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Human Cancer Epigenetics

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An altered pattern of epigenetic modifications is central to many common human diseases, including cancer. Many studies have explored the mosaic patterns of DNA methylation and histone modifications in cancer cells on a gene-by-gene basis, among them the seminal finding of transcriptional silencing of tumour suppressor genes by CpG island promoter hypermethylation. Epigenetic gene inactivation in transformed cells involves many "belts of silencing". We are in the process of completing the molecular dissection of the entire epigenetic machinery involved in methylation-associated silencing, such as DNA methyltransferases, methyl-CpG binding domain proteins, histone deacetylases, histone methyltransferases, histone demethylases and Polycomb proteins. The first indications are also starting to emerge about how the combination of cellular selection and targeted pathways leads to abnormal DNA methylation. In addition to classical tumour-suppressor and DNA repair genes, epigenetic gene silencing includes ncRNAs with growth inhibitory functions. Recent technological advances are now enabling cancer epigenetics to be studied genome-wide. It is time to "upgrade" cancer epigenetics research and put together an ambitious plan to tackle the many unanswered questions in this field using genomics approaches to unravel the epigenome.

Scientific Symposium (Sat, 24 Sep, 16:00−18:00) **Role of the Microenvironment in Lymphomas**

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The Microenvironment in B Cell Malignancies − a New Target for Therapy?

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In recent years, our knowledge on the pathogenesis of B-cell chronic Lymphoproliferative disorders, including Chronic Lymphocytic Leukemia (CLL), Follicular Lymphomas (FL) and Marginal Zone Lymphomas (MZL) has radically changed, thanks to a flurry of novel findings. Though genetic events play a fundamental role in initiating the disease with characteristic genetic lesions, stimuli originating from the microenvironment are indispensable for the onset as well as for the propagation of the neoplastic clone. In particular, several evidences suggest that non-neoplastic cells present in the invaded tissues, e.g. T lymphocytes, are involved in the maintenance of these diseases, providing key signals for the survival and accumulation of the monoclonal B cells. Among others, the CD40:CD40L interactions occurring between by-stander T cells and neoplastic B Lymphocytes have been shown to occur in several cases in the context of the tissues invaded by indolent lymphomas.
In addition, novel findings strongly support the possibility that stimulation through the B-cell antigen receptor (BCR) is crucial for the selection and expansion of the malignant clone. Direct and indirect signs of an in vivo antigen encounter are now evident in these diseases as suggested by distinct Heavy chain variable (IGHV) gene repertoires and the presence of somatic mutations in a large fraction of cases. More specifically, several groups have reported that CLL patients may express closely homologous if not identical ("stereotyped") complementarity-determining region 3 (CDR3) sequences on heavy and light chains, thereby strongly implying the recognition of discrete antigens or classes of structurally similar epitopes.
Finally, in few instances, the possibility of a role of inflammatory events as well as of infectious agents has been put forward if not clearly demonstrated.
For all these reasons, new therapeutic strategy can be envisioned for a better control of Chronic lymphoproliferative disorders, not only aiming at directly hitting the neoplastic clone but also at interfering the deadly interactions with the surrounding microenvironment. This could lead to less toxic though more effective treatments.

98 INVITED

The Stromal Cell Niche in Folliclar Lymphoma

Abstract not received

99 INVITED

The Microenvironment in Hodgkin Lymphoma − Pathogenic and Clinical Relevance

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Hodgkin lymphoma (HL) is among the most curable human neoplasms seen in adults and accounts for about 11% of all malignant lymphomas. Most of the patients can be cured with modern treatment strategies, whereas about 20% will die following relapse or progressive disease. HL is unique among virtually all cancers since the malignant Hodgkin Reed Sternberg (HRS) cells in classical Hodgkin lymphoma (cHL) and the lymphocyte predominant (LP) cells in nodular lymphocyte-predominant HL (NLPHL) cells are significantly outnumbered by non-neoplastic cells in the surrounding microenvironment. The clinical and pathological features of cHL reflect an abnormal immune response that is thought to be due to expression of a variety of cytokines and chemokines by the HRS cells shaping the cellular composition of affected lymph nodes and maintaining inflammation. This specific milieu contributes to the immune privilege of the malignant cells and recent studies have identified some of the genetic events underlying the unique crosstalk with the microenvironment. Moreover, gene expression signatures derived from non-neoplastic cells have been found to be associated with therapy outcomes and validation studies using immunohistochemistry identified certain cellular components as novel biomarkers for outcome prediction in HL. Unequivocally, the number of tumour associated macrophages and cytotoxic T cells have been linked to unfavorable outcome in retrospective studies. Incorporation of novel biomarkers such as tumour associated macrophages into prognostic models may improve risk stratification to guide treatment decisions, enhance our understanding of the biological correlates of treatment failure, and identify therapeutic targets at the interface between the malignant and reactive cells.

