QST and the Transformation in Drug Safety Assessment

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Howard Q Ferguson Distinguished Professor

Director, Institute for Drug Safety Sciences

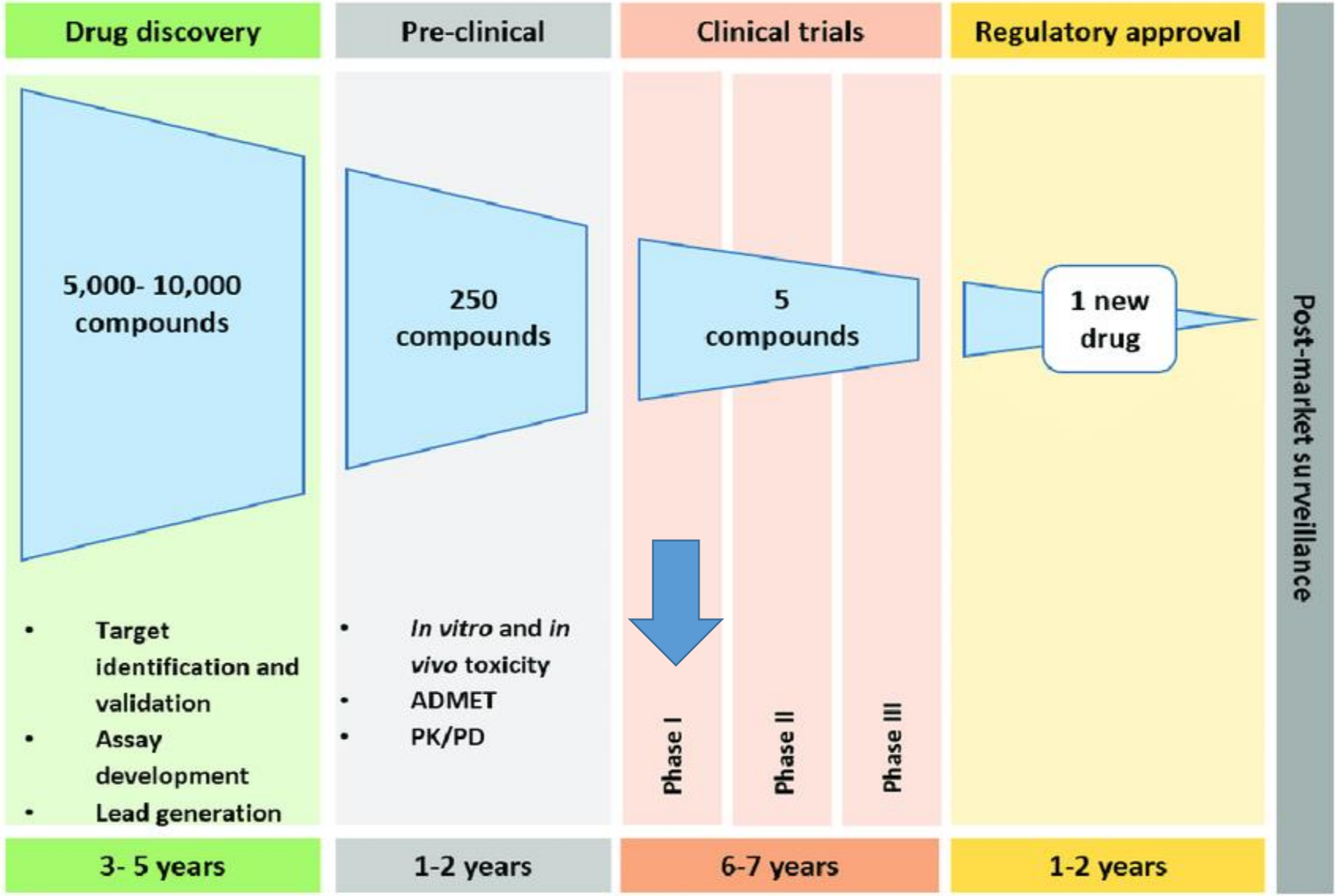
December 16, 2020

Disclosure

I chair the Scientific Advisory Committee for the DILI-sim Initiative and receive compensation for this.

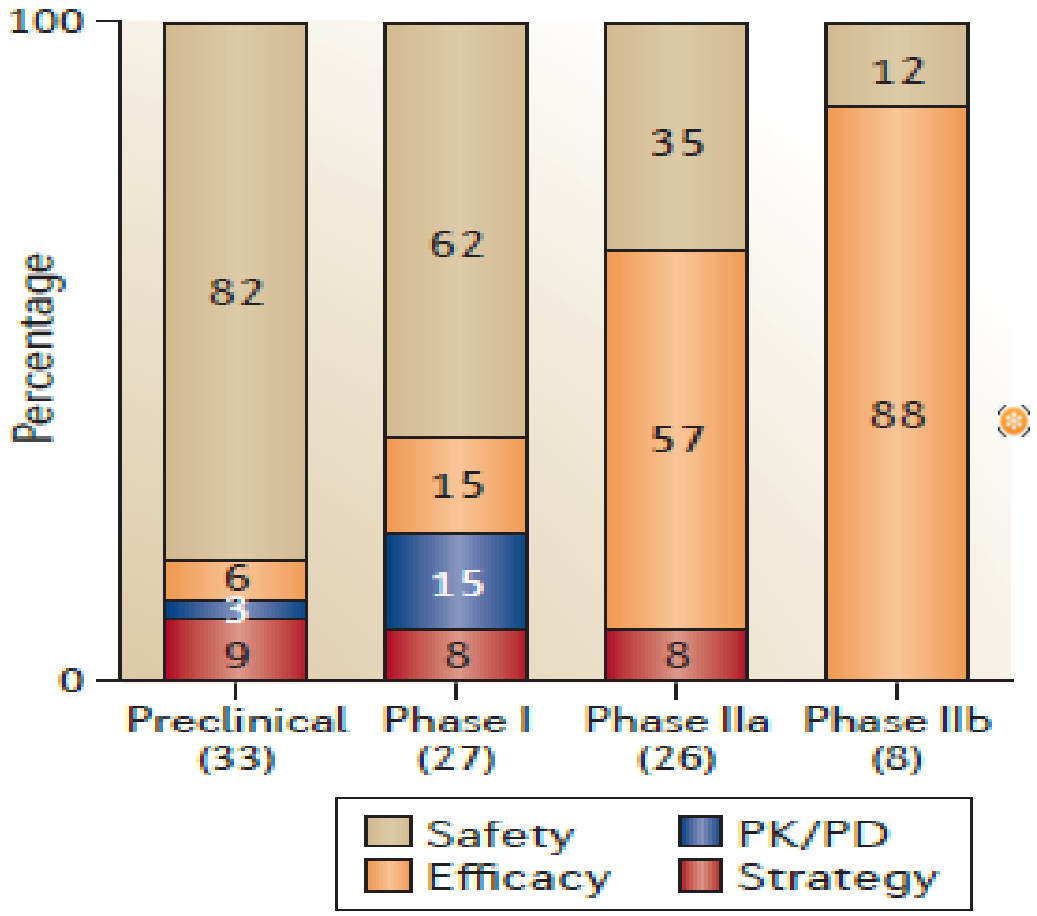
I no longer have a financial interest in the spin off company – DILIsym Services, Inc.- or its parent – Simulations Plus

Drug Development Pipeline



Up to 16 years and 2 $Billion to get a new treatment to market

Reasons for Termination of Programs



Safety concerns are the major causes of termination of drug development programs

NATURE REVIEWS | DRUG DISCOVERY VOLUME 13 | JUNE 2014 | 419

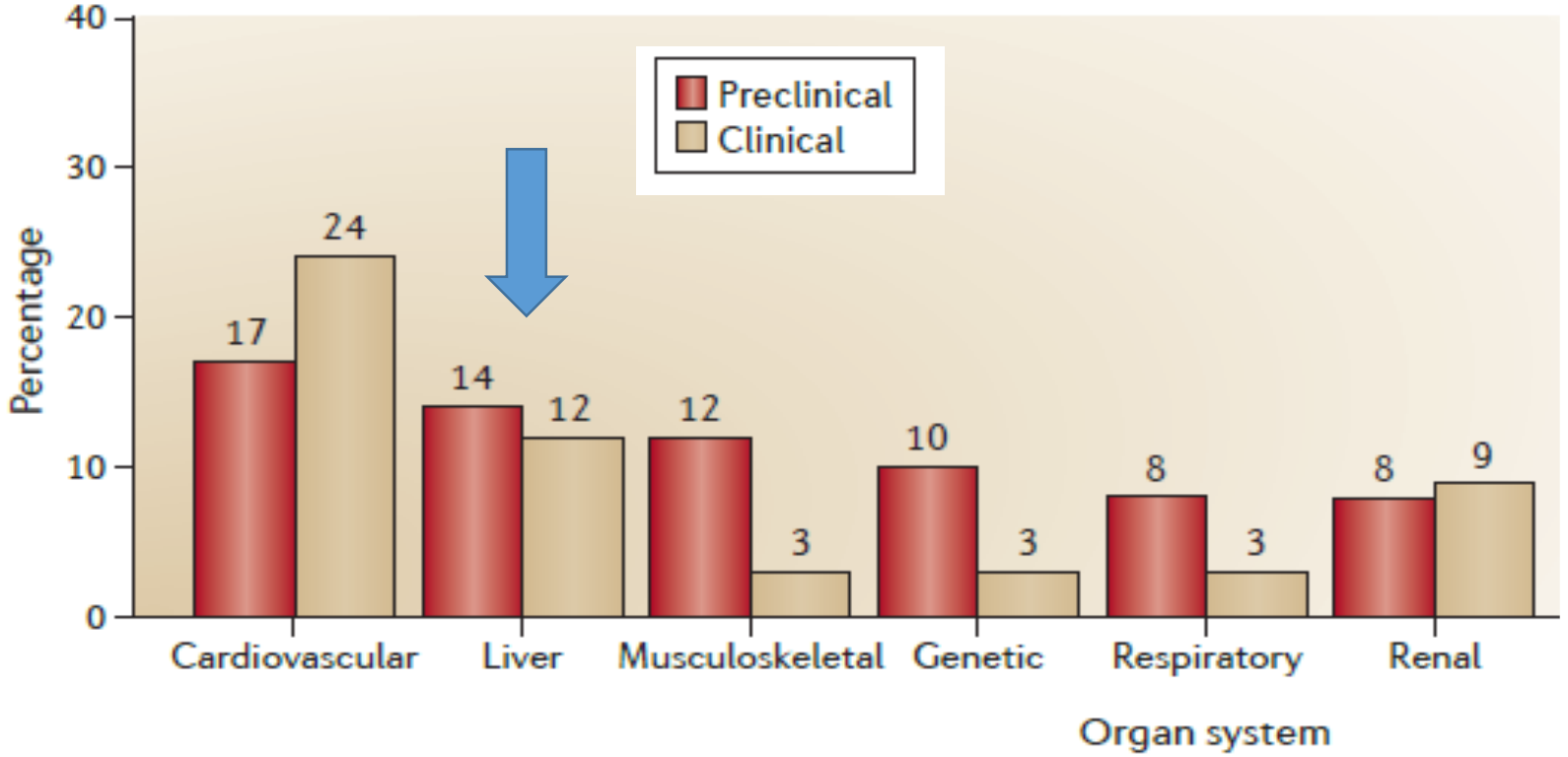
Predicting Drug Interactions from In Vitro Data

1993 – Institute of Medicine all day program on predicting drug interactions from studies in liver microsomes and expressed cytochromes-450.

Today – Data from such in vitro studies combined with physiologically based pharmacokinetic modeling can obviate need to conduct certain DDI clinical trials….

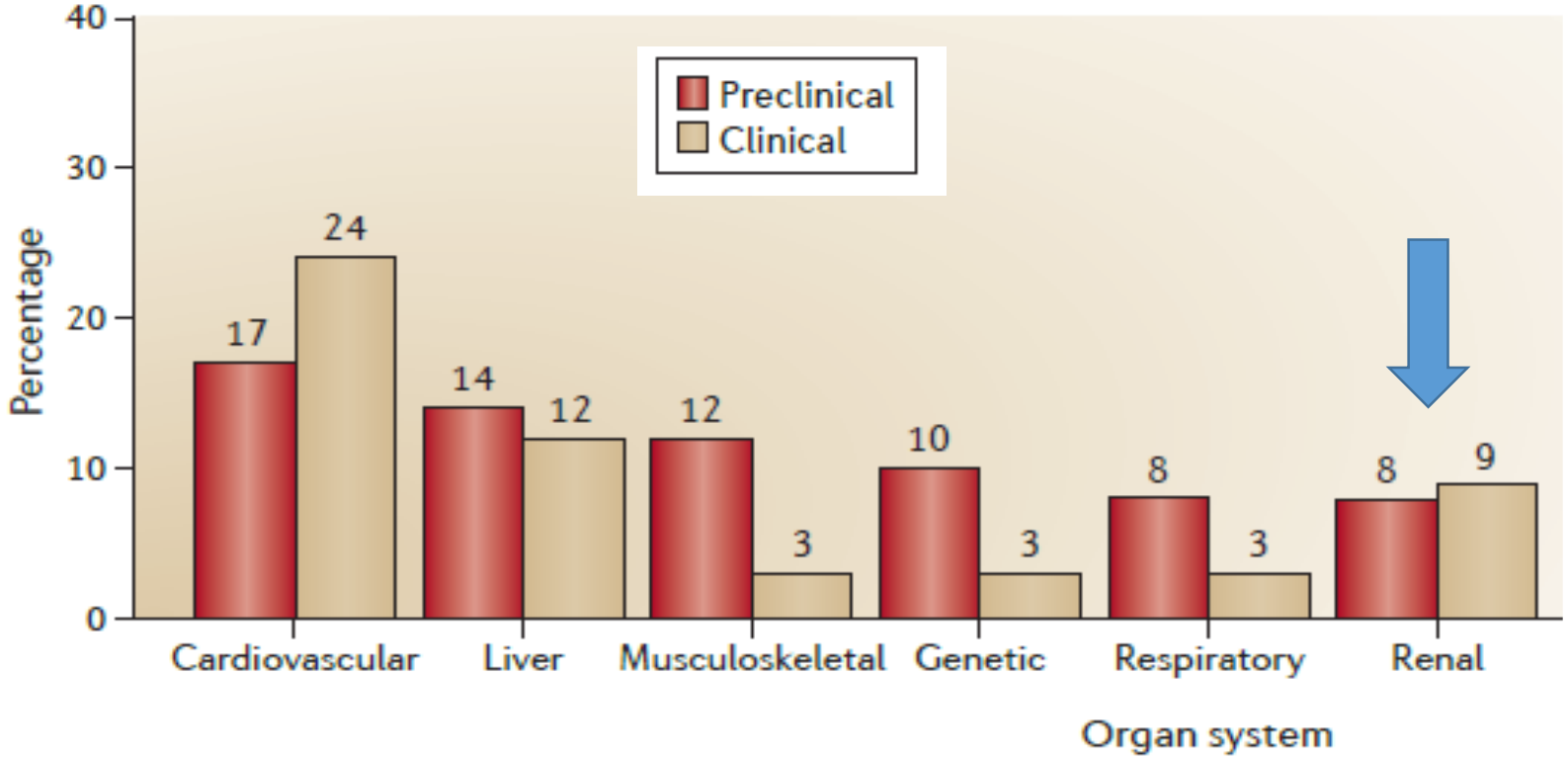
The software to predict DDIs has never undergone formal approval by the FDA.

