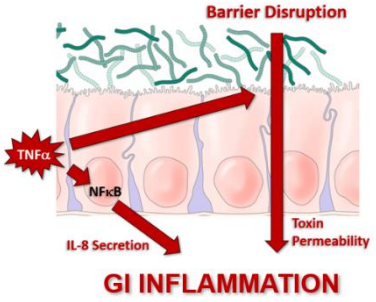
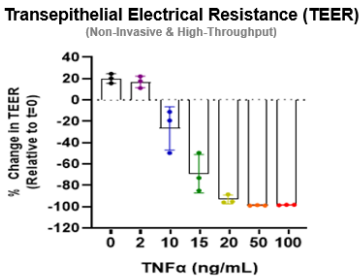
TNF-α is Critical to the Pathogenesis of Inflammatory Bowel Diseases

Tumor Necrosis Factor Alpha (TNF-a) is a potent cytokine that is over-expressed by cells during chronic intestinal inflammation[1]. Furthermore, TNF-α represents the most validated clinical target for ulcerative colitis (UC) and inflammatory bowel diseases (IBD) with multiple emerging neutralizing/inflammation-reducing therapeutics targeting this cytokine for inactivation[2]. TNF-α activation of intestinal epithelia can disrupt the intestinal barrier via mechanisms including that activation of the inflammatory master regulators, including NFkB-induced IL-8 production and secretion, as well as having direct effects on tight junction integrity and cellular apoptosis[2].



A Novel, High-Throughput Platform to Characterize Novel IBD Therapeutics

A.



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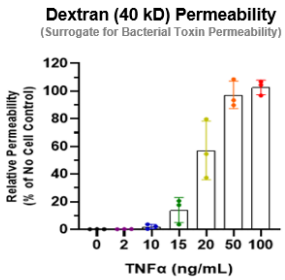

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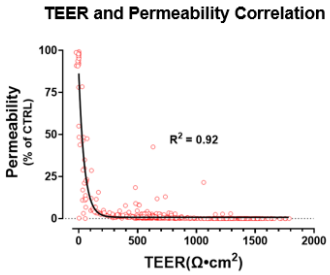
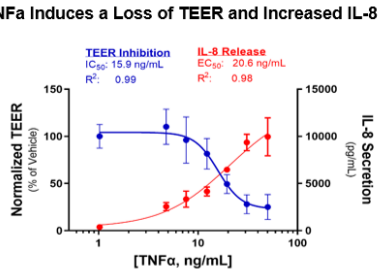


D.



Altis' RepliGut® Planar platform provides a novel, human primary culture cell system that both reprises the cellular complexity of the intestinal tract in vivo which is established using 12- and 96-well Tranwells® inserts to maximize throughput and dosing/assay flexibility. Altis has established a model of human IBD using RepliGut® planar designed to enable the screening and detailed characterization of novel therapeutic agents combining measures that bridge non-invasive and high-throughput testing with clinically relevant endpoints of the disease. In this model, TNF-α produces a dose-dependent decrease in TEER (electrical resistance, panel A), while increasing the permeability of organic molecules across the epithelium (panel B), which are highly correlated (panel C)—establishing a predictable response between TEER and the luminal permeability of surrogates of bacterial toxins. Furthermore, the Transwell format also enable easy sampling of the basolateral cell media which can be used to assay epithelial production of cytokines, including IL-8 (the major neutrophil-chemoattractant produced downstream of TNF-, panel D). Collectively, the RepliGut® planar model enables testing of novel IBD therapeutics which can be run in a 96-well plate format which can include relevant measures of barrier function and inflammation. Finally, as the experimental platform is highly flexible, additional endpoints including immunofluorescence, gene expression, and cell viability can be easily incorporated.

References:

1. Liu, T., Zhang, L., Joo, D. & Sun, S.-C. NF-κB signaling in inflammation. *Signal Transduct Target Ther* **2**, 17023 (2017).
2. Peyrin-Biroulet, L. Anti-TNF therapy in inflammatory bowel diseases: a huge review. *Minerva Gastroenterologica E Dietologica* **56**, 233–43 (2010).