Assessing the Role of Intracellular Binding Protein in Drug-Induced Bile Acid Transporter Inhibition Using Quantiative Systems Pharmacology (QSP) Modeling

November 6, 2018

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Biography and Contact Information

- Jeffrey L. Woodhead, Ph.D., DILIsym Services, Inc., a Simulations Plus company
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- Ph.D. in chemical engineering from North Carolina State University (Advisor: Dr. Carol Hall)
- Worked on the DILIsym software package for 7+ years
- Focused on representation of bile acid homeostasis and disruption by BSEP inhibitors
- Co-chair of Drug Safety Working Group within the ISoP QSP special interest group (with Dr. Lisl Shoda)

DILIsym Is Used to Predict Bile-Acid Mediated Drug-Induced Liver Injury

- DILIsym is a quantitative systems toxicology (QST) model of drug-induced liver injury (DILI)
- DILIsym has a good record of predicting DILI, including with drugs that are inhibitors of the bile salt export pump (BSEP)
  - Bosentan/telmisartan
  - Troglitazone/pioglitazone
  - Tolvaptan
  - TAK-875
- K_i determined from a vesicle assay is used to represent inhibition potency in the simulation

DILIsym Predicts Bile Acid-Mediated DILI Better Using Total Drug Concentration in the Liver

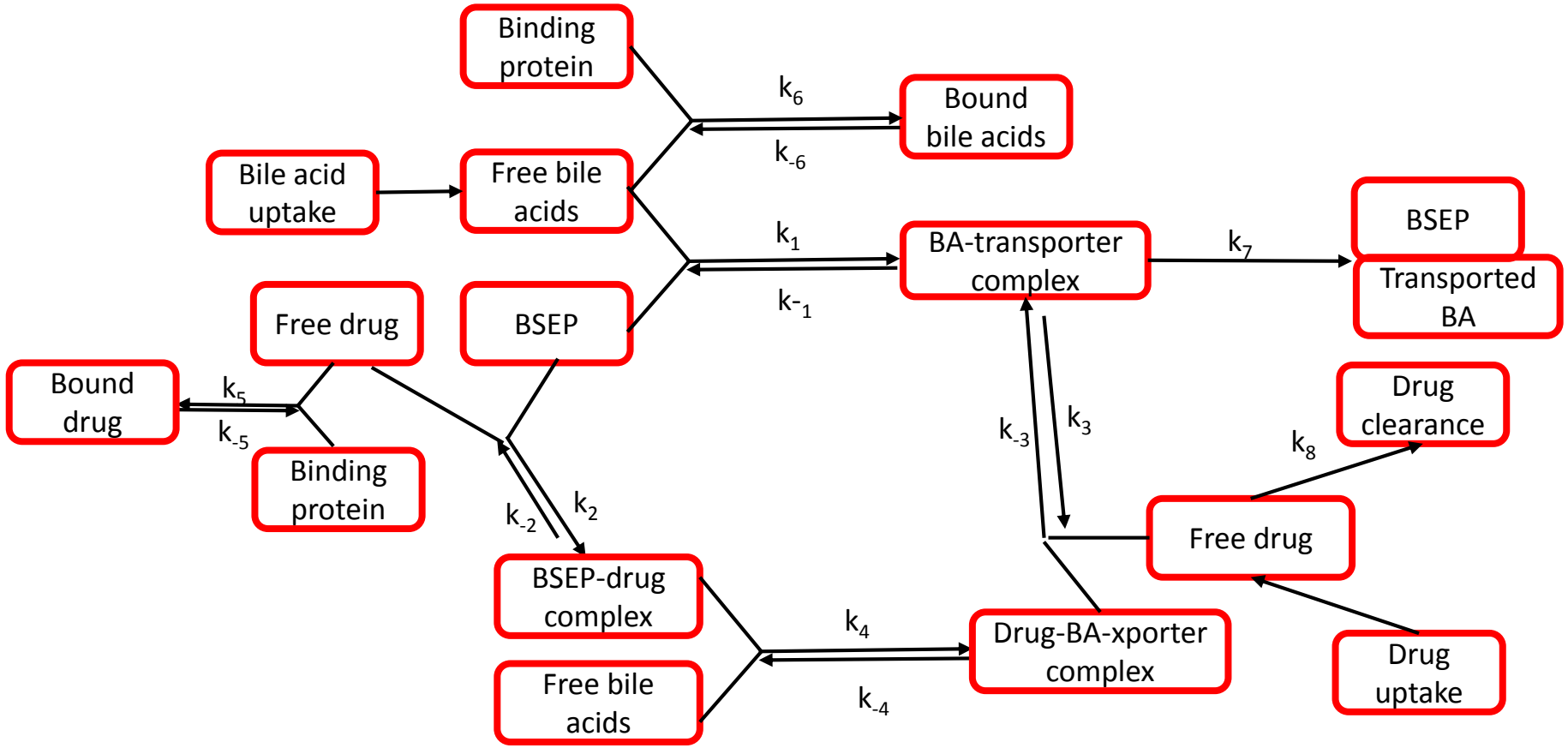
- DILIsym uses total drug concentration as the relevant concentration for BSEP inhibition
- The free drug hypothesis suggests that unbound drug concentration should be the relevant concentration
- Total concentration predicts toxicity better than free
- Several potential reasons this may be the case:
  - Non-specific binding in the vesicle assay
  - Complex binding kinetics within the cell

