Evaluation of the Clinical Stage FXR Agonist FXR314 in Human Primary Cell 3D Models of Crohn's Disease and Ulcerative Colitis

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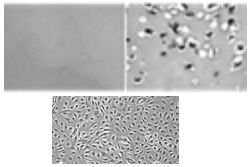
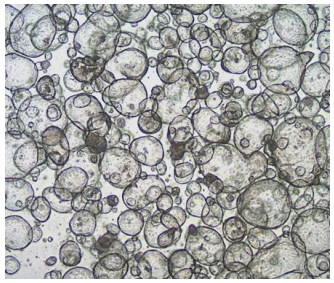
ONVO 3D Disease Models Can Enable Better Clinical Outcomes

- Organovo creates exceptional 3D models using bioprinting and other 3D tissue technologies
- Models created with cells isolated directly from IBD patients (Crohn's Disease or Ulcerative Colitis, biologic naïve or exposed, varying disease severity)
- Models faithfully replicate various aspects of the IBD disease process and human biology
- Models can be used to identify new mechanisms of action, validate novel targets via testing of various entities (chemicals, SiRNAs, …), and study the effects of clinically approved treatment paradigms
- Testing of broad donor sets from a biobank allows to understand population response to a drug or to target modulation

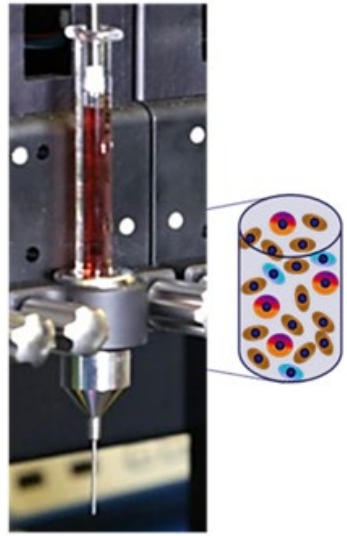
ONVO Bioprinting Inflammatory Bowel Disease Model

Cell expansion

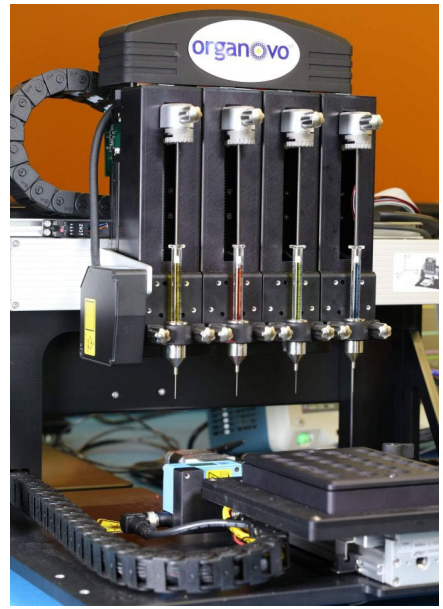




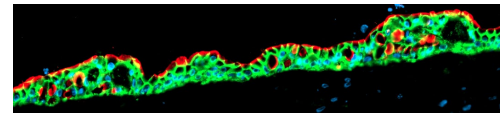
- Intestinal Crypts
- Endothelial cells
- Smooth muscle cells
- Fibroblasts

