DILIsym Services

A SIMULATIONS PLUS COMPANY

Webinar: Clinical DILI and State-of-the-Art Solutions

April 2, 2020

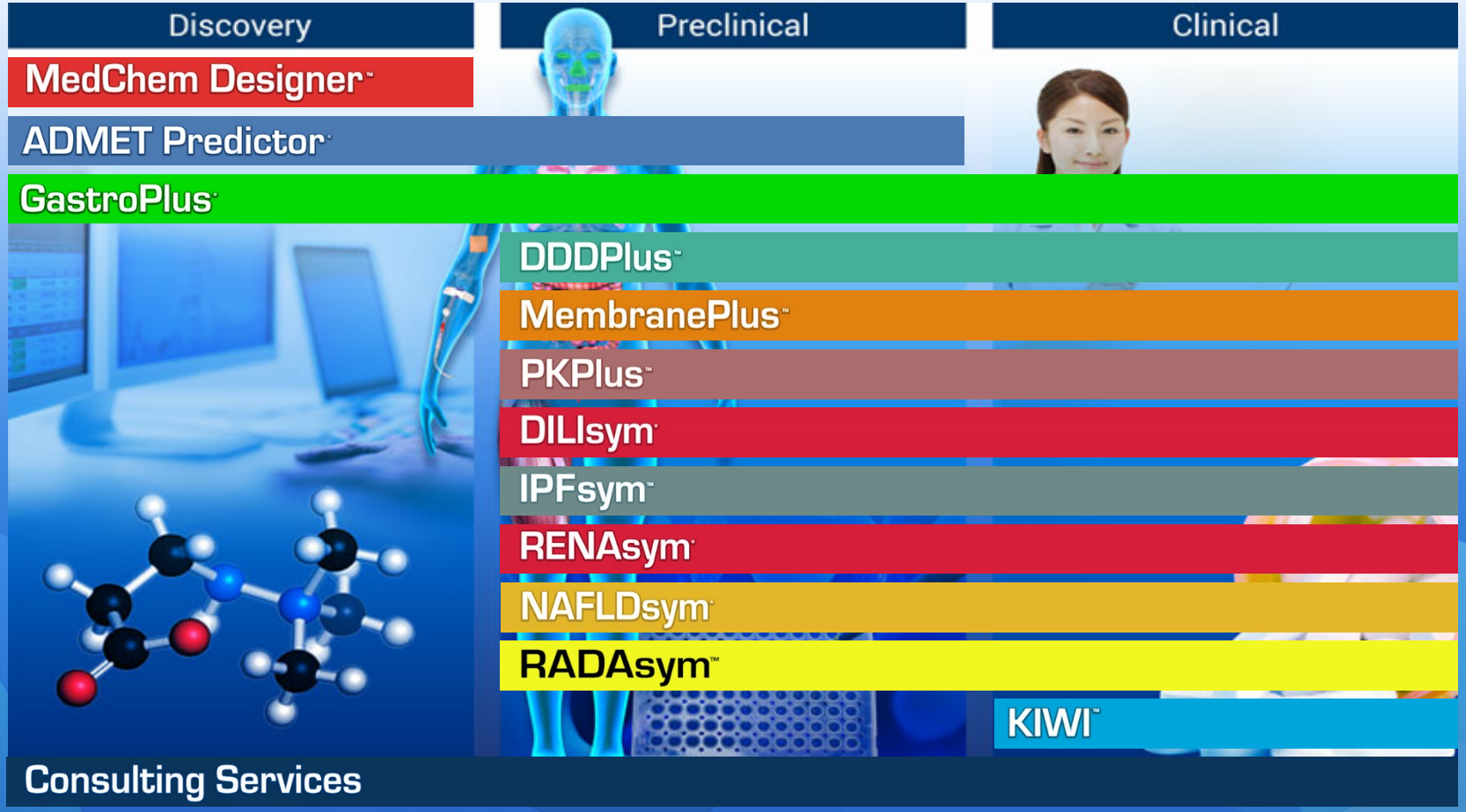
Drs. Paul B. Watkins and Lisl K.M. Shoda

SimulationsPlus | Cognigen | DILIsym Services

SCIENCE+SOFTWARE=SUCCESS

Where are you in the research process?

Save resources and get to market faster with our solutions.



DILIsym Services Inc., an SLP Company

"Our vision is safer, effective, more affordable medicines for patients through modeling and simulation."

- DILIsym Services, Inc. offers comprehensive program services:
  - **DILIsym** software licensing, training, development (DILI-sim Initiative)
  - **NAFLDsym** software licensing, training, development
  - **DILIsym** and **NAFLDsym** simulation consulting projects
  - Consulting and data interpretation; *in vitro* assay experimental design and management
  - **RENAsym** and **IPFsym** software in development

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Meet the Presenters

Paul B. Watkins
DILI-sim Initiative Founder and Scientific Advisory Board Chair
RTP, NC

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Chief Scientific Officer
Bay Area, CA

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Lancaster, CA

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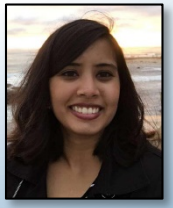

Vinal Lakhani
Scientist I
RTP, NC

Diane Longo
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Arlington, VA

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Scientist II
RTP, NC

Webinar Agenda

- Drug-induced liver injury (DILI): a clinical perspective on the problem
- DILIsym: a viable solution
- Live questions from the audience

Disclosure

I chair the scientific advisory committee for the DILI-sim Initiative and have a financial interest in the success of DILIsym Services Inc.

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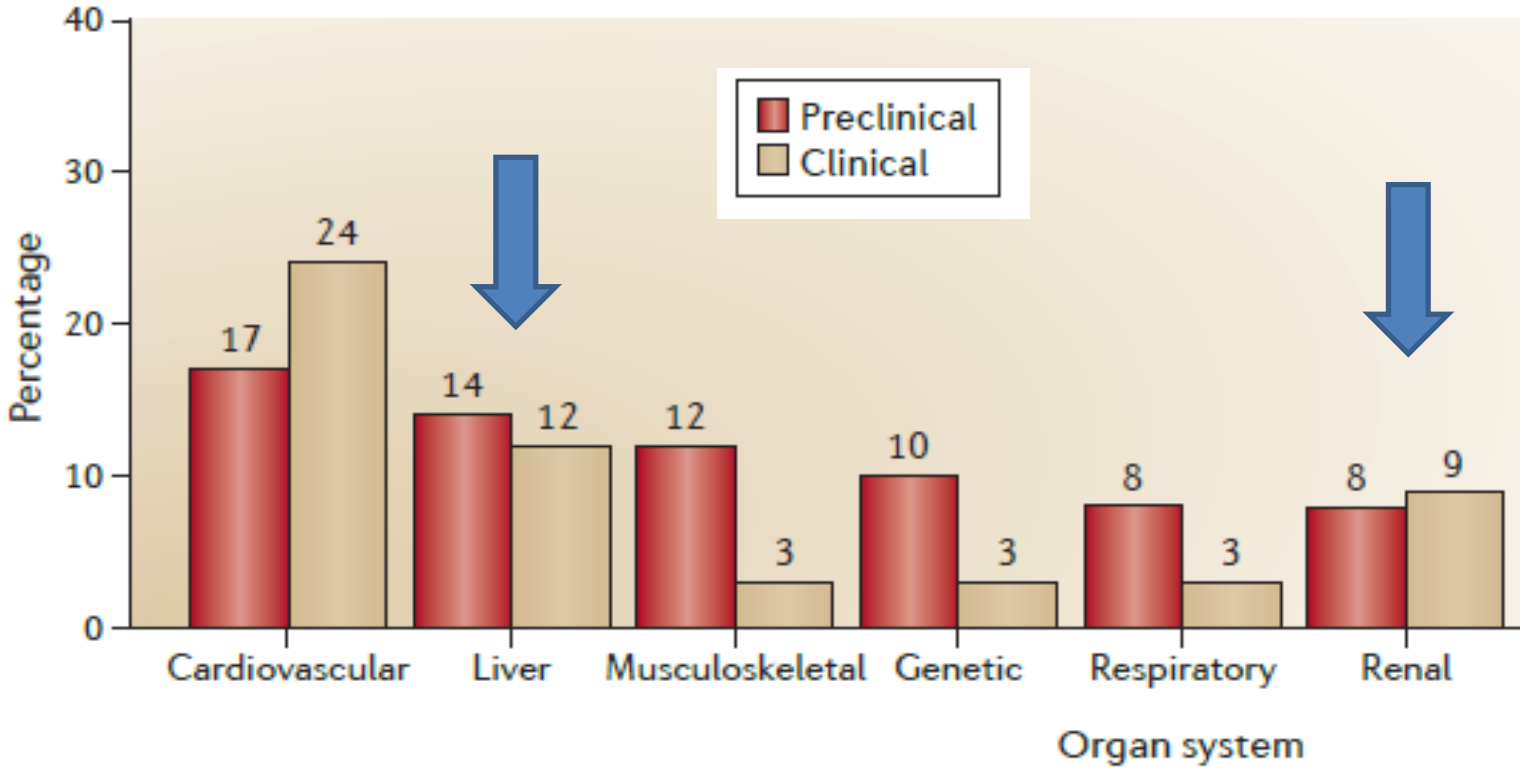
Reasons for Termination of Drug Programs Due to Safety by Organ System (Astra Zeneca Experience)



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Progress?

No drugs approved in the last decade have been withdrawn from the market in the U.S. due to liver safety concerns:

1). Drug developers and regulators and are smarter

but

2). Clinical trials are much bigger and longer now……

Then…and now

Rezulin (troglitazone) was approved in 1997 with less than 1,000 patients treated for 6 months

When rivaroxaban was approved, over 60,000 patients had been exposed to the drug

Motif Bio Shares Plummet After Additional Iclaprim Clinical Trial Blow (ALLISS)

LONDON (Alliance News) –
Alliance News 6 June, 2019 | 10:07AM

"On Thursday, Motif explained it had received the official minutes of its meeting with the FDA …(and) an **additional clinical trial will be needed before granting marketing approval to address continued concerns of the regulator about potential liver toxicity."**

"Rule of Three"
To exclude and event in 1:1,000, need a trial of 3,000 subjects

Economics of delay in FDA approval

If drug attains at least $1B/year in sales at the end of patent life

Every day of delay in approval >$2 million

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Don’t’ forget Herbal and Dietary Supplements!

