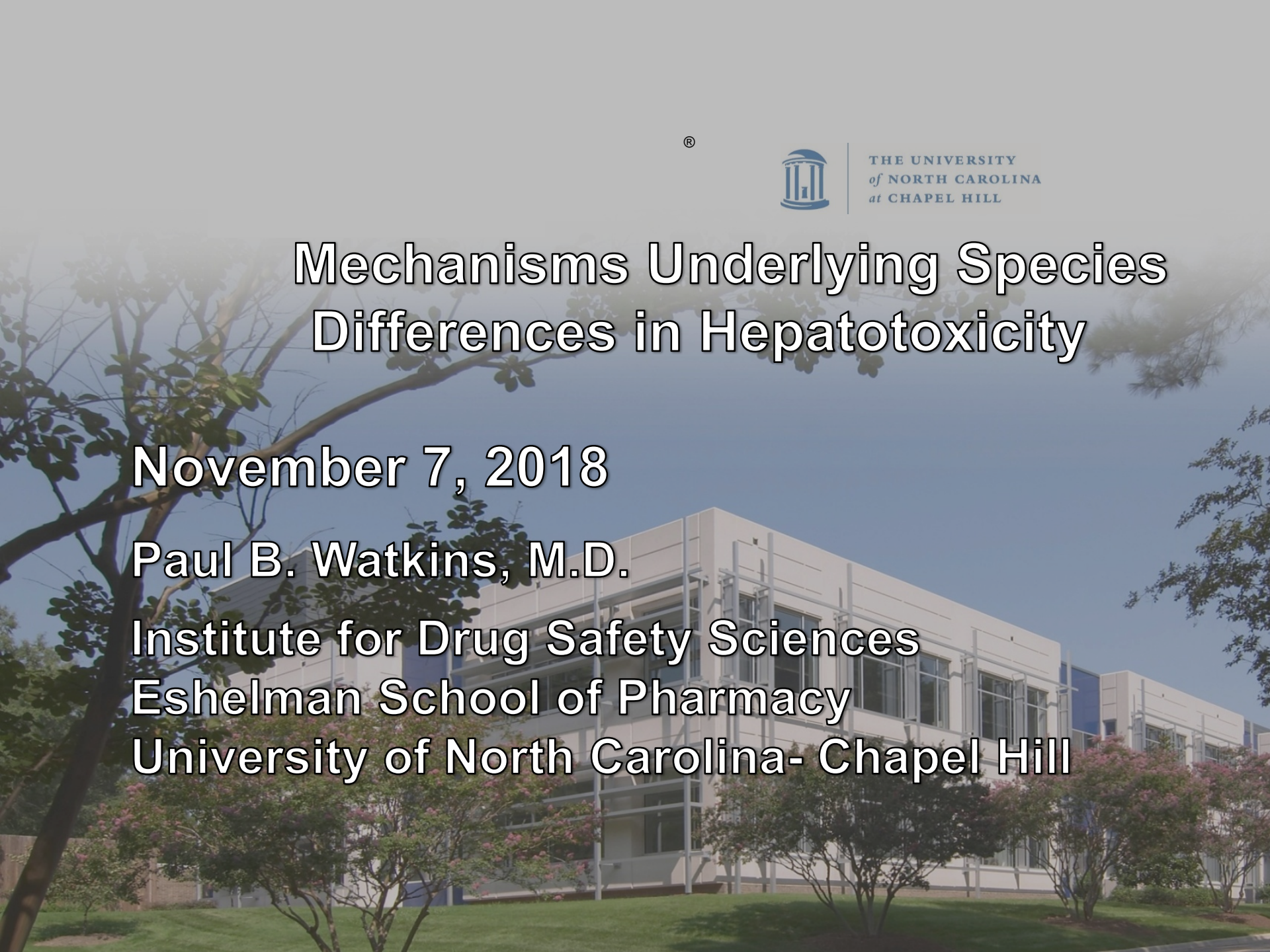


THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

Mechanisms Underlying Species Differences in Hepatotoxicity

November 7, 2018

Paul B. Watkins, M.D.

Institute for Drug Safety Sciences
Eshelman School of Pharmacy
University of North Carolina- Chapel Hill

Disclosure

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

Outline of Talk

1). The DILI-sim Initiative

2). Applications to understanding species differences

- a). AMG 009
- b). CKA
- c). troglitazone

3). Conclusions

UNC Institute for Drug Safety Sciences

DILIsym® Services

astellas

Pfizer

GILEAD

MERCK
Be well

In Silico Modeling

DILI-sim
Initiative

Mitsubishi Tanabe Pharma

janssen

gsk GlaxoSmithKline

FDA

Lilly

Bristol-Myers Squibb

Takeda

abbvie

Daiichi-Sankyo

Patients

Cutting Edge
Pre-clinical Models

In Vitro

DILI-sim Initiative Approach

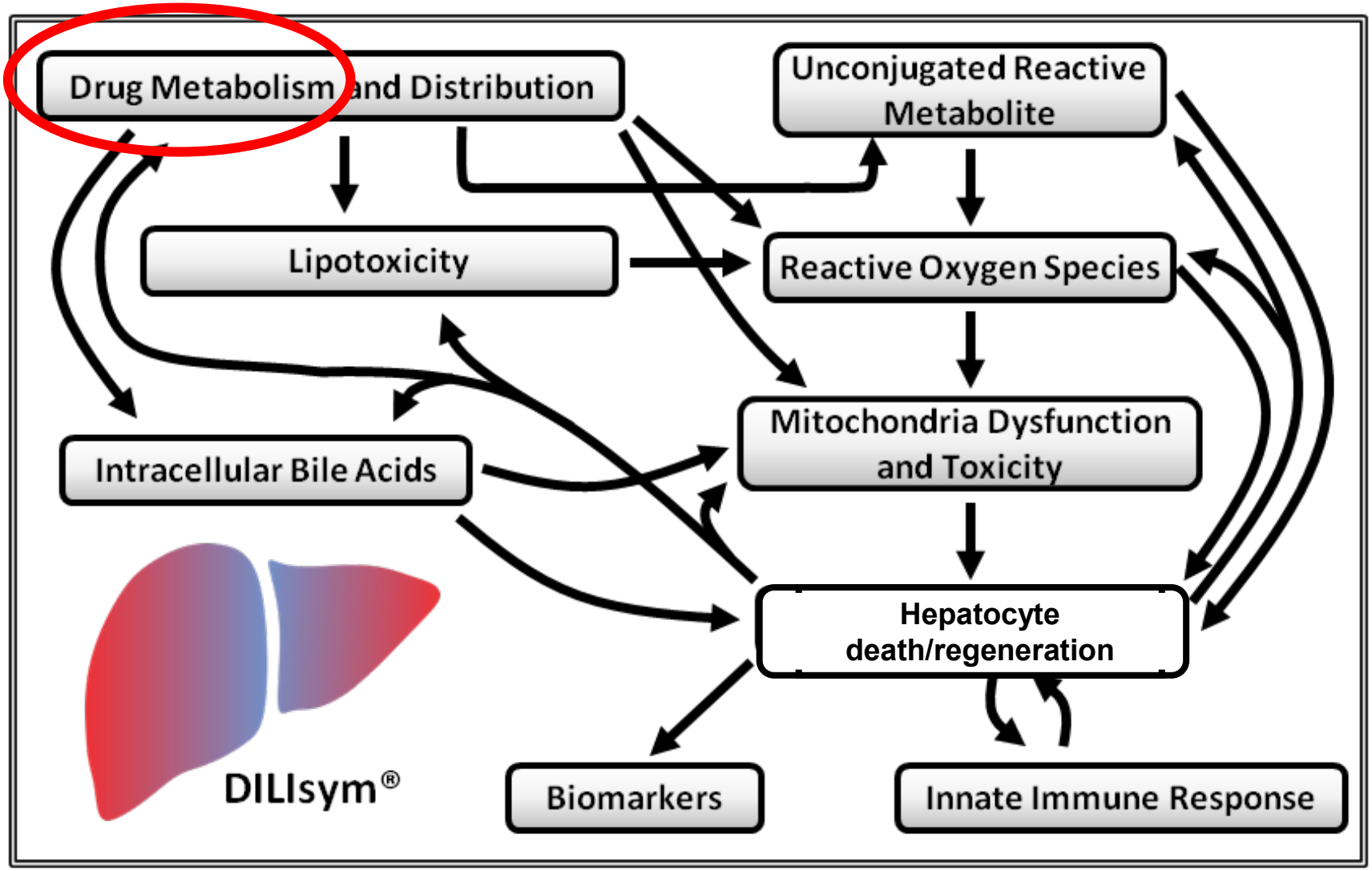
1). Build mechanistic “modules” using differential equations – perform experiments to fill in knowledge gaps.

