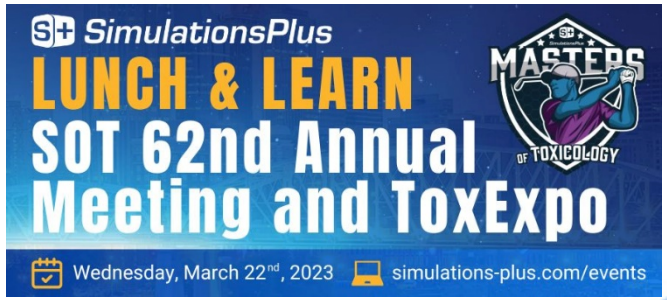


SimulationsPlus

SOT 2023: Updates from Simulations Plus, Your Partner in Safety Assessment

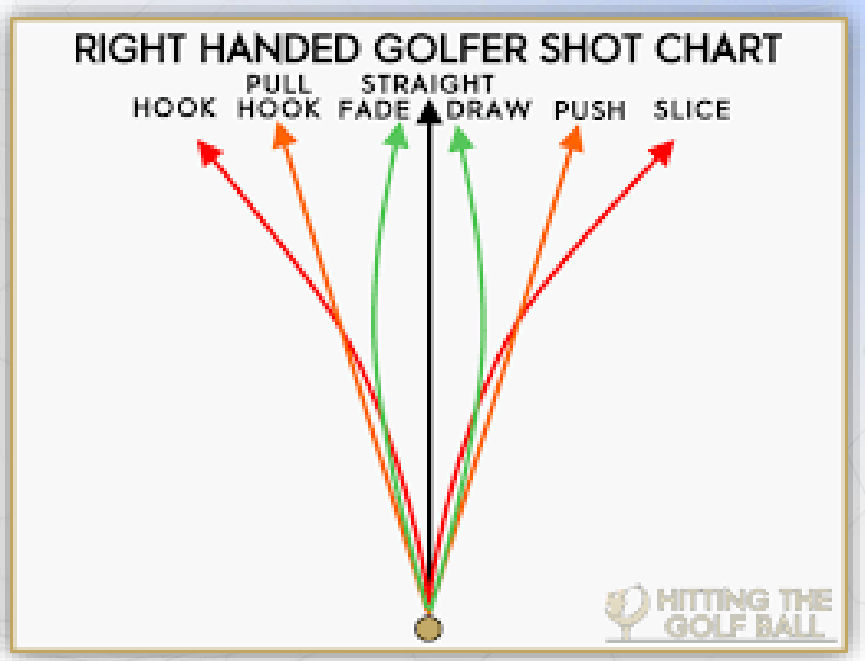
Simulations Plus Inc.

Josh Fohey and Brett Howell

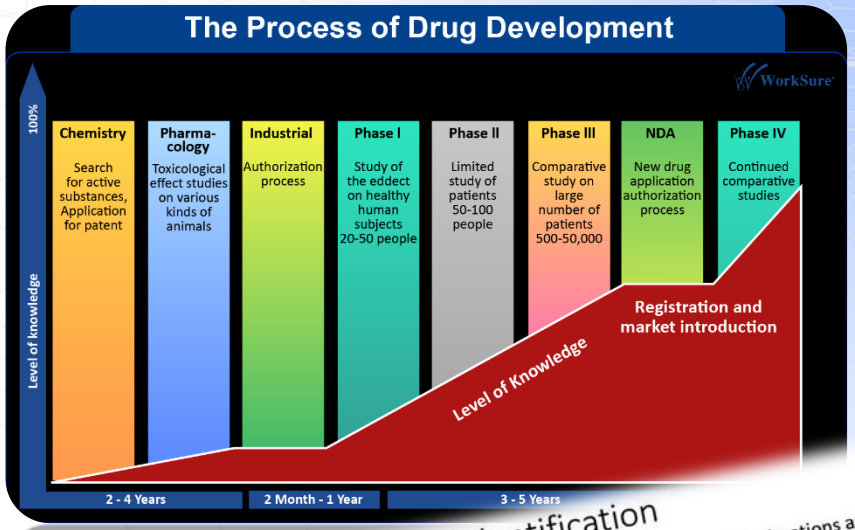
March 22, 2023

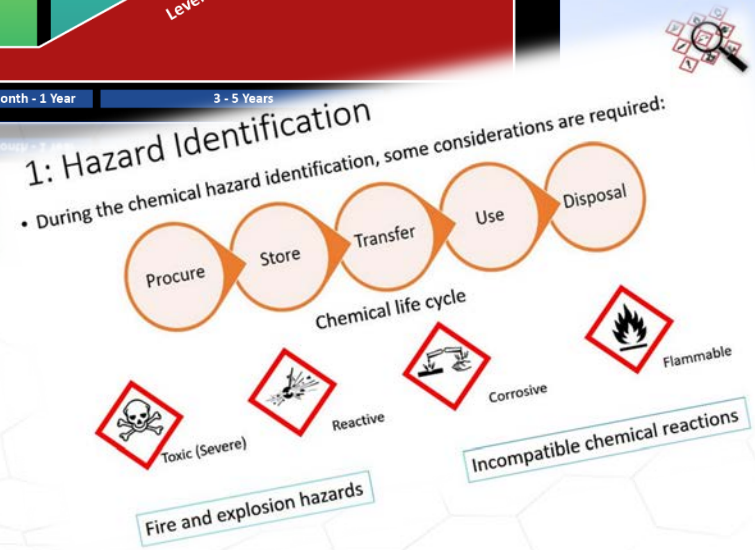
SOT 2023 SLP Lunch & Learn Shot Chart

- Simulations Plus – Your Strategic Partner in Safety and Risk Assessment!
- Exposure Related News and Updates
- Liver and Kidney Safety Related News and Updates
- Q&A



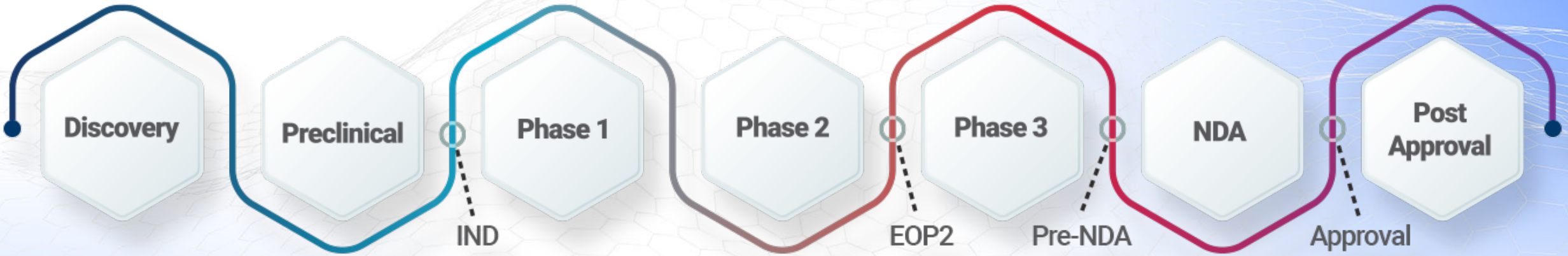
The Game of Golf is All About Strategy and the Right Tools…..Proper Safety Assessment is the Same

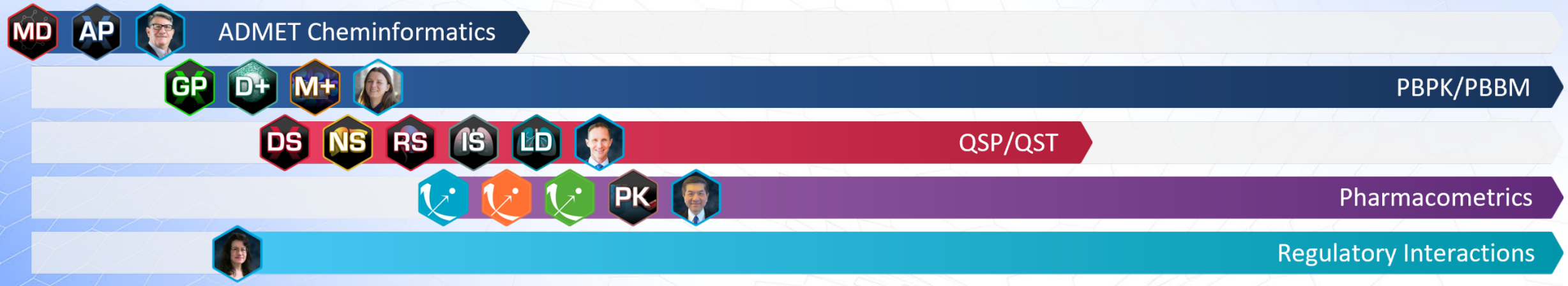




At *Simulations Plus* We Put It All Together

Our Solutions Inform the Entire Drug Development Process





Simulations Plus

"The Perfect Club" (Software) + "Expert Course Guides" (Services)

SOT 2023 SLP Lunch & Learn Shot Chart

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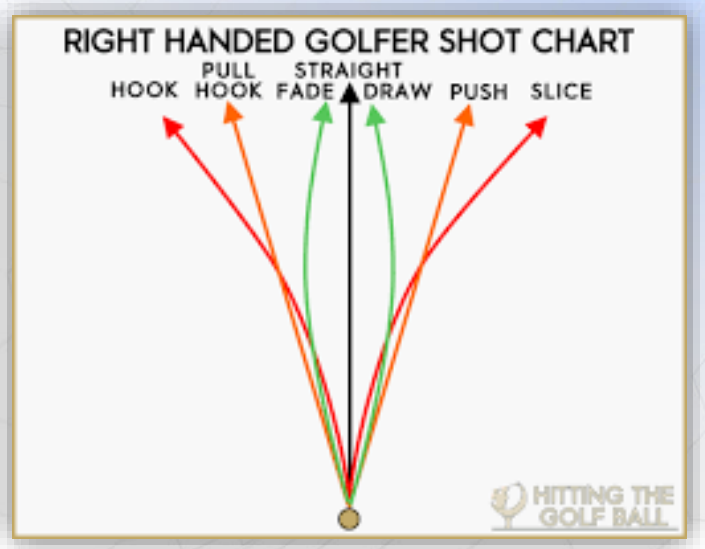

Your ACAT™/PBPK "Foundational" Model

Leverage your model!

Prediction of local and systemic exposure

- ➢ F Predictions
- ➢ teractions
- ant
- n
- s)
- tions
- fety

RENAsym

- ➢ Pred comes with QSP using P ns from G+, e.g.....

IPFsym ILDsym NAFLDsym

PBPK Model Deliverables:

- ➢ GastroPlus® database .mdb (w/input) files
- ➢ Simulation output files

GastroPlus®: By the Numbers…

200+
Companies licensing worldwide

10+
Regulatory agencies with reviewers trained on software

250+
Universities in 50+ countries with access to software

120+
Services projects executed over past 12 months

700+
Scientists received software training over past 12 months

65+
Peer-reviewed journal publications over past 12 months

SLP ♥ Academics

University+ Software Access

Internship+ Programs

SLP-funded Postdoctoral Research

Learning Services Support

Partners Driving Software R&D: Funded Collaborations

Includes 6 concurrent awards from the FDA for different routes!

FDA: Ocular model extensions

FDA: Pulmonary model extensions

Project Goals
- Develop and validate *in vitro* lung permeability assays
- Enhance PCAT™ model to include disease state physiologies
- Validate using clinical PK data for OIDPs

Interested in collaborating? Email us!

