DILIsym Services

A SIMULATIONS PLUS COMPANY

Utilizing DILIsym, a QST Platform, to Extract More from Your Data to Support Decisions

Solvo MEEX – Cambridge, September 2019

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DILIsym Services Inc., a Simulations Plus Company

The DILIsym Services Team

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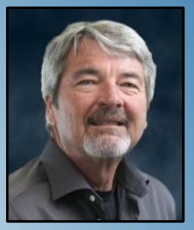

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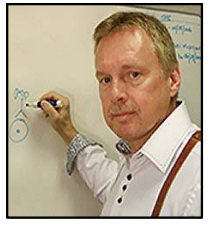

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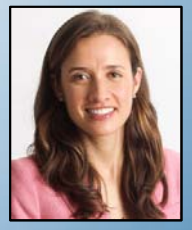

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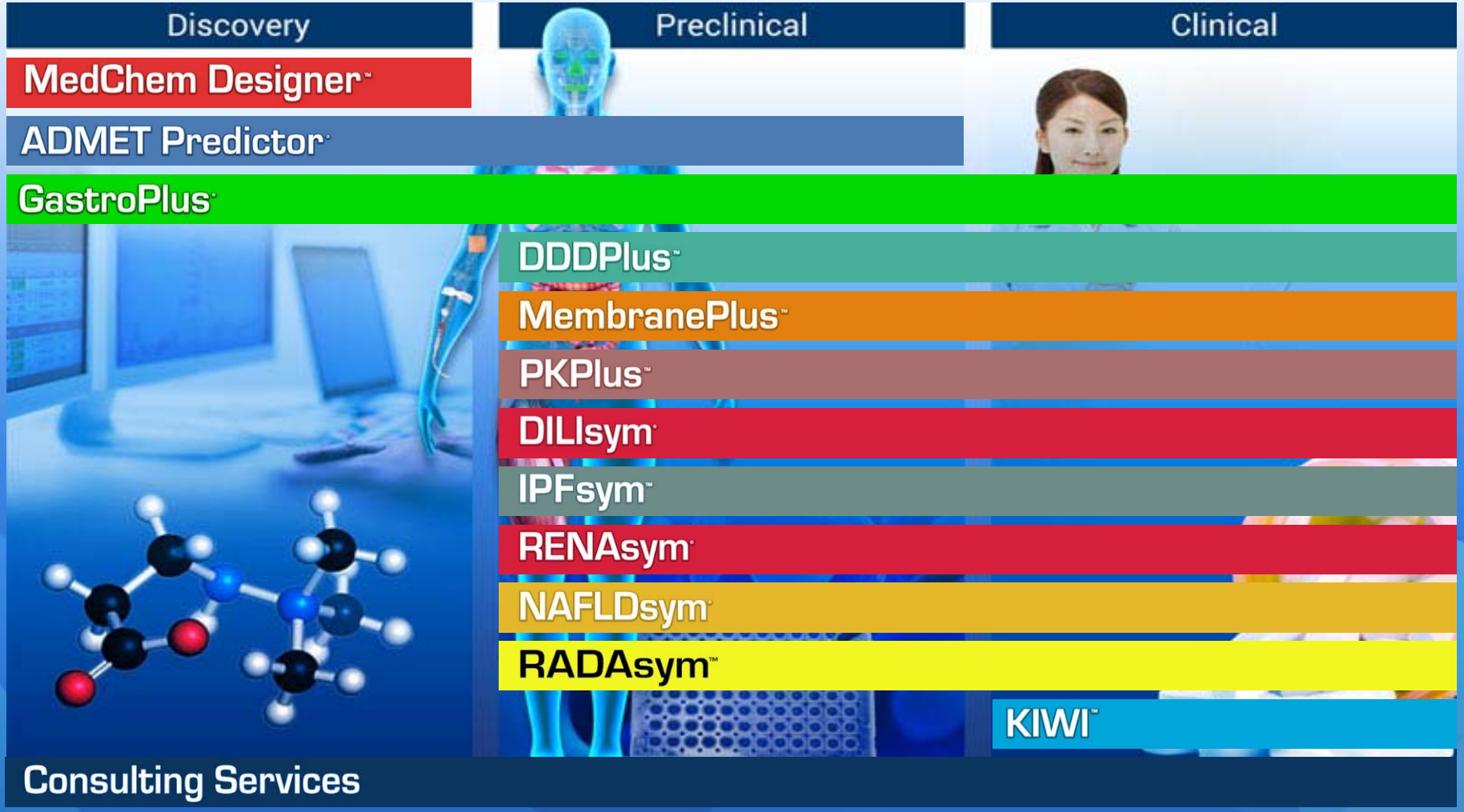
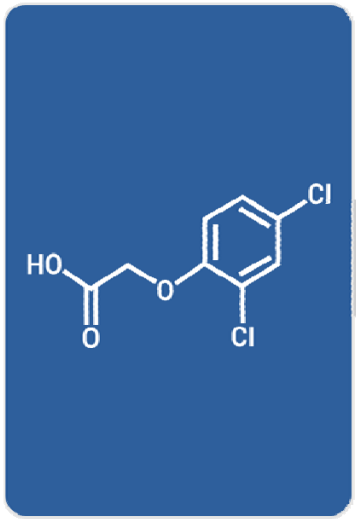
SCIENCE+SOFTWARE=SUCCESS

Where are you in the research process?

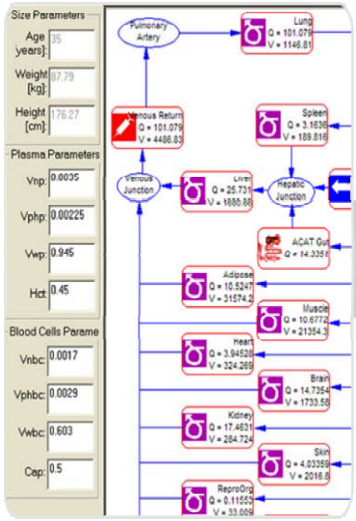
Save resources and get to market faster with our solutions.



