
# De-Risking Clinical Hepatotoxicity in Early Drug Discovery

Webinar

**December 3, 2024**

# Webinar Outline

- *Simulations Plus Overview*
- ***NEW! Liver Safety+ Package:*** *De-Risking Clinical Hepatotoxicity in Early Drug Discovery*
  - *Introduction to the ADMET Predictor DILIsym (APD) module*
  - *Development of machine learning models to predict DILIsym toxicity inputs*
  - *How to use the APD module and interpret its predictions for next steps*
  - *How to use APD module predictions in DILIsym and interpret its predictions*
- *Questions*

# 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



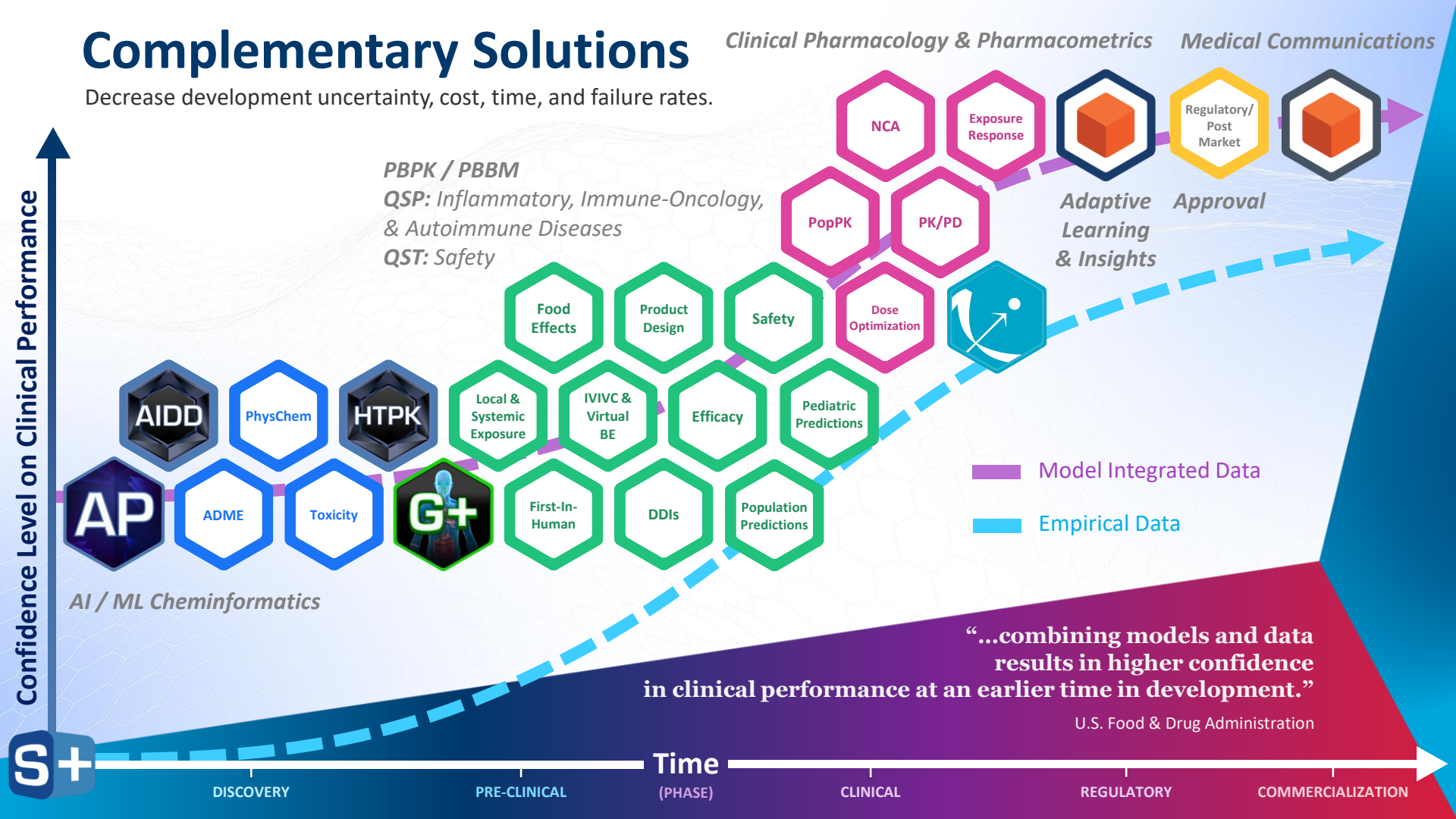


SimulationsPlus

# GastroPlus®/ADMET Predictor®: By the Numbers…

# Complementary Solutions

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




**"...combining models and data results in higher confidence in clinical performance at an earlier time in development."**

U.S. Food & Drug Administration

# 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

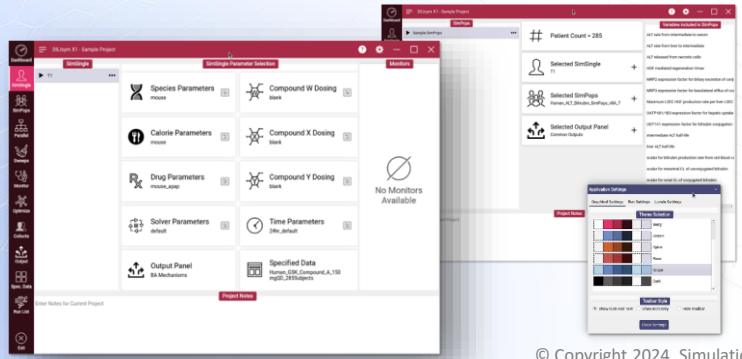
- Acute myeloid leukemia (AML)
- Diffuse large B-cell lymphoma (DLBCL)
- Multiple myeloma (MM)
- Myelofibrosis
- Solid tumor (NSCLC, melanoma, prostate cancer, colorectal cancer, ovarian cancer, endometrial cancer)

## 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)

# 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)

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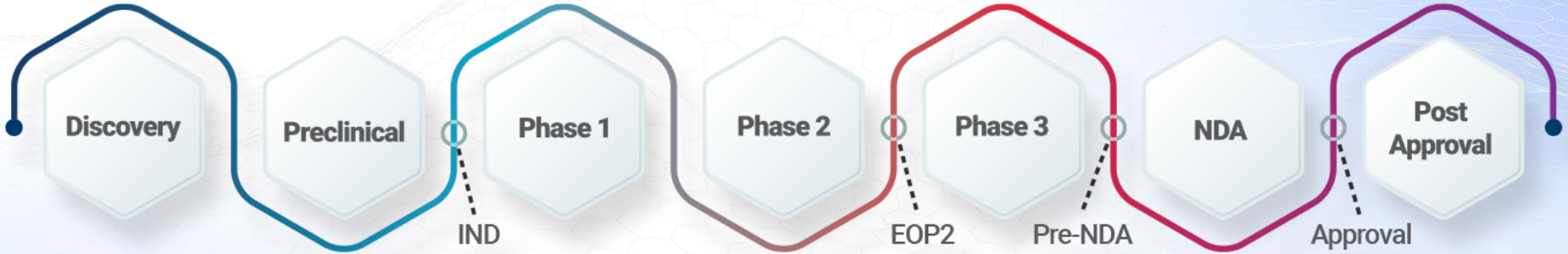
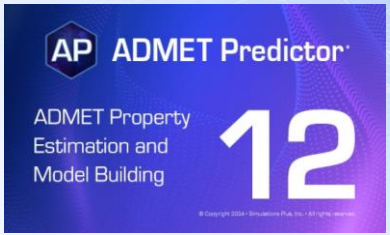
# The ADMET Predictor 12 DILIsym (APD) Module Adds Liver Safety Insights to Evidence Informing Compound Selection