Drug	Biophase	ALT > 3x ULN
Bosentan 500 mg BID	Total	24/285 (8.4%)
Bosentan 500 mg BID	Free	0/285
Clinical Observation	-	**8-18%**

Drug	Biophase	ALT > 3x ULN
AMG-009 100 mg QD	Total	112/285 (38.3%)
AMG-009 100 mg QD	Free	0/285
Clinical Observation	-	**12.5%**

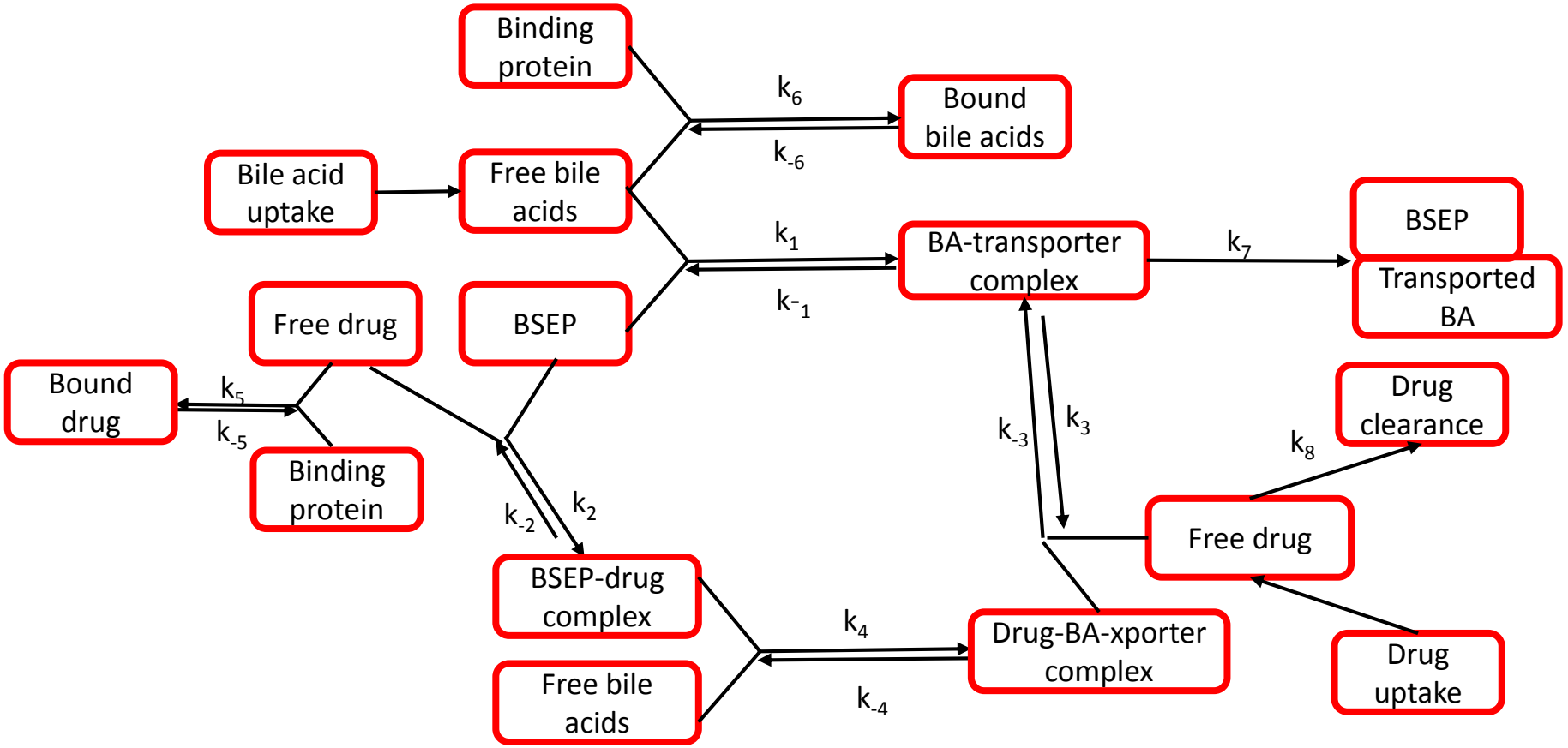
QSP Model of Bile Acid, Drug, and Binding Protein Kinetics Within the Hepatocyte Was Constructed