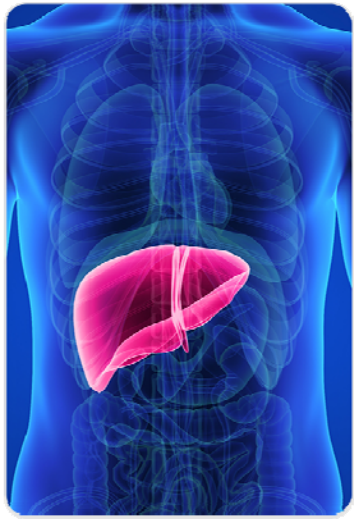
Saying “I do” to the QSAR / PBPK / QST marriage…



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 Services

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DILIsym Services, Inc.

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

- 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** and **IPFsym** software in development

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Summary of Key Points

- DILIsym is a mechanistic, mathematical model that has been constructed to support pharmaceutical risk assessment and decision making
- DILIsym has been applied to support decisions related to compound DILI risk throughout the clinical development pipeline
- DILIsym simulation results have been included in numerous communications with regulatory agencies
- Several key learnings related to transporters have emerged through the use of DILIsym

DILIsym Presentation Overview

- Overview of the DILI-sim Initiative
- Overview of the DILIsym Software
- 3 Lessons Learned – Examples
- Questions

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*

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- *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 $9 million total invested in project*

Support of the DILI-sim Initiative Has Led to Significant Research Achievements

- Eight versions of DILIsym released, including DILIsym v8A in Jan 2019
- At least **26** applications of DILIsym directly related to regulatory submissions for drug development (that we are aware of)
- More than **35** pharmaceutical companies have utilized DILIsym via consulting contracts for projects related to regulatory issues or applications, internal validation, or DILIsym use help internally
  - Insights go directly back into software for members
- **~80%** of the simulation scenarios evaluated within DILIsym have generally been predicted well (of the 66 cases and 59 compounds simulated)
- **30** accepted manuscripts and **5+** more in final preparation focused on DILIsym content
  - Many of these are co-publications between DILIsym Services and a member or non-member pharma company
- Academic and government licenses issued for teaching and research, including to FDA across multiple divisions

Relevant Recent DILIsym Publications

Several good publications in submission or preparation – mostly co-authored with sponsors

The DILI-sim Initiative: Insights into Hepatotoxicity Mechanisms and Biomarker Interpretation

Authors: Paul Watkins

Publication date: 2019/2/14

Journal: Clinical and translational science

Description: The DILI-sim Initiative is a public-private partnership involving scientists from industry, academia and the FDA. The Initiative uses Quantitative Systems Toxicology (QST) to build and refine a model (DILIsym®) capable of understanding and predicting liver safety liabilities in new drug candidates and to optimize interpretation of liver safety biomarkers used in clinical studies. Insights gained to date include the observation that most dose-dependent hepatoxicity can be accounted for by combinations of just three mechanisms (oxidative stress, interference with mitochondrial respiration, and alterations in bile acid homeostasis) and the importance of non-competitive inhibition of bile acid transporters. The effort has also provided novel insight into species and interpatient differences in susceptibility, structure:activity relationships, and the role of non-immune mechanisms in delayed idiosyncratic hepatotoxicity. The ...

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
Prabhavathi Fernandes[2] • Paul B. Watkins[3] • Scott Q. Siler[1] • Brett A.

Received: 24 September 2018 / Accepted: 27 January 2019 / Published onli

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 from the market by its provider due to liver toxicity. This work

Article: ***Quantitative Systems Toxicology (QST) Reproduces Species Differences in PF-04895162 Liver Safety due to Combined Mitochondrial and Bile Acid Toxicity***
Journal: Pharmacology Research & Perspectives

Congratulations on the acceptance of your article for publication in Pharmacology Research & Perspectives.

Generaux, Grant; Lakhani, Vinal; Yang, Yuching; Nadanaciva, Sashi; Qiu, Luping; Riccardi, Keith; Di, Li; Howell, Brett; Siler, Scott; Watkins, Paul; Barton, Hugh; Aleo, Michael ; Shoda, Lisl K.M.

Known DILIsym Applications Submitted to or Intended for Regulatory Agencies (Slide 1 of 2)

N	Agency	Context	Scenario	Simulation Type	Presented/ Submitted By
1	FDA	Simulation results included in formal, written correspondence to agency	Sponsor responding to concerns over liver safety signals	Hepatocyte loss (biomarker fitting)	Sponsor
2	FDA	Simulation results included in formal, written correspondence to agency	Sponsor responding to concerns over liver safety signals	Hepatocyte loss (biomarker fitting)	Sponsor
3	FDA	Simulation results included in formal, written correspondence to agency and presented during meeting	Sponsor responding to concerns over liver safety signals	Hepatocyte loss (biomarker fitting)	Sponsor and DILIsym Services
4	BARDA*	Simulation results presented to sponsor group at BARDA	Sponsor responding to concerns over liver safety signals	Mechanistic liver injury (predictive)	DILIsym Services and Sponsor
5	FDA and PMDA	Simulation results included in formal, written correspondence to agency and presented during meeting	Sponsor addressing concerns over liver safety in NDA submission	Mechanistic liver injury (predictive)	Sponsor and DILIsym Services
6	FDA	Simulation results included in formal, written correspondence to agency and presented during meeting	Sponsor repurposing compound that failed due to hepatotoxicity in IND submission	Mechanistic liver injury (predictive)	Sponsor and DILIsym Services
7	FDA	Simulation results included in formal, written correspondence to agency and presented during meeting	Sponsor addressing concerns over liver signals from other drug in same class with same indication	Mechanistic liver injury (predictive)	Sponsor
8	FDA and EMA	Simulation results included in formal, written correspondence to agency	Sponsor addressing concerns over liver safety in NDA submission, including DILI DDI concern	Mechanistic liver injury (predictive)	Sponsor
9	FDA	Simulation results included in formal, written correspondence to agency and discussed during call with FDA	Sponsor responding to concerns over liver safety signals	Hepatocyte loss (biomarker fitting)	Sponsor
10	FDA and other regulators globally	Sponsor intended to submit simulation results	Sponsor addressing concerns over liver safety signals	Hepatocyte loss (biomarker fitting) and Mechanistic liver injury (predictive)	Sponsor
11	FDA	Sponsor intended to submit simulation results	Sponsor addressing concerns over liver signals from other drug in same class with same indication	Mechanistic liver injury (predictive)	Sponsor
12	FDA	Sponsor intended to submit simulation results	Sponsor reformulating existing compound on the market	Mechanistic liver injury (predictive)	Sponsor
13	FDA	Sponsor intended to submit simulation results and present at meeting	Sponsor addressing concerns over liver safety signals	Mechanistic bilirubin (predictive)	Sponsor

