DILIsym Services

A SIMULATIONS PLUS COMPANY

Modeling DILI Drug-Drug Interactions with DILIsym

April 7, 2020

Live Stream Learning with SLP

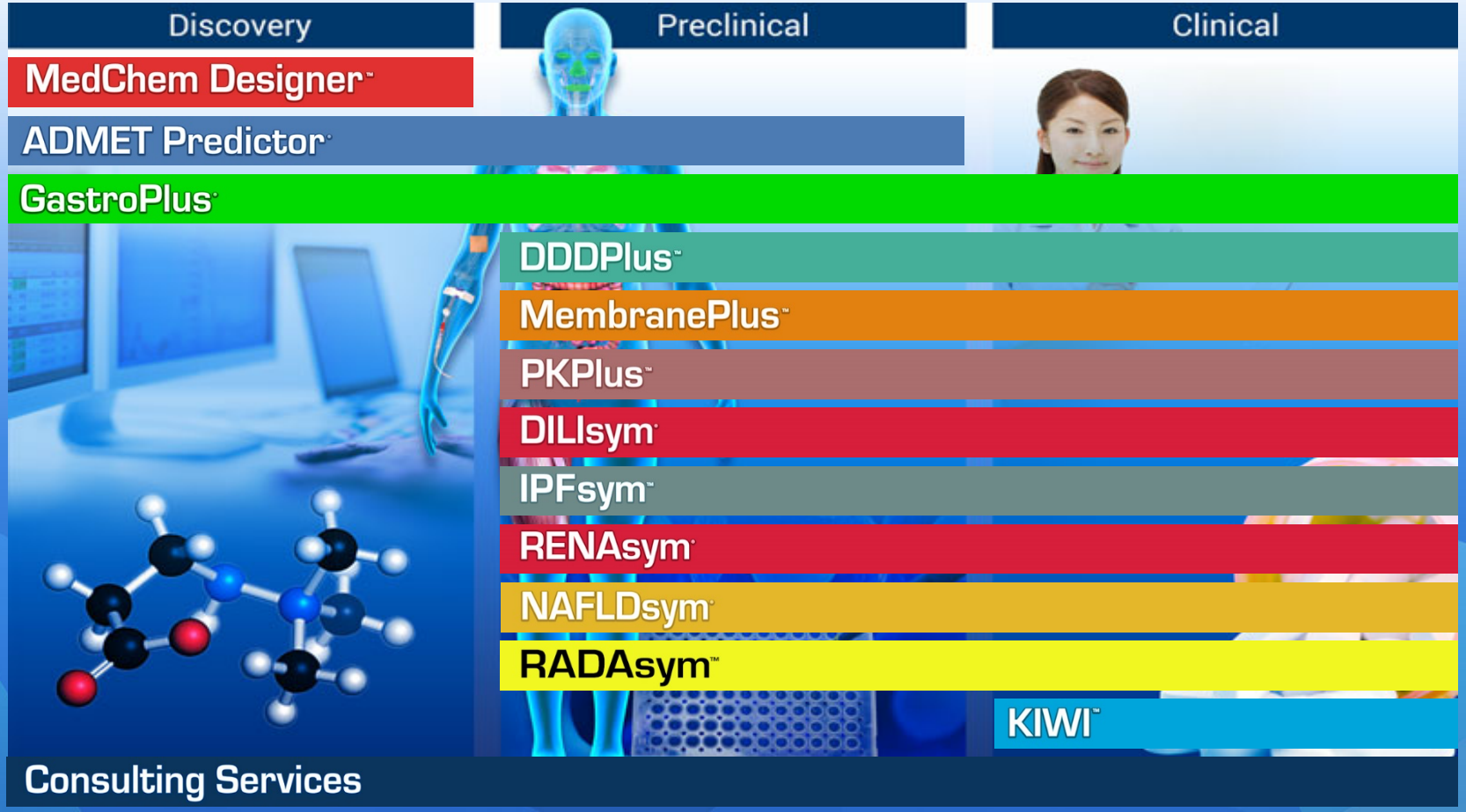
Brett A. Howell, Ph.D., President, DILIsym Services Division

SimulationsPlus | Cognigen | DILIsym Services

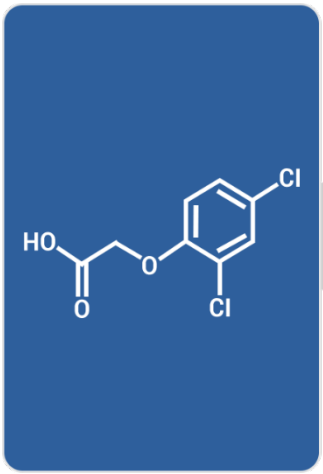
SCIENCE+SOFTWARE=SUCCESS

Where are you in the research process?

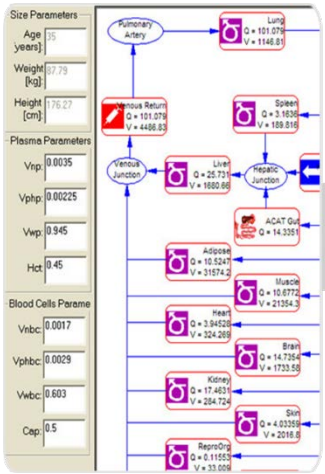
Save resources and get to market faster with our solutions.



Saying “I do” to the QSAR / PBPK / QST marriage…



Permeability, solubility vs. pH, pKa(s), logD vs. pH, Fup, blood:plasma ratio, tissue Kps, CLint, CLfilt



Local & systemic exposure, drug distribution, parent and metabolite levels, patient variability

Quantitative Structure Activity Relationships (QSAR)

ADMET Predictor™

Physiologically-Based Pharmacokinetics (PBPK)

GastroPlus™

Quantitative Systems Pharmacology/Toxicology (QSP/QST)

DILIsym®

DILIsym® RENAsym™

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DILIsym Services Inc., an SLP Company

"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

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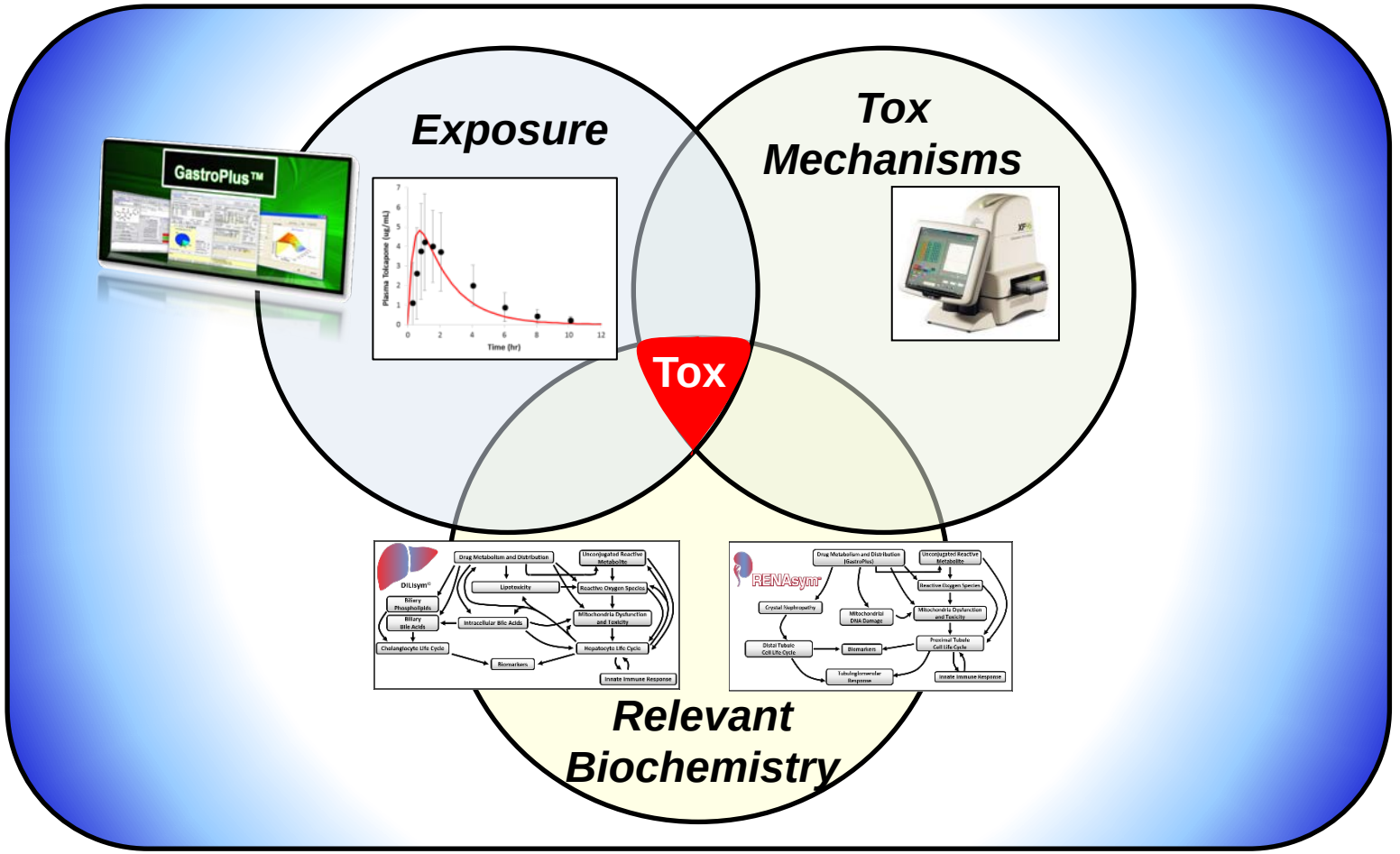
QST Predicts Tox via the Intersection Between Exposure, Mechanisms, and Inter-Patient Variability



