BALBc-hSLAMF7(CS1)

Strain Name: BALB/cJGpt-*Slamf7*$^{em1Cin(hSLAMF7)}$/Gpt
Strain Type: Knock-in
Strain Number: T055714
Background: BALB/cJGpt

Description

SLAMF7 (Signaling Lymphocytic Activation Molecule Family Member 7), also known as CS1 (CRACC), is a cell surface receptor belonging to the signaling lymphocyte activation molecule (SLAM) family. It is primarily expressed on natural killer (NK) cells, plasma cells, and a subset of CD8+ T cells[1]. SLAMF7 was initially identified as a molecule expressed on plasma cells and implicated in regulating their function. Subsequent studies revealed its broader expression pattern on immune cells, particularly NK cells, where it acts as a co-stimulatory receptor[1]. The binding of SLAMF7 with its ligand, CD319 (CRACC-L or SLAMF7-L), triggers signaling events that modulate immune responses[2, 3].

SLAMF7 plays a significant role in immune regulation and has emerged as an important therapeutic target in various diseases, including hematological malignancies and autoimmune disorders. Monoclonal antibodies targeting SLAMF7, such as elotuzumab, have shown promising results in multiple myeloma (MM) clinical trials. Elotuzumab functions by enhancing NK cell-mediated antibody-dependent cellular cytotoxicity (ADCC) against SLAMF7-expressing MM cells[4]. Strong correlation has been found between exhausted T cells and high SLAMF7 expression in the tumor microenvironment (TME), suggested that SLAMF7 might play an important role in modulating T cell function in the TME[5]. SLAMF7 has also been implicated in the pathogenesis of autoimmune disorders, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA)[6, 7]. Modulating SLAMF7 signaling may offer a novel approach to attenuate autoimmune responses and ameliorate disease symptoms.

The humanized SLAMF7 mice was created at GemPharmatech using gene editing technology whereby the coding sequence of extracellular domain of mouse Slamf7 was replaced with the human SLAMF7 counterpart on BALB/c background. The transmembrane and cytoplasmic regions of murine Slamf7 were completely retained and physiological cytoplasmic signal transduction was confirmed. This strain may be useful on anti-SLAMF7 drug screening and evaluation.

Applications

1. Targeted drug test (screening human SLAMF7 neutralizing antibodies or small molecule drugs that base on human SLAMF7 activity)
2. Studies on autoimmune diseases

Strategy

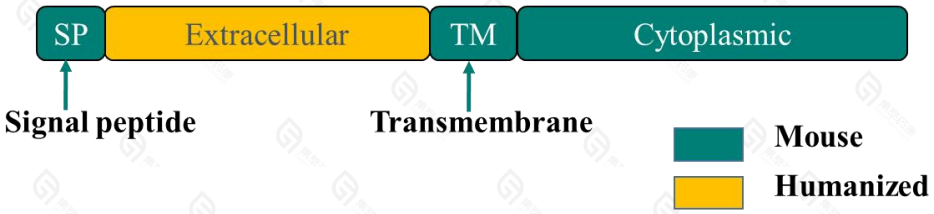
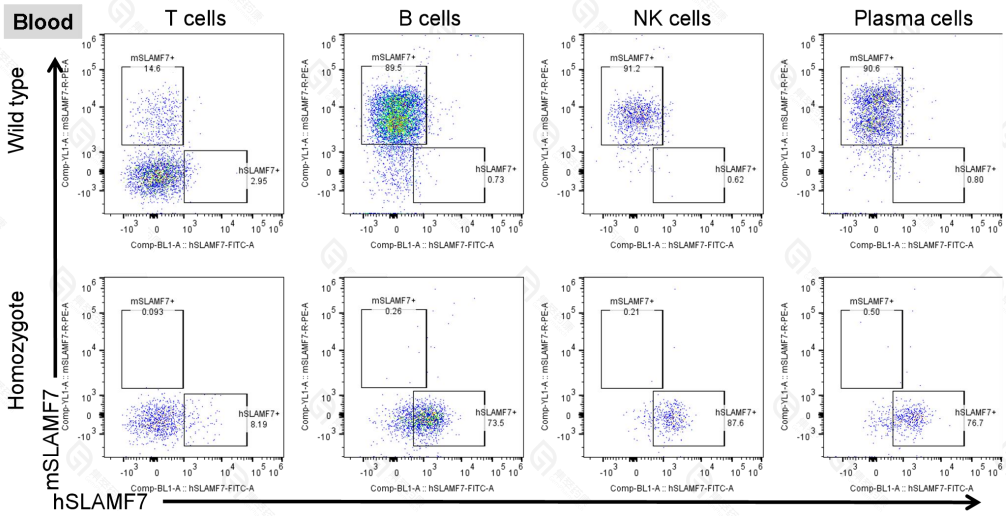


Fig 1. Schematic diagram of SLAMF7 humanization strategy.

