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Assessing Effects of Sublingual BHV-0223 and Oral Riluzole on Liver Function Test Parameters

March 13, 2019

Brett A. Howell, Ph.D., President, DILIsym Services Inc., a Simulations Plus Company

Society of Toxicology 2019 Annual Meeting

Conflict of Interest Statement

- *Brett A. Howell is an employee of DILIsym Services Inc., the producer of DILIsym software*

- *Brett A. Howell receives financial benefit from DILIsym software sales and consulting use*

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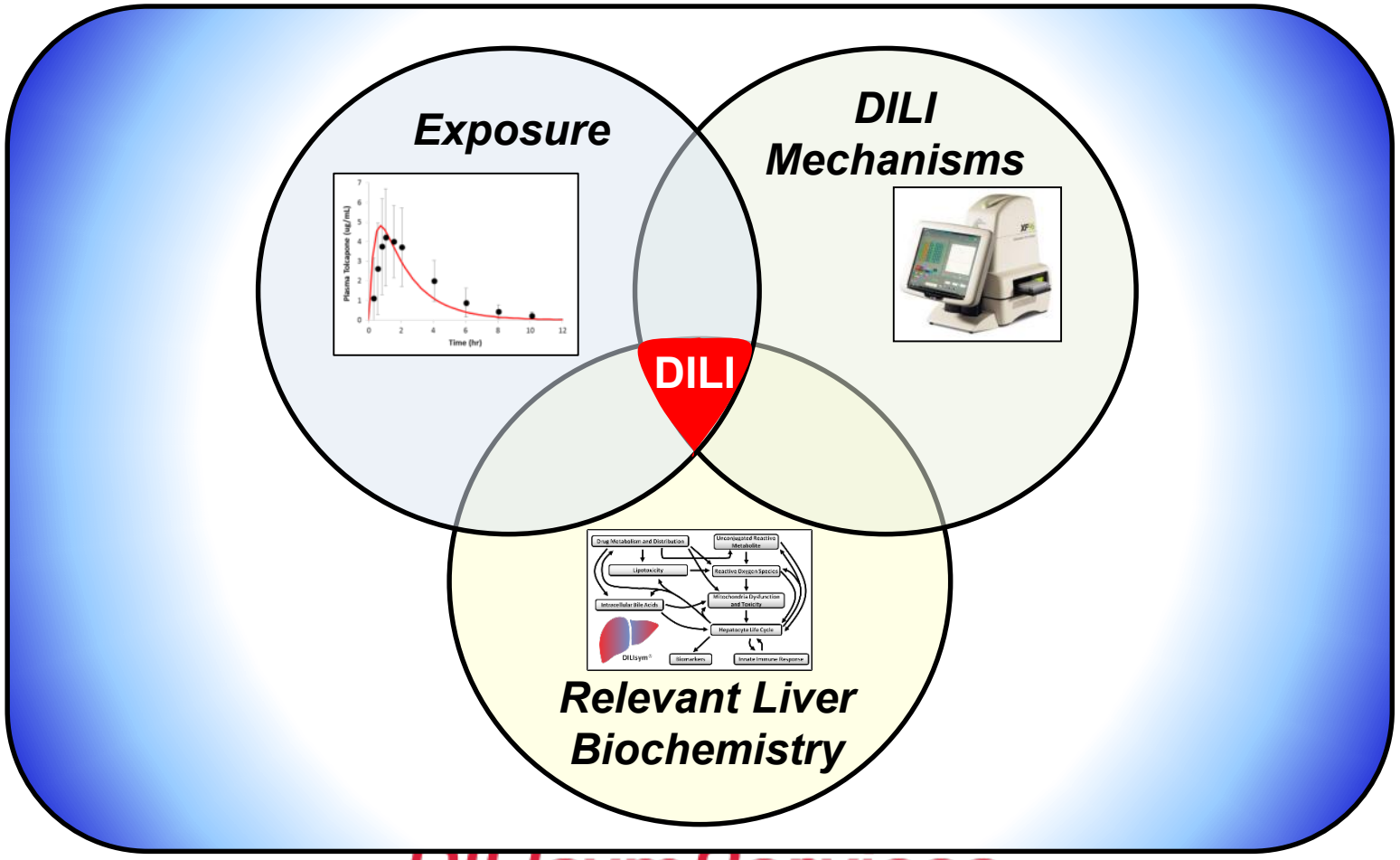
Summary of Presentation

- DILIsym is a mechanistic, mathematical model that has been constructed to support pharmaceutical risk assessment and decision making
  - Intersection of compound distribution and metabolism (PBPK), hepatotoxicity mechanisms, and patient variability
- DILIsym has been applied to support decisions related to compound DILI risk throughout the drug development pipeline
- DILIsym was used to compare the possible liver safety effects of two different formulations of riluzole, used to slow the progression of ALS

DILIsym Predicts DILI via the Intersection Between Exposure, Mechanisms, and Inter-Patient Variability



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

Scientific Advisory Board

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janssen

gsk GlaxoSmithKline

GILEAD

DILIsym

Mitsubishi Tanabe Pharma

Bristol-Myers Squibb

Sumitomo Dainippon Pharma

abbvie

Select Sample of Current Companies Licensing DILIsym

- *Overall Goals*
  - *Improve patient safety*
  - *Reduce the need for animal testing*
  - *Reduce the costs and time necessary to develop new drugs*
- *History*
  - *Officially started in 2011*
  - *19 major pharmaceutical companies have participated*
  - *Members have provided compounds, data, and conducted experiments to support effort*
  - *Over $9 million total invested in project*

