

## BALB/c-hHER2

**Strain Name:** BALB/cJGpt-*Her2<sup>em1Cin(hHER2)</sup>*/Gpt

**Strain type:** Knock-in

**Strain ID:** T009819

**Background:** BALB/cJGpt

### Description

HER2, also known as ERBB2, is a transmembrane receptor with tyrosine kinase activity but without a known ligand<sup>[1-2]</sup>. It belongs to the human epidermal growth factor receptor family that are involved in regulating cell growth, survival and differentiation. Overexpression of HER2 was found to occur in human breast cancer (BC), and HER2 signalling and transforming functions leading to the formation of aggressive tumor cells<sup>[3]</sup>.

The discovery that amplification or overexpression of HER2 was associated with extremely poor survival in BC ultimately led to the development of drugs targeting HER2. The dependence of the tumour on HER2, coupled with effective HER2-targeted drugs such as trastuzumab, pertuzumab and most recently, tucatinib and trastuzumab deruxtecan (T-DXd), have contributed to these survival improvements in patients with HER2-positive (HER2+) BC<sup>[4]</sup>. Besides, HER2-directed therapies have been used to treat other HER2-expressing tumor types such as gastric and lung cancers<sup>[5-6]</sup>. Recently, a specifically engineered HER2-directed antibody drug conjugate (ADC), named Enhertu has been jointly developed and commercialised by AstraZeneca and Daiichi Sankyo. The clinical results showed that Enhertu met the prespecified target for objective response rate (ORR) and demonstrated durable response across multiple HER2-expressing advanced solid tumours.

The BALB/c-hHER2 humanized model was created at GemPharmatech using gene editing technology whereby the coding sequence of the extracellular domain of the HER2 gene was replaced with the human counterpart on BALB/cJGpt background. The intracellular region of murine HER2 was completely retained for normal intracellular signaling transduction. This mouse will be useful for evaluation of drugs that targeting HER2.

