B6-hPD1/hTIM3

Strain Name: B6/JGpt - *Pdcd1*$^{em1Cin(hPDCD1)}$*Havcr2*$^{tm1(hHAVCR2)}$/ Gpt

Strain Type: Knock-in

Strain ID: T009737

Background: C57BL/6JGpt

Description

Tim-3 （T cell immunoglobulin domain and mucin domain-3）is an immune checkpoint receptor that limiting the duration and magnitude of Th1 (CD4+ T helper 1) and Tc1 (CD8+ T cytotoxic 1) T-cell responses. Dysregulation of Tim-3 expression has been associated with autoimmune diseases, cancer, etc. The interaction between galectin-9 and Tim-3 triggers cell death in effector Th1 cells, thereby dampening tissue inflammation leading to inhibition of autoimmune disease. And Tim-3 also plays as a key immune checkpoint in tumor-induced immune suppression, which may cooperate with the PD-1 pathway to promote the development of a severe dysfunctional phenotype in CD8+ T cells in cancer [1-5]. Currently, some TIM-3 antagonistic monoclonal antibodies, such as LY-3321367 and TSR-022, are in early-phase clinical development.

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 and inducing the escape of tumor cells. Blocking PD1/PDL1 signaling pathway with antibodies has become a standard method for tumor immunotherapy [7,8]. Another preclinical study showed that combination of anti-TIM-3 and anti-PD-1/PD-L1 monoclonal antibodies significantly suppressed tumor growth [6].

GemPharmatech develop the B6-hPD1/hTIM3 humanized model by breeding B6-hPD1 mice with B6-hTIM3 mice.The PD1/TIM3 humanization mice are ideal models to be used to evaluate the efficacy and safety of human PD1 inhibitors, anti-TIM3 and their combination.

Strategy

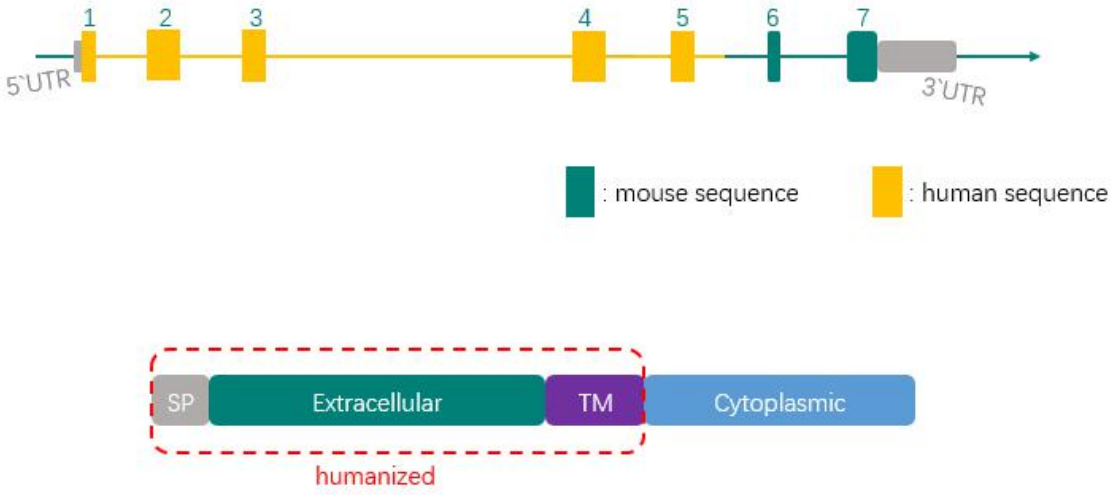

Fig 1. Schematic diagram of TIM3 humanization strategy in B6-hPD1/hTIM3 mice.

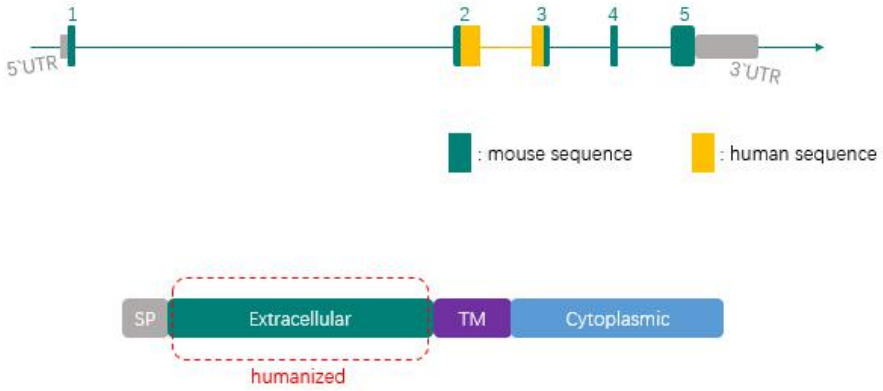

Fig 2. Schematic diagram of PD1 humanization strategy in B6-hPD1/hTIM3 mice.