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

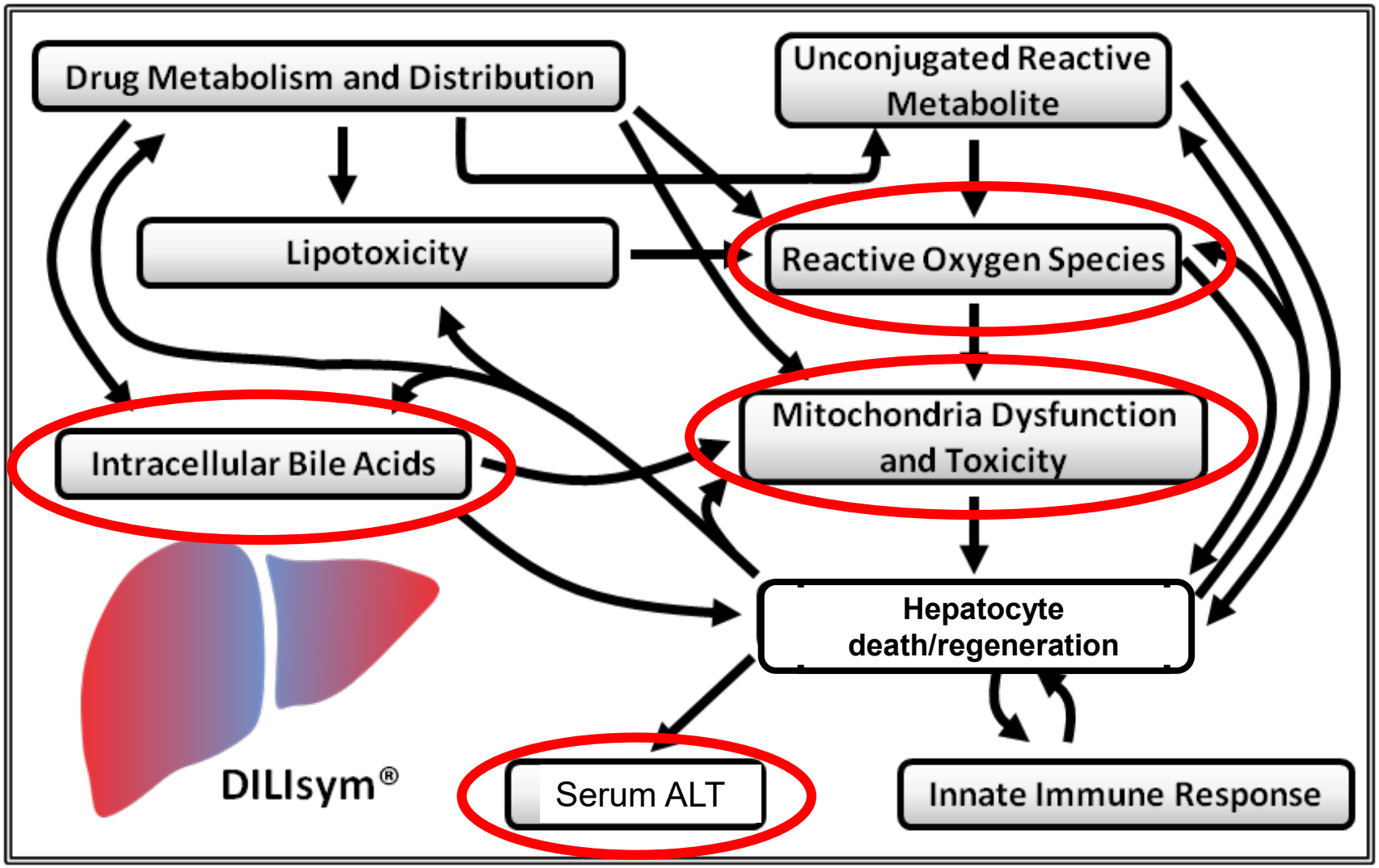
3). Vary model parameters to create simulated patient populations (SimPops™)

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

The model components- Rat and Human



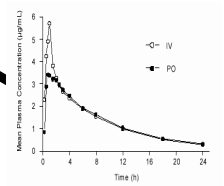
The model components- Rat and Human



DILIsym Input Data

Exposure

Pharmacokinetics



DILIsym®

Simulated Frequency & Severity of Liver Injury (ALT)

Outline of Talk

1). The DILI-sim Initiative

2). Applications to understanding species differences

a). AMG 009

b). CKA

c). troglitazone

3). Conclusions

AMG 009

No evidence of liver injury in multiple species

- Rats, mice, rabbits ***and non-human primates***

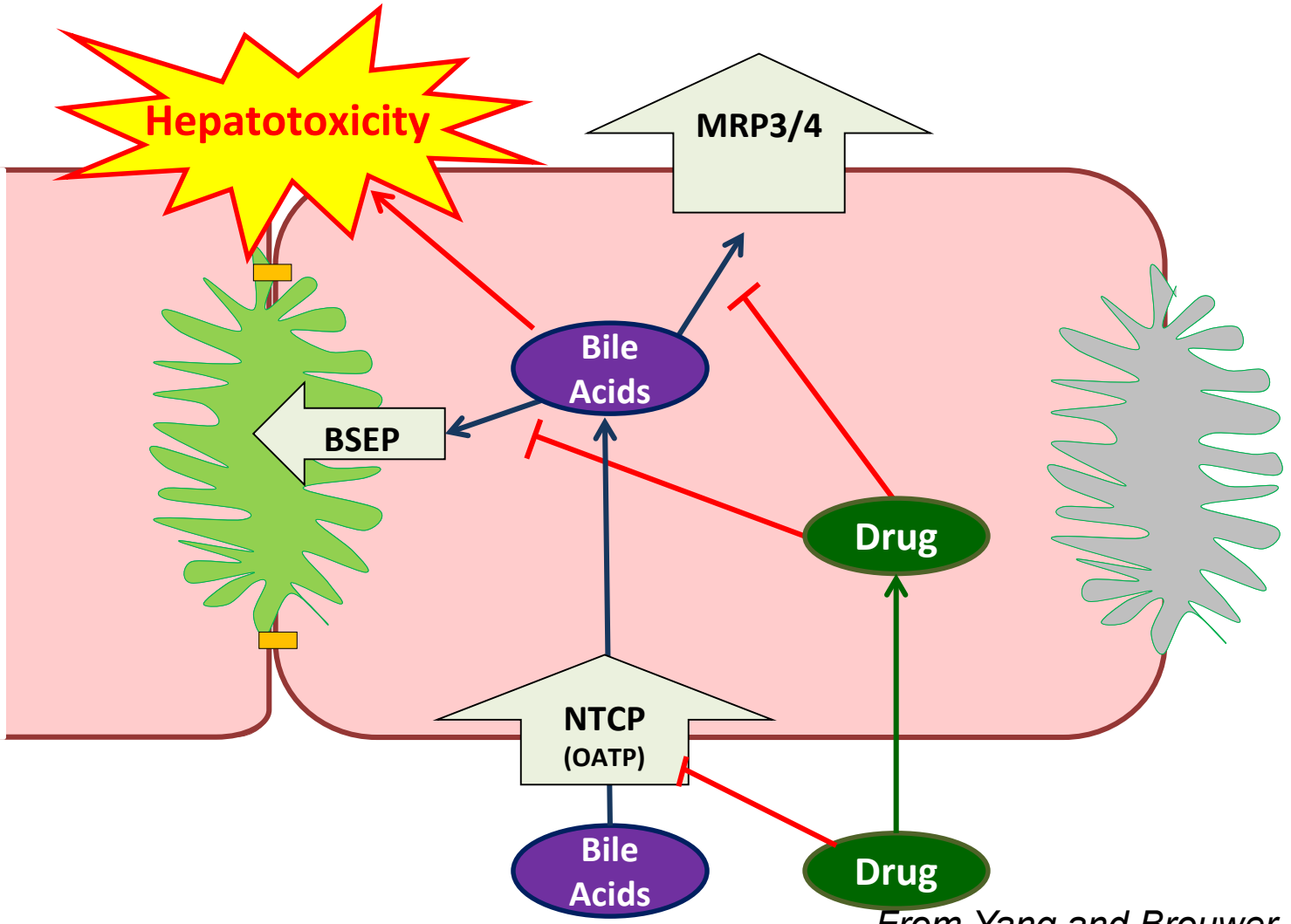
– During Phase I clinical trials in healthy volunteers, 5/8 patients showed significant ALT elevations at the highest dose.

– Development of AMG 009 was halted

– Bile acid transporter inhibition was the only mechanism identified as likely contributors to AMG 009 hepatotoxicity

- *No reactive metabolites, covalent binding, or mitochondrial toxicities were detected*

Drugs Can Inhibit Bile Acid Transporters

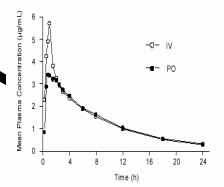


From Yang and Brouwer

DILIsym Input Data

Exposure

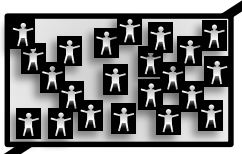
Pharmacokinetics



Mechanisms

Bile Acid Transporter Inhibition

Simulated Frequency & Severity of Liver Injury (ALT)