Data support

1. Humanized SLAMF7 protein expression analysis



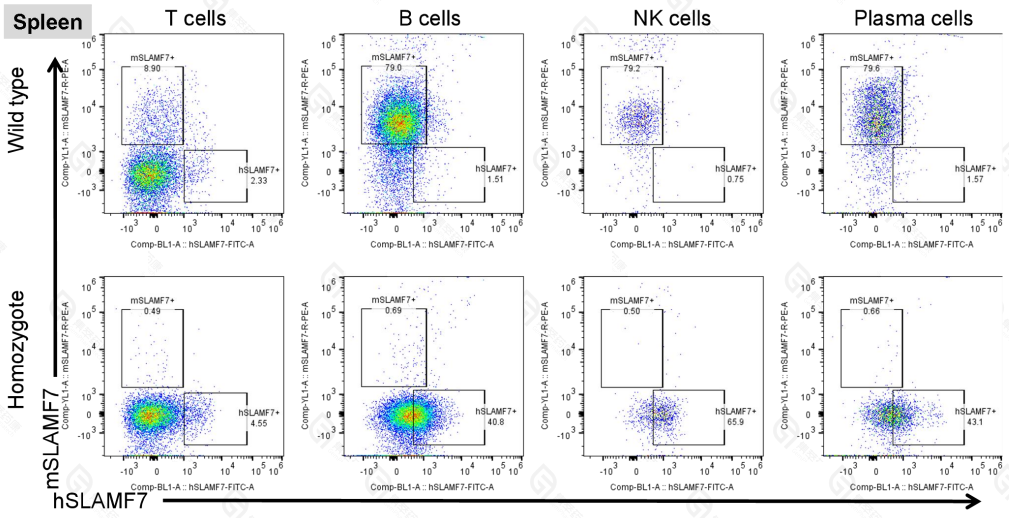
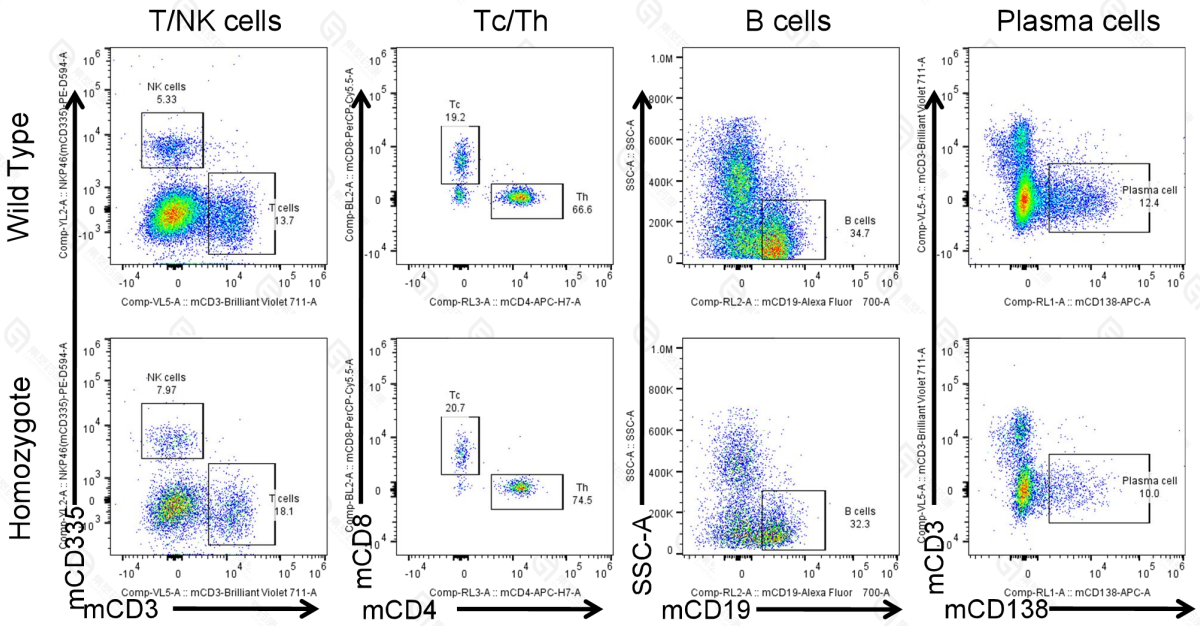


Fig 2. Detection of humanized SLAMF7 expression.

Blood and Spleen samples were collected from BALB/c and homozygous BALB/c-hSLAMF7 mice, and the expression of SLAMF7 was detected.

Expression of hSLAMF7 was successfully detected on the lymphocytes' surface of BALB/c-hSLAMF7 mice, but not in wild type mice.

