B6-hPD1/hOX40

Strain Name：B6/JGpt-*Pdcd1*$^{em1Cin(hPDCD1)}$*Tnfrsf4*$^{em1Cin(hTNFRSF4)}$/Gpt

Strain Type：Knock-in

Strain Number：T003532

Background：C57BL6/JGpt

Description

PDCD1（Programmed cell death protein 1，PD1），is a member of the extended CD28/CTLA-4 family of T cell regulators. Several lines of evidence suggest that PD-1 and its ligands negatively regulate immune responses.

Tumor necrosis factor receptor superfamily, member 4 (TNFRSF4), also known as CD134 or OX40 receptor, is a member of receptors of the TNFR-superfamily.

Although antagonist PD-1 or agonistic OX40 antibodies can promote the rejection of some murine tumors, however, poorly immunogenic tumors such as ID8 ovarian cancer does not respond to antibody therapy alone. Researchers showed that combined anti-PD-1/OX40 mAb treatment significantly suppressed ID8 tumor growth. Combination strategies to help increase antigen release and T cell activation, promote T cell activation and homing, improve the tumor immune microenvironment, can help understand the tumor immune-evasive mechanisms and maximize efficacy to ultimately benefit the majority of patients. Because the PD1/L1 checkpoint functions at the last step of effector T cell activation, a reasonable approach would be use PD1/L1 inhibitors as the backbone of this combination.

Murine OX40 was replaced with human OX40 by CRISPR/Cas9 technology on B6/c-hPD1 background. These mice are ideal models to be used to evaluate the efficacy and safety of human PD1 inhibitors, OX40 agonists and their combination.

Application

1、Screening of human OX40 agonists or human PD1 inhibitors

2、Evaluation of efficacy and safety of human OX40 agonist combine with human PD1 inhibitor