Reasons for Termination of Programs due to Safety by Organ System



NATURE REVIEWS | DRUG DISCOVERY VOLUME 13 | JUNE 2014 | 419

Reasons for Termination of Programs due to Safety by Organ System



NATURE REVIEWS | DRUG DISCOVERY VOLUME 13 | JUNE 2014 | 419

Liver Safety has Special Emphasis at the FDA

- March 21, 2000 – FDA withdrew Rezulin (Troglitazone) from the market due to severe liver toxicity.
- *Early 2000's – John Senior leads liver safety reviews at FDA*
- *Early 2021 – FDA plans to establish a liver safety evaluation team with standardized criteria to trigger a review*

Conclusion

- **Hepatotoxicity remains a major problem in drug development.**
- **Current preclinical testing has not eliminated this problem.**
- **FDA focus on liver safety has led to requirement of large safety trials and abandonment of promising new drugs.**

UNC Institute for Drug Safety Sciences

DILI-sim Initiative

DILIsym Services
A SIMULATIONS PLUS COMPANY

janssen
GILEAD
DILIsym
Mitsubishi Tanabe Pharma
Daiichi-Sankyo
gsk GlaxoSmithKline
Sumitomo Dainippon Pharma
Bristol-Myers Squibb
Roche
FDA

Patients

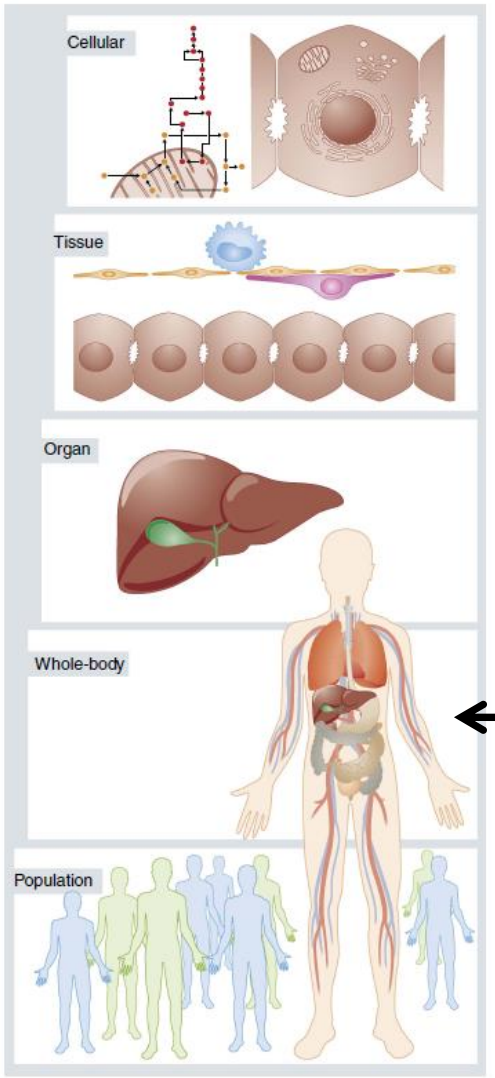
Cutting Edge Pre-clinical Models

In Vitro

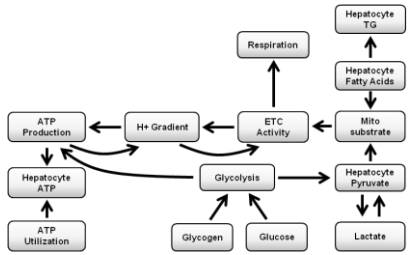
Quantitative Systems Toxicology (QST)

The use of mathematical equations to recapitulate relevant pathways whereby drugs or other chemicals can cause stress and death to cells, tissues, and organs.

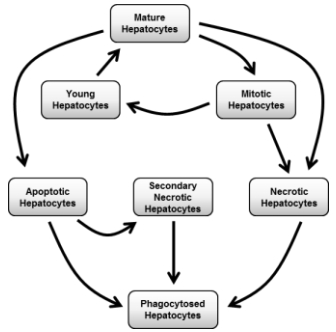
DILIsym® Is a Multi-Scale "Middle Out" QST Model



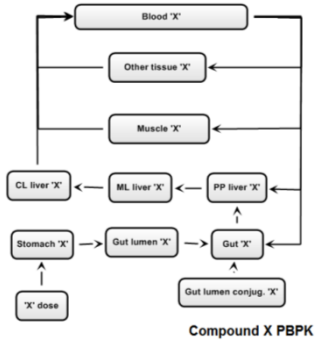
Mitochondrial dysfunction



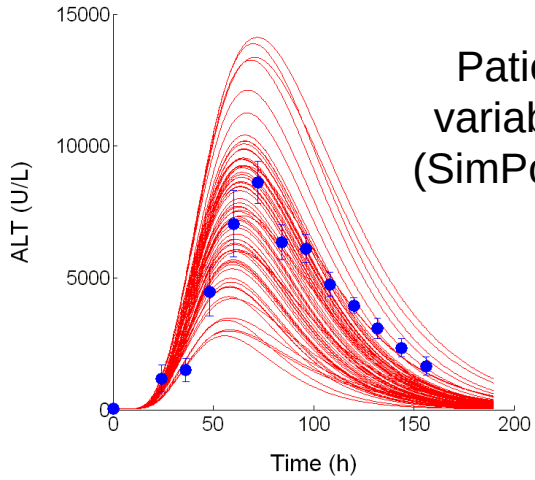
Cellular life-cycle



Drug distribution & metabolism



Compound X PBPK



Patient variability (SimPops®)

Kuepfer 2010, Molecular Systems Biology

UNC ESHELMAN SCHOOL OF PHARMACY

Institute for Drug Safety Sciences

DILI-sim Initiative Approach

1). Build mechanistic “modules” using differential equations – perform experiments to fill in knowledge gaps.

2). Integrate the modules with the outcome of hepatocyte death and release and clearance of traditional and novel serum biomarkers.

3). Vary model parameters to create simulated patient populations (SimPops™)

4). Refine the aggregate model through incorporating data obtained from successive “exemplar” drugs

QST software created by the DILI-sim Initiative (DILIsym®)

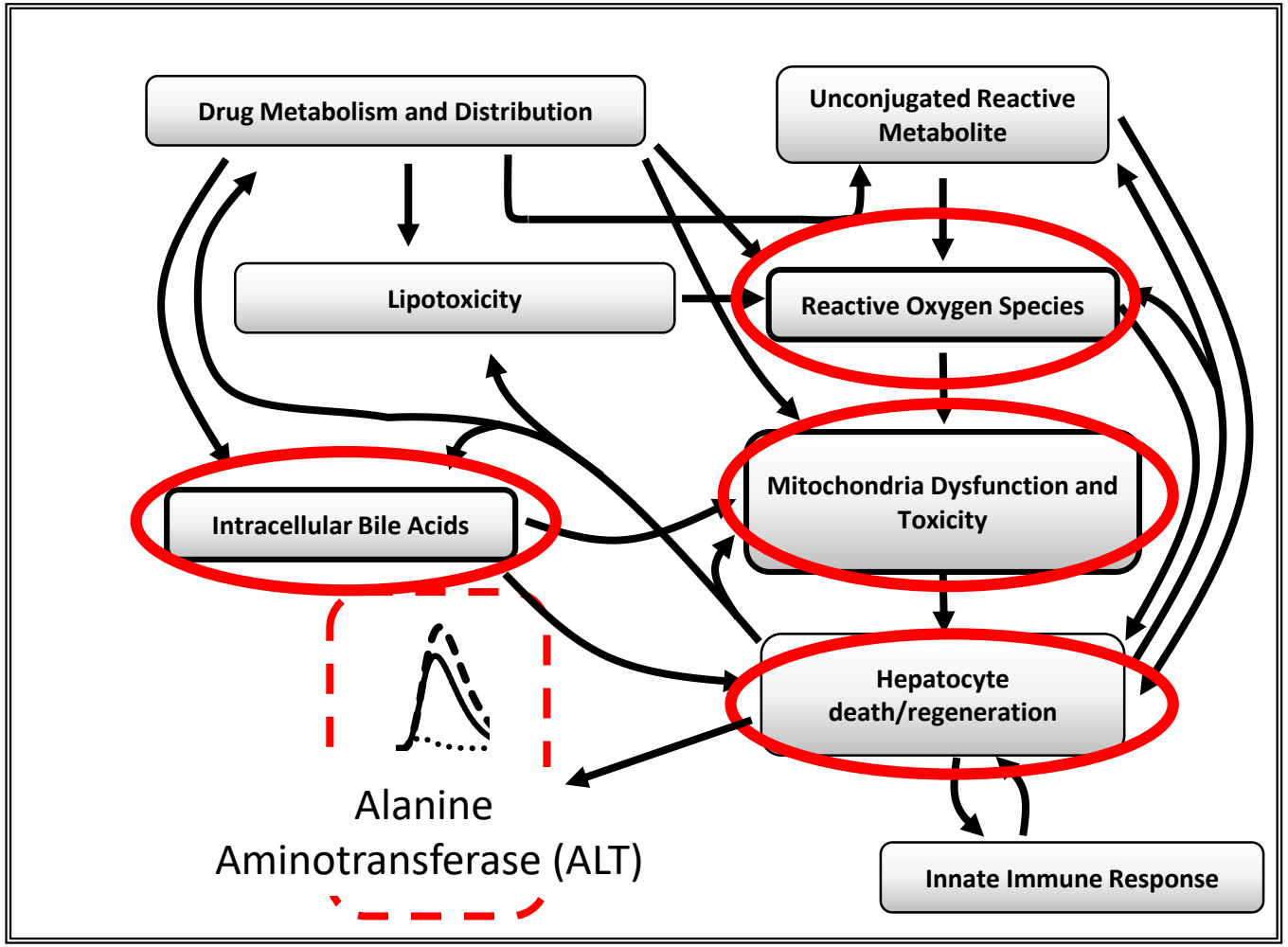


Table 1 Some mechanistic insights from the DILI-sim initiative.

	Insight	Comments	References
1).	Effects on just three processes account for the majority of dose-dependent DILI in patients	The data inputs in Figure 1 can predict ~80% of liver safety liabilities in a validation cohort of drugs.	[7]
2).	Dominant DILI mechanisms can vary among drugs that are closely related in structure	This was best shown for macrolide antibiotics	[33]
3).	Importance of bile acids in DILI	Bile acid accumulation has emerged as the most frequent contributor to DILI predictions	[7,11,29]
4).	Importance of mechanisms of BSEP inhibition	Although not typically assessed, mechanism of BSEP inhibition (competitive vesus noncompetitive) can have large effects on DILI potential	[11,29]
5).	Weak inhibition of BSEP can substantially contribute to DILI potential.	Although a recent consensus considered a BSEP IC50 > 25 uM as not a DILI risk factor, modeling has predicted a DILI risk contribution with IC 50 > 100 uM for some drugs (when one or both of the other mechanisms are involved).	[9,12,29]
6).	Species differences in DILI susceptibility	In addition to variation in toxic potential of bile acids, different effects on mitochondrial respiration can contribute	[6,9–11,13,15,29]
7).	DILIsym results may be relevant to prediction of delay idiosyncratic DILI	DILIsym has predicted DILI liability for troglitazone, tolcapone, TAK-875, and tolvaptan	[9,10,14,29]
8).	DILIsym can optimize interpretation of serum biomarkers	DILIsym provides estimates of hepatocyte loss and global liver function and has been used to refine interpretation of 'Hy's law cases'.	[27]
9).	Disease-associated changes in efflux transporter function could account increased susceptibility to DILI in patients	Alternations in biliary efflux of a major metabolite of tolvaptan (likely due to reduced MRP2 activity) could account for increased DILI susceptibility noted in patients with autosomal dominant polycystic kidney disease	[21]

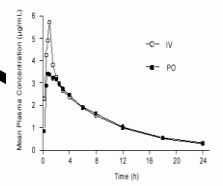
DILI, drug-induced liver injury; BSEP, bile salt excretory protein.

Current Opinion in Toxicology 2020, 23-24:67–73

DILIsym Input Data

Exposure

Pharmacokinetics



DILIsym®

Simulated Frequency & Severity of Liver Injury (ALT)

DILIsym has predicted *known* liver safety liabilities of drugs with greater than 80% accuracy.

Validation cohort, Unpublished data

The rates of serum ALT elevations due to antibiotics are reasonably predicted by DILIsym

Compound	Protocol	Peak ALT > 3X ULN	
		Observed	Simulated
Solithromycin	Oral (CE01-300)	5.4% (3.2%)	3.9%
	IV-to-Oral (CE01-301)	9.1% (5.5%)	6.0%
Erythromycin	500 mg QID 10 days	1-2%	2.8%
Clarithromycin	500 mg BID 7 days	1-2%	2.8%
Telithromycin	800 mg QD 10 days	0.0-0.8%	0%

Pharm Res (2019) 36: 48

Application of Systems Pharmacology to Explore Mechanisms of Hepatotoxicity

J Shon[1] and DR Abernethy[1]

[1]Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA. Correspondence: DR Abernethy (Darrell.Abernethy@fda.hhs.gov)

We look forward to future efforts to apply this model for prediction of hepatotoxicity that has not been clinically observed.

Clin Pharmacol Ther 2014 Nov;96(5):536-7.

