BALB/c-hIL1RL1

Strain Name: BALB/cJGpt-*Il1rl1*$^{em1Cin(hIL1RL1)}$/*Gpt*
Strain type: Knock-in
Strain ID: T054583
Background: BALB/cJGpt

Description

IL1RL1, also known as interleukin 1 receptor-like 1 and ST2, is a type I transmembrane glycoprotein that belongs to the interleukin 1 receptor (IL1R) family[1]. IL1RL1 is expressed on mast cells, activated Th2 cells, macrophages, and cardiac myocytes. IL1RL1 can be induced by proinflammatory stimuli, and is involved in the function of helper T (Th) cells[2].

IL33 is the only known ligand of ST2, which has been identified as a mediator of various inflammatory diseases such as asthma, cardiovascular diseases, and allergic diseases[3-4]. ST2 exists in two forms as splice variants: a soluble form (sST2), which acts as a decoy receptor, sequesters free IL-33, and does not signal, and a membrane-bound form (ST2), which activates the MyD88/NF-κB signaling pathway to enhance mast cell, Th2, regulatory T cell (Treg), and innate lymphoid cell type 2 functions[5]. Recently, a novel IL-33 antibody named REGN3500, has been developed by Sanofi and Regeneron Pharmaceuticals, Inc. The clinical results showed that REGN3500 monotherapy significantly reduced loss of asthma control and improved lung function compared to placebo[6]. Growing studies demonstrate that ST2/ IL33 signaling play an important role in inflammatory diseases and highlight potential avenues to intervene in ST2/IL-33 signaling as treatment options.

The BALB/c-hIL1RL1 humanized model was created at GemPharmatech using gene editing technology whereby the coding sequence of the extracellular domain of the IL1RL1 gene was replaced with the human counterpart on BALB/cGpt background. The intracellular region of murine IL1RL1 was completely retained for normal intracellular signaling transduction. This mouse will be useful for evaluation of drugs that targeting IL1RL1.

Strategy

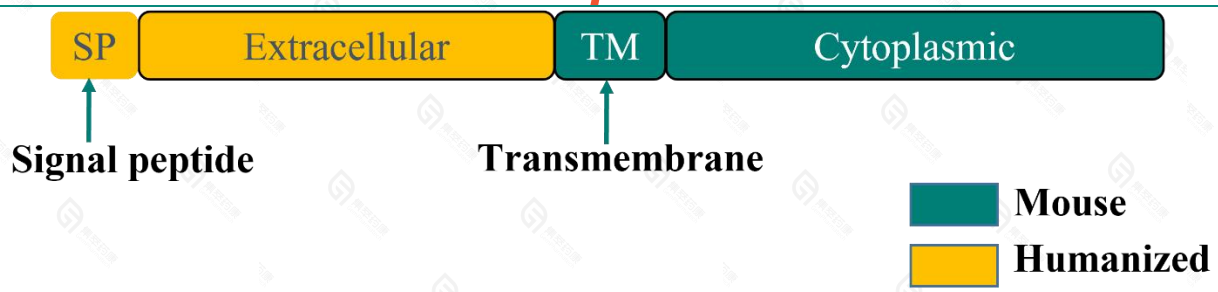

Fig.1 Schematic diagram of IL1RL1 humanization strategy in BALB/c-hIL1RL1 mice.

Application

1. Evaluation of efficacy and safety of human IL1RL1 drugs
2. Anticancer Drug Research and Development
3. Research on autoimmune diseases

Data support

1. hIL1RL1mRNA expression analysis

Fig.2 Detection of hIL1RL1 mRNA expression in BALB/c-hIL1RL1 mice.
Total RNA was isolated from large intestine of wild-type mice and homozygous BALB/c-hIL1RL1 mice, RT-PCR method was used to detect the mRNA expression of hIL1RL1. The expression of hIL1RL1 mRNA was only detectable in homozygous BALB/c-hIL1RL1, not in wild-type mice.