FDA: Long-acting injection model extensions

FDA: Oral cavity model extensions

FDA: Dermal model extensions

Large Pharma: ACAT™ model extensions

Large Pharma: Local GI disease extensions

Large Pharma: Virtual BE trial simulator

FDA: Oral absorption model extensions

Project Goals
- Perform *in vitro* dissolution studies in biorelevant conditions (healthy and disease states)
- Enhance ACAT™ model to include more segments and layers within the gut
- Validate using clinical GIT data for different population groups

Interested in collaborating? Email us!

Simulations Plus and Global Agrochemicals Leader to Collaborate on Machine Learning Models

Simulations Plus Enters New Collaboration to Enhance Machine Learning Models for Ionization Constants (pKa)

HTPK Simulation enhancements:

- Mouse added to rat/human selection
- New dose optimization criteria
- Full command-line/API integration

ADMET Predictor® v10.5:

- CYP inhibition & induction models – classification & regression for rapid DDI assessment
- 3D conformer generation & virtual screening capabilities

SOT 2023 SLP Lunch & Learn Shot Chart

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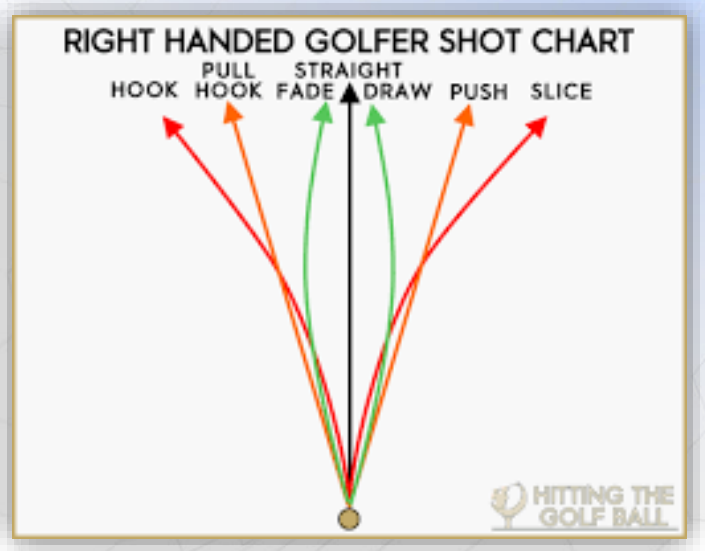
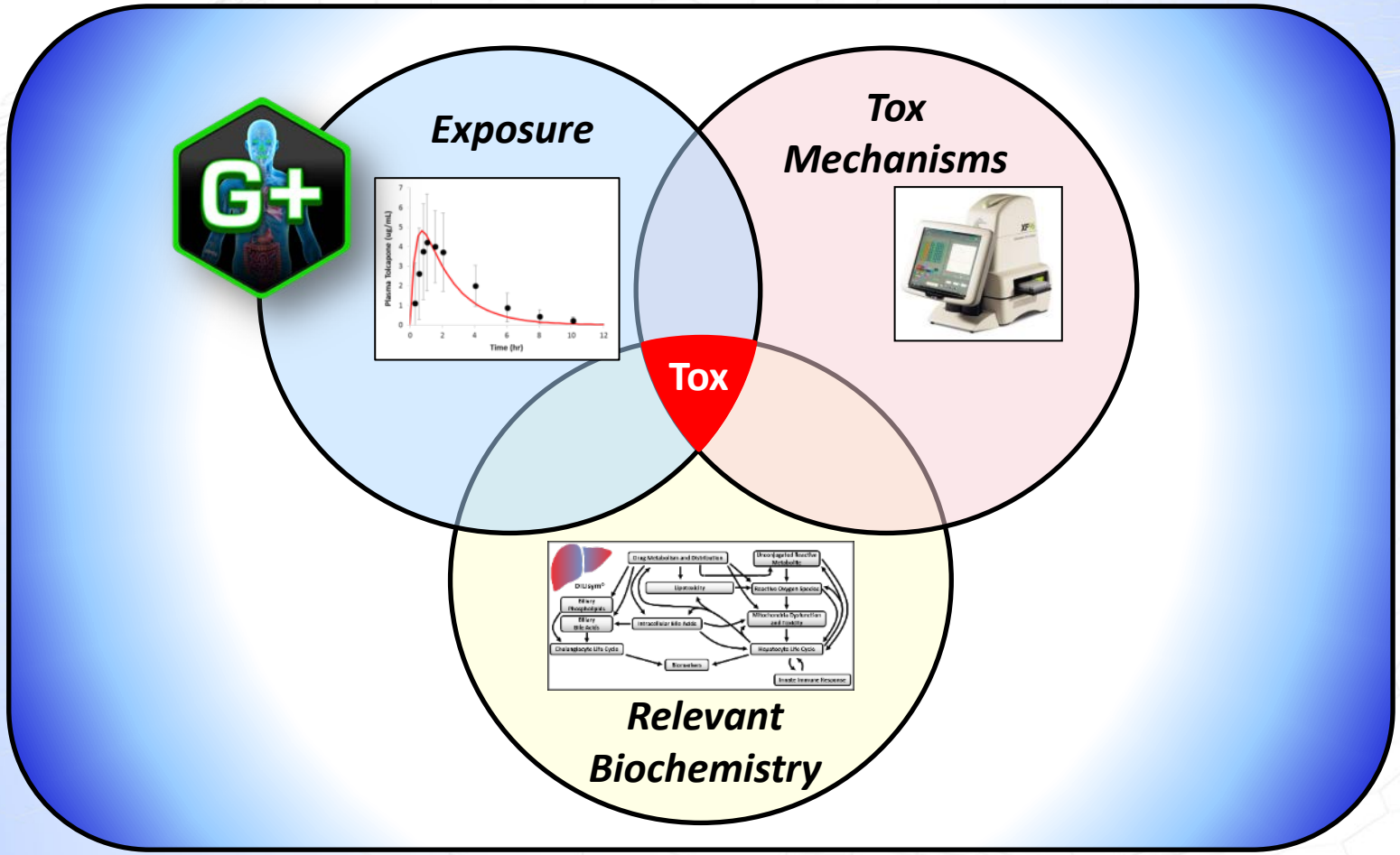


DILIsym Services QSP/QST Platforms

	Model	Disease area	Key References	Primary biomarkers included:	Number of compounds/ targets evaluated
QSP	NAFLDsym	Non-Alcoholic Fatty Liver Disease and Non-Alcoholic Steatohepatitis	Kenz 2020, Kenz 2019, Longo 2018, Siler 2018, Siler 2022	Histologic NAS, histologic fibrosis stage Liver fat (MRI), plasma ALT	25-30
	IPFsym	Idiopathic pulmonary fibrosis	Siler 2021	Forced vital capacity; high resolution computed tomography	6
	ILDsym	Interstitial lung disease	Kenz 2022	Forced vital capacity; high resolution computed tomography	5
	CARDIOsym	Cardiac recovery following myocardial infarction	Kenz 2021	Cardiomyocytes, myofibroblasts, collagen	2
	KIDNEYsym	Kidney diuresis	--	Urine volume; urinary sodium loss	3
	GOUTsym	Gout Emphasis on hyperuricemia	--	Uric acid	5
	MITOsym	Hepatocyte bioenergetics	Yang 2015	Oxygen consumption rate; ATP concentrations	>70
QST	DILIsym	Drug induced liver injury	Shoda 2017, Battista 2020, Eichenbaum 2020	Plasma ALT, plasma AST, plasma bilirubin	>70
	RENAsym	Drug induced kidney injury	Gebremichael 2020	Urine KIM-1, urine αGST, serum creatinine	10

QSP and QST models can also be newly developed for additional therapeutic areas

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



DILIsym Services QST Software Aids Decisions

- Predicts drug-induced liver disease
- v8A released Q1 2019
- Includes mechanistic representation of normal hepatic biochemistry
- Evaluated >80 compounds with 40+ companies

So how can DILIsym help my organization?

- Predict DILI liabilities beforehand and save **$$$**
- Choose the lead candidate ***most likely to succeed*** from a DILI standpoint
- Communicate with regulators on safety issues with information they have requested from others numerous times and from a platform they license (FDA) – ***33 projects completed / on-going with regulatory goals***
- ***Keep patients safer….***

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

Excellent Scientific Advisory Boards

gsk GlaxoSmithKline

janssen

Merck KGaA
Darmstadt, Germany

GILEAD

DILIsym
RENAsym

SERVIER

abbvie

AstraZeneca

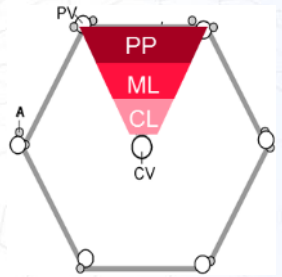
Current DILI-sim / RENAsym Members

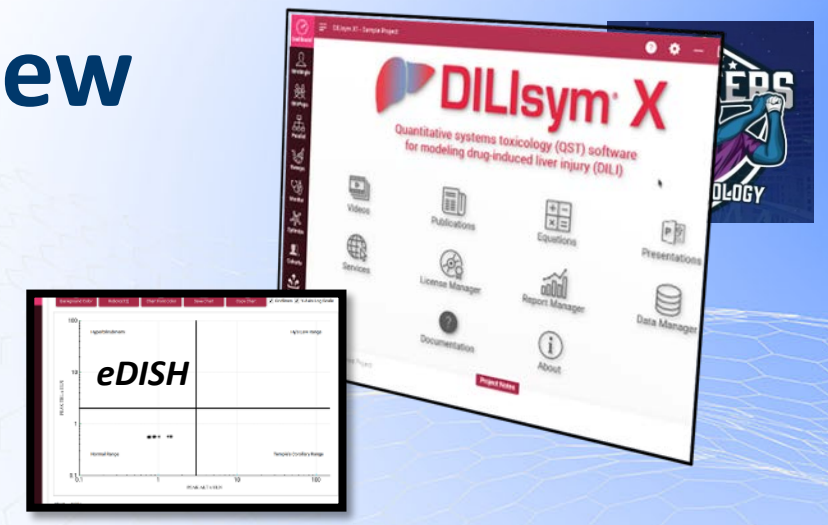
For a comprehensive review of progress, see *Watkins 2020, Current Opinion in Toxicology (23-24:67-73)*

