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QSP/QST Modeling Support for NASH Drug Development

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Quantitative Systems Pharmacology (QSP) Supports Clinical Development by Emphasizing Mechanistic Understanding of Pathophysiology and Treatment

Editorial: The emerging discipline of quantitative systems pharmacology

Tarek A. Leil and Sergey Ermakov*

Bristol-Myers Squibb, Clinical Pharmacology and Pharmacometrics/Exploratory Clinical and Translational Research, Princeton, NJ, USA

> There is an expectation that the use of QSP will reduce the cost of R&D and the risks associated with uncertainties and gaps in our knowledge while bringing new therapies to patients.

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- QSP models, such as NAFLDsym, help enhance the understanding of the disease pathophysiology and its treatment
  - Reduce knowledge gaps
  - Ability to predict response to combination treatments
- QSP models provide the ability to predict responses to treatments while accounting for inter-patient variability as well as mechanistic feedback loops
- QSP models can provide ability to predict disease progression
- QSP model validation adhering to similar framework as PBPK modeling (*Kuemmel 2019*)

Quantitative Systems Pharmacology: A Case for Disease Models

CJ Musante[1], S Ramanujan[2], BJ Schmidt[3], OG Ghobrial[4], J Lu[5] and AC Heatherington[1]

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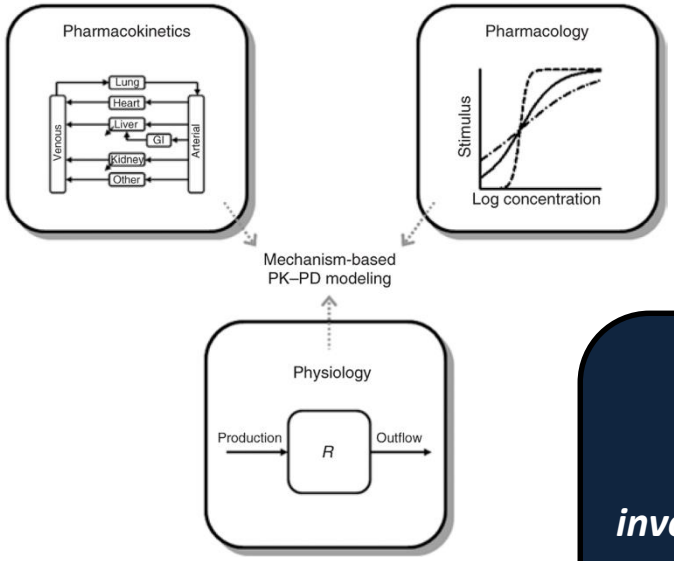
Mathematical Models Mechanistically Represent Disease Pathophysiology