Application

1. Efficacy evaluation of human TIM3 inhibitor

2. Toxicological evaluation of human TIM3 inhibitor

3. Research on autoimmune diseases

Data support

1. TIM3 protein expression analysis

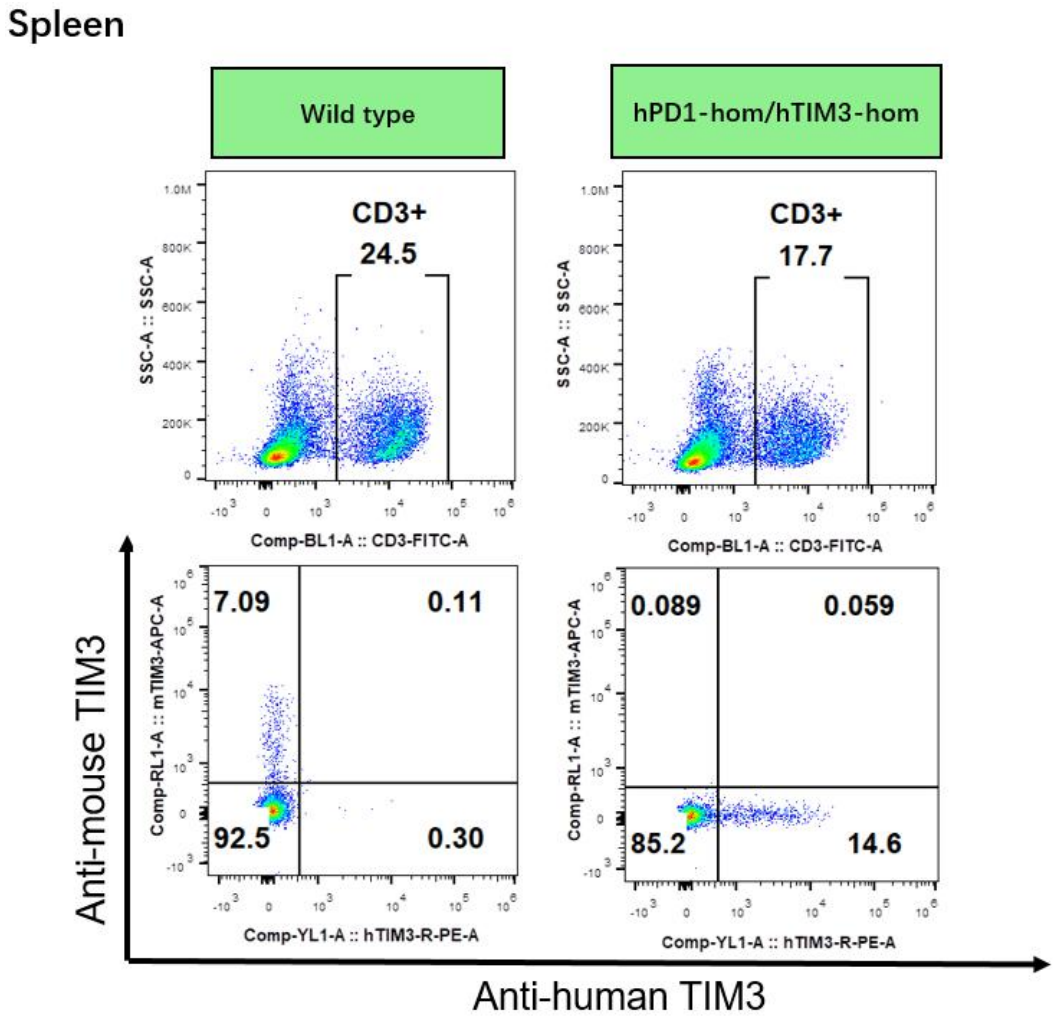

Fig 3. Detection of TIM3 expression in B6-hPD1/hTIM3 mice. After anti-CD3e stimulation, B6-hPD1/hTIM3 mice successfully express human TIM3 on the surface of T cells.

