INTRODUCTION

Emerging clinical data from several monoclonal antibodies, including ustekinumab (which targets IL-12/23) and MEDI2070, BI655066, and U3917828 (which target IL-23), strongly support 6-23 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) Selective for 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-18 or signaling through IL-12, 3) Cross-reactive towards rat and cynomolgus homologs, enabling in-vivo studies in these species; 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, a 2.6-tryptophan-tryptophan-aspartic acid (TNA) peptides model of IL-23. As there is interest in using pharmacodynamics (PD) biomarkers for early stage drug development, we sought to profile mechanism of action of PTG-200 and its related responses in these markers track with the inflammation and disease activity.

CONCLUSIONS

We demonstrate the in vivo activity of our lead candidate PTG-200, and show that PTG-200 exerts its effects via the IL-23 pathway in two preclinical models of IBD.

- In an acute TNBS-induced rat colitis model, blockage of IL-23-mediated signaling by oral treatment with PTG-200 leads to significant and dose-dependent attenuation of disease parameters, with activity comparable to that of a neutralizing anti-IL-23p19 antibody (mAbs).
- In the same TNBS-induced colitis model, oral treatment with PTG-200 leads to decreased colonic levels of NFκB, an indicator of neutrophil infiltration and of the innate immune response. More importantly, the levels of IL-17A and IL-22, two cytokines in the IL-23 signaling pathway, are also significantly reduced. Furthermore, the levels of pSTAT3, a transcription factor known to be regulated by IL-23, are restored to control levels. The dose-related responses in these markers track with PTG-200 treatment effects.
- In an acute DSS-induced rat colitis model, oral treatment with PTG-200 leads to significant decreases in the relative expression of genes encoding IL-23-directed cytokines (IL-17A, IL-17F, and IL-22) and in the abundance of IL-22 protein.

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

RESULTS: IN VIVO EFFICACY AND EFFICACY BIOMARKER RESPONSES IN AN ACUTE TNBS-INDUCED RAT MODEL OF IBD

**RESULTS: PD BIOMARKER RESPONSES IN AN ACUTE DSS-INDUCED RAT MODEL OF IBD**

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