1372 XMAB143, AN ENGINEERED IL18 HETERODIMERIC FC-FUSION, FEATURES IMPROVED STABILITY, REDUCED POTENCY, AND INSENSITIVITY TO IL18BP

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Background Interleukin-18 (IL18) is a proinflammatory cytokine that modulates both innate and adaptive immune responses. Mature IL18 promotes the expansion, survival, and cytotoxicity of T and NK cells expressing the heterodimeric IL18 receptor. Preclinical studies with recombinant IL18 have demonstrated anti-tumor activity in animal models, including impressive synergy with both immune checkpoint inhibitors and CAR-T therapy. However, clinical development as a single agent exhibited poor pharmacokinetics and an overall lack of efficacy despite heavy dosing. IL18 participates in a negative feedback loop with IL18 binding protein (IL18BP), a very high affinity natural inhibitor induced by IFNγ. As IL18BP upregulation was observed in early phase clinical trials, it likely limited the efficacy of recombinant IL18.

Methods Prior work at Xencor demonstrated that reduced-potency IL15/IL15Rα-Fc fusion proteins exhibited superior pharmacokinetics, pharmacodynamics, and safety in non-human primates through reduction of receptor-mediated clearance. Following that principle, we generated monovalent IL18-Fc fusions upon our XmAb® heterodimeric Fc platform and introduced substitutions that could modulate IL18 stability, affinity toward the IL18 heterodimeric receptor, and affinity toward IL18BP.

Results To address IL18's poor native stability, we engineered a disulfide bridge into the cytokine's structure which increased the thermal denaturation temperature from 45 °C to 65 °C. This had beneficial effects on the cytokine's yield and solution behavior, and translated into a significant improvement of PK in mice. Variants at IL18 positions along the IL18 receptor and IL18BP interfaces were explored in vitro by measuring PD-L1 induction on KG-1 cells, with and without a high concentration of IL18BP. Recombining hits generated a potency series with variants exhibiting over a 2,000-fold reduction in PD-L1 induction potency as compared to WT IL18-Fc. Importantly, we identified variants that no longer detectably bound IL18BP, relieving natural inhibition of our engineered IL18-Fc. In vivo immune-mediated inflammation by our lead IL18-Fc, XmAb143, was explored in human PBMC engrafted mouse models of graft versus host disease (GvHD). We observed dose-dependent exacerbation of GvHD, with corresponding dramatic increases in the numbers, activation, and IFNy release of T and NK cells as compared to a human PBMC only control. Conversely, XmAb143 pharmacodynamics in cynomolgus monkey pilot tox studies was observed only at higher doses, and serum half-life improved from hours to days over WT IL18-Fc.

Conclusions XmAb143, our engineered monovalent IL18-Fc fusion demonstrates insensitivity to IL18BP inhibition, robust inflammation activity in vivo, and improved pharmacokinetics in mice and cynomolgus monkeys.

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