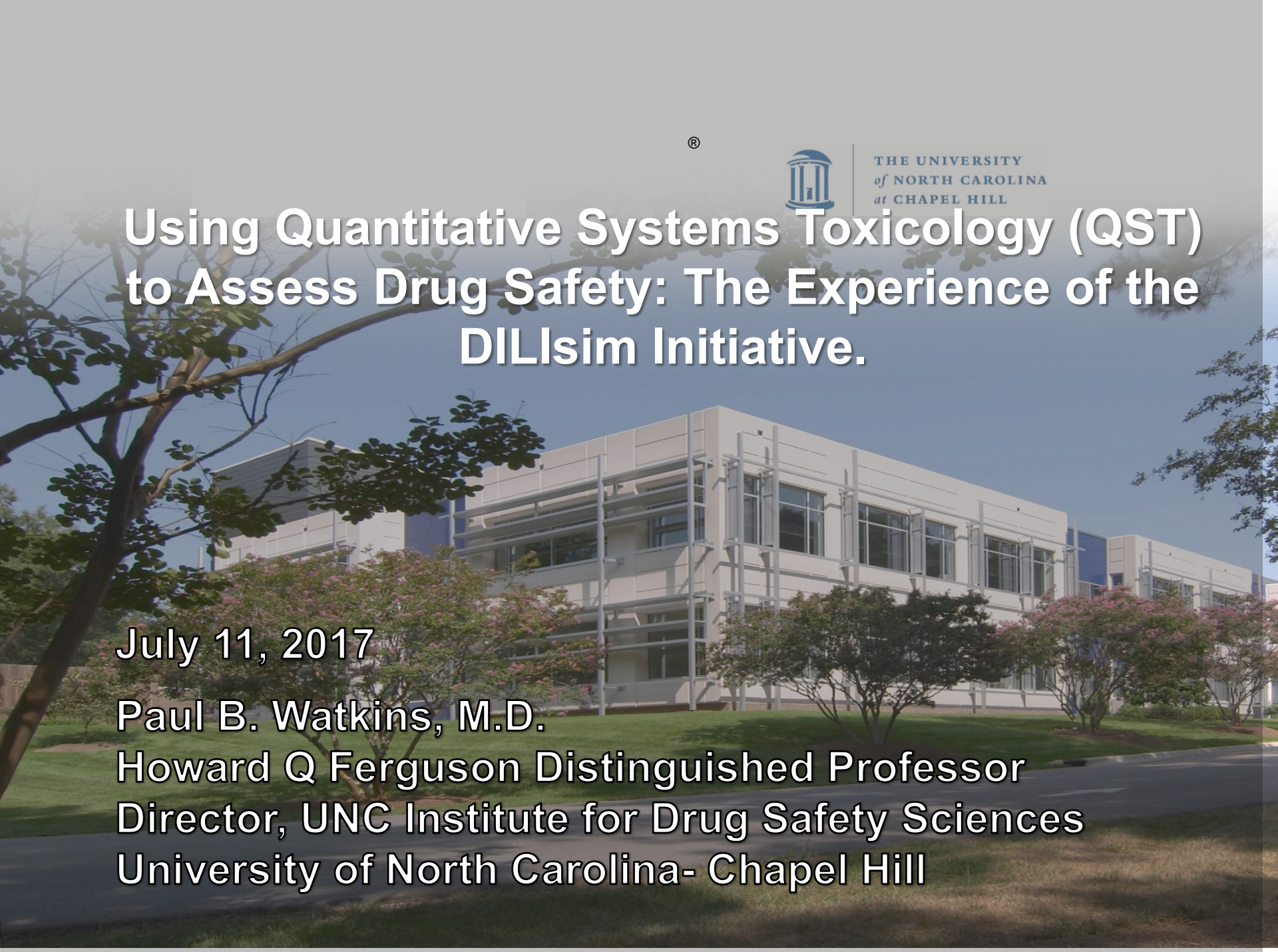


Using Quantitative Systems Toxicology (QST) to Assess Drug Safety: The Experience of the DILIsim Initiative.

July 11, 2017

Paul B. Watkins, M.D.
Howard Q Ferguson Distinguished Professor
Director, UNC Institute for Drug Safety Sciences
University of North Carolina- Chapel Hill

Disclosure

I am compensated to chair the scientific advisory committee for the DILIsim Initiative

I owned equity in the spin off company DILIsym Services, Inc. that was acquired by Simulations Plus June 1, 2017.

Drug-Induced Liver Injury (DILI)

1). Remains a major problem in drug development

2). The DILIsim Initiative is a public private partnership developing software capable to explaining and predicting DILI liability in new drug candidates.