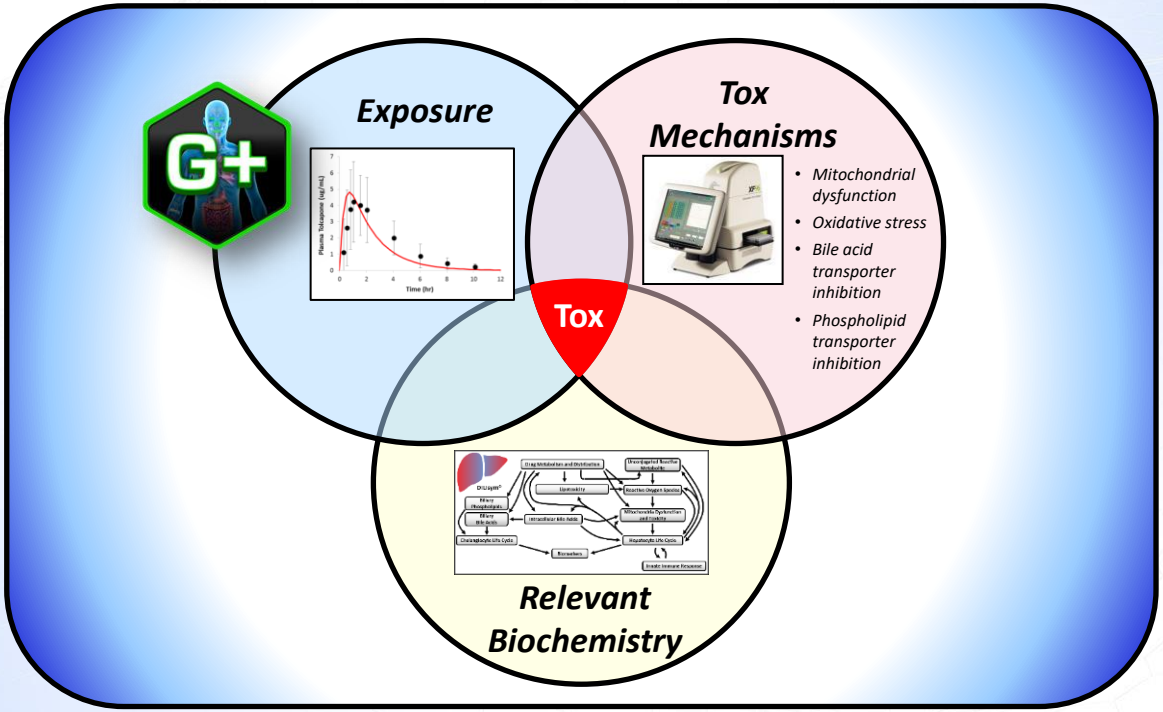

- Liver safety liabilities are commonly identified when a compound enters the clinic, sometimes as late as phase 3 clinical trials, imparting considerable expense and potential delays to drug development
- Historical use of DILIsym, a QST model of drug-induced liver injury, required extensive *in vitro* 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!

# 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



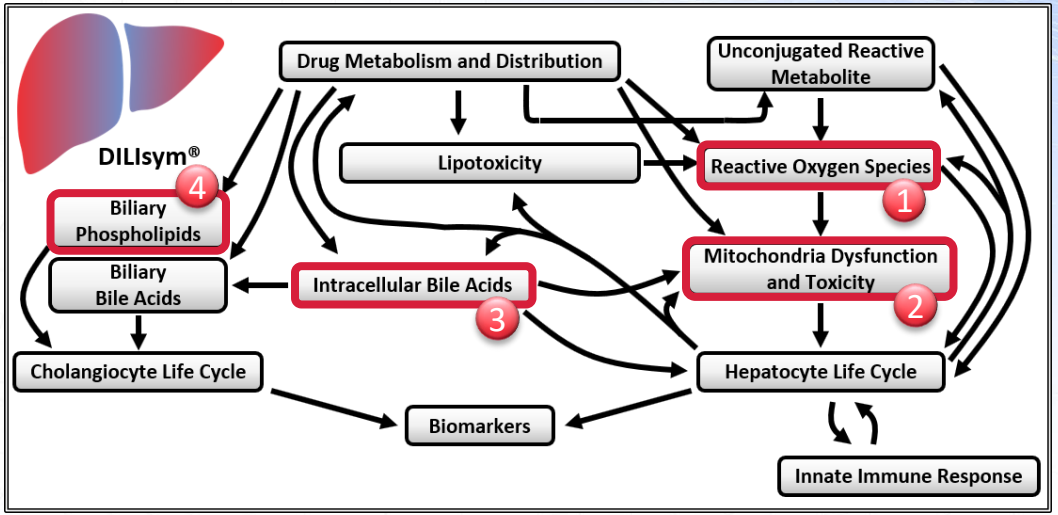

# DILIsym QST Model Predicts Liver Toxicity by Integrating Exposure, Mechanisms, and Inter-Patient Variability



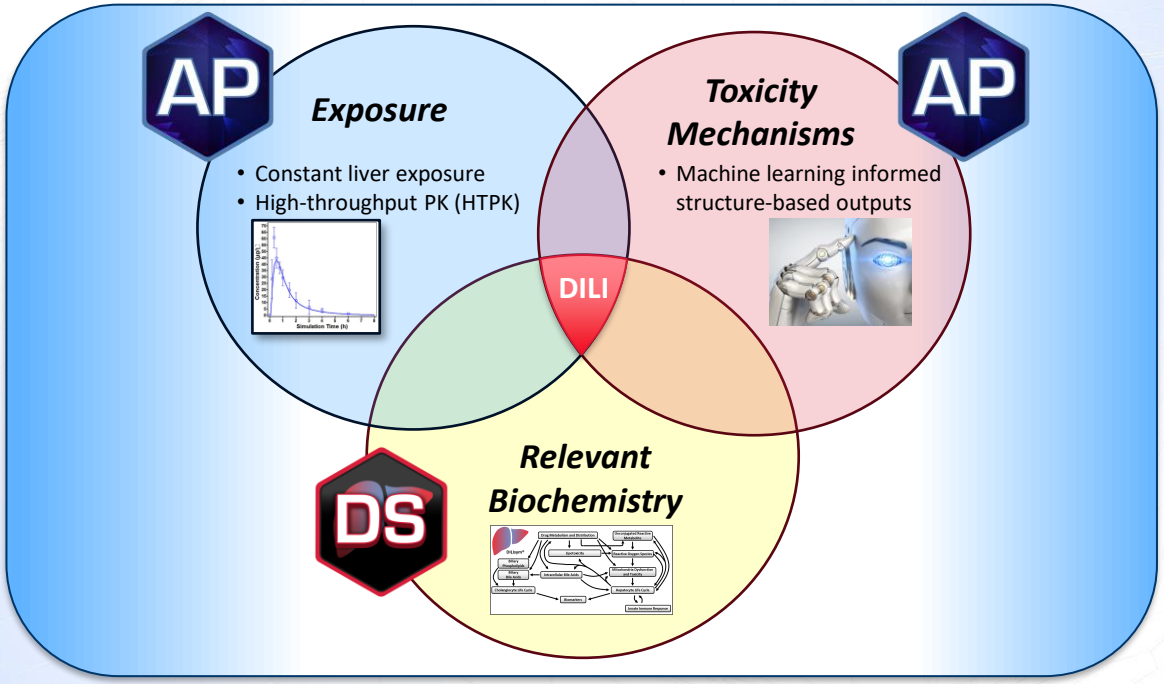
# Predicted Liver Exposure Interacts with Data-Defined Mechanisms of Toxicity in the DILIsym *In Vivo* Environment

