BALB/c-hPD1

Strain Name: BALB/cJGpt-Pdcd1 $^{em1Cin(hPDCD1)}$ /Gpt

Strain Type: Knock-in

Strain ID: T002726

Background: BALB/cJGpt

Application

1. Efficacy evaluation of human PD1 inhibitors
2. Assessment of human PD1 inhibitor safety
3. Research on immune system

Description

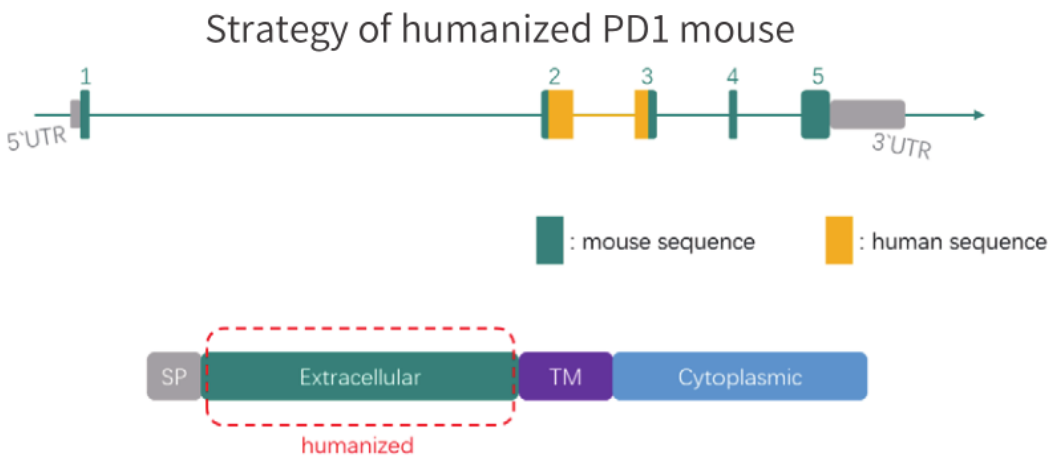
PDCD1（Programmed cell death protein 1，PD1），a member of the extended CD28/CTLA-4 family of T cell regulators，is involved in the regulation of T-cell function during immunity and tolerance.

PD1 has two ligands, PD-L1 and PD-L2, which are members of the B7 family. PD-L1 is highly expressed in several cancers. The expression of PDL1 has been correlated with the progression and poor prognosis of certain types of human malignancies. Tumour-induced PDL1 appears to utilize multiple mechanisms to facilitate the evasion of host immune surveillance, including the promotion of T cell anergy, exhaustion, unresponsiveness and apoptosis, inducing the expansion of Tregs as well as enhancing tumour-intrinsic resistance to killing and apoptosis. PD1 inhibitors, as a new class of drugs that block PD1, activate the immune system to attack tumors and are used to treat certain types of cancer.

BALB/c background can serve as a host and transplant almost all popular syngeneic murine tumor cell lines that currently available (e.g., CT26, 4T1, H22, Renca). Additionally, different from immune deficient models such as NCG and NSG, this strain has full functional immune system which could mimicking some human immune reactions. Therefore, this BALB/c-hPD1 strain will be a good model for anti-tumor drug evaluation and efficacy test.