2. T/B/NK cell population assay

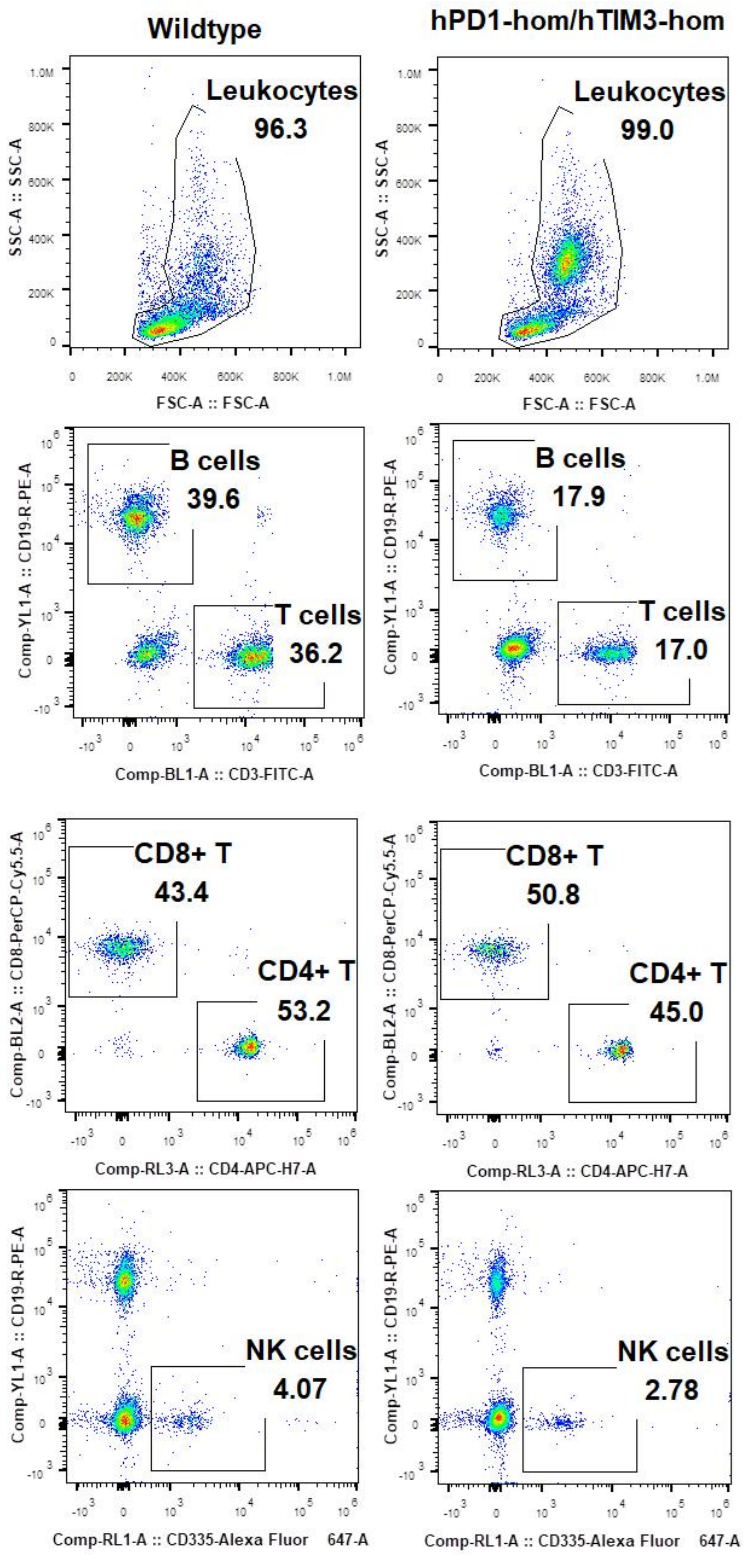

Fig 4. Detection of T/B/NK cells proportion in B6-hPD1/hTIM3 mice. There was no obvious difference of T/B/NK cells proportion between wild-type and B6-hPD1/hTIM3 mice.

References

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3. Anderson, Ana C., and David E. Anderson. "TIM-3 in autoimmunity." *Current opinion in immunology 18.6 (2006): 665-669.*

4. Sakuishi, Kaori, et al. "Emerging Tim-3 functions in antimicrobial and tumor immunity." *Trends in immunology 32.8 (2011): 345-349.*

5. Romero, Diana. "PD- 1 says goodbye, TIM- 3 says hello." *Nature Reviews Clinical Oncology 13.4 (2016): 202-203.*

6. Ngiow S F, von Scheidt B, Akiba H, et al. Anti-TIM3 antibody promotes T cell IFN-γ–mediated antitumor immunity and suppresses established tumors[J]. *Cancer research, 2011*.