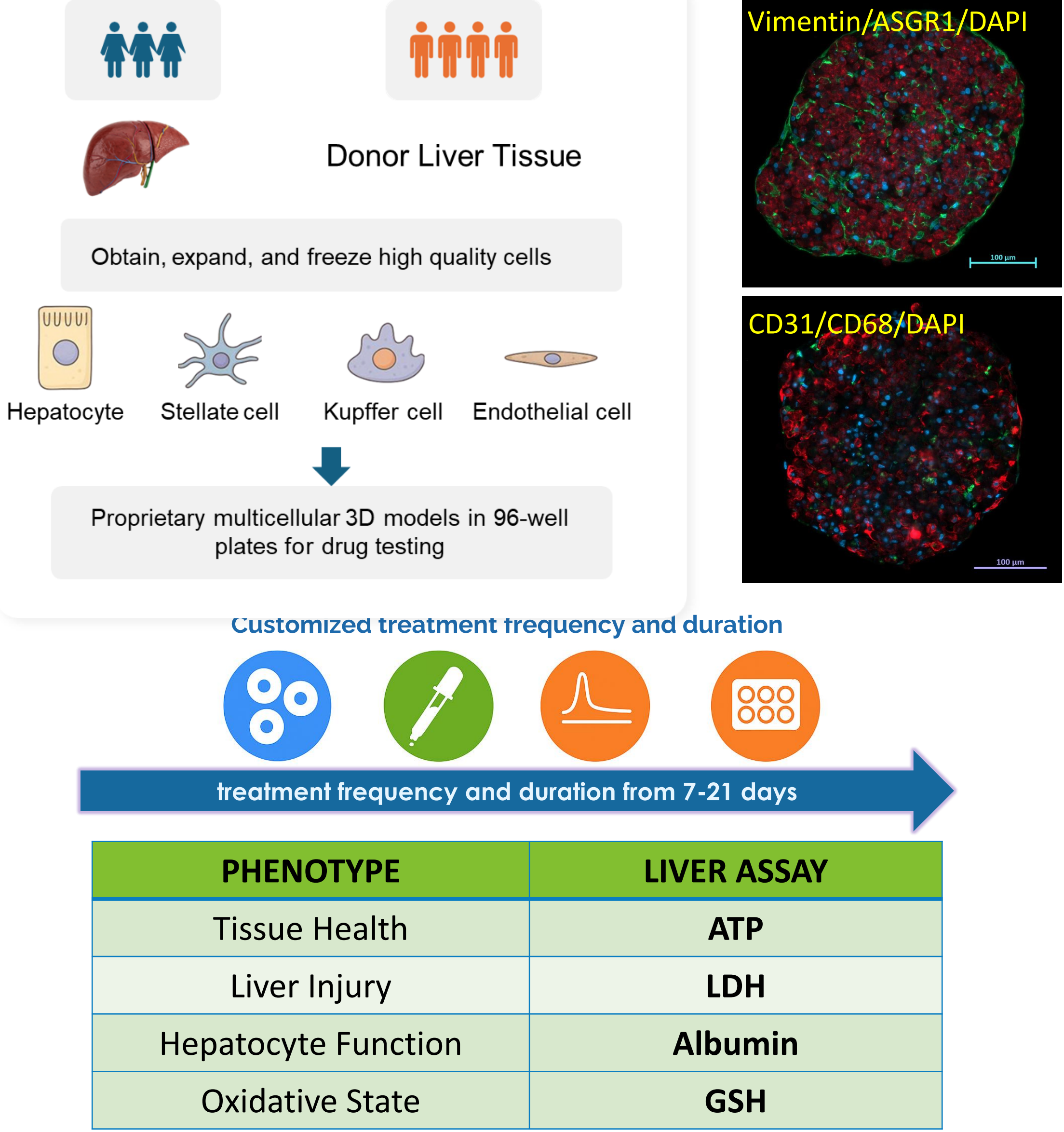


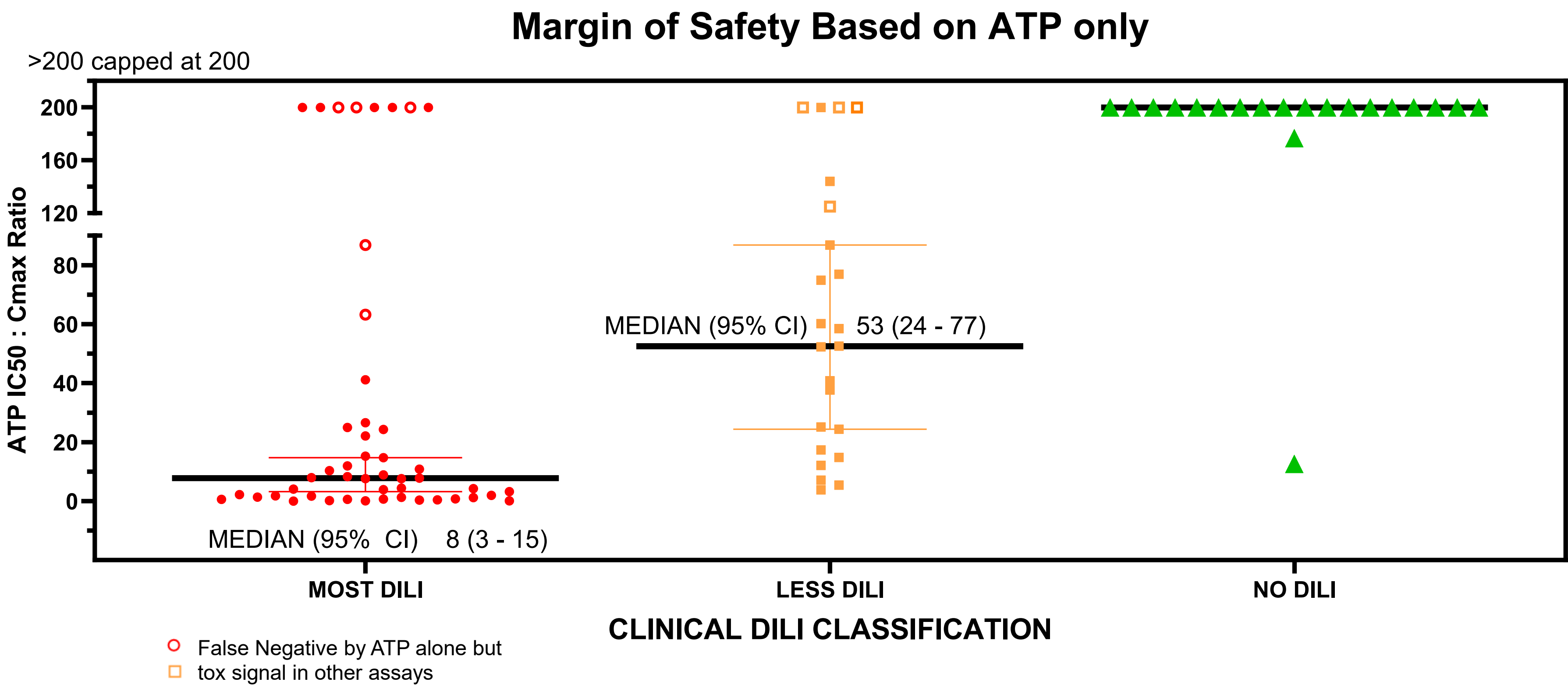
INTRODUCTION

Drug-induced liver injury (DILI) remains a major cause of clinical attrition and post-marketing withdrawal, highlighting the need for human-relevant models that capture cumulative toxicity under repeat dosing. Conventional in vitro systems often lack the complexity to reflect clinically relevant liver responses. Here, we evaluated a multicellular human 3D liver spheroid model (NAMkind™ Liver) incorporating