*Not a direct regulatory agency, but affiliated closely with NIH and FDA

**Several additional sponsors have declared intent to include results in regulatory communications in the future

***Additional drug development teams have implied that regulators have informally requested or recommended DILIsym simulations

Known DILIsym Applications Submitted to or Intended for Regulatory Agencies (Slide 2 of 2)

N	Agency	Context	Scenario	Simulation Type	Presented/ Submitted By
14	FDA	Sponsor intended to submit simulation results	Sponsor addressing concerns over liver safety signals	Mechanistic liver injury (predictive)	Sponsor
15	FDA	Sponsor intended to submit simulation results	Sponsor addressing concerns over liver signals from other drug in same class with same indication	Mechanistic liver injury (predictive)	Sponsor
16	FDA	Sponsor intended to submit simulation results	Sponsor addressing concerns over liver signals from other drug in same class with same indication	Mechanistic liver injury (predictive)	Sponsor
17	EMA	Sponsor intended to submit simulation results	Sponsor addressing concerns over liver safety signals	Mechanistic liver injury (predictive)	Sponsor
18	FDA	Agency reviewed results publicly available during evaluation	Agency addressing concerns over liver safety signals	Mechanistic liver injury (predictive)	Publicly available materials
19	FDA and EMA	Sponsor intended to submit simulation results	Sponsor addressing concerns over liver safety signals, including DILI DDI signal	Mechanistic liver injury (predictive)	Sponsor
20	FDA	Sponsor intended to submit simulation results to justify dose selection	Sponsor addressing concerns over liver safety signals and optimizing clinical trial design	Mechanistic liver injury (predictive)	Sponsor
21	U.S. State Agency	Sponsor intended to submit simulation results within regulatory submission	Sponsor addressing concerns over compound safety	Mechanistic liver injury (predictive)	Sponsor
22	FDA	Sponsor intended to submit simulation results	Sponsor addressing concerns over liver safety signals	Mechanistic bilirubin (predictive)	Sponsor
23	FDA	Sponsor intended to submit simulation results	Sponsor addressing concerns over liver safety signals	Mechanistic bilirubin (predictive)	Sponsor
24	FDA and EMA	Sponsor intended to submit simulation results	Sponsor proactively addressing concerns over liver safety due to concern that is difficult to test in animals	Mechanistic liver injury (predictive)	Sponsor
25	FDA	Sponsor intended to submit simulation results	Sponsor addressing concerns over liver safety signals for high unmet medical need compound	Mechanistic liver injury (predictive)	Sponsor
26	FDA	Sponsor intended to submit simulation results	Sponsor addressing concerns over liver safety signals within early clinical study	Mechanistic liver injury (predictive)	Sponsor

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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 1, 2018 ends June 30, 2021)
- Tier 2 (1 year contract) members - contracts on a rolling basis (e.g. starting July 1, 2018 ends June 30, 2019)

**License agreements can also be utilized to obtain access to DILIsym instead of membership*

Benefit: access to DILIsym software, equations, and support

- 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; Tier 2 (annual) members receive a 17% discount (compared to non-member pricing)
- 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
- Members gather in person once per year for a more comprehensive overview during the annual DILI-sim Face to Face Meeting
- Attendance, voting, and data generation are optional benefits of membership and are not required

DILIsym Software Licenses Are Available to Industry and Academia

- DILI-sim membership not required to license the DILIsym modeling software
- Training provided in various formats
  - Training courses and workshops
  - Web-based videos
  - User manual
  - Documentation
- Academic and regulatory licenses also available
- Access to the MITOsym modeling software is also provided

MITOsym®: A Mechanistic, Mathematical Model of Hepatocellular Respiration and Bioenergetics

Y. Yang • S. Nadanaciva • Y. Will • J. L. Woodhead • B. A. Howell • P. B. Watkins • S. Q. Siler

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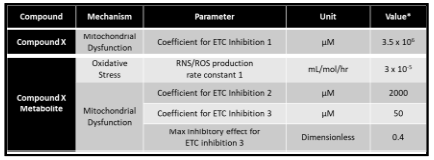
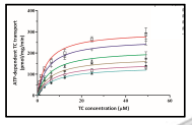
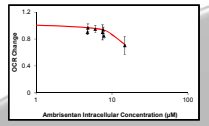
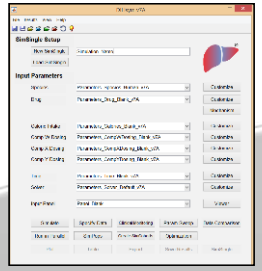
The DILIsym Discovery Support Program (DDSP) Enables Internal Use by DILI-sim Member Companies

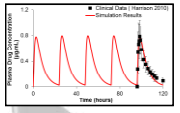


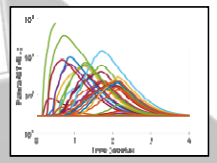
Compound	Mechanism	Parameter	Unit	Value*
Compound X	Mitochondrial Dysfunction	Coefficient for ETC Inhibition 1	µM	3.5×10^{6}
Compound X Metabolite	Oxidative Stress	RNS/ROS production rate constant 1	mL/mol/hr	3×10^{-5}
	Mitochondrial Dysfunction	Coefficient for ETC Inhibition 2	µM	2000
		Coefficient for ETC Inhibition 3	µM	50
		Max inhibitory effect for ETC inhibition 3	Dimensionless	0.4











Simulation support

- Preliminary simulations to aid with prioritization of internal efforts

DILIsym setup support

- Exposure setup
- Toxicity parameter setup

Data collection support

- On-going *in vitro* data collection management

- All components are optional to members
- The components can be utilized in isolation or together
- Deliverables are standardized outputs that facilitate the project, but do not complete it
- **Only** DILI-sim members can utilize these services
- The costs are much **lower** than full consulting projects conducted by DILIsym Services

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DILIsym Presentation Overview

- Overview of the DILI-sim Initiative
- Overview of the DILIsym Software
- 3 Lessons Learned – Examples
- Questions

DILIsym Services QST and QSP Models

DILIsym®

- Predicts drug-induced liver disease
- v8A released Q1 2019
- Includes mechanistic representation of normal hepatic biochemistry
- Evaluated >60 compounds with 25 companies

So how can DILIsym help my organization?

