DILIsym Services

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Please note: this presentation, including questions from the audience, is being recorded

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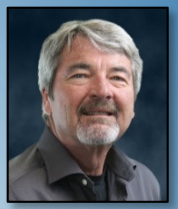

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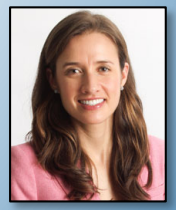

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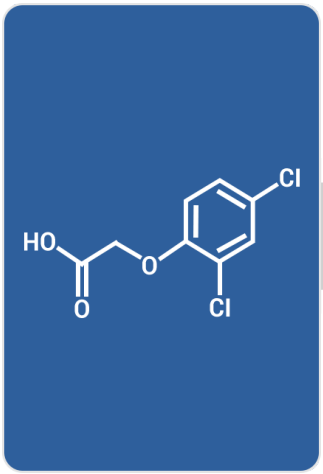
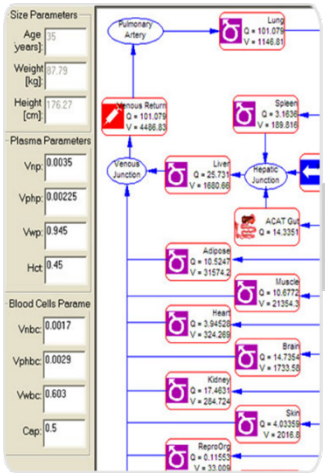
DILIsym v8A Release Webinar Agenda

- Introduction to DILIsym Software platform
- DILIsym version 8A highlights
- DILIsym v8A demo
- Questions

Simulations Plus (SLP) Family: Saying "I do" to the QSAR / PBPK / QST marriage…



Permeability, solubility vs. pH, pKa(s), logD vs. pH, Fup, blood:plasma ratio, tissue Kps, CLint, CLfilt



Local & systemic exposure, drug distribution, parent and metabolite levels, patient variability

Quantitative Structure Activity Relationships (QSAR)

ADMET Predictor™

Physiologically-Based Pharmacokinetics (PBPK)

GastroPlus™

Quantitative Systems Pharmacology/Toxicology (QSP/QST)

RENAsym™

DILIsym®

NAFLDsym®

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DILIsym Services QST and QSP Models

DILIsym®

- Predicts drug-induced liver disease
- v8A released Q1 2019
- Includes mechanistic representation of normal hepatic biochemistry
- Evaluated >60 compounds with 25 companies

RENAsym™

NAFLDsym®

So how can DILIsym help my organization?

- Predict DILI liabilities beforehand and save **$$$**
- Choose the lead candidate ***most likely to succeed*** from a DILI standpoint
- Communicate with regulators on safety issues with information they have requested from others numerous times and from a platform they license (FDA)
- ***Keep patients safer….***

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

Select Sample of Current Companies Licensing DILIsym

- *Overall Goals*
  - *Improve patient safety through QST*
  - *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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DILI-sim Initiative Membership Benefits

Access to DILIsym software, equations, and support

- DILI-sim members receive access to the DILIsym software during their active membership term
- DILI-sim members receive a PDF copy of all equations included in each version of the DILIsym software released during their active membership term
- DILI-sim members have exclusive access to DILIsym training materials and support, including 10 hours of one-on-one support, free training once per year at annual meeting, and reduced rates on off-site workshops
- DILI-sim members have access to online DILIsym documentation (i.e., software use, modeling rationale)
- Tier 1 (3 year) members receive a 31% discount on consulting; Tier 2 (annual) members receive a 17% discount (compared to non-member pricing)
- DILI-sim members have exclusive access to the DILIsym Discovery Support Program (DDSP); not available to non-members or academics

Influence over DILIsym development

- Member companies guide DILIsym development through voting
- DILI-sim members have option to donate data from current or failed compounds to serve as exemplars for DILIsym

Participation in regular meetings with colleagues

- Representatives from member companies attend quarterly DILI-sim update meetings to monitor progress and provide feedback, along with model design review sessions
- Members gather in person once per year for a more comprehensive overview during the annual DILI-sim Face to Face Meeting
- Attendance, voting, and data generation are optional benefits of membership

DILIsym Software Licenses Are Available to Industry and Academia

- DILI-sim membership not required to license the DILIsym modeling software
- Training provided in various formats
  - Training courses and workshops
  - Web-based videos
  - User manual
  - Documentation
- Academic and regulatory licenses also available
- Access to the MITOsym modeling software is also provided

MITOsym®: A Mechanistic, Mathematical Model of Hepatocellular Respiration and Bioenergetics

Y. Yang • S. Nadanaciva • Y. Will • J. L. Woodhead • B. A. Howell • P. B. Watkins • S. Q. Siler

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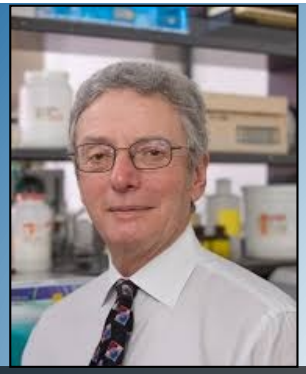
DILI-sim Scientific Advisory Board



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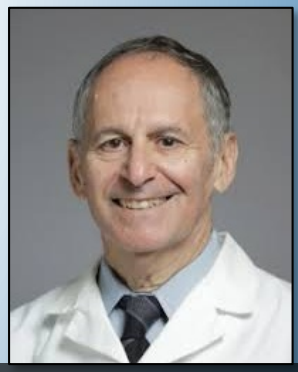
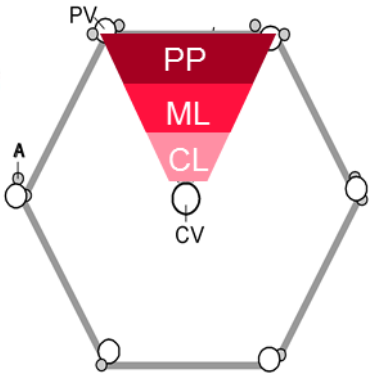
Michigan State University



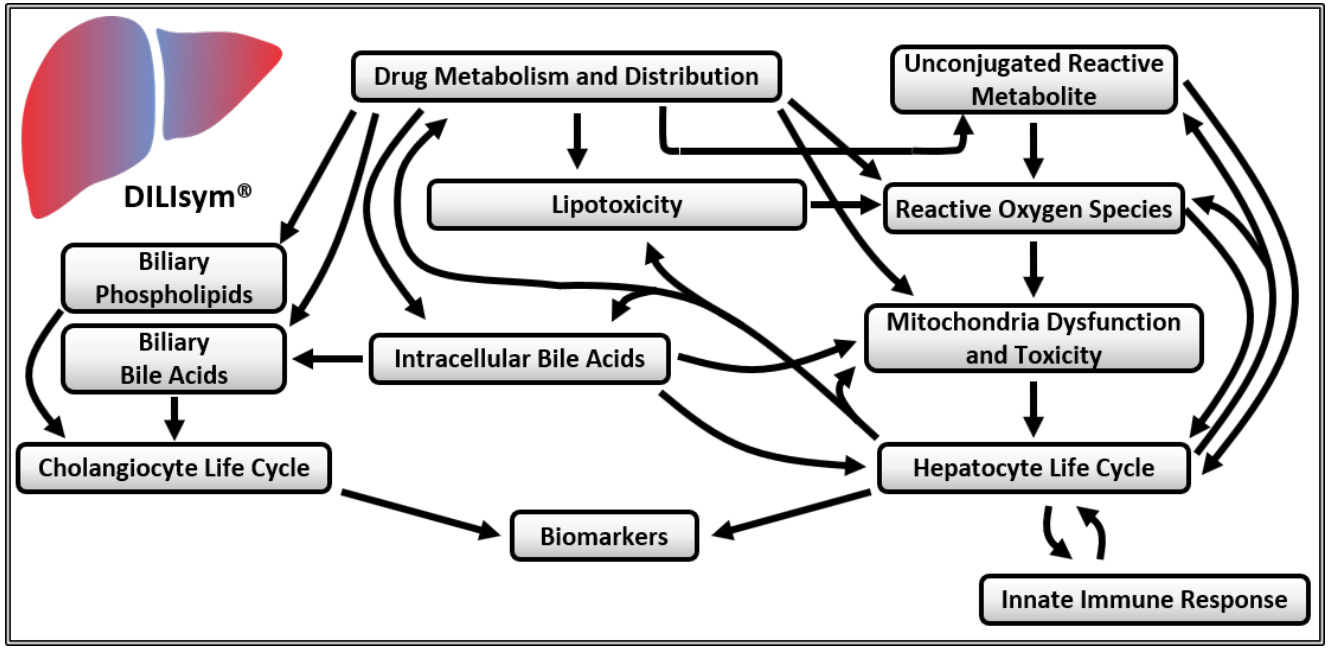
David Pisetsky
Professor of Medicine
Professor of Immunology
Member of the Duke Cancer Institute
Member of the Duke Human Vaccine Institute

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**



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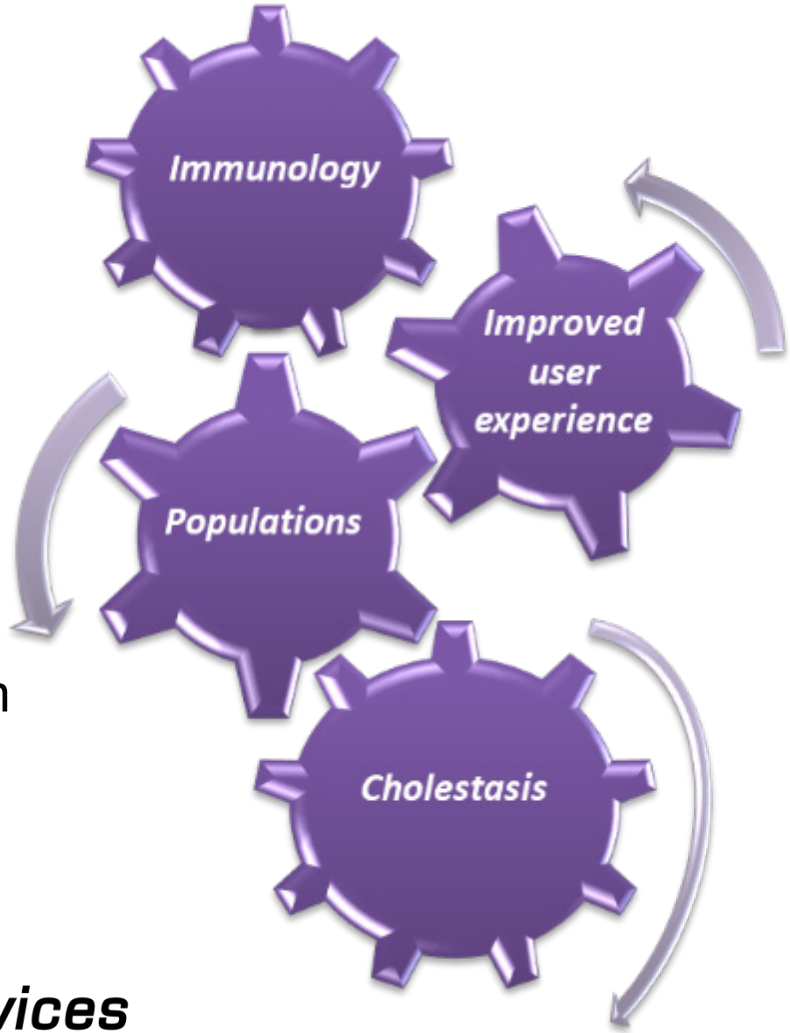
Immunology, Cholestasis, Population Variability and Enhanced Software Highlight Stage 3 Areas of Focus

