Application of Quantitative Systems Toxicology and Machine Learning Models in the Assessment of Drug-Induced Liver Injury

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(substituting for Kyunghee Yang)

ACS Fall 2025

Agenda

- Quantitative systems toxicology (QST) modeling of DILI
  - Liver safety assessment using DILIsym
  - Case study: application of QST modeling in the liver safety assessment of CGRP receptor antagonists
- Integrating QST and machine learning (ML) models for early assessment of hepatotoxic risk
  - Bridging compound structure to DILI mechanisms using ADMET Predictor
  - Application of QST-ML models in rank-ordering liver safety assessment of CGRP receptor antagonists
- Conclusions and perspectives

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

Predicted compound concentrations at site of toxicity using SLP PBPK modeling software

Toxicity mechanisms for given compounds (parent +/- metabolites) characterized by specifically-designed DILIsym input (in vitro) assays

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

Development and use of simulated populations provides inter-patient variability

SimulationsPlus

The DILI-sim and RENAsym Consortia are Partnerships Between DILIsym Services and Pharmaceutical Companies to Minimize Organ Injury

Excellent Scientific Advisory Boards

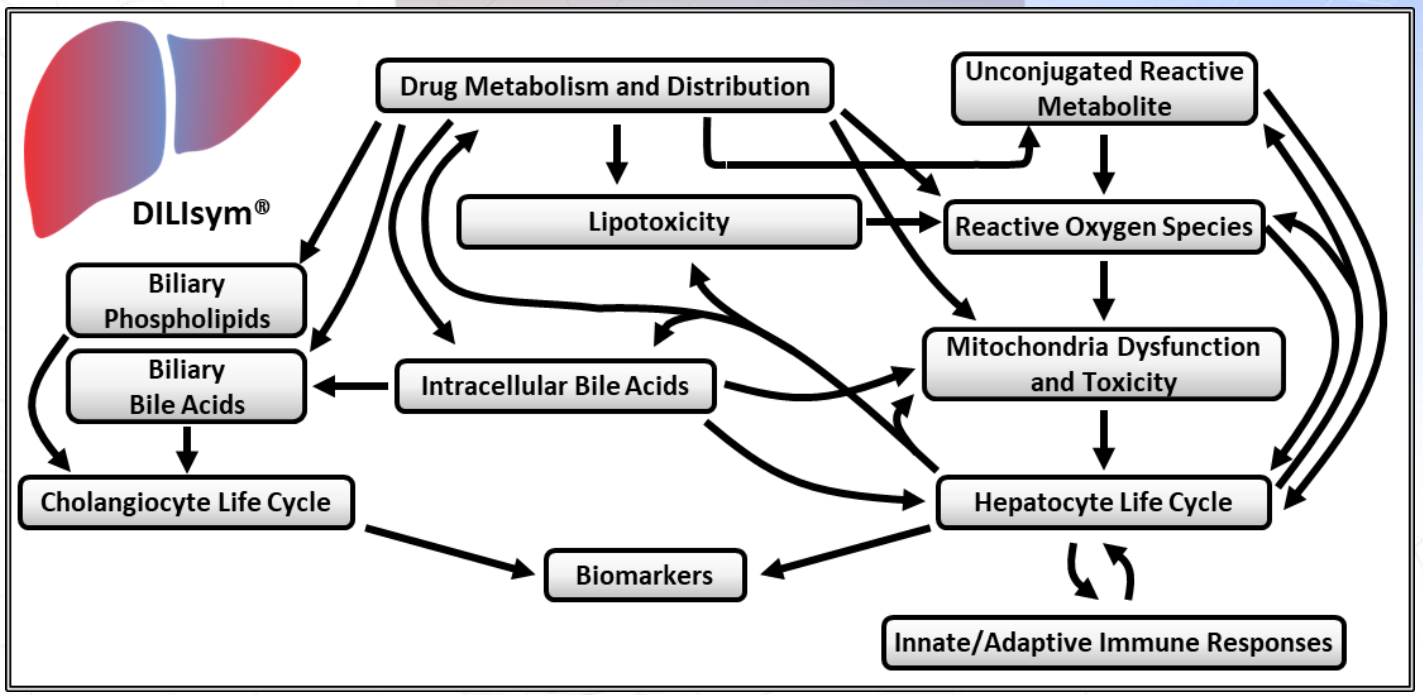
Current DILI-sim / RENAsym Members

For a comprehensive review of progress, see *Watkins 2020, Current Opinion in Toxicology (23-24:67-73)*

- *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*
  - *21 major pharmaceutical companies have participated*
  - *Members have provided compounds, data, and conducted experiments to support effort*
  - *Over $10 million invested in project*
- ***At least 30 cases of use for regulatory purposes***
- ***Over 30 publications***

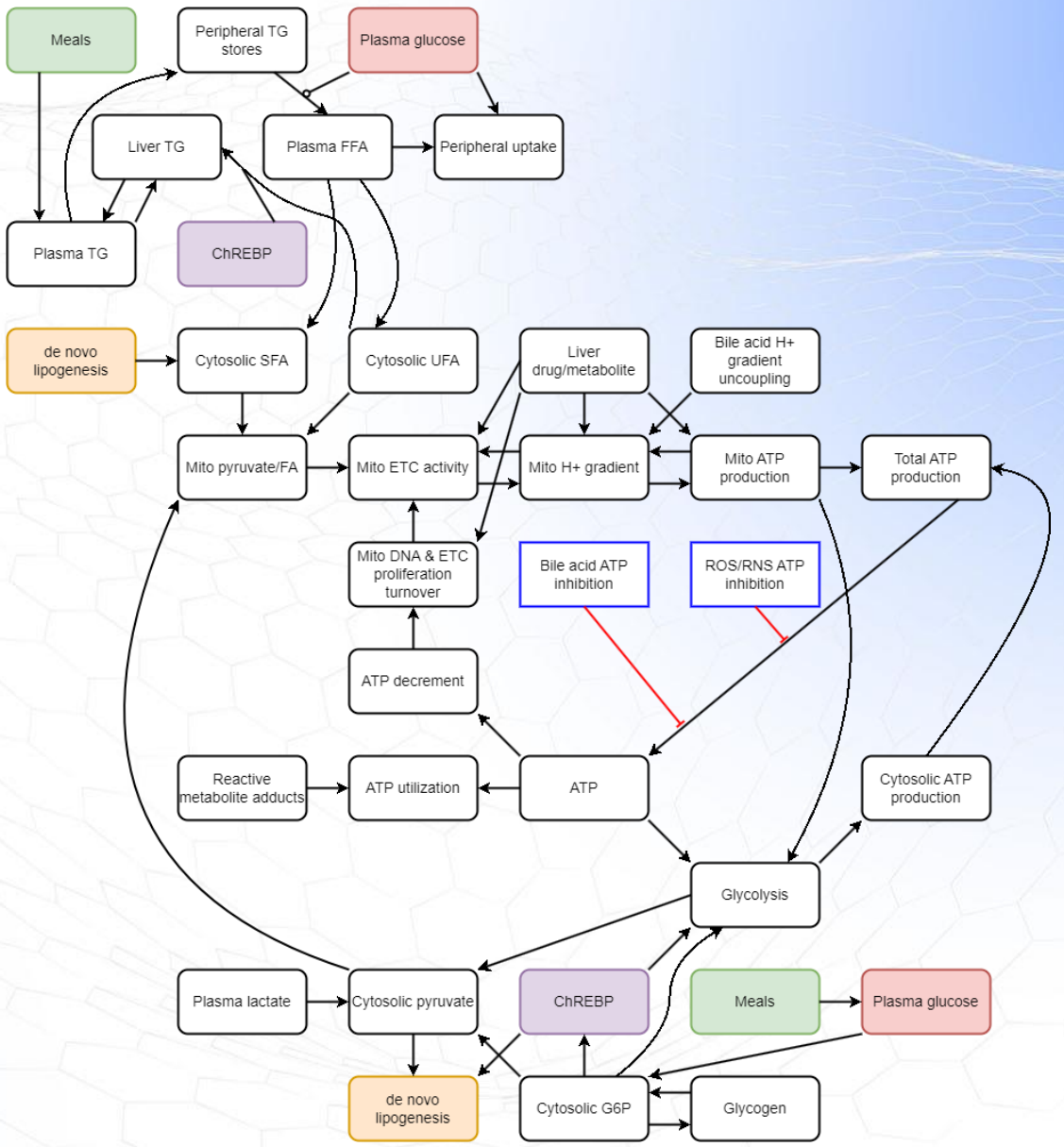
DILIsym Software Overview

- SimPops reflecting normal liver biochemistry and multiple disease states that affect liver
  - Adults and pediatrics (normal liver)
  - Rat, mouse, dog in addition to human
- Essential cellular processes represented to multiple scales in interacting sub-models
  - Key intrinsic hepatocellular injury mechanisms
  - Cholangiocyte injury and adaptive immune response representations updated in DS11
- ~90 detailed representations of validation compounds with >80% success and **zero false positive predictions**
- Single and combination drug therapies



