Use of a Quantitative Systems Pharmacology (QSP) Model to Predict Liver Toxicity in Simulated Populations

November 27, 2018

World Preclinical Congress Europe

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Disclaimer

- I am externally funded by DILIsym Services, Inc., a company that licenses the DILIsym software for commercial use and serves as the coordinating member of the DILI-sim Initiative.
- I have a financial stake in DILIsym Services, Inc.

DILIsym Summary

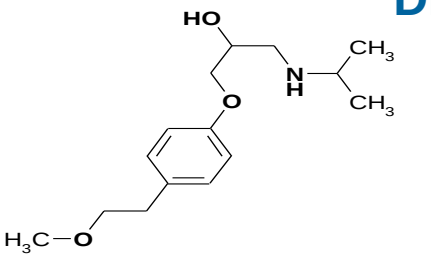
- DILIsym is a mechanistic, mathematical model that has been constructed to support pharmaceutical risk assessment and decision making
  - Intersection of compound distribution and metabolism (PBPK), hepatotoxicity mechanisms, and patient variability
  - Core focus on explaining and predicting drug-induced liver injury (DILI)
- DILIsym has been applied to support decisions related to compound DILI risk throughout the clinical development pipeline
  - Evaluated and interpret clinical biomarker signals in clinical trials
  - Optimized clinical trial design (dose selection, monitoring, inclusion/exclusion criteria)
  - Translated preclinical safety risk to first in human clinical trials
  - Ranked compounds by risk
- DILIsym simulation results have been included in over fifteen communications with regulatory agencies

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** software in development

Simulations Plus Inc. (NASDAQ: SLP): Your "End-to-End" Software Provider



Discovery

Preclinical

Clinical

ADMET Predictor™ ⟷ **GastroPlus™**

- **MedChem Studio™ MedChem Designer™**
- **DDDPlus™ MembranePlus™**
- **PKPlus™**
- **DILIsym®**
- **KIWI™**
- **NAFLDsym®**

Consulting Services and Collaborations

Outline

- Overview of the DILI-sim Initiative
- Overview of the DILIsym Software
- Application Example: *In vitro* to *in vivo* extrapolation
- Summary

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

DILIsym Services
A SIMULATIONS PLUS COMPANY

janssen
gsk GlaxoSmithKline
GILEAD
Mitsubishi Tanabe Pharma
DILIsym
Roche
Daiichi-Sankyo
Bristol-Myers Squibb
Sumitomo Dainippon Pharma
abbvie

Select Sample of Current Companies Licensing DILIsym

- *Overall Goals*
  - *Improve patient safety through quantitative systems toxicology (QST)*
  - *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 $8 million total invested in project*

The Evolution of the DILI-sim Initiative

2012 Stage 1	2015 Stage 2	2018 Stage 3
Mechanisms • Reactive metabolites • Oxidative stress • Mitochondrial toxicity • Bile acid toxicity	*Mechanisms* • Lipotoxicity • Innate immunity	*Mechanisms* • Adaptive immunity • Cholestasis • Improve *in vitro* assay systems
Patients and animals • Rats, mice, dogs • Healthy volunteers	*Patients and animals* • Healthy volunteers • Disease area patients	*Patients and animals* • Larger more robust SimPops and biomarkers • Disease area patients
Compounds • Exemplars for optimization	*Compounds* • Exemplars for optimization • Exemplars for validation	*Compounds* • Exemplars for optimization • Exemplars for validation

SLP Software Advances

Application of DILIsym in Drug Development

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

- Seven versions of DILIsym released, including DILIsym v7A in Jan 2018
- At least **18** 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
- **79%** 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
- DILIsym related publications have been cited **444** times as of September 2018
- Academic and government licenses issued for teaching and research, including to FDA across multiple divisions

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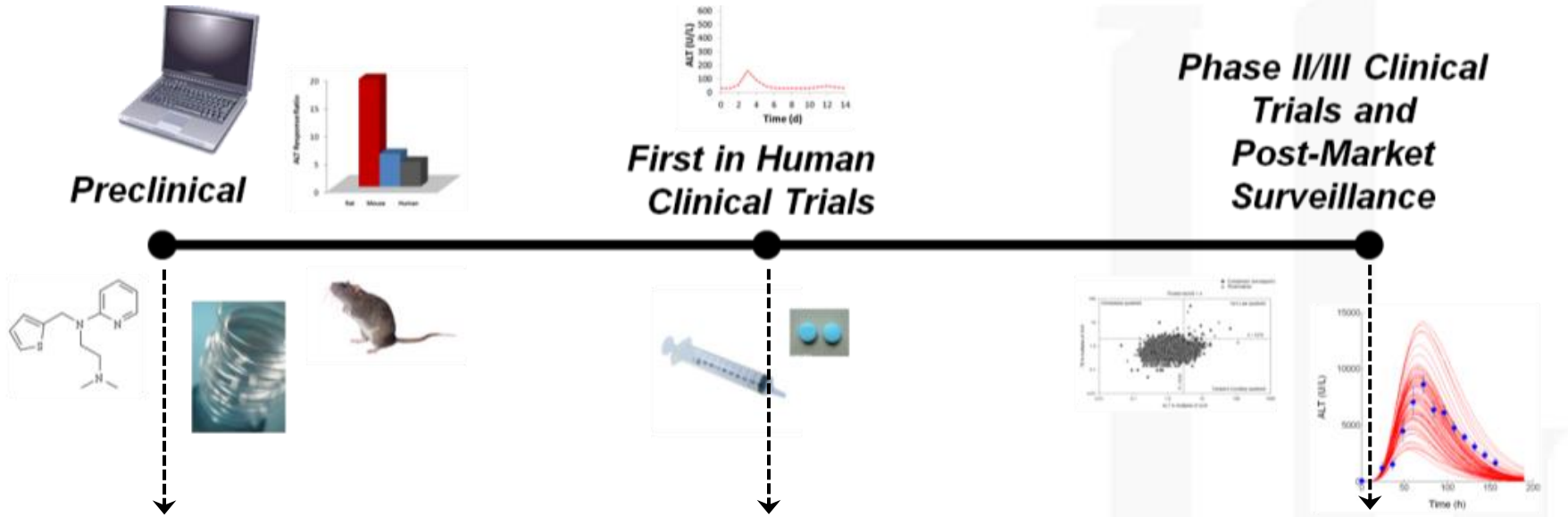
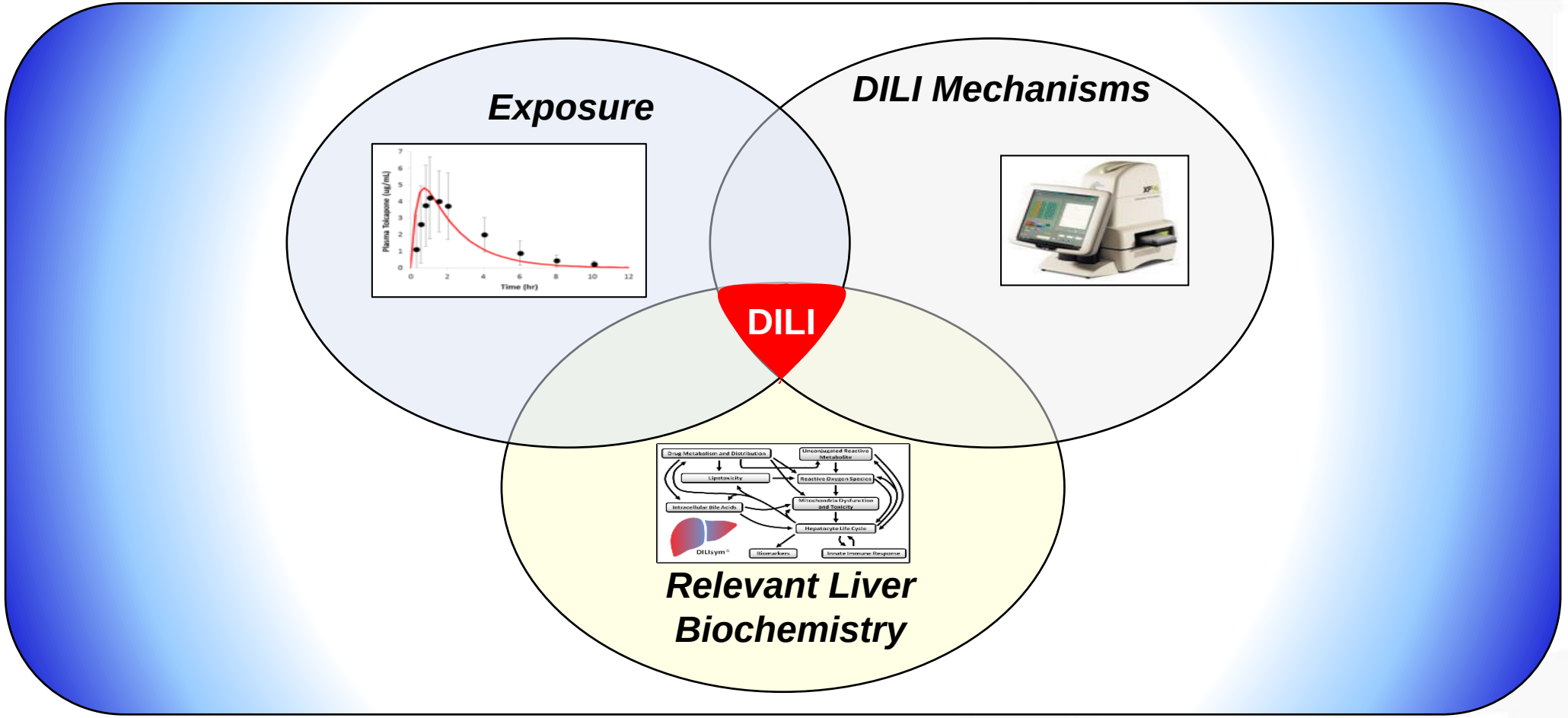
Applications of DILIsym Along the Drug Development Pipeline

