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Meeting Report

EACR-18: the best of European cancer research

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Abstract

EACR-18 was the 18th biennial meeting of the European Association for Cancer Research (EACR). It attracted more than 700 delegates, providing a pivotal European forum for basic scientists, translational researchers and clinical oncologists alike. It covered most of the key areas and recent developments in cancer research. This Review presents a meeting report.

Keywords: Meeting report; EACR; Cancer; Translational research; Tumour; Apoptosis; Oncogenomics

1. Introduction

The 18th biennial meeting of the European Association for Cancer Research (EACR-18) was held in Innsbruck, Austria, from 3rd to 6th July 2004. Innsbruck provided an inspiring setting, with the modern and spacious Congress Centrum located near the picturesque Old Town, surrounded by the stunning Tyrolian mountains. The meeting coincided with the final stages of the EURO 2004 soccer tournament and saw delegates crammed into bars and clubs to cheer on their favourites. It was a pleasure to witness the joy of our Greek colleagues at their country's memorable triumph.

A dense and stimulating scientific programme, covering cutting-edge research areas of experimental and translational oncology, was arranged by H. Grunicke, Conference and Scientific Chair, together with Co-Chair Edith Olah, the Scientific Programme Committee, and the secretariat of the Federation of European Cancer Societies (FECS). The programme contained educational lectures, plenary lectures and keynote lectures given by leading international authorities. These events were buttressed with basic science and translational research workshops and symposia, including several focused symposia organised by EACR, together with the national society members of the United Kingdom (UK) (BACR), Spain (ASEICA) and Italy (SIC). One hundred and eight talks were given in proffered paper sessions and 528 posters were presented. These free communications reflected the outstanding quality of the experimental research presented at EACR-18. A successful initiative at EACR-18 was the organisation by EACR with the American Association for Cancer Research (AACR) and Women in Cancer Research of a joint forum "Climbing the leadership ladder", to discuss womens' careers in science. There was great interest in all sessions, which resulted in a large attendance. It was especially gratifying to see the considerable numbers of young cancer researchers in the audiences. The conference dinner, held high in the mountains, provided a spectacular close to the meeting.

It was an honour and pleasure to be involved in such a stimulating and enjoyable experience. This report will attempt to provide you with an impression of the scientific excellence of EACR-18. We hope it will encourage you to attend EACR-19 in Budapest, 1st–4th July 2006.

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2. Mühlbock Lecture "Beyond the genome-what's next?"

P.G. Pelicci (Milan, Italy) delivered the opening lecture, named after Professor Otto Mühlbock, a founding member of EACR. He focused on the molecular biology of acute promyelocytic leukaemia (APL) and described how APL results from a chromosomal translocation that fuses the promyelocytic leukaemia gene (PML) with the retinoic acid receptor alpha gene (RARα). The PML–RARα chimera displays increased binding of enzymes involved in heterochromatinisation, including histone deacetylases and methyltransferases, and causes a block in differentiation. Binding of these enzymes can be blocked by retinoic acid, an established anti-leukaemic agent. In patients with APL, two different leukaemic cell types could be identified, a rapidly proliferating fraction and a slowly proliferating population. It was unexpected to learn that the slowly proliferating cells are responsible for sustained tumour growth. Evidence was presented that the slowly proliferating population originated from a reprogramming of progenitor cells to resemble stem cells.

3. Plenary lecture "Genes and the Environment: Nature, Nurture and Genetic Susceptibility"

The first plenary lecture of the meeting, by P. Pharoah (Cambridge, UK), gave a comprehensive overview on the importance of environment, genes and gene/environment interactions in the development of cancer. He first reviewed the general evidence for the importance of environmental factors and inherited factors in cancer. He then went on to describe some of his own data showing that polygenic inheritance is likely to account for much of the excess familial risk of breast cancer and reviewed methods for identifying such polygenes.The last part of the talk focused on the evidence that genetic factors interact with environmental factors, using as examples the variable penetrance of *BRCA1* and a putative interaction between host genotype and H. pylori genotype in determining gastric cancer susceptibility.

4. Symposium "Epigenetic reprogramming in cancer – implications for cancer chemotherapy"

Epigenetic mechanisms involving histone and DNA modifications regulate the heritable expression of genes without changing their coding sequences. Transcriptional repressive Polycomb-group (PcG) protein complexes and the counteracting Trithorax-group (Trx-G) of chromatin remodelling factors are also involved in these processes acting at the level of chromatin structure. Epigenetic abnormalities are frequently detected in cancer and novel epigenetic drugs targeting these alterations are currently under investigation in clinical trials and may be available for cancer treatment in the near future. U. Rapp (Würzburg, Germany) and M. van Lohuizen (Amsterdam, The Netherlands) provided novel data on the contributions of PcG proteins (PcGs) to the maintenance of stem cell fate and tumour formation, and on signalling pathways regulating PcG protein function. U. Rapp described links between mitogen activated protein kinase (MAPK) signalling and parts of the epigenetic memory system. He demonstrated that 3pK, a kinase activated by various MAPK signalling pathways, interacts with and phosphorylates the PcG protein, Bmi1, thereby influencing chromatin-association of PcGs. This suggests that PcGs do not act as static repressors of chromatin, but rather are part of dynamic complexes that are regulated by specific signalling pathways. M. van Lohuizen described Bmi1 expression patterns during brain development in mice and humans. Bmi1 is strongly expressed in proliferating cerebellar precursor cells, whereas the maintenance and proliferation of immature granule precursors is impaired in Bmi1-deficient mice. Moreover, Bmi1 is a target of the Shh signalling pathway and is overexpressed in a large fraction of primary human medulloblastomas. This extends the recently decribed role for Bmi1 as a renewal factor of haematopoietic and cortical neural stem cells, indicating a broader role for Bmi1-containing PcG complexes in the maintenance and expansion of stem cells and committed progenitor cells, as well as in events leading to tumour formation.

A. Roguev (Dresden, Germany) and M. Esteller (Madrid, Spain) focused on the methylation of histones and of DNA and its link to transcriptional regulation and propagation of chromatin structure and stability. A. Roguev provided new data on histone lysine methyltransferases (HKMTs) catalysing the methylation of highly conserved lysine residues at the N-terminal tails of histones H3 and H4. By sequential application of protein tagging, affinity purification and mass spectrometry, he charted the proteomic environment of the HKMT complex Set1C in fission and budding yeast. Although the compositions of Set1 complexes were found to be highly conserved in both yeasts, their overall proteomic environments differed substantially. The same principle emerged also by comparison of complexes containing Rad6, an E2 ubiquitin-conjugating enzyme involved in histone H2B ubiquitylation. Roguev suggested that the conservation of core complexes and the variability of associated proteins represent a common phenomenon in the evolution of eukaryotic proteomes.

M. Esteller presented novel data on the function of DNA methyltransferase 1 (DNMT1). He described a disorganisation of nuclear architecture and an altered pattern of histone H3 modification in human cancer cells lacking DNMT1. In addition, a loss of interaction of histone acetylases and Heterochromatin Protein 1 with histone H3 and pericentromeric repetitive se-

quences was found. These data suggest that the maintenance of distinct regions of genomic DNA methylation by DNMT1 contributes to chromatin organisation within the cell. Methyl-CpG binding proteins (MBDs) mediate histone deacetylase-dependent transcriptional silencing at methylated CpG islands. In order to identify novel epigenetically inactivated, hypermethylated genes in human cancer, he combined a chromatin immunoprecipitation (ChIP) assay of MBDs with a CpG island microarray (ChIP on chip). Among others, the homeobox gene PAX6, the prolactin hormone receptor and dipeptidylpeptidase IV displayed methylation-associated silencing in primary tumours and breast cancer cell lines. Furthermore, demethylating agents, such as 5-Azacytidine and Zebularine, and histone deacetylase inhibitors, such as LAQ824 and PXD101, had a potent cytostatic effect against tumour xenografts in nude mice and lymphomas in irradiated mice. In summary, this session provided novel data on various aspects of epigenetic reprogramming and indicated how this knowledge might be used to treat or prevent cancer.