The Drug Induced Liver Injury Network (DILIN) Cohort
September 2004 to May 2013

Top 10 therapeutic classes and individual agents to cause liver injury in the DILIN (N=899)

	Therapeutic Class	n
1	Antimicrobials	408
2	Herbal and dietary	145
3	CVS agent	88
4	CNS agents	82
5	Anti-neoplastics	49
6	Analgesics	33
7	Immunomodulatory	27
8	Endocrine	20
9	Rheumatologic	13
10	Gastrointestinal	12

Chalasani et. al. Gastroenterology 2015

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Drug-Induced Liver Injury (DILI)

1). Remains a major problem in drug development, driving up drug costs and delaying release of new drugs.

2). Is also a rising problem with herbal and dietary supplements.

Assessing Liver Safety of New Drug Candidates

1). Preclinical (non-clinical) studies

a). Variety of molecular screening tools

b). Animal models – rodent and non-rodent

Good drugs are being dropped at the preclinical stage due to toxicity concerns….

Acetaminophen

Ibuprofen

Assessing Liver Safety of New Drug Candidates

1). Preclinical (non-clinical) studies

a). Variety of molecular screening tools

b). Animal models – rodent and non-rodent

2). Clinical trials

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Serum Alanine Aminotransferase (ALT) is universally used to detect and monitor liver injury

- **Protein present inside hepatocytes**
- **Leaks into circulation during hepatocyte injury/death**
- **Elevations essentially liver-specific if there is no muscle injury.**

Problems with Serum ALT as a Biomarker for DILI in Clinical Trials

1). Some drugs cause ALT elevations yet are rarely associated with clinically important liver injury (e.g. statins, cholestyramine, heparins, tacrine)

2). ALT elevations generally resolve with continued treatment even for drugs that can cause liver failure

How do you tell when ALT elevations indicate serious DILI potential?

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General Approach to ALT elevations in Clinical Trials

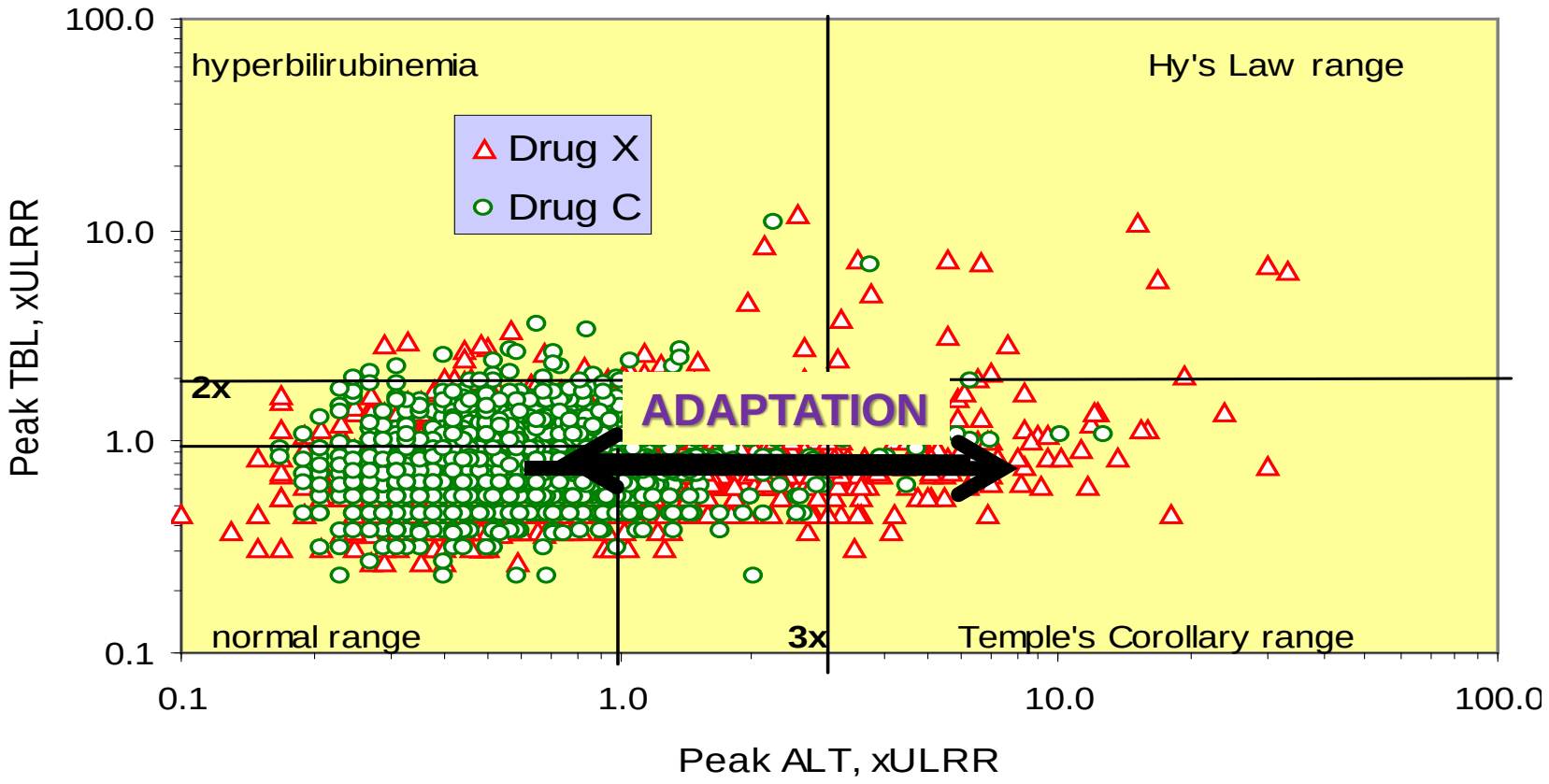
1). Continue to treat through the elevations to see if global liver dysfunction occurs

– i.e. a rise in serum bilirubin > 2 X ULN

("Hy's Law Case")

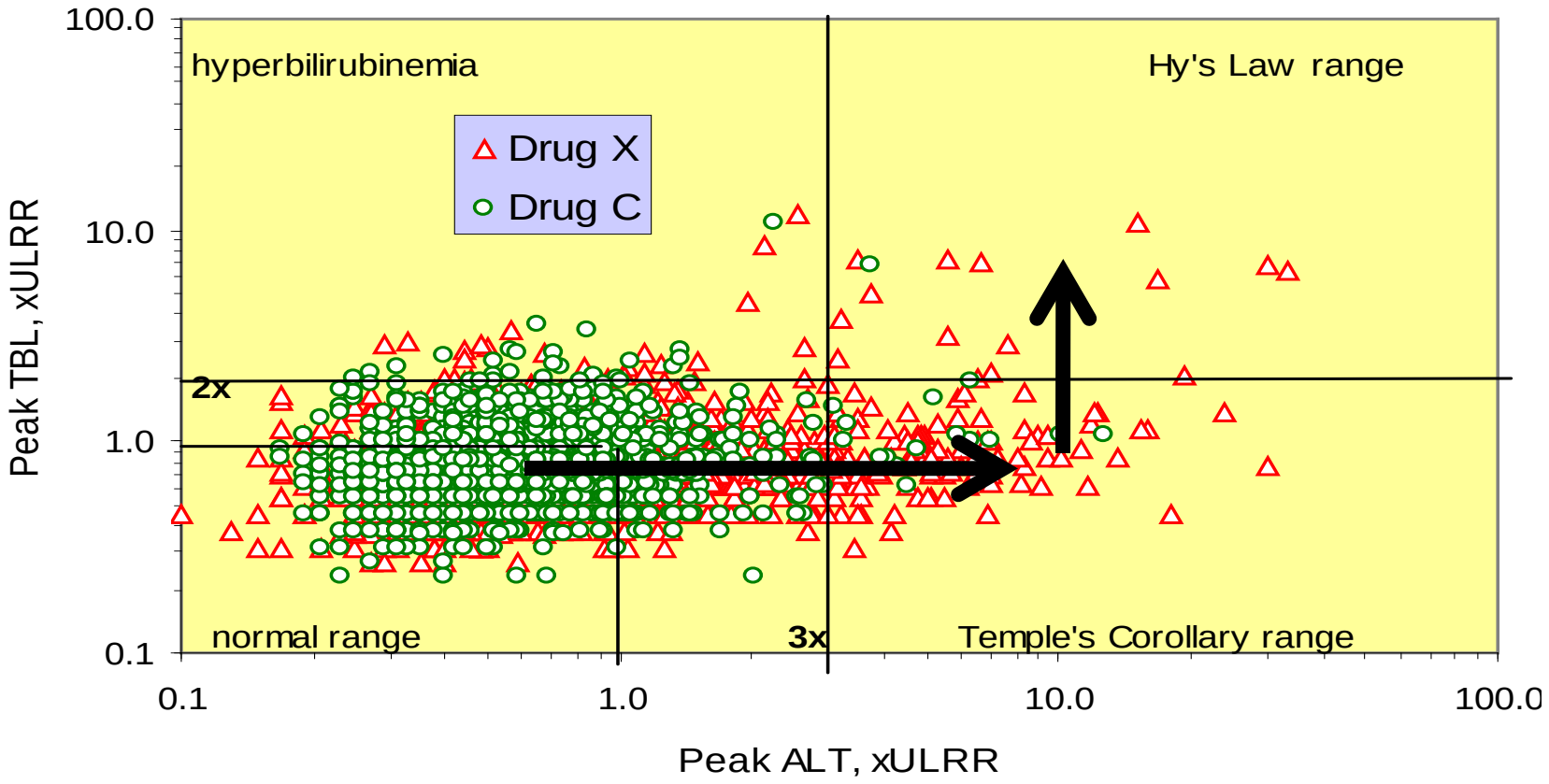
2). Large clinical trials may be needed to define risk

