



# Machine Learning ADMET Predictor Workflow for DILIsym Use Enables Earlier, Higher Throughput Use

ACT 2024 Lunch and Learn!

Monday, November 18, 2024



# Session Topics

- *Simulations Plus: Who We Are, and What We Do*
  - *Overview*
  - *News and Events*
  - *DILIsym Case Studies*
- **NEW! Liver Safety+ Package**
  - *Machine Learning ADMET Predictor Workflow for DILIsym Use Enables Earlier, Higher Throughput Use*
- *Questions Please!*

# Who We Are

NASDAQ: SLP



-  **Cheminformatics (CHEM)**  
Software & Services
-  **Physiologically Based Pharmacokinetics (PBPK)**  
Software & Services
-  **Clinical Pharmacology & Pharmacometrics (CPP)**  
Software & Services
-  **Quantitative Systems Pharmacology (QSP)**  
Software & Services
-  **Adaptive Learning & Insights (ALI)**  
Software & Services
-  **Medical Communications (MC)**  
Software & Services



>280

Pharmaceutical, biotechnology, chemicals, cosmetics, & consumer goods companies in the U.S., Europe, Asia, and South America

200+

Employees Worldwide

>25 yrs.

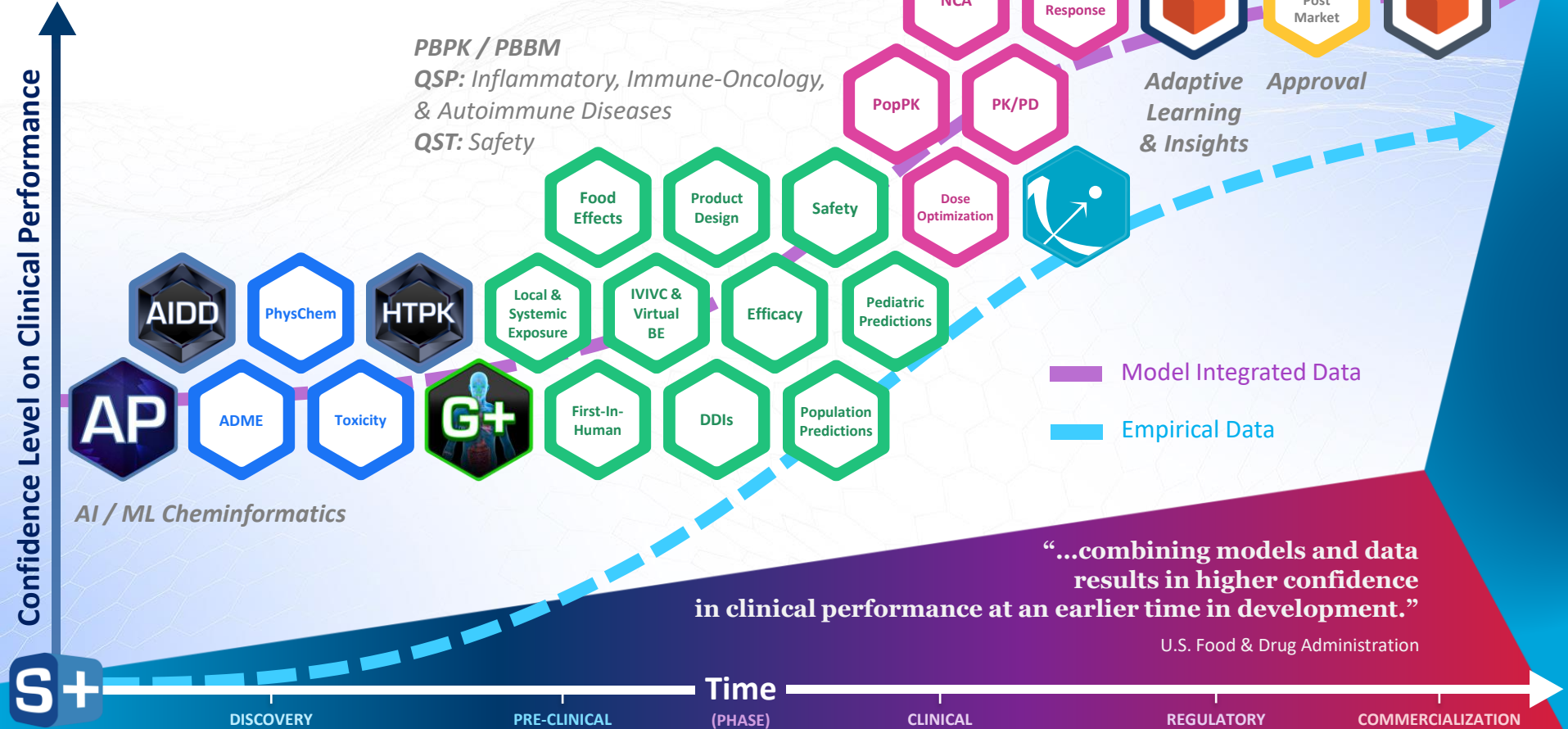
Established In 1996

# Complementary Solutions

Decrease development uncertainty, cost, time, and failure rates.

Clinical Pharmacology & Pharmacometrics

Medical Communications





# Simulations Plus Has the World's Largest Library of Platform QSP and QST Models to Predict Disease and Injury Outcomes



## QST: Liver and Kidney Safety

- Drug induced acute kidney injury
- Drug induced liver injury (DILI)



## QSP: Metabolic Diseases

- Non-alcoholic fatty liver disease / steatohepatitis (NAFLD/NASH or MASH)
- Obesity



## QSP: Immuno-Oncology

- Acute myeloid leukemia (AML)
- Diffuse large B-cell lymphoma (DLBCL)
- Multiple myeloma (MM)
- Myelofibrosis
- Solid tumor (NSCLC, melanoma, prostate cancer, colorectal cancer, ovarian cancer, endometrial cancer)







## QSP: Inflammation and Immunology (including fibrotic diseases)

- Asthma/COPD (*in development*)
- Atopic dermatitis (AD)
- Crohn's disease (CD)
- Dermatomyositis
- Dysregulation of alternative and terminal pathways (AP, TP) of complement
- Idiopathic pulmonary fibrosis (IPF)
- Interstitial lung disease (ILD) associated with systemic sclerosis
- Multiple sclerosis (MS, *in development*)
- Psoriatic arthritis (PSA)
- Psoriasis (PSO)
- Rheumatoid arthritis (RA)
- Systemic lupus erythematosus (SLE including CLE)
- Ulcerative colitis (UC)
- Uric acid disposition in gout
- Wound healing after myocardial infarction (MI)

# What's It Like to Work With Us?

We believe the relationships we build with our clients are critical for mutual success

**A highly interactive collaboration not only allows us to deliver results as quickly as possible, but also ensures a higher quality deliverable**

-  Regular interactions ensure the relevancy of results as the knowledge-base continues to evolve
-  Transparency provided by progress updates eliminates surprises
-  Synergies come from a shared knowledge-base of expertise and experience
-  Involvement, participation, and input from stakeholders outside of M&S is welcome



Legislation

Examples: hr5, sres9, "health care"



MORE OPTIONS

Home > Legislation > 117th Congress > S.5002

Citation | Subscribe | Share/Save | Site Feedback

## S.5002 - FDA Modernization Act 2.0

117th Congress (2021-2022)

BILL

Hide Overview

Sponsor: [Sen. Paul Rand \(R-KY\)](#) (Introduced 09/29/2022)

Latest Action: House - 09/29/2022 Held at the desk. ([All Actions](#))

Tracker:

Introduced

Passed Senate

More on This Bill

[CBO Cost Estimates \(0\)](#)

Subject — Policy Area:

Health

[View subjects >>](#)

Summary (2)

Text (2)

Actions (4)

Titles (3)

Amendments (0)

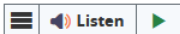
Cosponsors (11)

Committees (0)

Related Bills (2)

### Summary: S.5002 — 117th Congress (2021-2022)

[All Information](#) (Except Text)



There are 2 summaries for S.5002.

Passed Senate (09/29/2022)

[Bill summaries](#) are authored by [CRS](#).

Shown Here:

Passed Senate (09/29/2022)

FDA Modernization Act 2.0

This bill authorizes the use of certain alternatives to animal testing, including cell-based assays and computer models, to obtain an exemption from the Food and Drug Administration to investigate the safety and effectiveness of a drug.

The bill also removes a requirement to use animal studies as part of the process to obtain a license for a biological product that is biosimilar or interchangeable with another biological product.

Physiologic  
Pharmac  
Analyses —  
Cont  
Guidance fo

FDA Guidance

2018

document on the  
ation, validation and  
Physiologically Based  
models for regulatory  
purposes

OECD

ance Document

2021

ulationsPlus

# Breaking News...

June 20, 2023 8:00 AM

## Simulations Plus Acquires Immunetrics to Expand its Immunology and Oncology Drug Development Capabilities

*Acquisition increases breadth and depth of QSP expertise and range of therapeutic applications*

Simulations Plus, Inc. (Nasdaq: SLP) ("Simulations Plus"), a leading provider of modeling and simulation software and services for pharmaceutical safety and efficacy, today announced the acquisition of Immunetrics, Inc. ("Immunetrics"), a modeling and simulation company focused on

April 4, 2024 8:30 AM

## U.S. FDA Renews DILIsym® Software Licenses for 7th Year

*Predicting DILI risk supports informed decision-making regarding drug evaluations and approvals*

June 12, 2024 8:00 AM

## Simulations Plus Acquires Pro-ficiency, Creating One-of-a-Kind Platform Spanning the Drug Development Continuum

*Acquisition doubles the Company's TAM to \$8 billion*

July 30, 2024 8:30 AM

## Simulations Plus Releases ADMET Predictor® Version 12

*Enhancements in key models power HT-PBPK simulations and AI-driven drug design with unprecedented performance and accuracy*

Simulations Plus, Inc. (Nasdaq: SLP) ("Simulations Plus"), a leading provider of biosimulation, simulation-enabled performance and intelligence solutions, and medical communications to the biopharma industry, today announced the release of version 12.0 of ADMET Predictor® (AP12), its flagship machine learning (ML) modeling platform for the discovery, design, and optimization of new molecules.