Predictions of hepatotoxicity for humans and preclinical animal models

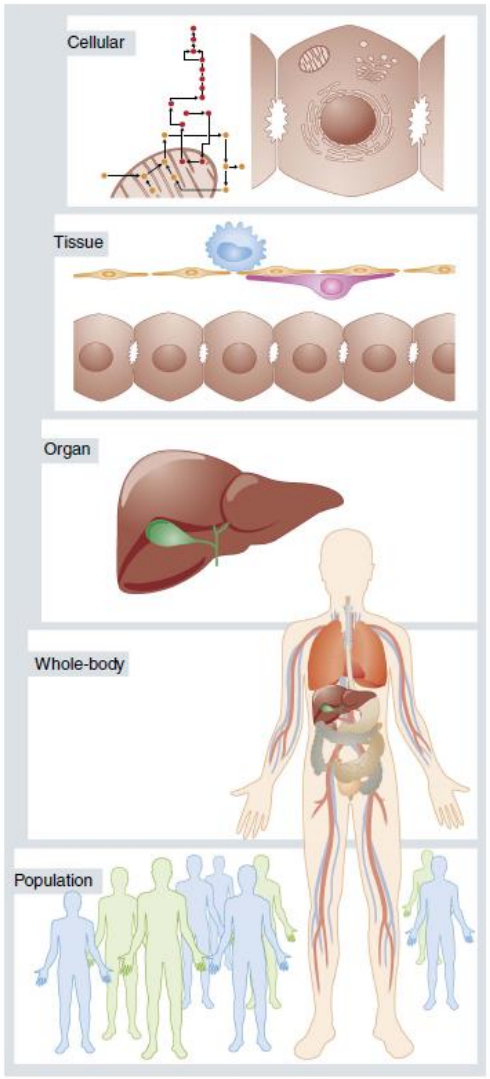


• Mechanism exploration • Rank candidates for DILI potential • Extrapolation from animal and *in vitro* findings to humans	• Dose optimization (risk versus presumed benefit) • Infer magnitude of injury based on measured biomarkers • Extrapolation from healthy volunteers to patient groups • Guide incorporation 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

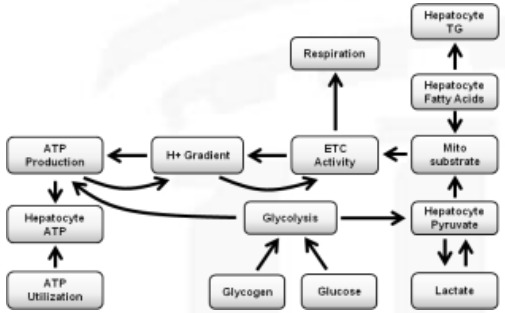
DILIsym Predicts DILI via the Intersection Between Exposure, Mechanisms, and Liver Biochemistry



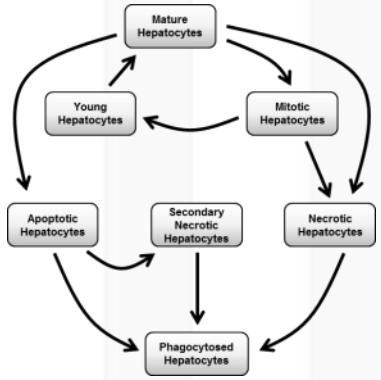
DILIsym: Quantitative Systems Toxicology



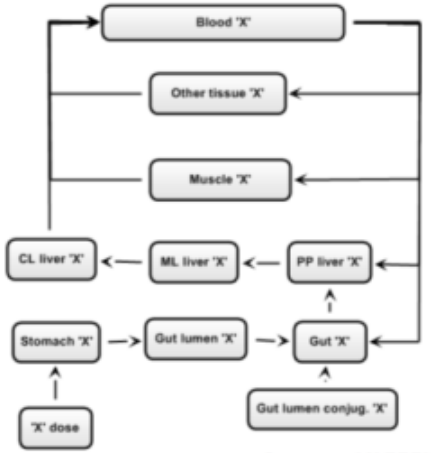
Mitochondrial dysfunction

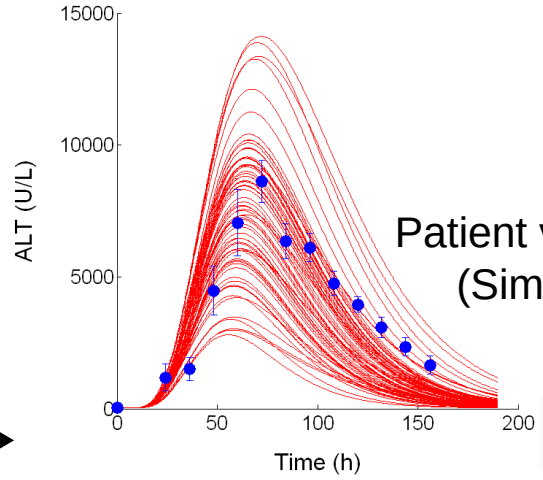


Cellular life-cycle



Drug distribution & metabolism





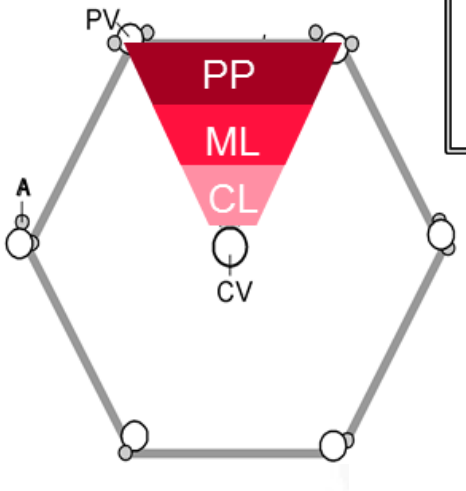
Patient variability (SimPops)