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DILIsym Services QST and QSP Models

DILIsym

- Predicts drug-induced liver disease
- DILIsym X release Q2 2020
- Includes mechanistic representation of normal hepatic biochemistry
- Evaluated >70 compounds with 40+ companies

RENAsym™

NAFLDsym

So how can DILIsym (and RENAsym in the near future) help my organization?

- ***Keep patients safer***
- Predict liabilities beforehand and save **$$$**
- Choose the lead candidate ***most likely to succeed*** from liver/kidney safety standpoint
- Communicate with regulators on safety issues with information they have requested from others numerous times and from a platform they license (FDA)

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Refactored DILIsym and GastroPlus Will Be Integrated for More Efficient and Powerful Predictions

Both DILIsym X and GastroPlus X will operate independently of each other but can be used seamlessly via export/import

- Integration will occur via an interoperability plugin
- During integration, DILIsym will utilize GastroPlus X's ODE system for running simulations
- RENAsym will be integrated in the future as well

RENAsym

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- Predicts treatment efficacy in non-alcoholic fatty liver disease (NAFLD) and steatohepatitis (NASH)
- v2A released Q2 2019
- Includes mechanistic representation of pathophysiology of NAFLD and NASH
- Evaluated 16 compounds with 6 companies

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DILIsym Services Has Secured Funding to Provide a Predictive Software Tool for Drug-Induced Kidney Injury: **RENAsym**

- Drug-induced kidney injury, or Acute Kidney Injury (AKI), is a major reason drugs fail
  - Failures due to cardiovascular and liver injuries also high
- The DILIsym development group has experience with:
  - Constructing QST frameworks focused on toxicity
  - Managing software development within the context of a consortium
- **DILIsym Services is now developing of a new QST tool, RENAsym**
- **DILIsym Services awarded a Fast-Track Small Business Innovation Research (SBIR) grant by the National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK) to develop RENAsym**

RENAsym™


BusinessWire

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Simulations Plus Subsidiary DILIsym Awarded Grant for up to $1.7 Million For Model Development

Novel in silico Drug-Induced Kidney Injury Model

July 23, 2018 08:30 AM Eastern Daylight Time

RESEARCH TRIANGLE PARK, N.C.--(BUSINESS WIRE)--DILIsym Services, Inc., a Simulations Plus company (Nasdaq: SLP) developing *in silico* modeling software, resources, and information for assisting the pharmaceutical industry to more efficiently develop safe and effective drug therapies, today announced it has been awarded a Fast-Track Small Business Innovation Research (SBIR) grant by the National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK). The grant, coauthored by Dr. Brett Howell (Principal Investigator) and Dr. Bud Nelson, is entitled "Software for predicting a drug's potential to cause acute kidney injury." The total award for this Fast Track SBIR grant is up to $1.7 million over the next 18-24 months. The initial award is for Phase I, at a level of $225,000, with Phase II beginning in January 2019, subject to successful completion of Phase I. Drug-induced kidney injury can be costly, and may require multiple interventions, including hospitalization. The goal of this project is to provide software that can be used in drug development efforts to predict a drug's potential to cause drug-induced kidney injury, as well as assess and improve the understanding of mechanisms of drug-induced kidney injury.

"Software for predicting a drug's potential to cause acute kidney injury."

Tweet this

Brett Howell, Ph.D., president of DILIsym Services, commented: "We are thrilled to see that the NIH supports our mission to help modernize drug development and reduce the time and costs associated with developing new therapies. This large research grant will provide the funding we need to produce the first version of RENAsym™, which will be marketed to the pharmaceutical industry for investigation and screening of possible drug-induced kidney damage. Our team had already begun development of RENAsym, and we will now ramp up to

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DILIsym Services Has Kidney Expertise

OXFORD

SOT | Society of Toxicology
www.toxsci.oxfordjournals.org

TOXICOLOGICAL SCIENCES, 2017, 1–12

doi: 10.1093/toxsci/kfx239
Advance Access Publication Date: November 6, 2017
Research Article

Multiscale Mathematical Model of Drug-Induced Proximal Tubule Injury: Linking Urinary Biomarkers to Epithelial Cell Injury and Renal Dysfunction

Yeshitila Gebremichael,* James Lu,† Harish Shankaran,‡ Gabriel Helmlinger,‡ Jerome Mettetal,‡ and K. Melissa Hallow*,1

*School of Chemical, Materials and Biomedical Engineering, College of Engineering, University of Georgia, Athens, Georgia; †IMED Biotech Unit, Astrazeneca Pharmaceuticals, Cambridge, UK; and ‡IMED Biotech Unit, Astrazeneca Pharmaceuticals, Waltham, Massachusetts

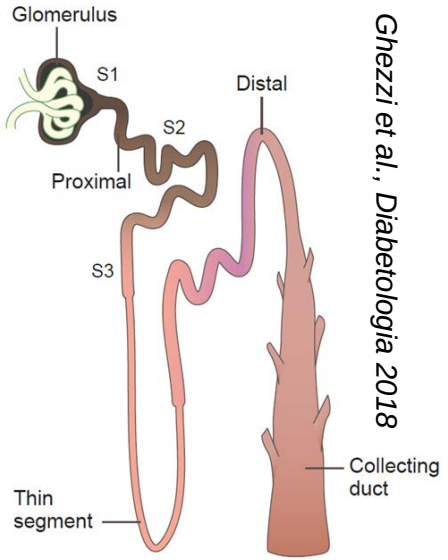
1To whom correspondence should be addressed at School of Chemical, Materials and Biomedical Engineering, College of Engineering, University o Georgia, 597 D. W. Brooks Dr., Athens, GA 30602. Fax: 706-542-2861; E-mail: hallowkm@uga.edu.