FDA

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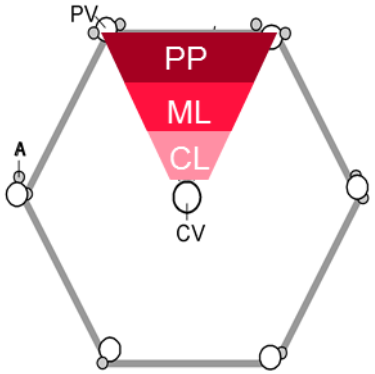
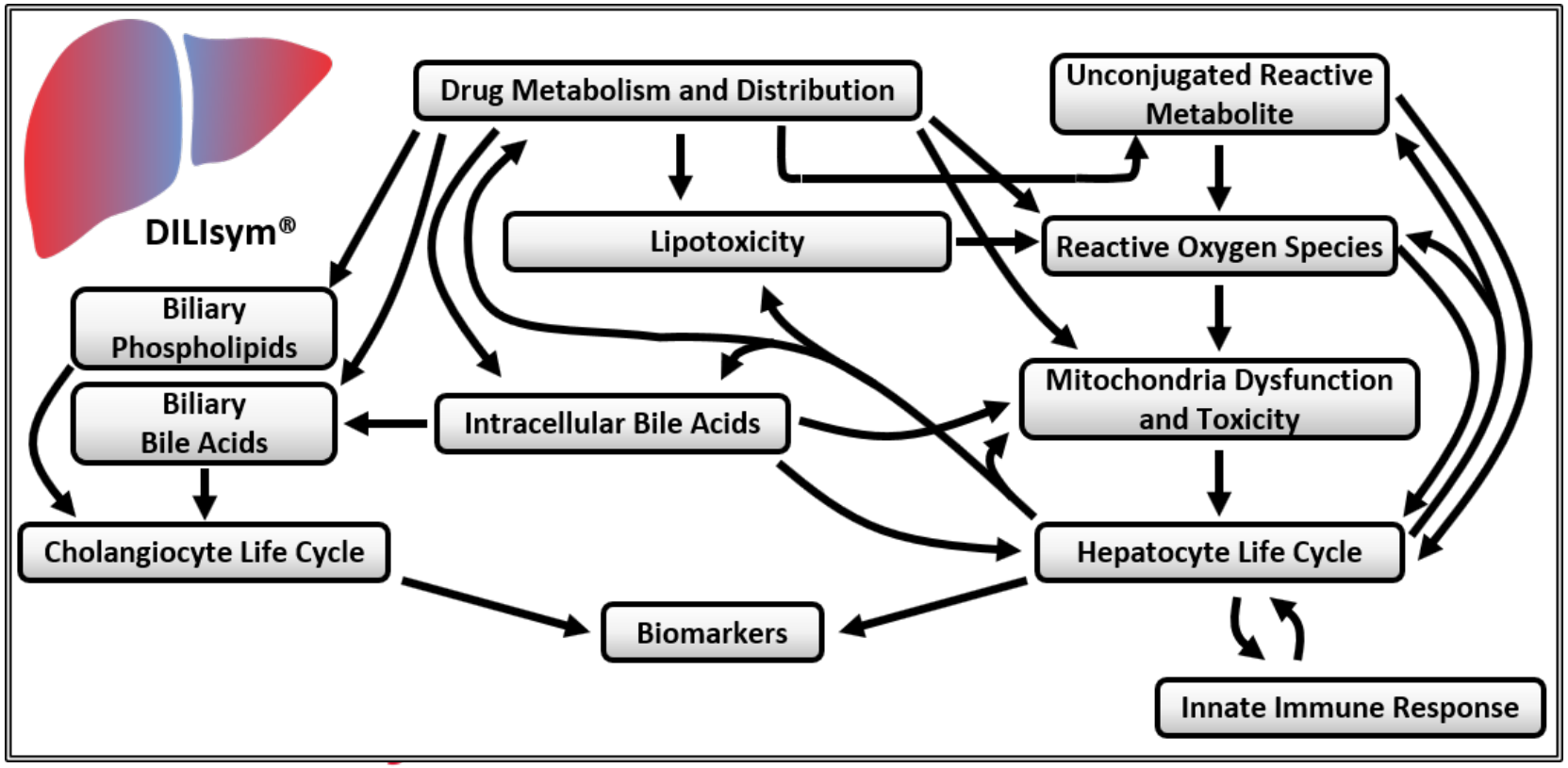
DILIsym Overview

- **Multiple species: human, rat, mouse, and dog**
  - Population variability
- **The three primary acinar zones of liver represented**
- **Essential cellular processes represented to multiple scales in interacting sub-models**
  - Pharmacokinetics
  - Dosing (IP, IV, Oral)
  - Transporter Inhibition
  - Drug metabolism
  - GSH depletion
  - Injury progression
  - Mitochondrial dysfunction, toxicity, DNA depletion
  - Bile acid mediated toxicity
  - Steatosis and lipotoxicity
  - Cellular energy balance
  - Hepatocyte apoptosis and necrosis, and proliferation
  - Cholangiocyte apoptosis and proliferation
  - Macrophage, LSEC life cycles
  - Immune mediators
  - Caloric intake
  - Biomarkers