- 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
- Software enhancements stemming from acquisition by Simulations Plus will propel user friendliness and speed
- Improved *in vitro* data to feed the software



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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*

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**

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 transporter inhibition**
  - *BSEP, MRP3 and 4, NTCP, (MDR3)*
- **Bilirubin transport/metabolism**
  - *OATP1B1, OATP1B3, UGT1A1, MRP2, MRP3*

Clinical Data

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

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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

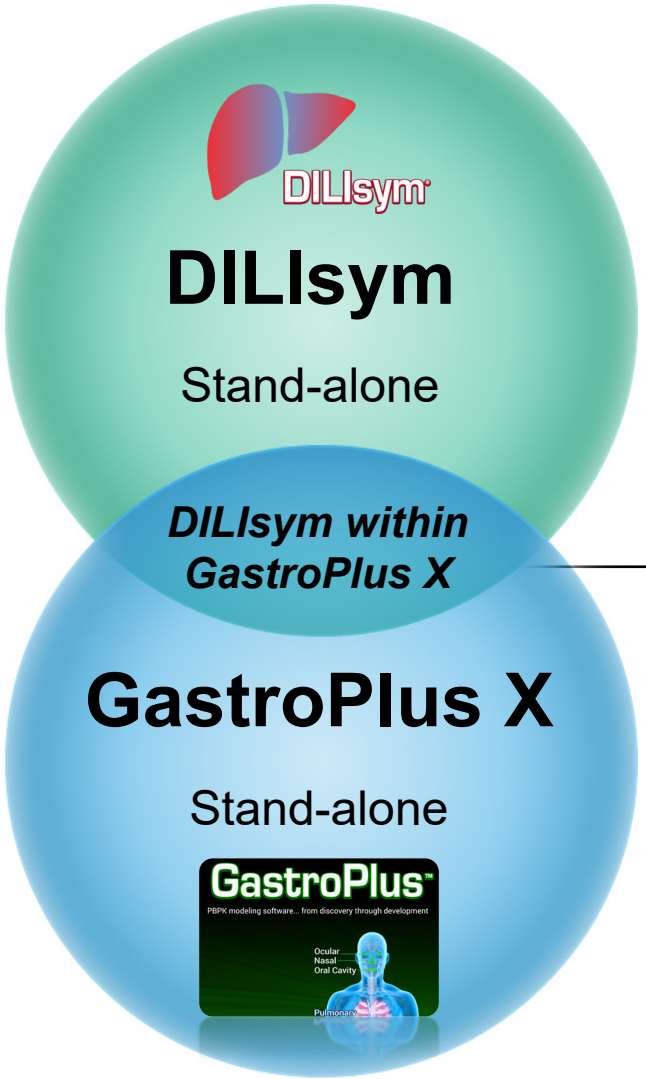
*Not a direct regulatory agency, but affiliated closely with NIH and FDA

**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

Refactored DILIsym and GastroPlus Will Be Integrated for More Efficient and Powerful Predictions

Both DILIsym and GastroPlus X will operate independently of each other



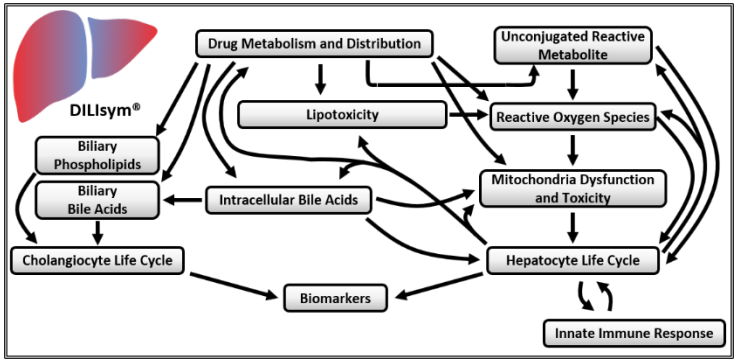
- Integration will occur via an interoperability plugin
- During integration, DILIsym will utilize GastroPlus X's ODE system for running simulations.

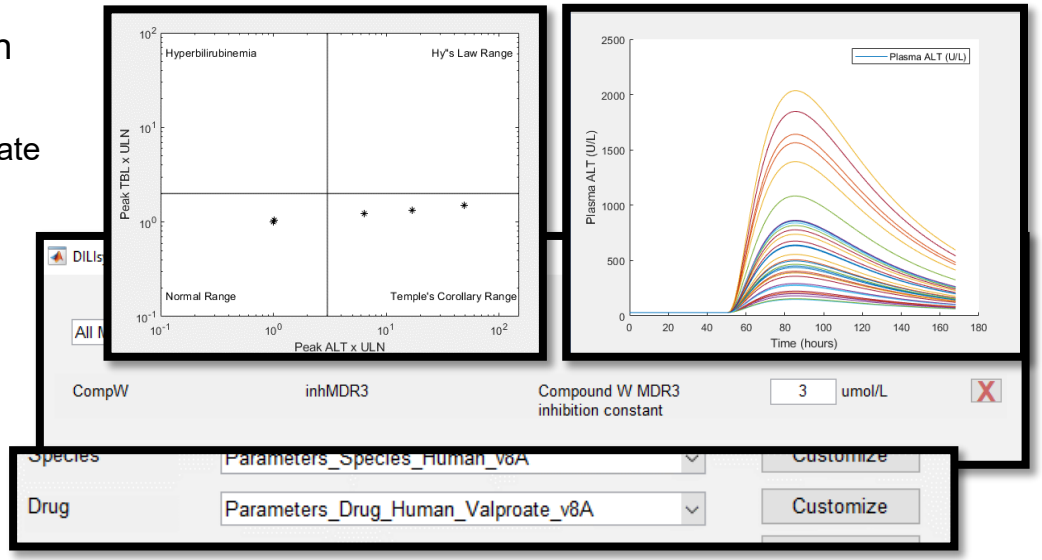
DILIsym v8A Release Webinar Agenda

- Introduction to DILIsym Software platform
- DILIsym version 8A highlights
- DILIsym v8A demo
- Questions

Highlights of DILIsym v8A (Released Jan 2019)

- 10 NEW exemplar Compounds included with varying clinical presentations
  - Includes several GSK compounds and valproate





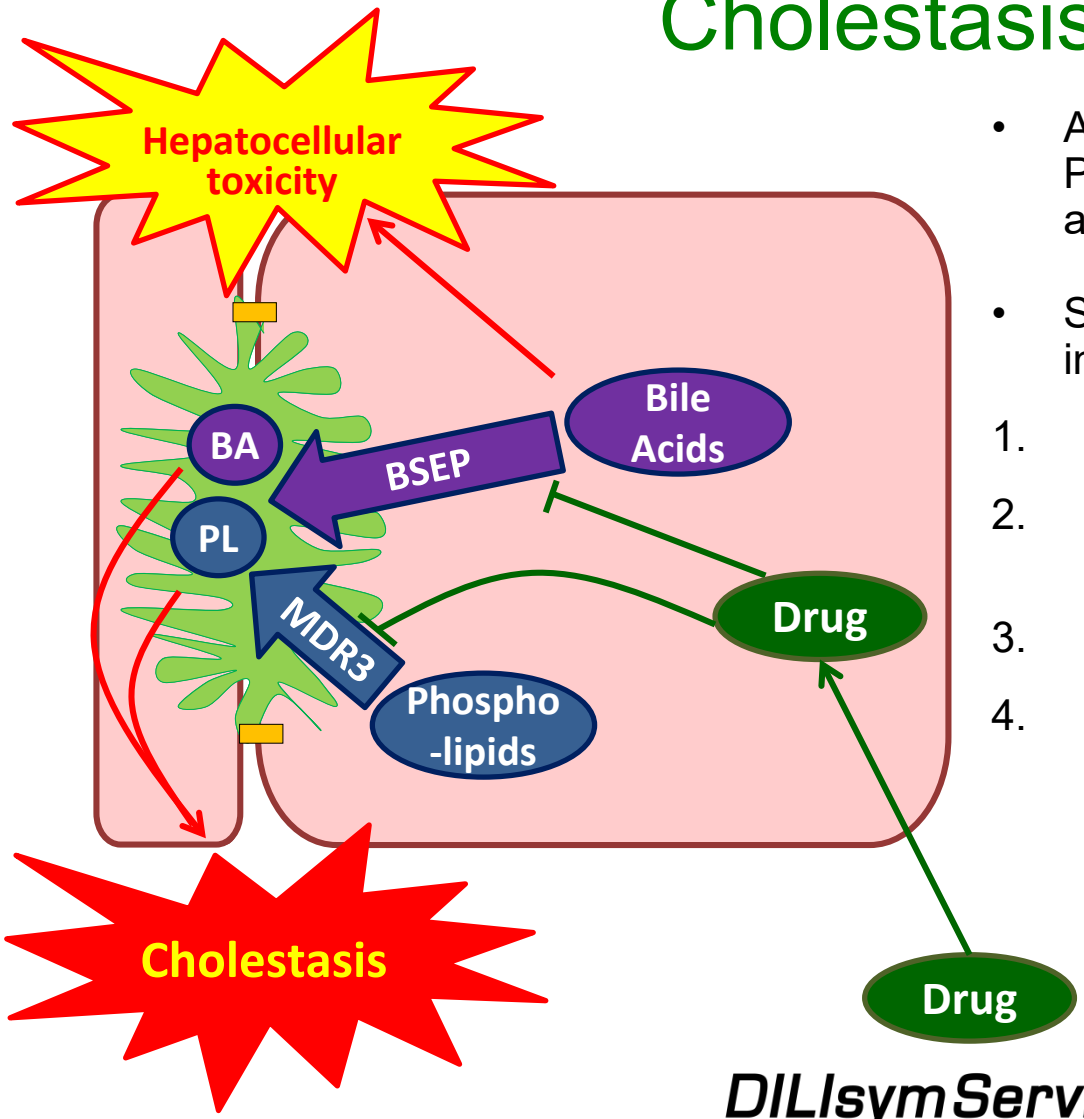
- NEW Cholestatic liver injury mechanism including MDR3 inhibition and phospholipid effects, with new associated biomarkers gamma glutamyl transferase (GGT) and alkaline phosphatase (ALP)
- NEW oxidative stress (ROS) NRF2 adaptation response framework
- NEW human SimPops with variability in bilirubin processing pathways
- NEW liver injury biomarker GLDH
- ADDED immune system components – neutrophils for all species
- UPDATES to the bile acid sub-model related to gut uptake / loss and renal clearance

- UPDATED SimPops with re-calibrated bile acid sub-model parameters: *note that many prior SimPops are no longer included and have been replaced*
- NEW Sweep feature with Specified Data
- Import / export feature for SimSingles to make changes across large numbers of SimSingles more easily within spreadsheet format
- NEW feature allowing for random shuffling of existing full SimPops or for random selection when creating SimCohorts
- DILIsym documentation website updated for new features, compounds and SimPops
- Improved simulation speed
- Built and compiled in MATLAB 2018b

