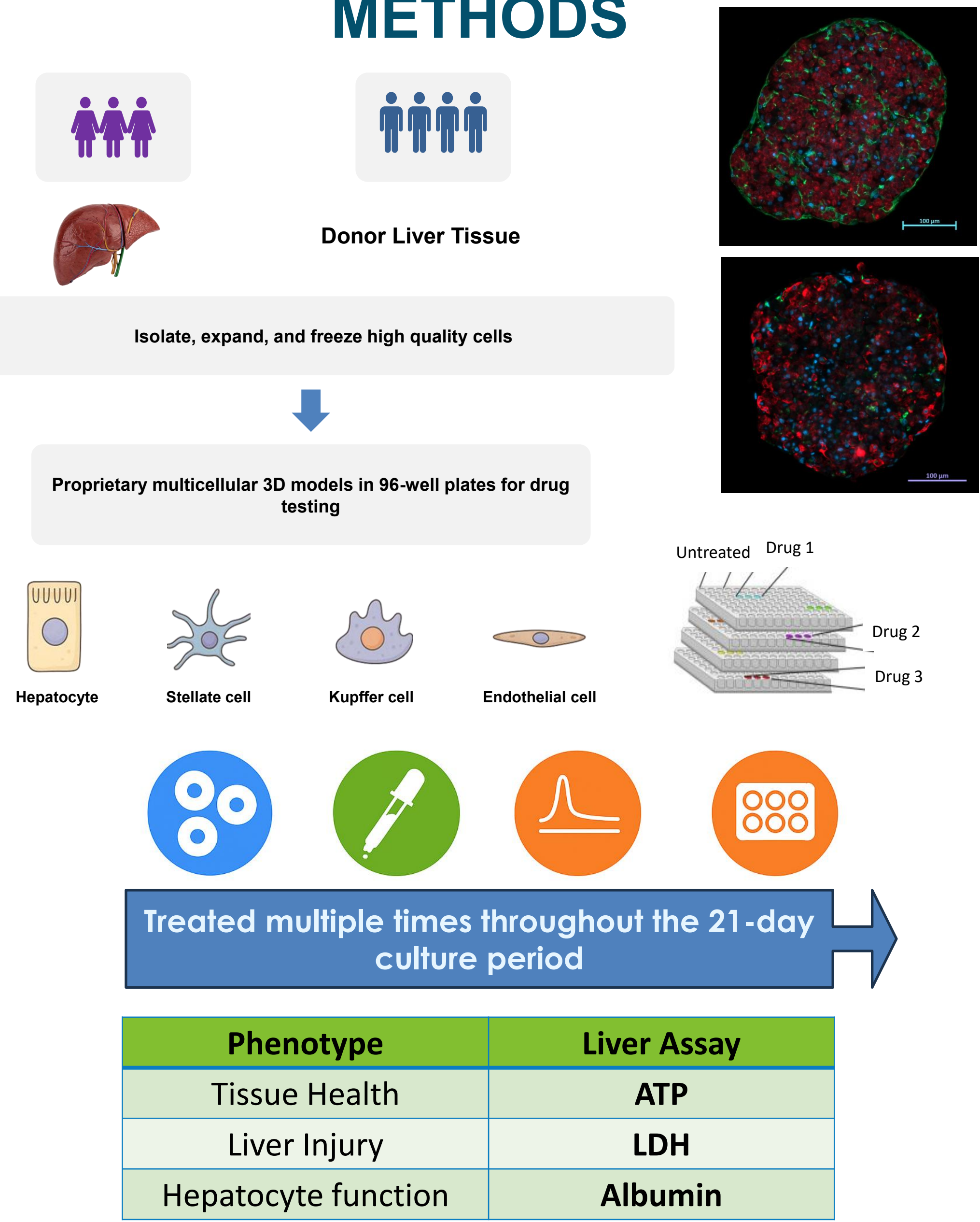


Mehrsa Mehrabi, Payton Olson, Cole Toohey, Rachel Dudum, Haylee Aidnik, Caridad Rosette, Keith Murhpy, Amar A. Sethi
VivoSim Labs, Inc, SAN DIEGO, CALIFORNIA, USA

AIM

To benchmark NAMkind™ liver performance for ADC-associated hepatotoxicity using five clinically used ADCs spanning on-target and off-target contexts. Specifically, we evaluated whether the model distinguishes (i) on-target hepatotoxicity, (ii) cleavable vs non-cleavable linker behavior, and (iii) permeable vs non-permeable payload classes at clinically relevant exposure (1× plasma Cmax) using Albumin, ATP, and LDH endpoints.