eDISH format for display of clinical trial liver safety data



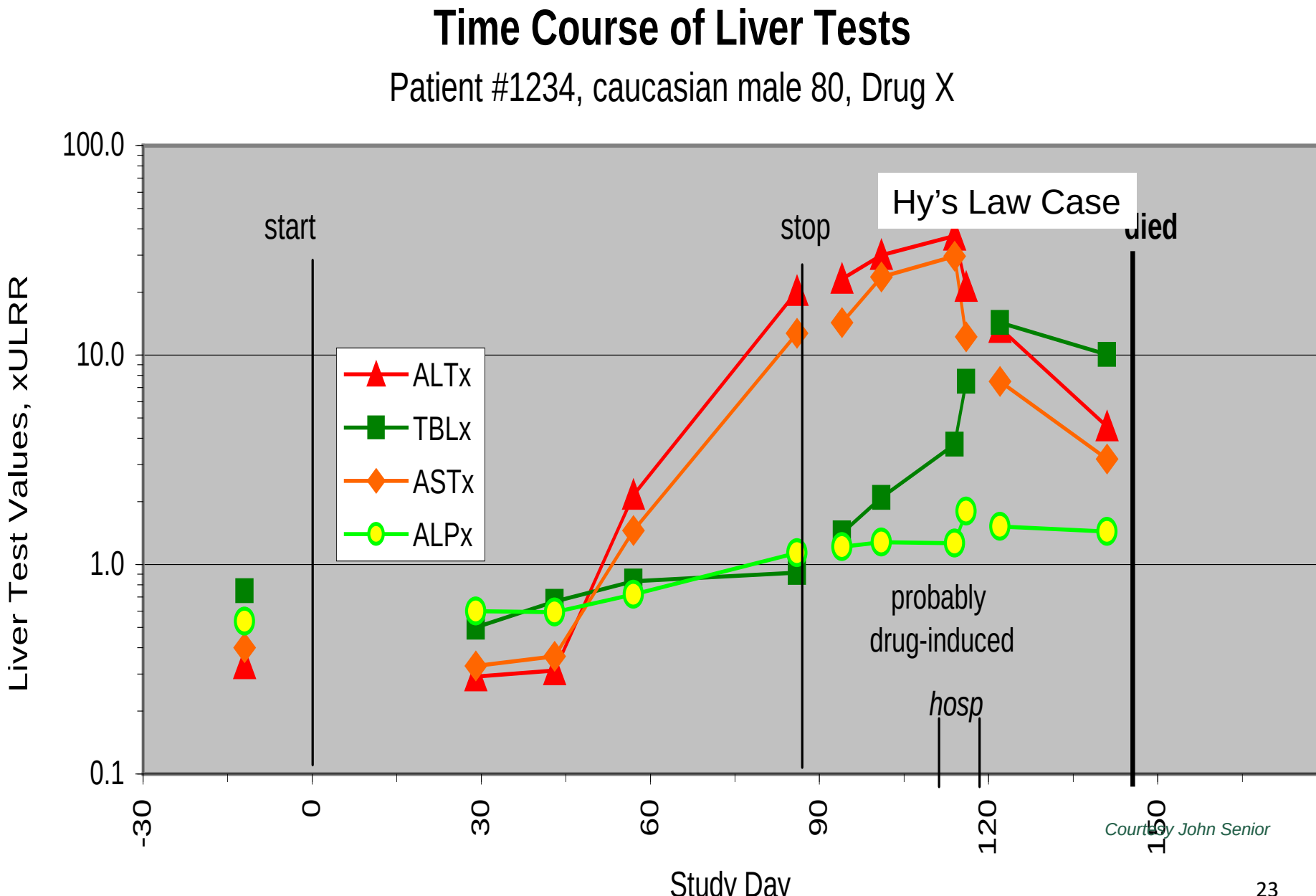
Ted Guo and John Senior

eDISH format for display of clinical trial liver safety data



Ted Guo and John Senior

Acute Idiosyncratic Hepatocellular DILI



Courtesy John Senior

Conclusions

The current clinical trial guidelines regarding assessing DILI potential demand large clinical trials and are putting some patients at risk.

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

Scientific Advisory Board

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janssen
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Select Sample of Current Companies Licensing DILIsym

For a comprehensive review of progress, see *Watkins 2019: Clin Transl Sci*

- *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*
  - *19 major pharmaceutical companies have participated*
  - *Members have provided compounds, data, and conducted experiments to support effort*
  - *Over $10 million total invested in project*
- ***At least 26 cases of use for regulatory purposes***
- ***Over 30 publications***

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FDA Continues to Receive Updates and Applications from DILIsym Software, and is Renewing Unlimited License Package

- Division of Pharmacometrics group has spearheaded a licensing agreement that provides FDA with DILIsym licenses to multiple divisions – ***renewal completed in April of 2020***

- DILIsym consulting projects continue to be associated with FDA interactions

U.S. FDA Renews DILIsym Software Licenses

Nachrichtenquelle: Business Wire (engl.) | 16.05.2019, 14:30 | 114 | 0 | 0

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 Drug Administration has renewed its multi-seat license for the company's flagship quantitative systems toxicology (QST) modeling software, DILIsym. The renewal provides DILIsym access to FDA employees across all FDA divisions

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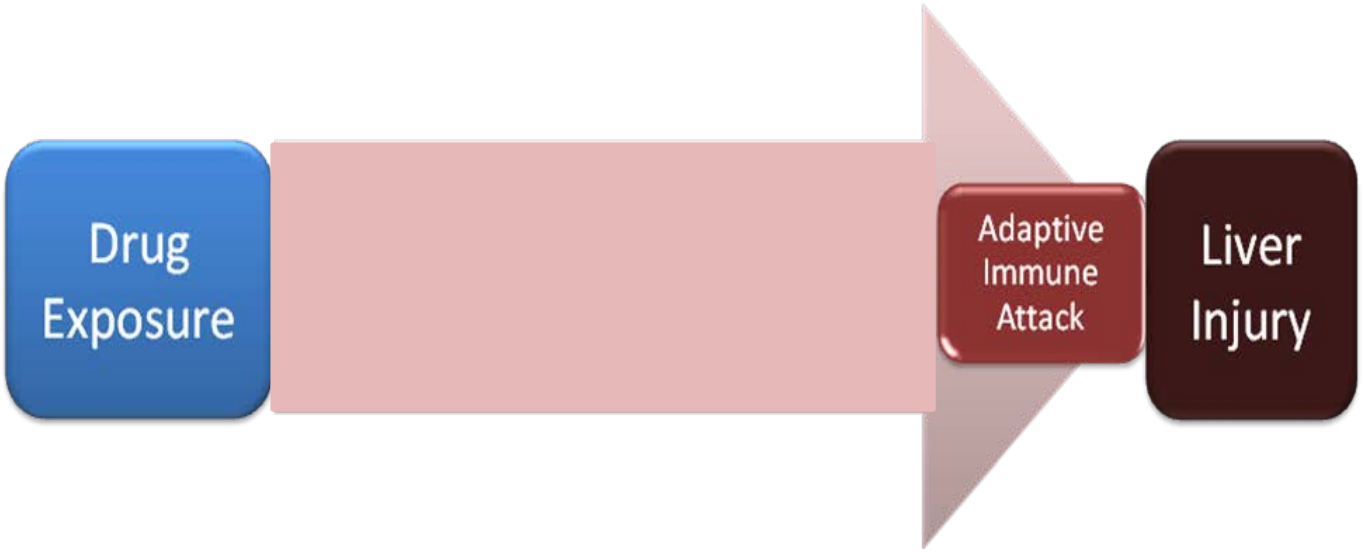
Question

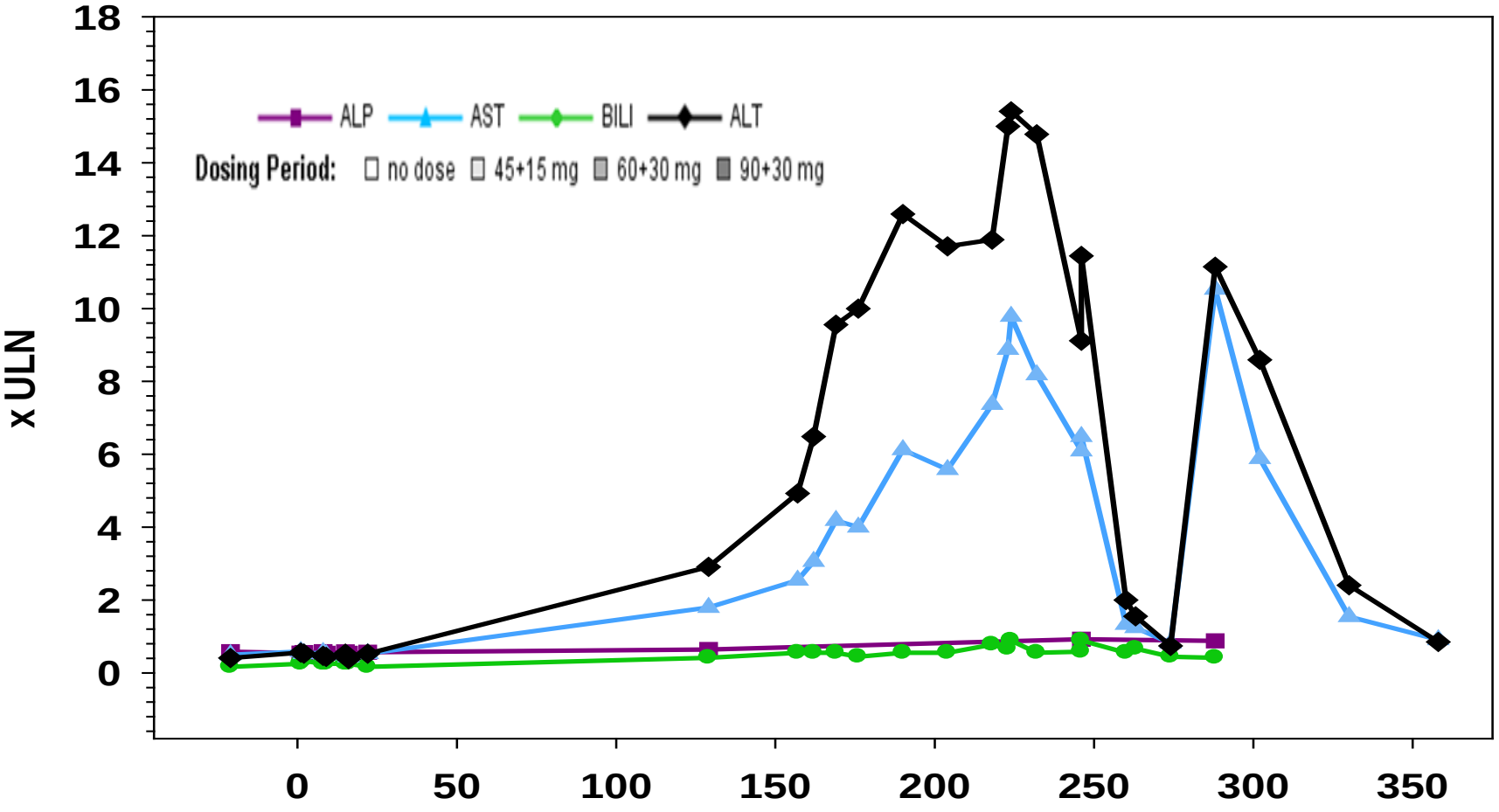
Does DILIsym predict idiosyncratic DILI?