Kuepfer 2010, Molecular Systems Biology

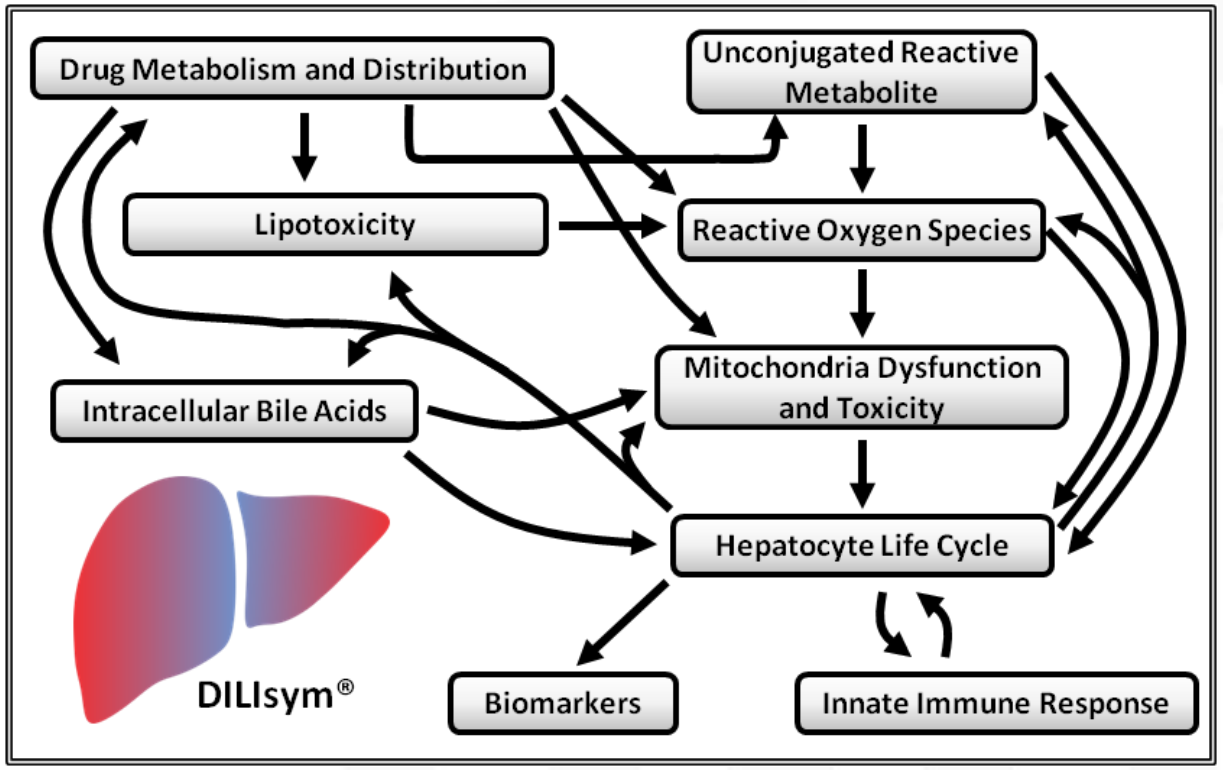
DILIsym Overview

- **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**
  - Pharmacokinetics
  - Dosing (IP, IV, Oral)
  - Transporter Inhibition
  - Drug metabolism
  - GSH depletion
  - Injury progression
  - Mitochondrial dysfunction, toxicity, DNA depletion
  - Bile acid mediated toxicity
  - Steatosis and lipotoxicity
  - Cellular energy balance
  - Hepatocyte apoptosis and necrosis, and proliferation
  - Macrophage, LSEC life cycles
  - Immune mediators
  - Caloric intake
  - Biomarkers



- **Over 30 detailed representations of optimization or validation compounds**
- **Single and combination drug therapies**

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*

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 transporter inhibition**
  - *BSEP, MRP3 and 4, NTCP*
- **Bilirubin transport/metabolism**
  - *OATP1B1, OATP1B3, UGT1A1, MRP2, MRP3*

Modeling & Simulation

DILIsym®

Simulations and Assays inform:

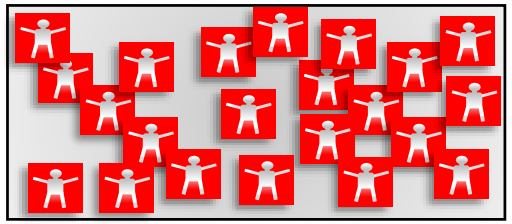
- **Prediction of DILI risk**
- **Participating DILI mechanisms**
- **Characteristics of patients at risk for DILI**
- **Drug dosing paradigms**
- **DILI monitoring strategies**

Clinical Data

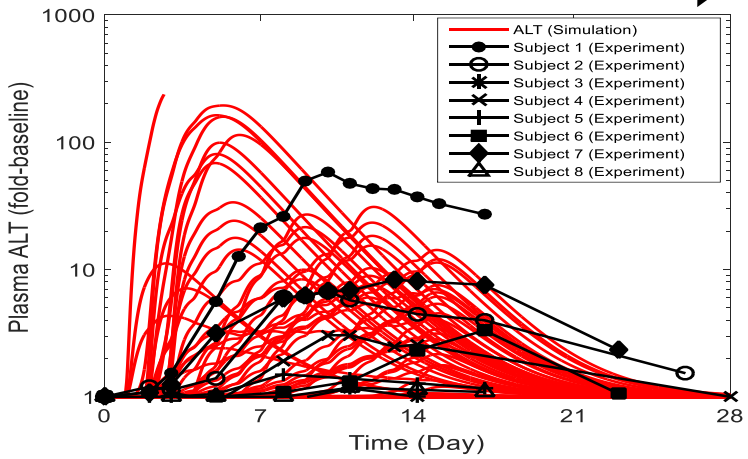
- **Dosing protocols, fasting/fed state, meal times**
- **Anthropometric data**
  - *Body weight, age, ethnicity*
- **Pharmacokinetic data**
  - *Absorption, extra-hepatic clearance, metabolites*

Range of Hepatotoxic Responses in SimPops Due to Variability in Underlying Biochemistry

- SimPops are population samples with variability in hepatotoxic drug responses
- Multiple parameters are varied to produce diverse simulated patients
- Numerous simulated patients are generated, consistent with range of observed response data and known parameter distributions
- SimPops compared with reported clinical data where available
- SimPops are subsequently used to predict responses to novel compounds



Variables Used to Construct SimPops
Body weight
Glutathione levels and synthesis
RNS-ROS clearance
Mitochondria function
Bile acid transporter function
Adaptive responses to bile acid levels
Apoptotic sensitivity to RNS-ROS
Necrotic sensitivity to ATP reductions
Hepatocyte regeneration



Clinical Data and Simulation Results

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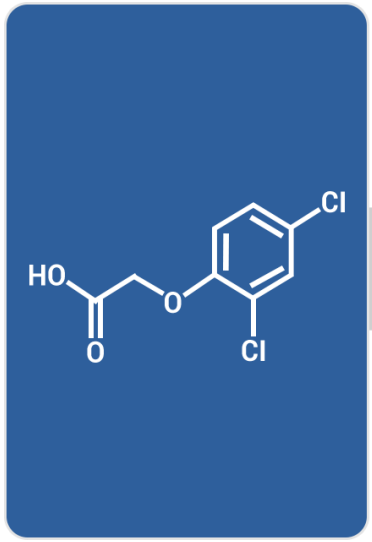
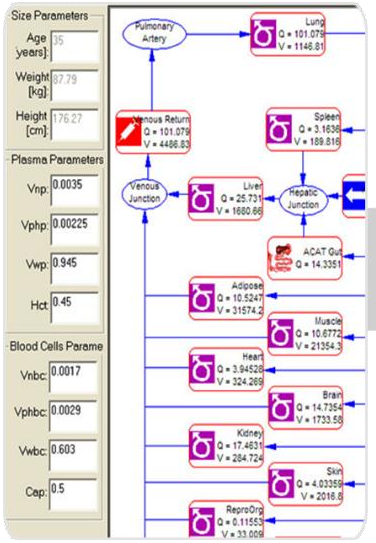
Example Project Goal – Assess Compound X and Compound Y

- The primary goal of this simulation work within the DILIsym software was to:
  - quantitatively and mechanistically assess the liver toxicity potential of Compound X and Compound Y combining clinical and mechanistic *in vitro* data with DILIsym and GastroPlus software simulations of previous or prospective clinical dosing paradigms.