10 New Compounds Included in DILIsym v8A

- Seven GSK compounds: Phenoxybenzamine, Zafirlukast, Fluconazole, GSK Compound A, GSK Compound B, GSK Compound C, and GSK Compound D
  - Represented by both GSK and DILIsym Services in parallel
  - DILIsym Services correctly predicted hepatotoxicity (or lack of toxicity) for six of the seven drugs
  - DILIsym Services version (of toxicity parameters) included in v8A
- Two tyrosine kinase inhibitors: Crizotinib and Pazopanib
  - Compounds for the treatment of non-small cell lung cancer (Crizotinib) or for the treatment of kidney cancer and some types of sarcoma (Pazopanib)
    - Frequent ALT elevations observed clinically for Crizotinib not recapitulated in default representation in DILIsym; ALT elevations predicted in DILIsym with inclusion of potential for Crizotinib to cause direct apoptosis
    - Low incidence of ALT elevations observed clinically for Pazopanib recapitulated in DILIsym
- Valproate
  - Anticonvulsant used to treat seizures and bipolar disorder
  - DILIsym valproate simulations with mitochondrial biogenesis adaptation showed ALT profiles consistent with clinical presentation (i.e. 5-10% of patients have ALT elevations that often resolve upon continued treatment)

MDR3 Inhibition Can Alter Canalicular Phospholipid Levels and Increase Cholestasis Risk



- Alterations in the canalicular ratio of BA to PL can increase risk of cholangiocyte death and cholestasis
- Steps to Incorporate Cholestasis Submodel into DILIsym :

1. Represent liver phospholipid homeostasis
2. Represent drug effects on phospholipid transport (MDR3 inhibition)
3. Represent cholangiocyte life cycle
4. Represent influence of extracellular bile acid to phospholipid ratio on cholangiocyte necrosis/ apoptosis and biomarker levels- alkaline phosphatase (ALP) , gamma glutamyl transferase (GGT)

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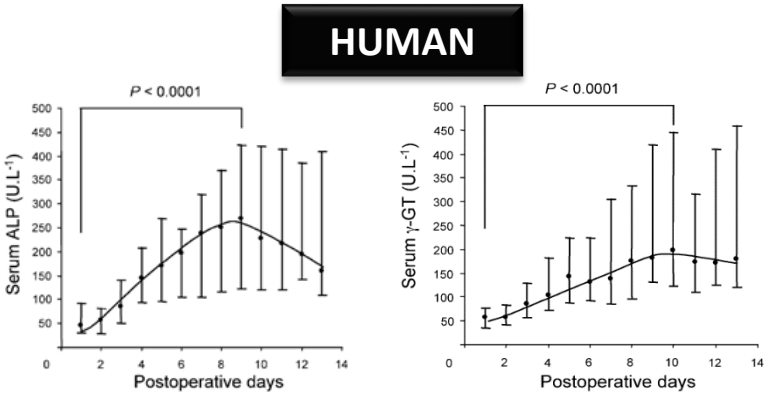
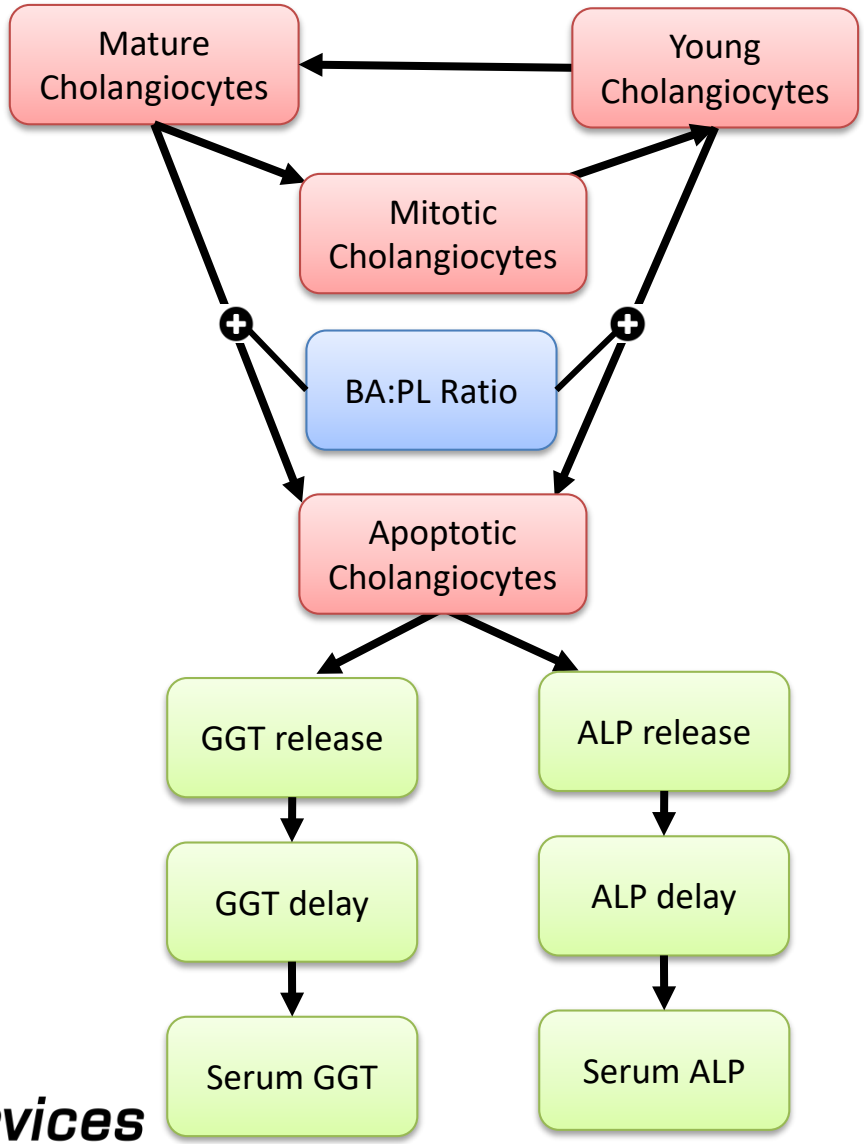
Cholestasis Sub-Model Constructed

- Cholangiocyte model consists of mature, mitotic, young, and apoptotic cholangiocytes
  - Cell numbers suggested by Barros 2009, Yoo 2016, Xia 2006
- BA:PL ratio modulation will increase cellular apoptosis (Chang 2018)
  - Normal ratio at 10; relationship between BA:PL ratio and cholangiocyte death given by continuous function
- Alkaline phosphatase (ALP) released by apoptotic cholangiocytes
  - Some delay in ALP release observed; potentially due to bicarbonate umbrella protecting cholangiocytes
  - Gamma-glutamyl transferase (GGT) represented as well



Geuken 2004



Clinical Data

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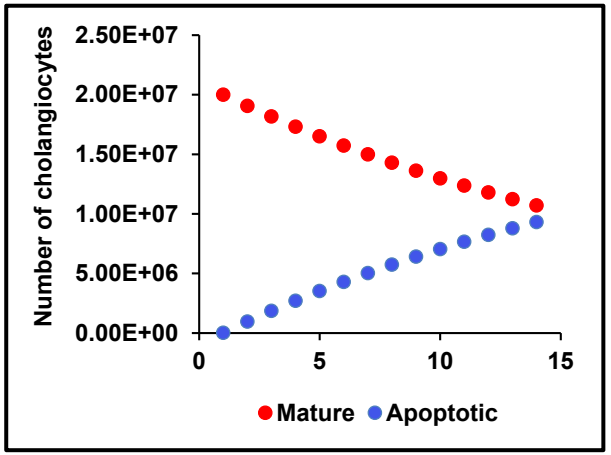
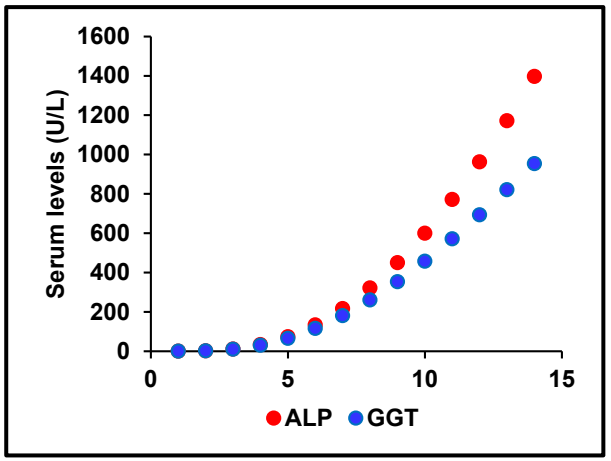
MDR3 Inhibition Can Lead to Simulated ALP Increases

HUMAN

- Theoretical MDR3 inhibitor introduced to cholangiocyte-phospholipid-bile acid system
  - Causes disruption in phospholipid transport, leading to increased BA:PL ratio
- Potential for cholangiocyte apoptosis and injury observed
  - Canalicular phospholipids decrease
  - Apoptotic flux increases, while number of mature cholangiocytes decreases
  - Serum ALP and GGT levels increase following a delay





Simulation Results

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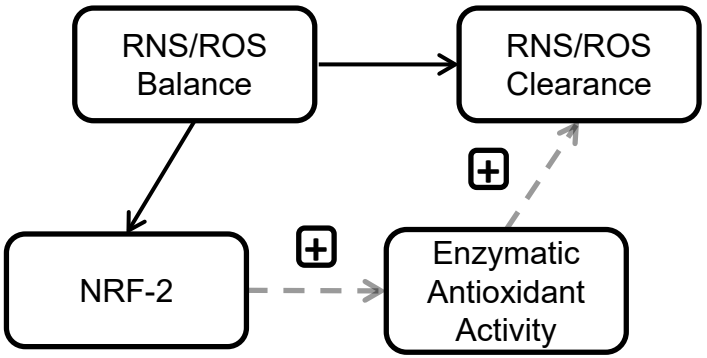
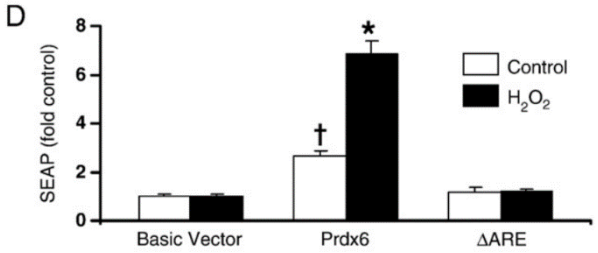
NRF-2 Based ROS/RNS Adaptation Framework in DILIsym v8A for Exploration

- DILIsym incorporates adaptive response to RNS/ROS levels in the form of NRF-2 induction of GSH synthesis, which can decrease levels of reactive species
- NRF-2 drives other responses to RNS/ROS, such as the induction of antioxidant enzymes superoxide dismutase (SOD) and peroxiredoxin (Prx), which directly decrease levels of RNS/ROS
- DILIsym v8A will include new equations which will allow for the exploration of NRF-2 adaptation dynamics; however, these dynamics will not be optimized
- Continuing to scope quantitative data to capture the effect of NRF-2 on antioxidant enzyme levels, and subsequent effects on RNS/ROS clearance





RAT

Chowdhury 2009

MICE

Rangasamy 2004

Table 2
Nrf2-dependent protective genes induced by CS in the lungs of *Nrf2* wild-type mice

