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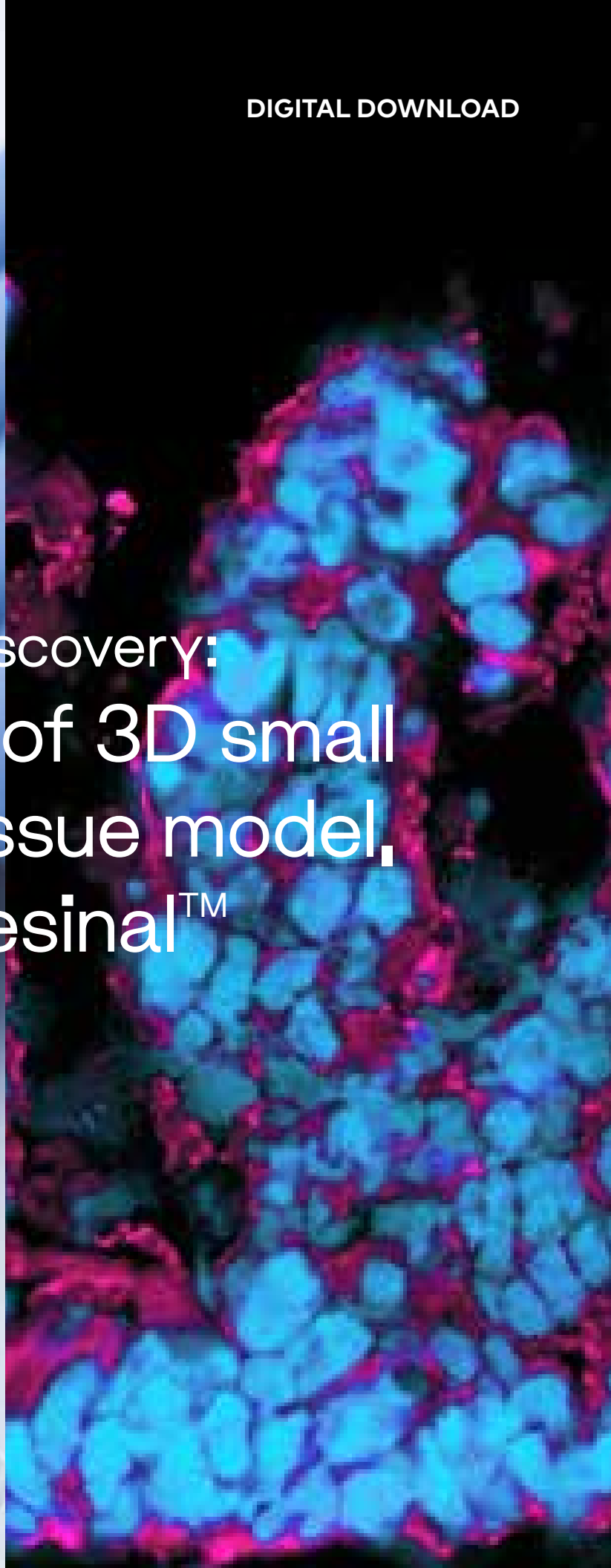

Drug Discovery: Relevance of 3D small intestine tissue model, EpiIntesinal™

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For More Information

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Introduction

Human relevant, organ specific models are increasingly prevalent in the toxicology and drug discovery fields. The differentiated structure and function of these tissue models cultured using normal, human cells, provide improved human in vivo relevance compared to animal models while also giving researchers a less expensive and faster alternative model. MatTek, a leader in the in vitro 3D field for the past 25+ years, creates highly differentiated 3D human relevant tissue models for use in pre-clinical studies. One such model, the organotypic EpiIntestinal™ model of the small intestine, can be used to address drug metabolism, drug absorption, compound efficacy, and gastrointestinal toxicity (GIT) in vitro. This paper describes the complexity of the small intestine, current small intestine in vivo and in vitro models, and the utility of EpiIntestinal in detecting drug-induced GIT.