Pathophysiology can be mathematically described to varying degrees of complexity

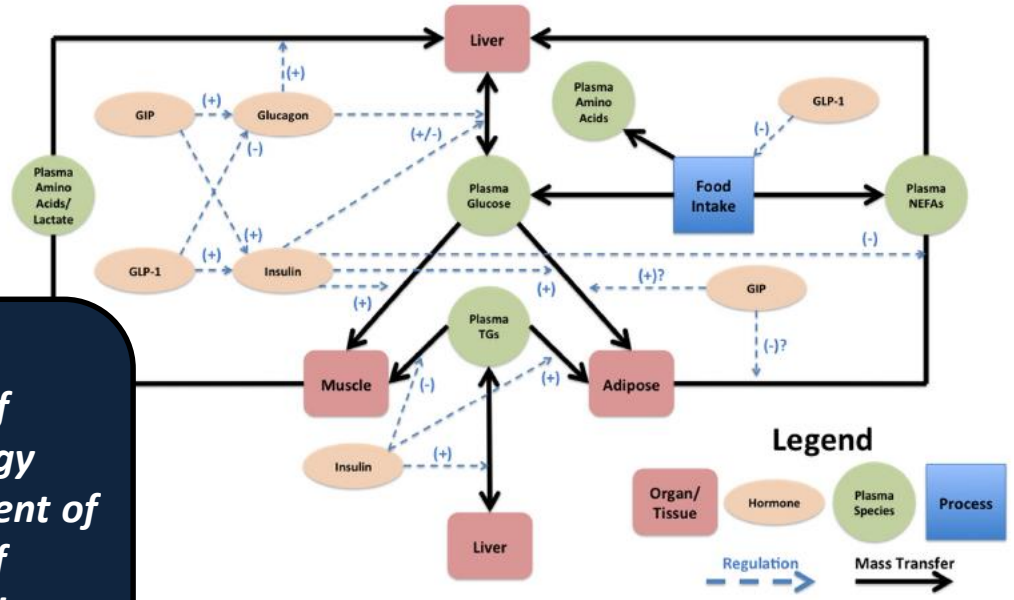
Mechanistic PK-PD



Mager and Jusko 2008

Complexity of pathophysiology invokes development of <u>QSP</u> model of NAFLD/NASH

QSP



Rieger and Musante 2016

Complexity

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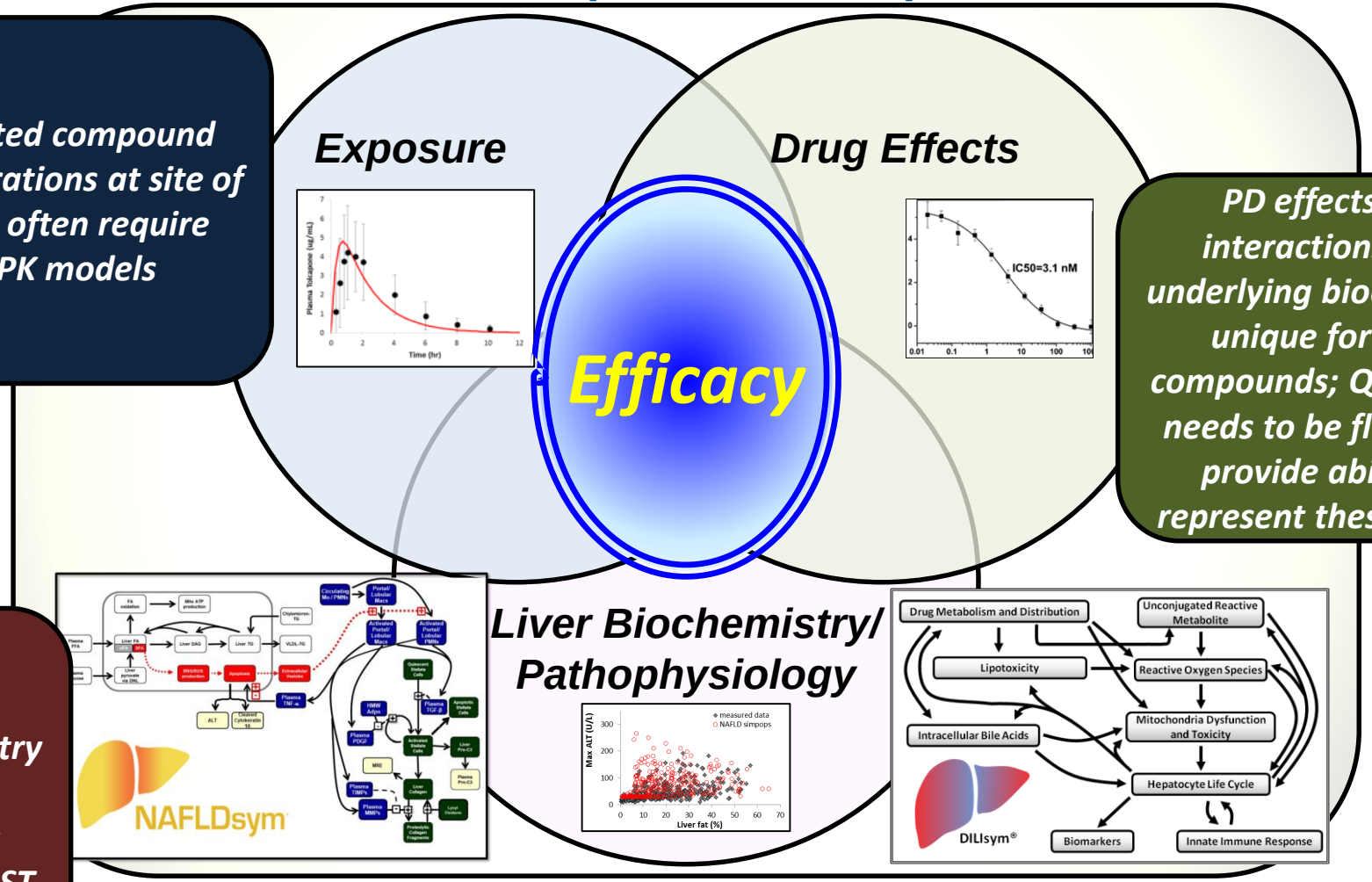
QSP/QST Models Predict Efficacy via the Intersection Between Pathophysiology Mechanisms, Compound Exposure, and PD