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

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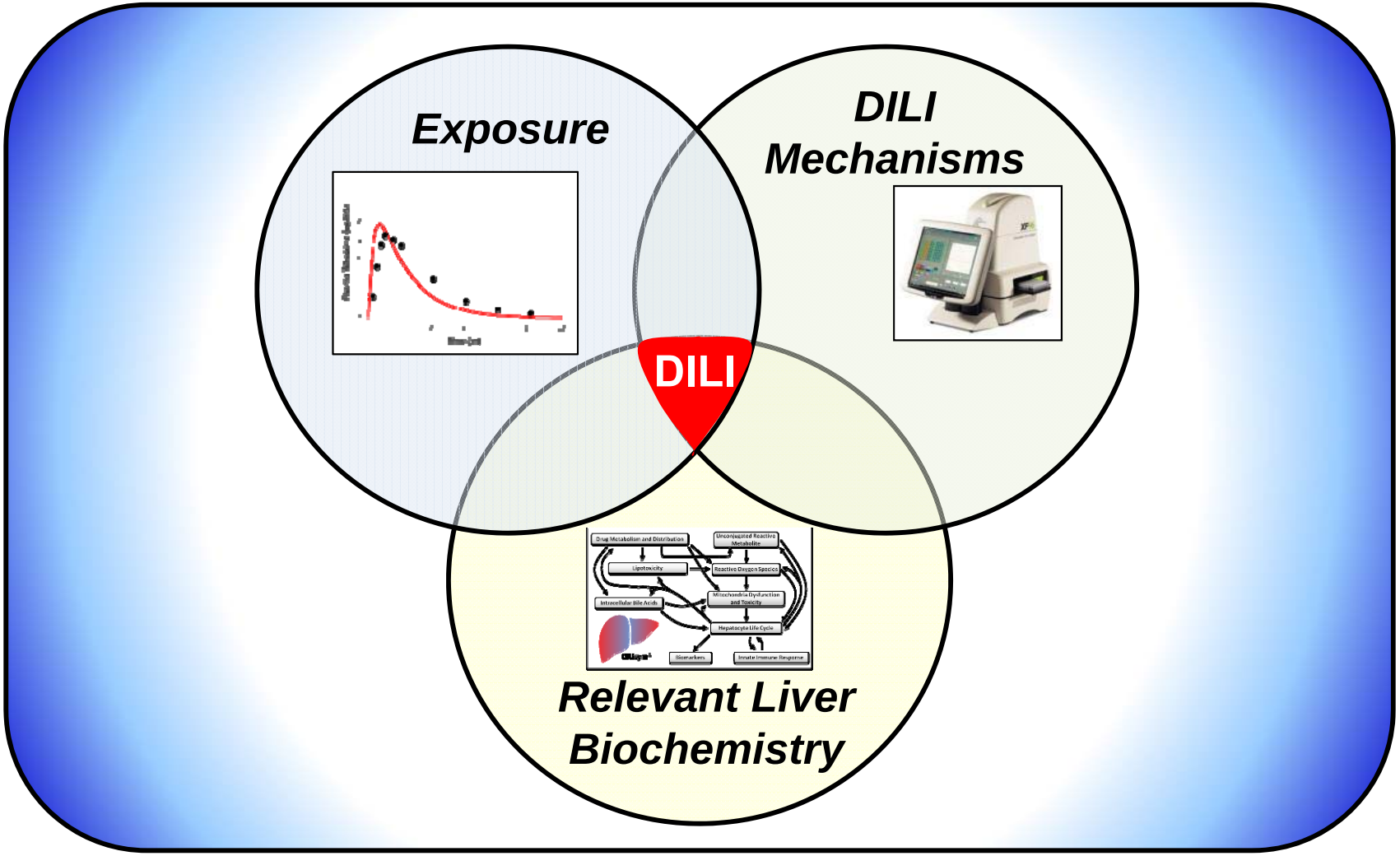
DILIsym Predicts DILI via the Intersection Between Exposure, Mechanisms, and Inter-Patient Variability



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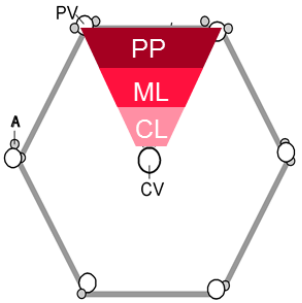
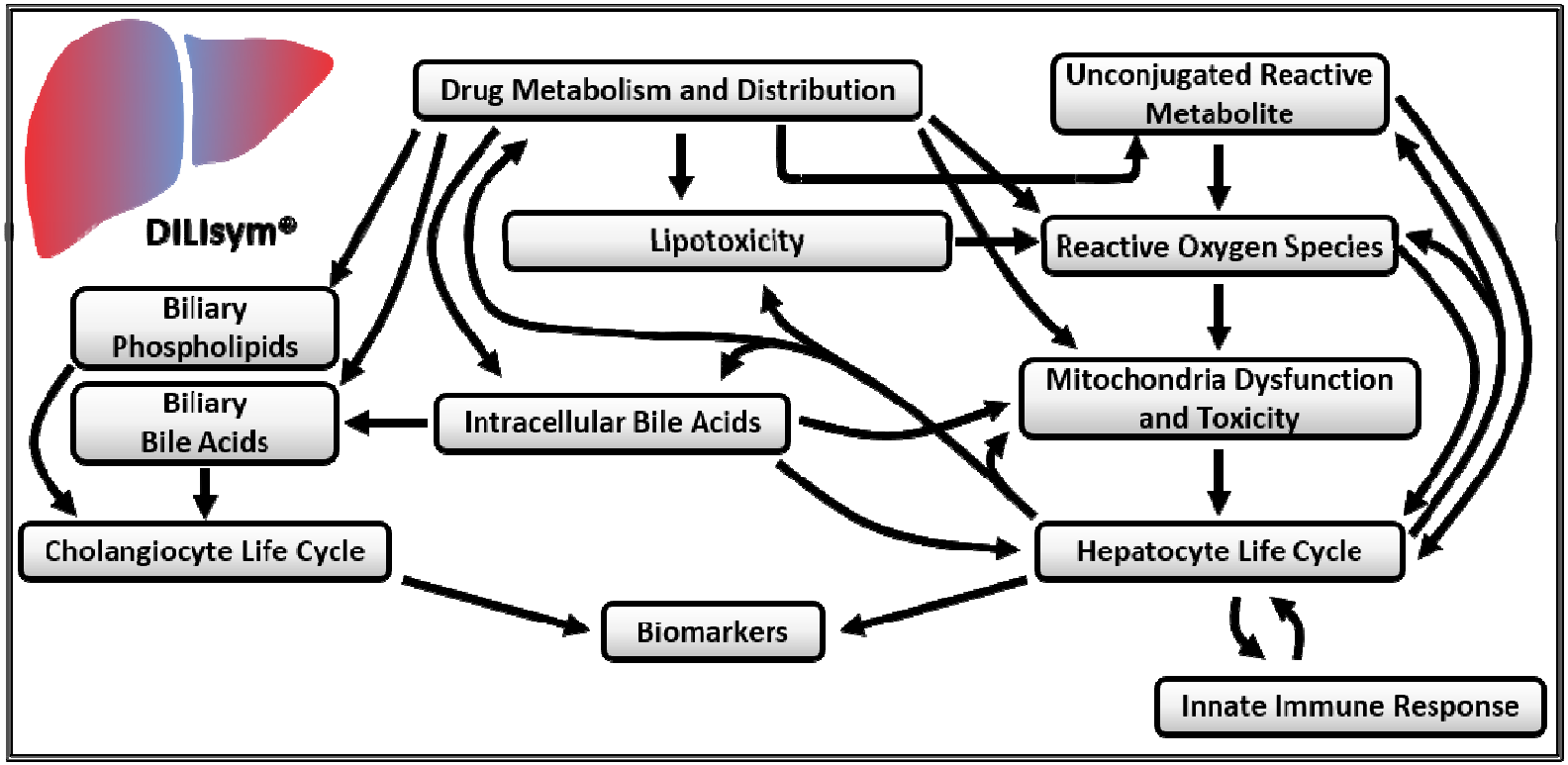
DILIsym Tool Overview

