

INTRODUCTION

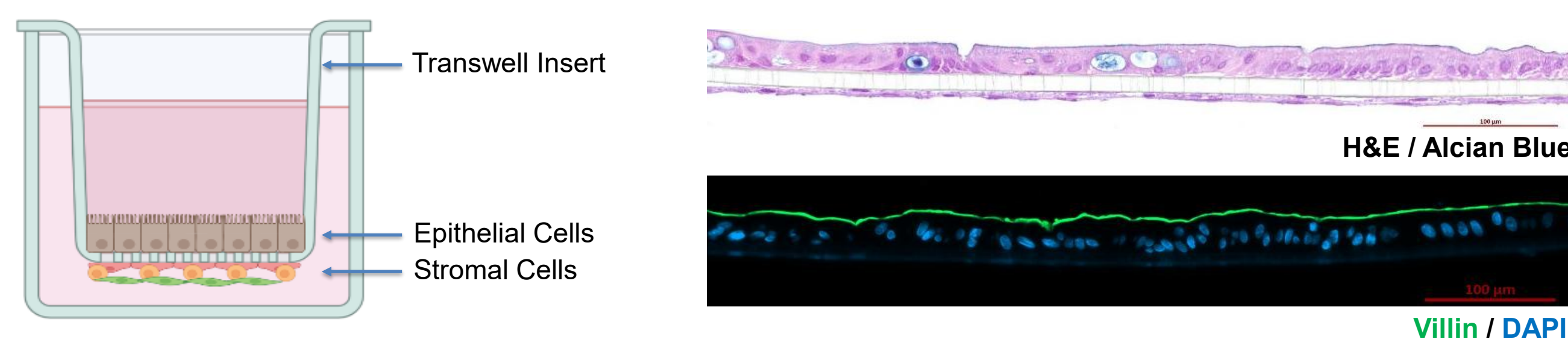
Drug-induced diarrhea is a frequent, dose-limiting GI toxicity with multifactorial mechanisms, and GI liability remains a persistent challenge during drug development. Only ~8% of drug candidates progress from Phase 1 to launch, where safety/toxicity can drive up to 59% of failures. GI toxicity is also featured among categories linked to post-marketing withdrawal. However, GI liabilities are often hard to anticipate early. Traditional animal studies are slow and costly and may miss human-specific liabilities, and routine *in vitro* assays suitable for GI toxicity screening are still limited despite the high clinical prevalence of GI adverse effects.

These gaps motivate predictive approaches that pair *in vitro* human intestinal models with machine learning to identify diarrhea liability earlier, prioritize safer chemistry within series, and guide candidate selection across modalities.

AIMS

- Build a human primary cell-derived, multicellular, high-throughput intestinal model that captures barrier integrity and tissue health to reflect clinical diarrhea liability and severity across drug modalities.
- Align model outputs with clinical diarrhea incidence and severity to train machine-learning models to predict diarrhea risk for new drug candidates and support candidate prioritization.

