mutations can also result in increased susceptibility to specific changes and situations. The concept that a particular mutation has deleterious consequences under specific conditions is known as synthetic lethality. Two genes are defined as synthetic lethal when cells die if they have both genes mutated but can survive if either gene alone is mutated. The approach of exploring synthetic lethal gene-gene interactions is attractive because it turns a hallmark of cancer cells, specific mutations, into a weakness that can be explored therapeutically. The development and application of the RNAi technology in mammalian cells has enabled us to systematically examine the consequence of inactivation of large numbers of individual genes in human (tumor) cell lines with defined tumor specific genetic alterations. This lecture will focus on the use of large collections of synthetic siRNAs in a screening model based on primary human cells with defined genetic alterations for the discovery of specific synthetic lethal interactions.

128 INVITED

Investigation of RAS and PI 3-kinase signaling networks in cancer using synthetic lethal screens

J. Downward[1]. [1]*London Research Institute, Signal Transduction Laboratory, London, United Kingdom*

The RAS oncogene is very frequently activated in human tumours and, as a result, the signaling pathways it controls have been well studied. However, effective targeting of these pathways as a therapeutic approach to cancer has remained elusive.
In order to find novel targets in RAS signaling pathways, we have undertaken a number of studies using large-scale RNA interference libraries. One has been a screen for genes that cause apoptosis in RAS oncogene addicted cells. In this way a number of pathways have been identified that are important for survival of RAS transformed, but not normal, cells. Some of these have not previously been implicated in RAS signaling. Further investigation indicates that some of these hits reflect true RAS oncogene addiction while others represent acute synthetic lethality of target knockdown with RAS signal. Targeting both mechanisms, synthetic lethality and oncogene addiction, together may provide optimal differential killing of cancer cells relative to normal cells.
An example of the potential power of blocking RAS signaling has been provided recently when we introduced point mutations into the gene encoding the phosphatidylinositol 3-kinase p110α, which block its ability to interact with activated RAS. Mice homozygous for the p110α mutation show a very dramatically reduced rate of cancer incidence in two models of RAS oncogene driven tumour formation. Failure of RAS to engage PI 3-kinase results in elevated rates of apoptosis in tumour precursor lesions and consequent failure of tumours to develop. Targeting this interaction may have clear therapeutic potential.

Special Session (Tue, 22 Sep, 13:30−14:30)
Breast cancer in the elderly

130 INVITED

Breast cancer in the elderly: a medical perspective

H. Wildiers[1]. [1]*U.Z. Gasthuisberg, Department of General Medical Oncology – Multidisciplinary Breast Centre, Leuven, Belgium*

Breast cancer is the most commonly diagnosed cancer and leading cause of cancer mortality in women worldwide. The elderly comprise a large part of the breast cancer population, and there are important specific considerations for this population. From the medical perspective, mainly the use of chemotherapy is challenging since toxicity increases with age and efficacy in terms of overall survival effect might decrease.
Certainly in the adjuvant setting, the balance between benefits and harm from chemotherapy can be delicate, and careful assessment of the patient including some form of geriatric assessment are crucial. Treatment with adjuvant chemotherapy should not be an age-based decision but instead take into account individual patients' estimated absolute benefit, life expectancy, treatment tolerance, and preference. Recent studies indicate that adjuvant chemotherapy is mainly beneficial for older people with hormone insensitive tumors and nodal involvement, while the benefit is much less clear for those with highly hormone sensitive tumors. However, there remains considerable uncertainty remains regarding the subgroups of older women most likely to benefit.
Also concerning the choice of chemotherapy, specific regimens/aspects can be considered. Anthracyclines are usually preferred over CMF in elderly patients with breast cancer. A recent phase III study showed that a 'soft' chemotherapy regimen like oral capecibatine is clearly inferior to classical AC/CMF in this population. Taxane regimens such as TC are a valuable alternative to anthracyclines without intrinsic cardiotoxicity.
In metastatic disease, quality of life is more important than quantity of life, certainly for older individuals. Preference is often given to chemotherapeutic agents with 'safer' profiles such as weekly taxane regimens, newer less cardiotoxic anthracycline formulations, capecitabine, gemcitabine, and vinorelbine.
Targeted therapies such as trastuzumab and bevacizumab have been shown to be useful in the treatment of breast cancer. The risk of side effects increases with age however, and certainly for antiangiogenic compounds, the balance between benefits and risks/costs should be carefully weighed.