- **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**
- **Over 70 detailed representations of optimization or validation compounds with 80% success**
- **Single and combination drug therapies**





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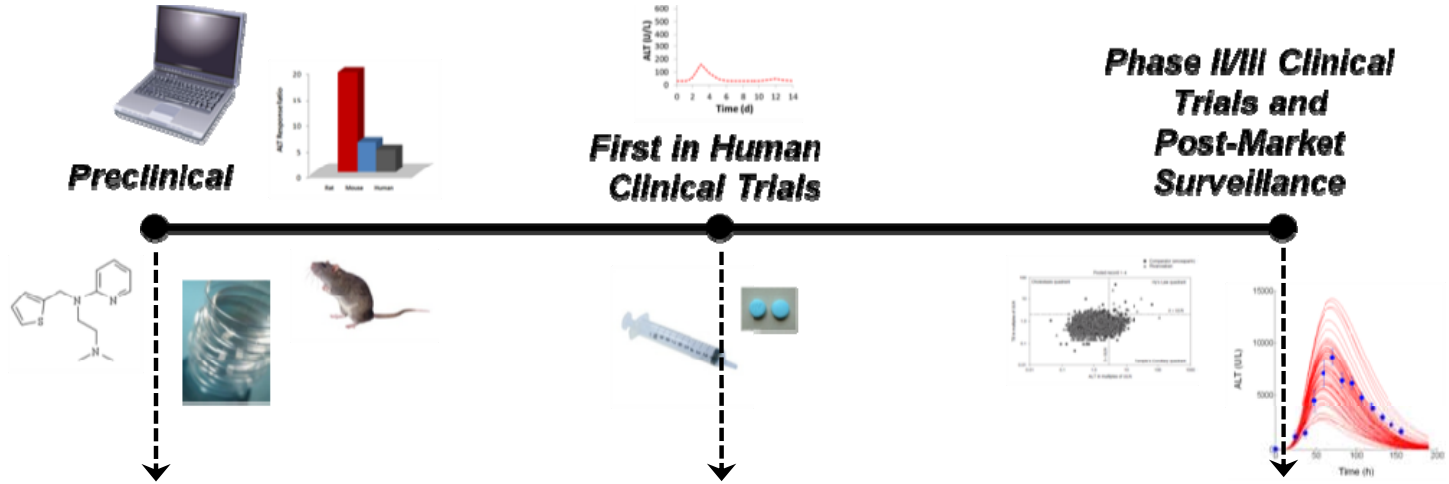
Applications of DILIsym Along the Drug Development Pipeline

Predictions of hepatotoxicity for humans and preclinical animal models



• Mechanism exploration • Rank candidates for DILI potential • Extrapolation from animal and *in vitro* findings to humans	• Dose optimization (risk versus presumed benefit) • Infer magnitude of injury based on measured biomarkers • Extrapolation from healthy volunteers to patient groups • Guide incorporation of emerging biomarker measurements in clinical trials • Analysis of mechanisms underlying observed liver signals	• Inform choice and timing of biomarker measurement • Aid identification of risk factors leading to personalized medicine approaches • Analysis of mechanisms underlying observed liver signals

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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

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*

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 Presentation Overview

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3 Lessons Learned Along the Way

1. Modest inhibition of transporters should not be ignored
2. The bigger picture (integration of different mechanisms of DILI) is important to consider
3. The mode (or mechanism) of transporter inhibition can be critical to outcomes

Case Study: DILIsym Illustrates the Combination of Mild Toxicity Mechanisms Accounts for Species-Specific DILI

Background

- PF-04895162 in development for epilepsy, did not demonstrate preclinical or early clinical liver toxicity (ALT >3x ULN)
- Development was halted when 300 mg BID for 14 days led to ALT elevations (Aleo et al. 2019)

Question

- Can mechanisms included in DILIsym account for the observed species differences?