AP12 includes:

- **Enhanced Models** : New and expanded models offer greater predictive accuracy, with an average 30% increase in training set sizes, for microsomal and hepatocyte clearance, protein binding, biorelevant solubilities, MDCK-LE/PAMPA permeability, and more.
- **High-Throughput Pharmacokinetics (HTPK)** : New options for solution dosing, adjusted free fraction outputs, and species-specific simulations enhance the flexibility and precision of HTPK studies.
- **Artificial Intelligence-Driven Drug Design (AIDD)** : Integration of 3D shape matching and tissue sensitivities (based on tissue Kp values) as new objectives, facilitating innovative lead optimization processes.
- **New DILI Module** : Introduction of the first drug-induced liver injury (DILI) endpoint models to support high-throughput (HT) DILIsym® predictions in early drug development.
- **Boosted ANN Regression Models** and added 37 new descriptors in ADMET Modeler™.
- **General Usability and Informatics Improvements**.

February 15, 2024 8:30 AM

## Simulations Plus Extends Collaboration with Major Toxicology Research Agency

*Research project with NIEHS includes focus on qualification of in silico methods for prioritization, assessment of risk, and identification of safety margins for chemical use*

May 15, 2024 8:30 AM

## Simulations Plus Releases GastroPlus® X, The Next Generation PBPK/PBBM Modeling & Simulation Software

*Redesigned platform offers ease-of-use, enhanced software engineering, and significant productivity gains for users*

July 11, 2024 8:30 AM

## Simulations Plus Announces New Research Project with the International Collaboration on Cosmetics Safety

*Objective to define best practices for the use of novel PBK modeling strategies to support animal-free safety assessment of new chemicals*

August 1, 2024 8:30 AM

## Simulations Plus Releases DILIsym® X

*Updated quantitative systems toxicology (QST) software investigates and predicts drug-induced liver injury (DILI)*

Simulations Plus, Inc. (Nasdaq: SLP) ("Simulations Plus"), a leading provider of biosimulation, simulation-enabled performance and intelligence solutions, and medical communications to the biopharma industry, has released the latest version of its flagship quantitative systems toxicology (QST) platform, DILIsym® version X.



# Upcoming Events

<p><b>NOV 18</b></p> <p>Webinars</p> <p><b>New Features of the IVIVC Module on the GPX™ Platform</b></p> <p>Nov. 18th, 2024 3:00- 4:00 pm BRT Online</p>	<p><b>NOV 26</b></p> <p>Live Workshops, Scientific Meetings</p> <p><b>PKUK Pre-Conference Workshop: Special Populations and DDI in GastroPlus® X</b></p> <p>Nov. 26th, 2024 9:00 am - 4:00 pm GMT Copplid Beech Hotel, Bracknell UK</p>	<p><b>NOV 27</b></p> <p>Scientific Meetings</p> <p><b>PKUK 2024</b></p> <p>Nov. 27th - 29th, 2024 All Day Copplid Beech Hotel, Bracknell UK</p>	<p><b>DEC 3</b></p> <p>Live Workshops</p> <p><b>Complimentary Introduction to GPX™</b></p> <p>Dec. 3rd, 2024 8:00 am - 12:00 pm EST Online</p>	<p><b>DEC 9</b></p> <p>Live Workshops</p> <p><b>GastroPlus® X Immersive Experience Workshop</b></p> <p>Dec. 9th - 13th, 2024 9:00 am - 12:00 pm CET Online</p>	<p><b>DEC 23</b></p> <p>On Demand Workshops</p> <p><b>ADMET Predictor Tutorial Series</b></p> <p>Dec. 23rd, 2024 On Demand (Available Now) Online</p>	<p><b>DEC 24</b></p> <p>On Demand Workshops</p> <p><b>ADMET Predictor® DDLsym™ Module Outputs to Assess Liver Toxicity Rankings...</b></p> <p>Dec. 24th, 2024 On Demand (Available Now)</p>		
<p><b>DEC 25</b></p> <p>On Demand Workshops</p> <p><b>Complimentary Introduction to GPX™</b></p> <p>Dec. 25th - 26th, 2024 On Demand (Available Now) Online</p>	<p><b>DEC 26</b></p> <p>On Demand Workshops</p> <p><b>GastroPlus® X Tutorial Series</b></p> <p>Dec. 26th - 27th, 2024 On Demand (Available Now) Online</p>	<p><b>DEC 27</b></p> <p>On Demand Workshops</p> <p><b>Complimentary Introduction to GastroPlus® for up to v.9.9</b></p> <p>Dec. 27th - 28th, 2024 On Demand (Available Now) Online</p>	<p><b>DEC 28</b></p> <p>On Demand Workshops</p> <p><b>GastroPlus® Introductory Workshop for up to v9.9 (Bundle)</b></p> <p>Dec. 28th - 29th, 2024 On Demand (Available Now) Online</p>	<p><b>DEC 28</b></p> <p>On Demand Workshops</p> <p><b>Introduction to Mechanistic Absorption Modeling (Bundle)</b></p> <p>Dec. 28th - 29th, 2024 On Demand (Available Now) Online</p>	<p><b>DEC 28</b></p> <p>On Demand Workshops</p> <p><b>Introduction to Biologics (Bundle)</b></p> <p>Dec. 28th - 29th, 2024 On Demand (Available Now) Online</p>	<p><b>DEC 28</b></p> <p>On Demand Workshops</p> <p><b>Introduction to IVIVC and Virtual Bioequivalence (Bundle)</b></p> <p>Dec. 28th - 29th, 2024 On Demand (Available Now) Online</p>	<p><b>DEC 28</b></p> <p>On Demand Workshops</p> <p><b>Introduction to PBPK Modeling (Bundle)</b></p> <p>Dec. 28th - 29th, 2024 On Demand (Available Now) Online</p>	
<p><b>DEC 28</b></p> <p>On Demand Workshops</p> <p><b>Introduction to DDI Predictions (Bundle)</b></p> <p>Dec. 28th - 29th, 2024 On Demand (Available Now) Online</p> <p>FIND OUT MORE</p>	<p><b>DEC 30</b></p> <p>On Demand Workshops</p> <p><b>Transdermal Administration (TCAT™) in GastroPlus® On Demand</b></p> <p>Dec. 30th - 31st, 2024 On Demand (Available Now)</p> <p>FIND OUT MORE</p>	<p><b>DEC 30</b></p> <p>On Demand Workshops</p> <p><b>Injectables (IM, SQ, IA) in GastroPlus® Including Biologics and LAIs...</b></p> <p>Dec. 30th - 31st, 2024 On Demand (Available Now)</p> <p>FIND OUT MORE</p>	<p><b>DEC 30</b></p> <p>On Demand Workshops</p> <p><b>Ocular Administration (OCAT™) in GastroPlus® On Demand</b></p> <p>Dec. 30th - 31st, 2024 On Demand (Available Now)</p> <p>FIND OUT MORE</p>	<p><b>DEC 30</b></p> <p>On Demand Workshops</p> <p><b>Oral Cavity Administration (OCCAT™) in GastroPlus® On Demand</b></p> <p>Dec. 30th - 31st, 2024 On Demand (Available Now)</p> <p>FIND OUT MORE</p>	<p><b>DEC 30</b></p> <p>On Demand Workshops</p> <p><b>Pulmonary Administration (PCAT™) in GastroPlus® On Demand</b></p> <p>Dec. 30th - 31st, 2024 On Demand (Available Now) Online</p> <p>FIND OUT MORE</p>	<p><b>DEC 30</b></p> <p>On Demand Workshops</p> <p><b>GastroPlus® ADR - 4 Course Bundle (TCAT™ / OCAT™) / ...</b></p> <p>Dec. 30th - 31st, 2024 On Demand (Available Now) Online</p> <p>FIND OUT MORE</p>	<p><b>DEC 30</b></p> <p>On Demand Workshops</p> <p><b>GastroPlus® ADR - 5 Course Bundle (TCAT™ / OCAT™) / ...</b></p> <p>Dec. 30th - 31st, 2024 On Demand (Available Now) Online</p> <p>FIND OUT MORE</p>	<p><b>JAN 7</b></p> <p>Live Workshops</p> <p><b>Complimentary Introduction to GPX™</b></p> <p>Jan. 7th, 2025 9:00 am - 1:00 pm CET Online</p> <p>FIND OUT MORE</p>

# DILIsym: By the Numbers...

57

Number of biopharmaceutical Sponsors that have engaged DILIsym\*

86

Mechanistic projects simulating liver injury based on in vitro data on mechanisms of toxicity

6

Biomarker fitting projects simulating hepatocyte loss consistent with measured transaminase profiles

