Heterodimeric FC-Fused IL12 Shows Potent Antitumor Activity and Low Toxicity

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Background Interleukin-12 (IL12) is a heterodimeric pro-inflammatory cytokine (70 kDa) composed of two different polypeptide chains: an α-chain (p35 subunit) and a β-chain (p40 subunit). IL12 could induce the proliferation and cytotoxicity of T and NK cell and production of interferon-γ (IFN-γ), promote the differentiation of T helper 1 (TH1) cells and regulate innate resistance and adaptive immunity. However, the clinical efficacy of IL12 has been hindered for its high dose-related toxicities and short serum half-life. Here we have developed heterodimeric Fc-fused IL12, HK054-Vx, with reduced potency to improve tolerability and prolong half-life.

Methods We assessed the binding, bioactivity, anti-tumor efficacy and safety of HK054-Vx. The binding ability of IL12-Fc lead variants to activated PBMCs was analyzed by flow cytometry. The bioactivity of HK054-Vx was determined by assessing the activated T-cell proliferation and IFN-γ production in human PBMCs, and STAT-4 phosphorylation in a reporter gene assay.

Murine surrogates was engineered to mimic HK054-Vx to evaluate the antitumor efficacy in MC38 and CT26 syngeneic tumor mouse models. In vivo anti-tumor activity was also assessed by engrafting MCF-7 cancer cells into human PBMC engrafted BNDG-B2m mice. Cytokine release assay was conducted by incubating HK054-Vx with peripheral blood mononuclear cells (PBMCs) from healthy donors.

Results Heterodimeric Fc-fused IL12, HK054-Vx, were designed with reduced potency. HK054-Vx were observed to stimulate the proliferation of activated T cells and NK cells and induce production of IFN-γ in a dose-dependent manner. HK054-Vx could activate pSTAT4 signal in luciferase reporter gene assay and showed up to 100-fold reduction of potency compared to wild-type IL12-Fc. HK054-Vx showed potent anti-tumor efficacy in human PBMC engrafted BNDG-B2m mice and was better tolerated than WT mIL12-Fc.

Conclusions These data demonstrate that HK054-Vx, heterodimeric Fc-fused IL12 with reduced potency, retain strong antitumor efficacy with a favorable tolerability profile, which may provide a practical alternative to the systemic administration of IL12 for antitumor therapy.