Quantitative Systems Toxicology (QST) Modeling Using BIOLOGXsym and Mechanistic Toxicity Data From a Biomimetic Liver Microphysiology System Predicts Biologics-induced Liver Injury (BILI) For Multiple Large Molecules

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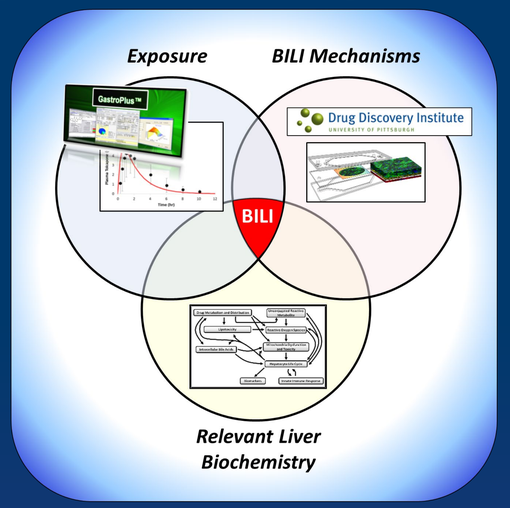
BACKGROUND: While biologics offer promise in addressing a range of unmet medical needs, clinically observed BILI events are concerning for drug developers, health care providers and patients. QST modeling, combined with *in vitro* data, can improve understanding of BILI mechanisms and help predict hepatotoxicity in humans.

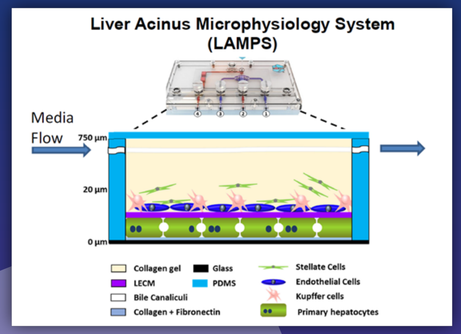
METHODS: BIOLOGXsym™ is a QST model developed in MATLAB 2021a to simulate BILI liabilities by mathematically representing relevant hepatic biochemistry and physiology, as well as pathways and mechanisms unique to biologics (*e.g.*, inhibition of IL-6 signaling by tocilizumab)[1]. Mechanistic toxicity assay readouts from 10-day experiments with the Liver Acinus MicroPhysiology System (LAMPS) were evaluated after treatment with different biologics (GGF2, tocilizumab, ipilimumab, infliximab, nivolumab, bevacizumab[2,3]) with and without BILI liabilities, and were used as BIOLOGXsym inputs to represent biologics mediated hepatocyte stress signals (e.g., oxidative stress). Physiologically based pharmacokinetic models were developed in GastroPlus® v9.8 to inform the exposure of these biologics in the hepatic interstitium at clinically relevant dosing protocols to drive the hepatotoxic effects in the BIOLOGXsym simulations[1,4].

RESULTS: BIOLOGXsym simulations, combining exposure, LAMPS-informed toxicity mechanisms, and a virtual population of normal healthy volunteers (NHV SimPops®, n=285) predicted plasma alanine aminotransferase (ALT) >3X upper limit of normal (ULN) for large molecules with clinical BILI liabilities: GGF2 (Sim: 0.7%, Data: 4.6% with ALT >3X ULN), tocilizumab (Sim: 6.7%, Data: 0.7-33.8% with ALT >1-5X ULN), ipilimumab (Sim: 15.1%, Data: 10.9% with ≥Grade 3), infliximab (Sim: 0.7%, Data: 0.7% with ALT >3X ULN), and nivolumab (Sim: 0.7%, Data: 1.4-1.5% with ≥Grade 3). For the negative control bevacizumab, no mechanistic LAMPS signal was observed, and no ALT elevations were simulated.

QST Modeling Using BIOLOGXsym



While Leveraging Data From LAMPS Experimentation



Has the Capacity to Predict Clinical Hepatotoxicity Caused by Biologics

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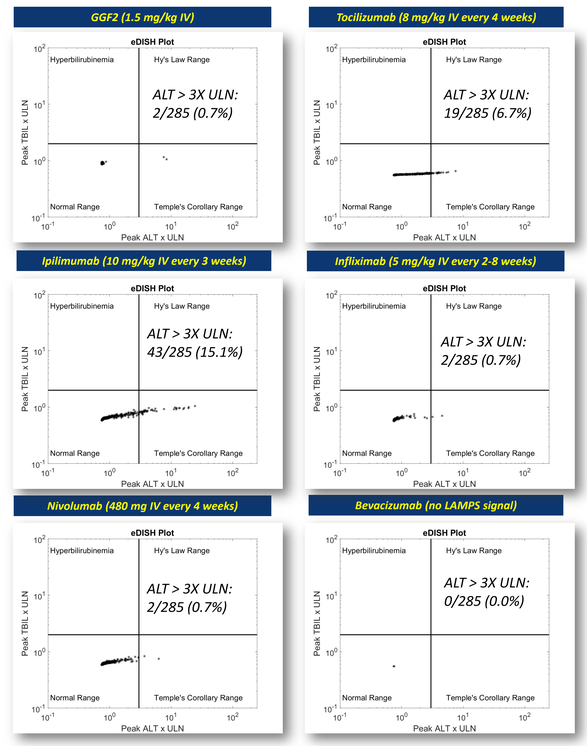
TABLE: Direct hepatocyte stress mechanisms from LAMPS and target-mediated mechanisms affecting hepatocytes that were or will be included in BIOLOGXsym

Compound	Direct hepatocyte stress mechanisms from LAMPS[†]	Target-mediated mechanisms affecting hepatocytes
GGF2	BA, Mito	None
Tocilizumab	ROS	Inhibits IL-6 signaling
Ipilimumab	Mito	Increases effector CD8+ T cell proliferation, mediator production, and cytotoxicity[‡]
Infliximab	BA, Mito	Inhibits TNF-α signaling[‡]
Nivolumab	BA, Mito, ROS	Increases exhausted CD8+ T cell proliferation, mediator production, and cytotoxicity[‡]
Bevacizumab	None	None

[†]BA, bile acid homeostasis alteration; Mito, mitochondrial dysfunction; ROS, reactive oxygen species formation
[‡]Not yet included in current simulations

FIGURE: Simulated evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plots for clinical protocols of biologics in the NHV SimPops (n=285)



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[2]Vernetti *et al*. SOT 63rd Annual Meeting & ToxExpo, Salt Lake City, UT, 2024 Mar 10-14.

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Additional references are available upon request.

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