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Development and Characterization of IBI3013, a Novel Half-life Extended Monoclonal Antibody Targeting Interleukin-15 (IL-15)

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Introduction & Objectives:

Vitiligo remains a global unmet medical need, with limited treatment, and is caused by auto-reactive CD8 T cells that recognize and induce cytotoxicity against melanocytes. It has been demonstrated that interleukin-15 (IL-15) promotes the activation, expansion, and survival of T cells as well as the formation of resident memory T cell population in barrier tissues such as the skin and intestine. Notably, serum IL-15 levels are elevated in vitiligo patients compared to healthy population. These observations position IL-15 as a potential key disease driver and an emerging therapeutic target for vitiligo. Here, we developed IBI3013, an IL-15 targeting monoclonal antibody (mAb) with high affinity, improved potency, superior pharmacokinetics (PK), and favorable safety profile.

Materials & Methods:

To evaluate the function of IBI3013 *in vitro* - with IL-15 reporter assay, immune cell expansion assay, and CD8 T cell activation assay - reporter cells, human peripheral blood mononuclear cells, and CD3/CD28-activated CD8 T cells were stimulated with either soluble IL-15 or IL-15/IL-15Rα complex and incubated with different concentration of IBI3013, followed by assessment of luciferase signal, cell number, and IFNγ production, respectively. In the skin inflammation model, IL-15/IL-15Rα complex was administrated by intradermal injection to stimulate skin infiltrating T cell activation and expansion. In the graft-versus-host disease (GvHD) model, IL-15/IL-15Rα complex was administrated by intraperitoneal injection to stimulate T cell expansion and enhance disease progression. In the *in vivo* studies, IBI3013 was administrated by intraperitoneal injection.

Results:

In *in vitro* functional assays, including IL-15 reporter assay, immune cell expansion assay, and CD8 T cell activation assay, IBI3013 showed superior blocking potency compared to a benchmark IL-15 mAb. Additionally, low dose of IBI3013 significantly suppressed IL-15 induced skin inflammation and IL-15 enhanced graft-versus-host disease in mouse models. Notably, cryogenic electron microscopy and Bio-layer interferometry revealed that IBI3013 targets a unique and differential epitope on IL-15, specifically antagonizing its interaction with Rγ without disrupting its binding to Rβ, potentially enabling the dominant negative function of antibody-cytokine immune complex. We also incorporated the clinically validated Fc engineering, YTE (M252Y/S254T/T256E), to prolong IBI3013's half-life. IBI3013 exhibited favorable developability, achieving a 200 mg/mL formulation suitable for subcutaneous dosing. In the monkey PK study, IBI3013 exhibited a half-life of 430 hours. Moreover, the toxicity study in monkey showed no adverse effect at doses up to 300 mg/kg, underscoring IBI3013's favorable safety profile.

Conclusion:

In summary, we developed a potent and half-life extended IL-15 mAb with potential as an effective, safe, and convenient treatment for patients with vitiligo and other IL-15 driving autoimmune diseases, including alopecia areata and celiac disease.