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)

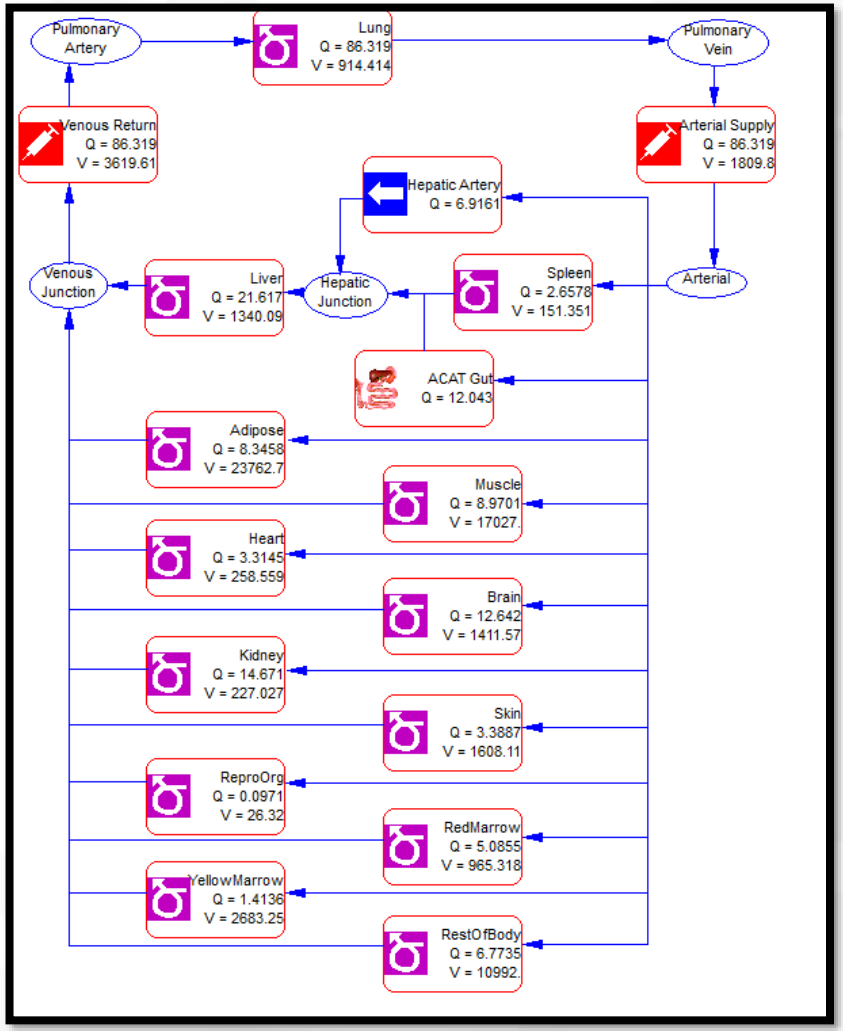
GastroPlus™

Quantitative Systems Pharmacology/Toxicology (QSP/QST)

DILIsym®

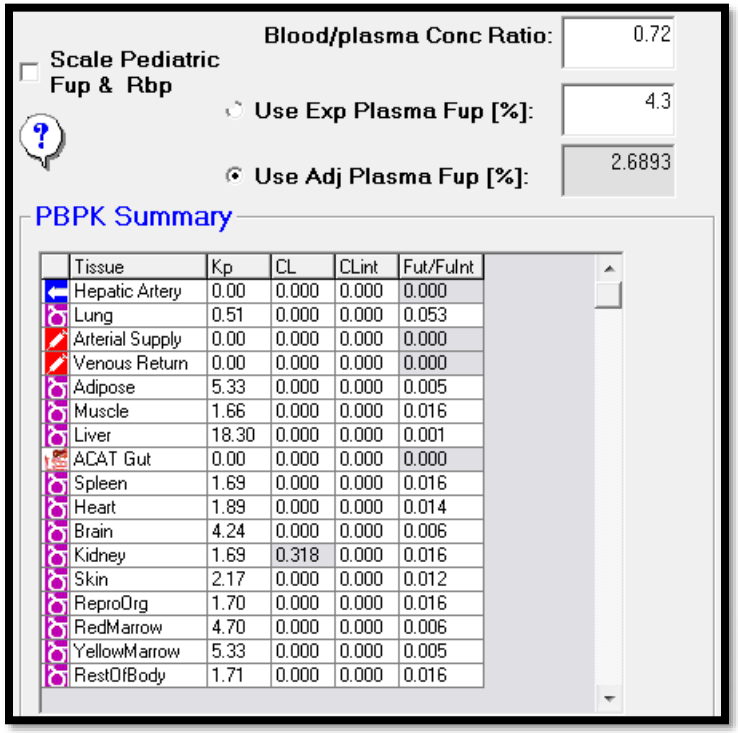
GastroPlus PBPK Model Used to Predict Liver Exposure of Compound Y and Compound X

- Data on Compound Y and Compound X pharmacokinetics not available in the literature
  - No plasma time courses available; no *in vitro* or animal studies available either
  - *In vitro* data on liver distribution available from intracellular data collected for this project
- Structure of each compound available online
  - QSAR modeling using ADMET Predictor and GastroPlus provided the best possible estimate of Compound Y and Compound X distribution and pharmacokinetics
- Plasma time course was estimated in GastroPlus and translated into DILIsym using “specified data” option
  - Liver:plasma partition coefficient was calculated from the cell:media ratio in the *in vitro* data and used as input into GastroPlus; the remainder of the parameters were calculated by ADMET Predictor
- Both compounds distribute significantly into the liver
  - Compound Y average cell:media was 18; Compound X average cell:media was 9



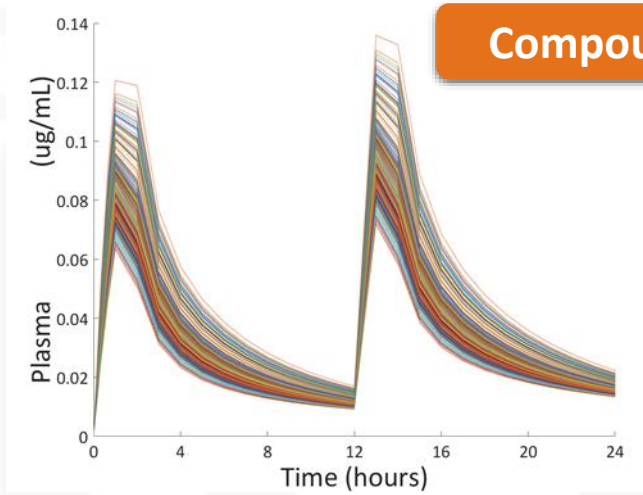
Compound Y PBPK Representation Calculated at Clinical Dose

