Cellular and Molecular Impact of the Melanocortin Receptor Agonist PL8177 in Dextran Sulfate Sodium (DSS)–Induced Colitis in Rats

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Introduction

- The melanocortin 1 receptor (MC1R)-specific agonist PL8177 and its main metabolite PL8274 have demonstrated broad anti-inflammatory activity in preclinical trials that mirrors that of α-melanocytederived peptide (α-MSH)–MC1R has been demonstrated to be effective in reducing inflammation in numerous experimental models.1,2
- Murine and human studies have found that MC1R is expressed on the colon luminal surface, and mouse models have demonstrated a role for MC1R in the mucosal inflammatory response in murine models of colitis.3

Methods

- Male Wistar rats (each group n=6) received 5% DSS in drinking water for 3 days to induce colitis. Rats in the placebo group received normal drinking water.
- At termination on day 8, 24 hours after the last dosing, colon tissues were harvested, dissected, and flash-frozen

Results

- **Single Nuclei RNA-Seq**
  - Expression of canonical genes was used to annotate clusters into broad groups of immune cell types (Figure 2).
  - UMAP analysis was performed to visualize clustering of single nuclei from different colon samples (Figure 2).

**Figure 2.** UMAP Plot Displaying Cell Type Clusters of Nuclei Derived From Placebo- and PL8177-Treated Colon Samples

- **Total Colitis Index and Histological Assessment**
  - Total colitis index was used to assess inflammatory damage to the colon (Figure 3).
  - Inflammation and histological scoring showed no significant difference between placebo and PL8177 cohorts.

**Figure 3.** Histopathological Assessment of Colon Tissue

- **Body Weight, Stool Consistency, and Fecal Occult Blood**
  - Body weight gain was similar between the vehicle control (placebo) and treated groups.
  - Fecal occult blood scores from 3 sections from each colon per animal. Separate scored items consisted of abnormalities of mucosal integrity, ulcers, and submucosal edema.

**Figure 4.** Box Plot of LC-MS DIA Data Shown a Trend Towards Lower CDXX Protein Expression in Mesalazine- and PL8177-Treated Colon Samples

- **Colon Length and Weight**
  - Oral mesalazine 300 mg/kg (positive control) was associated with significant reduction in colon length, but only moderate improvement (30%) in colon weight gain.

**Figure 5.** Changes in (A) Body Weight, (B) Body Composition, and (C) Fecal Occult Blood in DSS-Induced Colitis

Conclusions

- Colon samples from the DSS rat model showed significantly lower expression of the CDXX gene in macrophage cells in PL8177–treated animals when compared to placebo group. Protein levels of CDXX genes were likewise lower in PL8177-treated colon samples compared to the placebo.
- Colon histopathological examination showed injury and prominent ulcerations to the mucosa of the distal colon that extended for 2.5–7 cm in treated inflamed rats. Submucosal fibrosis and pronounced thickening of the colonic wall were also observed.
- Reported results are consistent with the ultimate aim of using PL8177 to treat inflammatory bowel disease in humans.