The DILIsim Initiative is in its sixth year

Approach

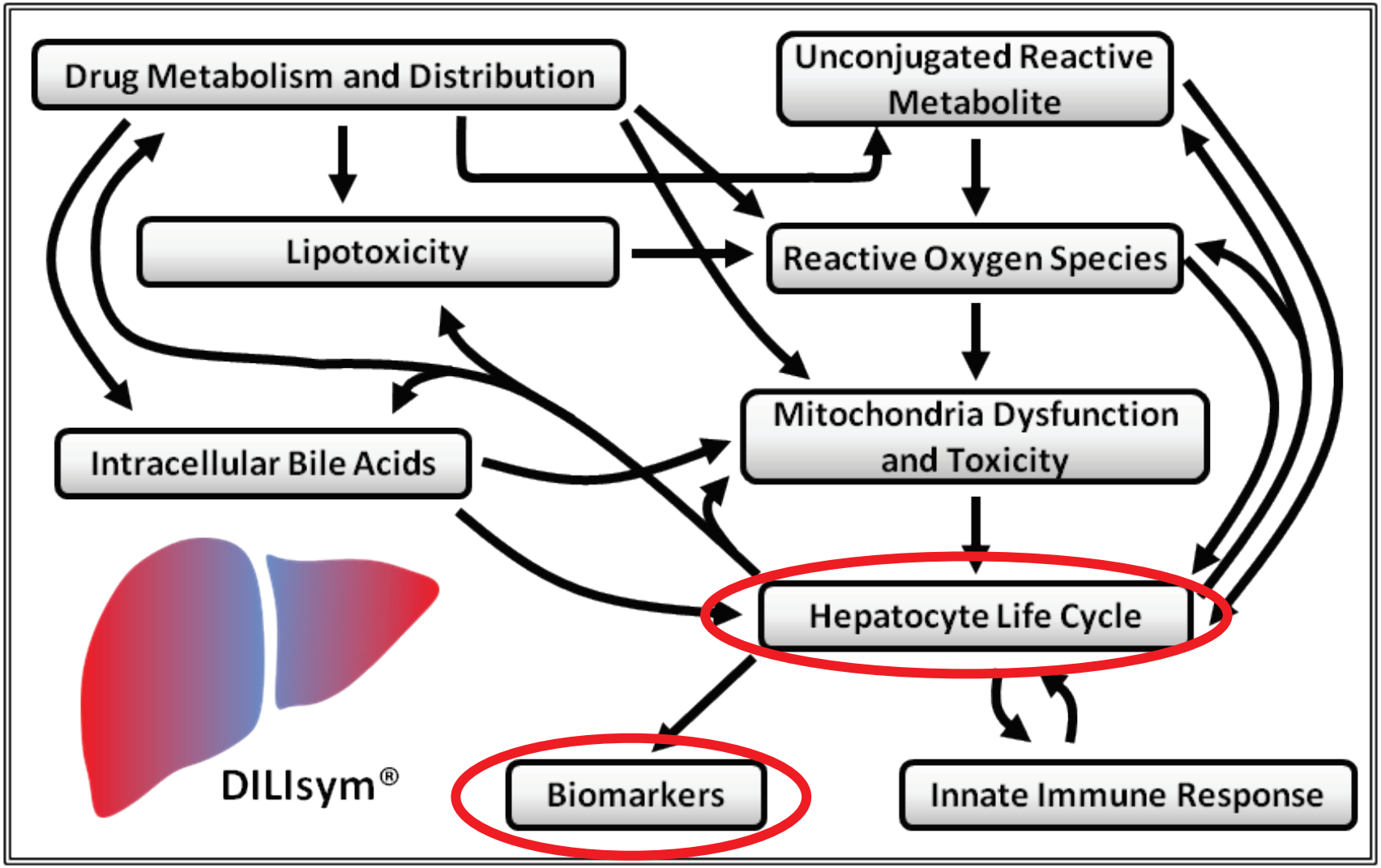
1). Build mechanistic “modules” using differential equations – perform experiments to fill in knowledge gaps.

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

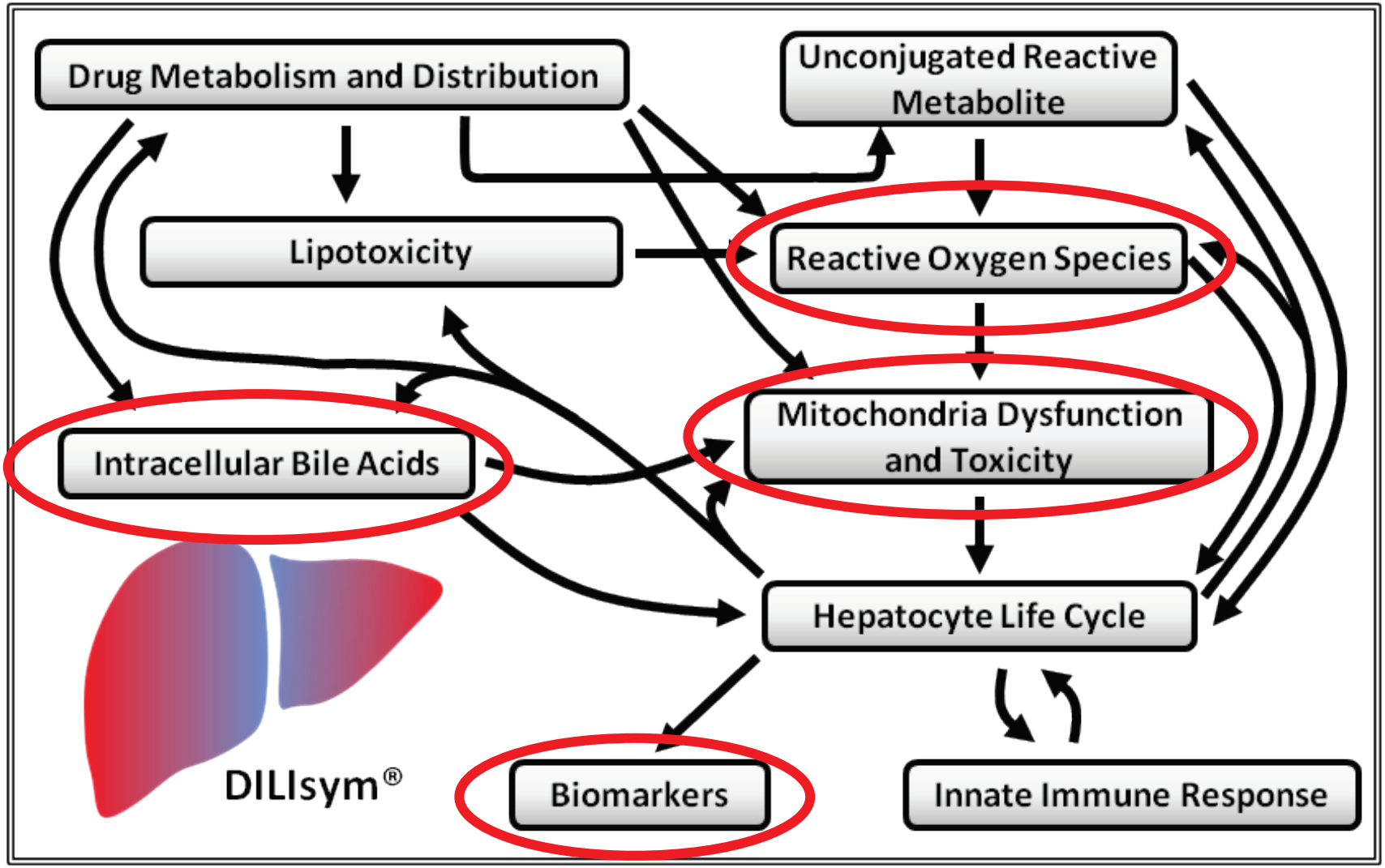
3). Vary model parameters to create simulated patient populations (Simpops®)

