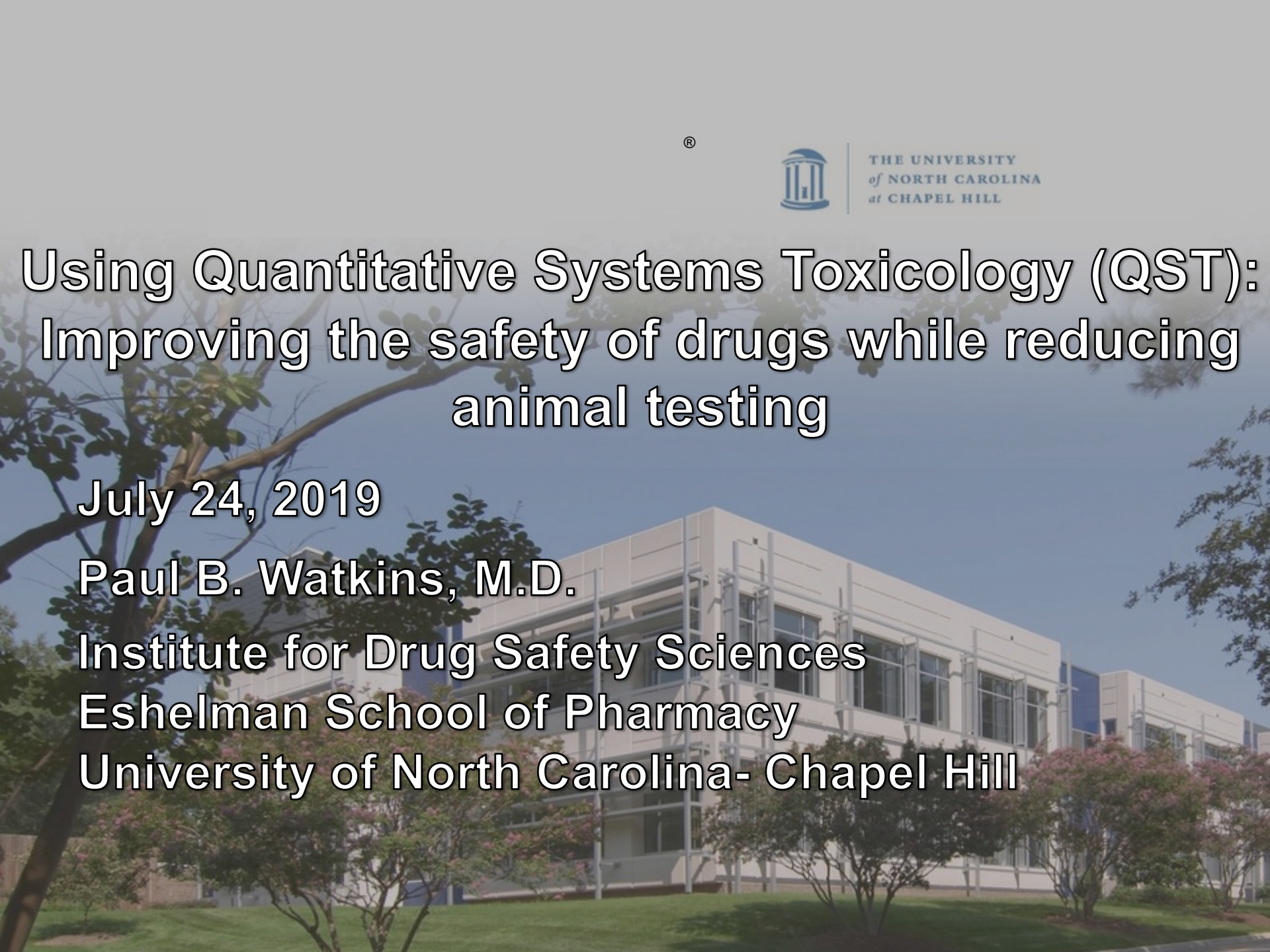


THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

Using Quantitative Systems Toxicology (QST): Improving the safety of drugs while reducing animal testing

July 24, 2019

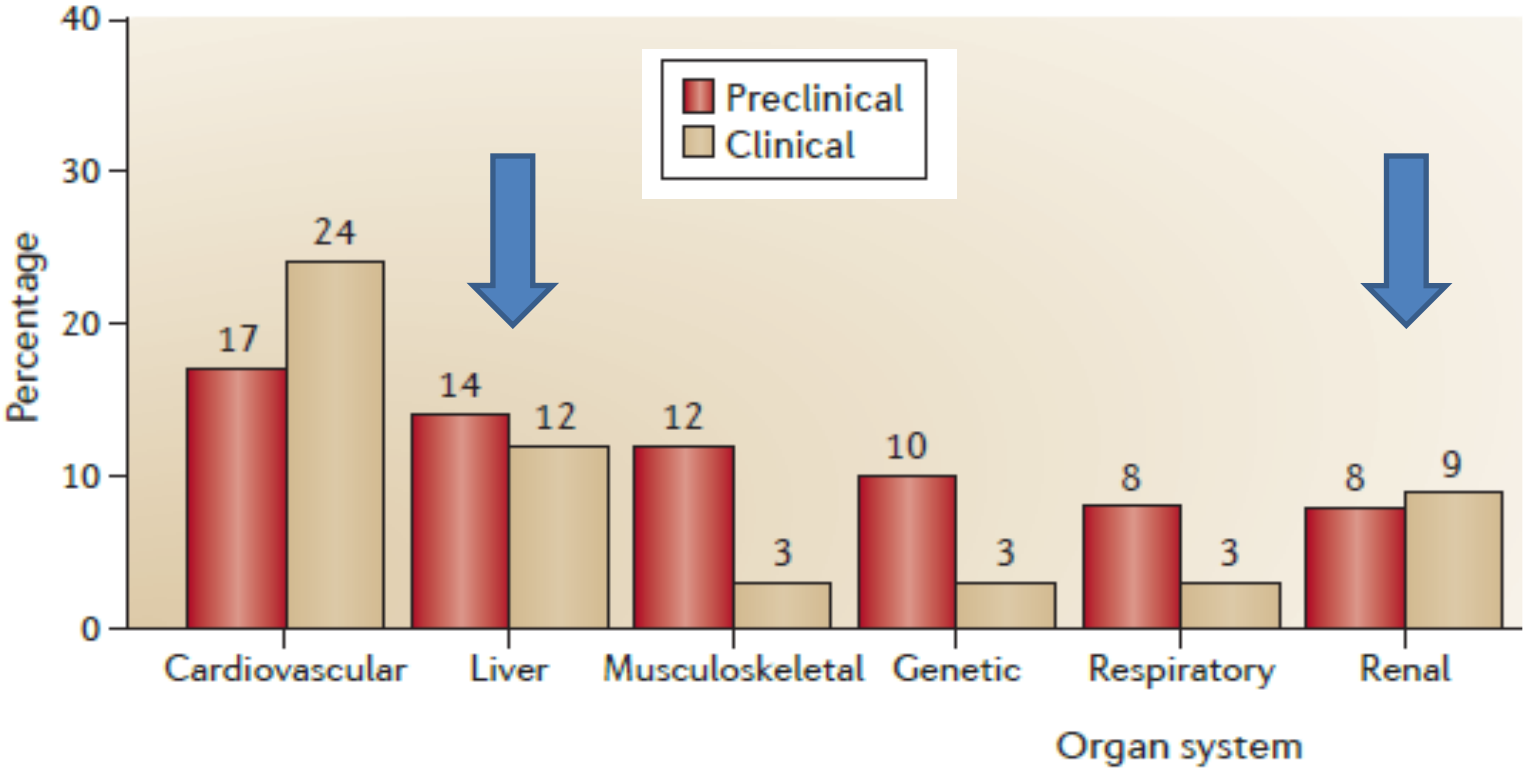
Paul B. Watkins, M.D.

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.

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



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

Outline of Talk

1). Problem of liver safety

2). Current process to assess the safety of new drug candidates

3). Progress in QST modeling – DILIsym®

4). Conclusions

Outline of Talk

1). Problem of liver safety

2). Current process to assess the safety of new drug candidates

3). Progress in QST modeling – DILIsym/Renasym

4). Conclusions

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No drugs approved in the last decade have been withdrawn from the market in the U.S. due to liver safety concerns: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

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.

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


Before
After
In only 6 weeks of drinking
FitTea™ Robert lost $500

Outline of Talk

1). Problem of liver safety

2). Current process to assess the safety of new drug candidates

3). Progress in QST modeling - DILIsym ®

4). Conclusions

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

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

- **Protein present inside hepatocytes**
- **Leaks into circulation during hepatocyte injury/death**
- **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?

General Approach to ALT elevations in Clinical Trials

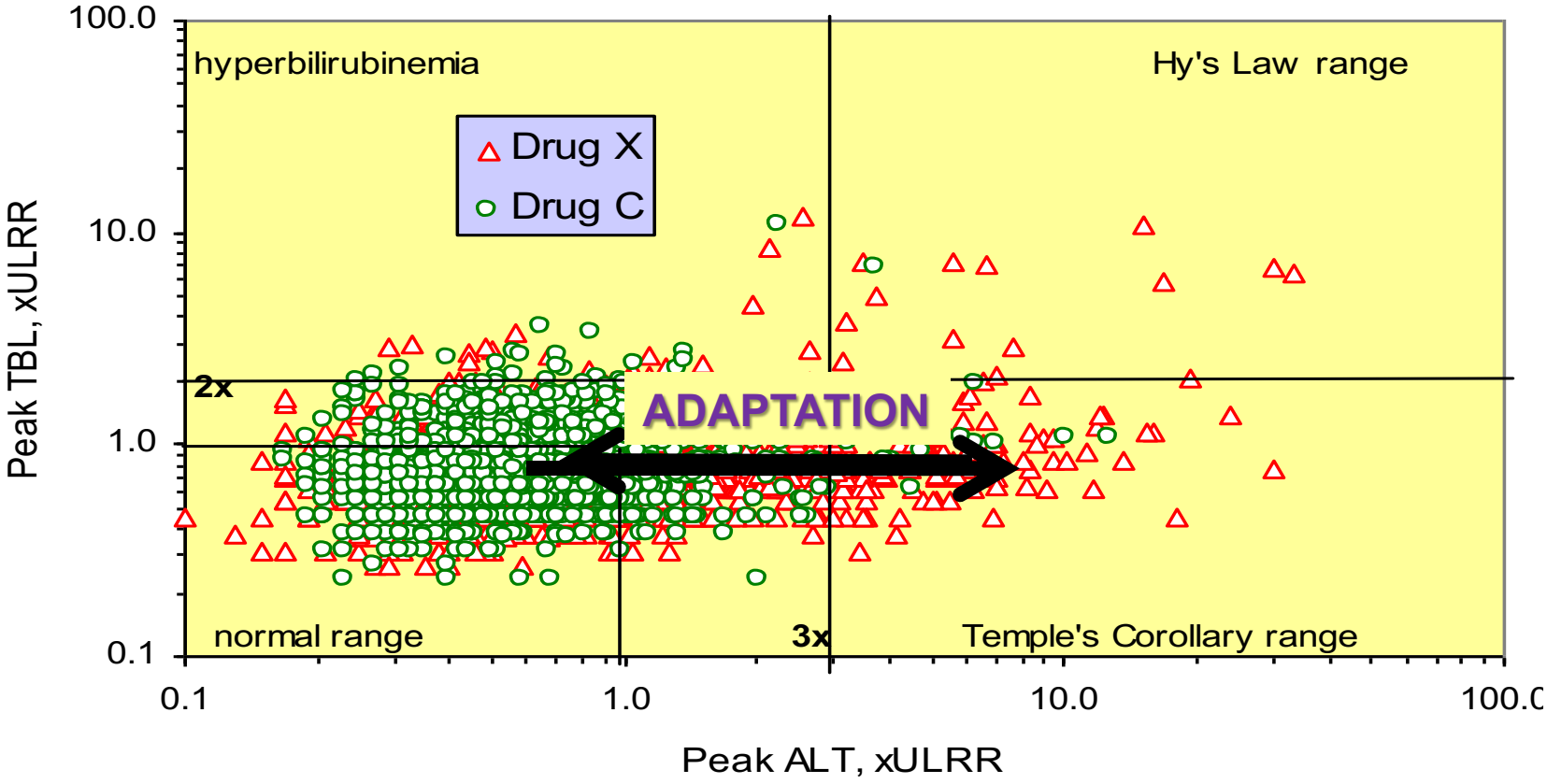
1). Continue to treat through the elevations to see if global liver dysfunction occurs