True Prediction Example #1: BAL30072

- **Antibiotic for multidrug resistant bacteria**

- **Dose-dependent ALT elevations observed in Phase 1 clinical trial**

Question: **Is there a dosing regimen that would maintain efficacy but be safe for the liver?**

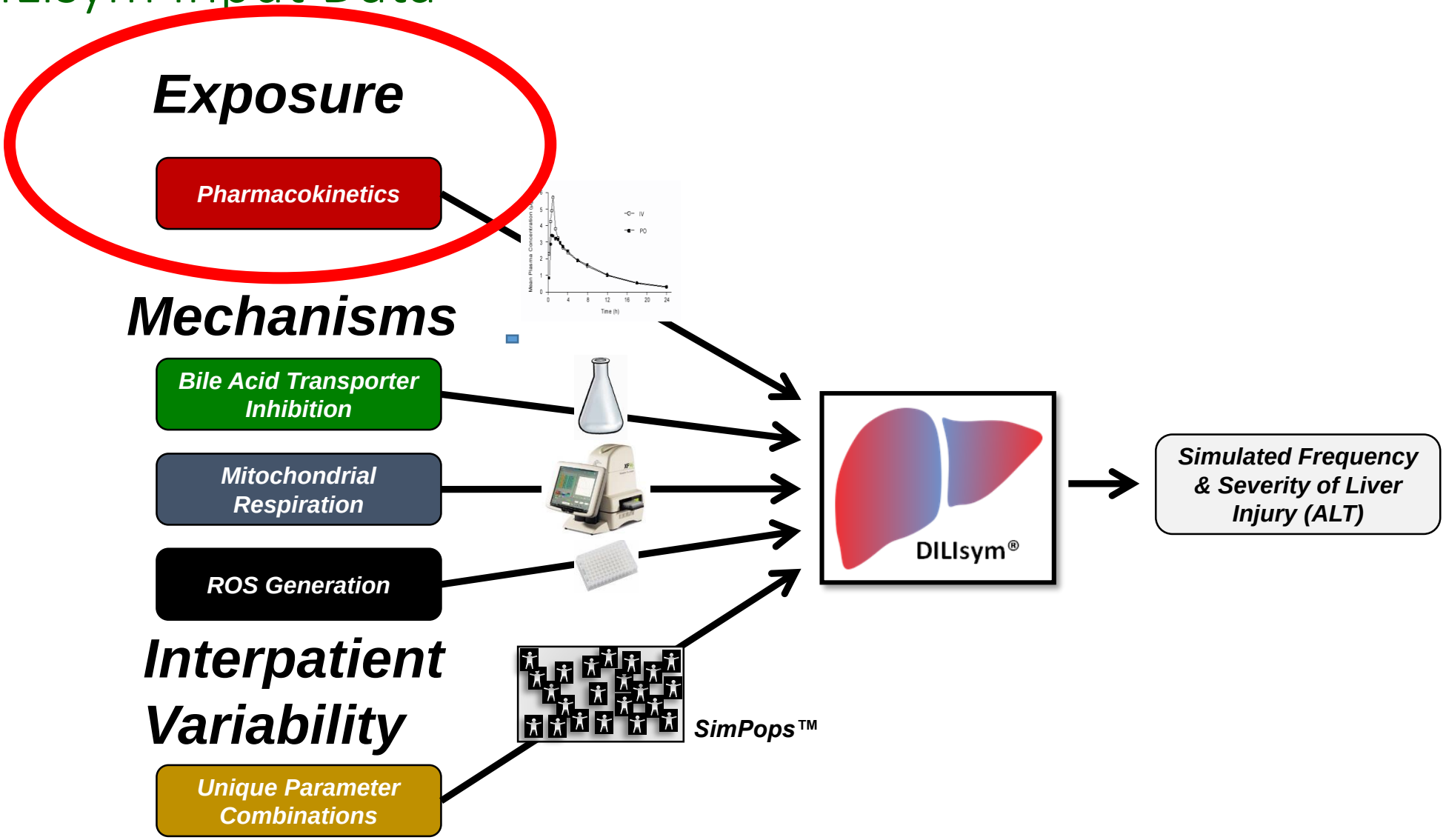
Citation: Clin Transl Sci (2018) 00, 1–8; doi:10.1111/cts.12560

ARTICLE

Prediction of Safety Margin and Optimization of Dosing Protocol for a Novel Antibiotic using Quantitative Systems Pharmacology Modeling

Jeffrey L. Woodhead[1,*], Franziska Paech[2], Martina Maurer[3], Marc Engelhardt[3], Anne H. Schmitt-Hoffmann[3], Jochen Spickermann[3], Simon Messner[4], Mathias Wind[3], Anne-Therese Witschi[3], Stephan Krähenbühl[2], Scott Q. Siler[1], Paul B. Watkins[1] and Brett A. Howell[1]

DILIsym Input Data



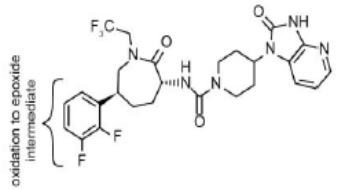
True Prediction Example #2 : Ubrogepant

Calcitonin gene-related peptide (CGRP) antagonist for treatment of migraines

Third in class

Development of first 2 in class terminated due to hepatoxicity

Calcitonin gene-related peptide (CGRP) antagonists for treatment of migraines

Parameter	Telcagepant[a]
Structure[d]	
Potency IC_{50}[e]	2.2 nM
Pivotal conventional nonclinical toxicology study liver findings	3M rat: <3 × ALT/AST with no liver histopathology at 15× exposure margin 6M rat: no liver safety signal at 7x margin 9M NHP: no liver safety signal at 7× margin 6M mouse: <2 × ALT/AST with no liver histopathology at 14× margin

Randomized controlled trial of the CGRP receptor antagonist telcagepant for migraine prevention

Tony W. Ho, MD
Kathryn M. Connor, MD
Ying Zhang, PhD
Eric Pearlman, MD, PhD
Janelle Koppenhaver, MA
Xiaoyin Fan, PhD
Christopher Lines, PhD
Lars Edvinsson, MD
Peter J. Goadsby, MD
David Michelson, MD

Randomized to telcagepant 140 mg, telcagepant 280 mg, or placebo twice daily for 12 weeks.

Neurology® 2014;83:958-966

Table 3 Summary of adverse events

	Telcagepant 140 mg (n = 263)	Telcagepant 280 mg (n = 265)	Placebo (n = 128)
Any adverse event	138 (52.5)	143 (54.0)	74 (57.8)
Drug-related adverse event[a]	81 (30.8)	74 (27.9)	38 (29.7)
Serious adverse event	3 (1.1)	2 (0.8)	1 (0.8)
ALT increased	6 (2.3)	12 (4.5)	0 (0.0)

But.. two symptomatic hepatitis cases with ALT > 30 X ULN occurring 3-4 weeks on treatment.

Original Article

Cephalalgia
An International Journal of Headache

International Headache Society

Cephalalgia
2016, Vol. 36(2) 148–161

DOI: 10.1177/0333102415584308
cep.sagepub.com

SAGE

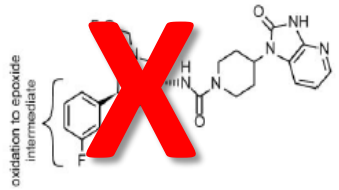
Randomized controlled trial of the CGRP receptor antagonist telcagepant for prevention of headache in women with perimenstrual migraine

Tony W Ho[1,a], Andrew P Ho[1,b], Yang (Joy) Ge[1], Christopher Assaid[1], Regina Gottwald[1], E Anne MacGregor[2], Lisa K Mannix[3], Willebrordus PJ van Oosterhout[4], Janelle Koppenhaver[1], Christopher Lines[1], Michel D Ferrari[4] and David Michelson[1]

n = 2660 on 140 mg qd X 7d each month vs n = 1336 on placebo

"In three patients, all in the telcagepant group, ALT elevations > 8 ULN were reported and were considered to be a serious laboratory adverse event."

Calcitonin gene-related peptide (CGRP) antagonists for treatment of migraines

Parameter	Telcagepant[a]
Structure[d]	
Potency IC_{50}[e]	2.2 nM
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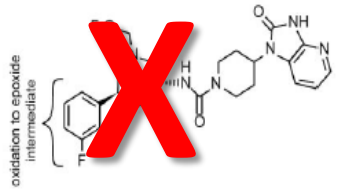
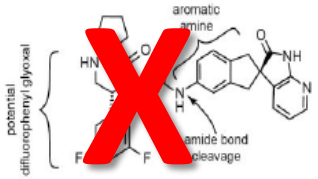
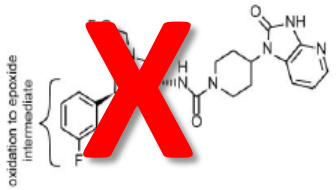
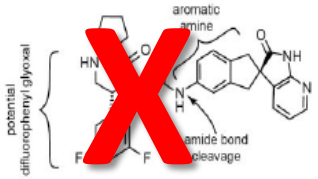
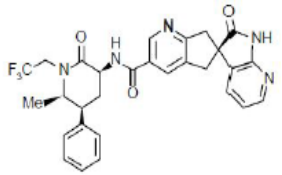
Smith et al, Tox Sci 1:177(1):84-93, 2020

Calcitonin gene-related peptide (CGRP) antagonists for treatment of migraines

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

Smith et al, Tox Sci 1:177(1):84-93, 2020

Calcitonin gene-related peptide (CGRP) antagonists for treatment of migraines

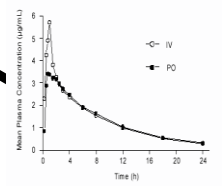
Parameter	Telcagepant[a]	MK-3207[b]	Ubrogepant[c]
Structure[d]			
Potency IC_{50}[e]	2.2 nM	0.12 nM	0.08 nM
Pivotal conventional nonclinical toxicology study liver findings	3M rat: <3 × ALT/AST with no liver histopathology at 15× exposure margin 6M rat: no liver safety signal at 7x margin 9M NHP: no liver safety signal at 7× margin 6M mouse: <2 × ALT/AST with no liver histopathology at 14× margin	6M rat: no liver safety signal at 25× exposure margin 9M NHP: no liver safety signal at 4× margin 6M mouse: no liver safety signal at 12× margin 1M dog: slight periportal vacuolation with <4 × ALT/AST associated with excessive body weight loss at 17x margin	6M rat: <2 × ALT with no liver histopathology at 70× exposure margin 9M NHP: no liver safety signal at 163× margin 3M mouse: no liver safety signal at 80× margin

Smith et al, Tox Sci 1:177(1):84-93, 2020

DILIsym Input Data

Exposure

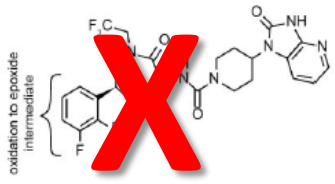
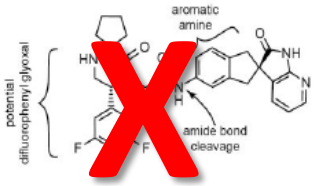
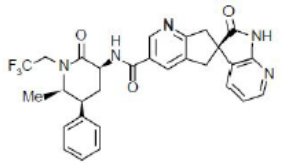
Pharmacokinetics



DILIsym®

Simulated Frequency & Severity of Liver Injury (ALT)

Calcitonin gene-related peptide (CGRP) antagonists for treatment of migraines

Parameter	Telcagepant[a]	MK-3207[b]	Ubrogepant[c]
Structure[d]	 X	 X	
Potency IC_{50}[e]	2.2 nM	0.12 nM	0.08 nM
Pivotal **DILIsym**	X	X	

Smith et al, Tox Sci 1:177(1):84-93, 2020

Predicted to be safe at 10 X dose planned

Original Article

Cephalalgia
An International Journal of Headache

International Headache Society

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

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DOI: 10.1177/0333102419869918
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Safety and tolerability of ubrogepant following intermittent, high-frequency dosing: Randomized, placebo-controlled trial in healthy adults

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

Table 3. Hepatic laboratory parameters.

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

For Immediate Release:
December 23, 2019

Food and Drug Administration today approved Ubrelvy (ubrogepant) tablets for the acute (immediate) treatment of migraine with or without aura (a sensory phenomenon or visual disturbance) in adults.

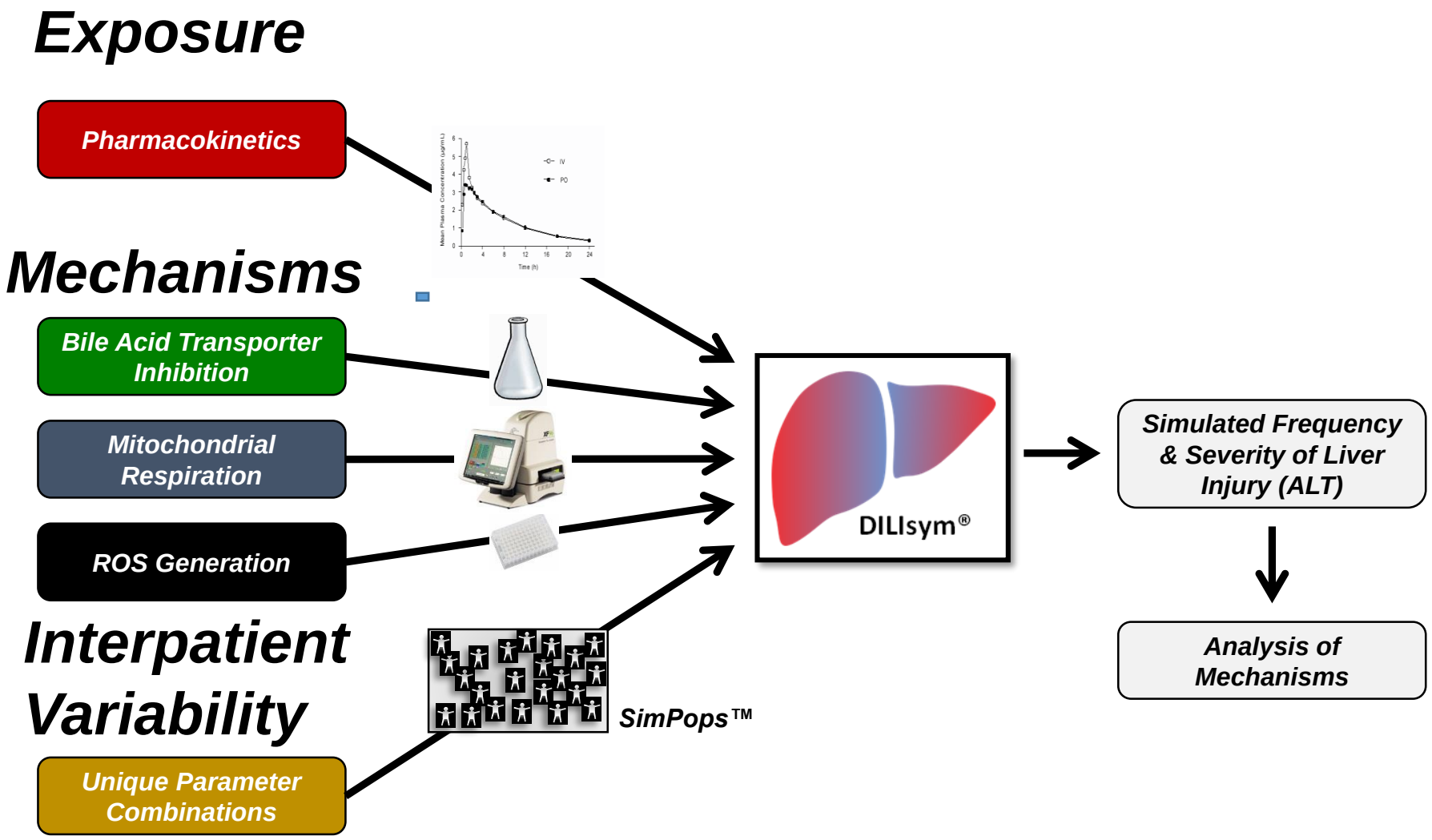
No liver safety warning in package insert!