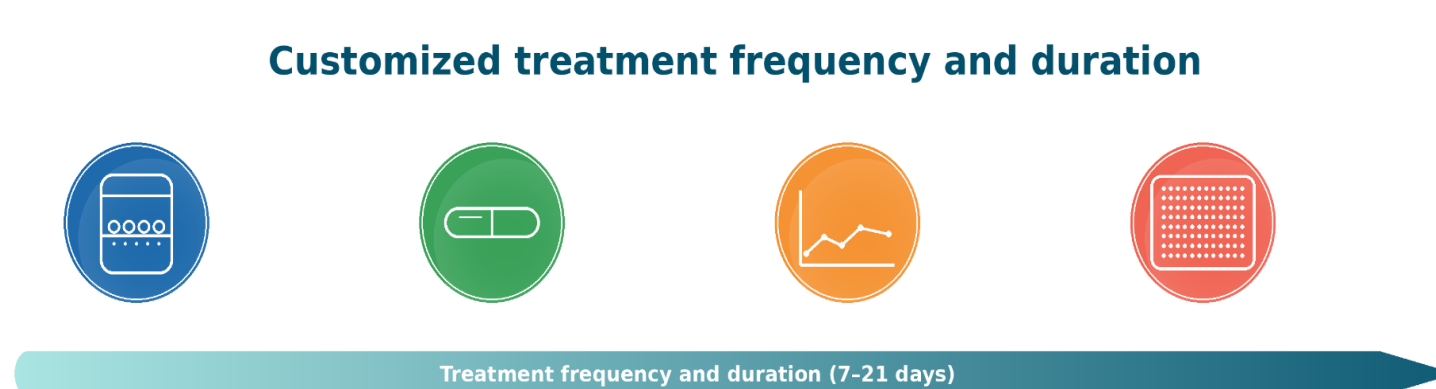
METHODOLOGY



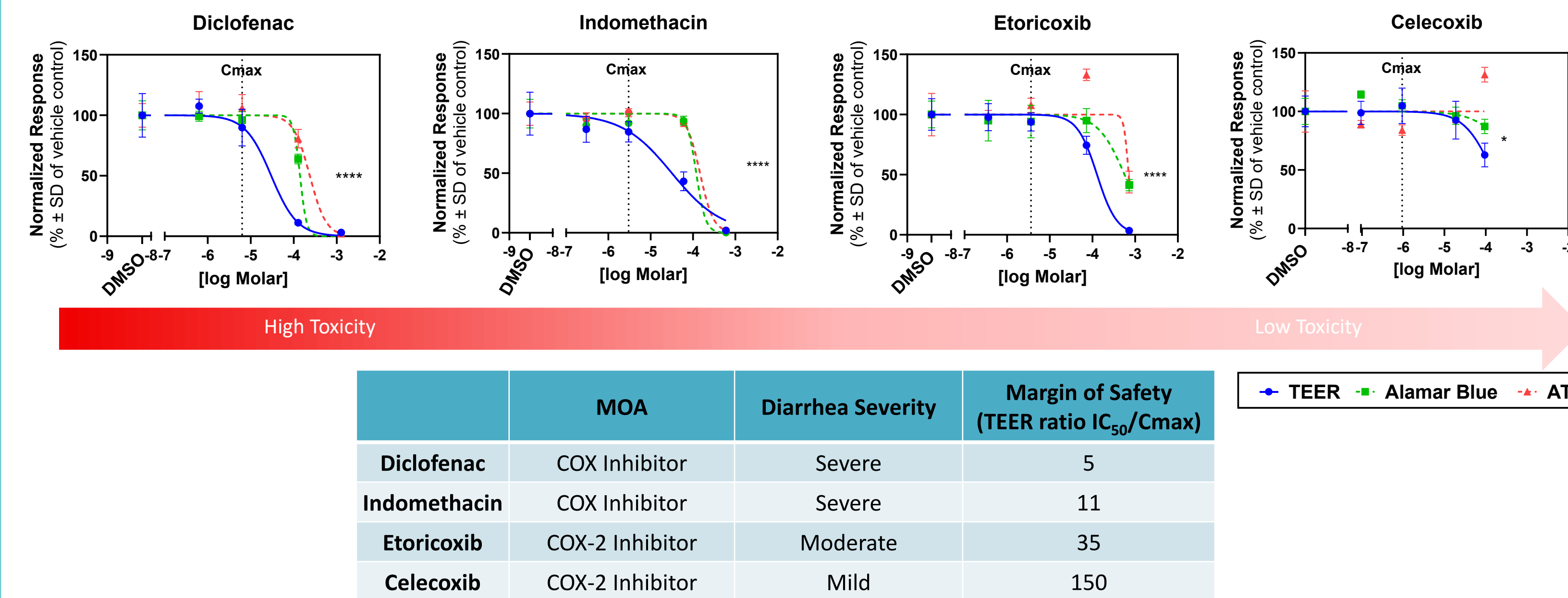
We developed a 3D human intestinal barrier model, NAMkind™ Intestine, for ileum and colon by incorporating epithelial and stromal cell components to preserve polarity and tight junctions. Assays measured barrier integrity (trans-epithelial electrical resistance), cell viability and redox state (ATP, and Alamar Blue) under repeat dosing. A machine learning model was trained on assay features and clinical incidence and diarrhea severity data using 5-fold cross-validation with thresholds calibrated for high sensitivity.

For ADC assessment, we performed comparative arms intact ADC, antibody-only, and payload-only, using the same exposure schedule and endpoints.