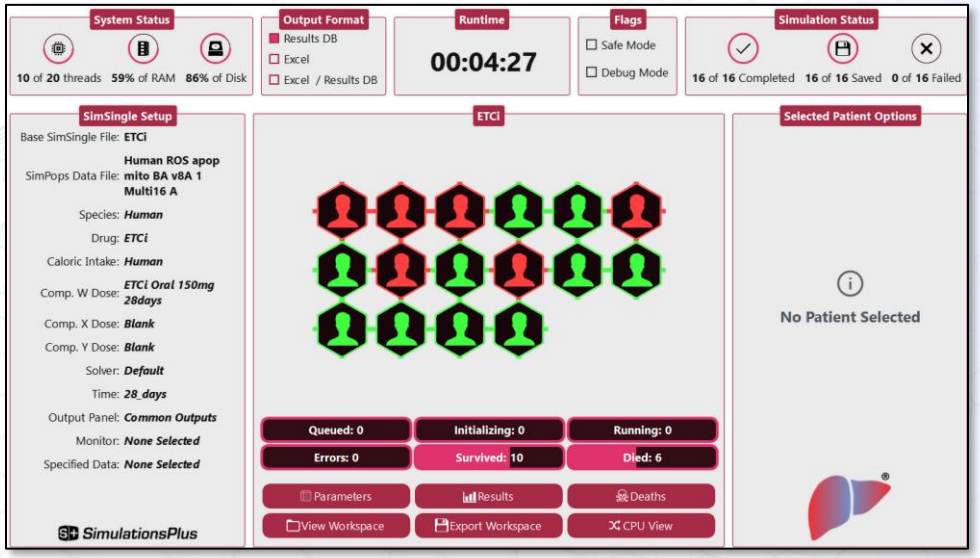
DILIsym Mitochondria Toxicity Sub-Model

- Mitochondria submodel enables prediction of bioenergetics in response to effects of drugs
- Mitochondria dynamics originally modeled in *in vitro* model, MITOsym
  - ATP turnover differs between species
- Plasma glucose provides substrate
  - Liver glycogen also contributes
- Plasma free fatty acids and triglycerides provide substrate
  - Also contributes to hepatocyte triglycerides
- Meals provide nutrient inputs
  - Typical feeding paradigm for each species is represented
- Trade-offs between pyruvate and fatty acids in supporting mito ATP generation are captured
  - Fasted: fatty acids sole substrate
  - Fed: fatty acids and pyruvate 50/50

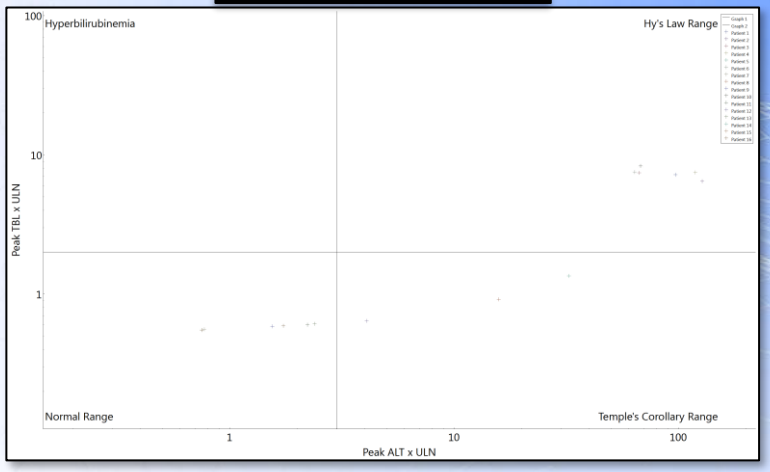


DILIsym Example: Theoretical ETC Inhibition

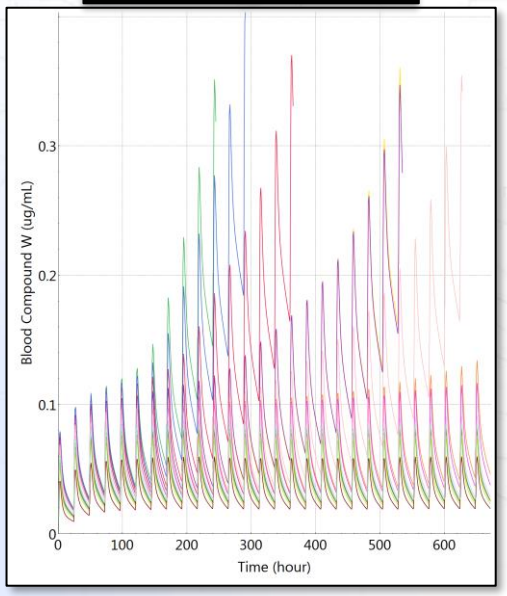
- Simulated administration of drug with electron transport inhibition properties in DS11
  - QD dosing for 28 days
  - SimCohort of 16 patients
- Hepatocyte ATP levels predicted to decrease
  - Drug Cmax has impact on hepatocellular bioenergetics
- Plasma ALT predicted to modestly increase over time in 3 simulated patients
  - Indicative of hepatocellular death
- Several patients had severe liver injury
  - Hy's Law quadrant of eDISH plot
  - DILIsym GUI shows death vs survival



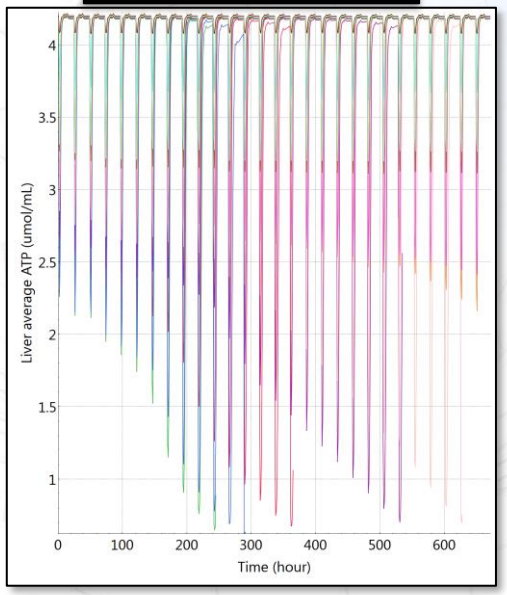
eDISH



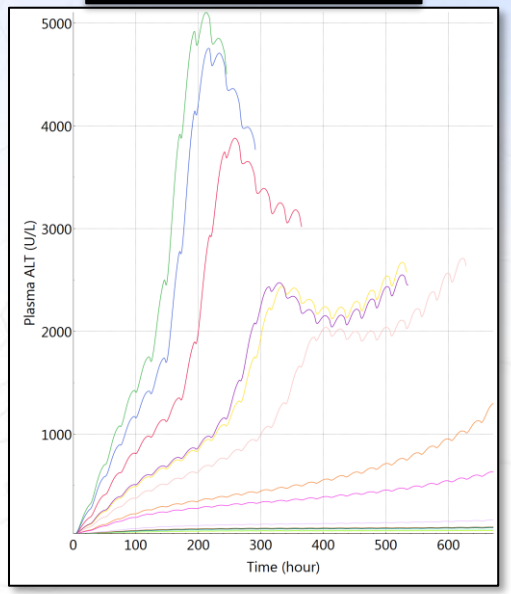
Drug PK



Hepatocyte ATP



Plasma ALT



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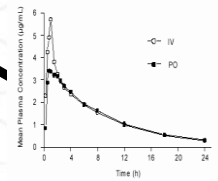
DILIsym Utilizes Various Data Types to Inform Decisions

Exposure (PBPK modeling)

Pharmacokinetics



Mechanisms

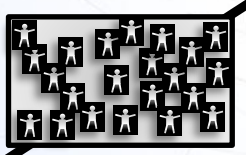
Bile Acid Transporter Inhibition

Mitochondrial Respiration

ROS Generation

Interpatient Variability

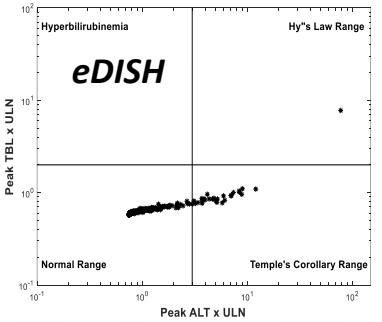
Unique Parameter Combinations

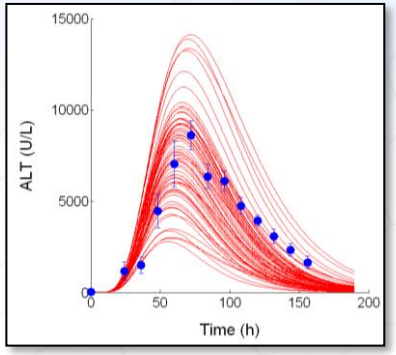


SimPops™

DILIsym®

Simulated Frequency & Severity of Liver Injury





SimulationsPlus

Biomarkers of Hepatocellular Function/Death and Cholestatic Injury Are Outputs of DILIsym

- Clinical biomarkers are outputs of DILIsym
  - Used for validation
  - Used for comparison with clinical and preclinical data
  - Functional, necrotic, and apoptotic indicators
- Dynamic simulations of biomarkers
  - Change over time based on extent of injury and recovery
- Additional DILIsym outputs include:
  - eDish
  - Fraction of viable hepatocytes
  - Liver ATP
  - Circulating, liver, and excreted drug and metabolites

Marker	Category
Alanine aminotransferase (ALT)[1,2,3,4,5]	**Necrosis**
Bilirubin (total, conjugated)[1,2,5,11]	**Function/Cholestasis**
Aspartate aminotransferase (AST)[1,2,3,4,5]	**Necrosis**
Alkaline phosphatase (ALP)[12]	***Cholestasis***
Gamma Glutamyl Transferase (GGT)[12]	***Cholestasis***
Prothrombin time [1,2]	*Function*
High mobility group box protein 1 (HMGB1)[1,10]	*Necrosis/Apoptosis*
Full length cytokeratin-18[1]	*Necrosis*
Cleaved cytokeratin-18[1]	*Apoptosis*
Sorbitol dehydrogenase (SDH)[1,6]	*Necrosis*
Arginase-1[9]	*Necrosis*
Liver derived mRNA[7] and miRNA[8] (miR122)	*Necrosis*