Conclusion

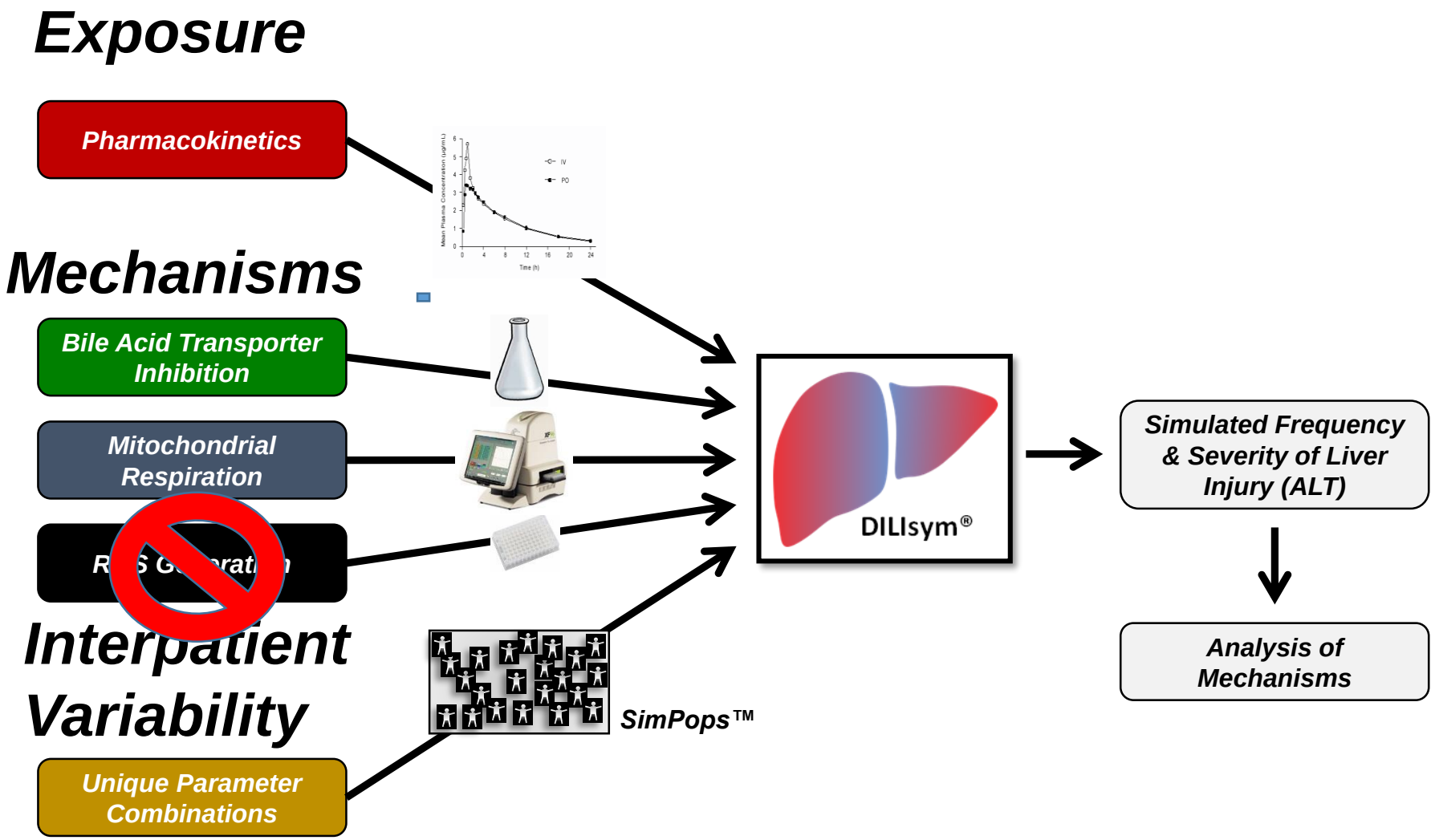
DILIsym modeling was part of the weight of evidence that *supported FDA approval* of Ubrogepant for the treatment of acute migraine headaches.

Can we use DILIsym to predict non-pharmacokinetic DDI leading to liver injury?

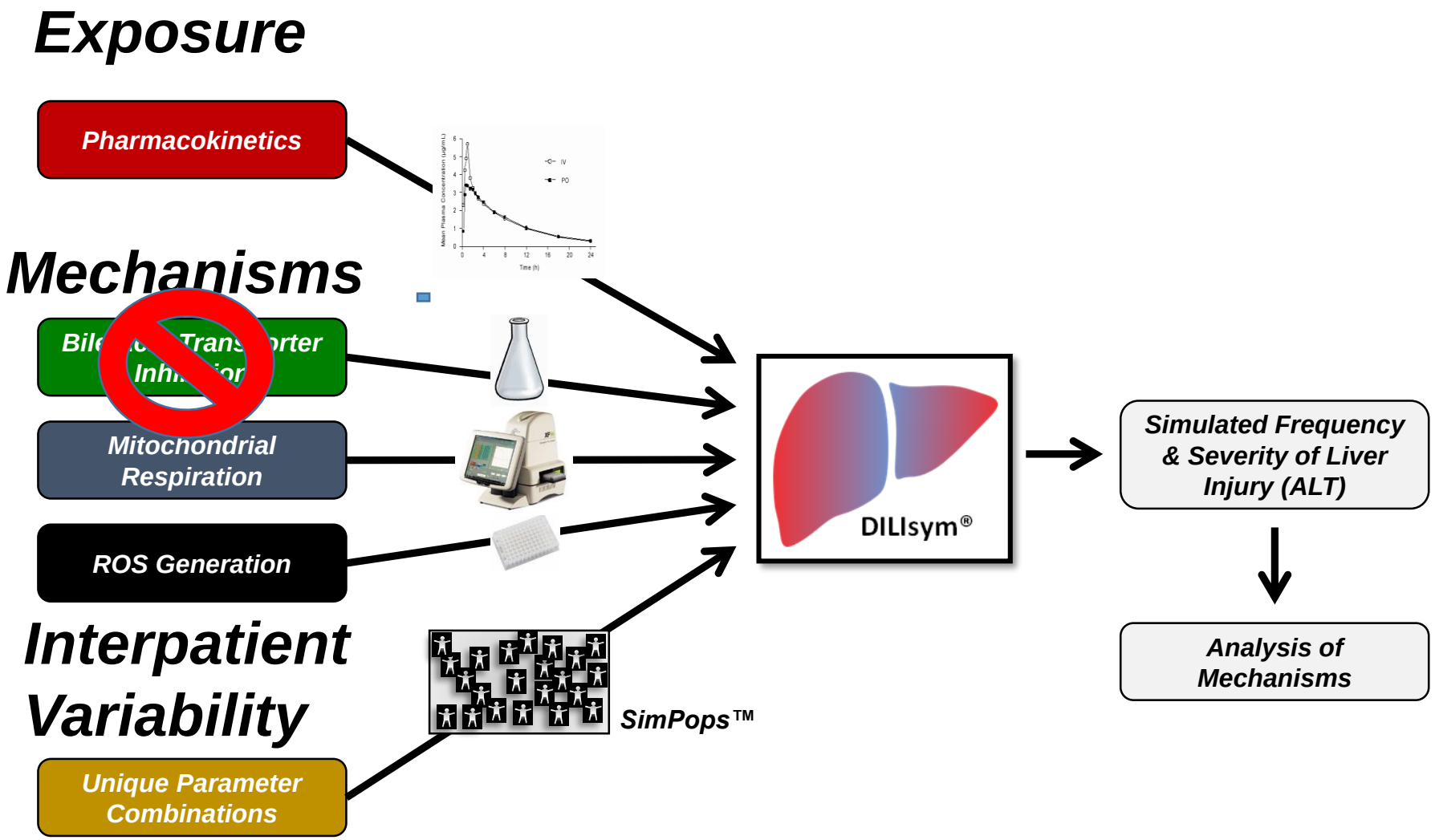
Using DILIsym to identify dominant mechanisms underlying DILI



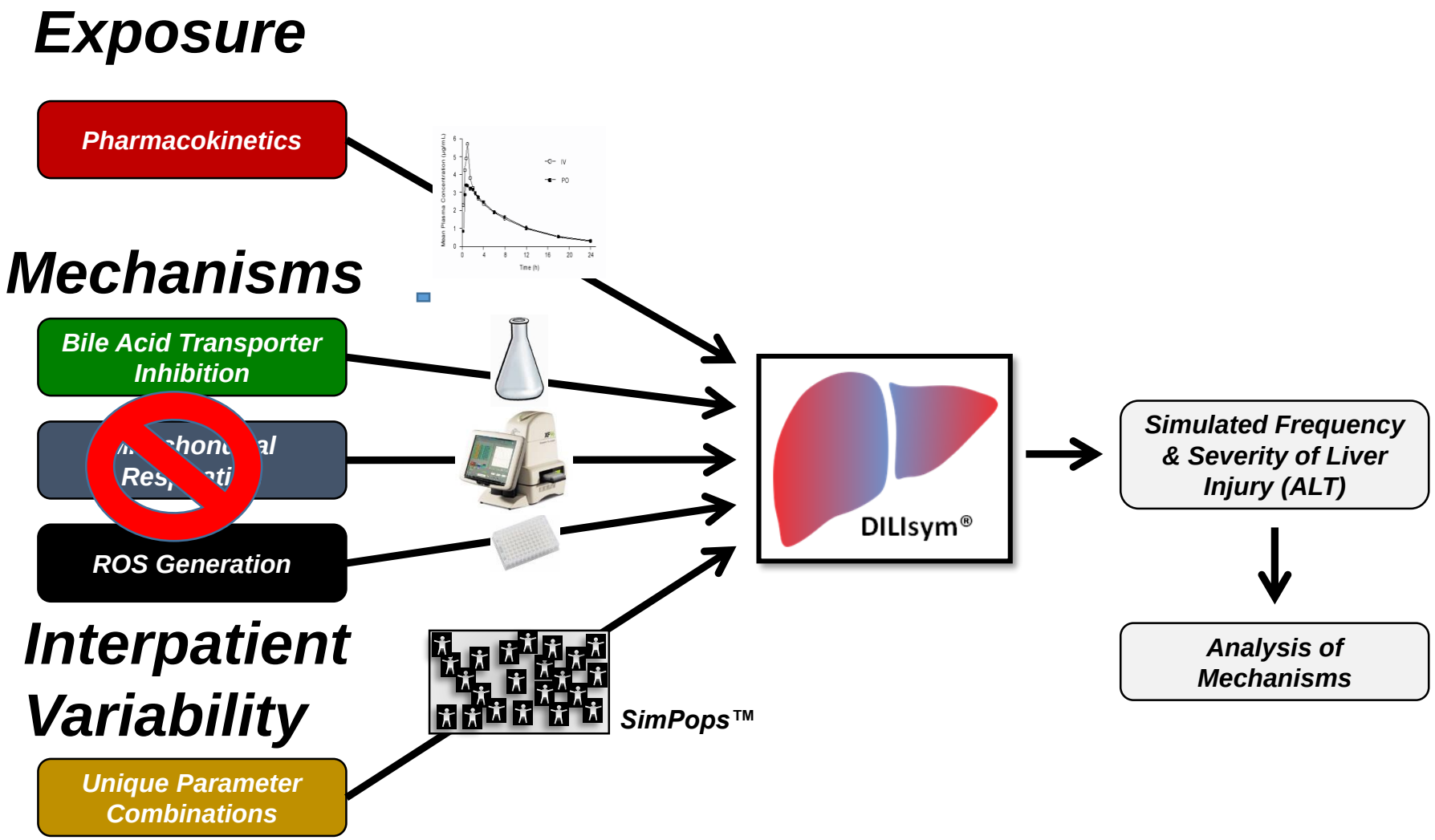
Using DILIsym to identify dominant mechanisms underlying DILI



Using DILIsym to identify dominant mechanisms underlying DILI



Using DILIsym to identify dominant mechanisms underlying DILI



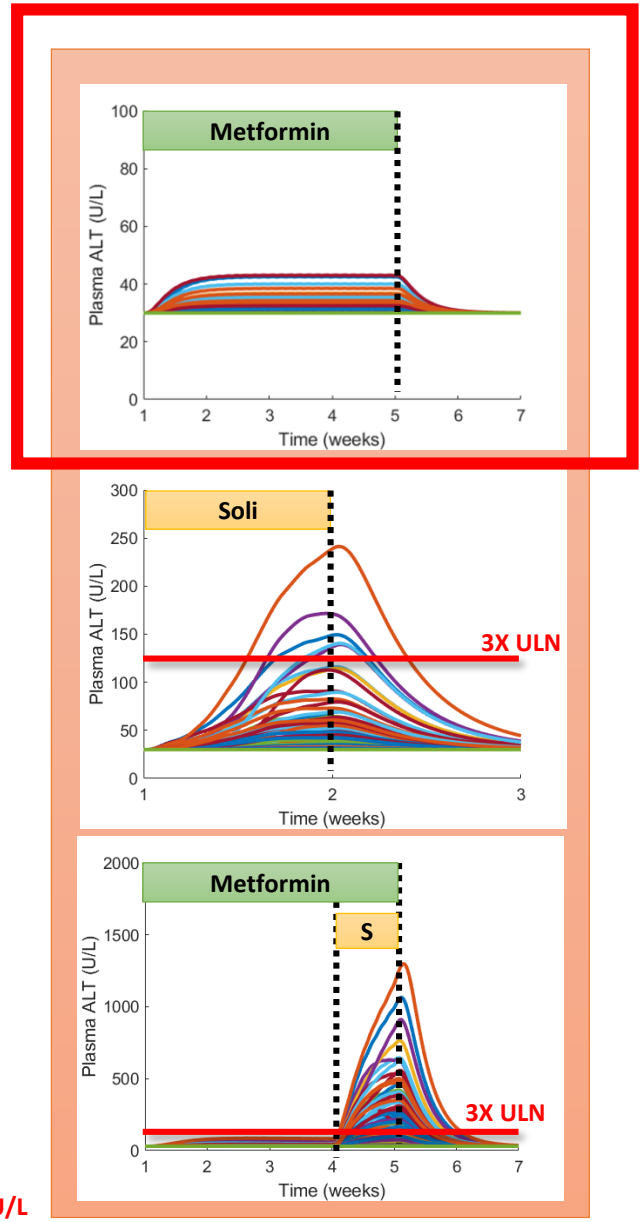
Contribution to Predicted ALT elevations in Simulated Human Population

DILI Mechanism	Solithromycin	Telithromycin	Erythromycin	Clarithromycin
Mitochondrial Respiration Inhibition	Predominant	None	None	Predominant
Oxidative Stress	None	None	Minor	None
Bile Acid Transporter Inhibition	Minor	Predominant	Predominant	Minor

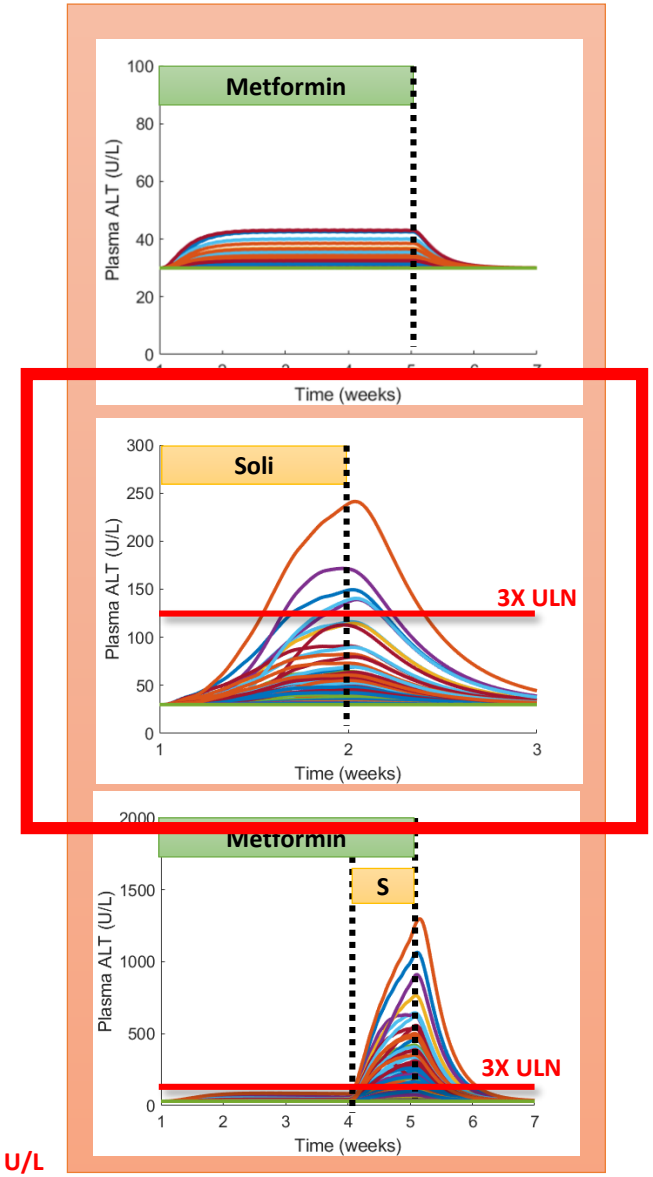
Data presented at Nov 4 2017 anti-infective Ad com

Question:

- What if a patients starts solithromycin but is already receiving another drug that also inhibits mitochondrial respiration, such as metformin?