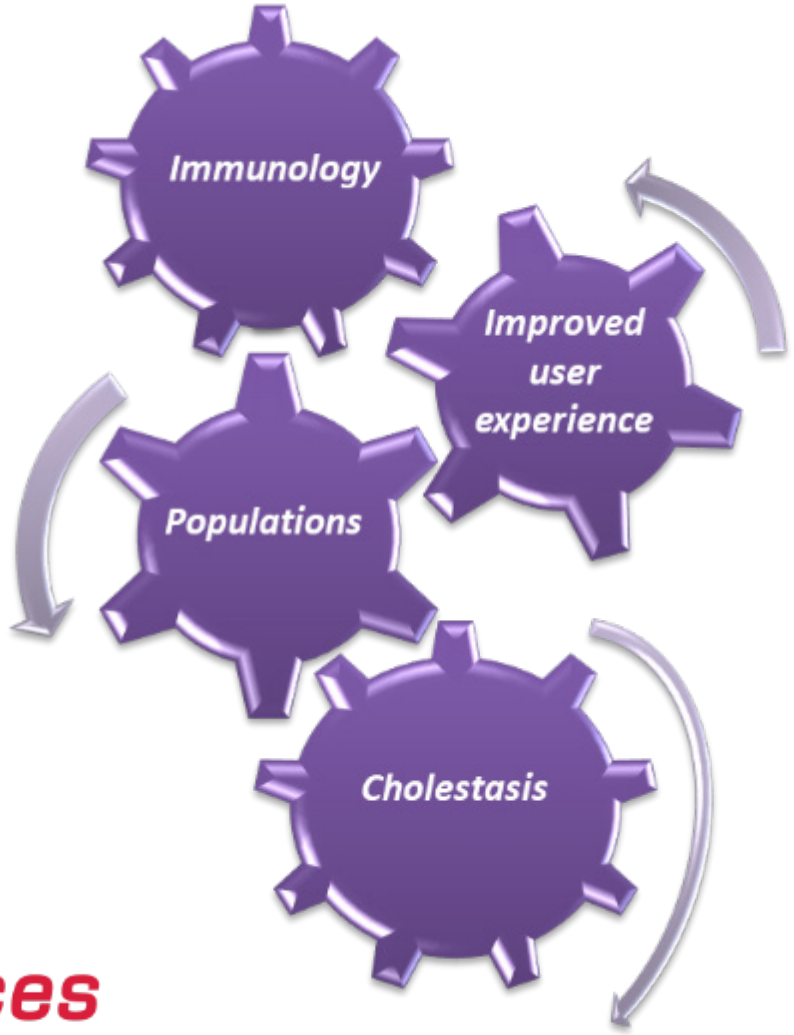


- **Over 60 detailed representations of optimization or validation compounds with 80% success**
- **Single and combination drug therapies**



Immunology, Cholestasis, Population Variability and Enhanced Software Highlight Stage 3 Areas of Focus

- Immunology is a critical area for latent DILI and many oncology related DILI events
- Cholestasis has become increasingly important from a regulatory standpoint
  - Phospholipids and MDR3 an important consideration
- Population variability must include all relevant factors such as disease, environment and genetics
- Improved user friendliness and speed
- Improved *in vitro* data to feed the software



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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 DILIsym Services
4	BARDA*	Simulation results presented to sponsor group at BARDA	Sponsor responding to concerns over liver safety signals	Mechanistic liver injury (predictive)	DILIsym Services and Sponsor
5	FDA and PMDA	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 DILIsym Services
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 and EMA	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 other regulators globally	Sponsor intended to submit simulation results	Sponsor addressing concerns over liver safety signals	Hepatocyte loss (biomarker fitting) and 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
14	FDA	Sponsor intended to submit simulation results	Sponsor addressing concerns over liver safety signals	Mechanistic liver injury (predictive)	Sponsor
15	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
16	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
17	EMA	Sponsor intended to submit simulation results	Sponsor addressing concerns over liver safety signals	Mechanistic liver injury (predictive)	Sponsor
18	FDA	Agency reviewed results publicly available during evaluation	Agency addressing concerns over liver safety signals	Mechanistic liver injury (predictive)	Publicly available materials

*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 Utilizes Various Data Types to Inform Decisions

Exposure Data

PBPK Modeling

- **Compound Properties**
  - Tissue partition coefficients
- **Tissue penetration studies**
  - *Liver to blood ratio*
- **Pharmacokinetic data**
  - *Absorption, extra-hepatic clearance, metabolites*
- ***in vitro* data**
  - *Metabolite synthesis, active uptake*

In vitro Mechanistic DILI Data

Assays performed to determine quantitative aspects of DILI mechanisms

- **Oxidative stress**
  - *Direct and reactive metabolite-mediated*
- **Mitochondrial toxicity**
  - *ETC inhibition*
  - *Uncoupling*
- **Bile acid / phospholipid transporter inhibition**
  - *BSEP, MRP3 and 4, NTCP, (MDR3)*
- **Bilirubin transport/metabolism**
  - *OATP1B1, OATP1B3, UGT1A1, MRP2, MRP3*

DILIsym Modeling & Simulation

Simulations and Assays inform:

- **Prediction of DILI risk**
- **Participating DILI mechanisms**
- **Characteristics of patients at risk for DILI**
- **Drug dosing paradigms**
- **DILI monitoring strategies**

Clinical Data / Information

- **Dosing Protocols, fasting/fed state, meal times**
- **Anthropometric data**
  - **Body weight, age, ethnicity**
- **Pharmacokinetic data**
  - **Absorption, extra-hepatic clearance, metabolites**

