INTRODUCTION

The recent regulatory approval of ustekinumab which targets IL-12/23 and clinical data from several anti-IL-23 monoclonal antibodies, MEDI2070, BI655066 and LY074428, support IL-23 as a therapeutic target for the treatment of inflammatory bowel disease (IBD).

To effectively treat IBD, Protagonist Therapeutics has generated a suite of oral peptides that would act locally in the gastrointestinal (GI) tissues and functionally block the IL-23 pathway by selectively antagonizing the IL-23 receptor (IL-23R). We have previously demonstrated that these peptides are: 1) Potential inhibitors of IL-23/IL-23R signaling in a human cell line and in human primary cells; 2) Selective for IL-23, and may not inhibit binding to IL-6R or signaling through the IL-32 receptor; 3) Cross-reactive towards rat and cynomolgus homologs, enabling in vivo studies in these species; and 4) Resistant to the proteolytic and reducing environments of the GI tract, resulting in high drug levels in intestinal tissues while limiting drug exposure in the circulation, potentially addressing safety concerns associated with systemically delivered therapeutics.

In this study, we investigate the therapeutic potential of orally delivered PTG-200 in a 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced rat model of IBD. As there is interest in using pharmacodynamics (PD) biomarkers for early stage drug development, we sought to evaluate mechanism-specific and disease-related efficacy biomarkers of oral PTG-200 in the colon, feces and serum of colitic rats.

CONCLUSIONS

We demonstrate the in vivo activity of our lead candidate PTG-200, and show that PTG-200 primarily exerts its effects via the IL-23 pathway in an acute TNBS-induced rat colitis model. Specifically, blockade of IL-23-mediated signaling by oral treatment with PTG-200 leads to: 1) Significant and dose-dependent attenuation of disease parameters, with activity comparable to that of a neutralizing anti-IL-23p19 antibody (mAb); 2) Significantly decreased colon levels of myeloperoxidase (MPO; an indicator of neutrophil infiltration), of IL-17A and IL-22 (cytokines downstream of IL-23 signaling), and of phosphorylated Signal Transducer and Activator of Transcription 3 (p38α); a transcription factor whose phosphorylation status is known to be regulated by IL-23). The dose-related responses in these markers track with PTG-200 treatment effects. Moreover, we show that in the diseased animals, the levels of Sipocin 2 (LCN2; an anti-inflammatory protein over-expressed in the inflamed colonic epithelium) are elevated in the serum, and MPO and LCN2 are increased in the feces. These inflammatory markers, MPO (in feces) and LCN2 (in serum and feces) are responsive to PTG-200 oral treatment, thus serving as non-invasive PD biomarkers for colitic activity.

Our results highlight the potential value of these biomarkers in translating preclinical efficacy to early clinical proof-of-concept for anti-IL-23R therapies.