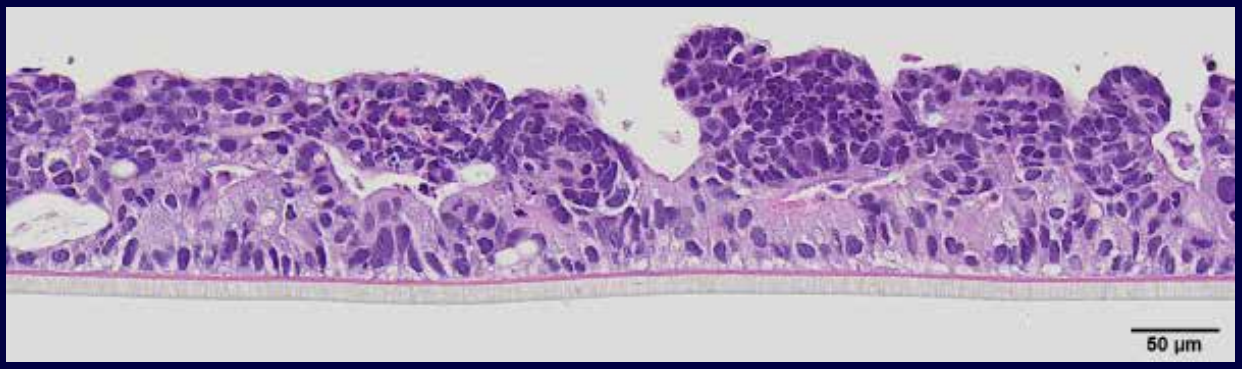
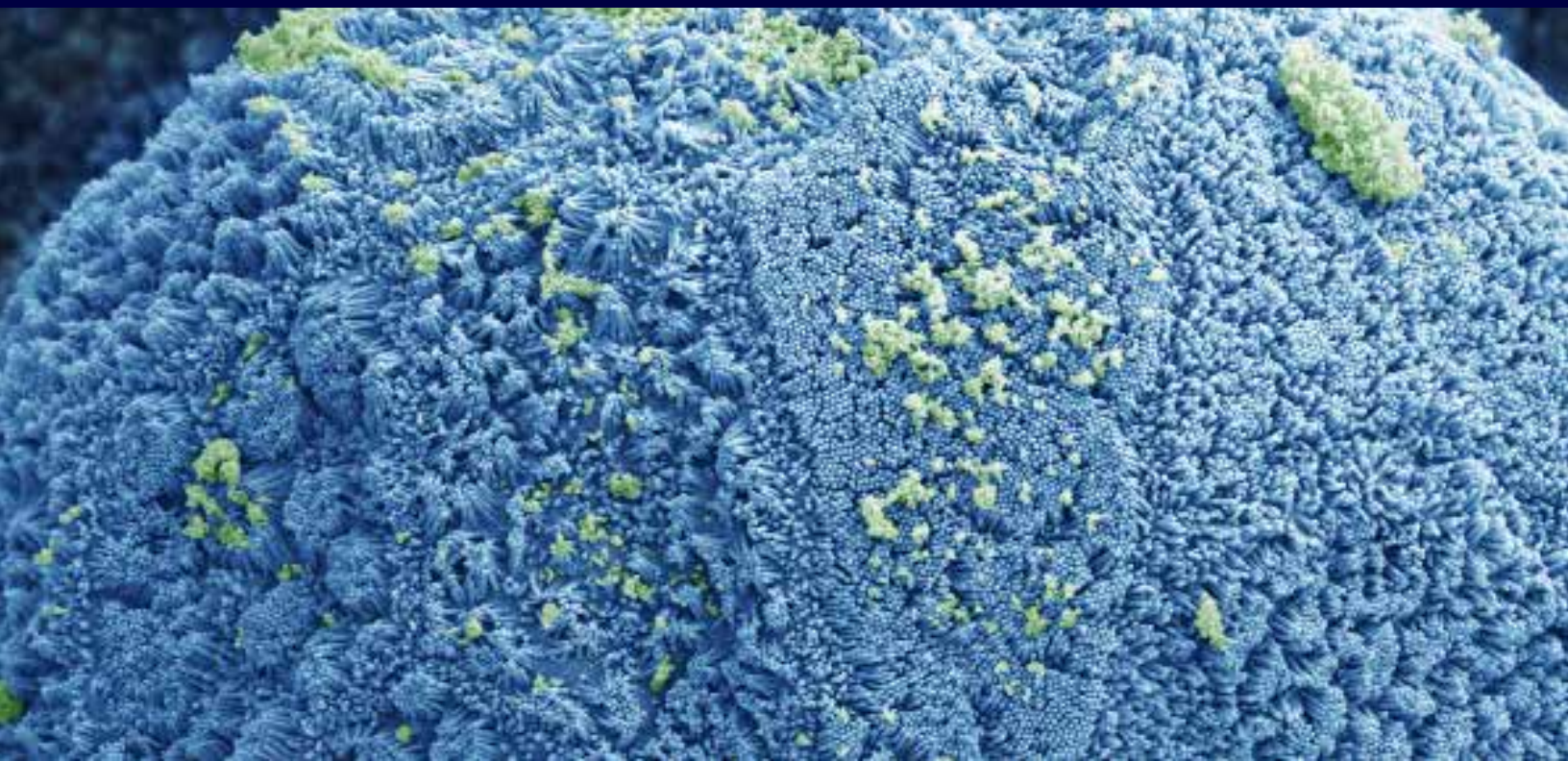