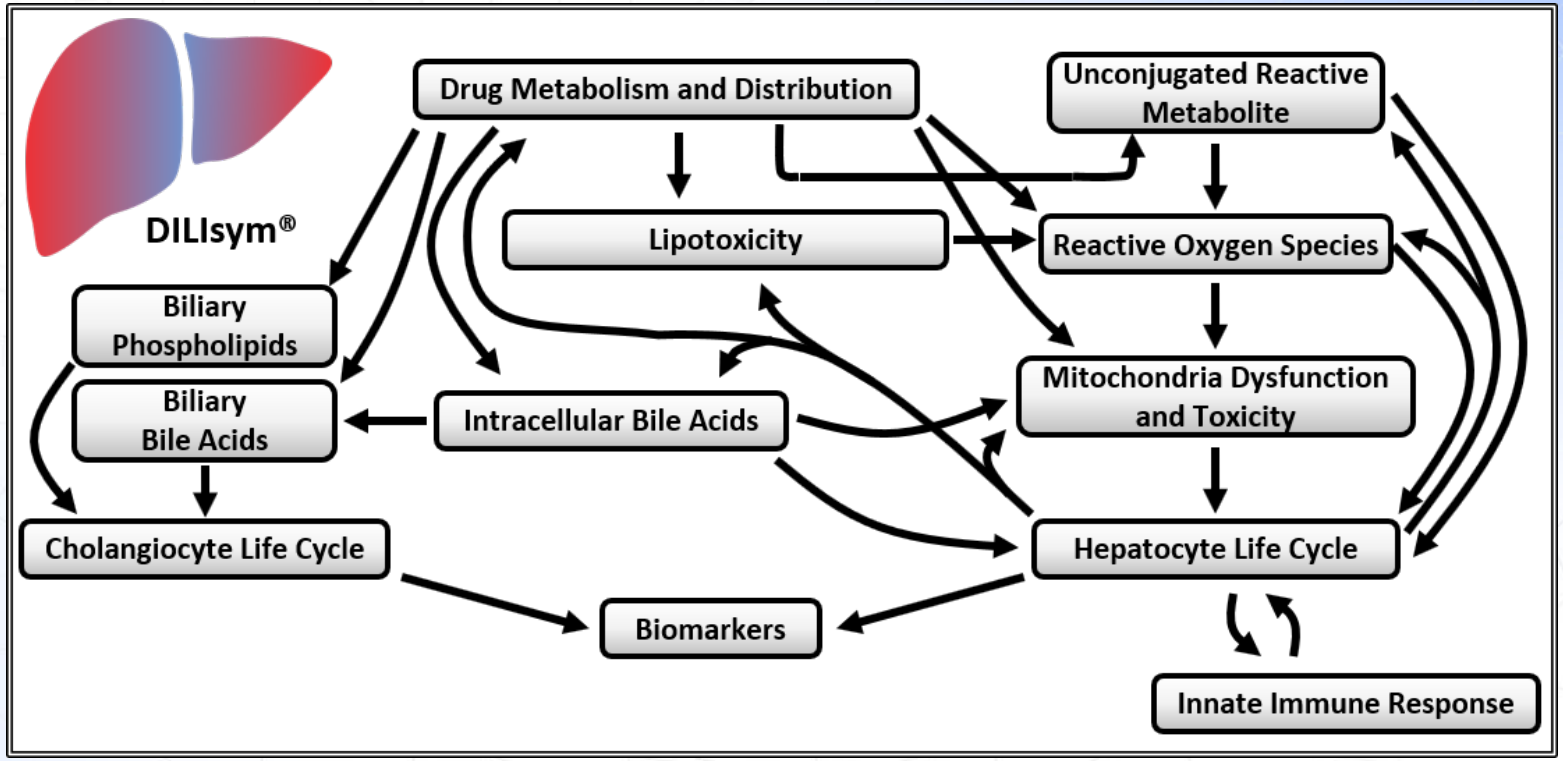
- *Overall Goals*
  - *Improve patient safety*
  - *Reduce the need for animal testing*
  - *Reduce the costs and time necessary to develop new drugs*
- *History*
  - *Officially started in 2011*
  - *21 major pharmaceutical companies have participated*
  - *Members have provided compounds, data, and 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

- Multiple species: human, rat, mouse, and dog
  - Population variability
- The three primary acinar zones of liver represented
- Essential cellular processes represented to multiple scales in interacting sub-models
- ~90 detailed representations of validation compounds with >80% success and **zero false positive predictions**
- Single and combination drug therapies







DILIsym Utilizes Various Data Types to Inform Decisions

DMPK and Exposure Data

PBPK modeling

- **Compound Properties**
  - Tissue partition coefficients
- **Tissue penetration studies**
  - *Liver to blood ratio*
- **Pharmacokinetic data**
  - *Absorption, extra-hepatic clearance, metabolites*
- ***in vitro* data**
  - *Metabolite synthesis, active uptake*

In vitro Mechanistic DILI Data

Assays performed to determine quantitative aspects of DILI mechanisms

- **Oxidative stress**
  - *Direct and reactive metabolite-mediated*
- **Mitochondrial toxicity**
  - *ETC inhibition*
  - *Uncoupling*
- **Bile acid / phospholipid transporter inhibition**
  - *BSEP, MRP3 and 4, NTCP, MDR3*
- **Bilirubin transport/metabolism**
  - *OATP1B1, OATP1B3, UGT1A1, MRP2, MRP3*

DILIsym®

Modeling & Simulation

Simulations and Assays inform:

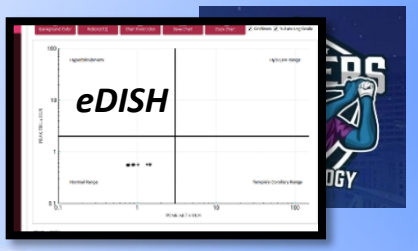
- **Prediction of DILI risk**
- **Participating DILI mechanisms**
- **Characteristics of patients at risk for DILI**
- **Drug dosing paradigms**
- **DILI monitoring strategies**

Clinical Data / Protocol Information

Client specified protocols

- **Dosing protocols, fasting/fed state, meal times**
- **Patient types (NHV, disease, etc.)**
- **Anthropometric data**
  - *Body weight, age, ethnicity*

Biomarkers of Hepatocellular Function and Death 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
- More biomarkers being added as data are becoming available
  - GLDH most recent addition
- Additional DILIsym outputs include:
  - Fraction of viable hepatocytes
  - Liver ATP
  - Liver glutathione
  - Circulating, liver, and excreted drug and metabolites
  - And more…..

Marker	Category
Alanine aminotransferase (ALT)[1,2,3,4,5]	Necrosis
Bilirubin (total)[1,2,5]	Function / Cholestasis
Aspartate aminotransferase (AST)[1,2,3,4,5]	Necrosis
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]Church *Exp Biol Med* 2017, [12]Yang *Clin Pharmacol Ther* 2017

Advancing Calcitonin Gene-Related Peptide Receptor Antagonists Using Quantitative Systems Toxicology Modeling to Characterize Next-in-Class Compounds Compared to the Hepatotoxic First in Class Telcagepant

Woodhead, Jeffrey L. (1); Siler, Scott Q. (1); Howell, Brett A. (1); Conway, Charles M. (3); Watkins, Paul B (2)

1. DILIsym Services, Inc., a Simulations Plus company, Research Triangle Park, NC, USA; 2. Institute for Drug Safety Sciences, UNC-Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, NC, USA; 3. Biohaven Pharmaceuticals, Inc., New Haven, CT, USA

AASLD The Liver Meeting® Nov. 12–15, 2021
DIGITAL EXPERIENCE

INTRODUCTION

While CGRP receptor antagonists have demonstrated efficacy in the acute and preventive treatment of migraine, two early CGRP signal-blocking compounds (gepants) showed liver injury signals in clinical trials. During clinical development of next-in-class gepants, confidence in compound safety was needed given the prior experience.

AIM

Biohaven enlisted DILIsym Services, Inc. (DSSI) to use DILIsym to independently assess the potential for liver toxicity to compare four next-in-class gepant compounds in clinical development to the hepatotoxic agent telcagepant.

MATERIAL & METHODS

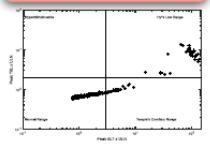
Models for telcagepant and four novel CGRP receptor antagonists (rimegepant, zavegepant, ubrogepant, and atogepant) were constructed in DILIsym v6A, a quantitative systems toxicology (QST) model of drug-induced liver injury. *In vitro* experiments were performed to measure the potential for each compound to inhibit bile acid transporters, produce oxidative stress, and cause mitochondrial dysfunction; physiologically-based pharmacokinetic (PBPK) models were produced for each compound to estimate liver exposure. Compounds were simulated at and above respective clinical dose regimens.

RESULTS

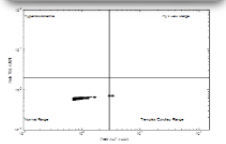
Telcagepant showed liver safety signals including: a) dose-dependent decrease in oxygen consumption rate (OCR) consistent with electron transport chain (ETC) inhibition, b) noncompetitive BSEP inhibition and c) liver exposure accumulation greater than in plasma resulting in an eDISH profile falling into Hy's Law range (see plots). Model-based elimination to identify the impact of contributors suggested synergy between bile acid accumulation and ETC inhibition as contributing to telcagepant toxicity. None of the other 4 novel gepants showed eDISH signals in Hy's Law range (see plots) and none showed simulated signals >1% frequency for ALT > 3X upper limit of normal (ULN) at clinical doses (see table). When clinical doses were exceeded only atogepant and ubrogepant showed simulated signals ≥10% frequency for ALT > 3X ULN. Simulations predicted rimegepant, zavegepant, atogepant, and ubrogepant would be safe at clinical doses.

RESULTS (cont'd)

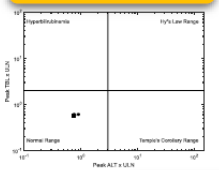
Telcagepant; 140 mg BID, 12 weeks, high ETCi



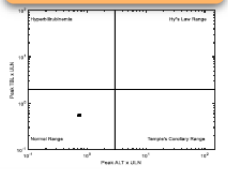
Rimegepant; 75 mg QD, alternate day dosing, 14 total doses over 28 days



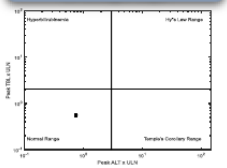
Atogepant; 60 mg BID, 12 weeks



Ubrogepant; 100 mg QD, 25 straight days



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



Compound	Oral Dosing Protocol	Simulated* ALT > 3X ULN	Observed ALT > 3X ULN in Clinic
Telcagepant – Original 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 – Alternate 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)	
	7.5 mg IV QD, 25 days, 25 total doses	0.0% (0/285)	
Atogepant	60 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, 25 days	0% (0/285)	
	500 mg QD, 25 days	1.4% (4/285)	
	1000 mg QD, 25 days	11.6% (33/285)	

*In vitro experiments led to the parameterization of each of the five CGRP compounds within DILIsym, with an alternate parameterization for telcagepant based on uncertainty in the *in vitro* data.

CONCLUSION

DILIsym correctly predicted the DILI liability of the first generation compound telcagepant. The four next-in-class compounds did not show the same signal for liver safety concerns as telcagepant. Subsequent clinical trials have validated these results, with rimegepant, ubrogepant and atogepant all approved by the FDA with no black-box warning for hepatotoxicity. Zavegepant continues in late-stage development. This work demonstrates the potential for QST modeling to prospectively differentiate between hepatotoxic and non-hepatotoxic molecules within the same class.

ACKNOWLEDGEMENTS

The DILI-sim Initiative, a partnership between pharmaceutical companies and DILIsym Services, Inc., has funded the development of DILIsym.

REFERENCES

1. Ho TW, Ho AP, Ge YJ, Assaid C, Gottwald R, MacGregor EA, et al. Randomized controlled trial of the CGRP receptor antagonist telcagepant for prevention of headache in women with perimenstrual migraine. Cephalalgia Int J Headache. 2016 Feb;36(2):148–61.

DISCLOSURES

Drs. Woodhead, Siler, and Howell are employees of DILIsym Services, Inc., developers of DILIsym. Dr. Conway is employed by Biohaven, developers of rimegepant and zavegepant.

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TOXICOLOGICAL SCIENCES, 00(0), 2022, 1–9

https://doi.org/10.1093/toxsci/kfac
Advance Access Publication Date 2022
Research article

Pfizer acquired Biohaven CGRP for $11B

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‡

*DILIsym Services, Inc., A Simulations Plus Company, Research Triangle Park, North Carolina 27706, USA; †Institute for Drug Safety Sciences, UNC-Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina 27599, USA; and ‡Biohaven Pharmaceuticals, Inc., New Haven, Connecticut 06510, USA

[1]To whom correspondence should be addressed at DILIsym Services, Inc., A Simulations Plus Company, 6 Davis Drive, Research Triangle Park, NC 27709, USA. E-mail: jeff.woodhead@simulations-plus.com.

