The DILI-sim Initiative: An Update

June 6, 2017

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Eshelman School of Pharmacy
University of North Carolina- Chapel Hill
Disclosure

I direct the DILI-sim Initiative and own equity in the spin off company DILIsym Services, Inc. which was acquired June 1, 2017 by Simulations Plus.
DILIsym Sub-Models

- Drug Metabolism and Distribution
- Unconjugated Reactive Metabolite

- Lipotoxicity
- Reactive Oxygen Species
- Mitochondria Dysfunction and Toxicity
- Hepatocyte Life Cycle

- Intracellular Bile Acids
- Biomarkers
- Innate Immune Response

DILIsym®
DILIsym Integrates Multiple Inputs to Simulate/Predict Hepatotoxicity

Exposure
- Pharmacokinetics

Mechanisms
- Bile Acid Transporter Inhibition
- Mitochondrial Respiration
- ROS Generation

Interpatient Variability
- Unique Parameter Combinations

SimPops™

Simulated Frequency & Severity of Liver Injury
# DILIsym Performance Review – the Validation Approach

<table>
<thead>
<tr>
<th>Drug</th>
<th>Injury Frequency</th>
<th>Injury Dose-Response</th>
<th>Injury Severity</th>
<th>Injury Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMG009 (DILI)</td>
<td></td>
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<tr>
<td>AMG 853 (Clean)</td>
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<tr>
<td>Tolcapone (DILI)</td>
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<tr>
<td>Entacapone (Clean)</td>
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<td></td>
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<tr>
<td>Methapyrilene (Clean)</td>
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<td></td>
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<tr>
<td>Bosentan (DILI)</td>
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<tr>
<td>Telmisartan (Clean)</td>
<td></td>
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<tr>
<td>Compound A (DILI)</td>
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<tr>
<td>Compound D (DILI)</td>
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<td></td>
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<tr>
<td>Compound B (DILI)</td>
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<tr>
<td>Compound C (DILI)</td>
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</tr>
<tr>
<td>Etomoxir (DILI)</td>
<td></td>
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</tr>
<tr>
<td>Compound E (DILI)</td>
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<td></td>
</tr>
<tr>
<td>Troglitazone (DILI)</td>
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<td>Pioglitazone (Clean)</td>
<td></td>
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</table>

## Color Key – Accuracy of DILIsym

- **Excellent**
- **Good**
- **Fair**
- **Poor**
- **Unavailable**

**Clinical Data and Simulation Results**
Conclusion

DILIsym modeling has been able to correctly predict the liver safety profiles of ~90% (21/23) of the validation set of drugs tested so far.
The Rates of Serum ALT Elevations In All Four Drugs Are Reasonably Predicted by DILIsym

Data presented at Nov 4 2017 anti-infective Ad com

<table>
<thead>
<tr>
<th>Compound</th>
<th>Protocol</th>
<th>Peak ALT &gt; 3X ULN</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Observed*</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Oral (CE01-300)</td>
<td>3.2%</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Oral (CE01-300)</td>
<td>2.8%</td>
</tr>
<tr>
<td>Telithromycin</td>
<td>Oral (CE01-300)</td>
<td>0.0%</td>
</tr>
<tr>
<td></td>
<td>IV-to-Oral (CE01-301)</td>
<td>5.5%</td>
</tr>
</tbody>
</table>

* Patients with normal ALT at baseline

Modeling work supported by Cempra
### The Rates of Serum ALT Elevations In All Four Drugs Are Reasonably Predicted by DILIsym

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</tr>
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<td>Clarithromycin</td>
<td>500 mg BID 7 days</td>
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* Patients with normal ALT at baseline
The rates of serum ALT elevations in clinical trials are reasonably predicted by DILIsym.

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<tbody>
<tr>
<td>Solithromycin</td>
<td>Oral (CE01-300)</td>
<td>5.4% (3.2%)</td>
<td>3.9%</td>
<td></td>
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<tr>
<td></td>
<td>IV-to-Oral (CE01-301)</td>
<td>9.1% (5.5%)</td>
<td>6.0%</td>
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<td>800 mg QD 10days</td>
<td>0.0-0.8%</td>
<td>0%</td>
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* Patients with normal ALT at baseline.
Conclusions

DILIsym predicted the incidence of elevations in serum ALT across the macrolide/ketolide class
DILIсим Интегрирует Многие Входы для Симулирования/Предсказания Гепатотоксичности

**Exposure**
- Фармакокинетика

**Mechanisms**
- Переносчик галогенов
- Митохондриальная резистентность
- Генерация ROS

**Interpatient Variability**
- Уникальные комбинации параметров

**Simulated Frequency & Severity of Liver Injury**

**Analysis of Mechanisms**
DILIsym Integrates Multiple Inputs to Simulate/Predict Hepatotoxicity

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Analysis of Mechanisms
Contribution to Predicted ALTelevations in Simulated Human Population

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The predominant mechanisms underlying dose dependent hepatoxicity can vary within a drug class.
Current uses of DILIsym®

1) Understand predict dose dependent serum ALT elevations, their implications, and how to avoid them.

2) Improve interpretation of traditional biomarkers
   a). Infer % hepatocyte death by necrosis vs apoptosis
   b). Explain elevations in serum bilirubin due to inhibition of transporters of UGT1A1
DILIsym Bilirubin Sub-Model Overview

Blood

UB ← OATP → UB

CB ← MRP3 → CB

Hepatocyte

UB ← UGT → CB

CB ← MRP2 → CB

TB: total bilirubin
UB: unconjugated bilirubin
CB: conjugated bilirubin

Systems Pharmacology Modeling of Drug-Induced Hyperbilirubinemia: Differentiating Hepatotoxicity and Inhibition of Enzymes/Transporters

The way forward

1) Incorporate adaptive immune responses

2) Model cholestasis and bile duct injury (eg. MDR3)

3) Vet metabolically competent liver cell culture systems to improve the efficiency of the modeling process

4) Priorities voted on by our partners.
The DILI-sim Team
The DILI-sim Scientific Advisory Board Includes World Class Scientists from Academia

- Neil Kaplowitz
- Paul Watkins
- Kevin Park
- Jack Uetrecht
- David Pisetsky
- Robert Roth

DILIsym®
Special Thanks to the DILI-sim Partners