Using Quantitative Systems Toxicology (QST) to Predict Liver Safety of New Drug Candidates

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UNC | ESHELMAN SCHOOL OF PHARMACY

Disclosure

I have no financial ties to DILIsym or to

Simulations Plus that provides this software.

Outline of talk

1). What is QST?

2). DILIsym

3). Pediatric representation: Dilisym V.11®

4). The future

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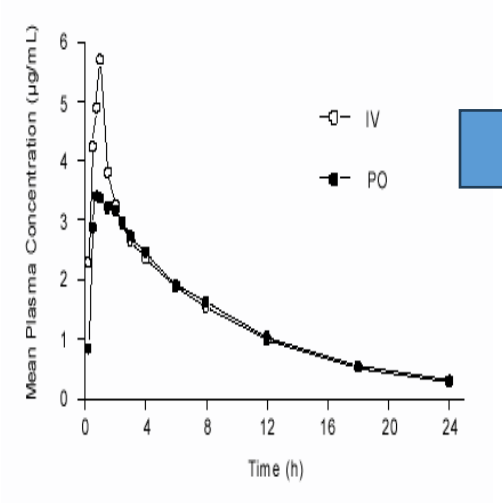
Quantitative Pharmacology

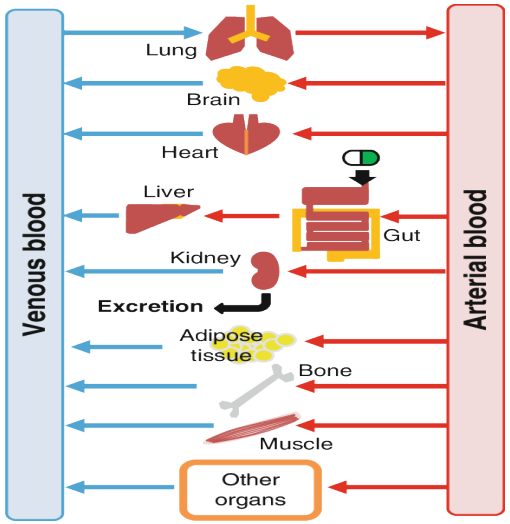
The use of mathematical and computational models to understand the relationship between drug concentration and effect over time.

History of Quantitative Pharmacology

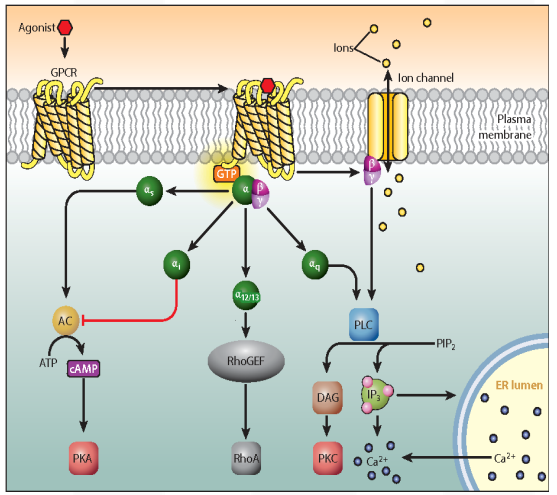
Pharmacokinetics (PK)



Physiologically-Based PK(PBPK)



Quantitative Systems Pharmacology (QSP)



Quantitative Systems Toxicology (QST)

Addition to PBPK of mathematical equations to recapitulate relevant intracellular pathways whereby drugs or other chemicals can cause stress and death to cells, tissues, and organs.