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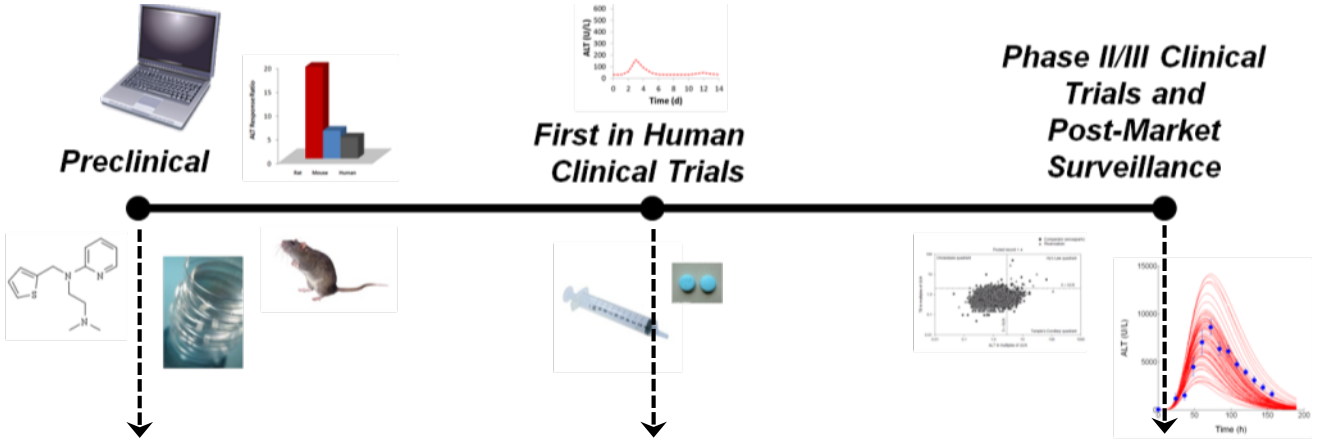
Applications of DILIsym Along the Drug Development Pipeline

Predictions of hepatotoxicity for humans and preclinical animal models



Preclinical	First in Human Clinical Trials	Phase II/III Clinical Trials and Post-Market Surveillance
• Mechanism exploration • Rank candidates for DILI potential • Extrapolation from animal and *in vitro* findings to humans	• Dose optimization • Infer magnitude of injury based on measured biomarkers • Extrapolation from NHV to patients • Guide incorporation of emerging biomarkers • Analysis of mechanisms underlying observed liver signals	• Inform trial design • Precision medicine • Analysis of mechanisms underlying observed liver signals

- Predict DILI liabilities beforehand and avoid patient risk and waste
- Choose the lead candidate ***most likely to succeed*** from a DILI standpoint
- Communicate with regulators on safety issues in an informed and mechanistic way

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ALS Riluzole Project Example Introduction

- Riluzole is used to slow the progression of ALS
  - Approved in 1995
  - Largely taken orally, which is difficult for late-stage disease patients
  - Associated with liver enzyme elevations in portion of patients

- Biohaven Pharma is developing an alternative, sublingual formulation (BHV-0223) with the following goals:
  - Improved delivery, compliance, and general ease-of-use for ALS patients, who often have trouble swallowing
  - ***Improved liver safety profile?***

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Clinical Incidence of ALT Elevations in ALS Patients ~10-15%

- *Bensimon 2004* – Riluzole in ALS patients
  - ALT elevations >3x ULN in 10-15% of patients
  - Elevations are dose-related
  - Median time to onset < 3 months
- No data on ALT elevations in healthy volunteers

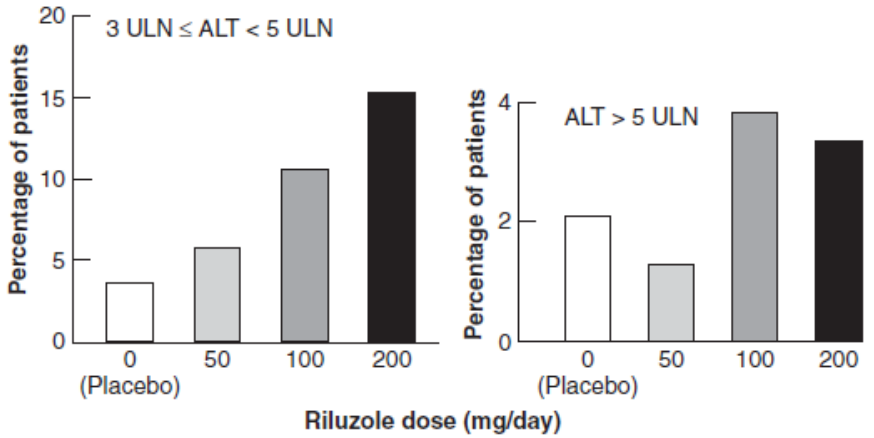

Figure 2. Dose-incidence relationship for transaminase elevations occurring with riluzole. Data are taken from [7].
ALT: Alanine aminotransferase; ULN: Upper limit of normal.

Table 2. Frequency of hepatic enzyme abnormalities in patients receiving riluzole (100 mg/day, 50 mg b.i.d.) or placebo.*

Enzyme		Riluzole (n = 395)	Placebo (n = 406)
ALT	3 – 5 x ULN	35 (9)	12 (3)
	> 5 x ULN	15 (4)	7 (2)
AST	3 – 5 x ULN	18 (5)	3 (1)
	> 5 x ULN	4 (1)	3 (1)

*Data [8,9] are given as numbers of patients % total.
ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; n: Number of patients; ULN: Upper limit of normal.

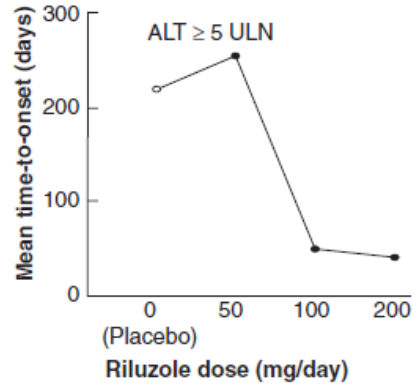

Figure 3. Relationship between riluzole dose and median time to ALT elevations. Data are taken from [16].