METHODS



CONCLUSIONS

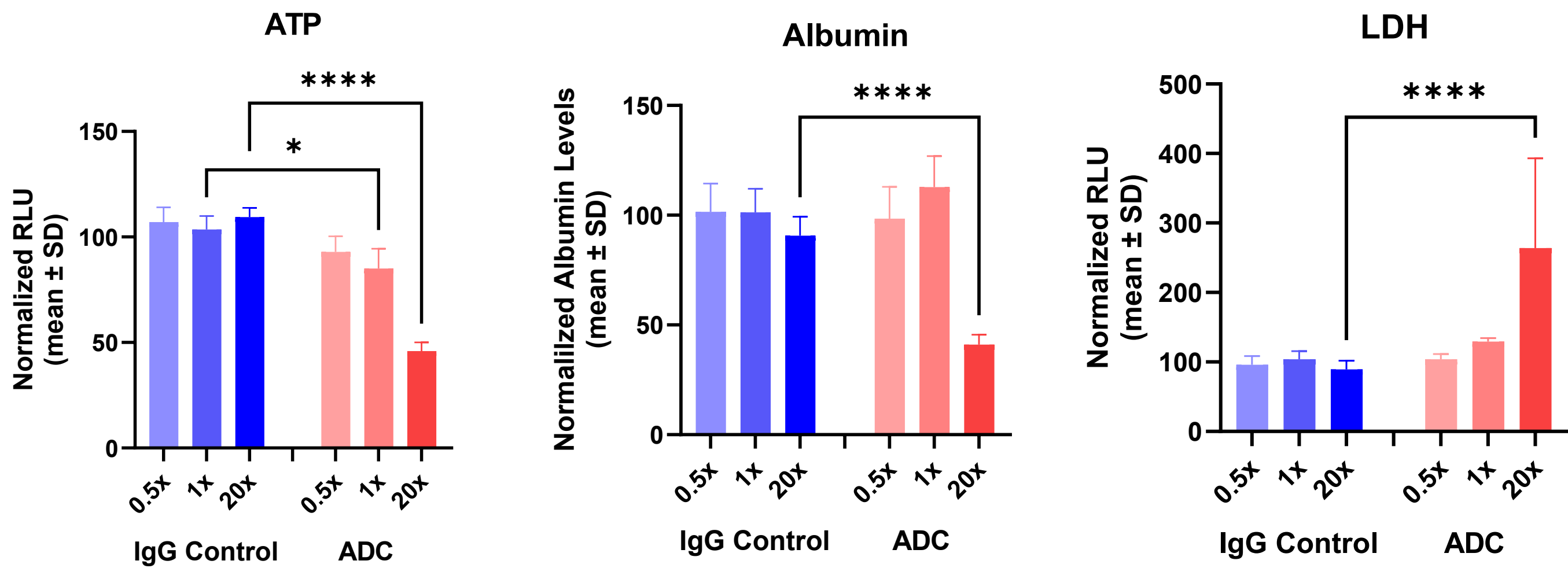
- Across five clinically used ADCs, NAMkind™ liver spheroids separated on target from off target liver liability using complementary functional and injury endpoints (Albumin, ATP, LDH).
- The CD33 targeted ADC gemtuzumab ozogamicin produced clear on target toxicity signals.
- Off target ADCs whose targets are not expressed in the model did not induce measurable liver injury under the tested conditions.
- Within HER2 targeted ADCs, NAMkind™ liver differentiated constructs consistent with conjugate design (DAR/linker/payload properties), yielding distinct response patterns across endpoints.
- Overall, NAMkind™ liver aligns with observed clinical hepatotoxicity patterns, with Brentuximab vedotin representing a notable exception driven primarily by susceptible patient subgroups not captured when using healthy donor cells.

INTRODUCTION

Drug-induced liver injury (DILI) remains a major cause of late-stage attrition in drug development, and this risk is increasingly relevant for complex modalities such as antibody-drug conjugates (ADCs). For ADCs, liver liability can be driven by conjugate design and exposure rather than payload potency alone. The mechanism of injury includes specific target engagement, non-specific scavenger receptor internalization, linker cleavability, drug-to-antibody ratio (DAR), and payload permeability.. Three-dimensional, multicellular NAMkind™ human liver spheroids enable human-relevant, throughput-compatible assessment of ADC liver risk using complementary functional and injury endpoints (Albumin, ATP, LDH) under repeat-dose schedules that can be tailored ro clinical dosing regimens..