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The DILI-sim Initiative – a Public Private Partnership

- ***History***
  - *Officially started in 2011*
  - *21 major pharmaceutical companies have participated*
  - *Members have provided compounds, data, and conducted experiments to support effort*

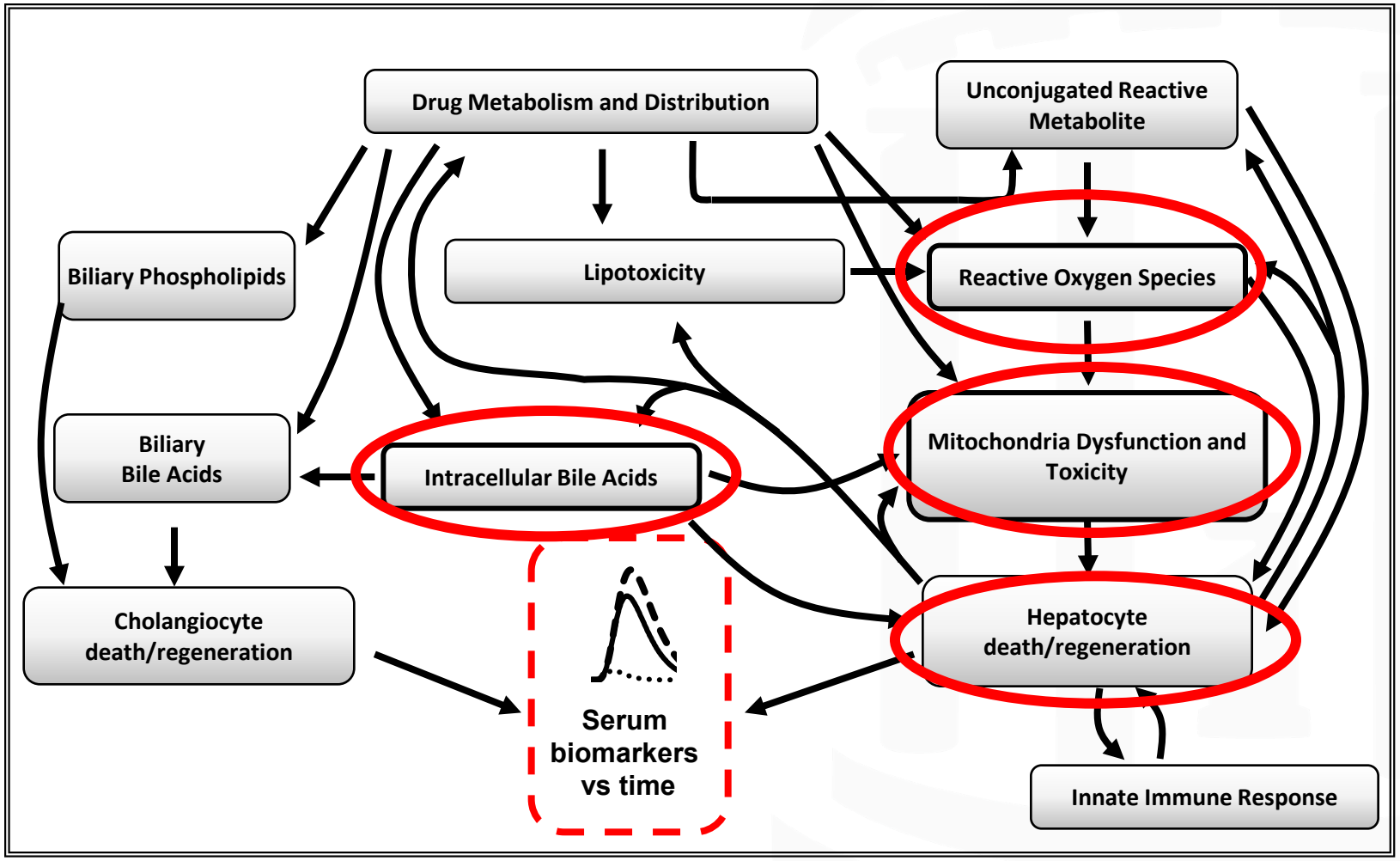
- ***At least 50 cases of use for regulatory purposes***

- ***Over 30 publications***

Current DILI-sim / RENAsym Members

For a comprehensive review
Watkins 2020, Current Opinion in Toxicology (23-24:67-73)

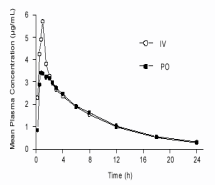
QST software created by the DILI-sim Initiative



DILIsym Input Data

Exposure

PBPK



DILIsym®

Simulated Frequency & Severity of Liver Injury (ALT)

DILIsym's role in successful drug development.