50+

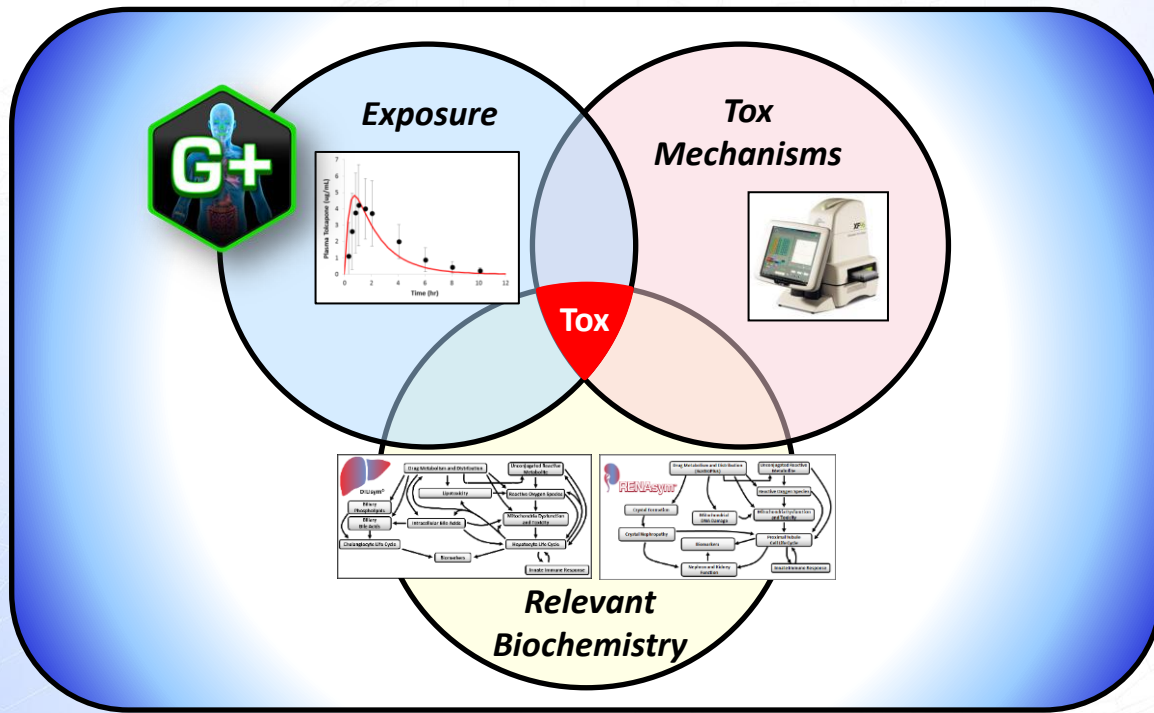
Known regulatory submissions

8

Marketed drugs in which it has been publicly disclosed that DILIsym contributed to liver safety decisions

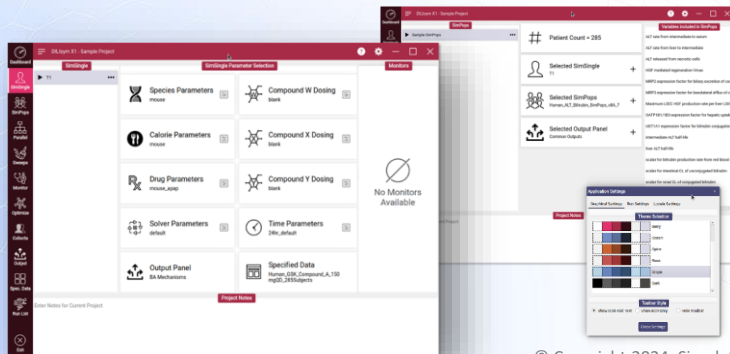
\* Total DILIsym clients, some with multiple projects / compounds

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



# Highlights of DILIsym Version X (DSX)

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





# Recent DILIsym (and BIOLOGXsym) Publications Showcase Various QST Model Applications and R&D

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 114 NUMBER 5 | November 2023

## Assessing Liver Effects of Cannabidiol and Valproate Alone and in Combination Using Quantitative Systems Toxicology

Vinal V. Lakhani<sup>1</sup>, Grant Generaux<sup>1</sup>, Brett A. Howell<sup>1</sup>, Diane M. Longo<sup>1</sup> and Paul B. Watkins<sup>2,3,\*</sup>

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 115 NUMBER 3 | March 2024

## Quantitative Systems Toxicology Modeling Informed Safe Dose Selection of Emvodostat in Acute Myeloid Leukemia Patients

Kyunghee Yang<sup>1,\*</sup>, Ronald Kong<sup>2</sup>, Robert Spiegel<sup>2</sup>, John D. Baird<sup>2</sup>, Kylie O'Keefe<sup>2</sup>, Brett A. Howell<sup>1</sup>

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 114 NUMBER 5 | November 2023

## Quantitative Systems Toxicology Identifies Independent Mechanisms for Hepatotoxicity and Bilirubin Elevations Due to AKR1C3 Inhibitor BAY1128688

Christina Battista<sup>1,\*</sup>, Lisl K.M. Shoda<sup>1</sup>, Paul B. Watkins<sup>2</sup>, Esther Groettrup-Wolfers<sup>3</sup>, Antje Rottmann<sup>4</sup>, Marian Raschke<sup>4</sup> and Grant T. Generaux<sup>5</sup>

frontiers | Frontiers in Pharmacology

Original Research  
PUBLISHED 17 January 2023  
DOI 10.3389/fphar.2022.1085621

## Investigating bile acid-mediated cholestatic drug-induced liver injury using a mechanistic model of multidrug resistance protein 3 (MDR3) inhibition

James J. Beaudoin<sup>1</sup>, Kyunghee Yang<sup>1</sup>, Jeffrey Adiwidjaja<sup>1,2</sup>, Guncha Taneja<sup>1†</sup>, Paul B. Watkins<sup>2</sup>, Scott Q. Siler<sup>1</sup>, Brett A. Howell<sup>1</sup> and Jeffrey L. Woodhead<sup>1\*</sup>

*Int. J. Mol. Sci.* 2023, 24, 9692. <https://doi.org/10.3390/ijms24119692>

## The Combination of a Human Biomimetic Liver Microphysiology System with BIOLOGXsym, a Quantitative Systems Toxicology (QST) Modeling Platform for Macromolecules, Provides Mechanistic Understanding of Tocilizumab- and GGF2-Induced Liver Injury

James J. Beaudoin<sup>1,†</sup>, Lara Clemens<sup>1,†</sup>, Mark T. Miedel<sup>2</sup>, Albert Gough<sup>2</sup>, Fatima Zaidi<sup>3</sup>, Priya Ramamoorthy<sup>3</sup>, Kari E. Wong<sup>3</sup>, Rangaprasad Sarangarajan<sup>3</sup>, Christina Battista<sup>1</sup>, Lisl K. M. Shoda<sup>1</sup>, Scott Q. Siler<sup>1</sup>, D. Lansing Taylor<sup>2</sup>, Brett A. Howell<sup>1</sup>, Lawrence A. Vernetti<sup>2,\*</sup> and Kyunghee Yang<sup>1,\*</sup>

XENOBIOTICA

2024, VOL. 54, NO. 7, 401–410

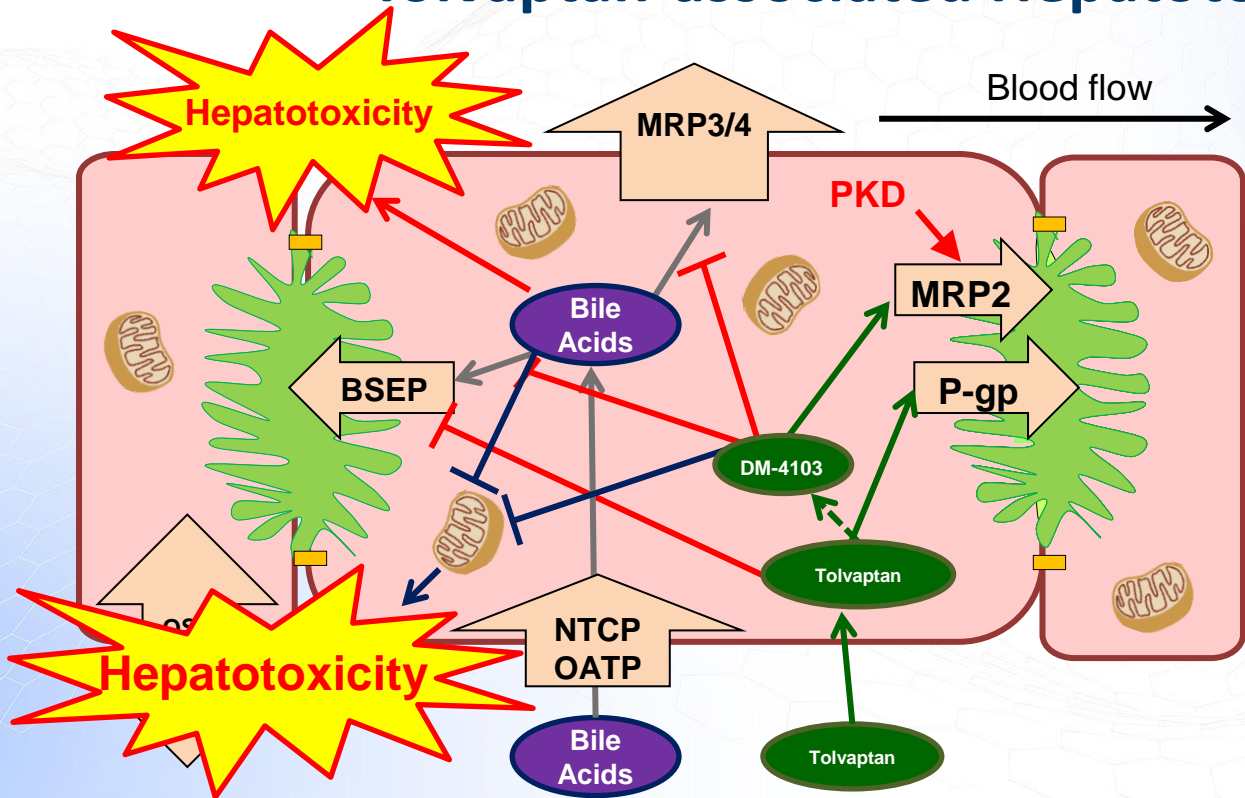
<https://doi.org/10.1080/00498254.2024.2361027>

## Prediction of the liver safety profile of a first-in-class myeloperoxidase inhibitor using quantitative systems toxicology modeling

Jeffrey L. Woodhead<sup>a</sup>, Yeshi Gebremichael<sup>b</sup>, Joyce Macwan<sup>a</sup>, Irfan A. Qureshi<sup>c</sup>, Richard Bertz<sup>c</sup>, Victoria Wirtz<sup>c</sup> and Brett A. Howell<sup>a</sup>



# Mechanistic Modeling and *In Vitro* Studies of Drug-induced Liver Injury Suggest a Role for Reduced Biliary Efflux in Tolvaptan-associated Hepatotoxicity



CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 109 NUMBER 2 | February 2021

Quantitative Systems Toxicology Modeling Predicts that Reduced Biliary Efflux Contributes to Tolvaptan Hepatotoxicity

James J. Beaudoin<sup>1</sup>, William J. Brock<sup>2</sup>, Paul B. Watkins<sup>1</sup> and Kim L. R. Brouwer<sup>1,2</sup>

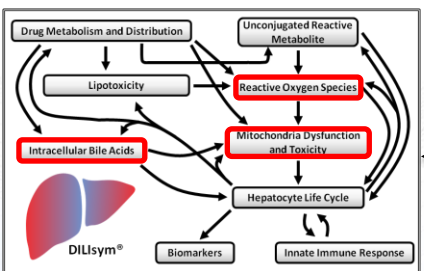
First DILIsym publication via academic license



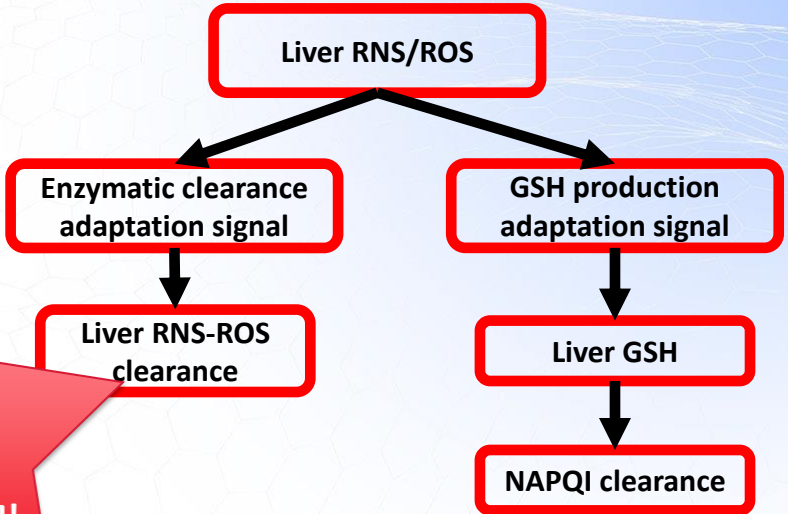
(Mitochondrion)

BSEP (Bile Salt Export Pump)  
 NTCP (Sodium-Taurocholate Cotransporting Polypeptide)  
 MRP (Multidrug Resistance-Associated Protein)  
 OATP (Organic Anion-Transporting Polypeptide)  
 P-gp (P-glycoprotein)  
 OST $\alpha/\beta$  (Organic Solute Transporter  $\alpha/\beta$ )

# QST Modeling of Otenaproxesul Liver Enzyme Elevations Leads to Prediction of Liver Safety for Acute Otenaproxesul Dosing

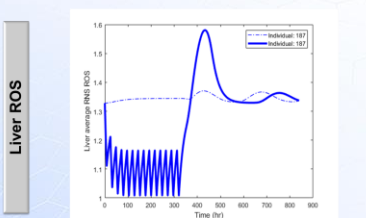


Mechanism	Parameter	Unit	Naproxen Value
BA Transport Inhibition	Inhibition constant for basolateral efflux	$\mu\text{M}$	93
Oxidative Stress	Liver RNS/ROS production rate constant 1	$\text{mL/nmol/hour}$	$2.8\text{e-}05$
Mitochondrial Dysfunction	Coefficient for ETC Inhibition 3	$\mu\text{M}$	347.2
	Max inhibitory effect for ETC inhibition 3	Dimensionless	0.372

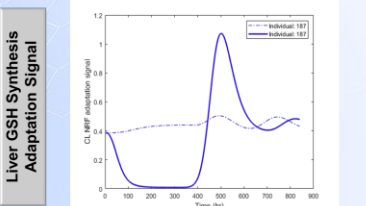


**Poster #P411 Today 5-6:30PM!**

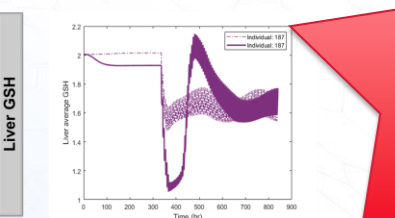
ATB-346 (750 mg QD) with APAP (medium exposure)



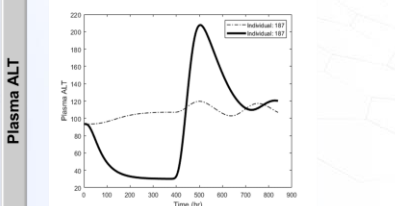
PMW SimPops No Enzymatic Adaptation



ATB-346 (750 mg QD) with APAP (medium exposure)



PMW SimPops No Enzymatic Adaptation



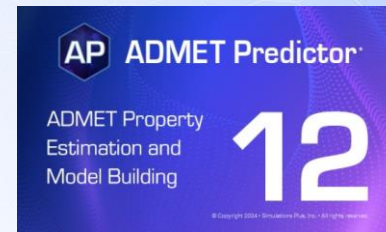
ATB-346 Dose (mg)	Duration (days)	Clinical On-Tx ALT Elevation	Simulated On-Tx ALT Elevation	Clinical ALT Rebound	Simulated ALT Rebound
250 mg QD	7	None Observed	None	Safe	0/261 (0%)
2000 mg QD	1				0/268 (0%)
75 mg QD	21			5% – 10%	7/263 (3%)
250 mg QD	10				163/261 (62%)

# Session Topics

- *Simulations Plus: Who We Are, and What We Do*
  - *Overview*
  - *News and Events*
  - *DILIsym Case Studies*
- **NEW! Liver Safety+ Package**
  - *Machine Learning ADMET Predictor Workflow for DILIsym Use Enables Earlier, Higher Throughput Use*
- *Questions Please!*

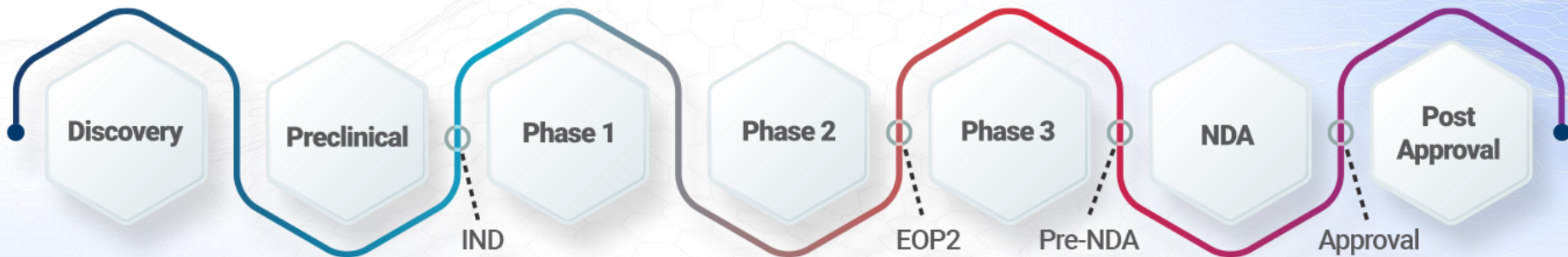
# Simulations Plus Has Developed a Roadmap to Derive an Early Assessment of Hepatotoxic Risk

- New DILIsym module in ADMET Predictor 12 generates outputs that can be used to inform inputs within the quantitative systems toxicology (QST) modeling platform DILIsym
  - Permissive of liver safety assessment during **early** drug discovery efforts!
  - Predictions of the current roadmap 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





# The ADMET Predictor 12 DILIsym (APD) Module Adds Liver Safety Insights to Weight of Evidence Informing Compound Selection



- Liver safety liabilities are commonly identified when a compound enters the clinic, sometimes as late as phase 3 clinical trials, imparting considerable expense and potential delays to drug development
- Historical use of DILIsym, a QST model of drug-induced liver injury, required extensive *in vitro* assay data and PK exposure modeling, making it less amenable for use in early drug discovery
- New APD module empowers DILIsym use at the drug discovery stage, without the need for typical DILIsym toxicity assay data!

