NOD-Scid-hNKp30

Strain Name: NOD/ShiLtJGpt-*Prkdc*^{em26Cd52}*Ncr3*$^{em1Cin(hNCR3)}$*/Gpt*
Strain type: Knock-in
Strain ID: T051430
Background: NOD/ShiLtJGpt

Description

In the past decade, therapeutic advances in immunotherapy have revolutionized the treatment of multiple cancers. Natural killer (NK) cells are lymphocytes with features of both innate and adaptive immunity. They contribute to immune defense by killing unhealthy cells, secreting soluble factors, and regulating the responses of antigen-presenting cells and adaptive T cells[1-2]. Preclinical evidences and early clinical successes have established NK immunotherapy as a safe, feasible, and promising therapeutic strategy[3-4].

Natural killer cells express many receptors that can activate their cytotoxic and secretory functions. The natural cytotoxicity receptors (NCRs, including NKp30, NKp44 and NKp46) are among the earliest identified NK cell activating receptors[5]. They are potent inducers of NK cell cytotoxicity, and are important for NK cell-mediated tumor immunosurveillance. NKp30 expression is mostly restricted to NK cells, although recent studies found this NCR to be present on the surface of additional immune cells, including γδ T cells and ILCs[6]. NKp30 is involved in NK cell-mediated killing of various tumor cell lines, viral-infected cells and also of autologous DCs during the so-called “editing” process. Recently, a novel class of NK-cell engager, named CTX-4419, binds to BCMA on MM cells and to NKp30 and CD16A (FcγRIIIA) on NK cells, specifically redirecting NK cells towards tumor cells expressing BCMA[7]. The preclinical results showed that CTX-4419 could significantly induces NK cell proliferation and lysis of tumor cells represents and is a promising candidate for MM treatment with the potential to be used as monotherapy or in combination with adoptive transfer of NK cells and/or other immuno-therapies.

GemPharmatech independently developed a humanized NOD-SCID-hNKp30 mouse model using gene editing technology. In this model, the human NKp30 gene contains human NKp30 promoters and regulatory elements was used to replace the mouse NKp30 pseudogene in situ. Meanwhile, NOD-SCID mice lack mature T/B cells due to prkdc gene deficiency, but its NK cells function normally. Therefore, the NOD-SCID-hNKp30 model is suitable for evaluating the efficacy and safety of drugs targeting for NKp30 only with the participation of the innate immune system.

Strategy

Fig.1 Schematic diagram of NKp30 humanization strategy in NOD-SCID mice.

Application

1. Evaluation of efficacy and safety of Anti-hNkp30 drugs
2. Anticancer Drug Research and Development
3. Immune system-related research