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



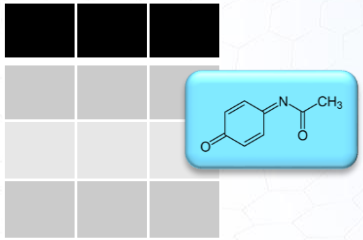
# APD Module Applies Machine Learning to Bridge from Compound Structure to DILIsym

***Compound Library In Vitro Assay Data***

- 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

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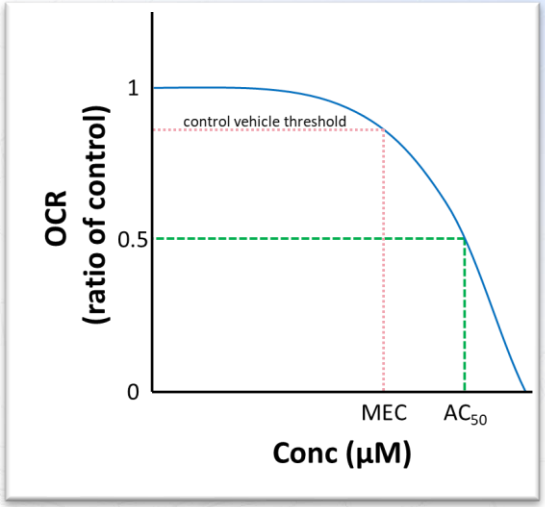
# The ADP Module Contains Three Mitochondrial Dysfunction Models

- 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% |

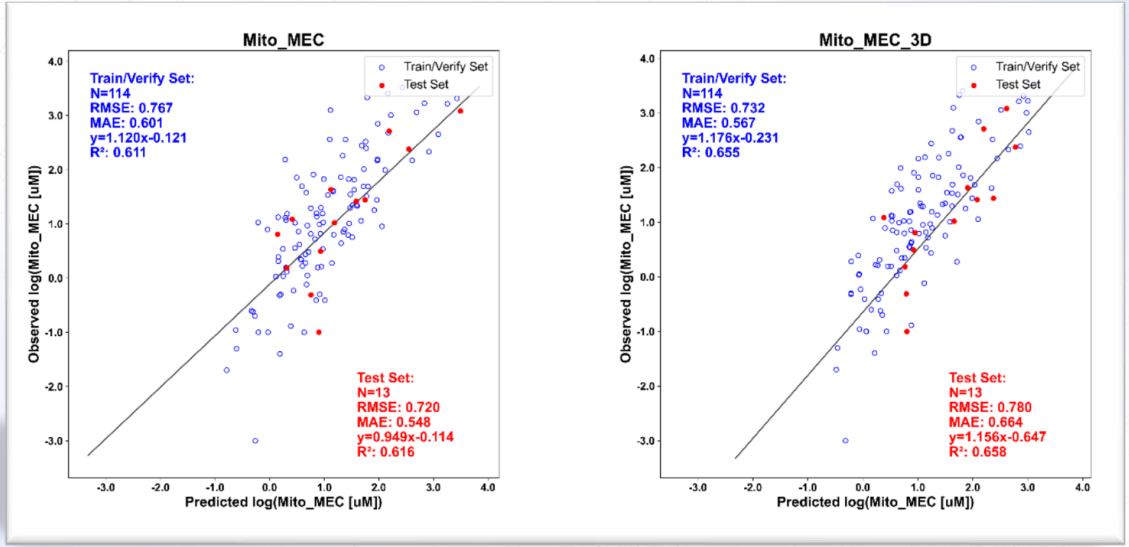
The single mispredicted negative from the test set is fenclozic acid, a compound that was withdrawn from the market due to jaundice




ETC inhibition with a complete knockdown of OCR at high concentrations

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

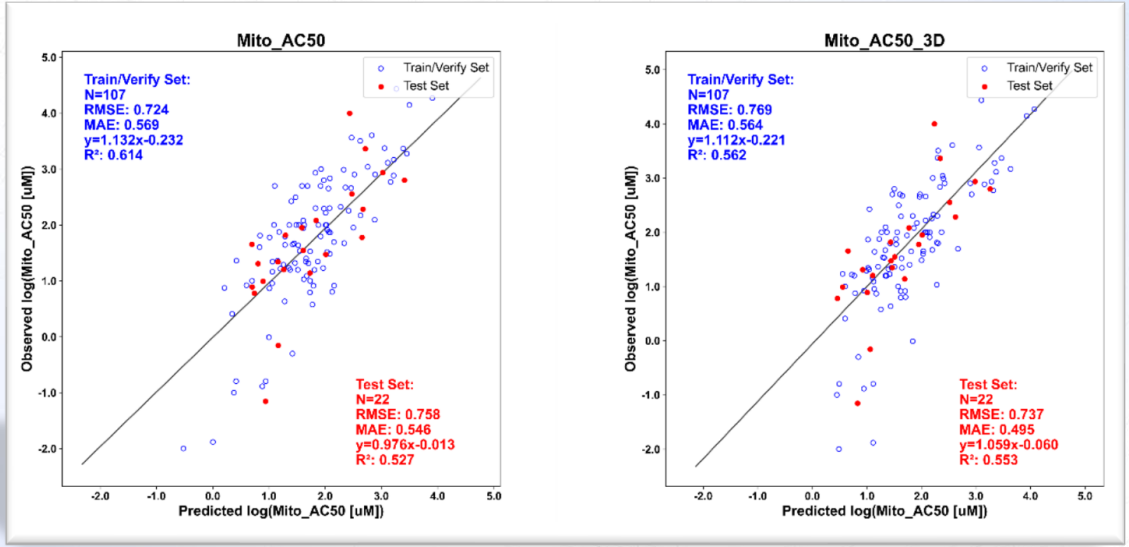
- The Mito_MEC dataset contains 127 compounds with 13 (~10%) in the test set
- The most active compound is rotenone, with an observed MEC value of 0.001 µM




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% |

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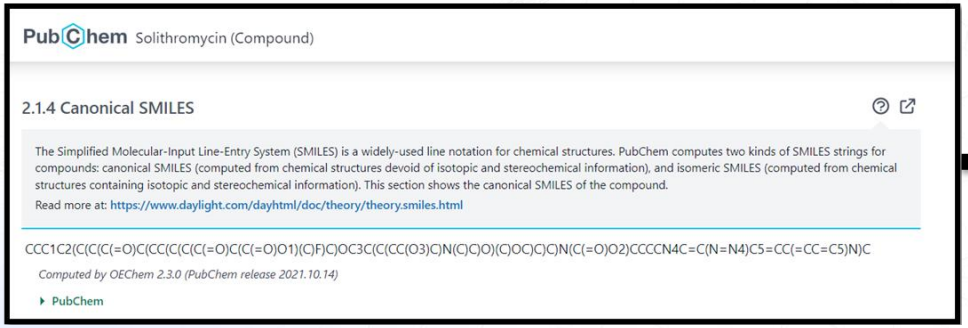
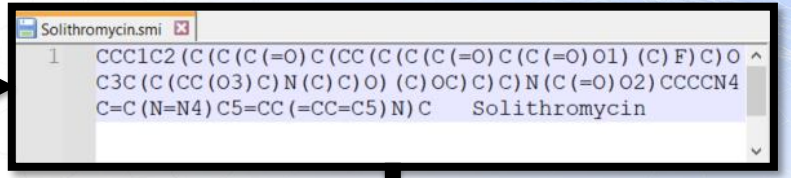
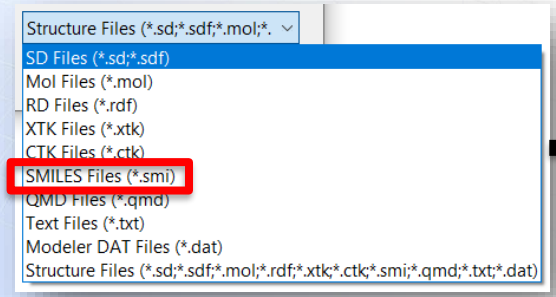
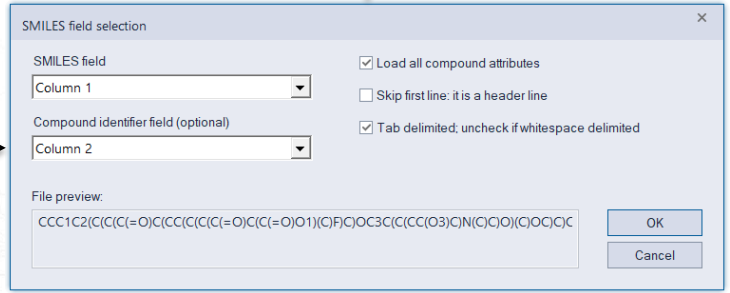
# Import/Load a Chemical Structure (e.g., SMILES) in ADMET Predictor