multi-endpoint readouts (ATP, LDH, albumin, GSH) to assess functional impairment and injury. Using clinically benchmarked datasets spanning small molecules and ADCs, we tested whether the platform could stratify DILI risk and support compound- and SAR-level decision making.

METHODS



NAMkind™ LIVER DETECTS TOXICITY AT LOW MARGIN OF SAFETY VALUES



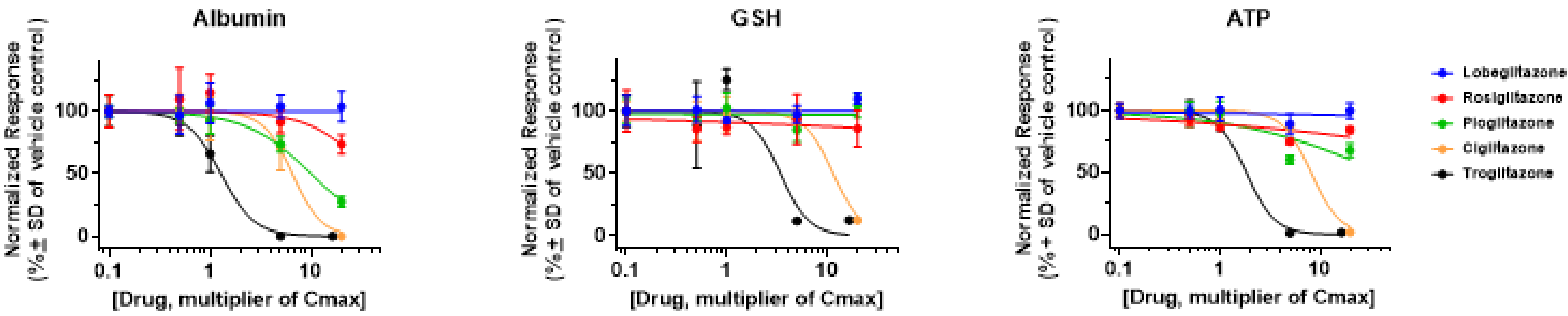
GROUP	N	MEDIAN ATP MOS	95% CI
MOST DILI	49	7.81	3.23 – 14.73
LESS DILI	23	52.56	24.42 – 76.96
NO DILI	20	200	200 - 200

