

NCG-HLA-A2.1

Strain Name: NOD/ShiLtJGpt-*Prkdc*^{em26Cd52}*Il2rg*^{em26Cd22}*H2-K1*^{emCin(HLA-A2.1)}/Gpt

Strain Type: Knock-in

Strain ID: T003278

Background: NOD/ShiLtJGpt

Description

HLA-A is a group of human leukocyte antigens (HLA) and coded by *HLA-A* gene. HLA is a major histocompatibility complex (MHC) antigen specific to humans. HLA-A is one of three major types of human MHC class I cell surface receptors which are heterodimer, and is composed of a heavy α chain and smaller β chain. The α chain is encoded by a variant *HLA-A* gene, which comprises the variable regions $\alpha 1$, $\alpha 2$ and the constant $\alpha 3$, transmembrane and intracellular regions. MHC I is expressed on all nucleated cell surfaces and it is responsible for antigen presentation, participation in CD8⁺ T cell maturation and CTL recognition [1]. Studies have confirmed that HLA-A2.1 restricted CTL response is stronger in HLA-A2.1/H2-Kb transgenic model which has a chimeric class I molecule consisting of the human $\alpha 1$ and $\alpha 2$ domains ligated to the murine $\alpha 3$, transmembrane and cytoplasmic H2-Kb domains than that in the whole humanized HLA-A2.1 transgenic mice. The studies indicated murine $\alpha 3$ domain is critical for CD8 binding in a species specific way [2-7].

GemPharmatech created an immune-compromised non-obese diabetic/SCID/IL2rg^{null} strain (NCG) with expression *HLA-A*02:01*[8] gene which has a great influence on the maturation process of human T cells. NCG background makes it possible to accept human hematopoietic stem cell transplantation. Human $\alpha 1$ and $\alpha 2$ can present antigens through the human HLA-A2.1 antigen binding region. Because the interaction between $\alpha 3$ and CD8⁺ T cell is species-specific, so the humanized $\alpha 3$ region which interacts with human CD8⁺ would promote T cell mature and CTL recognition. NCG-HLA-A2.1 is an ideal model for investigation of human immune responses against pathogens and the development of therapeutic strategies against human diseases.

Highlights

1. 100% NCG (NOD/ShiLtJGpt-*Prkdc*^{em26Cd52}*Il2R γ* ^{em26Cd22}/Gpt) background
2. The humanized MHC I molecule is a chimeric protein composed of mouse MHC I and human HLA (Type A*02:01);
3. Facilitate humanization of immune system, especially the maturation of CD8⁺ T cells

