huHSC-NCG (CH)

Strain name： huCD34+HSC-NOD/ShiLtJGpt-*Prkdc*^{em26Cd52}*Il2rg*^{em26Cd22}/Gpt(CH)
Strain type： Knock out
Strain number： T037620
Background： NOD/ShiLtJGpt

Description

NCG (NOD/ShiLtJGpt-*Prkdc*^{em26Cd52}*Il2rg*^{em26Cd22}/Gpt) is a severe immunodeficient strain obtained by knocking out the Prkdc (Protein kinase, DNA activated, catalytic polypeptide) and Il2rg (Common gamma chain receptor) genes in NOD/ShiltJGpt mice using gene editing techniques. The NOD/ShiltJGpt genetic background makes this strain naturally immunodeficient, e.g., complement system, macrophage defects, and the high affinity of this background Sirpα for human CD47 makes NOD/ShiltJGpt more suitable than other strains for colonization of human-derived grafts (e.g., tumor and human-derived cells). Prkdc gene loss of function results in V(D)J recombination does not occur normally, resulting in the failure of T and B cells to develop and mature.IL2RG is a common subunit of multiple interleukin cytokine receptors, and inactivation of IL2RG results in the absence of six different cytokine signaling pathways, resulting in NK cell defects. Therefore, NCG is one of the most complete mouse models of immune system deficiency to date, and is well suited for human derived tumor cell transplantation (CDX), human derived tumor tissue transplantation (PDX), human peripheral blood mononuclear cell (PBMC) and human derived hematopoietic stem cells (HSC). NCG has a long survival period (>89 weeks) and facilitates long-term transplantation and pharmacodynamic evaluation.

Application

1、Human-derived tumor cells, tumor tissue transplantation (CDX, PDX) ;
2、Pharmacodynamic evaluation (small molecule, large molecule, combination drug) ;
3、Human cancer models ;
4、Stem cell research.

Immune Reconstruction

Immune system humanized mice are mouse models with human immune system obtained by transplanting human hematopoietic cells, lymphocytes or tissues in severely immunodeficient mice (e.g. NCG), including huPBMC-NCG and huHSC-NCG mice. Immune system humanized mice combined with CDX or PDX molds can be used to study tumor growth in the human immune system environment, evaluate anti-tumor treatment options, and in particular, aid in the development of new drugs based on immunotherapy.

1. huHSC-NCG

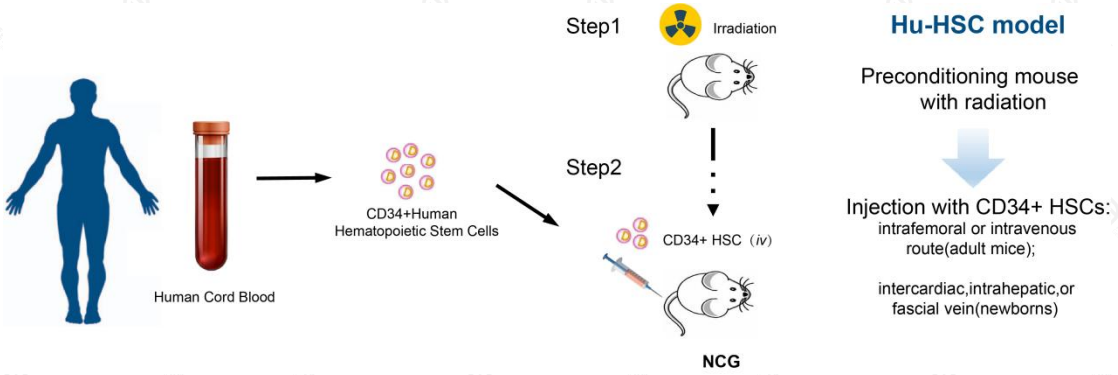

Figure 1. Flow chart of experimental design of huHSC-NCG mouse humanization model

huHSC-NCG mice are human hematopoietic stem cells ($CD34^+HSC$) transplanted into irradiated (80-100cGy) clear-marrow severely immunodeficient mice NCG and differentiated to produce various types of hematopoietic or immune cells, such as T cells, B cells and NK cells, to obtain a model of humanized immune system, and the reconstructed immune cell types are more abundant than those of PBMC humanized mice The reconstituted immune cell types were more abundant than those of PBMC humanized mice. The huHSC-NCG humanized mice were constructed using NCG mice as the recipient mice.

