Integration of models of drug-induced liver injury for risk assessment
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Facts & Figures
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Challenge
• Drug-induced liver injury (DILI) remains a major health, economic and regulatory issue.
• To date, there is no single definitive approach to testing new drug candidates for their liability to cause DILI in patients.
• Aim
  ➢ Gain a deeper understanding of current test systems to determine their value, limitations and translatability.
  ➢ To explore the use of novel computational models to help bridge the gap and inform assessment prior to first-in-man studies.

Approach & Methodology
• Basal hepatic protein expression in primary human hepatocytes (PHH), HepaRG, HepG2 and Upcyte cells were determined by mass spectrometry (ITRAQ).
• Cytotoxicity test was also performed in all four cell systems upon exposure to 13 compounds for 72 h.
• Translatability of preclinical test systems
  ➢ Mice and rats were dosed with the hepatotoxin paracetamol (APAP) for 24 h. Serum alanine transferase (ALT), hepatic covalent binding levels and histopathology were analysed.
  ➢ Primary human, mouse and rat hepatocytes were exposed in vitro to 10 mM APAP (+/- ABT, an inhibitor of drug bioactivation) over a 24 h period and analysed for viability (ATP) and glutathione (GSH) levels.

Results

Figure 1. TransQST concept scheme. Experimental validation:
• Determine and compare the response of mouse and rat in vivo to APAP.
• Determine translatability and human relevance of in vivo models by comparing with parallel experiments in primary human, mouse and rat hepatocytes as well as clinical data.
• Inform PBPK modellers and ‘omics experts for parameterisation and study design purposes.

Figure 2. Basal proteomic profiles of PHH, HepaRG, HepG2 and Upcyte cells.
(A) Common drug metabolising enzyme and transporter (DMET) proteins across all four cell systems. (B) Comparison of drug metabolising enzymes (CYP450) basal expression in HepaRG, HepG2 and Upcyte cells with PHH. With the exception of CYP3A4 in HepaRG cells, all other detected CYP450 proteins were less expressed in all three cell systems compared with PHH, including CYP2E1 which is responsible for APAP hepatotoxicity. Cytotoxicity testing was then carried out to determine each cell system’s ability to detect DILI (Figure 2).

Figure 3. Based on EC50 (A), no one cell system is better at predicting hepatotoxicity, however, when a safety margin is set (EC50/C50), PHH was the most predictive cell system (B). PHH alone cannot accurately predict DILI – explore new computational models but translatable data across preclinical test systems is key (Figures 4 – 6).

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Value of IMI collaboration
• Exchange of knowledge, expertise and resources
• Generation of robust and reliable data.
• Extensive learning opportunity and work experience for members in training.
• Implementation of knowledge gained from one IMI project to another.

Impact & take home message
• All test systems must be comprehensively phenotyped.
• PHH alone cannot robustly predict DILI in patients.
• Combining PBPK modelling and transcriptomics to generate new computational models could bridge the shortcomings of the test systems we have today.
• Translatability across the different test systems is key to ensure robustness of the models being built.

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