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CR-T1-T4, a tri-specific anti-inflammatory and anti-Th17 protein drug candidate for the treatment of hidradenitis suppurativa

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Introduction & Objectives:

Hidradenitis suppurativa (HS) is a chronic, recurrent, and debilitating inflammatory skin disease characterized by painful nodules, abscesses, and sinus tract formation, significantly impacting patients' quality of life. Although HS affects approximately 1% of the global population, the number of patients seeking treatment in the United States and Europe is comparable to that of psoriasis, with an estimated 350,000-400,000 patients in the United States alone. Historically, diagnosis was often delayed by 7-10 years; however, improved awareness has reduced this delay to 2-5 years, allowing for earlier intervention.

Despite advances in single-target biologic therapies targeting TNFα and IL-17 pathways, many patients fail to achieve sustained remission. The development of anti-drug antibodies (ADA) and increased risk of infections remain significant challenges. In this study, we aimed to evaluate the therapeutic potential of CR-T1-T4, a novel tri-specific soluble receptor TRAP protein designed to inhibit TNFα and IL-17 pathways while minimizing immunogenicity and infection risk. We present preclinical data from *ex vivo* analysis of HS patient skin samples, HS patient PBMC-based stimulation assays, an IL-17-driven inflammation *in vivo* model, and ADA assessments. Comparative analyses with existing therapies further support the potential of CR-T1-T4 as a promising new treatment option for HS.

Materials & Methods:

Human skin tissue and PBMC samples were obtained from HS patients with appropriate informed consent. Excised patient skin lesions were processed for *ex vivo* analyses, including cytokine profiling and comparative evaluation of therapeutic inhibitors. A genetically engineered double knock-in (KI) mouse model was used for the comparative evaluation of therapeutic agents.

Results:

We conducted efficacy comparison tests through *ex vivo* cultures of HS patient tissues to evaluate the neutralization of target cytokines and HS-specific biomarkers. Comparative evaluations of monotherapy and combination therapy were performed with competing agents Bimekizumab and Adalimumab in an HS-mimicking environment using human PBMCs. We also confirmed the low ADA response of CR-T1-T4 in human PBMCs, suggesting reduced immunogenicity.

Subcutaneous biological therapy with antibodies selectively targeting cytokine mediators involved in HS pathology was investigated. Efficacy evaluations using PASI scores and epidermal thickness were conducted in the IL-17A/F KI mouse model. Histopathological analysis and cytokine profiling post-treatment were used to confirm the efficacy of CR-T1-T4 compared to Bimekizumab, Etanercept, and et cetera. Overall, our results demonstrate that CR-T1-T4 effectively alleviates chronic inflammation and Th17-mediated skin lesions.

Conclusion:

CR-T1-T4 is a tri-specific soluble receptor TRAP protein that targets three key cytokines associated with HS. Our data shows that CR-T1-T4 exhibits a very low ADA response and low infection risk compared to current monoclonal antibody therapies in *ex vivo* models, while also demonstrating superior neutralizing effects in both *in vivo* and *ex vivo* studies. As a tri-specific Fc-fusion protein, CR-T1-T4 may offer a highly effective treatment option for HS patients who do not respond to, or relapse after, existing single-target antibody therapies.