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

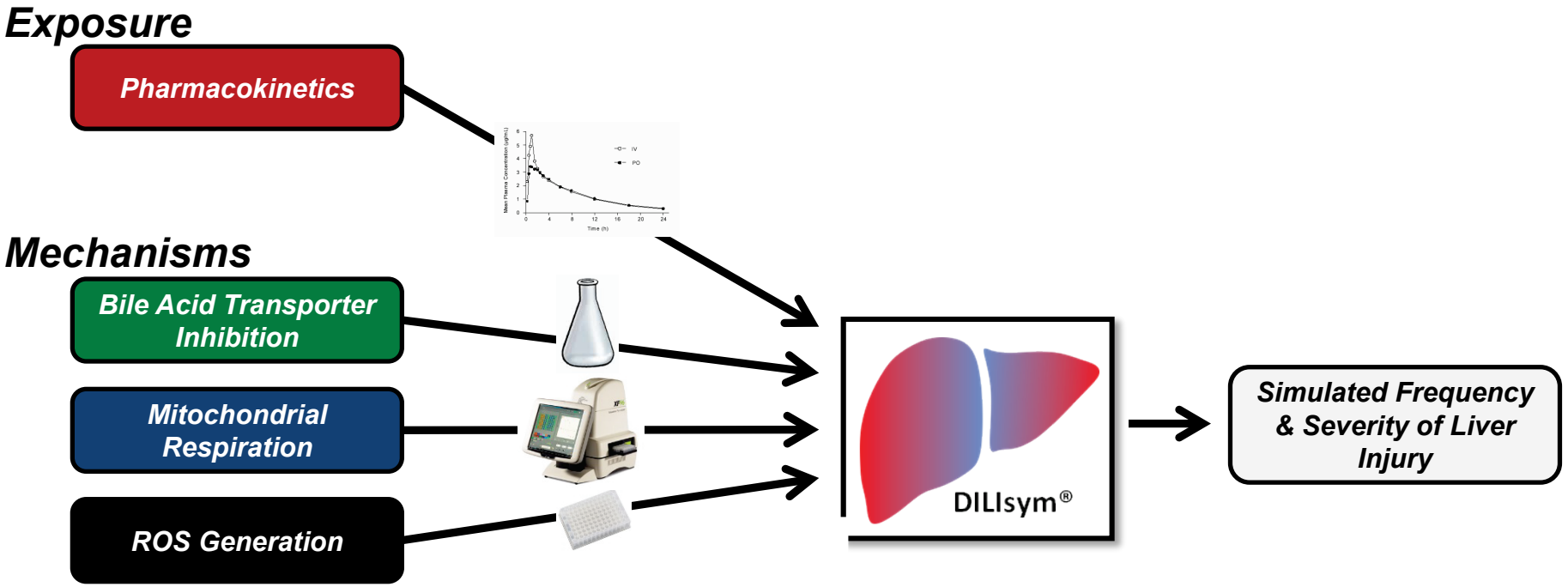
DILIsym Sub-Models



DILIsym Sub-Models



DILIsym Integrates Multiple Inputs to Simulate/Predict Hepatotoxicity



Conclusion

DILIsym modeling has been able to correctly predict the liver safety profiles of ~90% (24/27) of the validation set of drugs tested so far.

Outline of Talk

1). Problem of drug safety

2). The DILIsim Initiative

3). The solithromycin story

4). Conclusions

Posted: 5:17 p.m. Friday, Nov. 4, 2016

The Associated Press
WASHINGTON —

On Wednesday Cempra shares plunged more than 60 percent after the FDA posted an online review highlighting irregular liver enzyme measurements reported with the drug, called solithromycin……..

What exactly did the FDA say?