Functional classification and gene accession no.	Gene	Fold change ± SE
Antioxidants		
X56824 (X06985)	*Heme oxygenase 1*[A]	4.7 ± 0.4
U38261 (U10116)	*Superoxide dismutase 3*[B]	1.7 ± 0.4
X91864 (X68314)	*Glutathione peroxidase 2*[B]	2.7 ± 0.4
U13705 (X58295)	*Glutathione peroxidase 3*[B]	1.4 ± 0.4
U85414 (M90656)	*Gamma glutamylcysteine synthase (catalytic)*[A]	7.6 ± 0.5
U95053 (L35546)	Gamma glutamylcysteine synthase (regulatory)[A]	7.3 ± 0.5
AF090686 (M60396)	*Transcobalamine II*[B]	1.6 ± 0.3
L39879 (BC004245)	*Ferritin light chain 1*[A]	1.5 ± 0.3
AI118194 (X67951)	*Peroxiredoxin 1*[B]	1.5 ± 0.3
AI851983 (X15722)	*Glutathione reductase*[B]	3.3 ± 0.4
AB027565 (X91247)	*Thioredoxin reductase 1*[B]	4.3 ± 0.4

Preclinical Data

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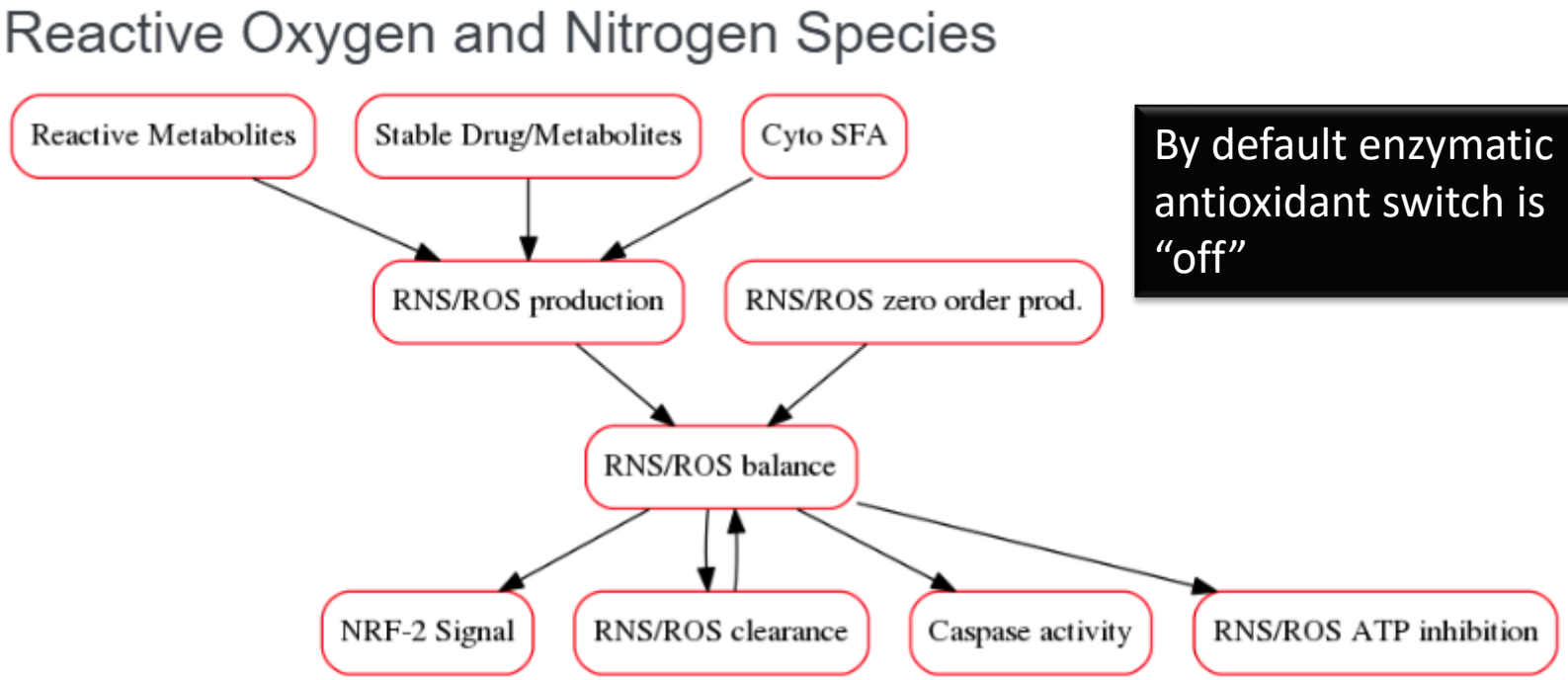
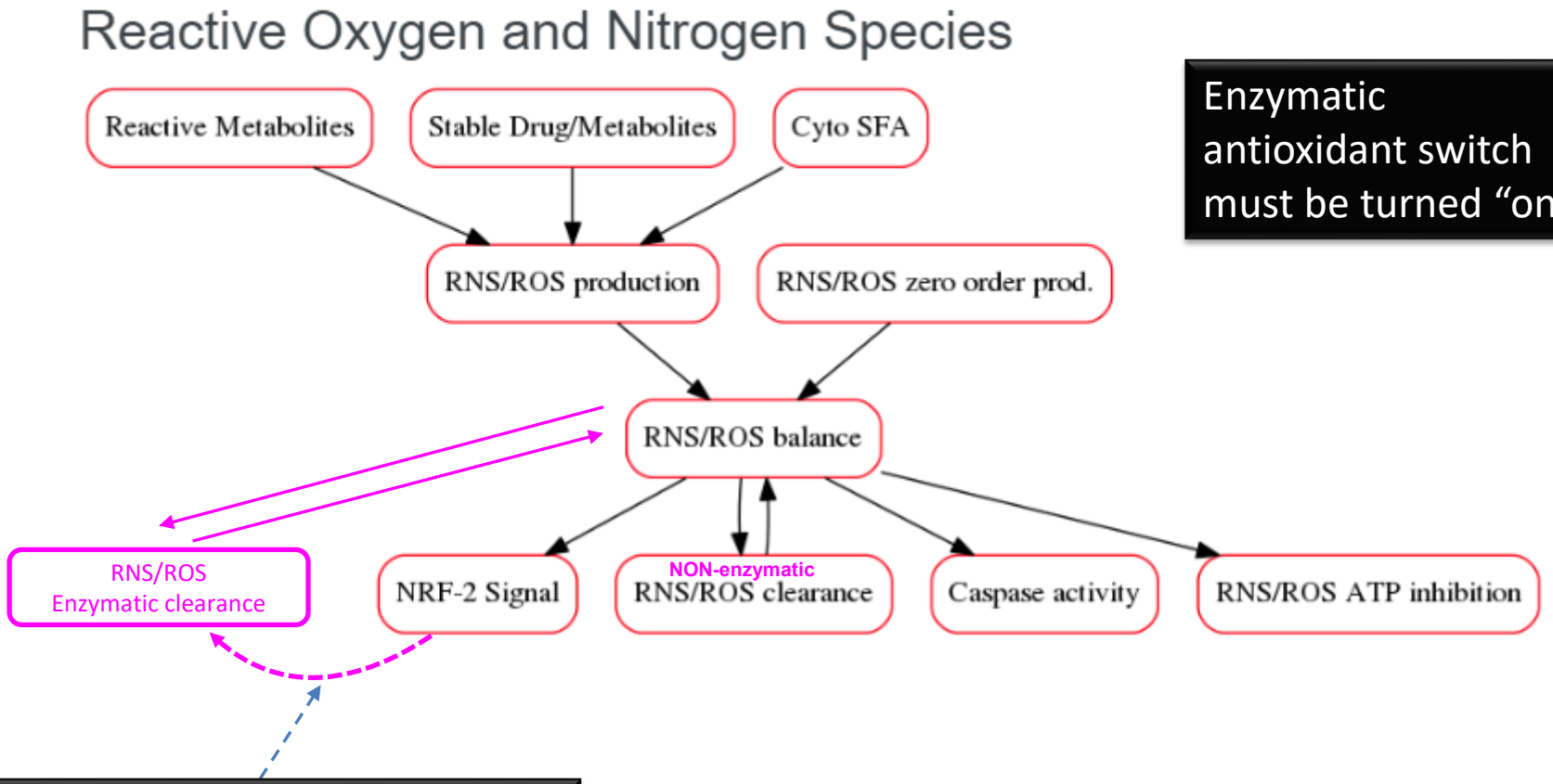
DILIsym v8A ROS (Oxidative Stress) Sub-model is Same as DILIsym v7A by default



By default enzymatic antioxidant switch is "off"

DILIsym v8A ROS Sub-model with Exploratory Enzymatic Antioxidant Mechanism



Enzymatic antioxidant switch must be turned "on"

Feedback: fold increase in NRF-2 leads to increased clearance from enzymatic sources

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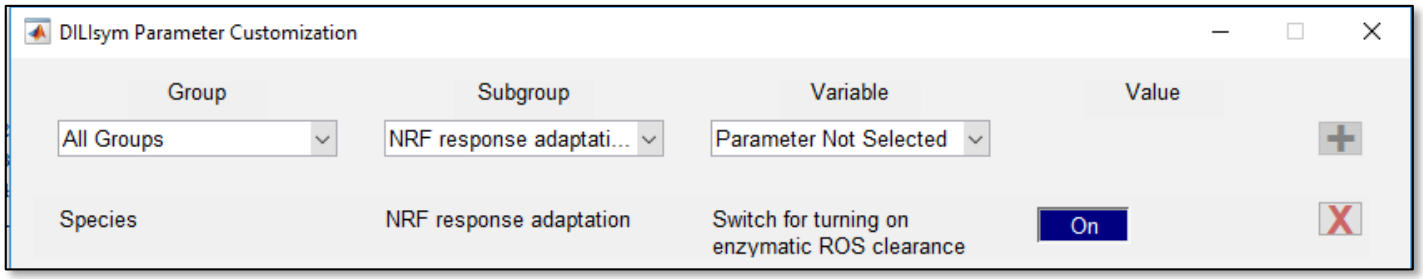
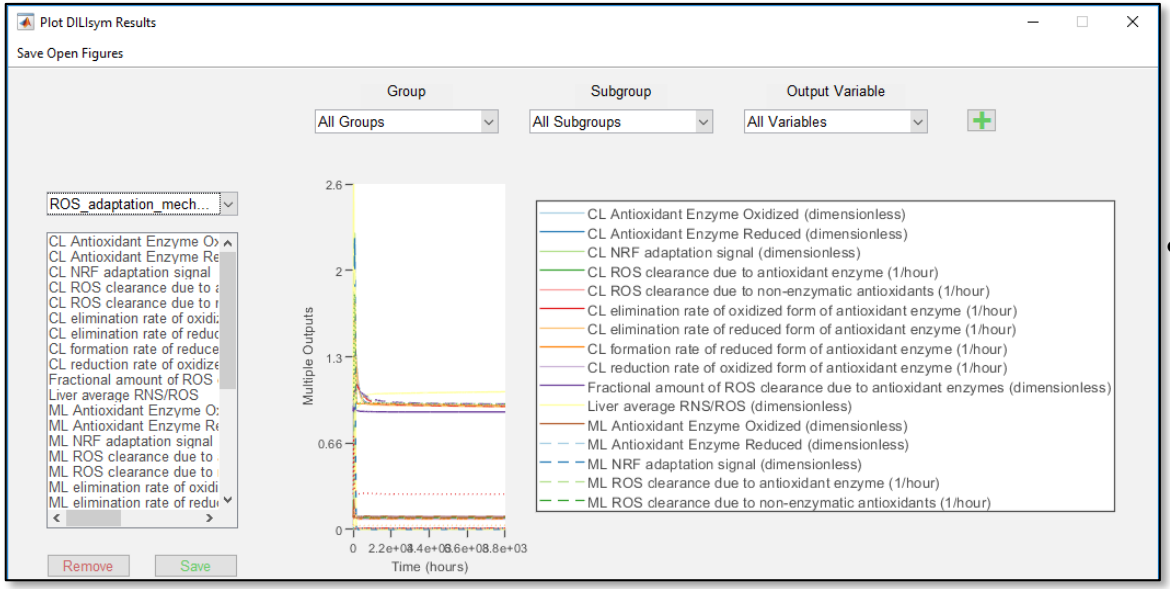
Access of Exploratory Mechanism Using Switch and Output Panel