Multiple Steps Involved in Idiosyncratic DILI



Mosedale, M, and Watkins, PB. Clin Pharmacol Ther. 2017 Apr; 101(4):469-480.

Idiosyncratic DILI due to Tolvaptan



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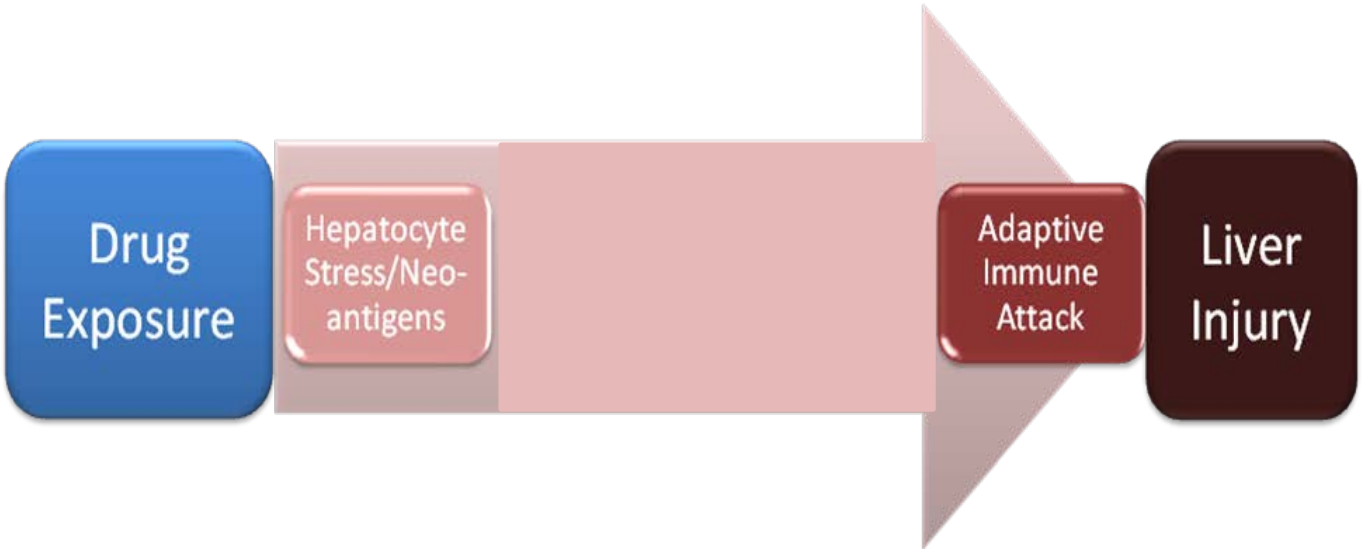
Multiple Steps Involved in Idiosyncratic DILI



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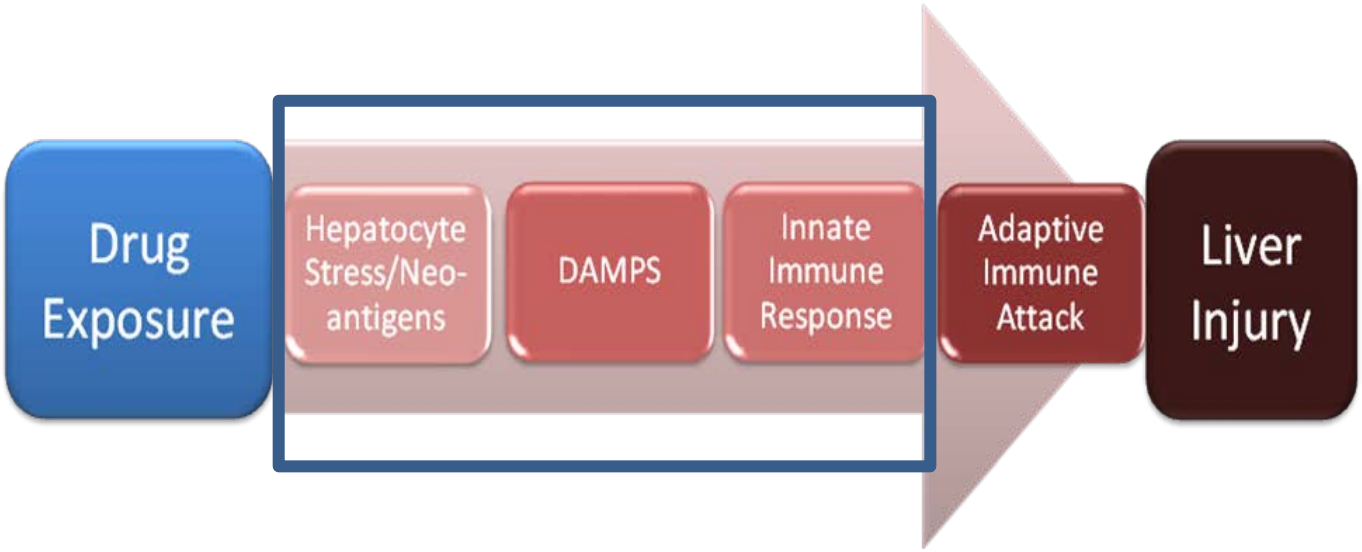
Multiple Steps Involved in Idiosyncratic DILI



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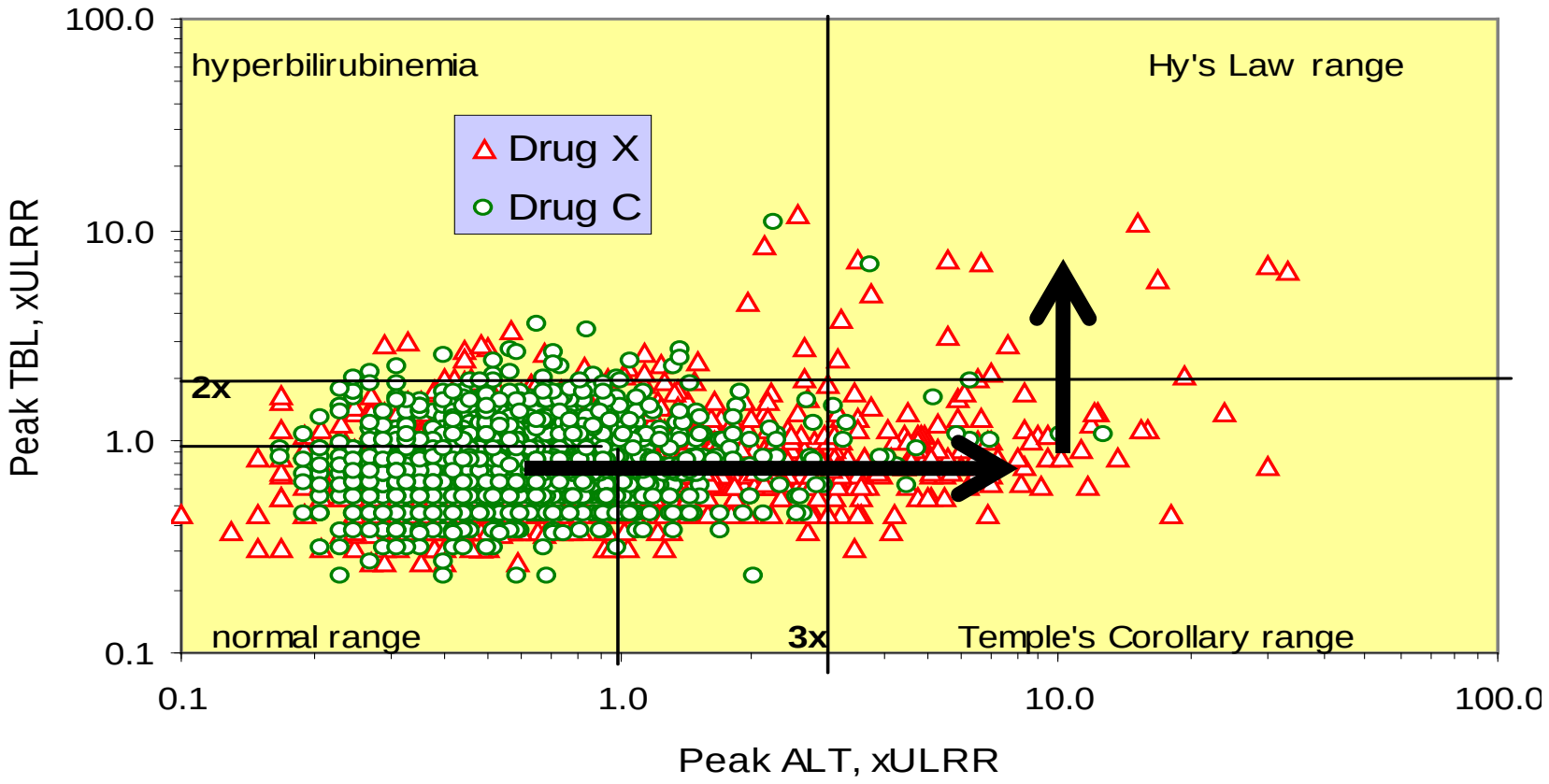

Ted Guo and John Senior

Webinar Agenda

- Drug-induced liver injury (DILI): a clinical perspective on the problem
- DILIsym: a viable solution
- Live questions from the audience

DILIsym Currently Includes Drug-Intrinsic and Inflammatory Toxicity

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Drug Exposure → Hepatocyte Death / Stress → Danger Signal → Innate Immune Response → Adaptive Immune Attack → Liver Injury

Drug-mediated HC death

Infl-mediated HC death

<u>Exposure-dependent mechanisms of toxicity:</u>
Bile acid transporter inhibition
Mitochondrial dysfunction
Oxidative stress

