# Enhancing Drug Safety and ADME Assessment with Organoids

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Poster P443

**Farzin Pourfarzad, Merel Derksen, Alessandra Merenda, Francisco Morales Rodriguez, Robert GJ Vries, Sylvia F Boj**

*HUB Organoids B.V. (HUB), Utrecht, the Netherlands*

**Introduction |** Selecting suitable *in vivo* preclinical drug development models for Absorption, Distribution, Metabolism, Excretion (ADME) and Toxicology (Tox) studies poses challenges due to inter-species variability, limited human relevance, and cost constraints. The FDA Modernization Act 2.0 has endorsed alternative *in vitro* models, with organoids emerging as valuable tools. Adult stem cell-derived HUB Organoids® from human and preclinical animal tissues have been shown to mimic tissue physiology accurately, offer high-throughput screening, and serve as a platform for drug toxicity, metabolism, and adverse event prediction (Kourula S. Derksen M. *et al.* 2023) for the intestinal tract. We have established adult stem cell-derived organoids from human and animal intestines and assessed drug toxicity, transport, permeability, metabolism and adverse immune events. Overall, this research highlights the utility of organoids supporting the evaluation of gastrointestinal (GI) toxicity for compounds, offering a transformative approach for comprehensive investigations of drug disposition, metabolism, and toxicity.

**Figure 1 | HUB Organoids human and animal adult stem cell-derived intestinal organoids.** **A|** Adult stem cell-derived organoids were established from epithelial organs, including different regions from small and large intestines from human and animal species, such as dogs, rats and mini-pigs. **B|** We developed specialized media formulations to expand and differentiate our organoids towards different epithelial cell fates, such as enterocytes, goblet, paneth and trans-amplifying cells. **C-D|** Representative images of human, dog and rat intestinal organoids in expansion **(C)** and differentiation media **(D)** stained for KI-67 and MUC2, denoting proliferative and differentiated cells, respectively.

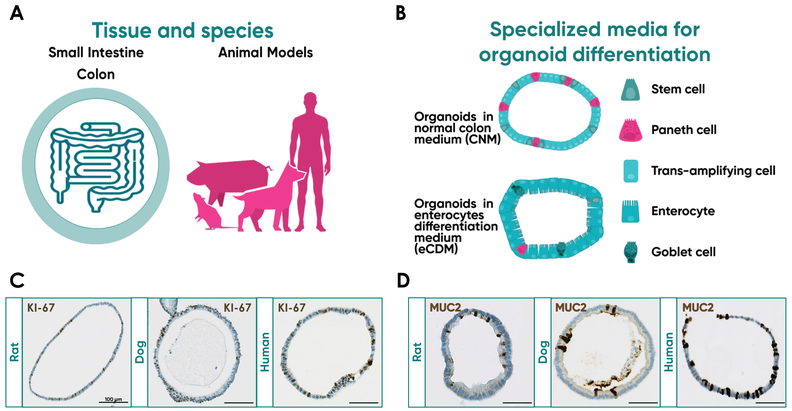



**Figure 2 | HUB Organoids support your derisking efforts when assessing GI drug safety**

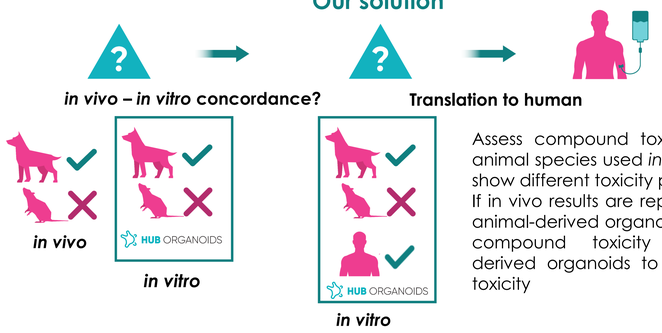
Ideal **scenario:** all *in vivo* models tested show a sufficiently wide therapeutic window


→ Compound can be tested in humans.

Challenging **scenario:** one or more *in vivo* models show a very narrow therapeutic window


→ What animal model is relevant to human translation?

**Our solution**




Assess compound toxicity in same animal species used *in vivo* and that show different toxicity profiles
If in vivo results are reproduced with animal-derived organoids, assess the compound toxicity in human-derived organoids to learn human toxicity

**Conclusions |** This study underscores the transformative value of human and preclinical animal organoids as *in vitro* platforms for in-depth investigations into drug disposition, metabolism, and toxicity in the intestinal tract. The versatility of organoids from diverse species and segments holds promise for cross-species and regional comparisons, aiding in the selection of appropriate animal models for preclinical studies and guiding dose escalation in clinical trials. The integration of organoids into drug development processes signifies a significant advancement, offering efficiency and accuracy in pharmaceutical research and safety assessment.

**Figure 3 | Animal-derived organoids reproduce *in vivo* toxicity for compounds such SN-38**
Animal-derived organoids from different species (rat, dog and minipig) and human-derived organoids from intestinal tract (duodenum) were exposed to a 6-dose response study for SN-38, a compound that has shown different *in vivo* toxicity profiles in rat and dog. Organoid viability was measured by ATP luciferase assay after 7 days in triplicate. Relative dose-response curves were plotted after normalisation to carrier.

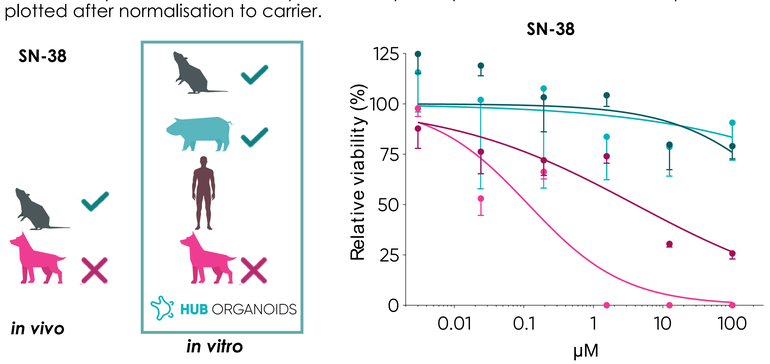
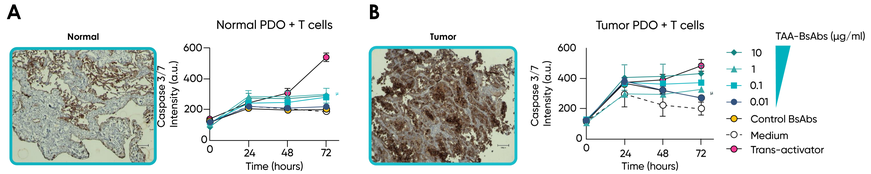



**Figure 4 | Organoids differentiate immune modulation specific response from immune adverse events.** **A|** Human normal and **B|** tumor-derived lung organoids cocultured with autologous T cells in the presence of increasing concentration of a Tumor Associated Antigen Bispecific Antibodies (TAA-BsAbs). T cell mediated organoid cytotoxicity was measured by Caspase 3/7 apoptosis dye intensity. Organoid apoptosis increased in a dose-dependent fashion in tumor, but not normal organoids thus demonstrating the feasibility of discriminating between an immune-specific response versus adverse events using organoids.




**#Reference**
*Kourula S. Derksen M., et. al.(2023); Journal of Pharmaceutical Sciences 188 (2023) 106481.*