Annotation: this strain is only available for heterozygous humanized mice

## Strategy

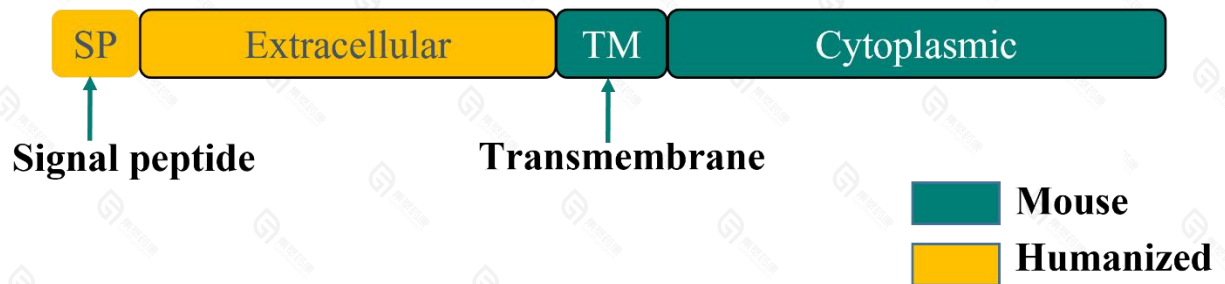


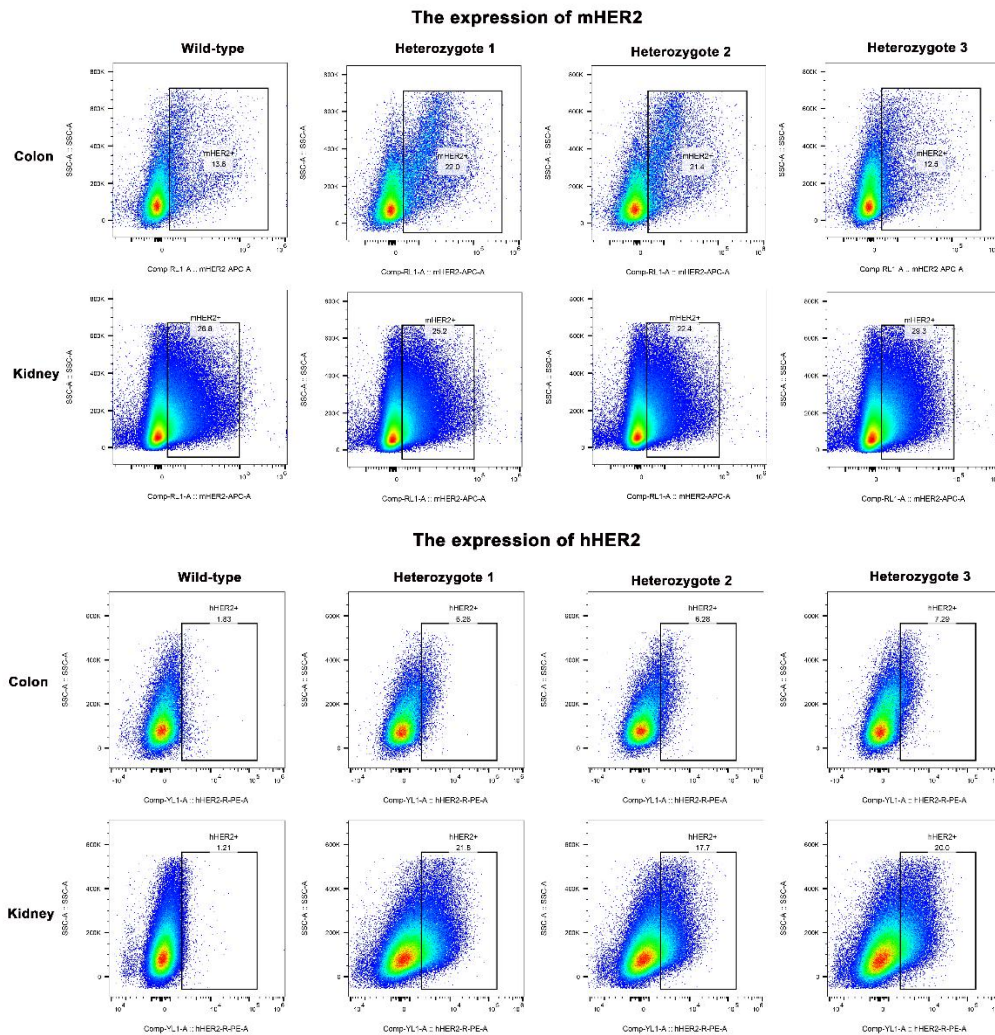
Fig.1 Schematic diagram of HER2 humanization strategy in BALB/c-hHER2 mice.

## Application

1. Evaluation of efficacy and safety of human HER2 drugs
2. Anticancer drug research and development
3. Development of cancer vaccines