- 1 new parameter as switch to activate enzymatic clearance



- New output panel

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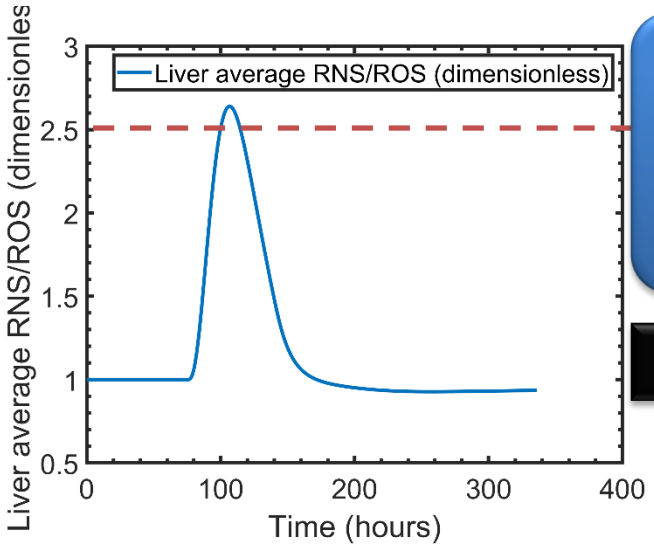
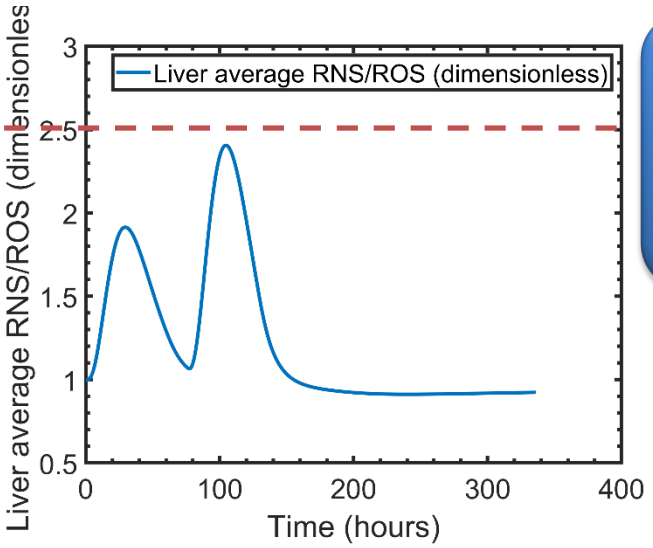
NRF-2 Adaptation Mechanism Reduces ROS Levels



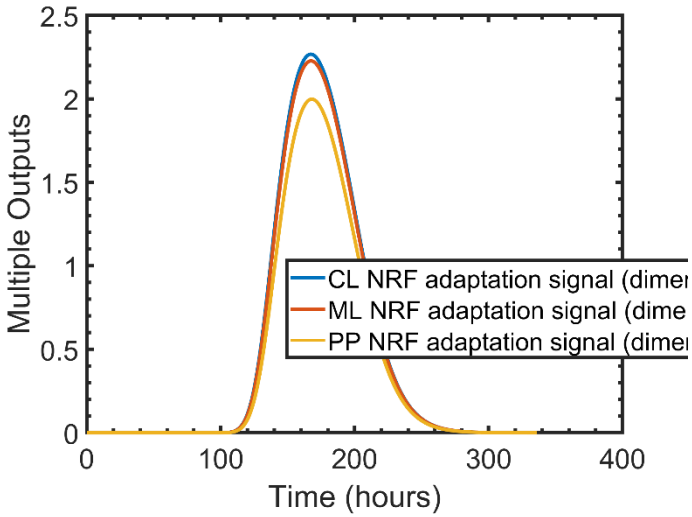
1x single dose of compound with oxidative stress

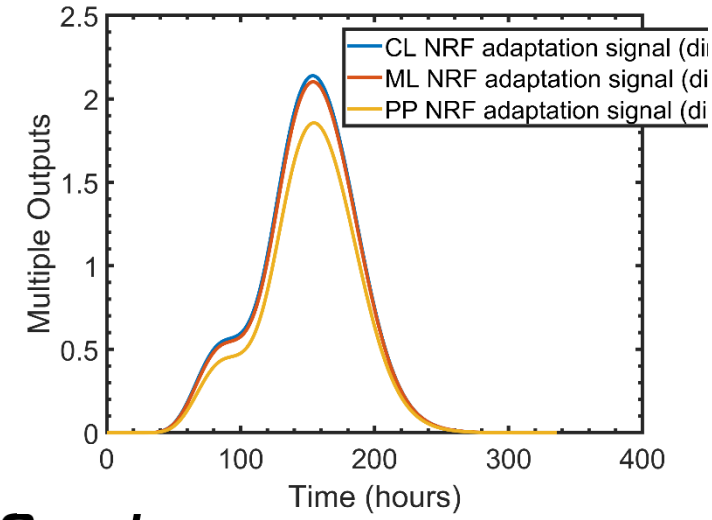
HUMAN



0.6x loading dose followed by 1x dose of compound with oxidative stress

HUMAN





Simulation Results

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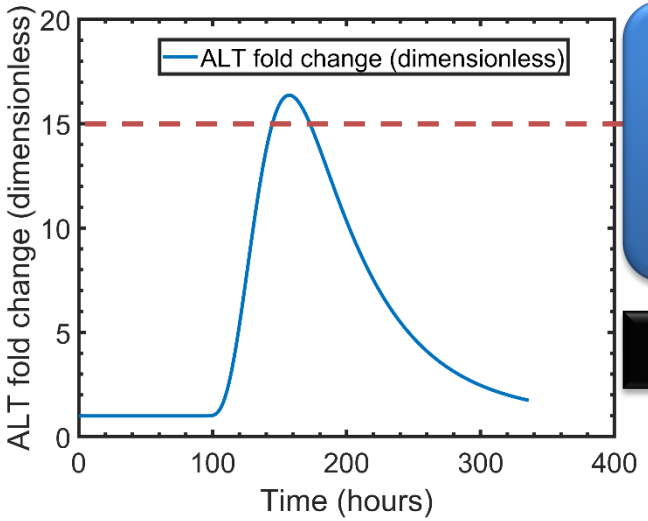
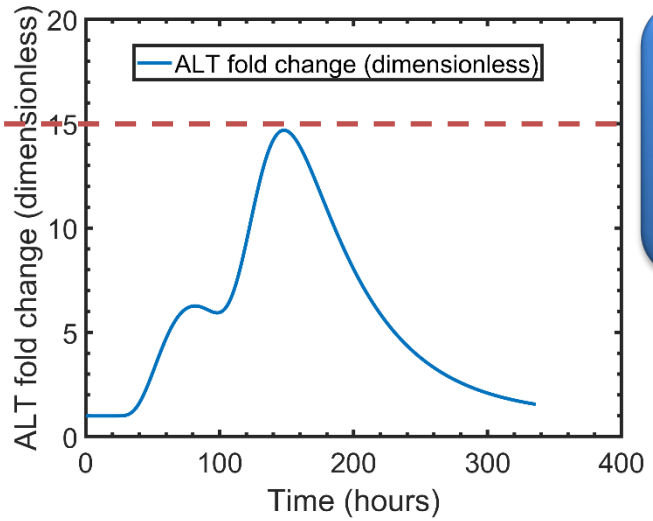
NRF-2 Adaptation Mechanism Reduces ALT



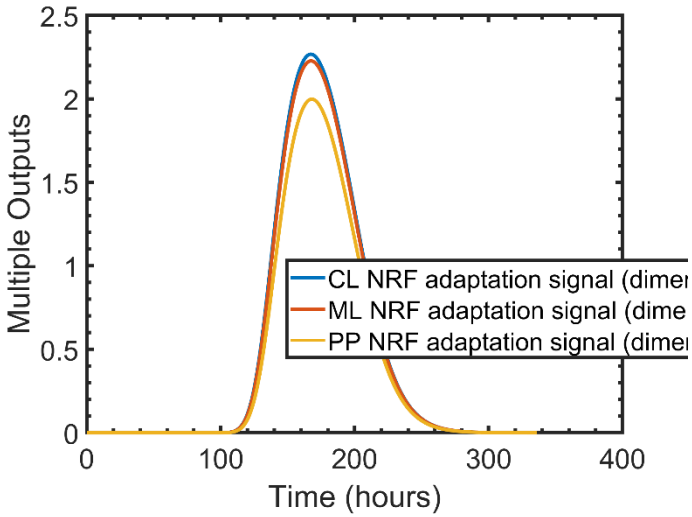
1x single dose of compound with oxidative stress

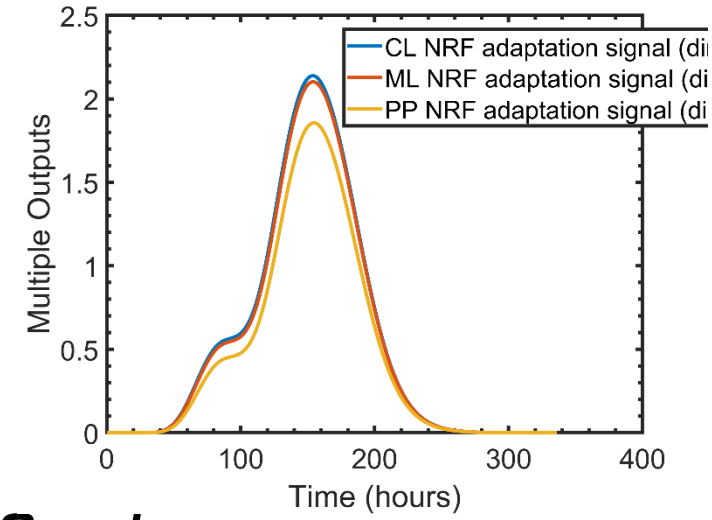
HUMAN



0.6x loading dose followed by 1x dose of compound with oxidative stress

HUMAN





Simulation Results

DILIsym Services

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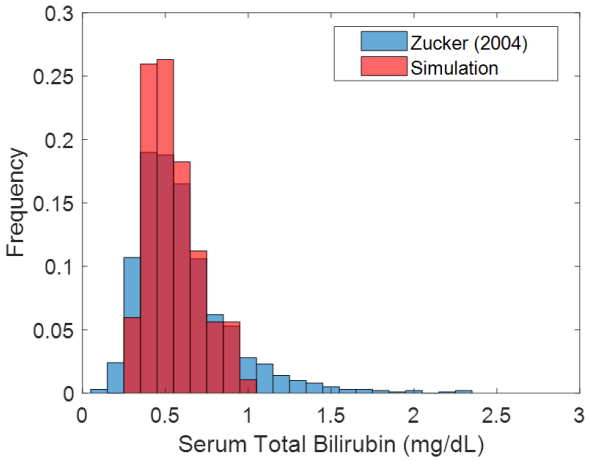
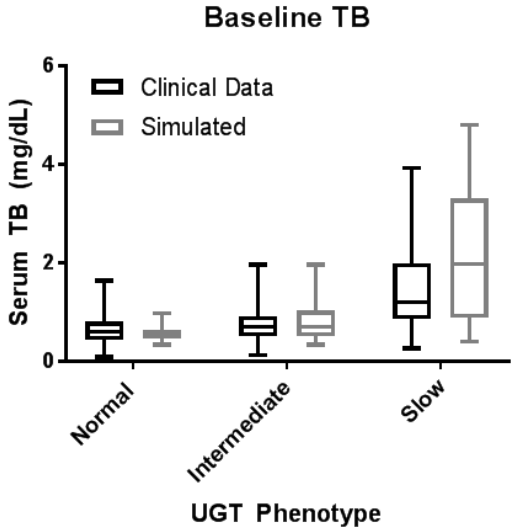
Bilirubin SimPops Allows Simulation of Variability in Response to Bilirubin Processing Perturbation

