Mechanism–based Integrated Systems for the Prediction of Drug-Induced Liver Injury

Project Overview
Drug-Induced Liver Injury

• Leading cause of acute liver failure and transplantation

• Health problem - implications for patients, health care professionals
  - 2-5% of patients hospitalized with jaundice and ~10% with acute hepatitis.
  - 40% due to acetaminophen, 12% idiosyncratic reactions / other medications.
  - 75% of idiosyncratic drugs reactions results in liver transplantation or death

• Major challenge for industry and regulatory agencies.
  - 1998-2008, 29% of drugs withdrawn for liver toxicity
  - ‘Blackbox’ warnings

Ostapowicz et al 2002; Lee 2009; Lee et al 2009; Ruben et al 2010; MacDonald and Robertson 2009;
Significance of DILI in Pharma R&D and post-marketing

**Message** – it doesn’t get any better moving from non-clinical to clinical ... only worse !!!!

‘Challenge of DILI increases from non-clinical - to post-marketing’

Stats: APBI 2008; Stevens and Baker 2008
## Clinical Development in 2013

<table>
<thead>
<tr>
<th>Drug</th>
<th>DILI finding</th>
<th>Impact</th>
<th>Time to onset</th>
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</thead>
<tbody>
<tr>
<td>Fasiglifam (Takeda)</td>
<td>liver enzyme elevations</td>
<td>PhIII termination</td>
<td>&gt; 1 Month&lt;sup&gt;1&lt;/sup&gt;</td>
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<tr>
<td>LY2888721 (Eli Lilly)</td>
<td>liver enzyme elevations</td>
<td>PhII termination</td>
<td>&gt; 1 Month&lt;sup&gt;1&lt;/sup&gt;</td>
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<td>Sovaprevir (Achillion)</td>
<td>liver enzyme elevations</td>
<td>PhII, clinical hold</td>
<td>&gt; 1 Month&lt;sup&gt;1&lt;/sup&gt;</td>
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<td>Ponatinib (Ariad)</td>
<td>Hepatotoxicity</td>
<td>PhIII, trial discontinued</td>
<td>&gt; 1 Month&lt;sup&gt;1&lt;/sup&gt;</td>
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<td>VX-135 (Vertex)</td>
<td>Liver enzyme elevations</td>
<td>PhII, partial clinical hold</td>
<td>&gt; 1 Month&lt;sup&gt;1&lt;/sup&gt;</td>
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<sup>1</sup> Inferred from clinical stage reached

## on Marketed Drugs 1998-2013

<table>
<thead>
<tr>
<th>Drug Year</th>
<th>DILI finding</th>
<th>Impact</th>
<th>Time to onset</th>
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<tbody>
<tr>
<td>1998</td>
<td>bomofenac, (Wyeth)</td>
<td>liver enzyme elevations; hepatotoxicity</td>
<td>Market withdrawal</td>
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<td>2006</td>
<td>troglitazone, (Park-Davies) 1997; 2000</td>
<td>liver enzyme elevations; hepatotoxicity</td>
<td>Market withdrawal</td>
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<td>2007</td>
<td>lumiracoxib, (Novartis) 2007</td>
<td>liver enzyme elevations; hepatotoxicity</td>
<td>Market withdrawal</td>
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<td>2009</td>
<td>lapatanib, (GSK)</td>
<td>liver enzyme elevations; hepatotoxicity</td>
<td>Label -black box warning</td>
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<td>2011</td>
<td>sitaxsentan, (Pfizer) 2011</td>
<td>liver enzyme elevations; hepatotoxicity</td>
<td>Market withdrawal</td>
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Drug-Induced Liver Injury

- Dose-dependent
- Species selective
- Selective individuals
- Idiosyncratic
- Immunological
1. Mitochondrial impairment hepatocyte necrosis microvesicular steatosis
2. Reactive metabolites hepatocyte necrosis immunoallergic toxicity
3. Lysosomal impairment phospholipidosis microvesicular steatosis
4. Inhibition of biliary efflux Intrahepatic cholestasis
Clinicopathological presentation of DILI

- Acute fatty liver with lactic acidosis
- Acute hepatic necrosis
- Acute liver failure
- Acute viral hepatitis-like liver injury
- Autoimmune-like hepatitis
- Bland cholestasis
- Cholestatic hepatitis
- Cirrhosis
- Immuno-allergic hepatitis
- Nodular regeneration
- Nonalcoholic fatty liver
- Sinusoidal obstruction syndrome
- Vanishing bile duct syndrome

Multi cellular and multifunctional organ
Multiple and variable forms of disease
Multi step pathologies

reviewed Tujios and Fontana
Nature 2011
• Current test systems are poorly predictive:
  ▫ Physiological gap between \textit{in vitro} test systems and human liver cells \textit{in vivo}

• Too little is understood about how the current test systems compare with human liver in the context of DRUG-INDUCED LIVER INJURY
Mechanisms relevant to DILI

- Multi cellular and multifunctional organ
- Multiple and variable forms of disease
- Multi step pathologies

Chemical Insult

- Metabolism
- Accumulation

HEPATOCYTE

- Function
- Viability
- Apoptosis
- Necrosis

Adaptation to stress & regeneration

Adaptive immune system

Innate immune system

Inflammation

Require new test systems & biomarkers
The Way Forward

- Need for physiology, pharmacology, toxicology evaluation of current and novel test systems using training compounds
  - Understanding fundamental mechanisms that occur in man
  - Complete integration of biological and chemical analysis in all model systems
  - Integration of ADME - PK and Drug Safety

