B6-hPD1/hPDL1/hTIGIT

Strain Name：B6/JGpt-*Pdcd1*$^{em1Cin(hPDCD1)}$*Cd274*$^{em1Cin(hCD274)}$ *Tigit*$^{em1Cin(hTIGIT)}$/Gpt

Strain Type：Knock-in

Strain ID：T006873

Background：C57BL/6JGpt

Description

PDCD1(Programmed cell death protein 1，PD1)，a member of the extended CD28/CTLA-4 family of T cell regulators，is involved in the regulation of T-cell function during immunity and tolerance. PD1 has two ligands, PD-L1 and PD-L2, which are members of the B7 family. PD-L1 is highly expressed in several cancers. Under physiological conditions, the PD-1/PD-L1 interaction is essential in the development of immune tolerance preventing excessive immune cell activity that can lead to tissue destruction and autoimmunity. Blocking PD1/PDL1 signaling pathway with antibodies has become a classic method for tumor immunotherapy[1,2].

TIGIT (T cell Ig and ITIM domain; also called Vsig9,Vstm3, or WUCAM), is an immune receptor present on NK cells. activated T cells, memory T cells, and a subset of regulatory T cells (Tregs). Blockade of TIGIT can reverse the exhaustion of cytotoxic T lymphocyte (CTL)-mediated anti-tumor immunity and inhibit tumor growth in preclinical tumor models [3].

Furthermore, anti-TIGIT displayed combination activity with anti-PD1 and anti-PDL1 in inhibiting tumor growth, promoting complete tumor rejection and significantly increasing mouse survival in the murine CT26 colon carcinoma model as compared to controls and single agents alone. Mice “cured” with anti-TIGIT/anti-PDL1 or anti-TIGIT/anti-PD1 combination treatments were protected from subsequent rechallenges with increasing numbers of tumor cells, suggesting the existence of immunologic memory.

B6-hPD1/hPDL1 mice were mated with B6-hTIGIT to obtain the B6-hPD1/hPDL1/hTIGIT mice. This strain is an ideal model for anti-PD1/PDL1 drug and anti-TIGIT drug combination evaluation and immunotherapy drug development.

Strategy

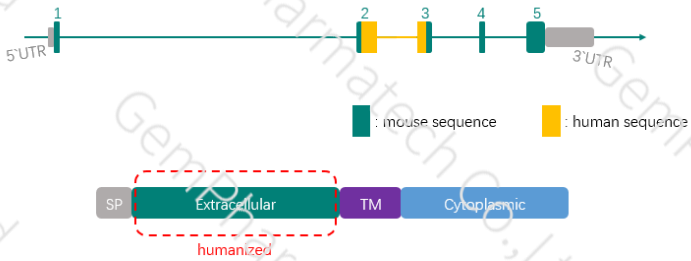

Fig.1 Schematic diagram of PD1 humanization strategy in B6-hPD1/hPDL1/hTIGIT mice.

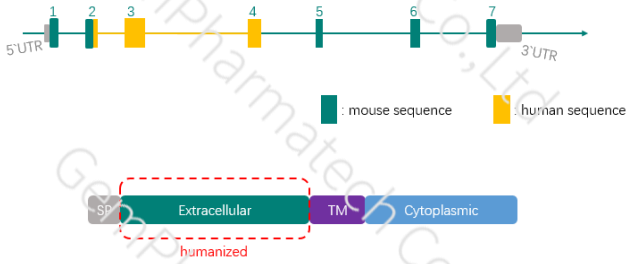

Fig.2 Schematic diagram of PDL1 humanization strategy in B6-hPD1/hPDL1/hTIGIT mice.

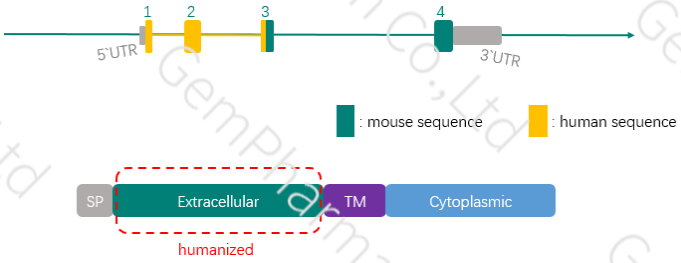

Fig.3 Schematic diagram of TIGIT humanization strategy in B6-hPD1/hPDL1/hTIGIT mice.

