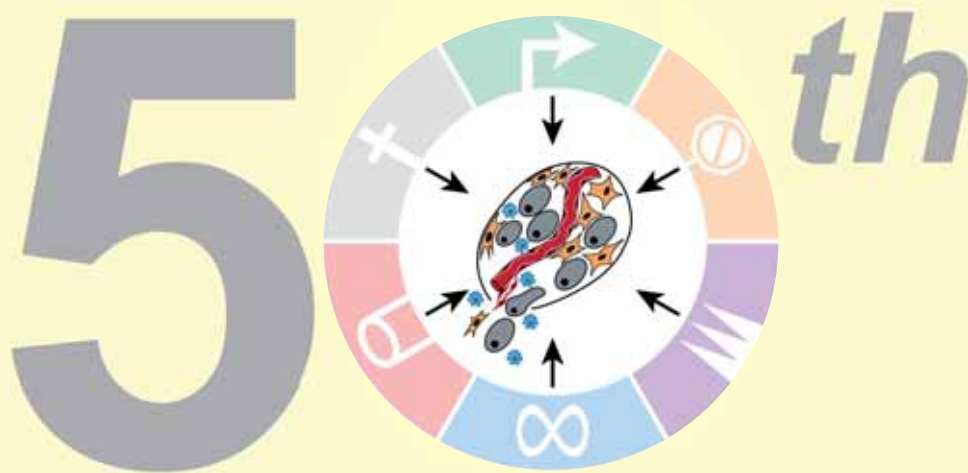




News

• British • Association • for • Cancer • Research •



Anniversary Meeting

**Hallmarks of Cancer:
From Mechanisms to Therapies**

Edinburgh, 13th – 15th June 2010

• Meeting Reports • News of Members •
• Forthcoming Meetings • BACR Awards •



Anniversary Meeting

**Hallmarks of Cancer:
From Mechanisms to Therapies**

Edinburgh, 13th – 15th June 2010

Registration Deadline Friday 16th April 2010

Confirmed Speakers include:

Doug Hanahan, Richard Marais, Hal Moses, Michael Pollak, Dennis Slamon, Roger Griffin, Dave Tuveson, Jerry Shay, Karen Vousden, Caroline Dive, Herbie Newell, John Condeelis, Margaret Frame, Adrian Harris, Tomasz Zaremba, Gareth Veal, Alan Ashworth, Richard Peto, Stephen Baylin, Paul Workman, Bruce Ponder, David Lane

The British Association for Cancer Research
Further details available from: bacr@leeds.ac.uk



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Letter from the Chairman



Dear colleagues

Welcome to the latest BACR Newsletter. 2010 will be a seminal year for the BACR as it is our 50th anniversary! We shall mark the event at the 50th anniversary meeting in June at Heriot-Watt University in Edinburgh, which will provide the propitious opportunity not only to celebrate and reflect on our past, but also to look forward to the next five decades of successfully supporting cancer research in the UK. Check the advert in this issue for details. The Executive Committee looks forward to seeing as many members of the association in Edinburgh as possible.

In 2009 we organized two focussed events, firstly the BACR/EACR joint back-to-back meetings on "Chromatin & Cancer" and "Transcription & Cancer" at Churchill College, Cambridge in July, and secondly a one-day conference in conjunction with the Oncology Section of the RSM, on "MicroRNAs and Translational Regulation in Cancer" in November in London. Both gatherings were academically excellent and well-attended. A report on the former will be published in the spring EACR Newsletter, whilst the latter is summarized on page X of this newsletter.

As in previous years, the BACR arranged two early morning workshops at the annual NCRI conference in Birmingham in October, one on "Early Phase Clinical Trial Design for Non-Clinicians" and the other on "How Do Cells Maintain their Integrity? An Introduction to DNA Double Strand Break Repair and its Relevance to Leukaemia" organized by Anne Thomas and Elaine Willmore, respectively. In spite of the early hour of these workshops, they attracted good numbers of punters, who were rewarded by stimulating and interesting expositions and discussions. The BACR-sponsored 2009 Tom Connors lecture at the NCRI meeting on "Drugging the Human Genome, Design of Personalised Cancer Medicines" was given by Prof Paul Workman (ICR Sutton), and his delivery was characterized by his indomitable enthusiasm and elegance.

For 2010 we are planning to stage two one-day meetings, in addition to the anniversary conference in Edinburgh in June. The first is on "Predictive Biomarkers of Response to Cancer Therapeutics" to be held on March 25th in London, organized jointly with the RSM, and the second on "Development of Cancer Medicines, (see advert on inside back page): Modelling of Disease and Preclinical Testing" to be held in November 2010, also at the RSM in London. In view of their popularity in previous years, we will again organise two workshops at the 2010 NCRI meeting in Liverpool in November.

I would like to remind you that assistance with putting on special conferences is one of the key objectives of the BACR. The Executive Committee is very happy to consider proposals from the membership for such conferences. So, if you have an idea for a meeting, please do not hesitate to submit scientific and financial details and rationale to the secretariat, so that we can consider them at our next meeting.

The following members retired in 2009 from the Executive Committee: Nicola Brown, Val Brunton, Liam Gallagher, Duncan Jodrell, and Kaye Williams. We thank them warmly for their enthusiastic and constructive contribution to running the association. The Executive Committee welcomes four new members: Sally Burtles (London), Chryso Kanthou (Sheffield), Ricky Sharma (Oxford) and Valerie Speirs (Leeds). The committee looks forward to working with them.

I am pleased to notify you that this year two new companies have become supporting partners: MedImmune and ABCAM

Finally, the unthinkable has happened: Barbara Cavilla has decided to retire from the administrative secretariat after the forthcoming anniversary meeting in Edinburgh. On a very positive note, I am happy to report to you that the BACR officers have successfully recruited a successor, Mrs Janet Alexander. Janet will commence her duties in January 2010, to allow her to learn the ropes from Barbara, a tall order indeed! Good luck, Janet! With this change the administrative secretariat will relocate to the Leeds Institute of Molecular Medicine to be accommodated in the environment of our honorary secretary. Please do take the opportunity to meet Janet at one of the forthcoming meetings!