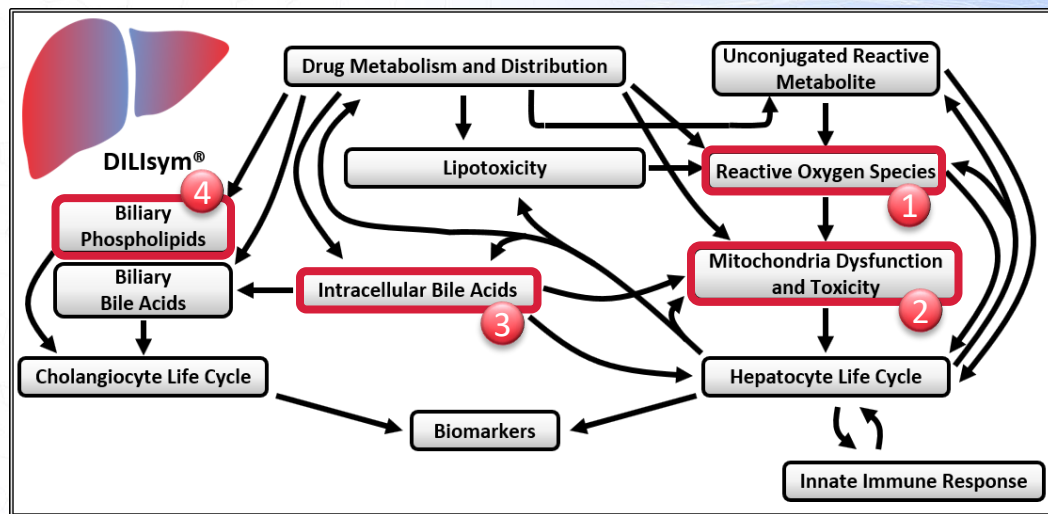




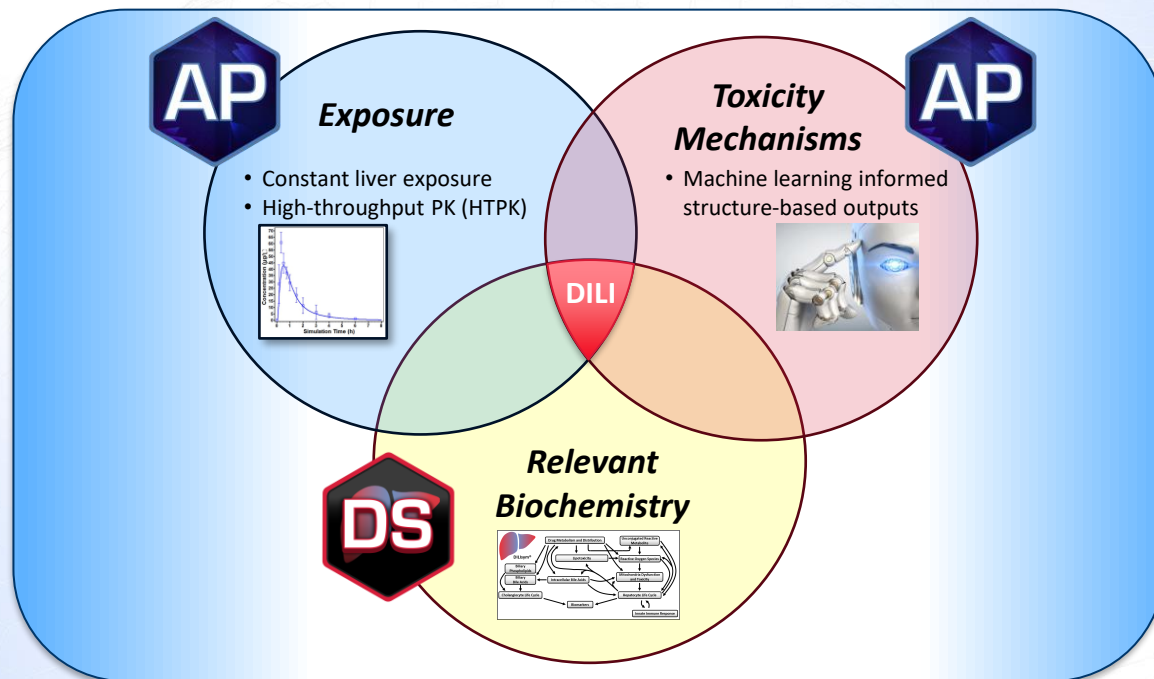
# Predicted Liver Exposure Interacts with Data-Defined Mechanisms of Toxicity in the DILIsym Simulated *In Vivo* Environment

## Mechanisms of toxicity in DILIsym

- 1 Reactive oxygen species (ROS)
- 2 Mitochondrial dysfunction
- 3 Bile acid transporter inhibition
  - Bile salt export pump (BSEP)
  - Multidrug resistance associated protein 3 or 4 (MRP3/MRP4)
  - Sodium-taurocholate cotransporting polypeptide (NTCP)
- 4 Phospholipid transporter inhibition
  - Multidrug resistance protein 3 (MDR3)

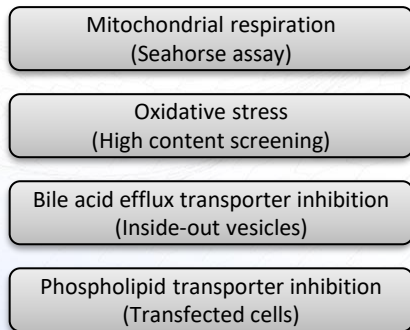


# Liver Safety+ Prediction Package Tailored for Early Discovery Data

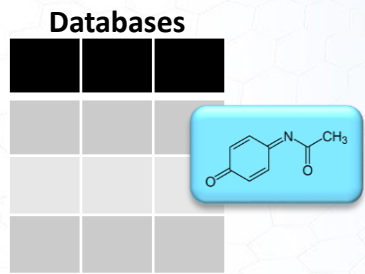


# APD Module Applies Machine Learning to Bridge from Compound Structure to DILIsym

## Compound Library In Vitro Assay Data



## Filtering, Automated Fitting, Translation



## Machine Learning Algorithms

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



# 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

Toxicity Mechanism	APD classification <sup>§</sup> output	APD MEC <sup>†</sup> output	APD AC <sub>50</sub> <sup>‡</sup> output	APD IC <sub>50</sub> <sup>  </sup> output
Mitochondrial dysfunction	✓	✓	✓	—
Reactive oxygen species	✓	✓	✓	—
BSEP inhibition	✓	—	—	✓
MRP3/MRP4 inhibition	✓	—	—	—
MDR3 inhibition	✓	—	—	✓

<sup>§</sup> yes/no prediction for *in vitro* signals

<sup>†</sup> minimum effective concentration (MEC) that significantly crosses vehicle control threshold

<sup>‡</sup> concentration at which 50% maximum effect is observed

<sup>||</sup> concentration at which 50% inhibition is observed



# Import/Load a Chemical Structure (e.g., SMILES) in ADMET Predictor

PubChem Solithromycin (Compound)

### 2.1.4 Canonical SMILES

The Simplified Molecular-Input Line-Entry System (SMILES) is a widely-used line notation for chemical structures. PubChem computes two kinds of SMILES strings for compounds: canonical SMILES (computed from chemical structures devoid of isotopic and stereochemical information), and isomeric SMILES (computed from chemical structures containing isotopic and stereochemical information). This section shows the canonical SMILES of the compound.

Read more at: <https://www.daylight.com/dayhtml/doc/theory/theory.smiles.html>

```
CCC1C2(C(C(=O)C(CC(C(C(=O)C(C=O)O1)(C)F)C)O)C3C(C(CC(O3)C)N(C)C)O)(C)OC)C)N(C(=O)O2)CCCCN4C=C(N=N4)C5=CC(=CC=C5)N)C
```

Computed by OEChem 2.3.0 (PubChem release 2021.10.14)

PubChem

```
Solithromycin.smi
1 CCC1C2(C(C(=O)C(CC(C(C(=O)C(C(=O)O1)(C)F)C)O)C3C(C(CC(O3)C)N(C)C)O)(C)OC)C)N(C(=O)O2)CCCCN4C=C(N=N4)C5=CC(=CC=C5)N)C Solithromycin
```

Structure Files (\*.sd;\*.sdf;\*.mol;\*.  
SD Files (\*.sd;\*.sdf)  
Mol Files (\*.mol)  
RD Files (\*.rdf)  
XTK Files (\*.xtk)  
CTK Files (\*.ctk)  
**SMILES Files (\*.smi)**  
QMD Files (\*.qmd)  
Text Files (\*.txt)  
Modeler DAT Files (\*.dat)  
Structure Files (\*.sd;\*.sdf;\*.mol;\*.rdf;\*.xtk;\*.ctk;\*.smi;\*.qmd;\*.txt;\*.dat)

SMILES field selection

SMILES field: Column 1

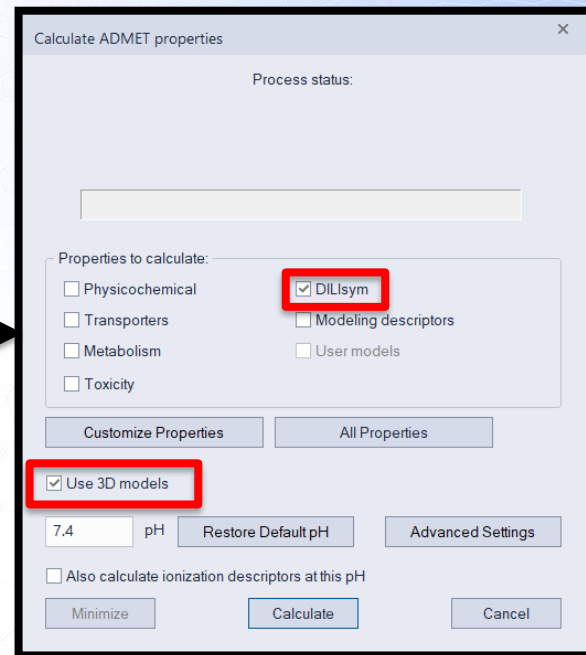
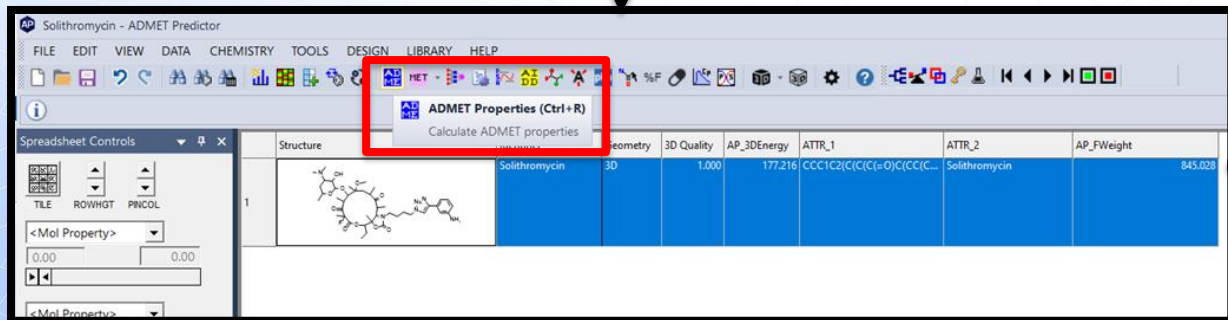
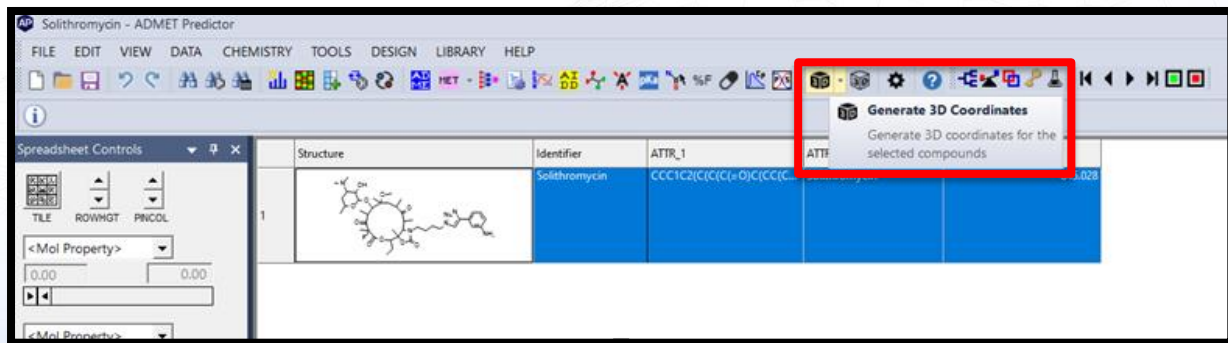
Compound identifier field (optional): Column 2