5. Biotherapy Development Association Symposium "Inhibition of epidermal growth factor signalling – from the bench to clinical application"

A satellite meeting organised by the Biotherapy Development Association covered preclinical and clinical data on the use of inhibitors of tyrosine kinase receptors. Y. Yarden (Rehovot, Israel) first gave a comprehensive overview on the structure and physiology of the ErbB family of receptors and their respective epidermal growth factor (EGF)-like ligands, which constitute important regulators of cell proliferation, migration and angiogenesis. A network of the four ErbB receptors and their diverse ligands ensures robust and highly regulated signalling. Deregulated function of this network contributes to the development of human tumours. For example, ErbB2/HER2 is frequently overexpressed in breast cancer. However, ErbB2/HER-2 represents an orphan receptor with no known ligands and is unable to signal in isolation. Heterodimerisation of this orphan receptor with other ErbB receptors, e.g. ErbB3 which has many ligands, but lacks an active intracellular kinase domain, allows the heterodimers to respond to growth factors. ErbB2/ErbB3 heterodimers potently activate the Ras-MAPK cascade leading to increased gene expression and cell proliferation. In parallel, improved recruitment of the phosphatidyl inositol-3-kinase/protein kinase B (PI3K/PKB) pathway results in decreased apoptosis. Furthermore, heterodimerisation with ErbB2 facilitates evasion from receptor endocytosis.

The ErbB signalling network offers a target for cancer therapy. Antibodies to ErbB receptors trigger rapid internalisation and degradation of the receptors, thereby inhibiting mitogenic and angiogenic signalling. In addition, those antibodies recruit natural killer cells to the ErbB2-overexpressing tumours. A second approach is the use of small molecule inhibitors of the common ErbB tyrosine kinase domain that interfere with the adenosine triphosphate (ATP) binding site, thereby blocking downstream pathways that require tyrosine phosphorylation. The use of Hsp90 antagonists that block Hsp90/ErbB2 interactions and facilitate degradation of ErbB2 in the proteasome constitutes another, less specific, approach to inhibit the growth of ErbB2 overexpressing tumours.

J. Buter (Amsterdam, The Netherlands) presented clinical data on the therapeutic use of small molecule inhibitors of ErbB receptor tyrosine kinases. Overexpression or mutation of the EGF receptor (EGF-R, ErbB1), which is often associated with a highly malignant phenotype, is commonly observed in tumours of epithelial origin. It therefore represents a promising target for treating epithelial tumours. Several low molecular weight inhibitors of the conserved ATP binding site of the common ErbB receptor tyrosine kinase domain have been developed. Overall, these inhibitors have relatively mild side-effects. Among these tyrosine kinase inhibitors, gefitinib (Iressa®) is most advanced in clinical development. However, despite some single agent activity of this highly specific EGF-R inhibitor in advanced non-small cell lung cancer (NSCLC), in second- and third-line, phase III trials evaluating the use of gefitinib in combination with standard chemotherapeutic agents failed to show any beneficial effect of the drug on the survival of patients. Similarly, despite some single agent activity, two large randomised trials with the EGF-R inhibitor, erlotinib (Tarceva®), in combination with carboplatin/paclitaxel or carboplatin/gemcitabine, failed to demonstrate increased survival of the patients compared with chemotherapy alone. Thus, despite promising preclinical data, clinical trials using small molecule tyrosine kinase inhibitors have been mostly disappointing. This may be for several reasons. First, chemotherapeutic agents and tyrosine kinase inhibitors may target and kill the same cell population. Second, tyrosine kinase inhibitors may lead to decreased sensitivity of the cells to chemotherapeutic treatment and *vice versa*. Most importantly, the lack of selection of an adequate patient population may have contributed to treatment failure. Thus, for future trials, sensitive patients harbouring mutations in the target (EGF-R) that are responsive to the treatment with EGF-R inhibitors need to be selected.

J. Tabernero (Barcelona, Spain) presented data on the mechanism of action and the clinical use of therapeutic antibodies to ErbB receptors. These antibodies prevent binding of the natural ligand, thereby blocking downstream mitogenic and anti-apoptotic signalling.

Interestingly, while responding and non-responding tumours similarly showed inhibition of EGF-R and the MAPK cascade, non-responding tumours fail to efficiently downregulate the PI3K/Akt pathway upon treatment. Apart from inhibitory effects on cell proliferation, these antibodies have been shown to downregulate pro-angiogenic factors and to induce immunological responses. The observed anti-angiogenic effects provided a rationale for the use in combination with vascular endothermal growth factor (VEGF)-inhibitors or VEGF antisense oligonucleotides.

Among the EGF-R-specific antibodies, Cetuximab is the most advanced in clinical trials. In contrast to the small molecule inhibitors of ErbB receptors, clear synergistic effects of cetuximab in combination with standard chemotherapeutic agents, ionising radiation and other targeted drugs have been demonstrated with beneficial effects in patients with advanced colorectal and head and neck cancer.

F. Ciardello (Naples, Italy) ended the symposium by discussing resistance and escape mechanisms, as well as strategies to overcome these. He pointed out that for a rational use of these EGF-R-targeted drugs, it is not only important to select potentially responding patients with a mutated EGF-R, but it is similarly important to analyse the cellular context of this deregulation to control intrinsic and acquired cellular resistance to the EGF-R-targeted agents. Concurrent overexpression of the EGF-R with mutations in PTEN can cause constitutive activation of PKB/Akt and resistance to apoptosis leading to intrinsic resistance to EGF-R inhibitors. In this case, reconstitution of PTEN restored sensitivity to EGF-R inhibitors. Furthermore, the selection of cells with EGF-R-independent activation of EGF-R downstream targets, such as VEGF, can cause acquired resistance to EGF-R inhibitors. Therefore, to avoid treatment failure by intrinsic or acquired resistance, it may be advisable to combine EGF-R inhibitors with other tumour cell-directed signal transduction inhibitors, in particular EGF-R antibodies and inhibitors of PKB/Akt, or inhibitors of EGF-R and VEGF-R.

6. Anthony Dipple Award Lecture "p53 from pathway to therapy"

For major contributions in the field of carcinogenesis, D. Lane (Dundee, UK) was presented with the Anthony Dipple Carcinogenesis Award. He provided a brief overview of the molecular function of p53 and reminded us of the price we pay for the protective activities of this key tumour suppressor, since recent work has shown that p53 can promote aging. Nevertheless, it is the basis for many cancer therapy schemes and he described some of the strategies which are currently being developed to exploit p53 in the clinic. In addition to his translational research, D. Lane also presented some of his recent findings concerning the molecular attributes of p53. These included data regarding the control of p53 function through covalent attachment of alternative short polypeptide chains. Most striking was his dramatic discovery that multiple isoforms of p53 are produced from the same gene, a fact which had been overlooked until now, despite the colossal research efforts that have focused on this molecule for many years. The full implications of this bombshell will take a long time to unfold, but they are likely to be far-reaching.