Best regards

Andy Gescher, *Chairman*

MicroRNAs and Translational Regulation in Cancer

Royal Society of Medicine 18th November 2009

The microRNAs and translational regulation in cancer meeting, a joint venture between BACR and the RSM Oncology section took place at the Royal Society of Medicine. Sponsorship and support for the event from Cancer Research UK, Association for International Cancer Research, Amgen AstraZeneca, Roche, Agilent Technologies, Applied Biosystems Europe BV, Enzyme Research Laboratories, Exiqon, Milleniy Biotec, PeproTech EC Ltd, PromoCell GmbH & Roche Diagnostics Ltd, is gratefully acknowledged.

During recent years it has become evident that alterations in microRNA (miRNA) gene expression contributes to the pathogenesis of cancer development. Alterations may be induced by a number of mechanisms including amplifications, deletions or mutations in miRNA loci, epigenetic silencing or transcription factor dysregulation that target specific miRNAs. Tumour cells appear to be dependent on miRNA gene dysregulation, which either control or are controlled by oncogenes or tumour – suppressor genes, therefore miRNA's provide important potential targets for miRNA- based therapies.

The morning session chaired by Professor Michael Seckl (Imperial College, London) was opened by Professor Anne Willis (Professor of Cancer Cell Biology, University of Nottingham) who described the importance of translation and the stages in the pathway where this process may be modified in disease. This clearly defined the mechanisms of translation on which the remainder of the day was based. A elegant series of studies using Non-Hodgkin lymphoma cell-lines derived from patients with diffuse large B-cell lymphoma (DLBCL), demonstrated an increase in eIF4B expression leading to enhanced protein synthesis and a global increase in translation. EIF4B stimulates the activity of eIF4A, the helicase which induces unwinding of secondary structures in 5'UTRs of growth factor and proto-oncogene mRNA's. Using polysome profiling Bcl-2, IGFR, migration and signalling proteins were upregulated whereas promoters of apoptosis (TRAIL Fas, eiF4B) are down-regulated at the level of translation. cMyc is translationally repressed in normal cells, but well translated in tumour cells, due to the absence of miR34, which leads to false replication firing and hence DNA damage. Data demonstrating that addition of miR34C and ATM inhibitors increases tumour cell apoptosis, was presented. Thus sequence elements in both 5' and 3' untranslated regions of these mRNA's contribute to altered translational regulation in NML and may offer targets for therapy.

Professor Martin Holcik (Apoptosis Research Centre, University of Ottawa), then gave an elegant presentation concerned with the role and regulation of X-linked Inhibitor of Apoptosis Protein (XIAP) the most potent intrinsic regulator of cell death. Anti-sense XIAP is currently undergoing Phase I & II clinical trials. Studies demonstrated that XIAP is translated by CAP-independent mechanism of translation initiation, mediated by a unique Internal Ribosome Entry Site (IRES). IRES are found in cellular mRNA's including growth factors, oncogenes and apoptosis. The IRES regulation of XIAP was then discussed in detail and is clearly a key mechanism in the control and regulation of apoptosis.

Professor Robert Schneider (Professor of Molecular Pathogenesis, NYU School of Medicine, US) then focussed on locally advanced breast cancer (LABC), and the ongoing clinical trials he is co-ordinating in USA, Mexico, India and Egypt. In tumours there is an increase in IRES-dependent translation, hypoxia and angiogenesis. Preclinical data using PTC299, a small molecule inhibitor of VEGF mRNA demonstrates inhibition of VEGF translation which is IRES dependent in tumour development but CAP mediated in normal tissues. Hypoxia in the tumour microenvironment inhibits mTor (which normally inactivates 4E-BPI), resulting in the elevation of eIF4GI and 4E-BPI, allowing translation of VEGF mRNA. The increased VEGF expression in response to lower levels of hypoxia induces increased tumour cell survival. eIF4GI and 4E-BPI are now used to predict LABC. The presentation also defined a role for translational regulation in an inflammatory breast cancer consortium. eiF4G is increased, with gene silencing decreasing VEGF expression. Clear evidence was provided that p120 catenin is also involved so the future strategy is to develop p120 catenin inhibitors of translation.

The morning session was ended by Dr Olivier Pardo (Imperial College, London) who discussed the development of lung cancer resistance to therapy. FGF2 is an independent prognostic factor for poor prognosis in small cell lung cancer and increases the expression of anti-apoptotic proteins (XIAP, C-IAP, Bcl-XL, Bcl-2 and Mcl-1)

triggering chemoresistance. This increase is mediated via increased protein translation, by the activation of S6K2. Using tandem affinity purification (TAP-Tag) members of the hnRNP family were identified as possible interactors with S6K2; hnRNPA1 but not hnRNPF and H was phosphorylated in response to FGF2 or an increase in S6K2 activity. Dr Pardo provided evidence that hnRNPF and H are involved in Bcl-XL/Xs splicing which is likely to contribute to cellular chemoresistance.

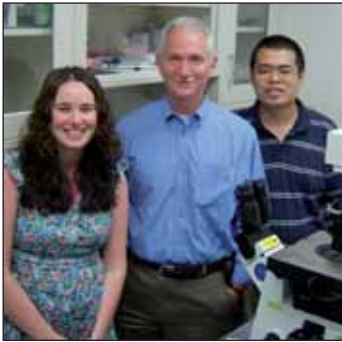
Following lunch and a successful commercial exhibition, the afternoon session was chaired by Professor Nicola Brown (University of Sheffield). Four short presentations selected from the abstracts discussed the novel components of the miRNA silencing pathway, use of miRNA microarray analysis to identify B-cell lymphoma phenotypes, translational control of CYP1B1, DNA damage, c-Myc and cell cycle arrest. There followed a presentation from Professor Robert White (Professor of Gene Transcription, Beatson Institute for Cancer Research) on RNA polymerase (POL) III which is the largest RNA polymerase, and makes short non-coding RNAs such as tRNA. mTOR controls POL III – transcribed tRNA and 5SRNA protein expression which is suppressed by rapamycin. Cell proliferation, translation and tumour formation in vivo is stimulated by overexpression of tRNA by POL III.

