

Invited Sessions

Keynotes – Panel Discussions – Round Table

K01-01

Identification of genes involved in phenobarbital-induced tumorigenesis: Emphasis on altered DNA methylation and expression

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Altered DNA methylation, an epigenetic mechanism, facilitates tumorigenesis. Hypomethylation can activate oncogenes, while hypermethylation can silence tumor suppressors. We utilize two model systems to investigate the effects of the nongenotoxic rodent liver tumor promoter phenobarbital (PB) on methylation and gene expression in liver of susceptible mice compared to their resistant counterparts. Hypothesis: At least some of the changes that occur uniquely in the sensitive animals play critical mechanistic roles during tumor formation. While the fundamental genes underlying cancer in mice and humans are likely the same, rodents exhibit an increased susceptibility, and methylation patterns in rodent cells are less stable than in human cells. We believe that humans and rodents differ regarding the regulation of epigenetic control resulting in enhanced sensitivity to tumor formation in the latter. Unique regions of altered methylation (RAMs) were discerned in susceptible B6C3F1 (compared to resistant C57BL/6) mice at 2 and 4 weeks, and in susceptible constitutive active/androstane receptor (CAR) wild type (WT), as compared to resistant knockout (KO) mice. Multiple genes exhibited methylation changes in identical regions in both susceptible groups. Furthermore, elucidation of unique expression changes in the B6C3F1 and CAR WT (pre-cancerous tissue and tumors) revealed perturbations of genes within signaling pathways, e.g., mitogen-activated protein kinase (MAPK), TGF- β and Wnt. Using 2 model systems, we have examined alterations in DNA methylation and expression of key genes that occur across a continuum of PB-induced liver tumorigenesis. PB affects both DNA methylation and critical signaling pathways uniquely in liver tumor-susceptible mice, potentially driving tumorigenesis.

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K01-02

Molecular aspects of adverse drug reactions – from molecule to man

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Adverse drug reactions (ADRs) can be classified as:

- *On-target* – which are predictable from the known primary or secondary pharmacology of the drug.
- *Off-target* – which are not predictable from the known pharmacology of the drug and exhibit marked inter-individual variability in susceptibility (idiosyncrasy).

On-target reactions are exemplified by the variation in response to the anticoagulant warfarin and the risk of bleeding. We now have a detailed understanding of both the molecular pharmacology of this oral anticoagulant. This has provided a better understanding of both inter- and intra-individual variation in drug response, which in turn should lead to a reduction in ADRs in the clinic. Excessive drug accumulation and/or the formation of chemically reactive metabolites have been implicated in a number of off-target (including idiosyncratic) ADRs. Studies with drugs such as acetaminophen have defined the chemical basis of the response of specific organs such as the liver to chemical stress with respect to adaptation and mechanisms of cell death. A number of idiosyncratic ADRs have the clinical hallmarks of hypersensitivity. Such reactions are usually rare but can be life threatening. Advances in cellular immunology have demonstrated the role of T cells in severe skin reactions, most notably by the demonstration of drug (metabolite)-specific effector T cells in the circulation and skin biopsies of affected individuals. The association of HLA B*5701 with abacavir hypersensitivity has demonstrated the role of genetic restriction in individual susceptibility, and the practical possibility of excluding susceptible patients from drug exposure, thereby preventing an ADR.

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K01-03

Panel discussion: The Innovative Medicines Initiative (IMI) – high hopes and first experiences

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The Innovative Medicines Initiative (IMI) is a public private partnership funded by the European Commission and the European Federation of Pharmaceutical Industries and Associations (EFPIA) with the aim to promote biomedical innovation on Europe and to address bottlenecks in the R&D process. This should allow for faster discovery and development of better medicines for patients by ensuring that Europe's biopharmaceutical sector remains a dynamic high technology sector (www.imi-europe.org).

Based on proposals from EFPIA member companies, IMI has published a first call for Expression of Interests (Eols) in 2008 with six topics for the sector Safety. Many consortia consisting of academic institutions and small enterprises submitted Eols in October 2008 which underwent a Stage I evaluation with external experts. For each of the six topics, one Eol was selected, and subsequently the public consortia were invited to submit a full project proposal together with the respective industry consortia by January 2009. In the Stage 2 evaluation by external experts four submissions were supported, whereas two were rejected.

The IMI panel session will discuss the expectations of the various stakeholders and specific strengths and weaknesses of the IMI concept, including lessons learned from the new IMI calls in 2009 and beyond.

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K01-04**Novel tools in predictive toxicity testing: Mathematical modelling of tissue damage and regeneration as well as control of cell states *in vitro* by manipulation of early signalling**

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Modern toxicology faces several major challenges. Particularly, the available toxicological data are insufficient for a large number of chemicals to which humans are exposed. Therefore, faster toxicity tests with higher predictive power are urgently required. The opinion that virtually all toxicity testing can be conducted in human cells *in vitro* supported by pharmacokinetic modelling is an easy one to have. Unfortunately, being able to experimentally deliver such results is extremely challenging. Clearly, a thorough understanding of the mechanisms occurring *in vivo* is a precondition for establishment of *in vitro* systems. In this lecture I will present a new technique that allows analysis of the spatial-temporal processes during toxic tissue damage and regeneration using the example of the regenerating liver. This multi-step procedure based on confocal laser scans, tissue reconstruction and mathematical modelling led to the identification of so far unrecognized key mechanisms of liver regeneration, such as the alignment of daughter hepatocytes along the orientation of the closest sinusoid. In a next step we studied which molecular mechanisms drive the dedifferentiation of primary hepatocytes *in vitro* compared to the *in vivo* situation. Using knockdown and overexpression strategies we identified focal adhesion kinase mediated MAP kinase signalling as a key mechanism of hepatocytes dedifferentiation *in vitro*. Interestingly, the phenotype could be directed towards an *in vivo* like state by manipulating early signalling network constellations. In this state, cultivated hepatocytes represent a promising tool for “omics” technologies.

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K01-05**Trisk: European advanced risk assessors accredited training programme for highly qualified toxicology experts**Corrado L. Galli^{1,*}, Helen Hakansson², Shirley Trice³, Bas J. Blaauboer⁴, Regine Kahl⁵, Marco Gerevini⁶

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The general objective of TRISK is to develop a training programme in risk assessment based on common European criteria, easily adoptable by institutions across Europe, and focusing on risk assessment methodology and procedure. TRISK fills an important need in the training of toxicologists into areas of risk assessment by establishing a clear and recognized definition of training criteria and a recognition mechanism to qualify risk assessors.

This project is aimed to fill the lack of training schemes and provide opportunities for practical, on the job training on the risk assessment approach for young scientists or new toxicologist graduates interested in pursuing this area of expertise, as well as trained toxicologist experts attracted by the opportunity to serve as member of the various scientific committees in regulatory, industry and governmental bodies engaged in risk assessment.

TRISK will contribute directly to the training of risk assessors across Europe in order to satisfy the constant needs for trained scientists to serve in the Commission Scientific Committees (SC) and ensure the sustainability of the EU risk assessment advice structure, while indirectly meeting the needs of industry and the private sector who also require trained risk assessors in order to satisfy the new regulatory requirements and development of new market products. It will contribute to regulatory decisions based on high-quality risk assessments, thus improving the health safety of the citizens in the Member States.

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