– i.e. a rise in serum bilirubin

("Hy's Law Case")

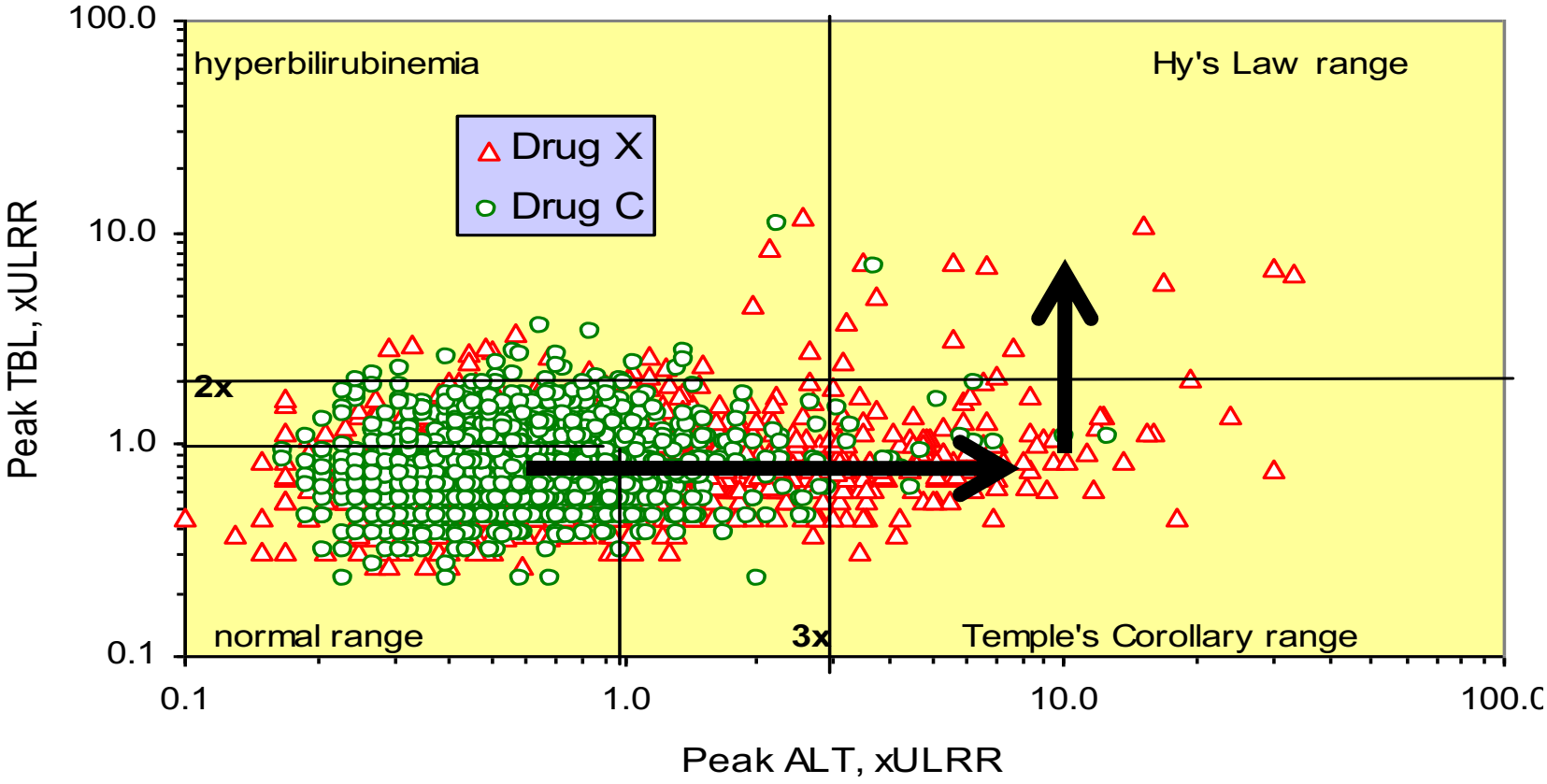
2). Large clinical trials may be needed to define risk

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

Outline of Talk

1). Problem of liver safety

2). Current process to assess the safety of new drug candidates

3). Progress in QST modeling – DILIsym ®

4). Conclusions

UNC Institute for Drug Safety Sciences

DILIsym Services
A SIMULATIONS PLUS COMPANY

The DILI-sim Initiative

janssen
gsk GlaxoSmithKline
GILEAD
DILIsym
Mitsubishi Tanabe Pharma
Bristol-Myers Squibb
abbvie

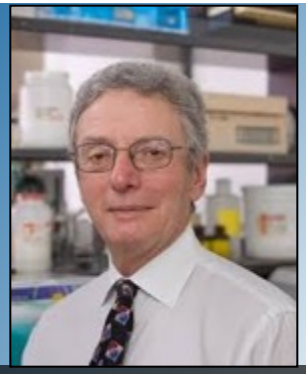
Some Current Companies In the Initiative

Patients

Cutting Edge Pre-clinical Models

In Vitro

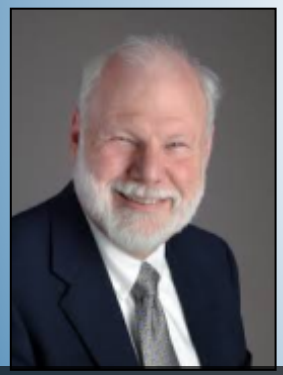
DILI-sim Scientific Advisory Board



Dr. Neil Kaplowitz
Professor of Medicine
USC Thomas H. Brem Chair in Medicine
Chief, Division of Gastroenterology and Liver Diseases

Dr. Paul B. Watkins
DIRECTOR, INSTITUTE FOR DRUG SAFETY SCIENCES
HOWARD Q. FERGUSON DISTINGUISHED PROFESSOR OF MEDICINE
UNC Eshelman School of Pharmacy

Dr. Kevin Park
Head of Institute of Translational Medicine / Director, MRC Centre for Drug Safety Science, University of Liverpool



Dr. Jack Uetrecht
Professor, Canada Research Chair in Adverse Drug Reactions
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

DILI-sim Initiative Approach

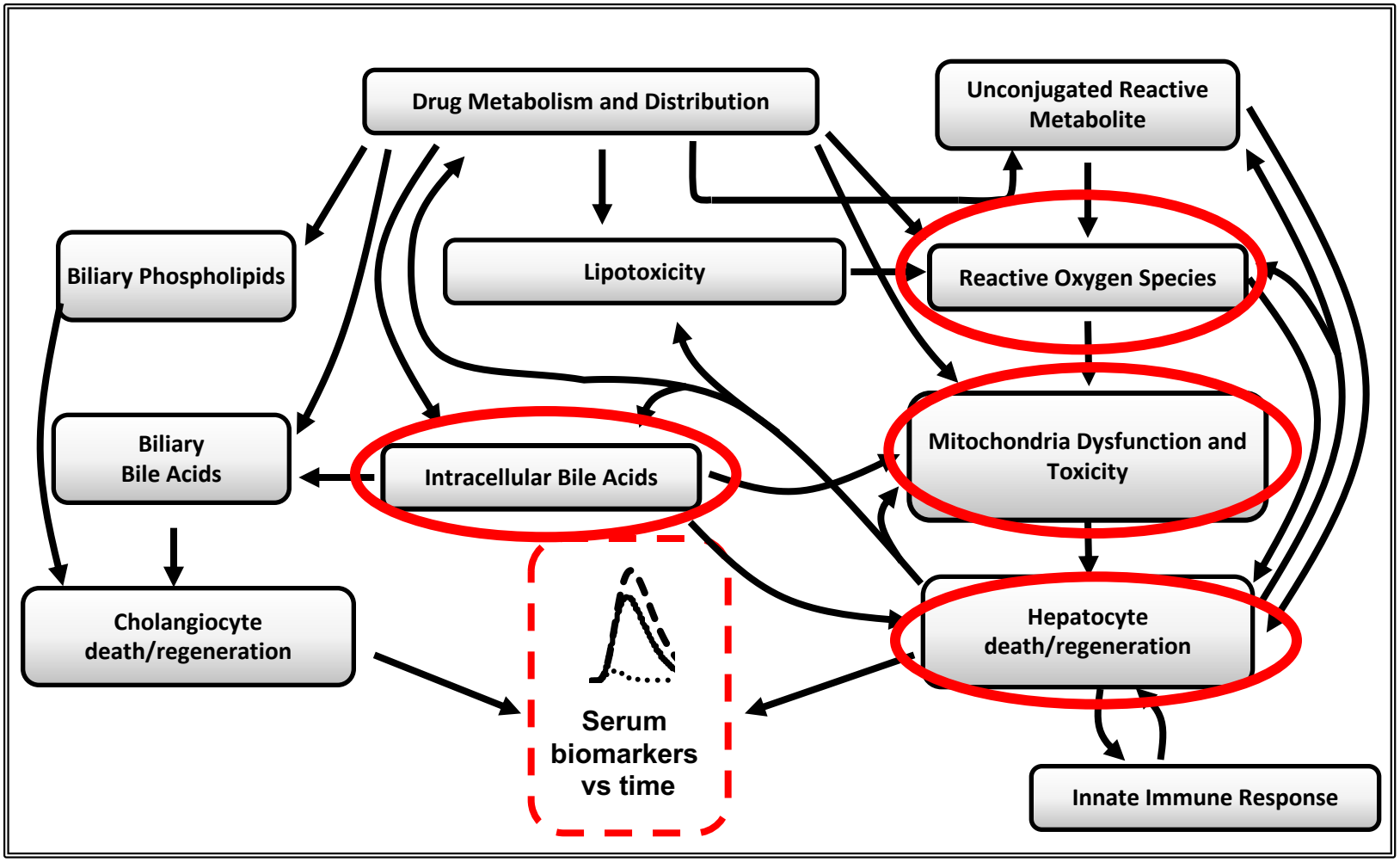
1). Build mechanistic “modules” using differential equations – perform experiments to fill in knowledge gaps.

