Modeling drug- and chemical-induced hepatotoxicity with systems biology approaches

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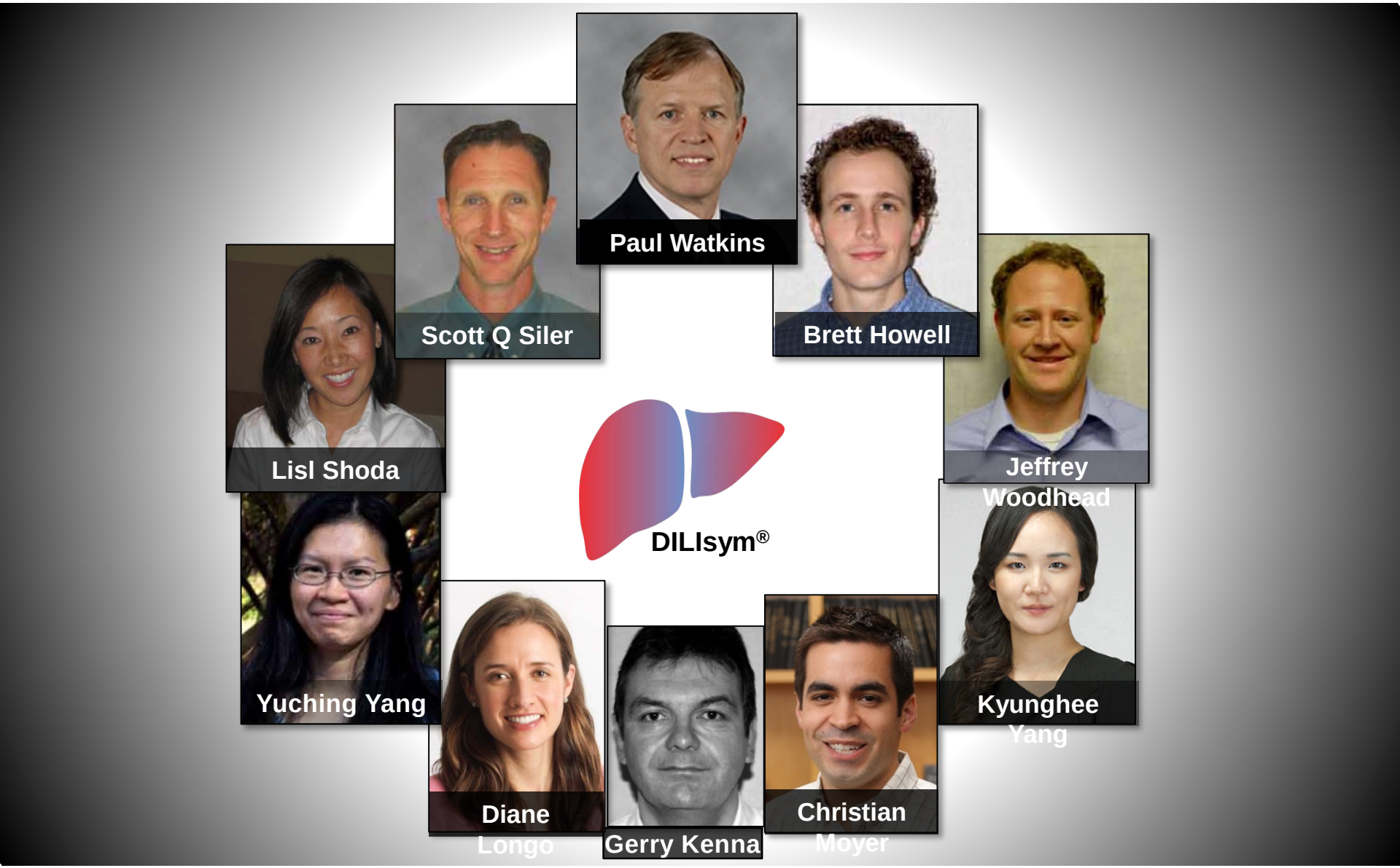
Lead Scientist and Manager, DILI-sim
The Hamner-UNC Institute for Drug Safety Sciences
Research Triangle Park, NC

The DILI-sim Initiative Is a Partnership between the Hamner Institutes and Pharmaceutical Companies to Minimize DILI

- *Overall Goals*
  - *Improve patient safety*
  - *Reduce the need for animal testing*
  - *Reduce the costs and time necessary to develop new drugs*

The DILI-sim Team and the SAB



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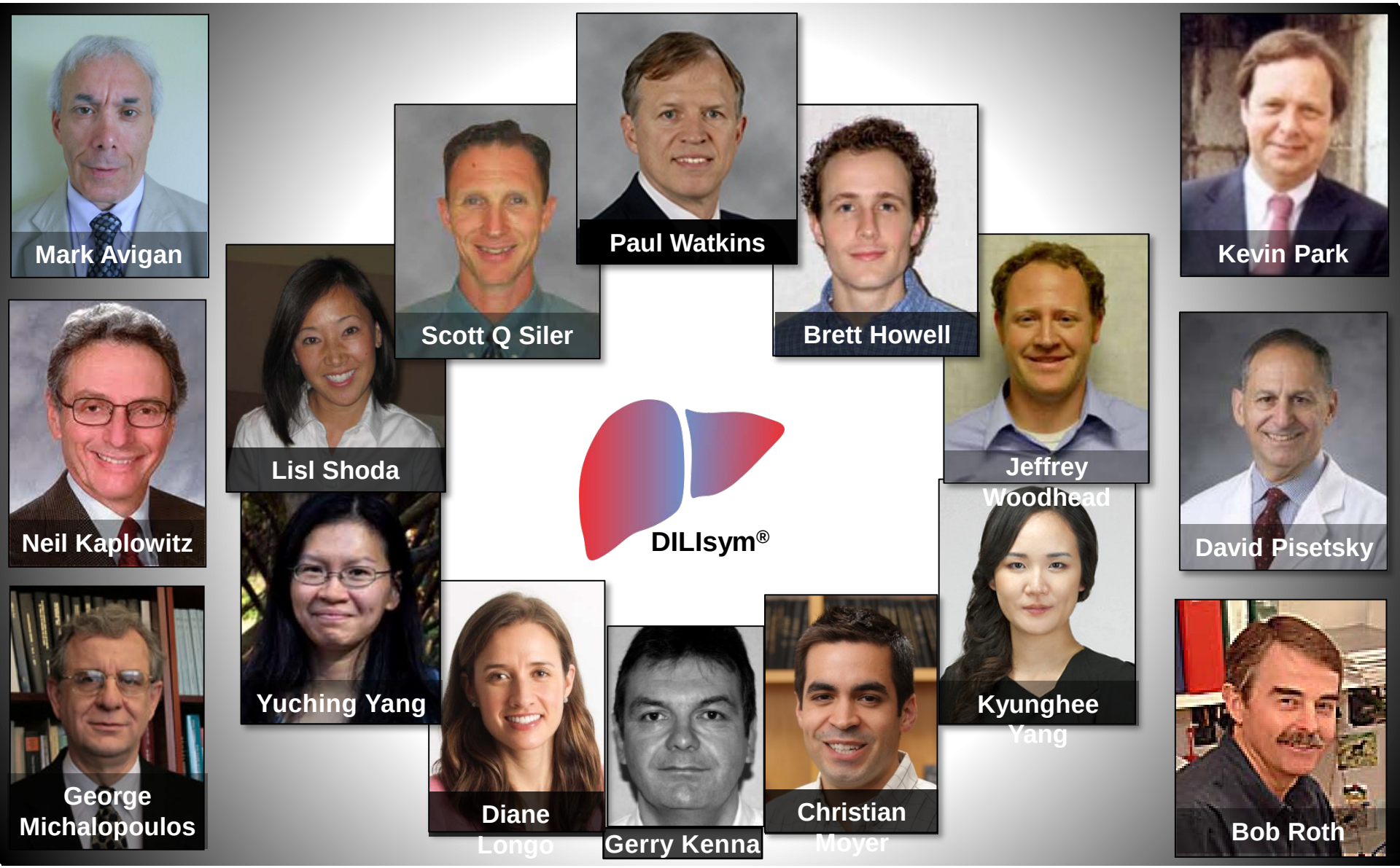

Goals of DILI-sim and Intended Applications of DILIsym®

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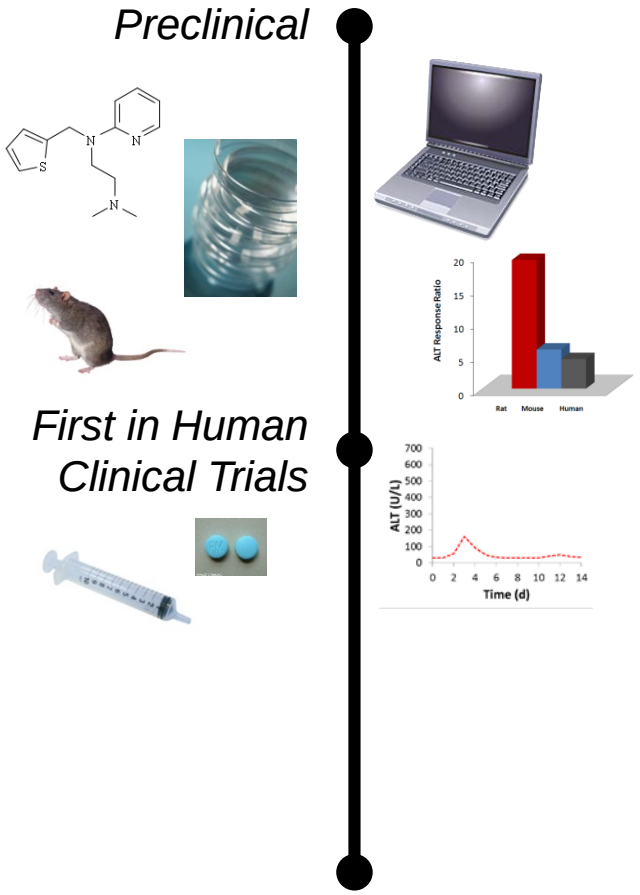
DILI-sim Stage 1 goals:

- Develop DILIsym® software to better inform safety decisions within early portion of drug development pipeline
  - 3 year cycle 2012-2014
  - *In vitro* to *in vivo*
  - Preclinical to first-in-human
  - Biomarker interpretation
  - *In vitro, in vivo,* and/or clinical data as inputs



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DILI-sim Stage 2 goals:

- Develop DILIsym® software to better inform safety decisions extending through late phases of drug development pipeline
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  - Inter-patient variability (with SimPops™)
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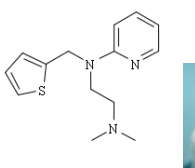
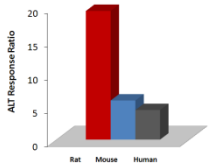
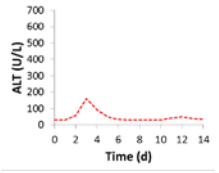
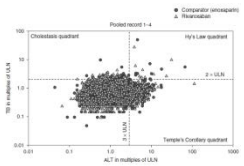
Preclinical

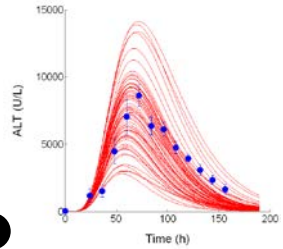




First in Human Clinical Trials







Phase II/III Clinical Trials and Post-Market Surveillance

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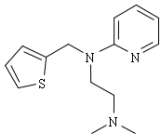
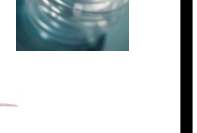
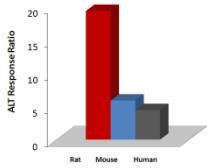
Intended applications:

- Predictions of hepatotoxicity risk for humans and preclinical animal models
- Enhanced understanding of elements contributing to observed liver signals in clinical trials

Preclinical







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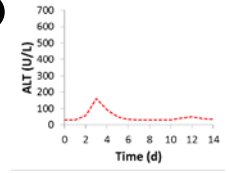

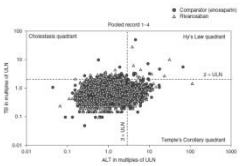

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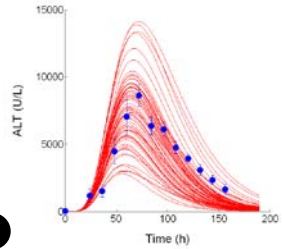
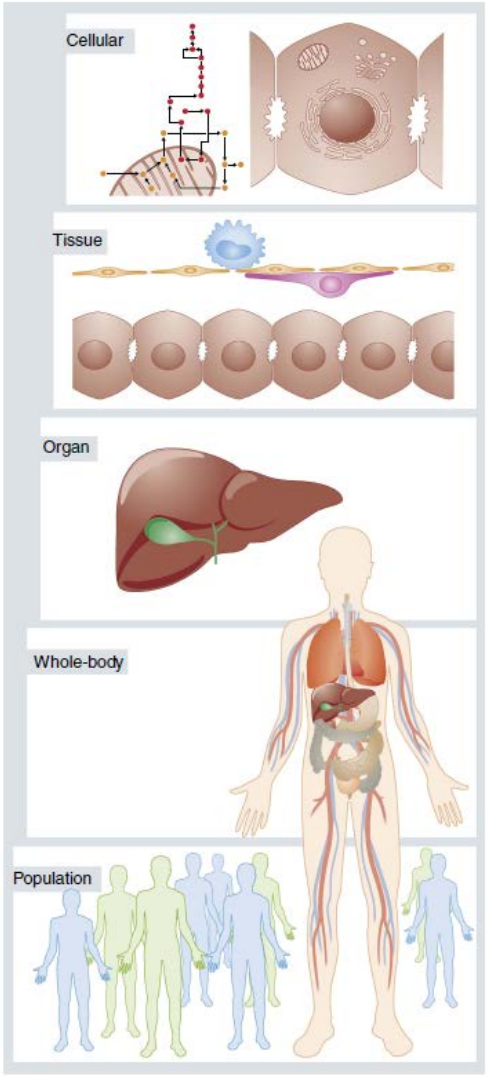


DILIsym®: 'Middle Out' and Multi-Scale



Kuepfer 2010, Molecular Systems Biology

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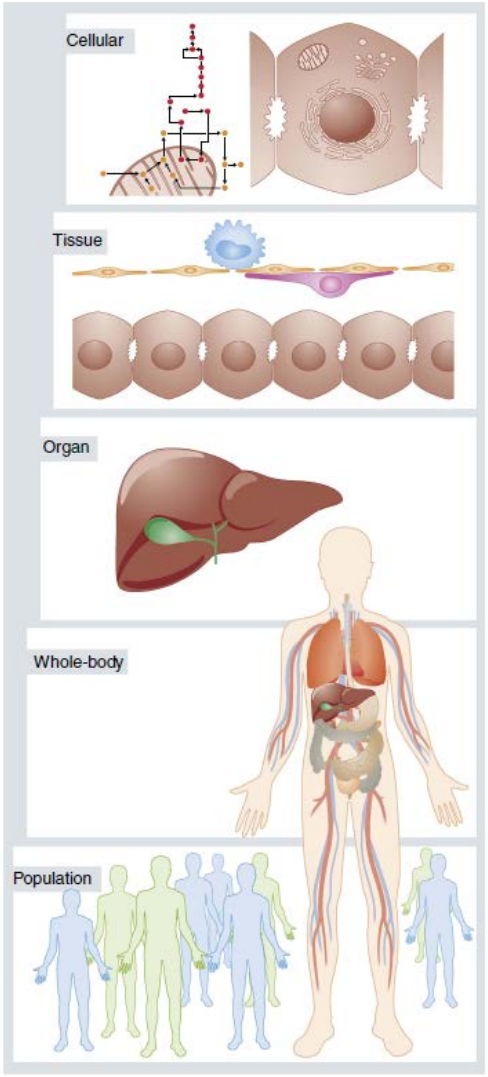
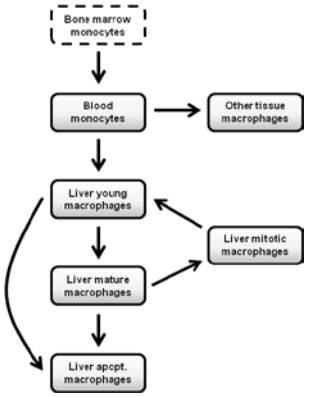