After transplantation of $CD34^+$ HSC in NCG mice, there was a slow rate of reconstruction relative to huPBMC, delayed onset of GvHD, and a survival cycle of more than 39 weeks, which prolonged the dosing window. huHSC-NCG mice had a high efficiency of immune reconstitution, mainly reconstituting T cells and a large number of immature B cells, as well as a small number of NK cells and macrophages, which can be used to perform the evaluation of tumor immunotherapeutic agents.

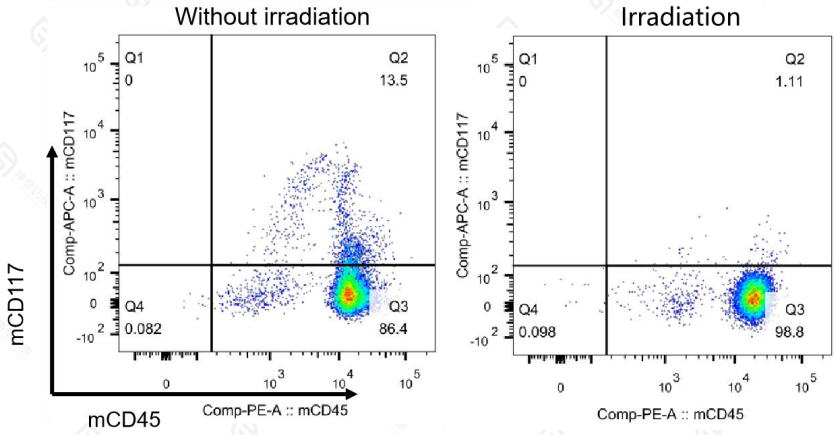

Figure 2. Detection of marrow clearing effect in NCG mice

The effect of irradiation on marrow clearance was examined using flow cytometry. Irradiation cleared hematopoietic stem cells from the bone marrow of mice, thereby increasing the level of reconstitution after human-derived HSC transplantation. The percentage of mCD45+mCD117+ cell population was 1.11% after irradiation, which was significantly lower than that of the unirradiated group (13.5%).

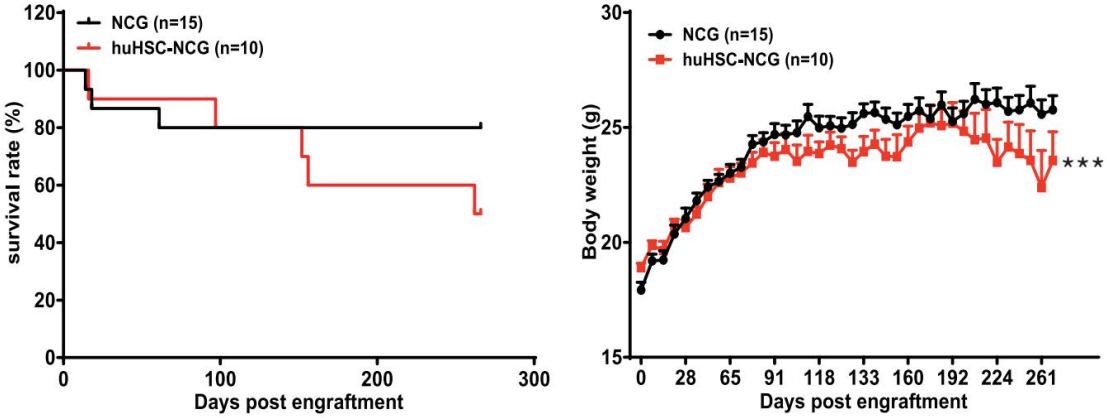

Figure 3. Survival curve and weight change of huHSC-NCG mice

The left panel shows that huHSC-NCG mice can survive longer than 37 weeks and the survival rate is not significantly different from that of NCG wild-type mice. The right panel shows that the body weight of huHSC-NCG mice increased with time, and there was no significant difference with the body weight of NCG wild-type mice.