Application

1. Vaccine research

2. Hematopoietic Stem Cell Transplantation
3. Establish the humanized immune system
4. Immune system research

Data support

1. HLA Protein expression analysis

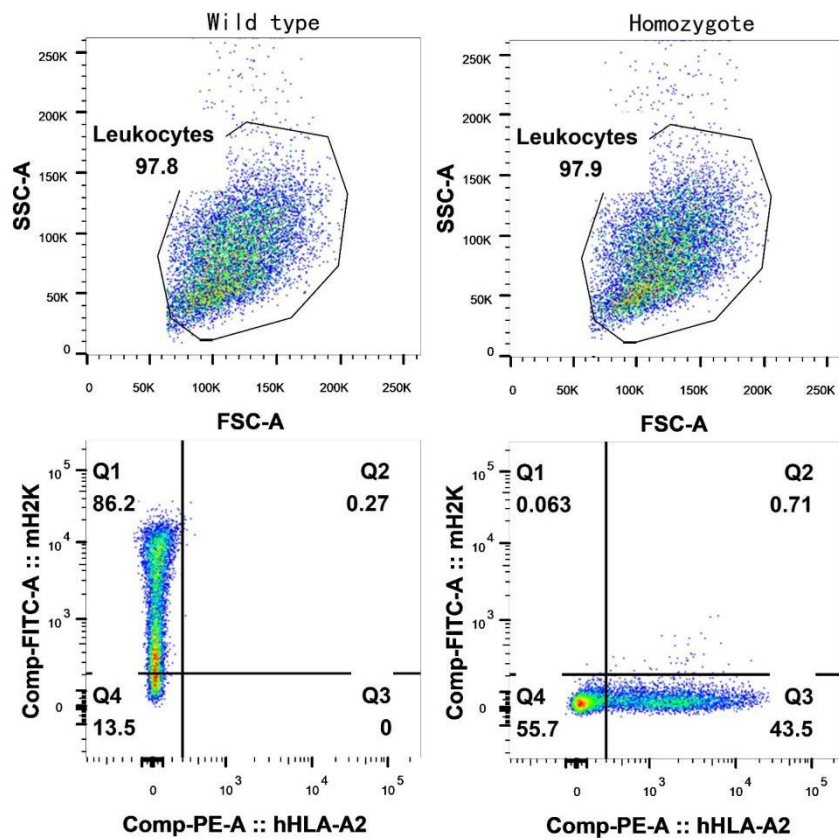


Fig.1 Detection of HLA expression in NCG-HLA-A2.1 mice.

HLA could be detected in the humanized homozygote mouse, only H2K in mouse spleen cells was detected in wild type mice.