REVIEW

Assessment of liver injury potential of investigational medicines in drug development

Naga Chalasani[1] | Paul H. Hayashi[2] | Debra Luffer-Atlas[3] | Arie Regev[4] | Paul B. Watkins[5]

Hepatology. 2025
Epub ahead of print.
PMID: 39999469

TABLE 3 Summary of nonclinical data assessed by DILI team at the U.S. Food and Drug Administration

Type	Examples of sources
In vitro	
Metabolic pathway	Dominant cytochromes, UDP
Lipophilicity	Log *P*
Reactive metabolite formation	Glutathione trapping; time-dependent CYP inhibition
Mitochondrial data	Mitochondrial injury/inhibition studies
Transporter inhibition	BSEP, MRP2, other drug transporters
In vivo (animal toxicology studies)	
Blood tests	Liver enzyme, bilirubin elevations
Liver histopathology	Inflammation, necrosis, fibrosis, zone of liver injury
Computer or modeling-based (as available and/or upon request)	
QST	DILISym
QSAR	Analysis by DARS
Rule-of-2; DILI risk score	Analysis by NCTR

Summary

DILIsym is increasingly used to predict the liver safety of new drug candidates.

….. but also to manage liabilities.

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DILI susceptibility can be different in children

Table 2. Selected Drugs Associated With cDILI.

Drugs	Age effect in humans	Age effect in animal models
Acetaminophen	Child < adult[12,73]	Child < adult[74,75,77,78,80,81] or child = adult[84]
Halothane	Child < adult[91]	
Valproic acid	Child > adult[103]	
Propylthiouracil	Child > adult[14]	
Isoniazid	Child < adult[115]	
Rifampicin plus isoniazid	Child = adult[129]	NA
Pyrazinamide	Child > adult[133]	NA
Ketoconazole	Child < adult[71]	NA

Abbreviations: cDILI, drug-induced liver injury in children; NA, not available.

WARNINGS: LIFE THREATENING ADVERSE REACTIONS

See full prescribing information for complete boxed warning

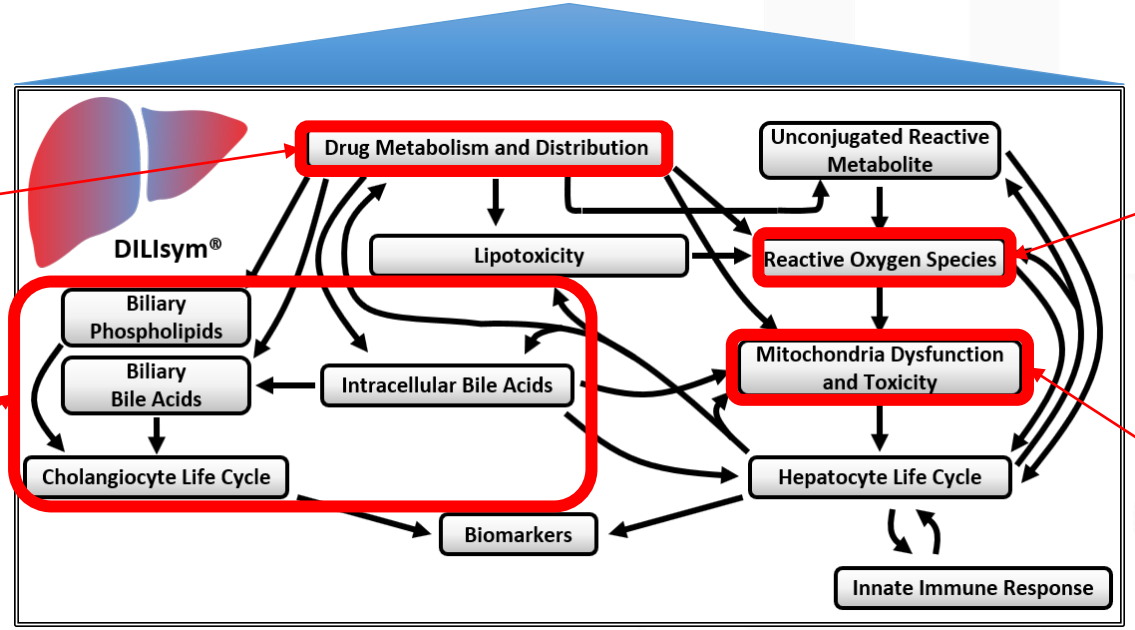
- **Hepatotoxicity, including fatalities, usually during first 6 months of treatment. Children under the age of two years and patients with mitochondrial disorders are at higher risk. Monitor patients closely, and perform serum liver testing prior to therapy and at frequent intervals thereafter (5.1)**
- **Fetal Risk, particularly neural tube defects, other major malformations, and decreased IQ (5.2, 5.3, 5.4)**
- **Pancreatitis, including fatal hemorrhagic cases (5.5)**

