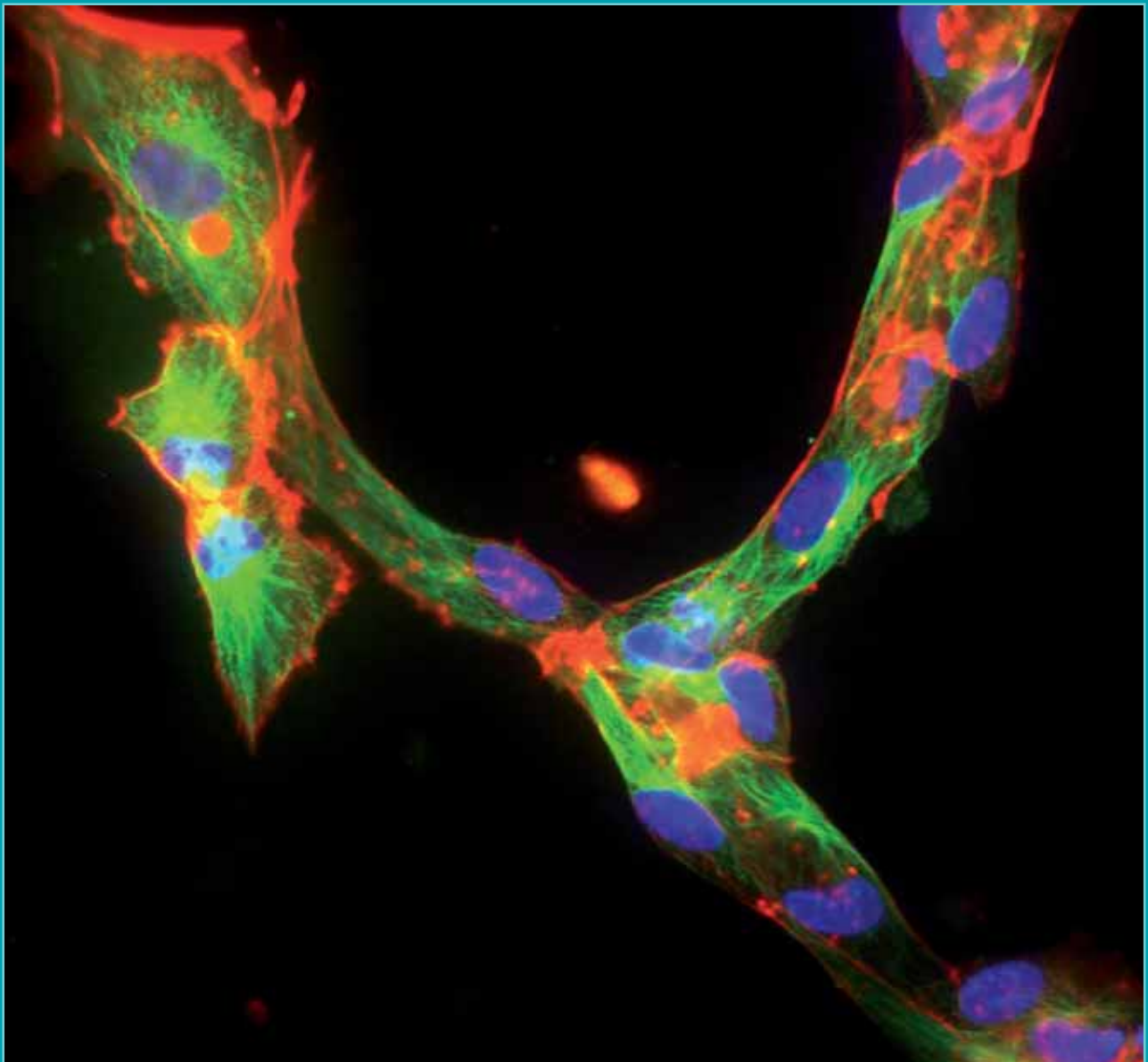


Spring 2008



News

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Front Cover

A three-colour fluorescent image of endothelial cells aligning to form tube-like structures in matrigel, showing cytoskeletal microtubules (green), actin (red), and nuclei (blue)

Dr Chyrso Kanthou
Academic Unit of Surgical Oncology
University of Sheffield

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Letter from the Chairman



Dear Colleagues,

Welcome to the Spring 2008 edition of the BACR Newsletter.

The BACR continues to expand its programme of focussed conferences and to support its members to attend other meetings. Competition for BACR awards continues to increase and the committee has had to work hard to support as many individuals as possible. During the year the BACR has provided in excess of **£37K** in support of both student (27 awards) and full members (13 awards) to attend meetings and 4 Travel Exchange Fellowships were awarded. See pages 21 / 23 for reports from recipients.

This issue also includes reports of the BACR Special Conferences: 'Diet & Cancer: susceptibility, prevention and therapy - June 2007, and 'Cell signalling and novel cancer therapeutics, November 2007.

The BACR also sponsored a number of meetings during the year:

- Nottingham Summer School and Symposium June 2007
- Mucins in Health and Disease (9th International Workshop on Carcinoma-associated Mucins) Cambridge, July 2007
- Genes & Cancer Meeting, Warwick, December 2007
- Metabre/BRECOSM, Rome, December 2007
- Life Sciences, Glasgow, July 2007

Topics for 2008 BACR Special Conferences are:

- Cellular immortality & cancer: from telomerase to cancer stem cells to be held in Stratford-upon-Avon on 3rd & 4th June, 2008
- Advances in Cancer Drug Discovery to be held in Cambridge on 7th/9th September, 2008
- BACR/RSM Oncology Section/APS meeting Pre-clinical models; biomarkers and targeted therapy to be held in London on 27th November, 2008.

Any member having a proposal for a Special Conference should submit details including a rationale for the subject directly to Barbara Cavilla at the Secretariat (b.cavilla@icr.ac.uk).

The 3rd NCRI Cancer Conference continues to be a successful meeting, bringing together laboratory and clinical cancer researchers, with over 1,700 delegates and a wide range of diverse sessions. Once again, the BACR was involved and ran two educational workshops, one on RNAi technologies and the other on Apoptosis which were both well attended despite the early start. A BACR reception for members was also well attended and it is anticipated that this event will run again this year. Plans are already under way for two BACR Educational workshops to be presented at the 4th Annual NCRI Cancer Conference 5th/8th October. Proposals for these workshops are "Small animal imaging and models" and "Tissue microarrays and image analysis".

We welcomed two new members to the Executive Committee at the AGM:

Stephen Hiscox (University of Cardiff) and Steve Wedge (AZ, Macclesfield) and Tomasz Zaremba (Newcastle) was elected as the student representative.

On behalf of the Executive, I would also like to express thanks to Moray Campbell and Michael Seckl, for their very valuable contributions to the Executive Committee and its sub-committees.

We would also like to give a huge vote of thanks to Dr Stewart Martin who has finally escaped from being Honorary Treasurer of the BACR. Stewart has worked tirelessly on behalf of the BACR to maximize our income and make sure the money was spent as effectively as possible. All of us recognize that the Honorary Treasurer of the BACR is lot of work with minimal thanks and lots of complaints. However, we didn't say that to Dr Andrew Westwell who has taken over as Honorary Treasurer!

In 2010 the BACR will have been supporting and promoting cancer research for 50 years. The Executive Committee is discussing events in 2010 to celebrate the past and future of the BACR and British cancer research. We would be keen to hear your thoughts and suggestions.

Robert Brown, *Chairman*

BACR Special Conference on 'Diet & Cancer: Susceptibility, Prevention and Therapy'

June 2007, Nottingham

Programme organisers:

Moray Campbell (Birmingham), Janet Cade (Leeds), Andy Gescher (Leicester), Ian Rowland (Reading) and Chris Wild (Leeds)

Diet In health

Review – Moray J. Campbell

The Opening session of the meeting was dedicated to establishing a view of the current understanding of Diet in Health, specifically in areas where the understanding of dietary impact is clearest.



Professor Martin Wiseman (Medical and Scientific Advisor, WCRF International) opened the meeting with an overview and provocative interpretation of the field to propose a series of future challenges. His presentation was extremely timely as the second edition of the WCRF/AICR Expert Report Food, *Nutrition and the Prevention of Cancer*: a global perspective is due for publication in Autumn 2007. Professor Wiseman outlined some familiar and novel background ideas in the field to demonstrate the significance of environmental factors, such as diet, on cancer initiation and progression. To develop these concepts further he stressed the importance of research developing away from traditional linear and single topic approaches, and outlined the requirements for future progress. He proposed the concept of a portfolio of evidence that draws on multiple strands of data, in a hierarchy, across fields and levels of study to inform policy accurately and precisely. Interestingly he highlighted several concepts addressed by subsequent speakers, not least of which was the importance of exercise to influence the impact of diet; a relationship that was examined more fully by the last speaker of the meeting, Professor David Alberts.



The second talk, by **Professor Ian Johnson** (Institute of Food Research, Norwich, UK), revealed the difficulties in establishing causal relationships between dietary factors and the incidence of colon cancer. His talk revealed how the complexity of these relationships is emerging. For example the protective effects of dietary fiber had appeared clear from epidemiological and ecological studies, however when applied in interventionist trials it proved equivocal. To resolve these issues there is a need for functional biomarkers, that reflect an integral of multiple dietary components, genotype, age, and physical activity. For example, with reduced physical activity there is increased adipocyte activity and secretion of cytokines, which in turn impact on the gut and liver function. Members of the IGF signaling axis appear to be emerging as a functional link between many of these factors and may prove to be important functional biomarkers which relate dietary intake, body mass index and physical activity. Finally Professor Johnson outlined ongoing human studies that are uniting findings from the mucosal biopsy of normal and malignant samples with metabolomic and proteomic Professoriles and lifestyle questionnaire data. This approach clearly reflected the concept of a portfolio of evidence as outlined by Professor Wiseman.



Professor Kenneth Muir (University of Nottingham) investigated several of these concepts further by addressing the links between folate metabolism and DNA methylation. This is an area of very active investigation and appears a route for chemoprevention with very significant potential. Consequently the concept of folate fortification of food stuffs is actively being investigated and debated. He outlined the supportive and negative findings, including recent data from his own group, that urged a note of caution as the relationships between folate metabolism and colon cancer initiation and progression depended upon gender, genotype, stage of disease and other factors and were not immediately distilled into simple causative relationships.

Finally two selected talks addressed further aspects of dietary factors required for maintenance of health and disrupted in malignancy. **Dr Alexandra Thurston** (University of Nottingham) summarized her work and previous findings from the group she works with on the relationships between dietary folate and the development of embryonic methylation patterns for example at the locus of imprinted genes. **Dr Paul Thompson** (University of Ulster) summarized new findings from his group on the role that nuclear receptors such as the vitamin D receptor, responding to dietary components, are able to induce a panel of xenobiotic-metabolising cytochrome p450s such as CYP3A4. These capacities appear to be suppressed in cancer models thereby allowing potentially damaging factors to exert geno-toxic effects.

Population Studies

Review - Janet Cade

The session opened with a fascinating talk by **Dr Georgia Salanti** (University of Ioannina, Greece) who spoke about the challenges of investigating gene-environment or gene-gene interactions. Studies are often limited by small sample size and Georgia put forward a new meta-analysis approach which enables combinations of studies to provide higher power to detect effects. The talk was illustrated by example of this new approach for studies of NAT1 and NAT2 genotypes and interaction with smoking in relation to bladder cancer.



