The DILI-sim Initiative

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Introduction

The costs of developing new drug therapies continue to rise. New methods and technologies are necessary to make the development of much needed therapies possible at a sustainable cost. Safety and efficacy concerns appear to contribute nearly equally to attrition of candidate drugs during clinical development. However, many clinical development no-go decisions that are attributed to lack of efficacy may simply reflect reluctance to dose-escalate based on margins of safety determined in preclinical animal models. ***Safety related issues are therefore the major reason drugs fail.*** Hepatotoxicity is one of the top safety concerns during drug development.

The DILI-sim Initiative represents a group of sponsoring organizations combining resources to support the development of the DILIsym® modeling software – a mechanistic, mathematical model of drug-induced liver injury in mice, rats, humans, and dogs. The Initiative is led by Dr. Paul B. Watkins, Director of the University of North Carolina Institute for Drug Safety Sciences, and operated by DILIsym Services Inc., located in the heart of Research Triangle Park, North Carolina. Mechanistic modeling offers scientists the opportunity to organize information and readily tests hypotheses. Regulatory agencies are increasingly interested in using computational tools to enhance efficiency:

> *"…the introduction of new measurement technologies and increasing knowledge about toxicity mechanisms and pathways offer important opportunities for advanced computational analyses that can promote the effective translation of non-clinical findings to the clinical setting."*
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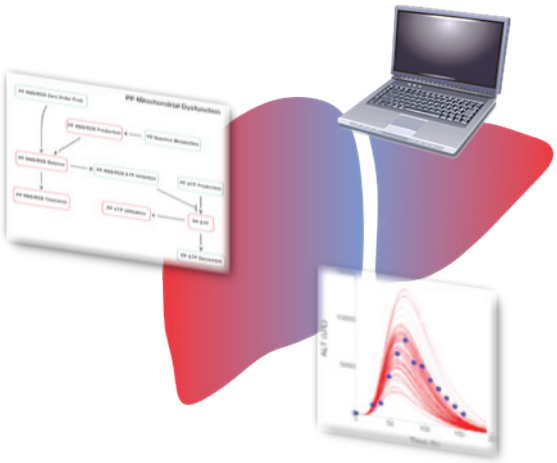
> - Advancing Regulatory Science at FDA, August 2011

Progress



DILIsym® software version 4B, based in the MATLAB® software environment, was made available to the DILI-sim members in September 2015. DILIsym® v4B introduces an entirely new and improved graphical user interface (GUI). With the new GUI, model simulations are more easily reproduced, changes to parameter sets are more readily tracked, inputs and outputs can be organized better into panels, and results are more easily exported to Excel. The GUI also features the ability to use PK simulation results from other software platforms to drive liver toxicity predictions, and contains built-in 'eDISH' plot capability. Additional capabilities and improvements include: new ASBT (gut transporter) inhibition module for bile acids; updated cytokeratin 18 parameter values based on new data; updated secondary necrosis function to be more biologically realistic, based on new data; additional SimPops™, capturing impact of variability in key pathways. The DILI-sim team also has launched MITOsym® software that mathematically models mitochondrial function in the in vitro setting. MITOsym® v2B was released in March 2015 and includes the ability to simulate inhibition of glycolysis, as well as reductions in ECAR in presence of compounds.

Thought leaders in the DILI scientific community are representing the DILI-sim Initiative members, which include: **AbbVie, Astellas, Bristol-Myers Squibb, Eli Lilly and Company, GlaxoSmithKline, Gilead, Janssen Research and Development, Merck, Mitsubishi Tanabe Pharma, Pfizer, and Takeda**. A scientific advisory board consisting of Dr. Mark Avigan, Dr. Neil Kaplowitz, Dr. George Michalopoulos, Dr. Kevin Park, Dr. David Pisetsky, and Dr. Robert Roth has been assembled.