ABSTRACT

Drug-induced nephrotoxicity is a major cause of acute kidney injury, and thus detecting the potential for nephrotoxicity early in the drug development process is critical. Various urinary biomarkers exhibit different patterns following drug-induced injury, which may provide greater information than traditional biomarkers like serum creatinine. In this study, we

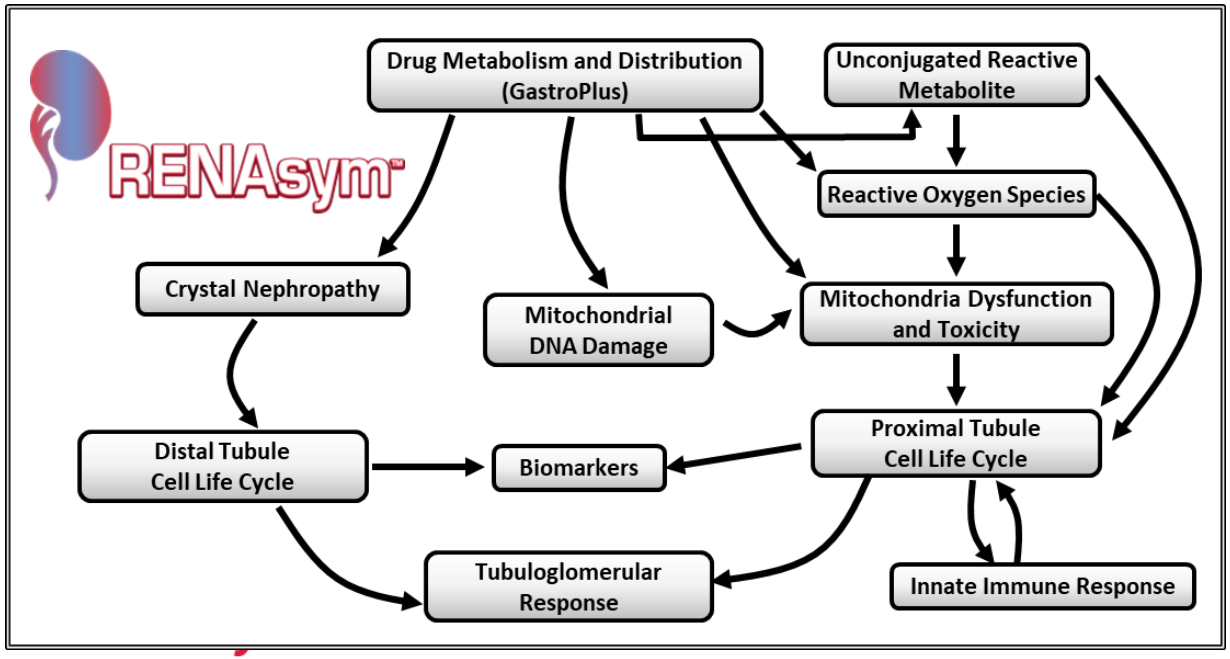
RENAsym Version 1A Preview

- **Species: human and rat**
  - Population variability
- **The three primary zones of the renal proximal tubule represented**
- **Some of the key cellular processes represented in multiple-scale, interacting sub-models**
  - GSH depletion
  - Injury progression
  - Mitochondrial dysfunction, toxicity, DNA depletion
  - Cellular energy balance
  - Crystal nephropathy
  - PTC and DTC apoptosis and necrosis, and proliferation
  - Immune cells contribution
  - Immune mediators
  - Caloric intake
  - Biomarkers of cell death and function
  - Renal function (tubuloglomerular response)



Ghezzi et al., Diabetologia 2018

- **Starting with well known kidney toxicants plus negative controls, such as cisplatin, gentamycin, and APAP**
- **Single and combination drug therapies to be examined**



RENAsym Will Utilize Various Data Types to Inform Decisions

Exposure Information

PBPK Modeling within GastroPlus

- **Compound Properties**
  - Tissue partition coefficients
- **Tissue penetration studies**
  - *Kidney to blood ratio*
- **Pharmacokinetic data**
  - *Absorption, extra-hepatic clearance, metabolites*
- ***in vitro* data**
  - *Metabolite synthesis, active uptake*

Modeling & Simulation

RENAsym™

Simulations and Assays inform:

- **Prediction of risk**
- **Participating mechanisms**
- **Characteristics of patients at risk for injury**
- **Drug dosing paradigms**
- **Biomarker monitoring strategies**

In vitro Mechanistic Tox Data

Assays performed to determine quantitative aspects of tox mechanisms

- **Oxidative stress**
  - *Direct and reactive metabolite-mediated*
- **Mitochondrial toxicity**
  - *ETC inhibition*
  - *Uncoupling*
- **Other assays to be added as well**

Testing *in vitro* systems with multiple providers

Clinical Data

- **Dosing Protocols, fasting/fed state, meal times**
- **Anthropometric data**
  - **Body weight, age, ethnicity**
- **Pharmacokinetic data**
  - **Absorption, extra-hepatic clearance, metabolites**

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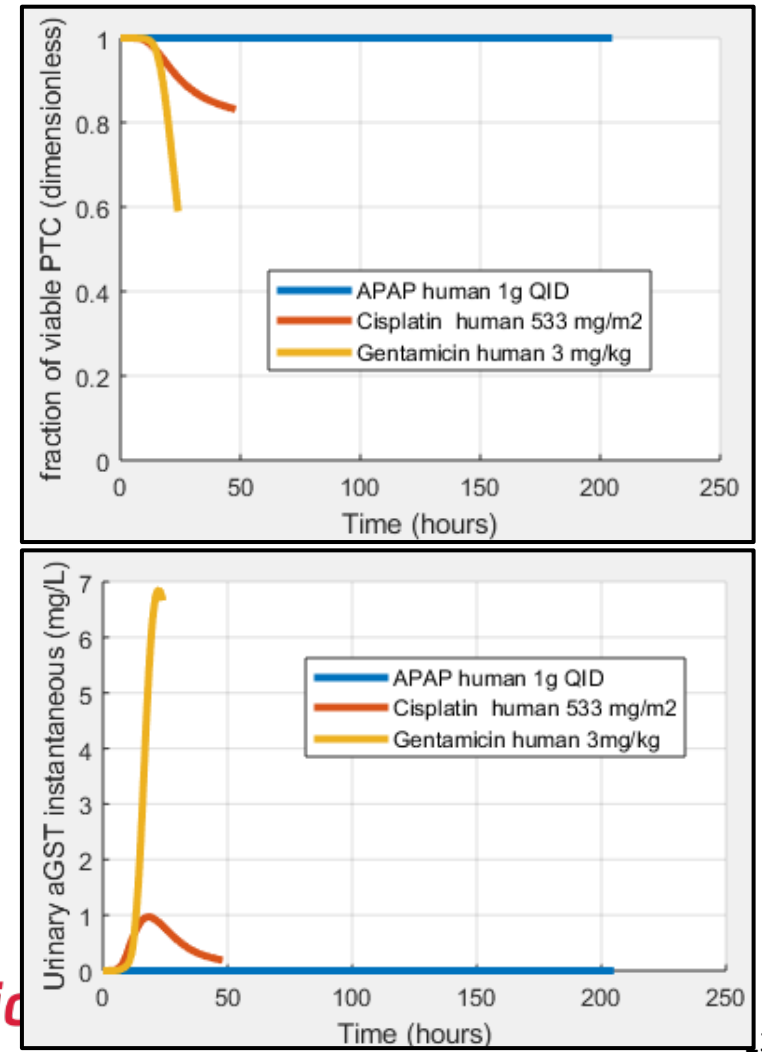
Comparison of the Toxicity Effect of Positive and Negative Control Drugs in Humans

HUMANS

- Toxic response comparisons of simulated human administered at multiple dose of 1 g QID APAP, single doses of 3 mg/kg gentamicin and 533 mg/m2 cisplatin
  - Simulation results show no cell death or αGST elevations from APAP exposure
  - Significant cell death and αGST elevations were observed with gentamicin
  - Mild cell death and GST elevation were observed with cisplatin

- **The in-progress model reproduces the expected qualitative behavior for the positive and negative control compounds**



Simulation Results

The RENAsym Consortium is Being Formed for Gathering Development Direction and Sharing of Important Compounds and Data