Cellular life-cycle



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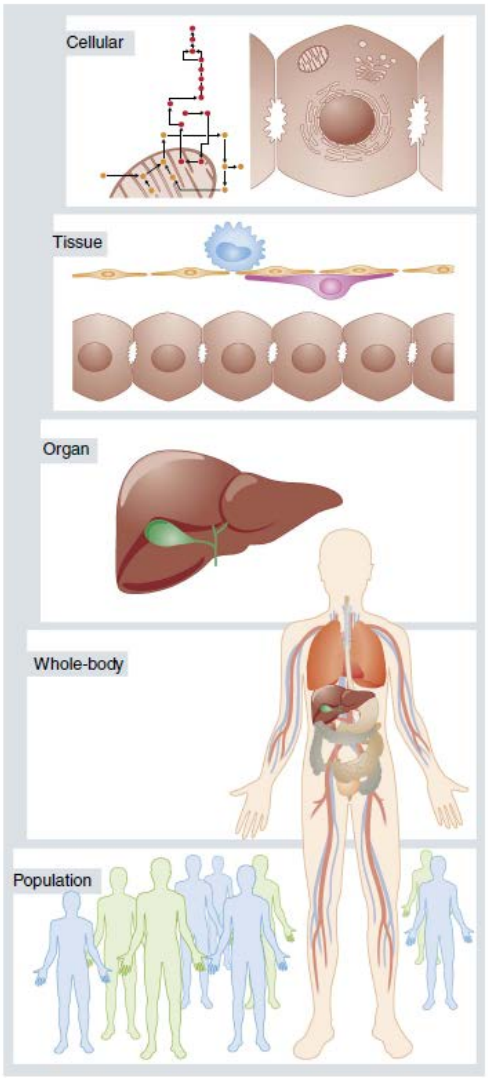
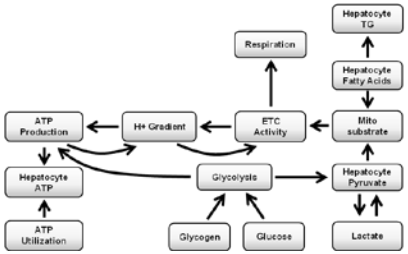


Mitochondrial dysfunction



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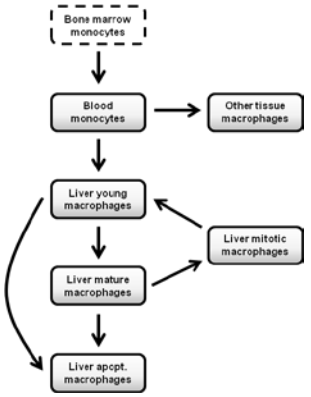

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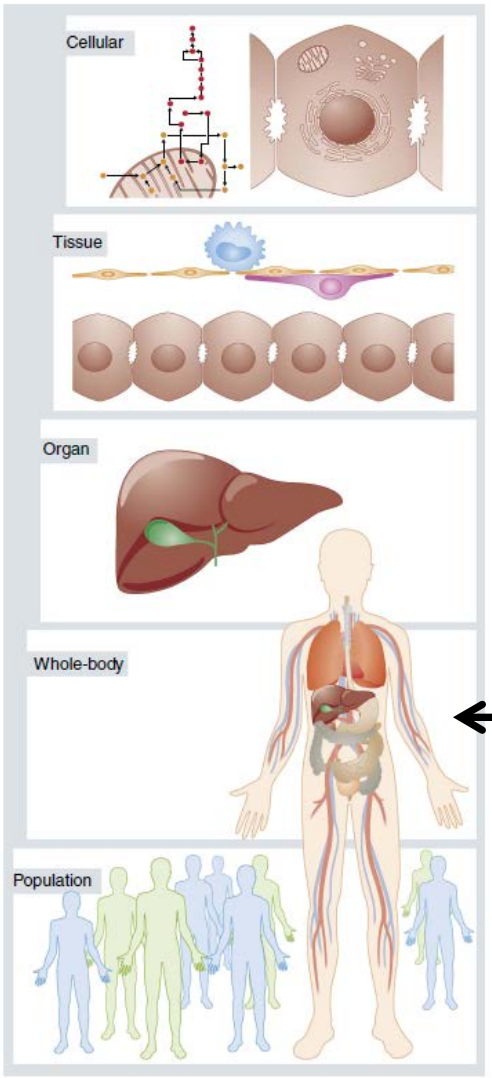

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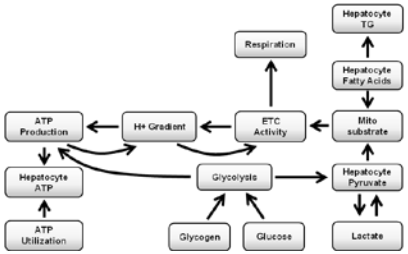

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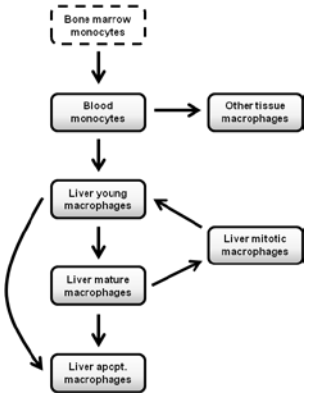
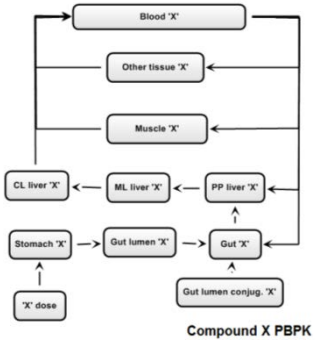


Drug distribution & metabolism



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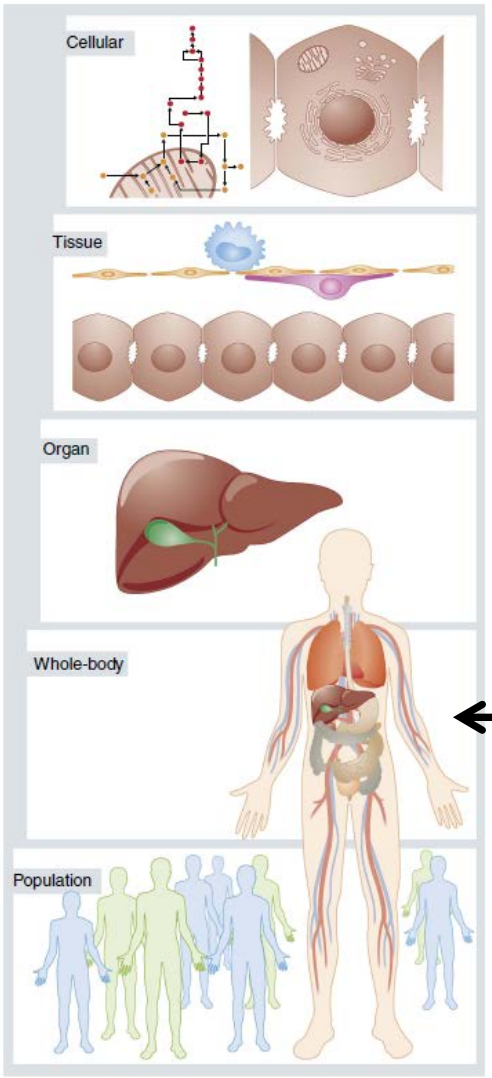

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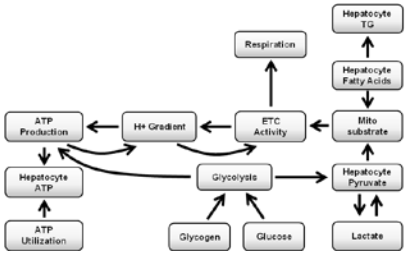

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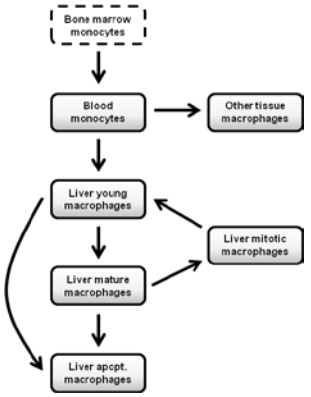

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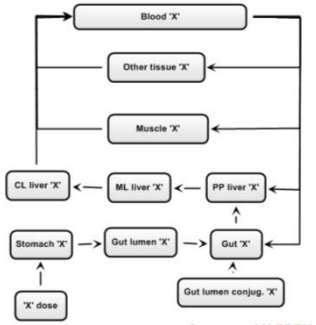
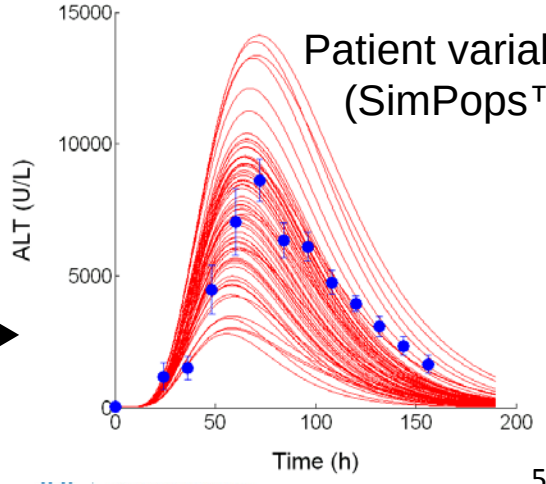


Compound X PBPK

Patient variability (SimPops™)



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DILIsym® Overview

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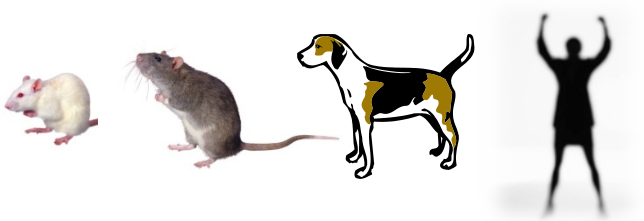

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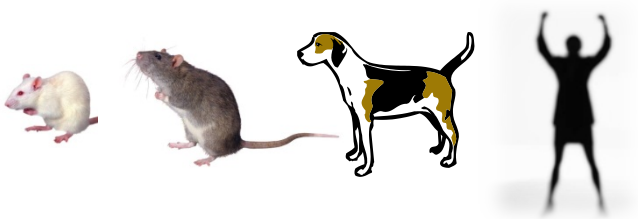

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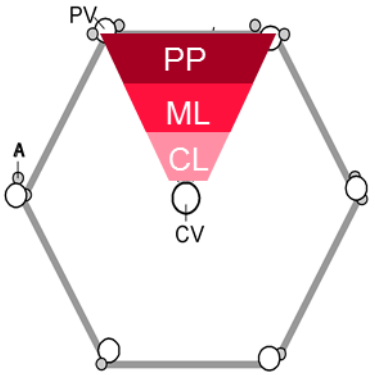

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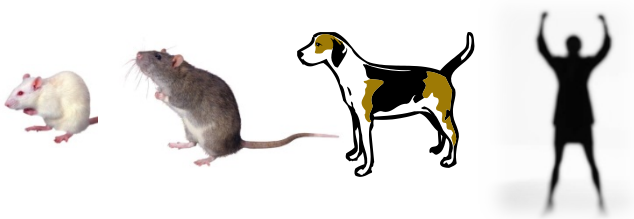

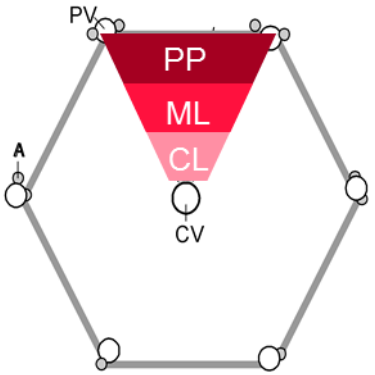

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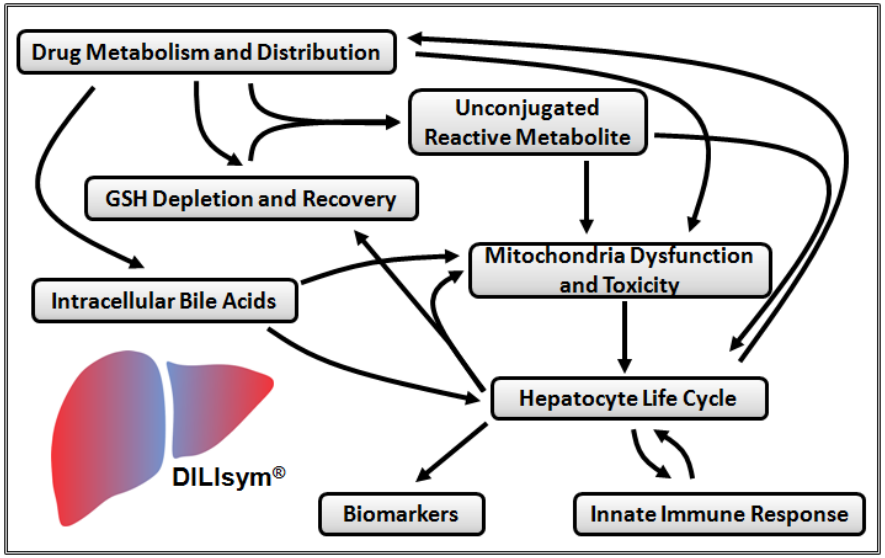

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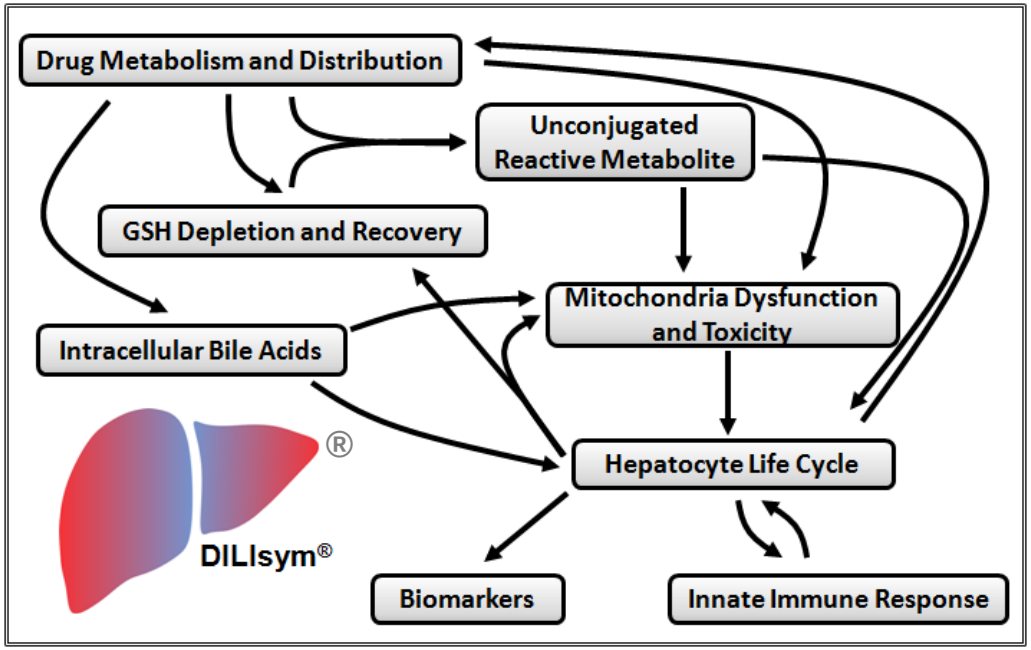
Key Areas for DILIsym® Data Inputs and Simulation Results Comparators

Drug Absorption and Distribution

Drug Metabolism

Proposed Hepatotoxicity Mechanism

Biomarkers



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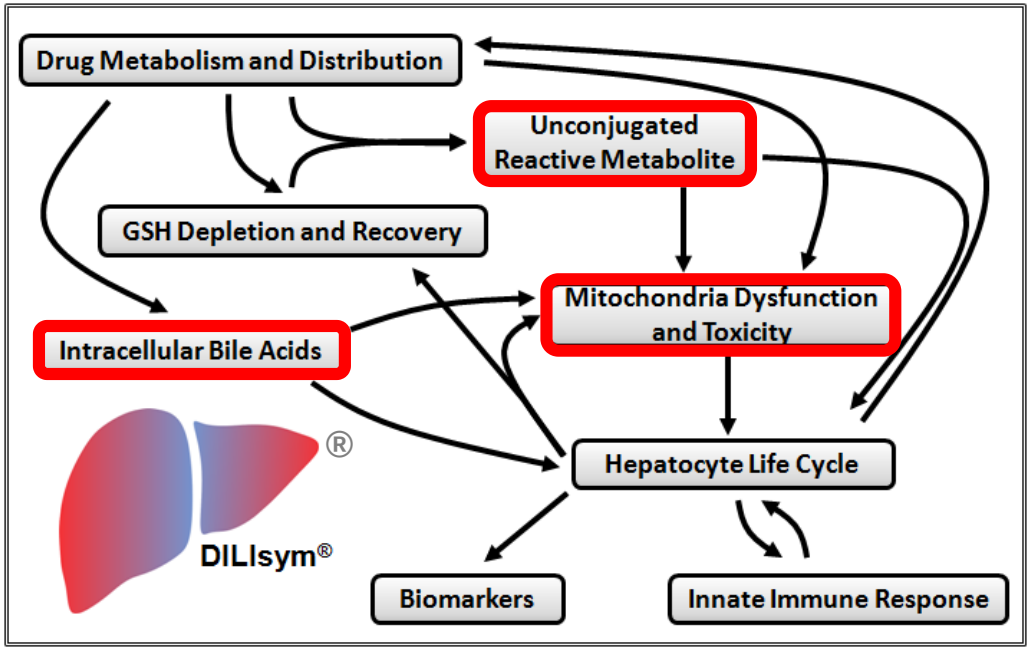