SimPops™

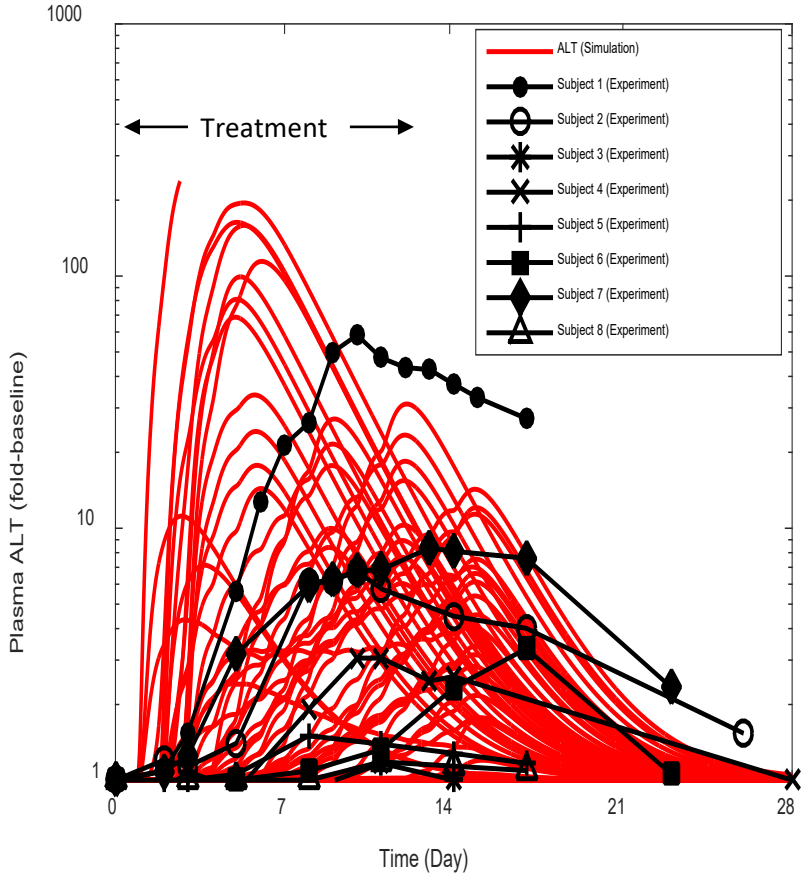
Interpatient Variability

Unique Parameter Combinations

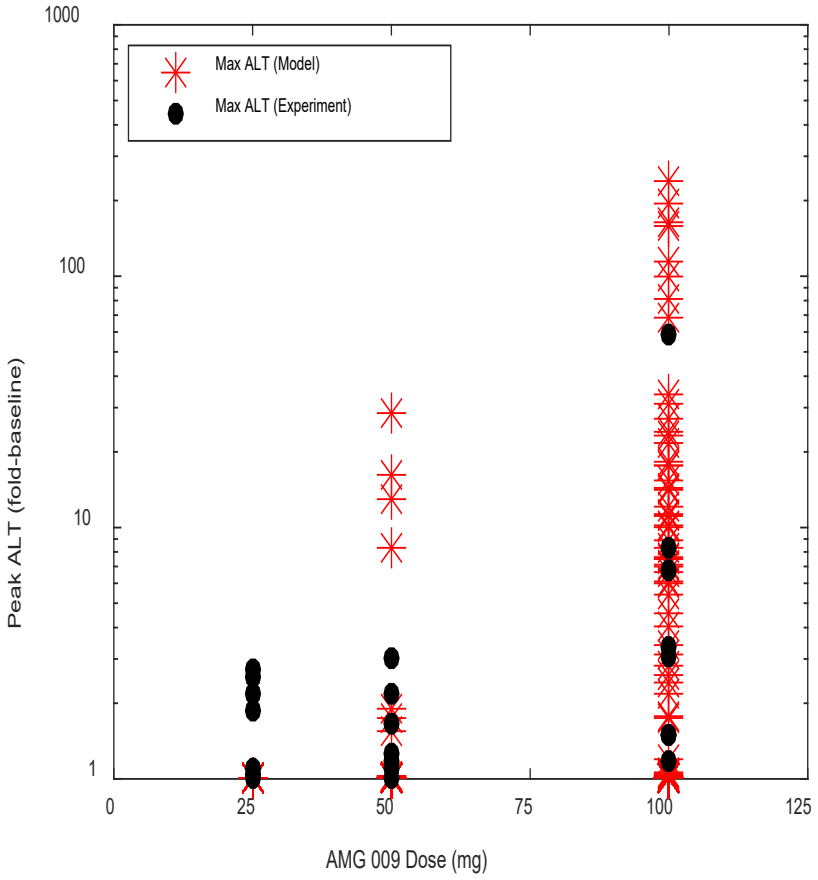
DILIsym® Predicts Dose- and Time-Dependent AMG 009 Hepatotoxicity in Human SimPops™

HUMANS

100 mg BID 14 d



Dose-Response
(25-100 mg BID 14 d)

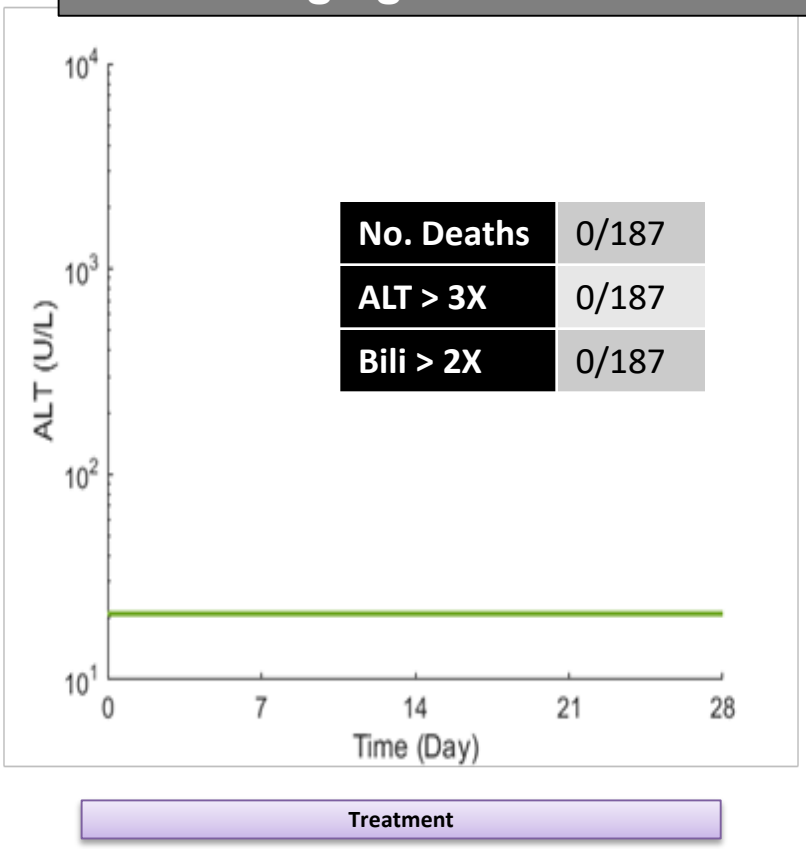


Clinical Data and Simulation Results

No Hepatotoxicity Predicted in the Rat SimPops™ Administered AMG 009

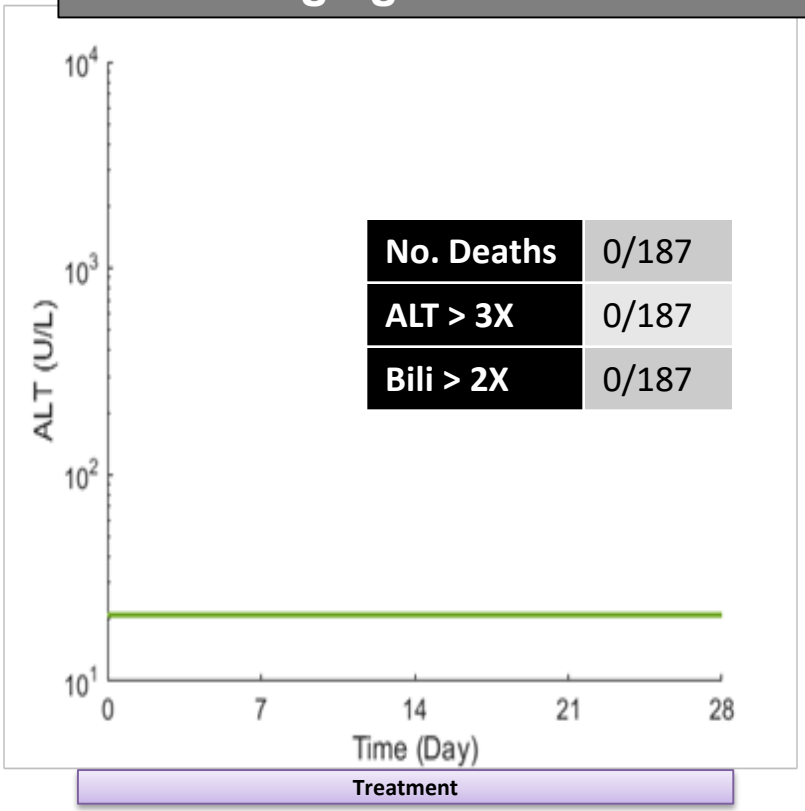
RATS

100 mg/kg IV for 1 month



No. Deaths	0/187
ALT > 3X	0/187
Bili > 2X	0/187

1500 mg/kg PO for 1 month



No. Deaths	0/187
ALT > 3X	0/187
Bili > 2X	0/187

Simulation Results

What was the basis of this species difference?

1). It was not exposure, which was 100-fold higher in rats than humans

2). Differences in inhibition of bile acid transporters played some role

Inhibition constants of AMG 009 for bile acid transport proteins in human and rat

Transporter	AMG 009
	Ki (µM)
Human BSEP	2.4 (1.8 – 3.1)
Rat Bsep	5.6 (4.8 – 6.3)
Human NTCP	126.5 (96.6 – 165.6) [a]
Rat Ntcp	48.2 (29.7 – 78) [a]

95% confidence interval in parenthesis.

[a] IC_{50} values

Ryan Morgan, Amgen

Conclusion

The major explanation for reduced susceptibility to AMG009 hepatotoxicity in rats vs humans is that the profile of bile acids in rats is inherently less toxic than in humans.