Predicted compound concentrations at site of target often require PBPK models

PD effects and interactions with underlying biochemistry unique for most compounds; QSP model needs to be flexible to provide ability to represent these effects

Mechanistic representation of underlying biochemistry describing pathophysiology is foundation of QSP/QST models



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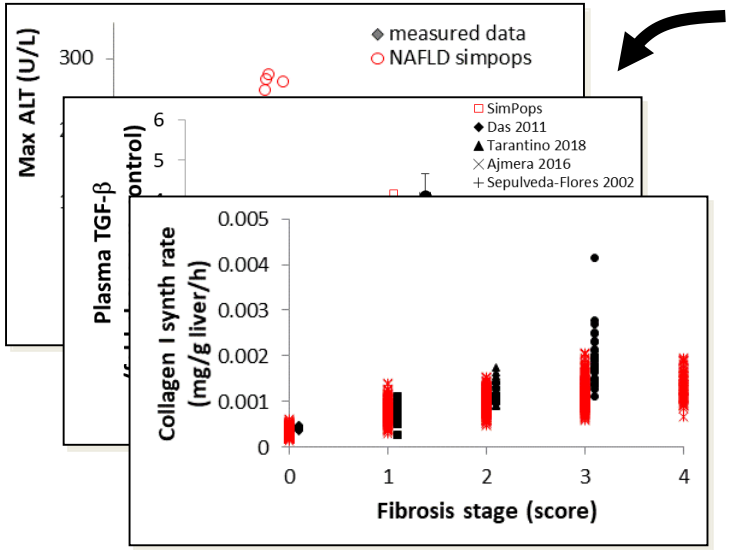
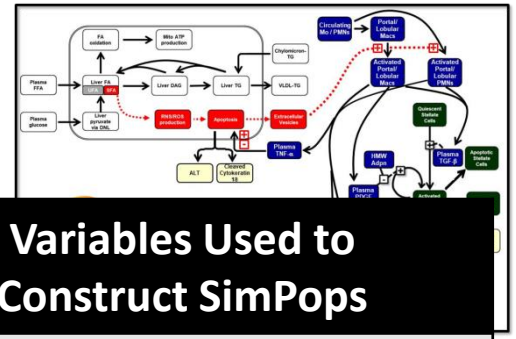
Pathophysiologic Variability Represented in NAFLD/NASH SimPops

- SimPops are population samples with variability across key areas of NAFLD/NASH pathophysiology
- Multiple parameters are varied to produce diverse possible simulated patients
- Simulated patients are compared with a multitude of clinical data to validate pathophysiology
- Response data (e.g., dietary intervention) have been used to validate the SimPops





Variables Used to Construct SimPops
Body weight
Adipose FA release
De novo lipogenesis
RNS-ROS clearance
Mitochondria function
VLDL-TG secretion rates
Plasma glucose
Hepatic glucose uptake
Plasma TG clearance
Apoptotic sensitivity to RNS-ROS
Necrotic sensitivity to ATP reductions
Hepatocyte regeneration
Extracellular vesicle release
Inflammatory mediator production
Stellate cell activation
Collagen synthesis and degradation

Measured data

Simulation results

Maximos 2015, Das 2011, Tarantino 2018, Ajmera 2016, Sepulveda-Flores 2002, Hasegawa 2001, Yin 2007, Wang 2011, Kim 2013, Park 2017, Decaris 2017, Masugi 2018