[1]Antoine *Xenobiotica* 2009; [2]Giannini *CMAJ* 2005; [3]Horn *Am J Clin Pathol* 1999; [4]Ozer J *Toxicology* 2008; [5]Hy's Law: Temple R *Pharmacoepidemiol Drug Saf* 2006; [6]Ozer *Toxicology* 2008; [7]Wetmore *Hepatology* 2010, [8]Yang *Tox Sci* 2012, [9]Murayama *Clin Chimica Acta 2008*, [10]Harrill *Clin Pharmacol Ther* 2011, [11]Yang *Clin Pharmacol Ther* 2017, [12]Beaudoin *Front Pharmacol* 2023

Known Use of DILIsym Simulation Results in Sponsor Communications with Regulatory Agencies

50+

Regulatory communications that included DILIsym simulation results

88

Percent of mechanistic liver injury projects

15

Percent of biomarker fitting projects, i.e., investigating underlying hepatocyte loss

7

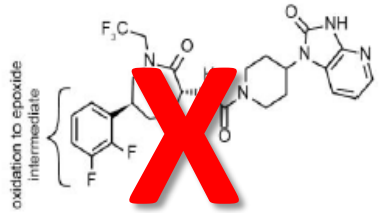
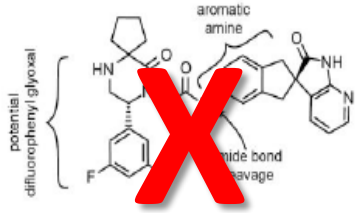
Instances in which DILIsym staff participated in presentation to regulatory agencies

5+

Distinct regulatory agencies

- *Use of simulation results in communications with regulators is generally governed by the sponsor, with imperfect visibility by the DILIsym team*
- *The following reflects our best understanding of their use*

Calcitonin Gene-related Peptide (CGRP) Receptor Antagonists for Treatment of Migraines

Parameter	Telcagepant[a]	MK-3207[b]
Structure[d]		
Potency IC_{50}[e]	2.2 nM	0.12 nM
Pivotal conventional nonclinical toxicology study liver findings	3M rat: <3 × ALT/AST with no liver histopathology at 15× exposure margin 6M rat: no liver safety signal at 7x margin 9M NHP: no liver safety signal at 7× margin 6M mouse: <2 × ALT/AST with no liver histopathology at 14× margin	6M rat: no liver safety signal at 25× exposure margin 9M NHP: no liver safety signal at 4× margin 6M mouse: no liver safety signal at 12× margin 1M dog: slight periportal vacuolation with <4 × ALT/AST associated with excessive body weight loss at 17x margin

Next-in-class Compounds

- Ubrogepant ?
- Rimegepant ?
- Atogepant ?
- Zavegepant ?

QST Modeling of CGRP Receptor Antagonists to Assess Liver Safety

- DILIsym simulations performed with telcagepant using clinical trial dosing protocols
  - Goal is to **recapitulate clinically observed toxicity**

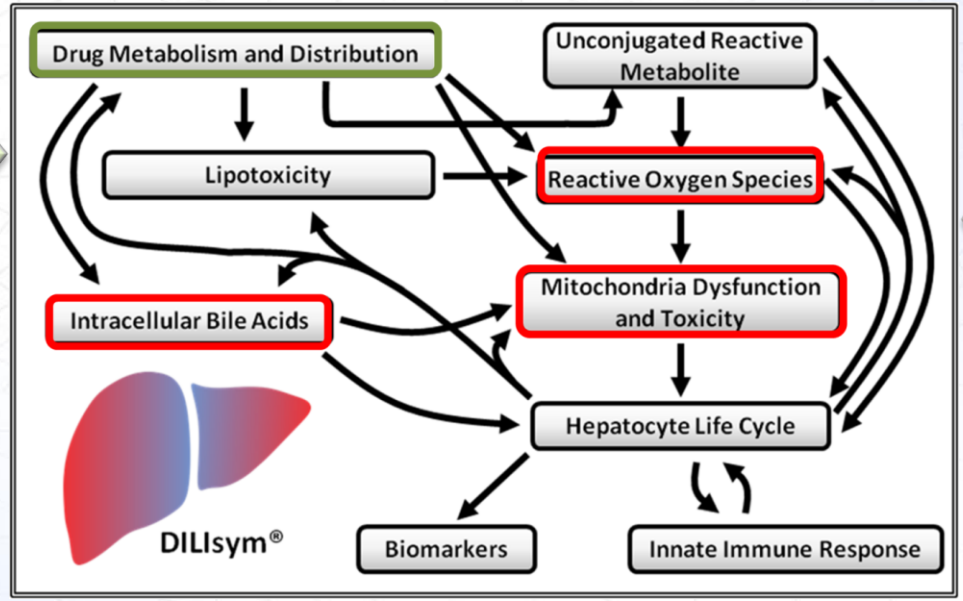
- DILIsym simulations performed with rimegepant, zavegepant, atogepant, and ubrogepant
  - Goal is to **predict likelihood of toxicity**

Woodhead et al., Tox Sci (2022)

QST Modeling of CGRP Receptor Antagonists to Assess Liver Safety

PBPK Input

- Physicochemical properties
- Absorption
- Tissue distribution
- In vitro metabolism/transport
- Renal and biliary clearance



DILIsym Input Panel

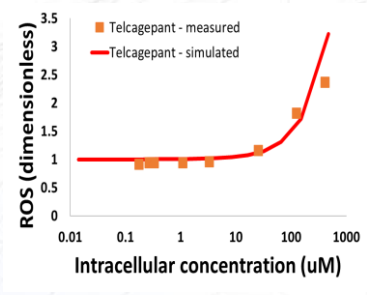
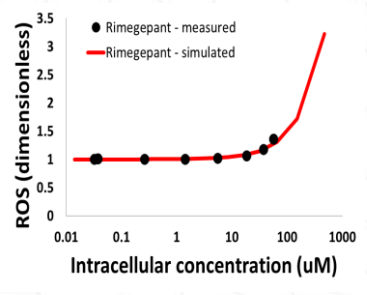
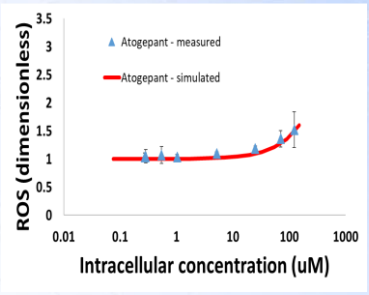
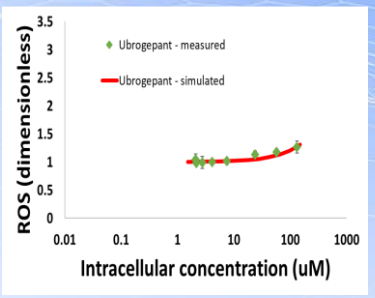
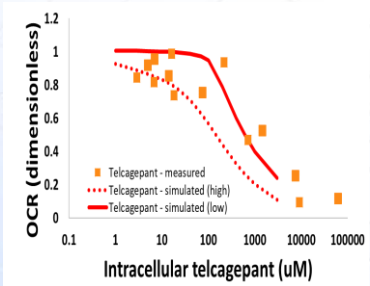
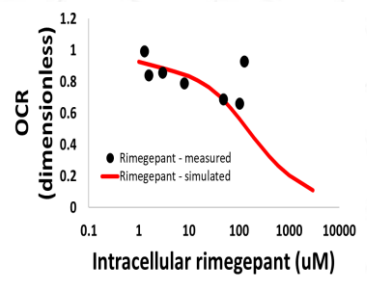
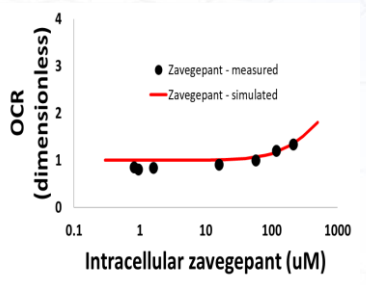
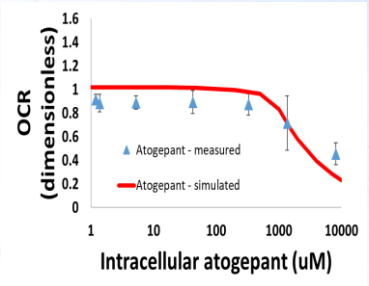
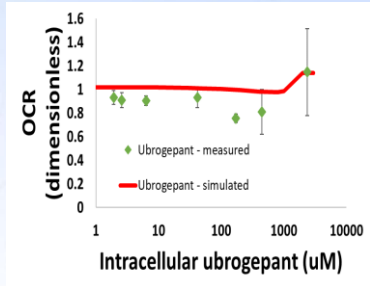
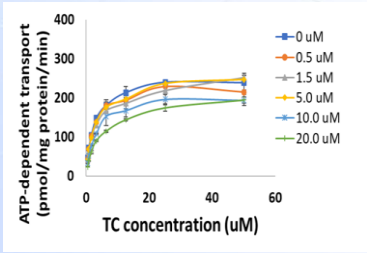
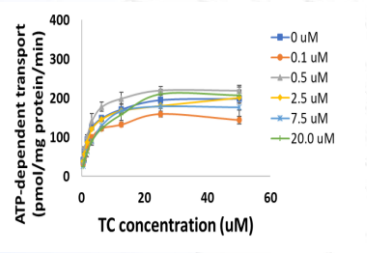
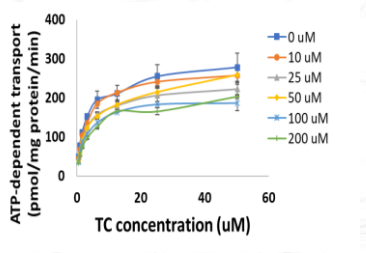
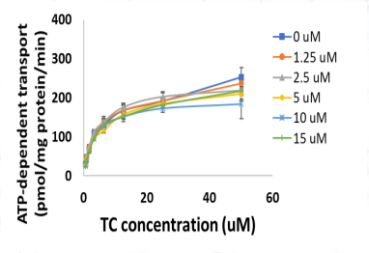
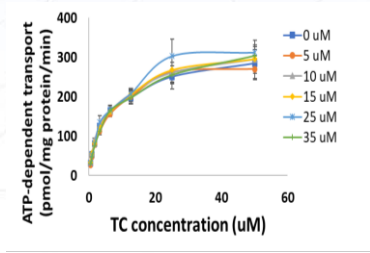
In vitro assays performed to determine quantitative aspects of DILI mechanisms