7. Eurolife Workshop "Signalling to programmed cell death"

For the first time, the EURO-life consortium, an European Union (EU)-sponsored network of seven European Universities (Centers of Excellence) in biomedical research, arranged several Workshops at EACR-18. The first workshop dealt with "Signalling to programmed cell death". Since resistance to apoptotic cell death is recognised as a major contributor to malignant transformation and as a main determinant of successful treatment, various aspects which contribute to this phenotype were addressed in this session. M. Henriksson (Malmo, Sweden) reported that induction of apoptosis by the commonly used cytotoxic drugs, etoposide, doxorubicin and cisplatin, requires c-Myc. Following drug treatment, rat cells expressing c-Myc showed higher activation than c-Myc-null cells of caspase 3, -8, and -9. Apoptosis was paralleled by c-Myc-dependent Bax activation and PKCδ cleavage. These findings suggest that Bax and caspase activation, together with PKCδ signalling, are involved in c-Myc-dependent drug-induced apoptosis.

A related topic was covered in the talk by A. Villunger (Innsbruck, Austria). Apoptosis provoked by DNA damage requires p53, but which of the many p53-regulated genes are critical has remained unclear. Two attractive candidates are the proapoptotic BH3 domain only members of the Bcl-2 family, Noxa and Puma. Fibroblasts of Noxa- or Puma-deficient mice show decreased DNA damage-induced apoptosis, but only loss of Puma protects lymphocytes from cell death. Puma deficiency also guards cells against diverse p53-independent cytotoxic insults, including cytokine deprivation and exposure to glucocorticoids or the kinase inhibitor, staurosporine. Hence, Puma and Noxa are important mediators of the apoptotic responses induced by p53 and other agents.

Hypermethylation of CpG island regulatory regions in genes leads to transcriptional silencing. This can affect cancer genes involved in cell proliferation, DNA repair and apoptosis and thus is an important contributor to transformation and a possible target for treatment.

S. Bader (Edinburgh, UK) presented his work on MBD4, a DNA glycosylase repair protein whose methyl-CpG binding domain is thought to direct its activity to mismatches within methylated DNA. The gene is secondarily mutated in mismatch-repair defective tumours causing loss of the glycosylase domain. Truncated MBD4 protein was able to inhibit competitively normal MBD4 in cell-free glycosylase assays, and, in microsatellite-unstable cells, the mutant form caused an increase in the mutation frequency of a lacI-lacZ shuttle vector. Thus, truncating mutations of MBD4 can give a dominant-negative phenotype. The spectra of mutations in the MBD4 mutant-transfected cells suggest a wider role of MBD4 in mismatch repair than just at methyl-CpG dinucleotides.

Finally, J. Troppmair (Innsbruck, Austria) reported work analysing the contribution of the stress kinase JNK (Jun N-terminal kinase) to the transformation process. JNK activation has usually been linked to apoptosis induction, but activated JNK has been reported in cells transformed by Ras and Raf, as well as primary tumours. Combined *in vitro* and *in vivo* data demonstrate that activated JNK behaves like a moderately transforming oncogene and stimulates proliferation without affecting cell survival. Moreover, JNK may favour tumour growth *in vivo* by promoting angiogenesis.

8. Proffered Paper Session "Oncogenomics"

Oncogenomics offers the potential for discovery of new cancer targets and the development of therapeutic agents against these. A presentation on molecular approaches to anti-angiogenic chemoprevention (angioprevention) was given by D. Noonan (Genova, Italy). This described the use of Affymetrix arrays to analyse differential gene expression when the angiopreventive drugs *N*-acetyl-cysteine, green tea flavonoid and chemopreventive retinoids were applied to HUVEC cells. The data revealed that the response to these drugs follows different pathways.

N. Rahman (Sutton, UK) described biallelic truncating mutations in *BRCA2* associated with familial Wilms' tumour. She reported an unusual Wilms' tumour pedigree in which both brothers developed a classic triphasic Wilms' tumour. Screening *BRCA2* identified a paternally inherited 2bp deletion and a maternally-inherited nonsense mutation present in both children. In conclusion, individuals homozygous for truncating mutations in *BRCA2* are viable, but have a high risk of malignancies in childhood. These findings contribute one more phenotype to the spectrum associated with *BRCA2* mutations.

R. Pascale (Sassari, Italy) presented work on polygenic control of hepatocarcinogenesis in a rat model. The data revealed that susceptibility to hepatocarcinogenesis in Cop rats is controlled by a complex array of genes, with several gene/gene interactions.

K. Birkenkamp-Demtröder (Aarhus, Denmark) described the identification of novel colorectal cancer-associated proteins. Microarray analysis on Affymetrix GeneChips identified 390 genes and expression sequence tags (ESTs) which were differentially expressed in normal mucosa compared with adenocarcinomas. Expression profiles were validated by reverse-transcriptase-polymerase chain reaction (RT-PCR). Immunostaining showed that differential protein expression was detectable in benign hyperplastic polyps, adenomas and adenocarcinomas.

B. Schäfer (Zürich, Switzerland) described the identification of rhabdomyosarcoma (RMS) subtypes using gene expression profiling and the detection of a novel t(2;2)(q35;p23) translocation fusing PAX3 to ncoa1. RMS, a paediatric tumour, is classified into ERMS (embryonal) and ARMS (alveolar), most of them carrying the PAX3(7)/FKHR-translocation. Using U133A Affymetrix microarrays, differential expression patterns were identified discriminating 15 ERMS from 10 translocation-positive ARMS and five translocation-negative ARMS. Tyrosine kinases and G-coupled receptors were among the differentially expressed genes. Moreover, the ARMS signature included a translocation generating a novel fusion protein, possibly playing an oncogenic role.

E. Tajara (Brazil) presented transcriptome analysis of head and neck and thyroid (HNT) tumours. 200,000 ESTs were derived from normal and tumour HNT tissue and clustered, mapped and classified according to putative function by Gene Onthology. More than 700 new human transcripts and alternative splicing isoforms were identified and some selected transcripts were validated by RT-PCR. These datasets might provide potential tumour markers in the form of new transcripts or splicing variants, thereby possibly providing a valuable tool for understanding HNT malignancies.

9. Proffered Paper Session "Signal transduction mechanisms in cancer"

Signalling pathways in eukaryotic cells are often controlled by specific signalosomes which are coordinated by scaffold and adaptor proteins. D. Teis (Innsbruck, Austria) described the identification of p14/MP1 as a novel member of the profilin adaptor superfamily involved in MAP kinase attachment to the late endosomes. Mutational analysis identified two highly conserved and hydrophobic protein docking sites working as an interface for MEK1 and ERK1 signal integration. This work was complemented by crystal structure studies of p14/MP1.

H. Sutterlüty (Vienna, Austria) presented work on the Sprouty family of MAP kinase modulator proteins that are frequently linked to receptor tyrosine kinase-mediated cell proliferation and malignancy. Ectopic expression of Sprouty2 in NSCLC cells characterised as low expressors inhibited cell proliferation and migration. These findings are part of a tentative model in which downregulation of Sprouty may contribute to uncontrolled proliferation, predominantly in squamous cell carcinomas of the lung.

D. Romero (Madrid, Spain) focused on the fact that expression of Smad4 decreases basal phosphorylations of ERK and Akt induced by oncogenic Ras, suggesting crosstalk between Ras and Smad, as well as Wnt and Smad cascades in human carcinogenesis.

The enhanced c-myc-driven telomerase activity in Philadelphia-positive myelogenous leukaemia cells is commonly discussed as a pivotal mechanism for drug resistance, including in the use of Imatinib mesylate (Gleevec™; Glivec). R. Bakalova (Takamatsu, Japan) gave insight into novel data on the interaction of c-myc and telomerase. RNAi demonstrated that c-myc downregulation is accompanied by significantly decreased hTERT, enhancement of TRF1 (negative regulator of telomerase), suppression of telomerase activity and sensitisation of LAMA-4 cells to Imatinib mesylate.