2. IL1RL1 Protein expression analysis

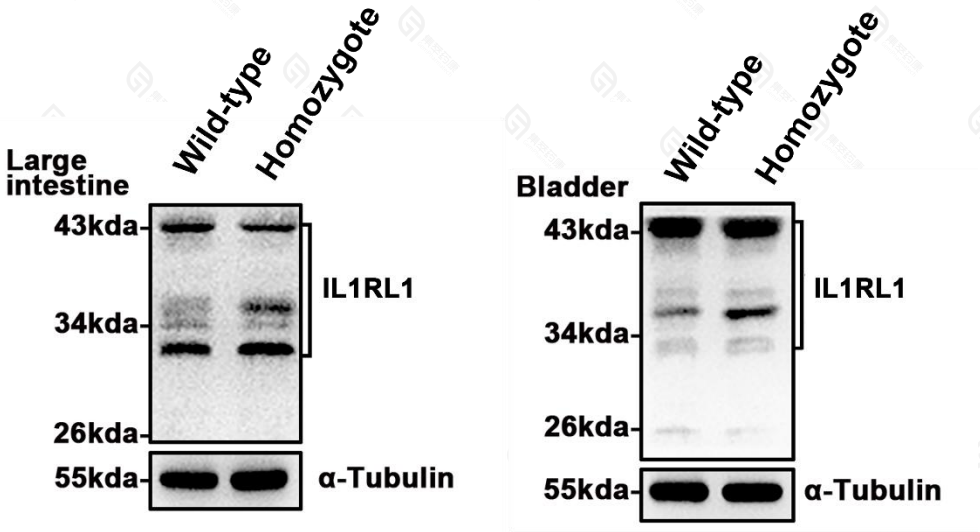

Fig.3 Detection of IL1RL1 expression in BALB/c-hIL1RL1 mice.
Large intestine and bladder tissues were collected from wild-type mice and homozygous BALB/c-hIL1RL1 mice, and analyzed by western blot with anti-IL1RL1 antibody. The anit-IL1RL1 antibody shows cross-reactivity with both human and mouse IL1RL1. IL1RL1 was detectable in both wild-type mice and homozygous BALB/c-hIL1RL1 mice.

3. Analysis of blood immune cell subpopulations in BALB/c-hIL1RL1 mice

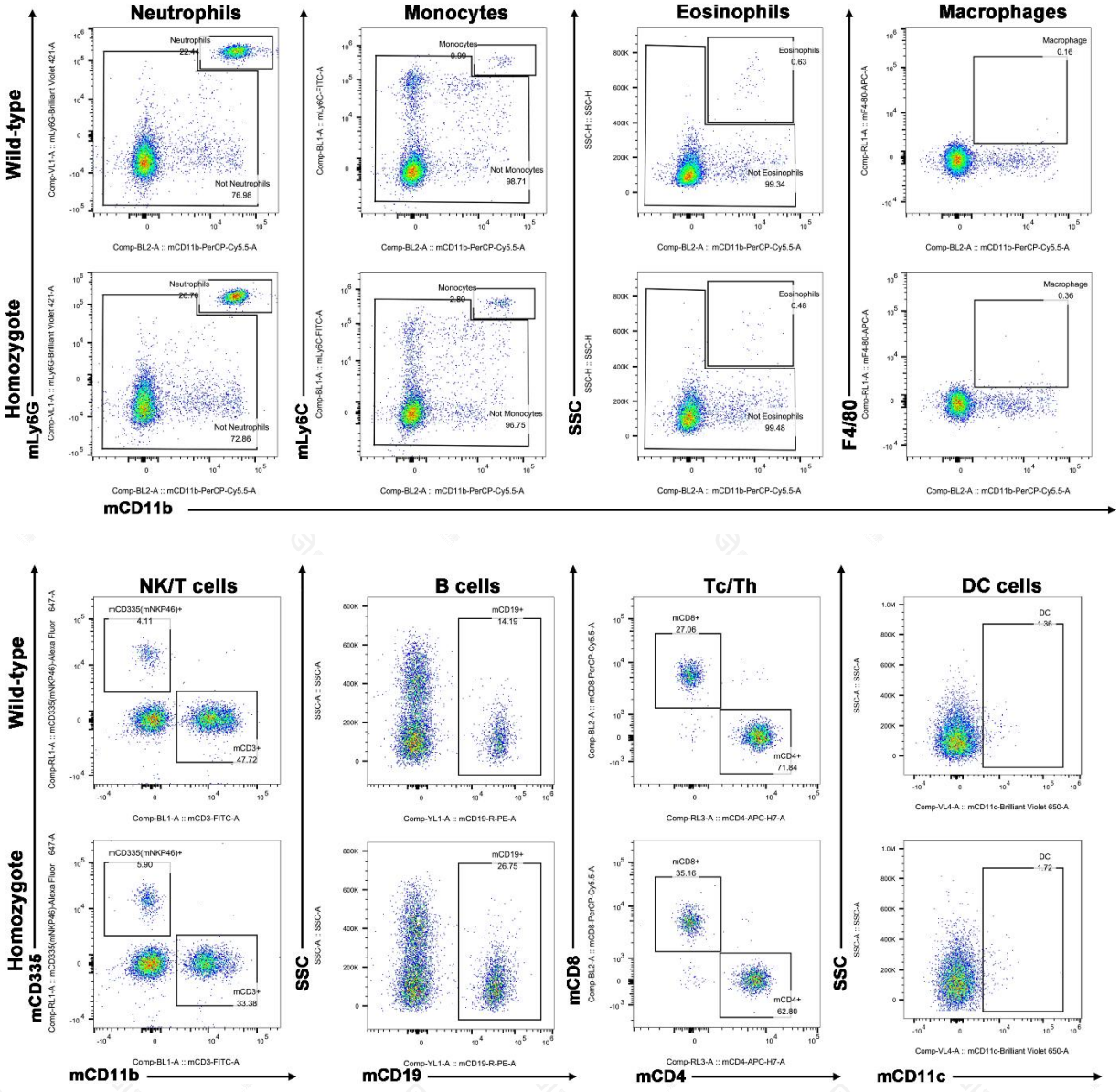

Fig. 4 The immune cell subpopulations in blood of BALB/c and BALB/c-hIL1RL1

Blood was taken from BALB/c and BALB/c-hIL1RL1 mice for flow cytometry analysis to assess immune cell subpopulations. As shown in Figure 3, the percentages of T cells, NK cells and neutrophils in BALB/c-hIL1RL1 mice were similar to those in BALB/c, indicating that the replacement of mIL1RL1 by hIL1RL1 did not alter the development, differentiation, and distribution of these cells in blood.