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

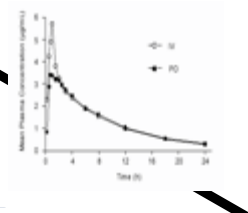
DILIsym® software created by the DILI-sim Initiative



DILIsym Input Data

Exposure

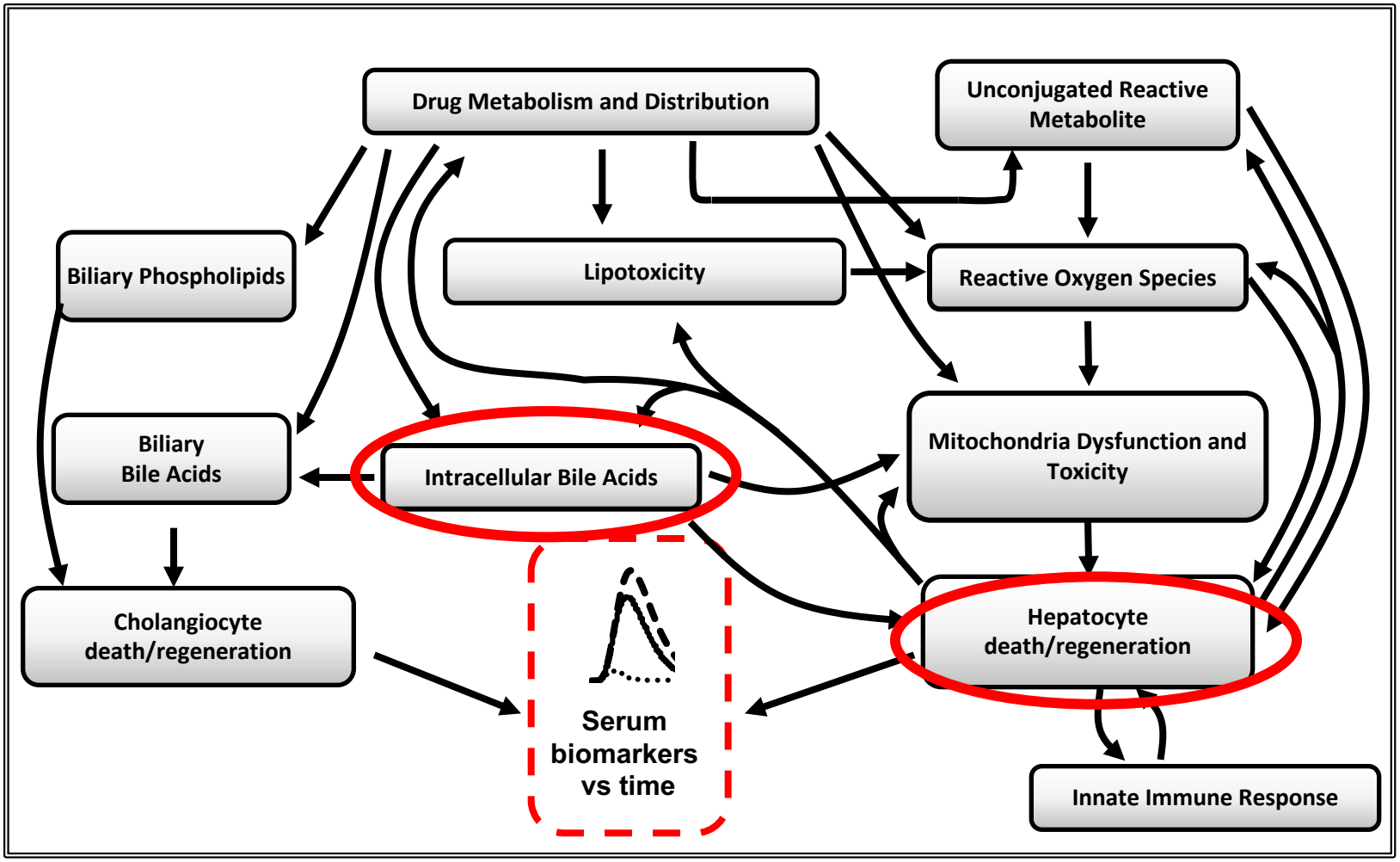
Pharmacokinetics



DILIsym®

Simulated Frequency & Severity of Liver Injury (ALT)

DILIsym® software created by the DILI-sim Initiative



AMG 009

No evidence of liver injury in multiple species

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

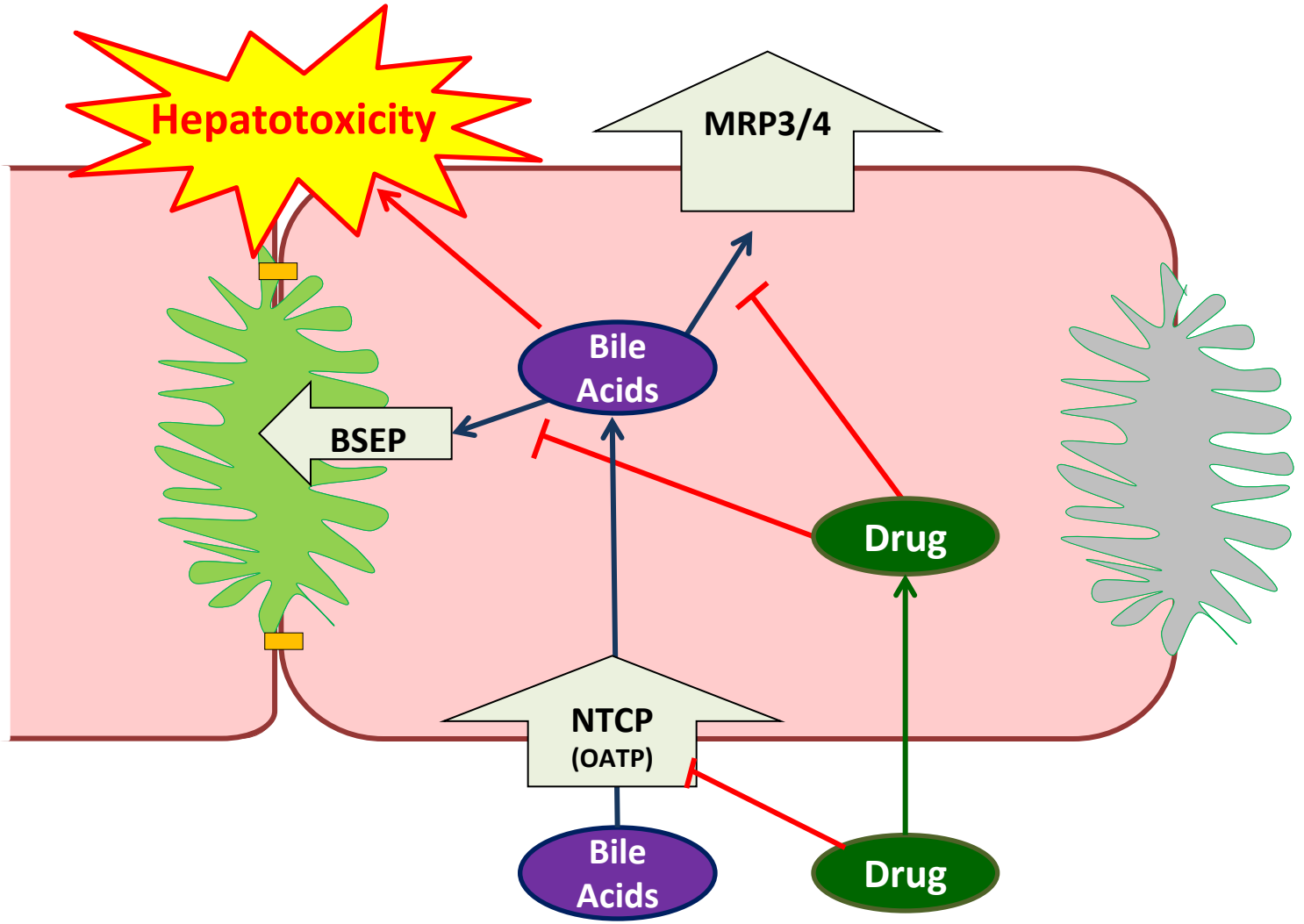
– During Phase I clinical trials in healthy volunteers, 5/8 patients showed significant and reversible transaminase elevations at the highest dose.

– Development of AMG 009 was halted

– BSEP and MRP3/4 inhibition was the only mechanism identified as likely contributors to AMG 009 hepatotoxicity

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

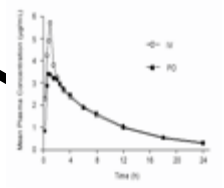
Drugs Can Inhibit Bile Acid Transporters



DILIsym Input Data

Exposure

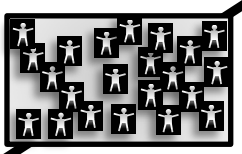
Pharmacokinetics



Mechanisms

Bile Acid Transporter Inhibition

Simulated Frequency & Severity of Liver Injury (ALT)



SimPops™

Interpatient Variability

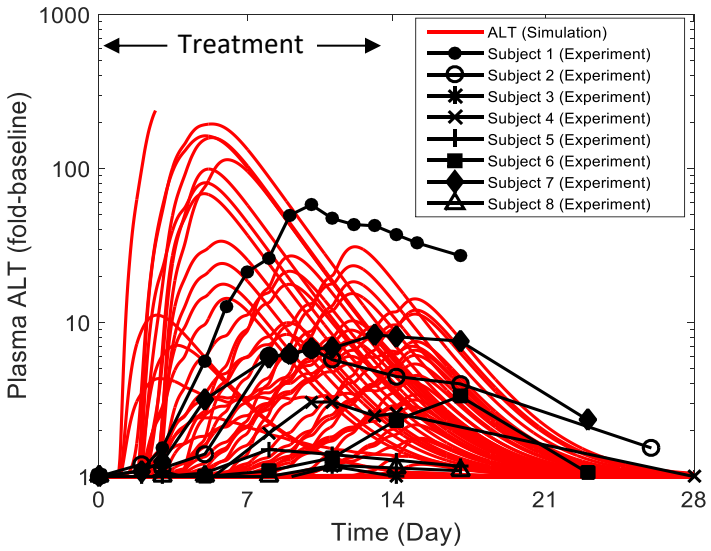
Unique Parameter Combinations

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

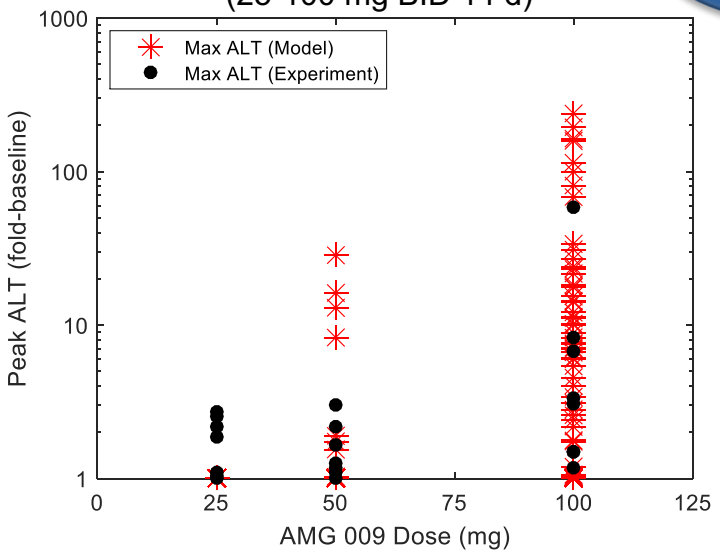
HUMANS

Stop criteria used

100 mg BID 14 d



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



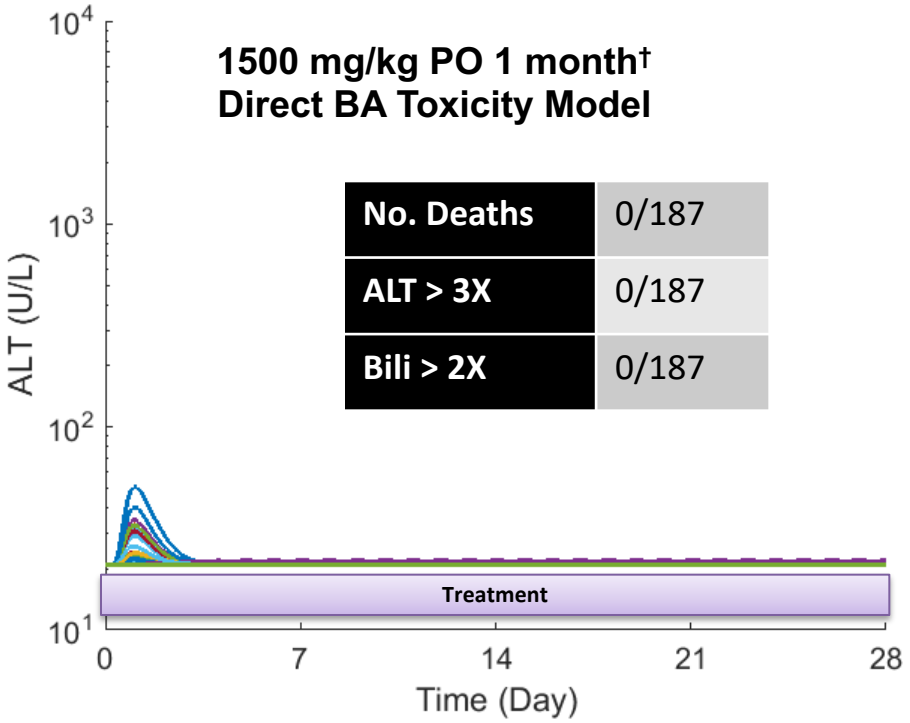
- DILIsym® predicts dose-dependent, delayed presentation of AMG 009 hepatotoxicity and recovery after discontinuation
- Incidence rates were fairly similar to observations