<u>Innate immune mediated toxicity:</u>
Macrophages
Neutrophils
TNF-R mediated cell death

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Ongoing DILIsym Development to Include Adaptive Immune-Mediated Toxicity

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Drug Exposure

Hepatocyte Death / Stress

Danger Signal

Innate Immune Response

Adaptive Immune Attack

Liver Injury

Drug-mediated HC death

Infl-mediated HC death

T cell-mediated HC death

<u>Requisite for adaptive immune attack:</u>
Neo-antigen formation
Antigen presentation
Altering tolerogenic liver environment

<u>Adaptive immune mediated toxicity:</u>
T cell activation, expansion, differentiation
T cell mediator production
T cell cytotoxicity
T cell tolerance mechanisms

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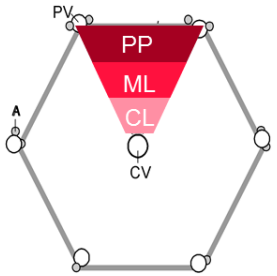
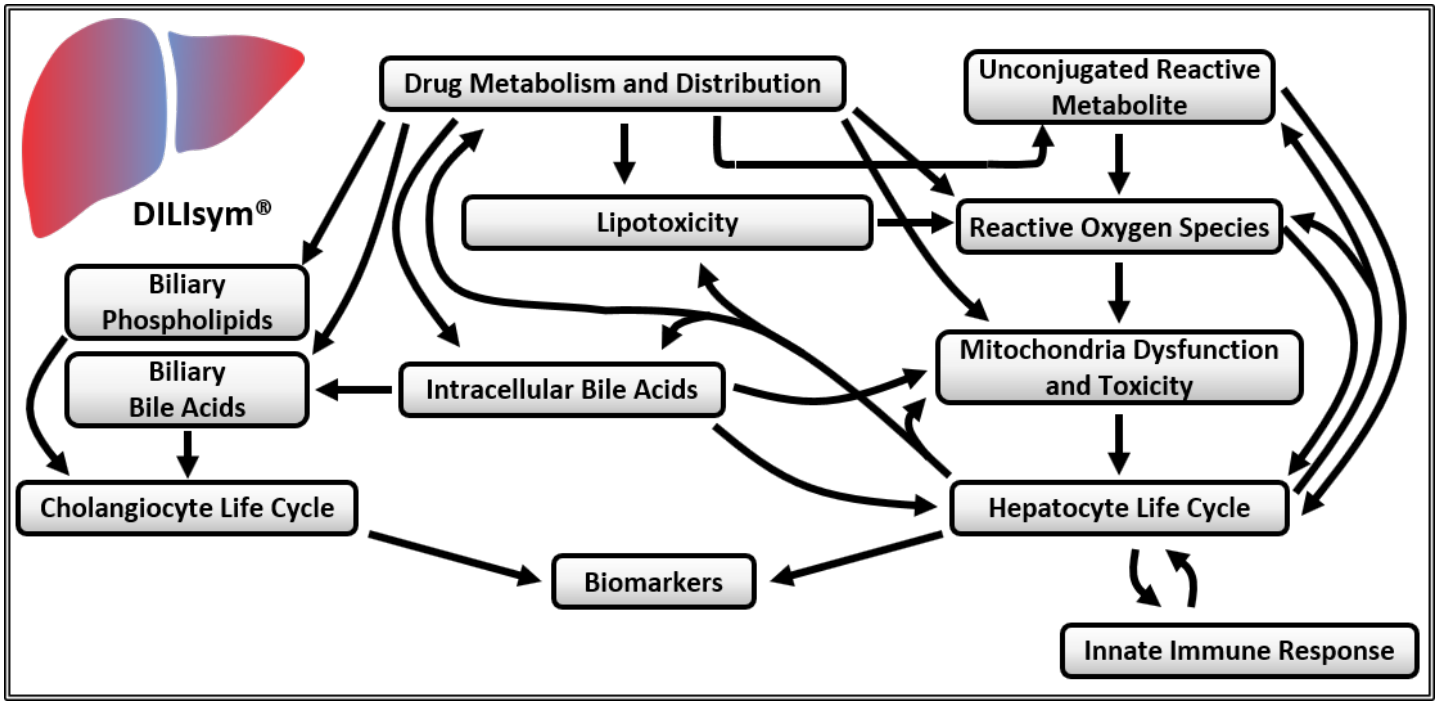
DILIsym Software Overview

- **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**
- **<u>Over 70</u> detailed representations of validation compounds with 80% success**
- **Single and <u>combination drug</u> therapies**





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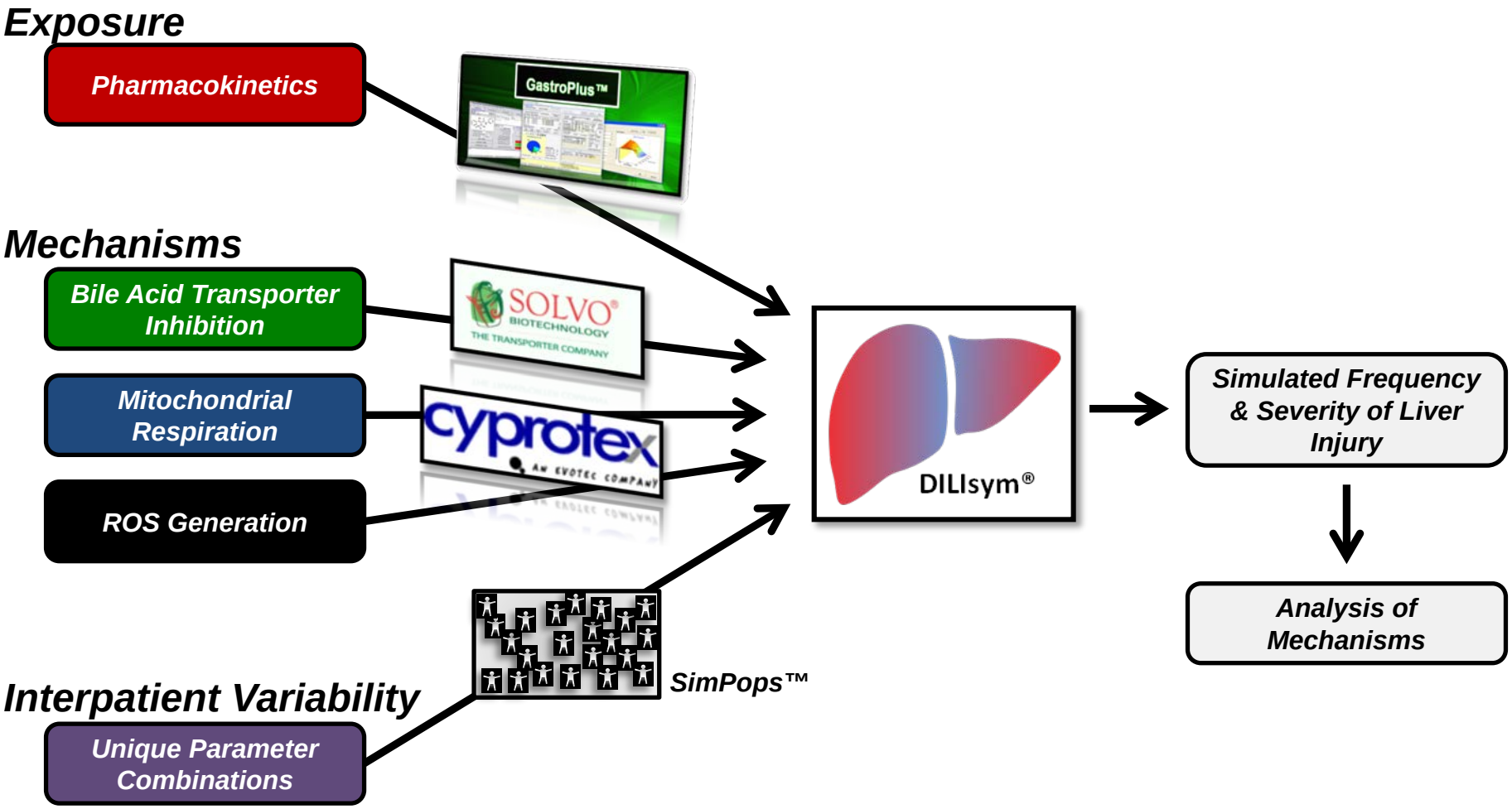
DILIsym Predicts Toxicity at the Intersection of Exposure, Mechanisms, and Patient Variability



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Relevant Recent DILIsym Publications

Quantitative Systems Toxicology Approaches to Understand and Predict Drug-Induced Liver Injury

Paul B. Watkins, MD

Clin Liver Dis 24 (2020) 49–60
https://doi.org/10.1016/j.cld.2019.
1089-3261/20/© 2019 Elsevier Inc.

KEYWORDS

• DILIsym • DILI • QST • Simulation • Modeling

KEY POINTS

- The DILI-sim Initiative is a public-private partnership that has applied quantitative systems toxicology modeling to develop software (DILIsym®) that has improved mechanistic understanding of DILI.

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 Disease Using Quantitative Systems Toxicology Modeling

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

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]

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[6]UNC Institute for Drug Safety Sciences, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina
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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]

Received: 24 September 2018 / Accepted: 27 January 2019 / Published online: 7 February 2019

ABSTRACT

Purpose Macrolide antibiotics are commonly prescribed treatments for drug-resistant bacterial infections; however, many macrolides have been shown to cause liver enzyme elevations and one macrolide, telithromycin, has been pulled

Conclusions The mechanisms responsible for toxicity can be significantly different within a class of drugs, despite the structural similarity among the drugs. QST modeling can provide valuable insight into the nature of these mechanistic differences.

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Relevant Recent DILIsym Publications

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

Check for updates

RESEARCH PAPER

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

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

Lixivaptan Background

- Lixivaptan is Palladio Bio's selective, competitive vasopressin V2 receptor antagonist
- **Palladio Biosciences acquired lixivaptan and intends to reposition lixivaptan for the treatment of Autosomal-Dominant Polycystic Kidney Disease (ADPKD)**

Lixivaptan DILIsym Project

DILI Background

- An approved compound in the same class had no DILI signals in hyponatremia, but signals were observed in ADPKD patients
- Lixivaptan has had no DILI signals in hyponatremia

Question

- Will lixivaptan experience similar DILI liability as the competitor in ADPKD patients?