The Ewing's family of tumours (EFT) harbours a chromosomal translocation joining the N-terminal region of the *EWS* gene with the C-terminal region of several transcription factors of the Ets family, mainly FLI-1. Presenting data on gene expression profiling experiments followed by functional luciferase reporter assays, M. Mendiola (Madrid, Spain) provided evidence that the orphan nuclear receptor DAX-1 is a specific target of the Ewing's sarcoma oncoprotein, EWS/FLI1. Since Dax-1 has been shown to be involved in differentiation of several cell lines and tissues, the findings suggest a role in EFT development.

D. Strand (Mainz, Germany) reported that loss of Hugl – the human homologue of the Drosophila tumour suppressor gene *lethal giant larvae* (lgl) – contributes to colorectal cancer progression. Hugl-1/2 is lost in a significant number of colorectal tumours and so this gene family may act as a human tumour suppressor. Regulation of Hugl function via survival kinases of the atypical PKC family was also discussed.

10. Proffered Paper Session "Tumour genetics and molecular epidemiology"

This session contained six talks that covered quite diverse aspects of tumour genetics and molecular epidemiology. In the first, J. Lacy-Colson (Stoke-on-Trent, UK) compared promoter haplotypes in the *CDH1* gene with protein expression as markers for disease progression in patients with colorectal cancer. A previously identified promoter SNP (−285 C allele) was shown to be an independent tumour marker, significantly associated with advanced stages of the disease. No association was found between disease progression and altered protein expression or with *CDH1* genotypes.

A PCR-based restriction fragment length polymorphic (RFLP) strategy was used by P. Mitrou (Cambridge, UK) and colleagues to investigate five different polymorphisms in three genes involved in detoxification pathways; *NQO1*, *mEH* and *MTHFR*. Their study comprised 206 patients with colorectal cancer and a distal polyp-free control group of 354 subjects. They concluded that the low activity allele mEH3 was associated with an increased risk for left-sided cancer in the colon that reached statistical significance, and this was particularly seen in men.

Low-penetrance susceptibility genes are thought to play an important part in non-high-risk familial breast cancer. R. Rodriguez-Lopez (Madrid, Spain) and colleagues investigated the role of six candidate low-risk alleles for the risk of breast cancer in 713 unselected cases of breast cancer and in 767 control cases. They found a statistically significant increased risk for two single nucleotide polymorphisms (SNPs), T241M (XRCC3) and P10L (TGFBeta), in particular for patients who were carriers of both variant alleles simultaneously.

Aberrant promoter methylation is a hallmark of cancer and P. Parella (San Giovanni-Rotondo, Italy) reported non-random distribution of methylation patterns in specific cancer genes in breast tumours. In particular, methylation of *ESR1* was associated with methylation also at the *CDH1*, *TRβ1*, *GSTP1* and *CDK2* loci. This hypermethylation, which appears to be an early event, characterised distinct cancer subsets that may represent specific biological entities with differences in disease outcome.

A. Ewis (Takamatsu, Japan) discussed the incidence of testicular germ cell tumours (TGCT) in relation to different Y chromosome haplotypes. Several Y haplotypes were studied in Japanese males with TGCT and in 104 unrelated healthy controls. Certain haplotypes were significantly overexpressed in the TGCT group, while others showed resistance to TGCT. The data do not reveal a causal relationship between Y haplotypes and the incidence of TGCT, but support the hypothesis that males from different Y lineages exhibit different susceptibilities for male-specific cancers, including prostate cancer and TGCT.

Lastly, X. Li (Huddinge, Sweden) presented a study on predisposition to early onset lung cancer in the Swedish population. Using a national register of familial cancer cases totalling over 10.2 million individuals, they found a higher risk by parental family history, in particular for adenocarcinoma and large cell carcinoma. They

concluded that there is an increased risk among siblings for all histological types of cancer when diagnosed under the age of 50 years and hypothesised that there might exist a highly-penetrant recessive gene(s) that predisposes to tobacco carcinogens.

11. Plenary Lecture "Translational cancer research in breast cancer: an integrated vision"

J. Celis (Copenhagen, Denmark) gave insights into the challenge of how to apply the "omic" technologies to clinically relevant samples and how to interpret and use the overwhelming amount of data obtained to the benefit of the patient. This was exemplified by a translational multicentre approach in breast cancer aiming at the identification of biomarkers for the disease, as well as the development of novel targeted therapies. He pointed out that the translation of discoveries from basic science to the clinics is a slow, expensive and very demanding process that requires contributions from numerous disciplines. However, using these multicentre approaches, molecular classification of individual patients and the prediction of tumour response to therapy may result in a real predictive, personalised therapy in the future.

12. Plenary Lecture "Molecular chemoprevention science: from cure of end-stage disease to early reversal of carcinogenesis"

Prevention is better than cure. This observation was made by Machiavelli, as H. Bartsch (Heidelberg, Germany) pointed out when introducing his lecture. He first presented data on the progress in identification of novel chemopreventive lead compounds and their mechanisms of action. In this regard, he summarised his very extensive studies on the cancer-preventive activities of xanthohumol, a substance purified from hops (*Humulus lupulus*). Xanthohumol has a broad range of actions that influence initiation, promotion and progression of cancer. It can modulate carcinogen metabolism by inhibiting the Cyp1A enzyme and is also a potent antioxidant. In terms of tumour promotion, xanthohumol has potent anti-oestrogenic activity in a rat uterotrophic assay. Furthermore, inhibition of pro-angiogenic factors, including metallo-proteases and VEGF, as well as reduced endothelial cell migration, could be demonstrated in culture. It also induces apoptosis in colon carcinoma cells.

H. Bartsch then turned to the development and validation of oxidative stress-related biomarkers for disease risk that could be used to screen for potential chemopreventive agents and, in conjunction with ultrasensitive analytical methods, to follow the drug response in clinical trials. He pointed out that oxidative stress leads to the formation of DNA adducts, which promote carcinogenesis. Inflammation, recognised since Virchow's days to be associated with carcinogenesis, may act partly in this way, via cyclooxygenases and lipoxygenases, leading to peroxidation of lipids, activation of the NFκB pathway and generation of reactive oxygen derivatives. In this regard, ethanodioxyadenine, which can be detected in premalignant liver lesions, is a potentially useful marker for monitoring the efficiency of chemopreventive trials.

H. Bartsch finished with recent findings on factors that determine the progression of head and neck cancers, where aneuploidy has been identified as a decisive prognostic factor Furthermore, the aneuploidy is strongly associated with increased expression of cyclooxygenase 2. This will form the basis of a large clinical chemopreventive trial using celecoxib.

13. Symposium "Pharmacogenomics–pharmacogenetics and individualised therapy"

M. Stratton (Cambridge, UK) described a novel approach to identify somatic mutations in protein kinase domains in cancer by a large-scale systematic screen using pharmacogenomics. This was based on the fact that among the known somatic mutations in protein domains, mutations in protein kinases are over-represented and may therefore constitute a promising target for cancer therapy. Using breast cancer as a model, no mutated protein kinase was found that frequently contributed to oncogenesis. In the many infrequently mutated protein kinases, no typical missense mutations in the kinase domain were detected. Therefore, protein kinase inhibitors may not be useful for the treatment of breast cancer.