Shi et al. International Journal of Toxicology 2017, Vol. 36(5) 365-379

Step-Wise Approach to Represent Pediatrics in DILIsym

1 ✓ Create “small adults” by scaling height, weight, and organ volumes

Pediatric-specific drug exposure simulated using GastroPlus



2 ✓ Develop and validate pediatric-specific bile acid homeostasis representations

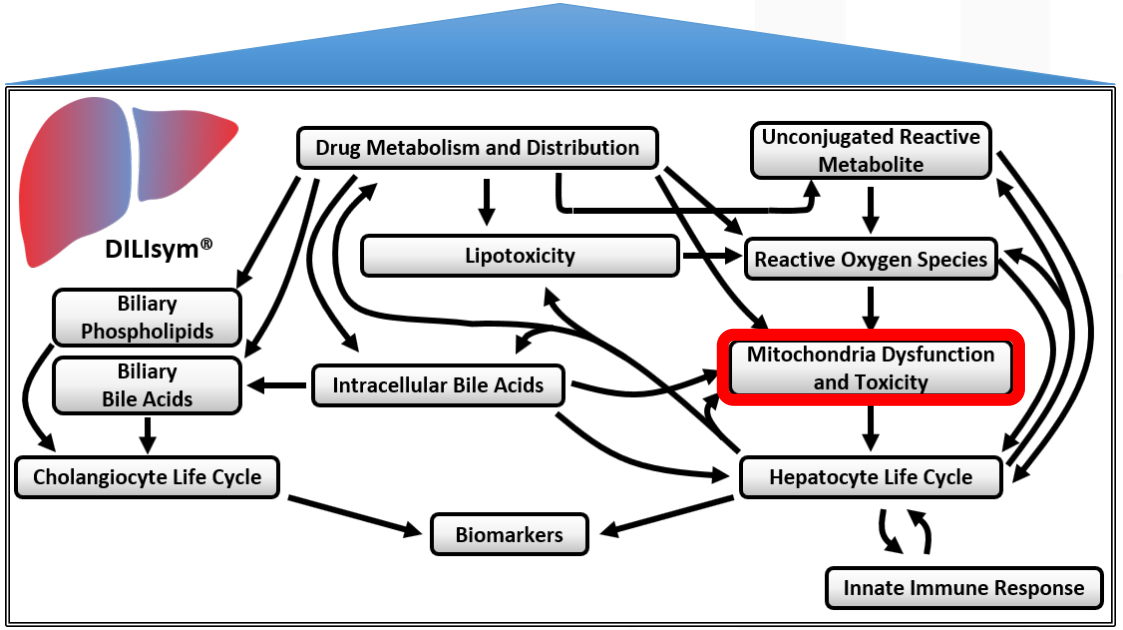
3 Develop and validate pediatric-specific re-dox representations