Clinical Data and Simulation Results

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Summary of DILIsym Toxicity Parameter Values For Riluzole

Mechanism	DILIsym Parameter	Unit	Value***
Mitochondrial Dysfunction	Coefficient for ETC inhibition	µM	382
Oxidative Stress	RNS/ROS production rate constant	mL/nmol/hr	6×10^{-4}
Bile Acid Transporter Inhibition	BSEP inhibition constant	µM	200*
	NTCP inhibition constant	µM	NA
	Basolateral inhibition constant**	µM	125*

*IC_{50} values; default assumption is mixed inhibition type with α = 5, based on the experience of the DSS team

**Basolateral inhibition constant represents the lowest IC_{50} of the experimentally derived MRP3 and MRP4 IC_{50} values

***Values shown in the table for DILIsym input parameters should not be interpreted in isolation with respect to clinical implications, but rather, should be combined with exposure in DILIsym to produce simulations that have predictive and insightful value

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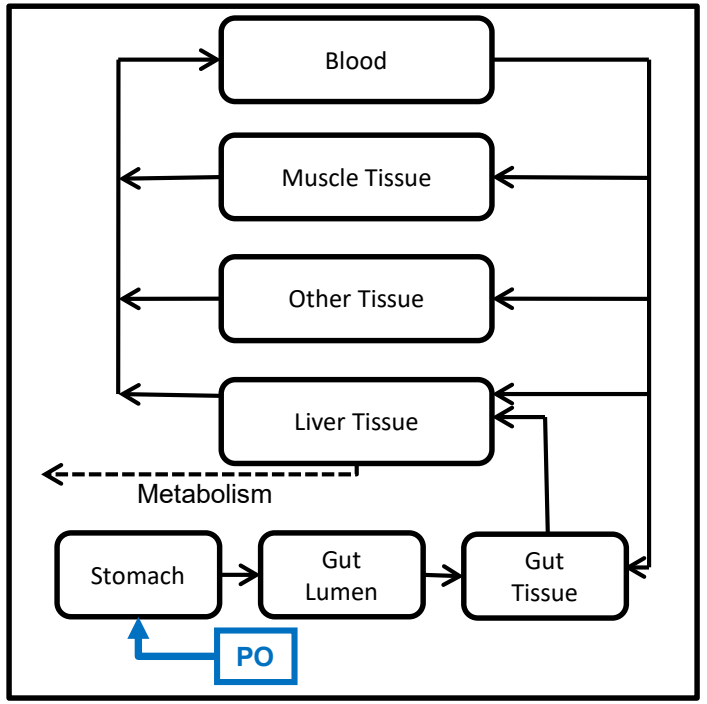
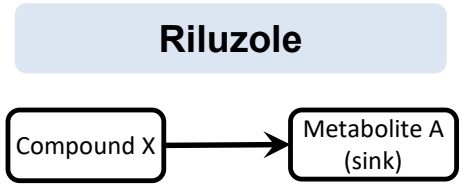
DILIsym PBPK Framework for Oral Riluzole (Rilutek)

- PBPK sub-model in DILIsym was used to represent riluzole disposition
  - Consists of blood, liver, gut, muscle, and other tissue compartments (Compound X scaffold)
- Riluzole metabolism represented by one metabolic pathway
  - Sink pathway (Metabolite A) represents aggregate of all riluzole metabolic pathways
  - Metabolites (Metabolite A) will not contribute to toxicity
- Riluzole is predominantly eliminated via hepatic metabolism
  - Excreted predominantly via urine in form of metabolites
  - Low urinary excretion of unchanged parent





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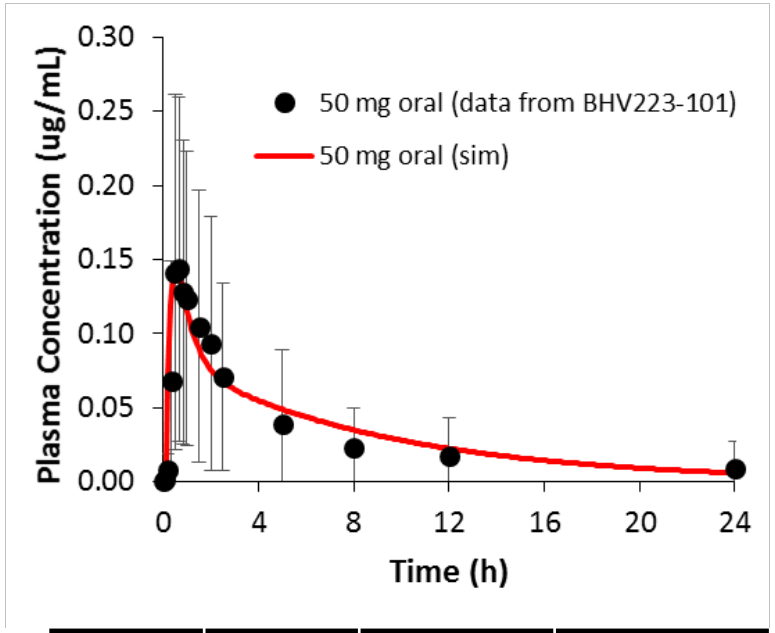
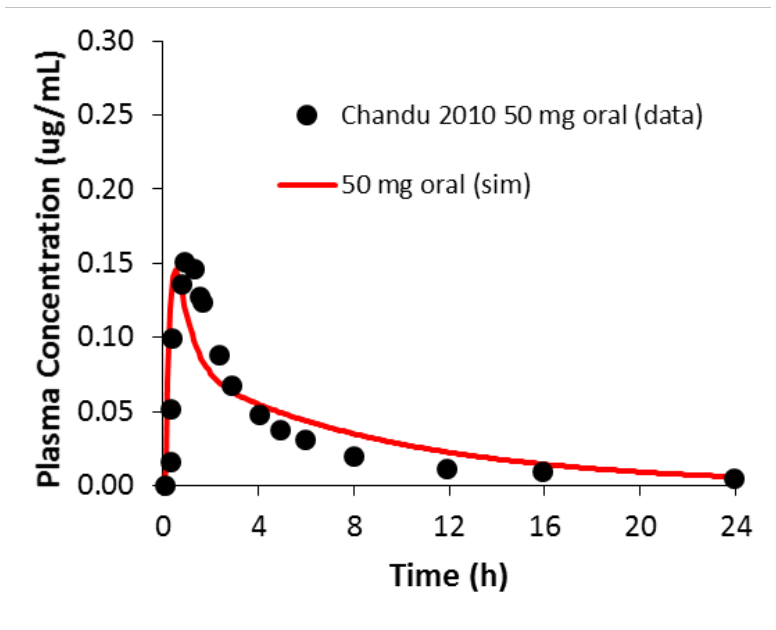
Oral Riluzole PBPK Representation in DILIsym Validated with Clinical PK Data