Quantitative Systems Toxicology (QST) Modeling Using DILIsym Informed Safe Dose Selection of Emvododstat in Acute Myeloid Leukemia (AML) Patients

Kyunghee Yang
kyunghee.yang@simulations-plus.com

BACKGROUND

Clinical investigation of emvododstat for the treatment of solid tumors was terminated after two patients who were heavily treated with other anticancer therapies experienced drug-induced liver failure. Subsequent investigations supported that emvododstat might be effective in treating AML at lower doses than administered in the solid tumor clinical trials. A QST model, DILIsym, was employed to predict liver safety of the proposed dosing of emvododstat in AML clinical trials.

METHODS

A PBPK model for emvododstat and its desmethyl metabolite was developed. In vitro assays were performed to assess effects of emvododstat and its desmethyl metabolite on bile acid transport, mitochondrial function, and oxidative stress (ROS). These data were integrated with in vivo exposure within DILIsym to predict hepatotoxicity responses in a simulated human population.

RESULTS

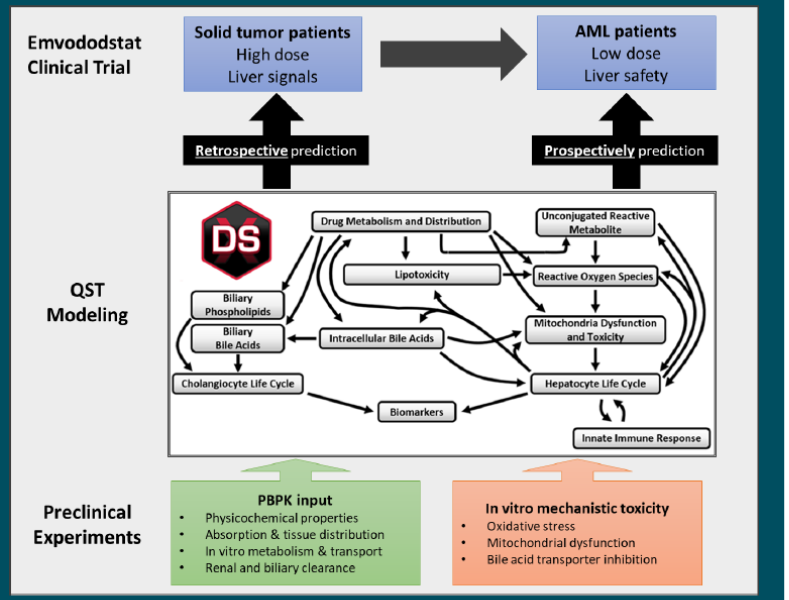
DILIsym simulations predicted the ALT elevations observed in prior emvododstat clinical trials for solid tumors, but ALT elevations were not predicted to occur with the emvododstat dosing proposed for the AML clinical trials. The modeling enabled regulatory approval to proceed with the AML clinical trial where significant liver safety concerns were not evident.

Protocol		Grade 1 (ALT 1-2.5X ULN*)		Grade 2 and above (ALT > 2.5X ULN)	
		Data	Sim	Data	Sim
Previous protocols	100mg BID 16 weeks	25% (13/52)	0.35% (1/285)	3.8% (2/52)	0.35% (1/285)
	160mg TID 16 weeks	14% (1/7)	8.4% (24/285)	0% (0/7)	22.5% (64/285)
	200mg TID 16 weeks	20% (1/5)	4.9% (14/285)	0% (0/5)	37.5% (107/285)
Prospective protocol (AML)	40mg (7)/20mg (21) QD 32 weeks†	3% 1/33	0% (0/285)	0% 0/33	0% (0/285)
	80mg (7)/40mg (21) QD 32 weeks†	3% 1/33	0% (0/285)	0% 0/33	0% (0/285)
	160mg (7)/80mg (21) QD 32 weeks†	3% (1/33)	N/A	0% (0/33)	N/A
	320mg (7)/160mg (21) QD 32 weeks†	3% (1/33)	N/A	0% (0/33)	N/A

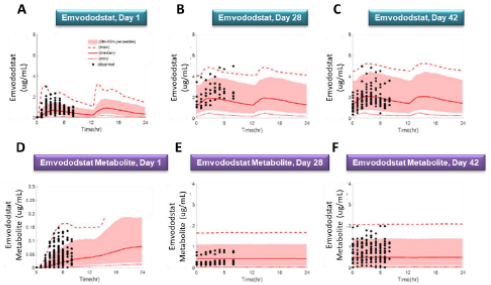
*Upper limit of normal (ULN) in DILIsym is 40 U/L.
†Prospective clinical protocols. Tablet doses converted to capsule based on the relative bioavailability of 40%. Numbers in parenthesis represent the number of loading doses. *Clinical data were not available when simulations were performed.*

QST modeling using DILIsym *retrospectively* predicted the liver safety liabilities of emvododstat in the treatment of solid tumors and *prospectively* predicted the liver safety of reduced doses of emvododstat in a clinical trial of patients with AML.

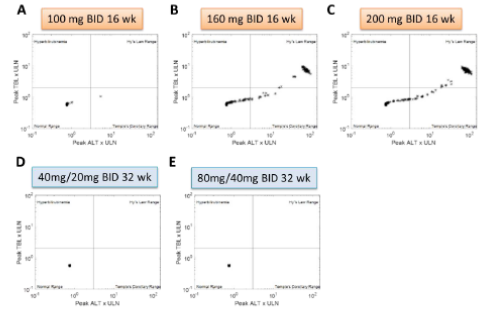
Take a picture for more information



Simulated (lines and shades) and observed (symbols) plasma concentration-time profiles of Emvododstat (a-c) and its desmethyl metabolite (d-f) after administration of 100 mg emvododstat (capsule formulation) BID for 42 days.



Simulated eDISH plots for previous (a-c) and prospective (d, e) clinical protocols of emvododstat in the Human SimPops (n=285).



Emvododstat (EMV) metabolite-mediated mitochondrial dysfunction and ROS were presumed responsible for predicted ALT signals.

Case	DILI Mechanism			Simulated Grade 1 ALT and Above
	EMV ETCi	EMV Metabolite ETCi	EMV Metabolite ROS	
I	On	On	On	15/16
II	**Off**	On	On	15/16
III	On	**Off**	On	14/16
IV	On	On	**Off**	15/16
V	**Off**	**Off**	On	14/16
VI	On	**Off**	**Off**	0/16
VII	**Off**	On	**Off**	14/16

Kyunghee Yang[1], Ronald Kong[2], Pius Maliakal[2], Robert Spiegel[2], John D. Baird[2], Kylie O'Keefe[2], Paul B Watkins[3], and Brett A Howell[1]

[1]DILIsym Services Division, Simulations Plus Inc. Research Triangle Park, NC
[2]PTC Therapeutics, Inc., South Plainfield, NJ
[3]UNC Eshelman School of Pharmacy, The University of North Carolina at Chapel Hill, NC

PTC THERAPEUTICS

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Prediction of the Liver Safety Profile of a First-in-Class Myeloperoxidase Inhibitor Using Quantitative Systems Toxicology Modeling

Jeffrey L. Woodhead[1], Yeshi Gebremichael[1], Joyce Macwan[1], Irfan Qureshi[2], Richard Bertz[2], Victoria Wertz[2], Brett A. Howell[1]

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CONTACT INFORMATION: jeff.woodhead@simulations-plus.com

SimulationsPlus

PURPOSE

The novel myeloperoxidase inhibitor verdiperstat was developed as a treatment for neuroinflammatory and neurodegenerative diseases. Phase 2 clinical studies had shown some promise for efficacy at the 600 mg BID dose; however, this is a large dose and verdiperstat had shown some *in vitro* signals suggesting possible liver toxicity. Mild liver signals had also been observed during Phase 1 trials, though it was unclear whether these were drug-related or not. In order to provide an added layer of confidence in the liver safety of verdiperstat before proceeding to Phase 3, a computational prediction of verdiperstat liver safety was performed using DILIsym v8A, a quantitative systems toxicology (QST) model of liver safety.

METHODS

A physiologically-based pharmacokinetic (PBPK) model of verdiperstat was constructed in GastroPlus 9.8, and the estimates for the liver and plasma time course of verdiperstat were input into DILIsym. *In vitro* experiments measured the likelihood that verdiperstat would inhibit mitochondrial function, inhibit bile acid transporters, and generate reactive oxygen species (ROS). Predictions of liver verdiperstat exposure from the PBPK model and parameters derived from the *in vitro* experimental results were used as inputs into DILIsym. Two alternate sets of parameters were used as inputs in order to fully explore the sensitivity of model predictions within the potential range of the *in vitro* data. Verdiperstat dosing protocols up to 600 mg BID were simulated for up to 48 weeks using a simulated population (SimPops) in DILIsym.

RESULTS

In vitro experiments were conducted in cell vesicles (for bile acid transport) and HepG2 cells (for ROS and ETC inhibition). These experiments showed verdiperstat to be a mild inhibitor of the bile acid transporter MRP4 (Figure 1), a mild generator of ROS (Figure 2), and a mild inhibitor of the mitochondrial electron transport chain (ETC, Figure 3). For ROS and ETC inhibition, the intracellular concentration was measured by mass spectrometry.

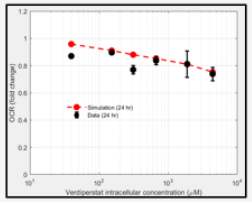


Figure 2. Relationship between measured intracellular verdiperstat and oxygen consumption rate, demonstrating a dose-dependent decrease in oxygen consumption and thus an inhibition of the electron transport chain.

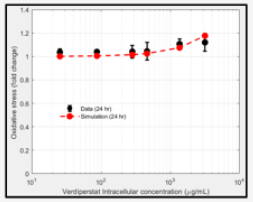


Figure 3. Relationship between measured intracellular verdiperstat and normalized TBARS generation, demonstrating a dose-dependent increase in oxidative stress.

Results from the *in vitro* experiments were used to calculate input parameters into DILIsym v8A, in the table below. OCR consumption was modeled in MITOsym v3B, a QST model of *in vitro* mitochondria, and translated into DILIsym; ROS generation was modeled in an *in vitro*-like parameterization in DILIsym (red lines in Figures 2 and 3). An alternate, conservative parameterization using an estimate of intracellular concentration as equal to the nominal concentration, which was suggested by the liver partition coefficient of 1 used in the PBPK model, was also developed; these parameters are also in the table below.

Mechanism	DILIsym Parameter	Unit	Alternate Verdiperstat Value	Primary Verdiperstat Value
BA Transport Inhibition	Inhibition constant for BSEP	μM	No inhibition	No inhibition
	Inhibition constant for basolateral efflux (MRP3/4)	μM	32.55**	32.55**
	Inhibition constant for NTCP	μM	No Inhibition	No Inhibition
Oxidative Stress	Liver RNS/ROS production rate constant 1	mL/nmol/hour	1.7×10^{-4}	1.15×10^{-6}
Mitochondrial Dysfunction	Coefficient for ETC Inhibition 1	μM	6.94×10^{5}	6.94×10^{5}
	Coefficient for ETC Inhibition 3	μM	2.43	243
	Max inhibitory effect for ETC inhibition 3	Dimensionless	0.39	0.39

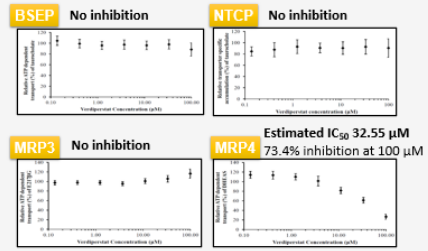
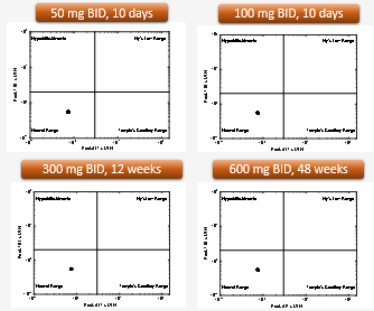
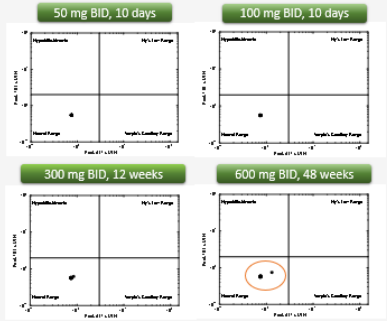


Figure 1. Inhibition of bile acid transporters by verdiperstat



In SimPops simulations (n = 285), no ALT elevations over 3x ULN were predicted using either the primary (above) or alternate (below) parameterizations. Mild ALT elevations (less than 3x ULN) occurred at the 600 mg BID dose in the alternate parameterization.