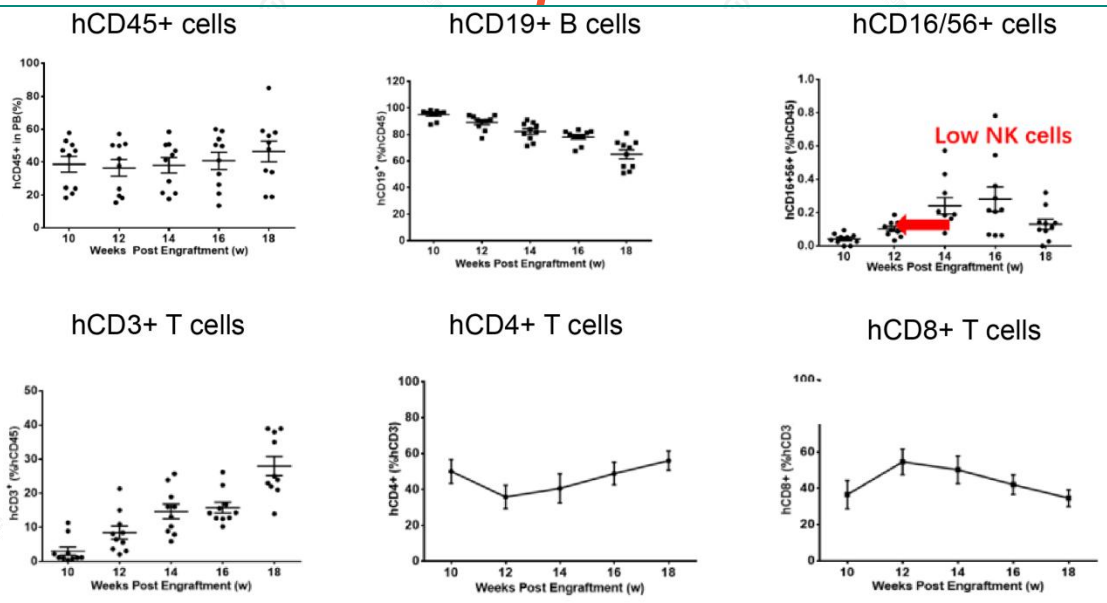

Figure 4. huHSC-NCG reconstruction effect evaluation

The huHSC-NCG mice were highly efficient in immune reconstitution, reconstituting mainly T cells and a large number of immature B cells, as well as a small number of NK cells.

2. Pharmacodynamic study based on huHSC-NCG mice

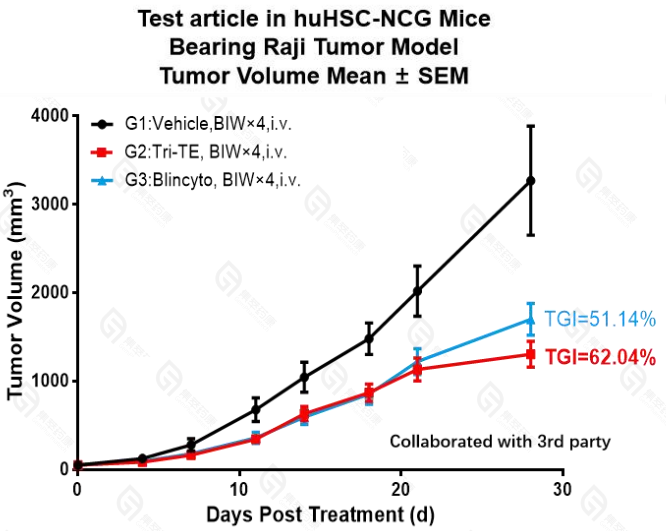

Figure 5. In vivo efficacy evaluation based on huHSC-NCG

Based on in vivo dosing test in huHSC-NCG mice. Raji cells, a logarithmic growth stage human lymphoma cell, were inoculated subcutaneously into huHSC-NCG mice, and when the tumors grew to an average volume of about 40-50 mm3, the mice were randomly divided into Vehicle group, Tri-TE administration group, and Blincyto administration group according to the tumor volume and body weight, and treated with the corresponding drugs. The results showed that the Tri-TE group (TGI=62.04%) and Blincyto administration group (TGI=51.14%) had an inhibitory effect on tumor growth on Raji cell-bearing mice with huHSC-NCG.

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