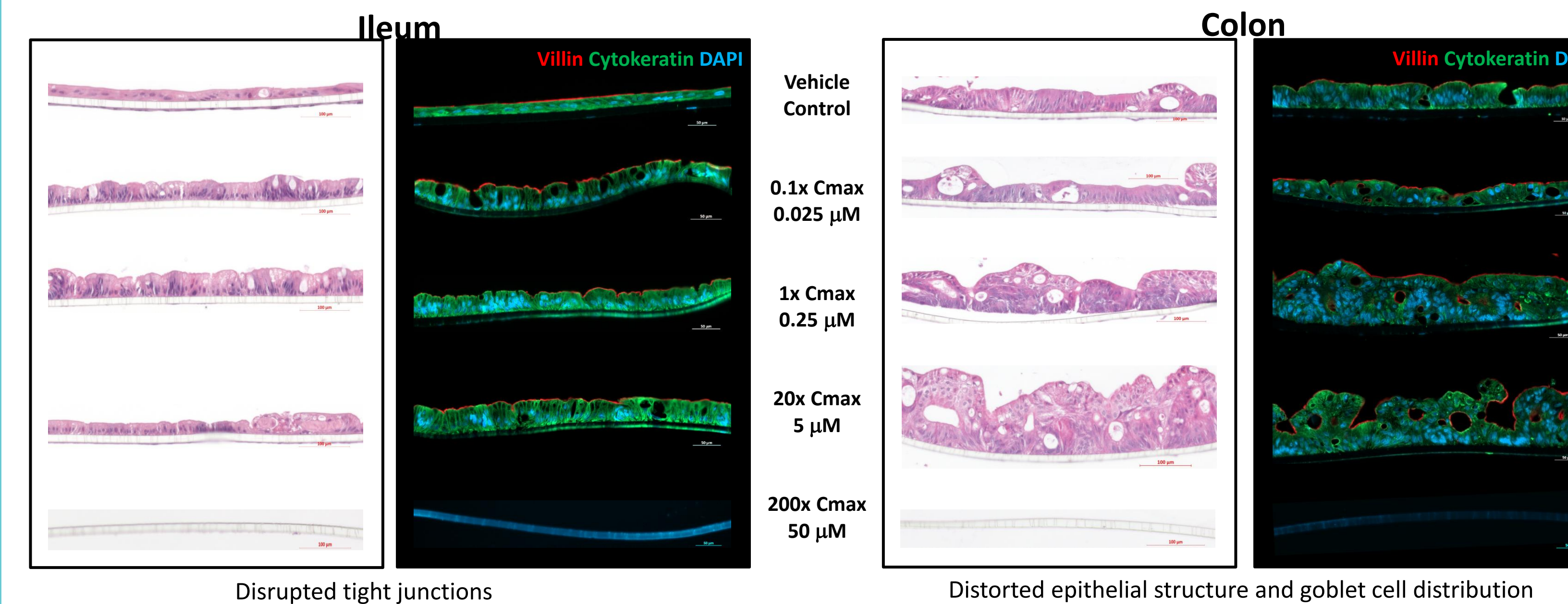
Phenotype	Intestine Assay
Mucosal Barrier Integrity	TEER
Tissue Viability	ATP
Metabolic Function	Alamar Blue



