Scientific Symposium (Mon, 26 Sep, 14:45−16:45)
High Throughput Technology Platforms for Biomarker Discovery − State of the Art

345 INVITED
Overview and Definition of Biomarkers (General Introduction)

Abstract not received

346 INVITED
Role of Gene Expression Profiling for Biomarker Discovery

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Gene expression profiling studies have made some important contributions to biomarker discovery, particularly in breast cancer, and in the process the limitations of the technology has also become clearer. Gene expression profiling using DNA microarrays is a powerful and robust technology to identify disease subsets that have large scale molecular differences. As a result of these studies it is now widely accepted that breast cancer is not a single disease with variable Estrogen Receptor (ER) expression and histology; but ER-positive and -negative cancers represent two fundamentally distinct diseases. Similar observations were made in other cancers including lymphomas, lung and prostate cancer although the clinical relevance of these new classification schemas is less well established for these cancers. The large mRNA expression footprint of proliferation and ER-signaling also proved useful to develop new multi-gene prognostic tests for ER-positive breast cancers that are now used in the clinic to aid adjuvant adjuvant treatment selection. However, it is also increasingly clear that gene expression profiling is not be able to identify small scale and variable mRNA expression differences that may be associated with many clinically relevant prediction problems. Robust prognostic signatures for triple-negative breast cancer or predictive-signatures with clinically relevant accuracy for any individual drug in any cancer remain elusive goals despite 15 years of research. An important lesson learned from these studies is that clinically important functions may be associated with limited and inconsistent mRNA expression footprints and substantially larger sample sizes will be required to solve these classification problems.

347 INVITED
Cancer Proteomics − From low Resolution to High Resolution to Study Lung Cancer Phenotype

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Proteome analysis aims to study the proteins on a systemic level in contrast to focusing the investigation on only one or a few proteins at a time. Proteomics is a collective term for techniques used for analysis of a proteome. In recent years, the development of both mass spectrometry (MS) based and antibody based proteomics methods has been tremendous. These advances in discovery proteomics have been propelled by improvements in instrumentation, sample pre-fractionation methods and improved bioinformatics pushing the field towards biological and clinical research. We have developed and used these methods especially to study clinical materials to understand how cancer cells responds to treatment and what, on the proteome level, defines a highly malignant cancer phenotype.
One of the major drawbacks in proteomics has been the lack of analytical depth, especially when studying complex proteomes such as the human proteome. This is manifested by lack of data on central regulators in cancer, such as transcription factors, their co-factors, tyrosine kinase receptors etc., in proteomics experiments. We have developed methods to increase proteome coverage in quantitative proteomics experiments on clinical material using high resolution fractionation (peptide isoelctric focusing) followed by mass spectrometry analysis. Here we present how this major leap in analytical depth in proteomics enables us to detect and study cancer pathways related to metastatic phenotype, cancer metabolism and therapy response to EGFR inhibition with focus on lung cancer.

348 INVITED
Full Genome Sequence Analysis

Abstract not received

349 INVITED
How Do We Study Network Pertubations in Clinical Specimens? How Do We Select "Drivers" of Malignancies?

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We need to develop an open innovation space where physicians, patients and scientists can together develop maps of cancer capable of driving better screening, diagnosis, treatment, and control of cancer. We will need to develop an infrastructure to manage this data and to provide an environment to build these maps of disease. This is not a problem that is solved by few but will involve large-scale involvement of the scientific and patient communities working together. Here are some of the issues to be discussed:

- Accessible but minimally usable clinical/genomic data- little care to annotate and curate data for other's use
- Mathematical models of disease are not built to be reproduced or versioned by others
- Data seen as supplemental materials after publications
- Assumption that those funded to generate data somehow own the data they generate
- Assumption that genetic alterations in human tumours can be owned
- Transient nature of sites where data models and tools for others are maintained
- Lack of standard forms for sharing data and future rights
- Most patients are not actively participating in donating samples and their outcome data
- Few cancer patients as activists demanding sharing data in the public forum
- Most clinical/genomic data generated by industry from trials is not shared
- Most academics feel they need to sequester data until their lab can complete publishing
- Rewards are for first/last authors who want to protect their unique contribution till after full article is published.