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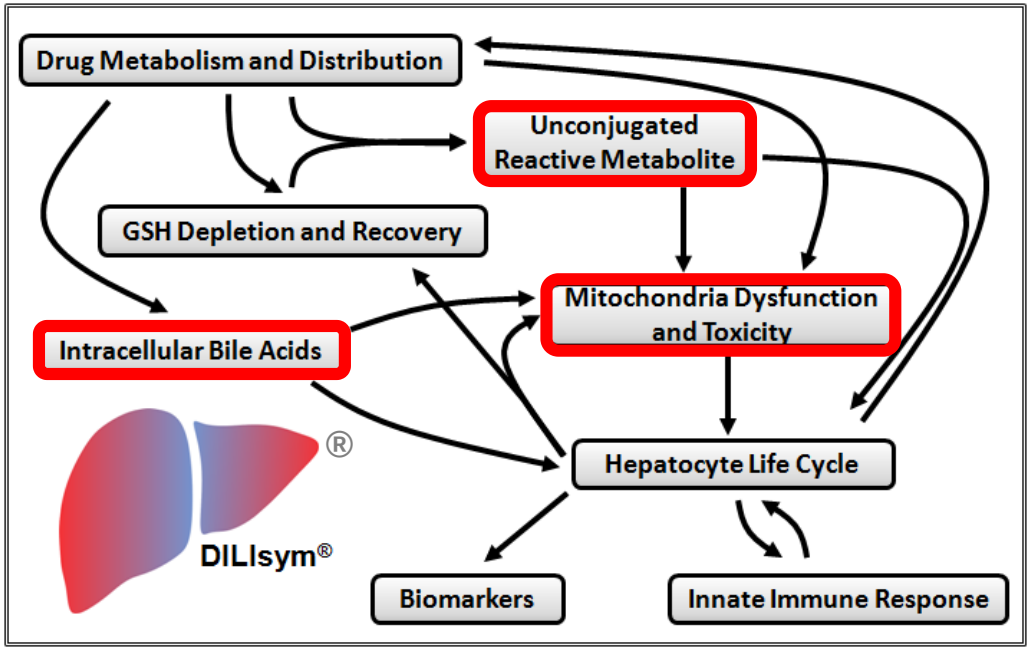


- *BSEP, NTCP, MRP Ki*
- *OCR, $\Delta\Psi m$*
- *ROS/RNS increases*
- *GSH depletion, adduct formation*
- *ATP depletion*
- *Apoptosis vs necrosis*

Examples of DILIsym® Applications

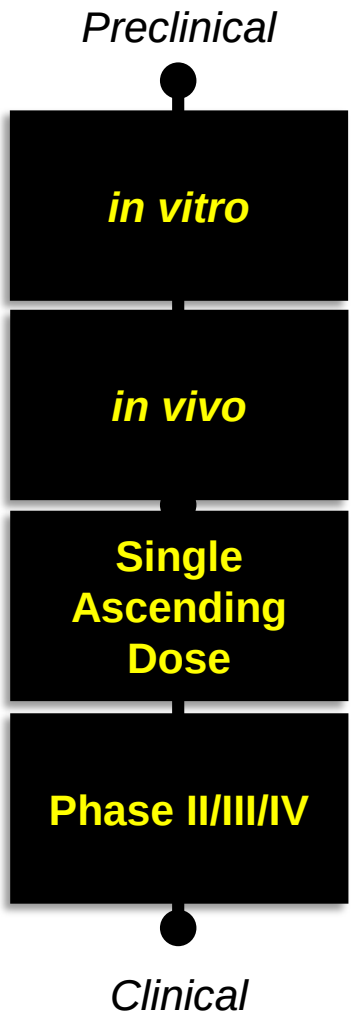
IVIVE

J Pharmacokinet Phar 39(5): 527-541. 2012.

Rank compounds by risk

Toxicol Lett 226(2): 163-172. 2014.

Preclinical biomarker study design



DILI Dose Response Estimation

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CPT Pharmacometrics Syst Pharmacol 3: e98. 2014.

Predicting variability in response

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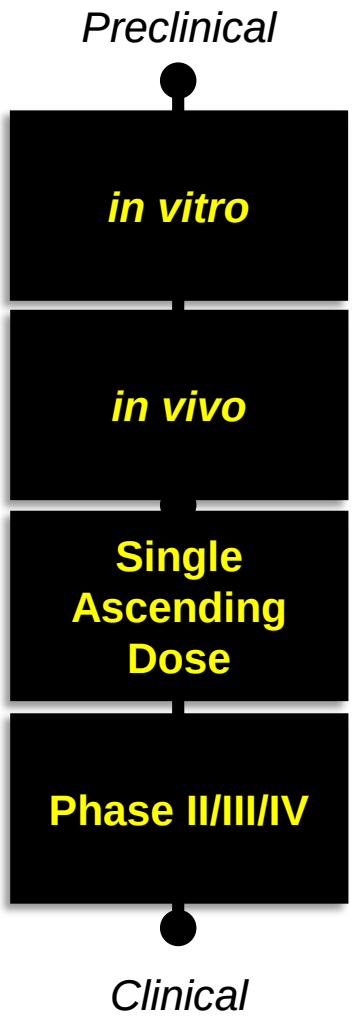

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- Entolimod (single dose) reduces radiation mortality by 40%
  - Satisfies FDA's animal rule for efficacy

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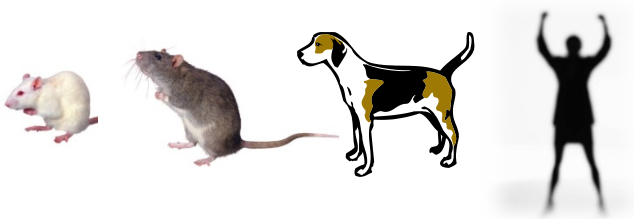

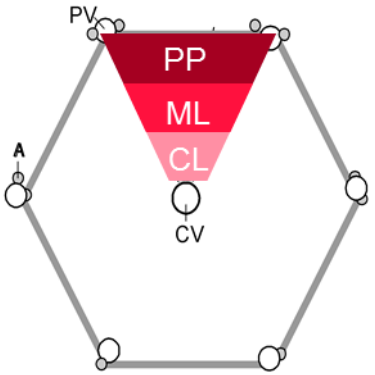

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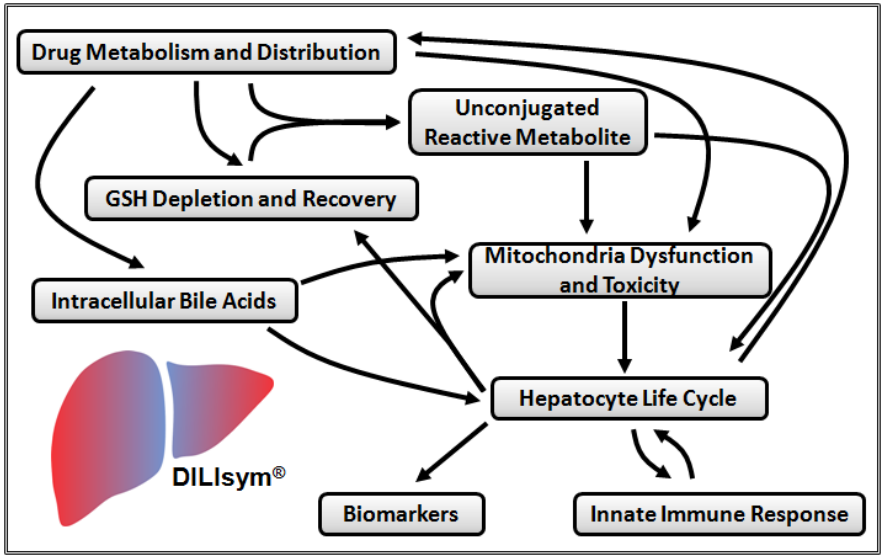

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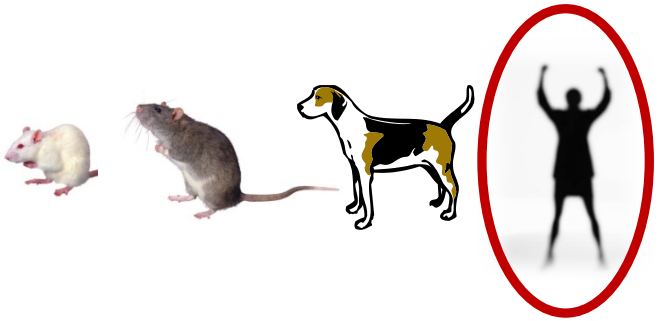

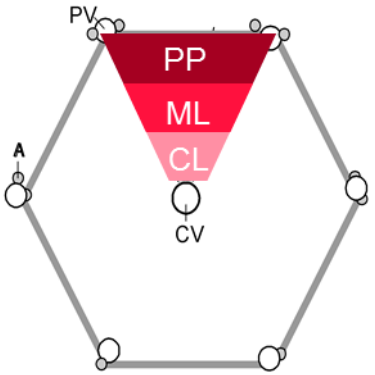

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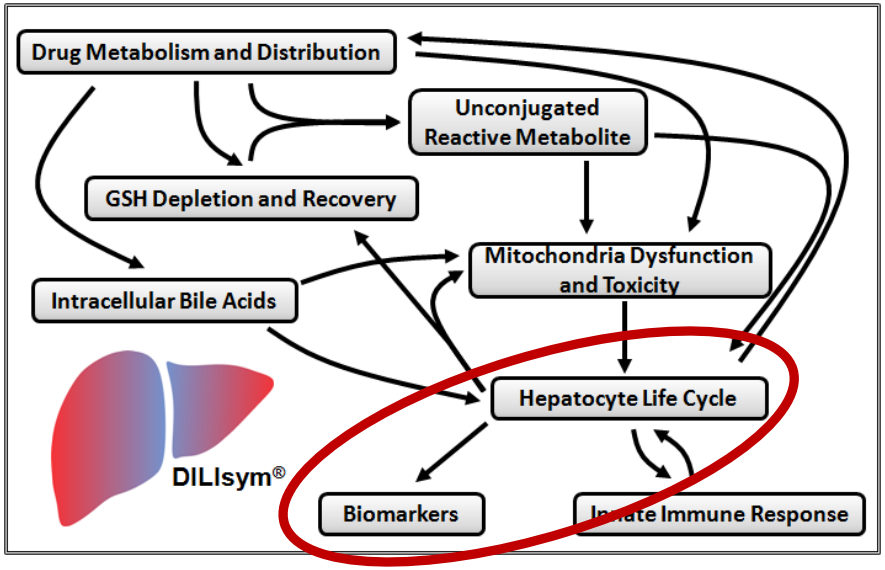
  - **Hepatocyte life cycle**
  - **Biomarkers**



®

Baseline Human Simulations Indicate Minimal Hepatocyte Loss with Entolimod

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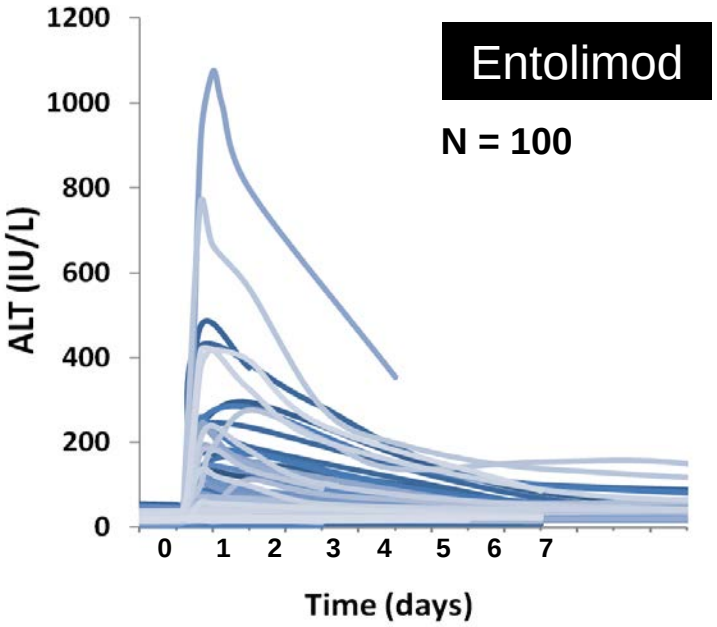
- ALT clinical data
  - Mostly minor elevations
  - Few higher elevations



Baseline Human Simulations Indicate Minimal Hepatocyte Loss with Entolimod

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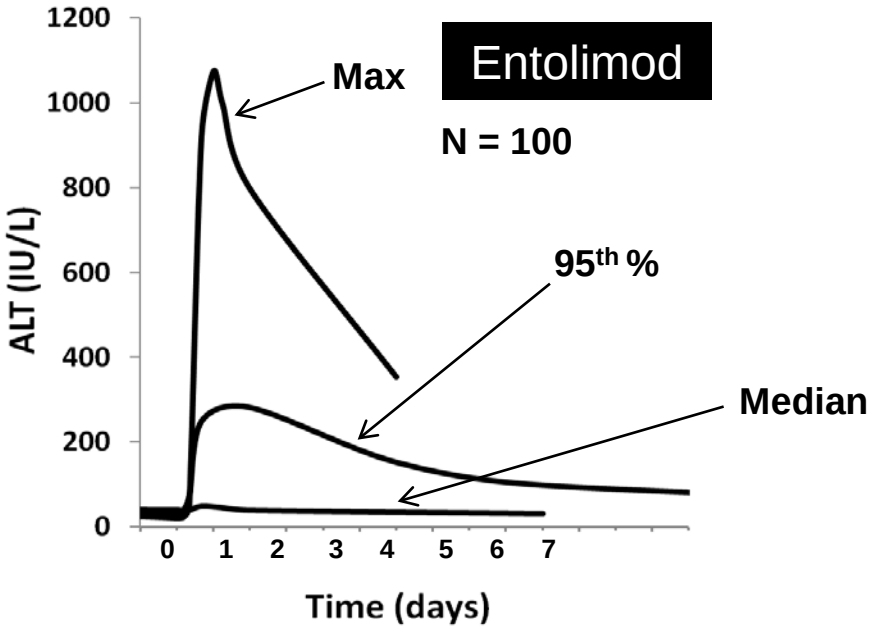
  - Few higher elevations
- Focused on max, 95th percentile, and median ALT levels