M. Eichelbaum (Stuttgart, Germany) then moved to pharmacogenetic aspects of colorectal cancer therapy. He proposed the use of genomics for the evaluation of the individual drug response of the patient regarding resistance and toxicity. In the case of 5-fluorouracil (5-FU), several genes involved in the conversion of 5-FU to nucleotides influence anti-tumour activity and the toxicity of the drug. Therefore, genetically determined differences in enzymatic activity can influence response to 5-FU. Apart from data on thymidylate synthase, M. Eichelbaum described a prospective clinical trial investigating the impact of genetical alterations in dihydropyrimidine dehydrogenase on the toxicity of 5-FU treatment in patients with solid tumours.

Moving again to target evaluation, P. Workman (Sutton, UK) lectured on the use of pharmacogenomics for drug discovery, development and clinical use. Upon completion of the human genome project, the development of high throughput techniques for sequencing, gene expression profiling, transcriptomics and

proteomics facilitated the identification of cancer genes. In this regard, P. Workman presented data on the identification of B-Raf and PI3K as targets for cancer therapy, as well as HSP-90 inhibitors as novel anticancer drugs. Rational use of these techniques will not only allow the identification of novel targets, but also permit personalised diagnoses and therapy with a molecular characterisation of the individual risk of disease and tumour response of patients in the future.

In the last talk of the symposium, H. McLeod (St. Louis, USA) focused on the clinical aspects of pharmacogenomics. Again, it was emphasised that pharmacogenomics should help introduce individualised cancer therapy. In this regard, evaluation of biomarkers is urgently needed that may help identify patients who may benefit from a given therapy. Furthermore, individual sensitivity and toxicity profiles for defined therapeutic approaches of a given patient should be available. Optimal timing for onset of the therapy should also be determined. Pharmacogenomics should no longer focus on the negative selection of patients with unwanted side-effects, but on the prospective selection of responsive patients.

14. EACR Young Cancer Researcher Award Lecture: "Molecular Portraits of Breast Cancer: Tumour Subtypes as Distinct Disease Entities"

The EACR Young Cancer Researcher Award is conferred in recognition of an outstanding contribution in the field of fundamental research in cancer. On the occasion of EACR-18, the award was presented to T. Sørlie from the Department of Genetics, Institute of Cancer Research, The Norwegian Radium Hospital, Oslo. In her award lecture, she presented data distinguishing different subtypes of breast cancer. These subtypes not only show differences in clinical outcome, such as overall and recurrence-free survival, but also differences in the risk of developing metastases. Furthermore, the response to specific chemotherapeutic agents depends on the tumour subtype (for more details, please see her Review that is published in this issue).

15. Proffered Paper Session "Tumour Biology"

The first presentation was given by J. Kim (London, UK), the winner of the EACR-OSI Translational Research Award. He spoke about the development of a fully "humanised" breast cancer model. A three compartment xenograft model of human breast cancer was obtained by xenografting MCF-7 mammary tumour cells together with human stroma; fresh primary human mammary endothelial cells and fibroblasts were immortalised and provided the stroma component of the model. It was also shown that the initial tumour growth was supported by the stromal cells before the host vasculature was recruited. This model now needs to be reproduced using fresh human breast cancer cells instead of the long-passaged MCF-7 line.

B. Luber (München, Germany) described changes in cell adhesion and motility derived from a single amino acid mutation of the cadherin gene (D370A) found in a case of gastric carcinoma. By using wild-type and mutant cadherin fused with enhanced green fluorescent protein, it was shown that wild-type localised to cell-cell contact sites, whereas the mutant was found in lamellipodia: this difference correlated with differences in cell motility and adhesion dynamics.

P. Gassmann (Münster, Germany) followed with a talk on tumour cell adhesion and migration *in vivo*. He outlined the consequences of injecting into the hearts of rats suspensions of colon cancer cells with different metastatic potentials. The kinetics of tumour cell arrest in metastatic target organs reflected specific adhesive interactions rather than mechanical size restrictions.

E. Caspani (Vienna, Austria) gave a very visual presentation on cytoskeleton re-organisation of glioblastoma cells. The study focused on the motile characteristics of two metastatic glioblastoma cell lines (U373 and U87) in different microenvironmental settings. It was shown that cell migration is driven by the extension of dendritic-like processes bearing ruffles and filopodia; cell body retraction appeared to be driven by the contraction of arrays of actin filaments underlying cell surfaces outside ruffling zones. It was also suggested that Rho-kinase plays a key role in glioblastoma cell motility.

In the last presentation, J. Morton (Glasgow, UK) showed that the RNA polymerase (pol) III transcription complex, which involves approximately 25 polypeptides and may represent a major obstacle to DNA repair, is cleared from genes *in vivo* when cells are treated with mutagens that induce DNA double-strand breaks. The pol III-specific transcription factor TFIIIC is a target for phosphorylation-mediated inactivation by DNA-dependent protein kinase (DNA-PK). Hyperphosphorylation of TFIIIC is followed by its degradation and release of the pol III transcription complex, prior to repair of damaged DNA.

16. Proffered Paper Session "Regulation of Apoptosis"

This session featured several aspects of cellular elimination through apoptosis.

P. Jansen-Dürr (Innsbruck, Austria) discussed papilloma virus (HPV) proteins E6 and E7 and their interactions with key molecules regulating the cell cycle and/or apoptosis. Depending on the cell type, HPV E7 may either block or promote apoptosis. Physical and func-

tional interactions have been described for multiple targets, including pRb, p130, p107, p27 and also p21. The pro-apoptotic activities of E7 involve the E2F-regulated genes p19ARF, p73 and Apo-1, and the chromatin modifiers, HDAC1 and Mi2. The apoptosis inhibitory activities are more obscure, but might be, in part, mediated by an interaction of E7 with insulin-like growth factor binding protein 3 (IGFBP-3), which may enhance proteosomal degradation.

A. Palmetshofer (Würzburg, Germany) described anti-tumour activities of nuclear factor of activated T cells (NFAT) transcription factors, which are regulators of T cell activation and elimination. NFAT protein expression may slow down lymphoma-genesis and progression, as several human lymphoma types have been found to lack NFATc1 expression. In mice, the *NFATc1* and *NFAT5* genes represent common integration sites for lymphotrophic retroviruses and, upon infection, mice deficient for *NFATc3* develop more aggressive tumours than wild-type animals.

Approaches to interfere with the EGF receptor signalling pathway only inhibit growth of a subset of NSCLCs. W. Berger (Vienna, Austria) discussed the relevance of autocrine fibroblast growth factor receptor (FGF-R) signalling loops to the malignant growth of these tumours. Overexpression of a dominant-negative FGF-R1 led to growth retardation and a partial induction of caspase-dependent apoptosis, which was associated with decreased Akt/PKB-activities. Blocking of both EGF-R and FGF-R was synergistic with regard to growth inhibition in several cases. A promising finding was that targeting the FGF-R pathway via overexpression of dominant-negative variants did not result in "escape" mutants in long-term clonogenic assays.

A. Villunger (Innsbruck, Austria) referred to p53-regulated BH3-only *PUMA* and *Noxa* genes. Puma-deficient mice show normal embryonic development and do not develop spontaneous tumours, but apoptosis is impaired in embryonic fibroblasts and lymphocytes. Both, PUMA and Noxa are important promoters of DNA damage-induced cell death and PUMA-deficient animals develop thymus hypercellularity and are cancer-prone. PUMA deficiency also protects cells against diverse p53-independent insults, including cytokine deprivation and glucocorticoids, suggesting that these proapoptotic BH3-only proteins may feature in tumour suppression and cancer therapy.

