale Lausanne (Switzerland), Weizmann Institute (Israel) and Instituto de Biologia Experimental e Tecnológica (Portugal).

PREDECT Website is at www.predect.eu

About the Innovative Medicines Initiative (IMI)

The five-year PREDECT project is funded by IMI (www.imi.europa.eu), a unique public-private partnership between the European Federation of Pharmaceutical Industries and Associations, EFPIA and the European Union, represented by the European Commission.

IMI aims to put Europe at the forefront of biopharmaceutical innovation and to support more efficient discovery and development of better medicines for patients.

IMI's innovative funding scheme has a budget of Euro 1 billion provided by the European Commission. That amount will be matched by in-kind contributions of at least another 1 billion euro from EFPIA members.

PREDECT Management is by Kurt Salmon (www.kurtsalmon.com) Formed by the merger of Kurt Salmon Associates and Ineum Consulting, Kurt Salmon is a global management consultancy of more than 1,600 consultants in 15 countries across five continents. Kurt Salmon includes a specialised department that provides assistance and consulting services for all types of entities in the identification, procurement and management of regional, national and international subsidies. This department also transfers its competencies and expertise through specialised and adapted seminars and training sessions.

For further details contact:

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Laurence Lapôtre: laurence.lapotre@kurtsalmon.com





Interested in becoming a member of the BACR or know someone who is!

The BACR is the largest cancer research association in the UK. It was formed in 1960 to “promote the advance of research in relation to all aspects of cancer and to encourage the exchange of information”

The Association’s membership represents all aspects of clinical and experimental research. The major functions of the Association are to organise scientific meetings/workshops on cancer research within the United Kingdom, and to provide a platform for presentation of original clinical and experimental research. To fund exchanges between laboratories to encourage knowledge transfer and engender collaborations both nationally and internationally; to provide opportunities for senior investigators to undergo further training to enable them to keep abreast of new investigative/research methods and opportunities for junior investigator and research students to present their work at other meetings/conferences.

APPLICATION FOR MEMBERSHIP

Please find overleaf a membership application form.

Please note that you can also join on line at:

<http://www.bacr.org.uk>

Membership of the Association is by election at the Annual General Meeting following application. A candidate for election should be proposed by **two Ordinary Members of the Association to whom he or she is personally known**. If you do not know any members, please contact the Secretariat for assistance

If you wish to be considered for election please complete the attached membership application and enclose a cheque for either **£50 or £25** (depending on full/student membership rate), made payable to “**British Association for Cancer Research**”, and return them to the BACR Secretariat. This payment will cover you until 30th September 2012.

However, you will be asked to complete a Direct Debit mandate in respect of future subscriptions, following election at the Annual General Meeting to take effect from 1st October 2013 and each October thereafter.*

If you are applying for student membership **you should attach a letter from your head of department confirming your student status**.

* NB **The exception to this rule is for those living overseas who do not have a bank account in the United Kingdom.**

If you require further information, please contact the BACR Secretariat at:

**c/o Leeds Institute of Molecular Medicine
Clinical Sciences Building
St James’s University Hospital
Leeds
LS9 7TF**

Tel/Fax: **0113 206 5611**

E-mail: **bacr@leeds.ac.uk**



BRITISH ASSOCIATION FOR CANCER RESEARCH

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I wish to apply for membership of the Association on the recommendations of the sponsors named below (who are ordinary members of the Association) and ask to be considered for election at the next Annual General Meeting.

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