Quantitative Systems Toxicology (QST) Modeling of Drug-Induced Liver Injury and Adaptation

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Session Description and Objectives

Description

- This talk will present how quantitative systems toxicology (QST) modeling can aid in evaluating potential drug-drug interactions (DDIs) at the hepatotoxicity mechanism level and exploring mechanisms underlying adaptation to drug-induced liver injury (DILI)
- A case study will be presented where DILIsym, a QST modeling platform, was employed to assess potential DILI DDIs between metformin and solithromycin

Objectives

- To understand drug-drug interactions (DDIs) at the hepatotoxicity mechanism level that may lead to enhanced drug-induced liver injury (DILI)
- To describe the application of quantitative systems toxicology (QST) modeling in prediction of DILI DDIs
- To describe how QST modeling can be employed to assess mechanisms underlying adaptation to DILI

Biography and Contact Information

- Scientist for DILIsym Services, Inc. and software developer working on the DILI-sim Initiative modeling team
- Research focuses on the quantitative systems toxicology (QST) modeling of drug-induced liver injury (DILI) regarding interference of bile acid transport, inhibition of mitochondrial function, and induction of oxidative stress by hepatotoxic drugs
- B.S. in pharmacy and M.S. in pharmacokinetics from Seoul National University, South Korea; Ph.D. in Pharmaceutical Sciences from University of North Carolina at Chapel Hill
- Published scientific papers in the areas of drug metabolism and transport, regulation of drug metabolizing enzymes during pregnancy, and QST modeling of DILI
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Introduction: Drug-Induced Liver Injury (DILI) and Adaptation

Drug-induced liver injury (DILI)

- One of the primary reasons for termination of drug development programs
- Induced by multiple mechanisms
- Can be enhanced by polypharmacy if co-administered drugs induce toxicity via mechanisms that have overlapping pathways (DILI-DDI)

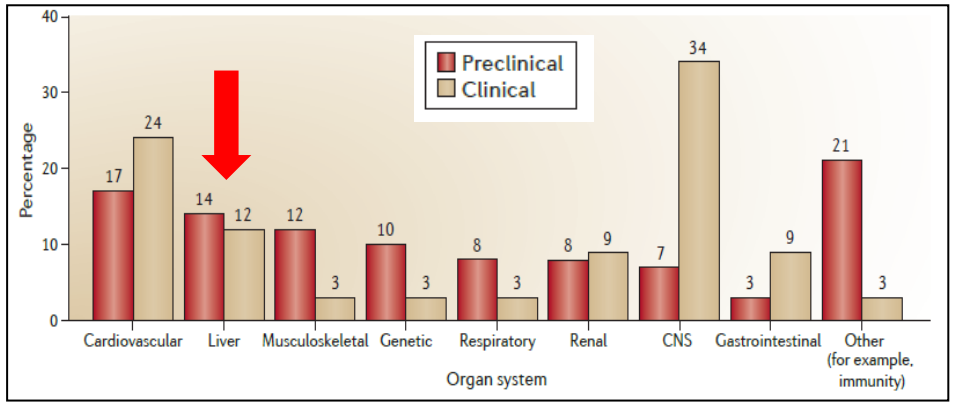
Adaptation

- Resolution of DILI despite continued drug dosing
- Commonly observed in clinical trials, but the underlying mechanisms behind this phenomenon remain unclear

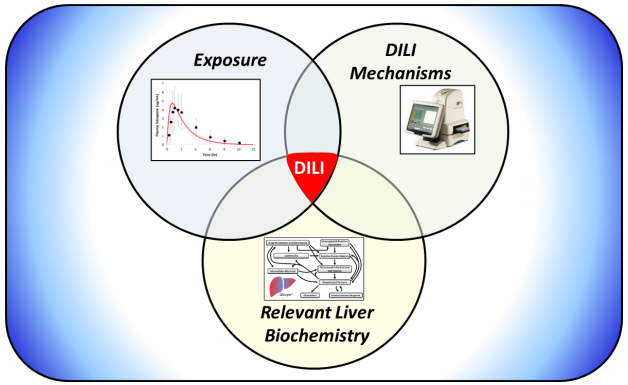
Quantitative systems toxicology (QST) modeling