Dose	Disease Status	Reference	Sim/Obs	
			Cmax	AUC
50 mg oral	Volunteer	BHV223-101	0.9	1.1



Dose	Disease Status	Reference	Sim/Obs	
			Cmax	AUC
50 mg oral	Volunteer	Chandu 2010	1.0	1.2

- Simulations reasonably capture plasma profiles of riluzole that were not used in optimization (pure validation results)

Clinical Data and Simulation Results

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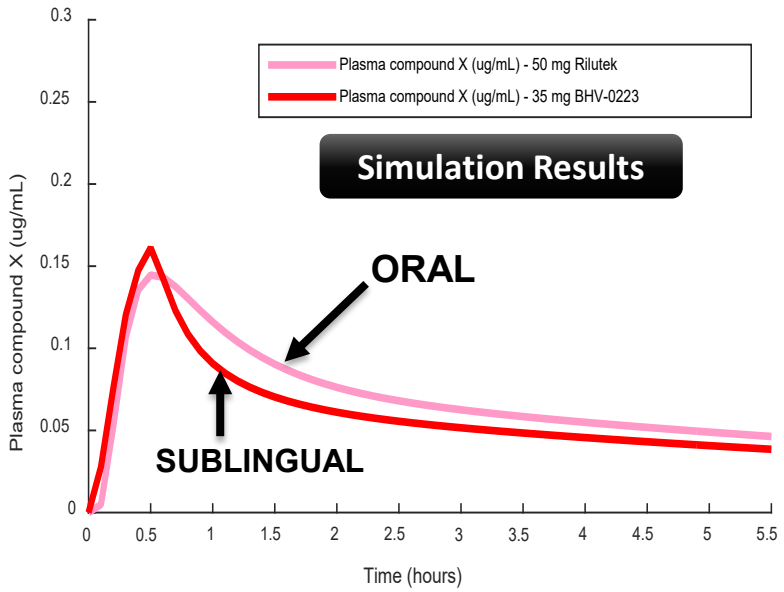
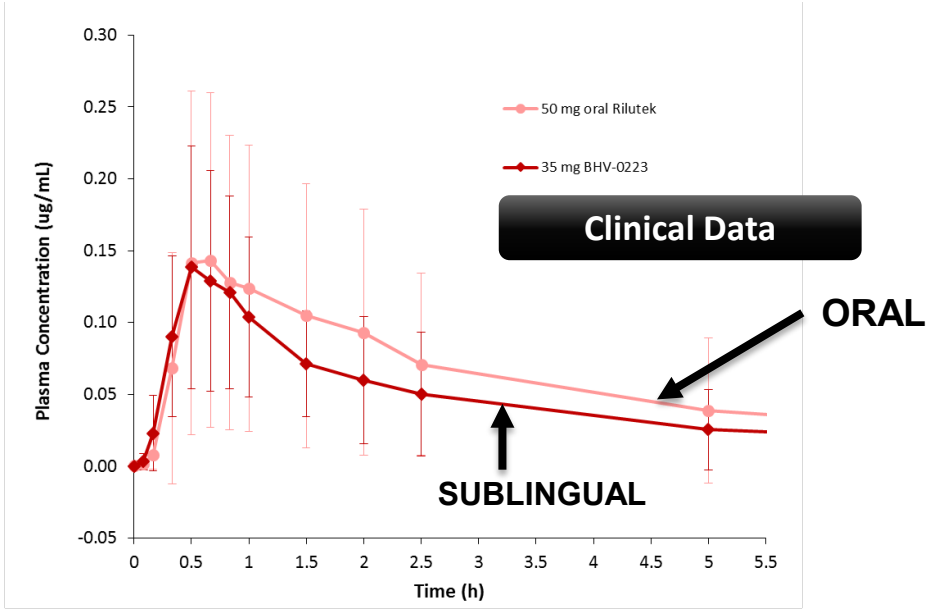
Plasma Profiles Simulated in DILIsym Comparable for 35 mg Sublingual Riluzole (BHV-0223) and 50 mg Oral Riluzole (Rilutek)





- Plasma Cmax and AUC for 35 mg BHV-0223 are comparable to plasma Cmax and AUC for 50 mg Rilutek
- Clearance dynamics also line up well with observed differences