Dr Gunter Kuhnle (MRC Dunn Human Nutrition Unit, Cambridge) spoke about his work with the large European Prospective Investigation of Cancer (EPIC) cohort exploring the risk associated with red meat intake and bowel cancer. Epidemiological studies have consistently demonstrated that red and processed meat consumption is associated with an increased risk of colorectal cancer. Increased intakes of red meat have been shown to increase faecal apparent total N-nitros compounds (ATNC) levels in a dose responsive manner. These may lead to adduct formation leading to mutation and cancer formation.

Faecal ATNC levels increase when a low meat diet is supplemented with haem; this is not seen with inorganic iron supplementation or when other sources of animal protein (fish, white meat) or vegetable protein are consumed. The majority of nitroso-compounds investigated have been shown to be carcinogens.

Professor Tim Key (University of Oxford) reviewed evidence linking diet, hormones and prostate cancer including from 150,000 men in the EPIC study from 8 countries with 2,700 incident cases of prostate cancer. There was no evidence that a high male sex hormone level was associated with increased prostate cancer risk. However, exploration of the insulin like growth factor (IGF) system showed that men who had the highest level of IGF1 adjusted for the IGF binding protein 3 had an increased risk of prostate cancer. There was no evidence that fruit and vegetable intake had an effect on risk, however, this may depend on the stage of disease. Increased intakes of lycopen and carotenoids reduced the risk of advanced disease.

Dr Y Y Gong (University of Leeds) spoke about the mycotoxins, fumonisins, as common contaminants of maize. They have been associated with liver and oesophageal cancer risk in some population studies and also may be a risk for neural tube defects. She reported work from Mexico where maize consumption is high. A biomarker for fumonisin B1 has been developed in the urine which is correlated with maize intake and so may be a marker for fumonisin intakes in some populations.

Dr Richard Hubner (The Institute of Cancer Research, Sutton) described his work on folate metabolism enzyme polymorphisms and their effect on colorectal cancer. Specifically, 3 polymorphisms in the thymidylate synthetase (TS) gene region and diet were explored in a colorectal adenoma case-control study. Subjects who were homozygous for the TS deletion polymorphism had a reduced risk of colorectal adenoma. There appeared to be an interaction between this genotype and intake of folate, B6 and B12 and the MTHFR C677T genotype, providing evidence that functional polymorphisms in folate metabolism genes may have a role in colorectal neoplasia.

Molecular Mechanisms of Functional Foods

Review – Moray J. Campbell

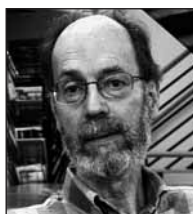
Several invited speakers were invited to highlight challenges and prospects in this extremely broad area.



Professor Gary Williamson opened the session. Professor Williamson had spent several years at the corporate research headquarters of Nestle Inc in Switzerland and had now taken up an academic position at the University of Leeds. Consequently he offered broad insight on Plant Flavenoids. This included a precise and clear overview of their classification (e.g. flavanones, isoflavonones, anthocyanins). These compounds are consistently highlighted in terms of cancer chemoprevention and attract considerable research interest. However the *in vivo* translation has been frustrated by bioavailability and metabolism issues. To obtain the optimal dose between dietary insufficiency and toxicity requires accurate measurement of plasma concentrations and robust functional tests. To move towards such studies Professor Williamson and colleagues are developing *in vivo* assays to model metabolic cascades in the gut, for example the capacity to induce phase II detoxification enzymes in response to food components combined with laser capture microdissection to measure gene induction precisely, conjoined with the use of gene knock out animals to demonstrate functional significance. Such comprehensive and convergent approaches appear to be very encouraging.



Dr Sarah Freemantle is a senior scientist in a large multi-disciplinary group working at Dartmouth Medical School, USA. The group examines ways to exploit retinoid signaling by dissecting basic mechanisms of gene regulation cell cross-talk. They model much of their work in murine and human lung cancer models and examine how retinoids interact with control of the cell cycle and other signaling mechanisms. Retinoids bind with high affinity to specific nuclear receptor transcription factors and govern a number of genes involved with control the cell cycle. In particular their group has examined ubiquitination processes which govern the half life of CYCLIN D1. This protein was subsequently used as functional tumour marker of retinoid responsiveness in Phase I and Phase II trials. Also using a range of transgenic murine models they have looked to exploit this understanding in chemoprevention settings. Again, the convergent use of *in vitro* cell models, *in vivo* murine transgenic animals and human Phase I and II trials underscore the multiple levels of evidence required to exploit dietary signaling processes.



Professor Andrew R. Collins, The University of Oslo, Norway, visited several of these themes in reviewing attempts that have been made to exploit the *in vitro* potential of anti-oxidant compounds such as vitamin E. Professor. Collins was part of an international consortium which aimed to harmonize the measurement of serum levels of key antioxidants. Such approaches only served to underscore how difficult this was, with divergence occurring when different member labs assayed the same samples. These discrepancies probably explain much of the ambiguity revealed by meta-analyses on the role of anti-oxidant compounds on cancer initiation and progression.

Three selected abstracts were also presented in this session. **Professor Marco Falasca**, UCL, London, outlined his groups' recent findings on the PI3K signaling pathway. Specifically his group have identified a novel inositol phosphate compound (Inositol(1,3,4,5,6) pentakisphosphate [Ins(1,3,4,5,6)P5]), which appears to act as a secondary messenger to antagonize AKT signaling. Synergisms were shown with standard cancer drugs and with a range of natural compounds; indeed Ins(1,3,4,5,6)P5 is itself derived from nuts and beans and therefore underscore the importance of diet in both chemoprevention and chemotherapy settings.

Dr Bernard Corfe, The University of Newcastle, UK, outlined the recent findings of his group examining non-histone targets of acetylation and deacetylation. Again, several dietary derived compounds, notably the butyrates, regulate this process. Using a proteomic approach they identified novel acetylated targets and demonstrated that the structural protein Cytokeratin 8 is a target, probably of HDAC5, and regulates anoikis. Importantly in human tumour samples they demonstrated the de-regulated CK8 was associated with intestinal hyperplasia.

Finally, **Marjo Malinen**, Kuopio University, Finland, explored several of these themes further, namely signaling via nuclear receptors, in particular the vitamin D receptor, and the regulation of gene promoter histone acetylation. She revealed that depending on cancer cell backgrounds (different breast cancer cell lines) the VDR targeted separate compliments of the cell cycle machinery and related these findings to the unique compliment of co-factors that assembled around the VDR.

Chemoprevention and Chemotherapy Dietary Capacity

Review - Andy Gescher

The emphasis of this session was on concepts pertaining to cancer chemoprevention with dietary agents. For many years the Division of Cancer Prevention of the US NCI has steadfastly and generously supported a plethora of diverse research activities devoted to advance the field of cancer chemoprevention. The development of novel agents originating from plants and herbs has been part of the NCI research portfolio.



Dr James Crowell (Chemopreventive Agent Development Research Group, Division of Cancer Prevention, NCI, Bethesda, USA) described the impressive spectrum of research programs on chemoprevention agent development, which the NCI currently supports. An example of an agent which has been shown promise in preventing experimental bladder cancer in rodents is the green tea catechin epigallocatechin gallate, which inhibits EGFR signalling among other effects. Unfortunately in humans catechins are less significantly eliminated in the urine than in rodents. Molecular reduction of diet-derived agents to active principles can lead to novel agents exploiting identification of molecular scaffolds and altering them by traditional medicinal chemistry synthesis. SR13668 is a molecule modelled on indole-3-carbinol, an exploratory IND is currently applied for it.



Dr Chris Parker (Institute of Cancer Research and Royal Marsden NHS Foundation Trust, Sutton) addressed clinical trials of chemoprevention strategies in prostate cancer. He conveyed to the audience in a most cogent and inspiring fashion that in the era of PSA testing prostate cancer is a different condition to what it used to be in pre-PSA times. This change asks for imaginative new prevention and treatment modes. "Active surveillance" is an increasingly popular approach in the management of early prostate cancer. This approach provides the opportunity for tertiary prevention trials to test interventions, conceivably dietary-derived agents, designed to slow disease progression. An efficacious agent, if found, would constitute a real advance as it would avoid the burden of adverse effects associated with conventional treatments such as surgery.



Dr David Alberts (Arizona Cancer Center, Tucson, USA) was unfortunately unable to attend the meeting due to illness. He kindly sent a CD with a fascinating and optimistic overview over how beneficial changes in life style and diet can reduce the risk of breast and colorectal cancer. He stressed the value of evaluating the progression from intraepithelial neoplasia to invasive cancer in the assessment of success or failure of a novel intervention. He described research at the University of Arizona dedicated to unravel the role of nutrients and physical activity in cancer prevention. His group has for many years pioneered cancer chemoprevention trials with diet-derived agents such as dietary fibre.

Finally, two interesting proffered papers illustrated the forefront of dietary cancer chemoprevention research and beautifully complemented the programme of the session. **Dr Hong Cai** (University of Leicester) described the chemopreventive efficacy *in vivo* of the flavones tricetin and apigenin in the *Apc^{Min}* mouse model, and **Dr Emma Coates** (University of Ulster) showed anticancer properties of raspberry polyphenols in colon cancer cells *in vitro*.

BACR/RSM Oncology Section conference “Cell Signalling and Novel Cancer Therapeutics”

November 2007, London

Programme Committee:

Michael J Seckl (London), Sue Burchill (Leeds), Ana Cost-Pereira (London)
Olivier Pardo (London), Julian Downward (London), Margaret Frame (Glasgow)

Receptors

Review - Sue Burchill

In the session on **Receptors** the success of targeting specific steps along the deregulated signalling cascade for therapeutic advantage was demonstrated by two speakers reviewing the development and current status of monoclonal antibodies and small molecule tyrosine kinase inhibitors (TKIs) targeting vascular endothelial growth factor and its receptors (SAB), and epidermal growth factor receptor (EGFR) (FS). The third speaker (JK) in this session described the importance of protein-protein interactions in the catalytic domain of the EGFR and how they might regulate signal transduction pathways.



Targeting VEGF and VEGFR (Sue Burchill, Leeds) Tumour neovascularisation plays a key role in the growth and metastases of most cancers; growth factors produced by the tumour cells stimulating endothelial cell proliferation, survival and migration to form a vasculature that delivers oxygen and nutrients to the growing tumour cells. Vascular endothelial growth factor (VEGF) and its tyrosine kinase receptors (VEGFRs) play a central role in this process, and are the targets for the design of both monoclonal antibodies and small molecule inhibitors. Blocking VEGF has a direct and rapid antivascular effect in both animal and human tumours, though this has not been beneficial therapeutically as a single agent. However inhibition of angiogenesis with the anti-VEGF antibody bevacizumab has improved the efficacy of standard cytotoxic therapy in a number of different cancers including colorectal, breast and NSCLC. The largest class of drugs that block angiogenesis are the TKIs targeting VEGFRs. Many of these are in development, though two are now on the market (sunitinib and sorafenib). These agents have activity when used as single agents and may also be synergistic or additive with traditional cytotoxics. Most of these inhibitors exert their therapeutic effect by targeting the VEGFR and inhibiting other pathways such as the RAF/MEK/ERK pathway. This lack of target specificity may explain some unexpected toxicity, but is also promising for improved therapeutic efficacy.