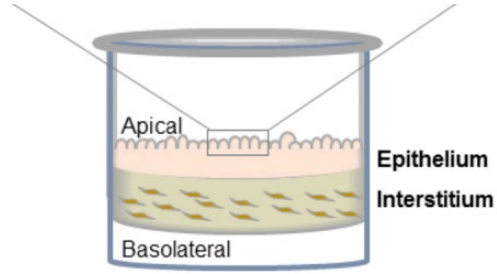


- Cell Mixture
- Proprietary Media
- Matrix



- Multimodal
- Biocompatible
- Spatial control
- Complex Geometries





- Reproducible
- Scalable
- Cell dense
- Physiologically accurate biology

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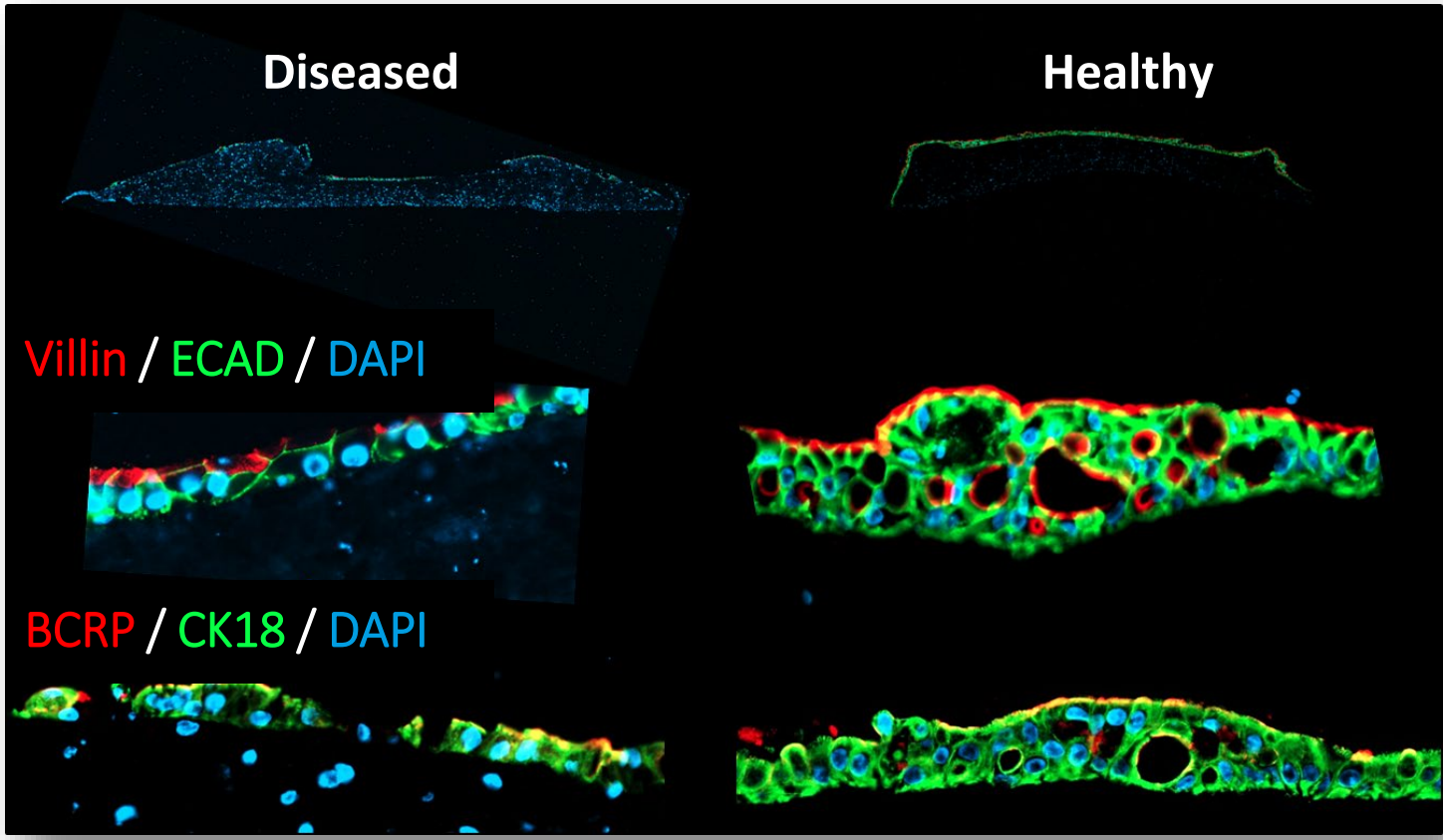
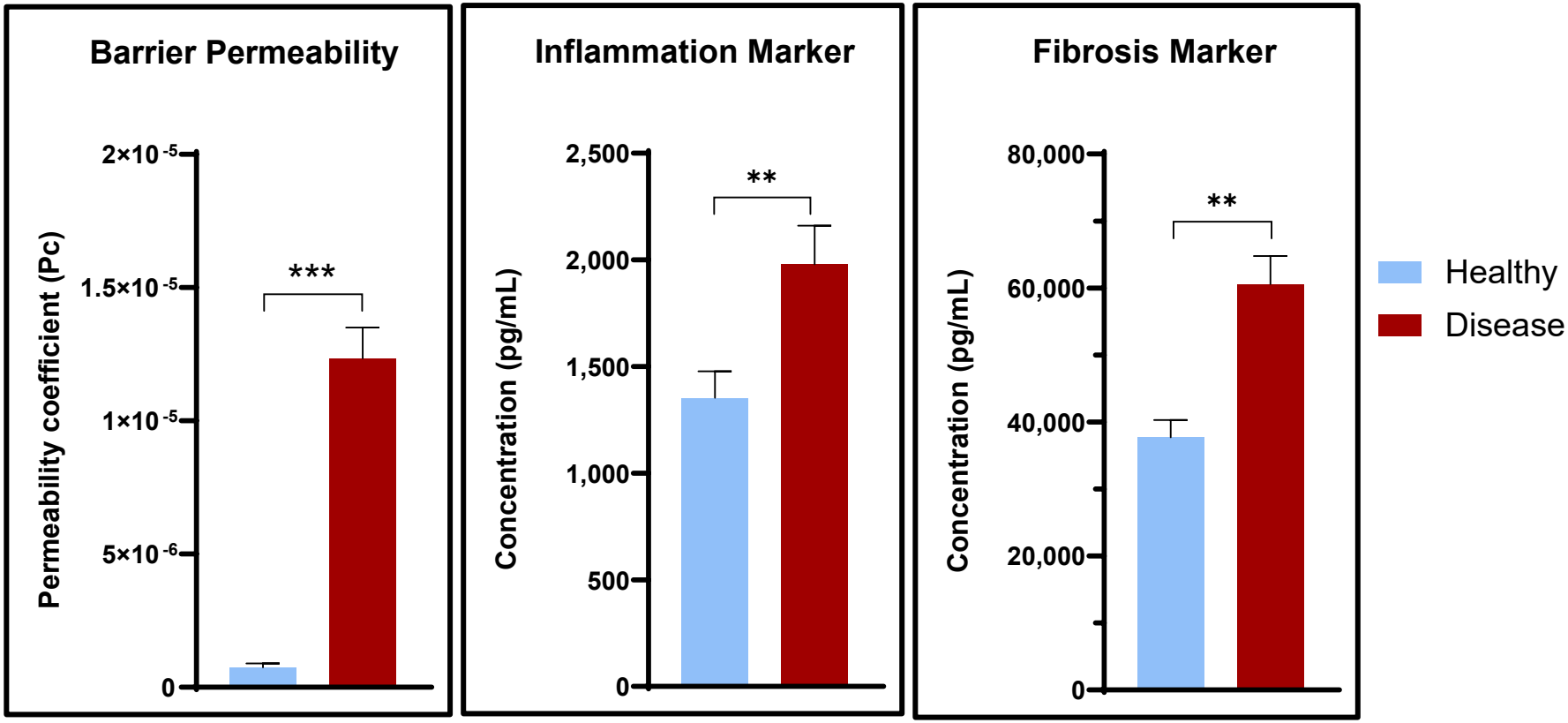
3D Bioprinting Recapitulates Cellular Organization of Diseased and Healthy Intestinal Cell Donors