The excellent plenary lecture delivered by Professor Frank Slack (Professor of Molecular, Cellular and Developmental Pathology, University of Yale) was entitled miRNAs: from worms to lung cancer therapies. It has been identified that Let -7 and lin-4 are the founding miRNAs. Let -7 miRNA is known to promote the cell cycle and differentiation, is 100% conserved in worms and flies, with mice and humans possessing 12 copies of the gene. Let -7c is highly expressed in developing and adult lung, with low expression in other organs. In lung cancer Let-7 is poorly expressed and is associated with reduced survival where as miR21 is upregulated in lung and other solid cancers. Let-7 regulates RAS (N, K and H), targets cyclin-dependent kinases and suppresses the cell cycle. In vivo studies using anti-sense to let -7g resulted in an elevation in hyperplasia and progression to low grade tumours, with Let -7g mapping to chromosome 3p21 which is lost early in lung cancer. Exciting in vivo studies using the Tyler Jacks mouse model elegantly demonstrated that treatment with Let-7 adenovirus resulted in minimal lung hyperplasia, with Let -7 lentivirus administered following tumour development resulting in tumour/hyperplasia regression, due to reduced proliferation. The data suggested that Let -7 could be used in both therapeutic and prophylactic settings. Clinical data showed that a SNP termed G allele is associated with a 2-3 fold increased risk of lung cancer if patients have a smoking history < 20 packs/year; a more subtle effect was seen in a second cohort of 2000 patients. The data clearly demonstrates that miRNA are good prognostic markers.



*From left back row: Frank Slack, Bob White, Martin Holcik & Olivier Pardo
From left front row: Robert Schneider, Anne Willis, Michael Seckl & Nicola Brown*

BACR Travel Fellowship – Visit to USA



Kim Reeves and colleagues

Dr Kim Reeves

*Academic Unit of Surgical Oncology
University of Sheffield*

The BACR travel grant funded my fellowship to the Dalton Cardiovascular Research Center, University of Missouri, USA. This is an International Center of Excellence in microcirculation, with state of the art imaging facilities adapted for studying vascular physiology and pathophysiology. The AFM technology is well established, and under the excellent guidance and expertise of Prof. Meininger and Dr Sun I was able to complete my proposed project successfully.

Prostate cancer is the most common male cancer in the UK and every year approximately 32,000 cases are diagnosed (1 in 6 men), resulting in 10,000 deaths each year. This number is likely to increase significantly to 60,000 men by the year 2020. Despite advances in the treatment of primary prostate cancer, mortality from the disease is increasingly linked to metastatic prostate disease in bone. For prostate cancer to metastasise to bone, tumour cells undergo a multistep process, with one critical step being the attachment to and extravasation through endothelial barriers by malignant cells possibly leading to the selectivity of metastatic sites. Tumour cells binding to endothelium involves two distinct steps, an initial docking step mediated via lectin-carbohydrate interactions followed by an integrin-mediated locking step. Several endothelial and tumour adhesion molecules have been associated with metastasis such as the ligand P-selectin and the integrin $\beta 1$.

AFM has previously been used to probe cellular mechanisms under physiological conditions and to characterise cancer cell stiffness, however it has not been used to identify tumour cell adhesion molecules. The aim of this project was to characterise tumour cell adhesion molecules and correlate with their ability to interact with the bone microvasculature using AFM. AFM operates by physical interaction of a cantilever tip with molecules on the cell surface, and was used to measure adhesion forces between prostate cancer cells (PC3) and bone marrow endothelial (BME) cells in vitro. During AFM probe retraction, if a specific adhesion has occurred, the rupture of this adhesion is detected as a small sharp shift (failure force) in the deflection curve compared with the smooth curve recorded during the tip approach.

BME cells were grown on a standard tissue culture dish while a single PC3 cell was coupled to the end of the AFM cantilever. Once baseline values for adhesion force had been measured, this technique was repeated with function blocking antibodies (20 mg/ml) anti-ICAM-1, anti-VCAM-1, anti-P-selectin and anti- $\beta 1$ to selectively determine the adhesion molecules involved in tumour cell adhesion with the bone microvasculature. A bone-sparing bisphosphonate, Zoledronic acid, which has previously been shown to reduce metastatic bone tumour growth, was also investigated, the results demonstrated a positive adhesion interaction between PC3 cells and BME cells. Anti- $\beta 1$, anti-ICAM-1, anti-P-selectin, all blocking antibodies combined and Zoledronic acid significantly ($p < 0.05$) reduced the adhesion forces between PC3 cells and BME cells compared to controls. Anti-VCAM-1 reduced the adhesion forces but this was not significant. Therefore we have identified possible adhesion molecules involved in the interaction of prostate cancer cells to the bone microvasculature using AFM, as well as developing a novel, highly sensitive method to quantify adhesive strength of tumour-BME cell interactions.

I would like to thank everyone at the Dalton Cardiovascular Research Center for their kind hospitality. Also the BACR for their generous continued support, as without the Fellowship I would not have been able to take advantage of such a fantastic opportunity. More importantly receipt of this funding has enabled me to develop a novel, highly sensitive method to quantify adhesive strength of tumour-BME cell interactions, which will now allow more detailed investigation into the mechanisms of tumour metastasis.

