

Poster

P30-47

NAMkind™ Liver & Intestine Toxicity Prediction Across Small Molecules and Antibody Drug Conjugates



EUROTOX 2026
VIENNA | AUSTRIA
13-16 SEPTEMBER 2026

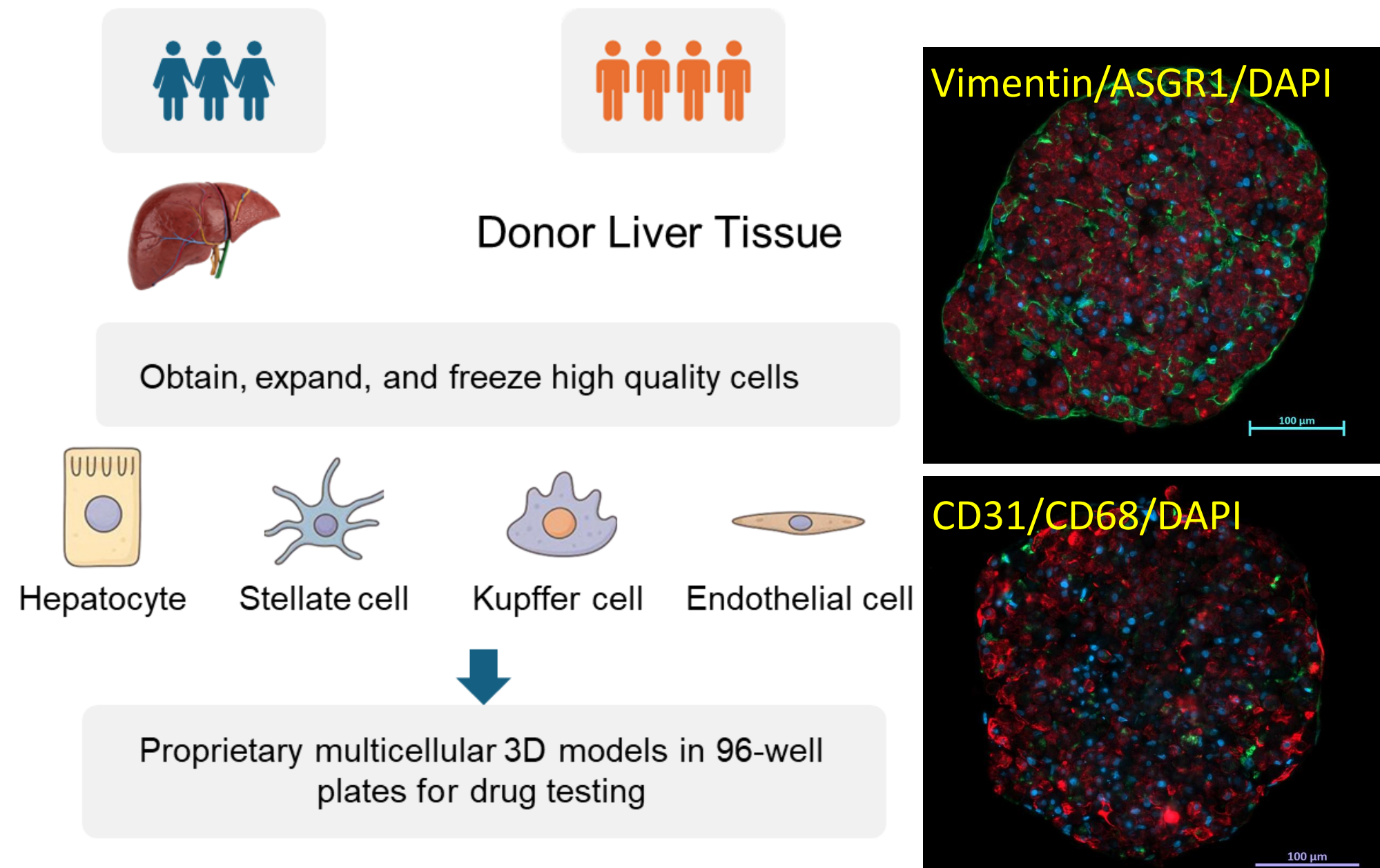
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INTRODUCTION