- Mitochondrial dysfunction
- Oxidative stress
- Bile acid transporter inhibition

Population Variability (SimPops)

- Collections of simulated individuals with parameter variability
- Designed to reflect appropriate biochemical and anthropometric ranges
- A standard human SimPops represents variability in body weight, mitochondrial function, caspase activation (apoptosis), bile acid disposition, and oxidative stress (ROS/RNS) susceptibility

In Vitro Mechanistic Toxicity Signals Observed for Telcagepant, Rimegepant, Zavegepant, Atogepant, and Ubrogepant

Mechanism	In Vitro Assay	Telcagepant	Rimegepant	Zavegepant	Atogepant	Ubrogepant
Oxidative Stress	HepG2 cells; High content imaging			***No ROS Signal***		
Mito-chondrial Dysfunction	HepG2 cells; Seahorse XF analyzer					
Bile Acid Transporter Inhibition	Membrane vesicles & transfected cells; Transport of taurocholate					

Woodhead et al., Tox Sci (2022)
SimulationsPlus

DILIsym Toxicity Parameters for Telcagepant, Rimegepant, Zavegepant, Atogepant, and Ubrogepant

Mechanism	Parameter	Unit	DILIsym Parameter Value					
			Telcagepant - High	Telcagepant - Low	Rimegepant	Zavegepant	Atogepant	Ubrogepant
Mitochondrial Dysfunction	Coefficient for ETC inhibition 1	µM	3,470	3,470	3,470	No inhibition	38,170	Not used
	Coefficient for ETC Inhibition 3	µM	1.89	-	1.89	No inhibition	0.1	4,217
	Max inhibitory effect for ETC inhibition 3	dimensionless	0.45	-	0.45	No inhibition	0.2	0.4
	Uncoupler 1 effect Km	mM	No effect	No effect	No effect	1,600	No effect	15,300
	Uncoupler 1 effect Vmax	dimensionless	No effect	No effect	No effect	2	No effect	22.5
	Uncoupler 1 effect Hill	dimensionless	No effect	No effect	No effect	1.5	No effect	4.3
Oxidative Stress	RNS/ROS production rate constant 1	mL/nmol/hr	3.5×10^{-4}	3.5×10^{-4}	3.5×10^{-4}	No ROS production	3.41×10^{-4}	1.65×10^{-4}
Bile Acid Transporter Inhibition	BSEP inhibition constant	µM	19.0	19.0	27.2	341	144.2	No inhibition
	BSEP inhibition alpha value	dimensionless	4.32	4.32	Competitive	1.368	0.64	No inhibition
	NTCP inhibition constant	µM	No inhibition	No inhibition	No inhibition	No inhibition	No inhibition	No inhibition
	MRP4 inhibition constant	µM	42.4	42.4	No inhibition	No inhibition	42	75.3

Woodhead et al., Tox Sci (2022)

CGRP Receptor Antagonists Modeling Results

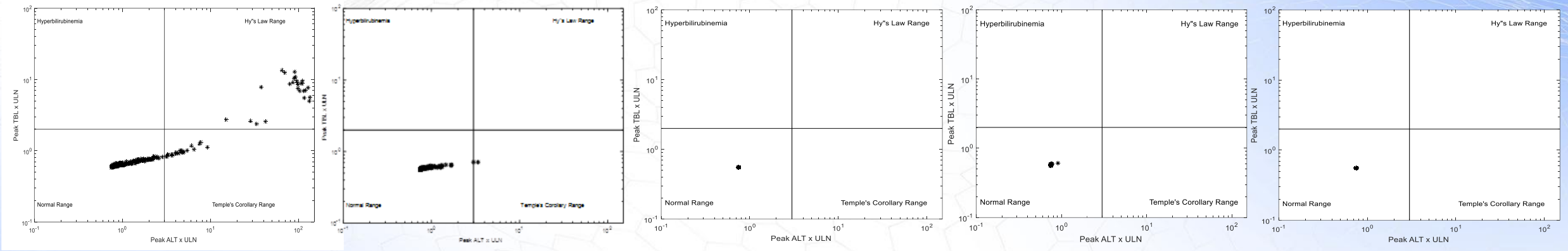
Telcagepant; 140 mg BID, 12 weeks, high ETCi

Rimegepant; 75 mg QD, alternate day dosing, 14 total doses over 28 days

Zavegepant; 20 mg IN or 750 mg PO or 7.5 mg IV, 25 straight days

Atogepant; 60 mg BID, 12 weeks

Ubrogepant; 100 mg QD, 25 straight days



- DILIsym modeling **retrospectively** predicted liver toxicity for telcagepant consistent with clinical experiences
  - The mechanisms involved in the predicted liver injury for *telcagepant* were mainly *inhibition of bile salt transport* and *mitochondrial ECT inhibition*
- DILIsym **prospectively** predicted liver safety for rimegepant, zavegepant, atogepant, and ubrogepant at clinically relevant doses
  - Liver safety confirmed by clinical trials, validating model prediction

Woodhead et al., Tox Sci (2022)

Liver Safety of Ubrogepant Confirmed in Clinical Trials

Original Article

Cephalalgia
An International Journal of Headache

International Headache Society

Cephalalgia
2019, Vol. 39(14) 1753–1761

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Safety and tolerability of ubrogepant following intermittent, high-frequency dosing: Randomized, placebo-controlled trial in healthy adults

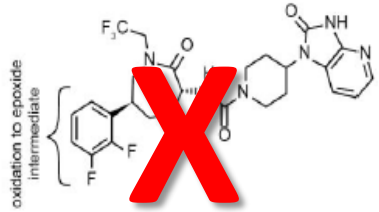
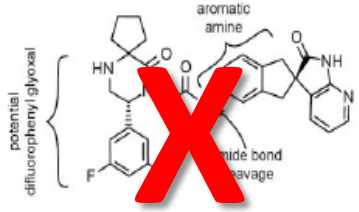
Peter J Goadsby[1], Stewart J Tepper[2], Paul B Watkins[3], Girma Ayele[4], Rosa Miceli[4], Matthew Butler[4], Lawrence Severt[4], Michelle Finnegan[4], Armin Szegedi[4], Joel M Trugman[4] and Abhijeet Jakate[4]

No significant liver signals shown at one of the simulated dosing protocols: 100 mg QD, 2 days on, 2 days off, for 56 days (28 total doses)

Table 3. Hepatic laboratory parameters.

	Placebo (n = 260)	Ubrogepant 100 mg (n = 256)
ALT, U/L	n = 258	n = 256
Baseline, mean (SD)	20.5 (7.2)	21.1 (9.1)
End of trial, mean (SD)	21.7 (7.7)	21.3 (8.7)
Change from baseline, mean (SD)	1.2 (7.4)	0.1 (8.4)
Post baseline ≥ 3 × ULN, n (%)	3 (1.2)	2 (0.8)

Calcitonin Gene-related Peptide (CGRP) Antagonists for Treatment of Migraines

Parameter	Telcagepant[a]	MK-3207[b]
Structure[d]		
Potency IC_{50}[e]	2.2 nM	0.12 nM
Pivotal conventional nonclinical toxicology study liver findings	3M rat: <3 × ALT/AST with no liver histopathology at 15× exposure margin 6M rat: no liver safety signal at 7x margin 9M NHP: no liver safety signal at 7× margin 6M mouse: <2 × ALT/AST with no liver histopathology at 14× margin	6M rat: no liver safety signal at 25× exposure margin 9M NHP: no liver safety signal at 4× margin 6M mouse: no liver safety signal at 12× margin 1M dog: slight periportal vacuolation with <4 × ALT/AST associated with excessive body weight loss at 17x margin

Next-in-class Compounds

- Ubrogepant
- Rimegepant
- Atogepant
- Zavegepant

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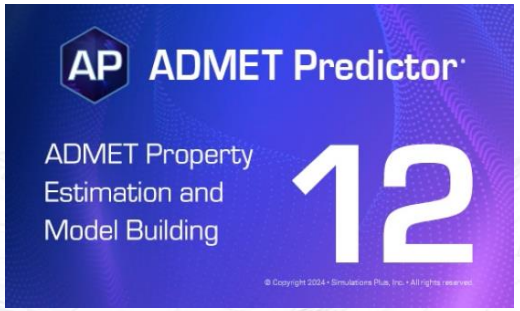
  - Liver safety assessment using DILIsym
  - Case study: application of QST modeling in the liver safety assessment of CGRP receptor antagonists
- Integrating QST and machine learning (ML) models for early assessment of hepatotoxic risk
  - Bridging compound structure to DILI mechanisms using ADMET Predictor
  - Application of QST-ML models in rank-ordering liver safety assessment of CGRP receptor antagonists
- Conclusions and perspectives

Combination of QST and AI Provide Efficient, Understandable Assessment of Compound DILI Risk



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Liver Safety+

AI

Predict mechanistic DILIsym Input Parameters from compound structure

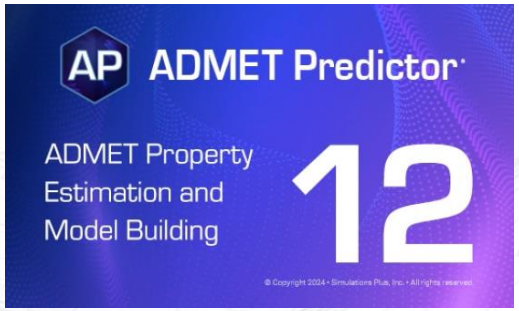
QST

Predict mechanistic DILIsym Input Parameters from compound structure

Efficient DILI risk assessment, readily applied to preclinical compound screening