Allosteric mechanisms in activation of EGFR (John Kuriyan, California, USA)

The clustering of receptor molecules is a key feature of activating signal transduction cascades. This clustering brings molecules into close proximity at high local concentrations to promote a number of protein-protein interactions that can lead to activation by phosphorylation of themselves, target proteins or ligands. EGFR is a transmembrane protein possessing an extracellular ligand-binding domain and an intracellular kinase domain that contains autophosphorylation sites that recruit signalling molecules when phosphorylated.

Recent studies have shown that enhanced local concentrations of the EGFR tyrosine kinase domain (that results from ligand stimulation) activates this kinase domain. This resembles the way in which cyclins control cyclin-dependent protein kinases, except the EGFR acts as its own “cyclin”. Understanding the regulation of such protein-protein interactions and how they may differ in normal and cancer cells to effect a response may lead to novel strategies for the development of targeted therapeutics.



EGFR inhibitors in the treatment of NSCLC (Frances Shepherd, Toronto, Canada)

The inhibition of epidermal growth factor receptor (EGFR) is established in the second and third-line treatment of patients with NSCLC. The small molecule inhibitors erlotinib and gefitinib have also been evaluated as first-line therapy, where it has been shown that they do not add to chemotherapy. In contrast, it appears that the addition of the monoclonal antibody cetuximab does result in higher response rates and longer survival. Several trials have shown that response to EGFR TKIs is higher in women, patients with adenocarcinoma, Asians and lifetime non-smokers. However, a differential survival benefit has only been shown in non-smokers.

The presence of somatic mutations in exons 19 and 21 is associated with higher response rates; however, the superior survival reported in patients who carry mutations in the single arm trials may reflect the prognostic power of these mutations rather than a significantly different response to treatment in patients with wild-type and mutated EGFR. Recent studies have also demonstrated that EGFR gene copy number and protein expression are associated with higher response rates, and a significantly greater survival benefit in some studies. The use of EGFR TKIs in the first-line setting in selected patients including those with EGFR mutations, remains experimental and the results of prospectively randomized trials comparing erlotinib or gefitinib to chemotherapy are awaited. The selection of patients based on EGFR status likely will be essential in future trials to establish the optimal strategy to exploit EGFR TKIs for therapeutic advantage, and to distinguish the prognostic and predictive power of EGFR protein expression, mutation status and gene copy number. Biomarker validation trials are planned in the North American cooperative clinical trial groups.

S6Ks + mTOR

Review – Michael J Seckl



Dr George Thomas (Genome Research Institute, University of Cincinnati) introduced the field of mTOR and S6K1 signalling demonstrating the importance of this pathway throughout the evolutionary tree for regulating growth and proliferation. He elegantly showed how mutations in TSC1/2, an upstream regulator of mTOR was associated with overactivity of mTOR and the human disease tuberose sclerosis. Moreover, tumours associated with the condition appear to regress with mTOR inhibitors. He then described work examining the nutrient sensing function of mTOR. Using a variety of techniques including inhibitors, RNAi, over-expression of wild-type and mutant proteins, his laboratory demonstrated that withdrawal of amino acids leads to mTOR and S6K1 activation through a pathway that is distinct from that used by insulin. The latter requires modulation of the upstream signalling molecules TSC1/2 and Rheb via class I PI3K. In contrast, amino-acid withdrawal requires input from the class III PI3Kinase, hVps34 and Rheb but not TSC1/2. The precise link between amino acid transporters and hVps34 is now actively being investigated.



Dr John Blenis (Harvard Medical School) focused on the mechanism coupling mTOR signalling to the translational machinery of the cell. Using tandem affinity purification his group discovered that the translation initiation factor eIF3 complex and the translation preinitiation complex (PIC), serve as scaffolds to promote growth factor- and nutrient-dependent initiation of mTOR-Raptor (mTORC1) signaling and phosphorylation of its two major effectors, the eIF4E binding proteins (4EBPs) and the S6 protein kinases (S6K1/2). Phosphorylation of these effectors results in their release from the PIC and promotes assembly of the translation initiation complex at the 5' mRNA cap. Once released from eIF3, S6K1 is activated and associates with the exon-junction complex (EJC) of newly synthesized and spliced mRNA via SKAR, a S6K1-specific interacting protein identified in a two-hybrid screen. At the EJC, the activated enzyme can phosphorylate targets involved in the pioneer round of translation. Thus, mTORC1 and S6K1 regulate assembly of the translational apparatus needed for pioneer and steady state translation, and connect growth factor signaling, nutrient availability and energy status to the energy consuming process of protein synthesis.



Professor Michael Seckl (Imperial College London) ended the session by providing a clinical view of mTOR/S6K1 and S6K2 signalling in small cell lung cancer (SCLC). The disease is driven by multiple growth factors so targeting individual receptors is insufficient. However, it was shown that multiple growth factors signal proliferation via mTOR and inhibiting this molecule with RAD001 blocks SCLC proliferation both in vitro and in vivo. Early clinical data look promising but since the effects are largely cytostatic there is a need to identify other targets which trigger cell death. He then described how S6K2, a homologue of S6K1 might be such a target. Using multiple approaches including RNAi, mutant kinases and knock-out cells FGF-2 but not other growth factors trigger the formation of a novel complex comprising BRAF/PKC β and S6K2 which enhances the translation of several antiapoptotic proteins. Inhibiting S6K2 or other components of the complex, induced apoptosis and reversed FGF-2 triggered multi-drug resistance. Similar effects were seen with an FGFR inhibitor both in vitro and in vivo. This new S6K2 mediated chemoresistance pathway provides a series of novel targets for new anticancer agents.

JAK/STAT

Review - Ana Costa-Pereira

JAK/STAT signal transduction pathways, initially identified as essential for signalling in response to the Interferons (IFNs), are central to the responses of most other cytokines and some growth factors. Consistent with this, JAKs (Janus kinases) and STATs (Signal Transducers and Activators of Transcription) are essential to the regulation of the immune system and can affect cell growth, cell differentiation and apoptosis.

JAK/STAT signalling is essential but not sufficient to mediate all aspects of the IFN- γ and IL-6 responses: additional signalling pathways are involved and 'cell status' clearly modulates the response.



Dr Ana P. Costa-Pereira (London, UK) opened the JAK/STAT session by describing JAK/STAT canonical pathways and, subsequently, some of the 'alternative signalling pathways' previously identified. She then described a powerful, robust flow cytometry-based quantitative short-interfering RNA (siRNA) screen which was used by her and her colleagues to identify additional kinases required for the IFN- γ response and molecules involved in an IL-6 mutational switch, previously identified by Dr Ian Kerr (London, UK) and his co-workers. Dr Costa-Pereira revealed the identity of a target identified through the IFN- γ screen and speculated how this molecule may be regulating aspects of the IFN- γ response. These screens pave the way for further elucidation of IFN/cytokine action and identification of additional targets for clinical intervention, and can be easily adapted to identify molecules involved in other biological responses and/or contexts.

There are 7 mammalian STATs, which function both as the signal transducers and transcription factors downstream of the JAKs. Interestingly, STATs are often deregulated in tumour cells, most notably STAT1, -3 and -5. STAT3, typically activated by IL-6, can act as an oncogene and promote cellular transformation. In contrast, STAT1 classically activated by IFN- γ has been identified as a tumour suppressor and has been implicated in a form of immune surveillance.



Professor Veronika Sexl (Vienna, Austria), however, provided highly compelling evidence for a dramatically different function for STAT1 in leukaemic cells: upon Abl- or Tel-Jak2-induced leukaemia, STAT1 can function as a tumour promoter. This re-emphasises the intricate nature of pathways involving JAKs and STATs and their highly context-dependent regulation. Professor Sexl also described the pivotal role that STAT5 plays in leukaemogenesis. In an elegant animal model, Professor Sexl's team has established that in the absence of STAT5 v-Abl and Bcr-Abl can no longer transform cells.



Dr Heike Hermanns (Aachen, Germany) gave a very compressive overview of STAT3, taking us on a journey from the key discovery of STAT3 (or APRF) by the groups lead by Professor Peter Heinrich (Aachen, Germany) and Professor. Toshio Hirano (Osaka, Japan), to its pivotal role in the acute phase response, ending with its most recent role as an oncogenic molecule. The role of STAT3 in immune evasion and, importantly, the relationship between STAT3 and pro-inflammatory mediators were also discussed.



Professor Tony Green (Cambridge, UK) closed the session by talking about mutations found in patients' JAK2 and the critical role that it plays in myeloproliferative diseases (MPDs). The relevance of the JAK2 V617F mutation was discussed and Professor Green provided clear evidence for additional JAK2 mutations found in MPD patients previously shown to be negative for V617F. The exciting new findings offer alternative avenues for diagnosis, classification and additional therapies for the MPDs.

The role of JAK/STAT signalling in tumourigenesis is in its early days but one can anticipate that much remains to be learned and this will be both a promising and an exciting field to explore from an oncological point of view in years to come.

Raf/MEK

Review – Olivier Pardo



Philippe Bastiaens (Dortmund, Germany) research focuses on understanding: (1) reaction-diffusion properties of protein reaction networks that generate spatial patterns of protein states in cells, and (2) how these reaction patterns regulate cellular signal transduction and morphogenesis. Philippe Bastiaens perfected mathematical models introduced by Boris Kholodenko to study differences in the MAP kinase signalling downstream of EGF and NGF stimulation in PC12 cells. EGF and NGF-mediated stimulation of the MEK/Erk pathway differ temporally in PC12 cells as NGF causes transient, and EGF sustained, Erk phosphorylation in this cell system. Using mathematical algorithms in conjunction with fluorescent cross-correlation spectroscopy (FCCS), Philippe Bastiaens team modelled differences in feedback loops to explain these divergent kinetics. Once perfected and extended, such models will allow to predict changes in signalling kinetics and intensity following single gene perturbation (eg. Activating mutation, siRNA...).



Richard Marais (London, UK) B-Raf activating mutations are common genetic alterations found in melanoma. Here, Richard Marais highlighted the phenotypic effects of B-Raf activation in mouse models and presented transcriptional events downstream of B-Raf signalling that may play a role in melanoma tumorigenesis. Early knock-in of kinase-active V600E B-Raf in mice leads to skin, brain, eye and heart defects. Inducible models first presented with local hyper-pigmentation and naevi (1/2 months), followed by eye-lids and anal hyper-proliferative lesions (3/5). However, these rapidly growth arrested (correlating with increased p16 expression) and did not spontaneously progress to form melanomas, requiring further insults to become cancerous. In a second part to his talk, Richard Marais presented data linking B-Raf to cell cycle regulation. This involved modulation of the transcription factor MITF, whose promoter activity was dependent on B-Raf signalling. MAPK signalling downstream of B-Raf is responsible for the transcriptional upregulation of BRN2 which binds to MITF's promoter to induce its upregulation. Data presented here suggest that disruptions of MITF's expression levels play a central role in B-Raf's oncogenic potentials.



Judith Sebolt-Leopold (Ann Arbor, US) presented clinical data on the use of MEK inhibitors currently on trial. To date, three MEK inhibitors have entered clinical trials: CI-1040, PD0325901, and ARRY-142886 (AZD6244). Significant target inhibition was observed in tumor biopsies and, importantly, signs of clinical activity. Attention was then given to differential response to these drugs based on ethnicity, sex and genetic alterations. BRAF mutations have been found, both *in vitro* and *in vivo*, to confer enhanced and selective sensitivity to MEK inhibition compared to RAS mutated or wild-type tumor cells. Thus, genetic profiling of human tumors prior to patient enrollment into clinical trials will likely play an important role in increasing our chances of eliciting activity with these agents. Based on the multiple genetic defects and heterogeneity found in human tumors, it seems unlikely that treatment with MEK inhibitors alone will be sufficient to totally eradicate tumor burden.