- Polarized epithelium with functional tight junctions, transporters (P-gp, BCRP)
- Specialized epithelial cell types
- Physiological barrier function



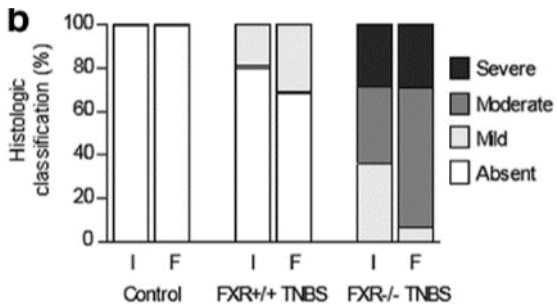
3D Models from IBD Patients Demonstrate Impaired Epithelial Barrier Function and Increased Inflammation and Fibrosis



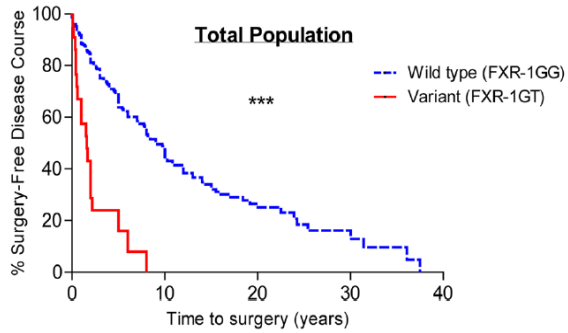
FXR Agonism Is An Important Effector in IBD