SimulationsPlus

Simulations Plus Has Developed a Roadmap to Derive an Early Assessment of Hepatotoxic Risk



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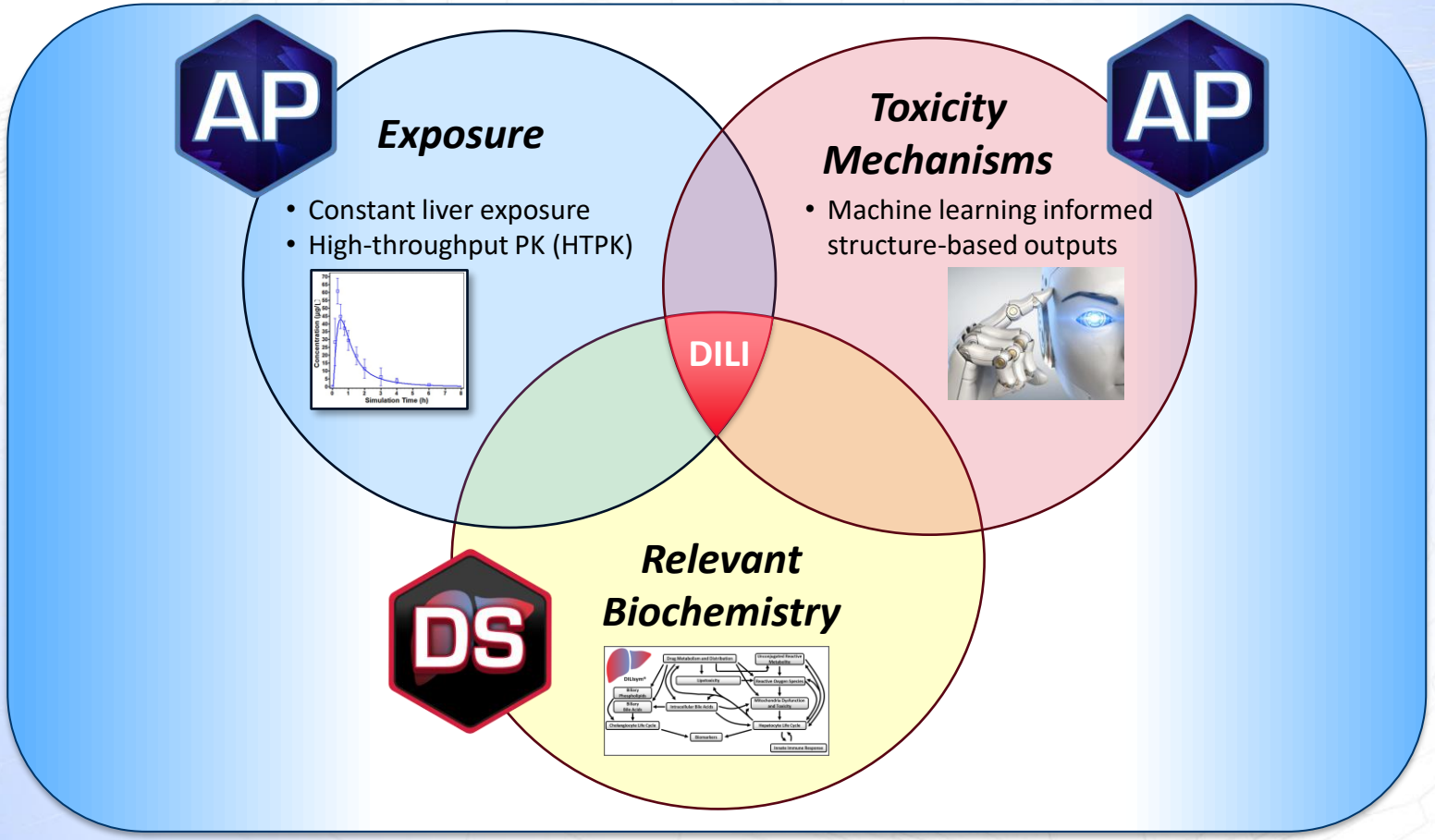
Liver Safety+

- New module in ADMET Predictor 12 generates outputs that can be used to inform inputs for DILIsym
  - Permissive of liver safety assessment during **early** drug discovery efforts!
  - Predictions of the current offering are qualitative
    - Yes/no toxicity mechanism classifications
    - Rank ordering of a compound's toxicity assessment with other in-class compounds
  - Accuracy and use of outputs will improve iteratively, as more data become available to inform predictions
- Workflow permissive for early discovery applications
  - No need for data from typical DILIsym *in vitro* assays
  - Leverages ADMET Predictor informed structure-based compound properties
  - Applies ADMET Predictor Machine Learning from a library of DILI/clean compounds
  - Use of constant liver exposure based on molar concentrations OR use of ADMET Predictor High-Throughput PK (HTPK) results
  - Integration of the above in the DILIsym *in vivo* context for early insights into liver liabilities

Liver Safety+ Prediction Package Tailored for Early Discovery Data



SimulationsPlus

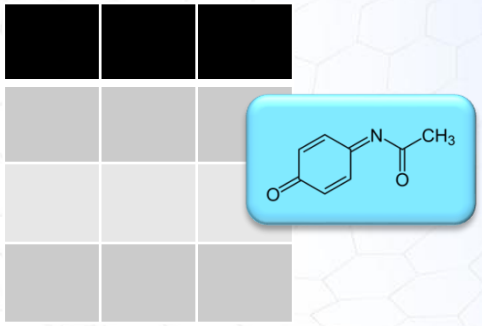
APD Module Applies Machine Learning to Bridge from Compound Structure to DILIsym

Compound Library In Vitro Assay Data

- Mitochondrial respiration (Seahorse assay)
- Oxidative stress (High content screening)
- Bile acid efflux transporter inhibition (Inside-out vesicles)
- Phospholipid transporter inhibition (Transfected cells)

Filtering, Automated Fitting, Translation

Databases



Machine Learning Algorithms

- Mitochondrial dysfunction
- Oxidative stress
- Bile acid efflux transporter inhibition
- Phospholipid transporter inhibition

ADMET Predictor 12
DILIsym module

DILIsym

Novel compound

SimulationsPlus

APD Module Outputs Include Values for Four Key Mechanisms of Hepatotoxicity

- APD module provides classifications (yes/no) and key parameter values for each of the four main mechanisms of toxicity represented in DILIsym
- Outputs are evaluated for potential toxicity
- If outputs suggest toxicity, user can move to identifying parameter values for DILIsym simulations
- Details on each of the APD module outputs and machine learning model construction are available in the ADMET Predictor 12 Manual, and will be summarized in the next section

Toxicity Mechanism	APD classification[§] output	APD MEC[†] output	APD AC_{50}[‡] output	APD IC_{50}[‖] output
Mitochondrial dysfunction	✓	✓	✓	—
Reactive oxygen species	✓	✓	✓	—
BSEP inhibition	✓	—	—	✓
MRP3/MRP4 inhibition	✓	—	—	—
MDR3 inhibition	✓	—	—	✓

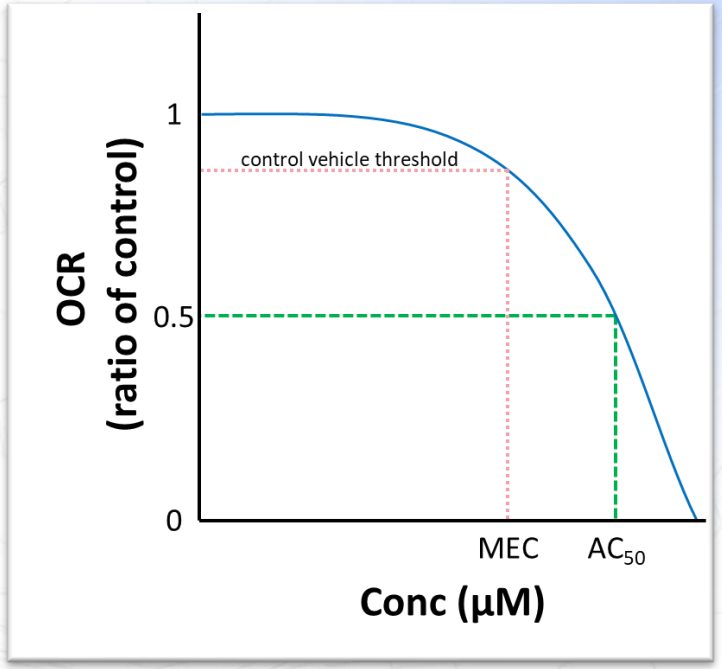
§ yes/no prediction for *in vitro* signals
† minimum effective concentration (MEC) that significantly crosses vehicle control threshold
‡ concentration at which 50% maximum effect is observed
‖ concentration at which 50% inhibition is observed

The ADP Module Contains Three Mitochondrial Dysfunction Models

- Mito_Tox
  - Classification model that predicts Yes or No for mitochondrial toxicity based on the Seahorse assay
  - Based on dataset containing 204 molecules with a large percentage (86%) of experimental positives
- Mito_MEC
  - Predict the minimum effective concentration (MEC) that significantly crosses the control vehicle threshold
- Mito_AC50
  - Predicts the concentration at which 50% maximum effect is observed

Model	Set	Negatives	Positives	Total	Correct	Concordance	Sensitivity	Specificity
Mito_Tox	Training	25	154	179	155	86.6%	85.7%	92.0%
	Test	4	21	25	20	80.0%	81.0%	75.0%