- ***RENAsym Consortium membership now included with DILI-sim Initiative membership for all Stage 4 renewals!***
- ***Please contact us today to join the consortium and get two memberships for the price of one!***
- Consortium of partners who will be privy to the progress being made on RENAsym along the way, in addition to the following:
  - Chance to offer advice and steer direction at multiple meetings each year
  - Chance to vote on certain RENAsym development items for prioritization
  - Stellar RENAsym SAB who will help guide software progress and overall design and goals
  - Software access including global floating licenses and cloud/server capabilities (upon initial release of the software)
  - Consulting and training discounts

RENAsym™

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Experts Who Have Agreed to Serve on the RENAsym Scientific Advisory Board

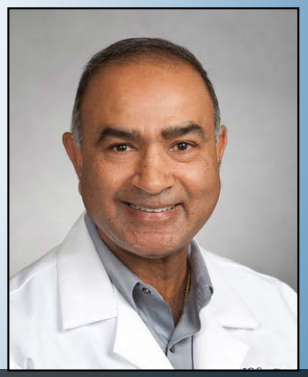
Dr. Paul B. Watkins
Director, Institute for Drug Safety Sciences
Howard Q. Ferguson Distinguished Professor Of Medicine
UNC Eshelman School of Pharmacy

Dr. K Melissa Hallow
Assistant Professor
School of Chemical, Materials, and Biomedical Engineering
University of Georgia

Dr. Zheng Dong
Leon H. Charbonnier Endowed Chair, Regents Professor
Medical College of Georgia
Senior Career Scientist, Director of Research
Charlie Norwood VA Medical Center

Lauren Aleksunes, PharmD, PhD, DABT
Associate Professor, Graduate Director
Pharmacology and Toxicology
Rutgers University

Dr. Frank Sistare
Former Executive Director of the Department of Laboratory Sciences and Investigative Toxicology within Safety Assessment at Merck
Former Co-Chair, Nephrotoxicity Working Group, PSTC
Formerly also with FDA/CDER for 15 years



Dr. Ravinder L Mehta
Professor of Medicine in the Division of Nephrology and Associate Chair for Clinical Affairs
Department of Medicine
University of California, San Diego (UCSD)

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The DILI-sim Initiative is a Partnership Between DILIsym Services and Pharmaceutical Companies to Minimize DILI

Scientific Advisory Board

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janssen
gsk GlaxoSmithKline
GILEAD
DILIsym
Mitsubishi Tanabe Pharma
abbvie
Bristol-Myers Squibb

Select Sample of Current Companies Licensing DILIsym

For a comprehensive review of progress, see *Watkins 2019: Clin Transl Sci*

- *Overall Goals*
  - *Improve patient safety*
  - *Reduce the need for animal testing*
  - *Reduce the costs and time necessary to develop new drugs*
- *History*
  - *Officially started in 2011*
  - *19 major pharmaceutical companies have participated*
  - *Members have provided compounds, data, and conducted experiments to support effort*
  - *Over $10 million total invested in project*
- ***At least 26 cases of use for regulatory purposes***
- ***Over 30 publications***

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Relevant Recent DILIsym Publications

Quantitative Systems Toxicology Approaches to Understand and Predict Drug-Induced Liver Injury

Paul B. Watkins, MD

Clin Liver Dis 24 (2020) 49–60
https://doi.org/10.1016/j.cld.2019.
1089-3261/20/© 2019 Elsevier Inc.

KEYWORDS

• DILIsym • DILI • QST • Simulation • Modeling

KEY POINTS

- The DILI-sim Initiative is a public-private partnership that has applied quantitative systems toxicology modeling to develop software (DILIsym®) that has improved mechanistic understanding of DILI.

Pharm Res (2020) 37:24
https://doi.org/10.1007/s11095-019-2726-0

RESEARCH PAPER

Comparison of the Hepatotoxic Potential of Two Treatments for Autosomal-Dominant Polycystic Kidney Disease Using Quantitative Systems Toxicology Modeling

J. L. Woodhead[1] • L. Pellegrini[2] • L. K. M. Shoda[1] • B. A. Howell[1]

Quantitative systems toxicology (QST) reproduces species differences in PF-04895162 liver safety due to combined mitochondrial and bile acid toxicity

Grant Generaux[1] | Vinal V. Lakhani[1] | Yuching Yang[1] | Sashi Nadanaciva[2] | Luping Qiu[3] | Keith Riccardi[4] | Li Di[4] | Brett A. Howell[1] | Scott Q. Siler[1] | Paul B. Watkins[5,6] | Hugh A. Barton[7] | Michael D. Aleo[3] | Lisl K. M. Shoda[1]

[1]DILIsym Services Inc., Research Triangle Park, North Carolina
[2]Compound Safety Prediction, Worldwide Medicinal Chemistry, Pfizer Inc., Groton, Connecticut
[3]Investigative Toxicology, Drug Safety Research and Development, Pfizer Inc., Groton, Connecticut
[4]Pharmacokinetics, Dynamics and Metabolism, Medicinal Sciences, Pfizer Inc., Groton, Connecticut
[5]UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina
[6]UNC Institute for Drug Safety Sciences, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina
[7]Translational Modeling and Simulation, Biomedicine Design, Pfizer, Inc., Groton, Connecticut

Pharm Res (2019) 36: 48
https://doi.org/10.1007/s11095-019-2582-y

RESEARCH PAPER

Analyzing the Mechanisms Behind Macrolide Antibiotic-Induced Liver Injury Using Quantitative Systems Toxicology Modeling

Jeffrey L. Woodhead[1] • Kyunghee Yang[1] • David Oldach[2] • Chris MacLauchlin[2] • Prabhavathi Fernandes[2] • Paul B. Watkins[3] • Scott Q. Siler[1] • Brett A. Howell[1]

Received: 24 September 2018 / Accepted: 27 January 2019 / Published online: 7 February 2019

ABSTRACT

Purpose Macrolide antibiotics are commonly prescribed treatments for drug-resistant bacterial infections; however, many macrolides have been shown to cause liver enzyme elevations and one macrolide, telithromycin, has been pulled

Conclusions The mechanisms responsible for toxicity can be significantly different within a class of drugs, despite the structural similarity among the drugs. QST modeling can provide valuable insight into the nature of these mechanistic differences.

DILI-sim Membership Details and Benefits

DILI-sim membership terms

- Tier 1 (3 year contract) members - contracts on a rolling basis (e.g. starting July 1st ends June 30, three years later)
  **License agreements can also be utilized to obtain access to DILIsym instead of membership*

Benefit: access to DILIsym software, equations, and support

- *RENAsym Consortium membership now included with DILI-sim fees!*
- DILI-sim members receive access to the DILIsym software during their active membership term
- DILI-sim members receive an electronic, secured copy of all equations included in each version of the DILIsym software released during their active membership term
- DILI-sim members have exclusive access to DILIsym training materials and support, including 10 hours of one-on-one support, free training once per year at annual meeting, and reduced rates on off-site workshops
- Tier 1 (3 year) members receive a 31% discount on consulting;
- DILI-sim members have exclusive access to the DILIsym Discovery Support Program (DDSP); not available to non-members or academics

Benefit: influence over DILIsym development

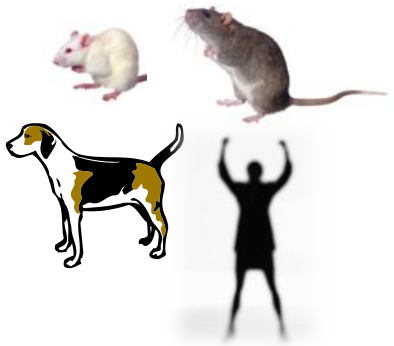
- Member companies guide DILIsym development
- DILI-sim members have option to donate data from current or failed compounds to serve as exemplars for DILIsym

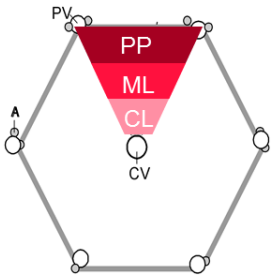
Benefit: participation in regular meetings with colleagues