Apoptosis

Review - Julian Downward



Professor Julian Downward (Cancer Research UK London Research Institute) described work exploring the link between Ras and PI 3-kinase signalling pathways in cancer. His lab has investigated the role of the direct interaction of Ras with the catalytic subunit of Type I PI 3-kinases in mouse development and oncogenesis. Mice were made with point mutations knocked into the gene encoding p110 γ that block its ability to interact with activated Ras. Fibroblasts from mice homozygous for this mutation showed strongly attenuated activation of PI 3-kinase in response to some growth factor, but not others, and also showed much reduced ability to be transformed *in vitro* by expression of activated Ras and EGFR mutants. Mice homozygous for the p110 γ mutation show a very dramatically reduced rate of lung cancer incidence when crossed onto the activated K-Ras LA2 knock in line. It is therefore clear that the Ras/PI3-kinase link is critical in promoting Ras driven tumorigenesis in mice and that this interaction might provide a novel oncology drug target.



Dr Stephen Fesik (Abbott Laboratories) described a long running programme to develop drugs targeting the anti-apoptotic Bcl-2 proteins, which have been shown to contribute to tumour initiation, progression and resistance to therapy. Using a nuclear magnetic resonance-based method for discovering lead compounds (structure activity relationship by NMR), parallel synthesis, and structure-based design, his group discovered a compound, ABT-737, that potently inhibits the ability of Bcl-2, Bcl-XL, and Bcl-W to bind to, and neutralise, pro-apoptotic Bak and Bax proteins. ABT-737 is synergistic with multiple chemotherapeutic agents and radiation for killing a wide variety of tumor cells in culture and has activity as a single agent in tumor cells derived from small cell lung carcinomas, lymphomas and leukemias in culture and xenograft models. The drug does not inhibit the Mcl-1 pro-survival Bcl-2 family member, but appears to synergise well with agent that suppress expression of this short-lived protein, including activators of the integrated stress response. The next generation Bcl-2 inhibitor, ABT-263, is entering clinical trials for lymphoma, CLL, and SCLC.



Professor Paul Workman (Cancer Research UK Centre for Cancer Therapeutics) described work on new inhibitors of PI 3-kinase) and the HSP90 molecular chaperone. His group and collaborators have developed potent and isoform-selective PI 3-kinase inhibitors by high-throughput screening (HTS) and subsequent optimisation by medicinal chemistry. These act to inhibit the growth of a variety of tumour cell lines as xenografts in nude mice. The molecular chaperone HSP90 is responsible for the stability and activation of a range of oncogenic client proteins and the discovery of new inhibitors has been enhanced by chemical biology, HTS and structure-based design. A proof of concept drug inhibiting HSP90, 17-AAG, has shown sufficient impact in clinical trials to drive the development of drugs targeting HSP90 with the potency needed to be clinical candidates, such as VER49009.



Professor Karen Vousden (Beatson Institute for Cancer Research) reported work on the p53 tumor suppressor protein which functions to prevent malignant progression, in part by inhibiting proliferation or inducing the death of potential tumor cells. The activity of MDM2, an E3 ligase that ubiquitinates p53, resulting in both proteasomal degradation and relocation of p53 from the nucleus to the cytoplasm, is regulated through interaction with a number of other proteins, including the MDMX – a related protein that does not have E3 activity itself, but can contribute to MDM2's function. MDM2 can drive the degradation of mutant p53 through a mechanism that does not depend on the E3 activity of MDM2. The contribution of MDM2 to the degradation of mutant p53 may reflect an ability of MDM2 to deliver the ubiquitinated mutant p53 to the proteasome.

Migration

Review: Margaret Frame



Margaret Frame (Beatson Institute for Cancer Research) described recent identification of a new function for the enigmatic focal adhesion kinase (FAK) FERM domain in regulating actin assembly via the Arp2/3 complex. Specifically, the FERM domain binds and recruits the Arp2/3 complex to peripheral adhesion sites, its subsequent release being linked to Arp2/3 actin nucleation activity and recruitment of actin into lamellipodia and cell polarisation. FAK is up-regulated in human epithelial cancers, and previous experiments had shown a key role for FAK in tumour initiation and progression in a number of tissues.

The new findings raise the possibility that FAK's role may be a function of its ability to regulate peripheral actin structures forming at early adhesion contacts, which, in turn control cell polarity and directional cell migration. FAK, and its upstream regulatory kinase Src, control cancer cell invasion and spread via mechanisms such as that described.



Georgia Mavria (Institute of Cancer research, Chester Beatty Labs, London) described studies on how signalling pathways determine movement of endothelial cells during endothelial tube formation studied in an organotypic tissue culture angiogenesis assay. Specifically, it appears that endothelial cells migrate in a 3-dimensional matrix shed by fibroblasts by extending cell protrusions. MAP kinase opposes Rho-kinase signalling to allow endothelial cell survival and sprouting. However, during establishment Rho-kinase activity is up-regulated at cell junctions and is apparently required for the maintenance of vessel quiescence. Inhibition of Rho-kinase switches established tubules to a sprouting phenotype that is Rac dependent. The work described suggests that actomyosin contractility, is a key determinant of angiogenic sprouting.



George Demetri (Dana-Farber Cancer Institute and Harvard Medical School, Boston) provided an overview of recent advances in the clinical use of signal transduction inhibitors, including the tyrosine kinase inhibitors imatinib (the BCR-Abl/c-Kit inhibitor), which has had excellent results in leukaemia and gastro-intestinal stromal tumours (GIST), and dasatinib (the dual BCR-Abl/Src inhibitor). The merits and issues associated with the clinical use of these, and other, molecular targeted agents were discussed. Interesting aspects included the re-engineering of imatinib to improve efficacy while reducing toxicity. There was an interesting discussion of the rationale for deciding how to combine new signal transduction inhibitors, and how best to evaluate their actions thinking about the right biomarkers and clinical endpoints. This talk was pertinent to a recurring theme of the meeting, *i.e.* evaluation and optimisation of molecular targeted therapies in the clinic.



Gordon Mills (MD Anderson Cancer Centre) rounded off the meeting with an excellent overview of the current big science omics approaches to addressing cancer biology with respect to predicting therapy response and patient survival. The enormous benefits of these approaches were balanced against the massive complexities in data handling, storage and analysis. Examples were given of how prediction using bioinformatics could already be helpful. However, the results generated still needed much verification. His groups recent work on establishing reverse-phase protein arrays to examine the combined proteome and phospho-proteome was also covered. Considerable progress has been made for a number of key cancer targets but there is still some way to go before most of the proteome can be said to be available for this type of analysis. The issues of understanding how individual proteins and their phosphorylation status are affected by tissue handling (length of time to fixation, methods of fixation and storage etc) as well as characterisation of antibodies available for each protein has required careful control. Overall, we have entered an exciting new era of drug development which will become increasingly dependent on bioinformatic predictions of response in individuals through novel high-throughput screening technologies.

Cancer Research at Nottingham (CRN) Summer School and EACR / BACR Symposium

University of Nottingham, U.K. 20th - 22nd June 2007

The fourth annual CRN Summer School “New Developments in Translational Research” and the equally popular EACR-BACR Symposium which follows took place from June 20th-22nd 2007. Sponsorship and support for the events from the British Association for Cancer Research (BACR), European Association for Cancer Research (EACR), Cancer Research U.K and the Association for International Cancer Research (AICR), along with ALMAC and Merck Biosciences is gratefully acknowledged.

CRN Summer School: ‘New Developments in Translational Research’

The Summer School followed the format of the previous year, mixing teaching (overview) presentations on contemporary topics with practical demonstrations of cutting-edge technology and equipment.

The first day focused on the design and therapeutic assessment of new cancer modalities. Charlie Laughton surveyed the pros and cons of a number of alternative approaches to drug discovery, then Tracey Bradshaw gave an overview of target-directed drug discovery, the predominant approach now used by the pharmaceutical industry. Sue Watson completed the morning session describing a number of in vivo models currently used in cancer research, and the increasingly sophisticated imaging technology available to support them. The afternoon session began with a talk from Fred Sablitzky on transgenic mouse, embryonic stem cell, and gene targeting technologies, then Jim Murray illustrated the realities of diagnostics developments – commercial and practical considerations may be at least as important as ‘clever’ science in getting a diagnostic test accepted. The afternoon tours and demonstrations covered computational methods in drug discovery and development, medicinal chemistry and structural biology. To wrap up, the major themes of the day were summarised in a review lecture given by Alan Perkins.

The second day focused on new target discovery and validation, and began with an overview of microarray (post genomic) technologies by Paddy Tighe. Peter Shaw then discussed proteomics, providing an overview of the principles, practicalities and perspectives involved in the rapid identification of proteins within biological samples. Next, Anna Grabowska presented a review of molecular technologies for target validation, focusing on methodologies for manipulating gene expression levels and for measuring protein expression. A wide-ranging discussion of the use of tissue microarrays, immunocytochemistry and image analysis was presented by Ian Ellis. The afternoon began with a talk from Stewart Martin, who overviewed the assessment of in vitro systems, encompassing cell proliferation, cytotoxicity, apoptosis and angiogenesis assays. Tim Gant then discussed how the varying genomics techniques discussed earlier in the day found practical applications in Cancer Research. The afternoon demonstration sessions featured a range of biological techniques, including flow cytometry, microarray technologies and confocal microscopy, then the events of the day and the theme of target discovery and validation were encapsulated in an summary presentation by Anne Willis.

All the speakers and demonstrators should be congratulated for their expertise in providing broad overviews of important themes in contemporary translational cancer research. The feedback from delegates was overwhelmingly positive, and it is clear that this annual event fulfils a valuable role in the education and training of cancer researchers.



EACR / BACR Symposium: 'Cancer Drug Discovery, Development and Evaluation'

For the last three years, the 1-day symposium on cancer drug discovery, development and evaluation that follows the summer school has provided an important opportunity to showcase the translation of recent advances in our understanding of the cellular and molecular biology of cancer into targeted therapeutic products providing real clinical benefit over existing therapies. This year's event, on the 22nd June, continued this theme and proved the most popular so far, being attended by about 100 delegates from the U.K. and overseas.