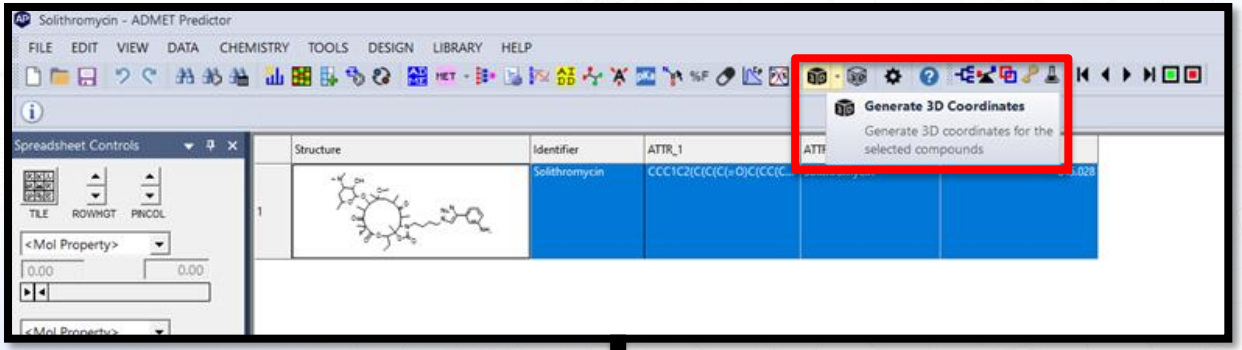


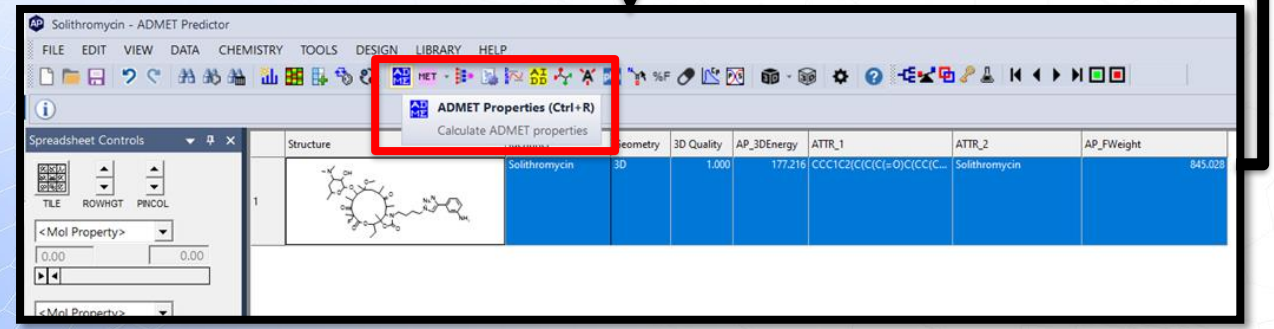



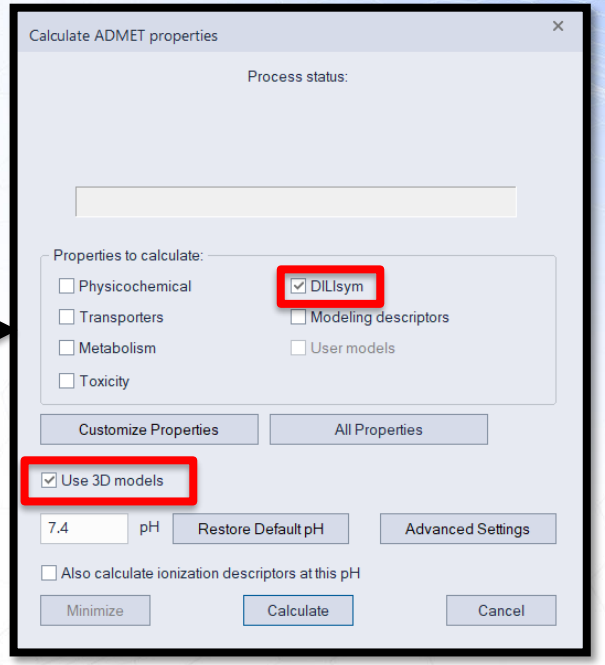



# Generate 3D Structure/Coordinates and Calculate ADMET: DILIsym Properties



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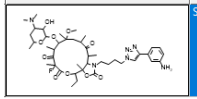
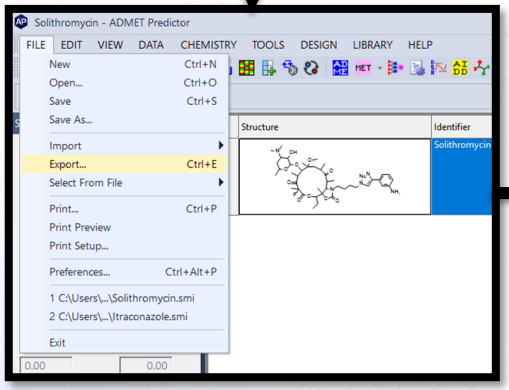
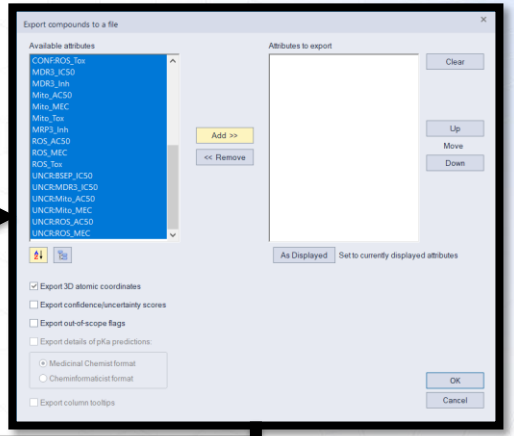
# Review and Export APD Module Results

| Structure | Identifier | Geometry | 3D Quality | AP_FWeight | BSEP_Inh | BSEP_IC50 | MDR3_IC50 | MDR3_Inh | Mito_AC50 | Mito_MEC | Mito_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%) |