A. Choudhury (Stockholm, Sweden) elucidated short interfering RNA (siRNA)-based approaches to interfere with aberrant fibromodulin expression in B cell chronic lymphocytic leukaemia (B-CLL), a strategy which induced apoptosis in B-CLL but not in untransformed human B or T lymphocytes and not in fibromodulin-positive fibroblasts. Therefore, blocking extracellular matrix proteins, such as fibromodulin, may provide a useful therapy for B-CLL.

In a series of electron microscope images, P. Debbage (Innsbruck, Austria) illustrated the mechanisms of radiation-induced vascular hyperpermeability and the dynamics of endothelial cell loss and replacement, using ectopically implanted glioblastomas in mice. Upon radiation, endothelial cells do not die of cytogenetic damage, but rather lose contact with the basement membrane, which is followed by apoptosis when the cells fail to re-attach.

17. Eurolife Workshop "Tumour immunology Workshop"

The "Tumour Immunology Workshop" was the second workshop organised by the EUROlife consortium. J. Hasenkamp (Göttingen, Germany) reported on a new Granzyme-B ELISPOT assay for the rapid detection of allo-reactive NK cells which will be used for further investigations on the possible effects of Kir-ligand mismatch on clinical relapse, engraftment and GvHD in allogeneic haematopoietic stem cell transplanatation.

M. Piesche (Göttingen, Germany) described efficient transduction of human T lymphocytes by an AD5/F35 chimaeric adenoviral system.

G. Brandacher (Innsbruck, Austria) reported that colon cancer cells can be induced by interferonγ (IFNγ) to express indoleamine 2,3-dioxygenase (IDO), which alters the tryptophan degradation pathway and is associated with T-cell depression. IDO levels in colorectal cancer patients were shown to correlate with poor clinical outcome and higher rates of liver metastases.

D. Wolf (Innsbruck, Austria) explained that regulatory T-cells, which have been implicated in immunosuppression in cancer, show telomerase activity during proliferation after stimulation *in vitro*. In contrast, T-reg cells isolated from cancer patients with proven expansion of these cells do not show telomere shortening.

Finally, C. Marth (Innsbruck, Austria) reported on a study showing that elevated expression of IFNγ in ovarian cancer is an independent predictor of favourable clinical outcome.

18. EACR Young Cancer Researcher's Forum

As the EACR is extremely keen to promote the involvement of researchers at early stages of their careers, a session was included that aimed specifically at these valuable members of the cancer research community. As well as an open discussion forum, it featured presentations from four highly successful young group leaders. A. Trumpp (Epalinges, Switzerland) spoke about his studies on haematopoietic stem cells. He described evidence for a specific *in vivo* microenvironment, in which stem cells are anchored by integrins and

cadherins into a niche where they undergo asymmetric division and self-renewal. If c-Myc is deleted from these haematopoietic stem cells in mice, their ability to differentiate is lost and severe anaemia results. The ability of c-Myc to alter the balance between self-renewal and differentiation will be of great importance to many malignancies in which c-Myc is deregulated.

J. Downs (Cambridge, UK) has used yeast as a model organism for studying the function of the abundant linker histone Hho1. Although linker histones are generally thought to repress gene transcription, this is not the case for Hho1 in *Saccharomyces cerevisiae*. However, Hho1 does inhibit homologous recombination and therefore suppresses one pathway for DNA repair and telomere maintenance. Nevertheless, lifespan is shortened by loss of Hho1, a counterintuitive discovery. She speculated that longevity may be compromised by aberrant recombination in the absence of Hho1, leading to chromosome fusions or translocations.

A. Nebrada (Heidelberg, Germany) discussed the p38 MAP kinases, which are important for regulating cellular responses to stress, but can also influence cell proliferation and survival. He used DNA microarrays to identify genes regulated by p38α (the most abundant p38 family member) in unstressed, normally proliferating cells and found that several genes encoding extracellular matrix components are upregulated in p38α–/– cells. These p38α-deficient cells are more resistant to apoptosis induced by various stimuli and this correlates with both decreased expression of pro-apoptotic proteins and upregulation of survival pathways. Moreover, p38α–/– fibroblasts transduced with oncogenic Ras show a more drastically transformed phenotype than wild-type fibroblasts, suggesting that p38 MAP kinases may protect against oncogene-induced malignant transformation.

T. Eisen (London, UK) referred to several new inhibitors of kinase signalling molecules that are in clinical development. They are multi-targeted drugs that inhibit a variety of kinases involved in the growth and development of cancers, including VEGFR, platelet-derived growth factor receptor (PDGFR), c-KIT, CRAF and BRAF. The most advanced in clinical development are the orally available sorafenib (formerly BAY43-9006) and SUO11248. BAY43-9006 was investigated in a very large phase II study involving patients with a variety of solid malignancies. The most encouraging results were obtained for patients with metastatic renal cell cancer. Approximately 1/3 of patients had significant shrinkage of their tumours, while another 1/3 had stable disease, often for prolonged periods. The main side-effects were skin rash and hypertension. SUO11248 produced similar results, although with less rash and more fatigue. It had been hoped that patients with melanoma, whose tumours express mutant BRAF in 2/3 of cases, would benefit from BAY43-9006. Whilst single agent BAY43-9006 was disappointing, encouraging signs are seen in combination with chemotherapy. These findings are relevant to other malignancies and the kinase inhibitors are likely to become an important group of anti-cancer drugs.

This excellent session finished with a presentation from R. Popescu (Lausanne, Switzerland) concerning the FLIMS Alumni Club.

19. Plenary Lecture "Human embryonic stem cells in medical research"

N. Benvenisty (Jerusalem, Israel) gave a lecture on the development of human embryonic stem cells suitable for use in medical research. He discussed his work exploring the effect of individual or combinations of exogenous growth and differentiation factors on the patterns of stem cell differentiation into different proportions of ectodermal, endodermal or mesodermal populations. He also described the use of lines stably expressing siRNA to β2 microglobulin to suppress MHC expression and thus immunogenicity in potential hosts.

20. Plenary Lecture "Mouse models for cancer"

A. Berns (Amsterdam, The Netherlands) presented new mouse models for a variety of tumours, developed using Cre/Lox-mediated switching of tumour suppressor genes and oncogenes and retroviral insertional mutagenesis. These models have been combined with sensitive *in vivo* imaging to follow tumour growth, metastatic spread and response to experimental therapies in real-time. One is a model for human malignant mesotheliomas, which, although rare, are increasing due to asbestos exposure. In the mouse models, mesothelioma can be induced at low frequency by inactivating Nf2 in the mesothelial lining of the thoracic and peritoneal cavity. A high incidence of these tumours, with a relatively short latency period, is then obtained by the concomitant loss of p53 or Ink4a/p19Arf. The second model deals with lung tumours, for which the genetic lesions associated with the two major histotypes, small cell lung cancer (SCLC) and NSCLC, include K-ras mutations, Myc deregulation, p53 loss and Rb inactivation. In mouse models, lung tumours can be efficiently induced by adenoCre-mediated switching of a floxed mutant K-ras allele or by the inactivation of both Rb and p53 floxed alleles. The two approaches resulted in different types of lung tumours: conditional activation of K-ras results in adenocarcinomas resembling NSCLC, whereas conditional inactivation of Rb and p53 yielded tumours with all of the features of metastatic SCLC, a tumour type not previously reproduced in a mouse model. Moreover, comparative genomic hybridisation (CGH) analysis of

these latter tumours revealed some aberrations also found in human SCLC. An interesting observation that emerged from these studies is that lung tumours develop from only a subset of cells expressing the conditionally-activated genetic lesion. This may imply that only a subset of normal lung cells (stem cell-like?) is prone to the neoplastic transformation or that earlier predisposing genetic alterations need to occur before the activation/inactivation of the relevant tumour-associated genes.