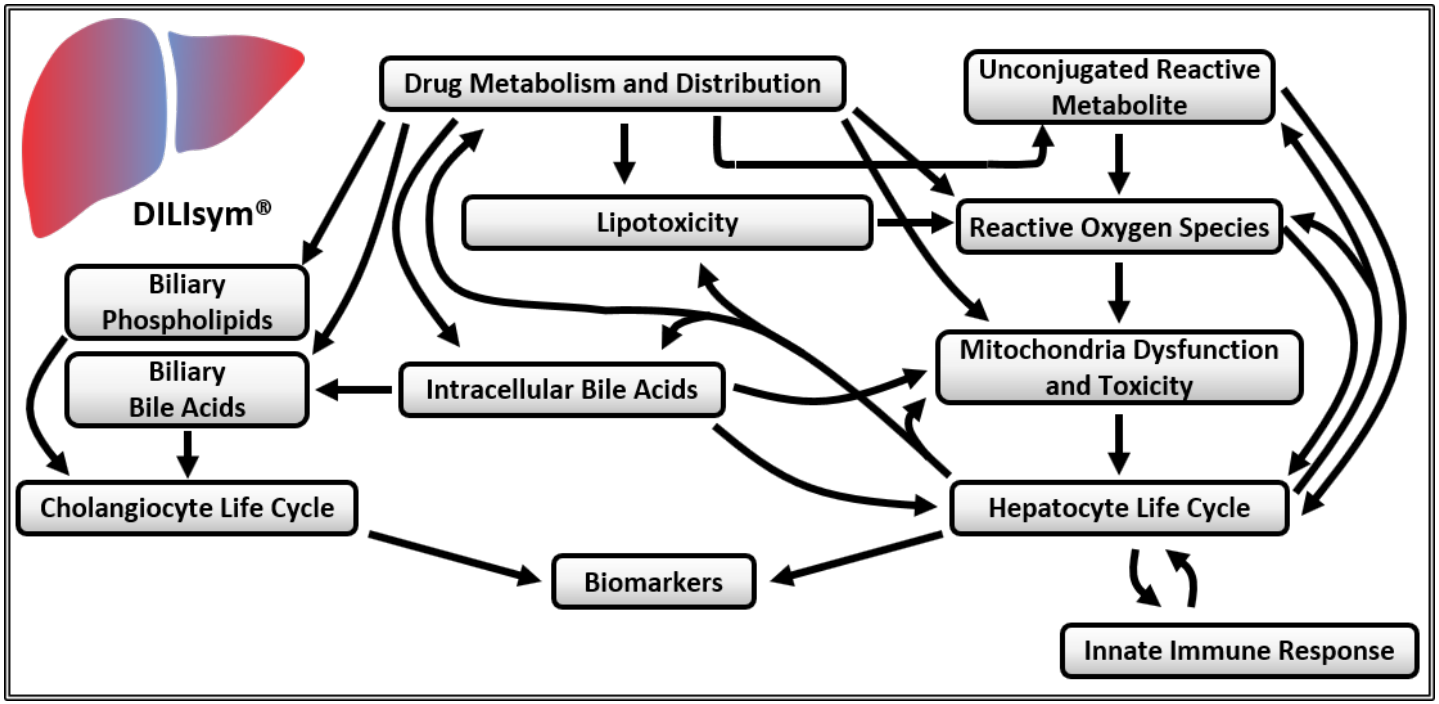
- Representatives from member companies attend quarterly DILI-sim update meetings to monitor progress and provide feedback, along with model design review sessions
- Attendance, voting, and data generation are optional benefits of membership and are not required

DILIsym Software Overview

- **Multiple species: human, rat, mouse, and dog**
  - Population variability
- **The three primary acinar zones of liver represented**
- **Essential cellular processes represented to multiple scales in interacting sub-models**
- **<u>Over 70</u> detailed representations of optimization or validation compounds with 80% success**
- **Single and <u>combination drug</u> therapies**







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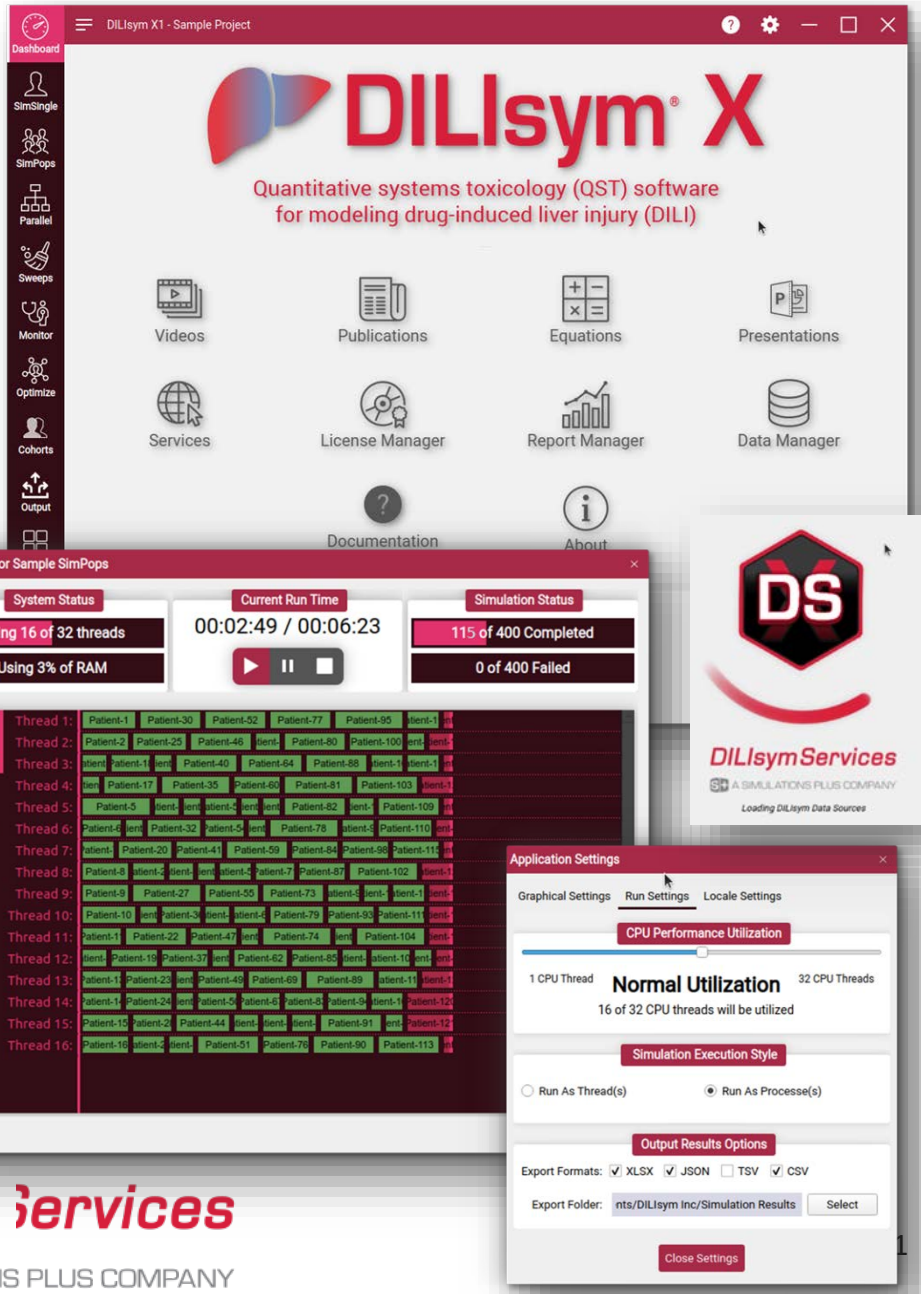
Highlights of DILIsym® Version X (DSX)