DILIsym Approach

- Represent and simulate PF-04895162 in rats and humans to determine if DILIsym mechanisms can account for species-specific observations

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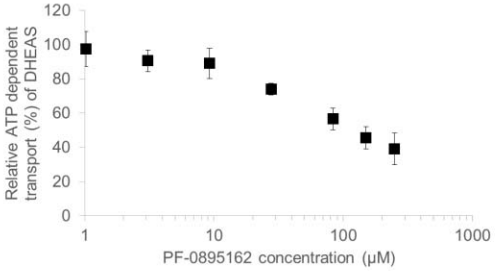
Evidence for Weak Interaction Between PF-04895162 and Bile Acid Transporters

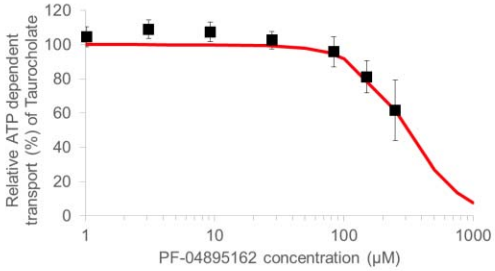
HUMANS

(A)



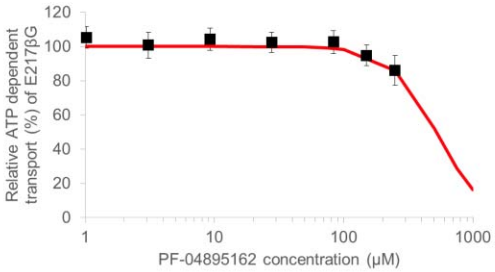
Measured IC_{50} 121 μM

(B)



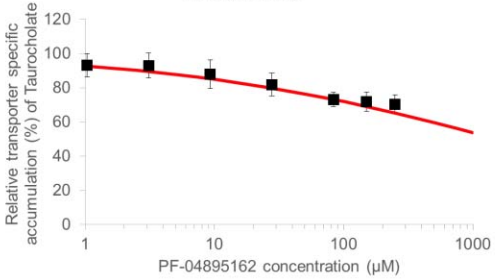
Extrapolated IC_{50} 311 μM

(C)



Extrapolated IC_{50} 519 μM

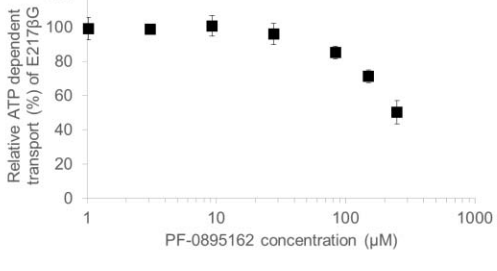
(D)



Extrapolated IC_{50} 1535 μM

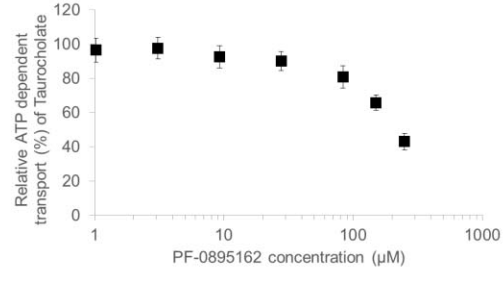
RATS

(A)



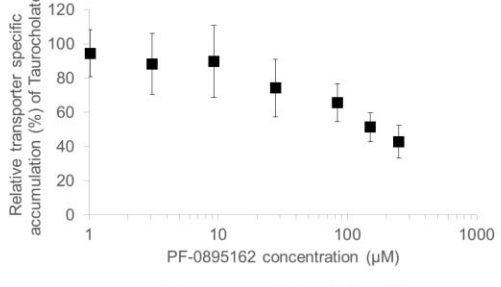
Measured IC_{50} 256 μM

(B)



Measured IC_{50} 229.6 μM

(C)



Measured IC_{50} 198 μM

Preclinical Data

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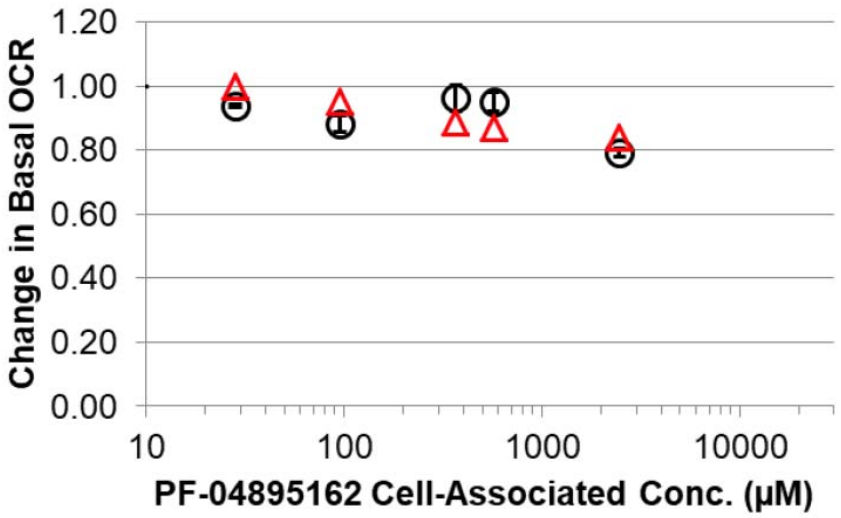
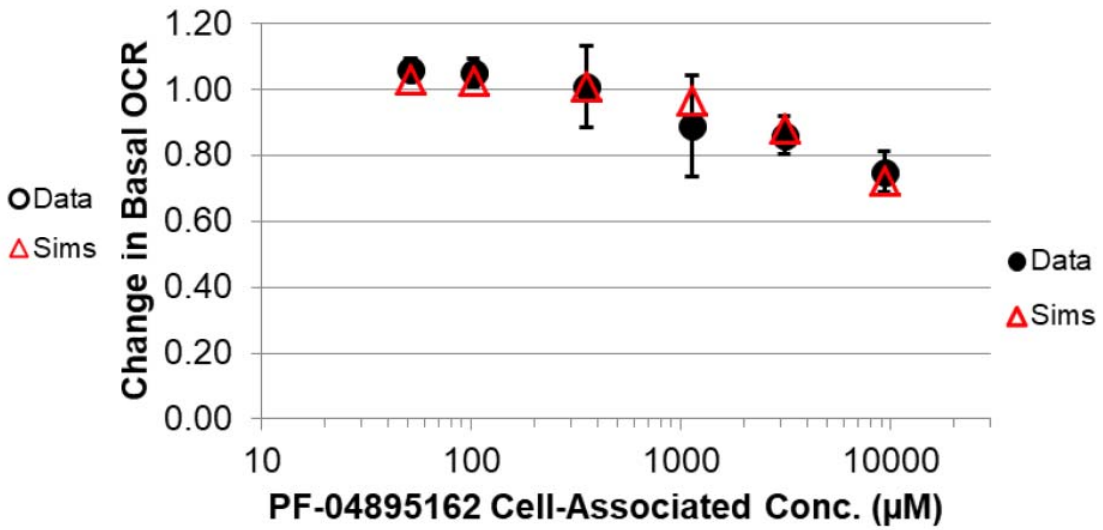
Evidence for Weak PF-04895162 Mediated Mitochondrial Dysfunction