3X ULN (upper limit of normal) = 120 U/L



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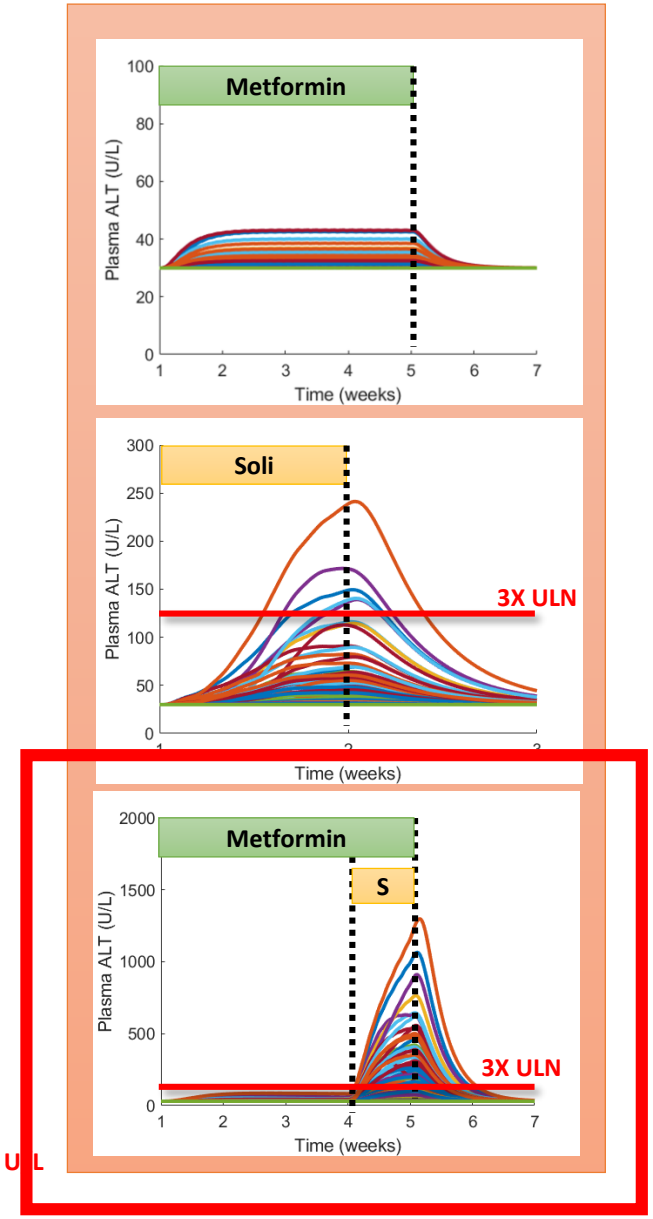

3X ULN (upper limit of normal) = 120 U/L

Does not happen

Reason: adaptation

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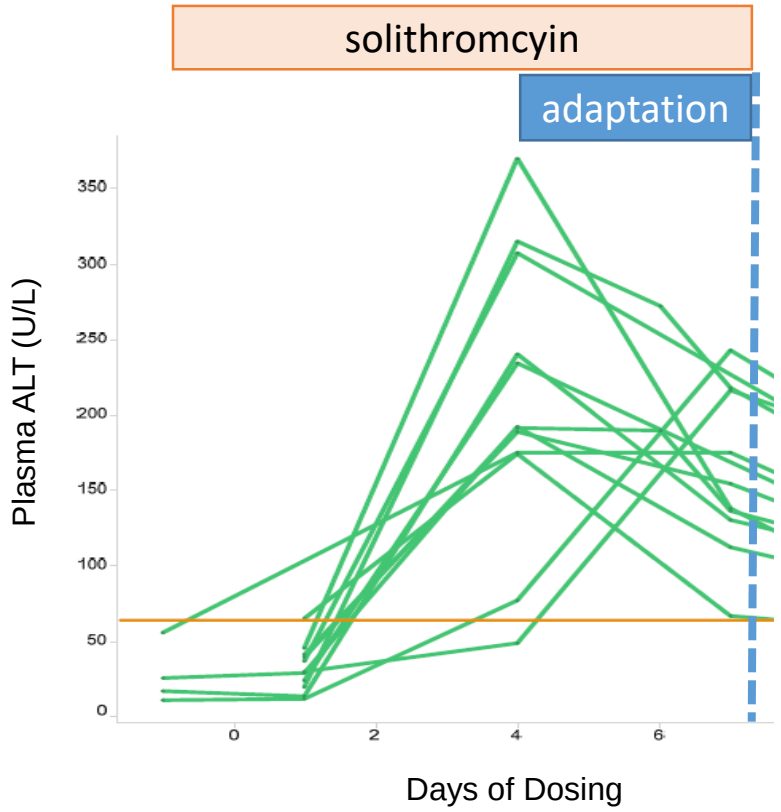
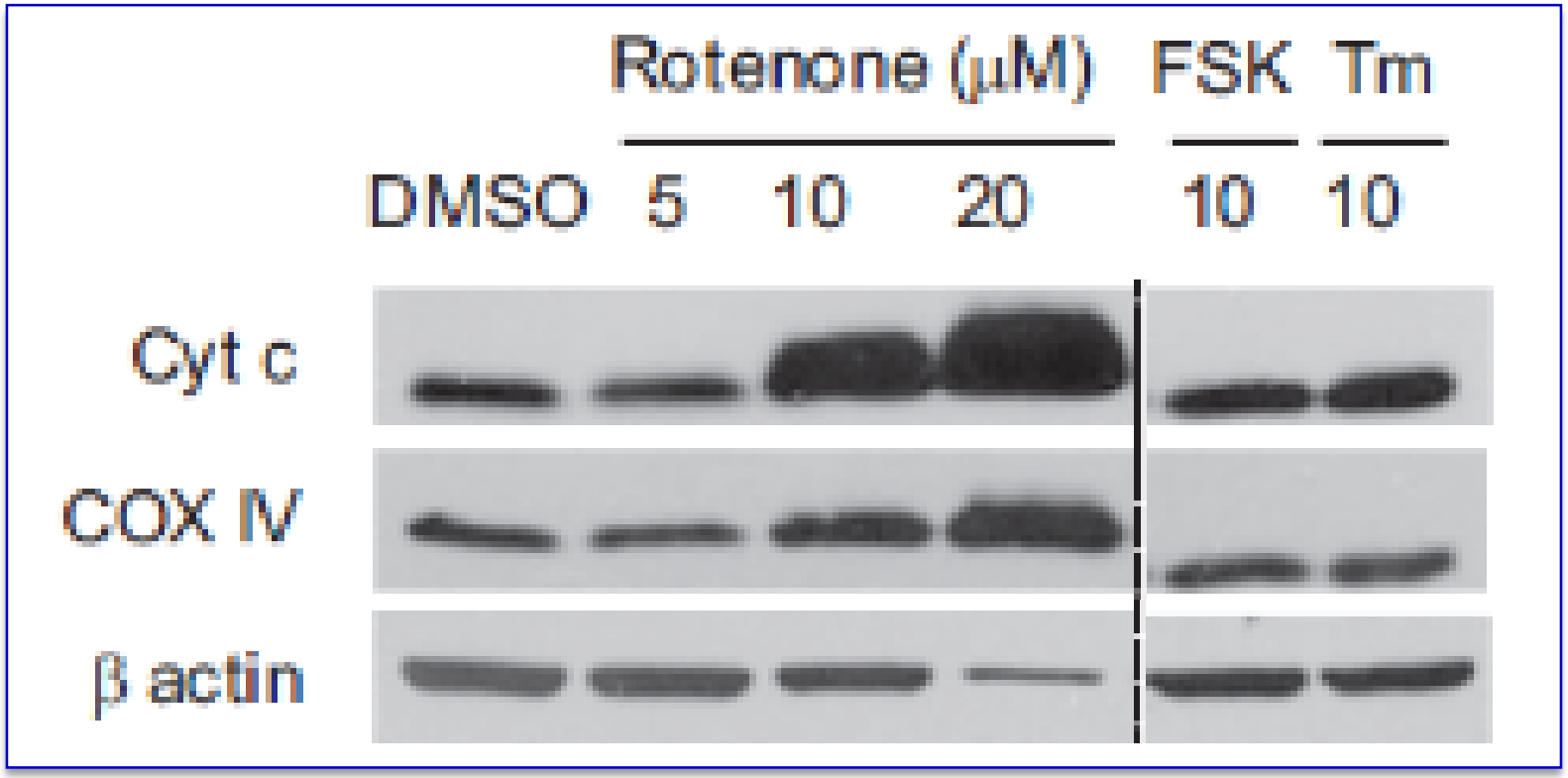
Clinical data – 7 day treatment with solithromycin



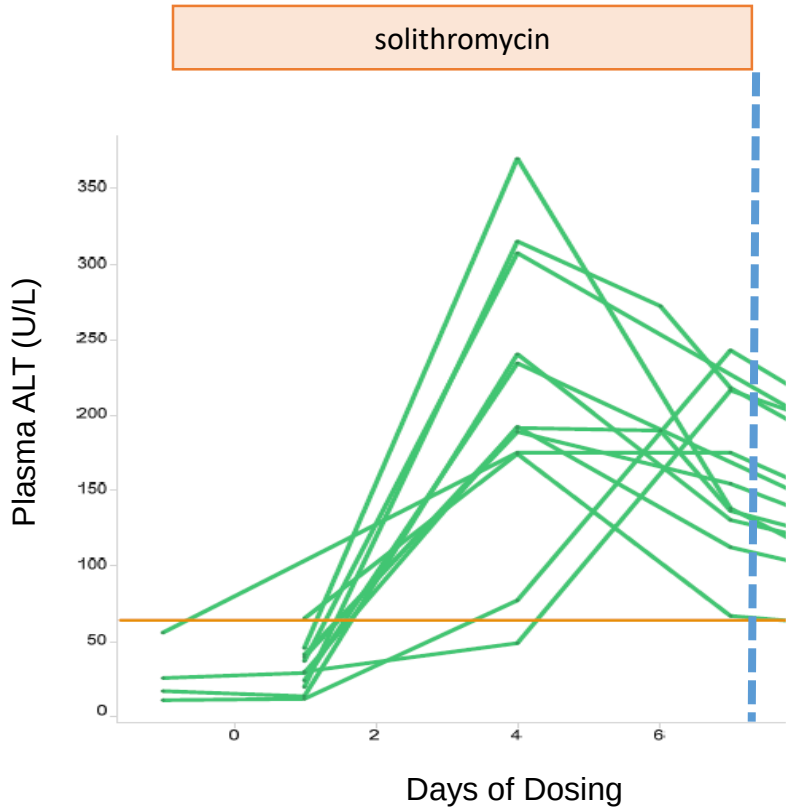
Mitogenesis in response to inhibition of mitochondrial respiration
(mouse hepatocytes)



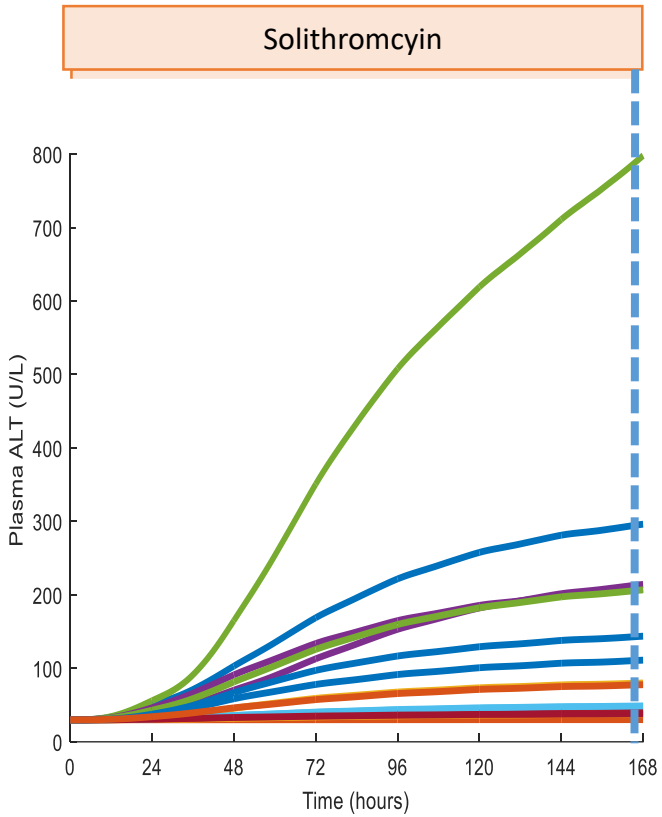
J Biol Chem. **2011** Jun 24;286(25):22047-54.