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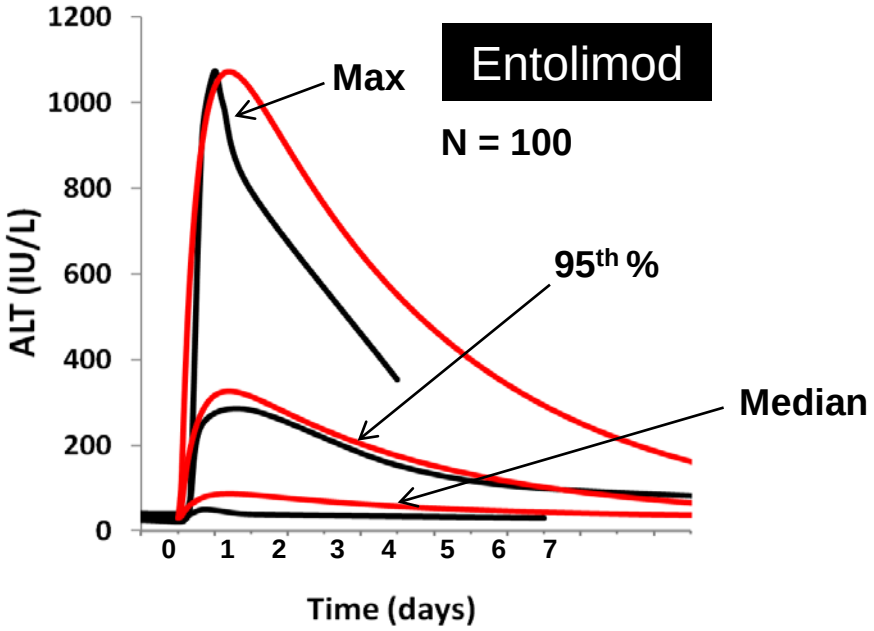
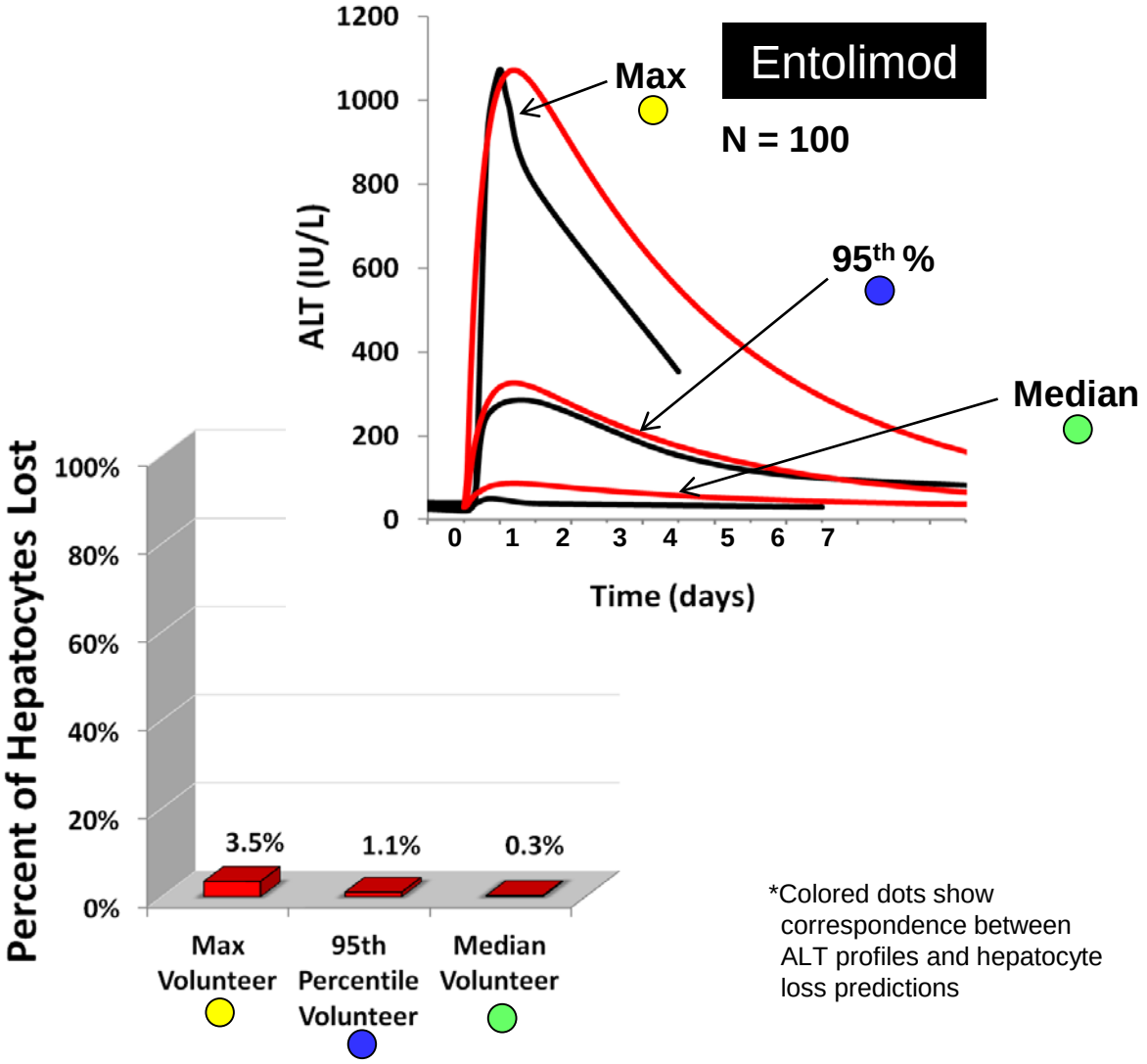


Clinical Data and Simulation Results

Baseline Human Simulations Indicate Minimal Hepatocyte Loss with Entolimod

- ALT clinical data
  - Mostly minor elevations
  - Few higher elevations
- Focused on max, 95th percentile, and median ALT levels
- Simulations agree with ALT clinical data by design
- Minimal hepatocyte inferred from ALT profiles

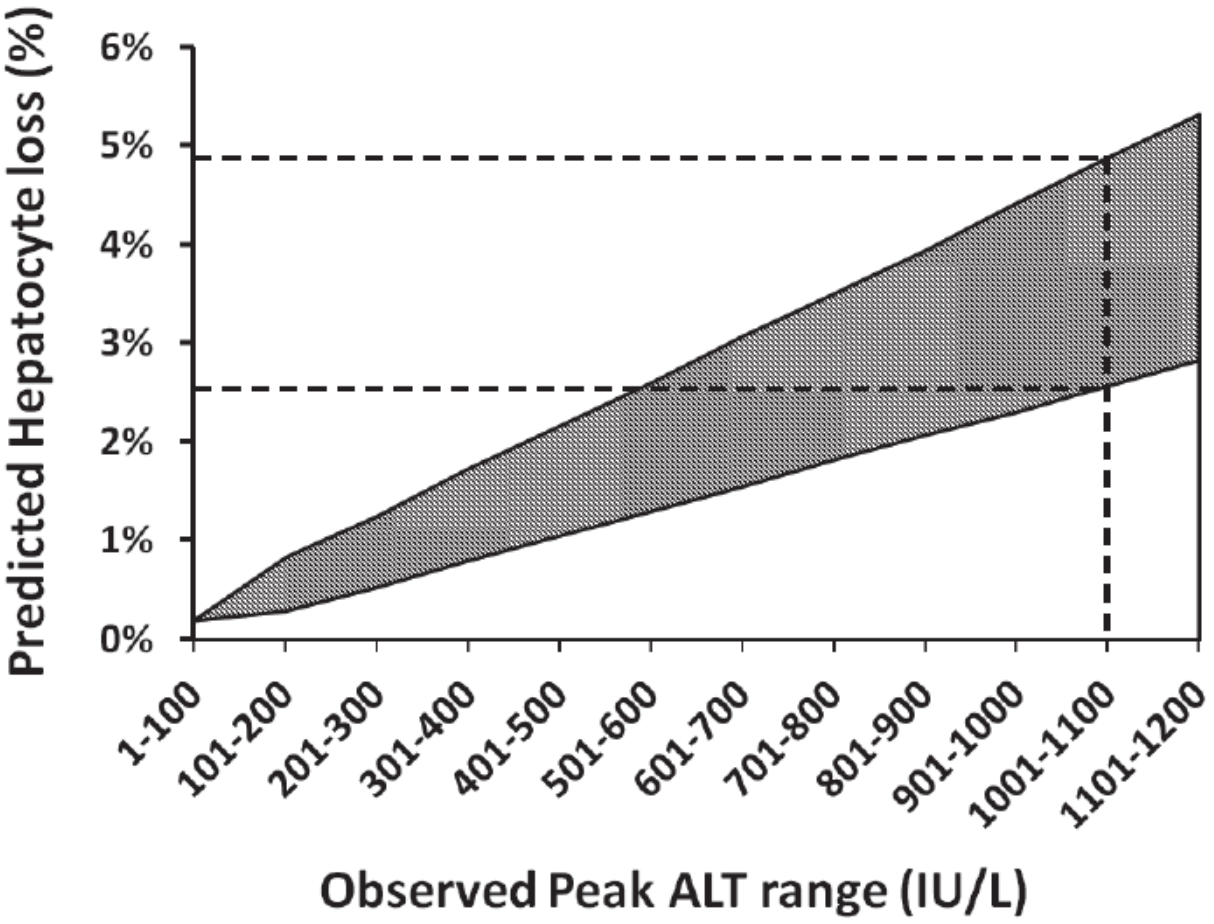


*Colored dots show correspondence between ALT profiles and hepatocyte loss predictions

Clinical Data and Simulation Results

Minimal Range of Hepatocyte Loss Predicted for Entolimod Using Population Sample

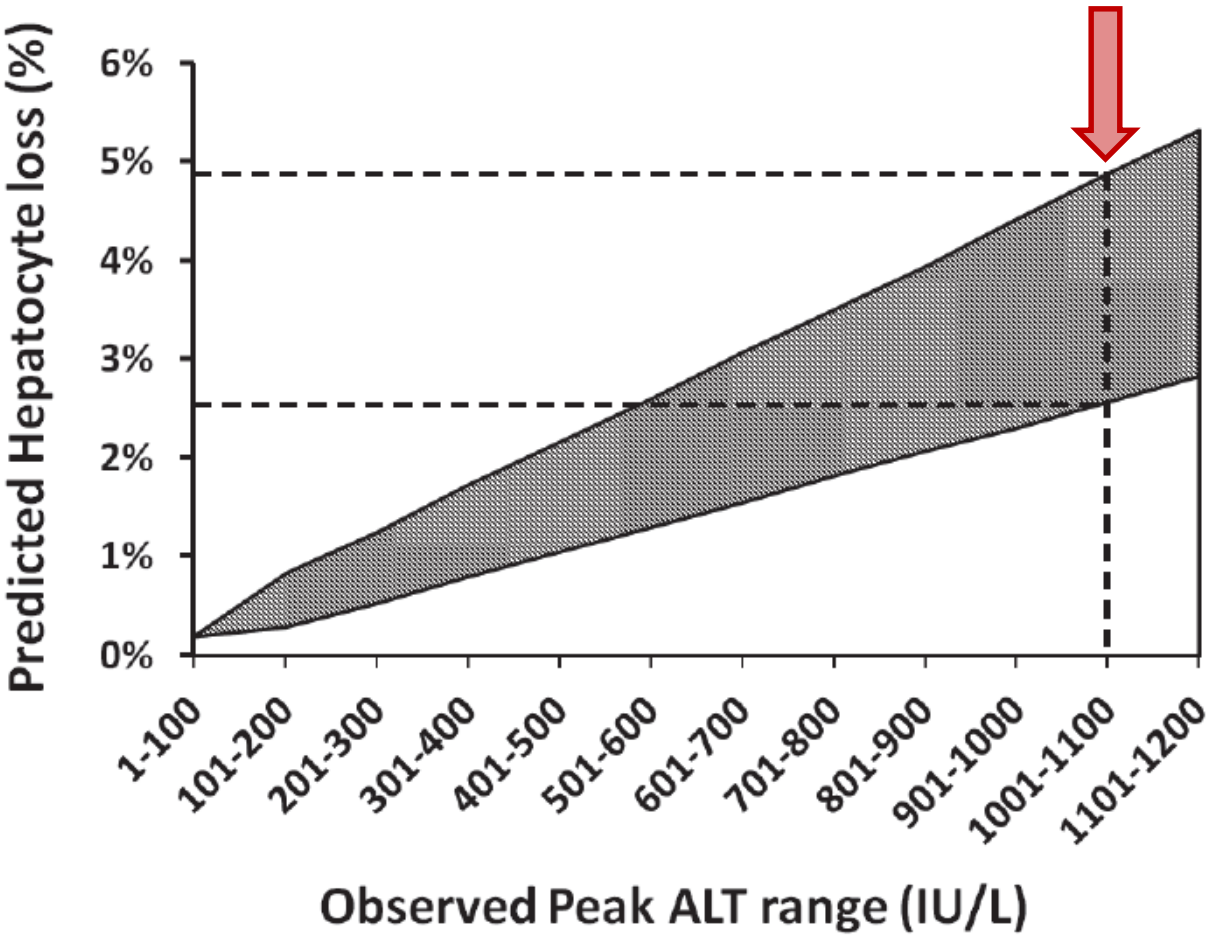
- Various levels of necrosis simulated for population sample



*Predictions only valid for time courses similar to those observed with Entolimod

Minimal Range of Hepatocyte Loss Predicted for Entolimod Using Population Sample

- Various levels of necrosis simulated for population sample
- Max observed ALT (1001-1100 U/L) corresponds with 2.6-4.6% predicted hepatocyte loss



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Project Summary

- Analyses indicate that volunteers with ALT elevations following Entolimod administration likely incurred hepatocyte losses of ≤5%
- The liver should have completely recovered in 2-9 weeks
- Literature review and modeling heparin-induced ALT profiles support the conclusion that the potential hepatocyte loss occurring in the Entolimod clinical trial did not represent a serious health threat
- DILIsym® simulation results were submitted to the FDA in support of the safety of Entolimod

Examples of DILIsym® Applications

IVIVE

J Pharmacokinet Phar 39(5): 527-541. 2012.

Rank compounds by risk

Toxicol Lett 226(2): 163-172. 2014.

Preclinical biomarker study design

DILI Dose Response Estimation

Clinical biomarker analysis

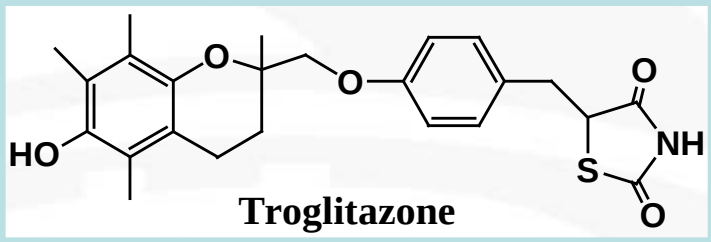
CPT Pharmacometrics Syst Pharmacol 3: e98. 2014.

Predicting variability in response

Modeling for Susceptibility Factors: The Case Study with Troglitazone

Kyunghee Yang
Division of Pharmacotherapy and Experimental Therapeutics
UNC Eshelman School of Pharmacy
The University of North Carolina at Chapel Hill

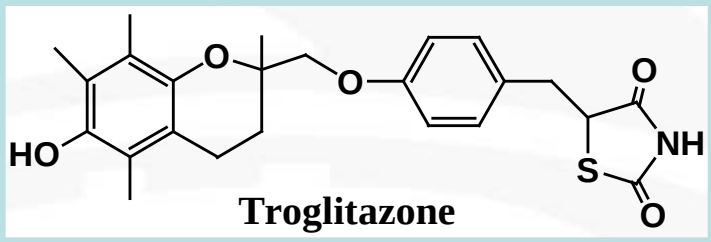
Troglitazone (TGZ)



Troglitazone

- First in thiazolidinedione class; PPARγ agonist
  - Reduces hepatic and peripheral insulin resistance
  - Approved for the treatment of type II diabetes

Troglitazone (TGZ)



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  - Hepatotoxicity was not detected in preclinical studies
  - 2% of patients developed ALT elevations >3X ULN in clinical trials
  - Withdrawn from the market due to idiosyncratic hepatotoxicity

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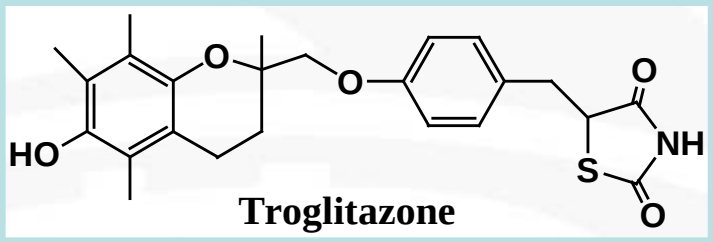

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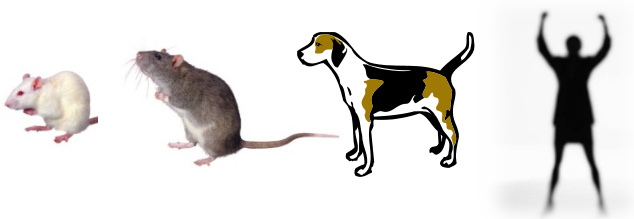
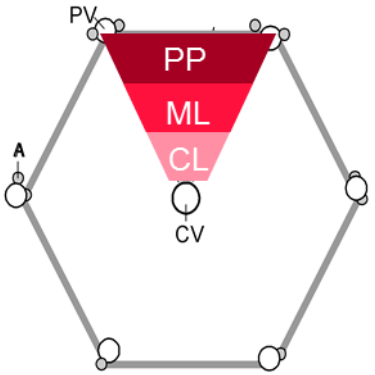
  - Withdrawn from the market due to idiosyncratic hepatotoxicity
- Mechanisms of hepatotoxicity remain unclear
  - Mitochondrial dysfunction
  - Induction of apoptosis
  - Formation of reactive metabolite(s)
  - **Impaired bile acid transport**