Scientific Symposium (Mon, 26 Sep, 14:45−16:45)
Drug Development in Paediatric Oncology

350 INVITED
4 Years Later − the Impact of the European Pediatric Medicine Regulation on Children and Adolescents in Europe

Abstract not received

351 INVITED
PARP Inhibition in Pediatric Malignancies

Abstract not received

352 INVITED
Targeting ALK in Paediatric Malignancies

Abstract not received

353 INVITED
Immunotherapy of Paediatric Malignancies

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Two major concepts have been recently identified in tumour immunity: the tumour immunoediting and the therapy-induced immunogenic cell death. Tumour immunoediting refers to 3 phases designed elimination, equilibrium, and escape. In the escape phase, tumour cells circumvent both innate and adaptative immune defences either by alteration occurring in edited tumour cells themselves, or by inhibition of the protective functions of the immune system, or by the generation of immunosuppressive cells. When cancer cells die through immunogenic cell death, they also alert the immune system, which mounts a therapeutic anti-cancer immune response and contributes to the control of residual tumour cells. Radiotherapy and some chemotherapy agents, in particular anthracyclines, can induce specific immune responses that result either in immunogenic cell death or in immunostimulatory side effects. Paediatric tumour immunology is of particular interest because (i) the environmental factors appears to play a minimal role in the genesis of cancer suggesting a more important role of host-related factors when compared with adult cancers, (ii) most of the tumours occur within the first years of life suggesting a special and

shorter tumour immunoediting process, and (iii) some tumours in infants can spontaneously regress arguing for a role of immune control.
This review will focus on the immune therapies that have been developed in paediatric solid tumours. Basically, immunotherapies could be classified into 3 categories: 1) Humoral therapy 2) Cellular therapy and 3) immunomodulatory agents. Monoclonal antibodies have been developed dramatically in the last decade and form one of the biggest classes of the new immune therapies with promising activities with IGF-1 receptor antibodies in sarcomas and anti-GD2 in neuroblastomas. Cellular therapies consist on T- or NK- or DC-based therapies and have been developed especially in high-risk neuroblastomas. Numerous immunomodulatory agents have been identified to date and some are of particular interest in paediatric solid tumours: immunomodulatory chemotherapies, Toll-like receptor agonists, mTOR inhibitors, epigenetic modulators (e.g., histone deacetylase inhibitors), and other immune modulators (e.g. muramyl tripeptide phosphatidylethanolamine in osteosarcomas). Although the impact of immunotherapy on the clinical management of most paediatric cancers is still negligible, it will certainly improve dramatically within the next years.

354 INVITED

Apoptosis Research in Paediatric Malignancies – New Targets for Therapy

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Resistance to apoptosis (programmed cell death) is a characteristic feature of human cancers including childhood malignancies. Further, evasion of apoptosis is a frequent cause of treatment resistance, since most anti-cancer therapies, for example chemo- or radiotherapy, act primarily by inducing cell death in cancer cells. Over the last two decades, the dissection of apoptosis pathways in pediatric tumours has resulted in the identification of many key molecules that may serve as molecular targets for drug discovery. Currently, components of the apoptotic cascade are exploited for the development of rationally designed molecular targeted therapies. For example, small molecule Smac mimetics that antagonize "Inhibitor of Apoptosis" (IAP) proteins prime childhood acute leukemia cells for TRAIL- or chemotherapy-induced apoptosis, bypass Bcl-2-imposed resistance and exert anti-leukemic activity in a NOD/SCID mouse model of pediatric acute leukemia. Besides overexpression of anti-apoptotic proteins, loss of expression or function of key pro-apoptotic proteins can confer apoptosis resistance. Caspase-8 is frequently epigenetically silenced in pediatric cancers. Re-expression of caspase-8 by e.g. histone deacetylase inhibitors restores sensitivity to death receptor-stimulated apoptosis. Furthermore, apoptosis signaling pathways can be impaired by aberrant activation of survival pathways. We identified increased PI3K/Akt signaling as a new negative prognostic factor in neuroblastoma. Importantly, small molecule dual PI3K/mTOR inhibitors sensitize neuroblastoma cells for death receptor- as well as for chemotherapy-induced apoptosis by shifting the balance between pro- and anti-apoptotic proteins and cooperate with TRAIL or chemotherapy to suppress neuroblastoma growth in vivo. Thus, this approach to target apoptosis signaling pathways is expected to generate new and more effective strategies for the treatment of childhood cancers.