- FXR is a nuclear hormone receptor critical for maintaining bile acid, lipid and intestinal homeostasis
- Studies in null mice demonstrate a protective role of FXR in IBD
- Human genetics studies have reported the existence of FXR SNP associated with intrahepatic cholestasis of pregnancy and IBD
  - FXR SNP rs56163822 (FXR-1G->T) leads to reduces protein expression
  - Patients with Crohn's disease (CD) carrying the FXR-1G->T variant exhibit greater disease severity and earlier progression to surgery
- The biomarker of intestinal FXR activity, FGF19, is reduced in CD patients

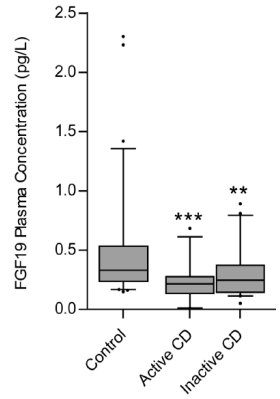
FXR protects mice from TNBS-induced colonic inflammation



FXR variant causes increased disease severity



Biomarker of FXR activity reduced in CD patients



FXR314 Potential Role in IBD – Study Design

- Evaluation of FXR314, a potent and selective non-bile acid FXR agonist

- Conducted in 3D models of IBD:
  - Crohn's disease: 5 human diseased donors
  - Ulcerative colitis: 3 human diseased donors

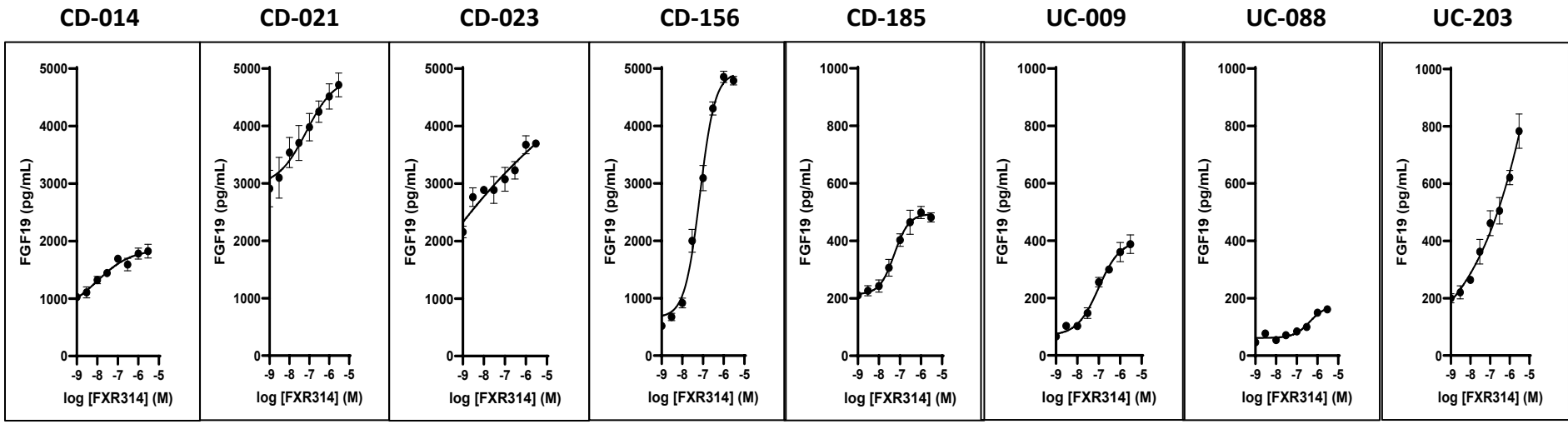
- Endpoints:
  - Target engagement: intestinal biomarker FGF19
  - Barrier permeability: FITC-Dextran 4 kDa (FD-4)
  - Fibrosis: Procollagen type I N-terminal propeptide (P1NP)