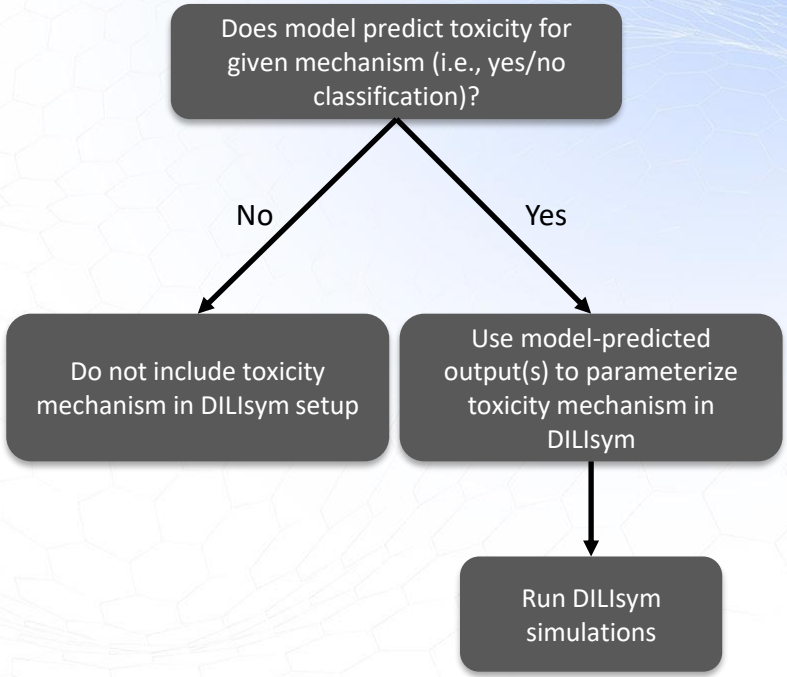




| A | B | C | D | E | F | G | H | I | J | K | L | M | N | O | P |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Identifier | Canonical | Canonical | Pair Count | Geometry | 3D Quality | AP_3DEne | AP_FWeig | ATTR_1 | ATTR_2 | BSEP_IC50 | BSEP_Inh | CONF:BSE | CONF:Mito | CONF:MRP | CONF:ROS |
| Solithromy | N(C1C(O)C | N(C1C(O)C | 0 | 3D | 1 | 177.2162 | 845.028 | CCC1C2(C | Solithrom | 8.860398 | Yes (83%) | 83 | 99 | 93 | 89 |

| Q | R | S | T | U | V | W | X | Y | Z | AA | AB | AC | AD | AE | AF |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| MDR3_IC5 | MDR3_Inh | Mito_AC50 | Mito_MEC | Mito_Tox | MRP3_Inh | ROS_AC50 | ROS_MEC | ROS_Tox | UNCR:BSE | UNCR:MDI | UNCR:Mito | UNCR:Mito | 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 | |

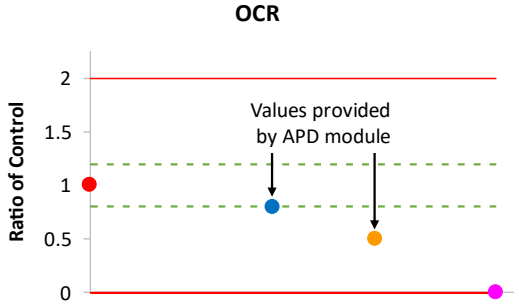
# Use and Interpretation of APD Module Classifications and Parameter Values

- 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 $AC_{50}$ for Mitochondrial Toxicity Used to Derive DILIsym Parameters for Mitochondrial Effects

**Example ETC inhibitor**




| Toxicity Mechanism | Data Point 1* | Data Point 2† | Data Point 3‡ |
|---|---|---|---|
| ETC inhibitor 1 (linear) **or** ETC inhibitor 4 (saturable) | (0.001 µM, 1) | (MEC µM, 0.8) | ($AC_{50}$ µM, 0.5) |

| Solithromycin points for mito parameterization | Data Point 1* | Data Point 2† | Data Point 3‡ |
|---|---|---|---|
| | (0.001 µM, 1) | (5.243 µM, 0.8) | (71.064 µM, 0.5) |

* Assume concentration of 0.001 µM causes no change in OCR compared to control
† Assume MEC causes OCR to drop to 0.8x control for ETC inhibitor
‡ Assume maximal reduction in OCR is complete inhibition (0x control)

- **MEC**: minimum effective concentration that significantly crosses vehicle control threshold
- **$AC_{50}$**: concentration at which 50% maximum effect is observed



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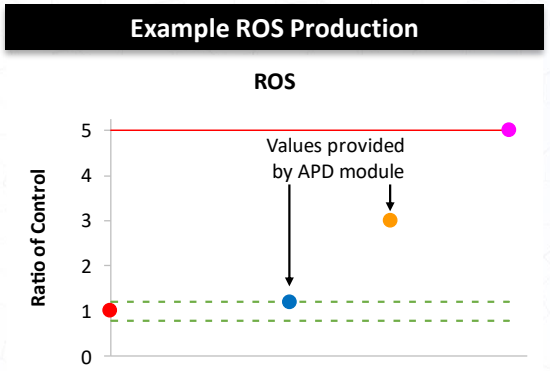
# Model-Predicted MEC and $AC_{50}$ for ROS Induction Used to Derive DILIsym Parameters for Effect on ROS Production

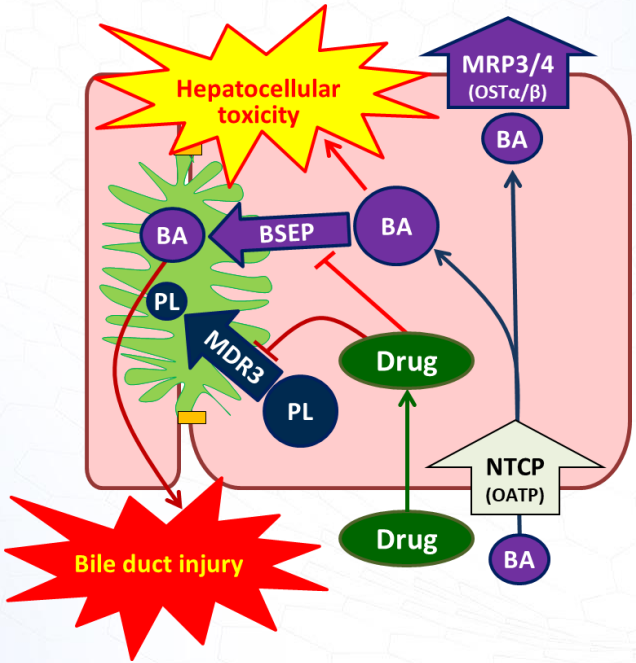



| Toxicity Mechanism | Data Point 1* | Data Point 2† | Data Point 3‡ |
|---|---|---|---|
| ROS production 1 (linear) **or** ROS production 4 (saturable) | (0.001 µM, 1) | (MEC µM, 1.2) | ($AC_{50}$ µM, 3) |
| **Solithromycin points for ROS parameterization** | **Data Point 1*** | **Data Point 2†** | **Data Point 3‡** |
| | (0.001 µM, 1) | (7.298 µM, 1.2) | (50.259 µM, 3) |

* Assume concentration of 0.001 µM 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

- **MEC**: minimum effective concentration that significantly crosses vehicle control threshold
- **$AC_{50}$**: concentration at which 50% maximum effect is observed