## Data support

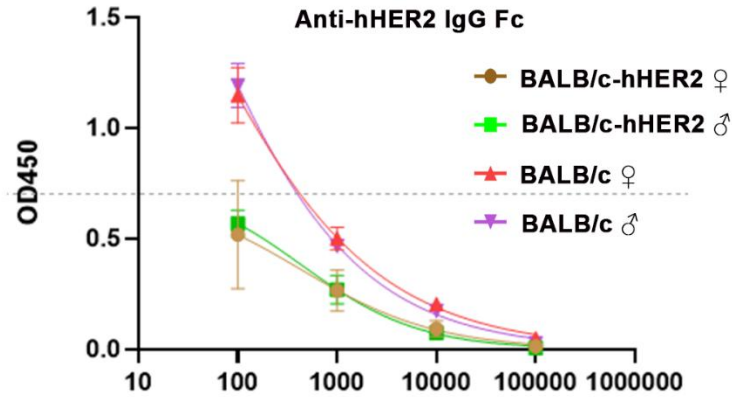
### 1. HER2 protein expression analysis



**Fig.2 Detection of HER2 expression in BALB/c-hHER2 mice.**

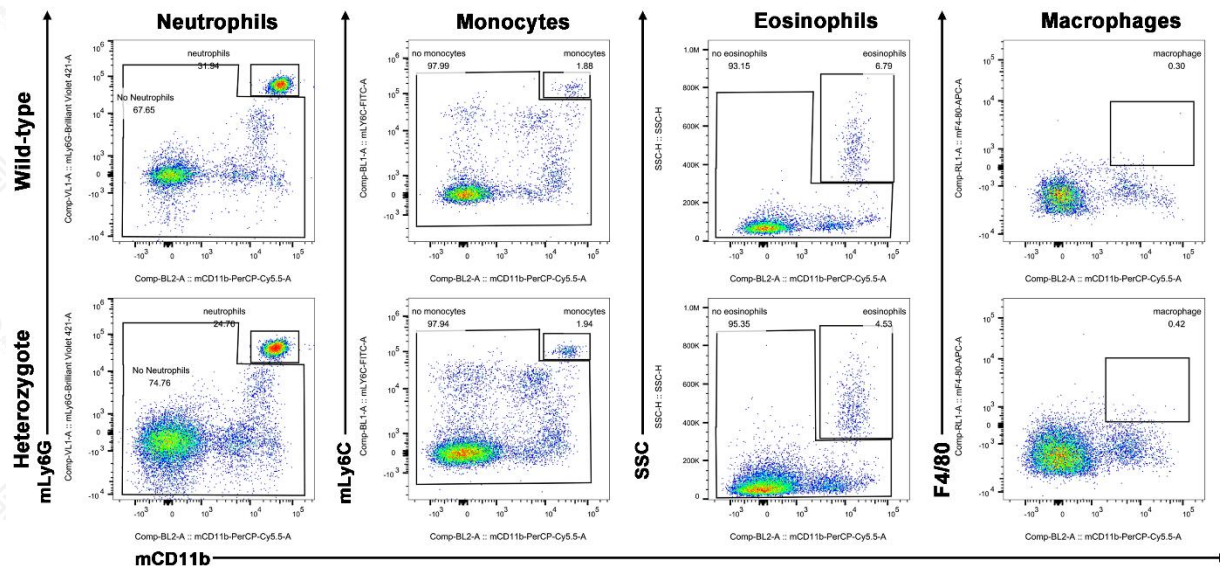
Colon and kidney tissues were collected from wild-type mice and heterozygous BALB/c-hHER2 mice, and analyzed by flow cytometry. mHER2 was detectable in both wild-type mice and heterozygous BALB/c-hHER2 mice, and hHER2 was only detectable in heterozygous BALB/c-hHER2 mice.