- Quantitative systems pharmacology (QSP) model of intracellular interaction among drug, bile acid, and binding protein constructed
  - Based on standard enzyme inhibition model with both drug and bile acids subject to protein binding
- Static, dynamic, and chaperoning models were constructed (dynamic model shown)



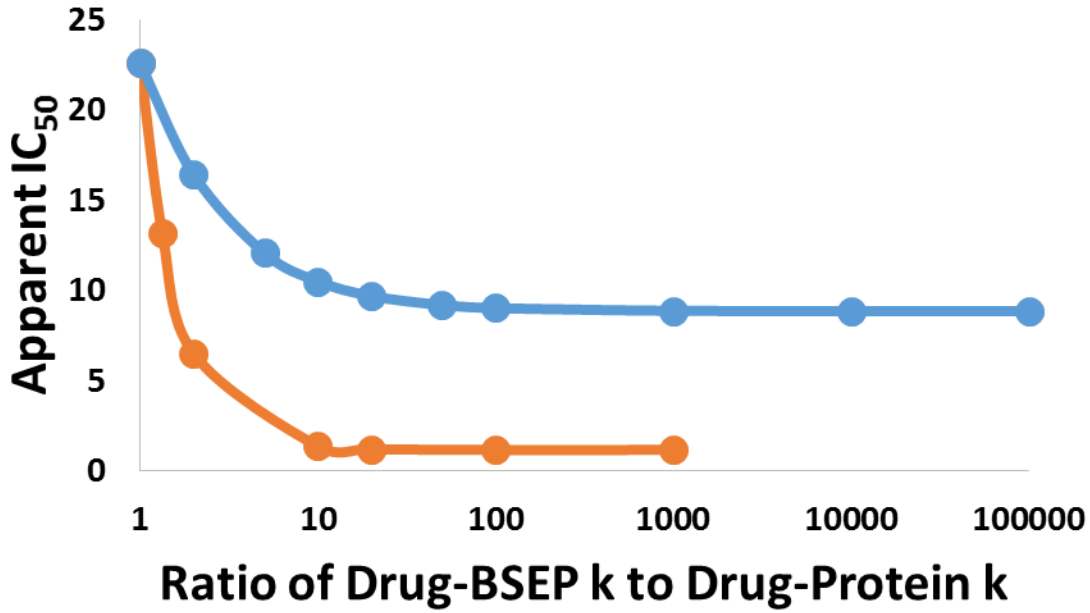
QSP Model of Bile Acid, Drug, and Binding Protein Kinetics Within the Hepatocyte Was Constructed

- Physiologically relevant concentrations assigned where plausible
  - Concentration of BSEP: 2.89 x 10^{-4} μM (Wisnewski 2016)
  - BA concentration : 61 μM (Setchell 1997)
  - Binding protein concentration: 100-400 μM (l-FABP concentration from Atshaves 2010)
- K values varied as well as initial binding protein concentration