3、Research on immune system

Data support

1. PD1 and OX40 protein expression analysis

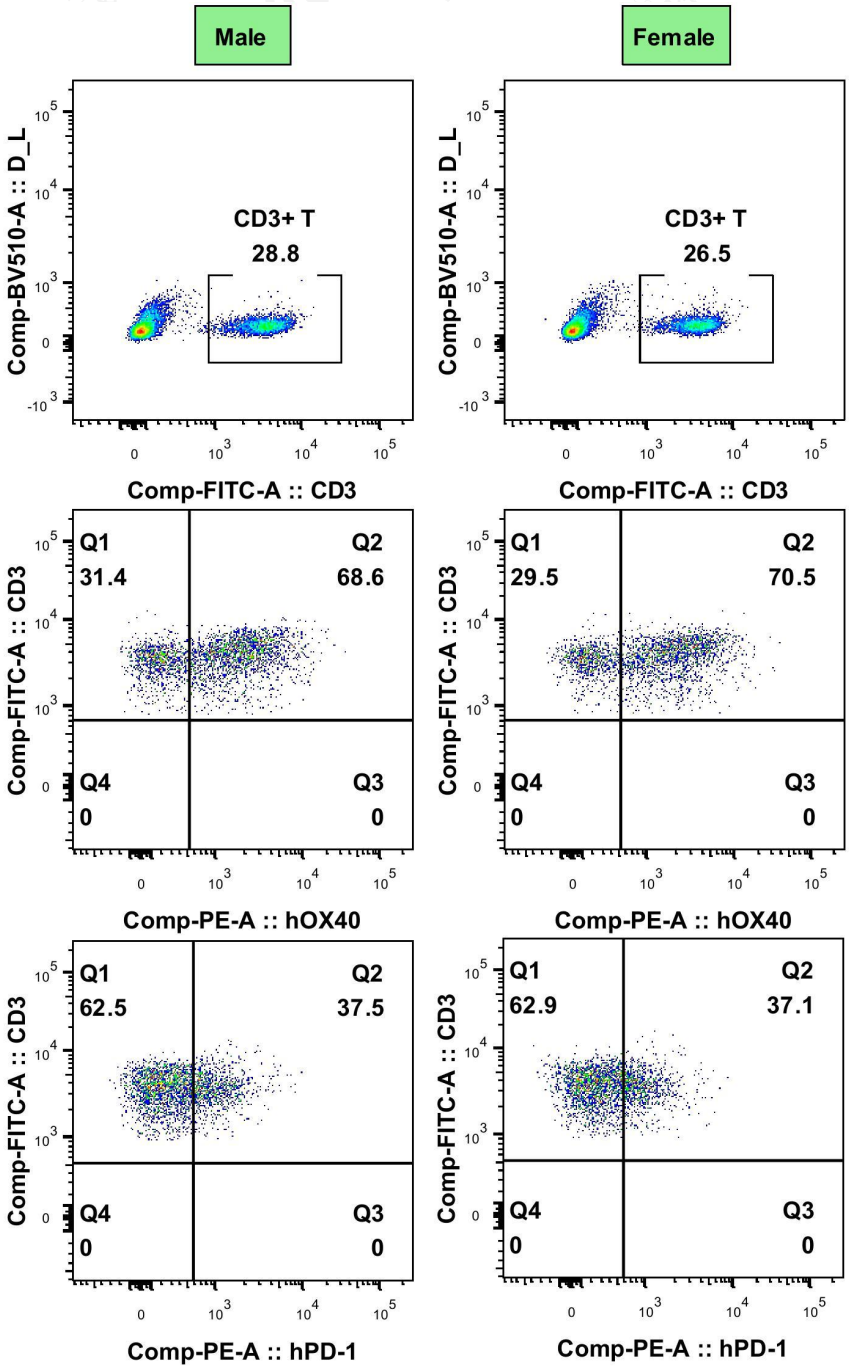
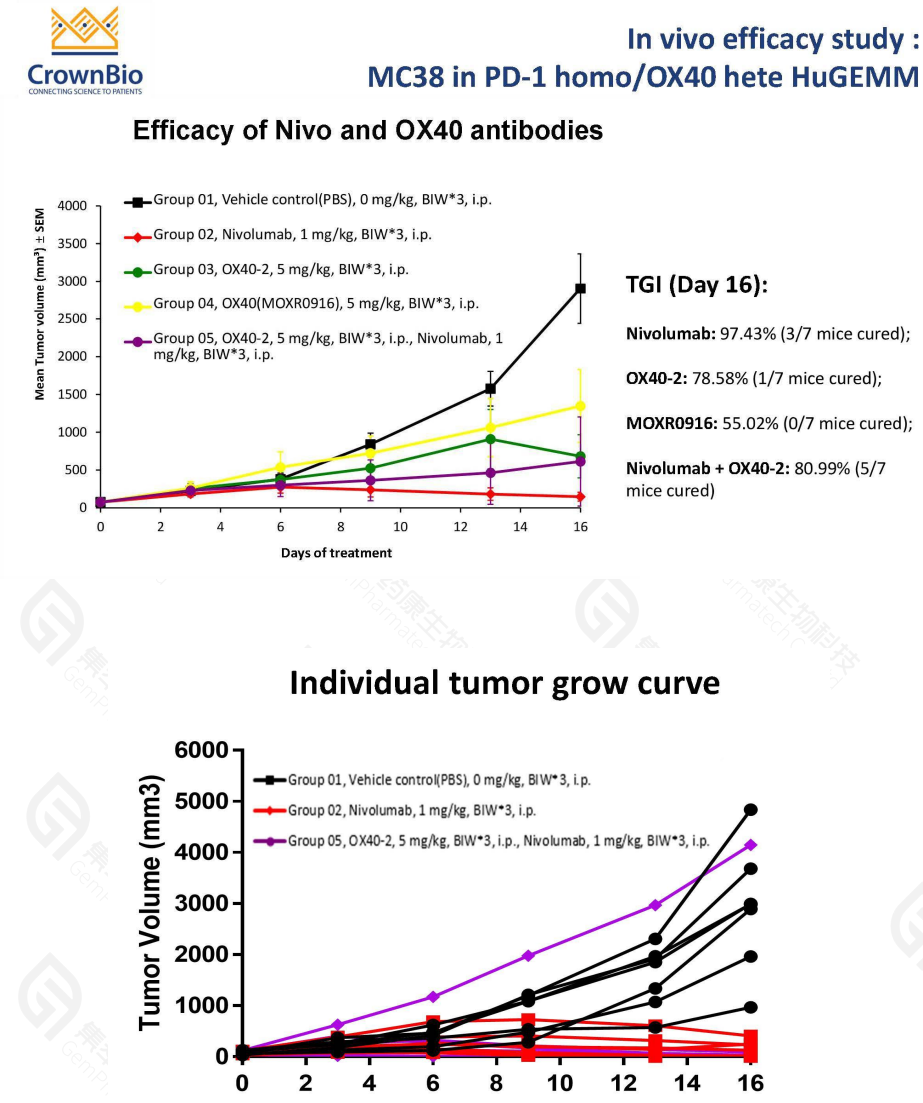
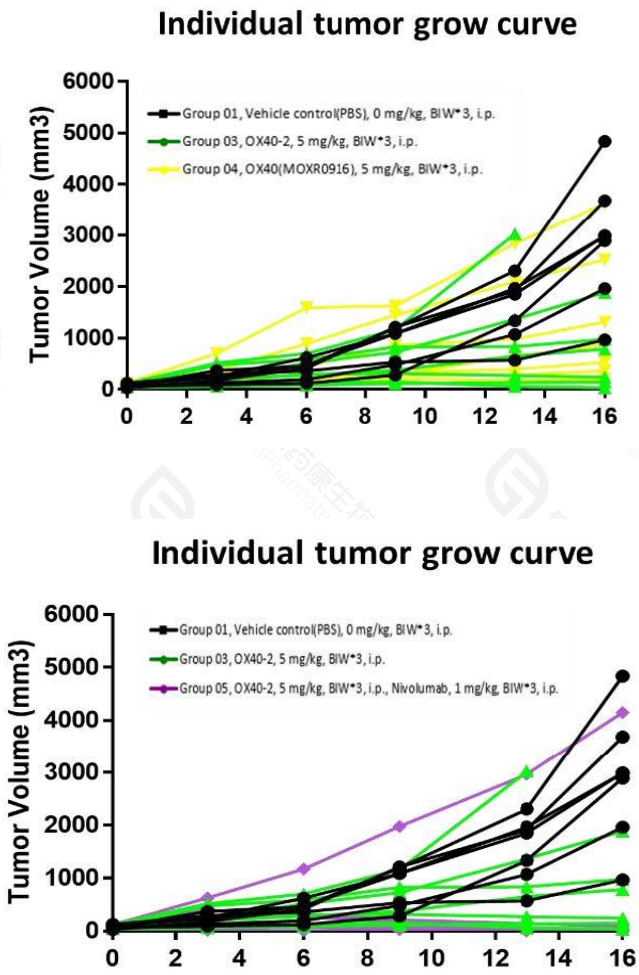


Figure 1. hPD1/hOX40 double humanized mice with B6 background can successfully express humanized PD1 and OX40 protein

2. Anti-tumor Efficacy Test (MC38, Data from CrownBio)





The efficacy of PDCD1 inhibitor (nivolumab), OX40 agonist1 (moxr0916) and OX40 agonist2 (OX40-2) on MC38 transplanted tumor in hpd1/OX40 mice was evaluated. PD-1 homo/OX40 hete mice were inoculated with MC38 cell line. The tumor growth inhibition effect of nivolumab combined with OX40-2 was significantly better than that of nivolumab or ox40-2 alone. The tumor of 5/7 mice was completely cleared.

Reference

1. Linch SN, McNamara MJ, Redmond WL: OX40 Agonists and Combination Immunotherapy: Putting the Pedal to the Metal. Frontiers in Oncology 2015, 5:34.