BACR Travel Fellowship – Visit to Milan



Stewart and colleagues

Dr Stewart Sale
University of Leicester

I am a lecturer at the University of Leicester with an interest focussed at cancer chemoprevention. In the past 18 months my research has focussed on the development of novel flavonoid compounds for the prevention of prostate and colorectal cancer. From performing a number of preliminary in vitro assays and also using two in vivo models we identified a lead compound whose mechanism of action seemed to be, in part, by the activation of p53. Within our research group we had very limited experience of p53 and the travel fellowship from the BACR gave me the unique opportunity to work with Dr Massimo Broggin, at the Mario Negri Institute in Milan to try and determine the importance of this p53 activation we observed in all of our model systems.

During my 6 week placement I performed experiments which furthered our understanding of the mechanisms engaged by this agent and I acquired some methodological and conceptual skills in the area of p53; including the use of p53 wild type and p53 null cell lines to elicit the effect of TMFol on cell growth. I also assessed the activity of p53 using promoter plasmids transfected into the p53 wild type cell lines which tentatively gave indications to the potential mechanism of action of TMFol. Having returned from my placement I am able to exploit all the techniques I learnt, as well as pass them onto other colleagues in Leicester.

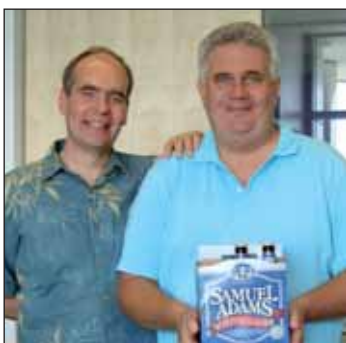
I also have a keen interest in the field of whole rodent imaging. In July 2007, the Mario Negri Institute moved to brand new facilities which houses state-of-the-art rodent tumour imaging equipment. During my 6 weeks I gained experience of some of these techniques and also observed the type of methods that could be useful in the in vivo preclinical development of cancer chemopreventive agents in Leicester.

This travel fellowship not only gave me the chance to learn new techniques but also the experience of working in a foreign country. Dr Broggin and his colleagues furnished me with a further understanding of the mechanism of action of the flavonol, and invaluable discussion offering their advice and assistance. They also allowed me to perform key experiments under the watchful eye of people with many years experience that could offer advice and assistance.

During my visit I was invited to give a seminar to the Oncology Department on my research and it allowed me to openly discuss my research with other scientists. This time in Milan has potentially led to the beginning of hopefully a very fruitful collaboration between the University of Leicester and the Mario Negri Institute. One to which I look forward to with excitement over the next few years.

I would like to thank the BACR committee for the support of my placement in Milan. It was a fantastic opportunity and pleasure to work within the laboratory of Dr Massimo Broggin. I would also like to thank all the other researchers that I met and spoke to in the Institute that offered help and assistance during my stay.

BACR Mid Career Fellowship – Visit to USA



*Richard Wheelhouse
& Brad Chaires*

Richard T Wheelhouse
Bradford School of Pharmacy

One of the great perks of BACR membership is access to support for travel, be it to a conference, a short research visit or a longer stay. The mid-career fellowship provides an opportunity to re-focus research, return to the lab and enjoy a spell of relief from the routine demands of one's home institution. In the summer of 2009, I spent 5 months at the Brown Cancer Center in Louisville, Kentucky, in the laboratory of Professor Brad Chaires.

Our two laboratories have collaborated for several years now on ligands that bind selectively to DNA·RNA hybrid duplexes (such as those formed by telomerase or RNase H). Through an intelligent screening process, we have identified hit compounds and the purpose of this visit was to define as much as possible about the precise molecular details determining the interaction using a barrage of biophysical techniques.

Using circular dichroism, isothermal titration calorimetry and other methods, we were able to identify and characterise a highly-unusual binding mode: intercalation but with a 10 base-pair binding site. Binding energies have been determined and some light shed on the role of interactions in the minor groove. Significantly, we have discerned a correlation between binding to DNA·RNA hybrids and binding to DNA triplexes, which should help inform the expansion of sequence and structure recognition properties in future compound design. Our first report should appear in the literature early in 2010. Importantly, the new skills and techniques learnt can be translated to Bradford.

Louisville is a quiet, small city at the Northern limit of the Southern states but is the venue for the high-society event of the year, the Kentucky Derby. For about a month in late April the whole city goes horse mad: brightly-coloured model horses on all the streets, a grand parade, fireworks, air display and horses everywhere except the menu. A bonus event this year was the 2nd International Conference on Quadruplex DNA.

Other scientific visits, a lecture tour in Michigan (Hope College and Grand Valley State University) and a family vacation on the Pacific Coast completed a memorable summer. Old friends, new techniques, new data and new ideas.

Gordon Research Conference (GRC) on Cell Contract & Adhesion New Hampshire – June 2009



Dr Elaine McSherry
Royal College of Surgeons in Ireland

I had the pleasure of attending the Gordon Research Conference (GRC) on Cell Contact & Adhesion in New Hampshire last June. Support from the BACR was crucial in facilitating my travel and participation in this landmark conference. The conference's aim is to promote an environment that welcomes young investigators from diverse backgrounds, while encouraging established scientists to embark on novel questions. Indeed, many leaders in the field were attending or presenting their work and there was a friendly informal atmosphere (happily-enforced by conference vice-chair Alpha Yap, who spoke with each attendee at least once). The conference format consisted of morning and evening lecture sessions, whilst also providing ample time for discussion and interaction between junior and senior scientists. I had the opportunity to speak with several leaders in my field (breast cancer cell adhesion) at communal meals and afternoon poster sessions, with a view to future collaborations and career opportunities. I also had the

opportunity to strengthen existing collaborative links at evening social events and also during an eventful mountain trek near the conference location.