2. The T/B/NK cells quantitation

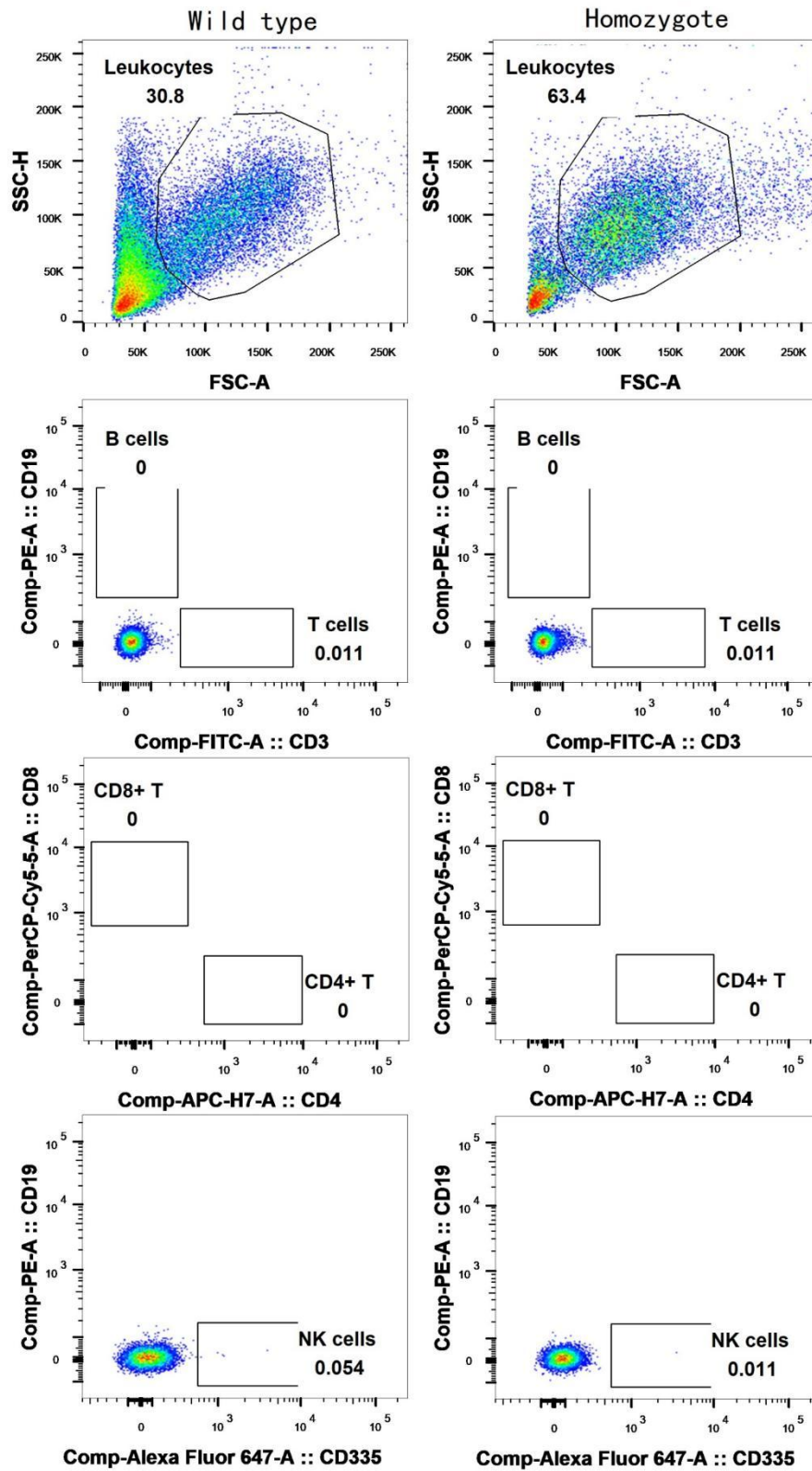


Fig.2 Detection of T/B/NK cells proportion in NCG-HLA-A2.1 mice.

There were almost no CD3⁺T (< 0.05%), CD19⁺B (< 0.1%), NK (< 0.1%) cells and

CD4⁺/CD8⁺ T cells in peripheral blood of HLA humanized mice, and the results were the same as wild type mice.

3. Anti-tumor efficacy test

Tumor efficacy of Ab-1 antibody was tested after subcutaneous inoculation of Raji-PBMC mixed cells in NCG-HLA-A2.1 mouse model

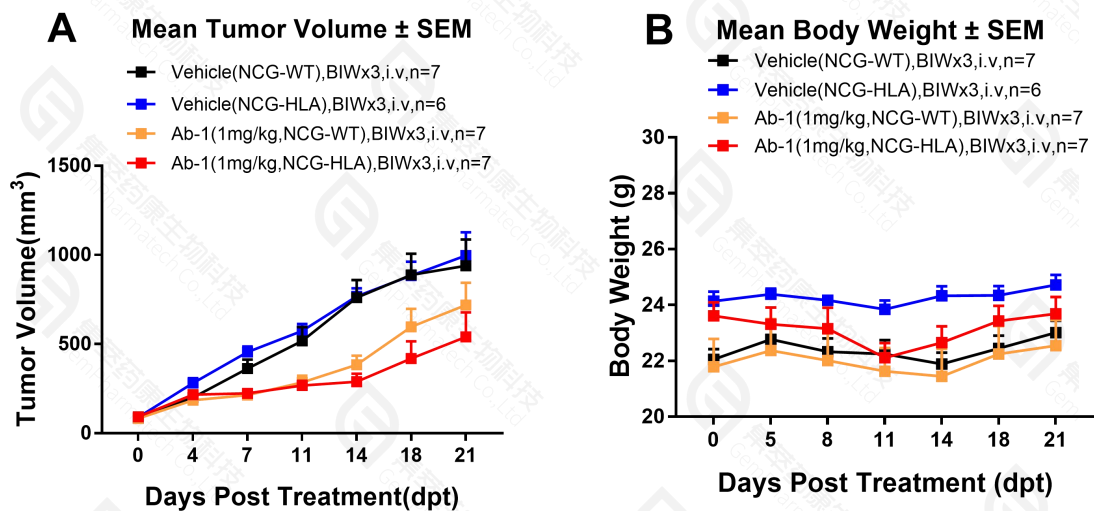


Fig.3 In vivo efficacy test based on NCG-HLA-A2.1 mice.

The logarithmic growth phase lymphoma Raji and HLA match PBMC cells were inoculated subcutaneously into NCG-HLA-A2.1 mice(6-8 weeks) and NCG, mice were randomly divided into 4 groups when the tumor average volume was about 70mm³. Each group was treated with Vehicle (black, NCG, n=7), Vehicle (blue, NCG-HLA-A2.1, n=6), Ab-1 (yellow, NCG, n=7) or Ab-1 (red, NCG-HLA-A2.1, n=7) twice a week for 6 times. The results showed that there was no difference between NCG and NCG-HLA-A2.1 mice on tumor growth curve, and Ab-1 antibody could inhibit tumor growth. Ab-1 (yellow, NCG) group TGI= 15.6%, Ab-1 (red, NCG-HLA) group TGI = 47.0%. The results demonstrate that NCG-HLA-A2.1 is an ideal model for investigation of human immune responses against tumor or other human diseases. (A) Tumor average volume ± SEM, (B) Mice average weight ± SEM. (Data from third-party)

References

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