2. Analysis of blood immune cell sub-population



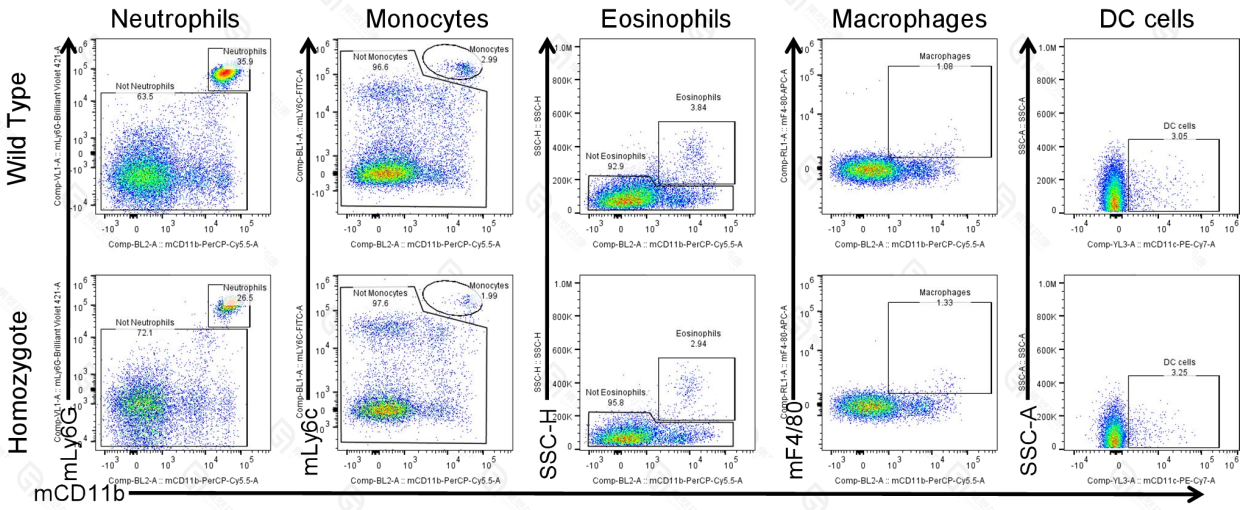
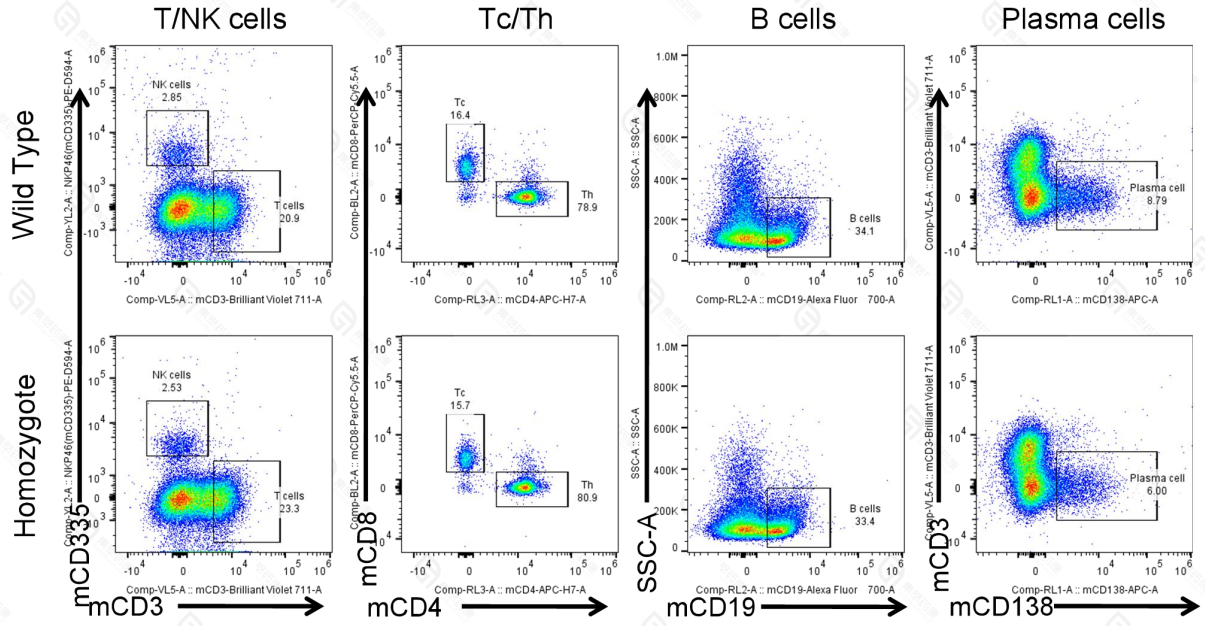


Figure 3 Blood immune sub-population ratio assay

Blood was isolated from female BALB/c (wild type) and BALB/c-hSLAMF7 (homozygote) mice for flow cytometric analysis to assess immune sub-populations. The percentages of T cells, NK cells, B cells, neutrophils, monocytes, and dendritic cells in SLAMF7 humanized mice were similar to those in BALB/c, indicating that the replacement of mSLAMF7 by hSLAMF7 did not alter the development, differentiation, and distribution of these cells in blood.