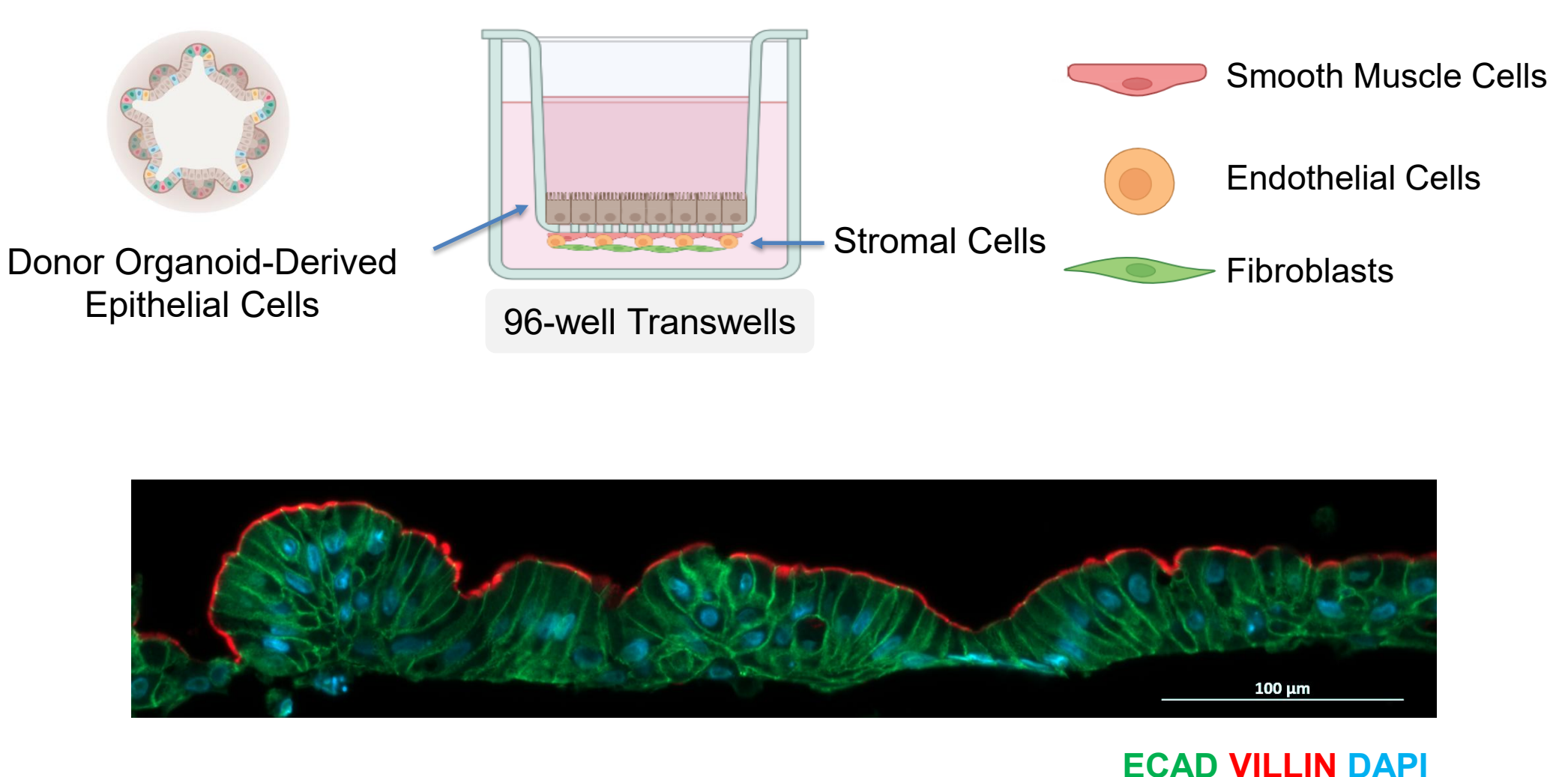
Drug-induced liver injury (DILI) and gastrointestinal (GI) toxicity are major causes of drug attrition, and Antibody Drug Conjugates (ADCs) introduce additional off-target liabilities driven by linker-payload properties, systemic exposure, and target expression in healthy tissues. Current in vitro models often fail to capture clinically relevant toxicities that arise under prolonged drug exposure. Here, we describe human primary cell-based NAMkind™ Liver spheroids and polarized NAMkind™ Intestine models to assess liver and GI safety across small molecules and ADCs. Using clinically annotated reference sets, including thiazolidinedione (TZD) compounds for liver injury risk and nonsteroidal anti-inflammatory drugs (NSAIDs) for intestinal toxicity risk, the platforms successfully differentiated compounds according to their known clinical safety liabilities and enabled quantitative ranking of toxicity risk. The predictive performance of both platforms was first established with these clinically benchmarked small-molecule datasets and then extended to the more complex ADC modality to evaluate their ability to discriminate payload- and linker-dependent toxicities. Through multiparametric functional readouts and repeat-dose exposure paradigms, the models were evaluated for their ability to predict toxicity, stratify safety risk, and support compound prioritization, ADC optimization, and preclinical decision-making.