# 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

# Webinar Outline

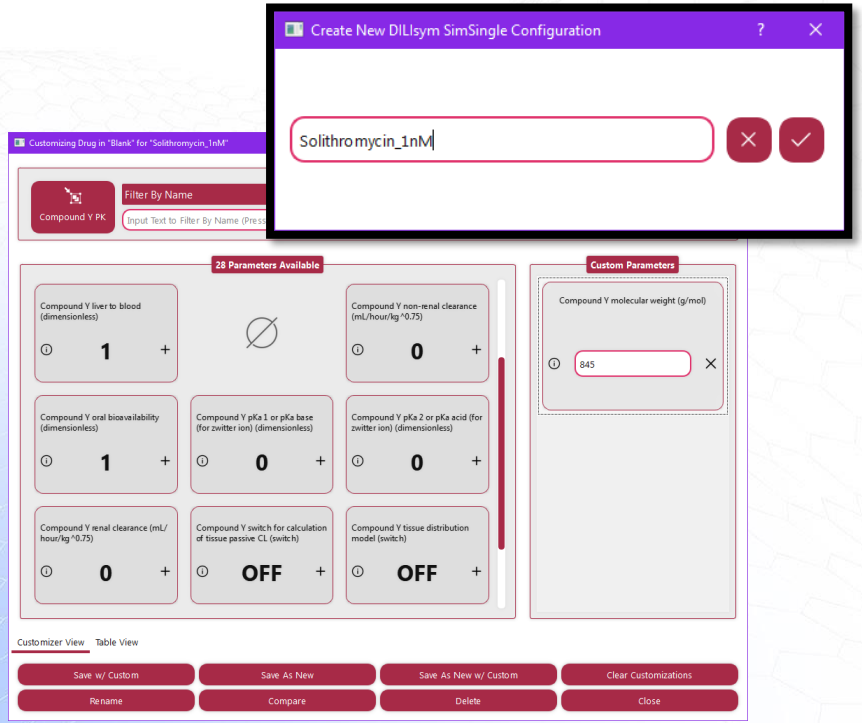
- *Simulations Plus Overview*
- ***NEW! Liver Safety+ Package:*** *De-Risking Clinical Hepatotoxicity in Early Drug Discovery*
  - *Introduction to the ADMET Predictor DILIsym (APD) module*
  - *Development of machine learning models to predict DILIsym toxicity inputs*
  - *How to use the APD module and interpret its predictions for next steps*
  - *How to use APD module predictions in DILIsym and interpret its predictions*
- *Questions*

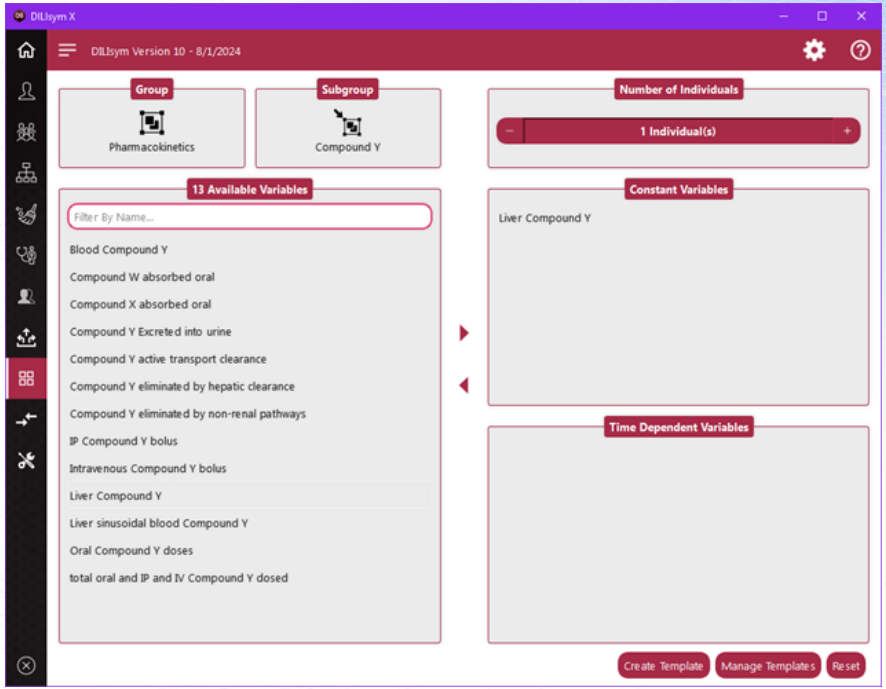
# Multiple Options for Liver Exposure in DILI Toxicity Ranking Process

- 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 webinar**]
     - *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

# DILIsym Drug Parameter Set and Use of Specified Data Feature to Define Constant Liver Concentrations



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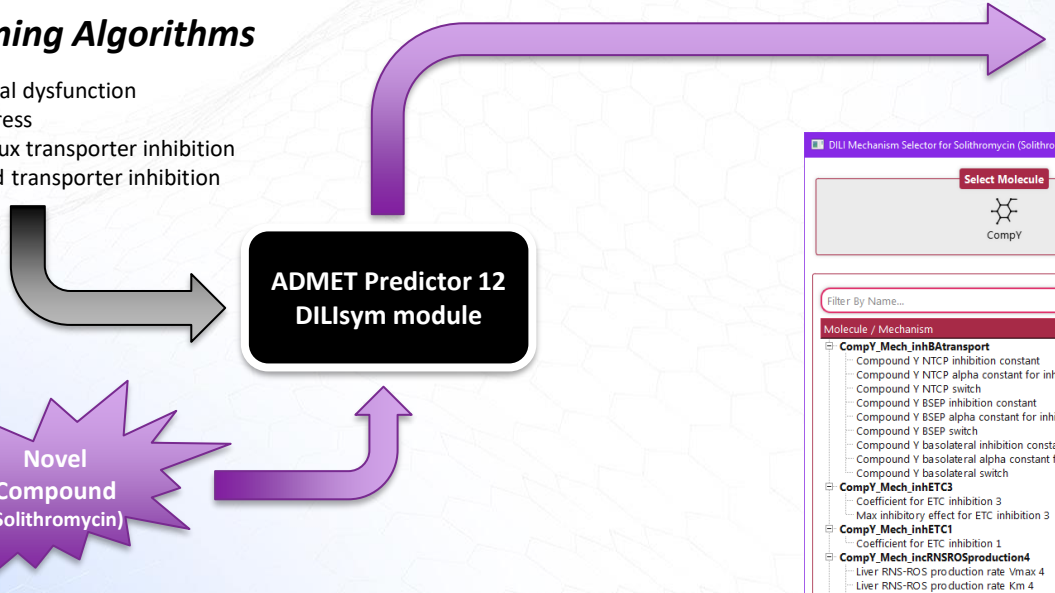
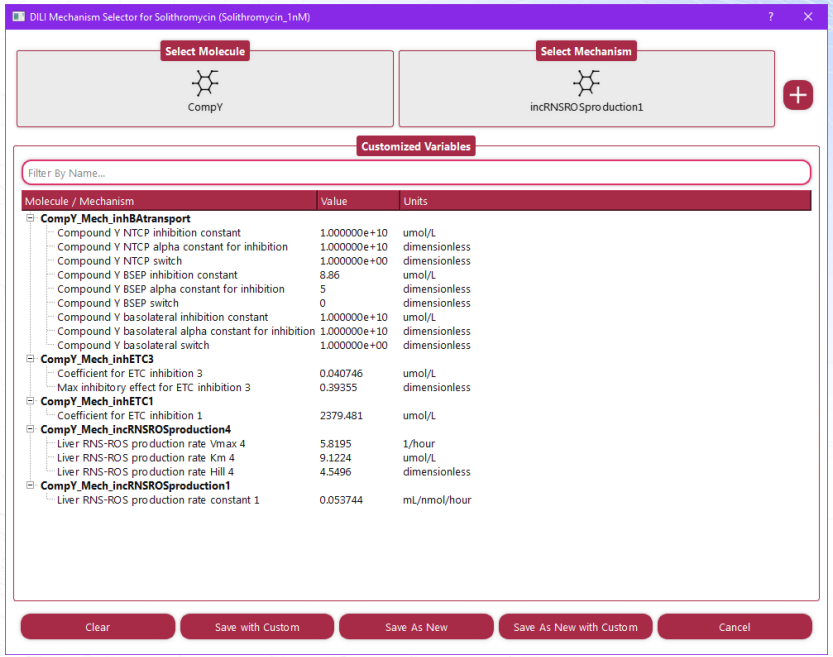
# APD Module Predictions Are Used to Set Up Active Toxicity Mechanisms in DILIsym