In addition, a model of pituitary tumours, induced by inactivating floxed Rb alleles, was shown to outline the power of the new tools provided by functional imaging to follow *in vivo* responses to therapy.

21. SIC–EACR symposium "Tumour microenvironment as a target for anticancer therapy"

A successful initiative at EACR-18 was the organisation of several focused symposia by the national society members. This session highlighted the ability of the tissue microenvironment to control malignancy and discussed approaches for therapeutic intervention.

Extracellular proteinases of the matrix metalloproteinase (MMP) family regulate many facets of normal and neoplastic cell behaviour. MMPs contribute to epithelial-stromal cross-talk and are centrally placed to modulate the balance of positive and negative growth and differentiation factors, invasion and metastasis. Z. Werb (San Francisco, USA) focused on the role of stromally-derived MMP-9 in tumour progression. She demonstrated that, in neuroblastoma, MMP-9 contributes to angiogenesis by promoting blood vessel morphogenesis and pericyte recruitment. However, MMP-9 also generates an endogenous inhibitor of angiogenesis and mice deficient in MMP-9 show accelerated tumour growth. Therefore, opposite properties of MMP-9 are integral to the overall tumour progression and need to be considered before using MMP inhibitors.

Initiation of angiogenesis depends largely on the cellular context and the microenvironment in which tumours develop. The hypoxia inducible transcription factor, HIF-1, plays a central role in cellular adaptation to low oxygen availability in physiological and pathophysiological processes, including angiogenesis and tumour growth. J. Pouyssegur (Nice, France) reported that HIF prolyl-hydroxylase 2 (PHD2) is a key oxygen sensor, setting low steady-state levels of HIF-1α in normoxia, and that PHD2 mRNA is upregulated by hypoxia. Since tumour hypoxia, malignant progression and treatment failure are often associated, recent findings on HIF-1α signalling should be considered in prognosis and therapy.

A complex network of cytokines and their respective receptors contribute to tumour cell growth and survival, and to the communication between malignant cells and stromal elements. F. Balkwill (London, UK) provided insight into tumour necrosis factor α (TNFα) signalling in tumorigenesis and provided a rationale for the use of TNF antagonists in the treatment of cancer. She showed that malignant cells from different cancer types differ in their profile of chemokine-receptor expression, with CXCR4 being most commonly found. CXCR4 expression is likely to be induced by genetic or microenvironment-mediated epigenetic events. However, given the complexity of the chemokine network, it is unlikely that an individual chemokine antagonist would have a powerful action in cancer. Inhibitors of cytokine-inducing cytokines could be useful. Research on the cancer chemokine network is revealing parallels between inflammation and malignancy, that may indicate new treatment approaches.

The immune system is a rational choice to target tumour growth and progression through the microenvironment. Inflammation can actively contribute to carcinogenesis, and appropriate immune stimuli can convert noxious inflammation into a specific antitumour response. Furthermore, immune activity is inherently systemic, allowing intervention at the level of tumour microenvironment through distant actions, such as vaccines. P.-L. Lollini (Bologna, Italy), pointed out that various vaccination strategies can be used to prevent (rather than cure) mammary carcinoma in HER-2/neu-transgenic mice, through the induction of persistent local and systemic immune responses based on γ-interferon and anti-HER-2/neu antibodies. Similar vaccines are also active in the prevention of a multigene cancer syndrome caused by the combination of HER-2/neu activation and p53 inactivation, thus raising the hope of future translation to humans at risk of cancer.

Since the tumour and host compartments interfere during tumour progression, the tumour stroma offers a target to control tumour growth and progression.

22. BACR–EACR Symposium "Functional imaging-molecules and cells"

BACRs initiative was to 'showcase' research exploring the dynamics of key cellular and molecular functions using 'state-of-the-art' optical imaging techniques. There have been tremendous improvements in technologies over the last decade enabling the molecular machinery of mitosis, for example, to be visualised as never before. It is clear that tumours, far from being static "lumps" are seething with activity – cells of different types jostling around, testing their environment, forming interactions, helping their neighbours or behaving in an antisocial manner – like a microscopic community.

J. Segall (New York, USA) showed stunning images of living cancers revealed by two-photon confocal microscopy in which the movement of cancer cells into the

tumour vasculature could be followed. Using multiphoton microscopy, he showed how macrophages and tumour cells communicate and jointly potentiate intravasation (found to be rate-limiting for metastasis) and invasion. Tumour cells can migrate along matrix fibres and also become polarised towards blood vessels, suggesting that they are responding to chemotactic gradients. His group is now combining this technology with magnetic resonance imaging (MRI) to obtain images deeper inside tumours and to glean 4-dimensional (4D) information.

P. Friedl (Würzburg, Germany) presented 5D imaging of cancer cell migration, using a variety of techniques including time-resolved bright field, confocal and multiphoton microscopy, to reconstruct the dynamics of cell motility. Individual cancer cells or populations of cells could be observed in 3D collagen matrices. As the cells moved, they left tracks of severed collagen fibres in their wake. He identified several different modes of tumour cell movement, including the classical integrin/protease-mediated formation of substrate focal contacts, stretch, release, retract model (mesenchymal movement) and integrin and protease-independent amoeboid movement. He showed how many escape mechanisms tumour cells have at their disposal and why interfering with motility and metastasis is so challenging.

Moving to the molecular level, J. Swedlow (Dundee, UK) used quantitative imaging and image informatics to reveal a phosphorylation network at the mitotic centromere. He is investigating using chromosome proteomics how chromosomes form and interact with the mitotic machinery. Kinetocore assembly is controlled by phosphorylation and dephosphorylation. By localising to the inner centromere, Aurora B is able to orchestrate the dynamics of microtubules. He identified PPIγ (a kinetochore component) as a possible Aurora B phosphatase and argued that kinase-phosphatase competition across the centromere may establish spindle orientation. Their exquisite ballet during mitosis could be followed using tagged proteins.

Finally, P. Nagy (Göttingen, Germany) described the use of quantitative optical and scanning probe microscopy and fluorescent resonance energy transfer (FRET) to explore interactions between c-erbB family receptor tyrosine kinases. He described both ligand-dependent and independent EGFR homodimers. The data suggest that in the absence of an activating ligand approximately 20% of the receptors are in a dimeric state. Ligand-less c-erbB-2 receptor is particularly prone to dimerise, perhaps explaining its potency in signalling. He also presented work with a new technique using Quantum Dots coupled with the ligand EGF to look at receptor clustering and internalisation. He showed that these are transported around filopodia and that there is differential endocytosis of c-erbB family receptors following ligand binding.

Overall, the Symposium gave a breathtaking overview of the possibilities of dynamic visualisation of many of the fundamental processes of cancer progression, including oncogenic signalling, mitosis and cell motility at both the cellular and molecular level.

23. ASEICA–EACR Symposium "Survival Pathways and Drug Resistance"

The ASEICA–EACR symposium on "Survival pathways and drug resistance" was another symposium organised by EACR together with a national society member, here the Spanish Association for Cancer Research.