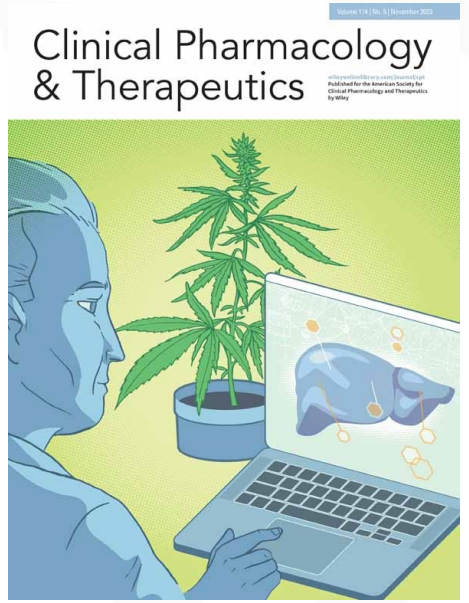
4 Develop and validate pediatric-specific representations of mitochondrial bioenergetics

5 Validate pediatric DILI responses by simulating drugs with known clinical DILI responses in pediatrics

DILIsym Predicts Valproate Hepatotoxicity in Adults

Dosing 10 mg/kg b.i.d.,
ALT elevations were predicted
in 33/285 (11.6%)





Assessing Liver Effects of Cannabidiol and Valproate Alone and in Combination Using Quantitative Systems Toxicology

Vinal V. Lakhani, Grant Generaux, Brett A Howell, Diane M. Longo and Paul B. Watkins.

Clin Pharmacol Ther 114(5)2023.