Data support

1. hNKp30 Protein expression on NK cells

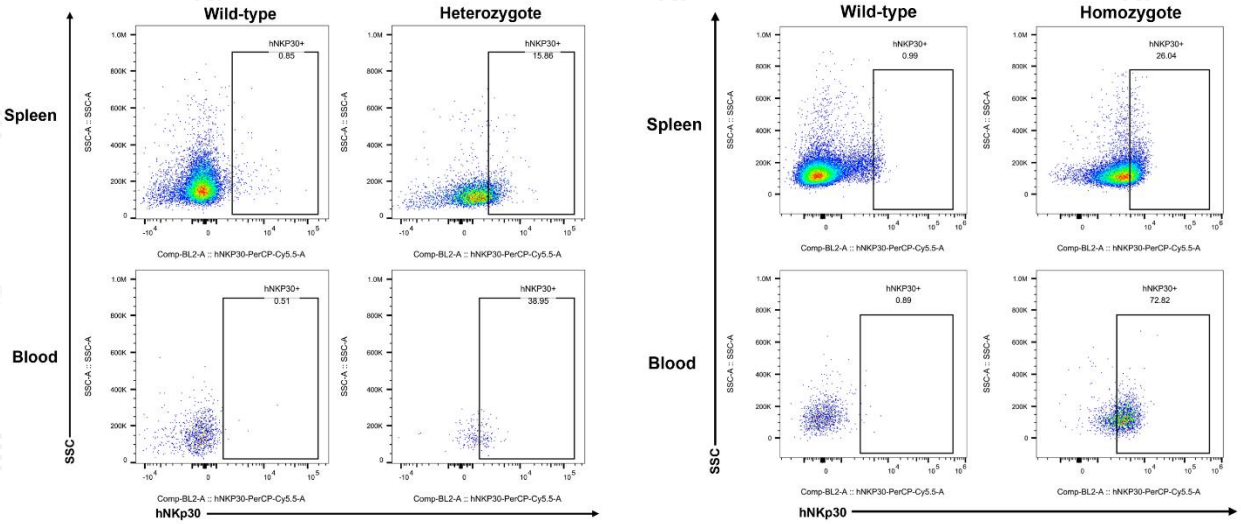
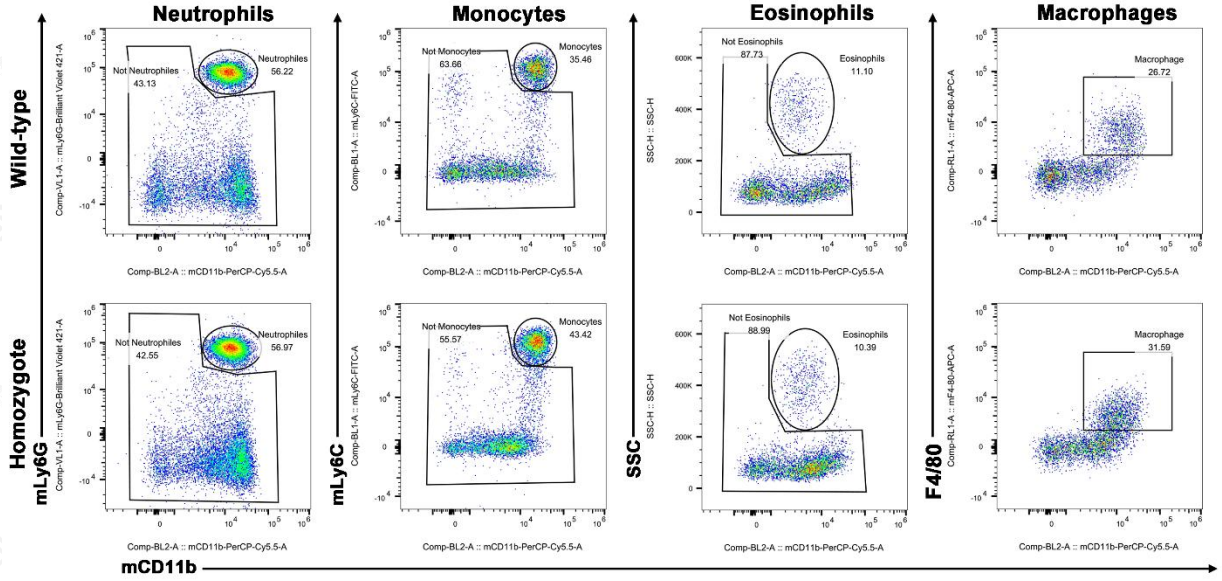


Fig.2 Detection of NKp30 expression in NOD-SCID-hNKp30 mice.

Splenocytes and blood were isolated from NOD-SCID, NOD-SCID-hNKp30 heterozygote and NOD-SCID-hNKp30 homozygote mice, and the expression of hNKp30 on the surface of NK cells was detected by flow cytometry. As shown in Figure 2, both NOD-SCID-hNKp30 heterozygote and homozygote mice successfully expressed hNKp30 on the surface of NK cells in blood and spleen.