Figure 1. Hematoxylin & Eosin stained EpiIntestinal™ model showing crypt-villus formation.



The forefront of pharmaceutical pre-clinical research

Small Intestine Biology

The small intestine is divided into the duodenum, jejunum, and ileum and is ~20 feet in length. It is lined with crypt-villi structures that create a highly absorptive organ. The crypt-villi structures found within the intestine are comprised of enterocytes, goblet, enteroendocrine, Paneth, and Lgr5+ stem cells. The Paneth cells are specialized secretory cells that help regulate the intestinal flora while the Lgr5+ stem cells are highly proliferative cells that continually renew the intestinal cells. Goblet cells secrete mucus while enteroendocrine cells produce hormones and peptides in response to stimuli. Enterocytes mature from the base of the crypt to the top of the villi where they become highly absorptive and are lined with microvilli on the apical surface. The cells within the crypt-villi structure play a critical role in intestinal health and absorption and in maintaining intestinal homeostasis. EpiIntestinal is grown to recreate the human small intestine environment, which is vital to accurately predicting drug responses in clinical settings.

Drug Discovery and the Small Intestine

Current preclinical gastrointestinal studies rely on in vivo tests in rodent, large mammal, and non-human primate models. However, data from these studies does not always predict clinical success in human clinical studies1,2. Compared to rodent and large mammal studies, primate models better predict human adverse effects of new pharmaceuticals, but they have significant challenges such as high cost and ethical considerations. Therefore, primate studies are normally used only for final compound screens3 and therefore alternative more affordable and relevant models are needed for preclinical drug screening assessment.

3D Small Intestine *In vitro* Models

Caco-2 cells are the industry standard for high-throughput drug absorption studies because the cells form tight monolayers and are highly absorptive. However, the Caco-2 monolayers lack stratification, only weakly express important intestinal metabolic enzymes such as CYP3A4, and do not provide reliable in vivo human data for carrier-mediated transport and paracellular permeation5. Also, this model is a single cell type instead of a co-culture with important intestinal cells (paneth, enteroendocrine, goblet cells, etc.). 3D organoids have been used for drug screening and toxicity assessment due to their improved 3D architecture and regenerative abilities that more closely mimic the in vivo environment. While organoids have improved in vivo relevance, the spherical nature does not allow for drug permeation experiments and measurement of efflux. Further, the orientation of the apical membrane inward limits which drugs can be easily screened3. MatTek has developed a highly differentiated EpiIntestinal™ 3D model that is derived from primary human cells, has well defined apical and basolateral surfaces, and expresses drug transporters and metabolizing enzymes found in the human intestine (Figure 1). This model can be used for moderate throughput studies and has shown high correlative abilities to in vivo responses.