DILIsym modeling of Valproate Hepatotoxicity in Children

Create “small adults” by scaling height, weight, and organ volumes

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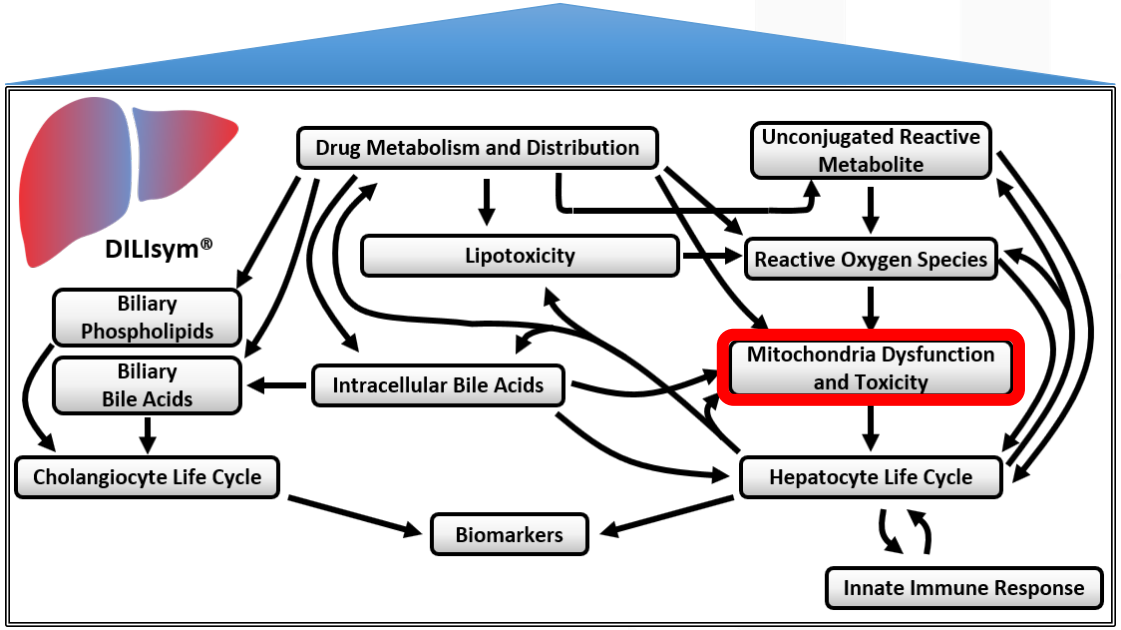
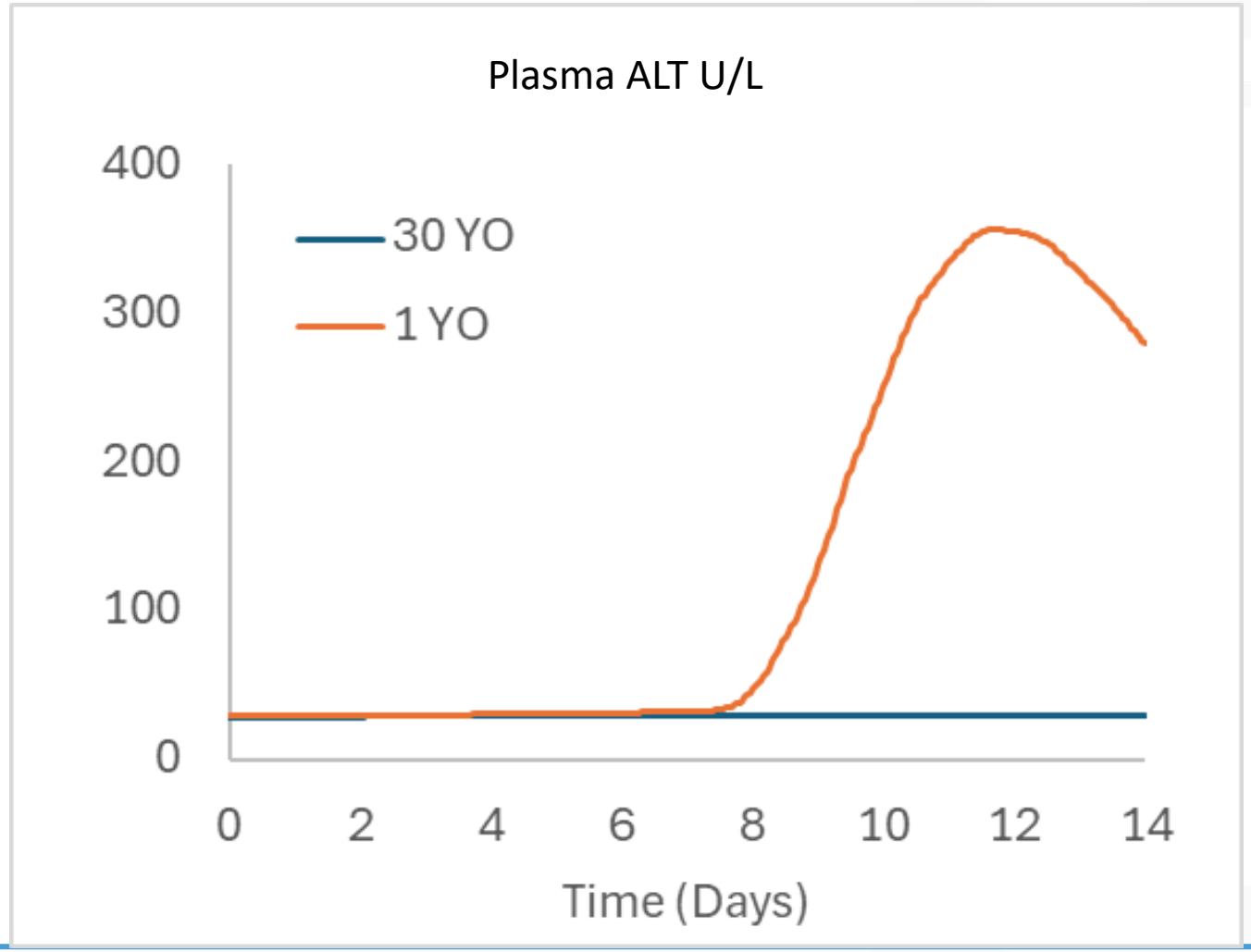


DILIsym Simulations Predicted Higher Susceptibility to VPA-Induced Hepatotoxicity in 1 Year Olds Compared to Adults