3. Analysis of spleen immune cell sub-population



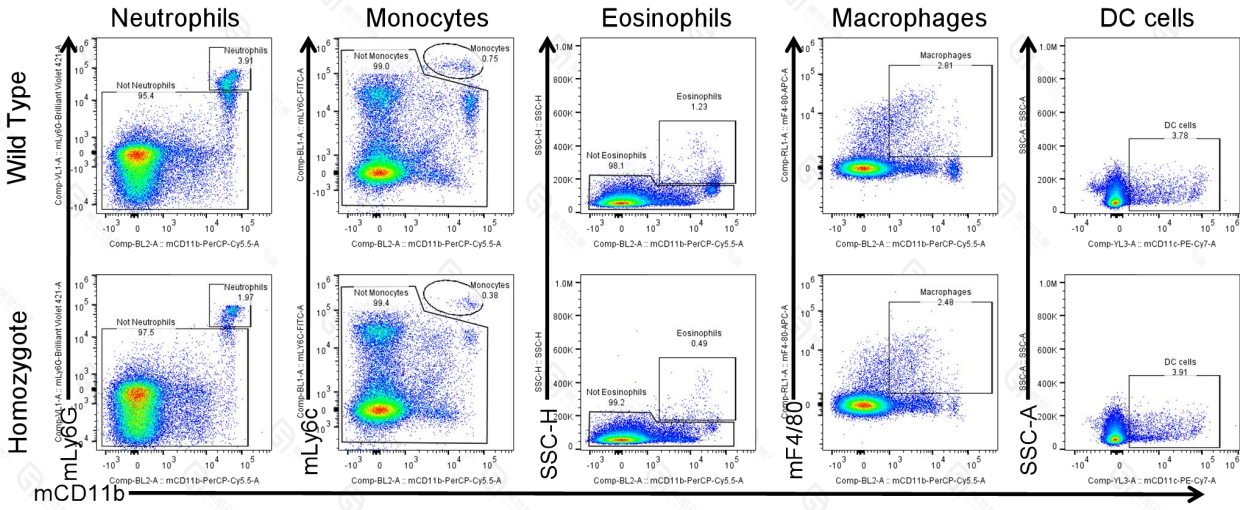


Figure 4 Spleen leukocyte sub-population ratio assay

Splenocytes were isolated from female BALB/c (wild type) and BALB/c-hSLAMF7 (homozygote) mice for flow cytometric analysis to assess immune sub-populations. The percentages of T cells, NK cells, B cells, neutrophils, monocytes, and dendritic cells in SLAMF7 humanized mice were similar to those in BALB/c, indicating that the replacement of mSLAMF7 by hSLAMF7 did not alter the development, differentiation, and distribution of these cells in spleen.

References

1. Cruz-Munoz, M.-E., et al., *Influence of CRACC, a SLAM family receptor coupled to the adaptor EAT- 2, on natural killer cell function.* Nature Immunology. **10**(3): p. 297-305.
2. Lee, J.K., K.S. Boles, and P.A. Mathew, *Molecular and functional characterization of a CS1 (CRACC) splice variant expressed in human NK cells that does not contain immunoreceptor tyrosine-based switch motifs.* European Journal of Immunology, 2004. **34**(10): p. 2791-2799.
3. Lee, J.K., et al., *CS1 (CRACC, CD319) Induces Proliferation and Autocrine Cytokine Expression on Human B Lymphocytes.* The Journal of Immunology, 2007. **179**(7): p. 4672-4678.
4. Weisel, K., *Spotlight on elotuzumab in the treatment of multiple myeloma: the evid ence to date.* OncoTargets and therapy. **9**: p. 6037-6048.
5. O'Connell, P., et al., *SLAMF7 Signaling Reprograms T Cells toward Exhaustion in the Tumor Microenvironment.* The Journal of Immunology, 2021. **206**(1): p. 193-205.
6. Simmons, D.P., et al., *SLAMF7 engagement superactivates macrophages in acute and chronic inflammation.* Science Immunology, 2022. **7**(68).
7. Comte, D., et al., *Signaling Lymphocytic Activation Molecule Family Member 7 Engagement R estores Defective Effector CD8+ T Cell Function in Systemic Lupus Eryt hematosus.* Arthritis & rheumatology (Hoboken, N.J.). **69**(5): p. 1035-1044.