- Bilirubin SimPops (n=285) with normal baseline serum total bilirubin (< 1 mg/dL) has been created
  - Variability added to several parameters related to bilirubin disposition
- Bilirubin SimPops that represent normal, intermediate, and slow UGT1A1 phenotypes created (n=100, each)
  - UGT1A1 parameter ranges determined from UGT1A1 protein expression and functional data in individuals with *UGT1A1*1/*1*, *UGT1A1*1/*28*, and *UGT1A1*28/*28*, respectively
  - Individuals with serum total bilirubin above clinical levels excluded





	Normal	Intermediate	Slow
UGT1A1 function*	80 – 120%	60 – 80%	40 – 60%
Serum TB†	< 1 mg/dL	< 2 mg/dL	< 5 mg/dL

*Bosma 1995, Rajimakers 2000
†Bosma 1995, Monaghan 1996, Persisco 2001, Rotger 2005, IU data

Clinical Data and Simulation Results

DILIsym Services
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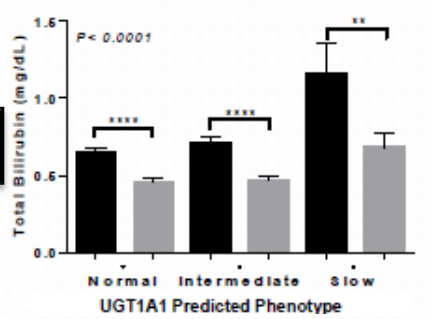
HUMAN

Influence of UGT1A1 Polymorphisms and Efavirenz on Serum Bilirubin Simulated

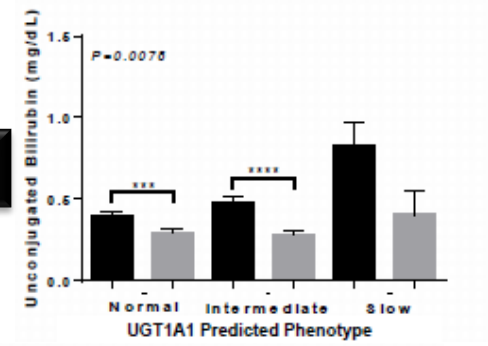
HUMAN

Clinical

TB



UB



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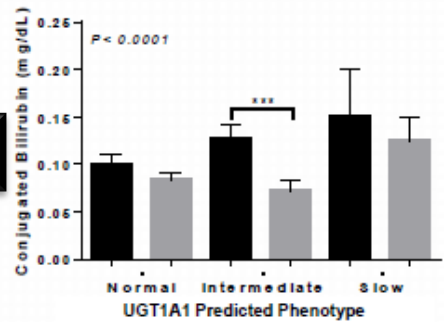


Burgess 2017 ASCPT

Black bar (screen); grey bar (exit); $^{**}P < 0.01$; $^{****}P < 0.0001$

Clinical Data

- Efavirenz monotherapy significantly reduced total, conjugated and unconjugated serum bilirubin levels
  - 600 mg/day efavirenz for 17 days
  - Serum bilirubin levels measured at study entry (screen) and 1 week after completion of dosing (Day 24; exit)
  - Data suggest that efavirenz is an effective inducer of UGT1A1, and potentially MRP2
- Efavirenz effects simulated with Bilirubin SimPops with normal, intermediate, or slow UGT1A1 function
  - Efavirenz PBPK not explicitly constructed
  - Induction effects simulated by directly modulating UGT1A1 and/or hepatic transporter (MRP2 or OATP1B1/1B3) function

Sim	Enzyme/Transporter Function		
	UGT1A1*	MRP2†	OATP1B1/1B3†
I	2X induction	↔	↔
II	2X induction	2X induction	↔
III	2X induction	↔	2X induction

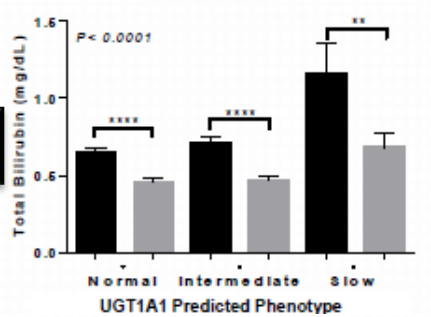
*Song 2014

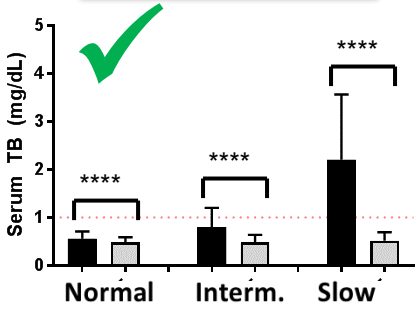
† 2-fold induction assumed because induction data were not available.

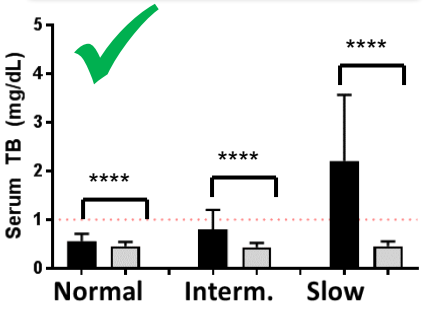
Influence of UGT1A1 Polymorphisms and Efavirenz on Serum Bilirubin Simulated

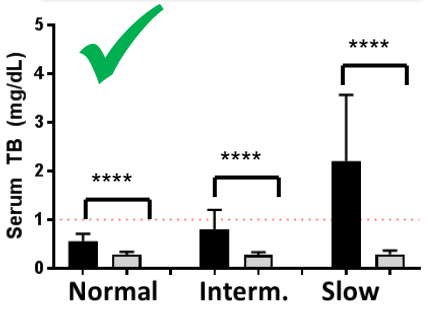
HUMAN | Clinical | Sim: UGT induction | Sim: UGT/MRP2 induction | Sim: UGT/OATP induction

TB









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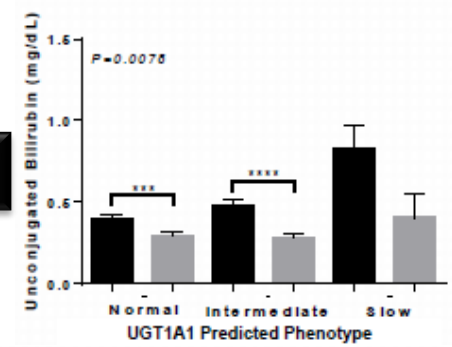

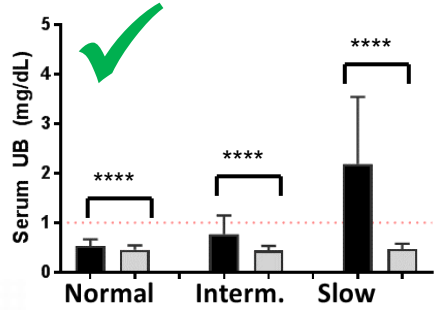

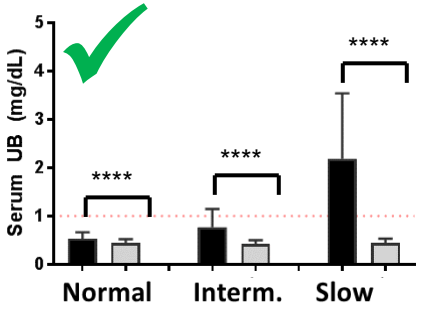

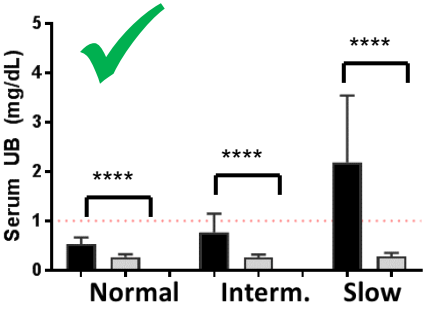

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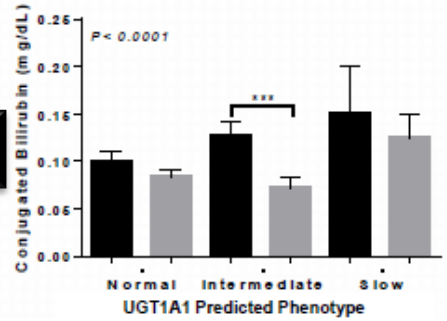
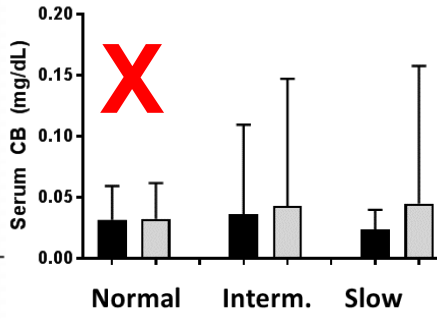
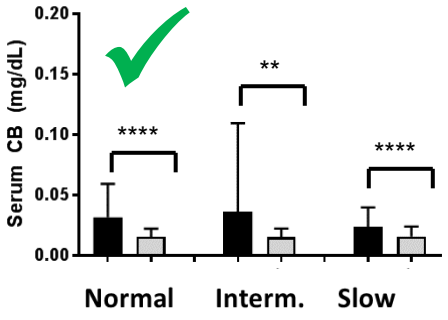
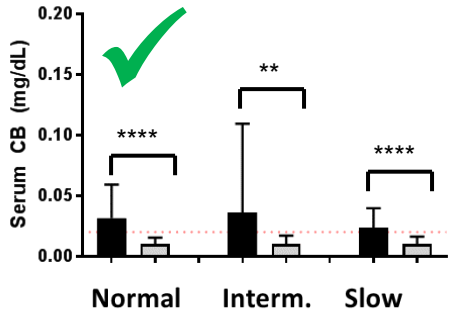