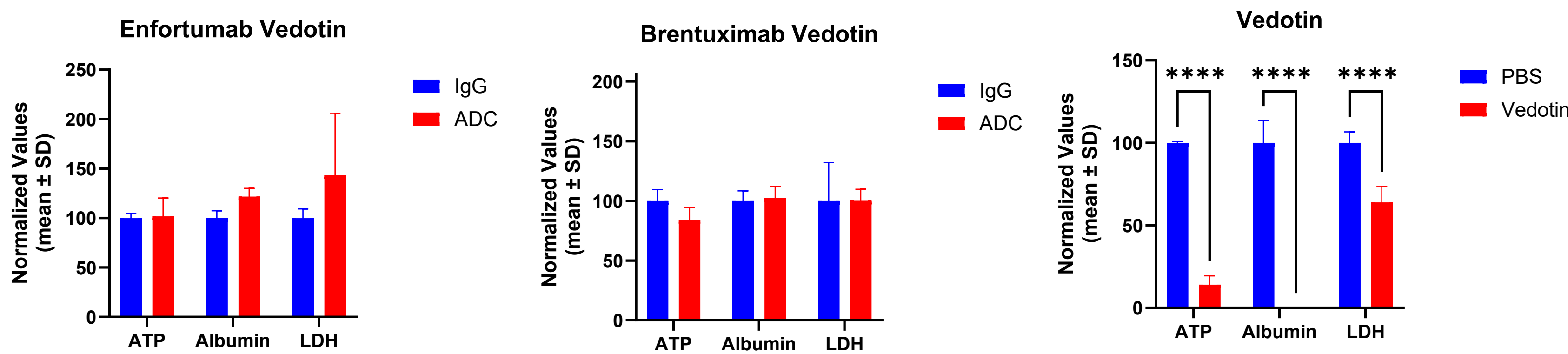
Clinically Aligned On-target Toxicity of Gemtuzumab-Ozogomycin

Drug	Target	Target Expression in Model	DAR	Linker Type	Payload Permeability	Payload Mechanism	Liver Toxicities
Gemtuzumab ozogamicin	CD33	Endothelial & Kupffer	2	cleavable	Yes	DNA disruption	Sinusoidal Obstruction Syndrome



Clinically Aligned No Toxicity with Off-target ADCs

Drug	Target	Target Expression in Model	DAR	Linker Type	Payload Permeability	Payload Mechanism	Liver Toxicities
Enfortumab vedotin	Nectin-4	none	4	cleavable	Yes	Tubulin inhibition	None
Brentuximab vedotin	CD30	none	4	cleavable	Yes	Tubulin inhibition	None (except in susceptible patients)