Special Session (Mon, 26 Sep, 17:00–18:00)
Co-Development of Investigational Agents: Industry Experience and Perspective

355 INVITED

Scientific Rationale for the Development of Targeted Agent Combinations

Abstract not received

356 INVITED

Big Pharma: Competitors or Collaborators?

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Successful treatment strategies in the challenging and at times frustrating field of cancer research are often reliant on development of fine-tuned novel combinations. However, agents for these scientifically promising combinations may belong to early phase portfolios of rival Pharmaceutical companies. Whilst true science knows no borders, the competitive nature of Pharmaceutical business will predictably pose questions as to how cross-company development is possible, if at all. In 2009, AstraZeneca and Merck embarked on such collaboration (NCT01021748), joining forces and paving the way to a new paradigm in early phase oncology drug development. This presentation focuses on practical aspects and early learnings from the on-going Phase I collaborative study.

357 INVITED

The Regulatory Perspective of Co-Development of Investigational Agents

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For some anticancer agents, it is expected that combinations are needed not only to optimise anti-tumour activity, but that they are actually necessary in order to obtain meaningful antitumour activity. The European Medicines Agency (EMA) has recently set up an Oncology Working Party to expand the current guideline for the development and evaluation of cancer drugs [1]. The guideline focuses on both exploratory and confirmatory studies for different types of agents. The current revision will address a number of topics, including the use of biomarkers as an integrated part of the drug development and the co-development of new compounds [2].
The rationale for using each drug in a combination should always be established based on appropriate nonclinical and clinical models. Furthermore, from a regulatory perspective, there is a need to establish the contribution not only of the combination of new agents but also of each individual agent in a combination. Concerning the latter, exploratory and confirmatory studies should aim to establish the benefit-risk balance of each individual agent intended to be used in combination with other agents, based on objective criteria of efficacy and safety. Incorporation of a reference treatment arm to enhance assay sensitivity is encouraged.
If based on exploratory clinical or nonclinical data it can be established convincingly that one or more agents do not have sufficient antitumour activity on their own, it maybe possible to further develop these agents using designs that only aim to establish the benefit-risk of these agents when used in combination. For instance, if based on convincing pharmacological and non-clinical data, one or more drugs have no or minimal antitumour activity on their own but are expected to enhance the anti-tumour activity of other drugs (for example, preventing the development of resistance), monotherapy phase 2 and phase 3 studies for the enhancing drugs may not be required. Similarly, when based on well powered phase 2 trials it can be shown that any drugs have each insufficient anti-tumour activity as single agents, but that the combination achieves sufficient antitumour activity to warrant further investigation, the design of phase 3 trials may omit monotherapy treatment arms. As the same targets may have a different impact in different malignancies, the role of each agent in a combination may need to be reassessed when exploring new indications.
The European regulatory requirements on co-development of investigational agents are currently under discussion. Until further guidance becomes available, regulatory advice is recommended in co-development programs.
Publication disclaimer: The views presented here are personal and should not be understood or quoted as those of the European Medicines Agency.

References

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[2] European Medicines Agency. Concept paper on the need to revise the guideline on the evaluation of anticancer medicinal products in man. 2010; Available from: http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500096730.

Special Session (Mon, 26 Sep, 17:00–18:00)
How to Write and Review a Good Article?

358 INVITED

The Point of View of a Statistician

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A mass of new medical information is published every day, bringing various levels of scientific evidence, unfortunately not always objectively presented,