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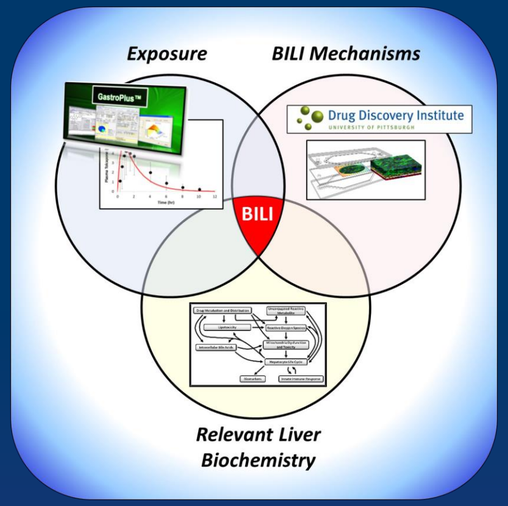
BACKGROUND: While biologics offer promise in addressing a range of unmet medical needs, clinically observed BILI events are concerning for drug developers, health care providers and patients. QST modeling, combined with *in vitro* data, can improve understanding of BILI mechanisms and help predict hepatotoxicity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

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 [illegible] Data From LAMPS Experimentation



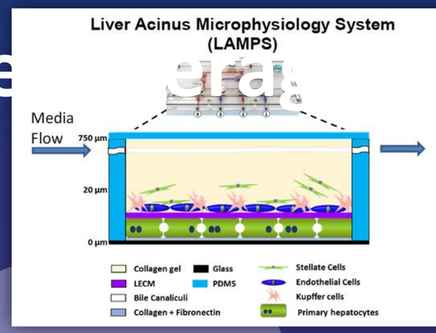
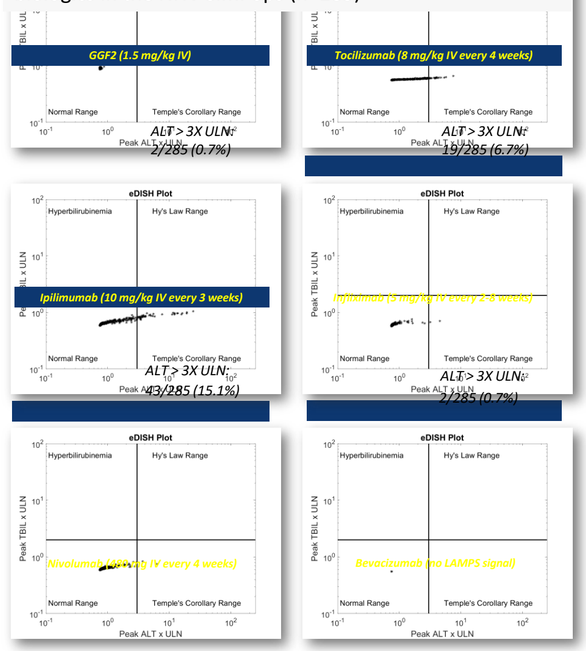


TABLE: Direct hepatocyte stress mechanisms from LAMPS and target-mediated mechanisms affecting hepatocytes that were or will be included in BIOLOGXsym

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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[1]Beaudoin *et al*. Int J Mol Sci. 2023 Jun 2;24(11):9692.

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

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

[4]Vallejo *et al*. Pharmaceutics. 2025 Mar 14;17(3):372.

Additional references are available upon request.

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Capacity to Predict Clinical Hepatotoxicity Caused by Biologics

ALT > 3X ULN:
2/285 (0.7%)

ALT > 3X ULN:
0/285 (0.0%)