Unpublished data

Clinical Data and Simulation Results

No Hepatotoxicity Predicted in the Rat SimPops™ Administered AMG 009

1500 mg/kg/day PO for 1 month



RATS

Unpublished data

Preclinical Data and Simulation Results

AMG 853

- **AMG 853 was the backup to AMG 009**
  - **No evidence of liver injury in preclinical species.**
  - **No evidence of human toxicity in clinical trials**

-- But..AMG 853 was a more potent BSEP inhibitor than AMG 009 with IC50's of 4.3 vs. 11.5 μM respectively

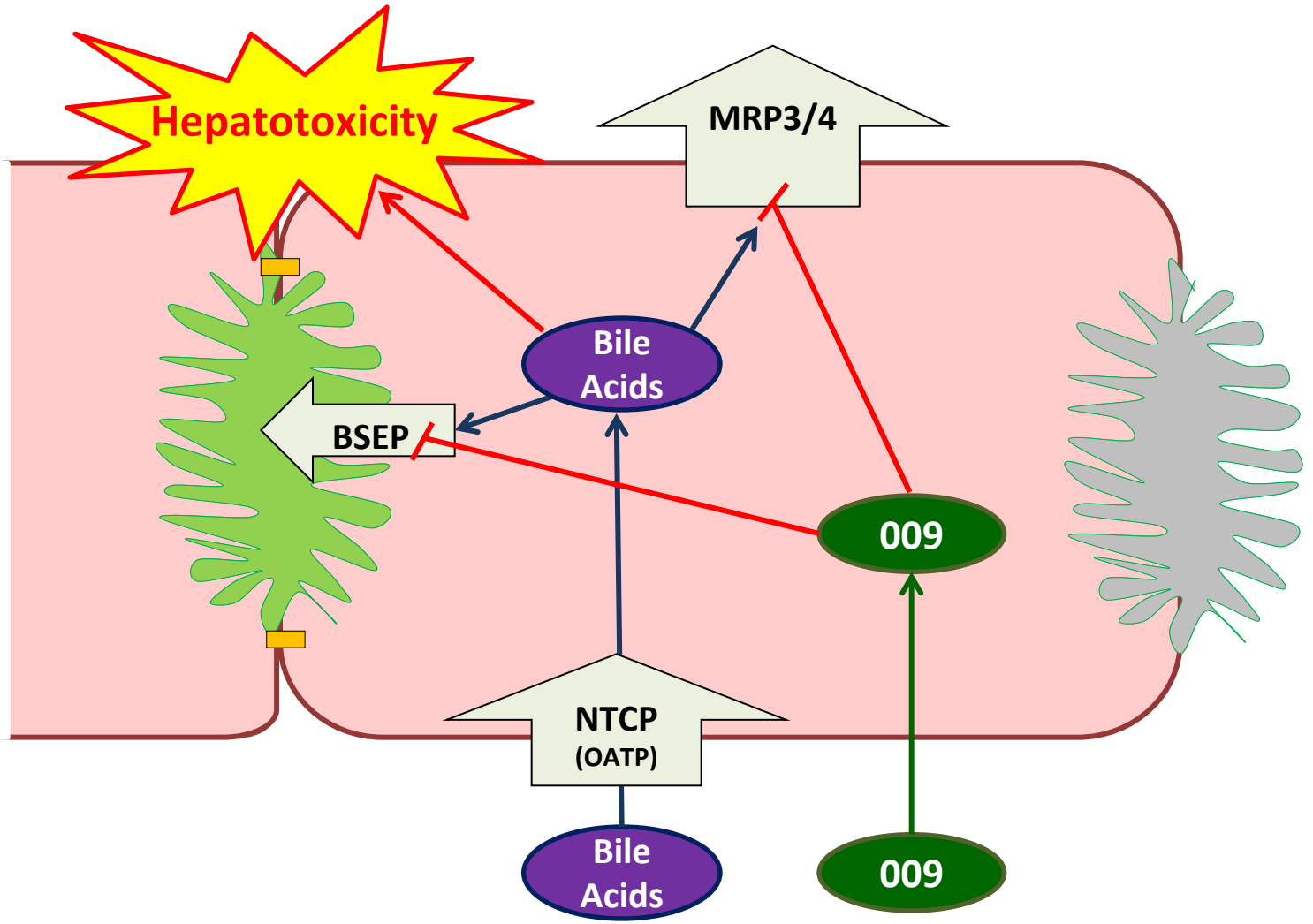
DILSYM Modeling of AMG 853

- DILIsym predicted that AMG 853 was safe in simulated humans (SimPops™)

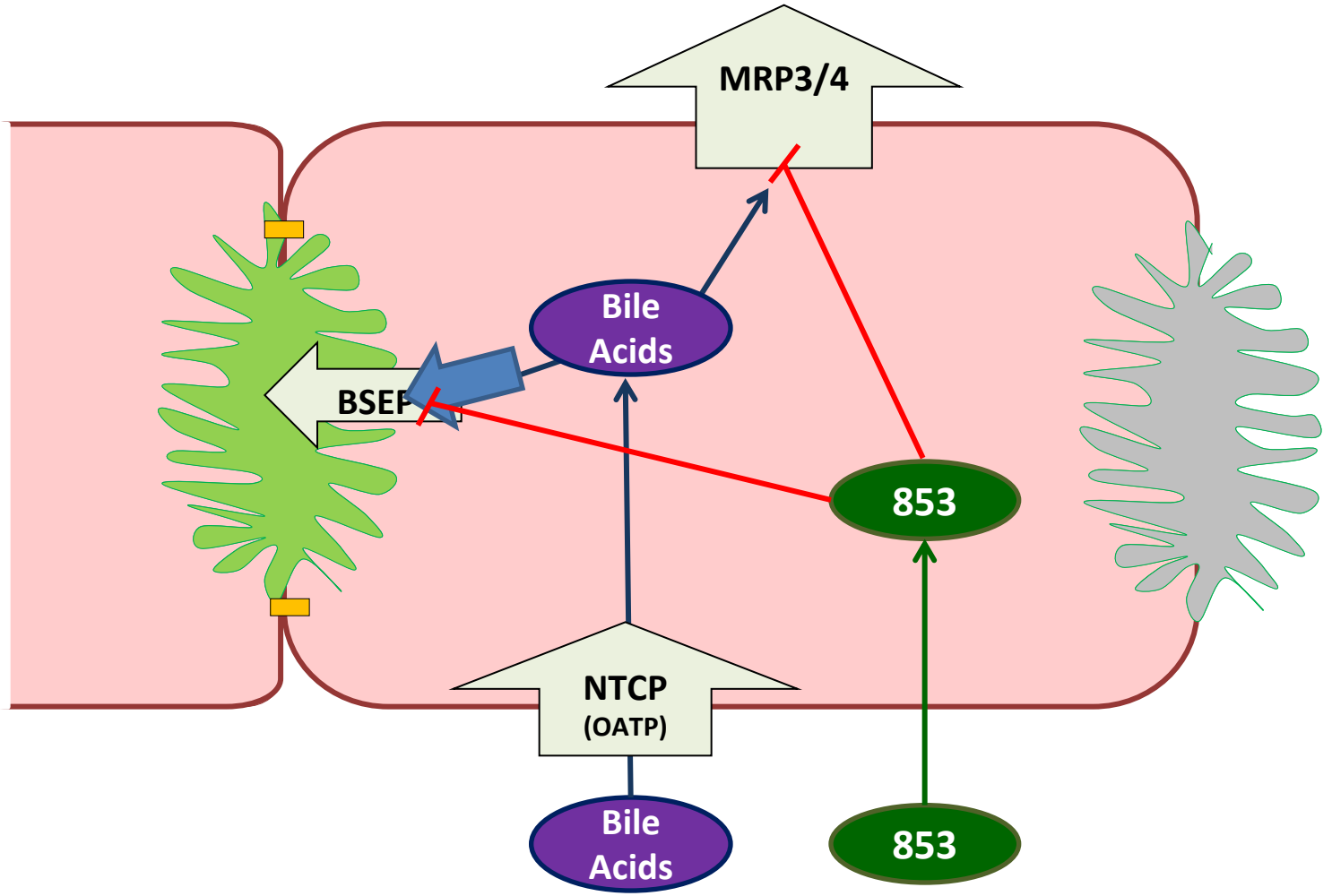
- Exposure to AMG 853 is lower compared to AMG 009 at comparable doses; however, higher doses were simulated in DILIsym up to 50X the clinical dose and AMG 853 remained safe

Why? - Inhibition type was the key

Why mechanism of transport inhibition matters



Why mechanism of transport inhibition matters



Conclusion

QST modeling was able to predict species differences in hepatoxic potential of AMG 009 and the safety of AMG 853 in man based on in vitro assessments of bile acid transporter inhibition

…. *Despite the fact that the BSEP IC50 (and Ki) were lower for 853 than 009*

TOXICOLOGICAL SCIENCES, 166(1), 2018, 123–130

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]

"DILIsym predicted that single doses of CKA caused serum ALT>3 X ULN in a subset of the simulated rat population, while single doses in a simulated Human population did not produce serum ALT elevations. Species differences were largely attributed to differences in liver exposure, **but increased sensitivity to Inhibition of mitochondrial respiration in the rat also contributed**".

OXFORD

SOT | Society of Toxicology

www.toxsci.oxfordjournals.org

TOXICOLOGICAL SCIENCES, 162(2), 499–508
2018

Advance Access Publication Date: December 20, 2017
Research Article

Measures of BSEP Inhibition *In Vitro* Are Not Useful Predictors of DILI

Rosa Chan and Leslie Z. Benet[1]

Department of Bioengineering and Therapeutic Sciences, Schools of Pharmacy and Medicine, University of California, San Francisco, California

[1]To whom correspondence should be addressed at Department of Bioengineering and Therapeutic Sciences, Schools of Pharmacy and Medicine, University of California, 533 Parnassus Avenue, Room U-68, San Francisco, CA 94143-0912. Fax: (415) 476-8887. E-mail: leslie.benet@ucsf.edu.

Comments from Will Proctor, Ph.D, Genentech Feb 25, 2018

We are targeting harder proteins such as GPCRs, ion channels, and previously "undruggable" targets by targeting them for degradation or affecting protein/protein interactions….. These (NMEs) are all typically BDDCS class 2 molecules, with high permeability, relatively low solubility, and high metabolism. They also have a high chance of hitting BSEP and other bile-acid transporters, affect mitochondrial respiration, and by metabolism alone higher chance of forming reactive metabolites. ...sometimes potency tracks with certain phys chem properties that build in higher risk….

…BSEP screening enabled us to progress and characterize the risk without killing molecules thoughtlessly. We could do the same for BDDCS class 2 molecules, assume there is higher DILI risk, however it doesn't give us something to inform on mechanism(s), a counter screen to use for back-up molecules, or help with monitoring strategies

Compound Y

1) Initially developed for one indication but Hy's Law Cases were observed in the first in man clinical trial resulting in termination of the program.