2. Analysis of blood immune cell subpopulations in NOD-SCID-hNKp30 mice



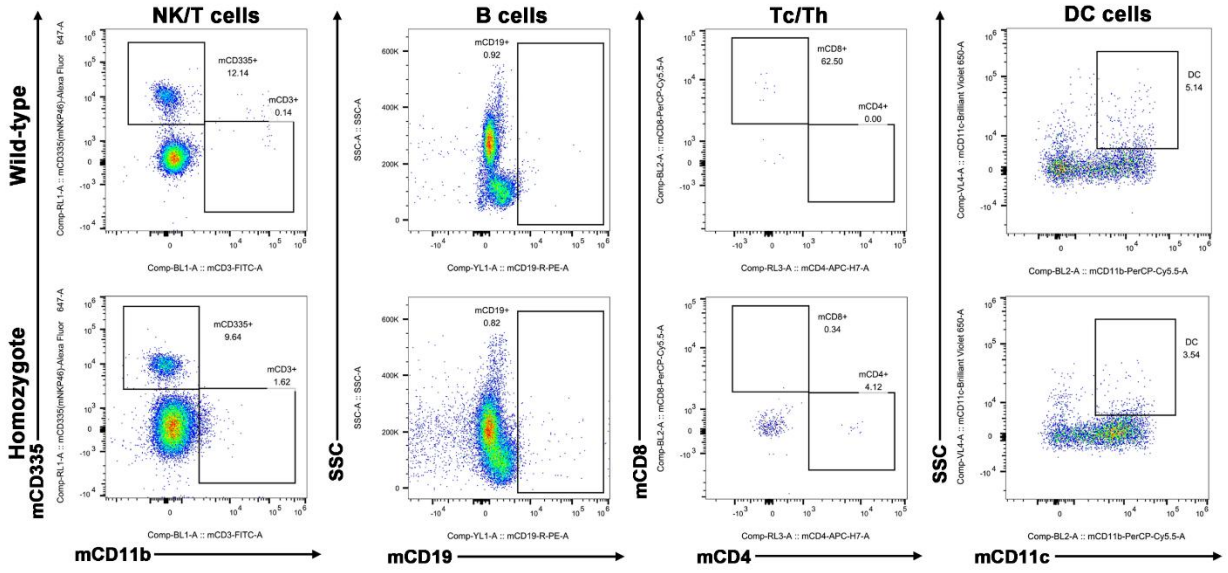
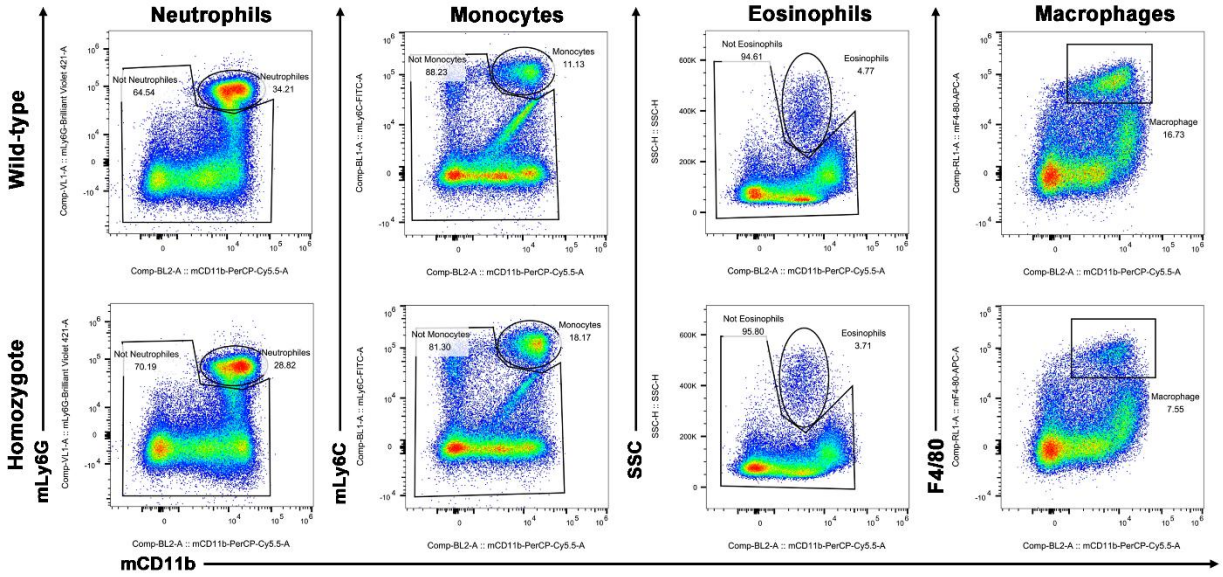


Fig.3 Analysis of blood immune cell subpopulations in NOD-SCID-hNKp30.

