GB004 exhibits protective effects directly on epithelial cells using ex vivo organoid and monolayer cultures

Kristen R. Taylor Meadows, Susan Murphy, Gregory J. Opteck, Barrett G. Levesque, Laura Carter, Luisa Satter-Cid
Gossamer Bio, Inc.

INTRODUCTION

• Inflammatory bowel disease (IBD) is characterized by a breach in intestinal barrier integrity, allowing influx of luminal antigens and setting up a vicious cycle of inflammation and epithelial injury

• Despite efficacy of IBD treatment with anti-tumor necrosis factor agents and anti-integrin agents, a large fraction of patients do not respond adequately to currently available therapies or biologics and do not achieve long-term remission

• GB004 is an oral, gut-targeted, small molecule that stabilizes hypoxia-inducible factor (HIF-1α), a key transcription factor involved in the adaptive and protective cellular responses at the intersection of hypoxia and inflammation (Figure 1)

• Preclinical efficacy of GB004 has been demonstrated in mouse models of colitis and correlated with HIF-1α stabilization in colonic epithelial cells, induction of HIF-1α target genes, downregulation of inflammatory cytokines, and improvement in histologic parameters of barrier function

• A phase 2 study evaluating two dosings of GB004 as a tablet formulation in mild to moderate UC is ongoing (NCT04556383)

OBJECTIVE

• To assess the effects of HIF stabilizer GB004 on gene expression, tight junctions, and barrier integrity using intestinal epithelial cells and organoids

METHODS

• Human RepliCult differentiated monolayers assays were performed at Attis Biosystems (Chapel Hill, NC) by proliferating and differentiating human-derived intestinal epithelial cells on a 2D monolayer platform. These monolayers were assessed with GB004 treatment under normal healthy conditions or with cytokine-stimulated conditions (25 ng/mL TNFα) to induce barrier damage. Barrier integrity was assessed through measuring Transepithelial Electrical Resistance (TEER) and a barrier integrity assay using FITC-dextran. HIF-1α target genes were assessed in cell lysates and tight junction formation and adhesion molecules were investigated by immunofluorescence staining. Three independent studies were performed to generate data presented in Figure 3, Figure 4, and Figures 5-7, respectively.

• Unless otherwise noted, data are presented as mean ± SD. Statistical analysis was carried out using GraphPad Prism and one-way ANOVA (*p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001)

RESULTS

• GB004 demonstrates direct protective effects on mouse organoid and human organoid epithelial cells

• GB004 induces HIF-dependent genes, specifically genes that drive barrier integrity, which are critical to mucosal repair in IBD

• This data complements data generated in mouse models of colitis demonstrating induction of HIF-1α-dependent genes, reduced barrier dysfunction and beneficial efficacy

REFERENCES


DISCLOSURES

KRTM, SWJ, GJO, ISGL, LC, and USC are employed by Gossamer Bio, Inc.