Clinical Data and Simulation Results

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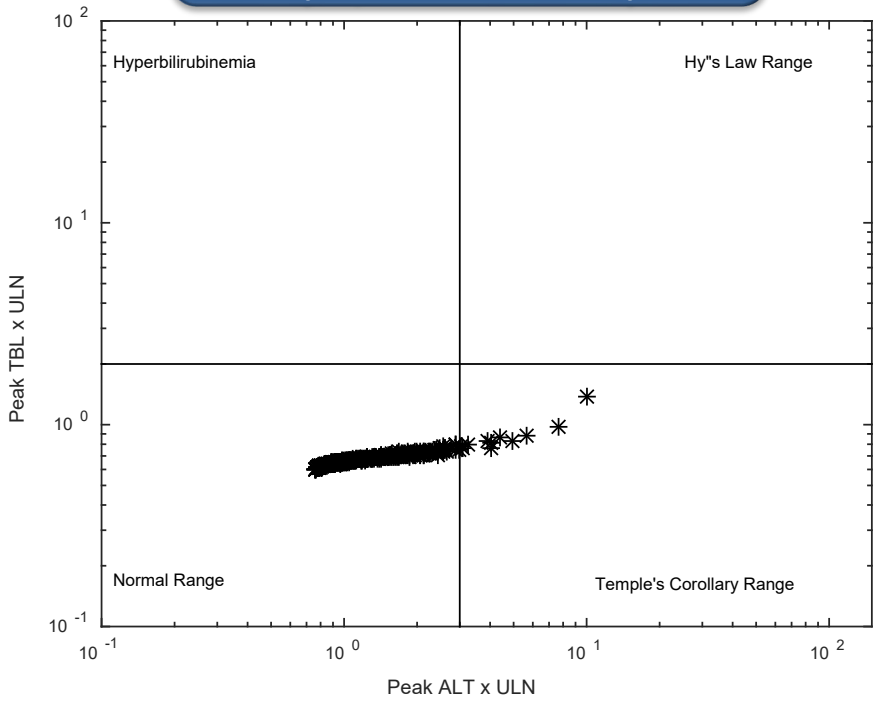
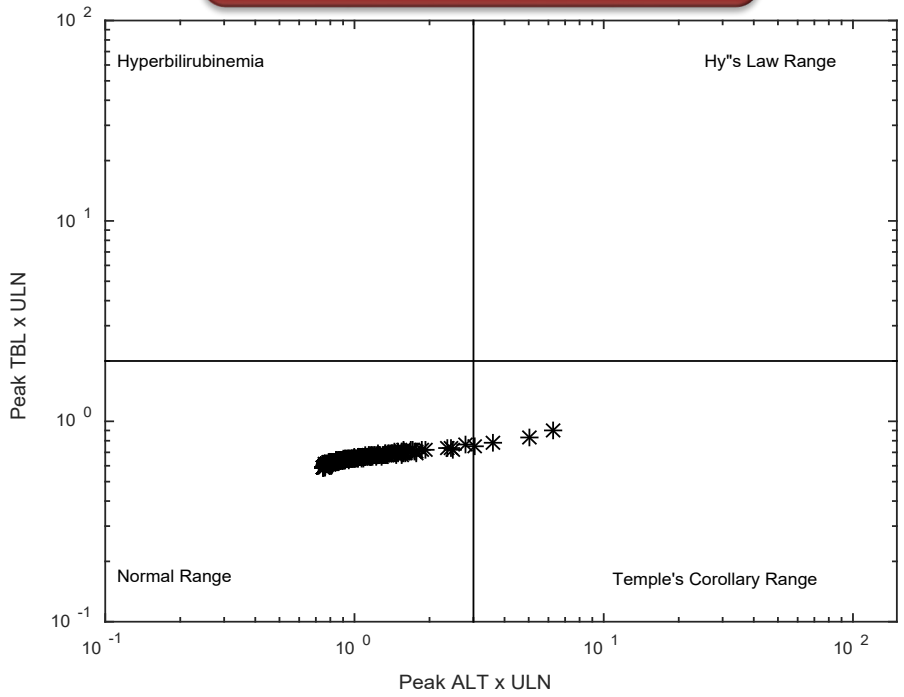
Riluzole Simulations in Normal Healthy Volunteer SimPops Show ALT Elevation Differences Between Oral and Sublingual Dosing with Certain Assumptions

Simulated eDISH Plots

Oral 50 mg BID 12 weeks
High PK, Liver Kb 10
(11/285 > 3x ULN*)



Sublingual 40 mg BID 12 weeks
High PK, Liver Kb 10
(4/285 > 3x ULN*)



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Upper limit of normal (ULN) in DILIsym is 40 U/L

Simulation Results

SimCohorts of N=16 Simulations Reveals Oxidative Stress as the Driver of Liver Injury in the DILIsym Riluzole Simulations

- Multi16 SimCohort includes 13 sensitive individuals and 2 insensitive individuals from the full n=285 SimPops and includes the baseline human
- **Liver injury predicted to be predominantly due to oxidative stress**
  - Oxidative stress is required for simulated ALT elevations
  - Mitochondrial toxicity is not required for simulated ALT elevations
  - Bile acid transport inhibition is not required for simulated ALT elevations

	Riluzole Dose and Duration	Parameter Settings	Mechanisms	ALT > 3X ULN*	ALT > 5X ULN*
Oral	Oral 50 mg BID for 12 weeks	High PK, Liver Kb 10	All	3/16	1/16
			No ROS	0/16	0/16
			No Mitochondrial Toxicity	3/16	1/16
			No BA Transport Inhibition	3/16	1/16
Sublingual	Sublingual 40 mg BID for 12 weeks	High PK, Liver Kb 10	All	1/16	1/16
			No ROS	0/16	0/16