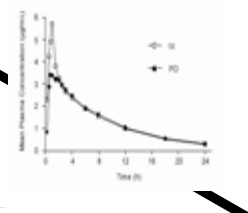
2). Discovered to have a very potent interaction with another disease target.

Question: Could lower dosing for this new disease indication be safe?

DILIsym Input Data

Exposure

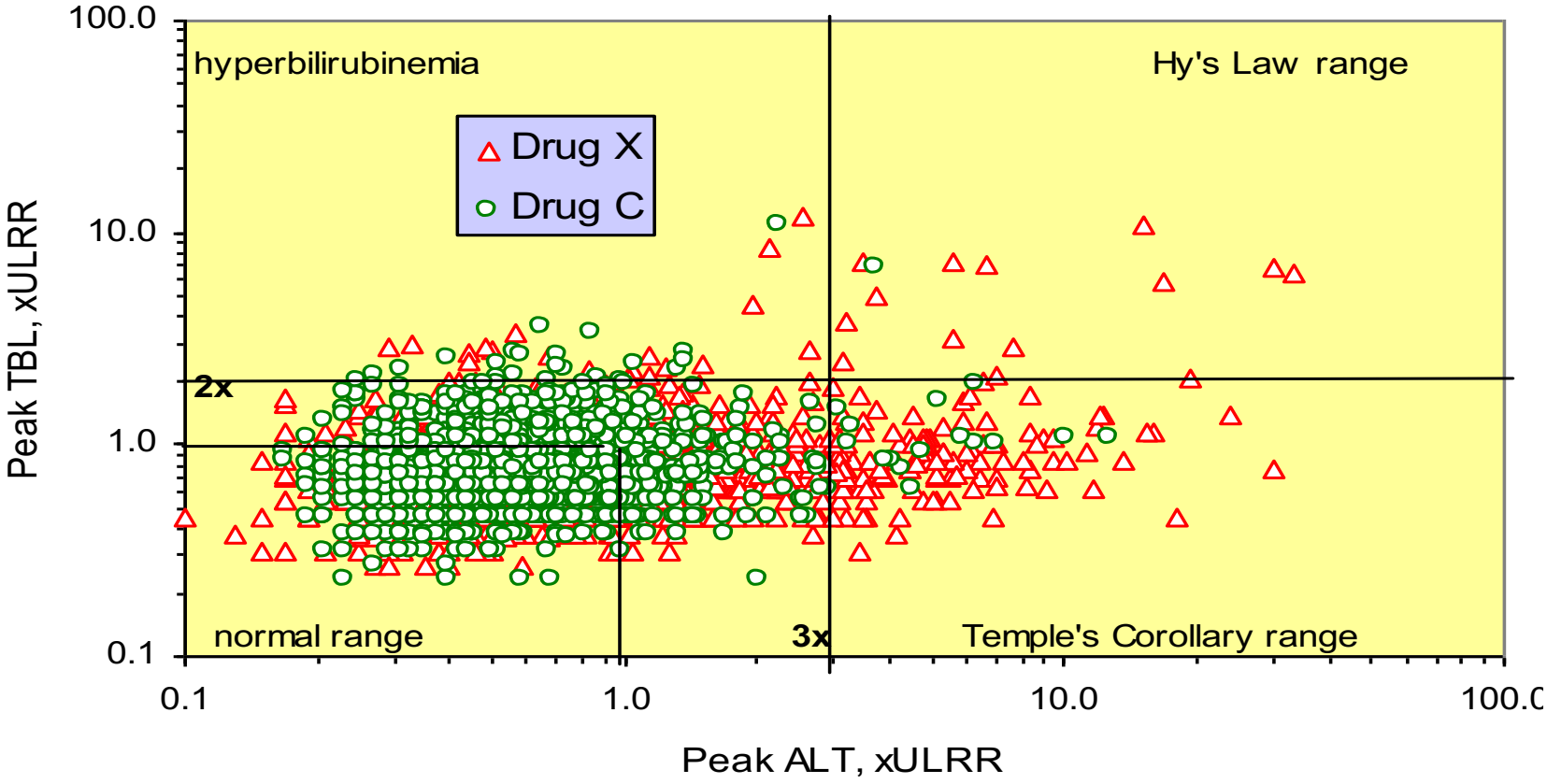
Pharmacokinetics



DILIsym®

Simulated Frequency & Severity of Liver Injury (ALT)

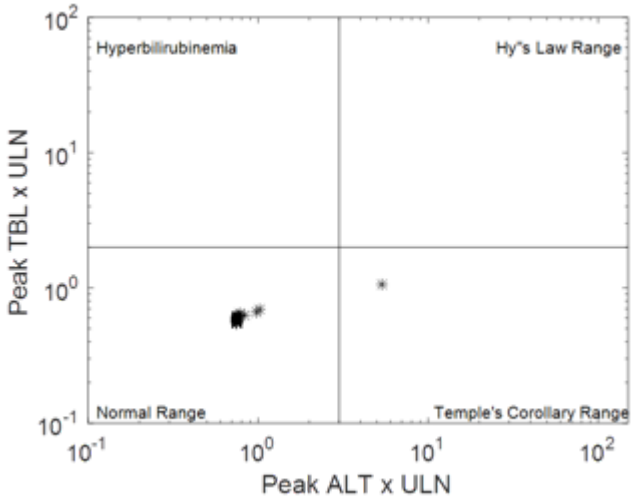
eDISH format for display of clinical trial liver safety data



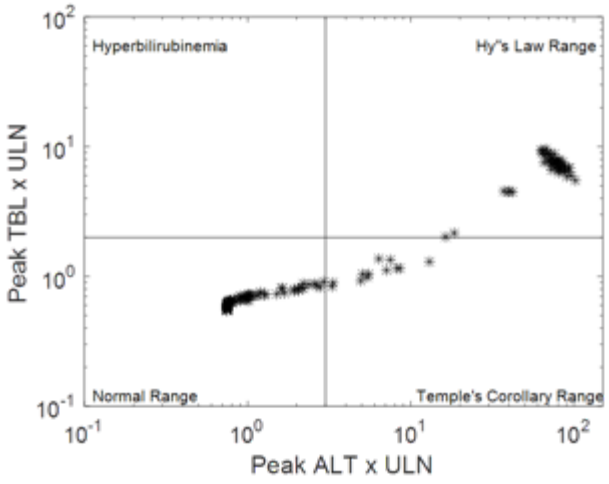
Ted Guo and John Senior

Hepatotoxicity Predicted for Prior Clinical Protocols

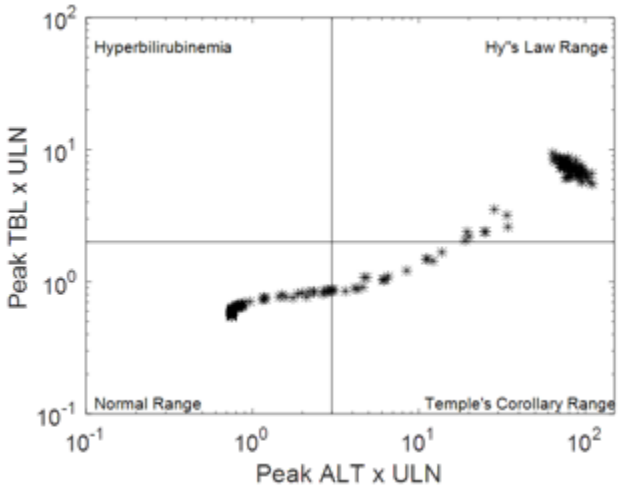
0.3X Compound Y Dosing



0.5X Compound Y Dosing



1X Compound Y Dosing

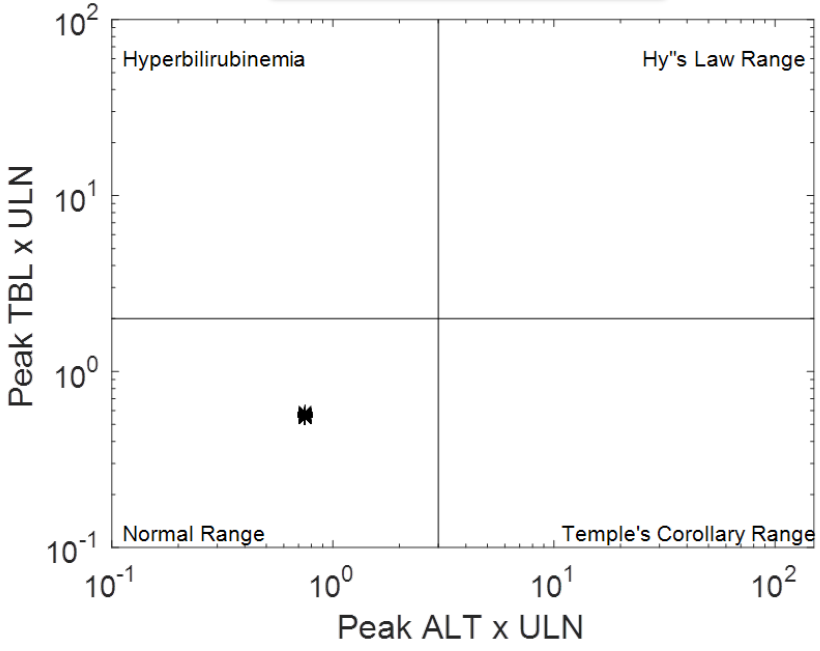


No clinical stop protocol

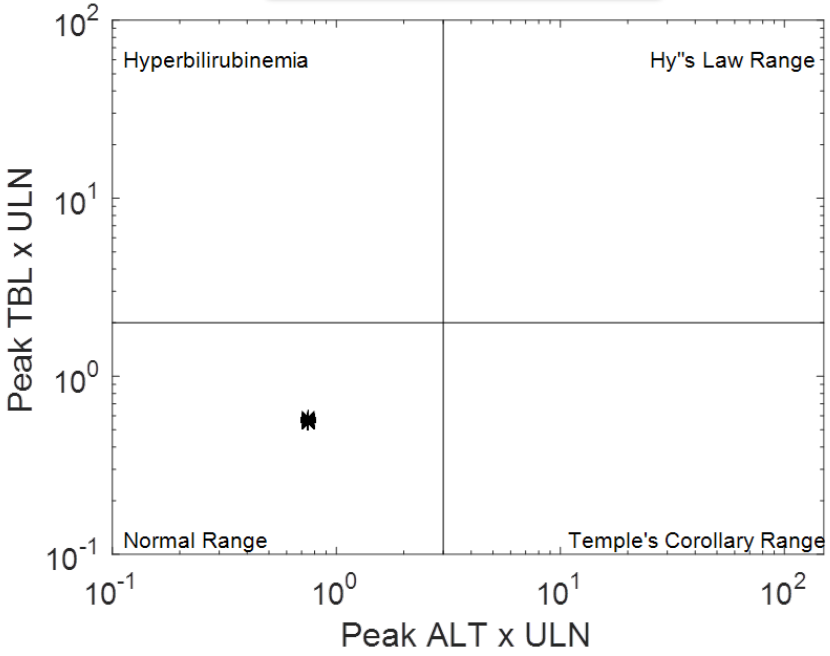
Simulation Results

No Hepatotoxicity Predicted for The Proposed Clinical Protocols

0.07X/0.03X Compound Y Dosing



0.13X/0.07 Compound Y Dosing



No clinical stop protocol

Presented at face to face meeting with FDA division

Conclusion

At the lower dosing regimens proposed, compound Y may have an acceptable liver safety profile for the new disease indication.

