DILIsym Services, Inc.

> ***"Our vision is safer, effective, more affordable medicines for patients through modeling and simulation."***

DILIsym **RENAsym** **IPFsym** **NAFLDsym** **RADAsym**

- DILIsym Services, Inc. offers comprehensive program services:
  - **DILIsym** software licensing, training, development (DILI-sim Initiative)
  - **NAFLDsym** software licensing, training, development
  - **DILIsym** and **NAFLDsym** simulation consulting projects
  - Consulting and data interpretation; *in vitro* assay experimental design and management
  - **RENAsym, RADAsym,** and **IPFsym** software in development

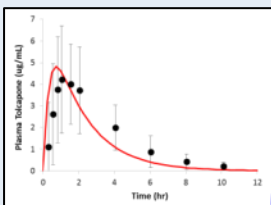**DILIsym Services**
A SIMULATIONS PLUS COMPANY

DILIsym Services Is Using QSP and QST Modeling to Predict Efficacy and Safety of Drugs in Development

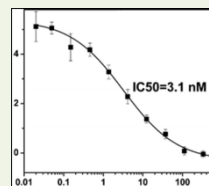**Predicted compound concentrations at site of target often require PBPK models**
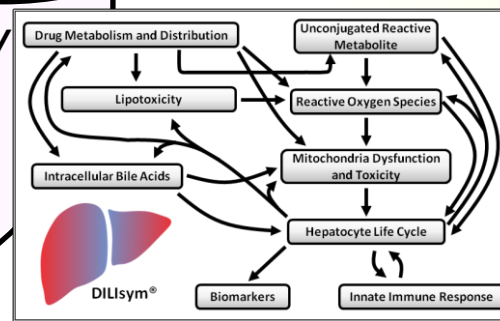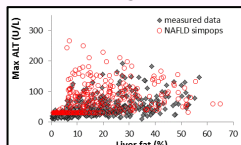
Exposure

Drug Effects

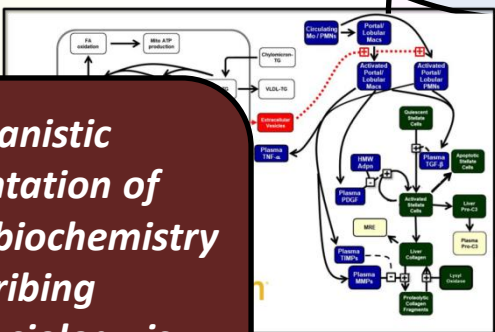**PD effects and interactions with underlying biochemistry unique for most compounds; QSP model needs to be flexible to provide ability to represent these effects**

Efficacy

Mechanistic representation of underlying biochemistry describing pathophysiology is foundation of QSP models

Liver Biochemistry/ Pathophysiology

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QSP Supports Clinical Development by Emphasizing Mechanistic Understanding of Pathophysiology and Treatment

Editorial: The emerging discipline of quantitative systems pharmacology

Tarek A. Leil* and Sergey Ermakov

Bristol-Myers Squibb, Clinical Pharmacology and Pharmacometrics/Exploratory Clinical and Translational Research, Princeton, NJ, USA

> "There is an expectation that the use of QSP will reduce the cost of R&D and the risks associated with uncertainties and gaps in our knowledge while bringing new therapies to patients."

- The complex, interconnected pathophysiology of many diseases poses challenges to developing effective treatments

- QSP models, such as NAFLDsym, help enhance the understanding of the pathophysiology and its treatment
  - Reduce knowledge gaps
  - Ability to predict response to combination treatments

- QSP models provide the ability to predict responses to treatments while accounting for mechanistic feedback loops as well as inter-patient variability

Quantitative Systems Pharmacology: A Case for Disease Models

CJ Musante[1], S Ramanujan[2], BJ Schmidt[3], OG Ghobrial[4], J Lu[5] and AC Heatherington[1]

> "Earlier and more thorough testing of mechanisms of action of novel agents have been proposed as critical for reducing attrition. With its focus on the interplay of pharmacological and biological mechanisms, QSP is well poised to support this call."

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QST Supports Clinical Development by Emphasizing Mechanistic Understanding of Pathophysiology and Toxicity

Editorial: The emerging discipline of quantitative systems pharmacology

Tarek A. Leil* and Sergey Ermakov

Bristol-Myers Squibb, Clinical Pharmacology and Pharmacometrics/Exploratory Clinical and Translational Research, Princeton, NJ, USA

> "There is an expectation that the use of QSP will reduce the cost of R&D and the risks associated with uncertainties and gaps in our knowledge while bringing new therapies to patients"

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COMMENTARY

Improving Interpretation of New and Old Serum Biomarkers of Drug-Induced Liver Injury Through Mechanistic Modeling

Paul B. Watkins

Quantitative systems toxicology

Peter Bloomingdale[1], Conrad Housand[2], Joshua F. Apgar[2], Bjorn L. Millard[2], Mager[1], John M. Burke[2], and Dhaval K. Shah[1]

[1]Department of Pharmaceutical Sciences, School of Pharmacy and Pharmaceutical The State University of New York at Buffalo, Buffalo, NY, USA

[2]Applied BioMath, LLC, 55 Old Bedford Road, Suite 208, Lincoln, MA 01773, USA

- The complex, interconnected nature of drug toxicity poses challenges to detection

- QST models (e.g. DILIsym and RENAsym) help enhance understanding of normal function and deviation via toxic pathways
  – Reduces knowledge gaps
  – Predict response to combination treatments
  – Patient Variability

> "Quantitative systems toxicology modeling maybe the solution to the long-range vision and strategy of the National Research Council (NRC) for the advancement of toxicity testing....."

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