DILIsym® Overview

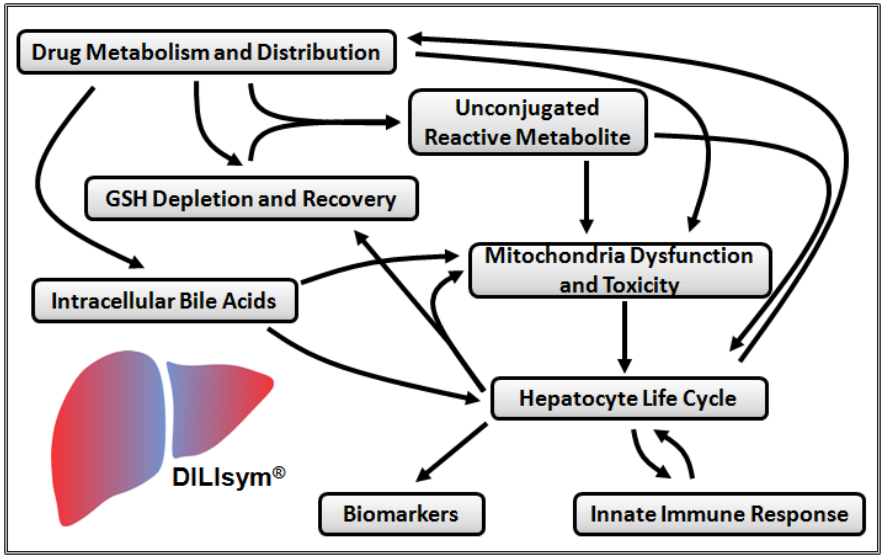
- **Multiple species: human, rat, mouse, and dog**
  - Population variability





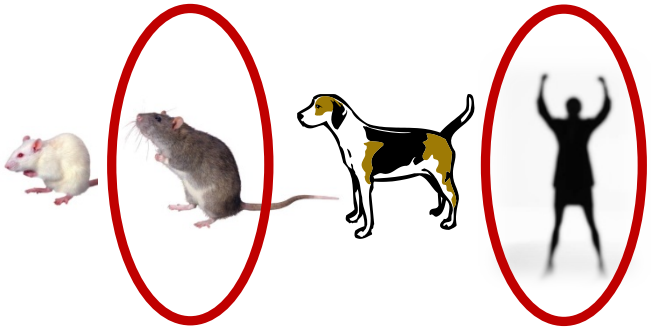
- **The three primary acinar zones of liver represented**

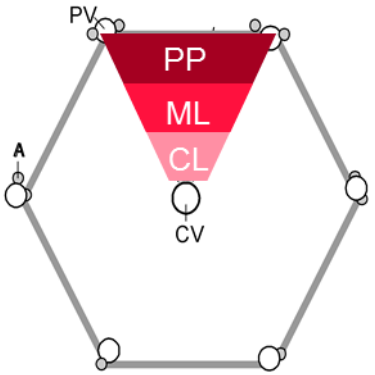
- **Essential processes represented to multiple scales in interacting sub-models**

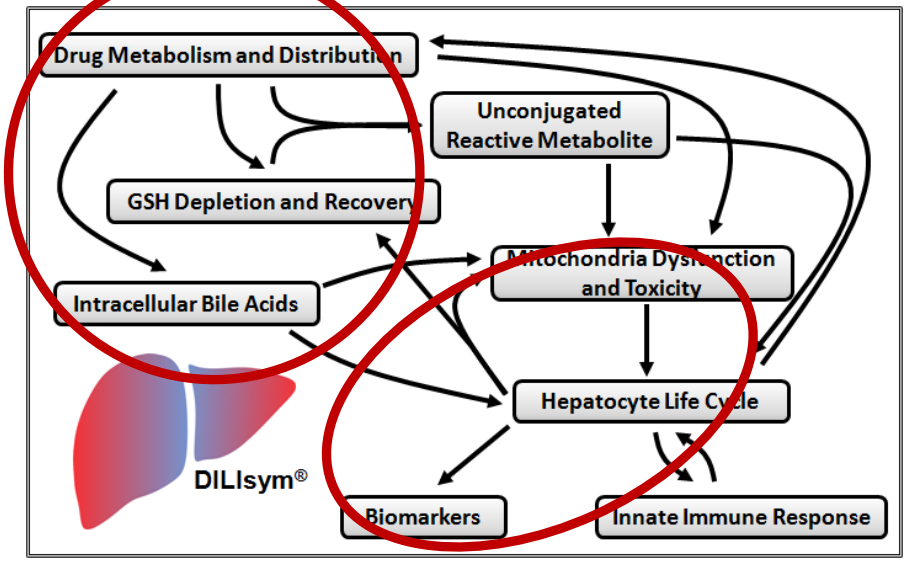


DILIsym® Overview

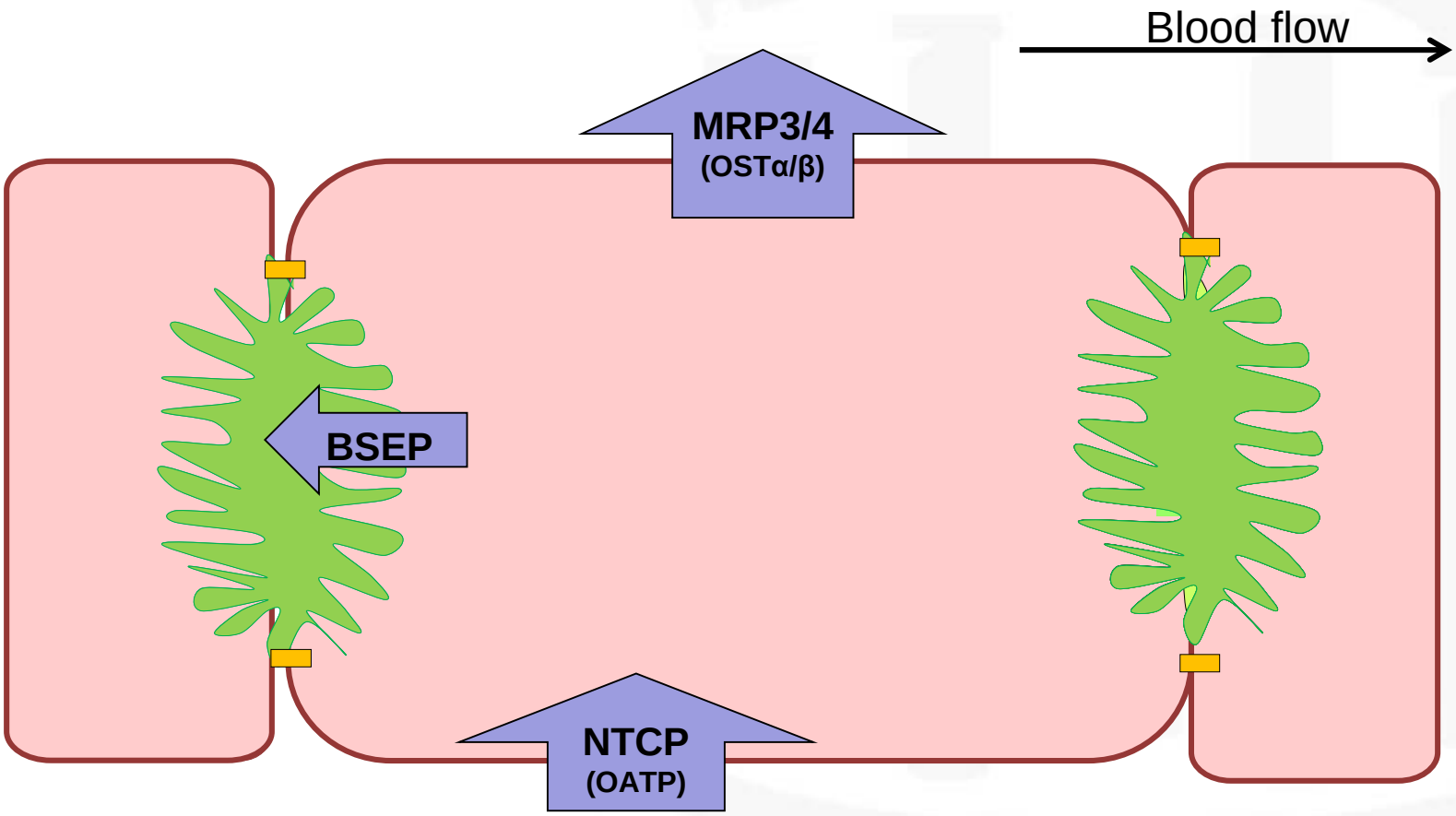
- **Multiple species: human, rat, mouse, and dog**
  - Population variability
- **The three primary acinar zones of liver represented**
- **Essential processes represented to multiple scales in interacting sub-models**
  - **ADME**
  - **Bile acid homeostasis**
  - **Hepatocyte life cycle**
  - **Biomarkers**







Mechanisms of DILI: Transport Protein-Mediated Bile Acid-Drug Interaction



BSEP (Bile Salt Export Pump);
NTCP (Sodium-Taurocholate Cotransporting Polypeptide);
MRP (Multidrug Resistance–Associated Protein);
OST (Organic Solute Transporter)

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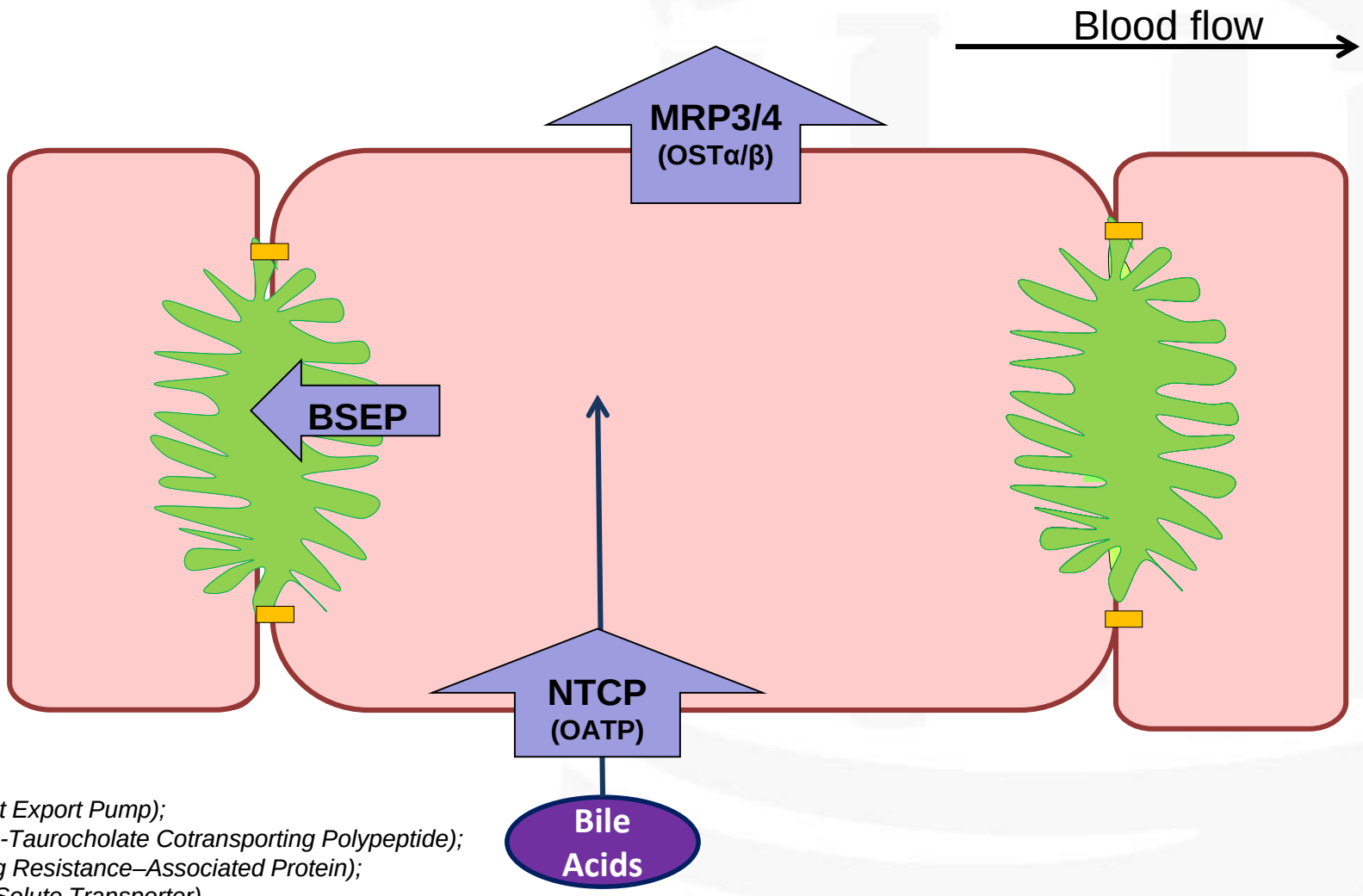

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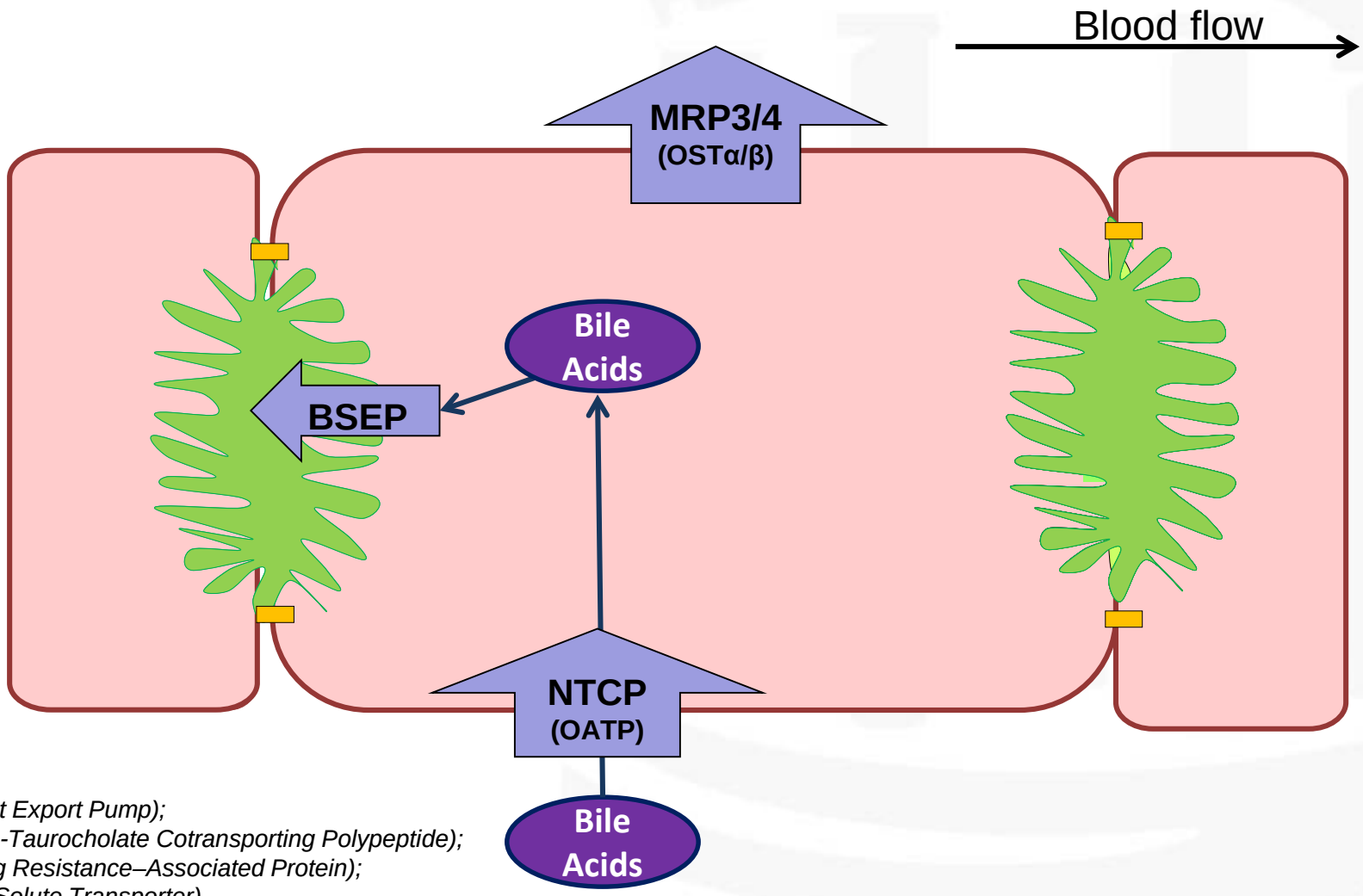