Known DILIsym Applications Submitted to or Intended for Regulatory Agencies

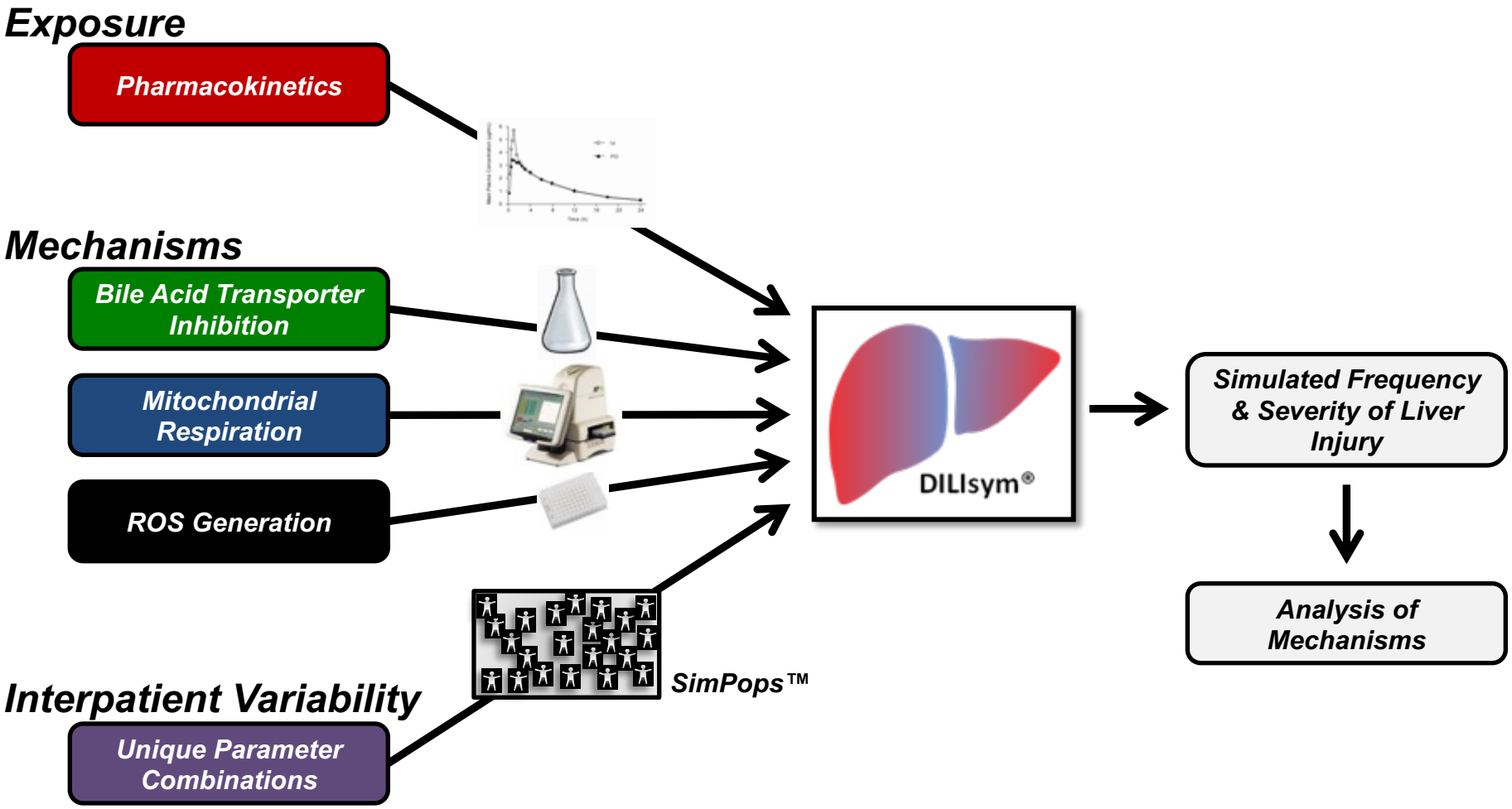
N	Agency	Context	Scenario	Simulation Type	Presented/ Submitted By
1	FDA	Simulation results included in formal, written correspondence to agency	Sponsor responding to concerns over liver safety signals	Hepatocyte loss (biomarker fitting)	Sponsor
2	FDA	Simulation results included in formal, written correspondence to agency	Sponsor responding to concerns over liver safety signals	Hepatocyte loss (biomarker fitting)	Sponsor
3	FDA	Simulation results included in formal, written correspondence to agency and presented during meeting	Sponsor responding to concerns over liver safety signals	Hepatocyte loss (biomarker fitting)	Sponsor and DSS
4	BARDA*	Simulation results presented to sponsor group at BARDA	Sponsor responding to concerns over liver safety signals	Mechanistic liver injury (predictive)	DSS and Sponsor
5	FDA and Japanese FDA	Simulation results included in formal, written correspondence to agency and presented during meeting	Sponsor addressing concerns over liver safety in NDA submission	Mechanistic liver injury (predictive)	Sponsor and DSS
6	FDA	Simulation results included in formal, written correspondence to agency and presented during meeting	Sponsor repurposing compound that failed due to hepatotoxicity in IND submission	Mechanistic liver injury (predictive)	Sponsor and DILIsym Services
7	FDA	Simulation results included in formal, written correspondence to agency and presented during meeting	Sponsor addressing concerns over liver signals from other drug in same class with same indication	Mechanistic liver injury (predictive)	Sponsor
8	FDA	Simulation results included in formal, written correspondence to agency	Sponsor addressing concerns over liver safety in NDA submission	Mechanistic liver injury (predictive)	Sponsor
9	FDA	Simulation results included in formal, written correspondence to agency and discussed during call with FDA	Sponsor responding to concerns over liver safety signals	Hepatocyte loss (biomarker fitting)	Sponsor
10	FDA and global regulators	Sponsor intended to submit simulation results	Sponsor addressing concerns over liver safety signals	Hepatocyte loss (biomarker fitting) Mechanistic liver injury (predictive)	Sponsor
11	FDA	Sponsor intended to submit simulation results	Sponsor addressing concerns over liver signals from other drug in same class with same indication	Mechanistic liver injury (predictive)	Sponsor
12	FDA	Sponsor intended to submit simulation results	Sponsor reformulating existing compound on the market	Mechanistic liver injury (predictive)	Sponsor
13	FDA	Sponsor intended to submit simulation results and present at meeting	Sponsor addressing concerns over liver safety signals	Mechanistic bilirubin (predictive)	Sponsor

*Not a direct regulatory agency, but affiliated closely with NIH and FDA

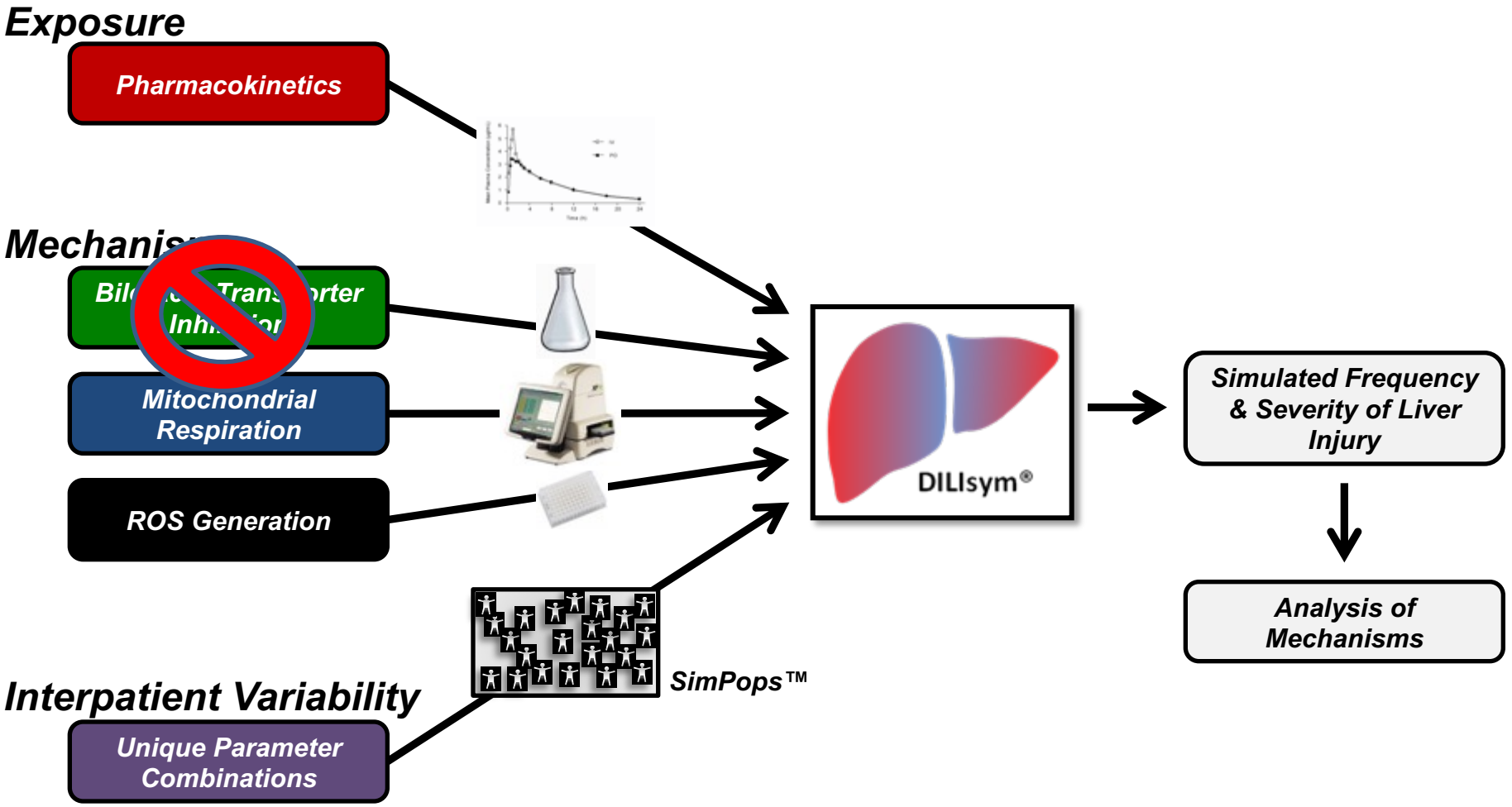
**Several additional sponsors have declared intent to include results in regulatory communications in the future

***Additional drug development teams have implied that regulators have informally requested or recommended DILIsym simulations