***Machine Learning Algorithms***

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



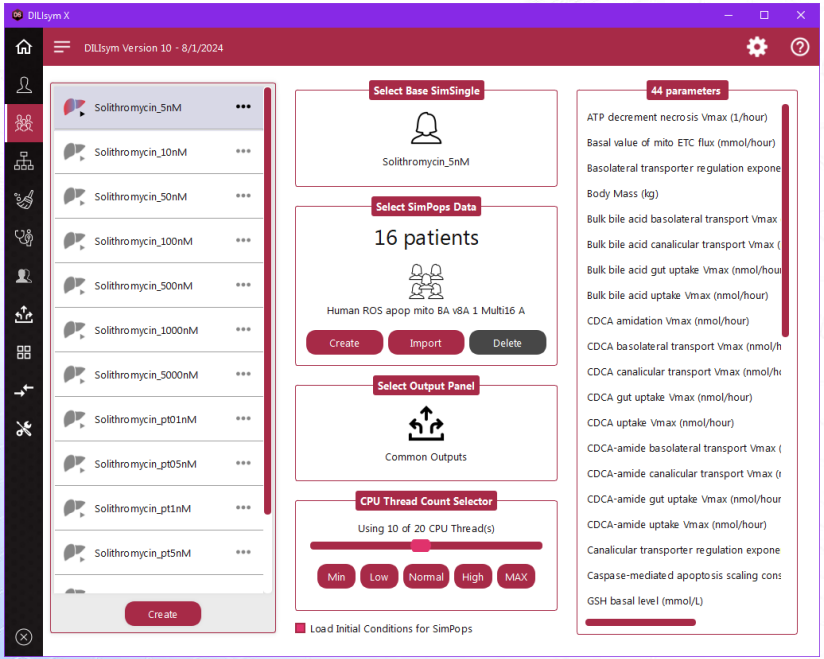

| Structure | Identifier | Geometry | 3D Quality | AP_FWeight | BSEP_Inh | BSEP_IC50 | MDR3_IC50 | MDR3_Inh | Mito_AC50 | Mito_MEC | Mito_Tox | MRP3_Inh | ROS_AC50 | ROS_MEC | ROS_Tox |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Solithromycin | 3D | 1.000 | 845.028 | Yes (83%)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






SimulationsPlus

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

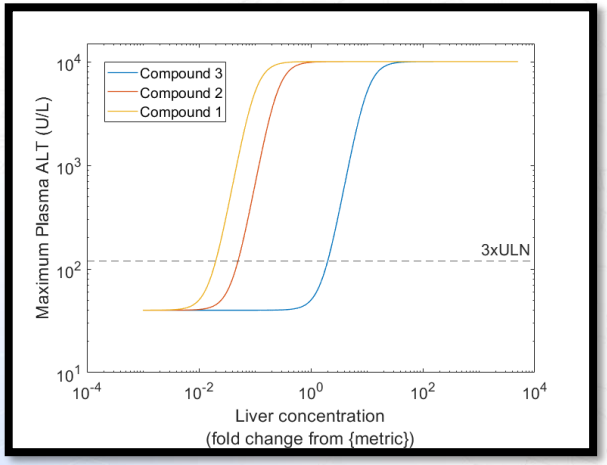



| Liver concentration (fold change from $IC_{50}$)* | Liver concentration (nM) | Maximum ALT (U/L) |
|---|---|---|
| 4.3e-7 | 0.01 | 30 |
| 2.2e-6 | 0.05 | 30 |
| 4.3e-6 | 0.1 | 30 |
| 2.2e-5 | 0.5 | 30 |
| 4.3e-5 | 1 | 30 |
| 2.2e-4 | 5 | 30 |
| 4.3e-4 | 10 | 30 |
| 2.2e-3 | 50 | 35 |
| 4.3e-3 | 100 | 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), $IC_{50}$ values for OATP1B1 were measured consistently for all compounds; $IC_{50}$ used as normalization metric in this example*

# Interpretation of Toxicity Ranking Results

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




**Compound 3**

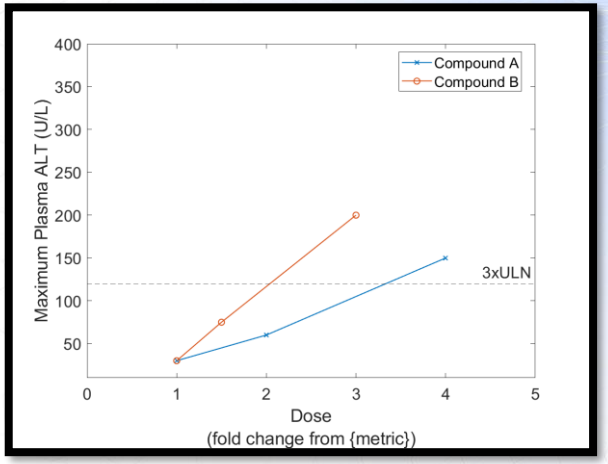
**Compound 2**

**Compound 1**

*Lowest potential for hepatotoxicity*

*Highest potential for hepatotoxicity*

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




**Compound A**

**Compound B**

*Lowest potential for hepatotoxicity*

*Highest potential for hepatotoxicity*





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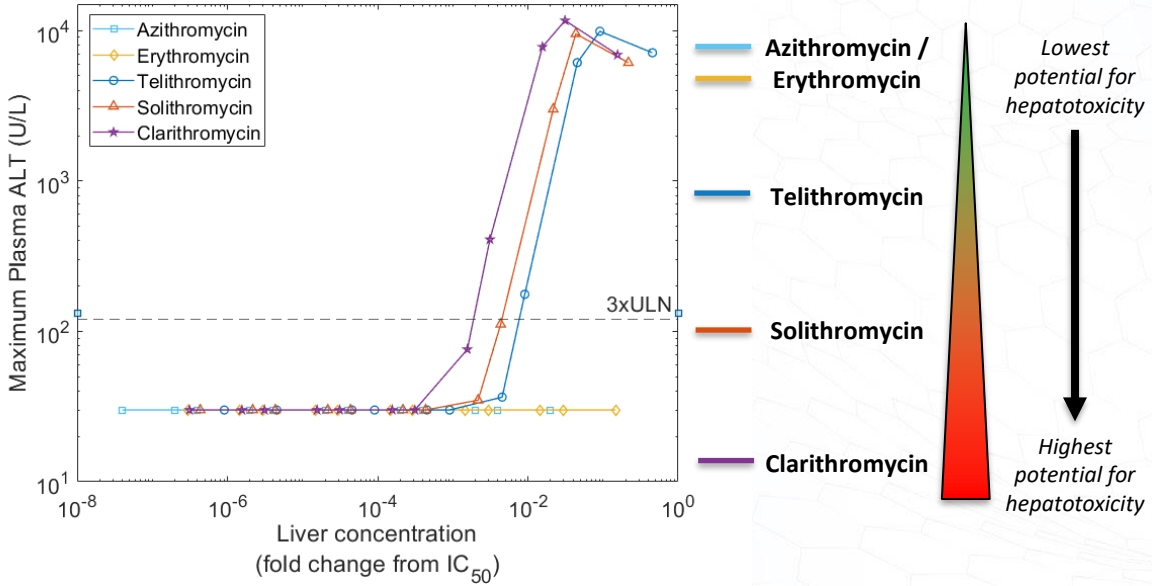
# APD Module Outputs Reproduce Clinical and Previous DILIsym Simulation Toxicity Rankings: Macrolide Antibiotics