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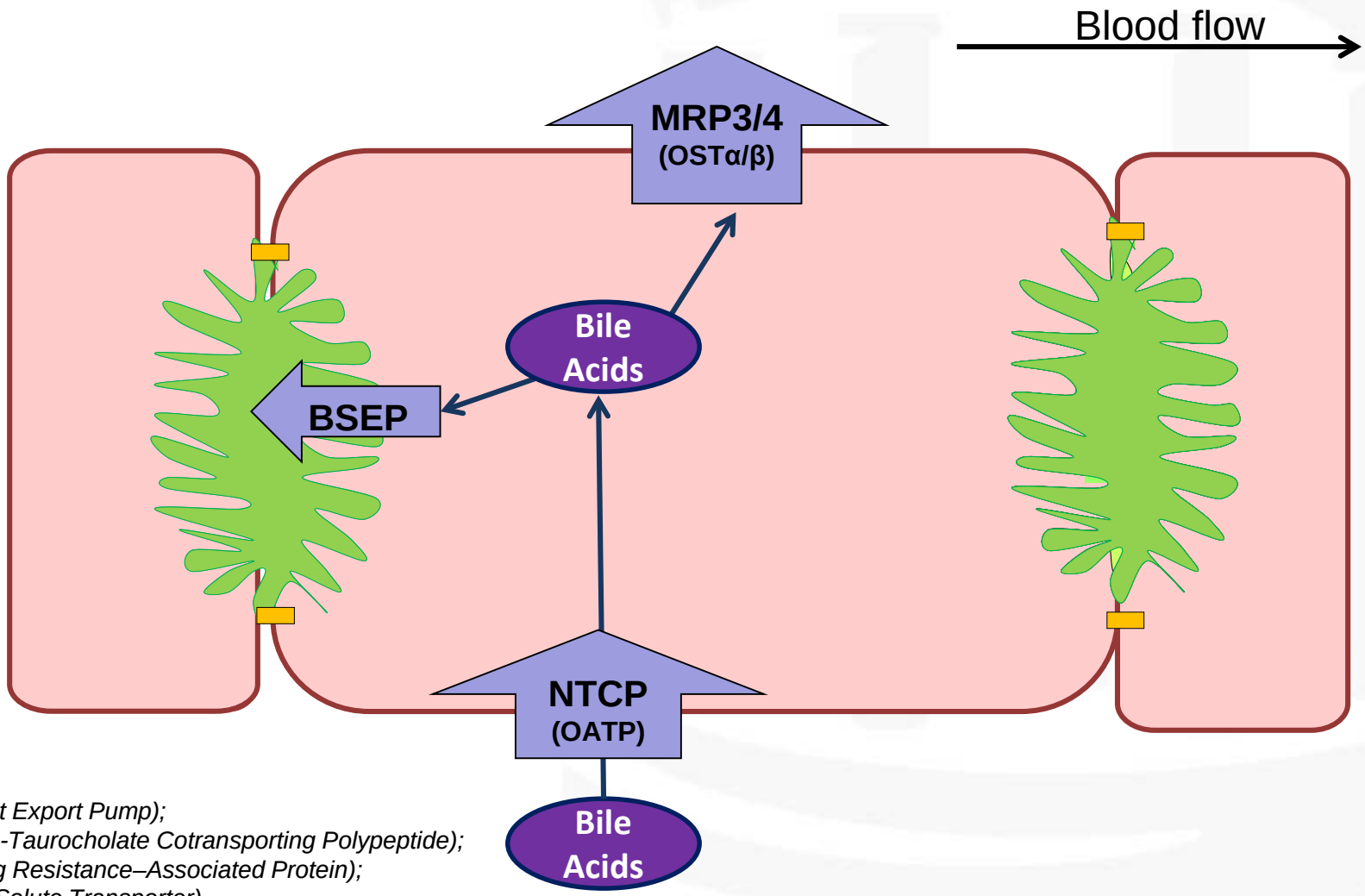

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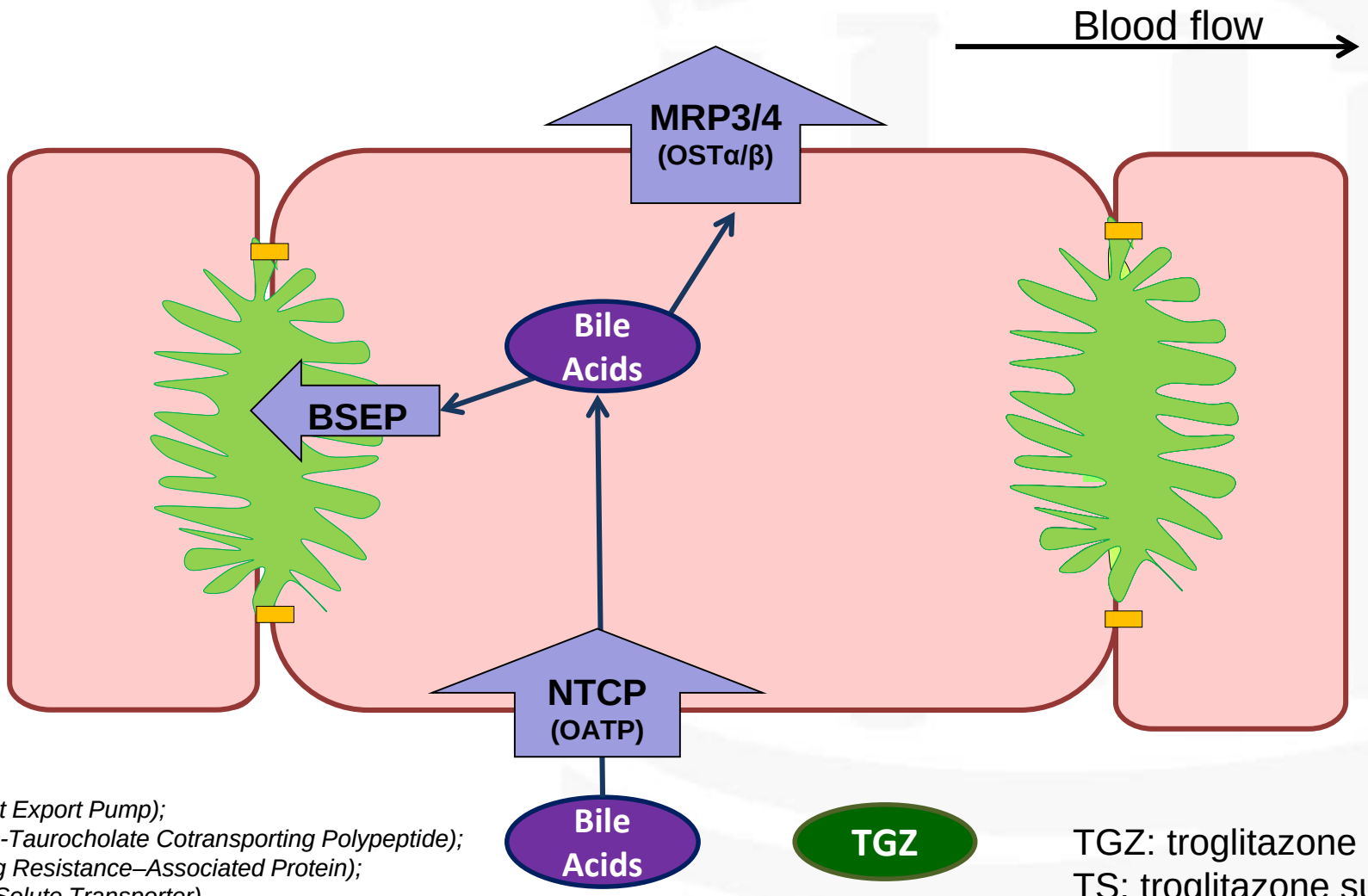

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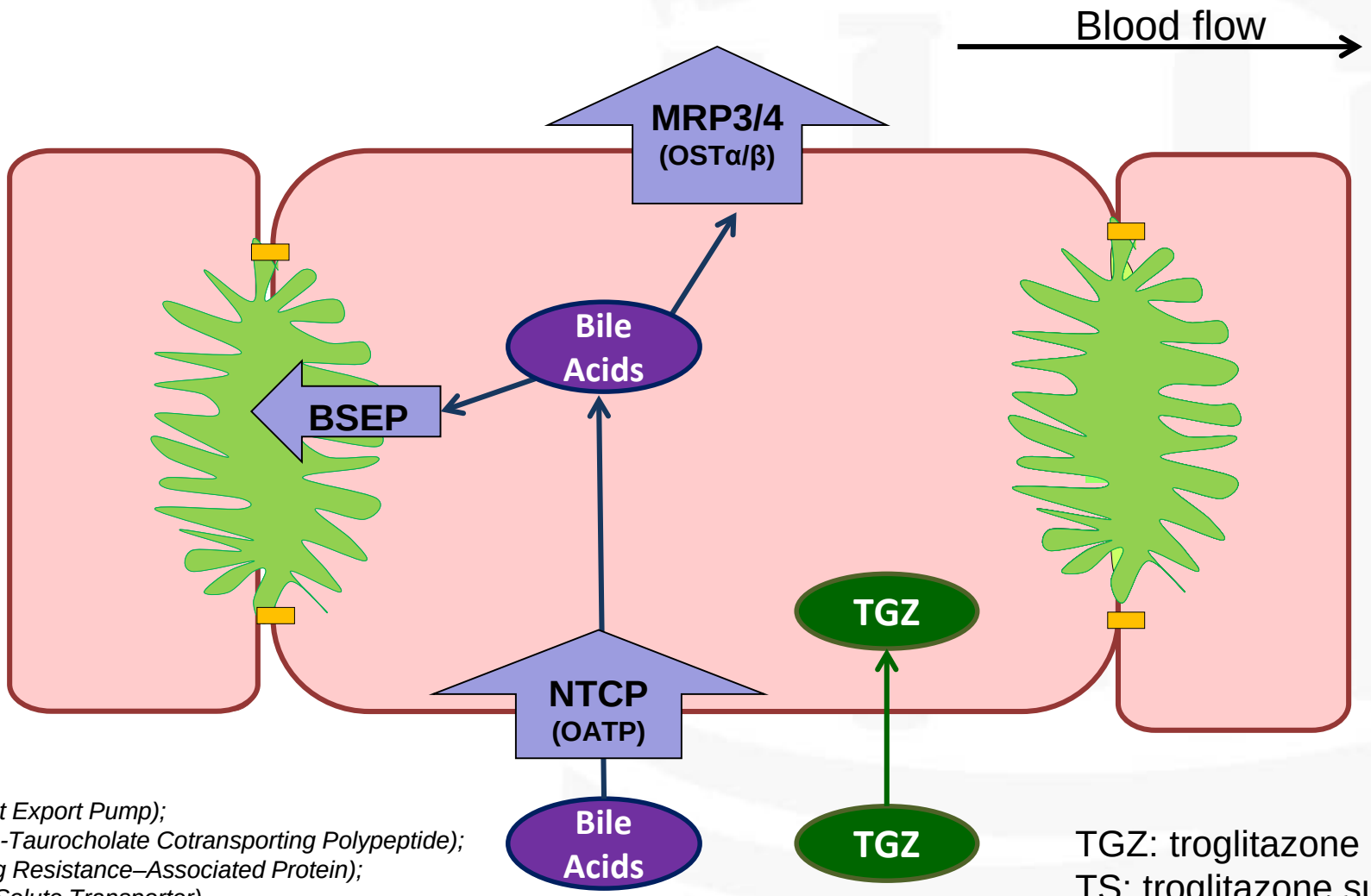

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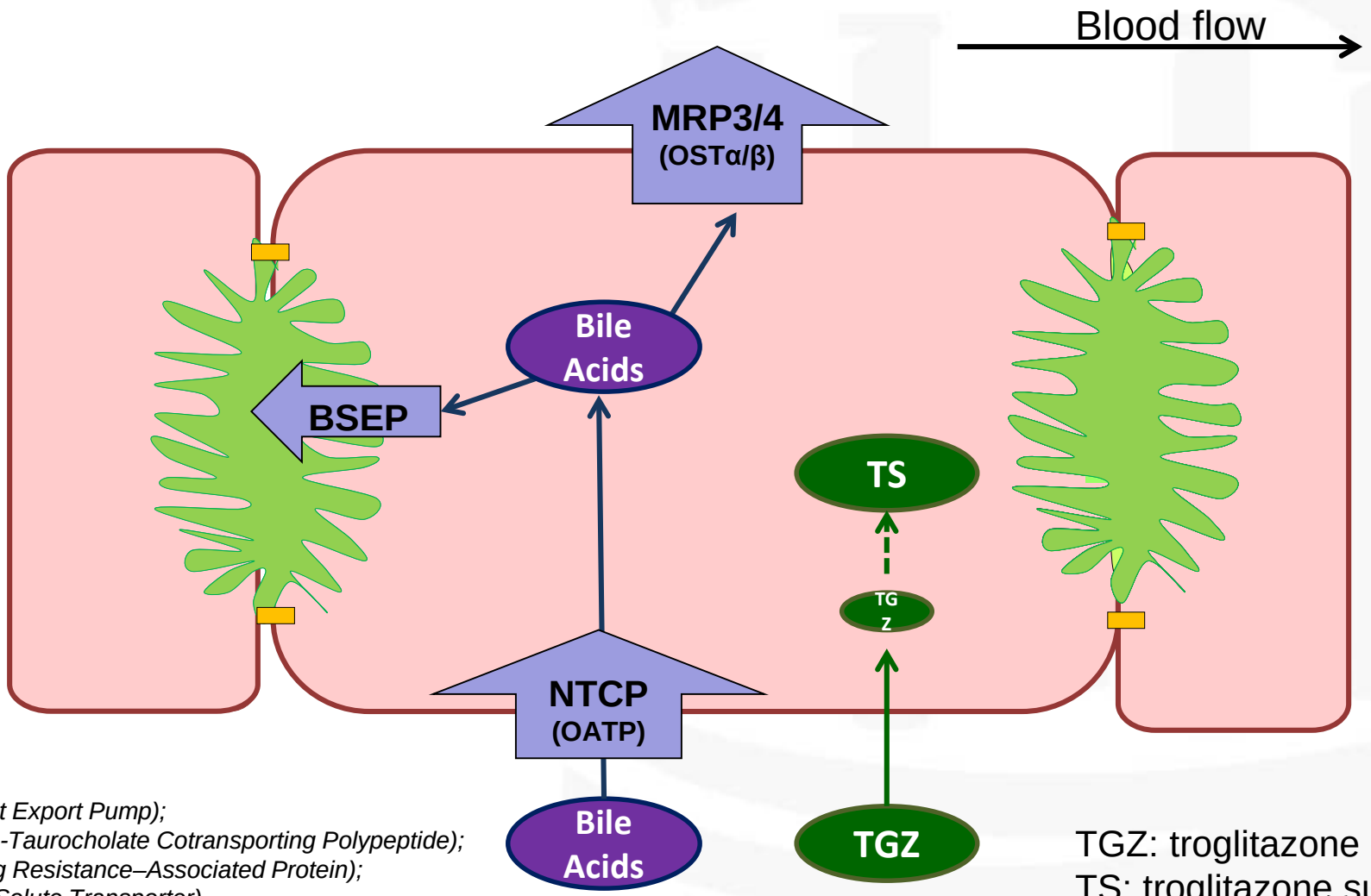