The morning session, chaired by **Richard Marais** (Institute for Cancer Research, Sutton, UK), started with two talks dealing with innovative treatment approaches in radiation oncology. **Verena Jendrossek** (Institute for Cell Biology, University of Duisburg-Essen, Germany) introduced the field in a talk entitled "Molecular radiation oncology: Targeting cell death pathways to overcome treatment resistance". She first described signalling pathways of radiation-induced cell death and associated resistance mechanisms of tumour cells and then gave several examples of molecularly targeted drugs which are actually tested in preclinical investigations and clinical trials in combination with ionising radiation. Next **Kaye Williams** (University of Manchester) in her talk "Therapeutic opportunities targeting hypoxia and HIF" discussed how hypoxia in tumours is associated with aggressive disease and treatment resistance. However a number of therapeutic approaches are being developed that can selectively target this tumour specific phenomenon. The presentation centred the exploitation of the transcription factor HIF-1 (hypoxia-inducible factor-1) in cancer therapy. HIF-1 plays a crucial role in the adaptation of cells to low oxygen tension. It is activated under hypoxic conditions and induces the expression of over 70 proteins associated with survival, angiogenesis, proliferation and metabolism, amongst others. HIF-1 can be targeted in two ways in cancer therapy- it can be used to drive the expression of exogenous cytotoxic and/or drug activating proteins specifically in hypoxic cells or it can be inhibited to alter how cells respond to the hypoxic environment. Data presented demonstrated that both approaches are therapeutically effective in pre-clinical studies, especially when combined with standard chemo- or radiotherapy where hypoxia and/or HIF-1 expression are associated with poor therapeutic response. **Joan Seoane** (Vall d'Hebron Research Institute, Spain) then described his research on the oncogenic role of TGF-beta in glioma. The TGF-beta oncogenic response has prompted the design of several compounds to be used as anti-TGF-beta therapies in cancer. However, it is crucial that the molecular pathways implicated in the malignant role of TGF-beta in oncogenesis are properly understood in order to select the patient population that may benefit from an anti-TGF-beta therapy. Joan's group has demonstrated that high TGF-beta-Smad activity is present in aggressive, highly proliferative gliomas and confers poor prognosis in patients with glioma. His work has also revealed that human glioma stem cell self renewal is regulated by TGF-beta. Glioma stem cells are considered to be responsible for glioma initiation, maintenance and recurrence, and hence are optimal therapeutic targets against this deadly disease. The morning finished with a talk from **John Hickman** (Institut de Recherches Servier, France) on targeting cancer cell survival mechanisms with small molecules. Suppression of apoptosis is one of the Hallmarks of cancer. Tumour-associated evasion of apoptosis stimulated by drug treatment, of either targeted therapies or antiproliferative cytotoxics may in addition be a major contributor to drug resistance. Targeting the increased "survival potential" of cancer cells permits selective tumour cell killing by coupling tumour-associated stimuli for the activation of apoptosis (genomic damage, aberrant expression of oncogenes) to cell death: these "drivers" of apoptosis are not present in normal cells, where there is no genomic instability nor aberrant oncogene expression. BCL-2 binds to and inhibits the pro-apoptotic activity of BAX through the binding of the alpha-helical BH3 domain of BAX to a hydrophobic pocket in BCL-2. Guided by structural biology (nmr and X-ray crystallography), elegant drug discovery programmes to generate BH3 mimetics – effectively small molecule inhibitors of this key protein-protein interaction - are providing potent and selective inducers of apoptosis in some tumours. These molecules are powerful cytotoxics but have a wide therapeutic margins in animal models. They are also able to potently synergise with minimally toxic targeted therapies, such as kinase inhibitors, since kinase inhibition initiates the canonical apoptosis pathways, inhibited by BCL-2 family members. Clinical trials of BCL-2 inhibitors are now in progress.

In the afternoon session, chaired by **Peter Fischer** (Nottingham), **Stephen Neidle** (School of Pharmacy, London) presented his recent work on "Structure-based design of small molecules targeting G-quadruplexes". DNA is the oldest therapeutic target in cancer. Descendants of the original mustard alkylators are still in clinical use, and have been joined by many other covalent and non-covalent DNA binding small molecules, some of which (such as cisplatin in testicular cancer), have been of major clinical benefit. However, it is also clear that cytotoxic therapy is unable to produce further significant improvements. The large amount of

knowledge that we currently have about the molecular basis of cancer has resulted in a fundamental change of emphasis, so that (small molecule) cancer drug discovery is now almost entirely concerned with targeting proteins and enzymes that are directly involved in initiating or maintaining the malignant phenotype. In his talk Stephen emphasised that this does not mean DNA is no longer a valid target. Cancer-selective proteins can be targeted either at the protein level – the preferred approach in industry at present – or at the individual gene level. Specific DNA sequences, for example in promoter regions, can be induced to form high-order guanine quadruplex structures. These structures may be stabilised by new types of DNA-binding ligands, which as a result modulate expression. He has recently characterised the unique fold of a quadruplex in the c-kit promoter sequence, which presents novel opportunities for small-molecule based selective inhibitors of this important target. Quadruplexes are also of significance in eukaryotic telomeres; their induction by small molecules can inhibit the action of the key immortalisation enzyme telomerase. Approaches to the design and development of these small-molecule quadruplex-binding agents were also discussed. The day finished with a talk from **Malcolm Stevens** (University of Nottingham), who very kindly stepped in at short notice for Ivan Dikic, who was unavoidably unable to attend. Malcolm provided a ‘chemist’s eye view’ of the process of translational research, in a wide-ranging and entertaining review of his own contributions to this area over a long and distinguished career. In an era when drug design and development is sometimes seen as a rather subsidiary activity to the investigation of cancer biology, his talk emphasised the many pitfalls and potholes along the road from “a target wannabe” to a drug molecule that really makes it in the clinic, and provided strong support for a higher profile for chemistry in the future, an aspiration that now seems to be gaining support in the guise of chemical biology and chemical genomics focussed initiatives.

The day provided the audience with a fascinating insight into cancer drug discovery and development from the bench to the clinic, and the speakers should be congratulated on the quality and breadth of their presentations, which will serve as an inspiration to researchers to more effectively translate basic research findings into therapeutic products that ultimately benefit the cancer patient.

Stewart Martin and Charlie Laughton



Genes & Cancer

December 2007, Warwick

As with previous meetings, the 2007 Genes and Cancer meeting proved to be an excellent conference, with a high calibre lineup of speakers who gave a series of outstanding talks. This year there were a record number of posters which created a vibrant poster session. The quality of the posters was very high making judging for the poster prize particularly difficult.

The conference was split into four sessions, loosely based around common topics. The first session was centred on various aspects of gene expression in cancer. **Barbara Graves** opened the conference with a talk on the ETS family of transcription factors. These are associated with various tumourigenic processes, but it is currently unclear how different family members give specific effects. By using ChIP-chip analysis Barbara nicely demonstrated that both the normal ETS transcription factors and oncogenic fusion proteins regulate overlapping and distinct sets of target genes. Subsequent talks focussed on the NF κ B pathway (by **Vishva Dixit** and **Michael Hottiger**) and highlighted the importance of posttranslational modifications such as acetylation in controlling transcription factor activity and polyubiquitin chains in promoting the assembly of signalling complexes. The theme of acetylation and ubiquitination was maintained through structural insights into histone acetyl transferases (**Ronen Marmorstein**) and the role of the E3 ligase arcadia in Smad pathway signalling (**Caroline Hill**). Insights into the control of p63 by ubiquitin-dependent proteolysis were provided by **Gerry Melino**. The last talk in this session by **Bob White** presented the incredible finding that overexpression of a tRNA molecule, and hence an increase in protein synthesis, is sufficient to cause cancer.

Steve West gave a fantastic keynote lecture focussing on defects in DNA repair and recombination in human diseases, and in particular nicely dissected the molecular mechanisms underlying neurodegeneration due to impaired repair of damaged DNA resulting from defective APTX function. Subsequent talks extended this theme of DNA repair defects in cancer with initial focus on the role of ubiquitination of RNA polymerase II in controlling the fate of polymerase stalled at DNA damage sites (**Jesper Svejstrup**). **Ashok Venkitaraman** discussed the interplay between BRCA2 and the Rad51 recombinase and demonstrated that Rad51 has an important role after the completion of S phase and hence DNA replication. Further studies on DNA replication demonstrated how cyclin-dependent kinases can control replication origin firing through promoting regulatory protein complex assembly (**John Diffley**). Further talks illustrated how double strand breaks initiate signalling events in the cell (**John Rouse**) and how kinetochores are controlled through microtubule attachment during the normal cell cycle (**Tomo Tanaka**).

The third session was on signalling and metastasis and **Peter Friedl** gave a fantastic talk with excellent movies that illustrated how tumour cells can metastasise by either amoeboid or mesenchymal like migration mechanisms. Interestingly, when adopting amoeboid like movement in dense matrices, the strain on the nucleus generated stress that gave rise to DNA damage foci, which is likely to be important in the context of cancer development. Further insights into metastatic mechanisms were provided by **Anne Ridley** in her discussion of RhoE and its activation. **Owen Samson** illustrated the importance of *myc* upregulation in response to Wnt signalling in colon cancer. Finally, we got a glimpse of the power of mass spectrometry applied to phosphoproteomics (**Forest White**). Studies focussed on the HER2 and EGFR receptors and how differing amounts could give rise to different signalling responses. This in turn could be used to predict key nodes for therapeutic intervention.

The final day revolved around senescence and apoptosis. **Eyal Gottlieb** illustrated how phospholipids and their aberrant metabolism could disrupt apoptotic mechanisms. The apoptotic theme was continued by **Pascal Meier** who used a Drosophila system to demonstrate the importance of IAP as a ubiquitin E3 ligase which causes polyubiquitination of caspase and hence its inactivation. An alternative form of death, mediated by lysosomes was also discussed and the importance of upregulation of Hsp70 proteins in promoting cancer cell survival by stopping lysosomal permeabilisation was illustrated (Marja Jaattela). Finally, two talks focussed on senescent pathways and their disruption in cancer cells. Two important findings were that PKC δ plays an important role in oncogene-mediated senescence through blocking cells in G2 (**Eiji Hara**) and that senescent cells are associated with a persistent DNA damage response (**Fabrizio d'Adda di Fagnana**).

Overall, the meeting was uniformly excellent and addressed many of the important key molecular questions in the cancer research field. We look forward in anticipation to another excellent meeting next year which will be the 25th consecutive annual meeting that has followed cancer research developments since people first began to begin to apply molecular biology to address this important area.

Andy Sharrocks (Chair of the organising committee, 2007)

BACR Award Presentations at NCRI Cancer Conference

October 2007, Birmingham



The BACR/AstraZeneca Young Scientist Frank Rose Award

was presented by Owen Sansom
University of Glasgow, Cancer Research UK Laboratories

Abstract

C-MYC deficiency rescues apc deficiency, prevents wnt dependent intestinal regeneration and is required for the dna damage response *in vivo*

A.Cole¹, V Meniel², TJ Phesse² JA Wilkins¹, V Muncan³, D.Athineos¹, H Clevers³, K Neufeld⁴, AR Clarke², Owen J Sansom¹

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The proto-oncogene c-Myc has been implicated in stem cell survival, proliferation, apoptosis and tumourigenesis within a number of tissues. Of particular interest is the role that c-Myc plays as a Wnt target gene in colorectal cancer. To elucidate the role c-Myc plays in the intestine following Apc loss, we have simultaneously deleted both Apc and c-Myc in the adult murine small intestine. Loss of c-Myc rescued the phenotypes of perturbed differentiation, migration, proliferation and apoptosis that occur upon deletion of Apc. Remarkably, this rescue occurred in the presence of high levels of nuclear β -catenin. Array analysis revealed that c-Myc is required for the majority of Wnt target gene activation following Apc loss. These data establish c-Myc as the critical mediator of the early stages of neoplasia following Apc loss.

We next investigated whether C-Myc was required for wnt dependent intestinal regeneration and found that C-Myc deficient intestines were unable to regenerate. Finally we investigated whether C-Myc is essential for the intestinal DNA damage response and found the C-Myc is essential for p53 induction and apoptosis following a range of different DNA damage lesions in the intestine. Take together our data establish that C-Myc is an essential regulator of intestinal homeostasis and tumourigenesis *in vivo*.