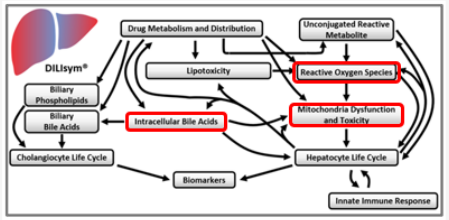


Diagram of the interactions between submodels in DILIsym v8A. In vitro *measurements of oxidative stress, mitochondrial dysfunction, and bile acid transport inhibition are used as inputs, and the DILIsym model of liver physiology computes the likelihood that those mechanisms will affect the hepatocyte life cycle, which will in turn affect biomarker release and immune system activation.*

CONCLUSION

Verdiperstat was predicted to be safe, with only rare, mild liver enzyme increases as a potential possibility in very highly sensitive individuals. Subsequent Phase 3 clinical trials conducted after the conclusion of this modeling work found that ALT elevations in the verdiperstat treatment group were generally similar to those in the placebo group. This validates the DILIsym simulation results and demonstrates the power of QST modeling to predict the liver safety profile of novel therapeutics.

ACKNOWLEDGEMENTS

- Biohaven Pharmaceuticals, Inc.
- The members of the DILI-sim and RENAsym Initiatives

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Relevant Recent DILIsym News / Publications

U.S. FDA Renews Annual DILIsym Software Licenses

FDA Maintains Access to Leading Liver Injury Software Program

May 06, 2020 08:30 AM Eastern Daylight Time

RESEARCH TRIANGLE PARK, N.C.--(BUSINESS WIRE)--DILIsym Services, Inc., a Simulations Plus company (Nasdaq: SLP) and a leading provider of simulation and modeling software for pharmaceutical safety and efficacy, today announced that the U.S. Food and

Application of the DILIsym® Quantitative Systems Toxicology drug-induced liver injury model to evaluate the carcinogenic hazard potential of acetaminophen

Gary Eichenbaum[a,*], Kyunghee Yang[b], Yeshitila Gebremichael[b], Brett A. Howell[b], F. Jay Murray[c], David Jacobson-Kram[d], Hartmut Jaeschke[e], Edwin Kuffner[a], Cathy K. Gelotte[f], John C.K. La

[a] Johnson & Johnson
[b] DILIsym Services In
[c] Murray & Associate

Pharm Res (2020) 37:24
https://doi.org/10.1007/s11095-019-2726-0

RESEARCH PAPER

Comparison of the Hepatotoxic Potential of Two Treatments for Autosomal-Dominant Polycystic Kidney Dis Using Quantitative Systems Toxicology Modeling

J. L. Woodhead[1] • L. Pellegrini[2] • L. K. M. Shoda[1] • B. A. Howell[1]

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

TOXICOLOGICAL SCIENCES, 00(0), 2022, 1–9
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[‡]

*DILIsym Services, Inc., A Simulations Plus Company, Research Triangle Park, North Carolina 27706, USA; †Institute for Drug Safety Sciences, UNC-Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina 27599, USA; and ‡Biohaven Pharmaceuticals, Inc., New Haven, Connecticut 06510, USA

1To whom correspondence should be addressed at DILIsym Services, Inc., A Simulations Plus Company, 6 Davis Drive, Research Triangle Park, NC 27709, USA. E-mail: jeff.woodhead@simulations-plus.com.

Available online at www.sciencedirec

ScienceDirect

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DILIsym: Quantitative systems toxicology impacting drug development

Paul B. Watkins

Clinical Pharmacology & Therapeutics

Article

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

James J. Beaudoin, William J. Brock, Paul B. Watkins, Kim L. R. Brouwer

First published: 03 August 2020 | https://doi.org/10.1002/cpt.2007

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Research Article

CrossMark

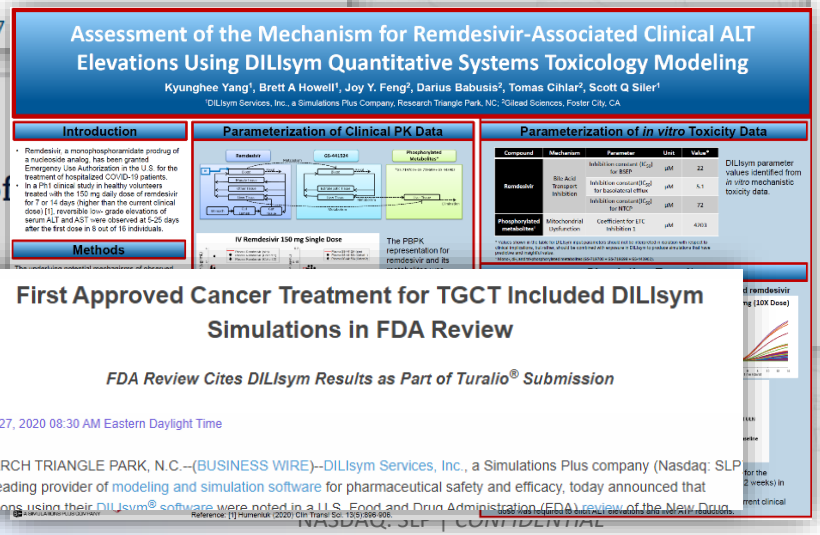
Analyzing the Mechanisms Behind Macrolide Antibiotic-Induced Liver Injury Using Quantitative Systems Toxicology Modeling

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]

Assessment of the Mechanism for Remdesivir-Associated Clinical ALT Elevations Using DILIsym Quantitative Systems Toxicology Modeling

Kyunghee Yang[1], Brett A Howell[1], Joy Y. Feng[2], Darius Babusis[2], Tomas Cihlar[2], Scott Q Siler[1]

[1]DILIsym Services, Inc., a Simulations Plus Company, Research Triangle Park, NC; [2]Gilead Sciences, Foster City, CA



Mechanistic Investigations Support Liver Safety of Ubrogepant

Brenda Smith,* Josh Rowe,*[,1] Paul B. Watkins,[†] Messoud A Jeffrey L. Woodhead,[§] Frank D. Sistare,[¶] and Peter J. Goadsby[||]

*Allergan plc, Irvine, California; †Eshelman School of Pharmacy and Institute for Drug Safety University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; ‡Department of Neu Headache Center, Faculty of Health and Medical Sciences, University of Copenhagen, Køben §DILIsym Services, Durham, North Carolina; ¶Merck & Co., Inc., West Point, Pennsylvania an

First Approved Cancer Treatment for TGCT Included DILIsym Simulations in FDA Review

FDA Review Cites DILIsym Results as Part of Turalio® Submission

October 27, 2020 08:30 AM Eastern Daylight Time

RESEARCH TRIANGLE PARK, N.C.--(BUSINESS WIRE)--DILIsym Services, Inc., a Simulations Plus company (Nasdaq: SLP) and a leading provider of modeling and simulation software for pharmaceutical safety and efficacy, today announced that simulations using their DILIsym® software were noted in a U.S. Food and Drug Administration (FDA) review of the New Drug

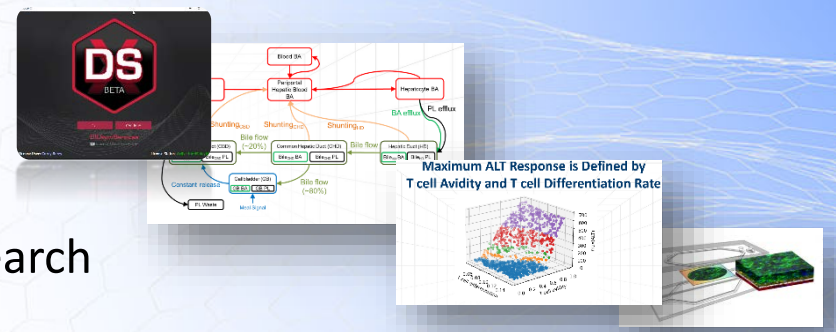
Quantitative systems toxicology (QST) reproduces species differences in PF-04895162 liver safety due to combined mitochondrial and bile acid toxicity

Grant Generaux[1] | Vinal V. Lakhani[1] | Yuching Yang[1] | Sashi Nadanaciva[2] | Luping Qiu[3] | Keith Riccardi[4] | Li Di[4] | Brett A. Howell[1] | Scott Q. Siler[1] | Paul B. Watkins[5,6] | Hugh A. Barton[7] | Michael D. Aleo[3] | Lisl K. M. Shoda[1]

[1]DILIsym Services Inc., Research Triangle Park, North Carolina
[2]Compound Safety Prediction, Worldwide Medicinal Chemistry, Pfizer Inc., Groton, Connecticut
[3]Investigative Toxicology, Drug Safety Research and Development, Pfizer Inc., Groton, Connecticut

The DILI-sim Initiative / RENAsym Consortium Will Continue Beyond 2023 into Phase 5 (~2024-2026)

Major Accomplishments of the Effort in Last Few Years



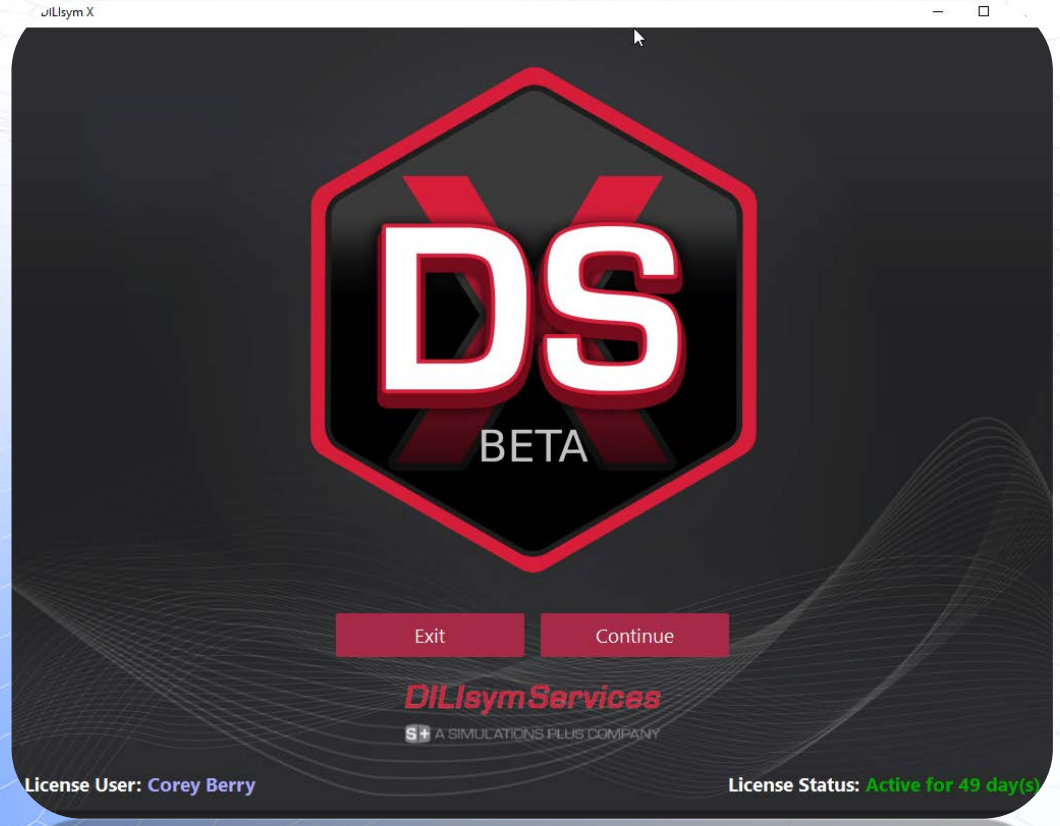
- Major software refactoring to increase user adoption - DSX
- MDR3 / cholestasis
- Immune
- Procured additional funding for wet lab, liver on chip program research
- Foundation laid for pediatric SimPops
- Many high-impact DILIsym applications (e.g. CGRP's, Turalio®, APAP carcinogenicity, Emvododstat, and more)

