Abstract N°: 5709

AI-Guided Design and Development of HXN-1011: A Potent Anti-TSLP Biparatopic Antibody

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Introduction & Objectives:

Thymic stromal lymphopoietin (TSLP) is a clinically validated therapeutic target associated with various inflammatory diseases. TSLP mediates its biological activity by binding to two distinct epitopes, Site I and Site II, on the TSLPR-IL7Rα receptor complex. By employing advanced AI-driven design strategies, we developed HXN-1011, a biparatopic antibody that simultaneously binds TSLP at both Site I and Site II. This dual binding provides superior inhibition of TSLP signaling compared to antibodies targeting only Site I, thereby enhancing therapeutic efficacy.

Materials & Methods:

The design, optimization, and epitope mapping of TSLP-targeting antibodies were guided by proprietary AI algorithms. Binding affinity was determined using surface plasmon resonance (SPR). Functional activity was evaluated through a series of in vitro assays, including TSLPR-STAT5-Luc reporter assays, TSLP-induced Baf3 cell proliferation assays, and CCL17 release from peripheral blood mononuclear cells (PBMCs). *In vivo* efficacy was assessed in inflammation models using hTSLP/hTSLPR transgenic mice, and pharmacokinetic properties were characterized in non-human primates (NHPs).

Results:

Epitope mapping confirmed that HXN-1011 simultaneously binds to both Site I and Site II, whereas other TSLP-targeting antibodies, including Tezepelumab, GSK5784283, and CM326, bind exclusively to Site I. HXN-1011 exhibited a binding affinity approximately 100-fold higher than Tezepelumab and achieved IC90 values 15- to 100-fold lower in functional assays. Notably, HXN-1011 completely inhibited TSLP activity at concentrations as low as 1.5–3 nM *in vitro*. Furthermore, in an OVA-induced asthma model using hTSLP/hTSLPR transgenic mice, HXN-1011 effectively reduced lung inflammation, as evidenced by decreased BALF cell counts, eosinophil levels, and CCL17 expression, outperforming both Tezepelumab and GSK5784283. Furthermore, in an MC903+OVA-induced skin and lung inflammation model, HXN-1011 demonstrated superior efficacy across all tested parameters including reductions in epidermal hyperplasia, immune cell infiltration and lung inflammation. Additionally, in pharmacokinetic (PK) studies in non-human primates (NHPs), HXN-1011 exhibited a significantly extended half-life compared to Tezepelumab.

Conclusion:

HXN-1011 is a next-generation biparatopic antibody exhibiting exceptional potency and holding significant potential to enhance clinical efficacy in the treatment of TSLP-driven inflammatory diseases, including atopic dermatitis, asthma, chronic obstructive pulmonary disease (COPD), and other related indications. Preclinical studies and IND-enabling research for HXN-1011 are currently underway.