EpiIntestinal™ predicts drug-induced adverse reactions

EpiIntestinal™ contains relevant cells that originate from primary human stem cells and maintain tissue function necessary for intestinal drug safety testing. Peters et al3 demonstrated the relevance of the model for studying drug-induced diarrhea (an adverse side effect which often compromises patient treatment) and showed EpiIntestinal™ had improved sensitivity and accuracy versus Caco-2 cells. Researchers treated Caco-2 cells and the EpiIntestinal™ model with validated compounds with known clinical side-effects. After drug treatment, the cells were assessed for barrier integrity (TEER) and toxicity (MTT). Using the TEER endpoint, the EpiIntestinal™ model better predicted drugs that induced clinical diarrhea than Caco-2 cells (Table 1) 3. In addition, the EpiIntestinal -TEER assay successfully predicted clinical side effects in drugs that had been pre-screened in 1-month animal studies without any apparent toxicity. These results are significant and indicate the utility of EpiIntestinal™ for predicting drug-induced gastrointestinal toxicity at an earlier stage of the drug development process.

Table 1. Validation results from EpiIntestinal and CaCo-2 TEER results using IC_{15}/C_{max} Ratio.

	EpiIntestinal Exp1	**EpiIntestinal** Exp2	**Caco-2**
No. Compounds Tested	31	30	31
Sensitivity	79%	71%	57%
Specificity	88%	94%	94%
Accuracy	84%	83%	77%

Note: Table modified from Peters et al[3].

EpiIntestinal™ in drug discovery

As 3D in vitro models continue to show relevance to in vivo predictions, researchers will need to consider which models best suit their needs. Caco-2 cells are readily used in drug absorption studies, but they are derived from a colon cancer line and are therefore less human relevant than primary, non-cancerous cells isolated from the small intestine. While organoids are more differentiated, their spherical geometry is limiting for many types of experiments. EpiIntestinal™ is a human relevant 3D tissue model that allows access to both the apical and basal tissue surfaces, contains the relevant primary cells isolated from the small intestine, can be cultured for long periods of time allowing for repeat dosing studies, and can be tested in medium-throughput studies (96 well). Importantly, EpiIntestinal's human origin allows for accurate prediction of drug-induced gastrointestinal toxicity (in some cases, better than animal models) and can play an important role in pre-clinical drug development.

References

1. Olson, H. et al. Concordance of the Toxicity of Pharmaceuticals in Humans and in Animals. Regulatory Toxicology and Pharmacology 32, 56–67 (2000).

2. Jones, T. W. et al. Current nonclinical testing paradigm enables safe entry to First-In-Human clinical trials: The IQ consortium nonclinical to clinical translational database. Toxicology and Applied Pharmacology 334, 100–109 (2017).

3. Peters, M. F. et al. Human 3D Gastrointestinal Microtissue Barrier Function As a Predictor of Drug-Induced Diarrhea. Toxicological Sciences 168, 3–17 (2019).

4. Ferrec, E. le et al. In Vitro Models of the Intestinal Barrier: The Report and Recommendations of ECVAM Workshop 461,2. https://doi.org/10.1177/026119290102900604 29, 649–668 (2019).

5. Balimane, P. v. & Chong, S. Cell culture-based models for intestinal permeability: A critique. Drug Discovery Today 10, 335–343 (2005)

6. Zhang, Y. et al. 3D organoids derived from the small intestine: An emerging tool for drug transport research. Acta Pharmaceutica Sinica. B 11, 1697 (2021).