The BACR Translational Award

was presented by Jorge Reis-Filho, The Institute of Cancer Research, Breakthrough Breast Cancer Research Centre (photo j.Reis-Filho)

Abstract

Basal-like carcinomas: from pathology to mouse-models and beyond

Jorge S Reis-Filho, MD, PhD, MRCPATH

The Breakthrough Breast Cancer Research Centre, Institute of Cancer Research, London

Basal-like breast carcinomas (BLCs) are poor prognosis breast cancers characterised by lack of hormone receptors and HER2 expression and by the expression of genes preferentially expressed in basal/ myoepithelial cells. As patients with BLCs are not amenable to treatment with current targeted therapeutic regimens, novel therapeutic targets for these tumours would be invaluable. Our group first focused on the high prevalence of EGFR expression in BLCs. Owing to the reported efficacy of EGFR tyrosine kinase inhibitors in tumours harbouring either *EGFR* activating mutations or gene amplification, we investigated whether one of these mechanisms would drive EGFR expression in BLCs. We found that although *EGFR* activating mutations are exceedingly rare in BLCs, *EGFR* gene amplification is found in 1/3 of cases with EGFR overexpression.

BLCs are remarkably similar in phenotype to 70-80% of tumours arising in *BRCA1* mutation carriers. We have demonstrated that *BRCA1* pathway is dysfunctional in BLCs, however the mechanisms leading to the significant reduction of *BRCA1* levels in BLCs vary: in sporadic invasive ductal BLCs, this seems to be due to overexpression of *ID4*, a negative regulator of *BRCA1*, whereas in metaplastic breast cancers, a rare type of BLC, *BRCA1* inactivation is due to gene promoter methylation. Consistent with this, pathological analysis of tumours arising in the conditional mouse model *BLG-Cre;Brca1^{F22-24/F22-24};p53^{+/-}* revealed that 78% were of basal-like phenotype and 88% showed metaplastic elements. Taken together, these results suggest that *BRCA1* pathway dysfunction is paramount for the biology of BLCs. Targeting defects in the *BRCA1* pathway with platinum based chemotherapy agents or PARP inhibitors or inhibiting *EGFR* pathway with specific tyrosine kinase inhibitors may provide novel therapeutic strategies for the management of BLCs.



The BACR Hamilton-Fairley Young Investigator Award

for the best poster presentation was won by Christopher Morrow, PICR University of Manchester

Abstract

The effect of PI3-kinase inhibition on the efficacy of chemotherapeutic agents used to treat colorectal cancer.

Christopher Morrow, Cristina Martin-Fernandez, Juliana Bales, Arkadiusz Welman, Caroline Dive Paterson Institute for Cancer Research, University of Manchester, United Kingdom

Class IA phosphatidylinositol 3-kinases (PI3Ks) are lipid kinases that, usually in response to growth factor stimulation, phosphorylate PtdIns(4,5)P₂, converting it to PtdIns(3,4,5)P₃. The generation of this secondary messenger causes the activation of AKT/PKB which, in turn, promotes cell survival, proliferation and growth, all characteristics important in tumorigenesis. Indeed, many tumours exhibit increased PI3K signalling, either as a result of aberrantly activated receptor or non-receptor tyrosine kinases or, more directly, due to altered levels or mutation of PI3K pathway components. Therefore, class IA PI3K inhibition represents an attractive potential therapeutic strategy for the treatment of cancer.

In order to determine the effect of inhibiting PI3K in colorectal cancer we have generated HCT116 and HT29 cells which can be induced to express a dominant negative subunit of PI3K, $\Delta p85\alpha$. Upon induction of $\Delta p85\alpha$ there is a decrease of phosphorylated AKT/PKB and GSK3- β , indicating that PI3K signalling has been impaired. Furthermore, both *in vitro* and *in vivo*, there is a reduction in the growth rate of the cells / tumours after $\Delta p85\alpha$ induction, which correlates with a reduction in cell proliferation, rather than an increase in apoptosis. Therefore, we have a robust genetic system by which to study the inhibition of PI3K signalling in colorectal cancer cells, without the issues of off-target effects inherent to studies using small molecule inhibitors. Here we will report findings on the effect of expressing $\Delta p85\alpha$ on the efficacy of chemotherapeutic agents commonly used to treat colorectal cancer, specifically oxaliplatin, 5FU and SN38, the active metabolite of irinotecan.

BACR Interview: Professor Len Seymour (Hybrid Systems)

In the second of our series of interviews with BACR members who are commercialising their research, Dr. Nick Miller from Beremans Ltd (www.beremans.com) interviews Professor Len Seymour, whose research is being commercialised through the vehicle of Hybrid Systems Ltd (www.hybridsystems.co.uk). Professor Seymour is Professor of Genetic Therapies in the Department of Clinical Pharmacology, University of Oxford, Head of the Cancer Research UK Gene Delivery Group, President of the British Society for Gene Therapy, and Supernumerary Fellow of Wolfson College, Oxford.



NM: Leaving aside the contract research and reagent provision aspect of Hybrid Systems, I believe the company is focussing on commercialisation of an enabling technology based on the polymer poly(hydroxypropylmethacrylamide). In particular, the company is looking at applications of the polymer in terms of coating recombinant virus particles in order to shield them from the immune system and from interactions with other non-target cells. This is anticipated to prevent clearance, increase serum half-life, and allow lower titres of virus to

be used in a therapeutic context. In particular, Hybrid Systems expects the polymer coating to facilitate use of recombinant viruses in two distinct but related areas, namely virotherapy (treatment of cancer by injection of a replication-competent lytic virus in order to cause a spreading infection that would eliminate disseminated cancer) and cancer vaccines (recruitment of an immune response against the cancer, by expression of an appropriate antigen in an appropriate host cell).

LS: Yes, that's right, although I should also say that the Hybrid Systems approach in fact is applicable to a very broad range of vaccines, not just cancer vaccines. It turns out that much of our early work is directly applicable to vaccine development, and the vaccine side of our business is becoming increasingly important. In addition, we are refining a number of different polymers, not just one.

NM: Can you tell us a little about how you came to discover the potential for the Hybrid Systems polymers in viral masking applications?

LS: The trigger was the discovery of unexpected activity in preparations of polymer-coated viruses. The anticipation had been that coating a virus with a synthetic polymer would kill it, but our work showed that if you introduced a novel ligand into the polymer coating, the coated virus could infect cells via new ligand-receptor interactions. This raised the possibility of constructing stealth viruses that could enter cells by ligands of our choice. We have since discovered that the adenoviral protease activated after cell entry retains its ability to cause shedding of the viral capsular proteins, along with the polymer bound to the capsular proteins. So the polymer system provides the ideal combination of features, in that it shields the virus while it is outside the cell, but does not interfere with viral functions post-cell entry, such as nuclear translocation and gene expression.

NM: What happens to the polymer in the body – for example, is it metabolised, excreted unchanged, or accumulated in tissue? How much clinical or animal safety data is there?

LS: The polymer is essentially non-biodegradable, so pretty much nothing happens to it in the body. In any case, we make the polymer chains small enough for them to be rapidly excreted. In terms of safety, this polymer has been through Phase I and II clinical trials with patients receiving gram doses of polymer with no apparent safety issues, and we are using quantities of polymer far smaller than that. We don't anticipate any significant safety concerns with this system.

NM: Could normal stealth / targeted liposome technology compete with your polymer?

LS: The problem with most systems that seek to deliver a drug cargo by targeting particular receptors is that the therapeutic effect may be limited by the number of receptors. Usually the numbers of cell-specific receptors are just not sufficient to internalise a dose of cytotoxic agent in quantities great enough to mediate a therapeutic effect, at least not with current cytotoxic agents. Our virotherapy approach has an intrinsic amplification step – once the virus enters a cancer cell, it replicates and provides a spreading lytic infection. Approaches which provide this type of amplification have obvious advantages over approaches which are limited by the numbers of available receptors on target cells.

NM: Is Hybrid Systems limiting itself to commercialising the polymer coating as an enabling technology for virotherapeutic or vaccine products developed by other companies, or is there any intention to generate intellectual property in, for example, proprietary targeting ligands for a virotherapy, or novel antigens for a vaccine?

LS: No, we are focussing on refining the enabling polymer technology for application to therapeutics or vaccines developed by other companies. It's a bit like wheels for sports cars – manufacturers of sports cars need good wheels to get optimal performance from their products, and some businesses focus on making the wheels. Hybrid Systems products are analogous to wheels, not the complete sports car.

NM: So the commercial potential of your technology is linked to that of virotherapy and vaccine products developed by other companies. How would you go about putting a relative value on your polymer technology vis-à-vis the various components of a virotherapy, for example, the vector backbone or the targeting ligand? I

ask this because one of the problems that dogged the commercialisation of gene therapy technologies in the 90s was the royalty stacking issue, whereby if you need several disparate technologies to make a gene therapy work, and if each technology comes from a separate commercial source each of whom demands a royalty on product sales, you may get a stack of royalties that makes the end product commercially untenable.

LS: A virotherapy product will need our delivery technology for intravenous administration, or it will be rapidly cleared by the innate immune system; and our technology will only form part of a therapy in conjunction with a virus. Both components are necessary, and once there is the opportunity to turn a combination of the two into a product, people will have to discuss and agree on commercial terms. I would say that at present the major problem to overcome is demonstration of proof-of-principle of virotherapy in a clinical context. Once that happens, everything else will rapidly fall into place.

NM: Moving away from technology issues, I think a lot of BACR members would be interested in learning about how you started your company, and what made you want to commercialise your academic research.

LS: It was largely precipitated by a PhD student who was capable and commercially motivated. Prior to that I had been writing patents on my own from time to time, but it really needed a team of two to make things happen. Our first point of contact with the commercial world came when we entered a BBSRC business plan competition – disappointingly, we only came third, but it was still very helpful, because it opened our eyes to the opportunities and problems involved in the commercialisation of science. Going down the commercial route seemed like a big step at the time – I felt like I was sullyng myself in some way, almost compromising my academic principles. I think this is a peculiarly British idea, that academic research is done for the love of knowledge and that money is somehow distasteful – but this is misguided, because if you don't patent and protect your research, it will be difficult to exploit it and use it to make a difference in the real world. And if you patent your research and take it forward commercially, there is a chance that you might see some reward from it – which seems appropriate, because scientists are not paid that well, and why should they not enjoy some return from their discoveries? I think that every group leader should make efforts to foster and exploit commercial links.

NM: What advice would you give other BACR members who might wish to get involved in technology commercialisation?

LS: I think that one of the problems in UK biotech in the past has been that a few scientists have overstated their data. This has resulted in a number of commercial failures and disappointments, and has damaged the credibility of the sector as a whole. In addition, it has called into question the integrity of some scientists. So one piece of advice would be, don't be tempted to overstate data and compromise your academic integrity. Another would be to stand up for yourselves in discussions with VCs. I have come across some investors who demand that the scientist puts his or her house on the line in return for business finance. That is ridiculous – the relationship is that the scientist contributes his time, expertise and inventions, while the VC contributes some of the fund that he is paid to manage. The scientist's house or other assets do not enter into the equation. Finally, although of course you hope that your business will make a major breakthrough and provide significant financial rewards, don't underestimate the value of a smaller additional income source, which may be a more realistic goal for many business propositions.

NM: What would you have done differently if you had to do it over again?

LS: Our model has been different from that of most other biotechs, in that we have only ever accepted about £250,000 investment money, which was from a seedcorn Challenge fund. Instead, from the beginning we have looked to raise financial support through commercial partnerships. Our reasoning was that commercial partnerships are a valuable source of expertise, market intelligence, route to market, and so on, which you just don't get from VCs. We entered into a relationship with Schering early on, which has been very useful to us. We have also got various monies through competitive grant applications, applications for EU funds, and similar sources. This is a slow method of growing the company, but frankly it suited the pace of development of the technology. However, we are now getting to the stage where we may consider looking for investor money. I think that our model has been correct and appropriate for what we were trying to achieve, and I would not change the way we went about things. The only thing that might have been done better would perhaps have



been to get a high-profile, experienced CEO, even on a part-time basis, to help us steer the commercial development of the technology faster and earlier in time. Also, having the company in closer physical proximity to my academic lab would have helped, but on the other hand the current location allows the business to take advantage of bioincubator facilities, so there are pros and cons to both locations.