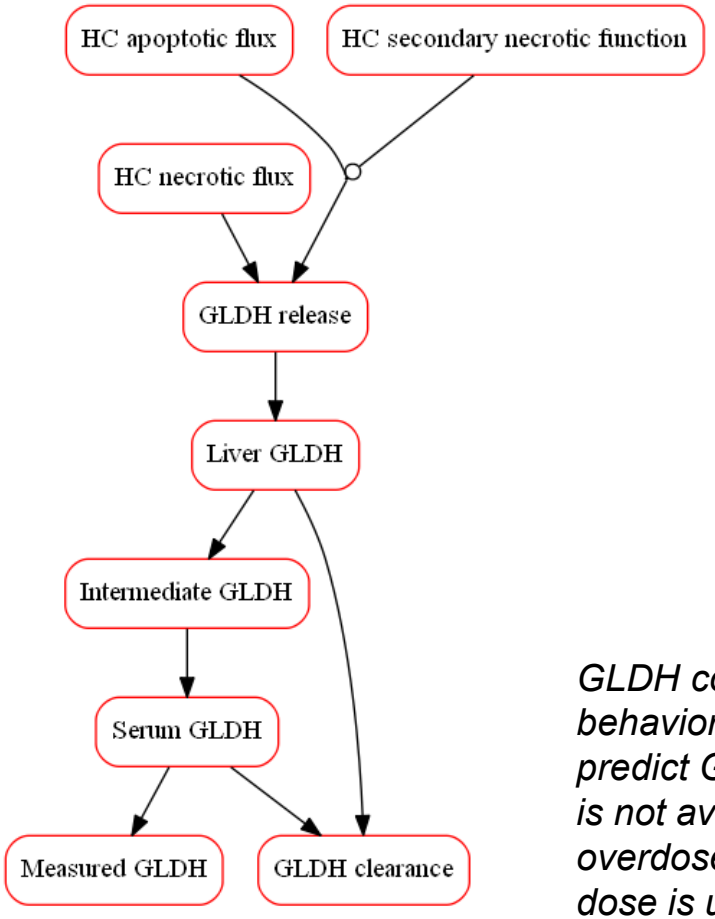
Burgess 2017 ASCPT

Black bar (screen); grey bar (exit); $^{**}P < 0.01$; $^{****}P < 0.0001$

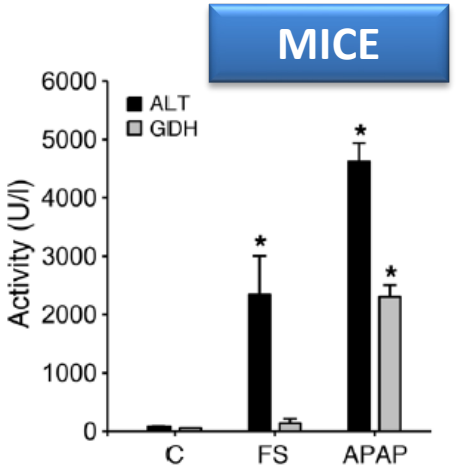
✓, consistent with clinical data; X, not consistent with clinical data

Clinical Data and Simulation Results

GLDH to Be Included in DILIsym v8A with Similar Mathematical Structure to ALT

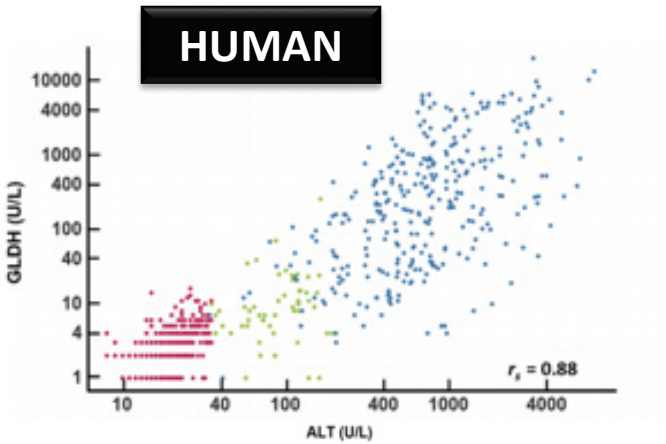


- GLDH is a mitochondrial enzyme primarily found in liver
- Similar to ALT, elevations of serum GLDH are a result of enzyme release due to hepatocellular necrosis and/or apoptosis
- Elevations in GLDH may provide a mechanistic understanding of liver injury
- GLDH release is greatest with mitochondrial toxicity (McGill 2012)



McGill 2012

GLDH correlates well with ALT, a behavior that may be exploited to predict GLDH when exposure data is not available, e.g., drug overdose clinical data where the dose is unknown



Shomaker 2013

Clinical Data and Preclinical Data

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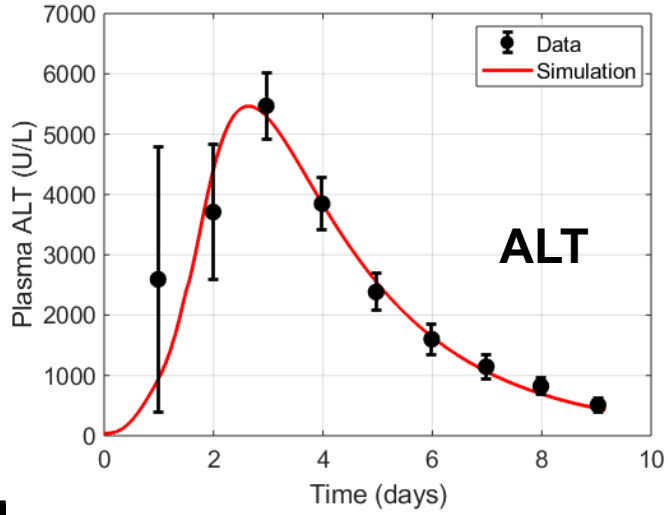
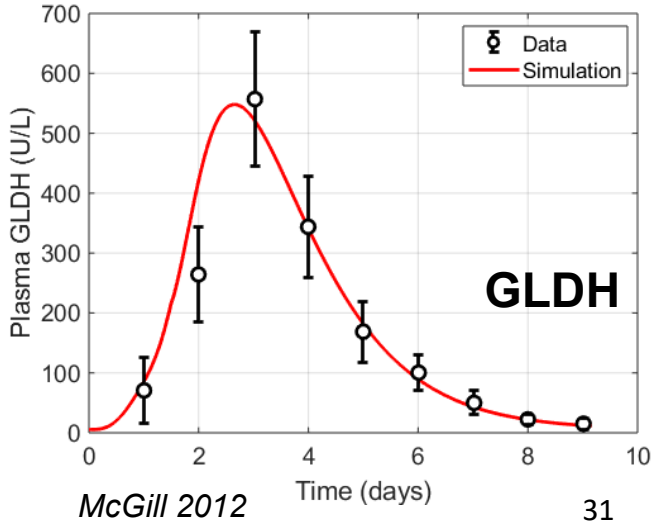
Human GLDH Sub-model Successfully Recapitulates GLDH Clinical Data

HUMAN

- The time profile of simulated ALT was determined by invoking the direct necrosis model implemented in the DILIsym
  - The amount of hepatocellular death was optimized using clinical ALT as a target signal (McGill 2012)
- Using hepatocyte death as injury driver, the time profile of simulated GLDH was determined based on the clinical GLDH response (McGill 2012)
  - Some key model parameters were extracted from the literature while others were optimized using the clinical GLDH activity as a target signal





McGill 2012

Key DILIsym Parameters	Value	Source (comment)
Baseline GLDH	5.5 U/L	Schomaker et al (2013), Tox. Sci 132:276-283. (reported value ranges 1 – 10 U/L)
Serum GLDH half-life	16 h	Church & Watkins (2017), Liver Int. 37 (11):1582–1590
Liver GLDH half-life	24 h	Jennissen (1995) Eur. J. Biochem. 23I, 1-30 (used a reported value for rat)
GLDH delay time constant, GLDH release from necrotic cells, and others	-	optimized

Clinical Data and Simulation Results

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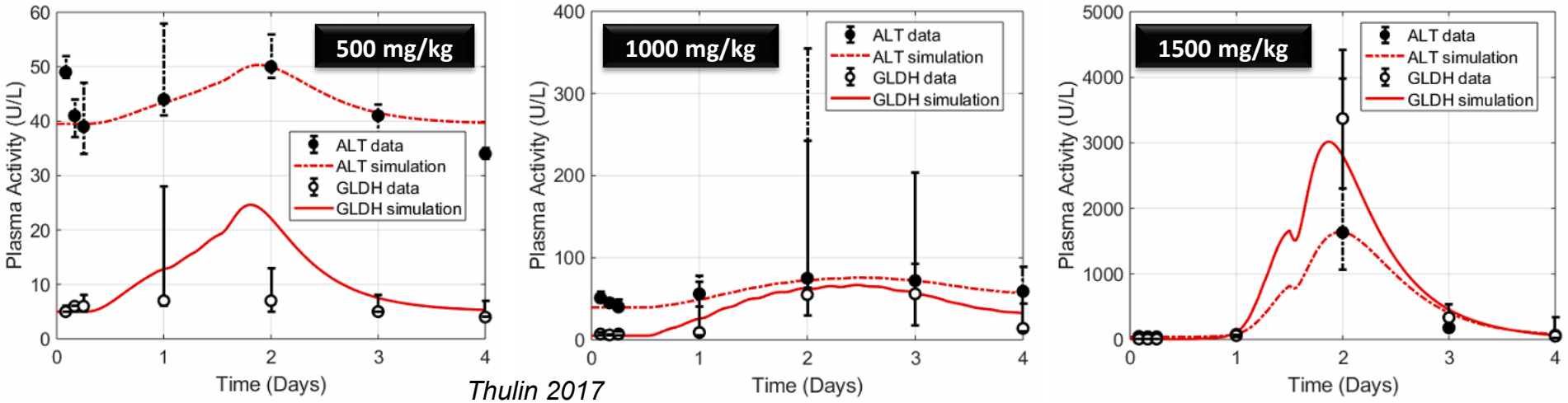
Rat GLDH Sub-model Recapitulates GLDH Preclinical Rat Data

RAT



Thulin 2017

- Preclinical Data: Groups of male Crl:WI (Han) rats 6 – 8 weeks of age received 500, 1000, or 1500 mg/kg of APAP p.o. (Thulin 2017)
  - *Some received a single dose while others received daily administrations of APAP for 2, 3, or 4 days before sacrificed*
- The model employed plasma ALT as a target for capturing the necrotic flux driving injury

Key DILIsym Parameters	Value	Source (comment)
Baseline GLDH	5 U/L	Thulin et al (2017), Biomarkers 22:461-469. (used the median of reported baseline values)
Serum GLDH half-life	8 h	Comprehensive Medicinal Chemistry III, pp 267
Liver GLDH half-life	24 h	Jennissen (1995) Eur. J. Biochem. 23I, 1-30
GLDH delay time constant, GLDH release from necrotic cells, and others	-	optimized

Preclinical Data and Simulation Results

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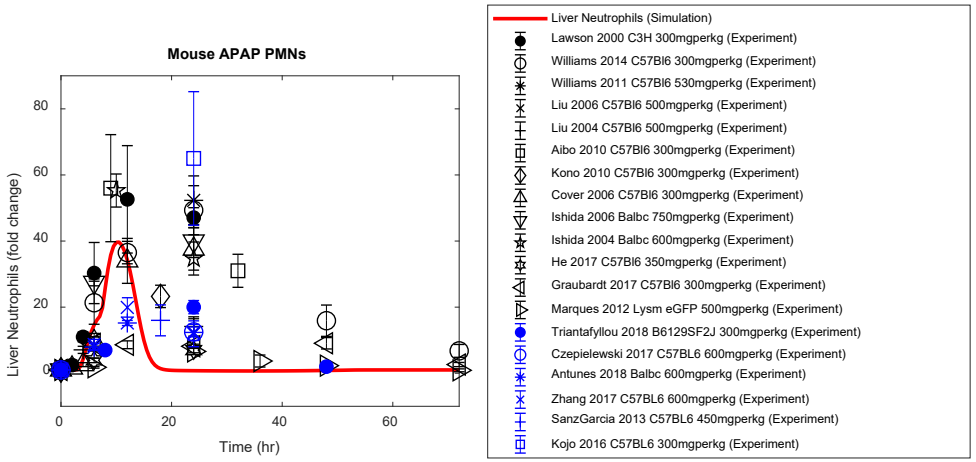
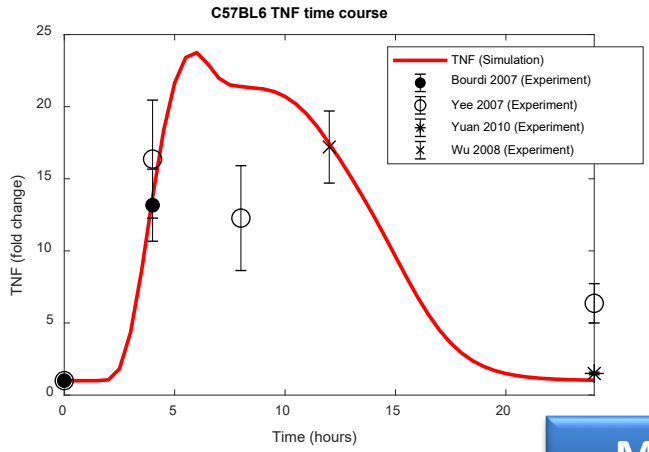
DILIsym v8A Includes Neutrophils