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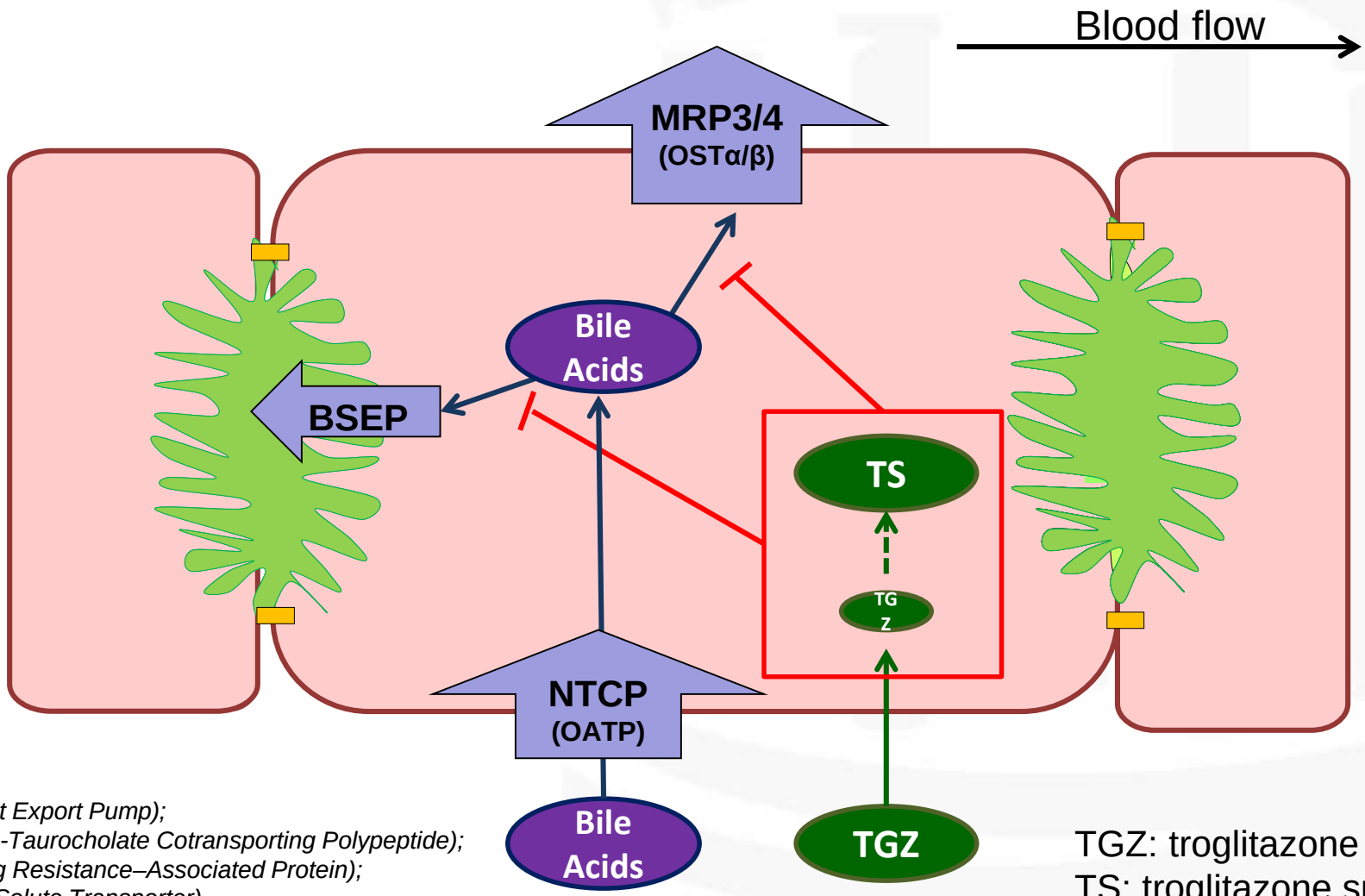

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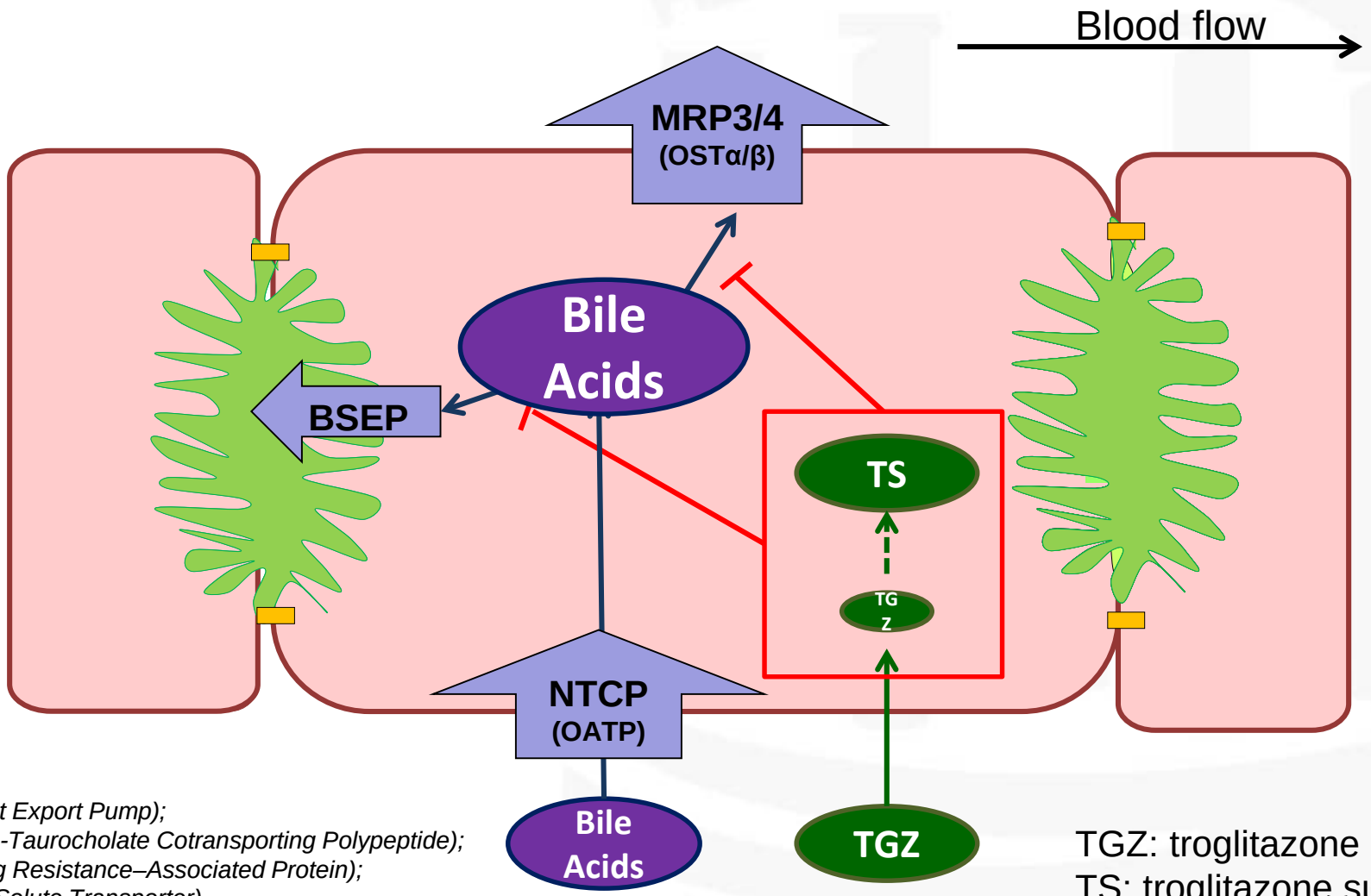

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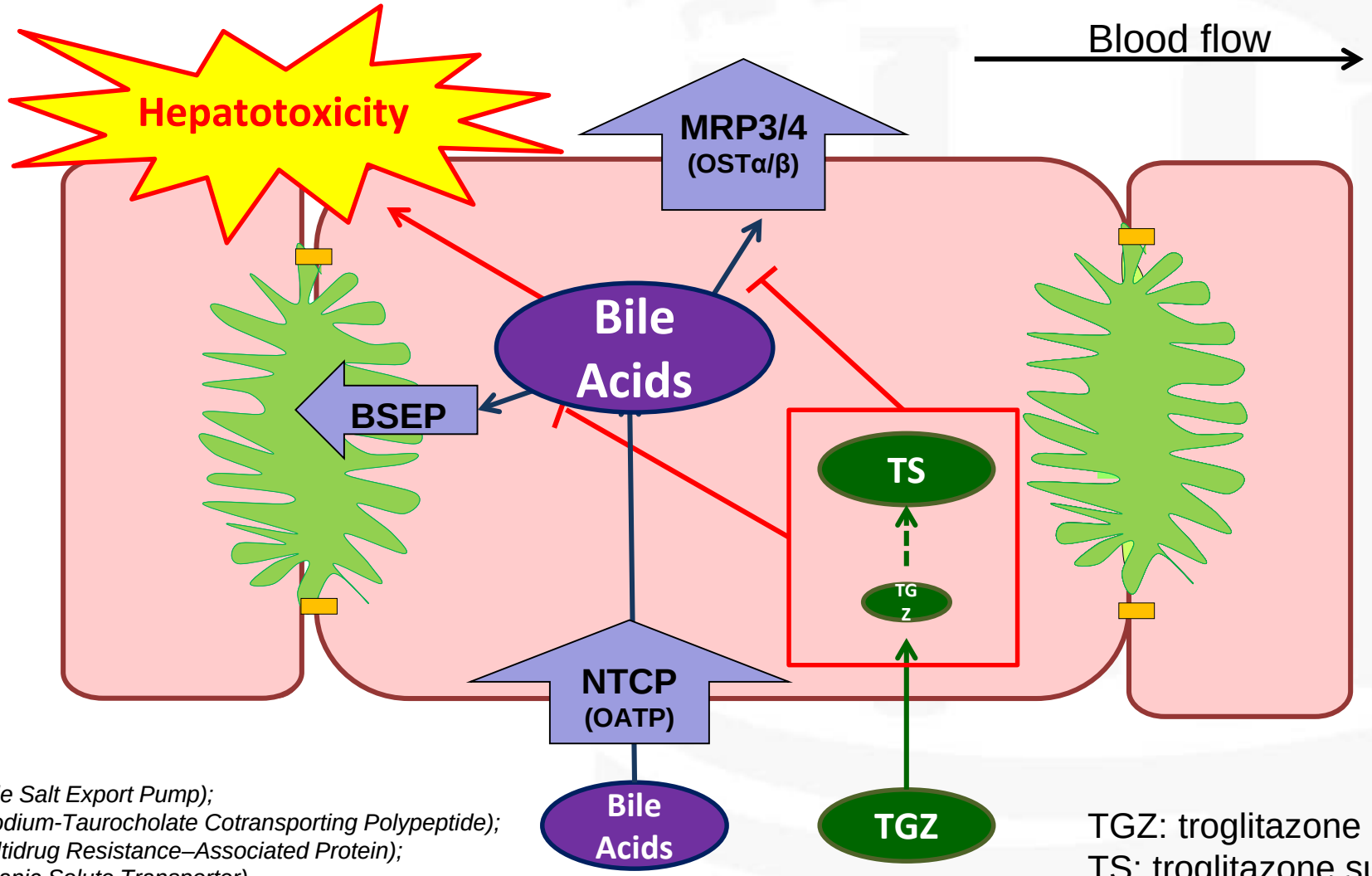

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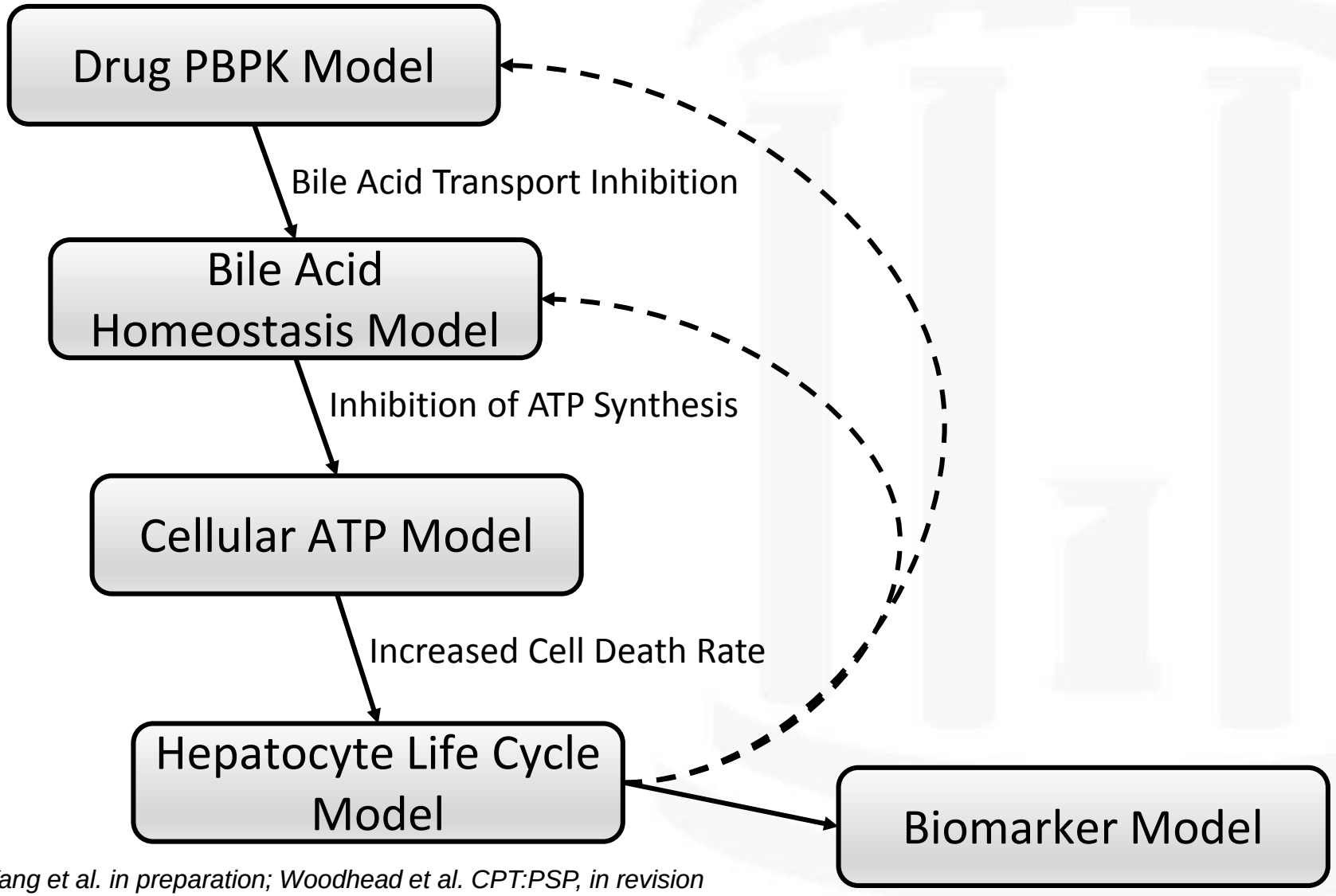
Construction of Human Sample Population (SimPops™)



Yang et al. in preparation; Woodhead et al. CPT:PSP, in revision

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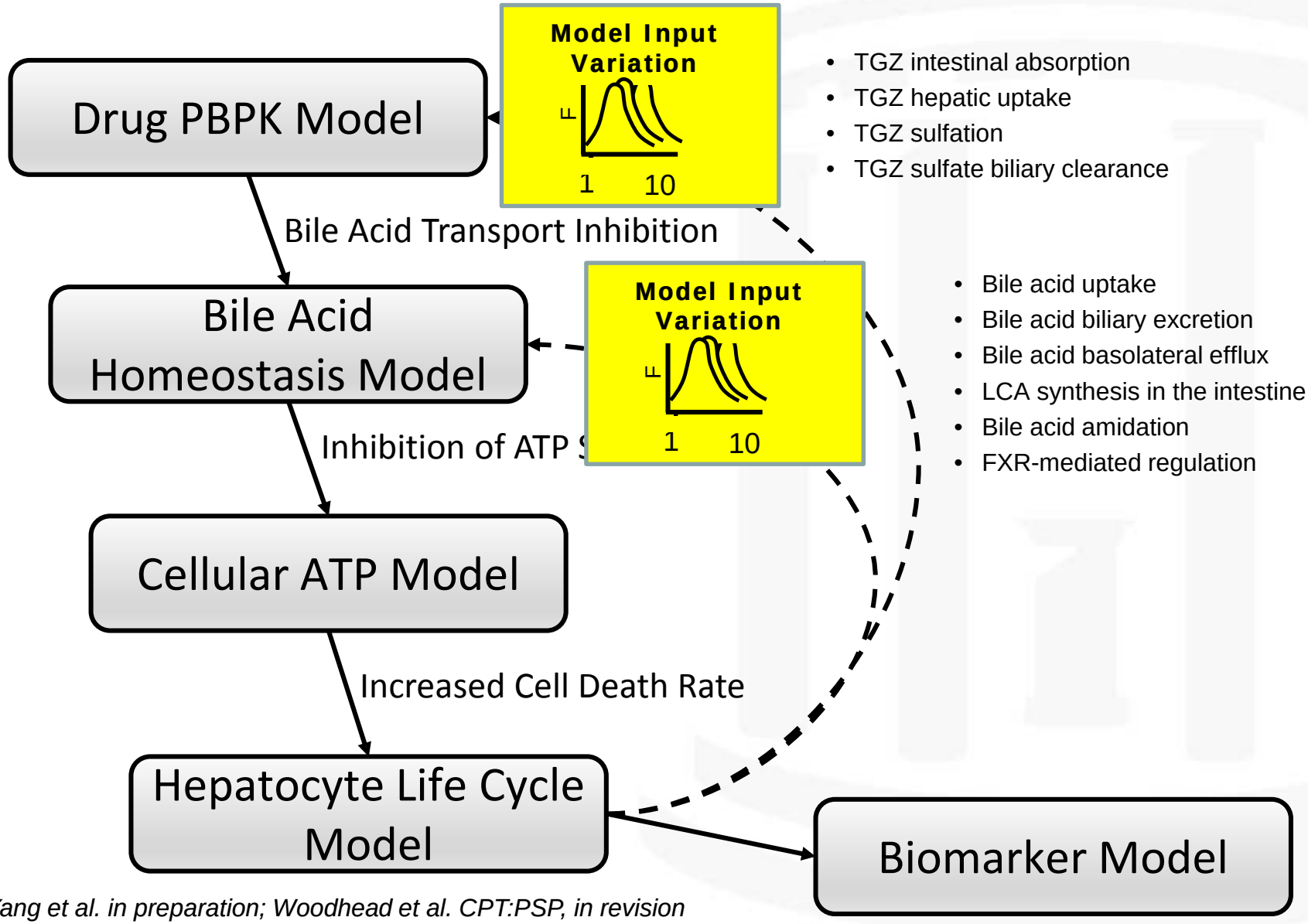