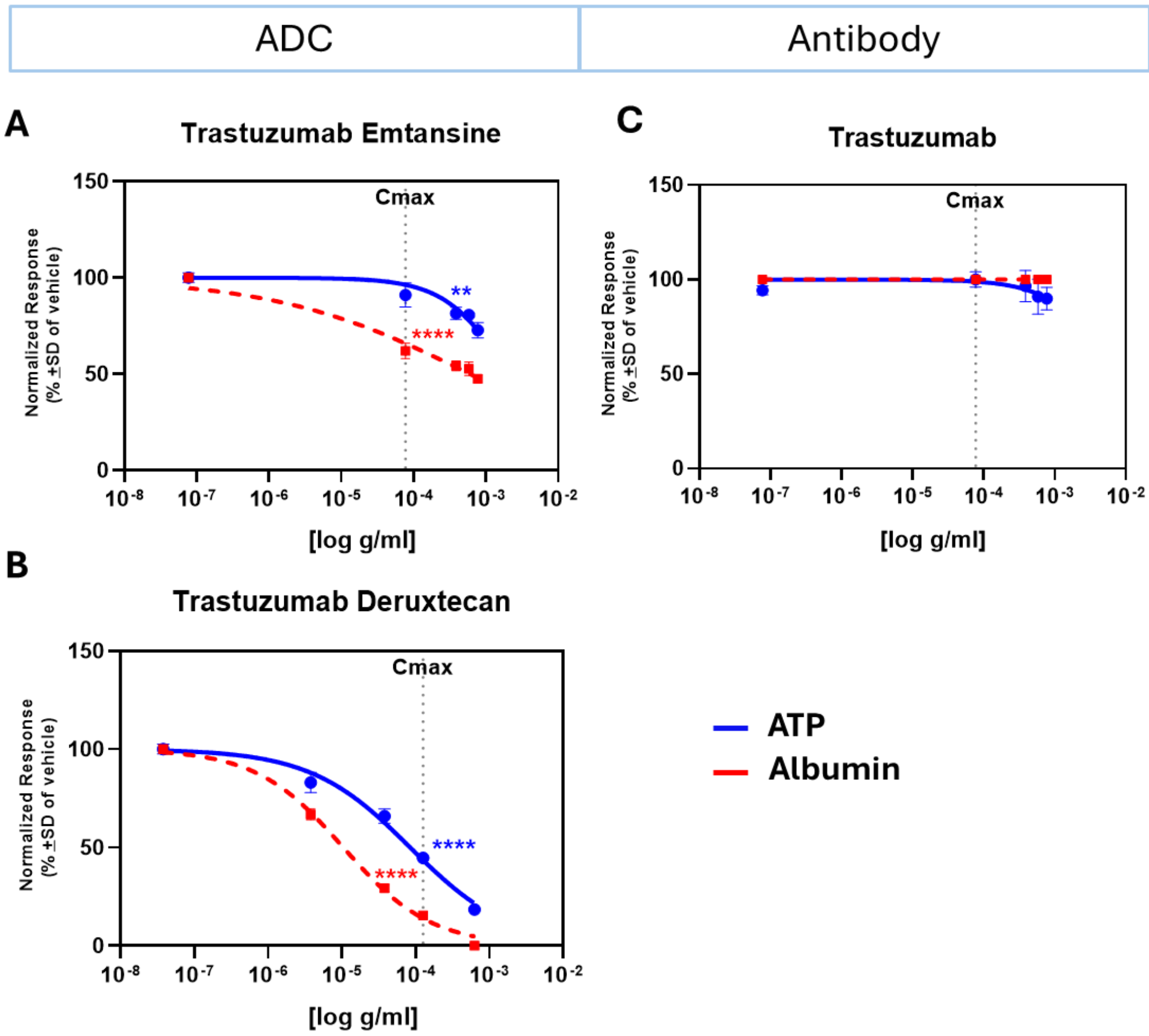


CONTACT INFORMATION

asethi@vivosim.ai <https://vivosim.ai/>
© VivoSim Labs, Inc.

NAMkind™ Liver Differentiates ADC Liver Risk by Linker/Payload Properties

Drug	Target	DAR	Linker Type	Payload Permeability	Payload Mechanism	Liver Toxicities
Trastuzumab	HER2	N/A	N/A	N/A	N/A	Very Low
Trastuzumab emtansine	HER2	4	non-cleavable	No	Tubulin inhibition	Rare Liver Sinusoidal Obstruction Syndrome
Trastuzumab deruxtecan	HER2	8	cleavable	Yes	Topo-I inhibition	Clinically significant hepatotoxicity



NAMkind™ Liver differentiates ADC liver responses in a manner consistent with key conjugate design features. Trastuzumab emtansine carries a DAR of 4 with a non-cleavable linker and delivers a tubulin inhibitor, whereas Trastuzumab deruxtecan carries a higher DAR of 8 with a cleavable linker and delivers a topoisomerase I inhibitor payload . These distinctions support the utility of the model for comparing ADCs with different payload classes, linker chemistry, and drug loading densities when assessing relative liver safety risk.

NAMkind™ Liver Aligns with Observed Clinical ADC Hepatotoxicity

ADC	CLINICAL	VivoSim
Gemtuzumab-ozogomycin	Toxic	Toxic
Trastuzumab-emtansine	Toxic	Toxic
Trastuzumab-deruxtecan	Toxic	Toxic
Brentuximab vedotin	Ambiguous	Safe
Enfortumab vedotin	Safe	Safe

LEGEND

Toxic

Safe

Ambiguous

The model shows strong concordance with clinical hepatotoxicity signals, with one notable exception. Brentuximab vedotin has clinically meaningful hepatotoxicity primarily in patients with baseline hepatic impairment. This mismatch likely reflects that the assay uses healthy donor cells and does not capture patient-specific vulnerability.