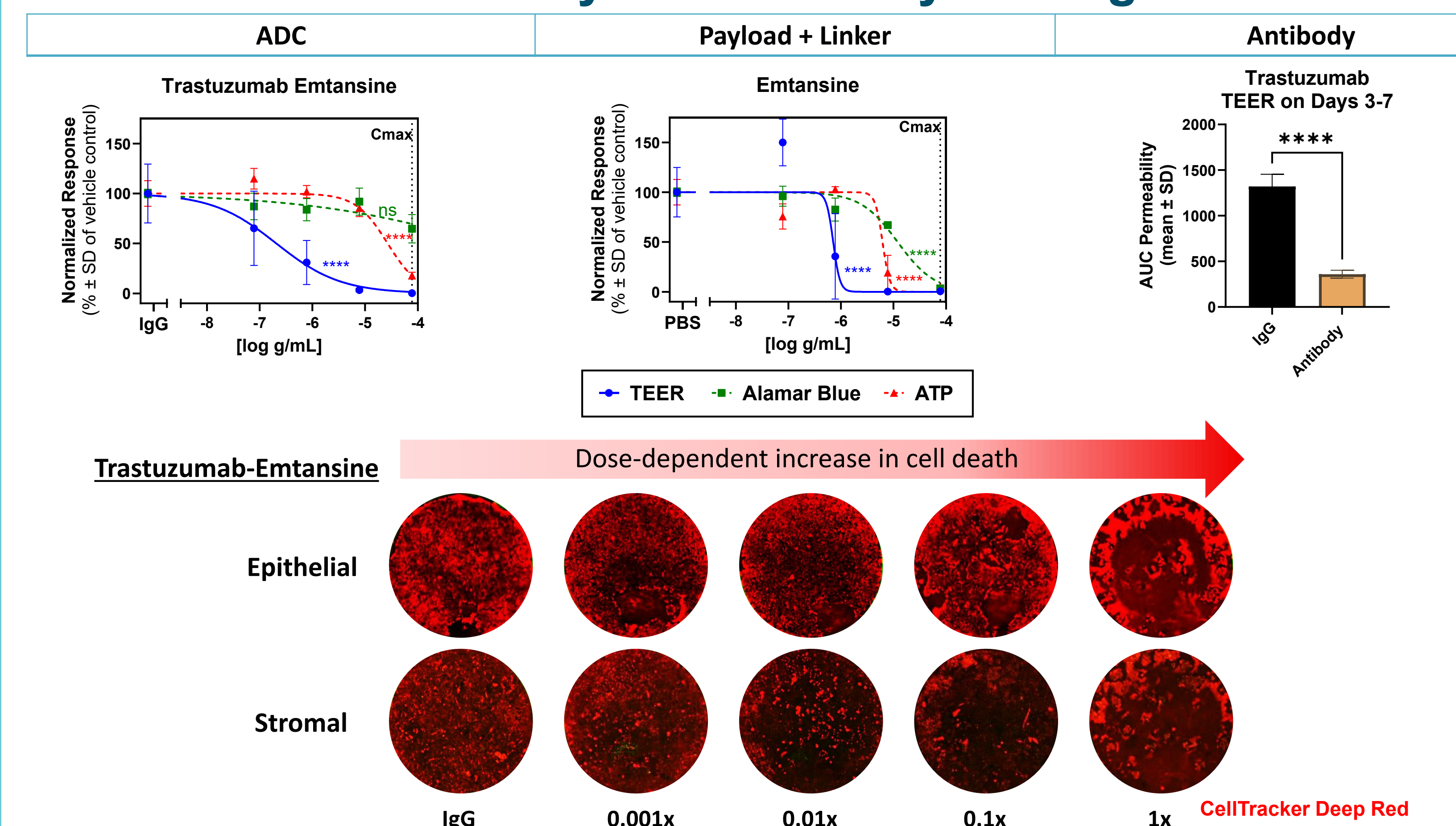
NAMkind™ Intestine Predicts Differential Toxicity Among Structurally Similar NSAIDs