Load all compound attributes  
 Skip first line: it is a header line  
 Tab delimited, uncheck if whitespace delimited

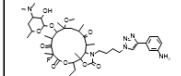
File preview:  
CCC1C2(C(C(=O)C(CC(C(C(=O)C(C=O)O1)(C)F)C)O)C3C(C(CC(O3)C)N(C)C)O)(C)OC)C)N(C(=O)O2)CCCCN4C=C(N=N4)C5=CC(=CC=C5)N)C

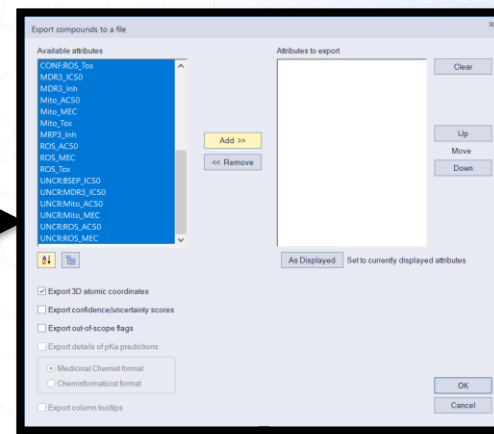
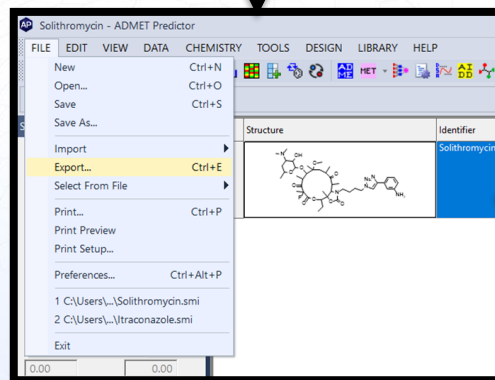
OK Cancel

# Generate 3D Structure/Coordinates and Calculate ADMET: DILIsym Properties



# Review and Export APD Module Results

Structure	Identifier	Geometry	3D Quality	AP_FWeight	BSEP_Inh	BSEP_IC50	MDR3_IC50	MDR3_Inh	Mito_AC50	Mito_MEC	Mito_Toxt	MRP3_Inh	ROS_AC50	ROS_MEC	ROS_Toxt
	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%)



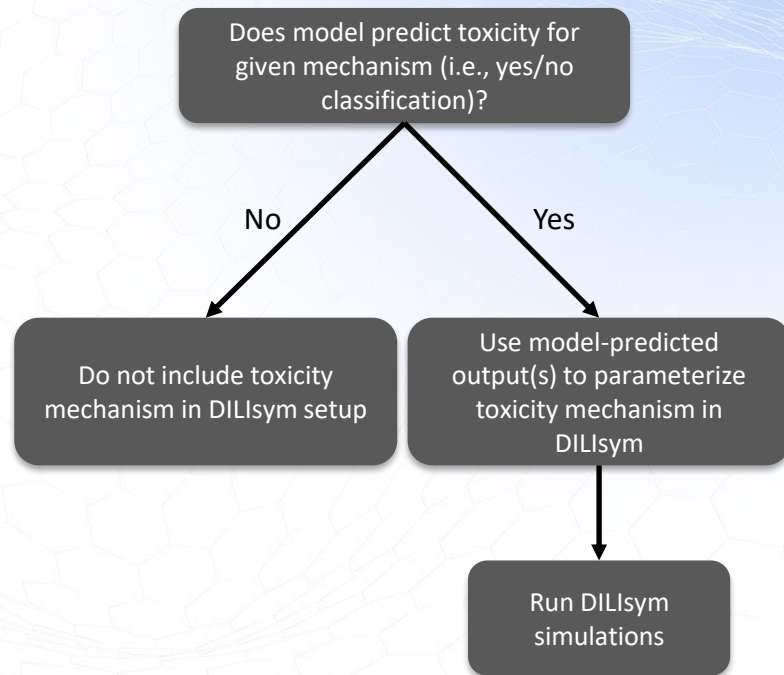
A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
Identifier	Canonical	Canonical	Pair Count	Geometry	3D Quality	AP_3DEnr	AP_FWeight	ATTR_1	ATTR_2	BSEP_IC50	BSEP_Inh	CONF:BSE	CONF:Mitc	CONF:MRI	CONF:ROS
Solithromy	N(C1C(O)(	N(C1C(O)(	0	3D	1	177.2162	845.028	CCC1C2(C	Solithrom	8.860398	Yes (83%)	83	99	93	89

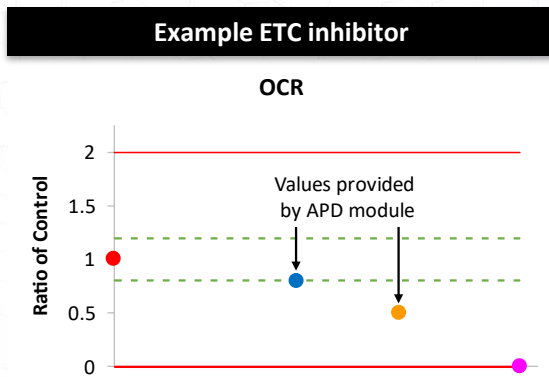
O	R	S	T	U	V	W	X	Y	Z	AA	AB	AC	AD	AE	AF
MDR3_IC50	MDR3_Inh	Mito_AC50	Mito_MEC	Mito_Toxt	MRP3_Inh	ROS_AC50	ROS_MEC	ROS_Toxt	UNCR:BSE	UNCR:MDI	UNCR:Mitc	UNCR:Mitc	UNCR:ROS	UNCR:ROS_MEC	
0.676589	No	71.06435	5.243293	Yes (99%)	Yes (93%)	50.25876	7.297704	Yes (89%)	0.35108	0.680241	0.781383	1.048154	0.341983	0.45848	

# Use and Interpretation of APD Module Classifications and Parameter Values

- Model provides yes/no classification predictions for active toxicity mechanisms based on compound structure
  - Mitochondrial dysfunction (*solithromycin: yes*)
  - ROS production (*solithromycin: yes*)
  - BSEP inhibition (*solithromycin: yes*)
  - MRP3 inhibition (*solithromycin: yes*)
  - MDR3 inhibition (*solithromycin: no*)
- Within current framework, Simulations Plus recommends prioritizing yes/no classification before utilizing the predicted, quantitative toxicity effects (MEC,  $AC_{50}$ ,  $IC_{50}$ ), if available
- The predicted MEC and  $AC_{50}$  values predicted for mitochondrial dysfunction and ROS production can be used for subsequent toxicity parameter estimation in DILIsym
- The predicted BSEP and MDR3  $IC_{50}$  values can be used directly as DILIsym input parameters



# Model-Predicted MEC and AC<sub>50</sub> for Mitochondrial Toxicity Can Be Utilized to Derive DILsym Parameters for Mitochondrial Effects



Toxicity Mechanism	Data Point 1 <sup>*</sup>	Data Point 2 <sup>†</sup>	Data Point 3 <sup>‡</sup>
ETC inhibitor 1 (linear) <u>or</u> ETC inhibitor 4 (saturable)	(0.001 μM, 1)	(MEC μM, 0.8)	(AC <sub>50</sub> μM, 0.5)
<b>Solithromycin points for mito parameterization</b>	<b>Data Point 1<sup>*</sup></b>	<b>Data Point 2<sup>†</sup></b>	<b>Data Point 3<sup>‡</sup></b>
	(0.001 μM, 1)	(5.243 μM, 0.8)	(71.064 μM, 0.5)

- **MEC**: minimum effective concentration that significantly crosses vehicle control threshold
- **AC<sub>50</sub>**: concentration at which 50% maximum effect is observed

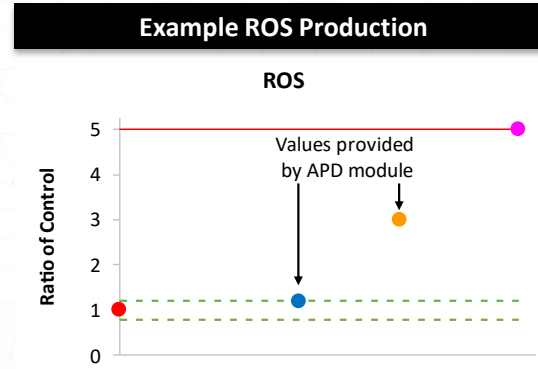
\* Assume concentration of 0.001 μM causes no change in OCR compared to control

<sup>†</sup> Assume MEC causes OCR to drop to 0.8x control for ETC inhibitor

<sup>‡</sup> Assume maximal reduction in OCR is complete inhibition (0x control)



# Model-Predicted MEC and AC<sub>50</sub> for ROS Mechanism Can Be Utilized to Derive DILIsym Parameters for Effect on ROS Production