- Predicts toxicity by integrating drug exposure, mechanisms, and inter-patient variability

Reasons for Termination of Programs due to Safety by Organ System [1]



QST Modeling of DILI

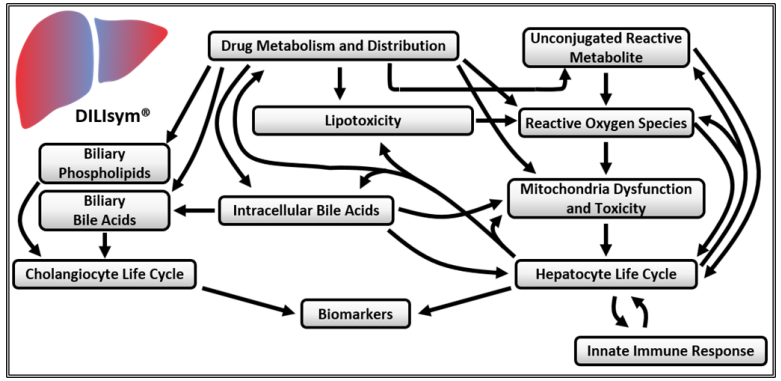


The objective was to predict potential DILI-DDIs of metformin and solithromycin and the impact of mitochondrial biogenesis on DILI using QST modeling

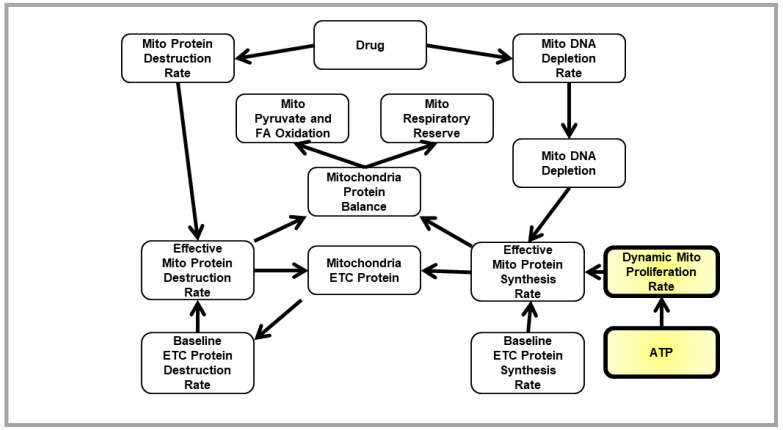
Methods: Quantitative Systems Toxicology (QST) Modeling of DILI-DDI and Adaptation

- DILIsym is a QST software platform that represents drug exposure, liver biochemistry, and multiple mechanisms contributing to DILI and adaptation
  - Constructed and qualified with clinical and experimental data [2-16]
  - Mitochondrial biogenesis added as a potential adaptation pathway
- A solithromycin model was previously constructed within DILIsym [17]
  - Inhibits hepatic bile acid transporters and mitochondrial electron transport chain (ETC)
  - Simulations recapitulated clinically observed mild ALT elevations
- Metformin model was constructed within DILIsym using clinical PK and *in vitro* mechanistic toxicity data
- DILIsym simulations performed using SimPops (n=285) with protocols below in the absence and presence of mitochondrial biogenesis:
  - Metformin 1 g BID for 4 weeks
  - Solithromycin IV 400 mg on days 1-3, PO 800 mg on day 4, PO 400 mg on days 5-7 (IV-to-Oral protocol)
  - Metformin 1 g BID for 4 weeks + Solithromycin IV-to-Oral protocol during the 4th week