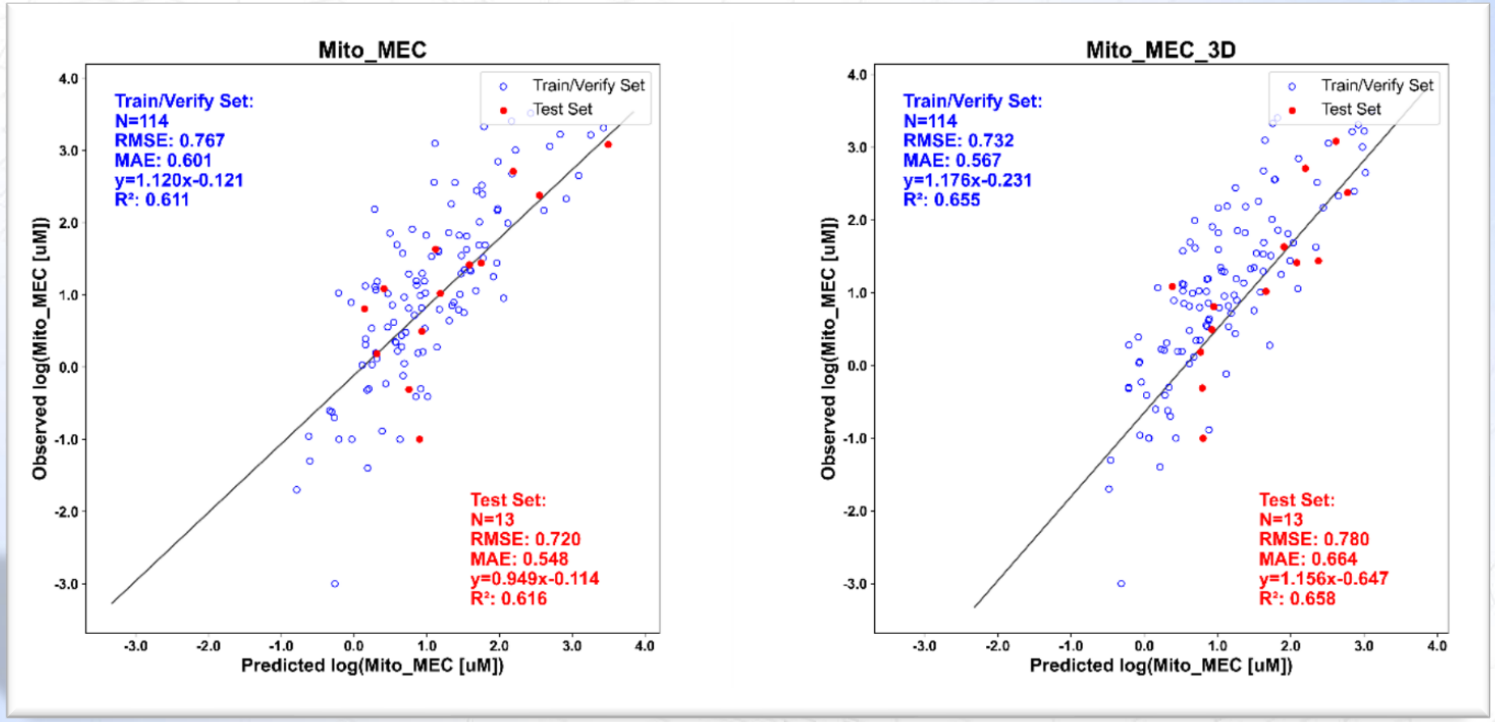
The single mispredicted negative from the test set is fenclozic acid, a compound that was withdrawn from the market due to jaundice



ETC inhibition with a complete knockdown of OCR at high concentrations

Mitochondrial Dysfunction Models With 2D and 2D+3D Descriptors Were Created: Mito_MEC

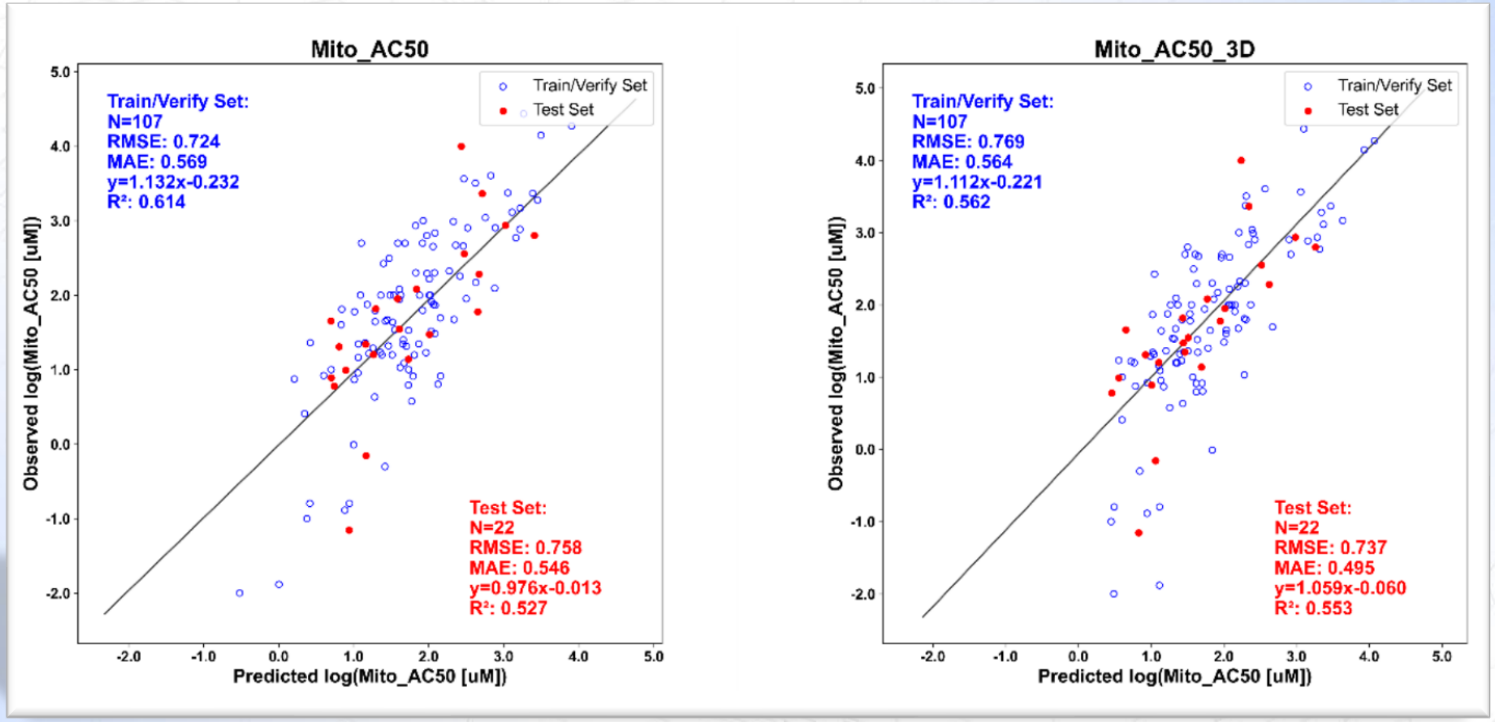
- The Mito_MEC dataset contains 127 compounds with 13 (~10%) in the test set
- The most active compound is rotenone, with an observed MEC value of 0.001 µM



Plots show the log of the experimental Mito_MEC value in micromolar units (µM) versus the log of the predicted value

Mitochondrial Dysfunction Models With 2D and 2D+3D Descriptors Were Created: Mito_AC50

- The Mito_AC50 dataset contains 129 compounds with 22 (~17%) in the test set
- The two most active compounds are antimycin A (Mito_AC50=0.01 µM) and rotenone (Mito_AC50=0.013 µM)



Plots show the log of the experimental Mito_AC50 value in micromolar units (µM) versus the log of the predicted value

The ADP Module Contains Three Reactive Oxygen Species Models

- ROS_Tox
  - Classification model that predicts Yes or No for reactive oxygen species formation
  - Based on dataset containing 243 molecules with 25 (~10%) in the test set
- ROS_MEC
  - Predict the minimum effective concentration (MEC) that significantly crosses the control vehicle threshold
- ROS_AC50
  - Predicts the concentration at which 50% maximum effect is observed

Model	Set	Negatives	Positives	Total	Correct	Concordance	Sensitivity	Specificity
ROS_Tox	Training	70	148	218	172	78.9%	80.4%	75.7%
	Test	6	19	25	22	79.8%	81.4%	76.3%

The ADP Module Utilizes the Existing BSEP Models in ADMET Predictor and Contains a New MRP3 Model for Bile Acid Transporter Inhibition

- BSEP_Inh
  - Classification model that predicts Yes or No for inhibition of the bile salt export pump (BSEP), a bile acid transporter on the canalicular membrane of hepatocytes
  - Based on dataset containing 615 compounds (Morgan et al. 2013), of which 127 inhibit BSEP below 60 µM
- BSEP_IC50
  - Regression model, using 155 compounds with half-maximal inhibitory concentration (IC_{50}) values below 133 µM, that predicts BSEP IC_{50} value
  - Test set consisted of 24 (~15%) compounds
- MRP3_Inh
  - Classification model that predicts Yes or No for inhibition of the multidrug resistance-associated protein 3 (MRP3), a bile acid transporter on the basolateral membrane of hepatocytes
  - Based on dataset containing 107 compounds (Köck et al. 2014, Ali et al. 2017), of which 43 inhibit MRP3 below 100 µM

Model	Set	Negatives	Positives	Total	Correct	Concordance	Sensitivity	Specificity
MRP3_Inh	Training	54	36	90	87	96.7%	94.4%	98.1%
	Test	10	7	17	15	88.2%	85.7%	90.0%

APD Module Predictions Are Used to Set Up Active Toxicity Mechanisms in DILIsym

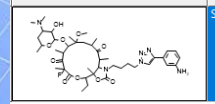
Machine Learning Algorithms

- Mitochondrial dysfunction
- Oxidative stress
- Bile acid efflux transporter inhibition
- Phospholipid transporter inhibition

ADMET Predictor 12
DILIsym module

Novel Compound (Solithromycin)

DILIsym

Structure	Identifier	Geometry	3D Quality	AP_FWeight	BSEP_Inh	BSEP_IC50	MDR3_IC50	MDR3_Inh	Mito_AC50	Mito_MEC	Mito_Tox	MRP3_Inh	ROS_AC50	ROS_MEC	ROS_Tox
	Solithromycin	3D	1.000	845.028	Yes (83%)	8.860	0.677	No	71.064	5.243	Yes (99%)	Yes (93%)	50.259	7.298	Yes (89%)

DILI Mechanism Selector for Solithromycin (Solithromycin_1nM)

Select Molecule: CompY

Select Mechanism: incRNSROSproduction1

Customized Variables

Filter By Name...