100 INVITED

Impact of the Tumour Microenvironment on Prognosis in Follicular Lymphoma

Abstract not received

Scientific Symposium (Sat, 24 Sep, 16:00−18:00) **Research Strategy of the Paediatric and Adolescents European Tumour Groups**

101 INVITED

Soft-tissue Sarcomas

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Soft tissue sarcoma (STS) accounts for around 7% of all malignancies in the paediatric age group. About 50% of these are rhabdomyosarcoma (RMS) and the remainder are a group of differing diseases (sometimes termed non-rhabdomyosarcoma soft tissue sarcoma or NRSTS), some of which are characteristically found in infants and young children (eg infantile fibrosarcoma, extracranial malignant rhabdoid tumours) and others, typically in older children and young adults, which occur also in the adult age group (eg synovial sarcoma, malignant peripheral nerve sheath tumour). A coordinated research strategy in Europe is possible for the commoner RMS but it is more difficult in NRSTS with small groups of disparate diseases: paediatric oncologists need to work with our adult colleagues to improve treatments in NRSTS tumours.
A number of key challenges remain in the management of RMS. These are to improve local control rate, to reduce distant relapses, especially in patients presenting with metastatic disease, to increase salvage in relapse and to minimize overall (early and late) morbidity. To address such questions in Europe requires collaborative studies.
The European Paediatric Soft Tissue sarcoma Group (EpSSG) was formed in 2000 to develop collaborative European studies in RMS and NRSTS. It has an open observational study in localized NRSTS (EpSSG NRSTS 2005). Its ongoing study in localized rhabdomyosarcoma (EpSSG RMS 2005) asks randomized questions about the role of the addition of doxorubicin to induction chemotherapy and the role of 6 months of maintenance therapy with vinorelbine and oral cyclophosphamide in high risk patients. The EpSSG, working with the ITCC (Innovative Therapies for Children with Cancer), has been closely involved in the development of the current BERNIE study in patients at first presentation of metastatic RMS or other STS. This pharma-sponsored randomized phase II study is the first European paediatric study to incorporate a novel agent, in this case the

antiangiogenic agent bevacizumab, in newly diagnosed patients with STS with the hope of improving EFS in these poor prognosis patients.
With the ITCC the EpSSG group has now developed a strategy for the introduction of novel agents in RMS and is expecting to open an investigator led, limited centre, randomized, phase II study in 2011 to define the optimal chemotherapy backbone in relapsed/refractory patients to which novel agents can subsequently be added. In addition, following a series of workshops, the EpSSG and ITCC have together defined a model paediatric investigation plan to guide the investigation of novel agents in children with RMS. The intention is that a clear research strategy and engagement with pharma at an early stage of drug development may help to realise some of the key challenges in improving the management of RMS.

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Recent Advancements for High Risk Neuroblastoma (HRN) in Europe Through the SIOP Europe Neuroblastoma Group (SIOPEN)

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Neuroblastoma, a cancer of the sympathic nervous system, is a heterogeneous disease with over 50% of patients having a high risk phenotype characterised by wide-spread dissemination or unfavourable biology in localised disease. Their long term survival is poor even if intensive multimodal treatments are used.
The HR-NBL1/SIOPEN trial randomised 2 myeloablative (MAT) regimens for this setting: BuMel (oral busulfan till 2006, $4\times150\,mg/m^2$ in 4 equal doses, or after 2006 intravenous use according to body weight and melphalan 140 mg/m^2/day) and CEM (carboplatin ctn. infusion ($4\times$AUC 4.1 mg/ml.min/day), etoposide ctn. infusion ($4\times338\,mg/m^2$day or $4\times200\,mg/m^2$/day*), melphalan ($3\times70\,mg/m^2$/day or $3\times60\,mg/m^2$/day*. *reduced if GFR <100 ml/min/1.73m^2)). A minimum of $3\times10E6$ CD34/kgBW PBSC were requested. VOD prophylaxis included ursadiol, but not prophylactic defibrotide. At randomisation closure, 1577 high risk neuroblastoma patients (944 males) had been included since 2002; with INSS stage 4 disease (1369 pts) >1 year, infants (65 pts) and stage 2&3 (143 pts) of any age with MYCN amplification. Response eligibility criteria prior to randomisation after Rapid COJEC Induction (J Clin Oncol, 2010) $\pm$ 2 courses of TVD (Cancer, 2003) included complete bone marrow remission and $\leqslant3$, but improved, mIBG positive spots. Local control included surgery and radiotherapy of 21 Gy. A total of 598 patients were randomised (296 BuMel, 302 CEM). The median age at randomisation was 3 years (1–17.2) with a median follow up of 3 years. A significant difference in EFS in favour of BuMel (3-years EFS 49% vs. 33%) was observed as well as for overall survival (3-years OS 60% vs. 48%, $p = 0.004$). This difference was mainly related to the relapse and progression incidence, which was significantly ($p < 0.001$) lower with BuMel (48% vs. 60%). Also the acute MAT toxicity profile favours the BuMel regimen in spite of a total VOD incidence of 18% (grade 3:5%). Thus BuMel was demonstrated to be superior to CEM and hence is recommended as standard treatment.
In addition, the HR-NBL1 trial established the prognostic value of semi-quantitative I-123 mIBG scintigraphy at diagnosis in high risk neuroblastoma. Patterns of skeletal 123I mIBG uptake were assigned numerical scores (Mscore). SIOPEN scoring of 123I mIBG imaging predicts response to induction chemotherapy and outcome at diagnosis in children with HRN and will help be a toll for risk based stratification.