- TGZ intestinal absorption
- TGZ hepatic uptake
- TGZ sulfation
- TGZ sulfate biliary clearance

- Bile acid uptake
- Bile acid biliary excretion
- Bile acid basolateral efflux
- LCA synthesis in the intestine
- Bile acid amidation
- FXR-mediated regulation

Yang et al. in preparation; Woodhead et al. CPT:PSP, in revision

Bile Acid Transport Inhibition Alone Predicted TGZ Hepatotoxicity in Human SimPops™

HUMAN

Simulation Results

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

Bile Acid Transport Inhibition Alone Predicted TGZ Hepatotoxicity in Human SimPops™

HUMAN

Simulation Results

Maximum Serum ALT (U/L)

	Simulations		Clinical Trials
	TGZ 400 mg (n=331)	TGZ 600 mg (n=331)	TGZ 200 – 600 mg (n=2510)
ALT > 3X ULN (%) *	**2.4**	**4.2**	**1.9**
ALT > 5X ULN (%) *	1.2	3.0	1.7
ALT > 8X ULN (%) *	0.9	2.4	0.9
ALT > 30X ULN (%) *	0	0.3	0.2
Bili > 2X (%)	**0.9**	**3.0**	N/A
Jaundice (%)	N/A	N/A	**0.08**
Hy's law (%)	**0.9**	**3.0**	N/A

*ULN = 34 in the clinical trials
N/A, not available

Simulation Results & Clinical Data

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

Watkins and Whitcomb (1998) NEJM; Yang et al. in preparation

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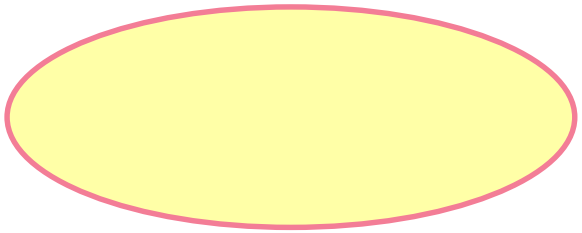

14 individuals with ALT>3X in simulation of 600 mg TGZ

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Mechanistic Model Reasonably Predicted Delayed Presentation of TGZ Hepatotoxicity

HUMAN

Simulation Results

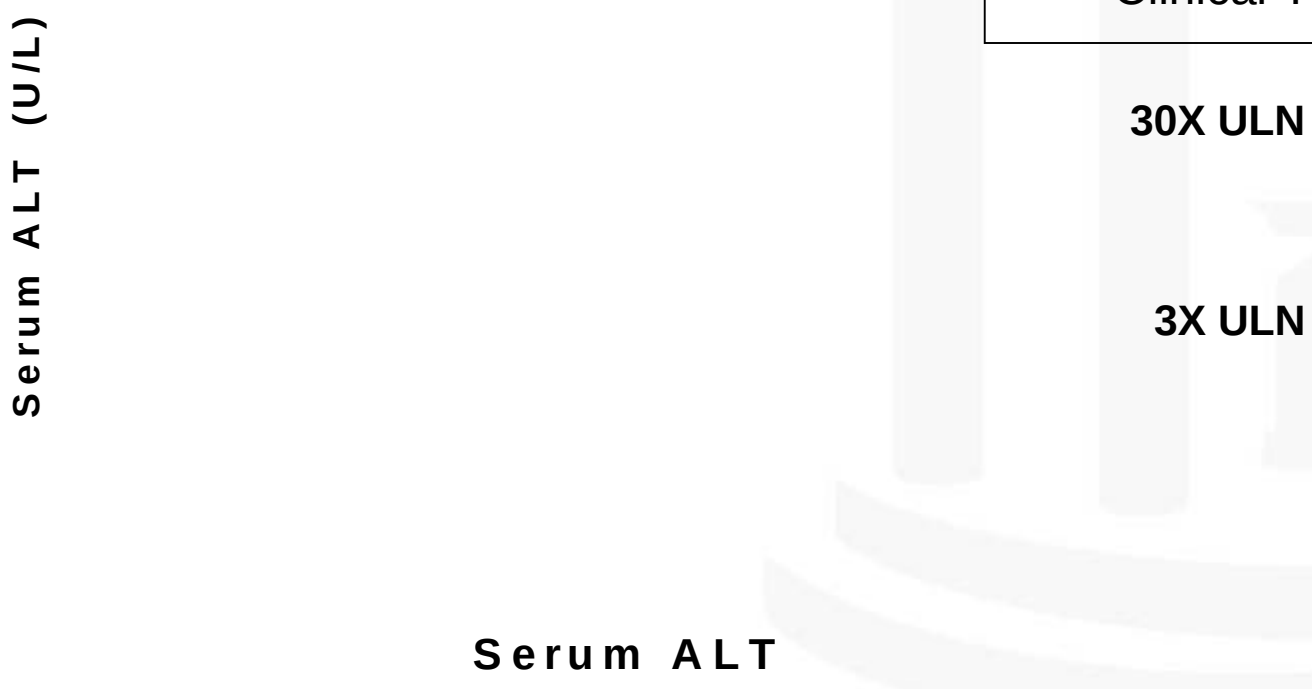
Yang et al. in preparation

Mechanistic Model Reasonably Predicted Delayed Presentation of TGZ Hepatotoxicity

HUMAN

Simulation Results

Time to peak ALT
- Simulated: 110 ± 62 days
- Clinical Trials: 147 ± 86 days



Yang et al. in preparation

Susceptibility Factors for TGZ Hepatotoxicity

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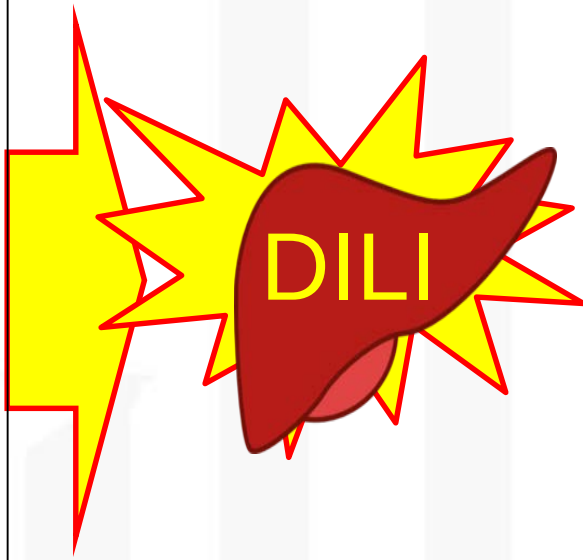
TGZ absorption
TGZ hepatic uptake
TGZ metabolism
↓ **TS biliary clearance**
↓ **Bile acid biliary excretion**
↓ **Bile acid basolateral efflux**
Bile acid hepatic uptake
Bile acid amidation
Bile acid sulfation
↓ **FXR-mediated feedback regulation**
↓ **Body weight**
↑ **LCA synthesis in the intestinal lumen**



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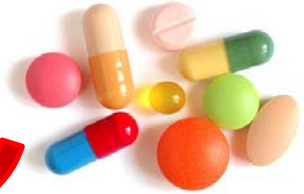

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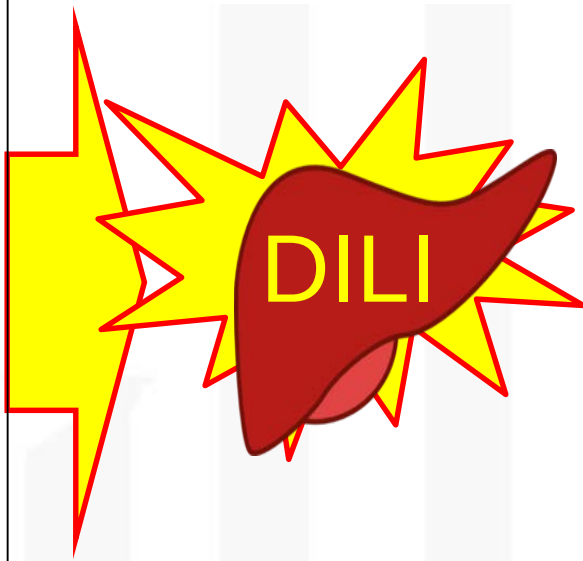

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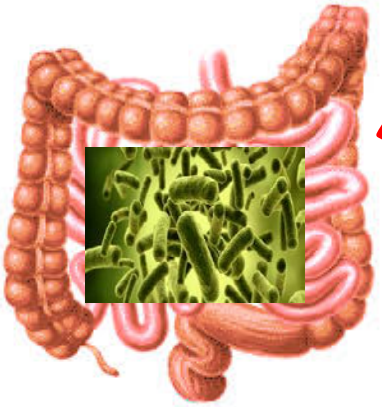

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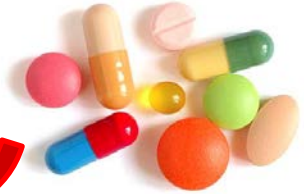
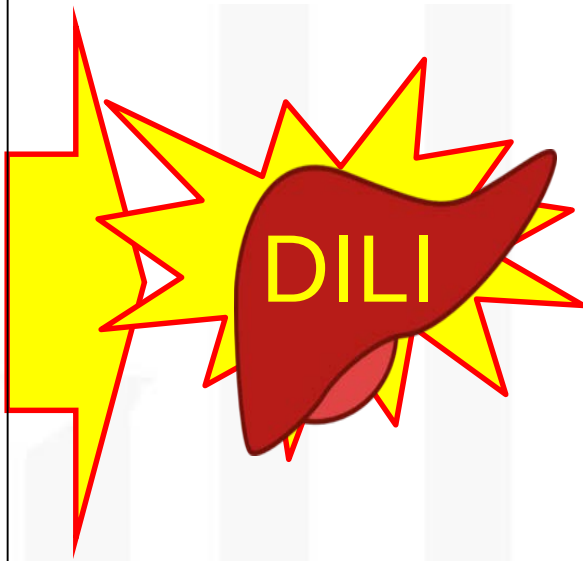
↑ **LCA synthesis in the intestinal lumen**





Species Difference in TGZ Hepatotoxicity Predicted

HUMAN

Maximum Serum ALT (U/L)

Species Difference in TGZ Hepatotoxicity Predicted

HUMAN

Maximum Serum ALT (U/L)

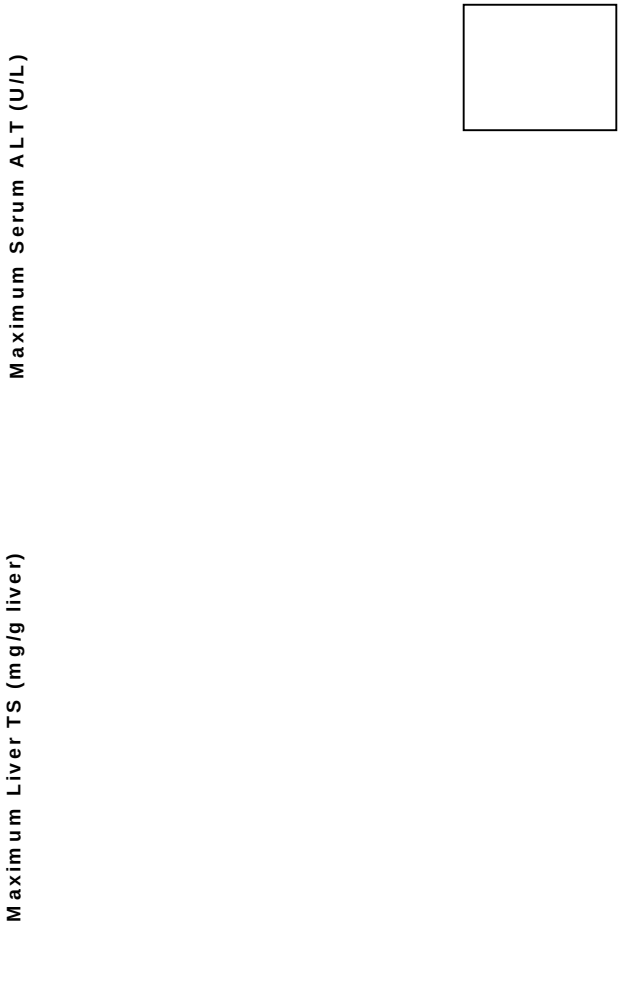
RAT

Maximum Serum ALT (U/L)

No hepatotoxicity observed in rat SimPops™

Species Difference in TGZ Hepatotoxicity Predicted

HUMAN



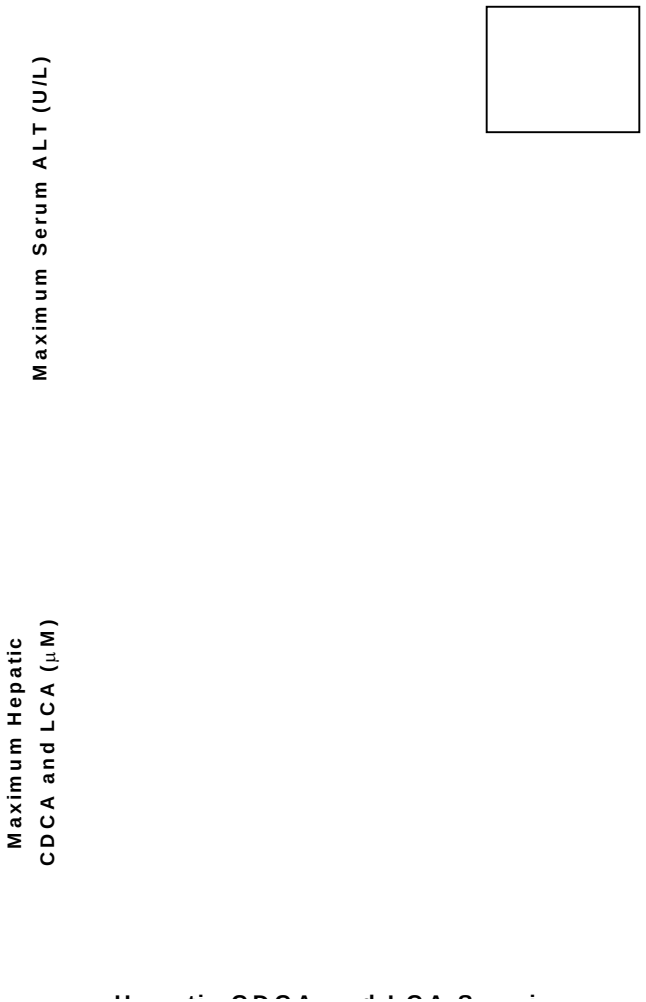
RAT

No hepatotoxicity observed in rat SimPops™

Hepatic TS concentrations were comparable in human and rat SimPops™

Species Difference in TGZ Hepatotoxicity Predicted

HUMAN



RAT

No hepatotoxicity observed in rat SimPops™

Hepatic toxic bile acid concentrations were lower in rat compared to human SimPops™

Conclusions and Perspectives

- Incidence and delayed presentation of TGZ hepatotoxicity was predicted in humans by TGZ-mediated bile acid transport inhibition alone
- Mechanistic modeling incorporating species-specific bile acid and TGZ disposition correctly predicted species differences in TGZ hepatotoxicity
- Mechanistic modeling incorporating data generated from human-derived *in vitro* systems could provide a framework for more accurate prediction of altered bile acid disposition and subsequent DILI risk in humans

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