NAMkind™ Liver



NAMkind™ Liver is a 3D human liver spheroid model composed of primary human hepatocytes, liver sinusoidal endothelial cells, hepatic stellate cells, and Kupffer cells that recapitulate key aspects of native liver microarchitecture. The spheroids remain viable and functional for up to 28 days, supporting long-term repeat-dose assessment of DILI. Using a clinically anchored panel of DILI-positive, DILI-negative compounds, and ADCs, the model quantifies complementary measures of hepatotoxicity, including cellular viability (ATP), hepatocyte function (albumin), oxidative stress (GSH), and cell injury (LDH), providing a human-relevant platform for liver safety screening and compound prioritization.

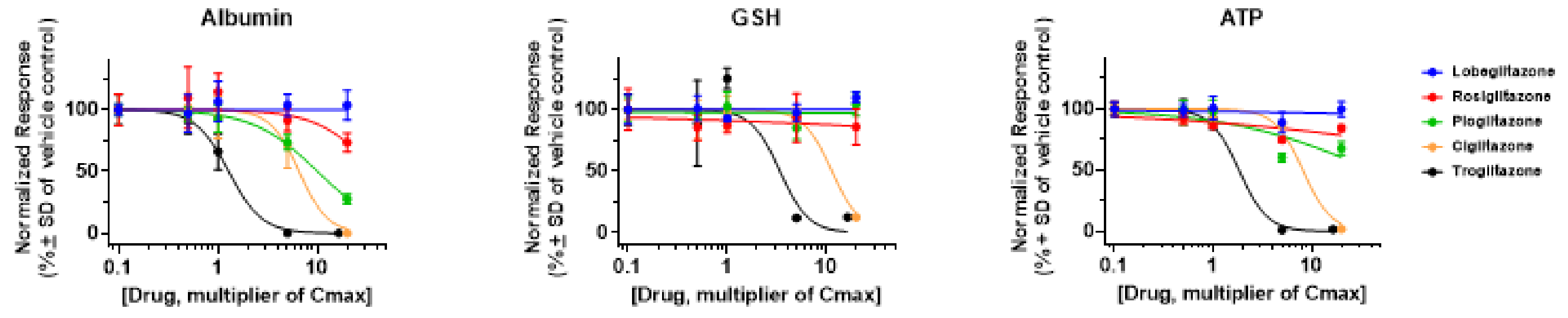
NAMkind™ Intestine: Colon & Ileum



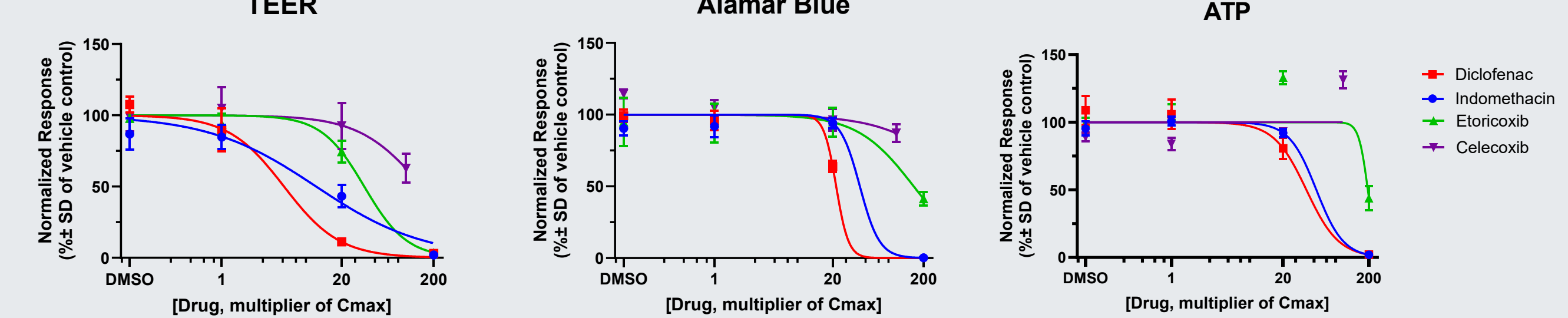
NAMkind™ Intestine is a 3D human intestinal barrier model established using epithelial cells from organoids derived from colon and ileum crypts. Along with stromal cells, the model maintains polarity and tight-junction integrity for greater than 3 weeks in culture. Under repeat-dose conditions, barrier function (TEER) and tissue health/redox state (ATP, Alamar Blue) were measured in a clinically anchored reference set of small-molecule compounds and ADCs with known diarrhea risk. Small molecules were added to the apical and basolateral sides of the transwell to mimic systemic exposure after oral dosing, while ADCs were added to the basolateral side only to mimic intravenous dosing.

