B6-hPD1/PDL1

Strain Name：B6/JGpt-*Pdcd1*$^{em1Cin(hPDCD1)}$*Pdl1*$^{tm1(hPDL1)}$/Gpt

Strain type：Knock-in

Strain number：T004022

Background：C57BL/6JGpt

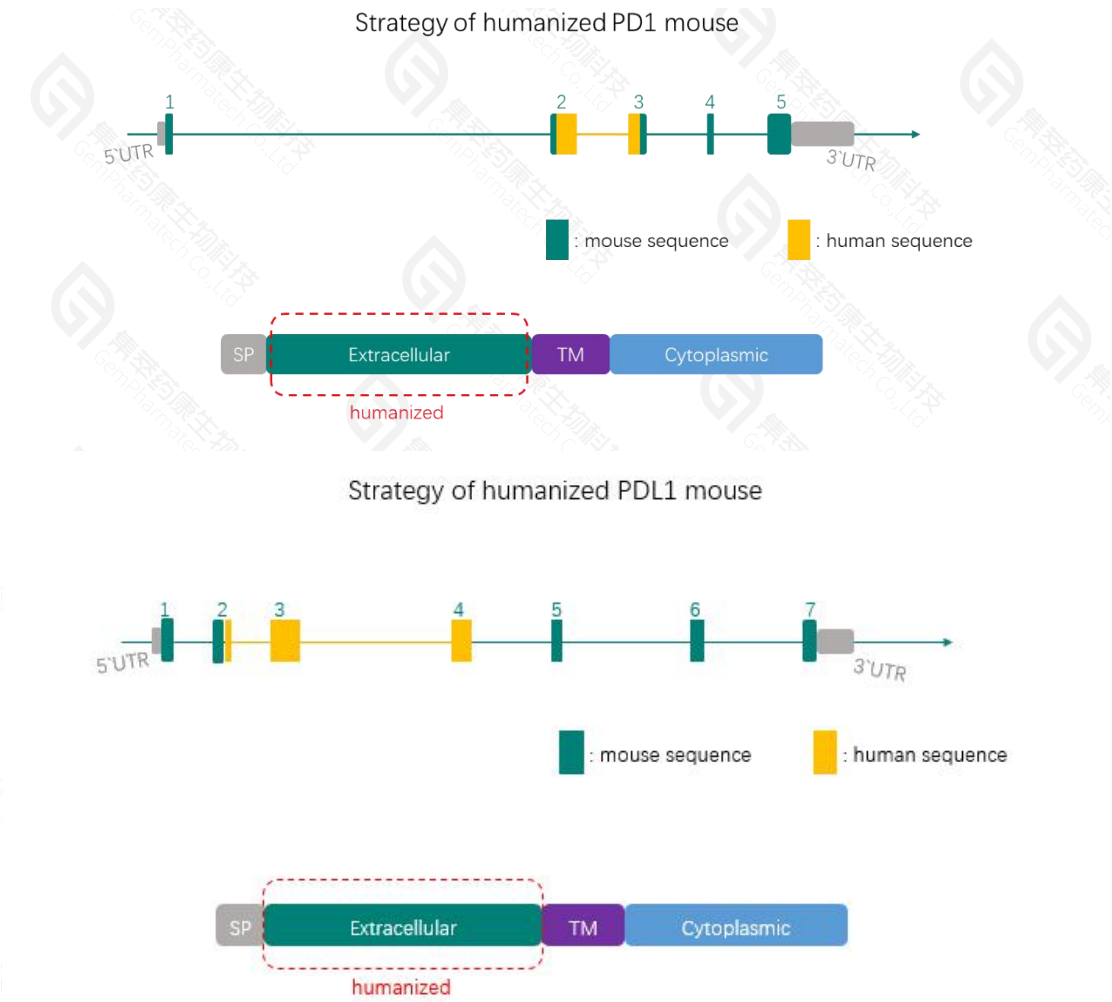
Description

Programmed cell death 1 ligand 1(PDL1),also known as cluster of differentiation 274 (CD274) or B7 homolog 1(B7H1), by *CD274* gene encodes a 40 kDa transmembrane protein [1].Under normal circumstances, the immune system responds to foreign antigens that accumulate in lymph nodes or spleen, promoting the proliferation of antigen-specific T cells. The combination of PD1 PDL1 can transmit inhibitory signals and reduce antigen-specific T cell proliferation[2-3].