At poster sessions (spread over two days to enable thorough discussion), I presented my post-doctoral study entitled “Junctional Adhesion Molecule- A (JAM-A), integrins and breast cancer – a new story?”. The results from this study suggest that over-expression of the tight junction protein JAM-A mediates increased cell migration, via downstream Rap1 and β 1-integrin signalling, in breast cancer cells. These results could have important implications for therapeutic modulation of breast cancer cell migration in the future. Indeed following discussions initiated at this conference, I have since applied with one investigator for a postdoctoral fellowship to investigate the in vivo relevance of these results at the University of Toronto, Canada from next summer.

In summary, I would like to thank the BACR for providing the support needed to attend this GRC conference. I would highly recommend this conference to others and would also hope to attend it again in the near future. Overall the conference provided a very encouraging, collaborative, and informative environment which further strengthened my enthusiasm for my current research studies.

Keystone Symposium: ‘Extrinsic Control of Tumor Genesis and Progression’ Vancouver – March 2009



Deborah Holliday

I am very grateful to the BACR for awarding me a travel fellowship enabling me to attend the above Keystone conference which took place in Vancouver in March 2009.

The conference, organised by Prof. Thea Tlsty and Prof. Mary Hendrix, centred on dissecting the complex interactions between cells and their microenvironments. These interactions not only have a role in development and organ homeostasis but are also critical in tumourgenesis and cancer progression.

My work, developing an in vitro 3d model of ductal carcinoma in situ (DCIS) to study functional aspects of fibroblast contribution to tumour cell invasion was presented as an oral presentation and as a poster both of which sparked some interesting discussions. Since my return I have been taking this forward to try and set up collaborations with scientists I met there.

The standard of the science presented was excellent and many of the talks presented novel unpublished findings alongside some published work. Prof. Pepper Schedin presented some elegant data showing the effect of tamoxifen treatment on peri-tumoural stroma. She showed that tamoxifen treated stroma exhibited altered extracellular matrix deposition and decreased expression of matrix degrading proteases. She went on to show that breast cancer cells cultured on tamoxifen treated stroma showed suppressed motility and invasion and that fibronectin in particular played a role in this. She concluded that tamoxifen induced remodelling of the stroma resulted in a microenvironment which was inhibitory to tumour cell progression.

Prof. Douglas Hanahan presented some thought provoking data on the treatment of mouse pancreatic tumours with anti-angiogenic therapies such as sunitinib. He showed that after the initial vascular dropout the tumour began growing again after ~4 weeks probably due to the upregulation of other proangiogenic factors such as FGFs and PDGFs. Of further concern was the observation that the relapsing tumours are more invasive than the initial tumours. He went on to present work from other groups which confirmed his findings, although so far this work has been carried out in animal models of cancer it has important implications for the long term use of these drugs in humans where they are currently in clinical trials.

I found the conference hugely interesting and inspiring and particularly enjoyed the opportunity to speak with other scientists at the informal poster sessions. I would once again like to thank the BACR for their support.

12th Annual MGED conference Phoenix, Arizona – October 2009



Karen Power


*School of Biomolecular and Biomedical Science
UCD Conway Institute
University College Dublin*

In October 2009, a successful application to the BACR for a travel fellowship enabled me to travel to Phoenix, Arizona and present my academic work at the 12th annual MGED conference. This meeting focused on translational genomics and high-throughput sequencing with emphasis placed on the computational challenges faced with these disciplines.

This conference was the first time I had the opportunity to present my PhD work internationally and it was well received, with many other attendees interested in similar work. My poster presented the contents of a paper we had published earlier in the year in PLoS One, based on a novel proteomics approach to detect undiscovered alternative splicing events. This method was tested on human platelet data but is applicable to any mass spectrometry dataset and we are currently using the same approach to elucidate novel alternative splicing events in melanoma cell lines.

A full day of workshops and tutorials launched the conference, which covered ‘deep sequencing analysis’. Meeting and interacting with some of the people behind powerful new analysis sequencing analysis techniques has been of unparalleled benefit. Three keynote speakers were the highlight of the program including Daniel Von Hoff, Chief Scientific Officer for US Oncology who spoke about personalized medicine and how it works in practice. Also, Prof. Henry Greely, a professor of law who encouraged discussions on the ethical challenges faced by the near-future genomic world.

I was inspired listening to the conference speakers at MGED and I am grateful to the BACR for giving me chance to attend such a relevant meeting.



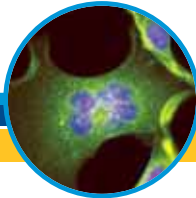
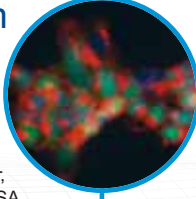
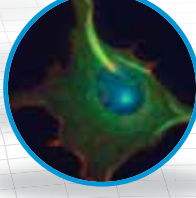
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VIIth International Melanoma Congress Boston, USA, November 2009



Dr Jane Armstrong

As a senior postdoctoral research scientist I am looking to progress my career towards becoming an independent investigator. The attendance at leading international conferences in my chosen field is therefore a vital aspect of my career development; the BACR Travel Award enabled me to attend the 2009 International Melanoma Congress, the foremost conference for melanoma research.

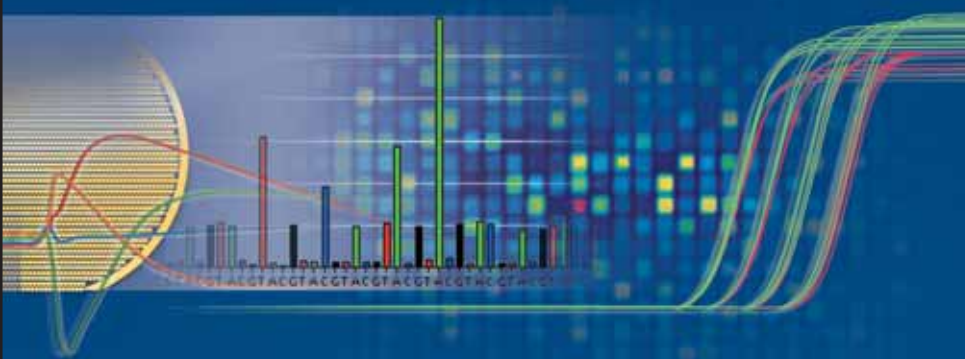
The spectrum of topics covered ranged from basic research to important clinical breakthroughs, with a format of presentations, workshops, as well as 'meet the professor' and poster sessions. There were a great number of highly interesting and relevant presentations, including the opportunity to hear two Nobel Laureates speak!