- Completely new software platform!
  - Much faster and more user friendly
  - Command line and GUI options
  - No reliance on MATLAB runtime or base MATLAB
  - Server/cloud computing capability coming soon…..
- 4 NEW exemplar Compounds included with varying clinical presentations
  - PF-04895162 *(Generaux 2019)*
  - Efavirenz
  - Anastrozole
  - Tamoxifen
- 2 New SimCohorts that include variability in susceptibility to liver injury and biomarker-related parameters (ALT and bilirubin)



DILIsym Utilizes Various Data Types to Inform Decisions

Exposure Data

PBPK Modeling

- **Compound Properties**
  - Tissue partition coefficients
- **Tissue penetration studies**
  - *Liver to blood ratio*
- **Pharmacokinetic data**
  - *Absorption, extra-hepatic clearance, metabolites*
- ***in vitro* data**
  - *Metabolite synthesis, active uptake*

Modeling & Simulation

DILIsym®

Simulations and Assays inform:

- **Prediction of DILI risk**
- **Participating DILI mechanisms**
- **Characteristics of patients at risk for DILI**
- **Drug dosing paradigms**
- **DILI monitoring strategies**

In vitro Mechanistic DILI Data

Assays performed to determine quantitative aspects of DILI mechanisms

- **Oxidative stress**
  - *Direct and reactive metabolite-mediated*
- **Mitochondrial toxicity**
  - *ETC inhibition*
  - *Uncoupling*
- **Bile acid / phospholipid transporter inhibition**
  - *BSEP, MRP3 and 4, NTCP, (MDR3)*
- **Bilirubin transport/metabolism**
  - *OATP1B1, OATP1B3, UGT1A1, MRP2, MRP3*

cyprotex AN EVOTEC COMPANY

SOLVO® BIOTECHNOLOGY THE TRANSPORTER COMPANY

Clinical Data

- **Dosing Protocols, fasting/fed state, meal times**
- **Anthropometric data**
  - **Body weight, age, ethnicity**
- **Pharmacokinetic data**
  - **Absorption, extra-hepatic clearance, metabolites**

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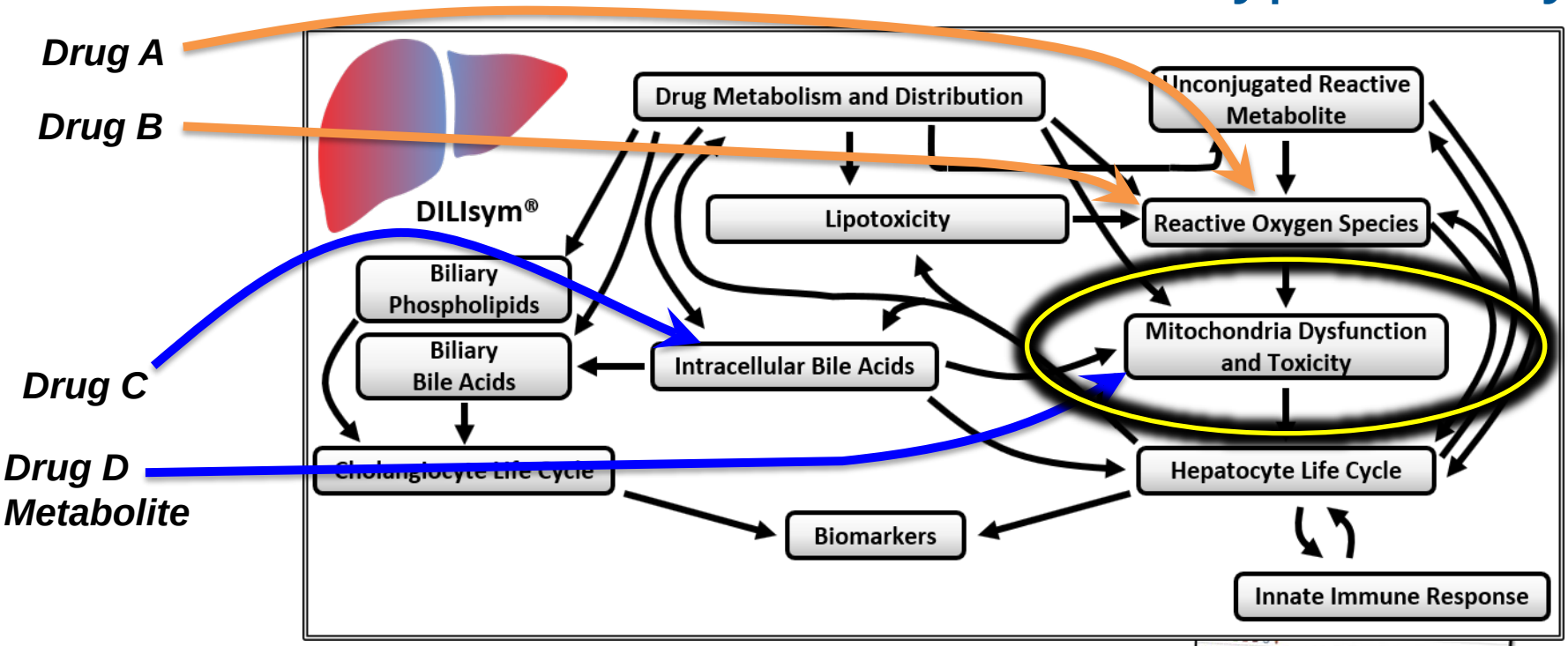
DILIsym Is Well-Suited to Predict the DILI Mechanism Interaction Effects of Polypharmacy



- Drugs can hit overlapping or different DILI mechanisms
- Effects can be similar or different when comparing NHV to patients
- Parent compounds and metabolites can contribute
- Mitochondria is common mechanistic intersection point

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Summaries of Current DILIsym *DILI-DDI* Simulation Applications

1. Increased ALT elevation frequencies observed in patients taking two drugs – data collection and simulations for each compound in isolation and combined
2. ALT elevations observed during PK-related DDI study in early clinical trials – data collected for candidate compound and available drugs studied in DDI study
3. ALT elevations seen in patients with APAP – drugs simulated as monotherapies and combination therapies
4. Drug targeted for patient population taking existing drugs that cause ALT elevations and drug has caused some elevations in isolation – pre-emptive simulations being conducted with co-meds

Valproate Leads to Liver Enzyme Elevations that Resolve with Continued Treatment

LiverTox

Clinical and Research Information on Drug-Induced Liver Injury

bout Us | Contact Us | Search Enter a drug name

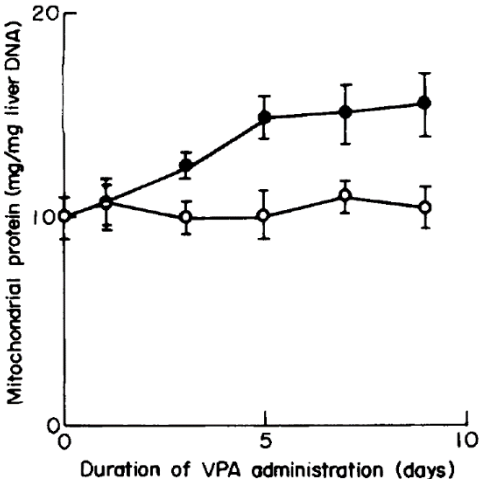
DRUG RECORD

VALPROATE

Hepatotoxicity

Prospective studies suggest that 5% to 10% of persons develop ALT elevations during long term valproate therapy, but these abnormalities are usually asymptomatic and can resolve even with continuation of drug. Unlike phenytoin and carbamazepine, valproate does not induce elevations