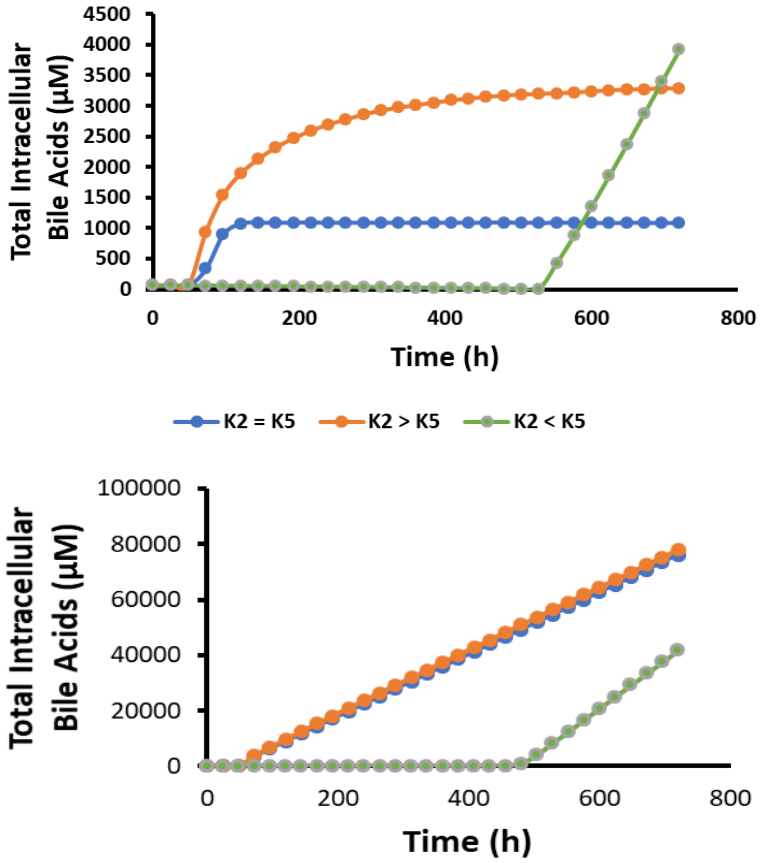
Results from Static Model Show Difference in Predicted Inhibition Potency When Drug Affinity for Protein and BSEP Is Modulated

- Rate constants for drug coupling with BSEP and binding protein varied in static model with inherent free-drug K_i = 1
  - BA and drug both 95% bound
- When BSEP and protein rate constants are similar, apparent IC_{50} of the system is in line with free drug hypothesis
- As drug-BSEP rate constant increases above unity, apparent IC_{50} decreases
  - Effect is more pronounced when drug-protein rate constant is decreased (orange) than when drug-BSEP rate constant is increased (blue)



Results from Dynamic and Chaperoning Models Demonstrate Complexity of Bile Acid-Drug-Protein System

- Dynamic flow of bile acids and drug introduced in order to better represent *in vivo* conditions (top)
- Chaperoning – potential for bile acid to go directly from bound to protein to bound to BSEP – introduced as a hypothesis exploration (bottom)
  - Some research suggests that some bile acid accumulation is due to disruption of chaperoning; this has been proposed as a toxicity mechanism for indomethacin
- In dynamic model, affinity difference leads to increase in BA accumulation
- In chaperoning model, affinity difference leads to little change in BA accumulation; significant accumulation occurs at affinity parity
  - Due to effect interference with BA protein binding has on transport
- In both models, high drug-protein affinity leads to high BA accumulation after time
  - Drug saturates protein binding sites, leading to increases in both free BA and free drug (which inhibits BA transport more efficiently)



Conclusions

- Improved predictivity of total drug vs. free drug can plausibly be explained by a number of hypotheses
  - Drug has higher affinity for BSEP than for binding protein
  - Drug interferes with bile acid chaperoning
  - Drug and bile acid combine to saturate intracellular protein binding sites
- Experiments can assist in determining likelihood for these hypotheses
  - Test for affinity difference between BSEP and l-FABP using BSEP inhibitors
- Behavior of bile acid-protein-drug system is quite complex and unlikely to be accurately described by an equilibrium binding ratio
  - Inclusion of binding model in DILIsym may be beneficial when system properties are understood further
- Implications for the use of the free drug hypothesis in pharmacology in general
  - Free drug hypothesis may underestimate – or overestimate – effect of drug on target (or on inhibition) depending on binding kinetics

Acknowledgments

- Dr. Guncha Taneja
- The DILIsym Services team
- Members of the DILI-sim Initiative
- Protein Binding Focus Group

Questions

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