My personal conference highlights included presentations describing the development of novel therapeutic approaches for the treatment of metastatic melanoma. Translation of basic research into the clinic has been exemplified by the development of a small molecule inhibitor of BRAF. Since BRAF mutations were first identified in melanoma seven years ago there has been intensive research to develop an inhibitor of this kinase. The first potent and specific BRAF inhibitor, PLX4032, has demonstrated impressive results in early clinical trials; nevertheless, the observed emergence of resistance highlights the complexity of targeting the RAS/RAF pathway and understanding the mechanisms of resistance is vital to the development of rational combination therapies. In this respect, the research I presented described for the first time how the presence of oncogenic BRAF mutations have a significant impact on the autophagic response in melanoma, potentially limiting the cytotoxic effect of chemotherapeutics.




Attendance at this meeting allowed me to network and discuss my work with key international researchers, which proved especially informative as I prepare my research for publication, as well as providing the opportunity to establish productive international collaborations. In summary, this meeting has been enormously beneficial at this stage of my career, which I could not have attended without funding from the BACR. The encouraging support and positive response to my presented research has additionally given me further confidence as I aim to acquire personal fellowship funding and establish my independent career.


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The BACR Hamilton-Fairley Poster Prize

Presented at the BACR/EACR “Chromatin& Cancer” Conference, July 2009



The DEAD-box RNA helicase p72 (DDX17) regulates ER α -estrogen-dependent transcription and cell growth, and is associated with improved survival in ER α -positive breast cancer”

Noel C Wortham¹, Eliyaz Ahamed², Simak Ali² and Frances Fuller-Pace¹
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The DEAD-box RNA helicases p68 (DDX5) and p72 (DDX17) have been shown to act as transcriptional co-activators for a diverse range of transcription factors, including p53, MyoD, Runx2 and estrogen receptor α (ER α). We have investigated the role of these proteins as co-activators of ER α and have shown that, while both p68 and p72 are able to co-activate ER α -dependent transcription in reporter gene assays, siRNA-mediated knockdown of p72, but not p68, results in a significant inhibition of estrogen-dependent transcription of endogenous ER α -responsive genes. Furthermore, knockdown of p72 results in inhibition of estrogen-dependent growth of MCF-7 breast cancer cells to a level similar to that observed through treatment with tamoxifen.

Microarray analysis of MCF-7 cells treated with siRNA against p72 showed effects on the expression of a large number of estrogen-regulated genes. Of particular interest was an increase in expression of ERBB2 (Her2), suggesting that p72 may be involved in estrogen-dependent repression of this gene.

Immunohistochemical staining of ER α -positive primary breast cancers for p68 and p72 demonstrated that p72 expression is significantly associated with increased relapse-free and overall survival, as well as being inversely associated with Her2 expression, in agreement with our microarray data. Conversely, p68 shows no association with relapse-free or overall survival, but is associated with increased expression of Her2, AIB-1 and increased tumour grade. Our data thus highlight a crucial role for p72 in ER α co-activation and estrogen-dependent cell growth and provide evidence in support of distinct, but important roles for both p68 and p72 in the pathogenesis of ER α -positive breast cancer.

7–10 November 2010, BT Convention Centre, Liverpool, UK



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NCR Cancer Conference

7-10 November, Liverpool, UK

Plenary speakers:

Doug Hanahan (Switzerland)

Robert Weinberg (USA)

Jose Baselga (Spain)

Patricia Ganz (USA)

Stan Kaye (UK)

Ted Lawrence (USA)

Edison Liu (Singapore)

Peter Selby (UK)

Derek Stewart (UK)

Thea Tlsty (USA)

Zena Werb (USA)

Chris Wild (France)

This year's keynote speakers are **Doug Hanahan** and **Robert Weinberg**. Ten years on from their prominent publication “**The Hallmarks of Cancer**”, these world-class researchers will provide the NCR Cancer Conference with an unrivalled opportunity to hear exciting new updates to the framework and principles within which to understand the complexities of cancer biology.

Also featuring symposia on:

<p>Biomarkers and imaging Hosted by Caroline Dive (UK)</p> <p>Early diagnosis of cancer Hosted by Nick Coleman (UK)</p> <p>Hard to beat cancers: when can we expect progress? Hosted by Herbie Newell (UK)</p> <p>Pathway specific therapeutics Hosted by Richard Marais (UK)</p>	<p>Stem cells and cancer Hosted by Tariq Enver (UK)</p> <p>Teenagers and young adults Hosted by Jeremy Whelan (UK)</p> <p>Tumour microenvironment and inflammation Hosted by Frances Balkwill (UK)</p>
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Important dates:

Abstract submission opens:
Monday **22 March** 2010

Abstract submission deadline:
Friday **14 May** 2010

Registration opens:
Tuesday **1 June** 2010

Late breaking abstract submission opens:
Friday **9 July** 2010

Earlybird registration deadline:
Monday **2 August** 2010

Late breaking abstract deadline:
Monday **9 August** 2010

Online registration deadline:
Friday **17 September** 2010

NCR Cancer Conference commences:
Sunday **7 November** 2010

www.ncri.org.uk/ncrconference

BACR Tom Connors Lecture

NCRI Cancer Conference 2009



Paul Workman

CR UK Centre for Cancer Therapeutics, The Institute of Cancer Research, Sutton, UK

In this lecture I will present our latest results on discovering and developing new drugs that are directed at exploiting those abnormalities in the genomes of cancer cells that are responsible for driving the process of malignancy. I refer to this as “drugging the cancer genome” (Workman, Cold Spring Harb Symp Quant Biol. 70:499-515, 2005; Workman Curr Opin Investig Drugs 8:445-6, 2007).

