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

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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

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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

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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

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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.