- Following APAP overdose, magnitude of simulated PMN accumulation is consistent with the majority of published data, by design
  - Baseline mouse shown; breadth of data provide extensive opportunity for creation of alternate simulated mice
  - Simulated macrophage accumulation updated
- Mediator production profiles updated to account for production by PMNs
  - Closer examination of the data revealed markedly lower TNF-α production by PMNs on a per cell basis (relative to macrophages)
  - Contribution of PMNs to injury or recovery dependent on cell accumulation
- Variability in the data allow for exploration of alternative mice
  - Greater or lesser PMN accumulation
  - Greater or lesser PMN mediator production





MICE

Preclinical Data and Simulation Results

DILIsym Services

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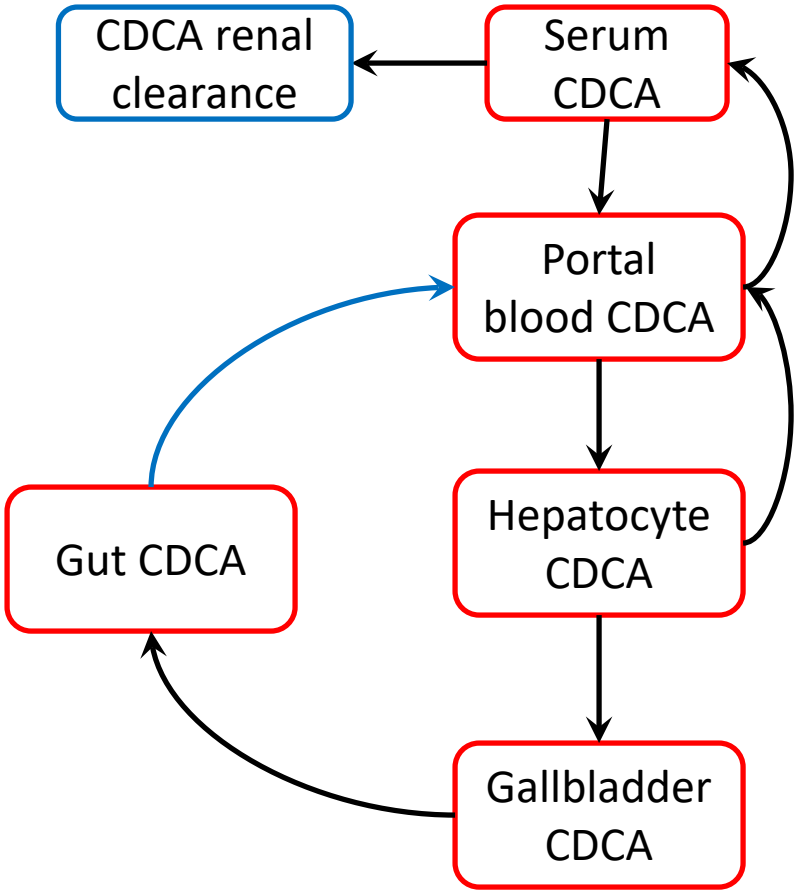
Bile Acid Renal Clearance and ASBT-Mediated Gut Reuptake Added for v8A

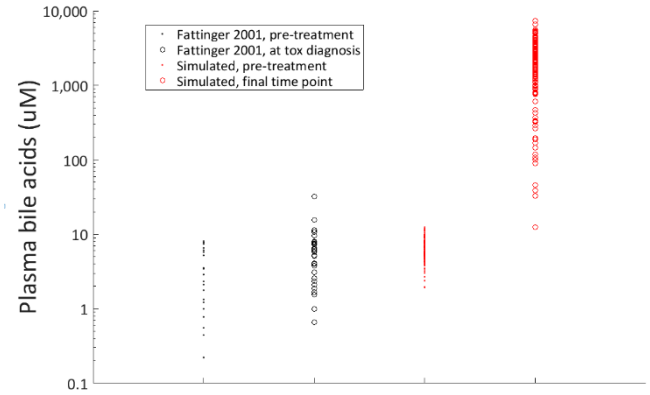
- DILIsym v8A includes the effect of renal clearance on plasma bile acids
- Saturable gut uptake implemented in v8A
  - Recirculation fraction used in v7A
- **All bile acid baseline models and SimPops re-optimized for v8A**



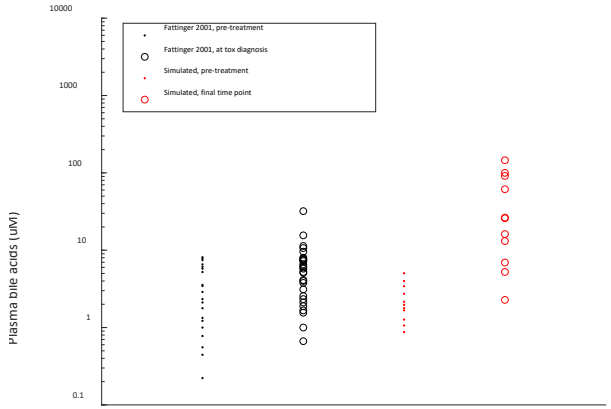
Human Plasma Bile Acids Recapitulate Literature Data Better in v8A

- v8A_1 SimPops used to model bosentan (500 mg BID, 30 days)
  - Bile acids at beginning and end of simulation compared to Fattinger data for individuals with ALT elevations that do not "die" in simulation
- Plasma bile acids do not increase as much as in v7A with v4A_1 SimPops

v4A-v7A



v8A



Clinical Data and Simulation Results

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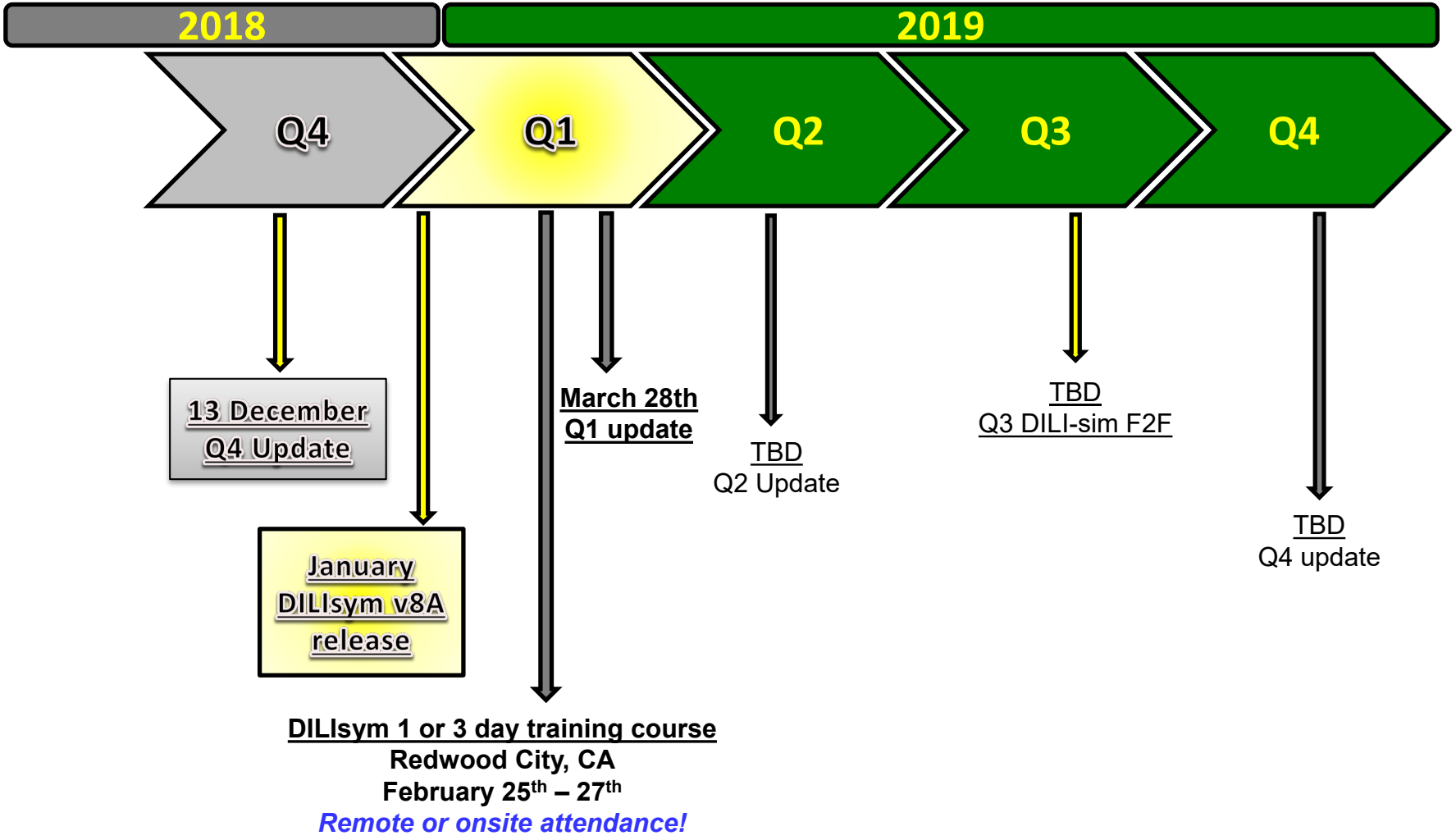
DILIsym v8A Release Webinar Agenda

- Introduction to DILIsym Software platform
- DILIsym version 8A highlights
- DILIsym v8A demo
- Questions

Key DILIsym Dates in 2019



DILIsym Services

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3 Day DILIsym Workshop Will Be Offered in Redwood City, CA in February Alongside GastroPlus Training: Remote Attendance Offered

- When: Feb. 25-27, 2019 (3 day workshop or mix and match days)
- Where: Seaport Conference Center, Redwood City, CA **or attend remotely**
- What: 3 day DILIsym workshop to include:
  - **Day 1**: General DILIsym Introduction (slides and demo)
  - **Day 2**: Step by step compound representation in DILIsym (hands-on)
  - **Day 3**: Advanced features (SimPops, Monitoring, Optimization, Specified Data; will be hands on)
  - Computers and software provided for onsite attendees if needed
- Who: beginning and advanced users of DILIsym
  - Feel free to attend 1 day or all 3 days for topics of interest
- Pricing per attendee
  - Tier 1 Members: $800 for 3 days ($400 for 1 day)
  - Tier 2 Members: $1,000 for 3 days ($500 for 1 day)
  - Non-members: $1,200 for 3 days ($600 for 1 day)
  - Discounted for academic / government

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Questions?

Contact Us Today for a Free Trial Version!

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