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AI-Guided Generation and Preclinical Evaluation of an OX40L-IL31 Bispecific Antibody

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Introduction & Objectives:

The itch-scratch cycle in atopic dermatitis (AD) is closely linked to skin inflammation exacerbation, which not only accelerates disease progression but also significantly impacts patients' quality of life. IL31 is a key factor in promoting itching, and antibodies targeting IL31Ra have shown promising therapeutic effect in AD patients in alleviating the disease symptoms, but with limited activity on the underlying skin inflammation and overall disease progression. In this study, we developed a bispecific antibody (bsAb), HXN-1022, that binds to and neutralizes both IL31 and OX40L, aiming to simultaneously inhibit OX40L and IL31 activities, thus providing a faster, deeper and more durable therapeutic efficacy to patients with AD and other autoimmune skin disorders.

Materials & Methods:

The binding affinity of bsAb to each target was evaluated using SPR, while its interaction with membrane-bound OX40L was measured with flow cytometry. The biological activity of HXN-1022 was examined through various in vitro assays, including IL31R-STAT reporter assay and HaCat cell activation assay for IL31, and OX40-NFκB-Luc reporter assay and Th2-diffierentiation assay for OX40L.

Results:

We generated a highly potent anti-IL31 antibody through an internal AI-guided design and optimization platform. The antibody significantly inhibits IL31 biological activity in the IL31R-STAT reporter assay and HaCaT cell activation, with an efficacy that is superior to the benchmark Nemolizumab and NM26-2198 analogs. Using this anti-IL31 antibody and an anti-OX40L antibody as the building blocks, we engineered a tetravalent bispecific antibody, HXN-1022, that is capable of simultaneously binding to IL31 and OX40L. HXN-1022 effectively blocks both IL31 and OX40L from interacting with and activating their respective receptors, with potency comparable to each of the parent antibodies. Moreover, HXN-1022 demonstrated a strong therapeutic efficacy in a human PBMC-reconstituted GvHD (graft-versus-host disease) mouse model. The bsAb significantly inhibited T cell proliferation, alleviated key GvHD symptoms, and prolonged the survival of the animals.

Conclusion:

HXN-1022 is a first-in-class bsAb that simultaneously targets IL31 and OX40L, two major pathogenic factors associated with skin inflammation and itch. The bsAb holds great potential as a more effective therapeutic option for patients with a variety of autoimmune skin disorders.