RANKING SAFETY RISKS WITH SMALL MOLECULE COMPOUNDS

Liver TZD Series



Intestine NSAID Series



Customized treatment frequency and duration

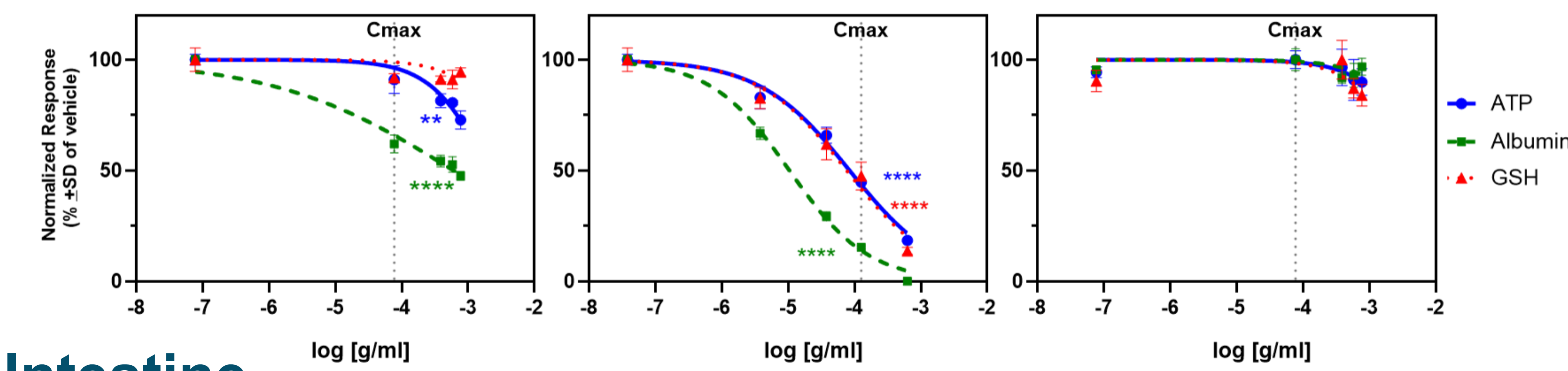


treatment frequency and duration from 7-21 days

TISSUE	PHENOTYPE	ASSAY
LIVER	Tissue Health	ATP
	Liver Injury	LDH
	Hepatocyte Function	Albumin
	Oxidative State	GSH
INTESTINE	Mucosal Barrier	TEER
	Tissue Viability	ATP
	Metabolic Function	Alamar Blue

NAMkind™ INTESTINE & LIVER DIFFERENTIATE ADC SAFETY RISK

Liver



Intestine

ADC	COLON	ILEUM
Trastuzumab Deruxtecan		
Trastuzumab Rezetecan		
Trastuzumab Emkansine		
Trastuzumab Antibody		

Legend: TEER (blue circle), Alamar (green square), CTG (red triangle)

• Trastuzumab deruxtecan showed the greatest hepatotoxicity, with marked reductions in ATP, albumin, and GSH.

• Trastuzumab emkansine caused modest liver toxicity, with albumin as the most sensitive endpoint.

• Naked trastuzumab showed minimal hepatotoxicity, with little effect on any endpoint.

• ATP, albumin, and GSH together formed a robust multiparametric panel for sensitive detection of liver injury.

• Overall liver liability ranked: deruxtecan > emkansine >> naked antibody.

Drug	DAR	Linker Type	Payload Permeability	Payload Mechanism	Liver Clinical Toxicities	GI Clinical Toxicities
Trastuzumab deruxtecan	8	Cleavable	Yes	Topo-I inhibition	Clinically significant hepatotoxic	29% Diarrhea 79% Nausea
Trastuzumab rezetecan	8	cleavable	Yes	Topo-I inhibition		11% Diarrhea 63% Nausea
Trastuzumab emkansine	4	non-cleavable	No	Tubulin inhibition	Rare sinusoidal obstructive syndrome	13 - 24% Diarrhea 36% Nausea