Outline of Talk

1). The DILI-sim Initiative

2). Applications to understanding species differences

- a). AMG 009
- **b). CKA**
- c). troglitazone

3). Conclusions

CKA

A chemokine receptor antagonist intended for treating inflammatory conditions, **produced dose-dependent hepatotoxicity in rats** but advanced into the clinic where single doses of CKA up to 600mg **appeared safe in humans.**

Using Quantitative Systems Toxicology to Investigate Observed Species Differences in CKA-Mediated Hepatotoxicity

Christina Battista,[*,†] Kyunghee Yang,[*] Simone H. Stahl,[‡] Jerome T. Mettetal,[§] Paul B. Watkins,[†] Scott Q. Siler,[*] and Brett A. Howell[*,1,2]

Tox Sci epub July 2018

DILIsym Integrates Multiple Inputs to Simulate/Predict Hepatotoxicity

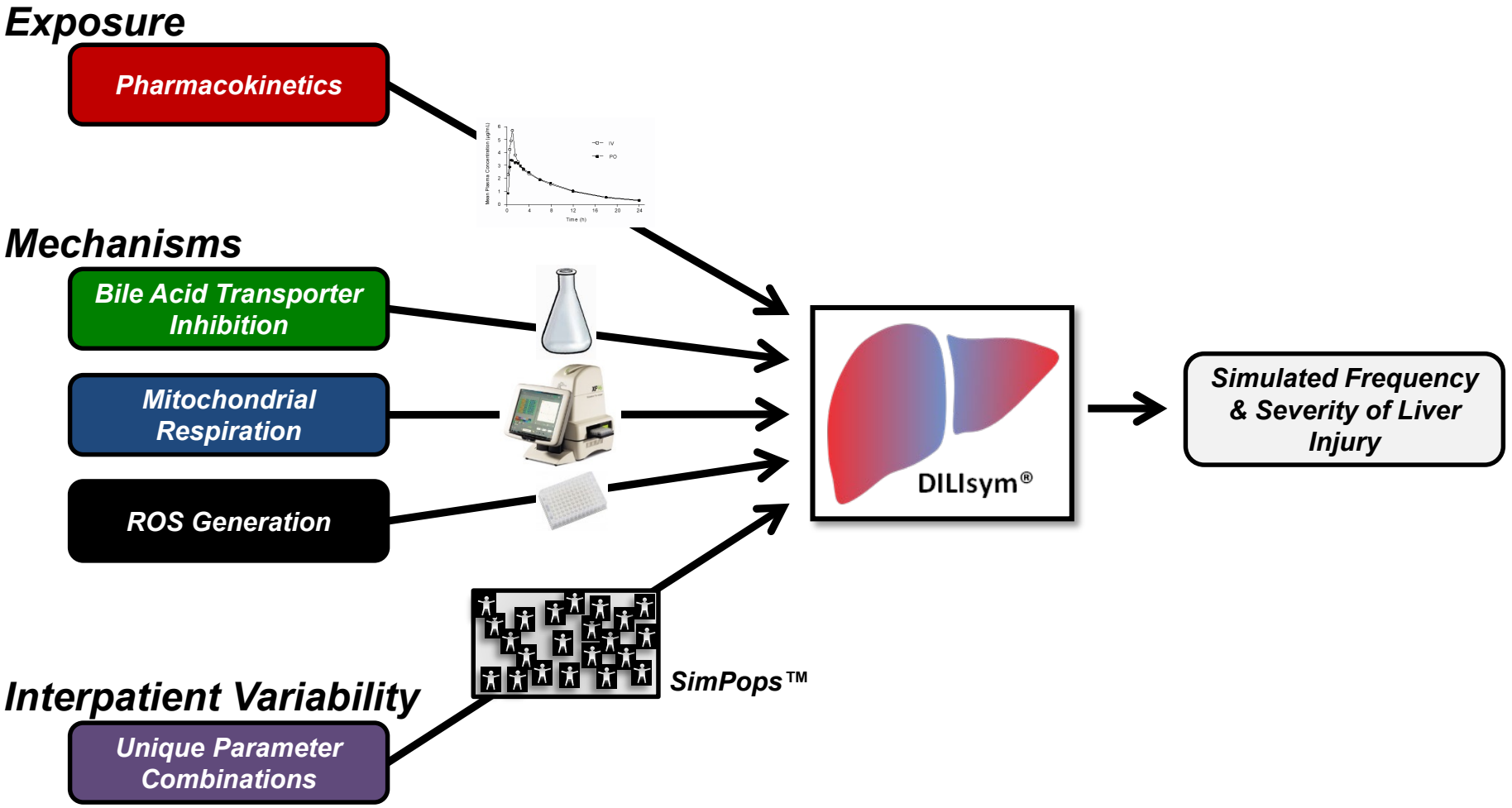


Table 2. Summary of CKA-Mediated Hepatotoxicity in Rat and Human SimPops and Preclinical and Clinical Observations

Species	Rat	Rat
		Simulations[a]
Dose	200 mg/kg	500 mg/kg
Population size	$n = 294$	$n = 294$
ALT $>$ 3$\times$ ULN (%)[b]	2.4	36.4
ALT $>$ 5$\times$ ULN (%)[b]	0	20.1
ALT $>$ 10$\times$ ULN (%)[b]	0	7.8

Battista et al Tox Sci epub July 2018

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ALT > 10× ULN (%)[b]	0	7.8
		Preclinical/clinical trials
Dose	200 mg/kg	500 mg/kg
Population size	$n = 8$	$n = 4$
ALT > 3× ULN (%)[b]	25	75
ALT > 5× ULN (%)[b]	0	50
ALT > 10× ULN (%)[b]	0	25

Battista et al Tox Sci epub July 2018

Table 2. Summary of CKA-Mediated Hepatotoxicity in Rat and Human SimPops and Preclinical and Clinical Observations

Species	Rat	Rat	Human	Human	Human
			Simulations[a]		
Dose	200 mg/kg	500 mg/kg	300 mg	600 mg	900 mg
Population size	$n = 294$	$n = 294$	$n = 285$	$n = 285$	$n = 285$
ALT > 3× ULN (%)[b]	2.4	36.4	0	0	0
ALT > 5× ULN (%)[b]	0	20.1	0	0	0
ALT > 10× ULN (%)[b]	0	7.8	0	0	0
			Preclinical/clinical trials		
Dose	200 mg/kg	500 mg/kg			
Population size	$n = 8$	$n = 4$			
ALT > 3× ULN (%)[b]	25	75			
ALT > 5× ULN (%)[b]	0	50			
ALT > 10× ULN (%)[b]	0	25			