DILIsym Mechanism-Based Model

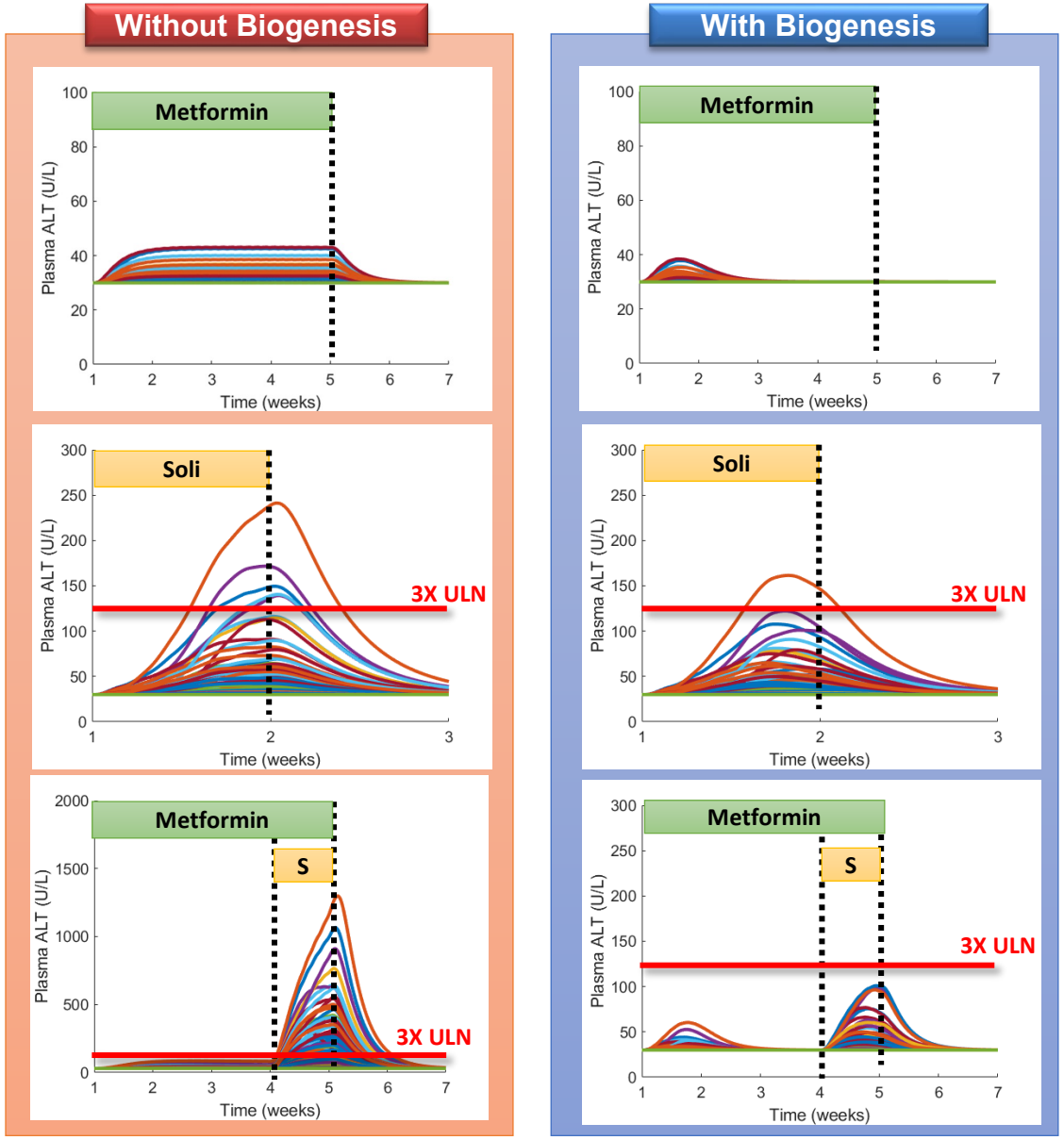


Mitochondrial Biogenesis Sub-model



Results

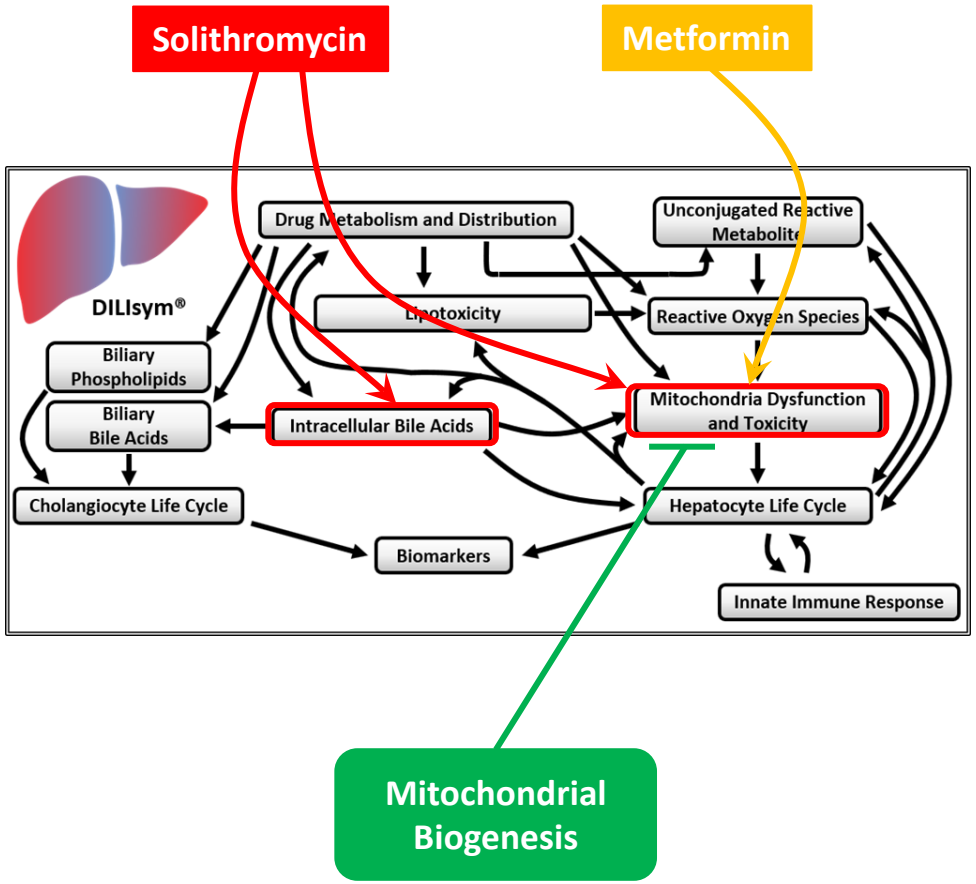
- Therapeutic dose of metformin (1 g BID) alone induced mild ALT elevations in a subset of simulated individuals which resolved with biogenesis despite continuing treatment
  - Consistent with known liver safety of metformin
  - Metformin is an inhibitor of mitochondrial ETC
- Solithromycin IV-to-Oral protocol alone induced modest ALT elevations in a subset of simulated individuals which resolved with biogenesis despite continuing treatment
  - Consistent with clinically observed ALT dynamics (by design) [17,18]
- Metformin enhanced solithromycin-induced hepatotoxicity in a subset of simulated individuals
  - Simulated DILI DDI was mitigated by mitochondrial biogenesis
  - A subset of patients who developed ALT elevations in solithromycin trials had a history of metformin treatment, but detailed information is lacking
  - Observed ALT elevations were modest suggesting a potential role of biogenesis, but additional data are needed to better quantitate the impact of biogenesis



3X ULN (upper limit of normal) = 120 U/L

Conclusion

- QST modeling can be employed to predict potential DILI DDIs due to interactions at toxicological mechanisms
- QST modeling can identify the potential mechanisms underlying DILI adaptation
  - More experimental data are needed to better quantitate the extent and inter-individual variability of biogenesis and to enhance the accuracy of prospective predictions of adaptation to DILI



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Acknowledgments

Questions

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