What the FDA Briefing Document Said

"serious liver safety concern"

"the number of study subjects treated with solithromycin should be increased from 924 to approximately 12,000 and carefully assessed for liver safety events…*in advance* of making a regulatory decision regarding approval"

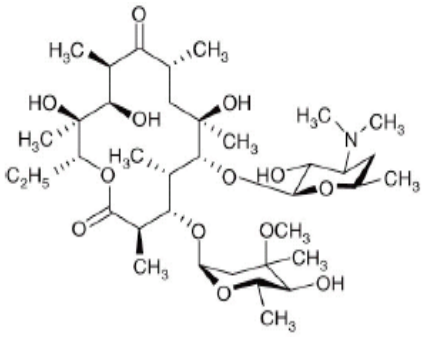
Solithromycin

“Quantitative Structure Activity Relationships (QSAR) show 85% similarity in structure to telithromycin and that hepatotoxicity would be expected with solithromycin use”

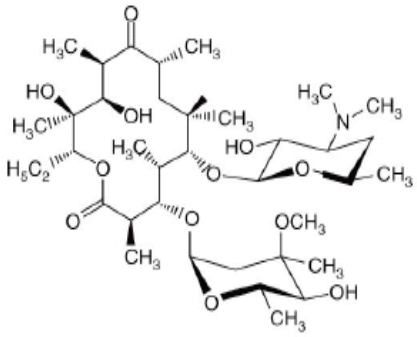
Raj Madabushi, PhD
FDA June 6, 2017

Institute for Drug Safety Sciences
THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