Treatment with solithromycin

Clinical data

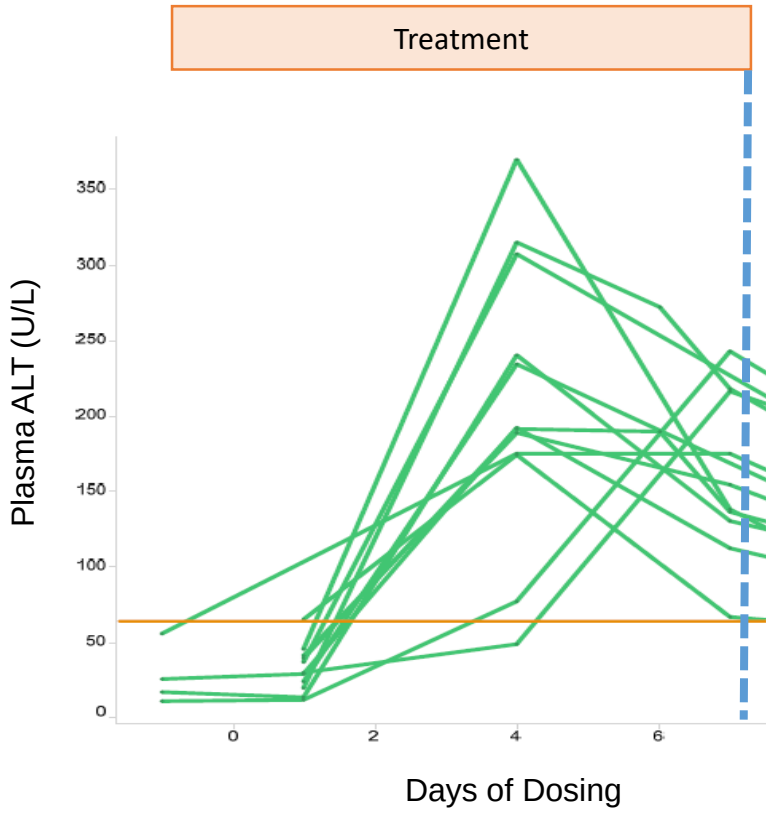


Simulation Results

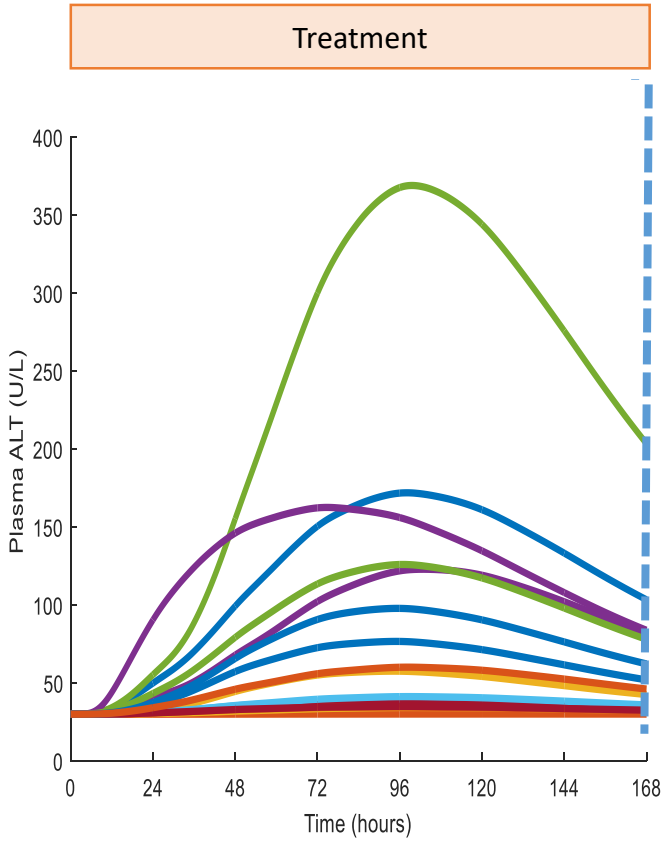


Treatment with solithromycin

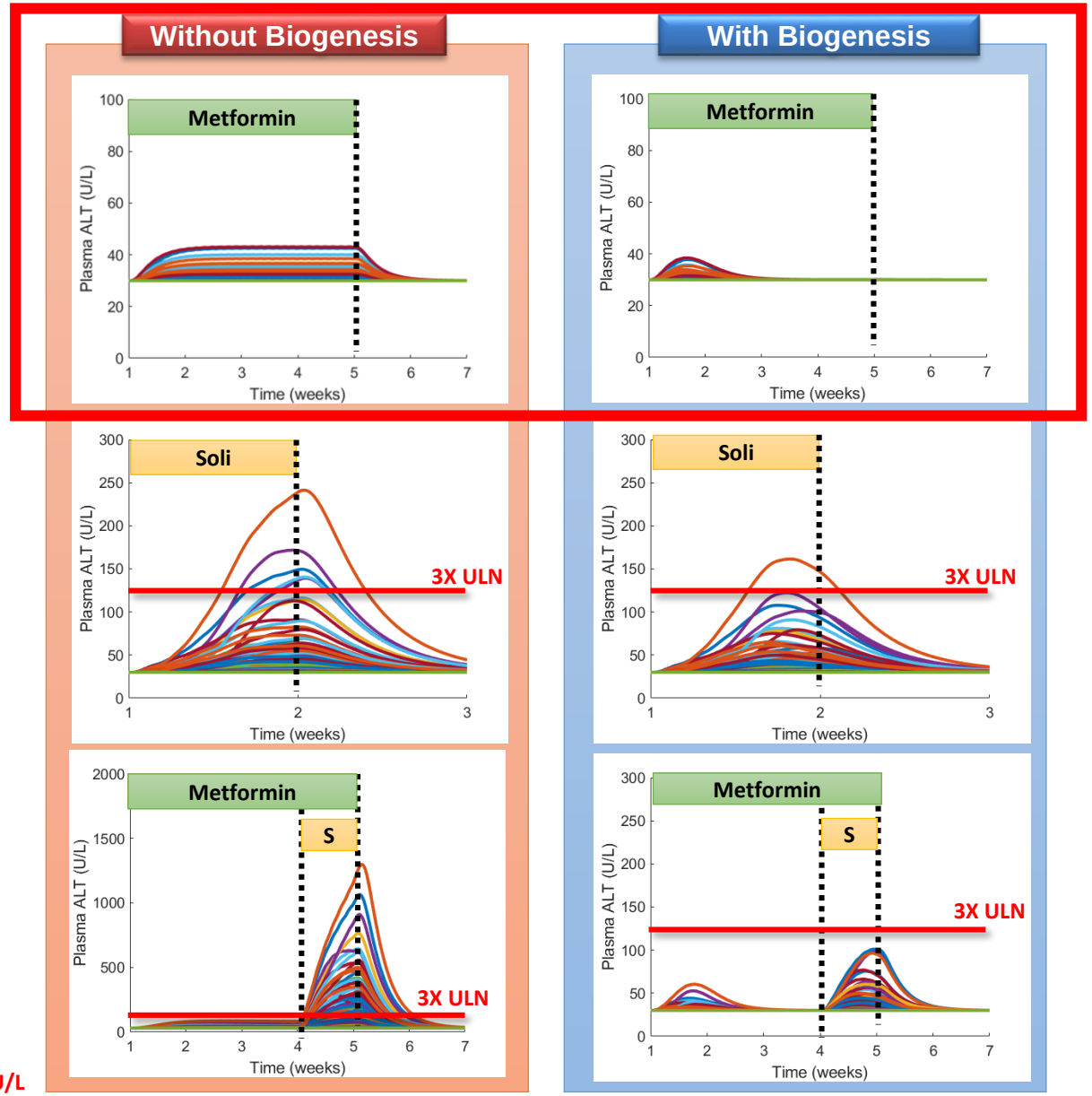
Clinical data



Simulation Results
With Mitogenesis



Fitted to drop in ATP



3X ULN (upper limit of normal) = 120 U/L

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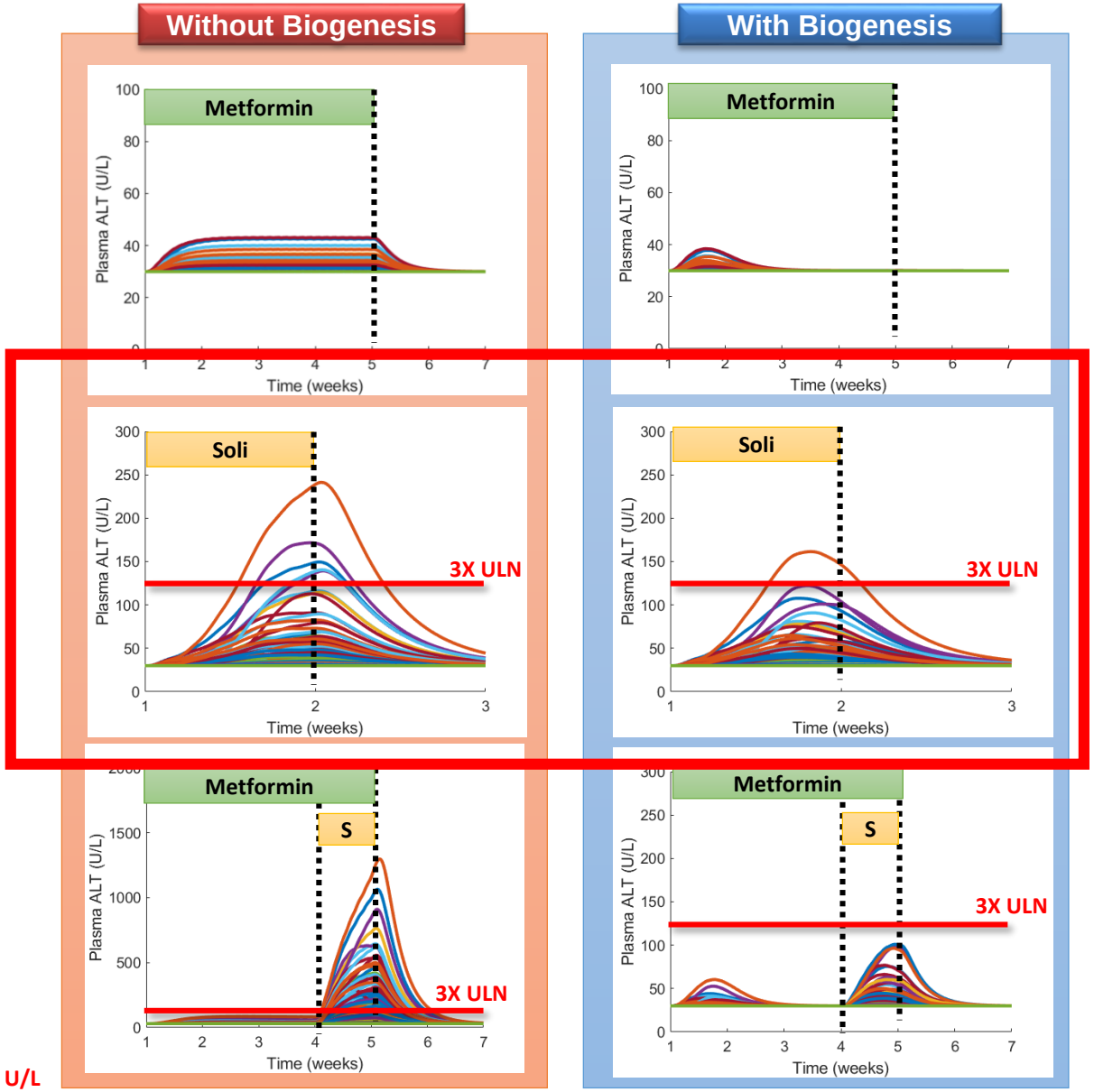

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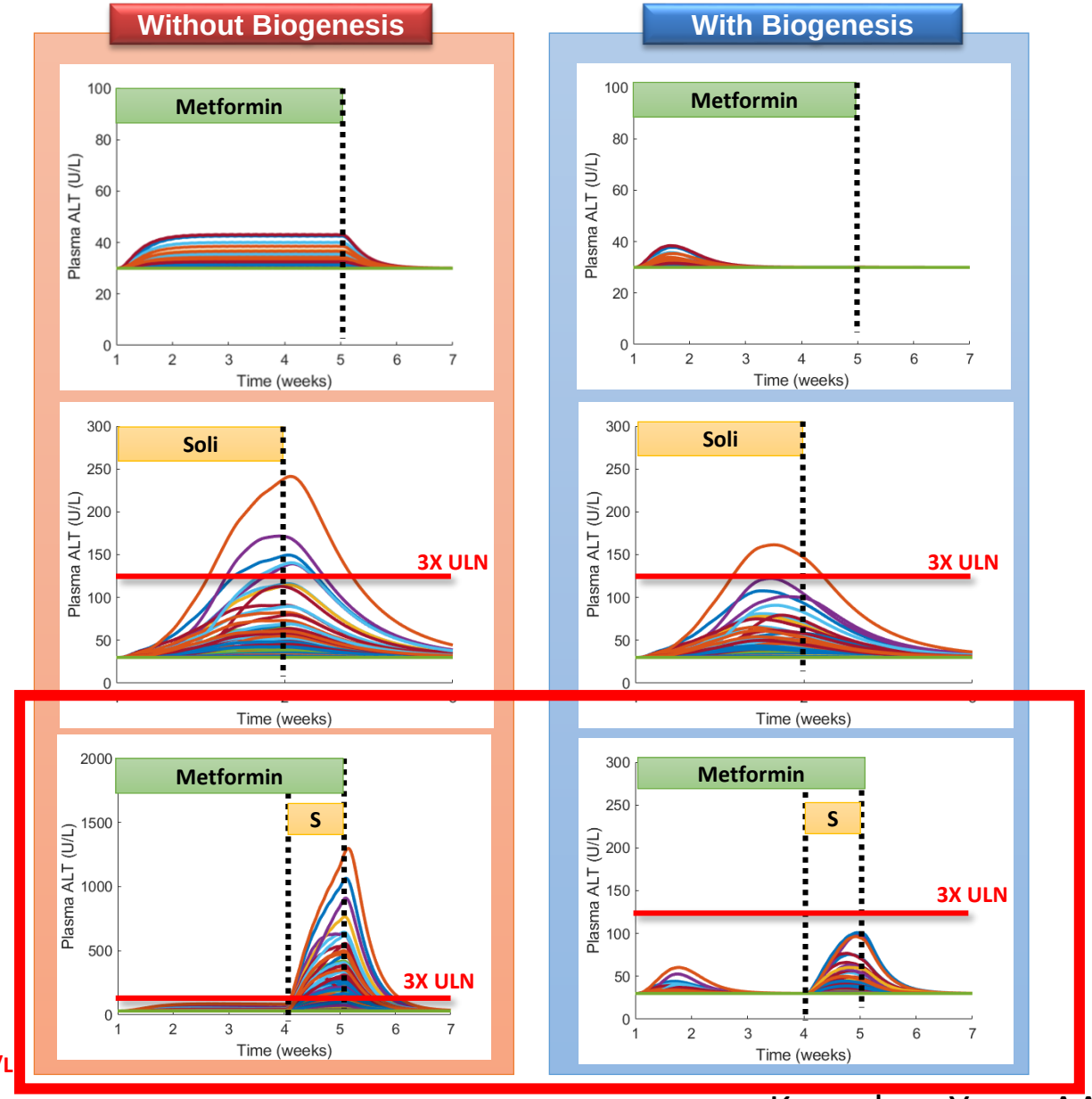
Kyunghee Yang, AAPS PharmSic360, October 2020



3X ULN (upper limit of normal) = 120 U/L

Kyunghee Yang, AAPS PharmSic360, October 2020

Drug X*

Causes very mild ALT elevations in some treated patients

Marked ALT elevations were observed in a Phase 1 DDI trial with a single dose of metformin

This was not due to a pharmacokinetic DDI

DILIsym modeling identified inhibition of mitochondrial respiration as the dominant mechanism.