### 2. Immunization of BALB/c-hHER2 mice with recombinant hHER2 proteins

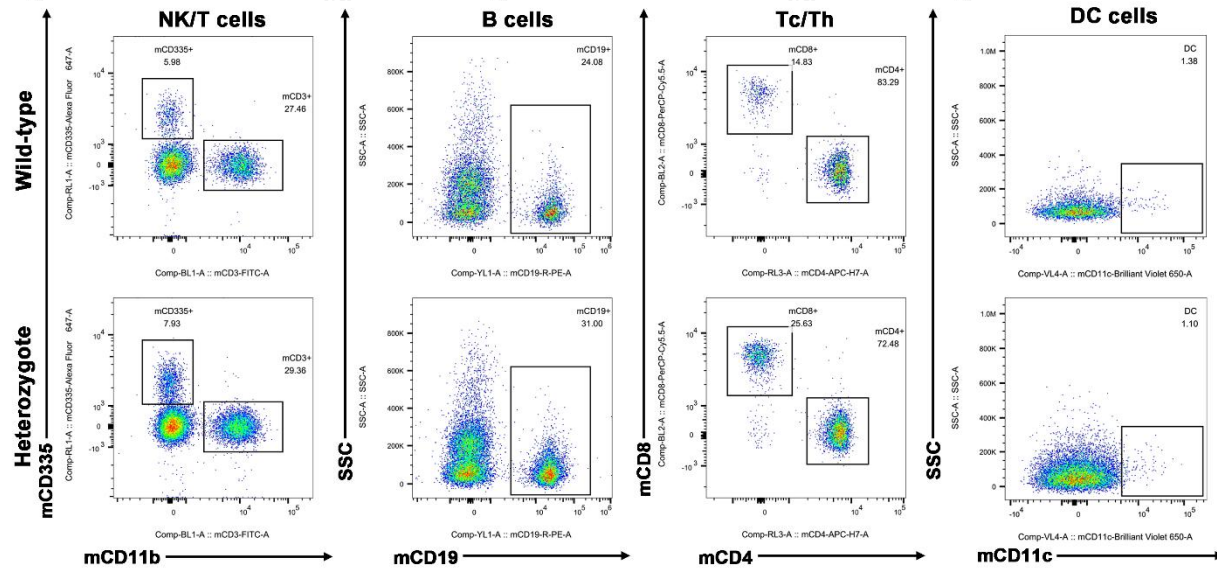


**Fig.3 The levels of anti-hHER2 antibodies in BALB/c-hHER2 mice(collaboration data).** BALB/c and heterozygous BALB/c-hHER2 mice were immunized with human recombinant HER2 protein. The results showed that the levels of anti-hHER2 antibodies in heterozygous BALB/c-hHER2 mice were much lower than those in BALB/c mice, suggesting that our heterozygous BALB/c-hHER2 mice endogenously express human HER2 protein.