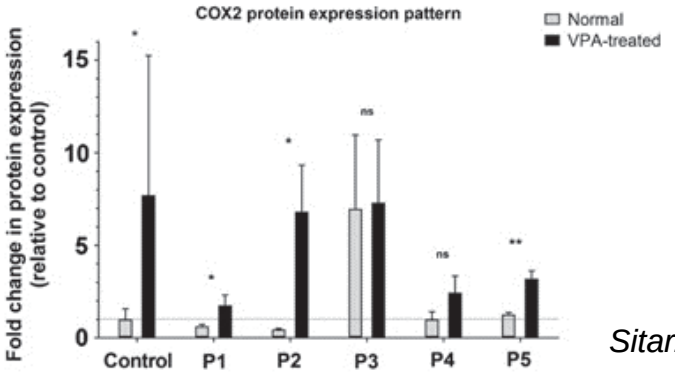
RAT



Hayasaka 1986

- Valproate causes ALT elevations in 5-10% of patients during long-term therapy
  - *In vitro* data indicates that valproate elicits mild mitochondrial ETC inhibition (Komulainen 2015 and internal data)
- *In vivo* and *in vitro* data indicate valproate causes mitochondrial biogenesis

Human Fibroblasts



Sitarz 2013

Preclinical Data

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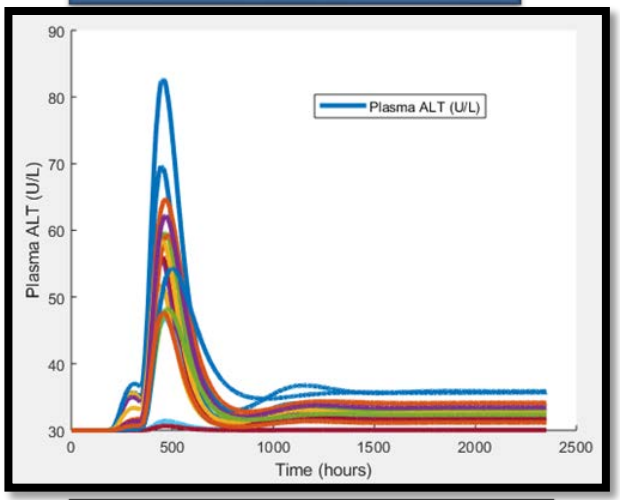
Plasma ALT from Compound X + Valproate Simulations Show Synergy and Adaptation

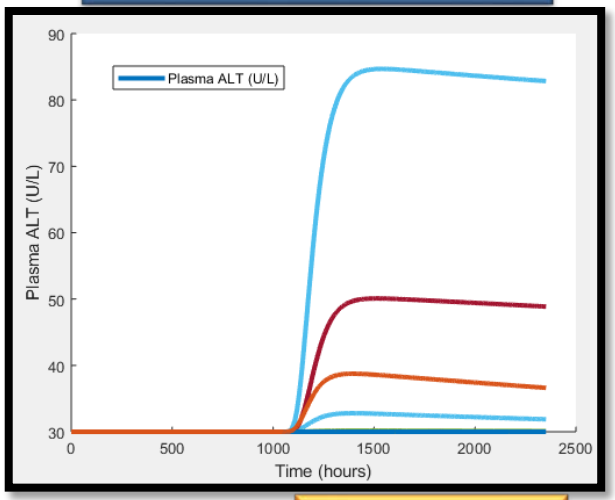
- Compound X in isolation causes minimal, mild ALT elevations
- Compound X + valproate leads to DILI DDI, with more bumps in ALT
- Resolution occurs
- One confidential case of two compounds leading to this response has already been noted – both compounds cause mild ETC inhibition

WITH MITOGENESIS



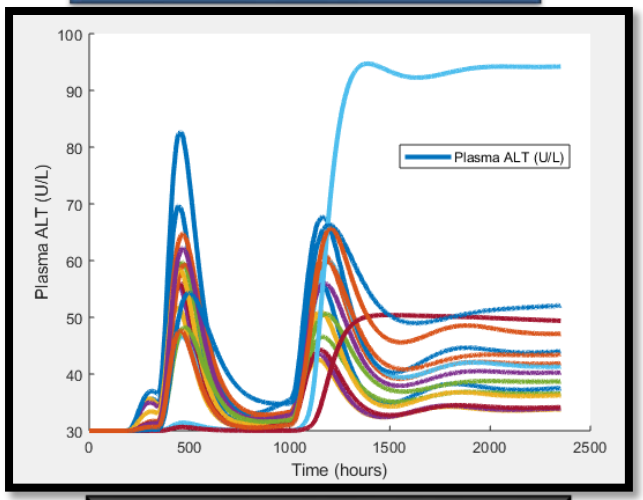
VPA Titrated to 15 mg/kg BID

WITH MITOGENESIS



Compound X

WITH MITOGENESIS



VPA Titrated to 15 mg/kg BID

Compound X

Simulation Results

HUMAN

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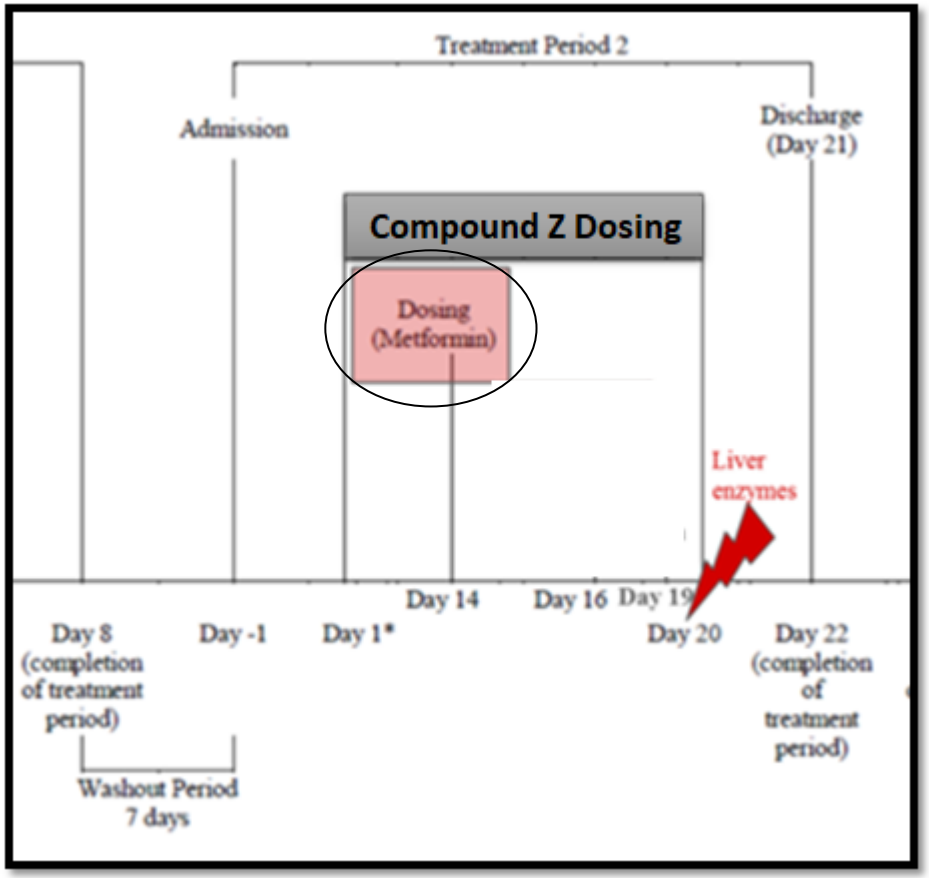
Drug-Drug Interaction Simulations Conducted To Test Plausibility of DILI-DDI That May Have Occurred During DDI Study

- ALT elevations > 20X ULN observed in DDI studies
  - Subject A: dosed with Compound Z and then a single dose of metformin (MFN) on day 14
- ***Simulations performed to investigate potential DDI with compounds within existing software (metformin) at the toxicity targets***
  - Metformin: a mild mitochondrial ETC inhibitor; PBPK model and toxicity parameters previously developed by DSS