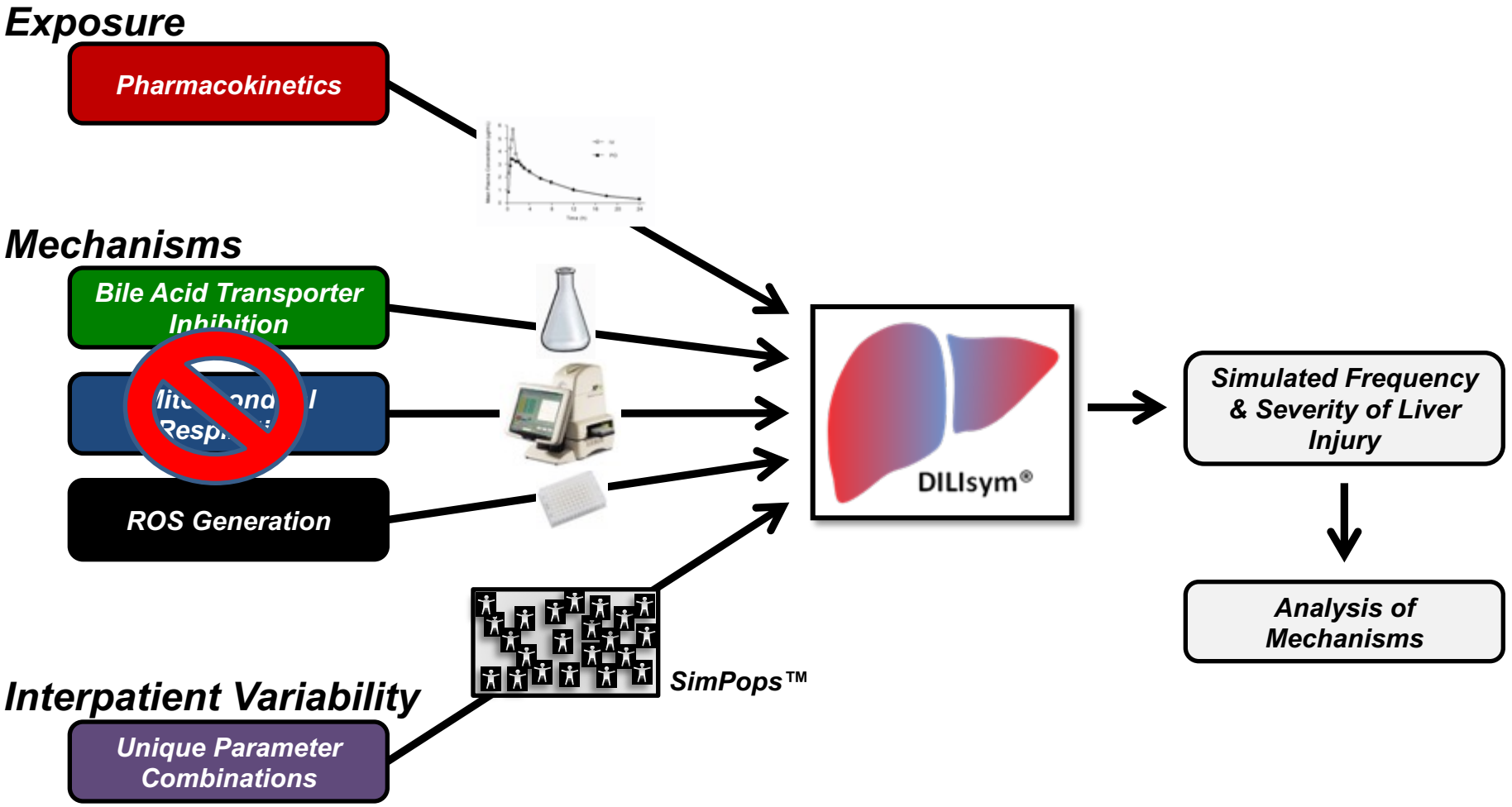
DILIsym Integrates Multiple Inputs to Simulate/Predict Hepatotoxicity



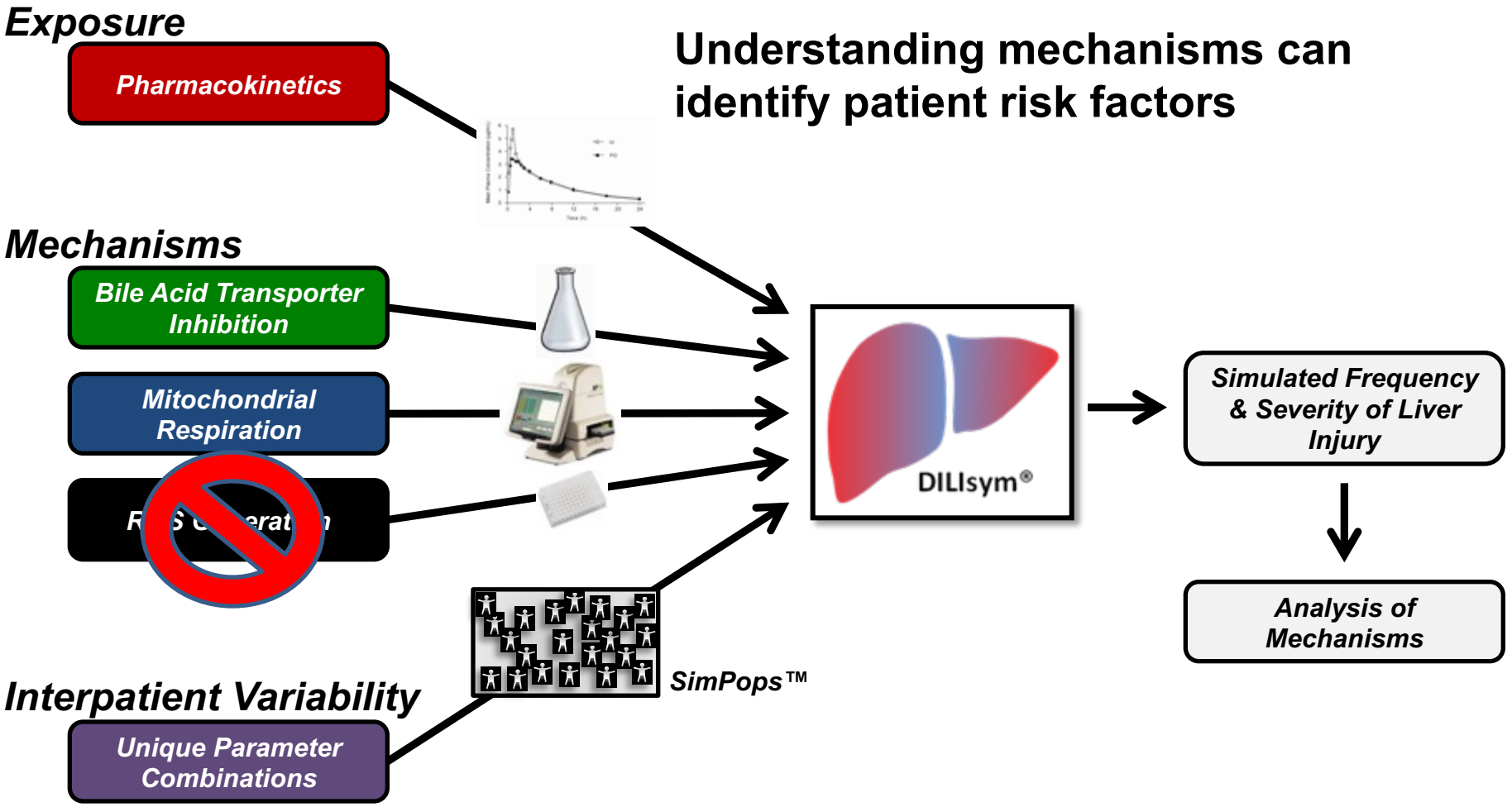
DILIsym Integrates Multiple Inputs to Simulate/Predict Hepatotoxicity



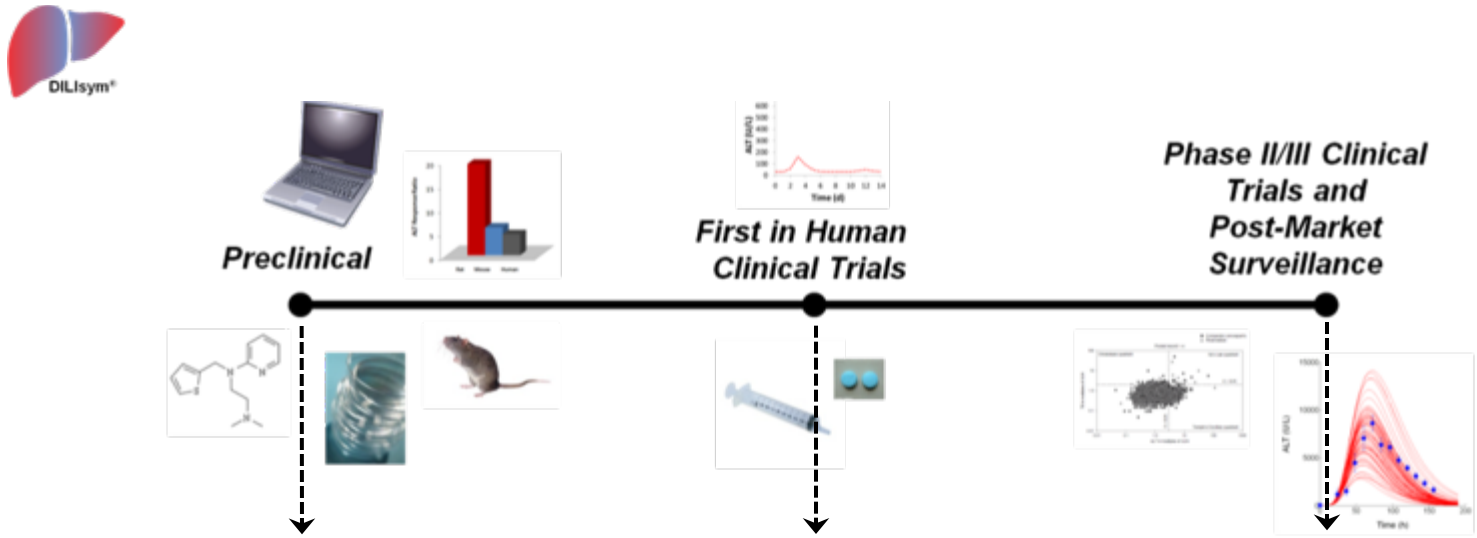
DILIsym Integrates Multiple Inputs to Simulate/Predict Hepatotoxicity