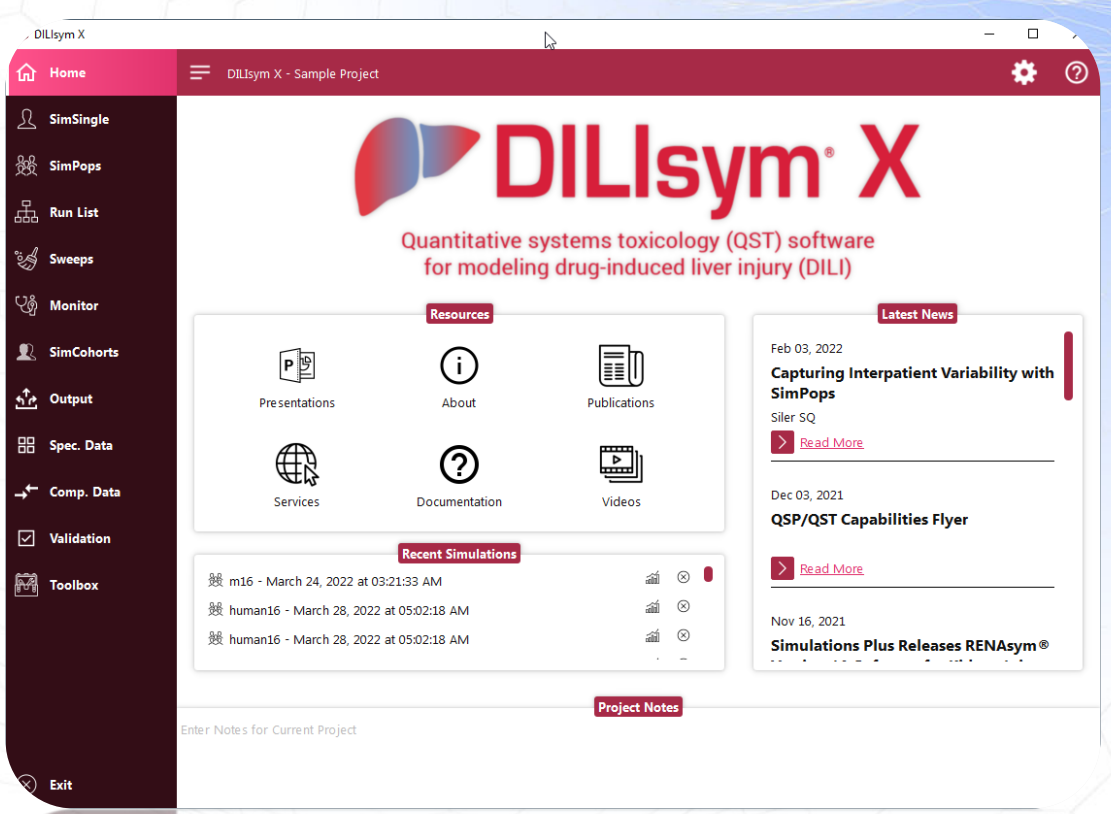
Major Areas of Continued Focus into Stage 5 (~2024-2026)

- Application of liver-on-a-chip data for large and small molecule safety – **all tools developed as part of additional grant funding will be included in DILIsym software for all members with no additional fees!**
- Release of adaptive immune response exploration framework within DILIsym
- Pediatric SimPops and other application focused SimPops
- Software enhancements – full integration with GastroPlus; conversion of RENAsym to C++
- Machine learning inputs – finalize machine learning models of DILIsym / RENAsym inputs for earlier use of QST in drug development

Corey Berry
Senior Software Engineer
Greensboro Area, NC

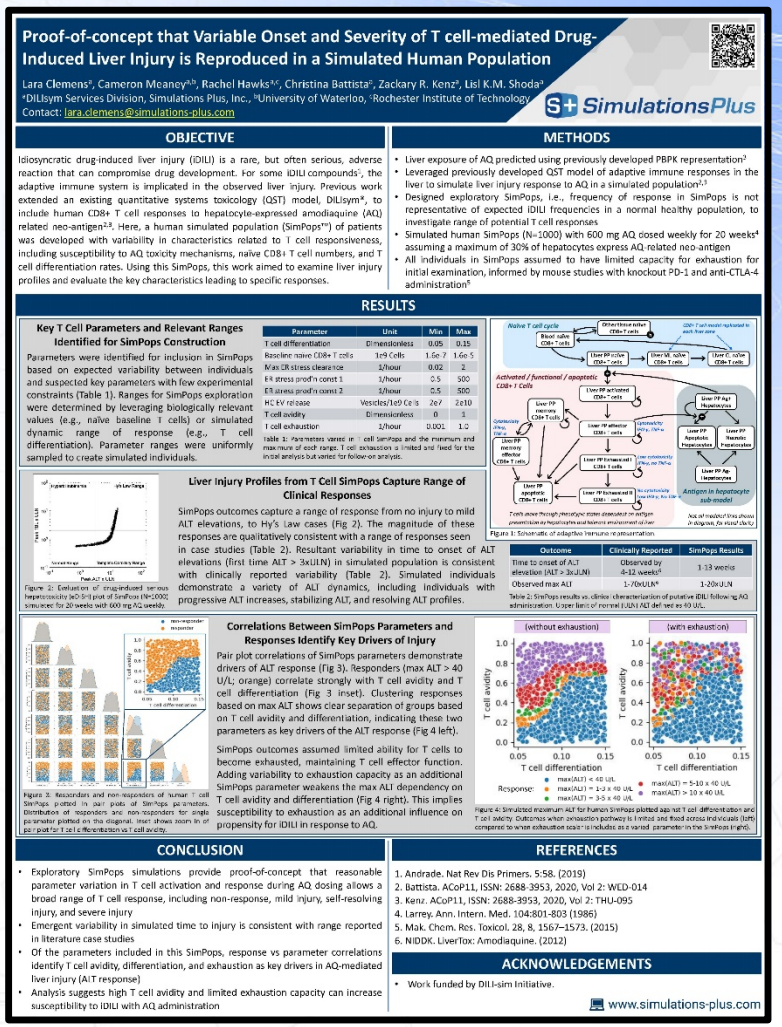
DILIsym version 10 (DSX) Beta Testing Version Available Now for Download





Adaptive Immune Sub-model Projected for Release in DILIsym v11

- Work ongoing to prepare exploratory adaptive immune sub-model for release in DILIsym v11
  - Addition of a sub-model switch to allow user to turn on/off adaptive immune response
  - Refinement of memory and rechallenge response based on available data
  - Evaluation of model outcomes during dose-response simulations, alternative compound administration
  - Finalizing exploratory human SimPops
  - Updating documentation and user guide
- Adaptive immune human SimPops work presented at ACoP13 (Oct 31, Denver CO)
  - Results shared with consortium at Q3 2022 meeting
  - Poster accessible through SLP website



Proof-of-concept that Variable Onset and Severity of T cell-mediated Drug-Induced Liver Injury is Reproduced in a Simulated Human Population

Lara Clemens[a], Cameron Mcaney[a,b], Rachel Hawks[a,c], Christina Battista[a], Zackary R. Kenz[a], Lisl K.M. Shoda[a]
[a]DILIsym Services Division, Simulations Plus, Inc., [b]University of Waterloo, [c]Rochester Institute of Technology
Contact: lara.clemens@simulations-plus.com

SimulationsPlus

OBJECTIVE

Idiosyncratic drug-induced liver injury (iDILI) is a rare, but often serious, adverse reaction that can compromise drug development. For some iDILI compounds[1], the adaptive immune system is implicated in the observed liver injury. Previous work extended an existing quantitative systems toxicology (QST) model, DILIsym®, to include human CD8+ T cell responses to hepatocyte-expressed amodiaquine (AQ) related neo-antigen[2,3]. Here, a human simulated population (SimPops™) of patients was developed with variability in characteristics related to T cell responsiveness, including susceptibility to AQ toxicity mechanisms, naïve CD8+ T cell numbers, and T cell differentiation rates. Using this SimPops, this work aimed to examine liver injury profiles and evaluate the key characteristics leading to specific responses.

METHODS

- Liver exposure of AQ predicted using previously developed PBPK representation[2]
- Leveraged previously developed QST model of adaptive immune responses in the liver to simulate liver injury response to AQ in a simulated population[2,3]
- Designed exploratory SimPops, i.e., frequency of response in SimPops is not representative of expected iDILI frequencies in a normal healthy population, to investigate range of potential T cell responses
- Simulated human SimPops (N=1000) with 600 mg AQ dosed weekly for 20 weeks[4] assuming a maximum of 30% of hepatocytes express AQ-related neo-antigen
- All individuals in SimPops assumed to have limited capacity for exhaustion for initial examination, informed by mouse studies with knockout PD-1 and anti-CTLA-4 administration[5]

RESULTS

Key T Cell Parameters and Relevant Ranges Identified for SimPops Construction

Parameters were identified for inclusion in SimPops based on expected variability between individuals and suspected key parameters with few experimental constraints (Table 1). Ranges for SimPops exploration were determined by leveraging biologically relevant values (e.g., naïve baseline T cells) or simulated dynamic range of response (e.g., T cell differentiation). Parameter ranges were uniformly sampled to create simulated individuals.

Parameter	Unit	Min	Max
T cell differentiation	Dimensionless	0.05	0.15
Baseline naive CD8+ T cells	1e9 Cells	1.6e-7	1.6e-5
Mas CR stress clearance	1/hour	0.02	2
ER stress prodn const 1	1/hour	0.5	500
ER stress prodn const 2	1/hour	0.5	500
HC EV release	Vesicles/1e9 Cells	2e7	2e10
T cell avidity	Dimensionless	0	1
T cell exhaustion	1/hour	0.001	1.2

Table 1: Parameters varied in T cell SimPops and the minimum and maximum of each range. T cell exhaustion is limited and fixed for the initial analysis but varied for follow-on analysis.

Figure 2: Evaluation of drug-induced serious hepatotoxicity (eDILI) risk of SimPops (N=1000) simulated for 20 weeks with 600 mg AQ weekly.

Liver Injury Profiles from T Cell SimPops Capture Range of Clinical Responses

SimPops outcomes capture a range of response from no injury to mild ALT elevations, to Hy's Law cases (Fig 2). The magnitude of these responses are qualitatively consistent with a range of responses seen in case studies (Table 2). Resultant variability in time to onset of ALT elevations (first time ALT > 3xULN) in simulated population is consistent with clinically reported variability (Table 2). Simulated individuals demonstrate a variety of ALT dynamics, including individuals with progressive ALT increases, stabilizing ALT, and resolving ALT profiles.

Figure 1: Schematic of adaptive immune representation.

