demonstrated by IFN γ production. Following intratumoral injection, exoIL-12 exhibited prolonged tumor retention and greater antitumor activity than rIL-12. Moreover, exoIL-12 was 100-fold more potent than rIL-12 in tumor growth inhibition. In the MC38 tumor model, complete responses were observed in 63% of mice treated with exoIL-12; in contrast, rIL-12 resulted in 0% complete responses at an equivalent IL-12 dose. This correlated with dose-dependent increases in tumor antigen-specific CD8 $^{+}$ T cells. Re-challenge studies of exoIL-12 in complete responder mice showed no tumor regrowth. Moreover, depletion of CD8 $^{+}$ T cells completely abrogated the antitumor activity of exoIL-12. Following intratumoral administration, exoIL-12 exhibited 10-fold higher intratumoral exposure than rIL-12 and prolonged IFN γ production up to 48 hr. Retained, local pharmacology of exoIL-12 was further confirmed using subcutaneous injections in non-human primates.

Conclusions This work demonstrates that tumor-restricted pharmacology of exoIL-12 results in superior in vivo efficacy and immune memory without systemic IL-12 exposure and related toxicity. exoIL-12 is a novel cancer therapeutic candidate that has the potential to overcome key limitations of rIL-12 and thereby create a therapeutic window for this potent cytokine.

Ethics Approval All animals were maintained and treated at the animal care facility of Codiak Biosciences in accordance with the regulations and guidelines of the Institutional Animal Care and Use Committee (CB2017-001).

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DEVELOPMENT OF IL-33 AS A NOVEL IMMUNOTHERAPY OF CANCER

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Background Immune-checkpoint-blockade (ICB) therapy has produced unprecedented survival benefits for cancer patients but such therapy has been limited by low response rates in most cancer. One major obstacle for ICB therapy is the reduced immunogenicity of tumor tissues due to genetically driven down-regulation of epithelial tissue cytokines. IL-33 is a member of the IL-1 gene family and its level is downregulated in many advanced carcinomas such as lung cancer, breast cancer and pancreatic cancer. It has recently been shown that IL-33 plays an important role in mediating cancer immune therapy. In addition, transgenic expression of the active form of IL-33 in tumor cells or administration of the recombinant IL-33 exerts strong antitumor effects. Mechanistically, IL-33 enhances the function of Th1 and CD8 $^{+}$ T cells in vitro and types 1 antitumor immune responses in vivo.

Methods In the current study, we have optimized the pharmacodynamics of IL-33 by engineering a fusion protein, called anti-HSA-IL-33, using IL-33 and an anti-human albumin antibody. We have used preclinical mouse tumor models to determine the efficacy and toxicity of this new molecule.

Results We have shown that anti-HSA-IL-33 has excellent antitumor activities alone and enhances the antitumor function of PD-1 mAbs. Despite causing increased inflammation, anti-HSA-IL-33 is well tolerated with limited toxicity in mice.

Conclusions These studies support further development of IL-33 as a novel cancer immunotherapy.

Ethics Approval The animal experiments have been approved by IACUC of University of Pittsburgh.

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HBM1022, A NOVEL ANTI-CCR8 ANTIBODY DEPLETES TUMOR-INFILTRATING REGULATORY T CELLS VIA ENHANCED ADCC ACTIVITY, MEDIATES POTENT ANTI-TUMOR ACTIVITY WITH KEYTRUDA

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Background CCR8-expressing CD4 and Foxp3 positive Treg (CCR8 $^{+}$ Treg) has been demonstrated to be a major driver for immunosuppression in solid tumors¹ <1> Superscript. Clinical studies have shown that CCR8 is selectively up-regulated by tumor resident Tregs in several tumor types including clear cell renal cell carcinoma (ccRCC)² <2> Superscript and breast cancer³ <3> Superscript. In these tumor types, CCR8 exhibit strong expression on tumor resident Tregs while it is rarely observed on Tregs in peripheral blood mononuclear cells (PBMCs). High expression of the CCR8 in tumor-infiltrating lymphocytes-Treg cells (TIL-Tregs) was associated with poor prognosis in breast cancer patients. These results suggest CCR8 as a promising therapeutic target; and anti-CCR8 mAbs could selectively inhibit a subpopulation of tumor resident Tregs in the tumor microenvironment (TME), to augment antitumor immunity.

Methods In vitro assay: HBM1022 binding on human, cynomolgus CCR8 and TIL-Tregs are evaluated via flow cytometry. Blocking and ADCC functional assay are all based on CCR8 overexpressing cell lines. In vivo efficacy study: HBM1022 anti-CCR8 antibody was administered after implantation ($\approx$ 100 mm³ <3> Superscript tumor volume) alone and in combination with anti-PD-1.

Results Anti-CCR8 antibody HBM1022 specifically binds to cell lines that over-express human or cynomolgus CCR8, as well as TIL-Tregs in multiple cancer types with the high affinity. HBM1022 potently blocks CCL1 binding to both human and cynomolgus CCR8. HBM1022 inhibits CCL1-induced migration and related GPCR signaling pathways. Furthermore, with enhanced antibody-dependent cell-mediated cytotoxicity (eADCC) activity, HBM1022 exhibits potent in vitro killing activity on CCR8-expressing cells. HBM1022 shows tumor growth inhibition as monotherapy in preclinical mouse syngeneic and humanized models. Moreover, HBM1022 shows enhanced antitumor activity with the combination of Keytruda[®] in preclinical efficacy models.

Conclusions Our finding reveals HBM1022 as an innovative immunotherapy targeting intra-tumoral suppressive Treg cells to change suppressive tumor to hot tumor. HBM1022 presents its great potential as exciting mono or combo anti-tumor therapies.

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