NM: Do you have any regrets?

LS: No, none. Hybrid Systems has not got in the way of my academic research, in fact it has helped it, in that it provides pointers on how things should develop.

NM: Are you seeking collaborations with other BACR members? Do you have any job opportunities in Hybrid Systems for BACR members?

LS: Yes, we are looking for people with vaccine experience. Although historically Hybrid Systems has focussed on virotherapy, the vaccine arm of the company seems likely to grow in importance, and we need somebody to lead that part of the business. We would be very interested in hearing from anybody with experience in developing antibody-resistant, cell-selective viral vaccines.

NM: Are there any final comments you'd like to share with BACR membership on the topics we have discussed?

LS: I suppose my experience suggests that when scientists step into the commercial arena, at first they don't know how much they don't know. We had to learn a lot of things that perhaps we would rather have learnt in a different way, rather than by learning from our mistakes. So I would say that it is advisable to talk to people with appropriate experience early on, and get advice on issues like tax credits and so forth. Learning from mistakes is not always the best way to go about things.



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Mariano Barbacid (Spain)
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Rakesh Jain (USA)
Tony Kouzarides (UK)

Paul Nurse (USA)
Martine Piccart (Belgium)
Howard Scher (USA)

Dates to Remember

Monday 3 March:
Abstract Submission Opens

Monday 19 May:
Abstract Submission Closes

Monday 2 June:
Registration Opens

Thursday 31 July:
Earlybird Registration Closes

Monday 1 September:
Registration Deadline



SPONSORED MEMBER'S EXCHANGE FELLOWSHIPS REPORTS

BACR EXCHANGE FELLOWSHIP – Visit to Cuba



Dr. Annette Byrne
*UCD School of Biomolecular and
Biomedical Science.
The Conway Institute
Dublin*

This report concerns collaborative work between the Dr Annette Byrne & Professor William Gallagher (UCD Conway Institute, University College Dublin) and the research group of Dr. Rolando Perez (Centre for Molecular Immunology (CIM), Havana) which was carried out by Dr Byrne between Dec 2006 and Feb 2007 while visiting CIM This visit was generously supported by a BACR Exchange Fellowship.

Metastatic breast cancer is the leading cause of death from cancer among women worldwide, accounting for more than 400,000 deaths per year¹. Epidermal growth factor receptor (EGFR) is believed to be an important effector of tumour metastasis in many cancers, including breast cancer². In very recent clinical studies with breast cancer patients, EGFR expression has now been associated with higher proliferation, genomic instability, HER2 over-expression, poor outcome and resistance to adjuvant hormonal and chemotherapy^{3,4}. Over-expression of EGFR during breast cancer metastasis has also been reported⁵. These studies provide an important rationale for studying anti-EGFR agents in metastatic breast cancer patients.

A crucial consideration for the successful translation of anti-EGFR therapeutics to the clinic for the treatment of breast cancer is the ability to understand the precise mechanisms involved in the anti-metastatic capacity of these new therapeutics. Most recently, it has emerged that passive 'immunotherapy' with mAb can further promote a "secondary" active specific anti tumour immunity and subsequent inhibition of metastasis. *In vivo* experiments⁵⁻⁷ studying the anti-metastatic effect of anti EGFR mAbs to date are limited, as they have been conducted with xenografts in nude mice. In this instance the utility of the nude mouse model is negligible, as these animals do not possess conventional T cell repertoires effectively precluding the assessment of immunologic mechanisms. A much more relevant pre-clinical strategy for the *in vivo* investigation of the anti metastatic capacity of mAbs would be the selection of immunologically normal individuals in a complete autologous scenario.

Dr. Rolando Perez and colleagues at the CIM currently hold the only globally available Mab specific to the murine EGFR extracellular domain, i.e. the 7A7 Mab⁸. Understanding the immunological and biochemical mechanisms associated with the anti-metastatic effect of anti-EGFR Mabs is a crucial step to optimising the use of these therapeutic agents and a task for which there is currently no substitute for the 7A7 Mab. The overall aim of Dr Byrne's visit to CIM, was to validate the utility of the 7A7 antibody for investigating secondary anti-metastatic immunological mechanisms of Mabs used to treat metastatic breast cancer.

Using 4T1 and M3 murine mammary cells, we confirmed expression of EGFR (Her 1) in both cell lines by Western Blot analysis noting a higher expression level in 4T1 cells. In addition, we demonstrated complement-dependant cytotoxicity (CDC) induced apoptotic effects in both cell lines again, with indication of a higher sensitivity evident in 4T1 cells. A similar result was seen when antibody dependant cytotoxicity (ADCC) was examined in both cell lines (ie more effect in 4T1 cells). These data argue for the use of 4T1 model for future *in vivo* and *in vitro* studies to assess anti-metastatic immunological methods of 7A7 antibody.

This award afforded Dr Byrne the opportunity to collaborate with a dedicated and experienced team of researchers focused on developing novel cancer immunotherapeutics and vaccines. The applicant had the opportunity to confirm the utility of 7A7 antibody for investigating secondary anti-metastatic immunological mechanisms of Mabs used to treat metastatic breast cancer. Moreover, during the visit there was the

opportunity to plan in detail future collaborative objectives, as well as discuss additional collaboration opportunities to generate novel anti-cancer monoclonal antibodies. Sincerest thanks to BACR for facilitating this important visit.

BACR EXCHANGE/TRAVEL FELLOWSHIP – Visit to Germany



Dr Sarah Haywood-Small
*Academic Unit of Surgical Oncology
University of Sheffield*

Munich is home to the Oktoberfest (known as the ‘Wiesn’ to the locals). This is the largest public festival in the world and attracts more than six million visitors each year. The celebrations began on 22nd of September, the same day that I arrived in Munich, and continue for 2 weeks. I was excited about spending 3 weeks working in the prestigious laboratory of Professor Gabriele Multhoff after obtaining a BACR Travel Fellowship. However, for my fellow travellers, the festivities began in the departure lounge of Manchester airport, giving me my first glimpse of lederhosen before we even boarded the flight!

The Multhoff laboratory has recently moved to the Technische Universität München which was recently declared as being one of Germany’s three ‘elite’ universities. I joined Professor Graham Pockley (Immunobiology Research Unit, University of Sheffield) who was undertaking a Visiting Professorship in the same laboratory to undertake a programme of work to investigate the influence of the stress protein Hsp70 on the activity of CD4⁺CD25⁺ regulatory T lymphocytes. This was an excellent opportunity to gain experience in the laboratory which originally identified the selective expression of Hsp70 on tumour cells. This laboratory has also demonstrated that membrane Hsp70 can act as a tumour-specific recognition structure for natural killer (NK) cells. My current studies at the University of Sheffield are aimed at providing insight into factors that influence the development and function of immunoregulatory T cell populations in cancer, and the influence of these cell populations on the induction of protective anti-tumour immunity. Given that soluble and cell membrane-bound Hsp70 can directly activate the cytolytic and migratory capacity of NK cells, we proposed that Hsp70 might influence the functional capacity of CD4⁺CD25⁺ regulatory T cells and thereby the development of anti-tumour immunity.

We evaluated whether Hsp70 can influence the activities of naturally-occurring CD4⁺CD25⁺ regulatory T cell populations and I acquired expertise in the measurement of cell surface expressed Hsp70. This Fellowship allowed the generation of compelling evidence to suggest that Hsp70 might indeed influence anti-tumour immunity and these findings are currently being prepared for submission. We feel that these studies are of clinical relevance, as they provide some insight into the regulation of T cell and NK cell mediated anti-tumour immune responses. The data generated are also being used to support competitive project grant applications.

I would like to thank everyone involved for their kind hospitality in the bustling city of Munich. I soon became accustomed to the unique dialect and had a wonderful time experiencing the colourful Bavarian lifestyle, which of course included frequent visits to the Oktoberfest! The enchanting fairytale castle of Neuschwanstein was an unforgettable day trip and well worth the journey. I would like to thank the BACR for their continued support, as without the Fellowship I would not have been able to take advantage of such a fantastic opportunity. I would highly recommend other BACR members to consider submitting Exchange Fellowship applications.

BACR TRAVEL EXCHANGE REPORT: Visit to Australia



Noor Atatreh
University of Manchester
School of Pharmacy &
Pharmaceutical Sciences

Src signalling and transduction, which involves protein phosphorylation, is directly involved in the processes of cell growth, cell cycle, malignant transformation and cell migration. It is thought that Src is linked to different diseases, including epithelial cancers. c-Src levels are elevated in colon cancer cells compared to non-malignant cells. Furthermore, there is a direct correlation between metastatic behaviour of colon cells and Src activity. The aim of my PhD project is to design small molecule inhibitors that selectively target the SH3/praline-rich complexes that are linked to the kinase-independent function of c-Src protein. Such inhibitors are potentially of use in, for example, colon cancer.

Based upon the crystal structure of an active form of Src (PDB entry code 1Y57, resolution 1.91 Å), flexible 3D ligand virtual screening was performed at the University of Manchester to generate a diverse set of potential small molecule leads. For compound docking of the ZINC purchasable database of ligands, the genetic algorithm-based docking program GOLD was employed. Selection of a shortlist of compounds was aided by the use of pharmacokinetic and drug-like filters. These hits required a high throughput screening assay, of which the fluorescence polarization (FP) technique developed for several SH3 proteins in Dr. Grant Booker's laboratory in Adelaide University, Australia was ideal.

The BACR travel grant funded my trip to Adelaide to complete FP testing of the ligands against a number of SH3-domain containing proteins including c-Src and Hck. Under the expert guidance of the Booker laboratory members, I gained experience in several biochemical techniques including handling genetically modified organisms, expressing several SH3 domains (including Src-SH3 domain) in *E. coli*, protein purification and quantification, and finally performing compound binding tests.

Fluorescence polarisation experiments were performed on a BMG Laboratories PolarStar Galaxy Plate Reader, using black BMG 96-well plates. This plate was blocked with 1% w/v casein for 2 h at 37 °C prior to conducting the experiments. Titration of the SH3-domain protein to determine the appropriate protein concentration required for the test was needed before commencing the ligand binding inhibition experiments. All compounds were tested in triplicate and the test was run for at least 5 cycles to get the correct measurement. Compound solubility was a big challenge, therefore a limited quantity of DMSO was used to overcome poor aqueous solubility of some compounds. From the FP test, one benzoquinoline derivative showed promising inhibitory action. This lead compound will be the subject of future *in vivo* testing and possible structural modification to enhance Src non-kinase inhibitory activity.

My PhD in medicinal chemistry requires several skills including computer-aided molecular design, organic chemistry and biological testing studies. Accomplishing the FP assay with Dr Booker and co-workers in Adelaide University has significantly supported my training in biological testing. This experience of a productive research collaboration in another university has been invaluable and my thanks go to Dr Booker and his lab members for their tremendous support. I am deeply grateful to the BACR for giving me this opportunity, which will have a great impact on my PhD project and future career prospects. In addition to it being a scientifically very stimulating trip, I have also appreciated the pleasant experience of living in Australia and visiting the kangaroo continent.