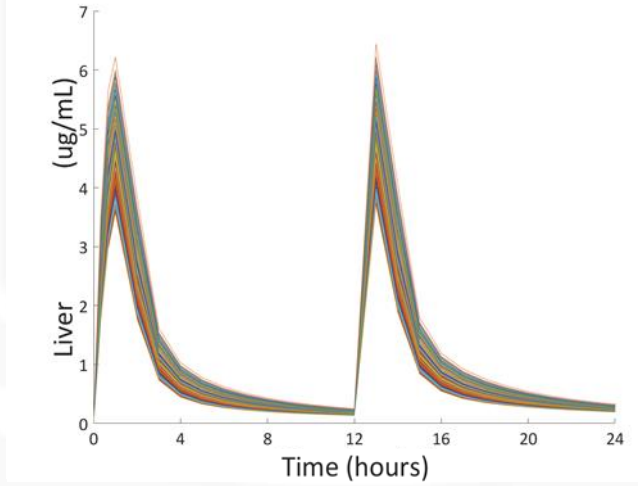
- GastroPlus predictions for liver and plasma at clinical dose shown at right
  - PBPK model specific predictions shown below
  - Dose escalation was simulated



Tissue	Kp	CL	CLint	Fut/FuInt
Hepatic Artery	0.00	0.000	0.000	0.000
Lung	0.51	0.000	0.000	0.053
Arterial Supply	0.00	0.000	0.000	0.000
Venous Return	0.00	0.000	0.000	0.000
Adipose	5.33	0.000	0.000	0.005
Muscle	1.66	0.000	0.000	0.016
Liver	18.30	0.000	0.000	0.001
ACAT Gut	0.00	0.000	0.000	0.000
Spleen	1.69	0.000	0.000	0.016
Heart	1.89	0.000	0.000	0.014
Brain	4.24	0.000	0.000	0.006
Kidney	1.69	0.318	0.000	0.016
Skin	2.17	0.000	0.000	0.012
ReproOrg	1.70	0.000	0.000	0.016
RedMarrow	4.70	0.000	0.000	0.006
YellowMarrow	5.33	0.000	0.000	0.005
RestOfBody	1.71	0.000	0.000	0.016

Compound Y

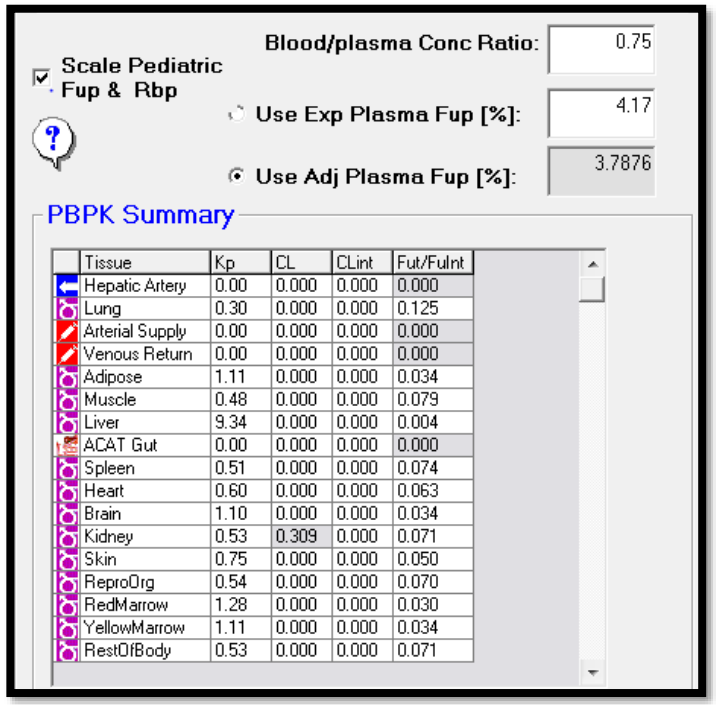




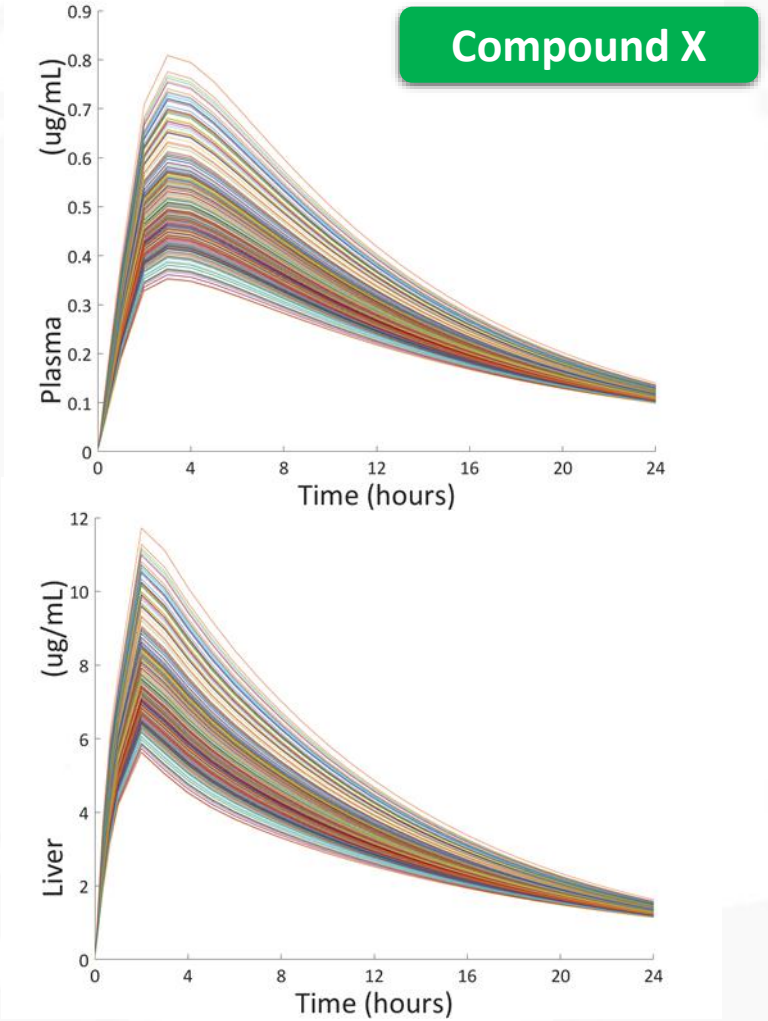
Simulation Results

Compound X PBPK Representation Calculated at Predicted Clinical Dose

- GastroPlus predictions for liver and plasma at clinical dose shown at right
  - PBPK model specific predictions shown below
  - Dose escalation and alternate protocols were also simulated



Tissue	Kp	CL	CLint	Fut/FuInt
Hepatic Artery	0.00	0.000	0.000	0.000
Lung	0.30	0.000	0.000	0.125
Arterial Supply	0.00	0.000	0.000	0.000
Venous Return	0.00	0.000	0.000	0.000
Adipose	1.11	0.000	0.000	0.034
Muscle	0.48	0.000	0.000	0.079
Liver	9.34	0.000	0.000	0.004
ACAT Gut	0.00	0.000	0.000	0.000
Spleen	0.51	0.000	0.000	0.074
Heart	0.60	0.000	0.000	0.063
Brain	1.10	0.000	0.000	0.034
Kidney	0.53	0.309	0.000	0.071
Skin	0.75	0.000	0.000	0.050
ReproOrg	0.54	0.000	0.000	0.070
RedMarrow	1.28	0.000	0.000	0.030
YellowMarrow	1.11	0.000	0.000	0.034
RestOfBody	0.53	0.000	0.000	0.071