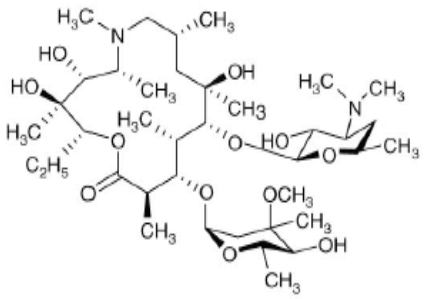
Structures of Macrolide Antibiotics



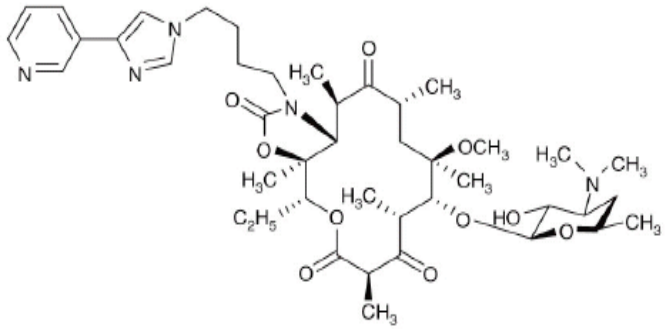
Erythromycin



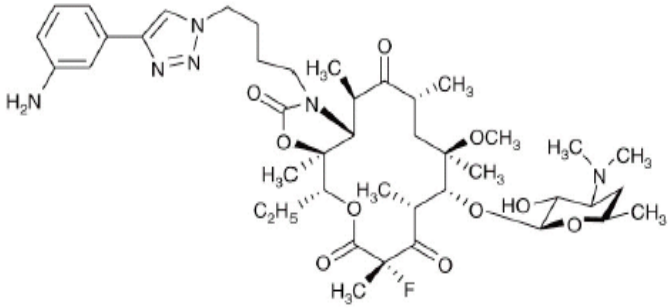
Clarithromycin



Azithromycin

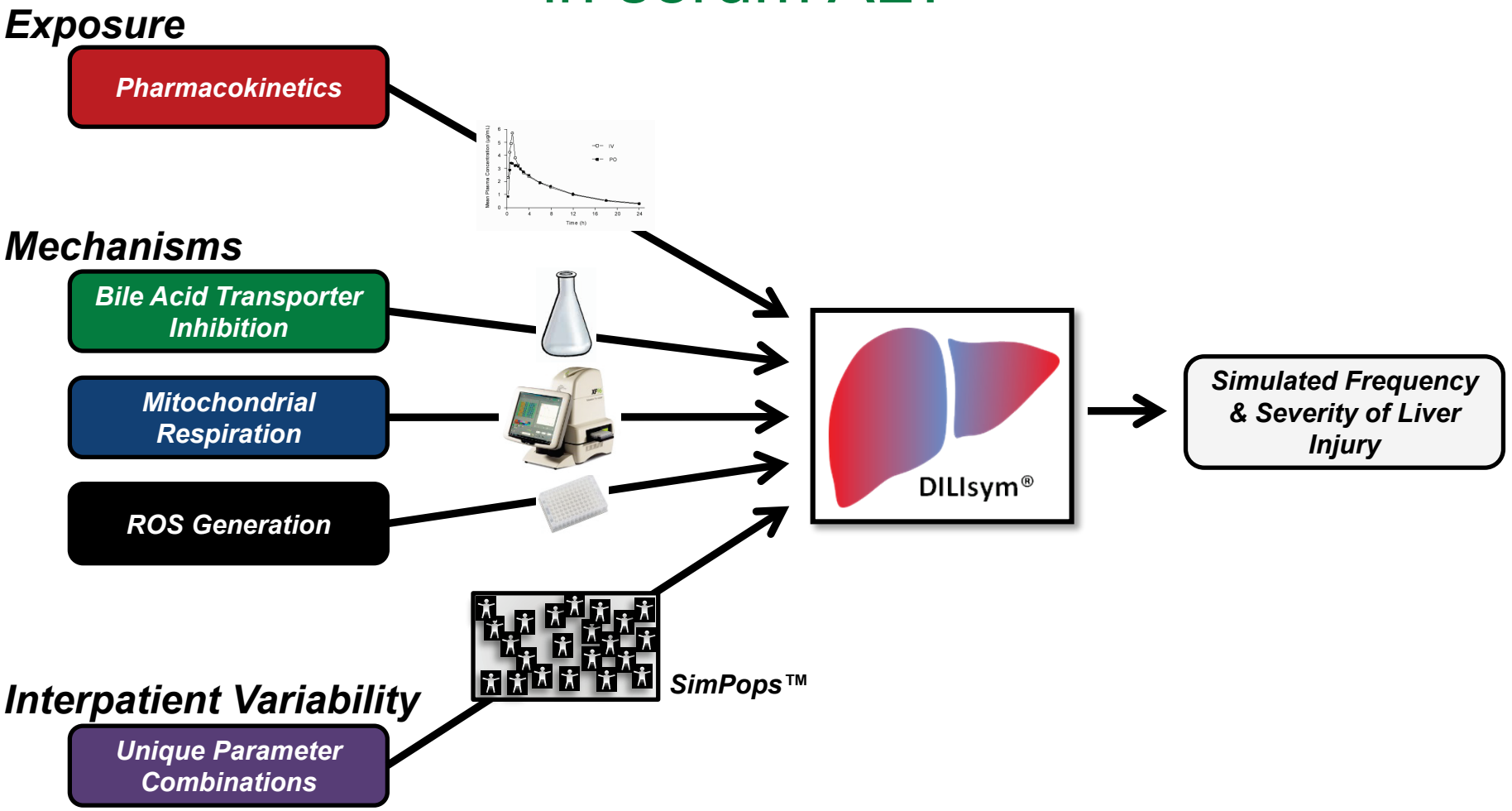


Telithromycin



Solithromycin

DILIsym prediction of solithromycin- and other macrolide/ketolide- induced elevations in serum ALT



The Rates of Serum ALT Elevations In All Four Drugs Are Reasonably Predicted by DILIsym

Data presented at Nov 4 2017 anti-infective Ad com

Compound	Protocol	Peak ALT > 3X ULN	
		Observed*	Simulated
Solithromycin	Oral (CE01-300)	3.2%	3.9%
	IV-to-Oral (CE01-301)	5.5%	6.0%

Modeling work supported by Cempra

* Patients with normal ALT at baseline

The Rates of Serum ALT Elevations In All Four Drugs Are Reasonably Predicted by DILIsym

Data presented at Nov 4 2017 anti-infective Ad com

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

Modeling work supported by Cempra

Excerpt from FDA Briefing Document

…. **A somewhat surprising additional unexplained gap in the analysis submitted by DILIsym Services is the absence of the parallel testing of telithromycin hepatoxicity in a simulated CAP population……The use of telithromycin as a "positive control" in the model with comparative liver test data would be highly relevant and might support the utility of the model…."**

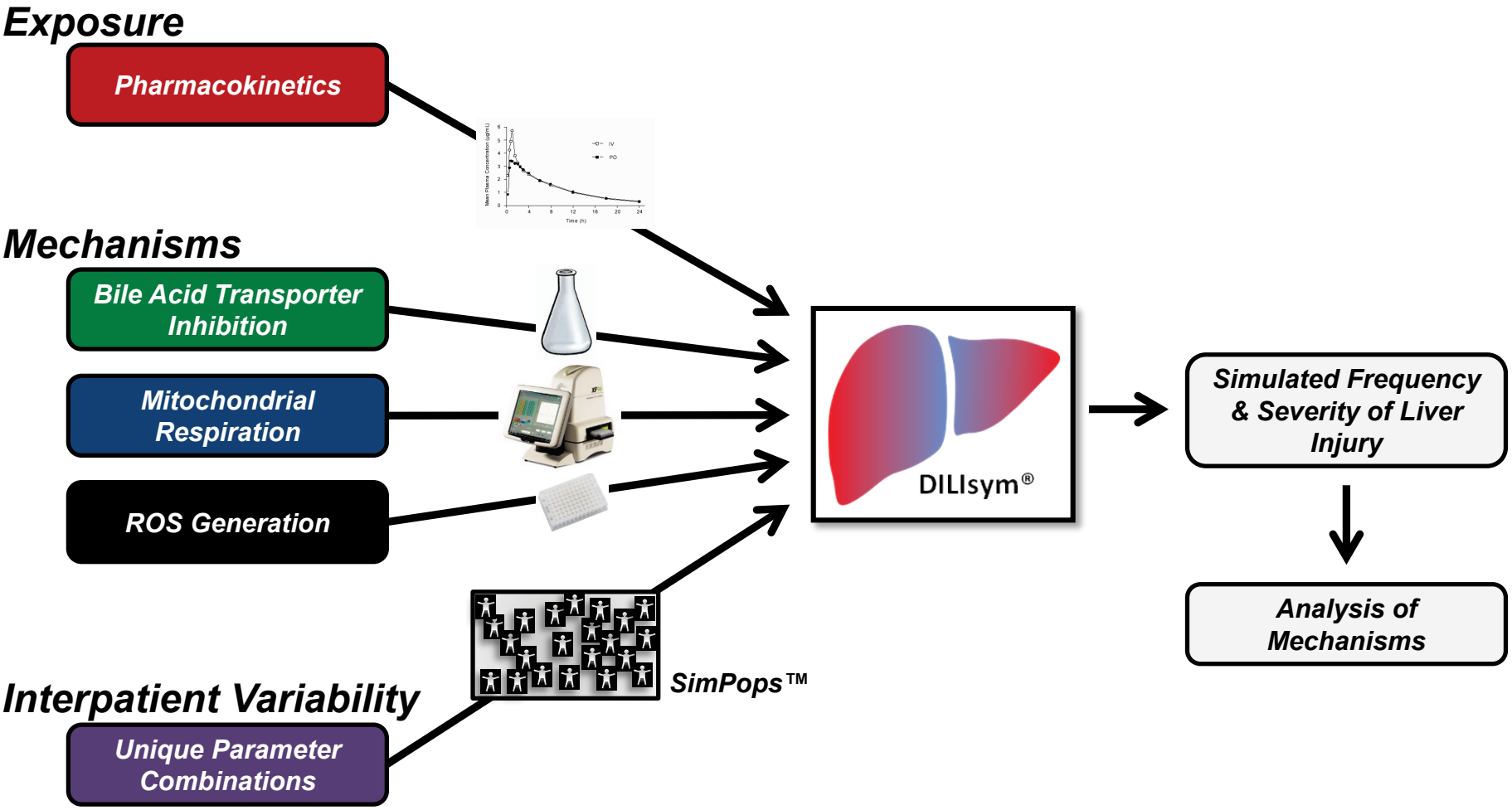
The rates of serum ALT elevations in clinical trials are reasonably predicted by DILIsym