Demonstrated Target Engagement by FXR314 in CD and UC

- Evaluated FGF19 a direct biomarker of intestinal FXR activity
- Potent and dose-dependent activation of FGF19 by FXR314 in all CD and UC donors
- Degree of activation varies between the different donors

	CD-014	CD-021	CD-023	CD-156	CD-185
Fold Act.	1.8	1.6	1.7	9.3	2.4
EC50 (nM)	100	70	54	71	53

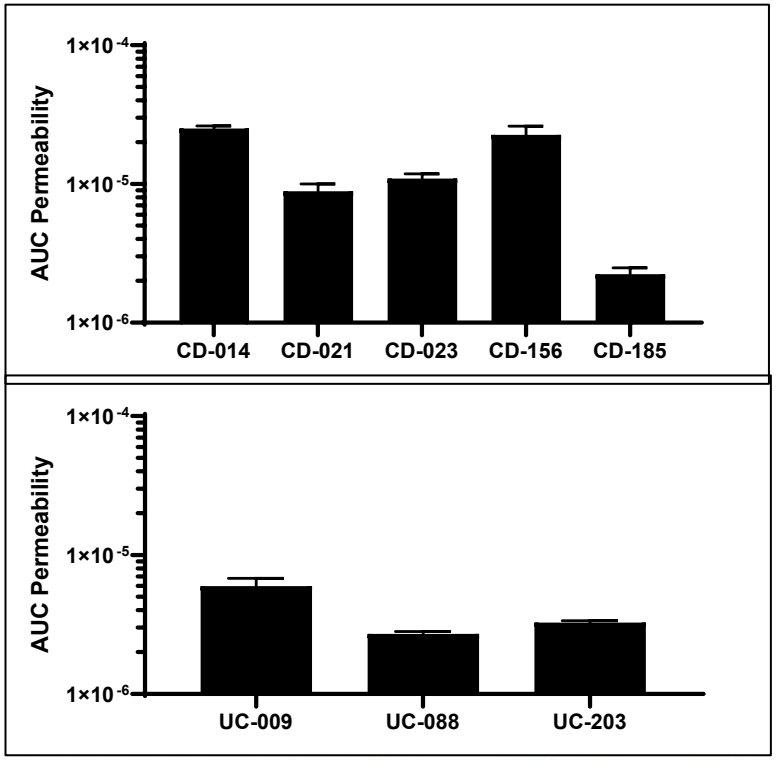
	UC-009	UC-088	UC-203
Fold Act.	5.9	3.4	3.9
EC50 (nM)	98	427	200



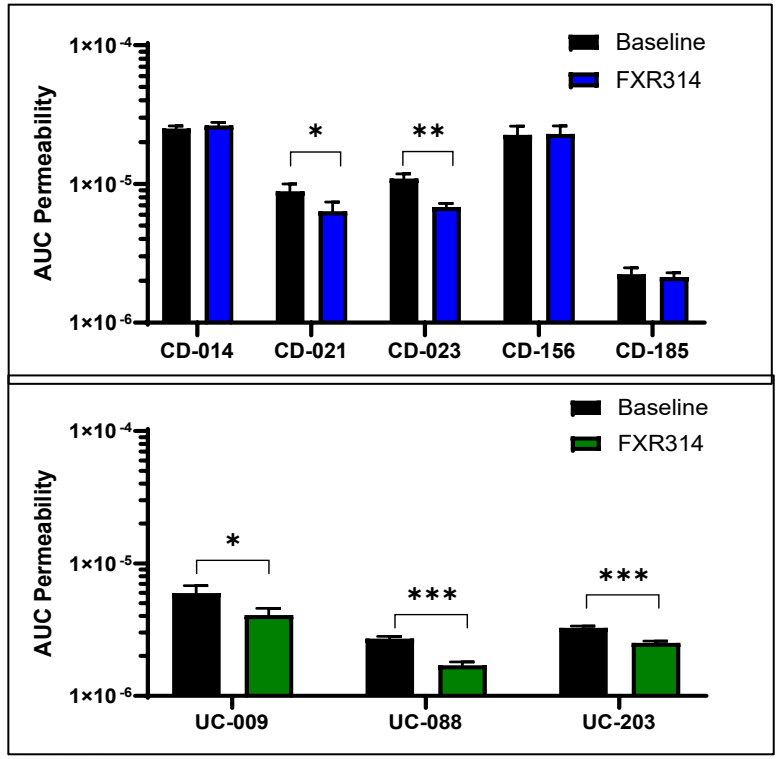
FXR314 Improves Barrier Integrity in CD and UC donors