Clinical Data and Simulation Results

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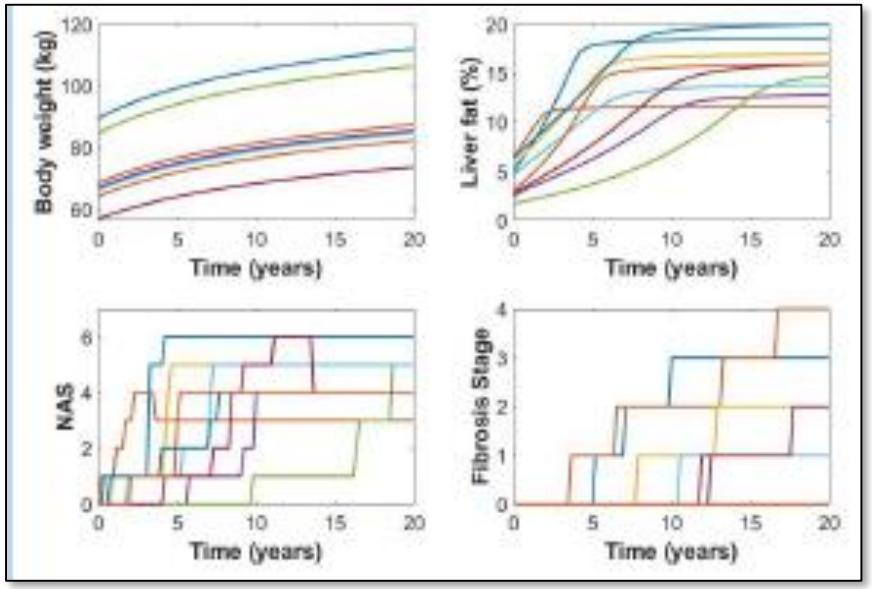
NASH SimPops Includes Progression of Disease due to Weight Gain

- Change in body weight has been reported to influence NASH disease progression (Wong 2010)
  - NASH patients studied longitudinally, including liver biopsies and histology
  - Based on histologic scoring
  - Patients with increased NAS had increased BMI
  - 3 year time interval between biopsies
- Simulated weight gain over 20 years in SimCohorts recapitulated NASH disease progression (Akpinar Singh 2019)
  - 20-30% increase in body weight via increased food intake (McTigue 2002)
  - Increase in food intake and weight gain elicit increases in steatosis
  - Increased NAS score over time due to lipotoxicity and increased hepatocellular apoptosis and hepatic inflammation
  - Release of pro-fibrotic mediators also drives increased fibrosis
- Enables prediction of disease status over time
  - Prediction of treatment vs. placebo in phase III clinical trials

Table 4 Factors associated with increased non-alcoholic fatty liver disease (NAFLD) activity score from baseline to month 36

Factors	Increased NAFLD activity score	Static or decreased NAFLD activity score	p
N	26	26	
Age (years)	45±9	44±9	0.65
Male gender, n (%)	16 (62)	18 (69)	0.56
Diabetes mellitus, n (%)	15 (58)	11 (42)	0.27
Hypertension, n (%)	12 (46)	14 (54)	0.58
Metabolic syndrome, n (%)	18 (69)	17 (65)	0.77
Body mass index (kg/m^2)	27.4±4.1	27.4±3.3	0.99
Change in body mass index (kg/m^2)*	0.6±1.6	−0.8±1.7	0.003
Waist circumference (cm)	92.8±11.1	92.5±6.7	0.91