MODEL PERFORMANCE 92 compounds based on ATP, LDH, ALBUMIN, GSH	MODEL PREDICTION
Accuracy	91%
Sensitivity	90%
Specificity	95%
Precision (Positive Pred Value)	99%

- Clear stratification of ATP MOS across clinical DILI risk groups
- Low MOS values for hepatotoxic compounds reflect sensitive detection of functional impairment
- Apparent MOS values are lower than typically reported in the broader in vitro liver safety field, suggesting detection closer to clinically relevant exposures
- Some compounds with high ATP MOS (non-filled symbols) appear negative by ATP alone. These compounds show toxicity in additional endpoints (LDH, albumin, GSH), reducing false negatives
- Multi-endpoint profiling improves detection of hepatotoxic liability versus ATP alone

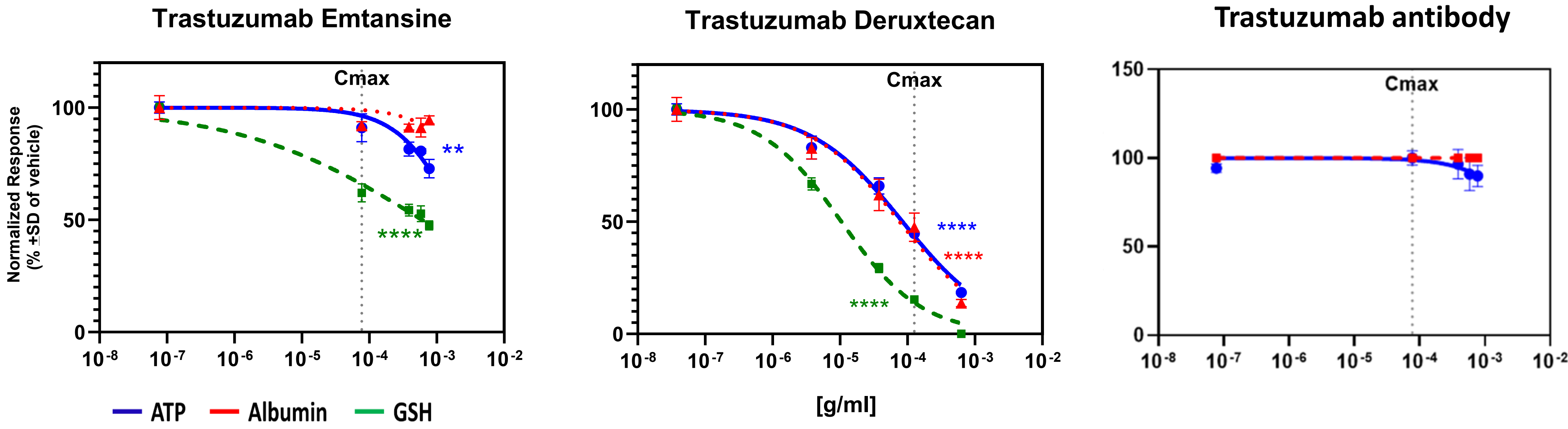
NAMkind™ LIVER PREDICTS DIFFERENTIAL TOXICITY BETWEEN CHEMICAL CLASSES

Compound	Clinical DILI	ALB MOS	ATP MOS	GSH MOS	LDH effect
Lobeglitazone	none	> 200	> 200	> 200	none
Rosiglitazone	mild	39	>200	>200	none
Pioglitazone	moderate	3	14	>200	significant
Ciglitazone	moderate-severe	2	3	4	High
Troglitazone	severe	0.2	0.3	0.6	high



- NAMkind™ Liver resolves intra-class TZD toxicity, matching known clinical safety (troglitazone >> ciglitazone > pioglitazone > rosiglitazone > lobeglitazone)
- MOS values across 3 assays and the LDH flag show clear gradients, enabling ranking within a chemical series for SAR-driven decisions.

NAMkind™ LIVER DIFFERENTIATES ANTIBODY DRUG CONJUGATE LIVER RISK BY LINKER/PAYLOAD PROPERTIES



- Trastuzumab Emtansine: more stable linker and intracellular payload release, yielding a localized toxicity profile
- Trastuzumab Deruxtecan: more labile linker with a membrane-permeable payload, enabling broader distribution and bystander effects
- Multi-endpoint readouts (ATP, LDH, albumin, GSH) capture these mechanistic differences, supporting risk stratification and optimization of ADC linker–payload combination

CONCLUSIONS

- VivoSim's NAMkind™ Liver is a human-relevant 3D platform for early liver safety prediction and lead optimization.
- In a clinically benchmarked small-molecule dataset of 92 compounds, the model demonstrates strong predictive performance ($\geq 90\%$ across metrics).
- Low MOS values indicate sensitive detection of toxicity near clinically relevant exposure levels, lower than typically reported in the broader field.
- Multi-endpoint profiling (ATP, LDH, albumin, GSH) captures toxicity missed by ATP alone, reducing false negatives.
- Supports compound ranking, SAR optimization, and early liver safety risk assessment across modalities.