4. Analysis of spleen immune cell subpopulations in BALB/c-hIL1RL1 mice

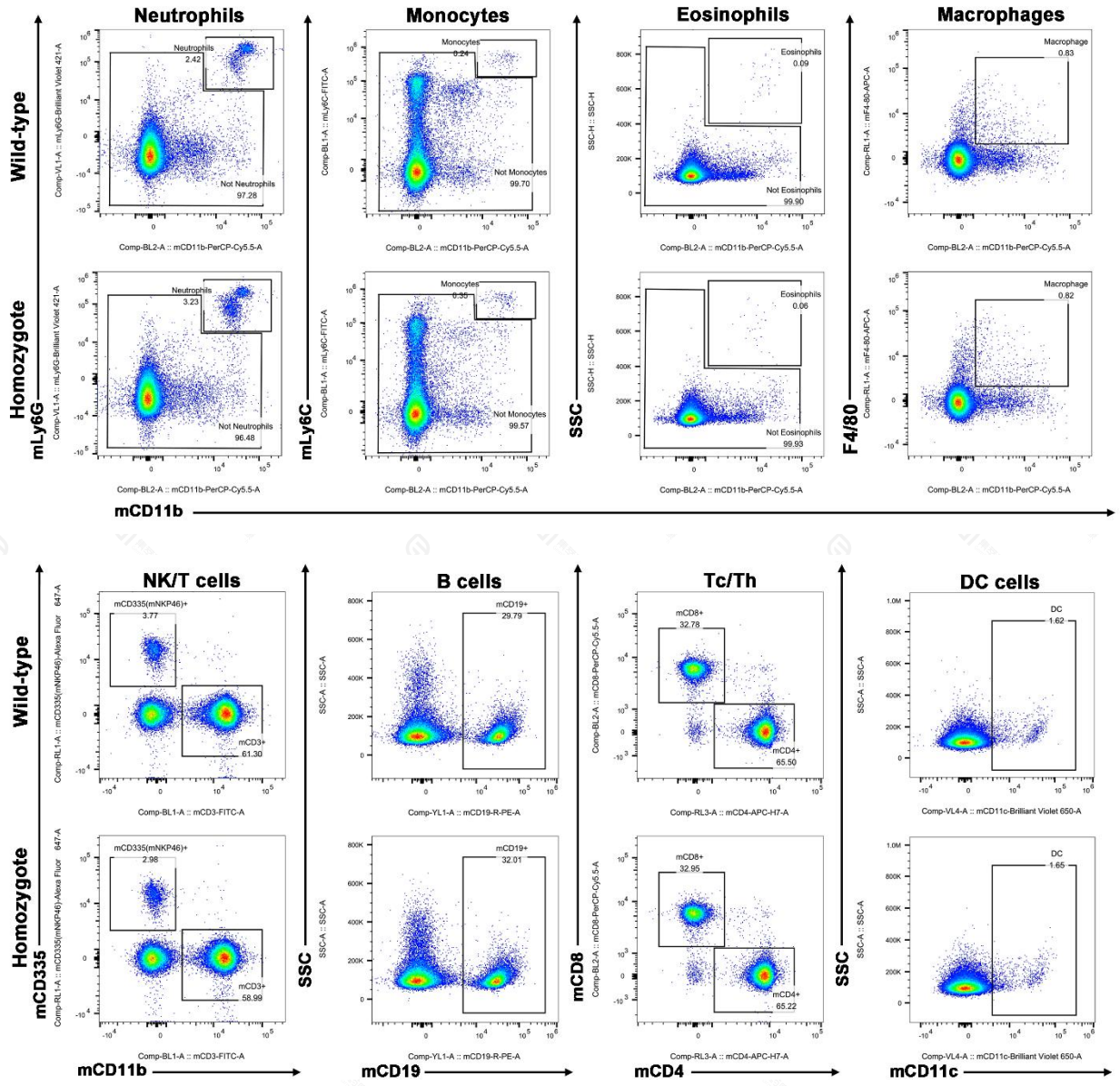

Fig. 5 The immune cell subpopulations in spleen of BALB/c and BALB/c-hIL1RL1

Splenocytes were taken from BALB/c and BALB/c-hIL1RL1 mice for flow cytometry analysis to assess immune cell subpopulations. As shown in Figure 4, the percentages of T cells, NK cells, B cells, neutrophils and dendritic cells in BALB/c-hIL1RL1 mice were similar to those in BALB/c, indicating that the replacement of mIL1RL1 by hIL1RL1 did not alter the development, differentiation, and distribution of these cells in spleen.

References

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