Wong 2010



Akpinar Singh 2019

Simulation Results

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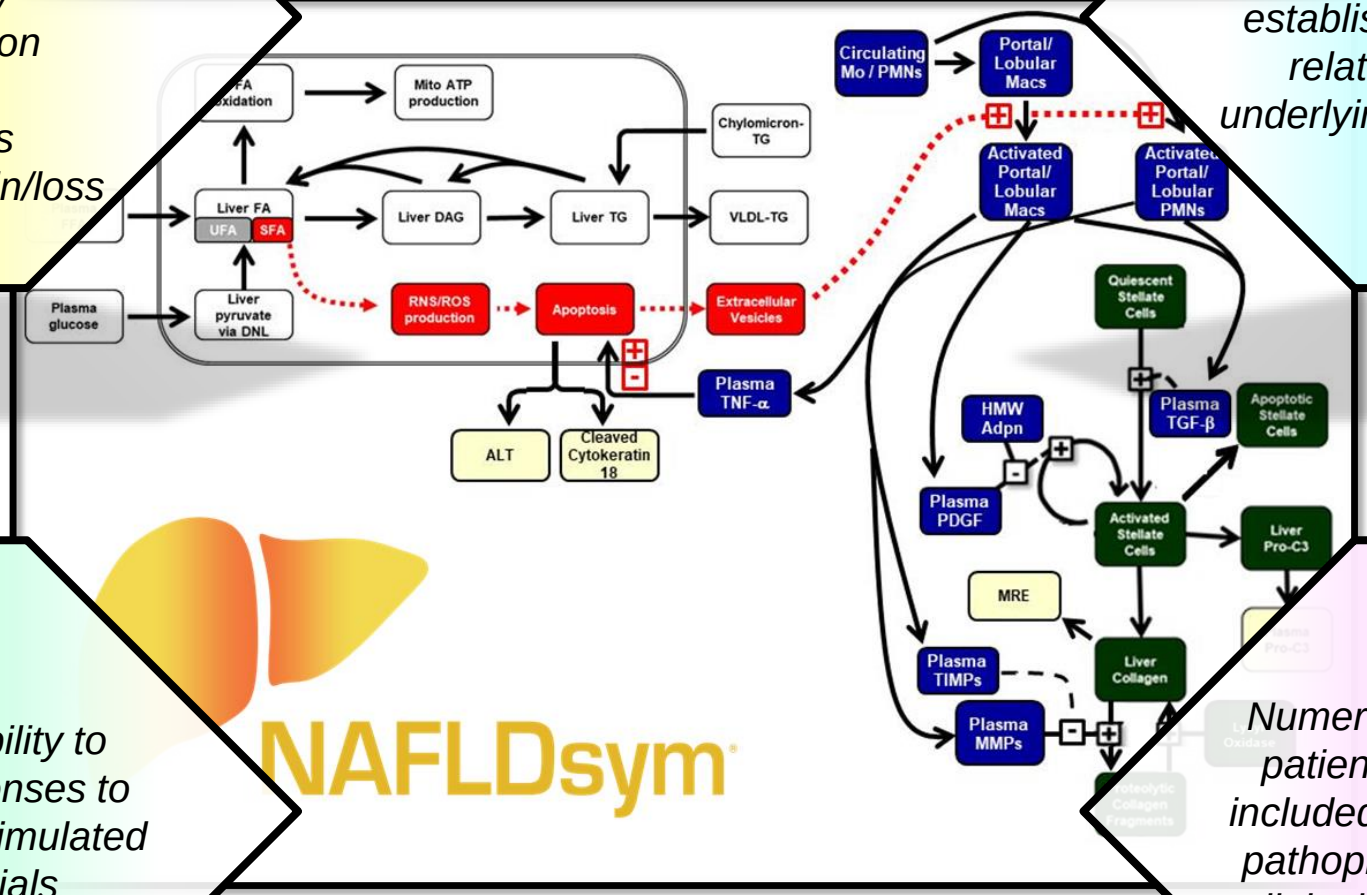
APPENDIX

NAFLDsym v2A Overview

Multiple interacting sub-models, including

- *Steatosis*
- *Lipotoxicity*
- *Inflammation*
- *Fibrosis*
- *Biomarkers*
- *Weight gain/loss*

Clinical data from literature used to establish quantitative relationships for underlying biochemistry



NAFLDsym

Provides ability to predict responses to treatment in simulated clinical trials

Numerous simulated patients (SimPops) included to account for pathophysiologic and clinical heterogeneity