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Research and Therapeutic Strategy of the European Intergroup for Children Non Hodgkin Lymphomas (EICNHL)

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In 1996, the EICNHL was created by several paediatric hemato-oncologists to meet, exchange data and design common studies on NHL.
The first studies were for ALCL (~10% of NHL in children). Based on a retrospective analysis of pooled data of several groups, prognostic factors were identified allowing designing the randomised ALCL99 study. This study demonstrated the possibility to do a large European study, including Japan (but before the European Directive). Besides conclusions on therapy, it allowed collecting clinical, pathological and biological data on more than 350 patients (pts). In parallel, was run a prospective study on relapses. The next randomised study will address the question of vinblastine in 1st line after stratification on biological data (MDD and ALK antibody title) with parallel biological studies, especially on antitumour immunity. EICNHL in collaboration with ITCC and COG is planning to study new drugs such as anti ALK or SGN35.
Lymphoblastic NHL (~25% NHL) was subject of the 2nd EICNHL study which randomised dexa vs pred in induction of the nonB-BFM 90 scheme. Unfortunately, the study had to stop because of toxic death rate higher than expected. However, it registered more than 300 pts treated homogeneously which should allow drawing conclusions on the disease.
For the B-cell NHL (~60%), the focus was first on PMBL which had poorer results with an attempt to develop a common strategy using rituximab. Then the other B-NHL (Burkitt and DLBCL) were considered: the 2 strategies developed in Europe since 1981 by the French LMB and the German BFM groups had allowed reaching >85% cure rates. Although using the same drugs in a same general strategy, the risk stratification, therapy and weight of treatment show dissimilarities. A study pooling data of 2 more recent studies of each group showed similar results, overall and by stage. This encouraged planning a common study to question the benefit of rituximab in advanced stage pts. Finally it will a LMB based protocol, with or without rituximab, considered as an investigational drug in children. This study will also be made with COG and maybe Hong Kong and Japan. The BFM group piloted an upfront window with 1 injection of rituximab 5 days before start of chemotherapy showing some response and will see how to go further with this information.
Conclusion: Despite regulatory processes being heavier after the EU directive, European studies for NHL must be encouraged because of the rarity of the disease.

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Relapsed Acute Lymphoblastic Leukemia

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Childhood ALL is characterized by a wide range of clinical and biological features at time of diagnosis. Age, leukemic cell count, CNS involvement, immunphenotype, and genetic subtype may be relevant for a first assessment of the immediate disease-related risk for the patient, and for determining the treatment strategy. Systematic evaluation of these features in the setting of cooperative clinical trials, however, has revealed the limitations to predict the risk of relapse. Therefore, the detailed analysis of early treatment response since the 1980's has revealed the large heterogeneity of in vivo treatment sensitivity, even within well-defined ALL subgroups. While estimates of relapse probabilities have improved over the past 20 years, individual parameters to predict relapse reliably are still missing. Thus, the vast majority of relapses occurs among patients with so-called intermediate risk features while the relatively highest proportion does occur among the rare high risk subsets such as children with translocation t(4;11) or t(9;22). Similar to first diagnosis, predictors of survival after 1st relapse relate to genetic and immunphenotypic subgroup, and clinical parameters such as involvement of extramedullary sites (Tallen G et al, J Clin Oncol 2010; Gaynon PS et al, Cancer 1998). Time of relapse from first diagnosis and response to second line therapy are strong prognostic parameters: Any relapse occurring during first line therapy is particularly unfavorable as this illustrates aggressive disease refractory to the wide range of antileukemic agents used in most contemporary protocols. No response to retrieval therapy is a strong adverse factor as is the slow response to 2nd line therapy measured by assessment of minimal residual disease (MRD) (Eckert C. et al, LANCET 2001). Recently, clonal heterogeneity in relapsed ALL when compared to initial presentation has been documented (Eckert C et al, LEUKEMIA 2011). Intensified chemotherapy can rescue a large proportion of relapsed patients. (Henze G et al 1994; von Stackelberg et al Eur J Cancer 2011). Relapsed ALL offers certainly also a window for clinical evaluation of new agents not used in standard frontline therapy. Recently it was shown in a U.K. study that mitoxantrone a drug which is frequently used in AML therapy, has a profound efficacy in relapsed ALL (Parker C et al, LANCET 2010). In some subsets, the introduction of allogeneic hematopoetic stem cell transplantation has further improved outcome (Borgmann A et al, Blood 2003). Recently, novel antibody constructs demonstrated high efficacy in relapsed ALL (Handgretinger R et al, Leukemia 2011). Cooperative clinical trials have contributed significantly to improve survival after first and subsequent disease recurrence. European approaches to combine diagnostic and research expertise and to develop innovative treatment in this difficult patient population are underway and will be described.