*proprietary new drug candidate

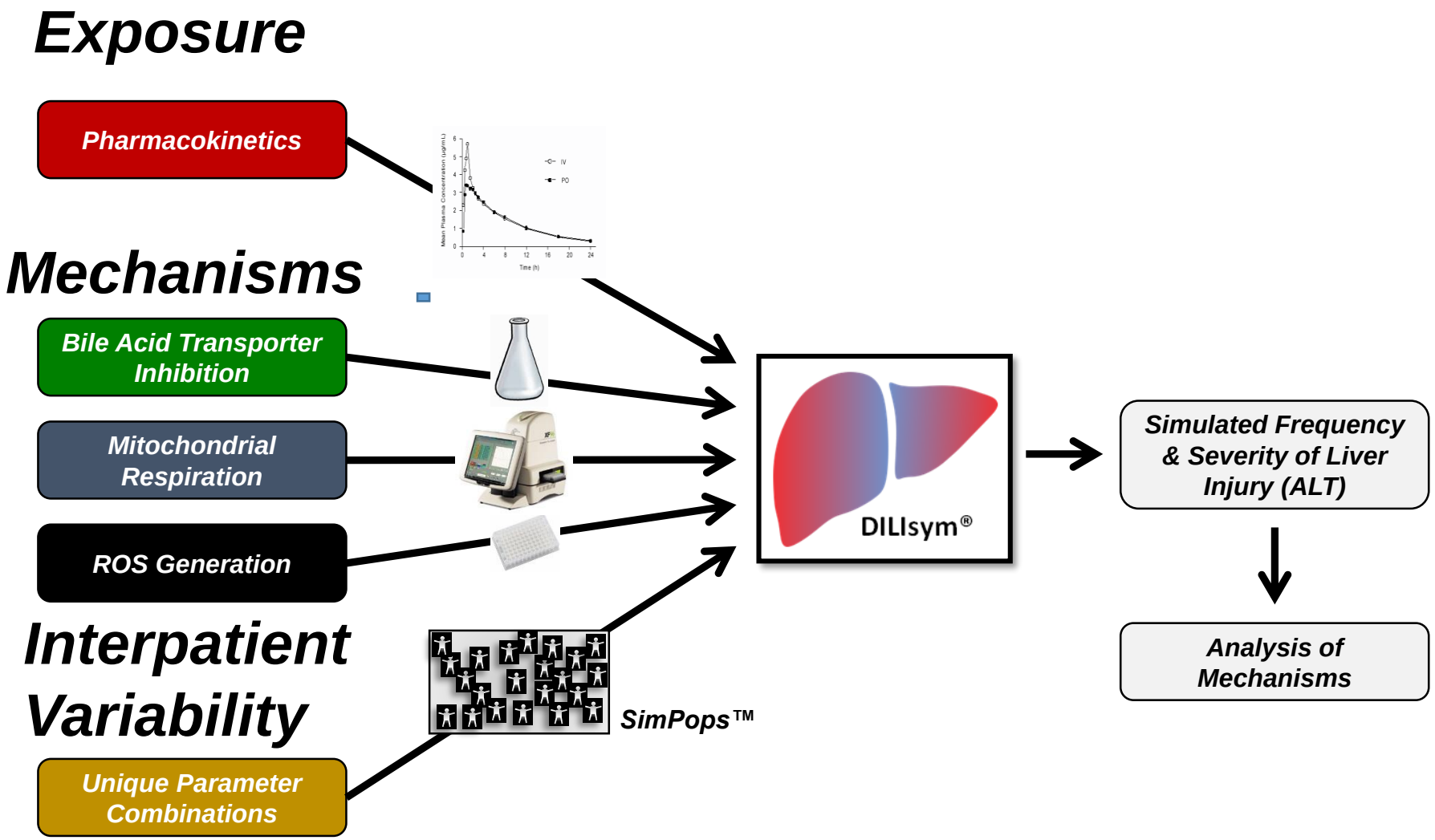
Conclusion

DILIsym can predict increased (mechanistic) susceptibility to liver toxicity due to another drug.

Question:

Can DILIsym predict patient populations at increased risk for liver injury due to a new drug candidate?

Using DILIsym to identify dominant mechanisms underlying DILI



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

James J. Beaudoin[1], William J. Brock[2], Paul B. Watkins[1] and Kim L. R. Brouwer[1,*]

[1]Division of Pharmacotherapy and Experimental Therapeutics, UNC Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina, USA; [2]Brock Scientific Consulting, LLC, Montgomery Village, Maryland, USA. *Correspondence: Kim L. R. Brouwer (klbrouwer@unc.edu)

Received April 6, 2020; accepted July 25, 2020. doi:10.1002/cpt.2007

First publication resulting from academic license of DILIsym

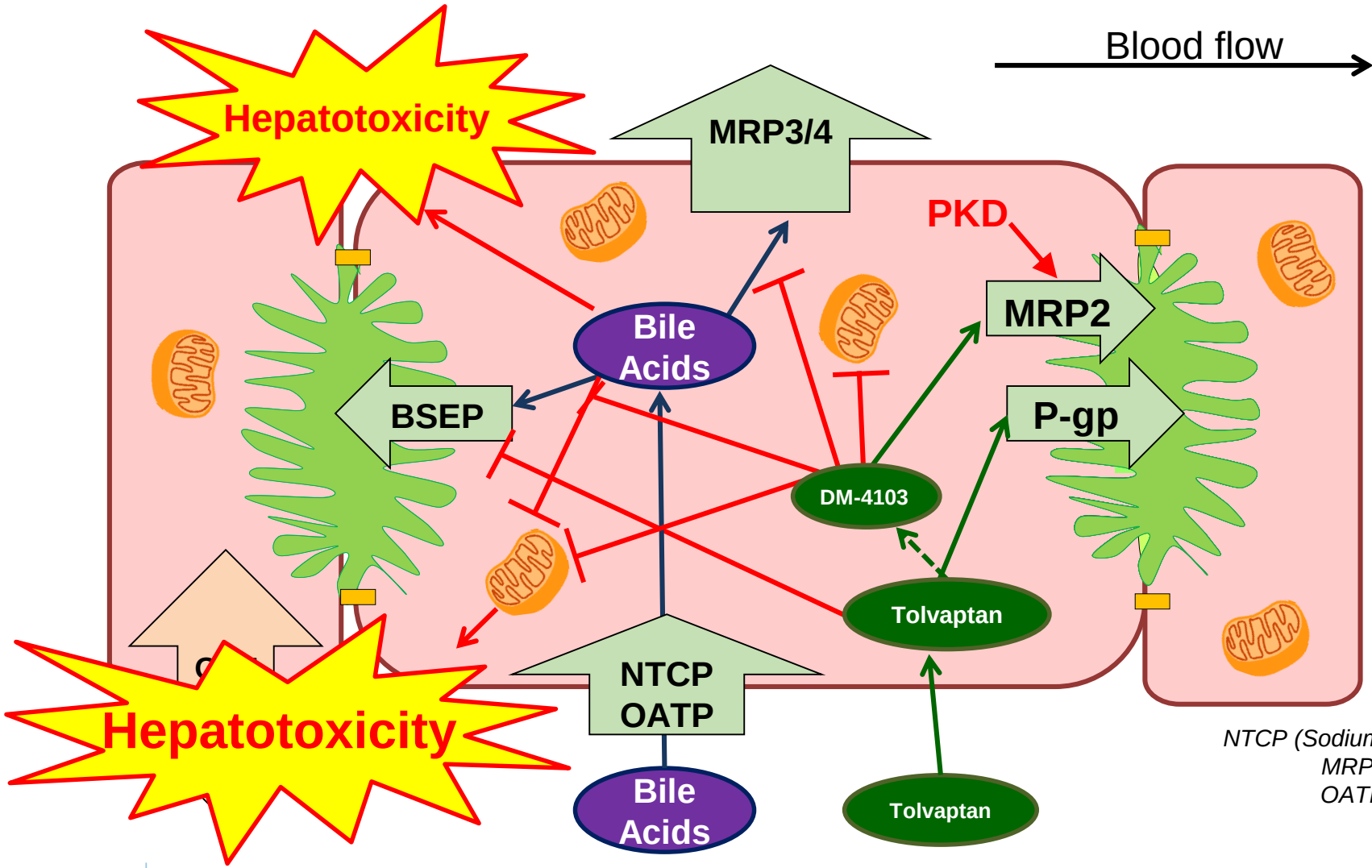
Tolvaptan Hepatotoxicity

1). Increase risk in patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD)

2). A rat model for ADPKD has reduced expression of MRP2

3). Inhibition or knock-down of MRP2 in human hepatocytes increases susceptibility to tolvaptan toxicity

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

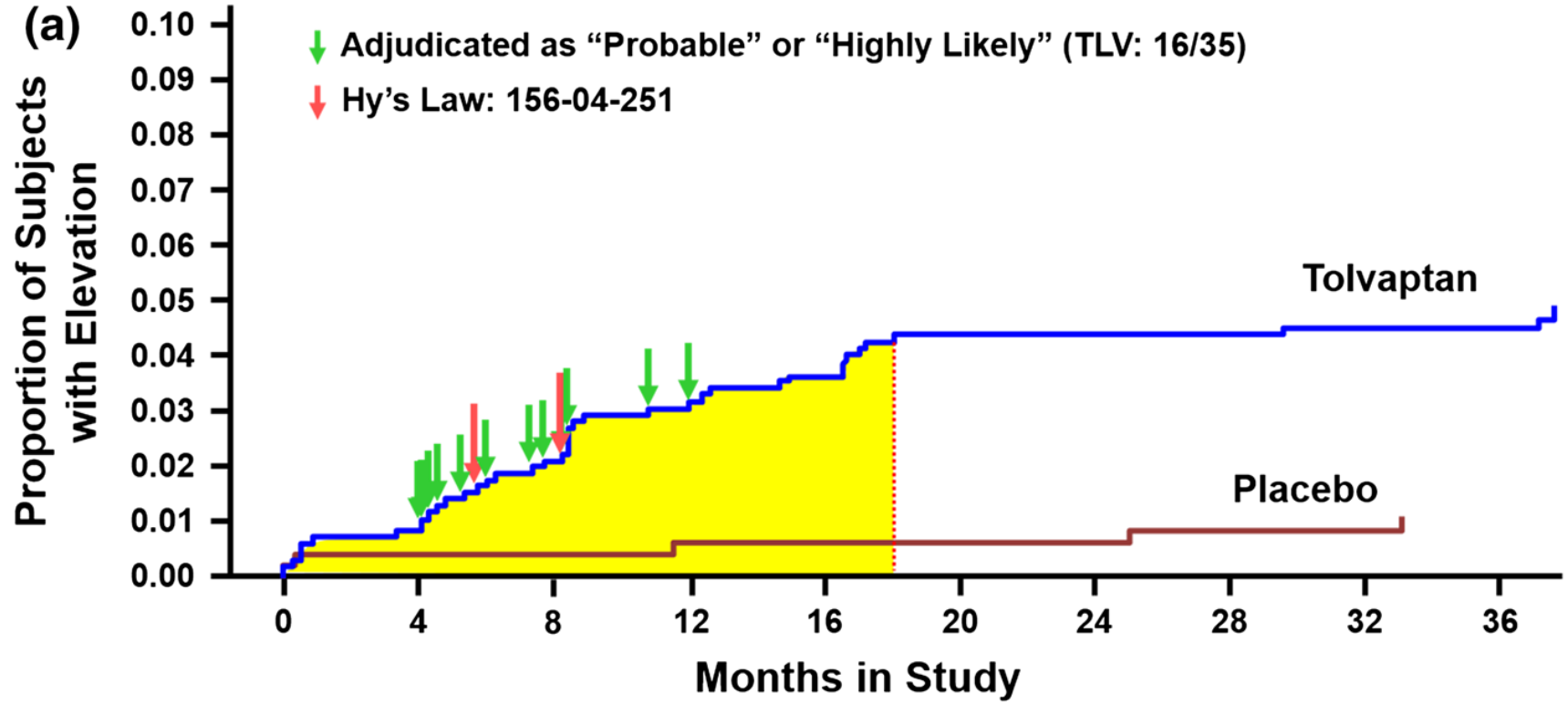


From Jim Beaudoin and Kim Brouwer

(Mitochondrion)

BSEP (Bile Salt Export Pump)
NTCP (Sodium-Taurocholate Cotransporting Polypeptide)
MRP (Multidrug Resistance–Associated Protein)
OATP (Organic Anion-Transporting Polypeptide)
P-gp (P-glycoprotein)
OSTα/β (Organic Solute Transporter α/β)

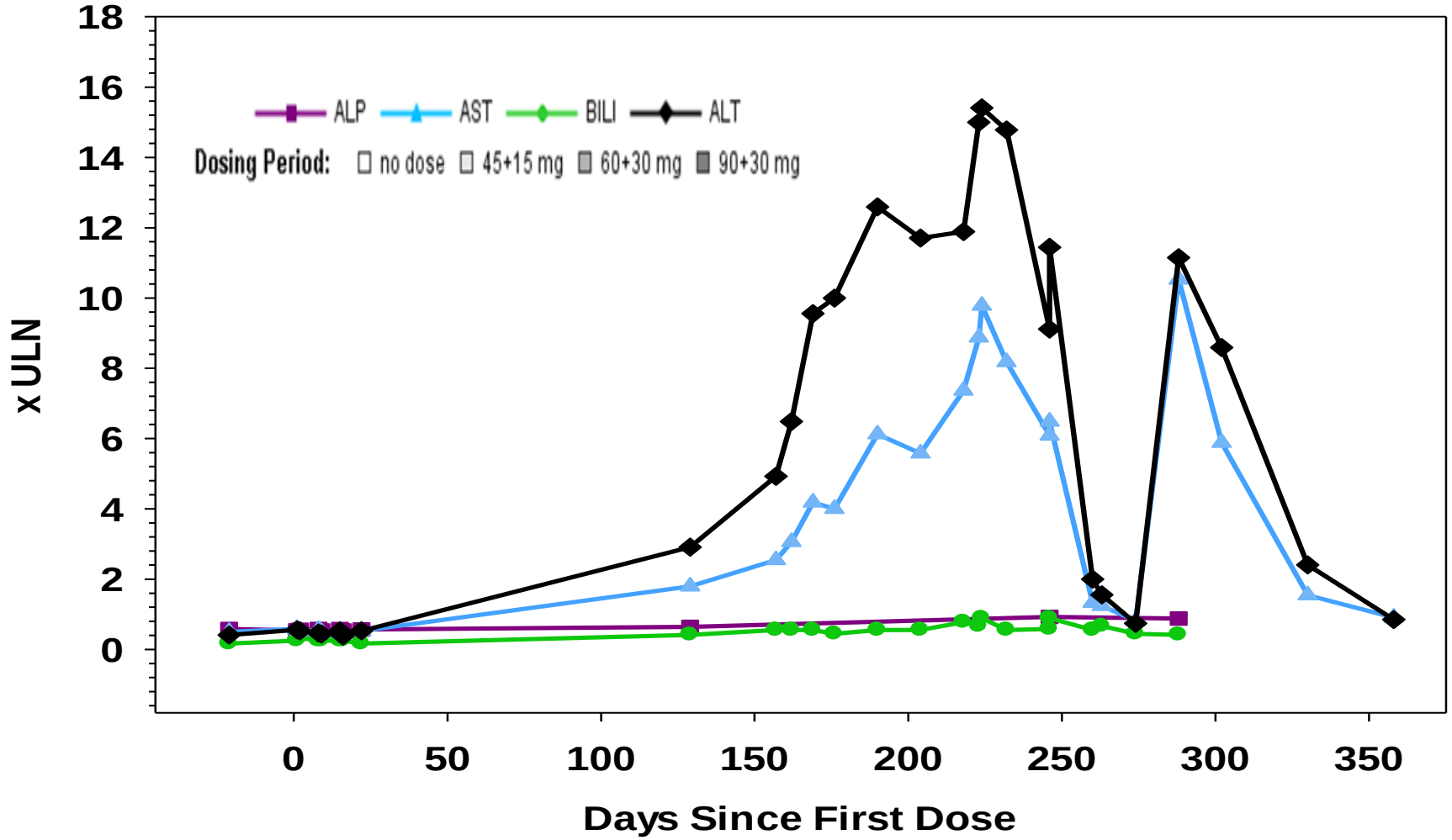
Incidence of hepatotoxicity vs. time



Days in Study	0	100	200	300	400	500	600	700	800	900	1000	1100
Tolvaptan N=	961	884	836	812	796	774	765	751	740	734	726	268
Placebo N=	483	476	468	459	452	445	442	433	425	422	415	147