HUMANS



RATS



Preclinical Data

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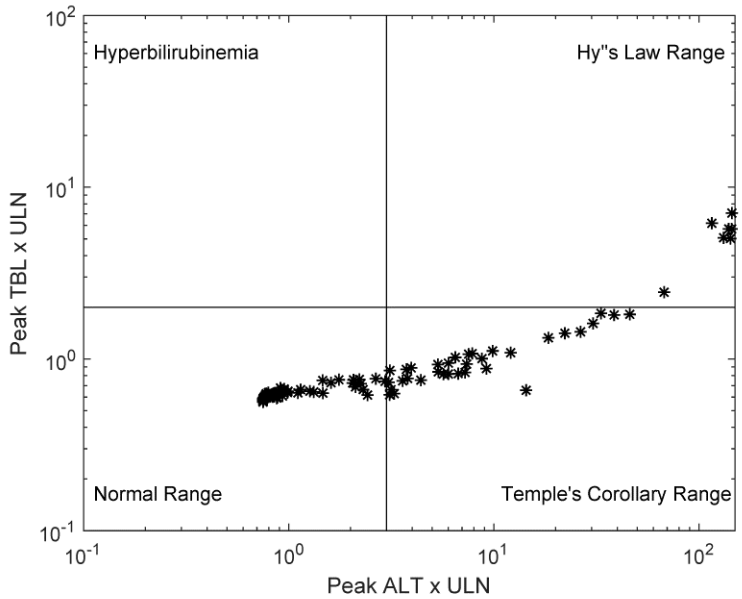
DILIsym Simulated Human, but Not Rat, Hepatotoxicity

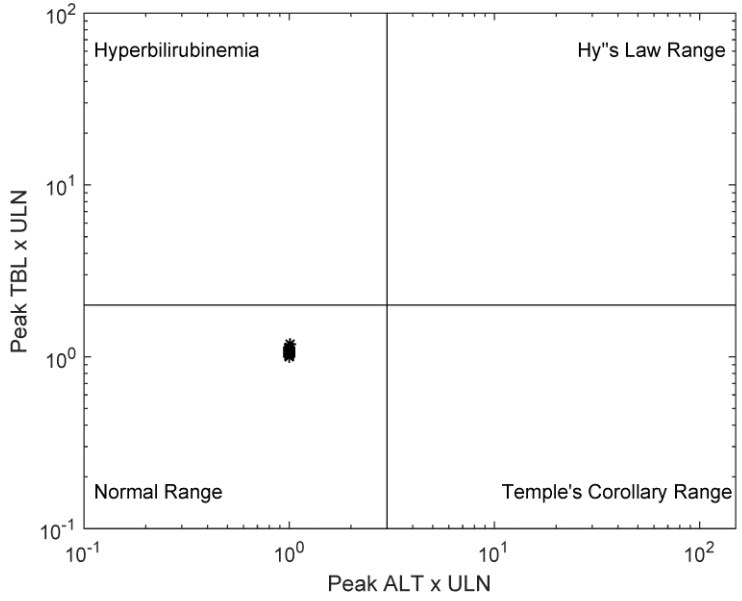
HUMANS

300 mg BID 14d, 14d follow



100 mg/kg/d, 28d

RATS



No clinical stop protocol

Simulation Results

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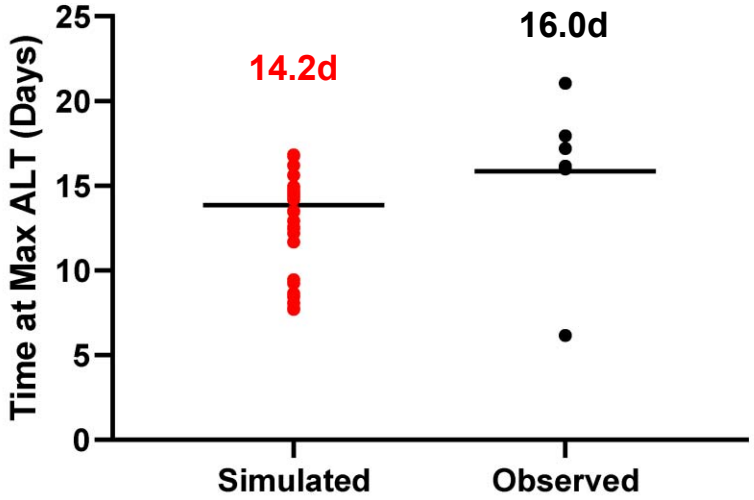
Simulated DILI Due to BA and Mitochondrial Toxicity Approximates Clinical Timing

HUMANS

Simulations	Mechanisms On	Mechanisms Off	ALT Elevations >3x ULN
300 mg po BID for 14 days in Multi16‡	ETCi, BAi	-	8/16
	ETCi	BAi	0/16
	BAi	ETCi	0/16

‡ Multi16 is the Human_ROS_apop_mito_BA_v8A_1_Multi16_A



Each point represents an individual

Median value represented above simulated and observed values

Clinical Data and Simulation Results

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Key Learnings

- Relatively **mild** mitochondrial dysfunction and BA transporter inhibition can **combine** to generate human hepatotoxicity
- Delayed ALT elevations were observed due to intrinsic mechanisms of toxicity
- *In vitro* toxicity data should consider compound concentration at the site of action
  - One of the first projects to demonstrate marked differences in simulation results depending on whether parameter values were based on nominal media concentrations vs. cell-associated concentrations
- Simulation results were better aligned with experimental data when input toxicity data were **species specific**
  - Initial simulations using all human in vitro toxicity data, with human *vs*. rat PK, reproduced species differences but not as well

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3 Lessons Learned Along the Way

1. Modest inhibition of transporters should not be ignored
2. The bigger picture (integration of different mechanisms of DILI) is important to consider
3. The mode (or mechanism) of transporter inhibition can be critical to outcomes

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Example Compound Comparison Project Scenario and Goal

- A backup drug candidate intended for the treatment of a central nervous system (CNS) disorder is in development
- The lead compound was terminated due to hepatotoxicity
- DILIsym was employed to assess the ability to differentiate liver safety between the two compounds