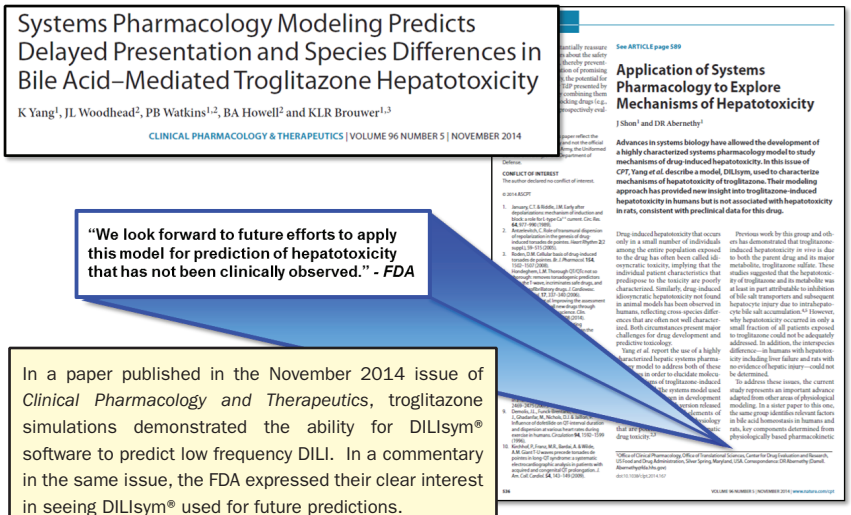
Contact information: Brett Howell, Ph.D., Associate Director, The DILI-sim Initiative

bhowell@dilisym.com or 919-558-1323

Project Overview

The primary objective of the DILI-sim Initiative is to develop and validate a mechanistically based, mathematical model (DILIsym® software) that integrates multiple data types relevant to drug-induced liver injury (DILI), in order to inform and improve decision making at key points in the drug development life cycle.

In the short term, it is envisaged that this information will be integrated with other key nonclinical safety data and will form a part of the weight of evidence for safety assessment prior to undertaking nonclinical in vivo regulatory safety studies or progression of compounds into man (FTIM). In the longer term, it is envisaged that use of the DILIsym® will improve human risk assessment and provide enhanced opportunities for customized clinical safety monitoring during all phases of clinical development.



In a paper published in the November 2014 issue of *Clinical Pharmacology and Therapeutics*, troglitazone simulations demonstrated the ability for DILIsym® software to predict low frequency DILI. In a commentary in the same issue, the FDA expressed their clear interest in seeing DILIsym® used for future predictions.

DILIsym® has been designed to include representations of human and nonclinical species (rat, mouse, and dog), and will be continuously developed based on existing literature, company data, and new laboratory data.

Deliverables and milestones for the DILI-sim Initiative will be specifically discussed and periodically revised by Initiative members and DILIsym Services Inc. at quarterly update meetings.

DILIsym® is now capable of addressing select liver safety concerns, particularly involving predictions across species and for biomarker study design and interpretation. The DILI-sim modeling team offers free consultations to review potential DILIsym® projects.

Deliverables

- A validated, predictive model of hepatocellular DILI, capable of evaluating the human toxicologic potential of novel compounds based on key nonclinical data, and improving the understanding of differences in DILI between nonclinical species. The model is based in the MATLAB® software environment, and delivered as a software package (DILIsym®).
- Citation of all reference data and literature used to construct the model, and descriptions of the modeling rationale.
- Identification and selection of non-standard mechanistically relevant DILI safety biomarkers and marker panels, which can be used to monitor early functional events that ultimately may result in DILI during clinical trials and so enable improved personalized healthcare.
- Descriptions of any biological insights discovered while constructing the model, including recommendations for, or outcomes of experiments based on those insights.

DILI-sim Initiative Current Status

- DILIsym® v4B and MITOsym® v2B are now available
- 8 dedicated FTEs
- Focus on predicting species differences in direct hepatotoxicity and margins of safety in man
- DILI mechanisms represented currently being expanded

Interested in knowing more about the DILI-sim Initiative?

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bhowell@dilisym.com or 919-558-1323