Battista et al Tox Sci epub July 2018

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Species	Rat	Rat	Human	Human	Human
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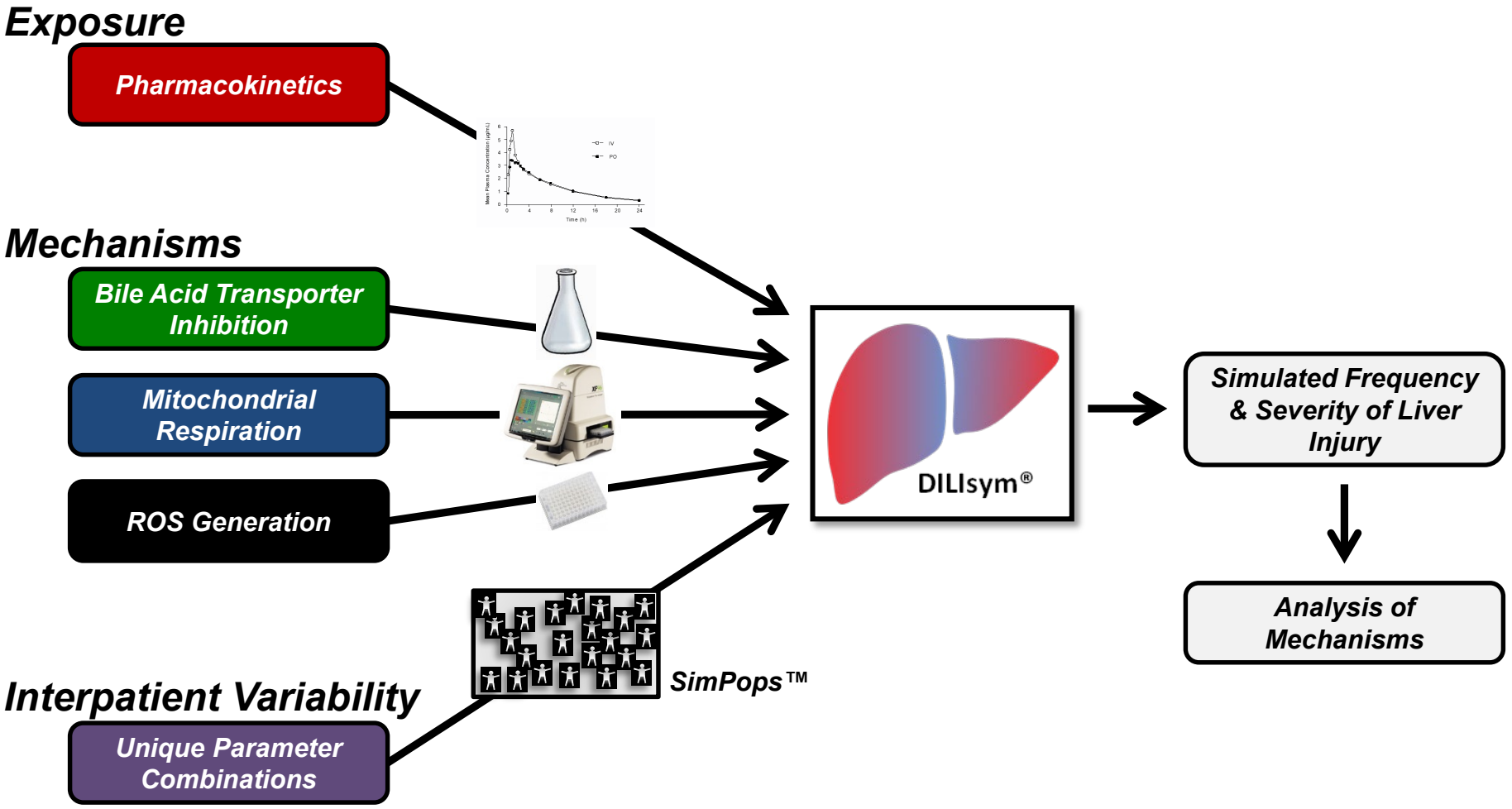
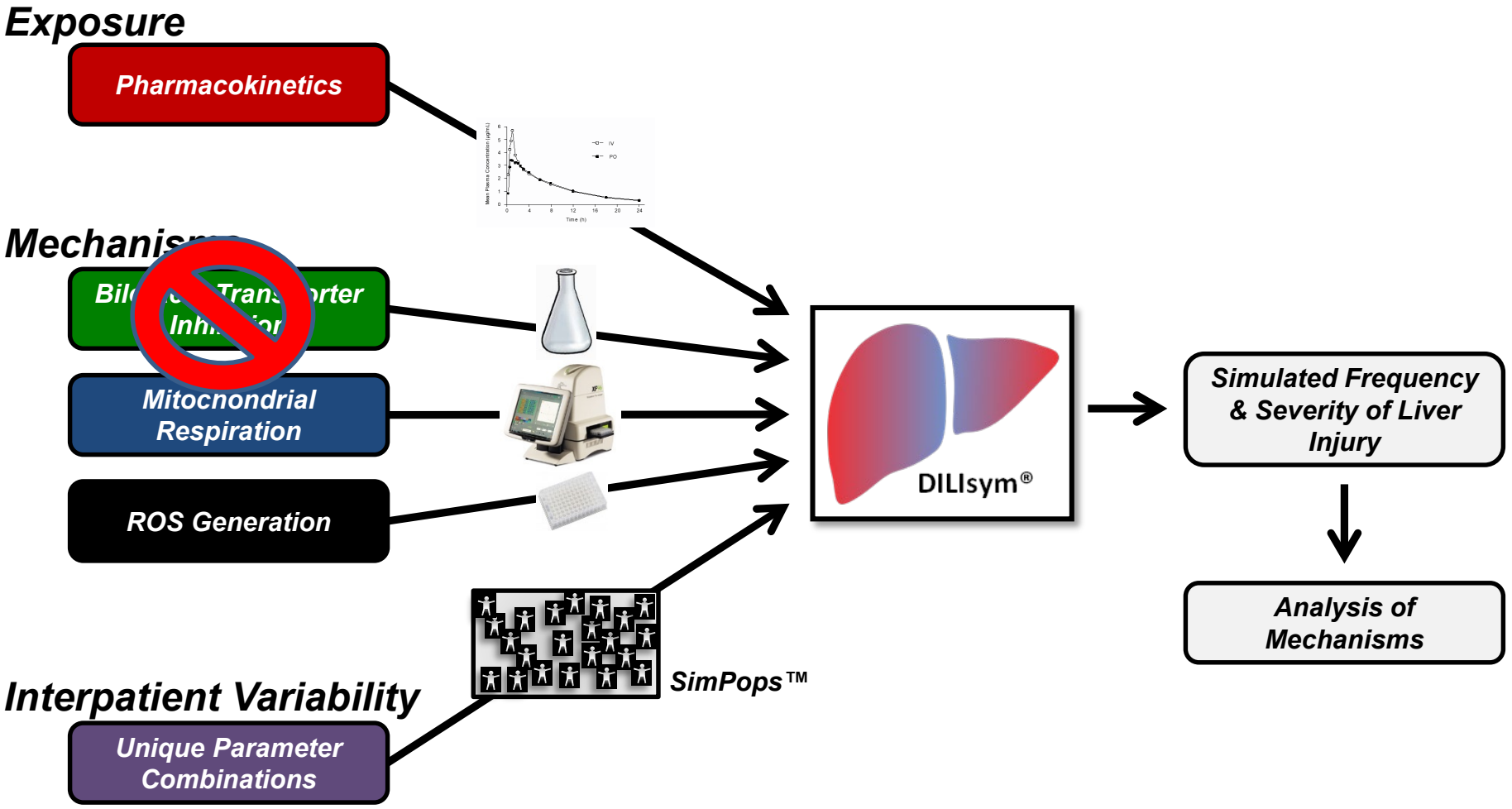
ALT > 5× ULN (%)[b]	0	20.1	0	0	0
ALT > 10× ULN (%)[b]	0	7.8	0	0	0
			Preclinical/clinical trials		
Dose	200 mg/kg	500 mg/kg	300 mg	600 mg	900 mg
Population size	$n = 8$	$n = 4$	$n = 5$	$n = 4$	$n = 6$
ALT > 3× ULN (%)[b]	25	75	0	0	16.7
ALT > 5× ULN (%)[b]	0	50	0	0	0
ALT > 10× ULN (%)[b]	0	25	0	0	0

Battista et al Tox Sci epub July 2018

DILIsym Integrates Multiple Inputs to Simulate/Predict Hepatotoxicity



DILIsym Integrates Multiple Inputs to Simulate/Predict Hepatotoxicity



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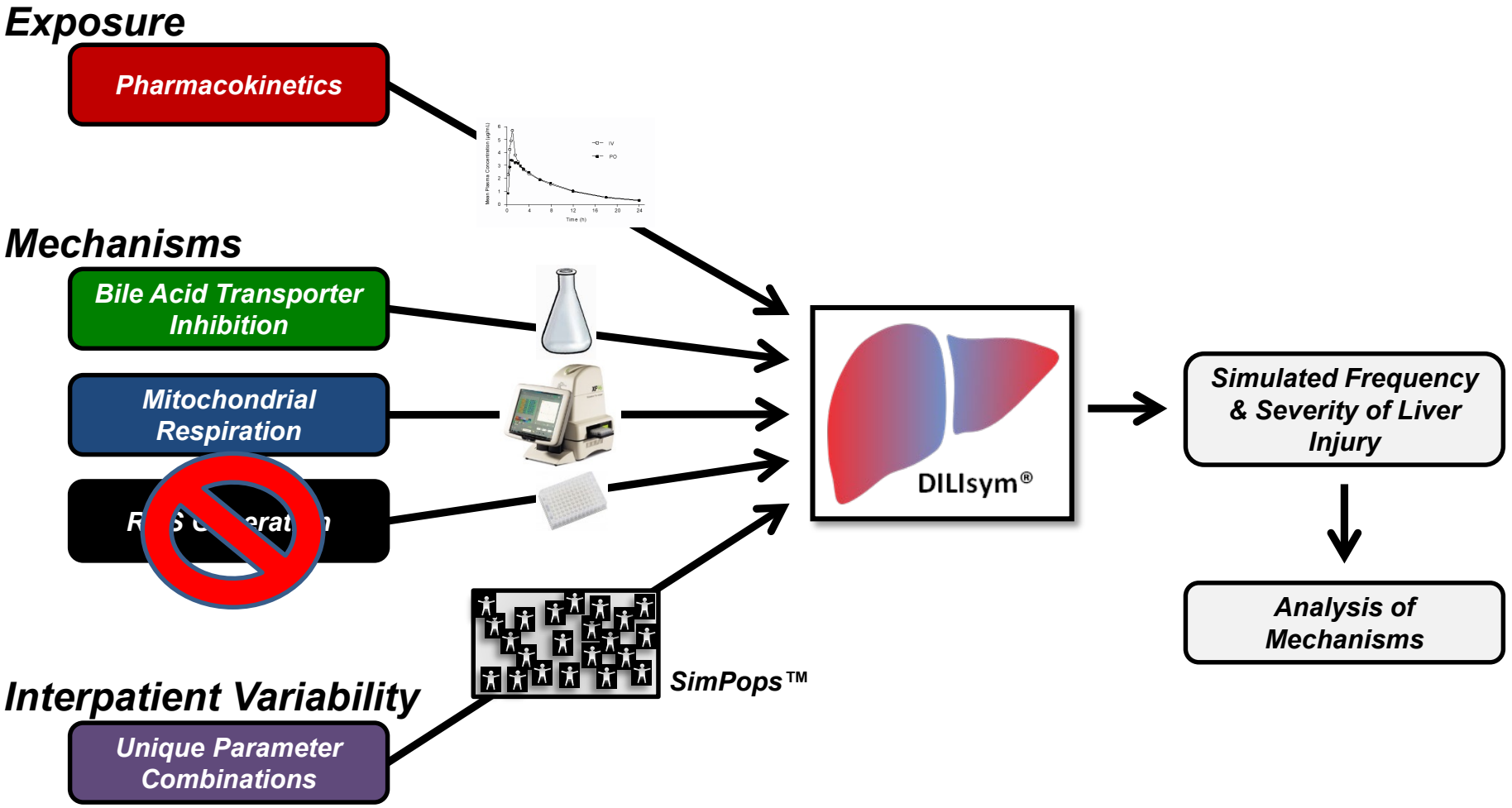