Toxicity Mechanism	Data Point 1*	Data Point 2†	Data Point 3‡
ROS production 1 (linear) <u>or</u> ROS production 4 (saturable)	(0.001 $\mu$ M, 1)	(MEC $\mu$ M, 1.2)	(AC <sub>50</sub> $\mu$ M, 3)
Solithromycin points for mito parameterization	Data Point 1*	Data Point 2†	Data Point 3‡
	(0.001 $\mu$ M, 1)	(7.298 $\mu$ M, 1.2)	(50.259 $\mu$ M, 3)

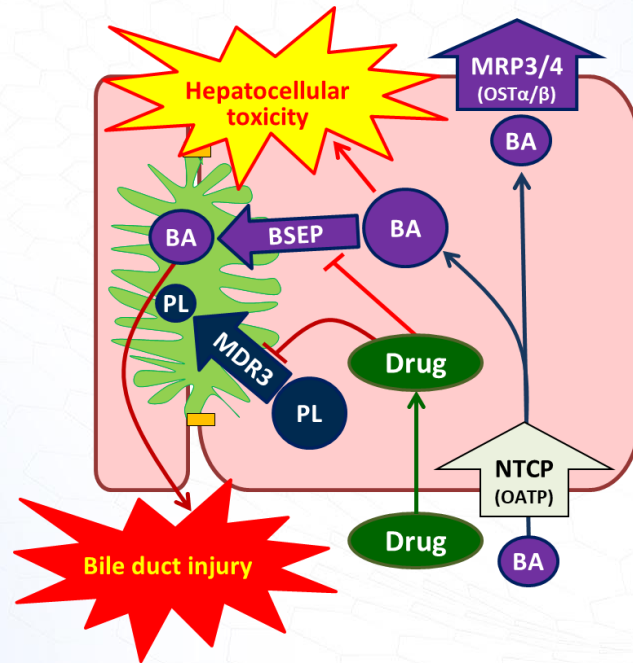
- **MEC**: minimum effective concentration that significantly crosses vehicle control threshold
- **AC<sub>50</sub>**: concentration at which 50% maximum effect is observed

\* Assume concentration of 0.001  $\mu$ M causes no change in ROS compared to control

† Assume MEC causes ROS production to increase 1.2x control

‡ Assume maximal ROS production response is 5x control

# Model-Predicted $IC_{50}$ Values for BSEP and MDR3 Can Be Utilized Directly as DILIsym Parameters for Bile Acid and Phospholipid Transport Inhibition Effects



- $IC_{50}$ : concentration at which 50% inhibition is observed

# 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 [**focus in today's Lunch and Learn**]
    - *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

# Setting up the Drug Parameter Set in DILIsym and Defining Constant Liver Concentrations Using the Specified Data Feature

The image displays the DILIsym X software interface for configuring a drug parameter set. A central dialog box titled "Create New DILIsym SimSingle Configuration" shows the drug name "Solithromycin\_1nM" entered in a text field. Below this, the "Customizing Drug in 'Blank' for 'Solithromycin\_1nM'" window is visible, showing a "Filter By Name" search bar and a grid of 28 parameters available for selection. The parameters include:

- Compound Y liver to blood (dimensionless): 1
- Compound Y oral bioavailability (dimensionless): 1
- Compound Y renal clearance (mL/hour/kg \*0.75): 0
- Compound Y non-renal clearance (mL/hour/kg \*0.75): 0
- Compound Y pKa 1 or pKa base (for zwitter ion) (dimensionless): 0
- Compound Y pKa 2 or pKa acid (for zwitter ion) (dimensionless): 0
- Compound Y switch for calculation of tissue passive CL (switch): OFF
- Compound Y tissue distribution model (switch): OFF
- Compound Y molecular weight (g/mol): 845

The main DILIsym X window shows the configuration for "Pharmacokinetics" and "Compound Y". It includes a "Number of Individuals" slider set to 1, a "Constant Variables" section with "Liver Compound Y" selected, and a "Time Dependent Variables" section. The "13 Available Variables" list includes:

- Blood Compound Y
- Compound W absorbed oral
- Compound X absorbed oral
- Compound Y Excrete into urine
- Compound Y active transport clearance
- Compound Y eliminated by hepatic clearance
- Compound Y eliminated by non-renal pathways
- IP Compound Y bolus
- Intravenous Compound Y bolus
- Liver Compound Y
- Liver sinusoidal blood Compound Y
- Oral Compound Y doses
- total oral and IP and IV Compound Y dosed

At the bottom of the DILIsym X window, there are buttons for "Create Template", "Manage Templates", and "Reset".



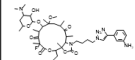
# APD Module Predictions Are Used to Set Up Active Toxicity Mechanisms in DILIsym

## Machine Learning Algorithms

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

ADMET Predictor 12  
DILIsym module

Novel  
Compound  
(Solithromycin)

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\_InM)

Select Molecule: CC1=CC=C(C=C1)C2=CC=CC=C2 CompY

Select Mechanism: CC1=CC=C(C=C1)C2=CC=CC=C2 incRNSRO\_Sproduction1

Customized Variables

Filter By Name...

Molecule / Mechanism	Value	Units
<b>CompY_Mech_InhBAttransport</b>		
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
<b>CompY_Mech_InhETC3</b>		
Coefficient for ETC inhibition 3	0.040746	umol/L
Max inhibitory effect for ETC inhibition 3	0.39355	dimensionless
<b>CompY_Mech_InhETC1</b>		
Coefficient for ETC inhibition 1	2379.481	umol/L
<b>CompY_Mech_incRNSRO_Sproduction4</b>		
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
<b>CompY_Mech_incRNSRO_Sproduction1</b>		
Liver RNS-ROS production rate constant 1	0.053744	mL/mmol/hour

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

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

DILIsym Version 10 - 8/1/2024

**Select Base SimSingle**  
Solithromycin\_5nM

**Select SimPops Data**  
16 patients  
Human ROS apop mito BA v8A.1 Multit16 A  
Create Import Delete

**Select Output Panel**  
Common Outputs

**CPU Thread Count Selector**  
Using 10 of 20 CPU Thread(s)  
Min Low Normal High MAX

**44 parameters**

- ATP decrement necrosis Vmax (1/hour)
- Basal value of mito ETC flux (mmol/hour)
- Basolateral transporter regulation expon
- Body Mass (kg)
- Bulk bile acid basolateral transport Vmax
- Bulk bile acid canalicular transport Vmax (
- Bulk bile acid gut uptake Vmax (nmol/hour)
- Bulk bile acid uptake Vmax (nmol/hour)
- CDCA amidation Vmax (nmol/hour)
- CDCA basolateral transport Vmax (nmol/h
- CDCA canalicular transport Vmax (nmol/h
- CDCA gut uptake Vmax (nmol/hour)
- CDCA uptake Vmax (nmol/hour)
- CDCA-amide basolateral transport Vmax (
- CDCA-amide canalicular transport Vmax (
- CDCA-amide gut uptake Vmax (nmol/hour)
- CDCA-amide uptake Vmax (nmol/hour)
- Canalicular transporter regulation expon
- Caspase-mediated apoptosis scaling cons
- GSH basal level (mmol/L)

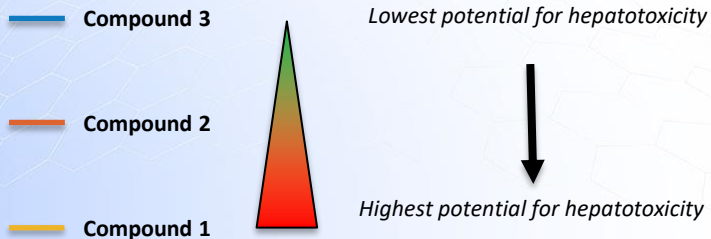
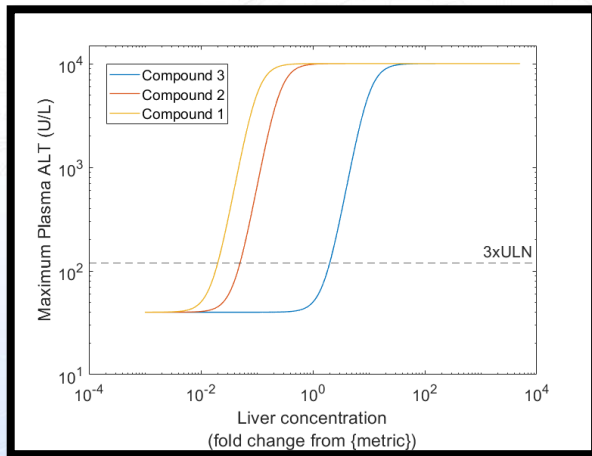
Load Initial Conditions for SimPops

Liver concentration (fold change from IC <sub>50</sub> )*	Liver concentration (nM)	Maximum ALT (U/L)
4.3e-7	0.01	30
2.2e-6	0.05	30
4.3e-6	0.1	30
2.2e-5	0.5	30
4.3e-5	1	30
2.2e-4	5	30
4.3e-4	10	30
2.2e-3	50	35
4.3e-3	100	112
2.2e-2	500	2999
4.3e-2	1000	9510
2.2e-1	5000	6114

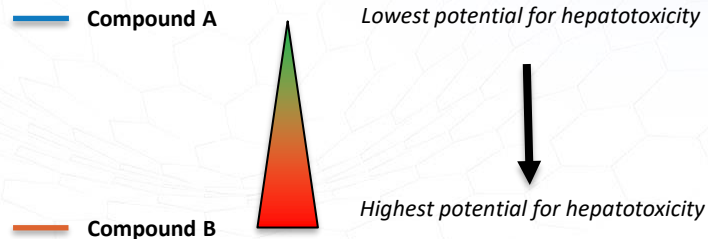
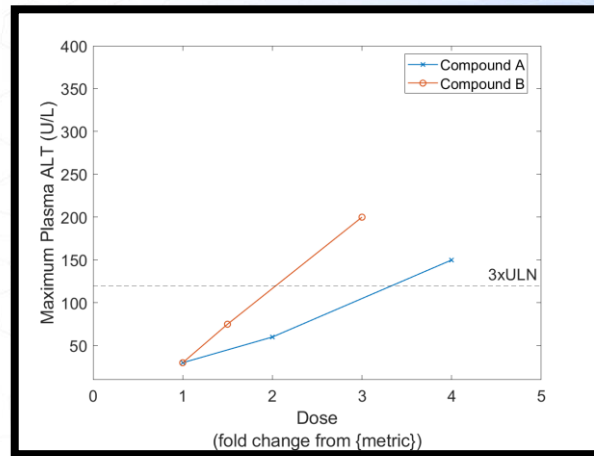
\* For the compounds tested in this class of compounds (macrolide antibiotics), IC<sub>50</sub> values for OATP1B1 were measured consistently for all compounds; IC<sub>50</sub> used as normalization metric in this example