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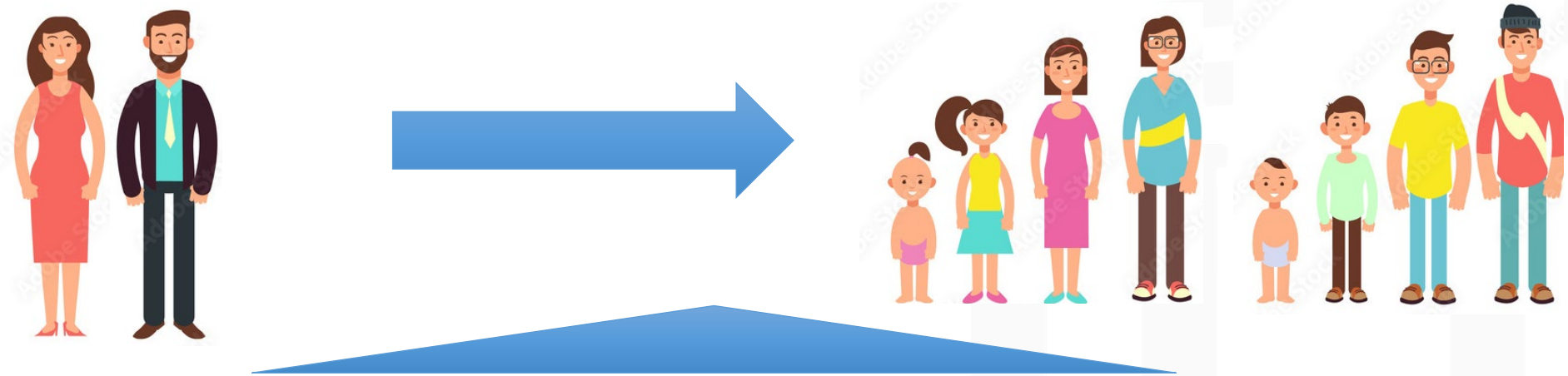
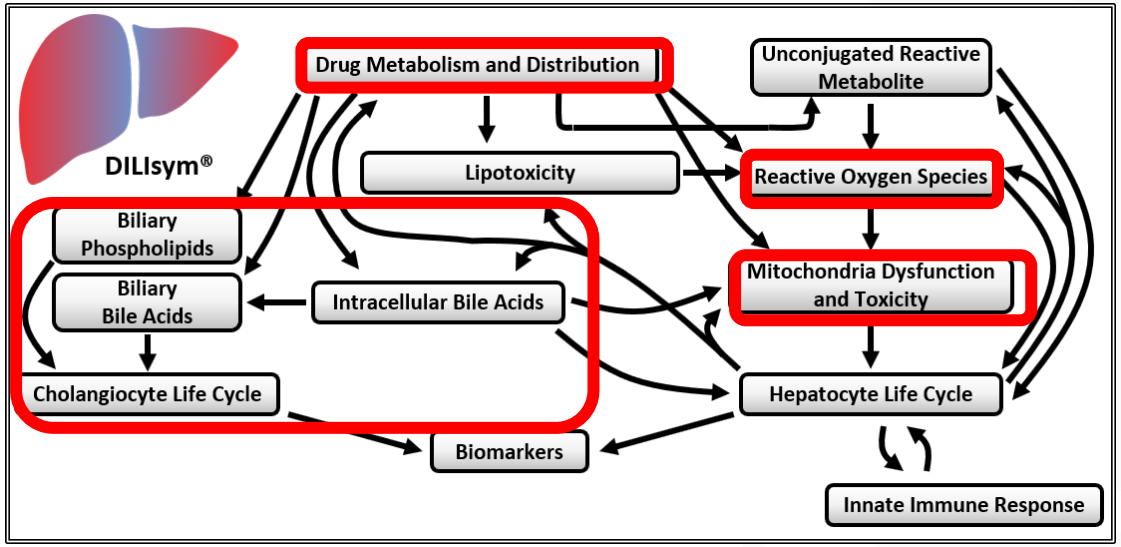
DILIsym Provides Mechanistic understanding



Predicts:

DILI susceptibility multiple drugs

Non-PK drug:drug interactions



Predicts effects of disease and genetic variation

Final Summary

DILIsym in an example of the potential of QST to improve the efficiency of drug development by identifying and guiding management of liver safety liabilities in new drug candidates.

Thanks to the DILIsym team

Sept.2019