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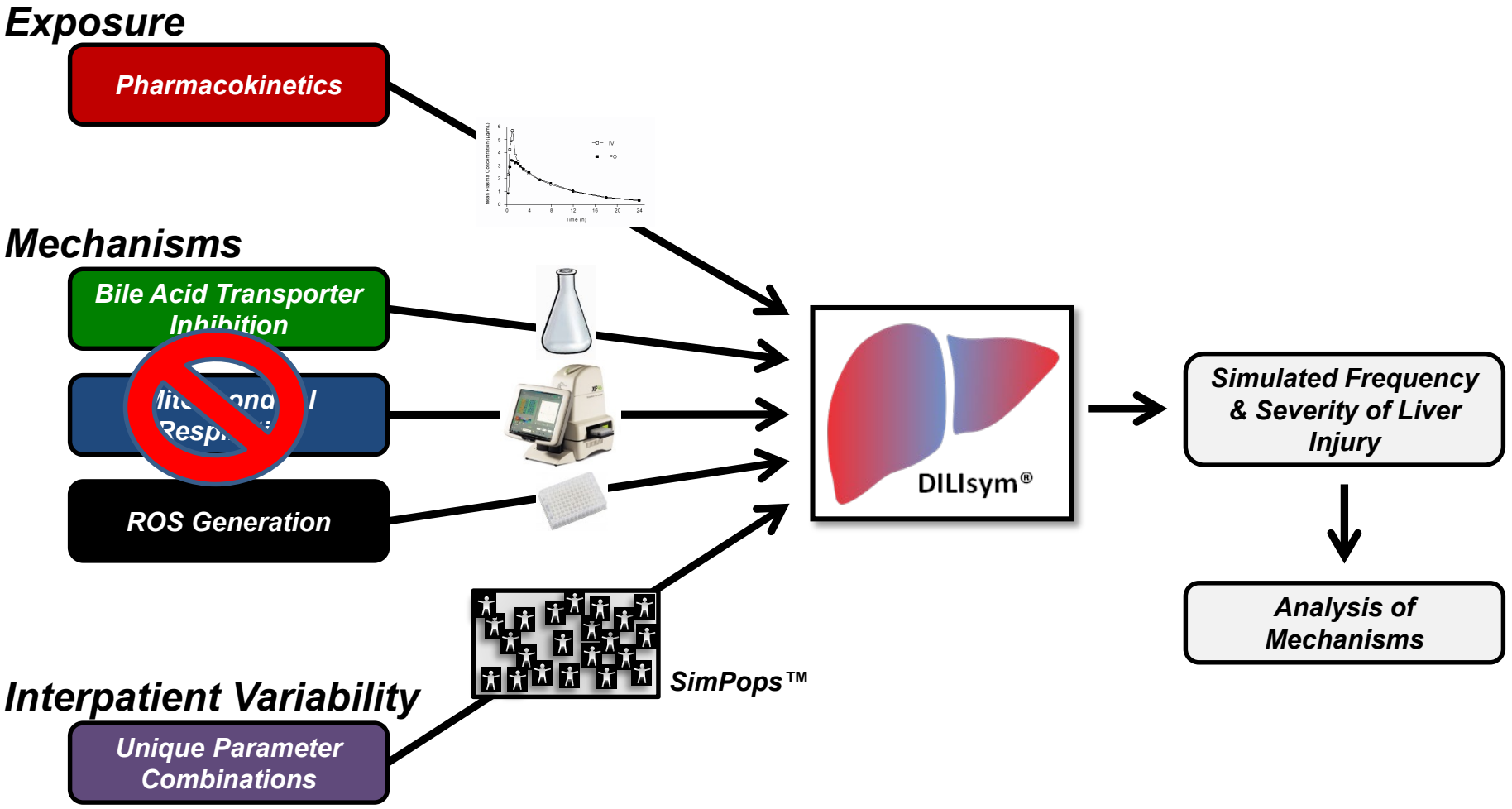


CKA DILIsym Parameters

Table 1. Toxicity Parameters for Human and Rat

	Human	Rat
Bile acid transporter inhibition constant (μM)		
BSEP	94[a]	129.7[b]
MRP3	11.2	11.2[c]
MRP4	12.3	12.3[c]
NTCP	19.5	19.5[c]
Mitochondrial toxicity constant (mM)		
ETC inhibition constant	14.2	1.42
ROS production constant (mL/mol/h)		
ROS production constant	7278	9705

Summary

The main reason for rats increased susceptibility to CKA hepatoxicity was increased susceptibility to interference with mitochondrial function.

Outline of Talk

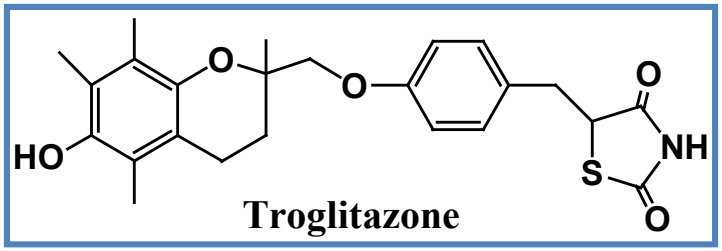
1). The DILI-sim Initiative

2). Applications to understanding species differences

- a). AMG 009
- b). CKA
- **c). troglitazone**

3). Conclusions

Troglitazone (TGZ)

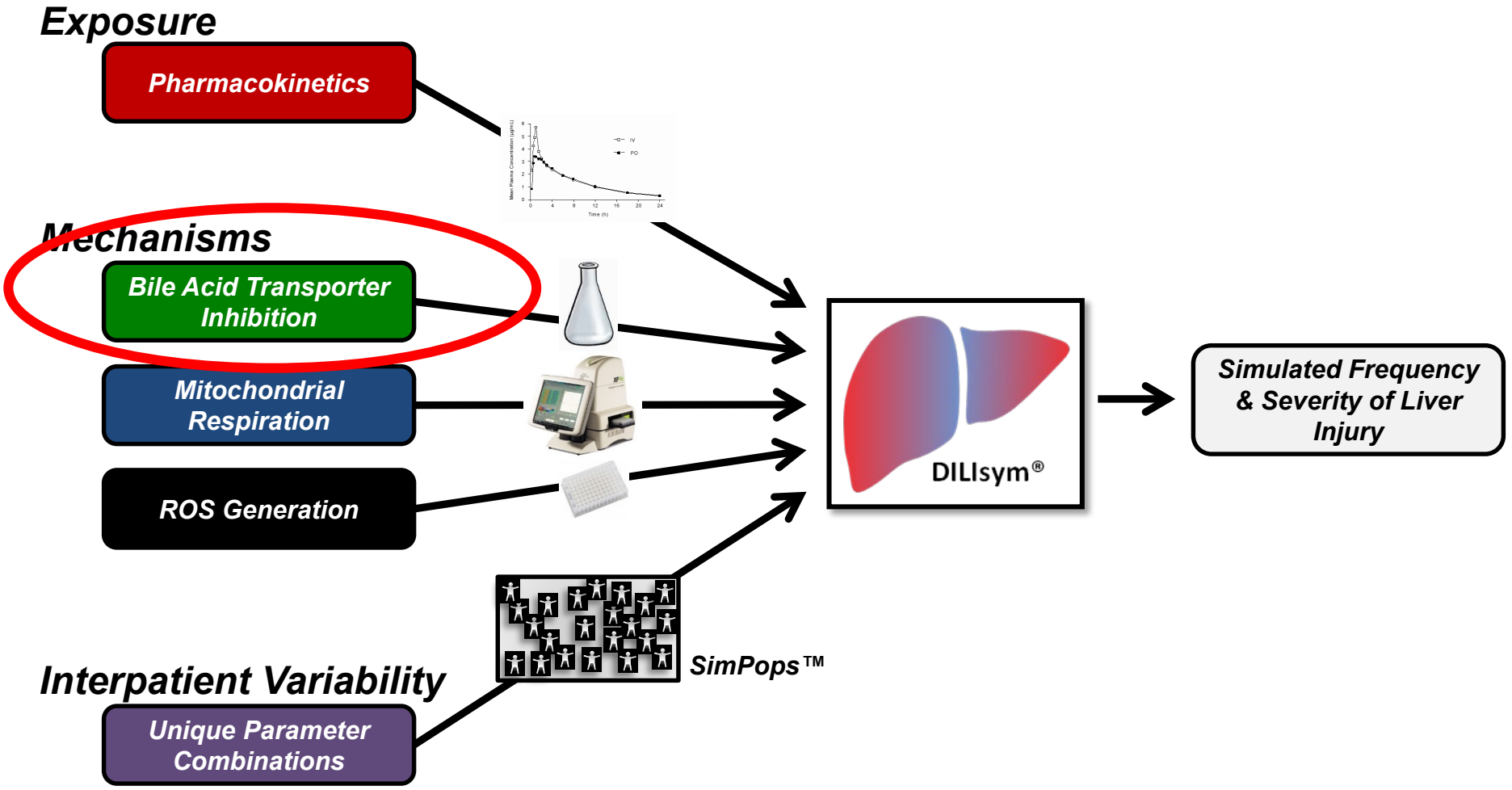


Troglitazone

- First in thiazolidinedione class; PPARγ agonist
  - -- Approved for the treatment of type II diabetes