## ML Tox Model Predictions




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

## 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<br>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

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]





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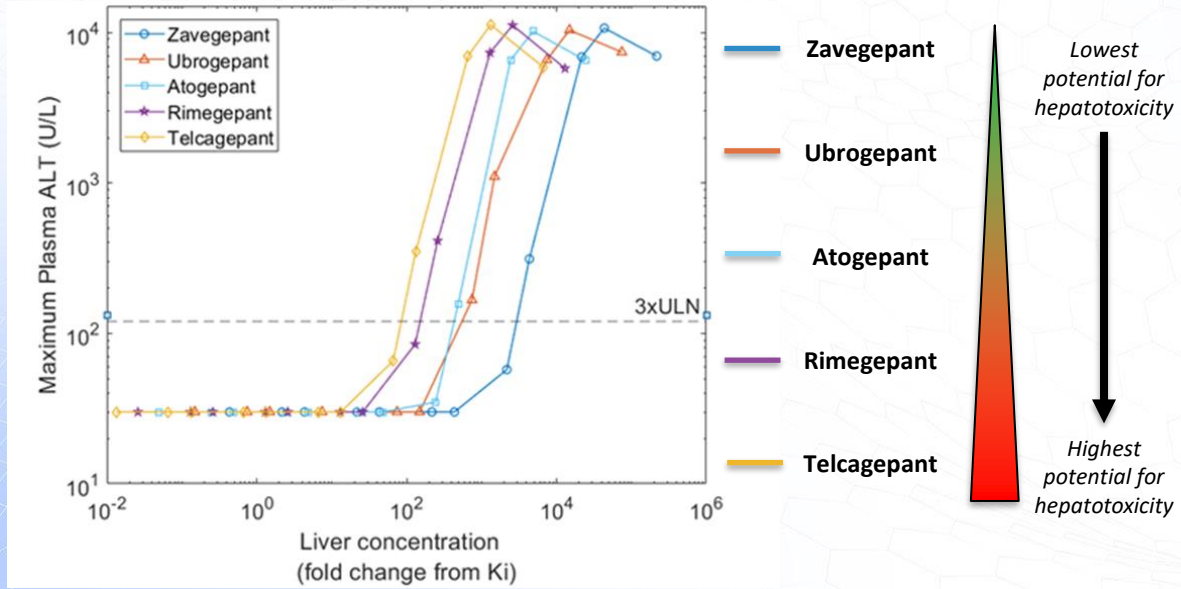
# APD Module Outputs Reproduce Clinical and Previous DILIsym Simulation Toxicity Rankings: CGRPR Antagonists

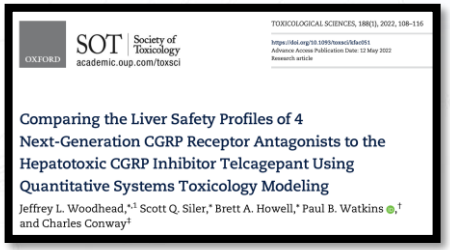
## ML Tox Model Predictions




## 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) | |




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



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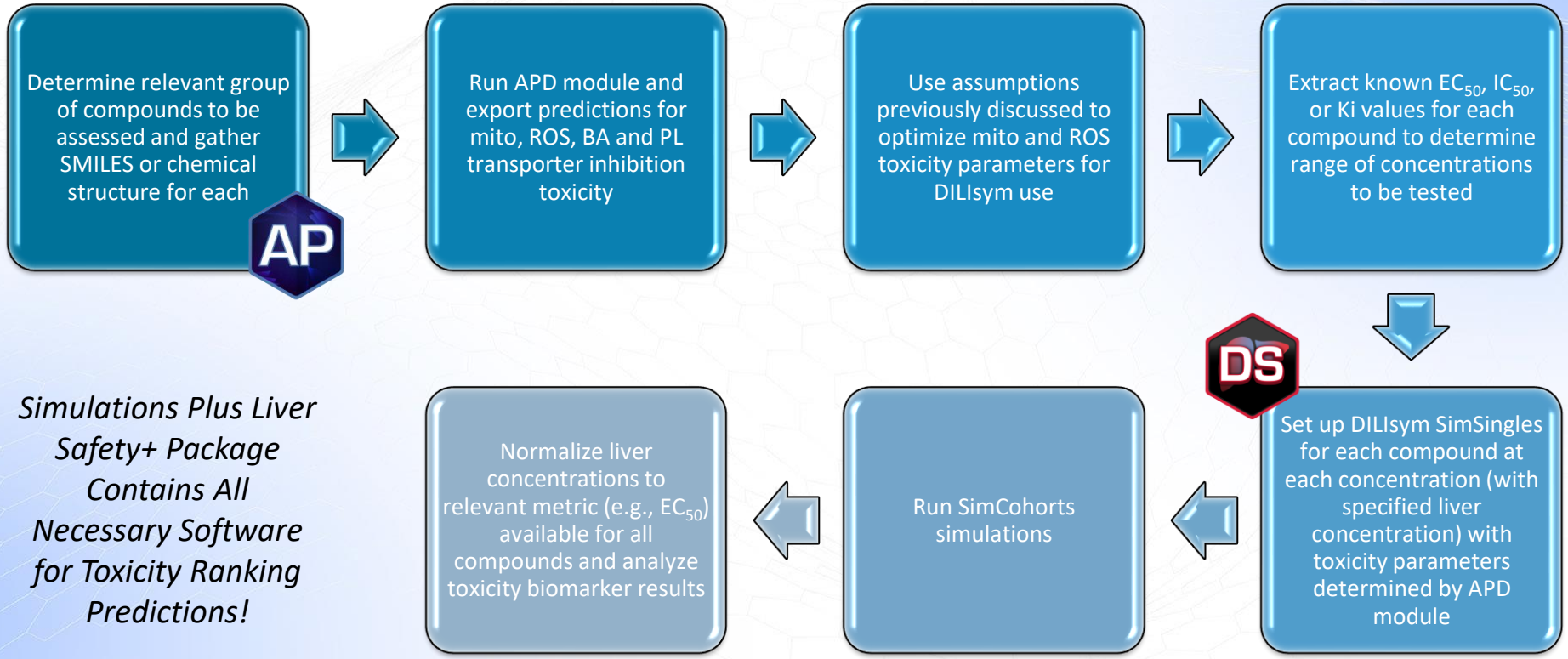
# Workflow: APD Module Enables Efficient Assessment of Hepatotoxic Rankings for In-Class Compounds at Any Stage of Drug Development!




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

# How to Engage with SLP?

**Business Development**

andrew.mueller@simulations-plus.com - Director, Business Dev.

**Today's Presenters**

lisl.shoda@simulations-plus.com – Vice President and Director of Immunology, Quantitative Systems Pharmacology

michael.lawless@simulations-plus.com – Senior Principal Scientist, Cheminformatics Solutions

james.beaudoin@simulations-plus.com – Senior Scientist, Quantitative Systems Pharmacology

christina.battista@simulations-plus.com – Senior Principal Scientist, Quantitative Systems Pharmacology

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