A large number of studies have confirmed that the expression of PDL1 on the surface of tumor cells is increased in the tumor microenvironment, and it binds to PD1 on activated T cells, transmitting negative regulatory signals, leading to apoptosis or immune disability of tumor antigen-specific T cells, thereby suppressing immune response, inducing the escape of tumor cells. Blocking PD1/PDL1 signaling pathway with antibodies has become a classic method for tumor immunotherapy[1,2]. The FDA has approved 5 drugs for the PD1/PDL1 pathway.

GemPharmatech use gene editing technology to replace the PDL1 extracellular domain of B6 mice for the corresponding fragment of human, and developed B6-hPDL1 humanized model independently. By humanizing the extracellular antibody binding sites while ensuring endogenous intracellular signaling transductions, this study generated a PDL1 humanized mouse strain which will be useful in developing anti-PDL1 immunotherapies. Mice expressing human PDL1 were propagated with B6-hPD1 to obtain the B6-hPD1/hPDL1 mice. The B6-hPD1/hPDL1 mice can be used for the evaluation of hPD1 inhibitors, hPDL1 inhibitors, and a combination of the two.

Strategy

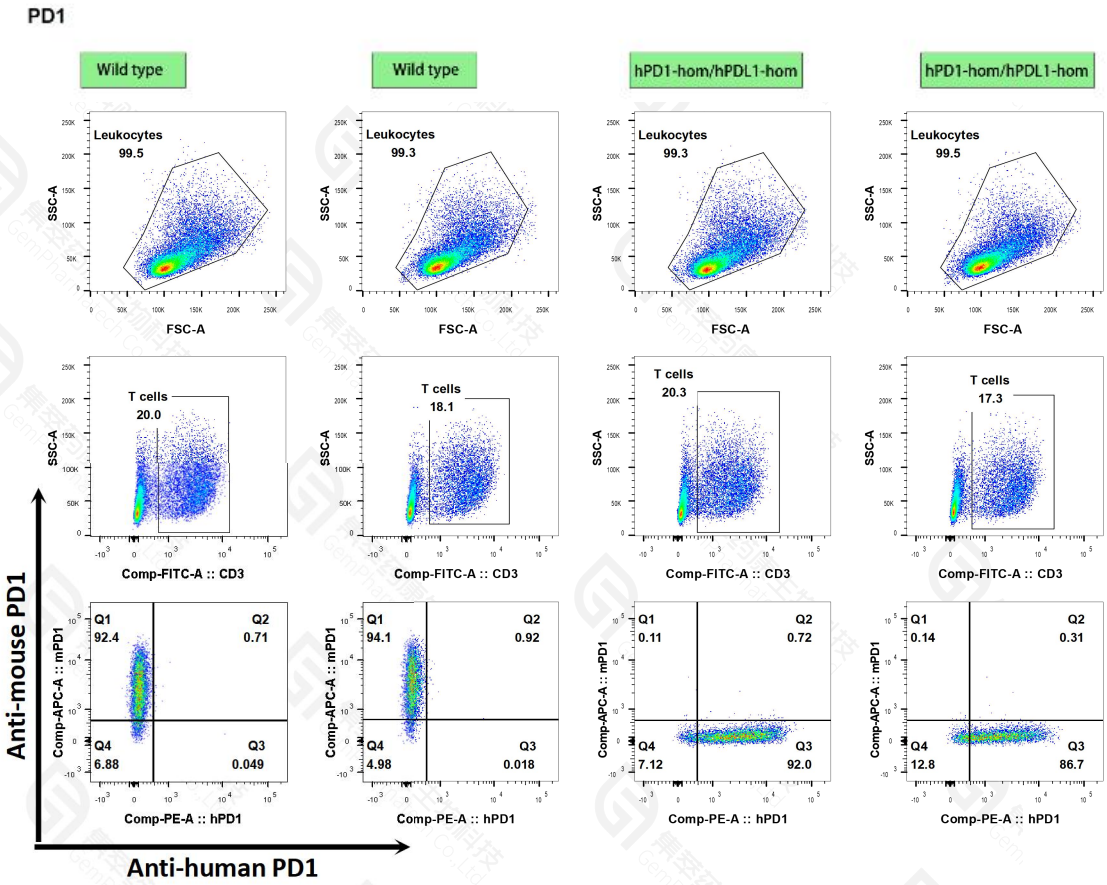


Application

1. Efficacy evaluation of human PD1 or PDL1 inhibitors.
2. Evaluation of efficacy and safety of human PDL1 inhibitor and human PD1 inhibitor combined.
3. Anticancer Drug Research and Development
4. Research on autoimmune diseases

Data support

1. Detection of PD1 and PDL1 expression



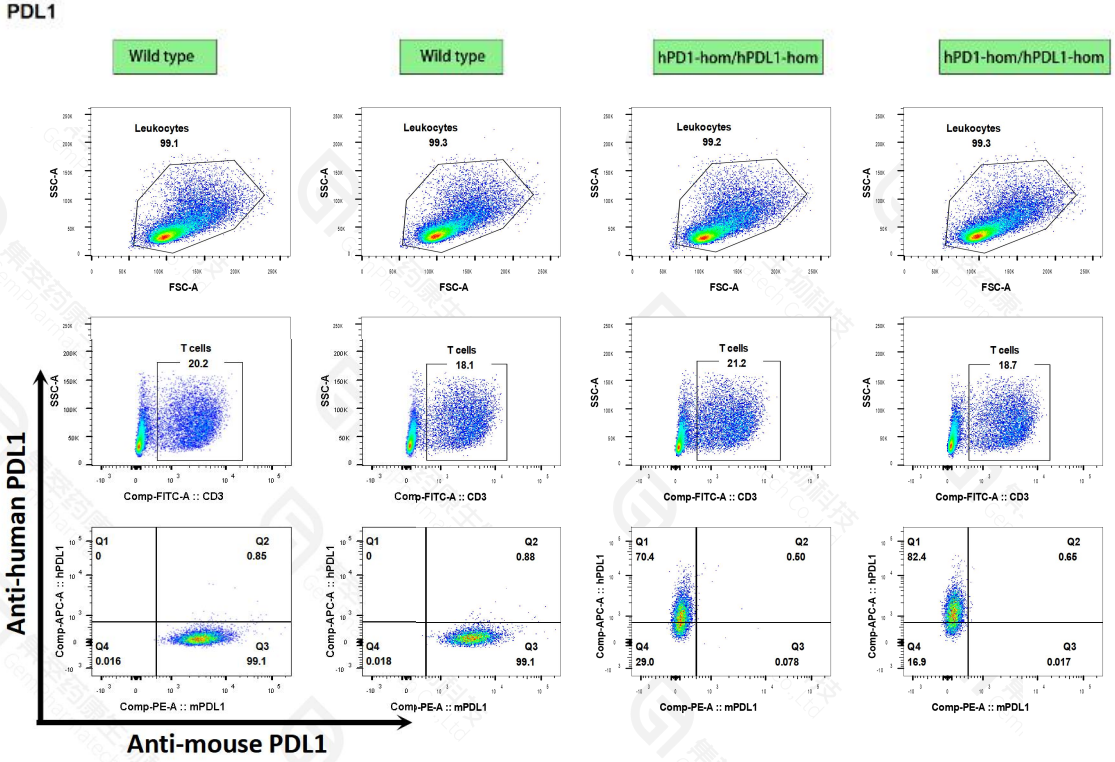


Fig.3 Detection of PD1 and PDL1 expression in B6-hPD1/hPDL1 mice.

After anti-CD3e stimulated, B6-hPD1/hPDL1 homozygous mice expressed hPD1 and hPDL1 on both T and B cell surfaces, the proportions were similar to the wild-type mice.