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%

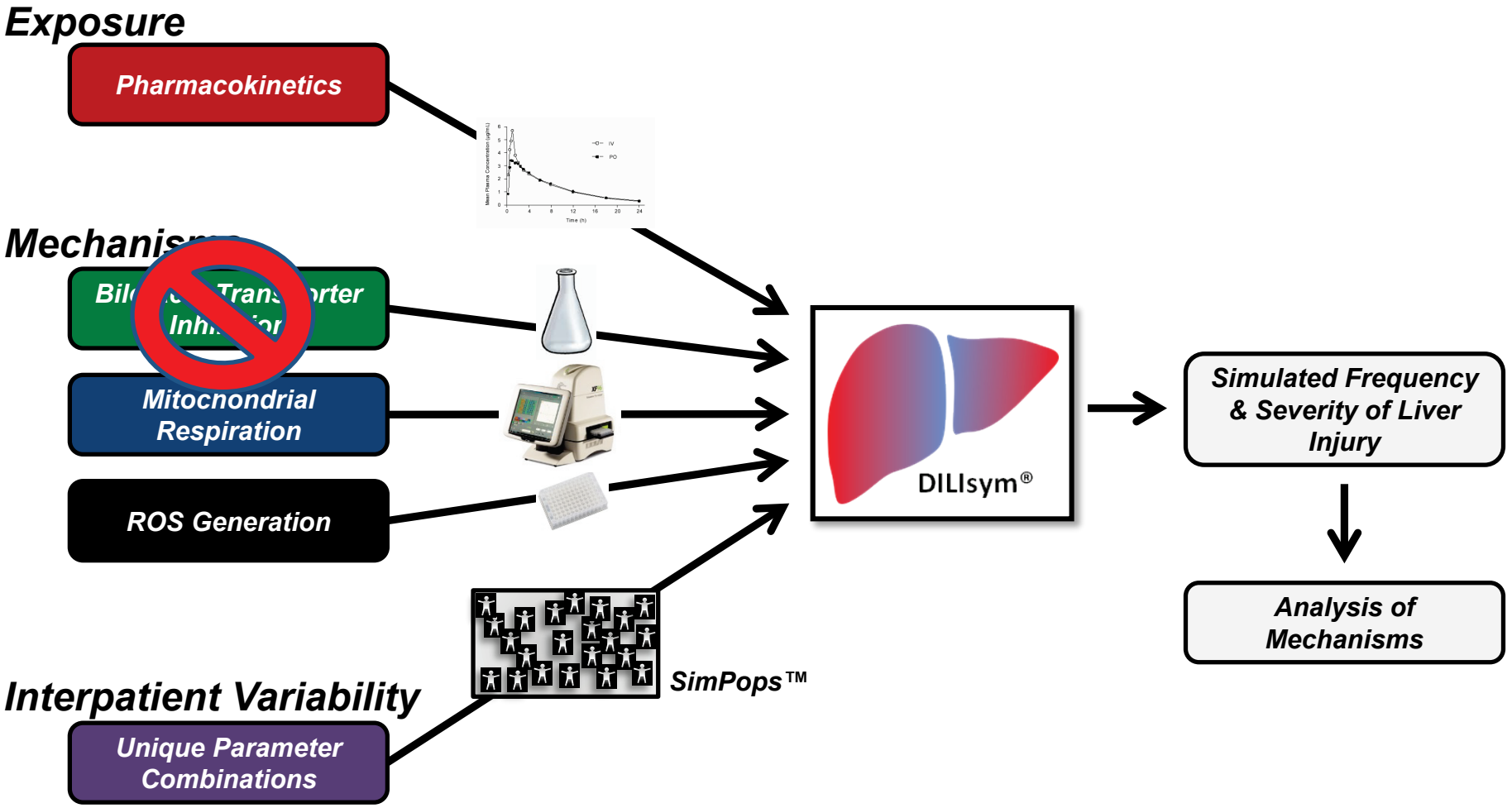
Conclusions

DILIsym predicted the incidence of elevations in serum ALT across the macrolide/ketolide class