### 3. Analysis of blood immune cell subpopulations in BALB/c-hHER2 mice



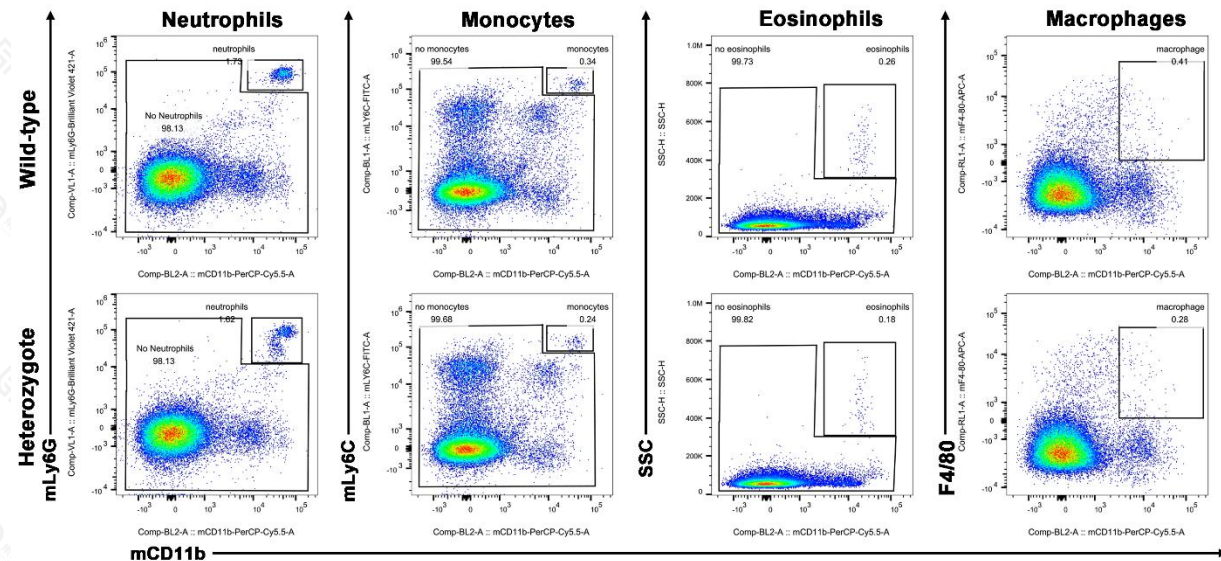


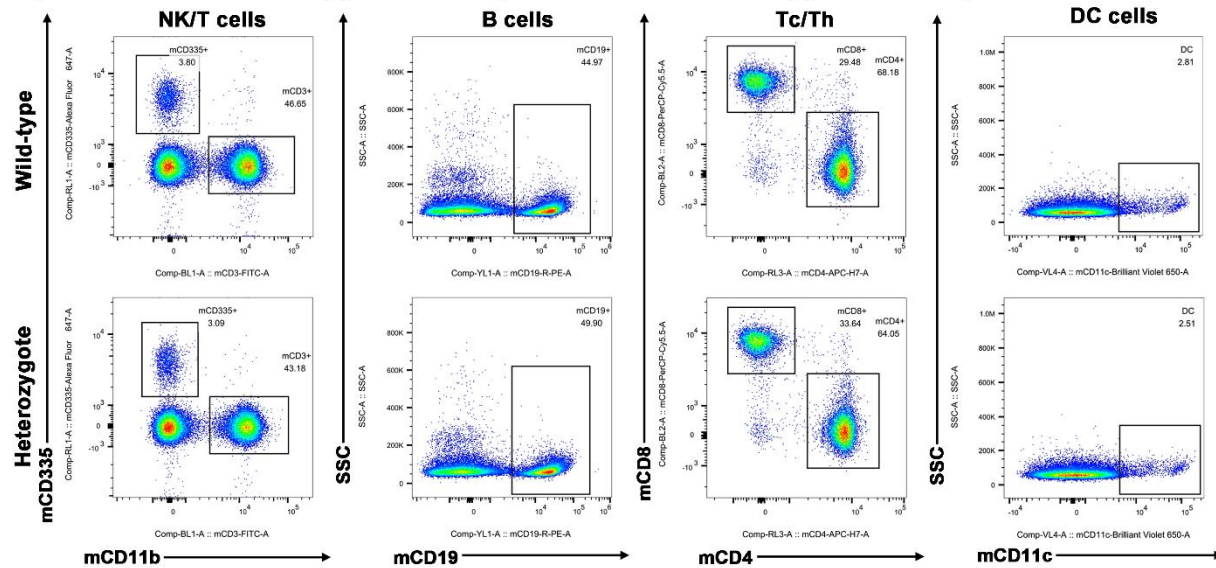


**Fig. 4 The immune cell subpopulation in blood of BALB/c and BALB/c-hHER2**

Blood was taken from BALB/c and BALB/c-hHER2 mice for flow cytometry analysis to assess immune cell subpopulations. As shown in Fig. 4, the percentages of neutrophils, monocytes, eosinophils, macrophages, B cells, T cells, NK cells and DC cells in BALB/c-hHER2 mice were similar to those in BALB/c, indicating that the replacement of mHER2 by hHER2 did not alter the development, differentiation, and distribution of these cells in blood.

#### 4. Analysis of spleen immune cell subpopulations in BALB/c-hHER2 mice





**Fig. 5 The immune cell subpopulation in spleen of BALB/c and BALB/c-hHER2**

Splenocytes were taken from BALB/c and BALB/c-hHER2 mice for flow cytometry analysis to assess immune cell subpopulations. As shown in Figure 5, the percentages of T cells, NK cells, B cells, neutrophils and dendritic cells in BALB/c-hHER2 mice were similar to those in BALB/c, indicating that the replacement of mHER2 by hHER2 did not alter the development, differentiation, and distribution of these cells in spleen.

## References

1. G. Carpenter, L. King, S. Cohen. Epidermal growth factor stimulates phosphorylation in membrane preparations in vitro. *Nature* 1978, **276**, 409-410.
2. A. Schechter, D. Stern, L. Vaidyanathan, et al. The neu oncogene: an erb-B-related gene encoding a 185,000-Mr tumour antigen. *Nature* 1984, **312**, 513-516.
3. D. Slamon, G. Clark, S. Wong, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 1987, **235**, 177-182.
4. S. Giordano, M. Franzoi, S. Temin, et al. Systemic therapy for advanced human epidermal growth factor receptor 2-positive breast cancer: ASCO guideline update. *J. Clin. Oncol.* 2022, **40**, 2612-2635.
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