Approach

- Develop a mechanistic representation of lixivaptan in DILIsym, a QST model of drug-induced liver injury (DILI), to assess the potential for liver toxicity with the intended dosing for lixivaptan

Lixivaptan DILIsym Parameters

Mechanism	DILIsym Parameter	Unit	Value****				
			Lixivaptan	WAY-138451	WAY-141624	WAY-138758	Tolvaptan**
Mitochondrial Dysfunction	Coefficient for ETC inhibition	µM	535	250	N/A	N/A	729
Oxidative Stress	RNS/ROS production rate constant	mL/nmol/hr	5.45×10^{-4}	2.12×10^{-3}	N/A	N/A	N/A
Bile Acid Transporter Inhibition	BSEP inhibition constant	µM	15*	8.6*	39.5*	5.6*	10***
	NTCP inhibition constant	µM	19*	N/A	85.8*	8.9*	N/A
	Basolateral inhibition constant**	µM	70*	54*	16.3*	4*	N/A

* Values are IC_{50} values; mode of inhibition was not measured *in vitro*

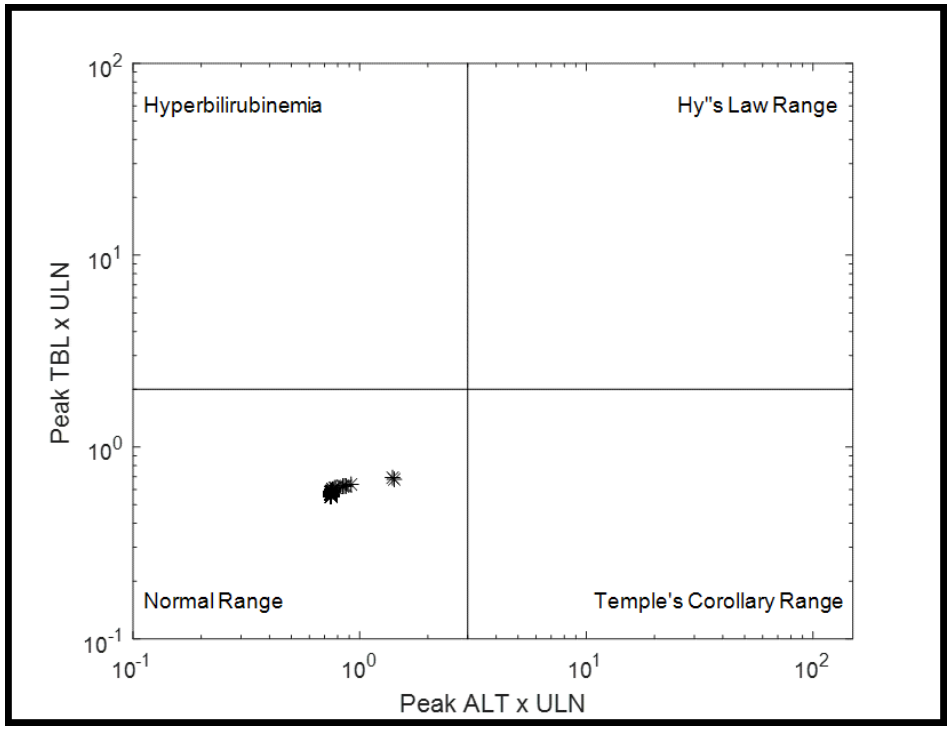
** Tolvaptan parameters are taken from *in vitro* experiments undertaken for this research. Previously published DILIsym parameters are available in Woodhead et al., Tox. Sci. 2017

*** IC_{50} value for tolvaptan was measured for this research. A K_i value was measured for the previously published tolvaptan work; the published value is somewhat higher than the value reported here. However, personal communication with the experimentalists suggested that the initial IC_{50} value calculated in that experiment was not substantially different from that measured here.

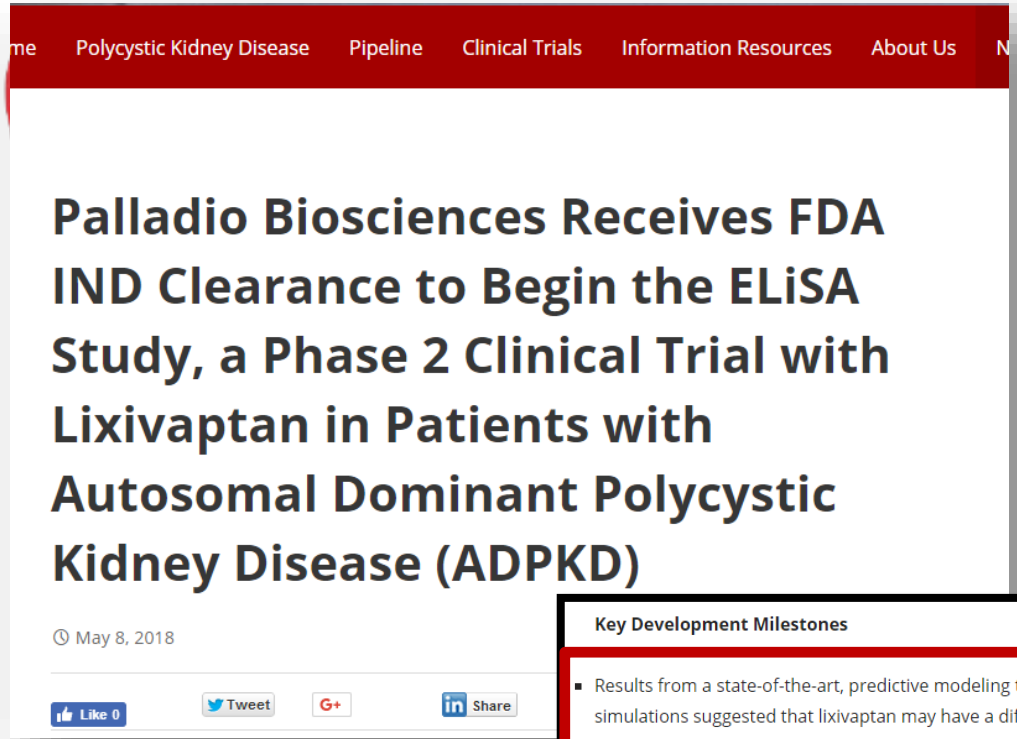
**** Comparisons of parameter values should be undertaken with caution, as they must be placed in context with exposure for their full usefulness.

Lixivaptan Simulations Predict Minimal ALT Elevations at 200/100 mg BID

- Lixivaptan simulated in SimPops of N = 285
- No ALT elevations simulated in 100 mg BID 60-day simulation
  - Consistent with observed clinical similarity to placebo (validation)
- **No ALT elevations simulated in 200/100 split daily dosing scenario for 12 weeks**
  - **Maximum intended clinical dosing for ADPKD**



Palladio Biosciences Website


me Polycystic Kidney Disease Pipeline Clinical Trials Information Resources About Us N

Palladio Biosciences Receives FDA IND Clearance to Begin the ELiSA Study, a Phase 2 Clinical Trial with Lixivaptan in Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD)

May 8, 2018

Like 0 Tweet G+ Share

Key Development Milestones

- Results from a state-of-the-art, predictive modeling tool based on in vitro inputs, physiologically based pharmacokinetic modeling and *in silico* simulations suggested that lixivaptan may have a differentiated safety profile compared to tolvaptan with respect to the potential to cause liver injury. Among other key findings, this investigation indicated that lixivaptan may have lower liver exposure than tolvaptan; that lixivaptan does not affect bile acid homeostasis and mitochondrial function, two key mechanisms of liver injury that may contribute to tolvaptan liver toxicity; and that lixivaptan, unlike tolvaptan, may not cause ALT elevations. These findings need to be confirmed in the clinics.
- The U.S. FDA Office of Orphan Drug Products designated lixivaptan as an orphan drug for treating ADPKD. The orphan drug designation is granted to support the development of drugs and biologics intended for the safe and effective treatment, diagnosis or prevention of diseases or disorders that affect fewer than 200,000 people in the U.S., or that affect more than 200,000 people but are not expected to recover the costs of drug development and marketing. Orphan drug designation provides eligibility for certain benefits, including seven years of market exclusivity following receipt of regulatory approval, tax credits for qualified clinical trials, and exemption from FDA application fees. It is an important milestone in the lixivaptan development program.
- In April 2018, the FDA granted IND (investigational new drug) clearance for the ELISA Study (Evaluation of Lixivaptan In Subjects with ADPKD), a Phase 2 clinical trial that will evaluate the safety, pharmacokinetics and pharmacodynamics of multiple doses of lixivaptan in patients with ADPKD with relatively preserved kidney function (chronic kidney disease stages CKD1 and CKD2) and moderately impaired renal function (CKD3). The study is expected to enroll 32 patients beginning the end of June 2018.

PALLADIO BIOSCIENCES
Working to bring new hope to patients with orphan diseases of the kidney

LIFE SCIENCES PA
CONNECT · ADVOCATE · ADVANCE

Bio Member

Please note that lixivaptan is for investigational use only.

Palladio Biosciences
12 Penns Trail
Unit A

Relevant Recent DILIsym Publications

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]

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[3]Investigative Toxicology, Drug Safety Research and Development, Pfizer Inc., Groton, Connecticut

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[5]UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

[6]UNC Institute for Drug Safety Sciences, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

[7]Translational Modeling and Simulation, Biomedicine Design, Pfizer, Inc., Groton, Connecticut

Case Study: DILIsym Illustrates the Combination of Mild Toxicity Mechanisms Accounts for Species-Specific DILI

Background

- PF-04895162 in development for epilepsy, did not demonstrate preclinical or early clinical liver toxicity (ALT >3x ULN)
- Development was halted when 300 mg BID for 14 days led to ALT elevations (Aleo et al. 2019)

Question

- Can mechanisms included in DILIsym account for the observed species differences?