- Intestinal permeability is determined by FD4 assay
- Diseased tissues (CD and UC) have intrinsically different baseline permeability values reflective of the disease state
- FXR314-induced decrease in barrier permeability observed in a subset of CD donors, and all UC donors

Baseline Barrier Integrity



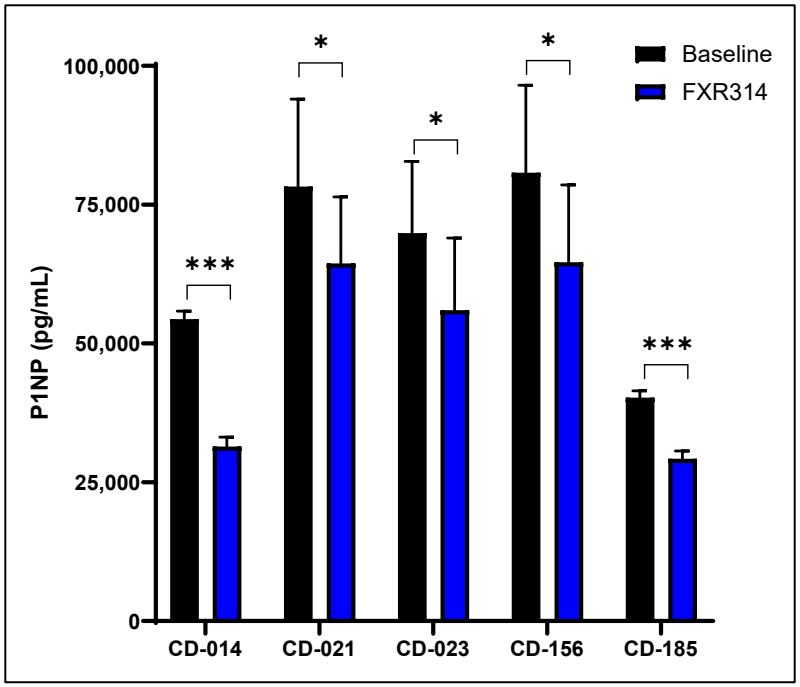
FXR314 Treated Donors



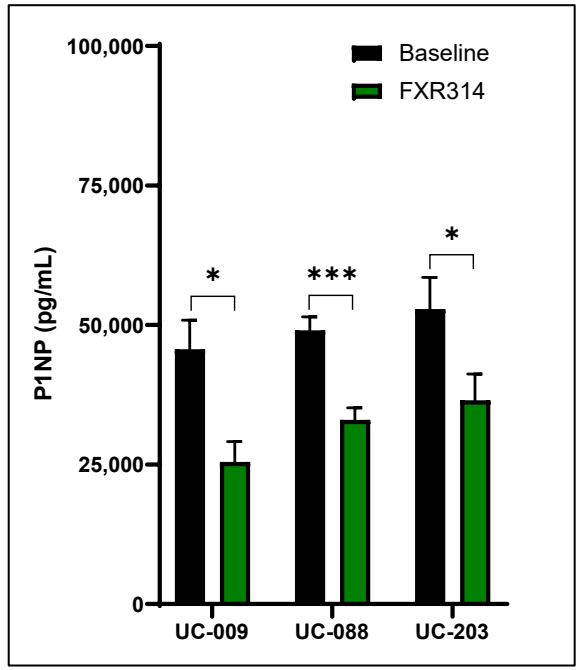
FXR314 Improves Fibrosis in CD and UC donors

- Evaluated P1NP as a marker of fibrosis
- FXR314-induced decrease in fibrotic marker observed in all CD and UC donors