Subject A



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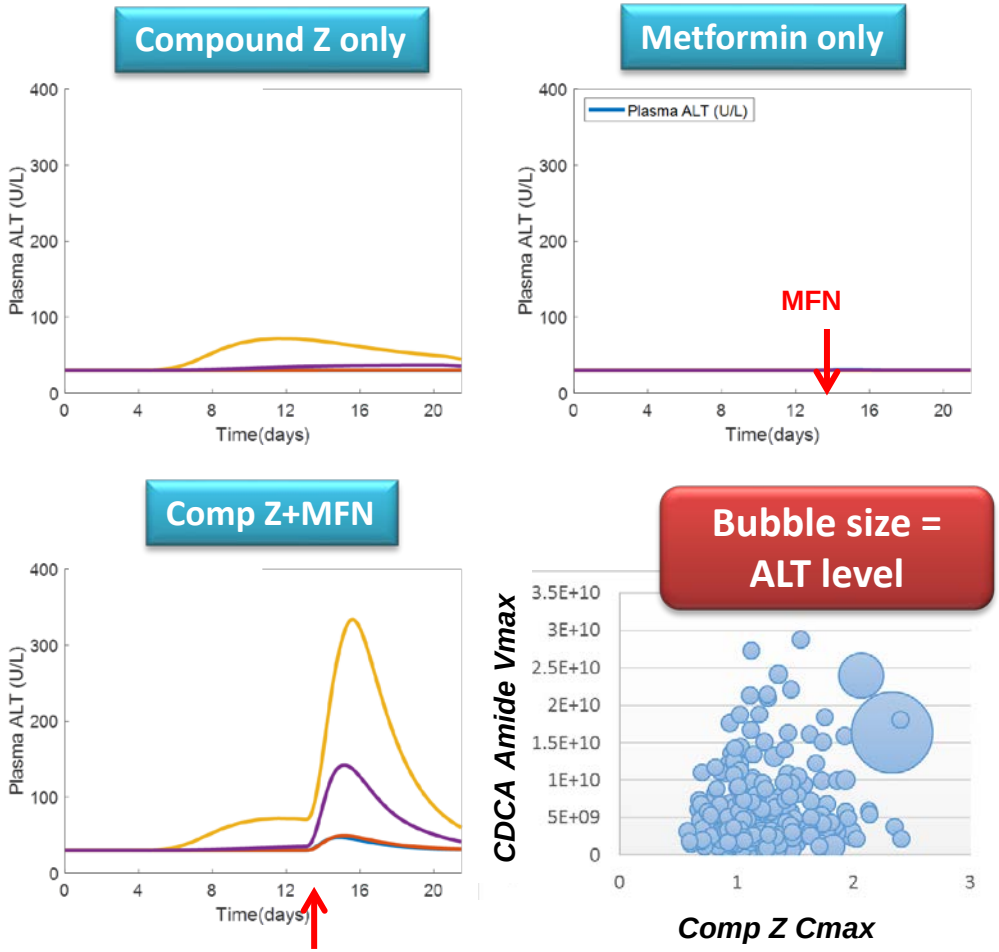
Simulations Show Plausibility of DILI-DDI Between Compound Z and Metformin

- Mild (< 3x ULN) ALT elevation predicted in one individual with Comp Z alone
- No ALT elevations predicted with a single oral dose of 500 mg Metformin
- Enhanced ALT elevations predicted when a single oral dose of 500 mg MFN was added to Compound Z
- High hepatic exposure of Compound Z (x-axis) and high capacity for formation of CDCA-amide (y-axis) led to susceptibility in simulated patients



Simulation Results

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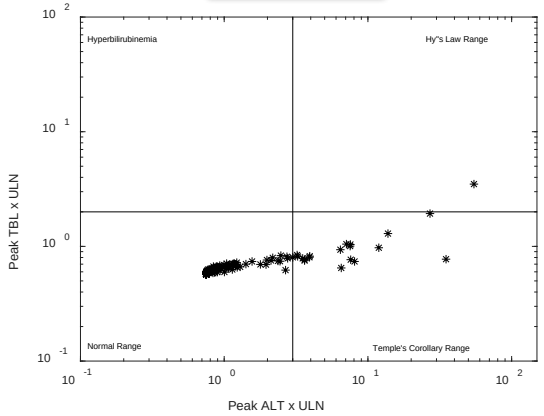
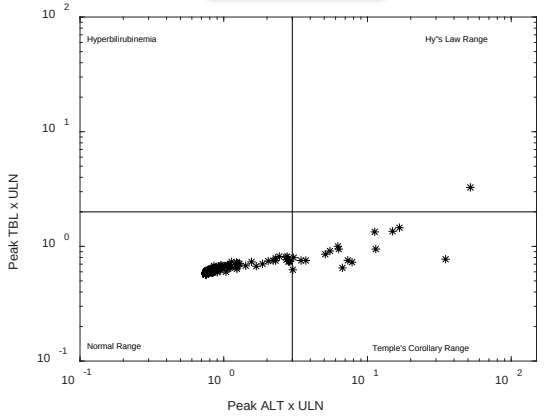
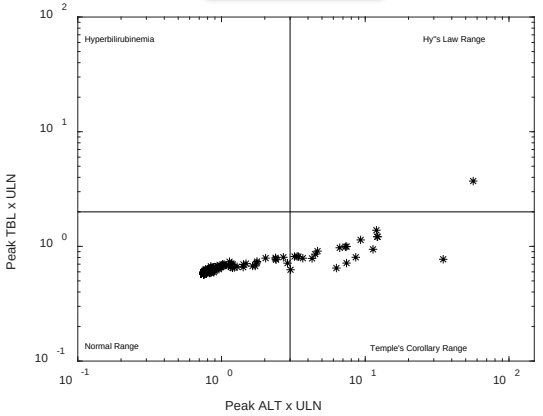
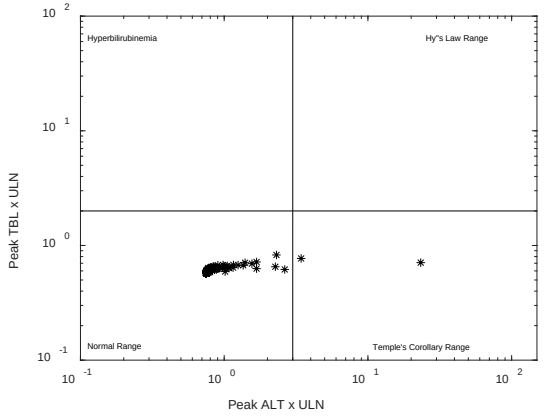
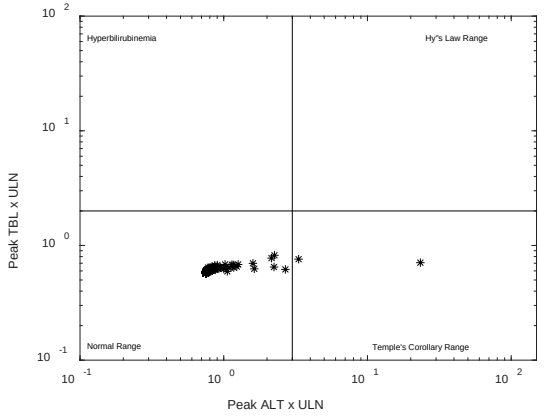
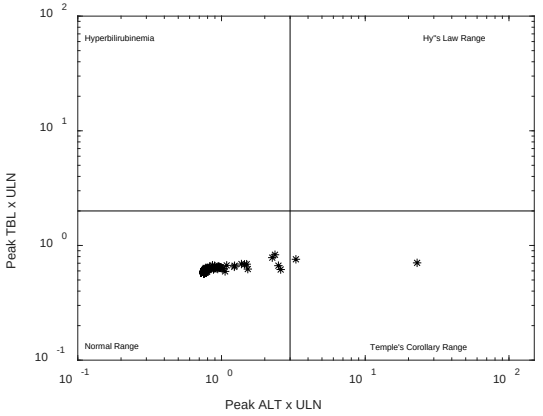
Mitochondrial Biogenesis Attenuated Predicted Hepatotoxicity with Therapeutic Dose of Metformin Combined with Compound Z

Comp Z + Metformin

	SimPops 1	SimPops 2	SimPops 3
No Biogenesis			
Biogenesis			

Simulation Results

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