96 INVITED

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