A Tribute to Chris Ralph Franks, MD (Lond) FACP FFPM (1 June 1937 - 9 May 2007) (BACR member 1971- 2007)



To achieve anything in research requires optimism, enthusiasm and stamina of a high order if only to overcome the slings and arrows of outrageous fortune, but all these qualities Chris had in full measure. After qualifying in medicine at Guy's Hospital in 1973 he stayed on to work in the ICRF Breast Unit on a variety of problems concerned with tumour transplantation. Despite this experience Chris never lost interest in cancer treatment and fundamentals of tumour biology.

Chris wanted particularly to improve cancer chemotherapy and this objective was strengthened by his experience as Medical Director of the Saskatchewan Cancer Center in Saskatoon, where he found the resistance of tumours to chemotherapy matched by some of the staff. Nothing daunted, Chris had an offer from Bristol Myers Squibb to act as their Medical Director for Anticancer Clinical Research covering Europe, Middle East and Africa with headquarters in Brussels; an offer he could not and did not refuse. BMS at that time had 2 new analogues of *cis* and of carboplatin in the clinic. Unfortunately, neither of them proved to be superior to cisplatin or carboplatin and consequently the company halted the project.

With another bite at the cherry, Chris accepted an offer from Eurocetus in Amsterdam as their Vice President (Medicine). The company was keen to obtain marketing approval for IL-2, a difficult task which Chris handled with aplomb, succeeding in getting PRO-LEUKIN on several European markets. However, indicators for its use were severely limited (melanoma and renal cell carcinoma) and Eurocetus was actively looking for other anticancer drugs.

Over lunch in Atlanta, Georgia, I managed to interest Chris in dexrazoxane which by then had had the most exhaustive preclinical investigations at the National Cancer Institute, Bethesda; at ICI (Pharmaceuticals) and in my lab at the ICRF as well as in a number of clinics including the Westminster Hospital where we appointed Chris as an Honorary Consultant. As a result it had become clear that dexrazoxane was highly effective in preventing the dose limiting cardiotoxicity of doxorubicin. It was not difficult to persuade someone as perceptive, enthusiastic and knowledgeable as Chris to take on the difficult task of running a multi-institutional clinical trial necessary to get dexrazoxane licensed in Europe. He also came up with the name – Cardioxane for dexrazoxane which has stuck. Getting the licensing authorities in Western Europe to approve Cardioxane was however an order of magnitude greater than anything Chris had tackled before. It is ironic that Chris (or anyone else) who was at a meeting in October 2006 dealing extensively with Cardioxane was unaware that Cardioxane had been licensed in the UK a few months before - just 35 years after the discovery of the cardioprotectant effect of Cardioxane and some 10 years after the United States FDA gave it accelerated approval. The UK license for Cardioxane was given to Chiron, the successors of Eurocetus, and for whom Chris continued as Vice President (Medicine) in Amsterdam until his retirement.

There are not many who have the tenacity and vision to see a drug through from the laboratory to the clinic to registration to the market, and to the patient - Chris Franks was one of that exclusive club and he will be greatly missed.

Professor Kurt Hellmann

July 2007

NEWS OF MEMBERS

Professor Bob Brown



Professor Bob Brown (Chair of BACR) has recently moved from the Centre for Oncology & Applied Pharmacology at the Beatson Laboratories Glasgow to a Chair of Translational Oncology at Imperial College London and Institute of Cancer Research. He will be spending the majority of his time at the Hammersmith Hospital campus (B.Brown@imperial.ac.uk), although he can be found at least one day a week at the Sutton site of ICR. Bob is continuing his Cancer Research UK programme of research on Drug Resistance and Pharmacodynamics, as well as expanding his work on epigenetics of cancer, particularly working with the Ovarian Cancer Action Unit at Imperial College.

Dr Val Brunton



Val Brunton has joined the University of Edinburgh as a Reader in Cancer Pharmacology. She will be part of the newly established Institute of Genetics & Molecular Medicine directed by Professor Nick Hastie, which is a partnership between the MRC Human Genetics Unit, Edinburgh University's Molecular Medicine Centre and the Edinburgh Cancer Research Centre. She will continue her work on developing therapeutic strategies to prevent tumour cell spread.

Professor Sue Burchill



Sue Burchill joined the Cancer Research Unit at St James's University Hospital, Leeds in 1992 to establish a paediatric oncology research group. Her achievement in original research and success in transfer and application of scientific knowledge and method from the laboratory to clinic was recognised by the University of Leeds in 2007, when she was awarded the title of Professor of adolescent and paediatric cancer research within the Section of Experimental Oncology, Leeds Institute of Molecular Medicine. She is an active member of the BACR, CCLG, AACR, SIOP and SIOPEN. The primary focus of her research is to investigate the biology of the Ewing's sarcoma family of tumours (ESFT) with the aim of identifying therapeutic targets for the development of new treatment strategies and clinically relevant biomarkers.

Professor Jeff Evans



Jeff Evans is Professor of Translational Cancer Research at the University of Glasgow and Honorary Consultant in Medical Oncology at the Beatson West of Scotland Cancer Centre, Glasgow. He has recently been appointed Honorary Group Leader (Translational Cancer Therapeutics Group) at the Beatson Institute for Cancer Research, Glasgow and Deputy Head of the Division of Cancer Sciences and Molecular Pathology, University of Glasgow. His clinical interests are in Upper GI Cancers and Melanoma, and his research interests are in the pre-clinical and clinical development of novel anti-cancer agents including molecular targeted therapies and gene therapy. He leads the Phase I clinical trials and drug development team in Glasgow, and runs the Analytical Services Unit. He is a former member of the Executive Committee of the British Association for Cancer Research.

STUDENTSHIPS : MSc Oncology

Cancer Biology – causation and treatment

The School of Molecular Medical Sciences is pleased to announce THREE Cancer Research UK sponsored studentships for the MSc in Oncology.

The MSc in Oncology, now in its 11th year of operation, is suitable for biology, biomedical and other graduates who wish to learn more about the causes and treatment of cancer, and for clinicians together with other health care professionals who require further training in the molecular aspects of oncology.

The degree is offered as a one-year full-time and two-year part-time course (day release format). The course draws upon a unique blend of scientific and clinical expertise, and benefits from strong ties between the clinic and laboratory. The course is particularly suitable for candidates wishing to pursue a research career in oncology or for candidates who wish to enter the pharmaceutical industry. The taught component, which includes subjects such as: The Molecular Basis of Cancer, Tumour Physiology, Tumour Immunology, Cancer Pathology, Radiation Biology, Cancer Chemotherapy, and Cancer Statistics & Epidemiology, partly fulfils the syllabus requirements for clinicians studying to sit Part I and Part II FRCR exams. The syllabus also meets the curriculum requirements for Higher Specialist Training in Medical Oncology. Full-time students conduct a laboratory based research project whereas part-time candidates conduct a work-based project in an oncology related subject.

Preference for the award of a studentship will be given to clinicians, those in professions allied to medicine or, if not clinically qualified, who have been at least 2 years from the date of their undergraduate degree.

Studentships will cover payment of tuition fees, a bursary for full-time students, registration fees for specified research meetings and a contribution towards the purchase of text books

Course duration: 1 year full-time or 2 years part-time (day release).



Further details:

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Informal inquiries :

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click on 'courses'

First Announcement

The Centre for Cancer Research Nottingham (CRN), in conjunction with the British and European Associations for Cancer Research (BACR and EACR), is pleased to announce the 5th annual

**Cancer Research Summer School on
“New Developments in Translational Cancer Research”
AND
1-day International Symposium on
“Cancer Drug Discovery, Development and Evaluation”**

The 2-day Summer School will be held on **18th and 19th June 2008** at the University of Nottingham and will be followed by the 1-day Symposium on **20th June 2008**.

Individuals can register for events separately or as a combined package. The Summer School will follow the highly successful format of previous years, mixing teaching (overview) presentations on contemporary topics in the field with practical demonstrations of cutting-edge technology and equipment. Early registration is advised. A number of places have been reserved for BACR and EACR members until 30th March.

Invited speakers at the 1-day symposium include:

Heiner Fiebig (Universitätsklinik Freiburg, Freiburg, Germany)

Michelle Garrett (Institute of Cancer Research, Sutton, UK)

Nadia Zaffaroni (Istituto Nazionale dei Tumori Milan, Italy)

Doriano Fabbro (Novartis Institutes for Biomedical Research, Switzerland)

Karol Sikora (Imperial College and Medical Solutions PLC, UK)

Juliane Jurgensmeier (AstraZeneca Pharmaceuticals, Cheshire, UK)

Claus Belka (Department of Radiation Oncology University of Tübingen, Germany)

Registration fees, that cover attendance, food and refreshments, are:

Summer School and Symposium: £150/£50 (Full rate/Student rate)

Symposium only: £70/£30 (Full rate/Student Rate).

Full programmes and registration details, will be available shortly and can be viewed either via the BACR or EACR websites (www.bacr.org.uk and www.eacr.org respectively). A limited amount of Travel Bursary Awards are available to non-UK based participants. Poster Prizes: 1 Winner and 2 “Highly Commended” Awards will be made on Friday 20th June 2008.

Further information is also available from: **Jane Doughty** jane.doughty@nottingham.ac.uk and **Kathryn Wass** kathryn.wass@nottingham.ac.uk University of Nottingham, UK



Cellular Immortality & Cancer: From Telomerase to Cancer Stem Cells



Organised on behalf of BACR by
Nicol Keith (UK) & Jerry Shay (USA)
3th & 4th June 2008
The Swan's Nest Hotel
Stratford upon Avon, UK



Aim of meeting

Research areas in cancer cell biology such as telomerase and cancer stem cells appear to be interrelated and may offer the potential for uncovering novel drug targets with potential to address common cancer phenotypes. In particular the meeting will focus on new findings in cellular self-renewal and immortalisation with a view to intervention strategies.

We will cover a number of topics in the meeting including:

- What mechanisms regulate self renewal & immortality in stem and cancer cells?
- How can we develop therapeutics that target cancer stem cells?
- What can we learn from telomerase as a target for therapeutic development?

Program

Jerry Shay, USA

Telomere biology & the cancer stem cell

Lenhard Rudolph, Germany

Telomere maintenance in stem cells

Maria Blasco, Spain

Telomerase regulation & stem cell behaviour

Tom Rando, USA

Stem cells, aging & immortality

Petra Boukamp, Germany

Epidermal tumour stem cells

Lea Harrington, UK

Stem and progenitor cell function in mice lacking the telomerase reverse transcriptase

Anne Collins, UK

Prostate cancer stem cells

Moustapha Kassem, Denmark

Immortalisation & the mesenchymal stem cell

Peter Dirks, Canada

Chemical genetic interrogation of cancer stem cells

Nicol Keith, UK

Signalling and cellular immortality

Masashi Narita, UK

Cellular senescence and tumour suppression

Tae Kook Kim, Republic of Korea

Small molecule-based reversible reprogramming of cellular lifespan

Cal Harley, USA

Clinical development of telomerase therapeutics

In addition there will be short talks selected from submitted abstracts, break-out sessions to address key issues, and a poster session.

Abstract deadline: 22nd February 2008; Registration deadline: 4th April 2008

Places are limited and will be on a first come first served basis so early registration advised.

Registration fees (covering conference attendance, all meals and refreshments):

BACR Members £275, Non-members £325

Further details from: BACR Secretariat, c/o The Institute of Cancer Research,
Cotswold Road, Sutton, Surrey SM2 5NG

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