We now understand in considerable detail the molecular defects that are involved in the causation and progression of cancer, but we don't know everything and it will take quite a while to figure out all the details. However, we do know enough to intervene therapeutically in a rational way (Collins and Workman, Nature Chem Biol 12: 689-700, 2006; Workman and De Bono, Curr Opin Pharmacol. 8:359-62, 2008). We understand the basic principles of oncogenesis, involving mutations in, and epigenetic changes to, key genes that regulate mission-critical pathways. We have sufficient knowledge to engage in mechanism-based drug development targeted to the genes and pathways that are hijacked in human cancers. We are achieving selective effects with new targeted therapies based on the exploitation of mechanisms such as oncogene addiction, other cancer dependencies including stress pathways, and synthetic lethality. We are exploiting new technologies to move faster from gene to drug, including high-throughput screening, structure-based design and biomarker discovery. And we are already seeing that patients are gaining considerable therapeutic benefit from our new targeted drugs. On the other hand, there are formidable challenges: in particular, overcoming drug resistance and feedback loops; the design of optimal combinatorial therapies; the targeting of heterogeneous tumour populations and of tumour stem cells; and the development of the best biomarkers to show proof of concept and select responsive patients.

I will explore progress and future potential in the design and development of small molecule inhibitors of oncogenic pathways, focusing on two areas of our work that are attracting considerable current interest and for which our first drugs are now undergoing early clinical trials: The HSP90/HSP70 chaperone pathway (e.g. NVP-AUY922; Eccles et al, Cancer Res. 68:2850-60, 2008) and the PI3 kinase pathway (e.g. GDC-0941; Raynaud et al, Mol Cancer Ther. 8(7): July 2009). Coupled with cancer genome sequencing and systems-based cancer network information, the discovery of targeted therapeutics is moving us inexorably towards the goal of personalized molecular cancer medicine.

BACR Award Presentation at NCRI 2009



BACR Translation Award presentation at NCRI Cancer Conference 2009

“Exploring hypoxia-mediated tumour progression”


Janine T Erler^{1,2,3,4}, Ian J Stratford², Caroline Dive³ and Amato J Giaccia⁴

¹Section of Cell and Molecular Biology, The Institute of Cancer Research, 237 Fulham Road, London SW3 6JB, UK ²School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Manchester M13 6AT, UK ³Clinical and Experimental Pharmacology, The Paterson Institute for Cancer Research, Manchester M20 4BX, UK ⁴Department of Radiation


Oncology, Stanford University, California 94305, USA

All solid tumours contain region of hypoxia (low oxygen). Tumour hypoxia is clinically associated with resistance to chemotherapy, patient treatment failure, metastasis and decreased survival of cancer patients. My research has identified two novel hypoxia-regulated genes, Bid and LOX, both controlled by hypoxia-inducible factor (HIF)-1 [Erler et al MCB 2004; Erler et al Nature 2006]. We demonstrated the therapeutic benefit of targeting these genes, to increase chemosensitivity (Bid) and to prevent metastasis (LOX). This work has provided insight into how hypoxic tumour cells have decreased apoptotic potential, and increased invasive and metastatic potential. In addition, this research has provided insight into how an extracellular matrix protein can mediate invasion and metastasis. We identified LOX as a prognostic marker and hypoxic biomarker. We were also the first to identify an enzyme secreted by the primary tumour that is directly involved in premetastatic niche formation [Erler et al Cancer Cell 2009]. This work provided insight into how signals from the primary tumour can regulate distant metastasis. We have provided pre-clinical evidence that anti-LOX therapy is effective at preventing and eliminating metastases. Our recent unpublished work shows effectiveness of anti-LOX therapy against advanced stage lung and pancreatic cancer, significantly reducing tumour burden and prolonging host survival. We are now developing LOX-targeting therapies to be used in clinical trials.

My team at the Institute of Cancer Research are continuing our translational research on hypoxic regulation of metastasis.



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BACR Award Presentation at NCRI 2009



BACR/Astrazenca Award presentation at NCRI Cancer Conference 2009

"Understanding how Pioneer factors regulate Estrogen Receptor function in breast cancer cells"

Kelly A. Holmes and **Jason S. Carroll**,
Cancer Research UK/Cambridge Research Institute,
Li Ka Shing Centre, Cambridge, CB2 0RE

Background: Estrogen Receptor (ER) regulation of target gene transcription is a significant factor in breast cancer development and progression. Recent work in characterising ER transcriptional activity has suggested that ER regulates gene expression from distal cis-regulatory elements and uses a large number of co-factors for modulating chromatin. We recently showed that ER binding to chromatin requires a novel class of proteins called Pioneer factors. FoxA1 and GATA3 were shown to be Pioneer factors, required for ER to maintain binding to the DNA at a select number of tested regions. Recent work has suggested that Groucho/TLE proteins may have Pioneer properties.

Methods: We use genomic technologies, such as high throughput sequencing (Solexa sequencing) in combination with Chromatin Immunoprecipitations (ChIP) and DNase sensitivity assays. This allows us to map transcription factor binding sites and chromatin structure on a global level.

Results: We now show that the Groucho protein TLE1 is an ER Pioneer factor required for ER DNA interactions. Our data suggest that TLE1 is necessary for ER to bind to more than half the ER binding sites within the genome and for estrogen mediated transcriptional activity. Furthermore, TLE1 is essential for efficient estrogen-mediated cell cycle progression and can predict outcome in ER positive breast cancer patients. We also confirm on a genome-wide level that FoxA1 and GATA3 are critical determinants of ER binding to the chromatin and overall chromatin structure.

Conclusions: These data provide insight into the mechanisms by which ER maintains chromatin interactions and suggests that Pioneer factors may be critical determinants of ER function in breast cancer cells.



