Patient-derived organoids as a relevant tool for preclinical IBD research and drug development

HUB ORGANOIDS

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Background

Chronic inflammation and epithelial barrier damage are two of the most important hallmarks of inflammatory bowel diseases (IBD). Currently available therapies target the chronic immune dysregulation, however recent drug development efforts focus on epithelial targets and restoring barrier integrity.

Patient-derived HUB Organoids (PDOs) represent a **clinically relevant IBD model** to study barrier integrity and other epithelial pathologies of IBD.

HUB Organoids IBD Biobank

- ✓ Crohn's disease and Ulcerative colitis patient
- ✓ Small intestine and colon (Ileum, proximal colon, distal colon, rectum)
- ✓ From uninflamed and inflamed regions
- ✓ 10 growth validated organoid models from IBD patients
- ✓ *PDOs from normal tissue available as controls*

Results

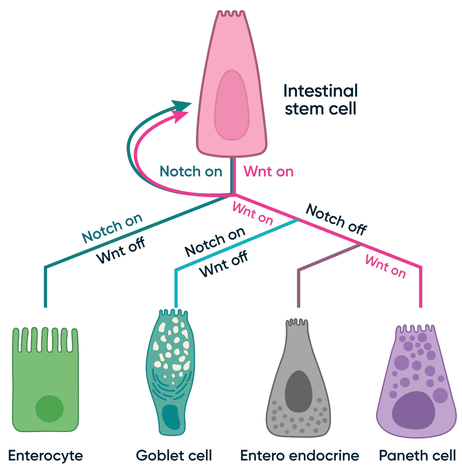
Intestinal organoids represent stem cells and fully differentiated epithelial cell types

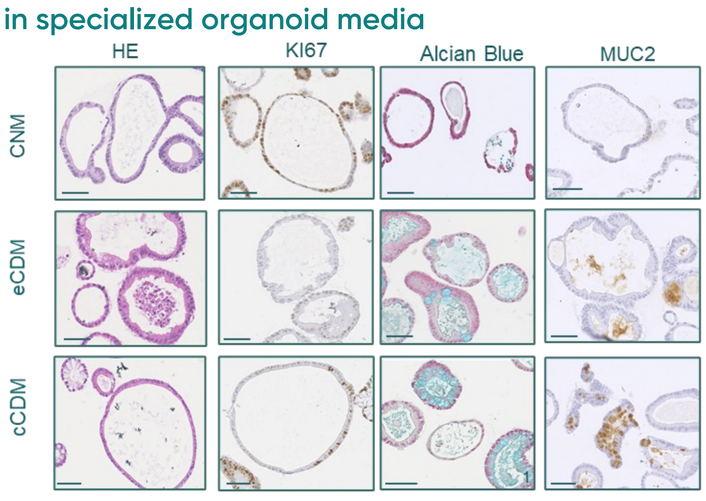
Table 1: Optimized organoid media to facilitate organoid expansion or differentiation

Cell types and supporting culture condition	Base*	Wnt	ip38	Nic	iWnt#	iNotch#	iMEK# (iEGF)
Stem and TA cells (CNM) Colon Normal Medium	WENR	50%	+	+			
Enterocytes (eCDM) enterocyte Colon Differentiation Medium	ENR				+		
All epithelial cell types (cCDM) combination Colon Differentiation Medium	WENR	10%				+	+

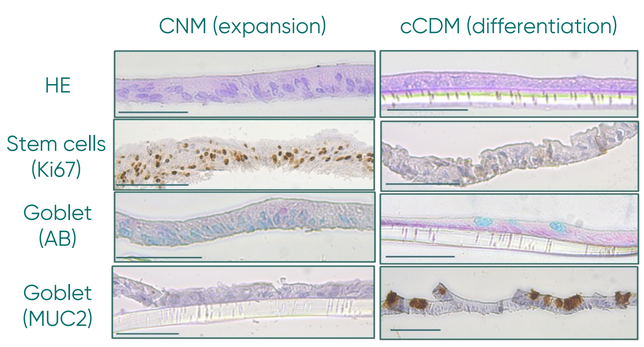
***W:** Wnt3a; **E:** EGF; **N:** Noggin; **R:** R-spondin 3; **SB202190**: p38 MAPK Inhibitor; **Nic**: Nicotinamide
#**i**: inhibition of the pathway involved

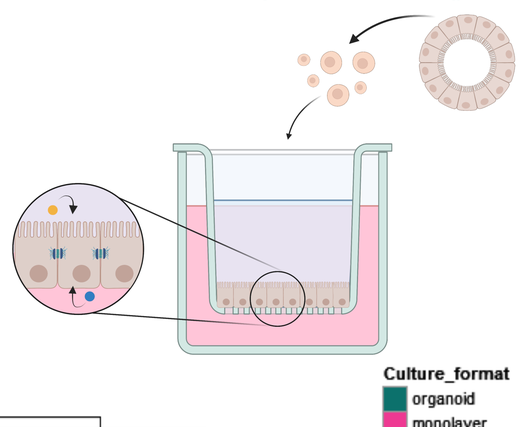
PDOs mimic *in vivo* differentiation in specialized organoid media