Special Session (Tue, 22 Sep, 13:30−14:30)
Individualisation of treatment based on pharmacokinetics and pharmacogenomics

131 INVITED

Population-based PK/PD modelling

S. Kaestner[1]. [1]*Plymouth hospitals NHS Trust, Medicines Managment Team, Plymouth, United Kingdom*

Cancer chemotherapy drugs are characterised by narrow therapeutic windows and significant intra- and inter-patient variability in therapeutic and toxic effects. In an attempt to reduce this variability most chemotherapy doses are traditionally individualised according to patient body surface area, but for many drugs this approach appears to have limited benefit. In addition, subsequent dose reductions or delays are usually made in response to excessive toxicity, while it is less common to increase doses for patients who tolerate treatment well to avoid the risk of under-dosing and suboptimal therapeutic effects.
The pharmacokinetics (PK) and pharmacodynamics (PD) of chemotherapy drugs and their metabolites may be influenced by various intrinsic and extrinsic factors, such as for example gender, age, body size measures, nutritional status, renal/hepatic function, disease, tumour characteristics, drug resistance, enzyme functions, genetics, concomitant medications, smoking and diet. It is therefore complicated to select a dose with maximal anti-tumour effects and acceptable levels of toxicity, but it is clear that an understanding of the sources of variability is crucial to the optimal individualisation of therapy. In population-based PK/PD modelling the potential contributions of these different factors to the intra- and interpatient variability in PK/PD are studied in large groups of patients. Statistical models can then be used to develop optimised prospective dosing strategies for specific populations, subpopulations, or individual patients based on the most relevant variables. Population PK and so called Bayesian models have been successfully developed and applied prospectively for various cytotoxic drugs, including paclitaxel and carboplatin. However, the clinical application of the approach may be limited by the lack of relationships between PK and PD for many chemotherapy drugs. Additionally, the difficulties in measuring the clinical effects of chemotherapy drugs most commonly results in the use of toxicity as the PD measure, and its use as a surrogate for clinical effect may not be appropriate in all settings. The clinical feasibility of PK/PD modelling therefore needs to be carefully assessed in each case.

132 INVITED

Individualisation of cancer treatment by pharmacogenetics

H.J. Guchelaar[1]. [1]*Leiden University Medical Center, Dept. Clinical Pharmacy & Toxicology, Leiden, The Netherlands*

Although in recent years, chemotherapeutic options for treatment of cancer have expanded, overall benefit – both with respect to efficacy and toxicity – could be improved. Pharmacogenetics studies the association between heritable functional variants in DNA (genotype) with outcome of therapy (phenotype). In recent years, pharmacogenetics in oncology has become an increasing field of research. Pharmacogenetics in oncology will ideally allow oncologists to individualise therapy based on a genetic test result. Severe toxicity and clinically significant underdosing may be avoided, whereas predicted non-responders can be offered alternative therapy.
In this presentation an overview of pharmacogenetics in oncology will be given including: thiopurine *S*-methyltransferase (TPMT) enzyme activity and 6-mercaptopurine (6MP) in treatment of acute lymphoblastic leukaemia (ALL); dihydropyrimidine dehydrogenase (DPD) enzyme activity and 5-fluorouracil (5FU) or capecitabine; uridine diphosphate glucuronosyl transferase (UGT) activity and SN-38 (active metabolite of irinotecan); glutathione S-transferase (GST) and platinum-based drugs or irinotecan; excision repair cross complementing group 1 (ERCC1) and platinum-containing compounds; cytochrome P450 2D6 (CYP2D6) enzyme and tamoxifen in treatment of breast cancer; methylene tetrahydrofolate reductase (MTHFR) and thymidylate synthase (TS) and 5FU.