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A Tribute to Professor Sheila Rodwell

7 March 1947 – 16 June 2009 (BACR Member 1998 – 2009)



Tribute to Professor Sheila Rodwell

The BACR is saddened by the early death in June 2009 of Professor Sheila Rodwell (known professionally as Sheila Bingham). Sheila was the Director of the MRC Centre for Nutrition and Cancer Prevention and Survival at the University of Cambridge. Sheila was an international leader in nutrition research with over 600 research publications. Her early work led her to realise that we needed better scientific evidence on the relationship between diet and health in people, and to understand the biological mechanisms via which diet might affect disease risk. She pioneered an enormous amount of research in these areas, running a laboratory as well as conducting detailed clinical and population studies. Sheila led the development and testing of accurate methods for assessing dietary intake and nutritional status suitable for use in the general population. She developed objective biomarkers for assessing dietary intake and nutritional status suitable for use in large population studies. Many nutrients that we believe may have important health effects, such as phytoestrogens, were hitherto difficult to measure. Sheila developed and validated the assessment of phytoestrogen concentrations in blood and urine, as well as dietary databases for phytoestrogens. She pioneered the use of urinary sugars to assess dietary sugar intake, and the measurement of faecal apparent N-nitroso compounds for the estimation of meat intake. Her insistence on understanding the effects of different diets on human metabolism led to detailed metabolic studies in human volunteers who received strictly controlled diets and provided urine and stool samples over several weeks for analyses. Sheila was one of the founding investigators of the European Prospective Investigation into Cancer (EPIC), the largest ever collaborative study of 10 countries with half a million participants initiated to provide substantive evidence on diet and cancer risk across the wide range of dietary patterns and variations cancer rates throughout Europe. Sheila led some of the early work demonstrating in this large cohort the inverse prospective association of dietary fibre with colorectal cancer risk, and an interaction between meat and fibre intake such that the adverse relationship of meat intake with increased risk of colorectal cancer was most apparent in those with low fibre intake. Sheila's huge contributions were recognized by numerous prizes and awards, prominent among them a fellowship of the Academy of Medical Sciences UK, honorary professorships from Cambridge and Coleraine and an OBE. Sheila's death is a huge loss to nutrition research and public health.

News of Members



Pfizer Excellence in Oncology Awards 2009

The prestigious Lifetime Achievement Award went to Professor Hilary Calvert, Director of the Northern Institute of Cancer Research, Newcastle Upon Tyne for his outstanding contribution to the field of oncology.

Hilary Calvert is Clinical Director of the Northern Institute for Cancer Research, Professor of Medical Oncology at the University of Newcastle Upon Tyne and Honorary Consultant in Medical Oncology at the Northern Centre for Cancer Care. He is one of the biggest names internationally, known in the oncology community for his seminal work on platinum-based

chemotherapy agent dosing and the development of the 'Calvert formula', which has benefited countless patients around the world.

Richard Sainsbury, chair of this year's judging panel and BOA president, commented: *"Hilary Calvert has had an outstanding career, making substantial advances in research and in anticancer drug development. His clinical commitment has led to innovative and lasting contributions that continue to benefit patients today. He is widely admired for his dedication and integrity, and for the respect with which he treats both patients and colleagues alike. This award is richly deserved."*



The ROYAL
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Development of Cancer Medicines: modelling of disease and preclinical testing

25th November 2010
Royal Society of Medicine, London

Programme:

Janine Erler (The Institute of Cancer Research, London)

Richard Marais (The Institute of Cancer Research, London)

Owen Sansom (Beatson Institute for Cancer Research, Glasgow)

Jos Jonkers (Netherlands Cancer Institute, Amsterdam)

Marie France Poupon (Institut Curie, Paris, France)

Steve Wedge (AstraZeneca, Macclesfield)

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Abstract deadline: Friday 22nd October 2010

Early bird Registration deadline 1st November 2010

Further details available from: <http://www.bacr.org.uk>

Email: bacr@leeds.ac.uk

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The Multiple Tiers of Gene Regulation in Cancer

Sunday July 4 – Wednesday July 7 2010 Glasgow, Scotland

Speakers and Sessions:

Keynote Address: Joseph Nevins (US)

Chromatin: Peter Adams (UK), Kristian Helin (DK), Peter Jones (US), Tony Kouzarides (UK), Irina Stancheva (UK)

Transcription Factors: Nick Dyson (US), Nick Hastie (UK), Gareth Inman (UK),
Daniel Peeper (NL), Eric So (UK), Karen Vousden (UK)

Non-Coding RNAs: Reuven Agami (NL), Joshua Mendell (US), Frank Slack (US), Robert White (UK)

Translation: Eric Holland (US), Stefan Huttelmaier (DE), Adrian Krainer (US), Davide Ruggero (US), Nahum Sonenberg (CA)

Systems: Joe Gray (US), William Hahn (US), Edison Liu (SG), Owen Sansom (UK)

Aims of the Conference

Misregulated gene expression plays a causal, or contributing, role in all cancers. This conference will focus on the various mechanisms, and their interactions, of gene control in cancer. Identifying and understanding these mechanisms and systems will lead to the development of novel diagnostics and treatments.

Short talks will be granted to the authors of outstanding abstracts. Some financial assistance will be available to the presenters of these short talks through sponsorship from the Association for International Cancer Research.

Website, on-line registration, payment and abstract submission instructions: <http://www.beatson.gla.ac.uk/conf>

For additional information please contact:

Tricia Wheeler, Conference Co-ordinator, Beatson Institute for Cancer Research, Garscube Estate,
Switchback Road, Bearsden, Glasgow G61 1BD, UK

Tel: +44 (0) 141 942 0855 Fax: +44 (0) 141 330 6426

E mail: t.wheeler@beatson.gla.ac.uk

Deadline for registration payment and abstract submission April 28 2010