*Upper limit of normal (ULN) in DILIsym is 40 U/L

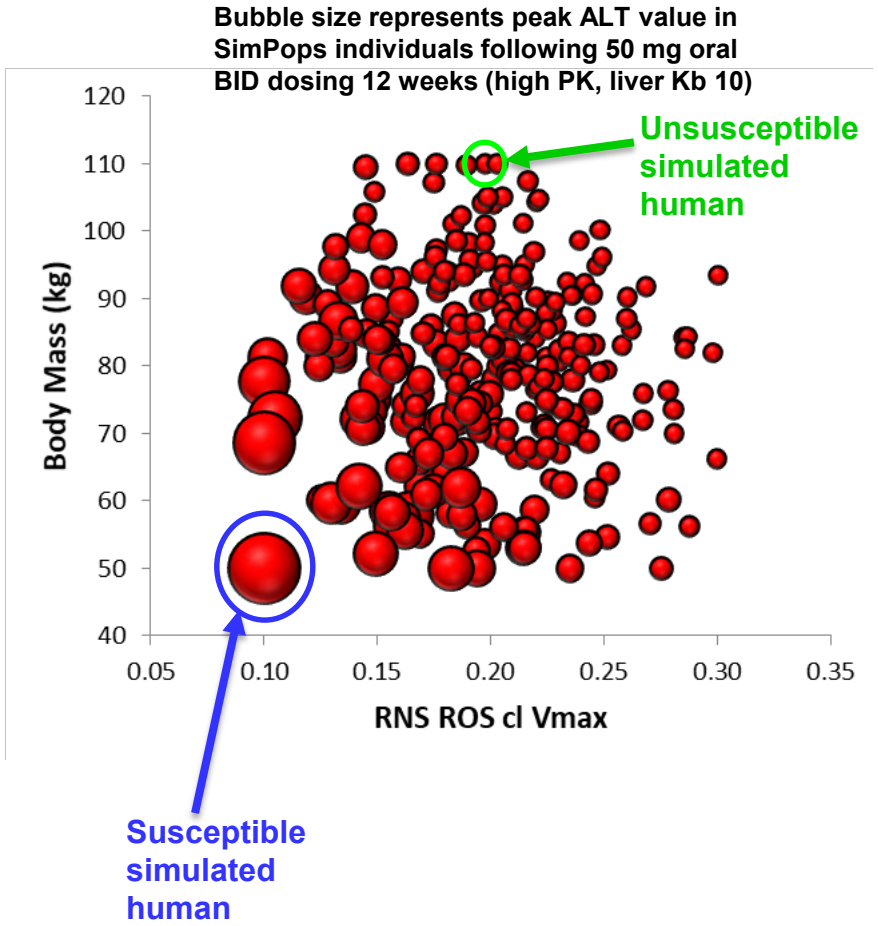
**Multi16 SimCohorts used is group of 16 individuals (n=16) among the full v4A_1 SimPops (n=285); 13 of the simulated individuals are sensitive to DILI mechanisms or combinations, 2 are insensitive, and 1 is the baseline (average) human

Multiple Factors Responsible for Differences in the Hepatotoxicity Response to Riluzole Among Simulated Individuals

- Differences in the hepatotoxicity response for the **unsusceptible individual** and the **susceptible individual** due to multiple factors (primarily the combined effect of differences in body mass and RNS/ROS clearance)
- Covariate analysis of the SimPops simulation results revealed 3 SimPops parameters that showed a statistically significant correlation with ALT elevations:

DILIsym Parameter	Parameter Description	P-value
RNS ROS cl Vmax	Liver RNS/ROS baseline clearance Vmax	7.6 E-39
Body mass	Body mass	8.3E-24
CAS apop scale	Caspase-mediated apoptosis scaling constant	1.4E-10

Regression analysis performed with peak ALT (oral BID dosing, high PK and liver Kb 10 assumptions) as the dependent variable and the 34 SimPops parameters as independent variables



Simulation Results

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ALS Riluzole Project Example: DILIsym Helped Biohaven Assess a Potential Safety Benefit of their Compound

- Riluzole is used to slow the progression of ALS
- Biohaven Pharma is developing an alternative, sublingual formulation (BHV-0223)

Primary Project Outcomes

- DILIsym was used to compare the liver safety profile for both formulations
  - Sublingual formulation is less likely to produce less ALT elevations
  - Benefit largely derived from the reduced dose needed
  - An exposure-response analysis helped to define possible safe exposure cut-offs and identified patient susceptibility factors

- ***The FDA has accepted the NDA filing for Nurtec™ and a final decision on approval is pending***

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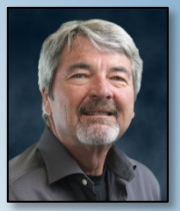
Acknowledgements - The DILIsym Services Team

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



Grant Generaux
Scientist II
Philadelphia, PA

Jeff Woodhead
Scientist II
RTP, NC

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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

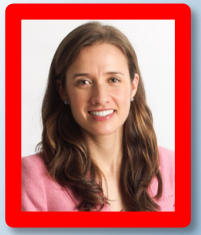
Zack Kenz
Scientist I
RTP, NC

Nader Hamzavi
Postdoctoral Fellow
RTP, NC

Guncha Taneja
Postdoctoral Fellow
RTP, NC

Shailendra Tallapaka
Postdoctoral Fellow
RTP, NC

Diane Longo
Scientist II
Arlington, VA



Yeshi Gebremichael
Scientist II
RTP, NC

Thank You - Questions?

Contact Information

www.DILIsym.com

www.Simulations-Plus.com

Emails: bhowell@DILIsym.com

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