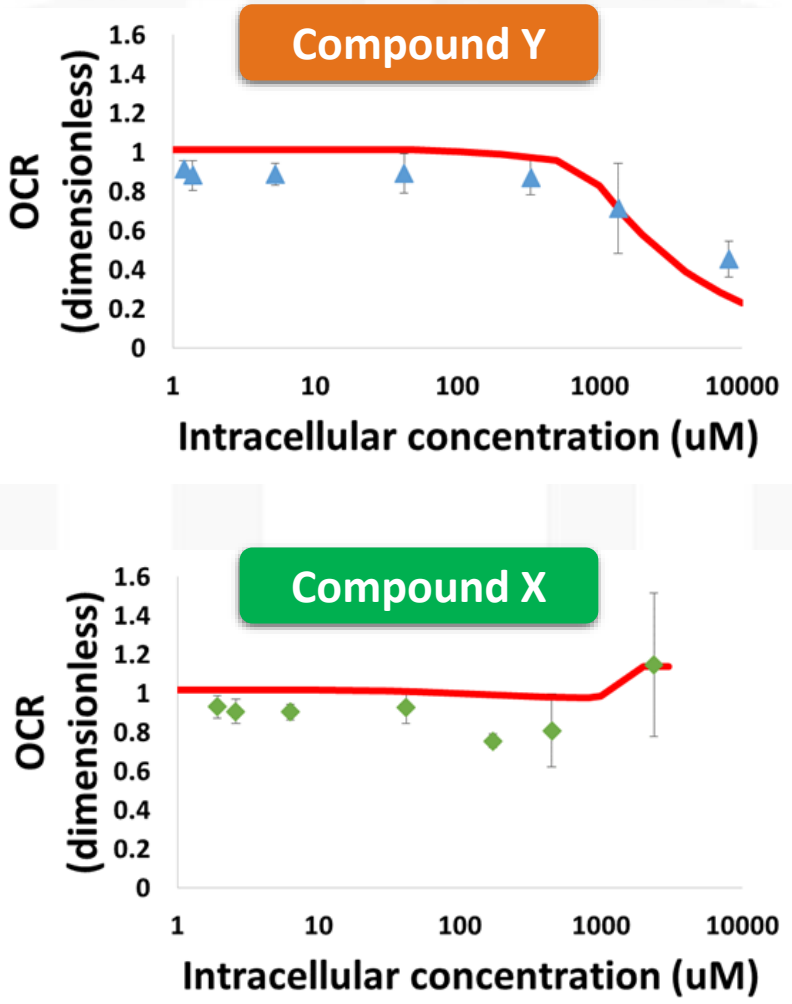
Simulation Results

Mitochondrial Toxicity Parameters Determined for Compound Y and Compound X

- Parameter values were fit to mitochondrial data for Compound Y and Compound X
  - Electron transport chain inhibition for Compound Y
  - Both electron transport chain inhibition and uncoupling for Compound X
  - 24 hour data used
- MITOsym and DILIsym used to parameterize both compounds

cyprotex AN EVOTEC COMPANY

DILIsym Parameter	Compound Y Value	Compound X Value	Units
Coefficient for ETC inhibition 1	38,000	Not used	µM
Coefficient for ETC Inhibition 3	0.1	4,200	µM
Max inhibitory effect for ETC inhibition 3	0.2	0.4 (max effect)	dimensionless
Uncoupler 1 effect Km	No effect	15,000	µM
Uncoupler 1 effect Vmax	No effect	22	dimensionless
Uncoupler 1 effect Hill	No effect	4	dimensionless



Preclinical Data and Simulation Results

Oxidative Stress Parameters Determined for Compound Y and Compound X

- Parameter values were fit to 24-hour ROS data for Compound Y and Compound X
- DILIsym representation of *in vitro* environment used to parameterize both compounds

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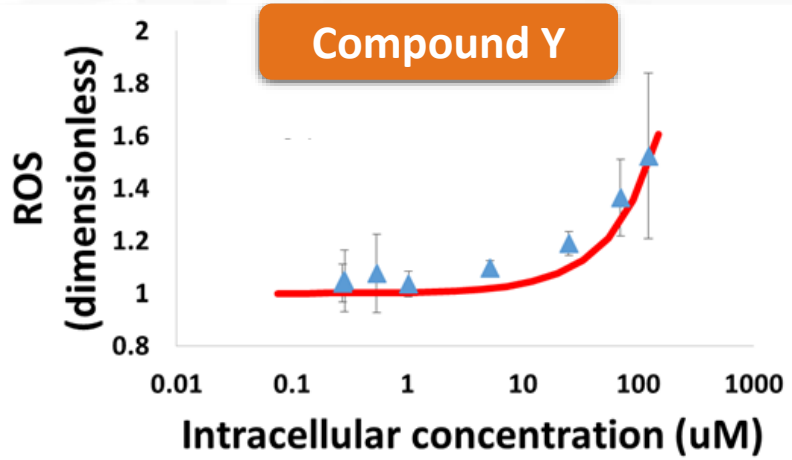
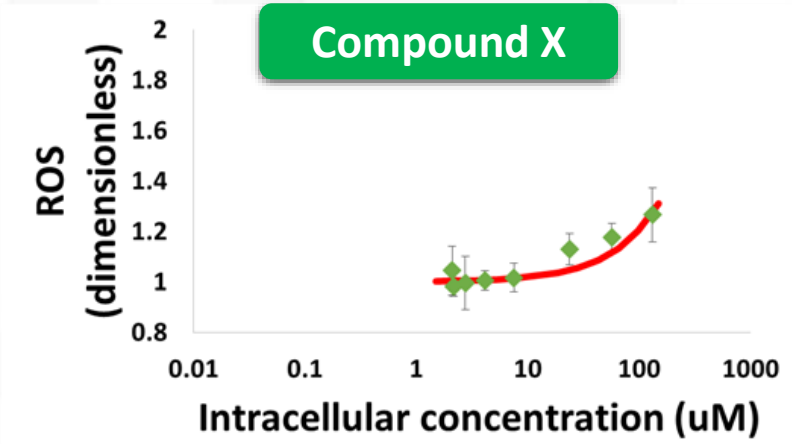
DILIsym Parameter	Compound Y Value	Compound X Value	Units
RNS/ROS production rate constant 1	3.4×10^{-4}	1.7×10^{-4}	mL/nmol/hr

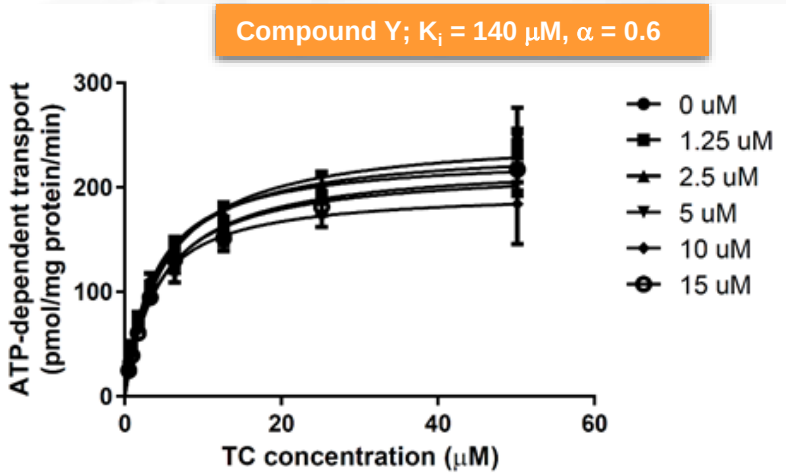


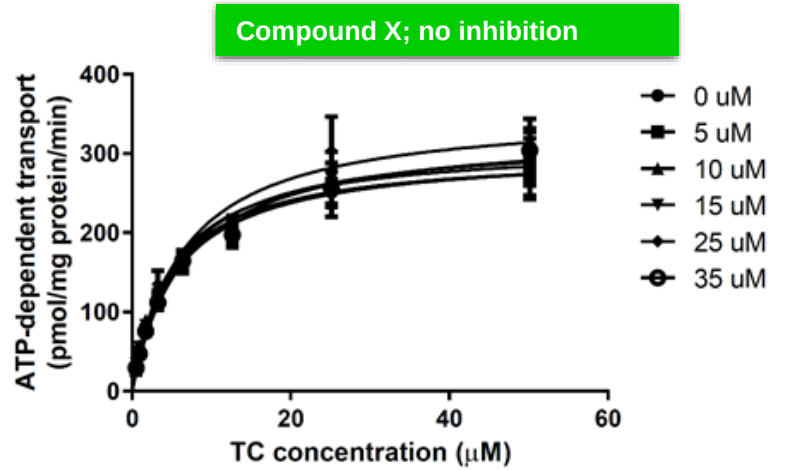


Preclinical Data and Simulation Results

Compound Y Weakly Inhibits BSEP; Compound X Does Not

- Compound Y is a low-potency inhibitor of BSEP
  - Compound Y also inhibits MRP4 transport (not shown)
- Compound X does not inhibit BSEP
  - No changes to V_{max} or K_m of transporters observed over course of assay
  - Compound X inhibits MRP4 transport (not shown)





