NCG-hHER2

Strain Name: NOD/ShiLtJGpt-*Prkdc*^{em26Cd52}*Il2rg*^{em26Cd22}*Her2*$^{em1Cin(hHER2)}$/Gpt
Strain type: Knock-in
Strain ID: T009813
Background: NCGJGpt

Description

HER2, also known as ERBB2, is a transmembrane receptor with tyrosine kinase activity but without a known ligand[1-2]. 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[3].

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[4]. Besides, HER2-directed therapies have been used to treat other HER2-expressing tumor types such as gastric and lung cancers[5-6]. 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 NCG-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 NCG background mice. 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

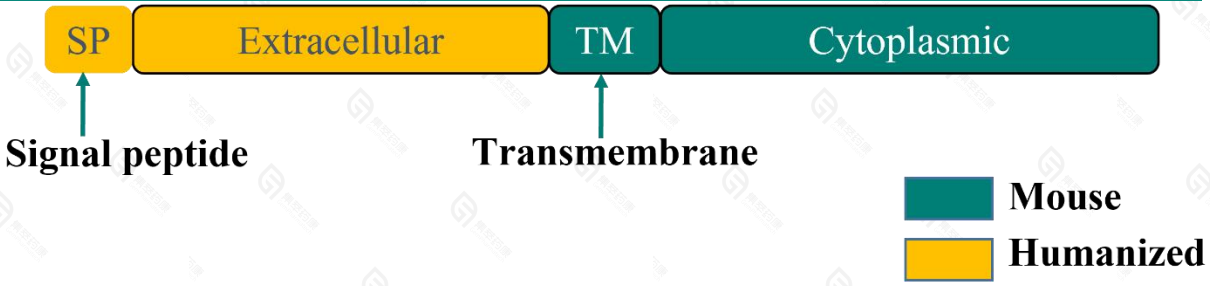

Fig.1 Schematic diagram of HER2 humanization strategy in NCG-hHER2 mice.

Application

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

Supporting data

1. HER2 mRNA expression analysis

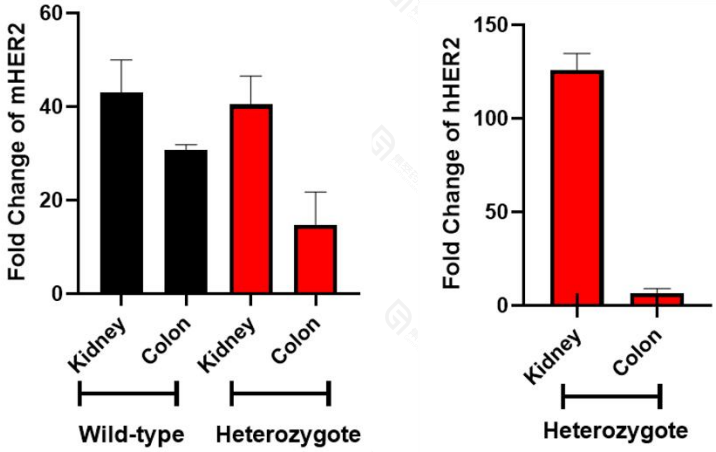

Fig.2 Quantitative PCR analysis of hHER2 mRNA expression in NCG-hHER2 mice.

Total RNA was isolated from kidney and colon of wild-type mice and heterozygous NCG-hHER2 mice, qPCR method was used to detect the mRNA expression of HER2. The results showed that the expression of mHER2 mRNA was detectable in both wild-type and heterozygous NCG-hHER2 mice. The expression of hHER2 mRNA was detectable in heterozygous NCG-hHER2.

2. HER2 Protein expression analysis

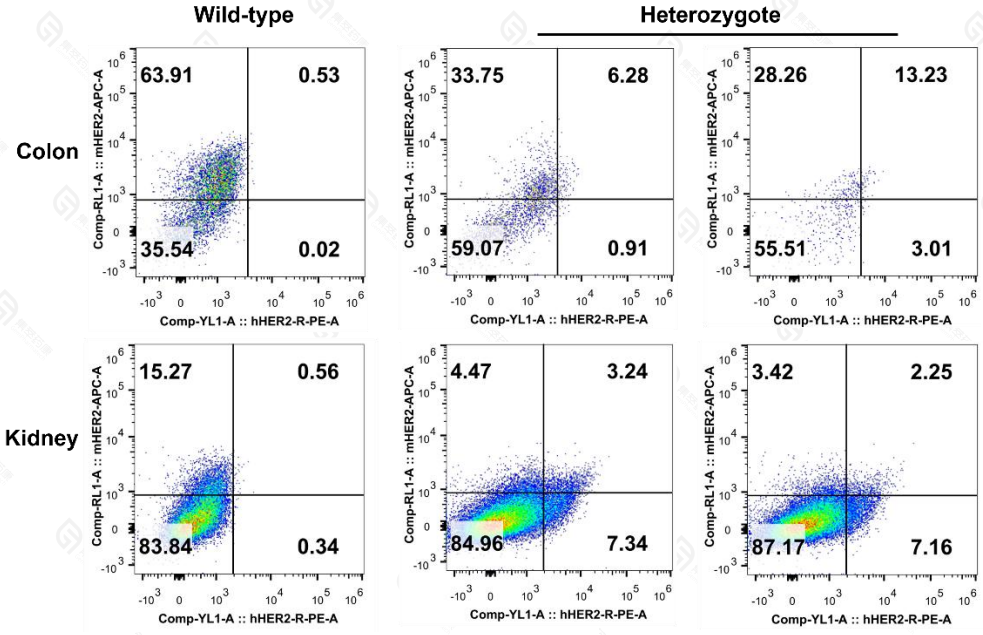

Fig.3 Detection of HER2 expression in NCG-hHER2 mice.

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

References

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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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