Comparison of Final DILIsym Input Parameters For Backup and Lead Compounds

Mechanism	Parameter	Unit	Value	
			Lead Compound	Backup Compound
Mitochondrial Dysfunction	Coefficient for ETC inhibition 1	mol/mL	1.7e-05	3.8e-06
Oxidative Stress	RNS/ROS production rate constant 1	mL/mol/hr	20,000	No Signal
Bile Acid Transporter Inhibition	BSEP inhibition constant*	µM	8 (Ki); Mixed inhibition (alpha = 4.5)	80.0† (Ki); Mixed inhibition (alpha = 2)
	NTCP inhibition constant*	µM	19^	15†^
	MRP3 inhibition constant*	µM	17†^	No inhibition
	MRP4 inhibition constant*	µM	17†^	No inhibition

*IC_{50} values unless indicated

†Lowest possible IC_{50} or K_i estimated by extrapolation based on the partial inhibition curve (assuming maximal inhibition of 100% at higher concentrations)

^Alpha values assumed to be consistent with measured BSEP alpha values for each compound (e.g. all alpha values assumed to be 4.6 for G and 2.1 for H)

Preclinical Data

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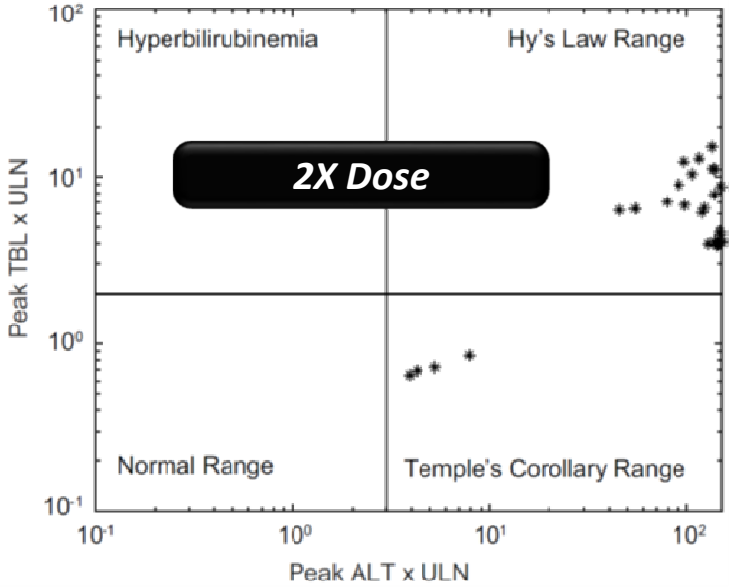
Frequency of Simulated Lead Compound Hepatotoxicity Generally Consistent with Clinical Data

Lead Compound



Protocol	Peak ALT > 3X ULN*	
	Observed	Simulated**
2X clinical dose (BID 12 weeks)	2.5-3.5%	12.6% (36/285)
1.5X clinical dose (BID 12 weeks)	No Data	2.1% (6/285)
1.25X clinical dose (BID 12 weeks)	No Data	0.7% (2/285)
clinical dose (BID 12 weeks)	**1-2%**	**0/285**

- Lead compound effects simulated in SimPops
- ALT > 3X ULN predicted in 0 – 12.6 % of population administered 1X – 2X doses over multiple weeks
  - Simulated time to reach ALT > 3X ULN was similar to observed timing
  - Validated DILIsym representation
- No ALT elevations predicted with alternative treatment protocol, consistent with clinical data

Clinical Data and Simulation Results

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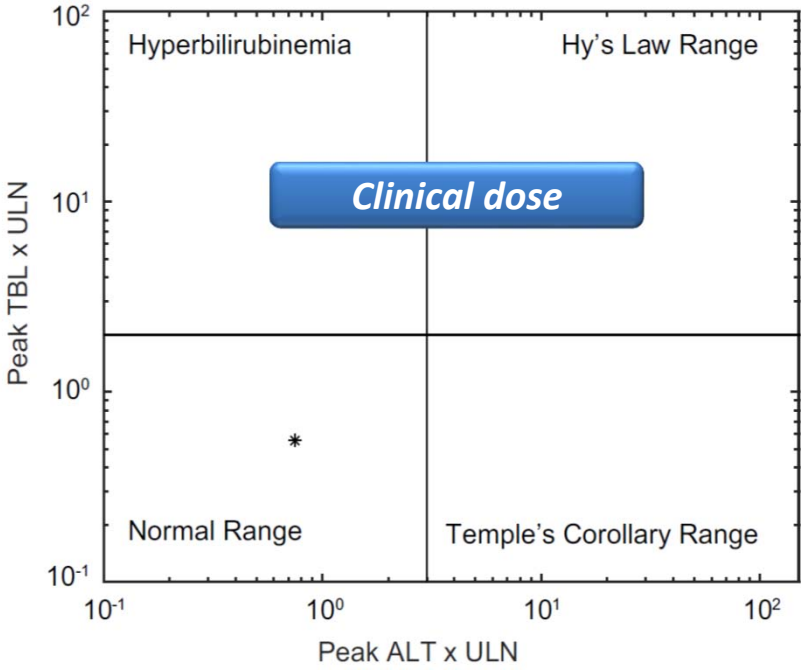
Simulations of Backup Compound in DILIsym SimPops at Clinical Dose Show No Liver Injury Responses

Backup Compound



Protocol	Peak ALT > 3X ULN*	
	Observed	Predicted**
clinical dose (BID 12 weeks)	**None reported for recent clinical trial**	**0/285**
1.5X clinical dose (BID 12 weeks)	*No data available*	0/285
2X clinical dose (BID 12 weeks)	*No data available*	0.7% (2/285)
3X clinical dose (BID 12 weeks)	*No data available*	7.4% (21/285)

- Backup compound effects simulated in SimPops
- Clinical dose for backup compound is <50% of dose for lead compound
- ALT > 3X ULN predicted in 0% of population administered clinically proposed dose of backup compound

Simulation Results

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Recently Completed Clinical Trial Indicates that DILIsym Backup Compound Predictions Were Correct

- DILIsym simulations suggested that the backup compound is considerably less likely to pose a DILI risk than the lead compound at the proposed clinical dosing regimens
- ***No liver signals reported for any dosing regimes for the backup compound in clinical trial completed in 2018***
- ***Combination of predicted and measured safety have enabled sponsor to confidently continue clinical development of the backup compound***

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Questions?

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