

Bridging the Translational Gap: Preclinical Efficacy Assessment of Biologics in Humanized Mouse Models for Inflammatory Bowel Disease

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Abstract

Inflammatory bowel disease (IBD) refers to chronic disease that leads to inflammation and fibrosis in the gastrointestinal tract. Recent advances in the development of various biologics shed light on novel therapeutic strategies against IBD, highlighting a growing demand on efficient, integrated biologic assessment pipeline. Here, we provide a comprehensive platform featured by various cell-based models and state of the art humanized mice for efficient and seamless evaluation of human- TNF-like ligand 1A (TL1A) - targeted biologics.

Experimental Design and Results

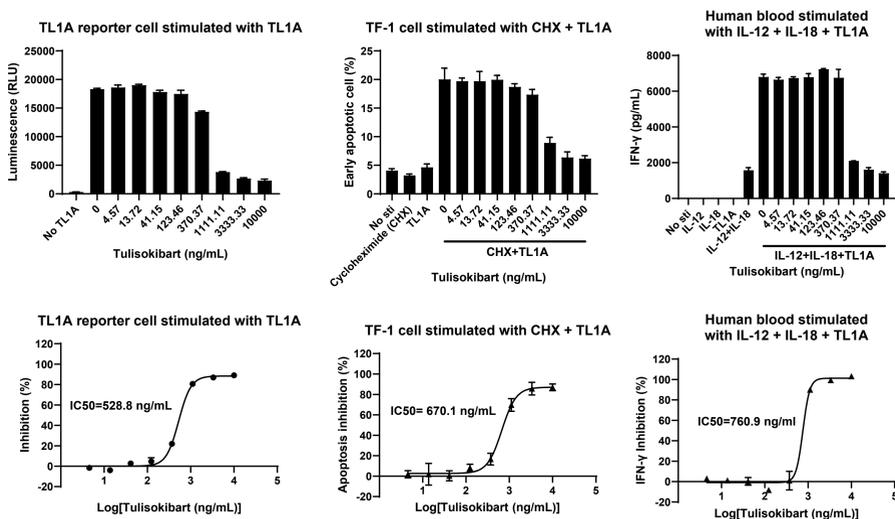
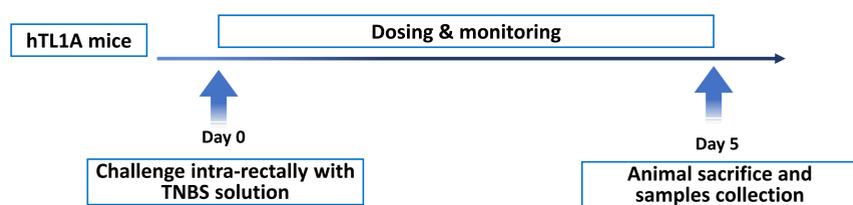


Figure 1. Tulisokibart suppresses luminescence signal, apoptotic rate and IFN- γ release. Tulisokibart effectively suppresses luminescence signal of reporter cells, apoptotic rate of TH-1 cells as well as IFN- γ release in stimulated human whole blood.



In vivo study shows that severe body weight loss and increased disease active index (DAI) scores in the Vehicle group confirmed the successful establishment of colitis in B-hTL1A humanized mice. Anti-TL1A treatment successfully reduced body weight loss, DAI scores (Fig 2A) and colon density in diseased mice. Histological analysis showed reverse inflammatory cell infiltration, crypt structure change (Fig 2B) and fibrosis in the treatment groups (Fig 2c). Cytokine detection results showed ameliorated inflammatory cytokines release in both colon mucosa (Fig 3A) and serum (Fig 3B).

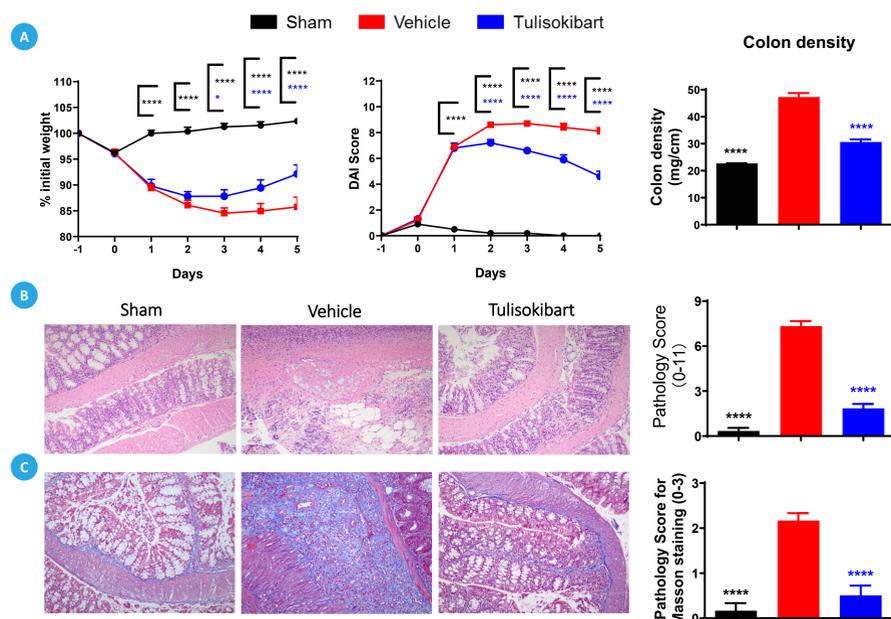


Figure 2. Tulisokibart administration alleviates TNBS-induced acute colitis in humanized TL1A mice. A) Body weight, DAI score over time and colon density at termination. B) H&E and C) Masson staining in colon of humanized TL1A mice.

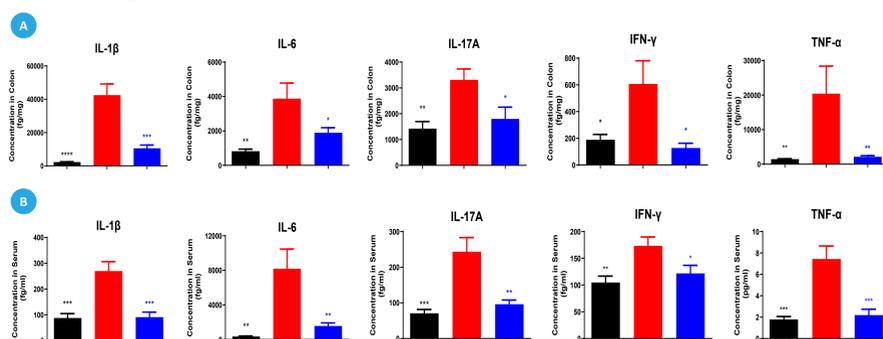


Figure 3. Expression of inflammatory cytokines IL-1 β , IL-6, IL-17A, IFN- γ , and TNF- α expression levels in A) colon mucosa and in B) serum detected by ultrasensitive CBA kits.

Summary

In this study, we have successfully established cell-based in vitro models and acute and chronic colitis models in TL1A humanized mouse strains for assessing TL1A-targeted biologics. Treatment with human TL1A antibody effectively alleviated the symptoms of colitis in the colitis-bearing mice. These results show our capability of evaluating drug efficacy against IBD, enabling precious opportunities and reducing R&D cycle for drug screening of novel therapeutic candidates, providing translational insights from bench work to clinical trial.

References

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