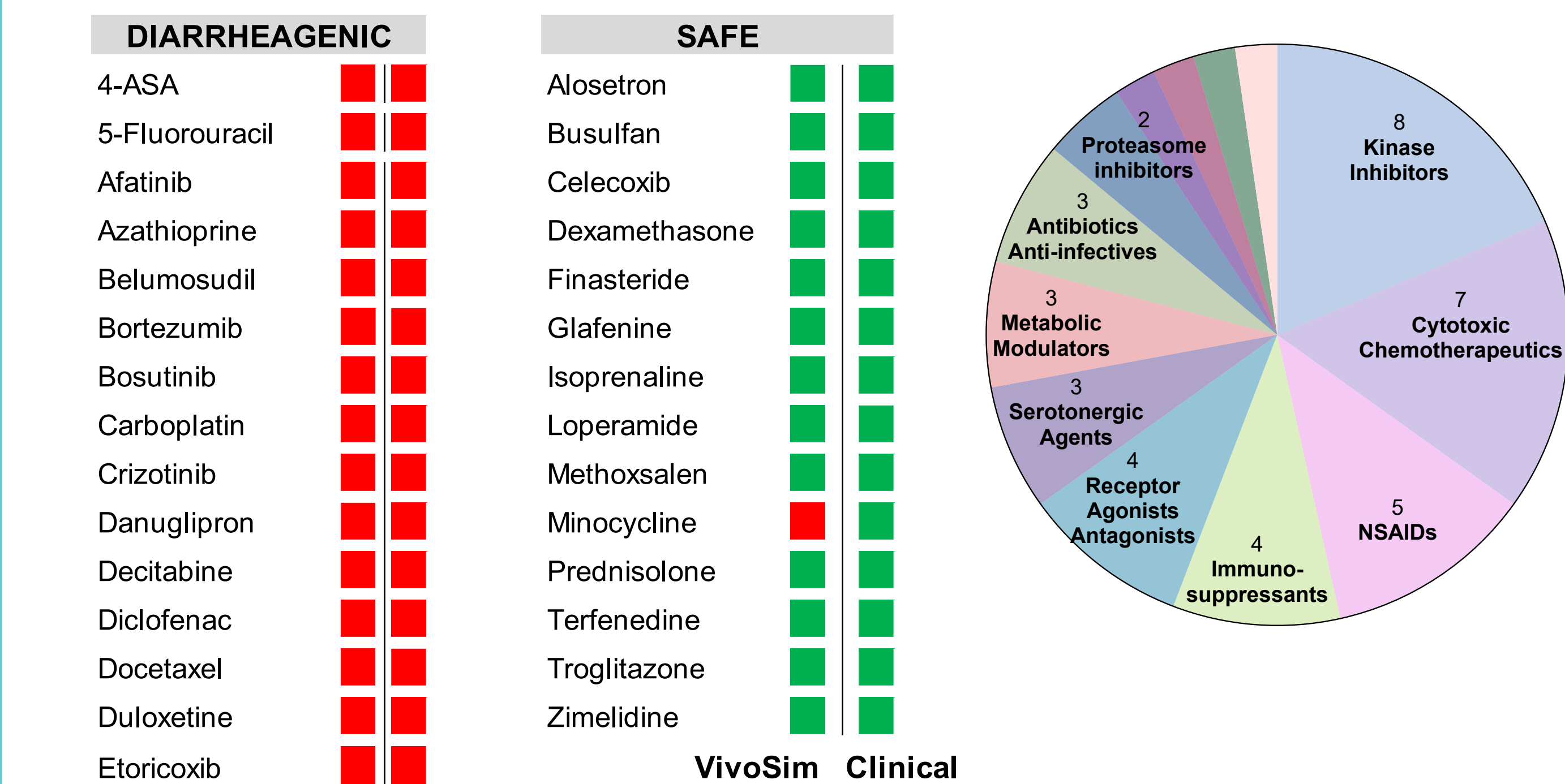
NAMkind™ Ileum and Colon Show Differential Susceptibility to Sunitinib



NAMkind™ Intestine Resolves ADC GI Liability via Parallel ADC/Payload/Antibody Testing



Validation of NAMkind™ Intestine Against Human Studies for 45 Small Molecules



	NAMkind Intestine Prediction
Accuracy	96%
Sensitivity	97%
Specificity	93%

- Heatmap and NAMkind™ Intestine prediction performance summary reflect robust alignment of NAMkind™ Intestine results with clinical diarrhea liability across a small-molecule reference set of 45 compounds.
- In determining the diarrhea liability, integrative scoring combines epithelial integrity and tissue health signals, and the inclusion of key stromal cell types enables detection of microenvironmental stress beyond epithelial injury.

CONCLUSIONS

- NAMkind™ Intestine is a multicellular, human primary-cell platform for diarrhea risk under repeat dosing.
- In a small-molecule reference set, the model aligns with clinical diarrhea outcomes and achieves high predictive performance (>93% predictive value) supporting early GI risk ranking across structurally similar compounds.
- Ileum and colon show different susceptibility, supporting multi segment testing.
- For ADC evaluation, parallel testing of intact ADC, antibody-only, and payload-only using the same exposure schedule enables resolution of component-dependent effects.
- In a proof-of-concept ADC dataset, the model detects dose-dependent injury consistent with clinical diarrhea reported for Trastuzumab antibody and the ADC Trastuzumab-Emtansine.
- Collectively, these results support NAMkind™ Intestine as an actionable preclinical tool to triage diarrhea risk earlier, guide candidate prioritization, and provide interpretable endpoints that can be integrated into a machine-learning framework trained on clinical incidence and severity.

CONTACT INFORMATION

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