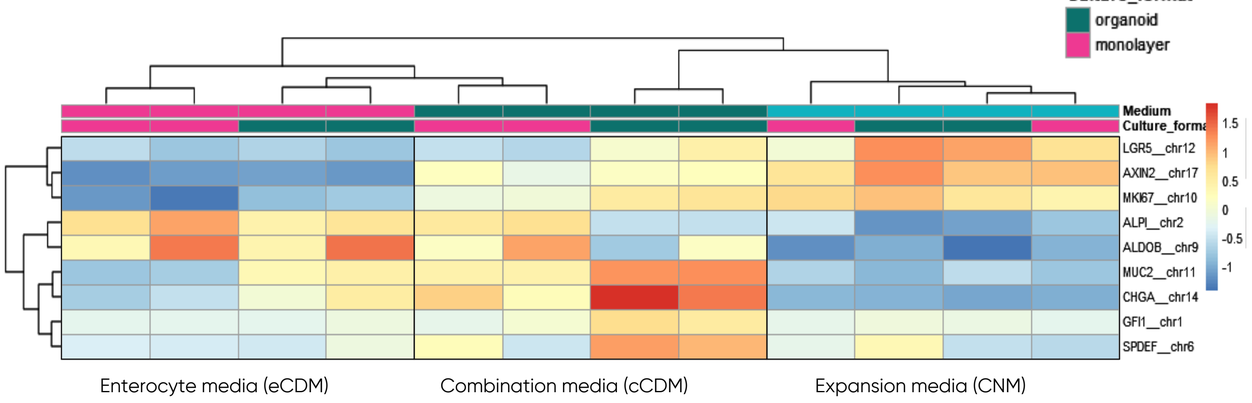




PDO monolayers establish on Transwells® and differentiate in specialized organoid media

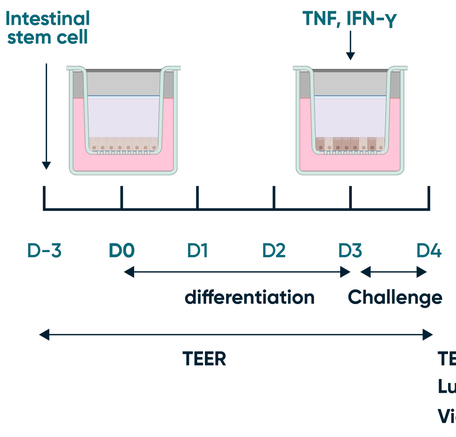


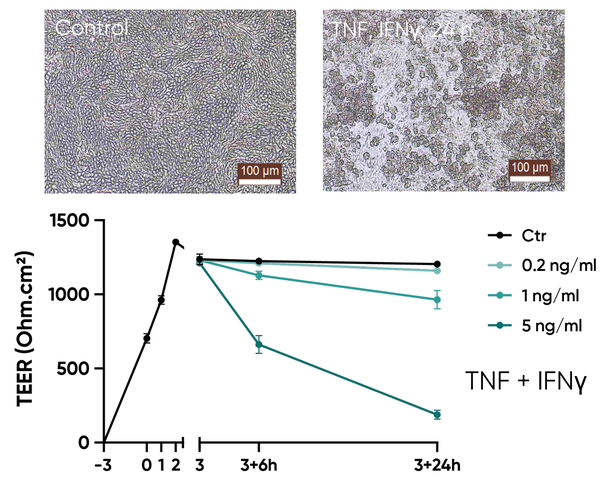




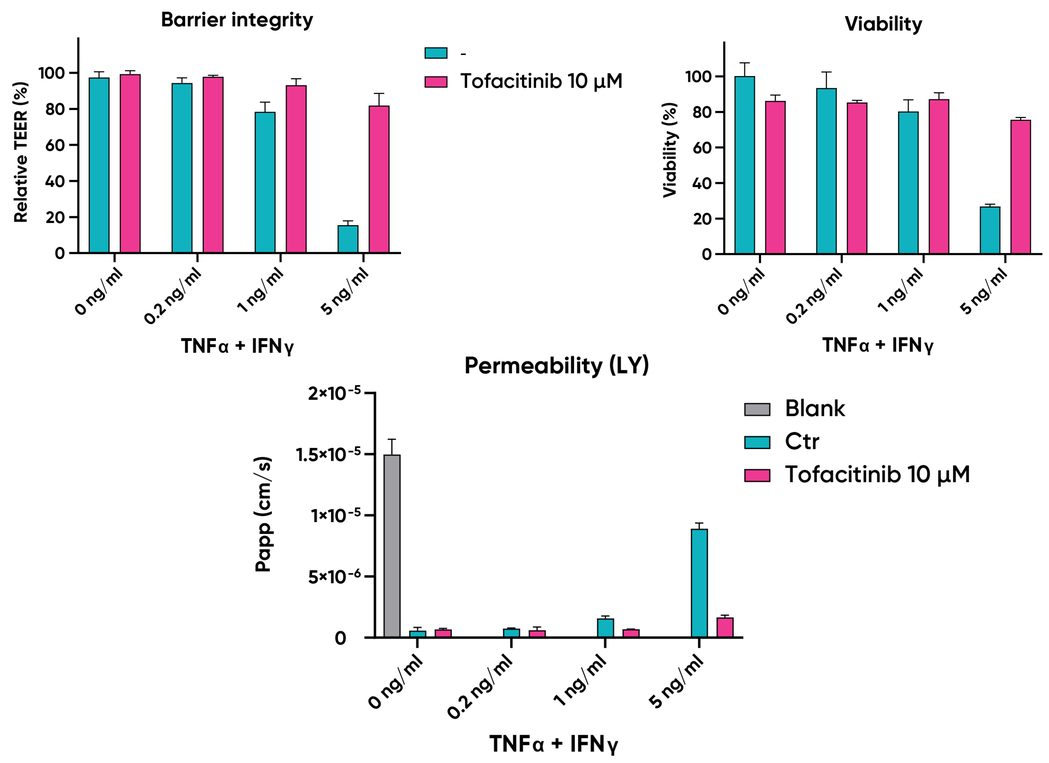
- ✓ Intestinal cell types are enriched in different medium compositions (IHC, IF, and RNAseq data)
- ✓ PDO intestinal monolayers are enriched for different cell types and allow barrier studies and access to the apical site.