The first two presentations dealt with survival pathways. M. Karin (La Jolla, USA) discussed the importance of the IKK-nuclear factor κB (NFκB) signalling pathway for tumour promotion. NFκB is a key transcription factor in the immune system regulating diverse aspects of immune cell development, function and survival. However, the relevance of the IKK-NFκB pathway in tumour initiation, promotion and maintenance is less defined. NFκB activation leads to the upregulated expression of key anti-apoptotic proteins, such as Bcl-2, Bcl-x_L, inhibitors of apoptosis (IAPs) and FLICE-inhibitory protein (FLIP), thereby interfering with death receptor as well as mitochondrial death pathways. By its pro-survival function, NFκB may bridge the gap between inflammation and cancer. In gastric cancer, H. pylori-induced inflammation in infected mucosa cells is closely associated with tumour initiation. The infection-induced permanent activation of NFκB prevents the elimination of cells with DNA damage caused by environmental carcinogens or inflammation-induced reactive oxygen species, thereby promoting growth of genetically altered cells. In addition, using mice in which NFκB signalling through IKKß is selectively ablated in mucosa or myeloid cells, the importance of IKKß in the development of chemically induced colitis-associated colon carcinoma was demonstrated, again linking inflammation and cancer.

P. Krammer described the importance of the CD95 (Apo-1/Fas)/CD95L system in activation-induced cell death (AICD) of T-lymphocytes. In this regard, two principal modes of apoptosis signalling can be distinguished. In so-called type I cells, binding of CD95-L to its receptor leads to efficient formation of a death-inducing signalling complex (DISC) with strong activation of an initiator caspase at the DISC and mitochondria-independent direct triggering of the effector caspase cascade. In contrast, DISC-formation is reduced in type II cells and efficient triggering of the effector caspase cascade requires an amplification of the death signal via the mitochondrial death pathway. In an *in vitro*

model for the initiation and downregulation phases of the immune response, freshly activated human T-cells turned out to be resistant to AICD triggered by CD95-L, despite high expression of CD95. Further analysis revealed that those resistant cells represent type II cells with a block in the mitochondrial death pathway due to the high expression of Bcl-x_L. In contrast, prolonged culture in the presence of interleukin 2 (IL2) led to a switch of the death phenotype from type II to type I cells that were now sensitive to CD95-mediated AICD. Finally, P. Krammer discussed the physiological relevance of these two T-cellular phenotypes with respect to the interaction of T-cells with tumour cells in the so-called tumour counter-attack.

The last two speakers discussed the relevance of death pathways to drug resistance. C. Dive (Manchester, UK) described the impact of tumour hypoxia on the regulation of cell death via Bcl-2 family members. Oxygen deprivation has been shown to render cells resistant to apoptosis induction by radiation and chemotherapy. In this context, the adaptive response of the cells is mainly mediated via the transcription factor HIF-1 and the altered expression of HIF-1-regulated genes. In colon cancer cell lines, acute hypoxia led to the downregulated expression of several pro-apoptotic proteins of the Bcl-2 family, namely Bax, Bad and Bid, without having any effect on the anti-apoptotic counterparts, Bcl-2 and Bcl-x_L. Hypoxia-mediated downregulation of Bid occurred via HIF-1-mediated transcriptional repression, while Bax and Bad were downregulated independently of HIF-1. In HCT116 xenografts, Bid and Bax levels were also decreased in hypoxic regions of the tumours, pointing to the physiological relevance of these findings. Thus, by regulating expression of pro-apoptotic Bcl-2 family proteins, hypoxia may modulate the apoptotic threshold, promoting clonogenic resistance to chemotherapeutic drugs and radiation.

Finally, G. Del Sal (Trieste, Italy) described a novel mechanism for regulation of p53 and its relative p73 in response to genotoxic stress. Full activation of p53 involves several post-translational modifications. Binding to Pin-1, a phosphorylation-dependent prolyl-isomerase, induces a conformational change selectively in phosphorylated p53, thereby increasing its transcriptional activity. Stabilisation of p53 in response to genotoxic stress is severely impaired in Pin1(–/–) cells, leading to a decreased apoptotic response. Similarly, a phosphorylation-dependent interaction with Pin-1 is also required to induce conformational changes in p73 in response to chemotherapeutic drugs; this is required for stabilisation of p73 and subsequent apoptosis induction.

Overall, the Symposium gave fascinating insights into diverse mechanisms for the regulation and fine-tuning of the apoptotic response. Knowledge of these mechanisms is a prerequisite for the successful targeting of these pathways in cancer therapy.

24. Eurolife Workshop "siRNA in cancer research"

A small workshop arranged by the EUROlife consortium addressed the development and possible utilisation of siRNA technology in cancer research. The primary aim was to bring together scientists who employ this technique for a brainstorming discussion.

D. Kube (Göttingen, Germany) described the use of RNA interference (RNAi) to deplete STAT3 and showed the importance of STAT3 in the proliferation and survival of classical Hodgkin's lymphoma cells.

To get further insight into the molecular mechanism(s) of Imatinib mesylate resistance in cancer, H. Rumpold (Innsbruck, Austria) employed a strategy based on a transposon-mediated vector for establishing RNAi-mediated P-glycoprotein-deficient cell lines. Depletion of P-glycoprotein in this way in the leukaemic cell line, K562, restored resistance to Imanitib mesylate.

In an effort to eliminate androgenic stimulation of tumour cells, I. Eder (Innsbruck, Austria) combined traditional antisense phosphorothioate oligonucleotides with siRNA technology to inhibit the expression of the androgen receptor, an approach which they are now testing in a xenograft prostate cancer mouse model. Finally A. Jama (Huddinge, Sweden) employed siRNA-based approaches to dissect the role of the peptidiyl-prolyl isomerase Pin1 in intracellular signalling by Bruton's tyrosine kinase.

25. Carcinogenesis Young Investigator Award Lecture: Telomere epigenetics: a higher order control of telomere length in mammalian cells

M. Blasco (Madrid, Spain) received the Carcinogenesis Young Investigator Award, for her outstanding work on telomeres. She described how mammalian telomeres are assembled into heterochromatin containing histone H3 that is trimethylated on lysine9 (H3K9). When marked by trimethylated H3K9, telomeres attract heterochromatin-binding proteins of the HP1 family. This is followed by trimethylation of histone H4 at lysine 20, in a process that is sensitive to the availability of Rb family members. Abnormal telomeric elongation results from knockout of the Suv39h methyltransferases responsible for H3K9 methylation. These data indicate that the length of mammalian telomeres is subject to epigenetic control. Errors in this process might contribute to the differential resetting of telomere lengths in cloned animals. Furthermore, defects in epigenetic regulation of telomere length may also impact on the pathologies of aging and cancer.

26. Mike Price Lecture: "Targeting Ras signalling pathways in cancer: past, present and future"

J. Downward (London, UK) gave the second memorial Mike Price Lecture. This lecture has been instituted to acknowledge the enormous contribution Professor Price made to the EACR over the 21 years he was its Secretary General. J. Downward reviewed the different intracellular pathways that Ras regulates and the clinical experience to date with using farnesyl transferase inhibitors to block Ras signalling. These have been somewhat disappointing for two main reasons; first, many tumours contain mutated K-ras genes which are not affected by the drugs; and, second, off target effects due to their inhibition of other cellular systems proved unacceptably toxic. He went on to describe new functional genomic approaches to identify targets in the Ras-activated pathways using libraries of siRNAs targeting several thousand gene products. For example, the transcription factor, Cutl1, was identified in an siRNA library screen for genes that affect cell motility in culture. Genome-scale screens have considerable potential to identify novel targets for cancer treatment.

Conflict of interest statement

None declared.

Acknowledgements

Because of the magnitude of EACR-18, it has not been possible to cover every session in this Review, let alone each of the excellent presentations, and we apologise for the omissions. We are extremely grateful to the chairpersons who kindly contributed summaries of their sessions for this report.