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THE TRANSPORTER COMPANY

Preclinical Data

DILIsym Toxicity Parameters for Compound Y and X

Mechanism	Parameter	Unit	DILIsym Parameter Value*	
			Compound Y	Compound X
Mitochondrial Dysfunction	Coefficient for ETC inhibition 1	µM	38,000	Not used
	Coefficient for ETC Inhibition 3	µM	0.1	4,200
	Max inhibitory effect for ETC inhibition 3	dimensionless	0.2	0.4
	Uncoupler 1 effect Km	µM	No effect	15,000
	Uncoupler 1 effect Vmax	dimensionless	No effect	22
	Uncoupler 1 effect Hill	dimensionless	No effect	4
Oxidative Stress	RNS/ROS production rate constant 1	mL/nmol/hr	3.4×10^{-4}	1.7×10^{-4}
Bile Acid Transporter Inhibition	BSEP inhibition constant	µM	140	No inhibition
	BSEP inhibition alpha value	dimensionless	0.6	No inhibition
	NTCP inhibition constant	µM	No inhibition	No inhibition
	MRP4 inhibition constant	µM	40	75

*Values shown in the table for DILIsym input parameters should not be interpreted in isolation with respect to clinical implications, but rather, should be combined with exposure in DILIsym to produce simulations that have predictive and insightful value

SimPops Results Show Compound X and Compound Y to be Safe at Clinical Doses; ALT Elevations Predicted to Occur at Higher Doses for Both Compounds

- Neither Compound Y nor Compound X are predicted to cause toxicity at the highest clinical dose
  - Some exposure variability included in these predictions due to GastroPlus population generation
- Both Compound Y and Compound X are predicted to cause mild ALT elevations at supratherapeutic doses
  - No bilirubin elevations or Hy's Law cases occurred in simulations with Compound X
  - 2 Hy's Law cases occurred at 10x clinical dose simulations with Compound Y

Compound Y **Compound X**

	Compound	Dosing Protocol	Simulated* ALT > 3X ULN**
Compound Y	Compound Y	1X Dose, 12 weeks	0% (0/285)
		2X Dose, 12 weeks	0% (0/285)
		5X Dose, 12 weeks	0.3% (1/285)
		10X Dose, 12 weeks	10.2% (29/285)
Compound X	Compound X	1X Dose, 15 days	0% (0/285)
		2X Dose, 15 days	0% (0/285)
		5X Dose, 15 days	1.1% (3/285)
		10X Dose, 15 days	11.6% (33/285)

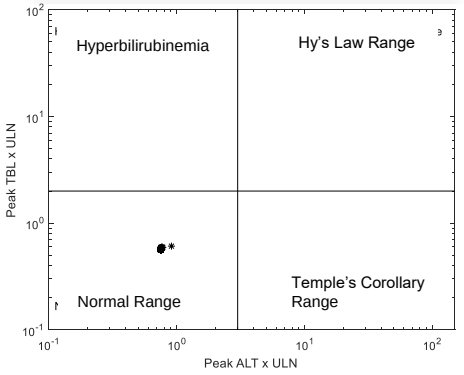
*The full v4A-1 SimPops (n=285) of normal healthy volunteers was used

**Upper limit of normal (ULN) in DILIsym is 40 U/L

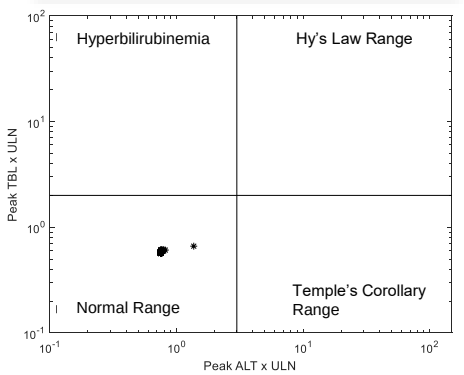
Simulation Results

SimPops Results Show Lack of Severe Liver Injury for Both Compound Y and Compound X at Clinical Doses