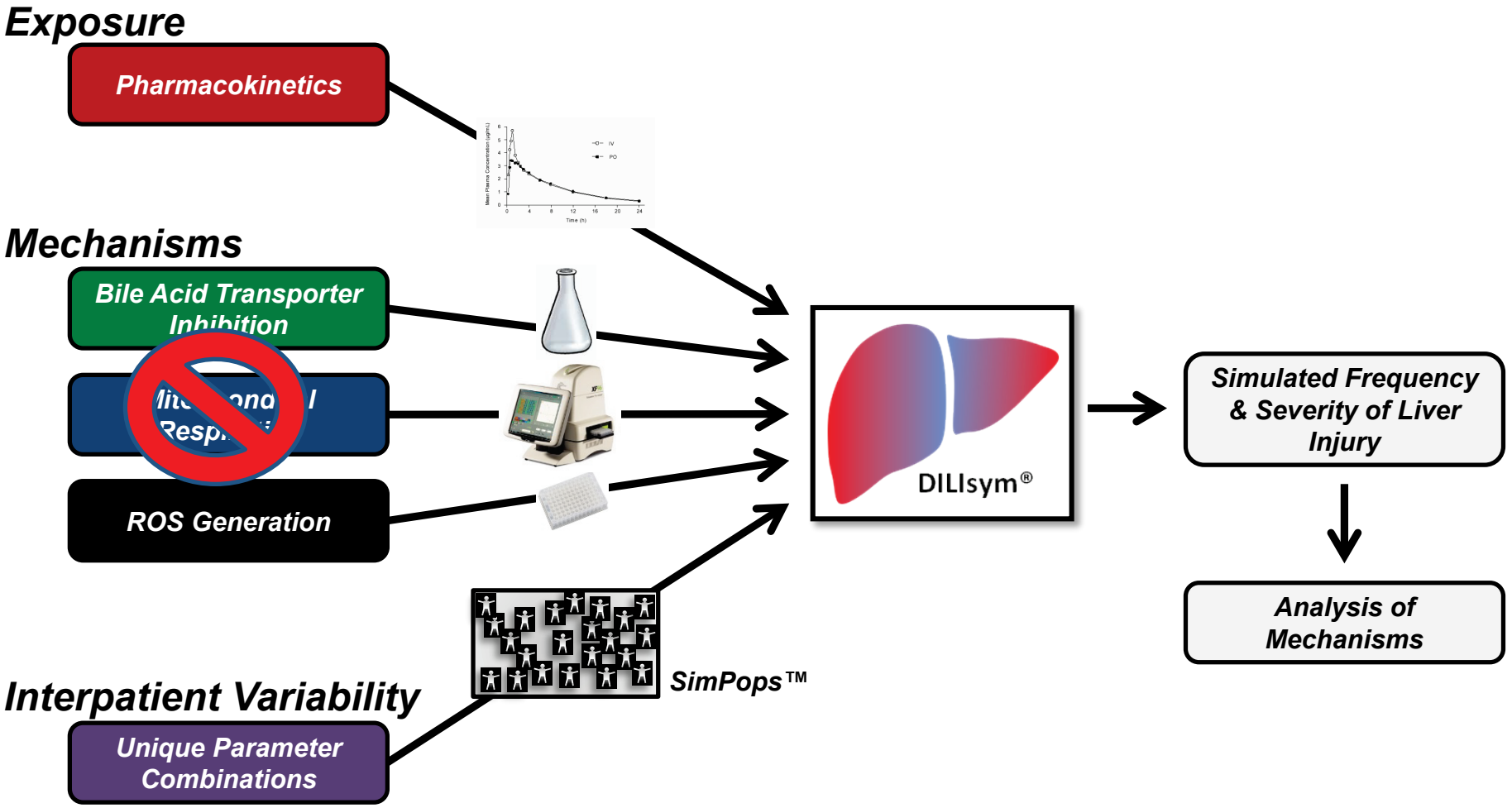
DILIsym Integrates Multiple Inputs to Simulate/Predict Hepatotoxicity