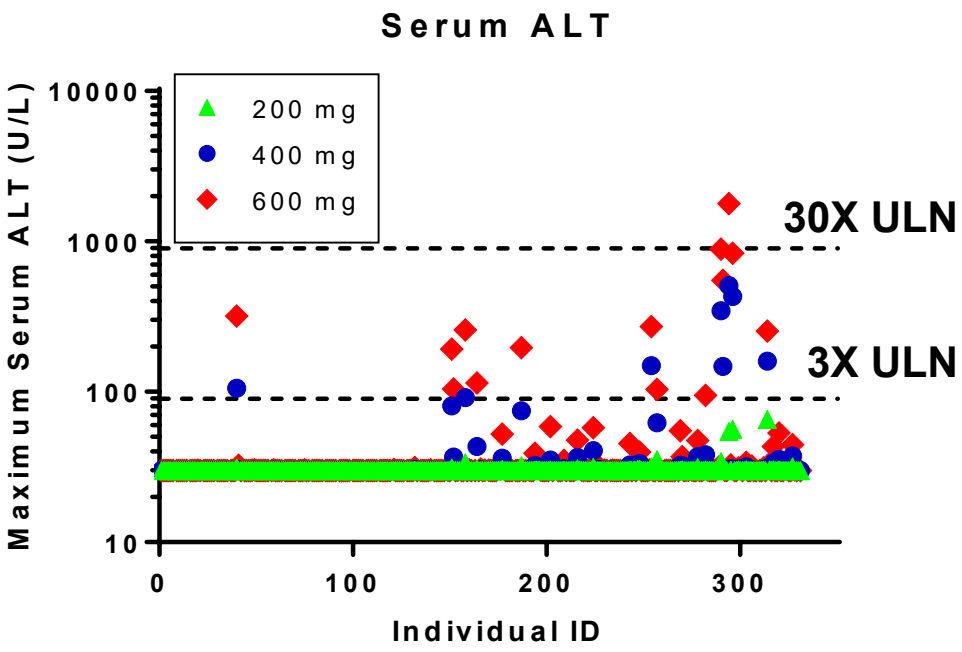
- Hepatotoxicity
  - **Not detected in preclinical studies**
  - Serum ALT elevations >3X ULN noted in the clinical trials
  - Withdrawn from the market due **to idiosyncratic hepatotoxicity**

DILIsym Integrates Multiple Inputs to Simulate/Predict Hepatotoxicity



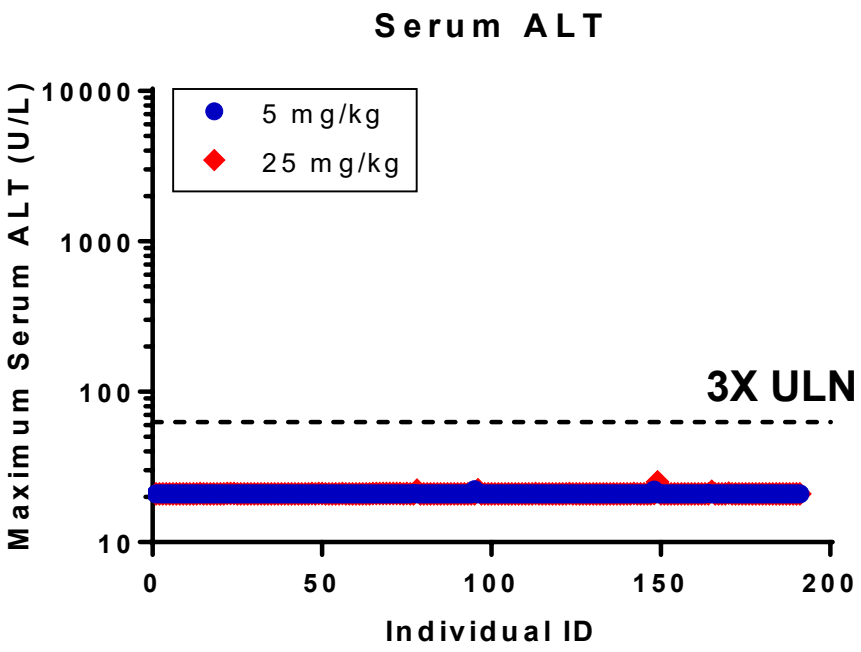
DILIsym Predicted Species Differences in TGZ Hepatotoxicity

HUMAN



Simulated DILI responses in human SimPop™ (n=331) administered 200, 400, or 600 mg/day TGZ for 6 months

RAT



Simulated DILI responses in rat SimPop™ (n=192) administered 5 or 25 mg/kg/day TGZ for 6 months

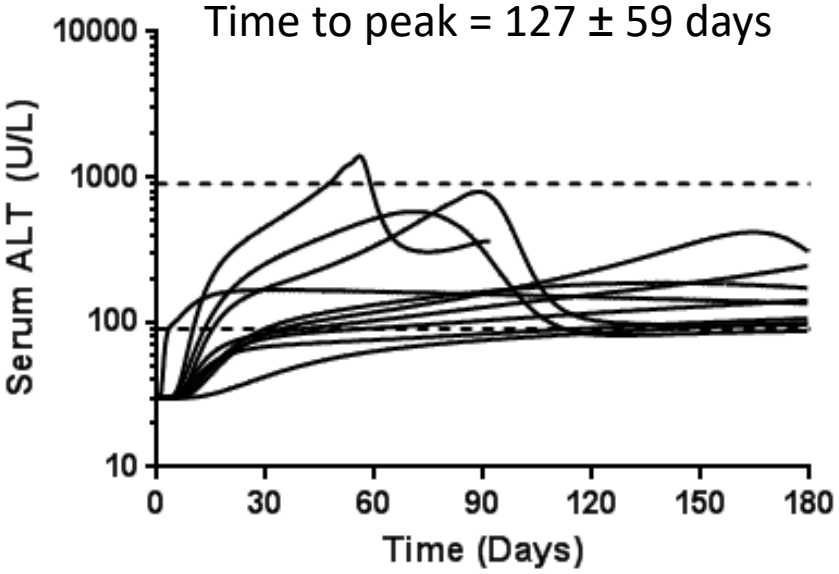
Yang … Brouwer CPT 96 (5) 2014

Mechanistic Model Reasonably Predicted Delayed Presentation of TGZ Hepatotoxicity

