

Drug Induced Liver Injury-sim Initiative (DILI-sim)

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Research Areas



Tool Development

At a Glance

- Status: **Active Consortium**
- Year Launched: **2011**
- Initiating Organization: **Institute for Drug Safety Sciences**
- Initiator Type: **Industry**
- Location: **North America**

Abstract

The DILI-sim Initiative is a precompetitive partnership between The Hamner Institutes for Health Sciences and a diverse set of stakeholders to develop a computational model that will predict whether new drug candidates will cause drug-induced liver injury (DILI) in patients. The goals of the initiative are to improve patient safety, reduce the need for animal testing, and reduce the costs and time necessary to develop new drugs. It is the intent of the initiative to make the model, in the form of DILIsym® software, broadly available so that it may be used by the pharmaceutical industry, the U.S. Food and Drug Administration (FDA), and other entities in academia, government, and industry.

Mission

The initiative represents a group of sponsoring organizations combining resources to support the development of the DILIsym — a mechanistic, mathematical model of drug-induced liver injury in mice, rats, humans, and dogs. The initiative is led by Paul B. Watkins, Director of the Hamner-University of North Carolina Institute for Drug Safety Sciences, located on the campus of The Hamner Institutes for Health Sciences in the heart of Research Triangle Park, N.C. Mechanistic modeling offers scientists the opportunity to organize information and readily tests hypotheses.

The vision for the initiative over the next three years is to build upon its foundation as a key resource in the pharmaceutical industry's preclinical toolbox by further optimizing and enhancing the DILIsym for the prediction of less frequent human DILI that may only become evident in late-stage clinical development or post-marketing.

DILIsym is designed to be used during drug development to provide enhanced understanding of the DILI hazard posed by individual molecules, and to provide deeper insight into the mechanisms responsible for observed DILI responses at various stages of the development process. 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 and prior to progression of drug candidate compounds into man. In the longer term, it is envisaged that use of DILIsym will improve human risk assessment and provide enhanced opportunities for customized clinical safety monitoring during all phases of clinical development.

Consortium History

DILIsym v4A, based in the MATLAB® software environment, was made available to the DILI-sim Initiative members in March 2015.

The DILI-sim team has also 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.

Structure & Governance

The DILI-sim Initiative efforts are reviewed by a scientific advisory board.

Data Sharing

Initiative members are granted access to the DILIsym modeling software. Modelers can participate in the model and software training provided to all members, rendering the tools and skills to predict the

hepatotoxic risk of compounds in-house. Training materials, such as recorded WebEx seminars and technical support, are available to initiative members through the members area of DILIsym.com.

Impact/Accomplishment

Initiative members meet three to four times per year, including one face-to-face meeting at the Hamner Institutes in Research Triangle Park, N.C. Members receive updates on model development progress, propose new model features and provide input on proposed additions, and engage in discussions regarding basic concepts and mechanisms related to DILI. Additional meetings are also held occasionally to discuss important scientific issues.

Each year, initiative members are provided with an updated version of DILIsym, along with training and access to the DILI-sim modeling team for support. Access is also granted to the members section of the DILIsym.com website, where the model and documentation can be downloaded and the members forum can be accessed. The members forum provides a medium for posting and reading technical and operational questions and answers, as well as engaging in interesting scientific discussions.

The initiative is currently open to new members. Academic and nonprofit researchers are also encouraged to contact the DILI-sim modeling team at the Hamner to receive information on accessing DILIsym.

MITOsym is a mathematical model similar to DILIsym, executed in MATLAB with code and graphical interface versions provided. Unlike DILIsym, MITOsym is a model of mitochondrial function in the in vitro setting, designed to help with parameter identification and data interpretation from experiments conducted to infer mitochondrial function using the Seahorse Bioscience XF Analyzer machines. Ideally, experiments are run on the XF Analyzer machine, data are interpreted and parameters identified with the MITOsym modeling software, and those parameters are then fed into DILIsym for in vivo extrapolation.

SimPops™ is a collection of simulated individuals that match a particular range and distribution of parameters and patient characteristics. SimPops allow DILIsym users to explore the inter-individual variability in response to potential DILI-causing drugs. SimPops introduces variability into several important model parameters, including baseline glutathione levels, cellular response to oxidative

stress, hepatocellular recovery speed, inflammation, and many more. Drug-specific SimPops includes variability in metabolism and distribution parameters. SimPops has been used in exploring the risk of methapyrilene toxicity across species and in assessing the effectiveness of varying courses of NAC treatment in humans.

Links/Social Media Feed

Homepage <http://www.dilisyms.com/>

Sponsors & Partners

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