Drug Saf (2015) 38:1103–1113

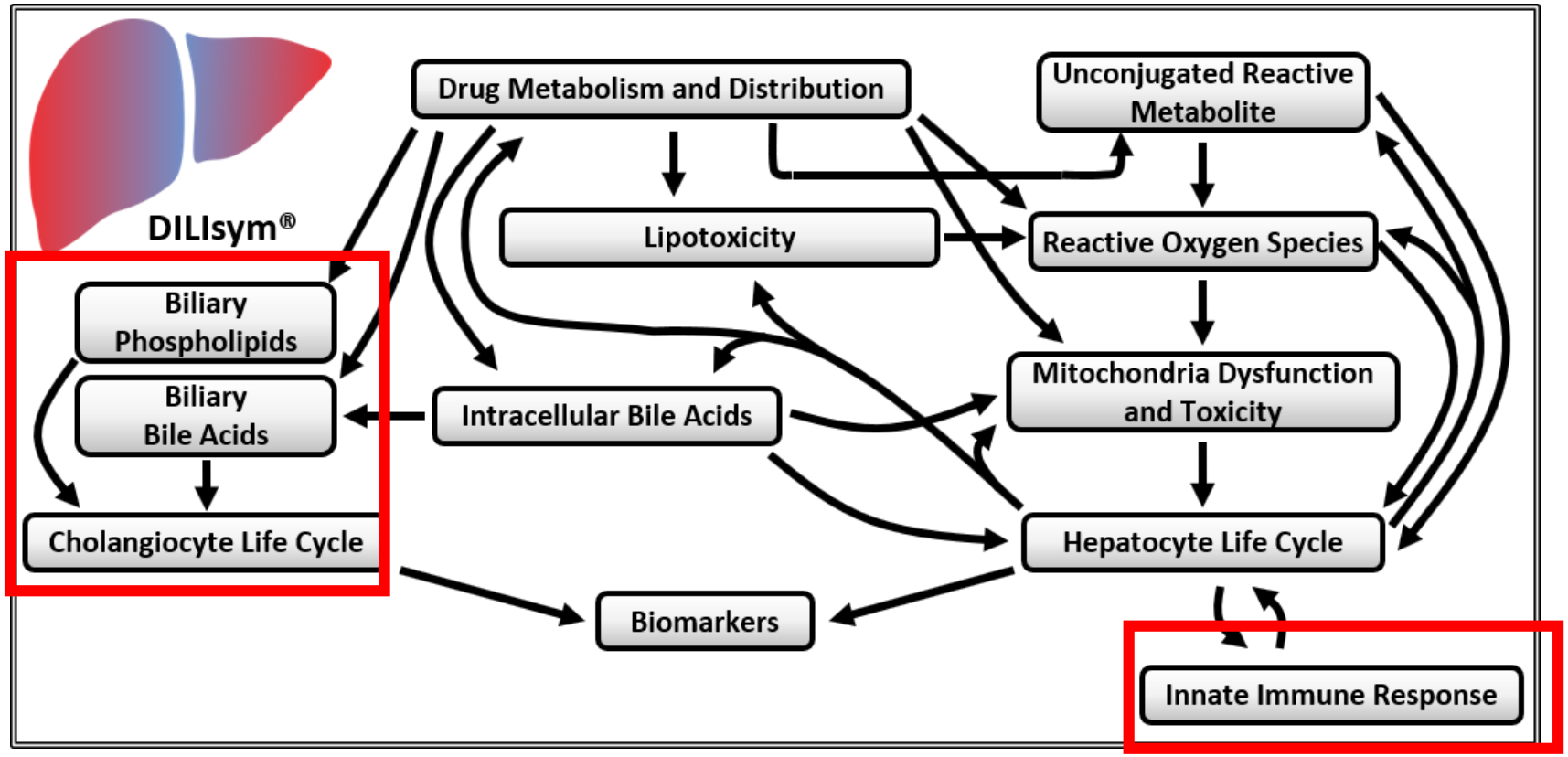
Idiosyncratic DILI with Prolonged Latency may not indicate an Adaptive Immune Attack on the Liver



UNC ESHELMAN SCHOOL OF PHARMACY

Institute for Drug Safety Sciences

Directions of the DILI-sim Initiative

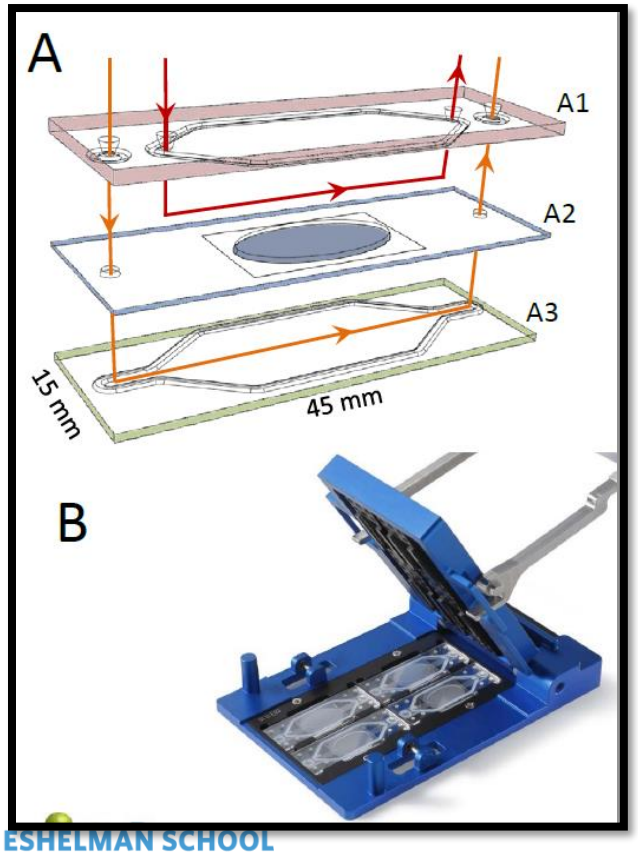


Directions of the DILI-sim Initiative

Collaboration with Lans Taylor

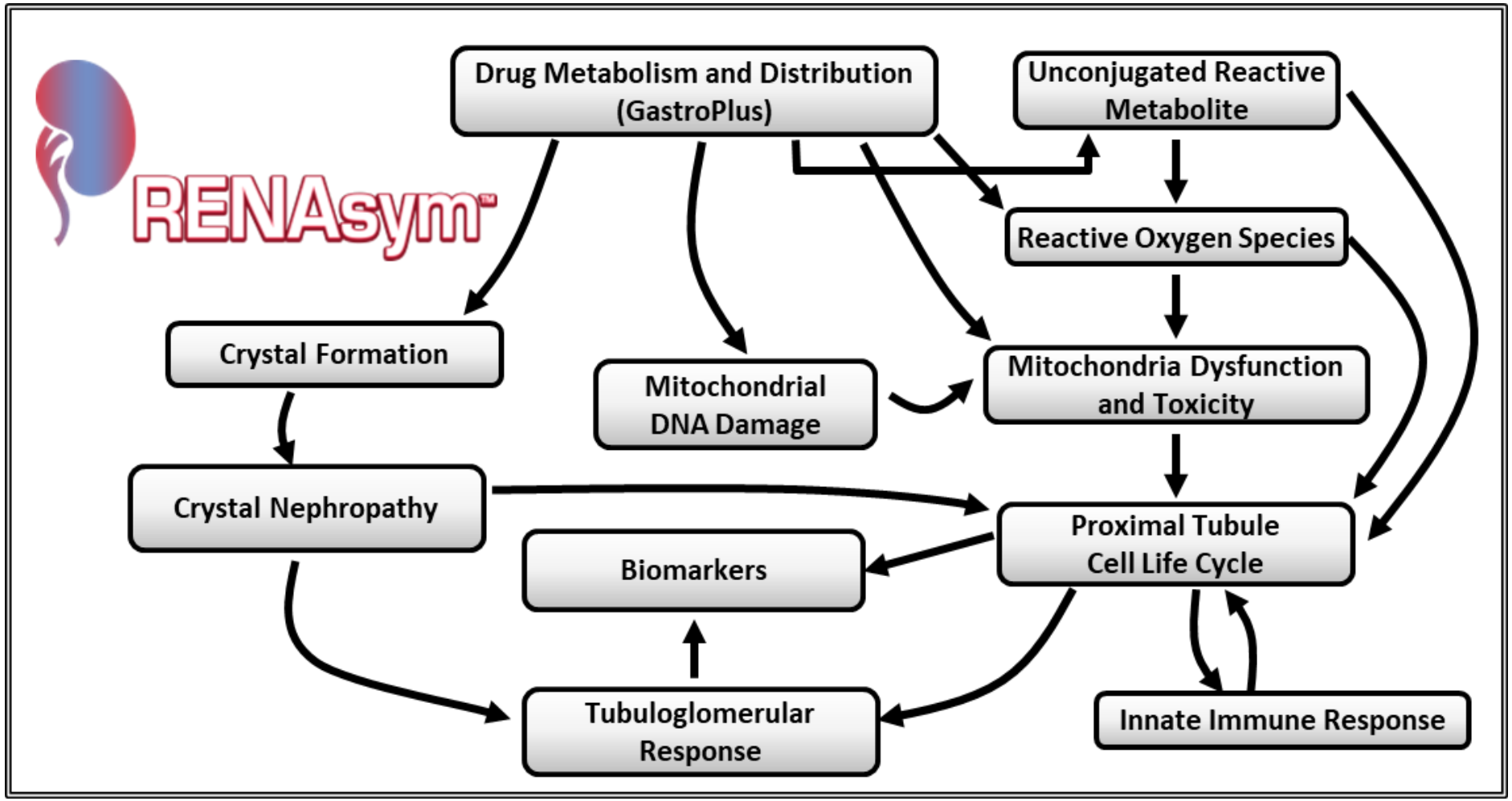
Drug Discovery Institute
UNIVERSITY OF PITTSBURGH

vLAMPS



Received score of 21 on SBIR proposal

Kidney Toxicity Modeling Supported by $1.7 M SBIR grant



Final Summary

DILIsym in an example of the potential of QST to greatly improve the efficiency of drug development by improving selection of lead candidates, supporting safety to drugs in development, and identifying patient risk factors.

"FDA's Center for Drug Evaluation and Research (CDER) is currently using modeling and simulation to predict clinical outcomes, inform clinical trial designs, support evidence of effectiveness, optimize dosing, **predict product safety**, **and evaluate potential adverse event mechanisms."**

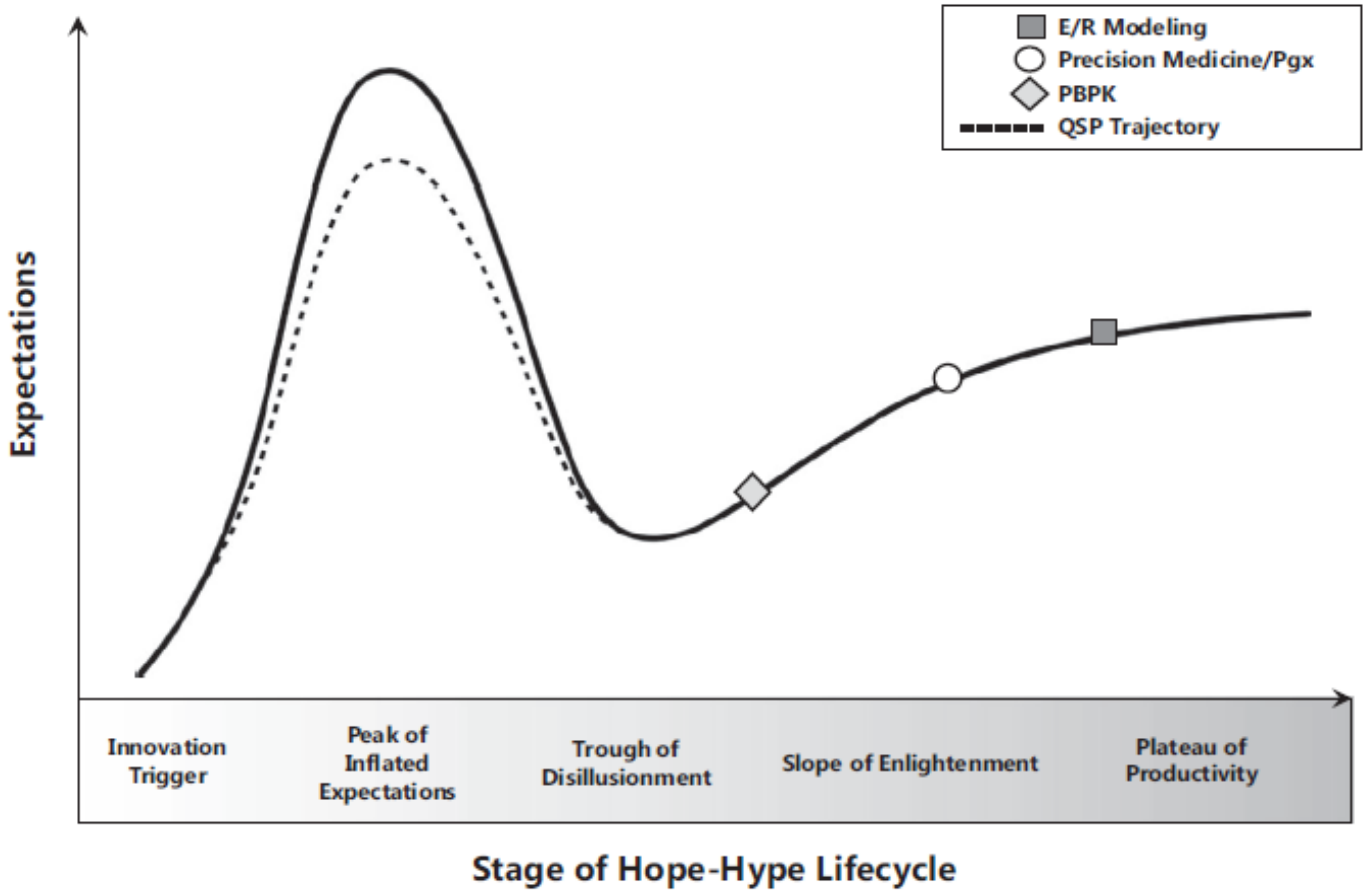
Posted on July 7, 2017 by FDA Voice

Scott Gottlieb, M.D
FDA Commissioner

The FDA Clin Pharm Perspective

QSP: A Regulatory Perspective on Translation
Zineh

PSP 2019



"QSP may be on track to progress through the hope-hype cycle more expeditiously than the previously discussed sciences largely because of a frontloaded effort to identify the specific applications of QSP that have the greatest values proposition"

Why will QST (vs QSP) lead the way?

1). Off-target toxicities (like hepatotoxicity) have common mechanisms across drug classes.

2). Animal rights activists are creating political pressure.

Senate Appropriations bill wording November 2020:

The Committee is aware that nonclinical approaches that **do not involve the use of animals** to evaluate new pharmaceuticals are being developed and might better predict some human outcomes **and reduce animal testing**. To help integrate these approaches, the Committee directs the FDA to review and modify regulations in 21 C.F.R. to clearly reflect the agency's discretion to accept valid nonclinical approaches. This could be accomplished, for instance, by **changing references to "animal" data to "nonclinical,"** which encompasses in vivo, in vitro, and **in silico approaches**. The Committee also directs the FDA to consider expanding its Drug Development Tools Qualification Program to include a program for evaluating and integrating in vitro and **computational approaches**.

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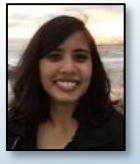

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