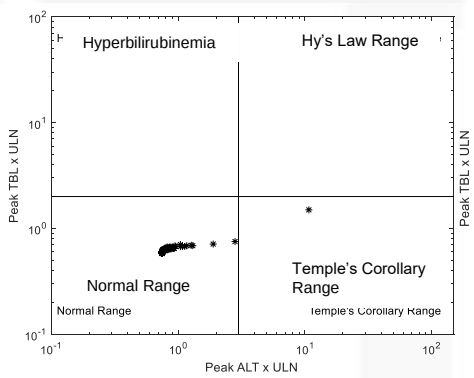
Compound Y; 1X Dose, 12 weeks



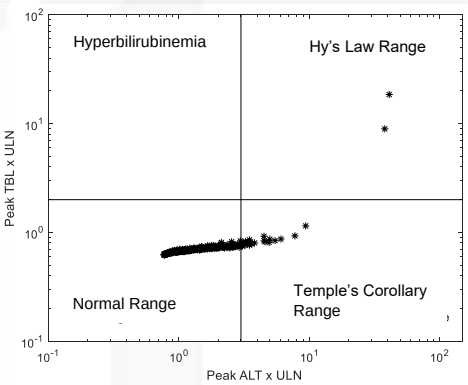
Compound Y; 2X Dose, 12 weeks



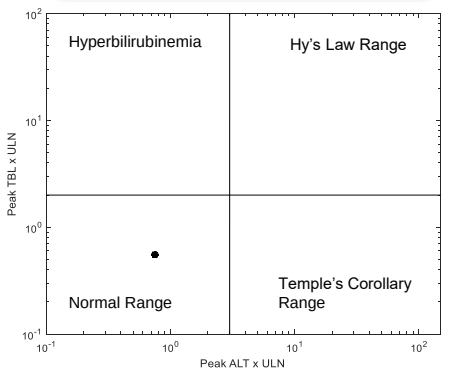
Compound Y; 5X Dose, 12 weeks



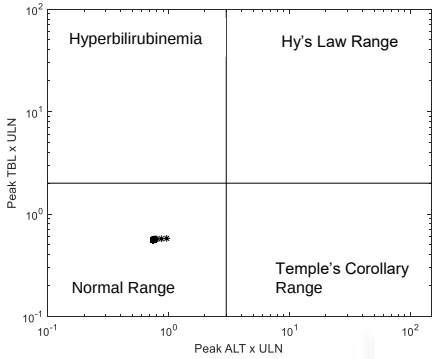
Compound Y; 10X Dose, 12 weeks



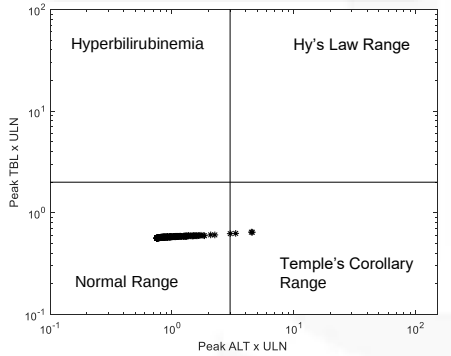
Compound X; 1X Dose



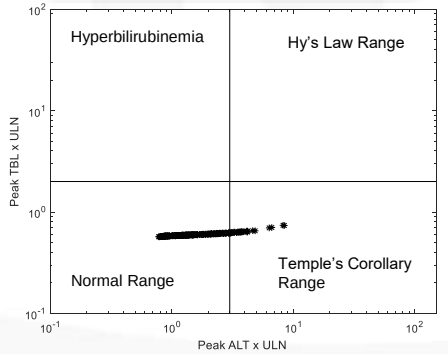
Compound X; 2X Dose



Compound X; 5X Dose



Compound X; 10X Dose

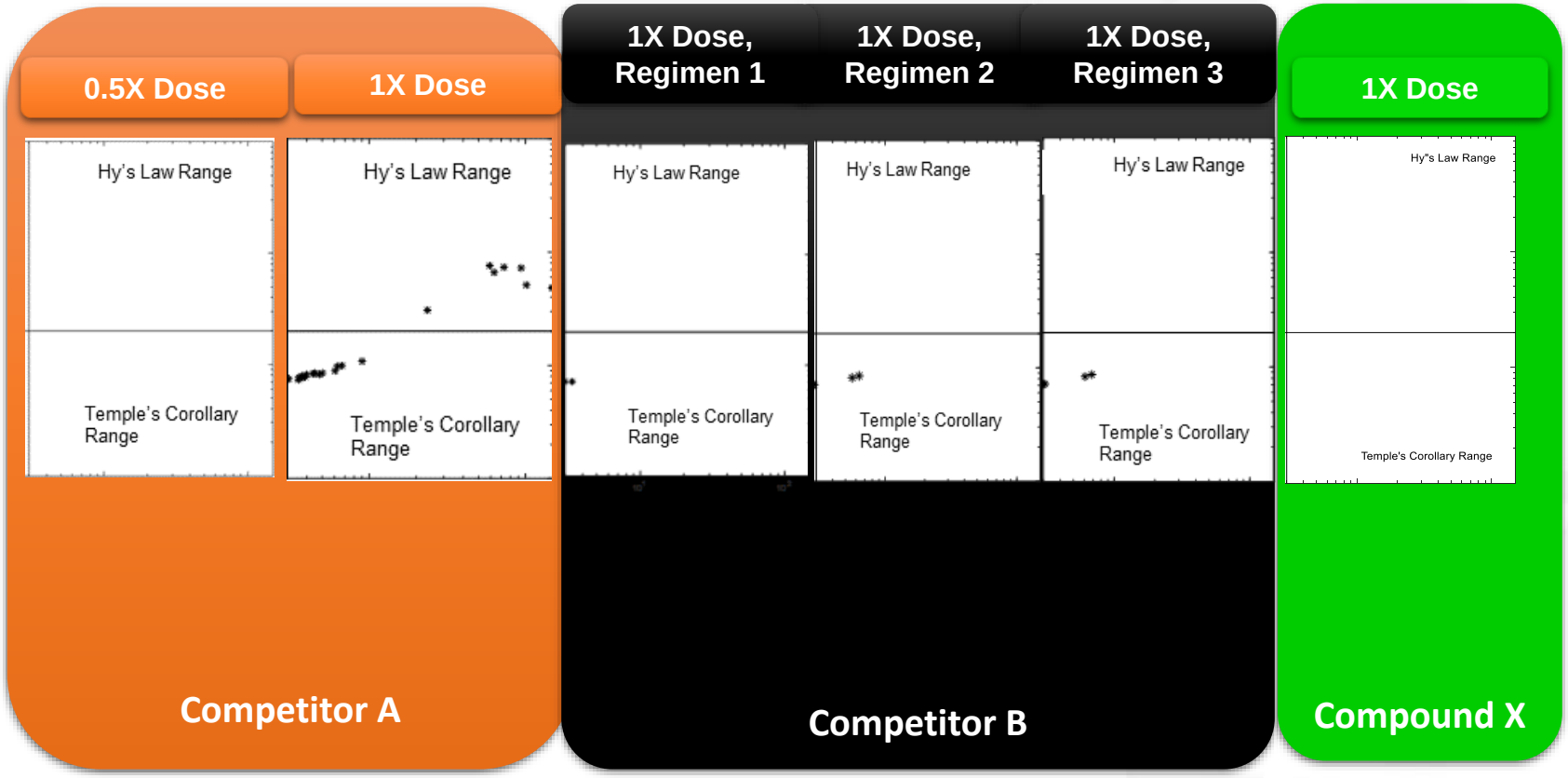


*The full v4A-1 SimPops (n=285) of normal healthy volunteers was used

**Upper limit of normal (ULN) in DILIsym is 40 U/L for ALT and 1 mg/dL for bilirubin.

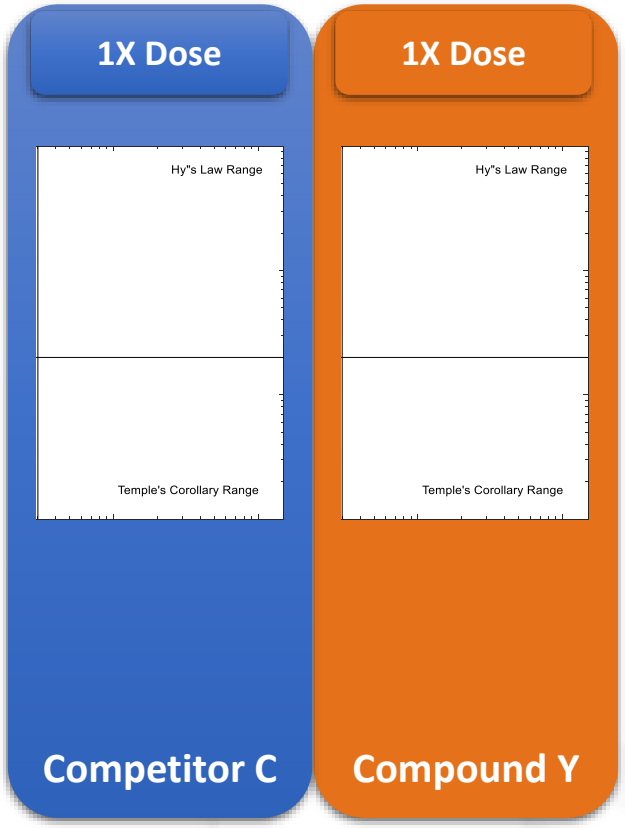
Simulation Results

Comparison with Competitors Suggests Compound X Has a Differentiated Liver Safety Profile



Simulation Results

Comparison with Compound Y Competitor Suggests Comparable Liver Safety Profile



Simulation Results

Example Project Summary

- ADMET Predictor™ and GastroPlus™ software, along with *in vitro* data, was used to construct PBPK representations to predict liver exposures for both compounds
- DILIsym parameters were successfully calculated from *in vitro* data for both compounds
- SimPops results show Compound X and Compound Y to be safe at projected clinical doses
- ALT elevations predicted within DILIsym at higher doses for both compounds
- SimPops results suggest that neither compound is likely to cause severe liver injury
- ***Phase IIb / III clinical trial results have subsequently confirmed the predictions for Compound Y***

Outline

- Overview of the DILI-sim Initiative
- Overview of the DILIsym Software
- Application Example: *In vitro* to *in vivo* extrapolation
- Summary

Summary

- A combination of multiple mechanistic, *in silico* modeling approaches can facilitate drug discovery (QSAR, PBPK, QSP and QST)
- DILIsym is a mechanistic, mathematical model that has been constructed to support pharmaceutical risk assessment and decision making
- DILIsym simulation results have been included in numerous communications with regulatory agencies
- DILIsym has been applied to support decisions related to compound DILI risk throughout the clinical development pipeline
  - Evaluated and interpret clinical biomarker signals in clinical trials
  - Optimized clinical trial design (dose selection, monitoring, inclusion/exclusion criteria)
  - Translated preclinical safety risk to first in human clinical trials
  - Ranked compounds by risk

Acknowledgements

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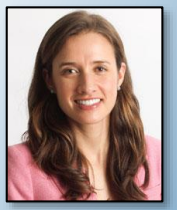

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