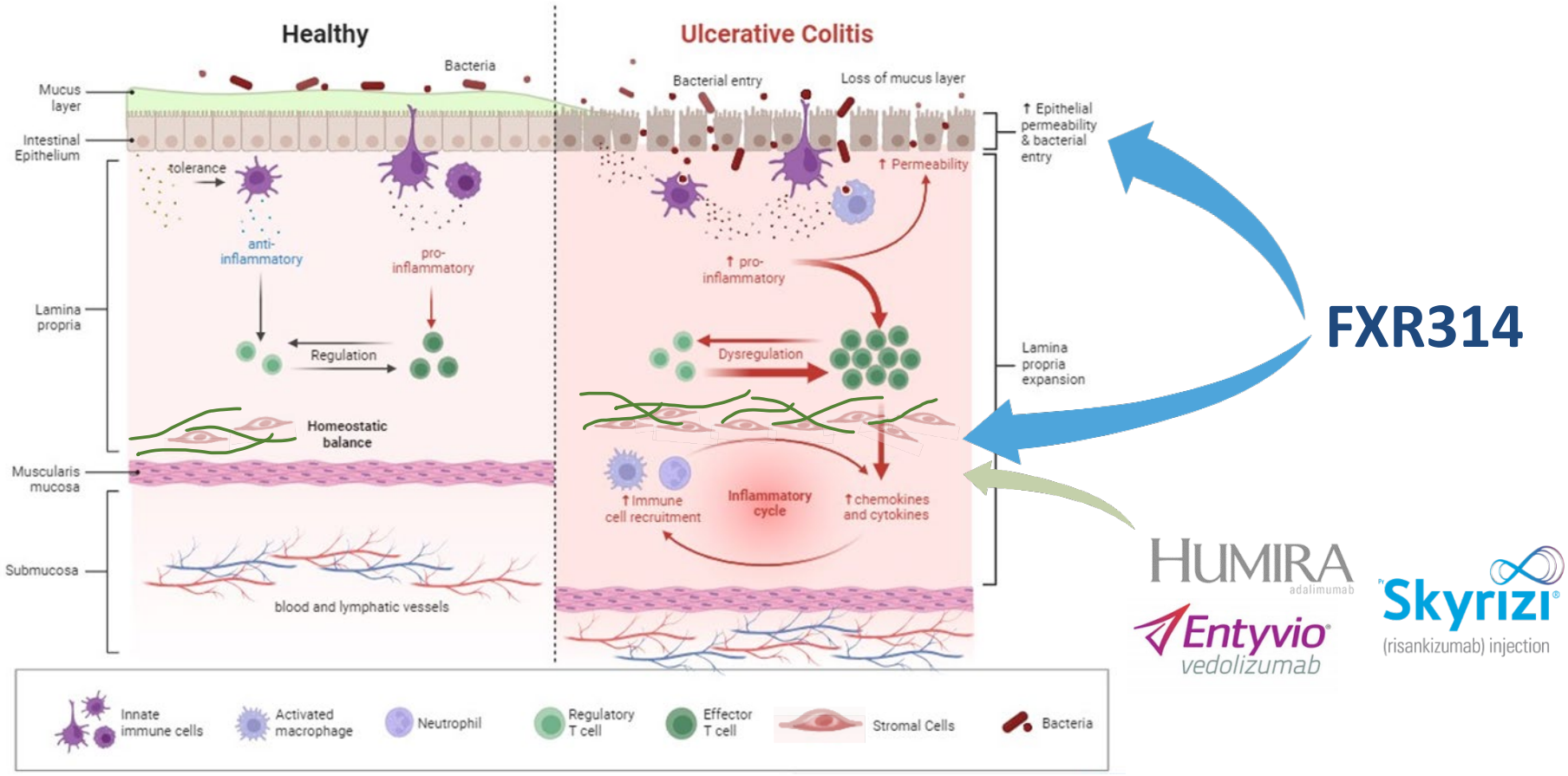
CD Donors



UC Donors



FXR314 MOA Linked to Epithelial Repair and Fibrosis Resolution Upstream of Anti-inflammatory Treatments



Conclusions

- Organovo 3D models (bioprinting and other tissue technologies) replicate various aspects of the IBD disease process and human biology
- 3D Models can be used to identify new mechanisms of action, validate novel targets, study the effects of clinically approved treatment paradigms and understand population response
- The potent non-bile acid FXR agonist FXR314 is effective in 3D models of Crohn's Disease and Ulcerative Colitis:
  - Demonstrated target engagement (FGF19) in all CD and UC donors
  - Improvement of intestinal barrier function in a subset of CD donors, and all UC donors
  - Improvement of fibrosis (P1NP marker) in all CD and UC donors
- A Phase 2 trial in Ulcerative Colitis is being planned