Barrier integrity: cytokine-induced damage assay

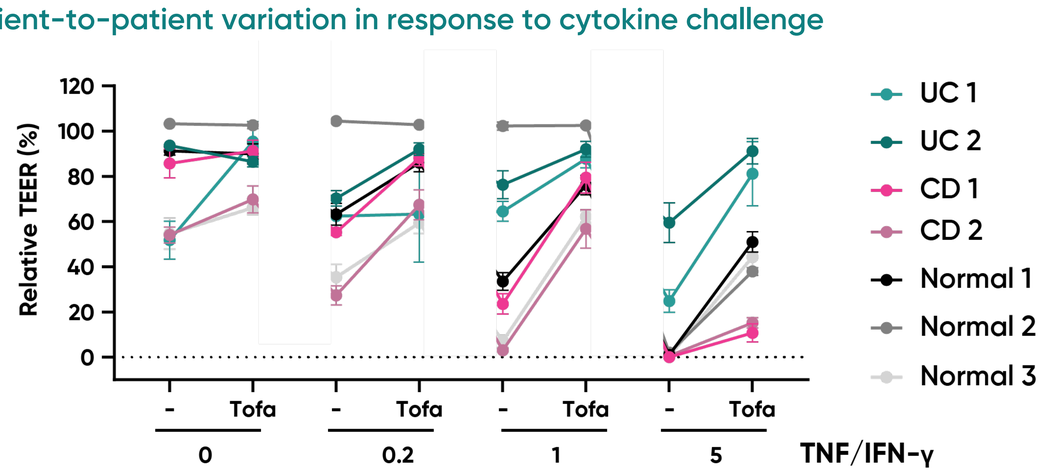




Tofacitinib's efficacy on barrier protection is recapitulated in cytokine-induced damage assay



Patient-to-patient variation in response to cytokine challenge



Summary

- ✓ PDOs recapitulate the cellular diversity and patient heterogeneity and provide a relevant platform to study the intestinal epithelium and its response to microbial or inflammatory challenges.
- ✓ HUB Organoid IBD Biobank contains UC and Crohn's disease patient samples.
- ✓ Specialized organoid media support the enrichment of distinct epithelial cell lineages.
- ✓ Intestinal PDO monolayers are enriched for differentiated cell types and allow barrier studies.
- ✓ Barrier damage during inflammatory conditions such as IBD can be studied with the Cytokine-induced barrier damage assay.
- ✓ The cytokine challenge robustly induces loss of barrier integrity across seven patient-derived monolayers.
- ✓ The barrier breakdown was ameliorated in all models by treatment with the IBD therapy Tofacitinib, demonstrating the suitability of the assay for IBD drug development efforts.

References

1. Wies T. M. van Dooremalen, Merel Derksen, Jamie Lee Roos, Celia Higuera Baron, Carla S. Verissimo, Rober G. J. Vries, Sylvia F. Boj, Farzin Pourfarzad, Organoid-derived epithelial monolayer: A clinically relevant *in vitro* model for intestinal barrier function, Jove 2021
2. Scott A. Jelinsky, Merel Derksen, Eric Bauman, Carla S. Verissimo, Wies T.M. van Dooremalen, Jamie Lee Roos, Celia Higuera Barón, Celia Caballero-Franco, Bryce G. Johnson, Michelle G. Rooks, Johanna Pott, Bas Oldenburg, Robert G.J. Vries, Sylvia F. Boj, Marion T. Kasaian, Farzin Pourfarzad*, and Charles V. Rosadini*, Molecular and functional characterization of human intestinal organoids and monolayers for modeling epithelial barrier, *IBD accepted*

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