Blood was taken from NOD-SCID and NOD-SCID-hNKp30 mice for flow cytometry analysis to assess immune cell subpopulations. As shown in Figure 3, the percentages of NK cells, neutrophils, eosinophils, monocytes, macrophages and dendritic cells in NOD-SCID-hNKp30 mice were similar to those in NOD-SCID, indicating that the replacement of mNKp30 by hNKp30 did not alter the development, differentiation, and distribution of these cells in blood. Meanwhile, no T cells or B cells was detected in NOD-SCID-hNKp30 mice, as well as in NOD-SCID mice.

3. Analysis of spleen immune cell subpopulations in NOD-SCID-hNKp30



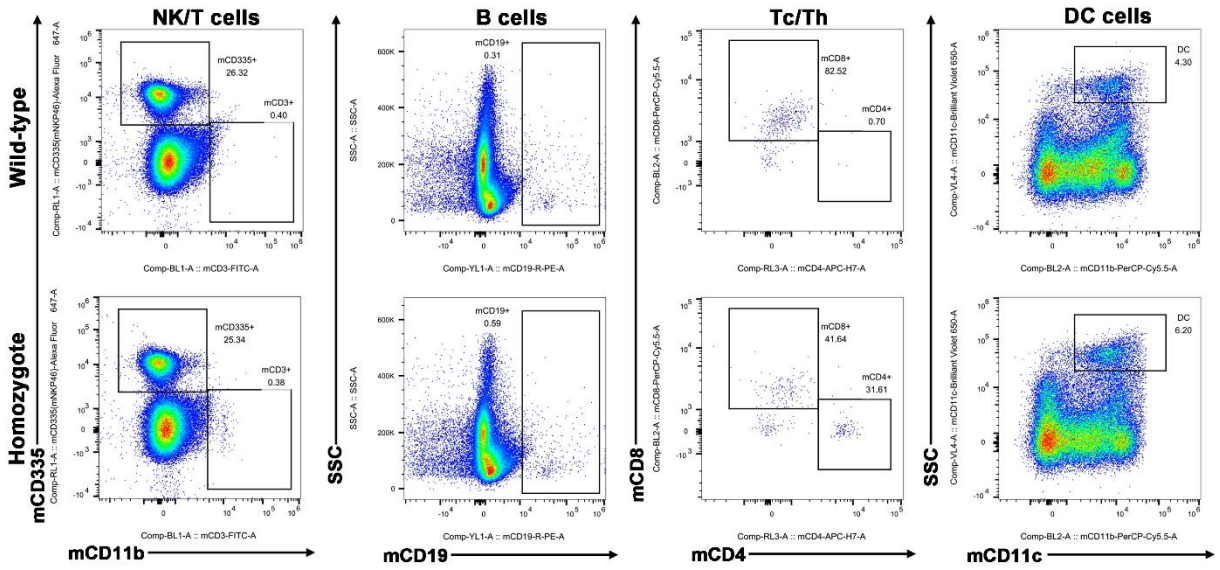


Fig.4 Analysis of spleen immune cell subpopulations in NOD-SCID-hNKp30

Splenocytes were taken from NOD-SCID and NOD-SCID-hNKp30 mice for flow cytometry analysis to assess immune cell subpopulations. As shown in Figure 4, the percentages of NK cells, neutrophils, eosinophils, monocytes, macrophages and dendritic cells in NOD-SCID-hNKp30 mice were similar to those in NOD-SCID, indicating that the replacement of mNKp30 by hNKp30 did not alter the development, differentiation, and distribution of these cells in spleen. Meanwhile, no T cells or B cells was detected in NOD-SCID-hNKp30 mice, as well as in NOD-SCID mice.

References

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