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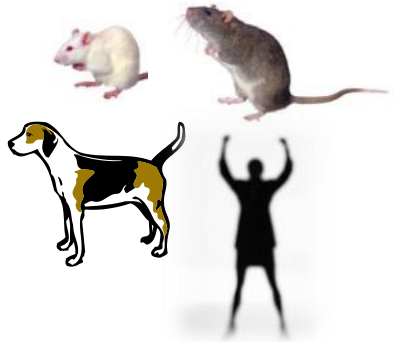
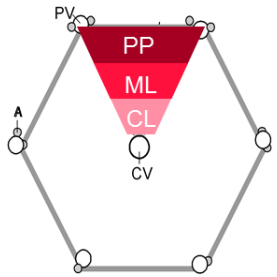
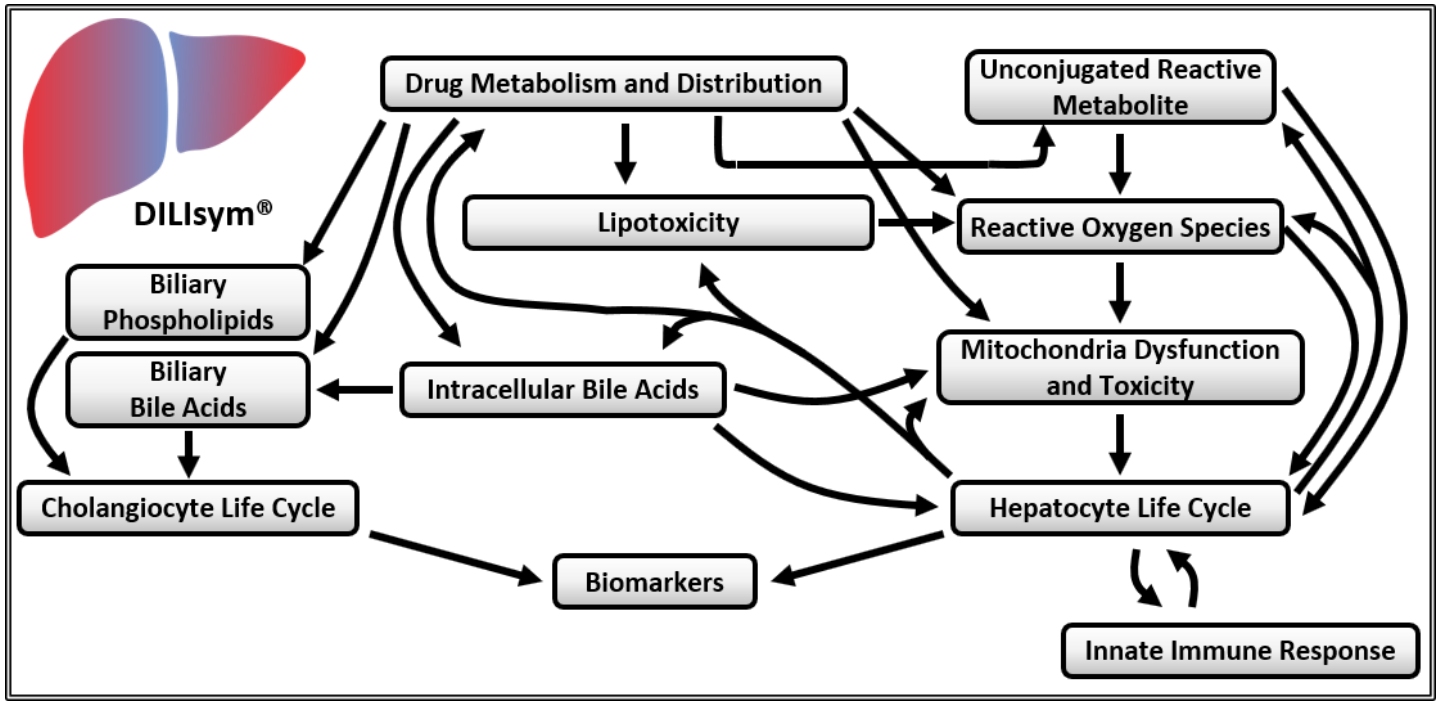
DILIsym Software Overview

- **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**
- **<u>Over 70</u> detailed representations of optimization or validation compounds with 80% success**
- **Single and <u>combination drug</u> therapies**







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"Our vision is safer, effective, more affordable medicines for patients through modeling and simulation."

- DILIsym Services, Inc. offers comprehensive program services:
  - **DILIsym** software licensing, training, development (DILI-sim Initiative)
  - **NAFLDsym** software licensing, training, development
  - **DILIsym** and **NAFLDsym** simulation consulting projects
  - Consulting and data interpretation; *in vitro* assay experimental design and management
  - **RENAsym, RADAsym,** and **IPFsym** software in development

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