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TARGETING TREG CELLS BY TNFR2 ANTIBODY INDUCES TUMOR REGRESSION IN VIVO

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Background: Tumor necrosis factor receptor 2 (TNFR2) is considered an appealing target due to its low-level expression on immune cells, but it could be upregulated on regulatory T cells (Tregs) in the tumor microenvironment which plays key roles in Treg proliferation and function. It has been demonstrated that Tregs with high TNFR2 expression were the most suppressive subsets among all Treg populations in the tumor. While early studies showed that TNFR2 co-stimulates naïve T cells, it has been revealed later that TNFR2 also limits CD8+ T-cell-mediated viral clearance and anti-tumor immunity by inducing rapid contraction of CD8+ T cells. Consistent with these findings, several publications reported that anti-TNFR2 antibody treatment exhibited robust antitumor efficacy. In short, TNFR2 signaling is critical in regulating immune response in different diseases. In the current study, the anti-human TNFR2 antibody SBT-1901 was developed and the anti-tumor activity was evaluated.
Materials and methods: SBT-1901 was generated through hybridoma and humanization technologies. The binding affinity and specificity were tested by ELISA, FACS, and OCTET. The function of SBT-1901 was tested in TNFR2-Fas overexpressing Ramos cells and in Treg proliferation assay. The *in vivo* anti-tumor activity and pharmacokinetics of SBT-1901 were evaluated in the human TNFR2 transgenic mouse model (Biocytogen) bearing MC38 tumor.
Results: SBT-1901 binds to the extracellular domain of human and cynomolgus TNFR2 with the affinity of single digit-nanomolar. It competes with TNFα for binding to TNFR2 receptor and inhibits TNFα-induced TNFR2-Fas overexpressing RAMOS cell death. SBT-1901 also blocks TNFα induced Treg proliferation in human PBMC. In addition, SBT-1901 significantly inhibits MC38 tumor growth in a dose-dependent manner as a monotherapy and enhances anti-tumor efficacy of mPD-1 antibody in a combination study in human TNFR2 transgenic mouse model. SBT-1901 is currently under preclinical development.
Conclusions: Our studies show that SBT-1901 exhibits a very potent anti-tumor efficacy *in vivo* as a single agent or the combination. Therefore, it is highly valuable to further develop SBT-1901 for human cancer treatment.