The proof of concept of pharmacogenetics, namely that drug response is a heritable trait, is accepted. However, despite emerging evidence, pharmacogenetic testing has not yet found its way to routine patient care. Replication of earlier findings and validation in prospective trials are required to establish clinical value and cost-effectiveness of pharmacogenetic testing in oncology. Moreover, pharmacogenetics will increasingly be used in discovery and development of future anticancer drugs.

Advocacy Session (Tue, 22 Sep, 13:00–14:30)
Cancer in the workplace

134 INVITED

EU Plan for a safer workplace: the Community Strategy on Health and Safety at Work 2007–2012

F.J. Alvarez Hidalgo[1]. [1]*European Commission, Unit "Health Safety and Hygiene at Work", Luxembourg, Luxembourg*

Thanks to the adoption and application in recent decades of a large body of Community laws on the protection of the health and safety of workers at work, it has been possible to improve working conditions in the EU Member States and make considerable process in reducing the incidence of work-related accidents and illnesses.
The most recent data available show that, during the period of the previous Community strategy 2002–2006, the rate of fatal accidents at work fell by 17% while the rate of workplace accidents leading to absences of more than three days fell by 20%.
In spite of the progress achieved, the number of accidents at work and the incidence of occupational illnesses are still too high. This situation takes a heavy human toll in terms of the suffering endured by workers and their families, but also generates considerable economic repercussions which have an impact on business competitiveness and productivity.
It is therefore important to pursue a joint action strategy in this area at national and Community level determining the objectives and priorities which must be targeted in order to achieve the change in attitudes needed if regulatory provisions are to be applied effectively; this strategy should be accompanied by measures to provide information and training as well as technical assistance to SMEs and to promote a healthy working environment.
An ongoing, sustainable and uniform reduction in accidents at work and occupational illnesses continues to be the prime objective of the Community strategy for the period 2007–2012, adopted by the European Commission the 21 February 2007. In the Commission's view, the overall objective during this period should be to reduce the incidence of accidents in the EU by 25%.
In order to achieve this ambitious goal, the following main objectives are contained in the new Community Strategy:
- guarantee the proper implementation of EU legislation;
- support SMEs in the implementation of the legislation in force;
- adapt the legal framework to changes in the workplace and simplify it;
- promote the development and implementation of national strategies;
- encourage changes in the behaviour of workers and encourage their employers to adopt health-focused approaches;
- develop methods for identifying and evaluating new potential risks;
- improve the tracking of progress;
- promote health and safety at international level.