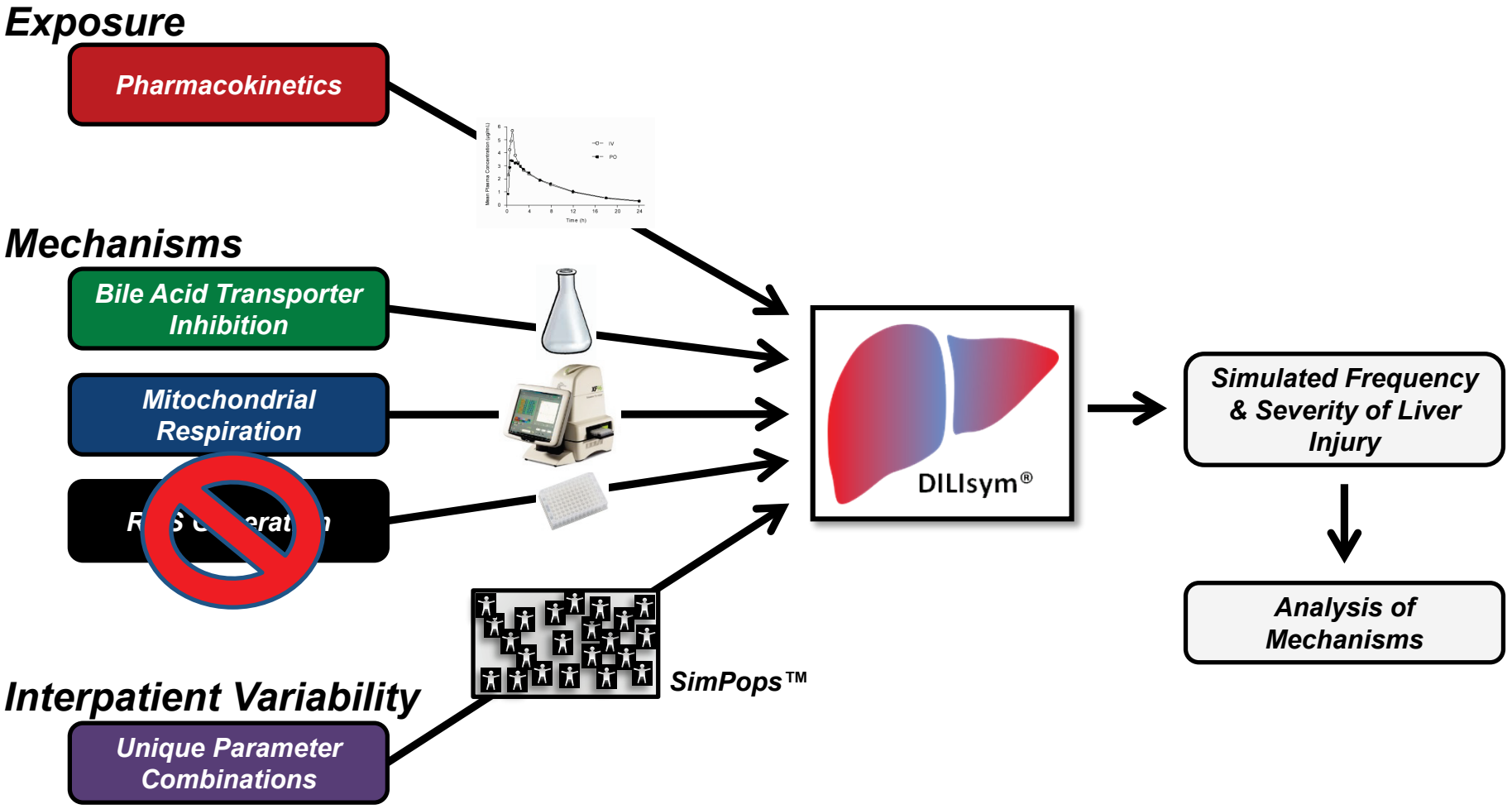
DILIsym Integrates Multiple Inputs to Simulate/Predict Hepatotoxicity



DILIsym Integrates Multiple Inputs to Simulate/Predict Hepatotoxicity



DILIsym Integrates Multiple Inputs to Simulate/Predict Hepatotoxicity



Contribution to Predicted ALT elevations in Simulated Human Population

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

Data presented at Nov 4 2017 anti-infective Ad com

Contribution to Predicted ALT elevations in Simulated Human Population

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

Data presented at Nov 4 2017 anti-infective Ad com

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

Conclusion

The predominant mechanisms underlying dose-dependent hepatoxicity can vary within a drug class.

FDA panel narrowly backs Cempra antibiotic
Posted: 5:17 p.m. Friday, Nov. 4, 2016

The Associated Press
WASHINGTON —

The Food and Drug Administration's outside experts voted 7-6 in favor of the drug, saying its effectiveness outweighed risks of liver toxicity seen in company studies. The vote is nonbinding but the FDA often follows the advice of its panelists.

Conclusion

Quantitative Systems Toxicology is already having an impact on drug development decisions within industry and has appeared in regulatory submissions. Its impact should rapidly increase in the years ahead.

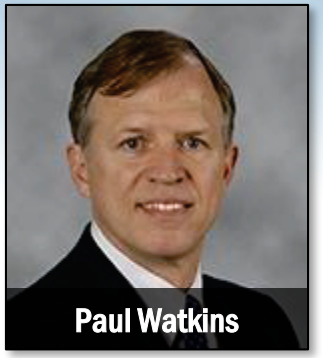
The DILI-sim Initiative Team

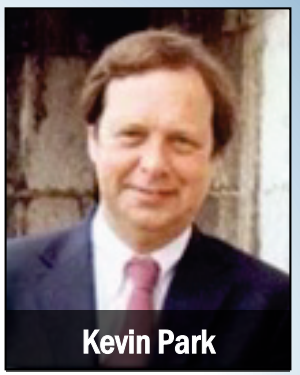
Partners

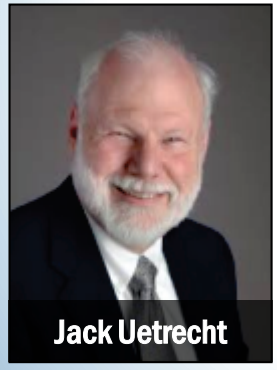
Abbvie
Astellas
BMS
Daiichi-Sankyo
Gilead
GSK
Janssen
Lilly
Merck
MitsubishiTenabe
Pfizer
Takeda

CDER –
ORISE Fellow

The DILI-sim Initiative Scientific Advisory Board







DILIsym®