HUMAN

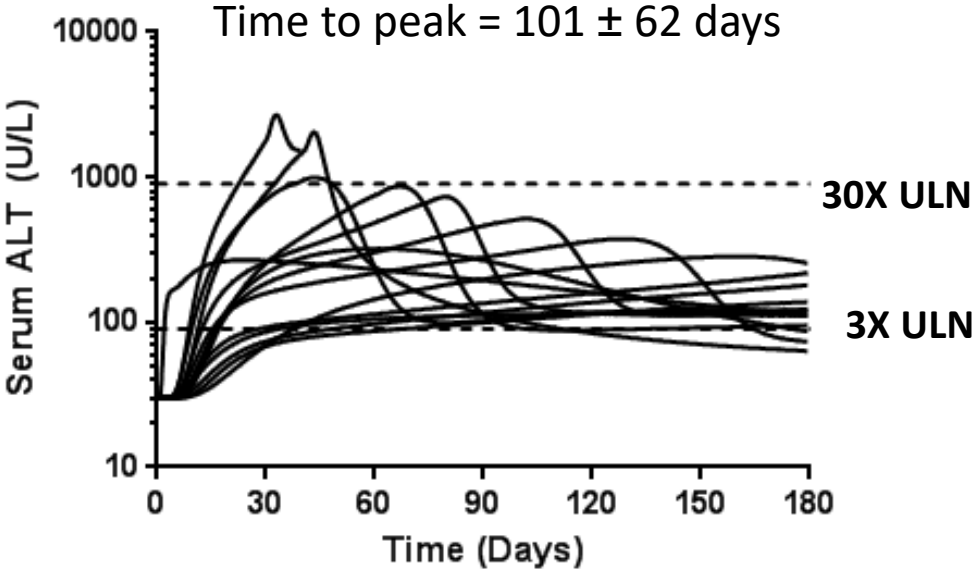
Serum ALT: 400 mg TGZ

Time to peak = 127 ± 59 days



Serum ALT: 600 mg TGZ

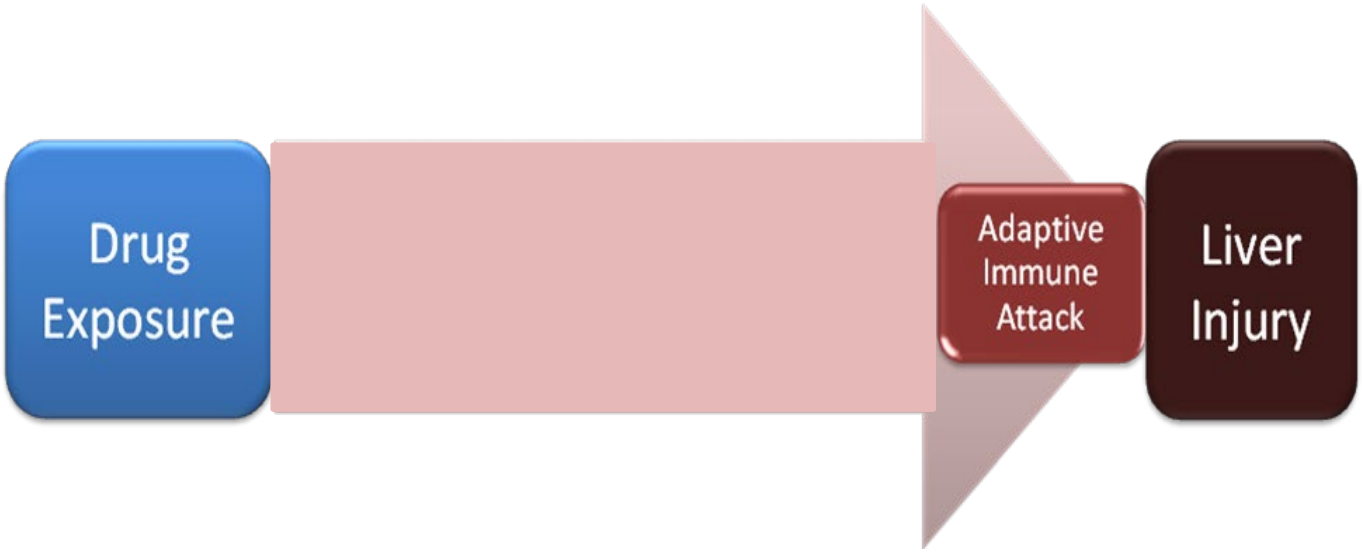
Time to peak = 101 ± 62 days



Time to peak ALT in clinical trials: 147 ± 86 days

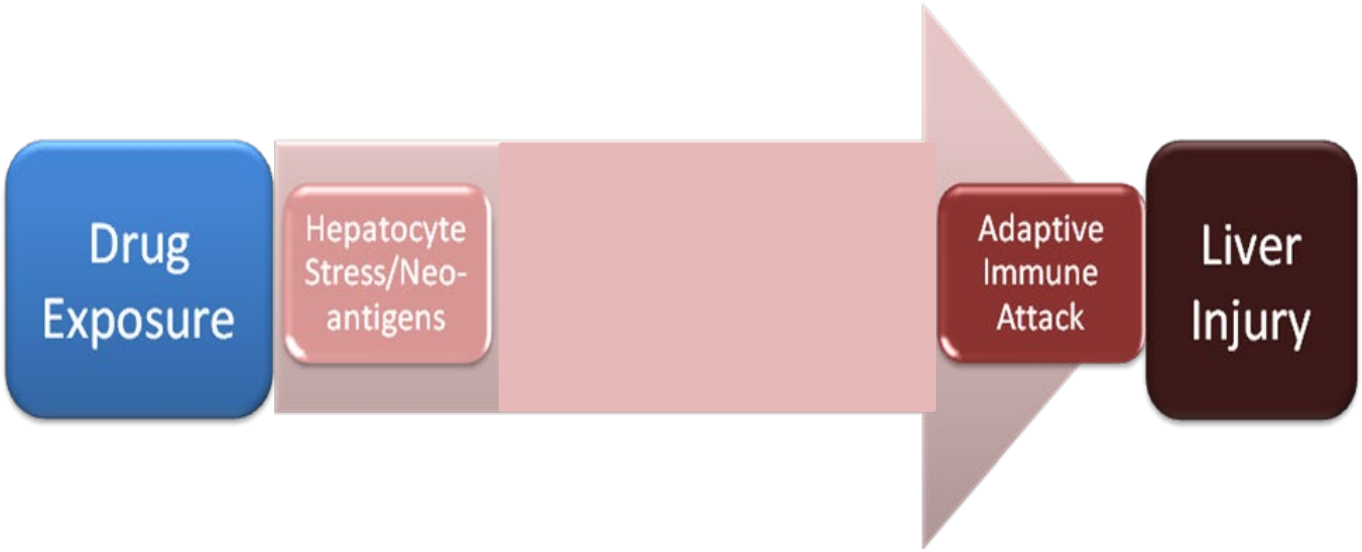
Yang … Brouwer CPT 96 (5) 2014

Involvement of Adaptive Immunity in Idiosyncratic DILI



Clin Pharmacol Ther. 2017 Apr;101(4):469-480.

Involvement of Adaptive Immunity in Idiosyncratic DILI



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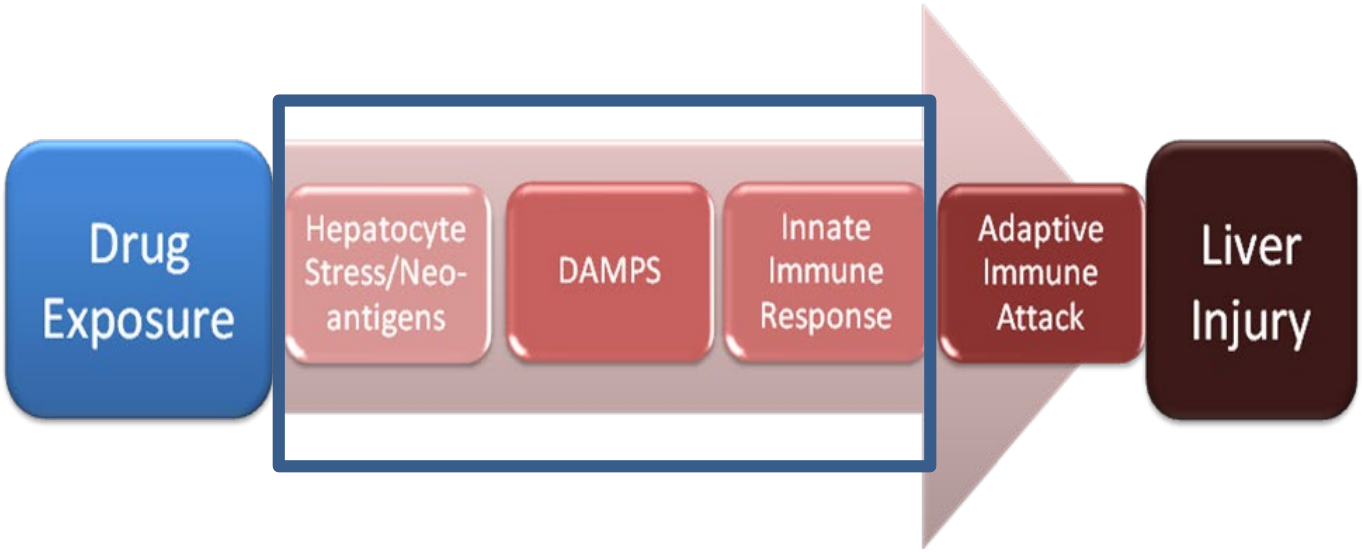
Involvement of Adaptive Immunity in Idiosyncratic DILI



Clin Pharmacol Ther. 2017 Apr;101(4):469-480.

DILIsym Predicts Liability for Idiosyncratic DILI

1). Title: Application of a Mechanistic Model to Evaluate Putative Mechanisms of **Tolvaptan** Drug-Induced Liver Injury and Identify Patient Susceptibility Factors

Authors: Jeffrey L. Woodhead,* **William J. Brock,† Sharin E. Roth**,‡ Susan E. Shoaf,‡ Kim L.R. Brouwer,§ Rachel Church,§,¶ Tom N. Grammatopoulos,k Linsey Stiles,k Scott Q. Siler,* Brett A. Howell,* Merrie Mosedale,§,¶ Paul B. Watkins,§,¶ and Lisl K.M. Shoda*,1

Tox Sci: 155(1), 2017, 61-74, 2017

2). Title: Quantitative Systems Toxicology Analysis of *In Vitro* Mechanistic Assays Reveals Importance of Bile Acid Accumulation and Mitochondrial Dysfunction in **TAK-875**-induced Liver Injury

Authors: Diane M. Longo*‴, Jeffrey L. Woodhead*, Paul Walker†, Krisztina Heredi-Szabo‡, Karoly Mogyorosi‡, **Francis S. Wolenski§, Yvonne P. Dragan**§, Merrie Mosedale¶‖, Scott Q. Siler*, Paul B. Watkins*¶‖, Brett A. Howell*

Tox Sci 2018 – epub

Conclusions

1). Quantitative Systems Toxicology (QST) modeling can explain and predict species differences in dose-dependent hepatotoxicity.

2). Species differences in the profile of bile acids often underlie unexpected hepatoxicity in the clinic - species differences in susceptibility to mitochondrial toxicity can also contribute.

3). Dose dependent hepatotoxicity may be relevant to delayed, idiosyncratic hepatoxicity even if its immune-mediated.

DILIsym Services Inc. Team

Scott Q Siler
Chief Scientific Officer
Bay Area, CA

Brett Howell
President
RTP, NC

Grant Generaux
Scientist II
Philadelphia, PA

Jeff Woodhead
Scientist II
RTP, NC

DILIsym Services

A SIMULATIONS PLUS COMPANY

Lisl Shoda
Principal Scientist
Bay Area, CA

Corey Berry
Senior Software Engineer
RTP, NC

Vinal Lakhani
Postdoctoral Fellow
RTP, NC

Guncha Taneja
Postdoctoral Fellow
RTP, NC

Zack Kenz
Postdoctoral Fellow
RTP, NC

Christina Battista
Scientist I
RTP, NC

Kyunghee Yang
Scientist I
Middleton, DE

Bud Nelson
Director of Operations
RTP, NC

Patti Steele
Executive Assistant
RTP, NC

Diane Longo
Scientist II
Arlington, VA

Yeshi Gebremichael
Scientist II
RTP, NC

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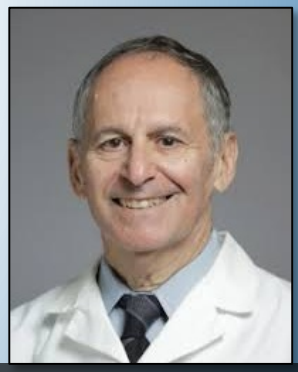
University of Toronto

Dr. Robert Roth
Distinguished Professor of Pharmacology & Toxicology
Director, Graduate Training Program in Environmental and Integrative Toxicological Sciences, Center for Integrative Toxicology
Michigan State University



David Pisetsky
Professor of Medicine
Professor of Immunology
Member of the Duke Cancer Institute
Member of the Duke Human Vaccine Institute