are well designed, the study group well defined and the treatments and assessment of long term outcome (including toxicity) are standardised.

Keynote Lecture (Wed, 23 Sep, 11:15−12:00)
Insights into the cancer cell, stem cell interface through systems biology

223 INVITED

From RNAi screens to molecular function: A systematic pipeline for gene function in mammalian cells

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RNAi screens typically deliver a large number of candidate genes that play a role in a biological process. The validation of these candidates and the dissection of the molecular mechanism are often time consuming and cumbersome. Hence, RNAi libraries employed during the screening process should be of high quality to avoid tedious downstream work. We have developed endoribonuclease prepared (e)siRNAi libraries for efficient and specific RNAi screening. The advantages of esiRNAs will be discussed and example screens will be presented. We have also developed a pipeline using BAC recombineering technology and tissue culture transgenesis to streamline the analysis of hits identified in large scale RNAi screens. Together, these resources represent a seamless pipeline for the systematic analysis of mammalian genes.

Special Session (Wed, 23 Sep, 13:30−14:30)
What is new in the pathogenesis of urothelial cancer?

224 INVITED

Hereditary factors in bladder cancer

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First degree relatives of patients with bladder cancer have a two-fold increased risk of bladder cancer but high-risk bladder cancer families are extremely rare. There is no clear Mendelian inheritance pattern that can explain the increased familial risk. This makes classical linkage studies for the mapping of susceptibility genes impossible. The disease is probably caused by a combination of exposure to exogenous carcinogens and a large number of susceptibility genes with modest effects.
Genome-wide association studies (GWAS) are better suited to identify these genes. Three of these studies are ongoing of which one reported the first results. In this presentation, an overview will be given of hereditary factors in bladder cancer and the relevance of the results of the GWAS will be discussed.

225 INVITED

Histopathological profile of bladder cancer

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Bladder tumors represent a heterogeneous group of cancers that include those that are:
1. Papillary in nature and limited to the mucosa (Non-invasive, stage Ta).
2. High grade and flat confined to the epithelium (Non-invasive, stage Tis)
3. Invasive into the lamina propria or submucosa (Early invasive, stage T1)
4. Invasive into the muscularis propria or beyond (Invasive, stage T2-T4).

The natural history of these bladder cancers is that of recurrence of disease and progression to higher grade and stage disease. Furthermore, recurrence and progression rates of superficial bladder cancer vary according to several tumor characteristics, mainly tumor grade and stage. The most recent World Health Organization (WHO) classification of tumors of the urinary system includes epithelial abnormalities and metaplasia as well as urothelial dysplasia and carcinomas in situ as flat lesions. The papillary lesions are broadly subdivided, following the current WHO classification, into benign (papilloma and inverted papilloma), papillary urothelial neoplasia of low malignant potential and non-invasive papillary carcinoma (low or high grade). Invasive papillary carcinoma and non-papillary (solid) carcinomas are subdivided into low and high grade neoplastic lesions. Each of these lesions is defined with strict morphological criteria to provide more accurate information to urologists and oncologists in managing patients. There is still debate in the literature as to whether the 2004WHO system should be the only one to be used in clinical practice. The key points of the latest World Health Organization (WHO) classification of non-invasive urothelial tumors are: a. The description of the categories has been expanded in the current version to improve their recognition, b. One group (papillary urothelial neoplasm of low malignant potential) with particularly good prognosis does not carry the label of 'cancer', c. It avoids use of ambiguous grading such as grade 1/2 or 2/3 (according to the WHO classification published in 1973, d. The group of non-invasive high grade carcinoma is large enough to contain virtually all those tumors that have biological properties (and a high level of genetic instability) similar to those seen in invasive urothelial carcinoma. e. This scheme is meant to replace the 1973 WHO classification. From the practical point of view, the use of both the 1973 and the latest WHO classifications is recommended until the latter is sufficiently validated. This presentation summarizes the recent literature concerning important issues in the pathology and the clinical management of the patients with bladder urothelial carcinoma. The initial proposal of the WHO has been achieved with most reports clearly recognizing that categories are better defined than in previous classifications. Questions such if PUNLMP remains as a clinically useful category or if this category should be expanded including all low grade Ta lesions (PUNLM and Low grade papillary carcinoma) as a wider low malignant potential neoplastic category not labelled as cancer needs to be discussed in the near future. In this presentation, emphasis is placed on macroscopic appearance, and synchronous or metachronous presentation (field disease vs. monoclonal disease with seeding), classification and microscopic variations of bladder cancer with clinical significance, TNM distribution and the pathologic grading according to the most recent WHO proposal.