Outcome	Clinically Reported	SimPops Results
Time to onset of ALT elevation (ALT > 3xULN)	Observed by 4-12 weeks[6]	1-13 weeks
Observed max ALT	1-70xULN[6]	1-20xULN

Table 2: SimPops results vs. clinical characterization of putative iDILI following AQ administration. Upper limit of normal (ULN) ALT definition as 40 U/L.

Figure 3: Responders and non-responders of human T cell SimPops plotted in pair plots of SimPops parameters. Distribution of responders and non-responders for single parameter plotted on the diagonal. Inset shows zoom in of pair plot for T cell differentiation vs T cell avidity.

Correlations Between SimPops Parameters and Responses Identify Key Drivers of Injury

Pair plot correlations of SimPops parameters demonstrate drivers of ALT response (Fig 3). Responders (max ALT > 40 U/L; orange) correlate strongly with T cell avidity and T cell differentiation (Fig 3 inset). Clustering responses based on max ALT shows clear separation of groups based on T cell avidity and differentiation, indicating these two parameters as key drivers of the ALT response (Fig 4 left).

SimPops outcomes assumed limited ability for T cells to become exhausted, maintaining T cell effector function. Adding variability to exhaustion capacity as an additional SimPops parameter weakens the max ALT dependency on T cell avidity and differentiation (Fig 4 right). This implies susceptibility to exhaustion as an additional influence on propensity for iDILI in response to AQ.

Figure 4: Simulated maximum ALT for human SimPops plotted as a function of T cell differentiation and T cell avidity. Outcomes when exhaustion pathway is limited and fixed across individuals (left) compared to when exhaustion scale is included as a varied parameter in the SimPops (right).

CONCLUSION

- Exploratory SimPops simulations provide proof-of-concept that reasonable parameter variation in T cell activation and response during AQ dosing allows a broad range of T cell response, including non-response, mild injury, self-resolving injury, and severe injury
- Emergent variability in simulated time to injury is consistent with range reported in literature case studies
- Of the parameters included in this SimPops, response vs parameter correlations identify T cell avidity, differentiation, and exhaustion as key drivers in AQ-mediated liver injury (ALT response)
- Analysis suggests high T cell avidity and limited exhaustion capacity can increase susceptibility to iDILI with AQ administration

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6. NIDDK. LiverTox: Amodiaquine. (2012)

ACKNOWLEDGEMENTS

- Work funded by DILI-sim Initiative.

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New SimPops Utilizing the Refined Cholestatic Liver Injury Submodel Is Undergoing Further Optimization and Validation

The human bile acid (BA) and phospholipid (PL) submodels within DILIsym have been updated with new features relevant to cholestatic liver injury:

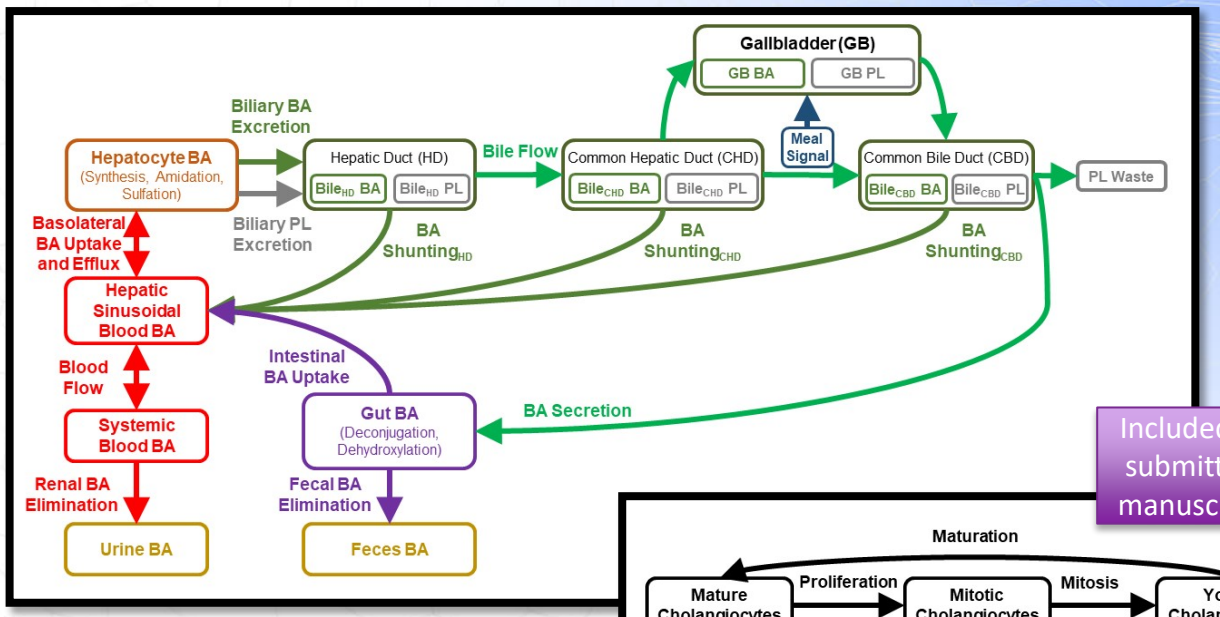
(1) Cholehepatic shunting of BAs

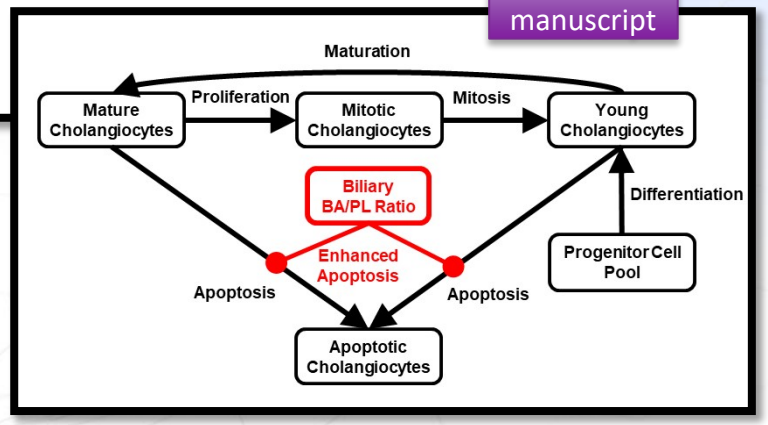
(2) Biliary HCO_3^- secretion and its impact on:
- ❖ Bile flow
- ❖ BA shunting
- ❖ Cholangiocyte toxicity

(3) Different modes of MDR3* inhibition

(4) Non-MDR3-mediated PL efflux

(5) Cholangiocyte regeneration





Included in submitted manuscript

- New SimPops that represents variability in both BA toxicity and cholestasis mechanisms is undergoing development
  - ❖ Calibration/validation underway with numerous no-treatment and with-treatment data
- The updated BA and PL submodels and the new SimPops will be added to DILIsym v11
- Manuscript describing the development of the new BA and PL submodels and the new SimPops has been submitted for (invited) publication; currently under review

**MDR3: Multidrug Resistance Protein 3, a PL floppase on the canalicular membrane of hepatocytes often implicated in cholestatic hepatotoxicity*

Pediatric SimPops Development Progress

Q4 2021 | Q4 2022 | Q4 2023 and beyond

✓ Step 1: Initial testing of pediatric representations in DILIsym

- Imported G+ PEAR physiology to create representative pediatrics (1 yo, 4 yo, 10 yo, 14 yo)
- Scaled down bile acid parameters
- Created four pediatric SimCohorts (n=16) representing 1 yo, 4 yo, 10 yo, and 14 yo
- Simulated responses to BAi, mito tox, ROS mechanisms using a "dummy" drug

Step 2: Implement age-dependent PEAR physiology and bile acid mechanism in DILIsym code

- ✓ Implement G+ PEAR physiology in DILIsym code
- ✓ Implement age-specific scaling factors in BA and cholangiocyte parameters (e.g., liver volume, transporter ontogeny)
- Optimize pediatrics BA/cholangiocyte sub-models with clinically observed reference ranges of plasma/liver BA profiles
- Develop/test pediatric SimPops

Release in DILIsym 11

Step 3: Further develop pediatric physiology in DILIsym

- Incorporate age-related differences beyond organ volume and BA mechanism where data available (e.g., glutathione, mito function)
- Predict DILI susceptibility of exemplar compounds in pediatrics
- Implement continuous physiological changes for longer-term simulations

Release in future DILIsym versions

DILIsym Preclinical Use Strategy (DPUS) Program Justification

- **Why use DILIsym (and RENAsym in future) during preclinical stages of drug development?**
- **What are the main advantages at each stage?**
- **Disadvantages and challenges of preclinical use**
- **General contrasts between preclinical and clinical use cases**

- Higher probability of successful candidates
- Early candidate kills save more time and money
- Faster implementation of DILIsym in clinic later if needed
- Better FIH design / dose projection / margin projection
- Reduce suspicions surrounding program early
- Better anticipate possible DDI's
- Better anticipate special population issues based on indication
- Prediction / extrapolation tools are critical at this stage

- Less information available
- Less funding within the program
- Less confidence in modeling results
- Less personnel / resources
- Less information about projected dose(s) for efficacy

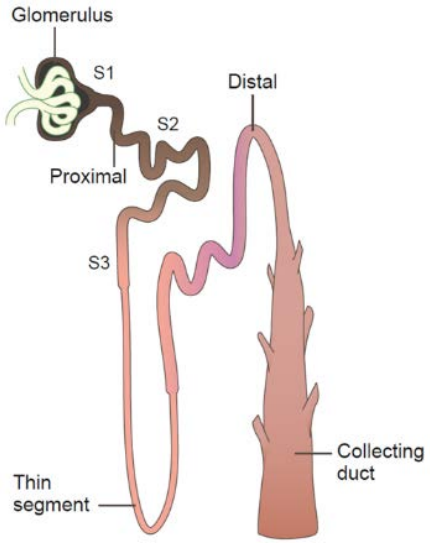
- Less involvement from regulators (at least by necessity)
- Lower threshold for accuracy (rank order, etc.)
- More driven by proactive mindset
- Important to define the context of use and risk tolerance
- Less focused on exact dose evaluation

DILIsym Preclinical Use Strategy (DPUS)
Impact Vision: Example High Impact Scenarios

- ***Sponsor desires streamlined yet very logical and organized data + modeling and simulation approach to preclinical development (lead optimization/candidate selection) liver safety assessment program*** – DILIsym preclinical use and associated assay inputs implemented as regular and high impact component of development plan for entire pipeline (either through internal software use or outsourcing)
- ***A liver safety signal is seen with a sponsor's candidate in one animal species but not the other*** – DILIsym preclinical use helps elucidate true risk in clinic
- ***A clear unambiguous liver safety signal was seen not in animals but rather in an early clinical trial*** – DILIsym preclinical use helps define best preclinical de-risking strategy for backups
- ***Sponsor learns that a competitor's very similar molecule being developed against the same therapeutic target has run into a liver safety liability either in animals or in humans*** – DILIsym preclinical use differentiates against competitor early