2. T/B/NK cell ratio assay

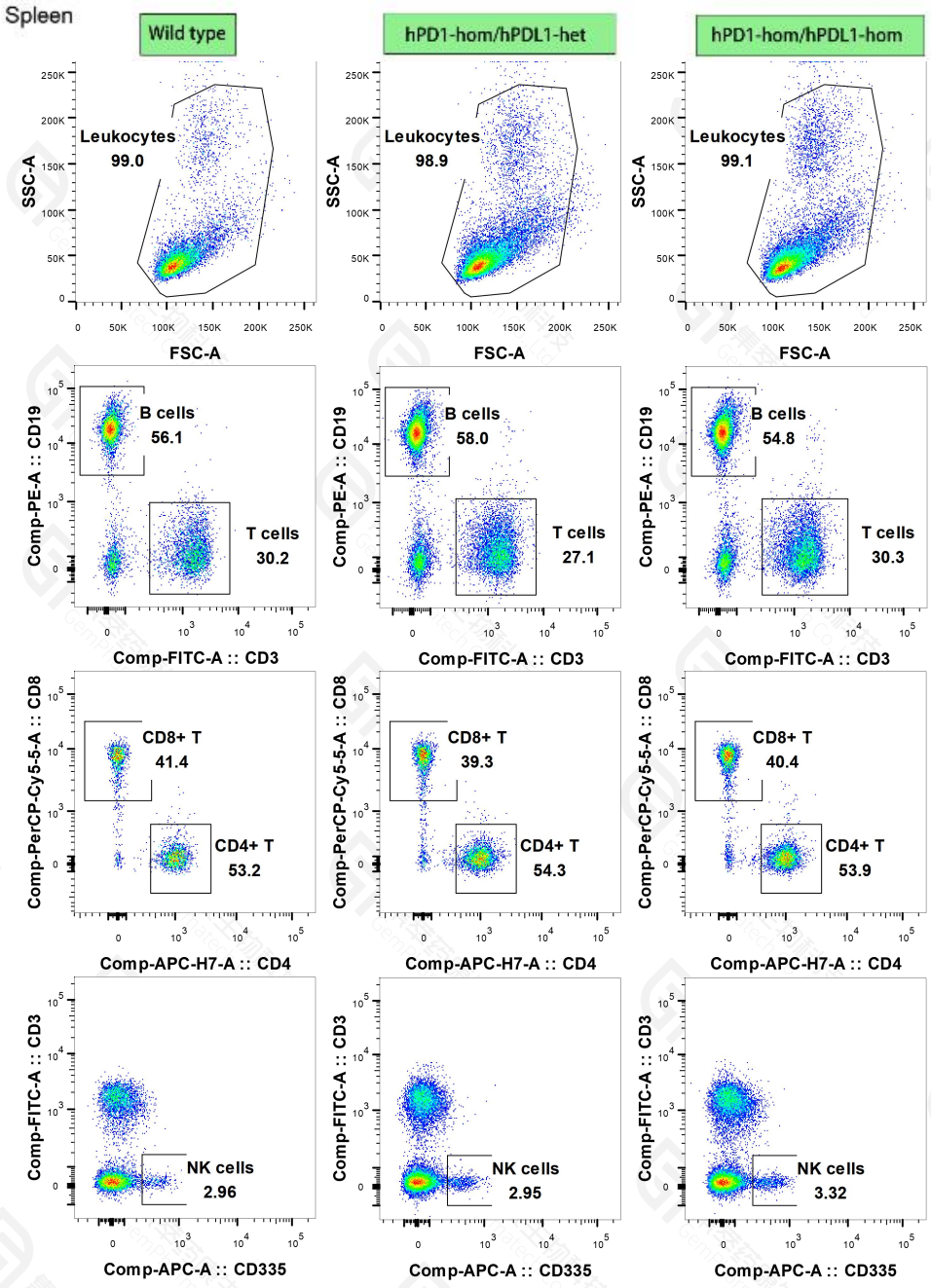


Fig.4 Detection T/B/NK cell ratio in B6-hPD1/hPDL1 mice.

There were no difference of T/B/NK cells proportions in wild-type, heterozygote 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. Xu, W., et al. "The Upregulation of Immune Checkpoint Ligand Pd-L1 in Tumour Microenvironment." *Scand J Immunol* 80 1 (2014): 71-2.