226 INVITED

Genomic alterations in urothelial carcinoma subgroups

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Bladder tumors are heterogeneous in their histopathology and clinical behaviour. Currently, assessment of risk for recurrence and progression to invasive disease is not precise and response to specific therapies cannot be predicted accurately. It is anticipated that a thorough knowledge of the molecular alterations that are involved in the development and progression of bladder cancer will lead to greater predictive power and the application of targeted therapies. The current state of knowledge of genomic alterations found in urothelial carcinoma will be summarised.

Special Session (Wed, 23 Sep, 13:30−14:30)
Immune system and ovarian cancers

228 INVITED

Antigen specific active immunotherapy for ovarian cancer

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Introduction: Epithelial ovarian cancer is the most frequently diagnosed malignancy of the ovaries. Standard therapy consists of cytoreductive surgery, an attempt to remove as much tumour bulk as possible, followed by platinum-containing chemotherapy. Although initial response rates to primary therapy are high, the majority of patients with advanced stage disease relapse. The observation that survival rates were higher in patients with certain intra-tumoral immune cells (i.e. T-lymphocytes), suggested that the stimulation of anti-tumour immune responses, i.e. immunotherapy, might be a useful approach to improve the prognosis of patients with ovarian cancer. In this survey, the feasibility of antigen-specific active immunotherapy is evaluated. As immunotherapy is a relatively novel treatment strategy for ovarian cancer, not only randomised controlled trials, but also early phase studies were included in this review.
Material and Methods: Thirty studies evaluating antigen-specific active immunotherapy in 1230 patients with ovarian cancer were identified with a systematic search of study reports published between 1966 and 2008. Information on clinical responses, survival, immunological responses, and adverse events was available for 18, 18, 29, and 22 studies respectively.
Results: the most frequently described strategy (1134 patients in 14 studies) was the administration of antibodies targeting CA-125, better known as a tumour marker for ovarian cancer. Most of these studies were

non-randomised studies, primarily evaluating safety and immunological responses to treatment. Five studies described grade III/IV flu-like symptoms and gastro-intestinal events in 7−30% of patients. Anti-CA-125 antibodies and CA-125 specific T-lymphocytes were frequently detected, albeit response rates varied between studies. Despite the promising immunological responses in these studies, two randomised placebo controlled trials found equal progression free and/or overall survival rates for patients treated with placebo or CA-125 directed antibody.
Antigen-specific active immunotherapy studies were generally small phase I or II studies primarily investigating safety and immunogenicity of a vaccine. Overall, treatment was well-tolerated, with local inflammatory side effects at the site of immunisation most frequently reported. Anti-tumour immune responses, i.e. tumour-specific antibodies and T-lymphocytes, were induced by most strategies studied. Whether these are also clinically active, still has to be evaluated in large randomised controlled trials.
Conclusion: A general observation of this review, which forms a major limitation for reliable conclusions regarding the achievability of immunotherapy as a treatment for ovarian cancer, is the lack of uniformity in trial conduct, clinical and immunological response definitions and trial reporting. An additional concern is the observation that although the majority of studies were phase I or II trials, adverse events were often not or only sparsely mentioned. We strongly advocate the adoption of universally accepted immunological and clinical response definitions, guidelines for adverse events reporting, as well as internationally accepted directives for trial conduct and reporting to ensure that in the future it will be possible to make reliable inferences about the feasibility of immunotherapy as a treatment for ovarian cancer.

Special Session (Wed, 23 Sep, 13:30−14:30)
Cancer stem cells and radiation resistance

229 INVITED

Radioresistance of cancer stem cells

T. Brunner[1], O. Al-Assar[1], R.J. Muschel[1], W.G. McKenna[1]. [1]*Churchill Hospital, Gray Institute for Radiation Oncology and Biology University of Oxford, Oxford, United Kingdom*

Recent publications are providing increased support for the role of cancer stem cells (CSC) in different human malignancies. CSC are defined as a subpopulation of tumour cells which have the capacity to self-renew and to generate the heterogeneous lineages of cancer cells within a tumour. CSC were initially isolated from human acute myeloid leukaemia, and were subsequently identified in a number solid cancers. It is postulated that CSC are responsible for recurrences and metastases after anticancer treatment because they escape conventional therapies. This implies that better knowledge of the biological differences between CSC and non-CSC may improve tumour therapy dramatically. To achieve an improved curative effect of radiation therapy only the radiosensitivity of cancer stem cells should matter since these are the cause of local tumour recurrences after complete responses. The isolation of CSC from solid tumours can be done with sorting methods for Hoechst dye excluding side populations (SP) cells and more importantly with CSC-specific cell surface markers. Radiation is one of the main modalities used in the treatment of solid tumours. Our own work tested the hypothesis that cancer cell lines would contain a subpopulation of CSC with lower intrinsic radiation sensitivity compared to the non-CSC in the same culture based on several studies which have demonstrated the relative radioresistance of CSC in brain tumours, and breast cancer. In this study, we used a panel of cell lines from five tumour types to examine the clonogenic survival and γH2AX foci formation of CSC isolated using the respective markers for the corresponding tumour type. While in some of the cell lines we could confirm a less radiosensitive phenotype the majority of the lines did not. In conclusion we can state that, although we reliably identified CSC in cell lines we could not confirm the radioresistant phenotype in this model in general. This is critical to consider in exploring models essential for assessing the biological advantage of CSC.