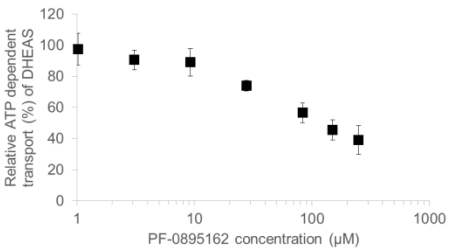
DILIsym Approach

- Represent and simulate PF-04895162 in rats and humans to determine if DILIsym mechanisms can account for species-specific observations

Evidence for Weak Interaction Between PF-04895162 and Bile Acid Transporters

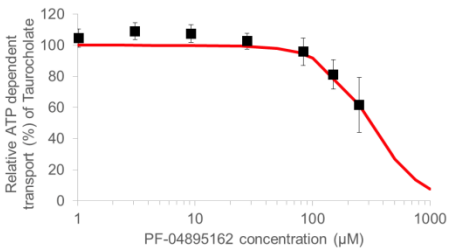
HUMANS

(A)



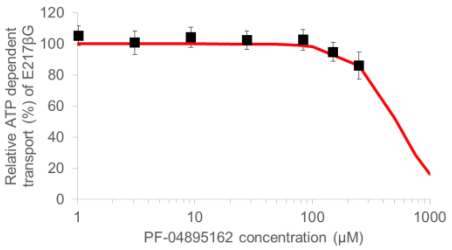
Measured IC_{50} 121 μM

(B)



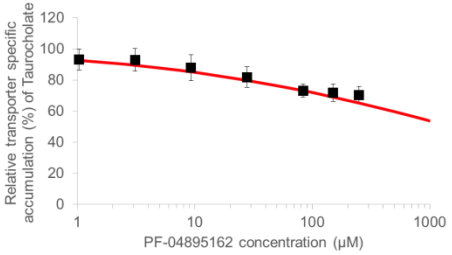
Extrapolated IC_{50} 311 μM

(C)



Extrapolated IC_{50} 519 μM

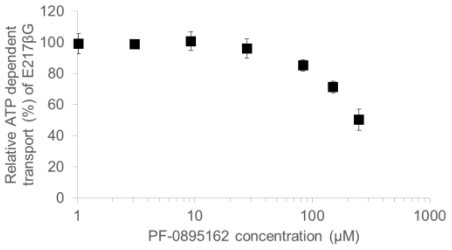
(D)



Extrapolated IC_{50} 1535 μM

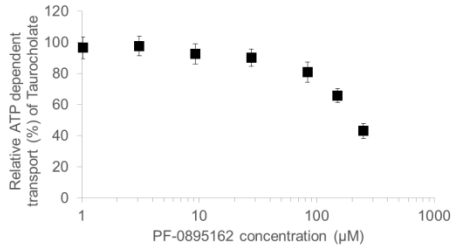
RATS

(A)



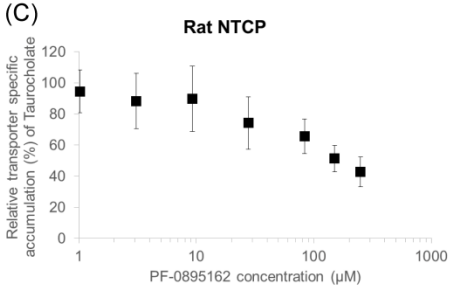
Measured IC_{50} 256 μM

(B)



Measured IC_{50} 229.6 μM

(C)



Measured IC_{50} 198 μM

Preclinical Data

DILIsymServices

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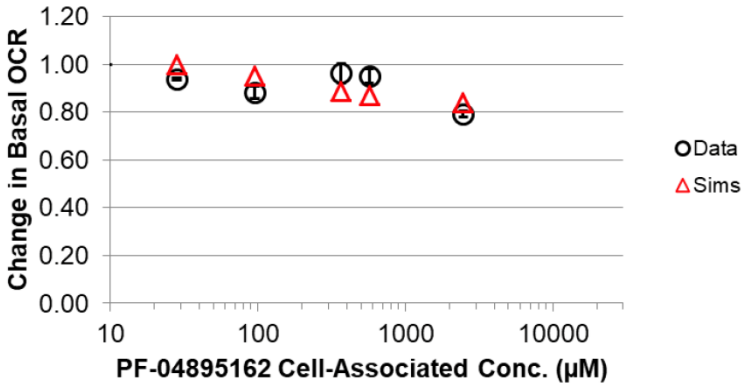
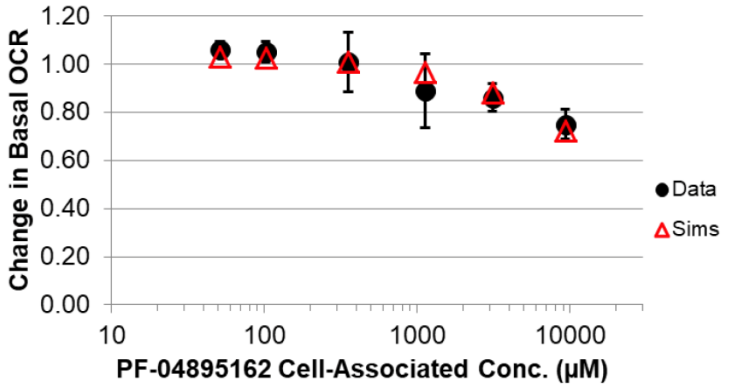
Evidence for Weak PF-04895162 Mediated Mitochondrial Dysfunction

HUMANS



RATS



Preclinical Data and Simulation Results

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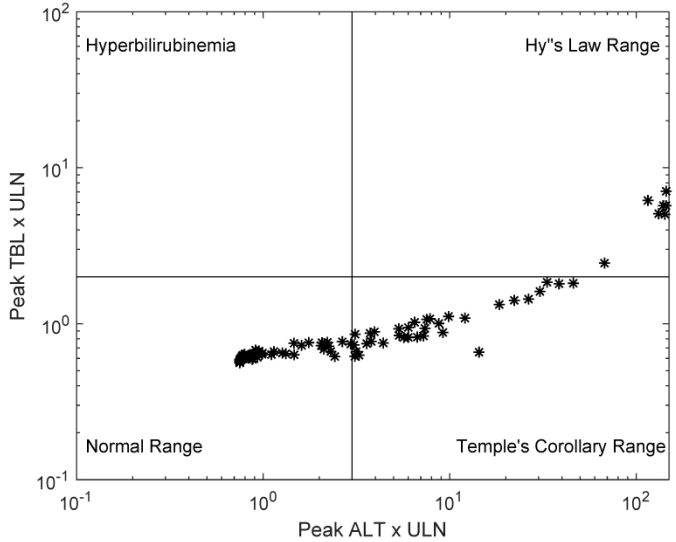
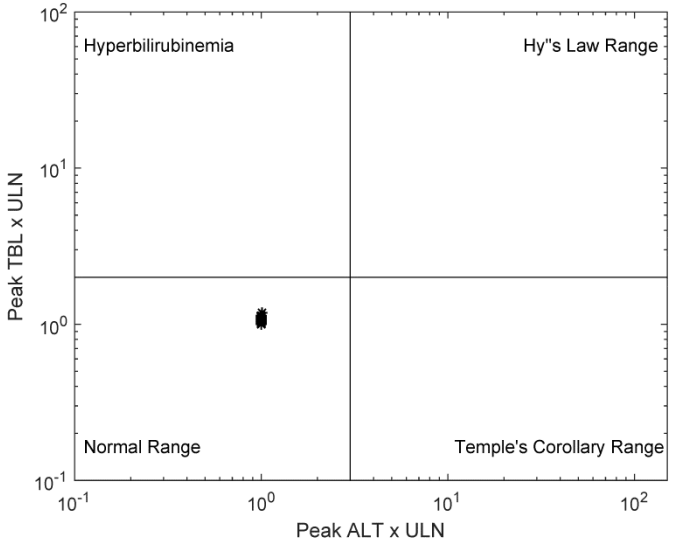
DILIsym Simulated Human, but Not Rat, Hepatotoxicity

HUMANS | **300 mg BID 14d, 14d follow** | **No clinical stop protocol** | **100 mg/kg/d, 28d** | **RATS**



N=285 simulated patients



N=294 simulated rats

Simulation Results

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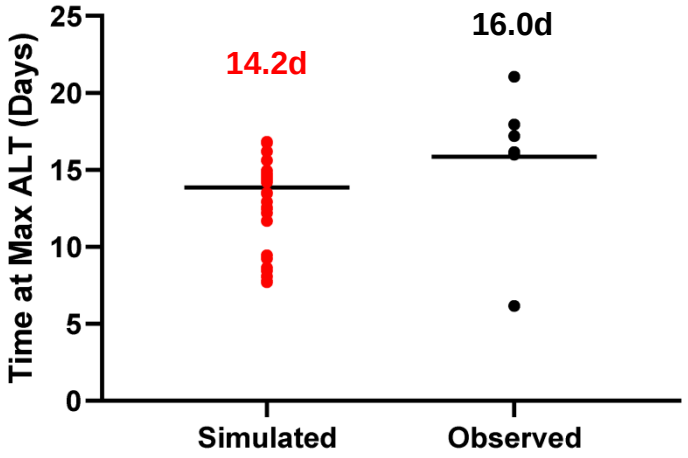
Simulated DILI Due to BA and Mitochondrial Toxicity Approximates Clinical Timing

HUMANS

Simulations	Mechanisms On	Mechanisms Off	ALT Elevations >3x ULN
300 mg po BID for 14 days in Multi16‡	ETCi, BAi	-	8/16
	ETCi	BAi	0/16
	BAi	ETCi	0/16