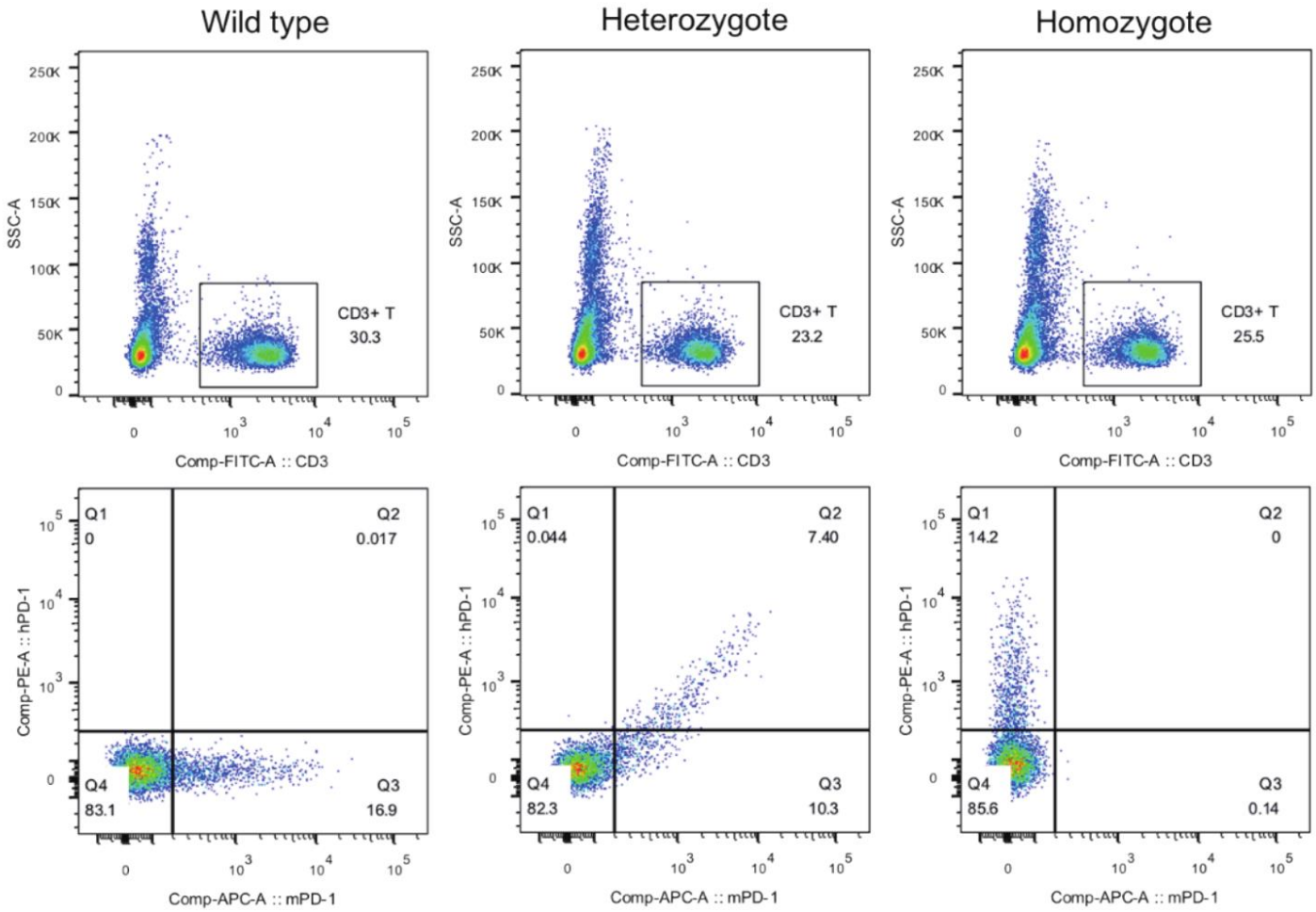
GemPharmatech use gene editing technology to developed BALB/c-hPD1 humanized model independently. The coding sequence of extracellular domain of PD1 is replaced with human counterpart on BALB/c background. Intracellular region of murine PD1 was completely retained and normal intracellular signal transduction was guaranteed. hPD1 expression in homozygous BALB/c-hPD1 mice were similar to mPD1 expression in wild type. These mice are ideal models for anti-PD1 drug evaluation and immunotherapy drug development.