230 INVITED

Cancer stem cells as determinant of tumour radioresistance

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Recent experiments which combined isolation of tumour cell population based on specific surface markers with tumour transplantation assays support that cancer stem cells are a specific subpopulation of all cancer cells. The proportion of cancer stem cells in most tumours appears to be very small compared to the vast majority of cancer cells which are non-tumourigenic. An overview of experimental and clinical data will be given to explore methodology to measure stem cell biology for radiotherapy and the question which role the number of cancer stem cells, their intrinsic radiosensitivity, and other radiobiological parameters play in tumour radioresistance will be given. Recurrent tumours after radiotherapy originate by definition from at least one surviving cancer stem cell while permanent local tumour control requires inactivation of all cancer stem cells. Local tumour control assays therefore functionally measure survival of the subpopulation of cancer stem cells, and can be considered as a gold standard in this respect. In contrast changes in tumour volume after therapy, i.e. tumour response, are governed by the changes in the mass of tumour cells, i.e. primarily by the non-stem cells. Today the vast majority of preclinical studies in cancer research use volume dependent parameters such as tumour regression or tumour growth delay as experimental endpoints. This carries the substantial risk that new treatments may be optimized for their effect on the bulk of non-stem cancer cells, with no improvement in the curative potential. Experimental data provide evidence for the importance of cancer stem cell number and density for local tumour control and suggest that the response of cancer stem cells and non-tumourigenic cells to radiation and combined treatment may dissociate. The question whether cancer stem cells are intrinsically more radio resistant than non-stem cells can not be answered unequivocally at the present time but is important, particularly for the development of bioassays to predict radioresistance before or during radiotherapy.

Special Session (Wed, 23 Sep, 13:30−14:30)
Imaging in drug development

231 INVITED

Imaging in early drug development-the pharmacology audit trail

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Novel imaging technologies offer unprecedented opportunities to image tumor biology. Rather than merely documenting site, size and morphology of tumors we can now image microvascular function, hypoxia, tumor metabolism and proliferation, and apoptosis. Currently anatomical imaging measurements for measurement of tumor response are used in late phase trials as a surrogate for the clinical endpoint of change in overall survival and in early phase trials as an indicator of anti-tumor activity. However anatomical techniques may be inadequate to determine if a drug is worth taking forward to Phase II for compounds which produce prolongation of stable disease rather than tumor shrinkage and for drugs targeting pathways which may only be driving tumor growth in a subset of tumor types. In these cases, other imaging techniques such as Dynamic Contrast Enhanced MRI (DCE-MRI) to measure changes in tumor microvasculature, ^{18}Fluoro-Deoxy Glucose PET (FDG-PET) to measure changes in tumor metabolism and glucose transport, and ^{18}Fluorine-Labeled Thymidine PET (FLT-PET) to measure changes in tumor metabolism, can be used to document the 'pharmacology audit trail'. This 'audit trail' requires demonstration that the drug achieves biologically relevant exposures, that it modulates the target of interest, that this target modulation translates into anti-tumor activity, and support for selection of a dose or dose range, and the dose schedule to take forward into Phase II trials.
Effective use of these imaging tools in early phase development requires some modification of 'traditional' early phase trials design and implementation. Ideally the same techniques planned for early phase clinical trials should be used in pre-clinical models to compare dose response and time course of the imaging endpoint with dose response for anti-tumor efficacy. Use of the above imaging techniques may require expansion of cohorts to ensure an effect of clinical relevance can be measured. This requires a larger investment in Phase I, but would allow a 'proof of confidence' decision, and a No Go if no/limited effects are seen in the tolerable dose range. The more novel techniques are by their nature less standardized, with significant differences in methodology between centers even for such a widespread technique as FDG-PET. There is frequently a lack of data on repeatability between and within patients and sites and over the timepoints of interest. Knowledge of the multi-center repeatability is required to adequately size cohorts for assessment of treatment effect. Image analysis methodology needs validation, with quality control of initial image acquisition. If data are to be shared across multiple sites there is a need for a centralized database, compatible with the different hardware and software at each site. Industry needs to work with academia to develop acceptable standards for these steps. The presentation will discuss updates on repeatability in multi-center trials for dynamic MRI, FDG and FLT-PET, and illustrations of how decision-driving data utilizing these techniques have been obtained in preclinical and clinical experiments for compounds in the BMS pipeline including brivanib, a FGFR and VEGFR2