The concept of MIP DILI
• To identify and validate an improved panel of in vitro “best practice assays” for predicting DILI in the human population - PRIMARY GOAL

• To explore and understand the relationship between in vitro assay signals and DILI in vivo, in preclinical test species and in man - SUPPORTIVE GOAL

• To develop and validate novel modelling approaches that integrate multiple preclinical data types to improve prediction of DILI in man - SUPPORTIVE GOAL

• To enhance shared understanding, between academia, pharmaceutical and regulatory agencies, of the value and limitations of new and existing approaches for DILI hazard identification and risk assessment - SUPPORTIVE GOAL
Project Strategy

 ITERATIVE

**in vitro** test systems

- Current and emerging cell systems
- Refined cell systems
- Multi-cell systems

**compound training sets**

- Mechanism specific hepatotoxins
- Pathway selective compounds
- Diagnostic test sets

**in vivo models**

- Current and emerging in vivo models
- Refined in vivo models
- Humanized in vivo models

**MECHANISMS**

**MECHANISMS**

Novel mechanism-based systems for DILI prediction
Project Structure

WP1: Compound and Assay Selection
DATA CURATION

WP2: Established in vitro systems
Novel in vitro systems

WP3: in vivo models
In vitro-in vivo correlations

WP4: Bioanalysis, Toxicological Function & Phenotype

WP5: Systems Analysis, Biomathematical & ADMET Modelling

WP7: Project management

Outcomes MIP-DILI
WP6: Communication & Dissemination
Roadmap for MIP-DILI Activities

Tier 1
- Drug
  - Cell health
    - HepG2
      - Cytotoxicity
      - Mitotoxicity
    - Proteome
  - Phenotype
  - Pharmacological liability
    - Hepatocyte suspension (1-4h)
      - Accumulation
      - Bioactivation
  - Cell function
    - Specialised cell systems
      - Transporter inhibition
      - Cholestasis

Tier 2
- Multi-cell culture
- Long term culture
- 2D, 3D Spheroids

Tier 3
- Complex systems
  - Viral infection
  - HLA restriction
  - T cells

Patient dependent factors

Transcriptome
Proteome
Cytotoxicity
Signalling from innate immune system
  - TNF
  - IL-6

modelling
Bridging Biomarkers
Project Achievements (month 18)

• Development of informatics infrastructure for background and foreground data

• Year 1/2: Characterisation current in vitro models and response to training compounds
  ▫ Physiological, pharmacological, toxicological

• Emerging EFPIA consensus on current test platforms

• Piloting of cutting edge in vitro models

• Greater definition of mechanisms of idiosyncratic DILI
Synergy, complementarity and novelty

**eTOX**
Database of pharmaceutical industry legacy toxicology reports and public toxicology data
  - In silico toxicity modelling
  - All types of toxicity

**STEM CELLS FOR SAFER MEDICINES & STEMBANCC**
  - Production of hepatocytes from embryonic stem cells

**SAFER AND FASTER EVIDENCE-BASED TRANSLATION**
  - Qualification of new specific and sensitive safety biomarkers for drug-induced kidney, liver and vascular injury

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**MIP-DILI**

- **EFPIA**
- **iSAEC**
- **SC4SM StemBANCC**
- **SAFE-T**
- **Virtual liver**
- **Improved validated assays**
- **EMA**
- **FDA**

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**INTERNATIONAL SERIOUS ADVERSE EVENT CONSORTIUM (iSAEC)**
  - Identification of DNA-variants for predicting the risk of drug toxicity

**PREDICT-IV**
  - Development of non-animal preclinical safety screens

**VIRTUAL LIVER**
  - Development of a dynamic model that represents, rather than fully replicates, human liver
• MIP-DILI will deliver a panel of well characterised in vitro and computational models reflecting the key mechanisms of drug induced hepatotoxicity.
  ▫ This panel may form a major aspect of the future pre-clinical DILI screening paradigm used in industry and consequently reduce the occurrence of drugs with DILI that eventually reach regulatory assessment.

• Understanding human-specific and idiosyncratic hepatotoxicity is highly challenging (complex, multifactorial nature of the mechanisms that are unique to specific drugs and to specific patients).
  ▫ Through the mechanistic insights that we will deliver, we hope to support the regulatory dialogue by informing the scientific community which forms of DILI can and cannot be predicted.
  ▫ To further progress it will be critical to integrate the output for MIP-DILI with other international research initiatives.
Executive Summary

• DILI is a major health problem and challenge for the pharmaceutical industry

• MIP-DILI is developing an improved panel of in vitro “best practice assays” and mechanistic knowledge for predicting DILI in the human population
  ▫ If successful, MIP-DILI will change the DILI screening paradigm and reduce the occurrence of drugs with DILI that reach regulatory assessment.

• This a highly challenging scientific area and through developing mechanistic insights the consortium also aims to enhance regulatory understanding of which forms of DILI can and cannot be predicted.
  ▫ To further progress it will be critical to integrate the output for MIP-DILI with other international research initiatives.
## Acknowledgements

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<td>Magnus Ingelman-Sundberg (KI)</td>
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