Strategy



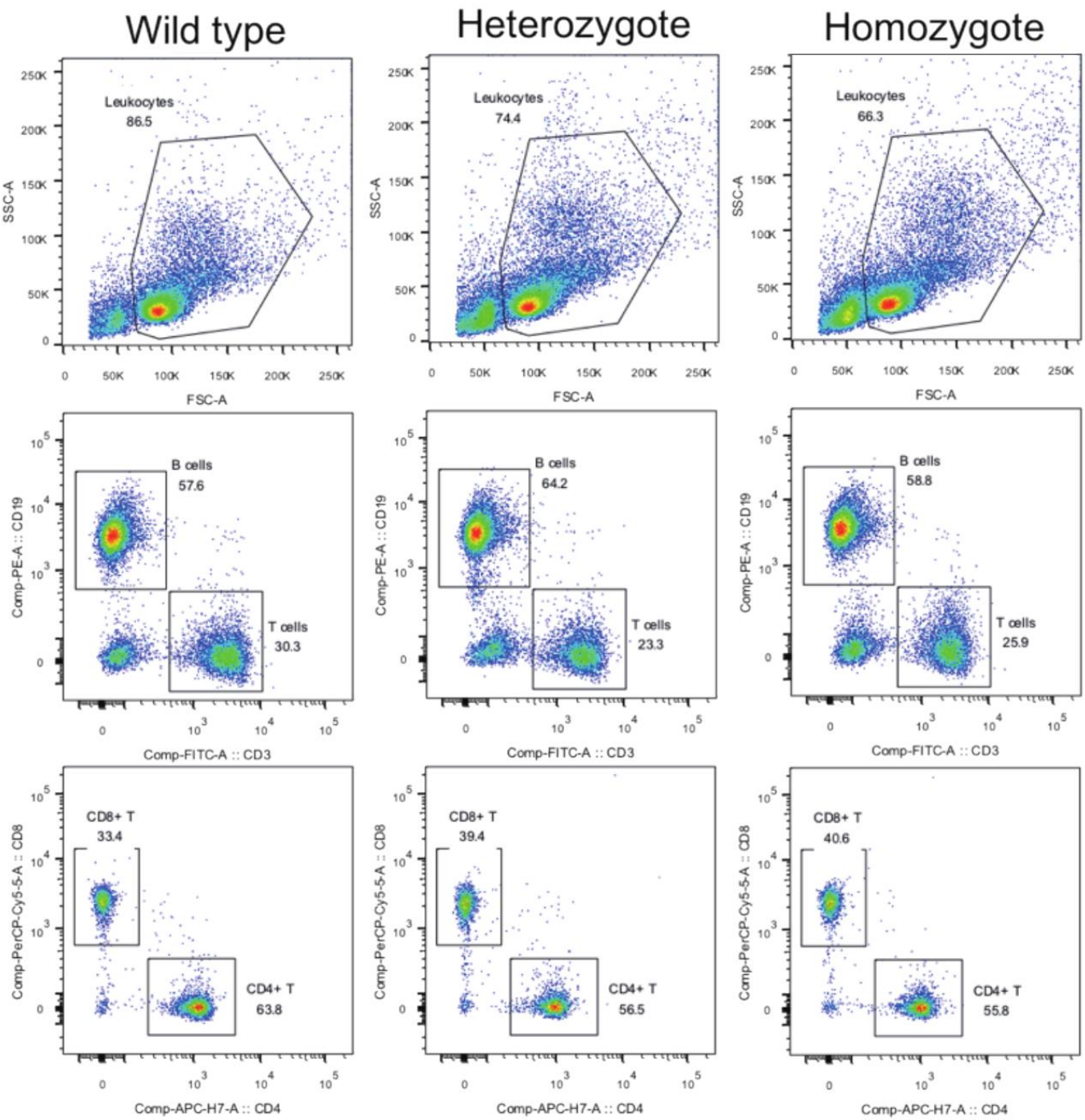
Data support

Detection of PD1 expression



Detection of hPD1 expression on BALB/c-hPD1 mice.hPD1 is expressed at comparable level in homo as mPD-1 expressing the wild type mice

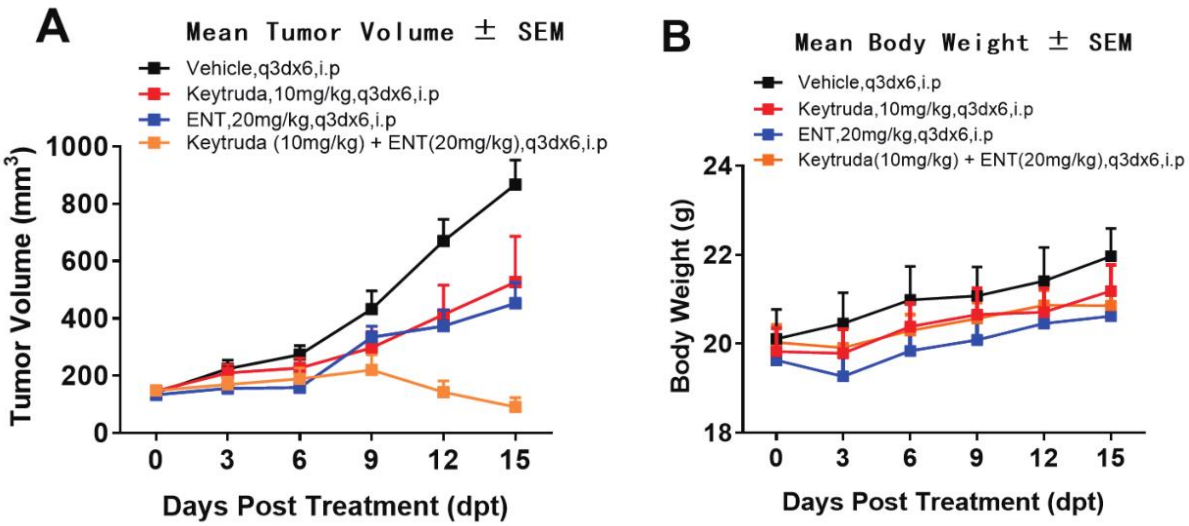
T/B/NK cell ratio assay



The proportion of T and B cells in spleen of BALB/c-hPD1 mice is similar between wild type, heterozygous and homozygous, and there was no significant difference in CD4+/CD8+ T cells.

In vivo efficacy test

Anti-hPD1 antibody KEYTRUDA® alone and KEYTRUDA® combined with Ent for tumor suppressor efficacyafter subcutaneous inoculation of CT26 tumor cell line in BALB/c-hPD1 mouse model



In vivo combination drug test on BALB/c-hPD1 mice

KEYTRUDA® or Entinostat inhibits tumor growth when used alone (TGI indicated 45.3% and 44.6%, respectively). Particularly, in Keytruda/ENT combo group, tumor size was significantly smaller comparing with single drug treatment(TGI=89.5%)(A)Mean tumor