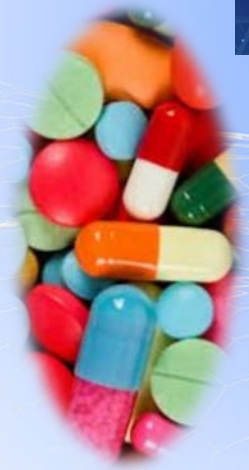
RENAsym Software Overview

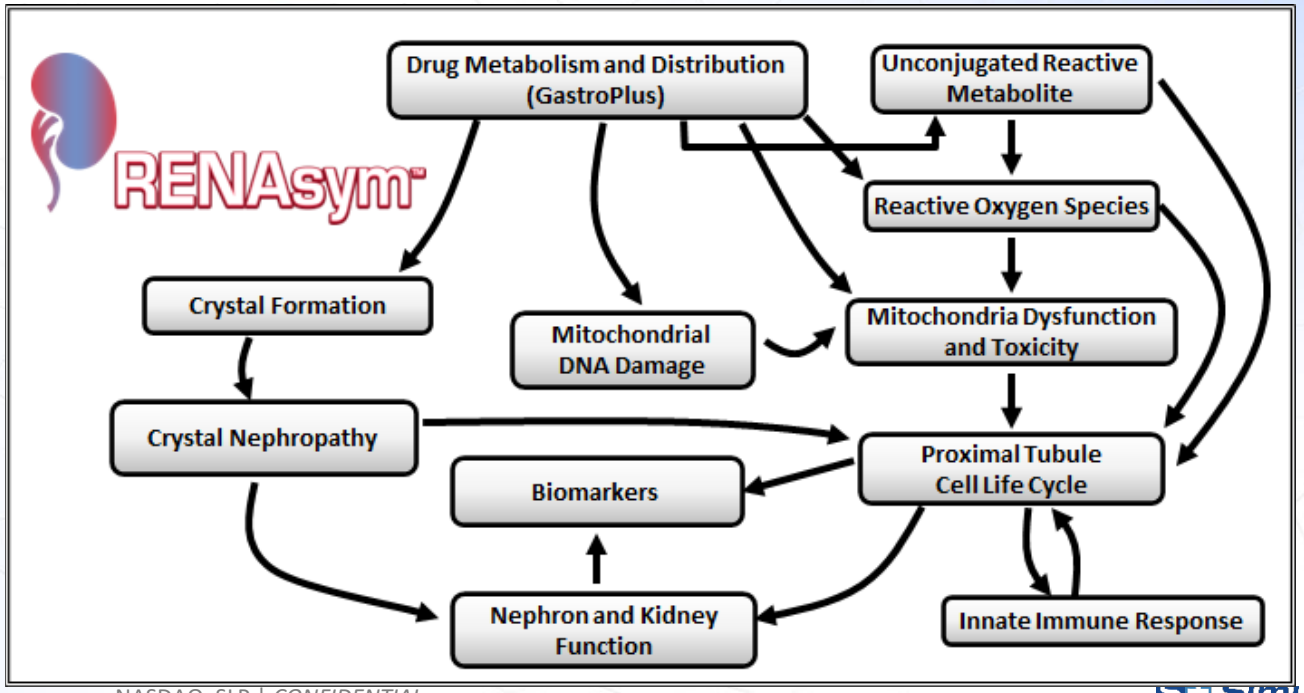
- **Species: human and rat**
  - Population variability
- **Primary focus is nephron proximal tubules**
- **Multiscale biology**
- **Proximal tubule cells (PTC)**
  - Cellular energy balance
  - Apoptosis and necrosis, and proliferation
  - GSH depletion
  - Mitochondrial dysfunction, toxicity, DNA depletion
  - Crystal nephropathy
  - Inflammatory response
  - Neutrophils, macrophages, DCs
  - HMGB1, TNF-α, IL-1β, IL-6, IL-10, IL-18, HGF
- **Biomarkers**
  - Biomarkers of cell death and function (alpha GST, KIM-1)
  - Emerging biomarkers (uIL-18)
  - GFR, creatinine, RBF
- **Renal function**
  - Hemodynamics
  - Na+, Water reabsorption
  - RAAS modulation



Ghezzi et al., Diabetologia 2018

- **Drugs**
  - Cisplatin
  - Gentamicin
  - Piroxicam
  - Cyclosporin A
  - Acyclovir
  - Indinavir
  - Valproate





Relevant Recent RENAsym News / Publications

Simulations Plus Releases RENAsym® Version 1A Software for Kidney Injury

By: Simulations Plus, Inc. via Business Wire News Releases — November 16, 2021 at 08:30 AM EST

SimulationsPlus

Simulations Plus, Inc. (Nasdaq
announced that its DILIsym Se
for predicting and investigatin

Dr. Brett Howell, president of
RENAsym, our newest QST pla
well, thereby expanding the re

Dr. Jeffrey Woodhead, Princip
injure the kidneys of preclinic
the QST side, allowing us to sc

Mechanistic Modeling of Cyclosporine A-induced Acute Kidney Injury with RENAsym®

Pallavi Bhargava[a], Christina Battista[a], Viera Lukacova[b], Jeffrey L. Woodhead[a]
[a]DILIsym Services, Inc., Research Triangle Park, NC; [b]Simulations Plus Inc., Lancaster, CA

ABSTRACT

OBJECTIVES: The use of Cyclosporine A (CsA) can cause tubular damage leading to a decline in renal function as determined by decreases in serum creatinine levels, glomerular filtration rate (GFR), and ATP[1]. This work uses RENAsym®, a quantitative systems toxicology (QST) model of acute kidney injury (AKI), to recapitulate clinical outcomes following CsA administration in humans.

METHODS: The effects of CsA on mitochondrial function and reactive oxygen species (ROS) production were assessed to define the potential for CsA-induced kidney injury. Human renal proximal tubule epithelial cells (RPTECs) were treated with CsA and its effects on

RESULTS

Figure 1: RENAsym is comprised of submodels that interact with one another to predict kidney injury outcomes. RENAsym combines data from *in vitro* toxicity studies, predictions of metabolism and distribution, as well as inner workings of kidney

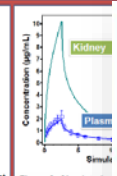


Figure 2: Simulated a of CsA, 4 mg/kg, for 2 plasma concentration

METHODS

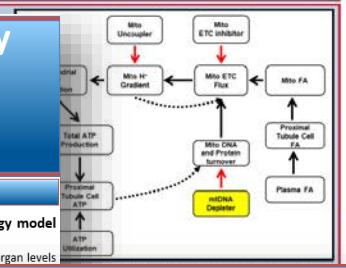
Development of Quantitative Systems Toxicology Model to Predict Drug Induced Acute Kidney Injury via mtDNA Depletion Pathway

Shailendra B. Tallapaka, Nader Hamzavi, Yeshitila Gebremichael, Scott Q. Siler, Jeffrey L. Woodhead
DILIsym Services, Inc., a Simulations Plus company, Research Triangle Park, NC, USA

ABSTRACT

Objective: Treatment of chronic viral infections like HIV, Hepatitis B etc.,

METHODS



CONCLUSION

- mtDNA depletion has been incorporated into the mitochondrial dysfunction sub-model of RENAsym.
- In the baseline simulated individual, model predicts decline in ATP but not PTC viability upon adefovir treatment.
- Sensitivity analysis indicates model is likely to predict toxicity in simulated populations.
- These results show that RENAsym shows promise in being a useful tool to predict drug induced AKI
- Model will be refined by collecting more in vitro data and representing more exemplar compounds.

REFERENCES

1. Lewis, W., Day, B. & Copeland, W.

Quantitative Systems Toxicology (QST) Modeling of Drug-Induced Acute Proximal Tubule Epithelial Cell Injury and Associated Renal Hemodynamic Responses

Nader Hamzavi[a], Yeshitila Gebremichael[b], Jeffrey L. Woodhead[a], Sergey Ermakov[c], and Brett A. Howell[a]
[a]DILIsym Services Division, Simulations Plus company, Research Triangle Park, NC, [b]Valo Health, Boston, MA, [c]Daiichi Sankyo, Inc, Hayward, CA

INTRODUCTION

- Renal proximal tubule epithelial cells (RPTEC) are vulnerable to drug-induced toxicities which often result in acute kidney injury (AKI).
- Drug toxic effects range from mild sub-lethal RPTEC injuries to cellular death via multiple cellular damage mechanisms. At the systems level, decline in glomerular filtration rate (GFR) is a common manifestation of AKI.
- The complexity of pathophysiological responses (cellular, neurohormonal, hemodynamic) that lead to impaired filtration pose a challenge for reliable prediction of AKI.

RESULTS

- The model quantitatively relates cellular injury and biomarker changes with renal hemodynamic responses.
- Nephrotoxic drugs such as cisplatin are used to as
- At the cellular level, urinary biomarkers such as KI represent cellular injury (ROS/Mito dysfunction/Cr following cisplatin exposure. RENAsym was able to and αGST in rats treated with cisplatin.
- At the systemic level, functional biomarkers such a

CONCLUSION

We developed a quantitative systems toxicology model of drug-induced acute kidney injury

- RENAsym represents kidney function at cellular and organ levels

Mechanistic Modeling of Kidney-Injury Molecule 1 (KIM-1) as a biomarker for Cisplatin-Induced Acute Kidney Injury

Nader Hamzavi[a], Yeshitila Gebremichael[b], Jeffrey L. Woodhead[a], Sergey Ermakov[c], and Brett A. Howell[a]
[a]DILIsym Services Division, Simulations Plus company, Research Triangle Park, NC, [b]Valo Health, Boston, MA, [c]Daiichi Sankyo, Inc, Hayward, CA

INTRODUCTION

Kidney Injury Molecule 1 (KIM-1) is a specific and sensitive biomarker for drug-induced acute kidney injury (AKI) prediction

Despite growing interest in clinical use of KIM-1 as a key biomarker for AKI diagnosis, a mechanistic model of KIM-1 that accurately predicts the kinetics of KIM-1 is still lacking.

Unlike normal conditions where urinary Kim-1 is not detectable, it is significantly expressed during acute kidney injury. Kim-1 was detected at high levels in proliferating bromodeoxyuridine-positive and dedifferentiated vimentin-positive epithelial cells in regenerating proximal tubules (Ichimura 1998).

We developed a mechanistic model of KIM-1 as part of a quantitative systems toxicology (QST) model to predict urinary

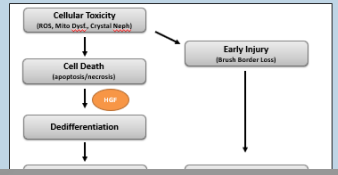
RESULTS

- Kim-1 is considered an inducible biomarker that significantly upregulated during AKI and released into the urine
- In our model, the production of Kim-1 mainly originates from upregulated Kim-1 in dedifferentiated cells and early shedding of Kim-1 comes from existing Kim-1

$$\text{Kim1 Excretion} = \text{Basal Kim1}^{(1)} + \text{Exisiting Kim1}^{(2)} + \text{Kim1 upregulation}^{(3)} - \text{Kim1 shedding}$$

1. The basal Kim-1 production at steady state is set to be very low in line with the basal shedding rate of Kim-1 reported in control healthy individuals (Peters 2011)
2. Urinary Kim-1 is reported before dedifferentiation process begins, and it may be attributed to proximal tubule brush border loss
   - An existing level of Kim-1 is assumed to be sitting on PTCs and its shedding rate into the urine is determined based on ATP decrement
3. Kim-1 is markedly upregulated in regenerated PTCs and mechanistically linked with the flux of dedifferentiated cells in RENAsym

Kim-1 Mechanistic Model



CONCLUSION

Developed a mechanistic model of urinary Kim-1 biomarker response to characterize cisplatin-mediated acute kidney injury

- Kim1 model recapitulate the Kim-1 profile in rats treated with cisplatin as well as the Kim-1 peak in humans and mice
- Kim-1 upregulation is determined to be the main contributor to urinary Kim-1 during AKI
- Using dedifferentiation as the driving signal for Kim-1 upregulation, the timing of predicted Kim-1 peak aligns with the clinical and preclinical data
- As dedifferentiation starts with a delay, we could capture the early increase in urinary Kim1 by assuming the shedding of existing Kim-1 sitting on PTCs

SOT 2023 SLP Lunch & Learn Shot Chart

- Simulations Plus – Your Strategic Partner in Safety and Risk Assessment!
- Exposure Related News and Updates
- Liver and Kidney Safety Related News and Updates
- Q&A