Molecule / Mechanism	Value	Units
CompY_Mech_inhBAtransport		
Compound Y NTCP inhibition constant	1.000000e+10	umol/L
Compound Y NTCP alpha constant for inhibition	1.000000e+10	dimensionless
Compound Y NTCP switch	1.000000e+00	dimensionless
Compound Y BSEP inhibition constant	8.86	umol/L
Compound Y BSEP alpha constant for inhibition	5	dimensionless
Compound Y BSEP switch	0	dimensionless
Compound Y basolateral inhibition constant	1.000000e+10	umol/L
Compound Y basolateral alpha constant for inhibition	1.000000e+10	dimensionless
Compound Y basolateral switch	1.000000e+00	dimensionless
CompY_Mech_inhETC3		
Coefficient for ETC inhibition 3	0.040746	umol/L
Max inhibitory effect for ETC inhibition 3	0.39355	dimensionless
CompY_Mech_inhETC1		
Coefficient for ETC inhibition 1	2379.481	umol/L
CompY_Mech_incRNSROSproduction4		
Liver RNS-ROS production rate Vmax 4	5.8195	1/hour
Liver RNS-ROS production rate Km 4	9.1224	umol/L
Liver RNS-ROS production rate Hill 4	4.5496	dimensionless
CompY_Mech_incRNSROSproduction1		
Liver RNS-ROS production rate constant 1	0.053744	mL/nmol/hour

Clear | Save with Custom | Save As New | Save As New with Custom | Cancel

SimulationsPlus

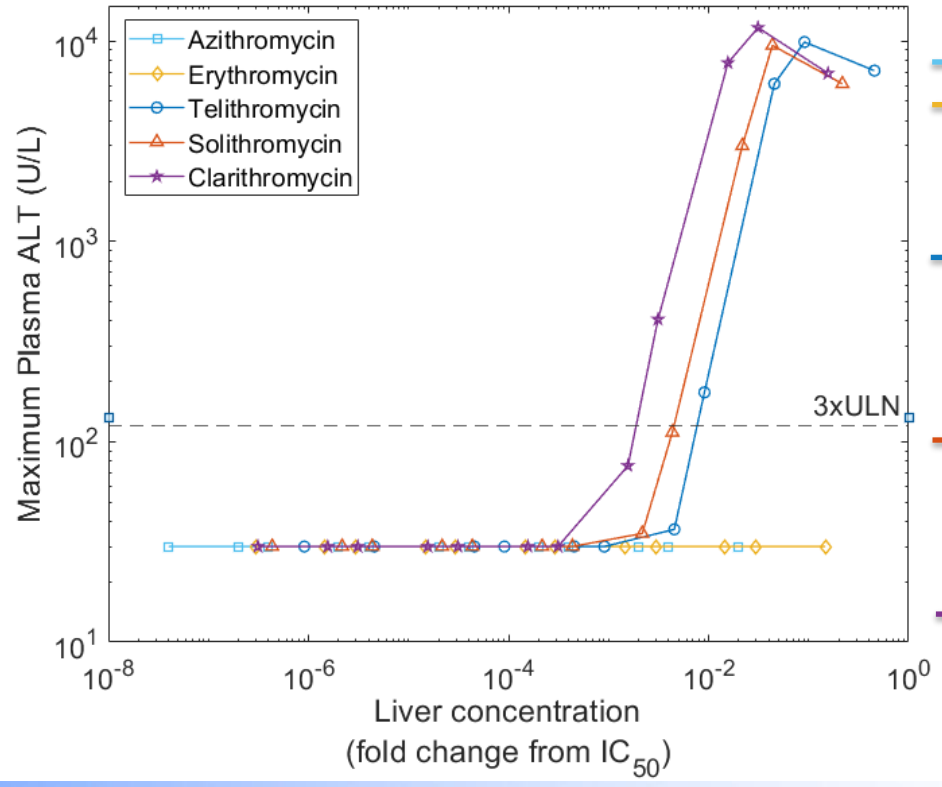
Multiple Options for Liver Exposure in DILI Toxicity Ranking Process

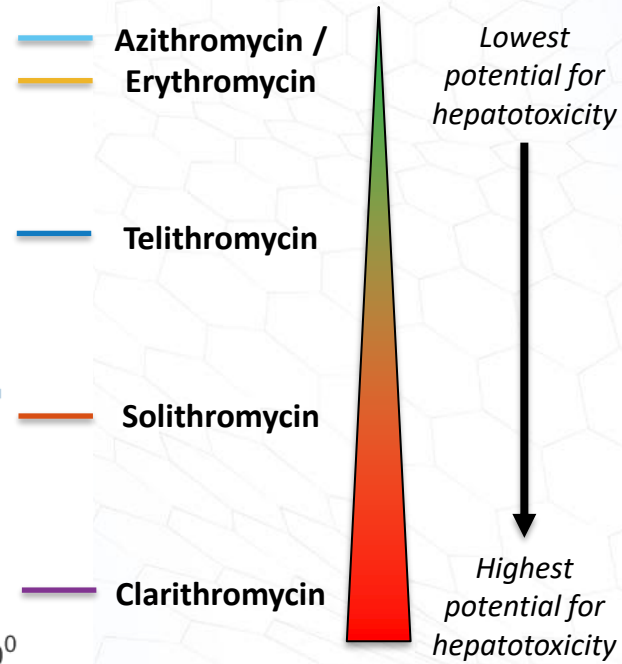
- APD module is designed to provide insight into DILI toxicity rankings at any stage in the drug development pipeline
- Based on where a compound is in the drug development pipeline, different information about exposure in humans is available
  - Compounds further along in the pipeline likely have more information available to define exposure
  - Compounds very early on in development may have minimal data to inform exposure

- Potential options for liver exposure to drive hepatotoxicity mechanisms in DILIsym:
  1. Constant liver exposure based on molar concentrations
     - *DILIsym simulations to be performed at a range of constant liver concentrations*
     - *For rank-ordering hepatotoxicity risk of multiple in-class compounds using the "constant liver exposure" approach, liver concentrations need to be normalized using a relevant metric which provides consideration to compound-specific efficacy ranges*
  2. Assume or estimate liver profiles from preclinical PK data
  3. Estimate liver exposure from ADMET Predictor HTPK using predicted C_{max} and liver partition coefficient from user-specified doses
  4. Predict liver exposure from GastroPlus PBPK model

APD Module Outputs Reproduce Clinical and Previous DILIsym Simulation Toxicity Rankings: Macrolide Antibiotics

ML Tox Model Predictions





Clinical Data & Previous DILIsym Simulation Results

Table III Results in the v4A_1 SimPops for Each of the Five Macrolides in DILIsym v5A Compared to Reported Clinical data. Observed Data are from the Literature (3,10,31)

Compound	Protocol	Peak ALT >3X ULN	
		Observed	Simulated**
Solithromycin	Oral (CE01–300)	5.4%[a] (22/411)	3.9% (11/285)
	IV-to-Oral (CE01–301)	9.1%[b] (38/417)	6.0% (17/285)
Clarithromycin	500 mg BID 7 days	1–2%	2.8% (8/285)
Erythromycin	500 mg QID 10 days	1–2%	2.8% (8/285)
Telithromycin	800 mg QD 10 days	~0.5%	0%
Azithromycin	500 mg QD day 1 250 mg QD days 2–5	1.2%	0%

Upper limit of normal (ULN) in DILIsym is 40 U/L
[a] (9); 2.8% among patients with normal baseline ALT
[b] (8); 6.6% among patients with normal baseline ALT