‡ Multi16 is the Human_ROS_apop_mito_BA_v8A_1_Multi16_A



Each point represents an individual

Median value represented above simulated and observed values

Clinical Data and Simulation Results

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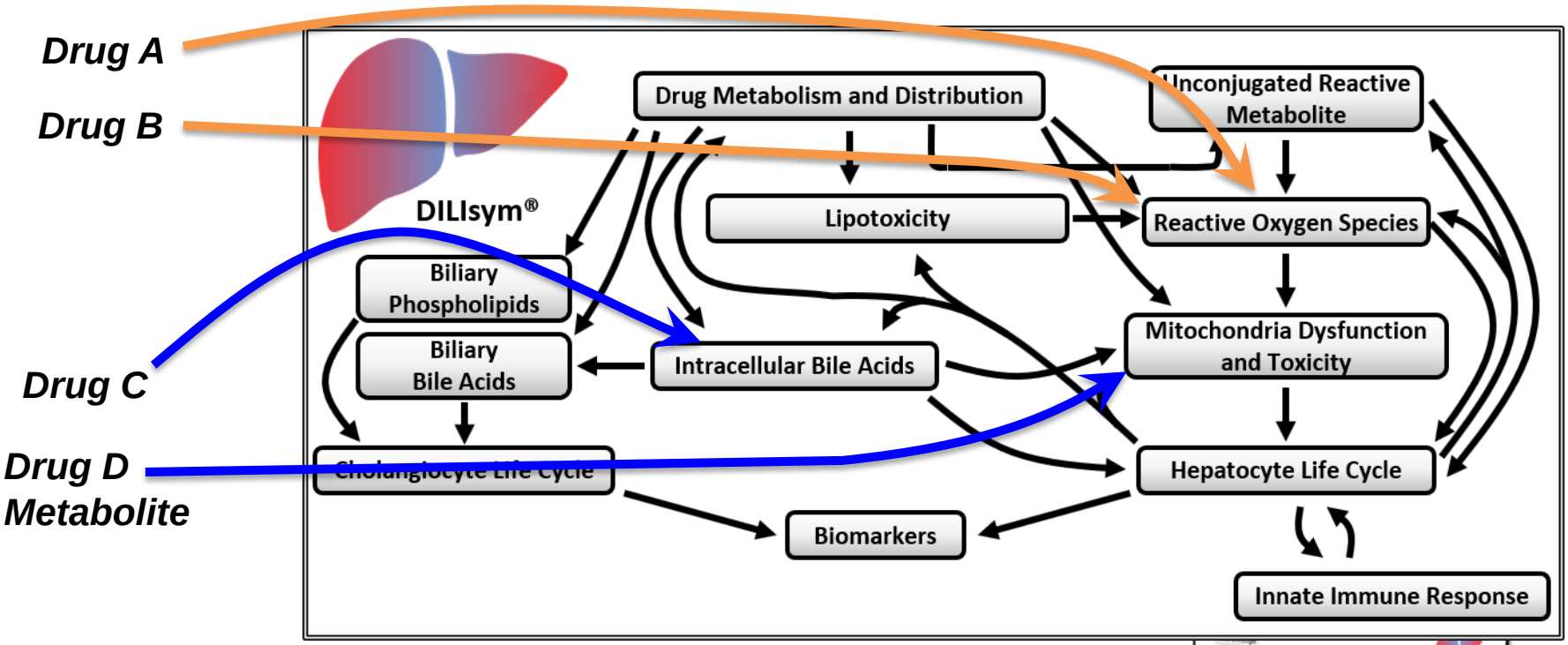
Key Learnings

- Relatively **mild** mitochondrial dysfunction and BA transporter inhibition can **combine** to generate human hepatotoxicity
- Delayed ALT elevations were observed due to intrinsic mechanisms of toxicity
- *In vitro* toxicity data should consider compound concentration at the site of action
  - One of the first projects to demonstrate marked differences in simulation results depending on whether parameter values were based on nominal media concentrations vs. cell-associated concentrations
- Simulation results were better aligned with experimental data when input toxicity data were **species specific**
  - Initial simulations using all human in vitro toxicity data, with human *vs*. rat PK, reproduced species differences but not as well

DILIsym Is Well-Suited to Predict the DILI Mechanism Interaction Effects of Polypharmacy



- **Drugs can hit overlapping or different DILI mechanisms**
- **Effects can be similar or different when comparing NHV to patients**
- **Parent compounds and metabolites can contribute**

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DILI-sim Initiative

Consortium Distributing and Developing Software for
Predicting and Preventing Drug-Induced Liver Injury (DILI)

Dr. Paul B. Watkins
Director, DILI-sim Initiative;
Chair, Scientific Advisory Board

Join Today and Support Cutting Edge Research to Make Patients Safer!

DILIsym®

Benefits of Stage 4 DILI-sim Membership

- Two global, floating end-user licenses to the current version of the DILIsym® software package
- Includes integrated GastroPlus® version, when available
- Licenses to an add-on feature of DILIsym that enables use of server/cloud parallel computing with unlimited nodes (upcharge for non-members)
- 31% discount on consulting services related to DILIsym
- 10 total hours of private training for employees of the Member company related to DILIsym use
- The right to vote on DILIsym software development items going forward
- Attendance at DILI-sim research, development, and software update meetings/discussions (typically held quarterly)
- Access to the DILIsym Discovery Support Program (DDSP), a Members-only, lower cost program for enabling internal software use

*Now includes **RENAsym™ Consortium** membership at no additional cost!*

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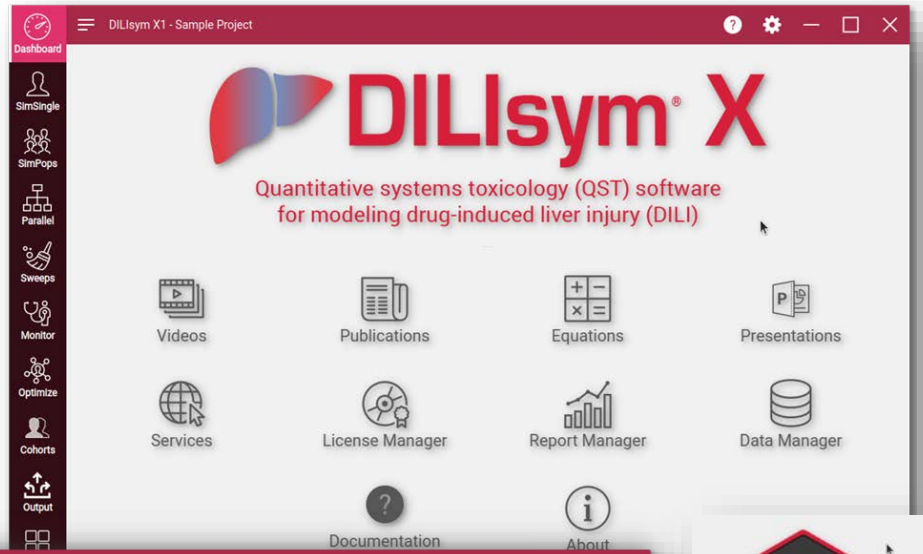
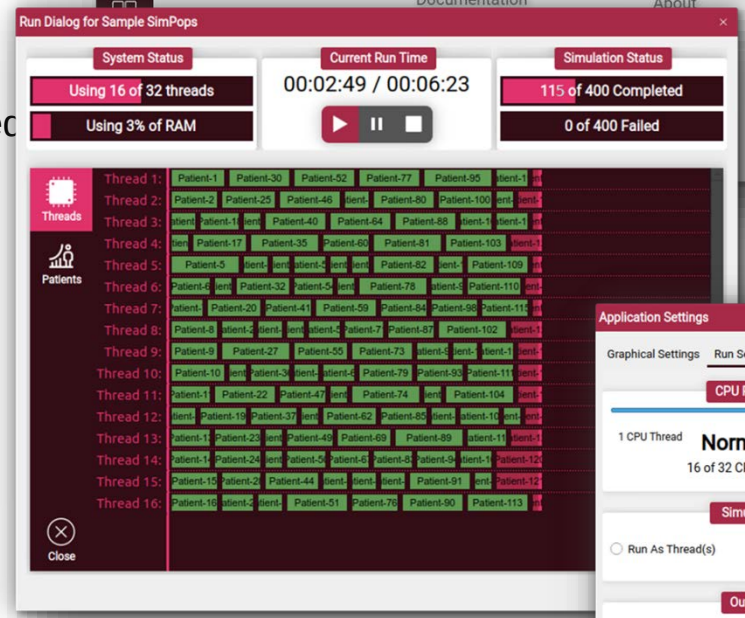
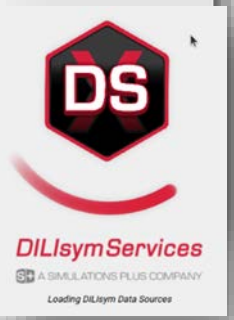
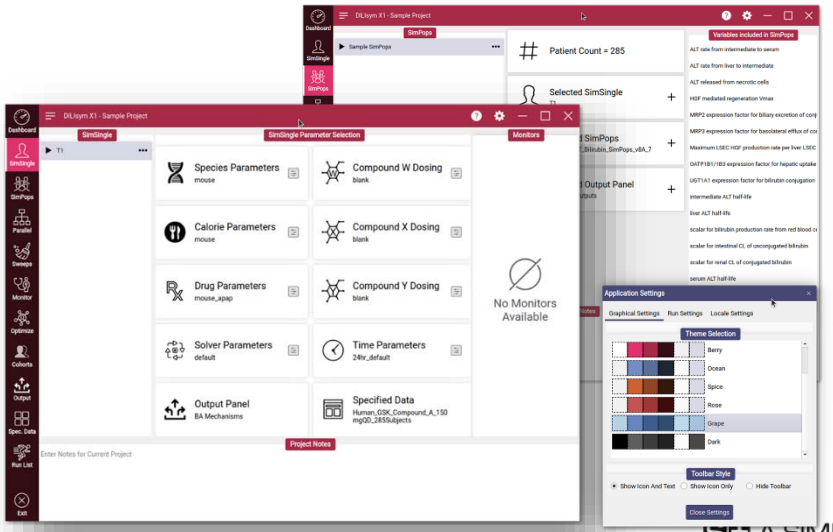
Highlights of DILIsym® Version X (DSX)

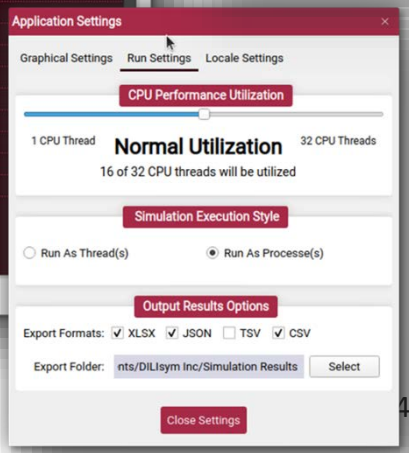
- Completely new software platform!
  - Much faster and more user friendly
  - Command line and GUI options
  - No reliance on MATLAB runtime or base MATLAB
  - Server/cloud computing capability coming soon…..
- 4 NEW exemplar Compounds included with varying clinical presentations
  - PF-04895162 *(Generaux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











Webinar Agenda

- Drug-induced liver injury (DILI): a clinical perspective on the problem
- DILIsym: a viable solution
- Live questions from the audience

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