Trastuzumab	Na	na	na	na	Rare	5 - 10% Diarrhea 10- 20% Nausea

• Trastuzumab deruxtecan caused the greatest TEER loss, with stronger effects in the ileum than colon.

• Trastuzumab rezetecan also reduced TEER, again showing greater ileum sensitivity.

• Trastuzumab emkansine reduced TEER and viability markers (Alamar Blue, CTG) at higher concentrations, consistent with both barrier injury and cytotoxicity.

• Naked trastuzumab had minimal effects, with only modest TEER reductions in the ileum.

• TEER was the most sensitive endpoint, detecting toxicity before changes in tissue viability.

• Overall, the ileum was more sensitive than the colon and the models distinguished payload-dependent intestinal toxicity.

CONCLUSIONS

• Clinically validated NAMkind™ Liver and Intestine models accurately predict organ-specific toxicity risk across diverse small-molecule datasets.

• Multi-endpoint, repeat-dose profiling improves sensitivity for detecting clinically relevant liver and GI liabilities.

• Both platforms differentiated ADC toxicities driven by linker and payload properties, demonstrating translational relevance for complex drug modalities.

• Integrated liver and intestine testing provides a human-relevant strategy for compound prioritization, ADC optimization, and earlier safety-informed decision making.

• Integrated TEER, ATP, and Alamar Blue measurements capture complementary aspects of intestinal injury, enabling mechanistic assessment of GI toxicity associated with clinical diarrhea.

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