136 INVITED

Working with cancer – how to benefit from staying in employment

P. Litchfield[1]. [1]*BT Group plc, Chief Medical Officer, London, United Kingdom*

The European population is ageing at the same time as working lives are being extended. The early detection of cancers is improving as is the effectiveness of treatment. The consequence of these long term trends is that more people in work are developing cancer and more employees are surviving to continue their careers. Employers therefore need to give greater consideration to cancer as a workplace health issue and how to improve the effectiveness of their policies, procedures and practices in managing people who become ill. The moral case for supporting people who develop cancer to remain in work is underpinned by increasing legislative requirements and the prohibitive costs of medical retirement.
In many societies cancer remains a taboo subject which is rarely spoken about. Consequently knowledge of the effects on people of cancer and its treatment is not well understood by the general population. The great majority of healthcare professionals are poorly informed about the nature of work outside their own industry and are rarely skilled at assessing functional capability. Neither patient nor practitioner may see work as an important outcome measure of cancer treatment although it is now well established that work can have positive health effects and that unemployment is significantly detrimental. Educating the various stakeholders is therefore an essential precursor to improving employment rates of those with cancer.
Overcoming the barriers to remaining in employment during and after treatment for cancer can appear daunting but, in practice, is usually straightforward. The majority of adjustments required are attitudinal and administrative rather than physical and therefore requiring capital expenditure. Recognising the nature of common problems, such as fatigue, allows managers to apply common sense in adjusting work load and time without having to rely overly on professional guidance which introduces delay and expense. Making time to listen and having access to guidance on what (or what not) to say are simple measures that can be applied universally and which make a huge difference. Returning to work can be a stressful time for both patient and manager but realistic planning can diffuse much of the stress and greatly improve the chances of success. After initial rehabilitation most people need few if any adjustments and reminding managers of the effectiveness of modern treatment when they are considering the recruitment or promotion of cancer survivors may be necessary.
The key to staying in employment with cancer is strong partnership working between the individual concerned and their manager. Patients need to be honest and open about their capability and managers need to listen and avoid making assumptions – both need to be realistic. Third parties such as family, treating clinicians and occupational health professionals should ensure that the wants and needs of the cancer sufferer remain paramount, within the constraints of what is practicable, and resist being either overprotective or cavalier with their advice.

Scientific Symposium (Tue, 22 Sep, 14:45–16:45)
Targeted therapy in breast cancer

137 INVITED

Optimising anti-HER2 therapy in early breast cancer

M. Piccart[1], P. Bedard[2], E. de Azambuja[3]. [1]*Institute Jules Bordet – BIG aisbl, Medicine Department, Brussels, Belgium;* [2]*Institute Jules Bordet – BIG aisbl, Medicine, Brussels, Belgium;* [3]*Institute Jules Bordet, Breast, Brussels, Belgium*

Results are now available from six trials randomizing more than 13,000 women with HER-2 positive early breast cancer to trastuzumab versus non-trastuzumab based adjuvant chemotherapy. Aside from the negative PACS 04 trial (528 HER-2 positive patients only), these studies demonstrate remarkably consistent results: the addition of trastuzumab significantly reduces recurrence by approximately 50% and improves overall survival by 30% irrespective of tumour size, nodal status, schedule of administration, and type of chemotherapy. Nevertheless, there remain many unanswered questions regarding optimal adjuvant trastuzumab, such as: i) the relationship between trastuzumab efficacy and markers of HER2 assessment (HER2 protein expression, gene copy number, and chromosome 17 polysomy), topoisomerase II co-amplification, c-MYC and PTEN; ii) the selection of patients for non-anthracycline based chemotherapy; iii) the decision to administer trastuzumab in a sequential or concurrent manner with chemotherapy; iv) the minimal effective duration of trastuzumab and v) the treatment of small (<1 cm) node-negative HER-2 positive tumours. Longer follow-up from the adjuvant trastuzumab trials suggests that trastuzumab-induced cardiac toxicity may be time-limited and reversible with discontinuation of trastuzumab and the introduction of cardiac medications. However, longer follow-up is required to further confirm this hypothesis. Future studies with promising novel anti-HER2 agents, such as the ongoing ALTTO trial with lapatinib, will use cutting edge technologies to prospectively identify biomarkers for rational tailing of anti-HER-2 targeted therapy.

138 INVITED

Anti-HER2 therapy treatment after progression

G. von Minckwitz[1]. [1]*German Breast Group, GBG Forschungs GmbH, Neu-Isenburg, Germany*

Treatment with anti-Her2 agents, especially trastuzumab, has been proven in vitro and clinically to be highly synergistic in combination with various cytotoxic and endocrine agents. Blocking of the down-stream proliferation signal of the HER2 receptor, either by binding of an antibody to the external domain or of an tyrosine-kinase inhibitor to the intracellular ATP binding site of this receptor is considered as the main mechanism of action. Further mechanisms under discussion are the prevention of the cleavage of the