DILIsym Integrates Multiple Inputs to Simulate/Predict Hepatotoxicity

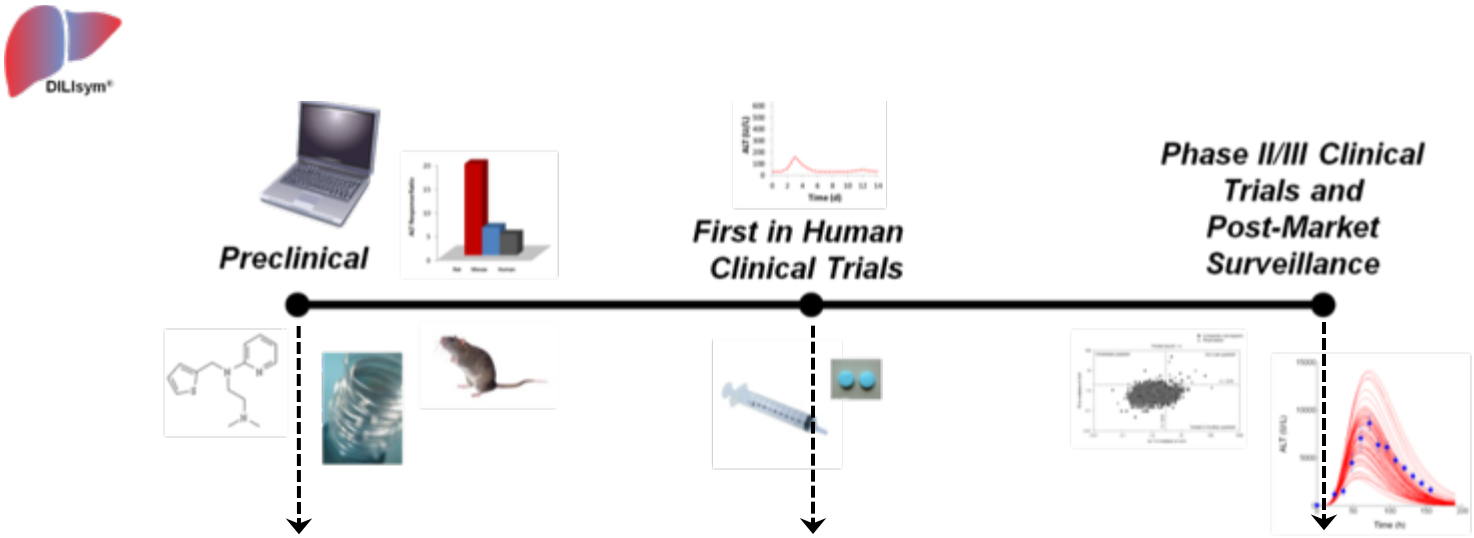


Applications of DILIsym Along the Drug Development Pipeline



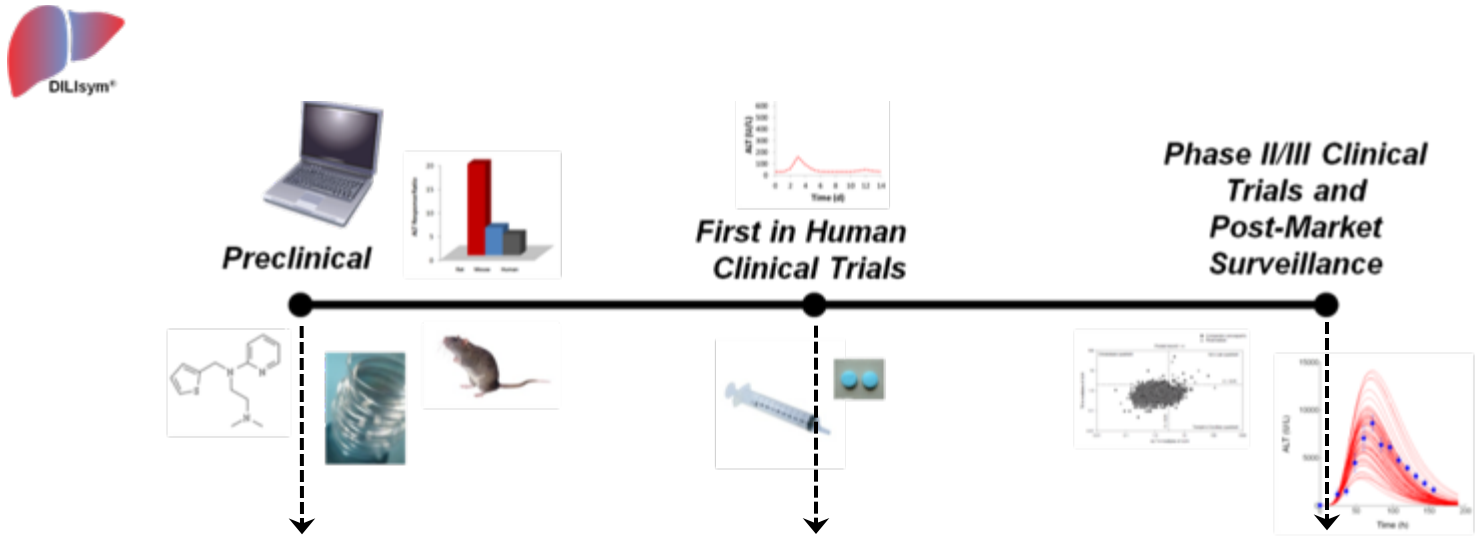
	• Dose optimization (risk versus presumed benefit) • Infer magnitude of injury based on measured biomarkers • Extrapolation from healthy volunteers to patient groups • Guide incorporation of emerging biomarker measurements in clinical trials	

Applications of DILIsym Along the Drug Development Pipeline



	• Dose optimization (risk versus presumed benefit) • Infer magnitude of injury based on measured biomarkers • Extrapolation from healthy volunteers to patient groups • Guide incorporation of emerging biomarker measurements in clinical trials	• Aid identification of risk factors leading to personalized medicine approaches

Some Applications of DILIsym Along the Drug Development Pipeline



• Rank candidates for DILI potential • Extrapolation from animal and *in vitro* findings to humans	• Dose optimization (risk versus presumed benefit) • Infer magnitude of injury based on measured biomarkers • Extrapolation from healthy volunteers to patient groups • Guide incorporation of emerging biomarker measurements in clinical trials	• Aid identification of risk factors leading to personalized medicine approaches

How to access DILIsym

Academia: Low cost licenses available

Industry: 1). Join DILI-sim Initiative

2). Licensing options

For more information, google “DILIsym” or contact Brett Howell at bhowell@dilisym.com

New Renasym Consortium

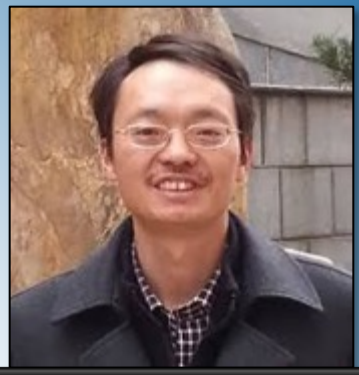
1). $1.7 M Phase1/2 SBIR awarded.

2). Merck is first to join and will share data on species differences in kidney toxicity of NMEs including newer urine biomarker data.

Experts Who Have Agreed to Serve on the RENAsym Scientific Advisory Board

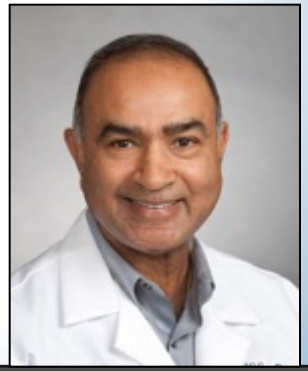
Dr. Paul B. Watkins
Director, Institute for Drug Safety Sciences
Howard Q. Ferguson Distinguished Professor Of Medicine
UNC Eshelman School of Pharmacy

Dr. K. Melissa Hallow
Assistant Professor
School of Chemical, Materials, and Biomedical Engineering
University of Georgia



Dr. Zheng Dong
Leon H. Charbonnier Endowed Chair, Regents Professor
Medical College of Georgia
Senior Career Scientist, Director of Research
Charlie Norwood VA Medical Center

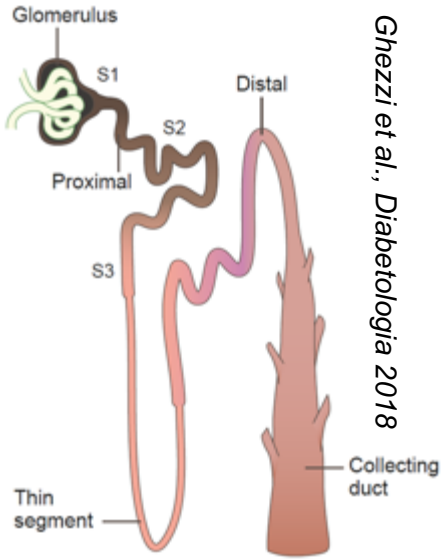
Dr. Lauren Aleksunes
Associate Professor, Graduate Director
Pharmacology and Toxicology
Rutgers University



Dr. Ravinder L. Mehta
Professor of Medicine in the Division of Nephrology and
Associate Chair for Clinical Affairs
Department of Medicine
University of California, San Diego (UCSD)

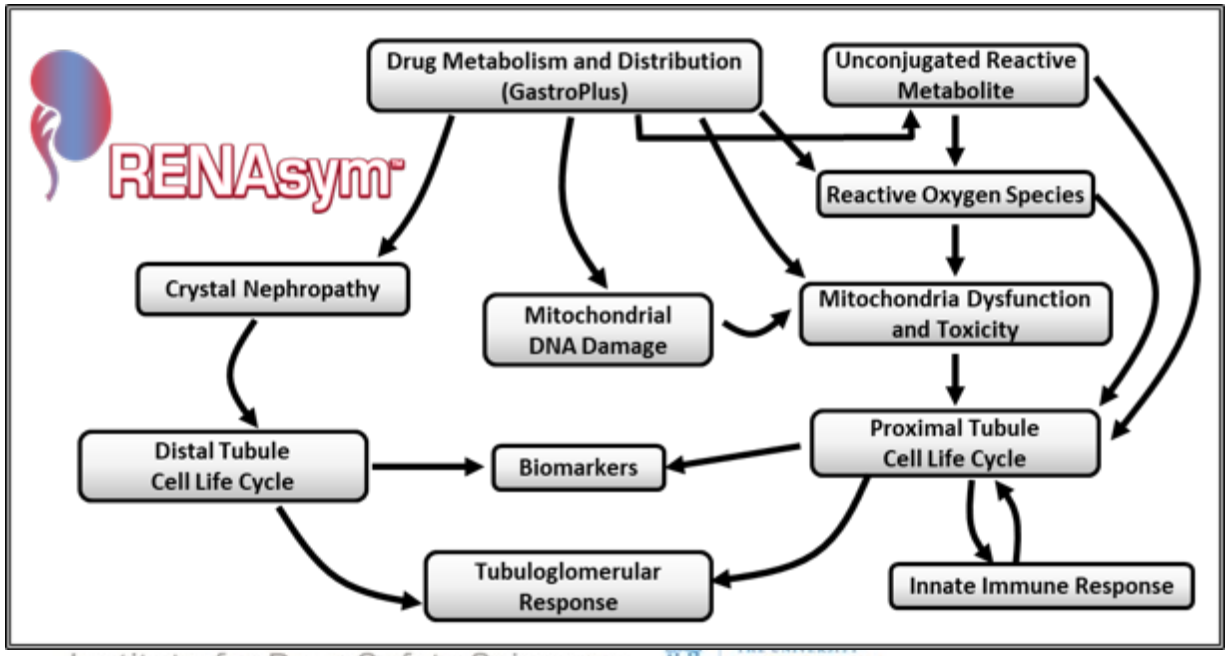
RENAsym Version 1A Preview

- **Species: human and rat**
  - Population variability
- **The three primary zones of the renal proximal tubule represented**
- **Some of the key cellular processes represented in multiple-scale, interacting sub-models**
  - GSH depletion
  - Injury progression
  - Mitochondrial dysfunction, toxicity, DNA depletion
  - Cellular energy balance
  - Crystal nephropathy
  - PTC and DTC apoptosis and necrosis, and proliferation
  - Immune cells contribution
  - Immune mediators
  - Caloric intake
  - Biomarkers of cell death and function
  - Renal function (tubuloglomerular response)



Ghezzi et al., Diabetologia 2018

- **Starting with well known kidney toxicants plus negative controls, such as cisplatin, gentamycin, and APAP**
- **Single and combination drug therapies to be examined**



Outline of Talk

1). Problem of liver safety

2). Current process to assess the safety of new drug candidates

3). Progress in QST modeling – DILIsym ®

4). Conclusions

Conclusions

- **QST modeling is having a significant impact on decision making in drug development.**

- **Its application should lead to reductions in improved safety of new drugs, smaller and smaller clinical trials, and reduction in animal testing.**

How FDA Plans to Help Consumers Capitalize on Advances in Science

Posted on July 7, 2017 by FDA Voice

By: Scott Gottlieb, M.D

New FDA Commissioner

"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."**

How FDA Plans to Help Consumers Capitalize on Advances in Science

Posted on July 7, 2017 by FDA Voice

By: Scott Gottlieb, M.D

New FDA Commissioner

"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."**

"We'll be putting out additional, updated guidances on how aspects of these in silico tools can be advanced and incorporated into different aspects of drug development."

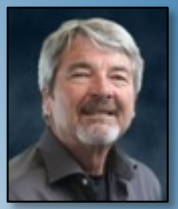
The DILIsym Services Team

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

Scott Q Siler
Chief Scientific Officer
Bay Area, CA

Brett Howell
President
RTP, NC

Shawn O'Connor
CEO, Simulations Plus Inc.
Lancaster, CA



DILIsym Services
A SIMULATIONS PLUS COMPANY

Grant Generaux
Scientist II
Philadelphia, PA

Jeff Woodhead
Scientist II
RTP, NC

Lisl Shoda
Principal Scientist
Director of Immunology
Bay Area, CA

Kyunghee Yang
Scientist II
Middleton, DE

Vinal Lakhani
Scientist I
RTP, NC

Corey Berry
Senior Software
Engineer
RTP, NC

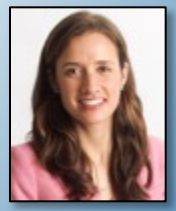
Bud Nelson
Director of Operations
RTP, NC

Patti Steele
Executive Assistant
RTP, NC

Christina Battista
Scientist I
Buffalo, NY

Zack Kenz
Scientist I
RTP, NC

Diane Longo
Scientist II
Arlington, VA



Yeshi Gebremichael
Scientist II
RTP, NC

Nader Hamzavi
Postdoctoral Fellow
RTP, NC

Guncha Taneja
Postdoctoral Fellow
RTP, NC

Shailendra Tallapaka
Postdoctoral Fellow
RTP, NC