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

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

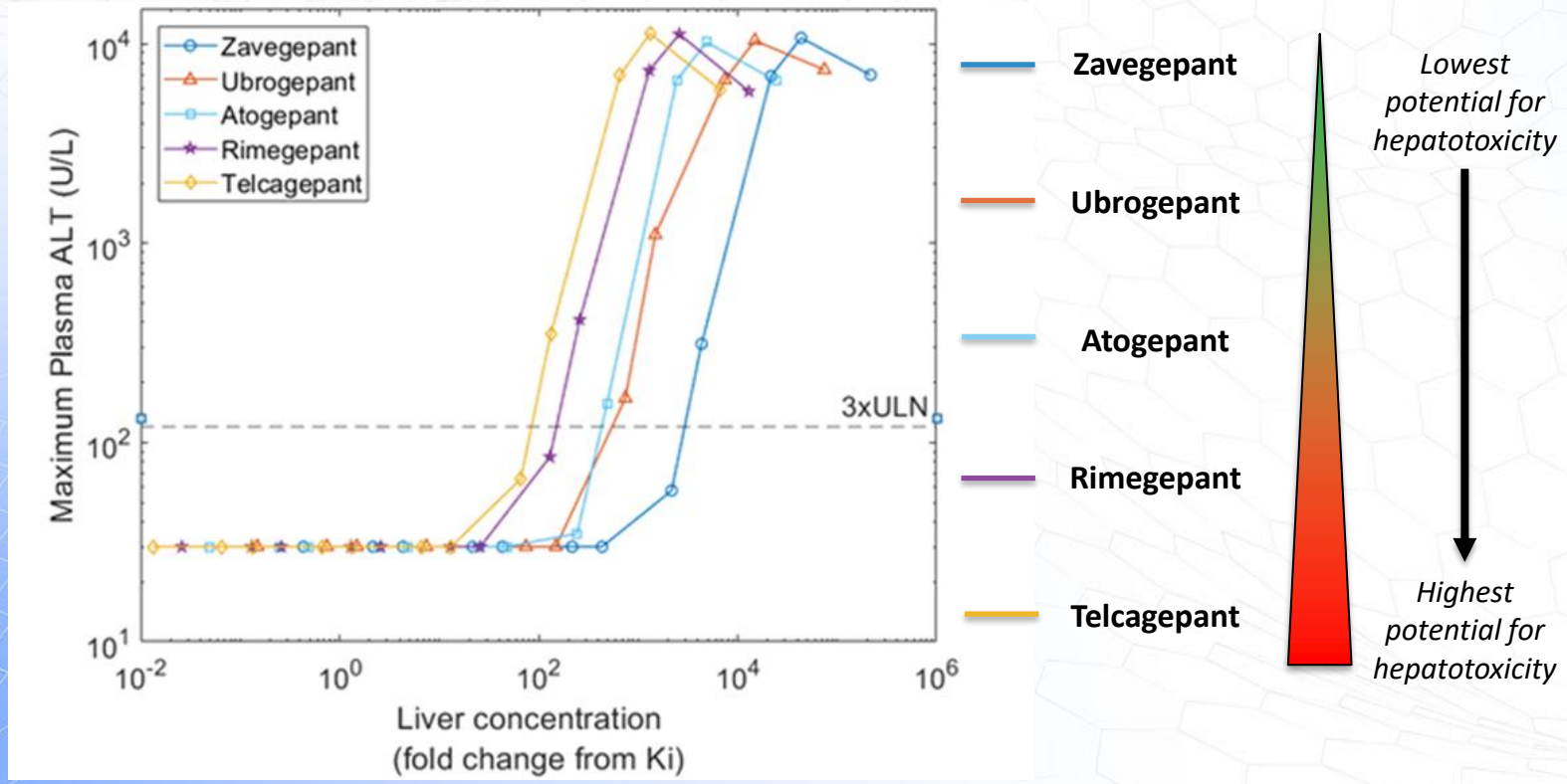
Jeffrey L. Woodhead[1] · Kyunghee Yang[1] · David Oldach[2] · Chris MacLauchlin[2] · Prabhavathi Fernandes[2] · Paul B. Watkins[3] · Scott Q. Siler[1] · Brett A. Howell[1]

- Liver concentrations were normalized to OATP1B1 IC_{50} values for macrolide antibiotics

SimulationsPlus

APD Module Outputs Reproduce Clinical and Previous DILIsym Simulation Toxicity Rankings: CGRPR Antagonists

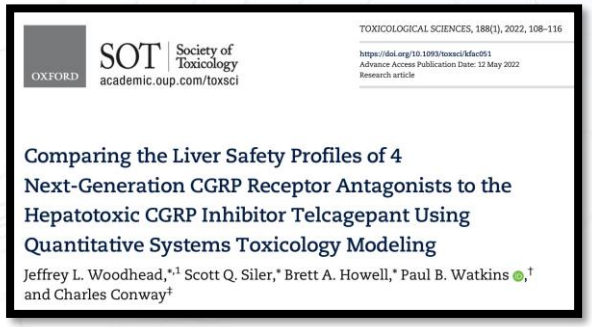
ML Tox Model Predictions



Clinical Data & Previous DILIsym Simulation Results

Table 2. Simulated ALT Elevations in the v4A_1 SimPops for Each of the CGRP Compounds

Compound	Oral Dosing Protocol	Simulated ALT > 3X ULN[a]	Observed ALT > 3X ULN in Clinic
Telcagepant—High ETC	140 mg BID, 12 weeks	17.5% (50/285)	1.9% (5/263)
	280 mg BID, 12 weeks	76.1% (217/285)	3.2% (8/265)
Telcagepant—Low ETC	140 mg BID, 12 weeks	0.0% (0/285)	1.9% (5/263)
	280 mg BID, 12 weeks	7.72% (22/285)	3.2% (8/265)
Rimegepant	75 mg QD, alternate day dosing, 14 total doses	0.35% (1/285)	—
	75 mg QD, 5 days on, 1 day off, 25 total doses	0.7% (2/285)	—
	75 mg QD, daily dosing for 25 days, 25 total doses	1% (3/285)	—
Zavegepant	750 mg oral QD, 25 days, 25 total doses	0.0% (0/285)	
	75 mg oral QD, 25 days, 25 total doses	0.0% (0/285)	
	20 mg IN QD, 25 days, 25 total doses	0.0% (0/285)	
	2 mg IN QD, 25 days, 25 total doses	0.0% (0/285)	
	0.75 mg IV QD, 25 days, 25 total doses	0.0% (0/285)	
	7.5 mg IV QD, 25 days, 25 total doses	0.0% (0/285)	
Atogepant	60 mg BID, 12 weeks	0% (0/285)	
	120 mg BID, 12 weeks	0% (0/285)	
	300 mg BID, 12 weeks	0.3% (1/285)	
	600 mg BID, 12 weeks	10.2% (29/285)	
Ubrogepant	100 mg QD, 15 days	0% (0/285)	
	200 mg QD, 15 days	0% (0/285)	
	500 mg QD, 15 days	1.1% (3/285)	
	1000 mg QD, 15 days	11.6% (33/285)	
	100 mg QD, 25 days	0% (0/285)	
	200 mg QD, 25 days	0% (0/285)	
	500 mg QD, 25 days	1.4% (4/285)	
	1000 mg QD, 25 days	11.6% (33/285)	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academic.oup.com/toxsci
TOXICOLOGICAL SCIENCES, 188(1), 2022, 108–116
https://doi.org/10.1093/toxsci/kfac051
Advance Access Publication Date: 12 May 2022
Research article

Comparing the Liver Safety Profiles of 4 Next-Generation CGRP Receptor Antagonists to the Hepatotoxic CGRP Inhibitor Telcagepant Using Quantitative Systems Toxicology Modeling

Jeffrey L. Woodhead,*,[1] Scott Q. Siler,* Brett A. Howell,* Paul B. Watkins,[†] and Charles Conway[‡]

- Liver concentration were normalized to CGRP receptor Ki values for CGRP receptor antagonists

SimulationsPlus

Workflow: APD Module Enables Efficient Assessment of Hepatotoxic Rankings for In-Class Compounds at Any Stage of Drug Development!

Determine relevant group of compounds to be assessed and gather SMILES or chemical structure for each

Run APD module and export predictions for mito, ROS, BA and PL transporter inhibition toxicity

Use assumptions previously discussed to optimize mito and ROS toxicity parameters for DILIsym use

Extract known EC_{50}, IC_{50}, or Ki values for each compound to determine range of concentrations to be tested

Set up DILIsym SimSingles for each compound at each concentration (with specified liver concentration) with toxicity parameters determined by APD module

Run SimCohorts simulations

Normalize liver concentrations to relevant metric (e.g., EC_{50}) available for all compounds and analyze toxicity biomarker results

Simulations Plus Liver Safety+ Package Contains All Necessary Software for Toxicity Ranking Predictions!

SimulationsPlus

Agenda

- Quantitative systems toxicology (QST) modeling of DILI
  - Liver safety assessment using DILIsym
  - Case study: application of QST modeling in the liver safety assessment of CGRP receptor antagonists
- Integrating QST and machine learning (ML) models for early assessment of hepatotoxic risk
  - Bridging compound structure to DILI mechanisms using ADMET Predictor
  - Application of QST-ML models in rank-ordering liver safety assessment of CGRP receptor antagonists
- Conclusions and perspectives

The QST Model DILIsym Provides More Comprehensive Predictions of DILI Risk than Artificial Intelligence Models

	DILIsym (QST model)	Artificial Intelligence models
Primary methodology	Predict DILI in SimPops based on PBPK predictions of hepatocellular drug (parent + metabolites) and primary cellular mechanisms of DILI	Predict DILI based on in vitro signals and correlations with known DILI-causing drugs
Based on compounds that do and do not cause DILI	DILIsym has been used to characterize compounds that do and do not have DILI liabilities, providing a balanced predictiveness	AI models are unlikely to include many (if any) negative controls because they are relying on database of clinical DILI cases
Mechanistic contributions as identified with in vitro assays	Compounds predicted to have DILI risk with DILIsym include contributions from multiple mechanisms, some of which are synergistic	AI models cannot account for synergistic, mechanistic interactions underlying DILI risk
Include liver to plasma ratio within predictions	DILIsym can be used to identify clinically relevant, safe dosing paradigms thanks to the inclusion of hepatocyte drug (parent + metabolites) concentrations in the predictions	AI models cannot account for differences in media and intracellular drug concentrations, where hepatocyte concentrations are frequently much greater than extracellular
Ability to identify susceptible patients	The use of SimPops to account for inter-patient variability and disease status provides ability to identify individuals potentially susceptible to DILI	AI models do not account for inter-patient differences or disease status
User to understand basis for predictions	DILIsym (and most QST models) provides the ability to quantify the contributions from various mechanisms at clinically relevant doses	AI models appear to be a black box to users, with limited to no ability to provide a mechanistic basis for predictions of DILI risk