FPT155, a novel therapeutic CD80-Fc fusion protein, with potent anti-tumor activity in preclinical models

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Introduction

T cell regulation involves the integration of multiple signaling pathways; signaling via the TCR complex and through co-signaling receptors, both co-stimulatory and co-inhibitory. CD80 is a transmembrane protein and a well-characterized co-signaling ligand. It is expressed on professional antigen presenting cells (APC), such as dendritic cells and activated macrophages. Following TCR recognition of peptide-major histocompatibility complex (MHC), CD80 acts as a co-stimulatory ligand via interactions with its receptor, CD28, expressed on T cells. In addition to signaling via CD28, CD80 also interacts with co-inhibitory molecules (CTLA4 and PD1). CD80 interactions with CTLA4 are central for dampening the T cell response once activated T cell responses are no longer needed, while the biological significance of the CD80 interaction with PD1 is not as well understood. Together, the co-stimulatory and co-inhibitory ligands ensure both tolerance to self-antigens and the ability to mount an appropriate immune response to non-self antigens.

Screening using Five Prime's Rapid in vivo Protein Production System (RPPS™) identified a soluble version of CD80 as one of the most potently inhibiting CT26 tumor growth among a library of 440 extracellular proteins evaluated. The activity of soluble CD80 was comparable or superior to that of other T cell agonists such as GITRL, OX40L, and 4-1BB.

RPPS® Screen of Soluble Extracellular Proteins in the CT26 Tumor Model

We are developing FPT155, a soluble CD80 fusion protein, for the treatment of solid tumors. FPT155 is a recombinant fusion protein composed of the extracellular domain (ECD) of human CD80 fused with human IgG1 with a flexible Fc domain. FPT155 is designed to act as a potent stimulator of anti-tumor immunity and efficiently co-ordinates primary human T cells in the presence of antigenic stimulation. A murine surrogate molecule mFPT155 was constructed for preclinical studies, comprising the ECD of murine CD80 fused with mouse IgG2a type Fc domain. mFPT155 demonstrates potent anti-tumor activity in vivo and induces a favorable microenvironment for an effective anti-tumor immune response. We are currently performing IND-enabling studies and plan to initiate a clinical study with FPT155 in 2018.

FPT155 stimulates primary T cells in a TCR-dependent fashion

FPT155 potently co-stimulates naive and memory CD4+ T cells to proliferate and secrete IFNγ in a dose-dependent fashion in the presence of “artificial APC” (aAPC) that co-express anti-CD2 and a non-signaling CD64. Importantly, memory CD4+ T cells are not stimulated by FPT155 with aAPC that do not express the CD80 molecule, demonstrating that FPT155 must be co-presented with TCR to activate T cells.

To confirm that FPT155 does not have superagonistic, TCR-independent activity, we evaluated it in the Splittas "wet-coating" assay, in which the test article is presented to PBMC in a highly-crosslinked, immobilized form. This assay format predicts the cytokine release syndrome (CRS) induced in patients by the anti-CD28 superagonist antibody TGN1412. By contrast, FPT155 does not induce the spontaneous release of CRS-associated cytokines, even at high concentrations, unless it is co-immobilized with anti-CD2 (5 donors shown). We thus conclude that FPT155 is not a CD80 superagonist and does not pose the same clinical risk as TGN1412.

FPT155 co-stimulates murine T cells

mFPT155 has potent single-agent anti-tumor efficacy

mFPT155 exerts dose-dependent inhibition of CT26 tumor growth following one or three administrations starting at a starting tumor volume of 80-100 mm³. Tumor growth is significantly inhibited even following a single administration at 0.1 mg/kg, and we observe complete tumor regressions with a single administration of 0.2 mg/kg mFPT155. mFPT155 controls the growth of EMT6 and MC38 tumors following three administrations.

mFPT155 has synergistic combination activity with anti-PD1

mFPT155 exerts partial anti-tumor activity in the CT26 model when administered at a large starting tumor volume (3 doses of 0.3 mg/kg at starting at 200 mm³). Combination with anti-PD1 (RMP1-14, mouse IgG2a-anti-155, 3 administrations of 5 mg/kg) synergistically enhances tumor growth control (p < 0.03 compared to monotherapy). The combination regimen also increases the number of complete tumor regressions to 9 of 15, compared to 5 of 15 with mFPT155 alone.

Conclusions

FPT155 promotes T cell responses in the presence of antigenic stimulation but is not a CD28 superagonist.

Tumor control induced in vivo by mFPT155 is accompanied by robust effector T cell infiltration into the tumor and an increased effector T cell to Treg ratio. mFPT155 demonstrates potent anti-tumor activity in combination with PD1 pathway blockade.

In summary, FPT155, a CD80-Fc fusion protein, has potent anti-tumor activity in preclinical models and is a promising modality for the treatment of cancer.