of the intact liver. What is now required is a concerted multidisciplinary research effort, embracing academic, industry and regulatory partners, to deliver a portfolio of robust and well characterised predictive platforms that are fit for purpose according to well-defined criteria. It is clear that no one system is fit for purpose as a universal test for DILI in man. DILI is too complex a pathophysiological process to allow that. We therefore need a roadmap for the development of an integration of established and emerging test systems, based on an approach, whereby the complexity of the model increases from single cell 2D to multi cell 3D systems.

http://dx.doi.org/10.1016/j.toxlet.2015.08.107

W05-3
Mechanistic Insights in TNF Signaling and Drug-Induced Liver Injury: Towards a Predictive Preclinical Toolbox

B. van de Water

Leiden University, Leiden Academic Centre for Drug Research, Leiden, Netherlands

There is an increasing body of evidence that various drugs can sensitize hepatocytes to TNF-mediated killing. This interaction is likely due to perturbations of the normal hepatocyte physiology that triggers a pro-apoptotic TNFR pathway when TNF is present in the system. We have focussed on the effects of DILI compounds on endoplasmic reticulum (ER) stress as well as the Nrf2-mediated oxidative stress adaptive toxicity pathways and how these two pathways converge with adverse TNFR signaling. Moreover, we have deepened our understanding on effects of DILI compounds on the TNFR-mediated NF-kappa B regulation. We have integrated primary human hepatocyte transcriptomics data with live cell imaging adaptive stress response GFP-reporter data to unravel in detail the interaction between different adaptive stress pathways and TNF/drug cytotoxic synergy. Moreover we have applied RNA interference screening to identify key modulators of these signaling pathways that define this synergistic toxic interaction. Our data provide suggestions on the toolbox components that can be used in a preclinical drug safety testing phase to assess safety liabilities for a drug/cytokine interplay in the development of DILI. This work is part of the MIP-DILI project supported by the Innovative Medicines Initiative (grant agreement n° 115336), and the FP7 SEURAT-1 DETECTIVE project (grant agreement 266838).

http://dx.doi.org/10.1016/j.toxlet.2015.08.108

W05-4
Role of the immune system in DILI; lessons learned from animal studies

R. Pieters

Utrecht University-IRAS, Utrecht, Netherlands

Drug induced liver injury (DILI) is a major concern for industry as well as society as it is the major cause of liver failure and mostly not predicted preclinically. In these often idiosyncratic cases, non drug-related factors are involved in the induction of liver toxicity, e.g. patient-specific inheritable or environmental, situation-specific factors, such as infections. Presently there are no strategies to preclinically predict whether a new drug entity can possibly cause DILI in patients. The IMI-MIP-DILI project aims to fill that gap by providing translational battery of *in silico* and *in vitro* tests that can reliably predict the risk of DILI in man. To ultimately provide such a battery of tests and related functional biomarkers, mechanistic information from *in vivo*, animal models and human patients, which are both scarce, is needed used to feed into these tests. In the presentation, a review will be provided on available *in vivo* data obtained in mice and rats with known DILI-related drugs. Data shows the importance of the immune system by drug-induced changes in both innate and adaptive immune components. It will be clear that findings do not yet provide an overall and clear picture on the mechanisms. Often, inflammatory, danger-related changes are observed, whereas adaptive immune changes are only suspected based on the occurence of T cell-related cytokines. Data from mouse studies performed within the MIP-DILI project, using ximalagatran and trovafloxacin as examples of DILI-drugs, point to an important role of danger-associated cytokine-mediated death of liver cells, initiated by sterile or infectious inflammation. Excessive cell death, possibly combined with disturbed immune regulation (causing break of tolerance) may eventually initiate liver damage. Remarkably, there are only few animal reports showing neoantigen-specific (e.g. hapten-specific) T cells, despite the fact that in human patients DILI is often associated with skin rashes and other clinical effects that are reminiscent of T cell sensitization. The role of innate (danger-associated) versus adaptive (hapten/neoantigen associated) immune components will be discussed in view of personalized and environmental risk factors and in relation to possible use in human risk assessment.

http://dx.doi.org/10.1016/j.toxlet.2015.08.109

W05-5
Unravelling the impact of hepatotoxic drugs by dynamic pathway modelling

U. Klingmueller

DKFZ, B200, Heidelberg, Germany

Deciphering hepatotoxicity not only needs to consider effects caused by the parent drug or its metabolites, but also the impact of synergistic drug-cytokine interactions. These interactions are often multifactorial and complex, and the outcome of different signalling pathways can be altered dramatically under certain conditions, leading to hepatotoxicity and eventually liver failure. We have focused on TNFa- and HGF-signalling pathways as examples for key mediators of inflammatory and regenerative responses, in combination with two liver injury inducing drugs, diclofenac and acetaminophen. Both are ranked among the top ten causes of drug induced liver injury. However, underlying mechanisms remain elusive. Mathematical modelling offers a powerful tool to study the intracellular signalling networks and cellular responses to perturbations. By combining cell population and single cell data, we have established time-resolved dynamic pathway models for TNFa- and HGF-signalling pathways. In particular, this enables us to study the immediate, early effects on the specific pathways thereby elucidating processes at the beginning of a cellular decision.

http://dx.doi.org/10.1016/j.toxlet.2015.08.110