QST Modeling Using BIOLOGXsym and Mechanistic Toxicity Data from a Biomimetic Liver Microphysiology System Predicts Increased Susceptibility to Nivolumab-Mediated Hepatotoxicity in MASLD Patients

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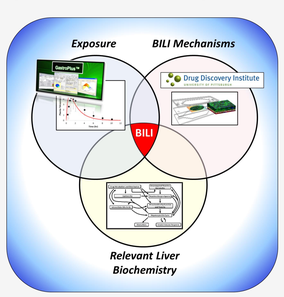
BACKGROUND

Immune checkpoint inhibitor-related hepatotoxicity is a significant clinical concern. A retrospective analysis identified metabolic dysfunction-associated steatotic liver disease (MASLD) as a possible risk factor for PD-1 inhibitor-associated hepatotoxicity[1], but underlying mechanisms remain unclear. In this study, quantitative systems toxicology (QST) modeling was performed to investigate susceptibility and mechanism of nivolumab-induced hepatotoxicity in MASLD patients.

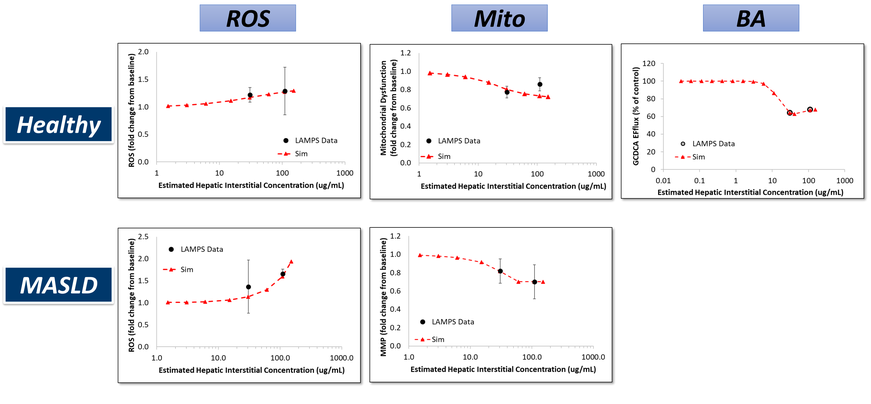
METHODS

BIOLOGXsym is a QST model that represents liver physiology and hepatotoxicity mechanisms[2]. Simulated populations (SimPops) for healthy (n=285) and MASLD (n=263) liver conditions were developed. Mechanistic toxicity data from healthy and MASLD liver acinus microphysiology system (LAMPS) was used as model inputs to represent nivolumab-induced hepatocyte stress. Hepatotoxicity following intravenous nivolumab (480 mg Q4W for 12 weeks) was simulated within BIOLOGXsym using PBPK-based exposures[3]. Mechanism analysis was performed using sensitive SimCohorts (n=16) by systematically removing individual pathways to identify key drivers of toxicity.



RESULTS

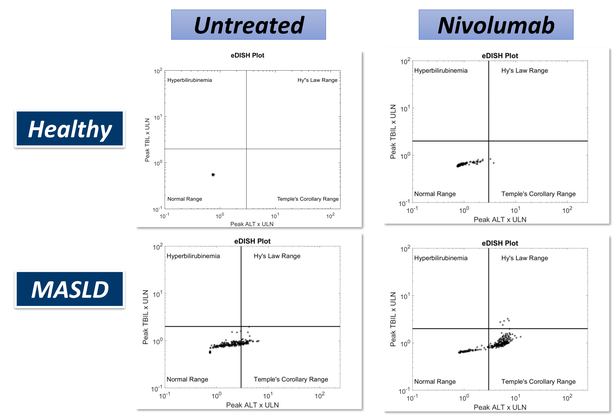
Liver Acinus Microphysiology System (LAMPS) Data and Toxicity Parameterization



Mechanism	Parameter	Parameter Value	
		Healthy	MASLD
Mitochondrial Dysfunction	Biol. Coefficient for ETC inhibition 3 (μM)	0.03	0.1
	Biol. Max inhibitory effect for ETC inhibition 3 (dimensionless)	0.4	0.5
Oxidative Stress	Biol. RNS/ROS production rate Vmax 4 (1/hr)	0.015	0.03
	Biol. RNS/ROS production rate Km 4 (μM)	0.19	0.19
	Biol. RNS/ROS production rate Hill 4 (dimensionless)	1	1
Bile Acid Transport	Biol. Basolateral efflux impact delay (1/hr)	0.0417	N/A
	Biol. Basolateral efflux impact Vmax (dimensionless)	-0.65	N/A
	Biol. Basolateral efflux impact Km (μg/mL)	10	N/A
	Biol. Basolateral efflux impact Hill (dimensionless)	3.75	N/A

- In healthy LAMPS, nivolumab significantly increased oxidative stress (ROS), reduced mitochondrial function (Mito), and reduced bile acid (BA) efflux
- In MASLD LAMPS, nivolumab significantly increased oxidative stress (ROS) and reduced mitochondrial function (Mito), but did not significantly change BA efflux

Hepatotoxicity Simulations



- In healthy SimPops, ALT > 3X ULN was predicted in 0.7% (2/285) with nivolumab treatment compared to 0% without treatment
- In MASLD SimPops, ALT > 3X ULN was predicted in 75.7% (199/263) with nivolumab treatment compared to 19.4% (51/263, due to oxidative stress driven by lipotoxicity) without treatment

Mechanism Analysis

Drug	Mechanisms	Peak ALT (U/L)	
		Healthy SimCohorts	MASLD SimCohorts
Nivolumab	All mechanisms	103 ± 44	337±55
	ROS removed	83 ± 30	215±50
	Mito removed	36 ± 6	307±45
	BA removed	73 ± 28	-
Untreated		30	178 ± 45

ROS: oxidative stress, Mito: mitochondrial dysfunction, BA: bile acid

- In healthy SimCohorts, nivolumab hepatotoxicity was mainly driven by Mito and BA mechanisms
- In MASLD SimCohorts, nivolumab hepatotoxicity was mainly driven by ROS with minor contribution from Mito

CONCLUSION

- QST modeling integrating LAMPS data successfully recapitulated the modest ALT elevations observed clinically following nivolumab treatment and predicted increased susceptibility to nivolumab-induced hepatotoxicity in MASLD patients.
- Simulations identified ROS as the predominant mechanistic driver, exacerbating the underlying oxidative stress characteristic of MASLD.
- Together, these findings provide proof of concept that QST modeling informed by organ-on-a-chip data can function as a new approach methodology (NAM) to assess hepatotoxicity risk.

REFERENCES

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CONFLICT OF INTEREST

Kyunghee Yang, Lara Clemens, Francisco Huizar, Celeste Vallejo, Lisl K.M. Shoda, and James J. Beaudoin are employees of Simulations Plus Inc., which received a National Institutes of Health Small Business Innovation Research Award in collaboration with the University of Pittsburgh Drug Discovery Institute to develop a QST platform for the evaluation of liver injury induced by biologics.

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