# Interpretation of Toxicity Ranking Results

For drugs early on in development pipeline  
(using constant liver exposure method)



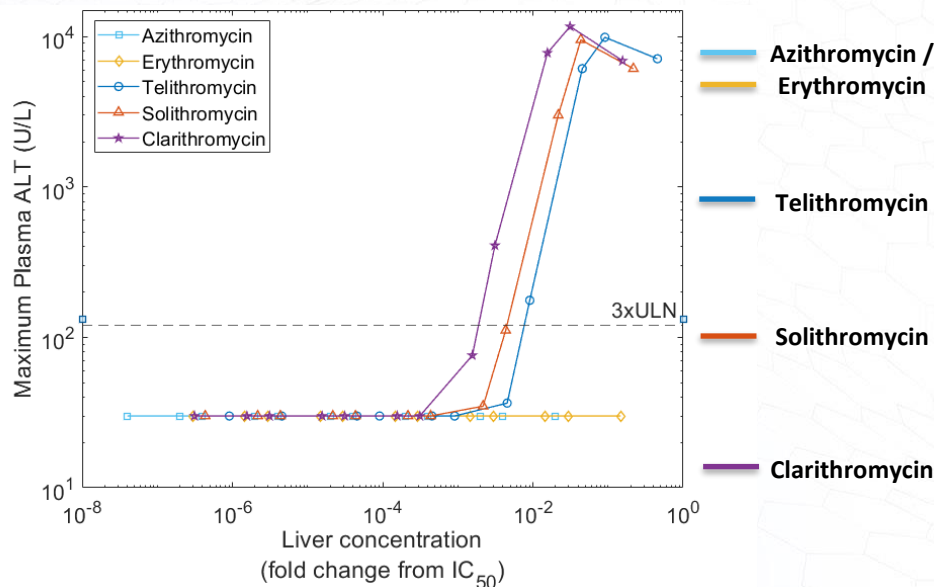
For drugs further along in development pipeline  
(using known liver concentrations or predicted using  
ADMET Predictor HTPK module or PBPK model)



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

## ML Tox Model Predictions

## Clinical Data & Previous DILIsym Simulation Results



Lowest potential for hepatotoxicity

Highest potential for hepatotoxicity

**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% <sup>a</sup> (22/411)	3.9% (11/285)
	IV-to-Oral (CE01-301)	9.1% <sup>b</sup> (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)
	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  
<sup>a</sup>(9); 2.8% among patients with normal baseline ALT  
<sup>b</sup>(8); 6.6% among patients with normal baseline ALT

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

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

RESEARCH PAPER

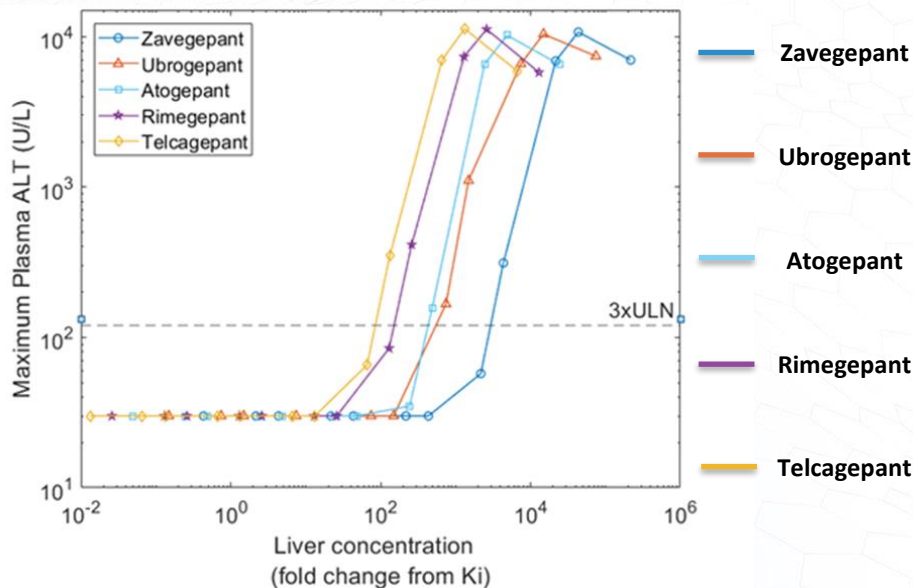
**Analyzing the Mechanisms Behind Macrolide Antibiotic-Induced Liver Injury Using Quantitative Systems Toxicology Modeling**

Jeffrey L. Woodhead<sup>1</sup> · Kyunghye Yang<sup>1</sup> · David Oldach<sup>2</sup> · Chris MacLauchlin<sup>2</sup> · Prabhavathi Fernandes<sup>2</sup> · Paul B. Watkins<sup>3</sup> · Scott Q. Siler<sup>1</sup> · Brett A. Howell<sup>1</sup>



# APD Module Outputs Reproduce Clinical and Previous DILIsym Simulation Toxicity Rankings: CGRP Receptor Antagonists

## ML Tox Model Predictions



Lowest potential for hepatotoxicity

Highest potential for hepatotoxicity

## 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*	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% (8/263)
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% (8/263)
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)	—
Ubrogapant	600 mg BID, 12 weeks	10.2% (29/285)	—
	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)	—
Atogepant	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)	—

- Liver concentration were normalized to CGRP receptor  $K_i$  values for CGRP receptor antagonists

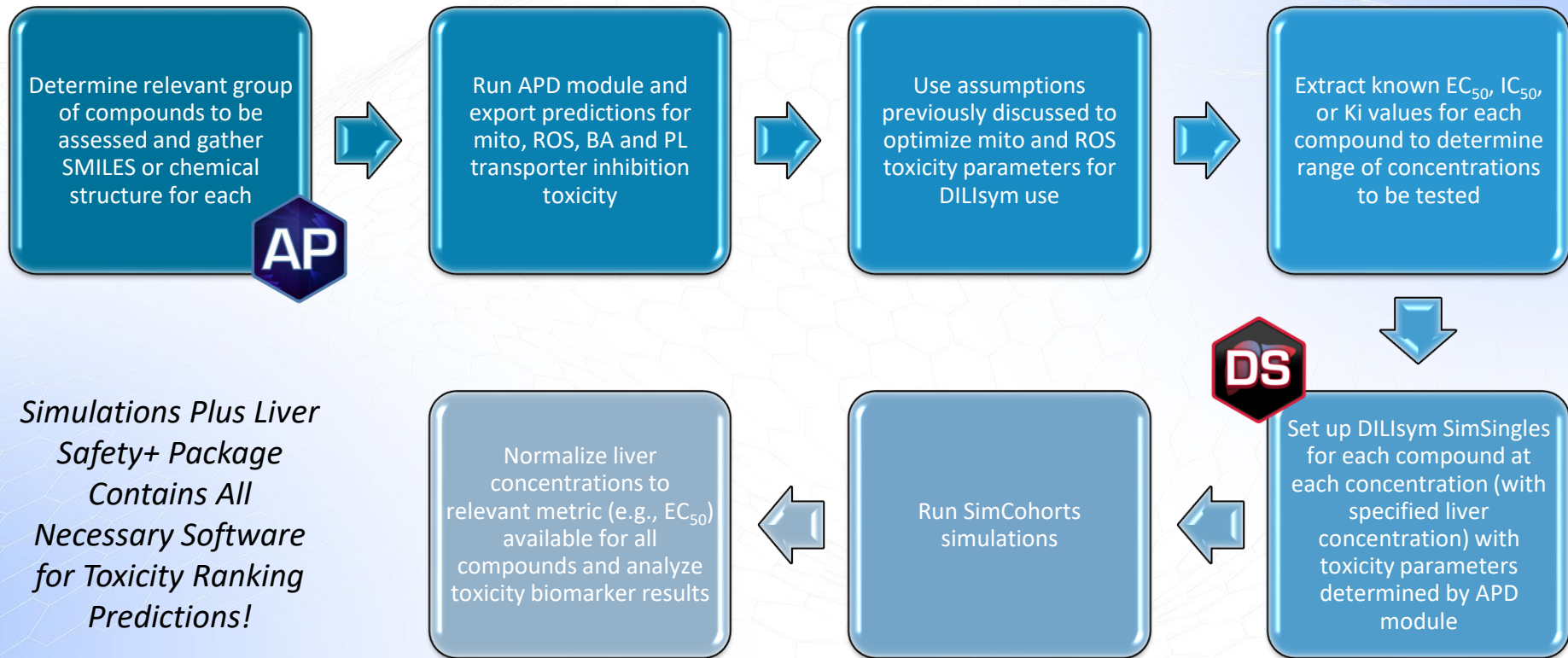
OXFORD | SOT | Society of Toxicology | academic.oup.com/toxsci

TOXICOLOGICAL SCIENCES, 188(1), 2022, 108–116  
<https://doi.org/10.1093/toxsci/kfab11>  
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 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

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



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

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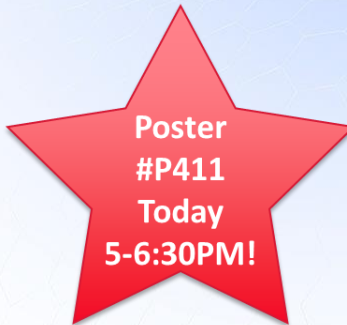
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