Application

1. Screening of human TIGIT inhibitors or human PD1/PDL1 inhibitors
2. Evaluation of efficacy and safety of human TIGIT inhibitors combine with human PD1/PDL1 inhibitor
3. Research on immune system

Data support

1、PD1, PDL1, TIGIT expression level detection

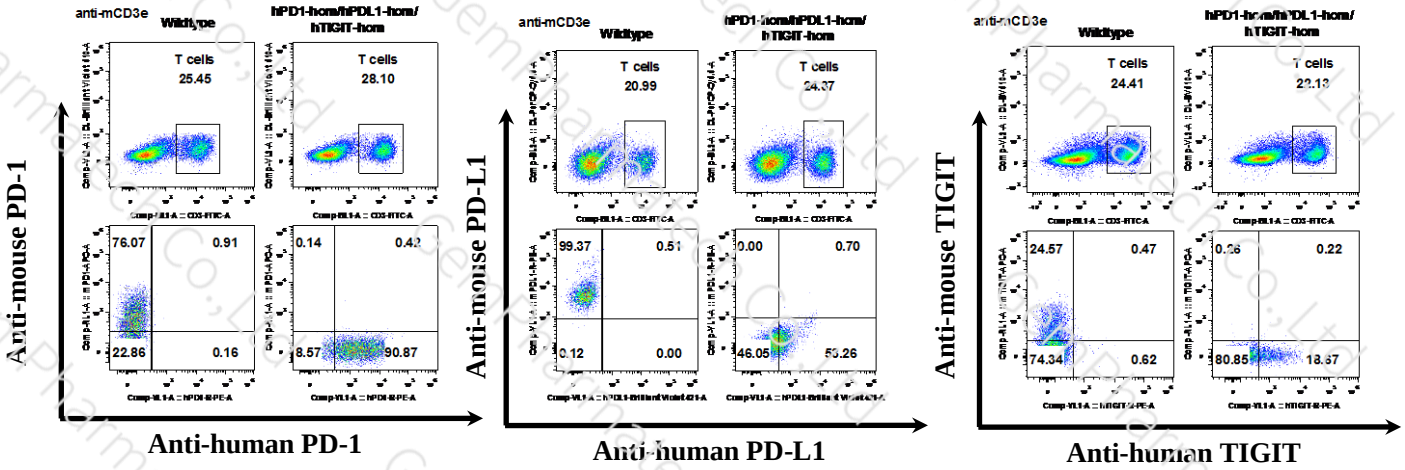

Fig.4 Detection of PDCD1 and TIGIT expression in mice

B6-hPD1/hPDL1/hTIGIT mice can successfully express hPD1、hPDL1 and hTIGIT on the surface of T cells after anti-CD3e treatment.

2、T/B/NK cell ratio dectection

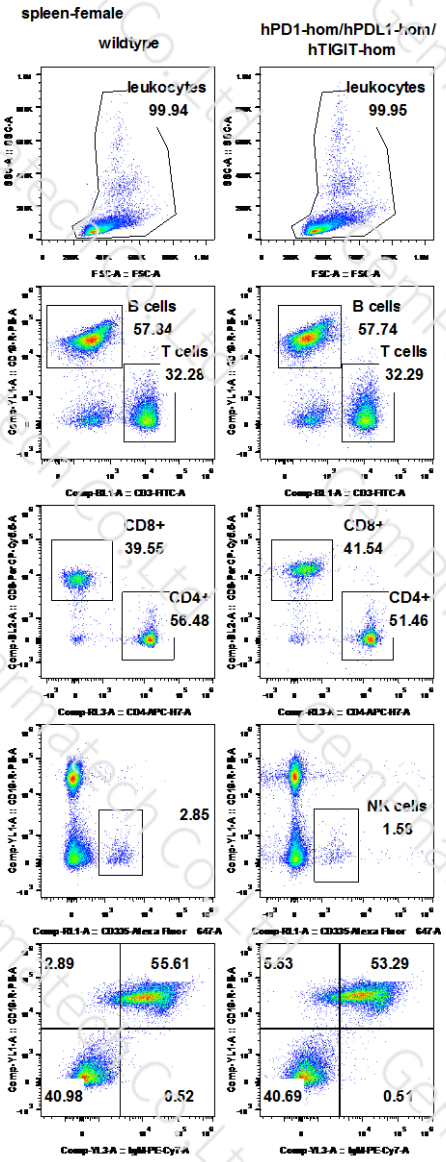

Fig.5 Detection of T/B/NK cells proportion in B6-hPD1/hTIGIT mice

There was no obvious difference of T/B/NK cells proportion between wild-type and homozygote mice.

References

1. Liang, S. C., et al. "Regulation of Pd-1, Pd-L1, and Pd-L2 Expression During Normal and Autoimmune Responses." Eur J Immunol 33 10 (2003): 2706-16.

2. Mamalis, A., M. Garcha, and J. Jagdeo. "Targeting the Pd-1 Pathway: A Promising Future for the Treatment of Melanoma." Arch Dermatol Res 306 6 (2014): 511-9.

3. Joller, Nicole, et al. "Cutting edge: TIGIT has T cell-intrinsic inhibitory functions." *The Journal of Immunology* 186.3 (2011): 1338-1342.