Efficacy Evaluation Models of Immune Checkpoint Antibody Drugs

Immune Checkpoint Humanized Mouse Models
Our vision is to provide researchers all over the world with comprehensive, convenient and professional animal model services to facilitate a simplified and highly-efficient approach to uncover the mysteries of life.

Founded in September 2000, Shanghai Model Organisms Center, Inc. (SMOC) specializes in model organisms and is dedicated to gene editing and life decoding.

We provide customized solutions such as genetically engineered animal models, phenotype analysis and high-throughput screenings to advance life science research and drug discovery. SMOC owns a rapidly-growing repository of Research-Ready models, including immunodeficient and humanized mouse models to advance R&D for cancer immunotherapy.

Our breeding facility is equipped with 60,000 specific pathogen-free (SPF) cages which can hold up to 300,000 rodents. Health and safety procedures for animal handling are strictly complied. Animal welfare is highly prioritized by SMOC and which has earned us the AAALAC accreditation.
Immune Checkpoint Humanized Mouse Models

Checkpoint inhibitor immuno-oncology (I-O) treatments, the new breed of immuno-oncology therapies, have led to important clinical advances and provided a new weapon against cancer, which have won the 2018 Nobel Prize!

However, In vivo efficacy testing of potential therapeutic antibodies is still a major challenge for preclinical scientists. Drug candidates developed to interfere with human proteins may not comparably interact with their murine counterparts, making it challenging or even impossible to perform in vivo tests on wild-type rodents.

Therefore, we have generated over 60 humanized immune checkpoint knock-in mouse models to evaluate the in vivo efficacy of human I-O antibodies, including single knock-in models and double knock-in models.

66 Immune Checkpoint Humanized Mouse Models generated by SMOC

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For more detailed information, please visit www.modelorg.com
Humanized PD-L1 Mouse

Strain Name: C57BL/6J-Cd274<sup>em1(hPD-L1)/SMOC</sup>  Strain Background: C57BL/6J

PD-L1 (Programmed Death Ligand 1, also known as B7-H1), which is encoded by the CD274 gene, is an immune checkpoint expressed on the surface of tumor cells or on the surface of host immune cells adjacent to the tumor microenvironment. PD-L1 binds to the PD-1 receptor expressed on the surface of T lymphocytes and transmits an inhibitory second signal, thus inhibiting the activation of T cells or other immune cells. Because T lymphocytes play an important role in anti-tumor immunity by mediating the adaptive anti-tumor immunity, the high expression of PD-L1 in the tumor microenvironment can significantly inhibit the function of tumor infiltrating T cells, thereby allowing tumor cells to escape immune surveillance.

Generation strategy

On the C57BL/6J genetic background, the protein coding sequences for human PD-L1 were inserted into the ATG position of the mouse Pd-l1 (Cd274) gene, so that the expression of endogenous Pd-l1 in the mouse was replaced by the expression of fully humanized PD-L1 protein.

Validation data

**Figure 1.** Expression of PD-L1 in the spleen lymphocytes collected from homozygous humanized PD-L1 mice and wild-type mice is detected by FACS. The results showed that the expression of human PD-L1 can be detected in both T cells and B cells collected from the spleen of homozygous humanized PD-L1 mice. ( Completed in collaboration with CrownBio)

**PD-L1 antibody anti-tumor efficacy validation**

**Figure 2.** In vivo validation of anti-tumor efficacy in a MC38 tumor-bearing model of humanized PD-L1 mice. Homozygous humanized PD-L1 mice were inoculated with MC38 colon cancer cells (expressing human PD-L1 rather than murine Pd-l1). After the tumors grew to 100 mm<sup>3</sup>, the animals were randomly assigned into a control group and a treatment group (n=5). The results showed that the antibody targeting human PD-L1 was associated with a very significant anti-tumor effect (TGI: tumor growth inhibition, p < 0.001), demonstrating that the humanized PD-L1 mice are a good in vivo model for validating the efficacy of antibodies targeting human PD-L1.

**Body weight changes in anti-tumor validation**
Humanized PD-1 Mouse

Strain Name: C57BL/6J-Pdcd1<sup>em1(hPDCD1)/SMOC</sup>  Strain Background: C57BL/6J

The PD-1 receptor (also known as CD279), which is encoded by the PDCD1 gene, is expressed on the surface of activated T cells and its ligand PD-L1 is usually expressed on the surface of dendritic cells or macrophages. Upon the binding of PD-L1 to PD-1, an inhibitory second signal is transmitted to reduce the production of cytokines by T cells and inhibit the proliferation of T cells. This regulatory system ensures that the immune system is activated at an appropriate time to reduce the likelihood of chronic autoimmune inflammation.

Generation strategy

On the C57BL/6J genetic background, the protein coding sequences for human PDCD1 gene were inserted into the ATG position of the mouse Pdcd1 gene, so that the expression of endogenous Pdcd1 in the mouse was replaced by the expression of full length PDCD1 protein of human.

Validation data

![Unstaining ctrl](image1)  ![WT](image2)  ![hPdcd1](image3)

**Figure 3.** Expression of PD-1 in the activated spleen lymphocytes of humanized PD-1 homozygous mice is detected by FACS.

![Vehicle, 10 ml/kg, biwkx2, i.v.](image4)  ![Keytruda, 10 mg/kg, biwkx2, i.v.](image5)

**Figure 4.** In vivo validation in a MC38 tumor-bearing model of humanized PD-1 mice. Homozygous humanized PD-1 mice were inoculated with MC38 colon cancer cells. After the tumors grew to 100 mm<sup>3</sup>, the animals were randomly assigned into a control group and a treatment group (n=8). The drug was given twice a week for a total of 4 administrations. The results showed that Keytruda, a drug targeting human PD-1, exerted a very significant anti-tumor effect (p<0.001), demonstrating that the humanized PD-1 mice are a good in vivo model for validating the efficacy of antibodies targeting human PD-1. (Data were obtained in cooperation with Genscript)

![PBS b.i.wx2 i.p.](image6)  ![Opdivo 5mpk b.i.wx2 i.p.](image7)  ![Opdivo 2.5mpk b.i.wx2 i.p.](image8)  ![Opdivo 1.25mpk b.i.wx2 i.p.](image9)

**Figure 5.** In vivo dose validation in a MC38 tumor-bearing model of humanized PD-1 mice. Homozygous humanized PD-1 mice were inoculated with MC38 colon cancer cells. After the tumors grew to 100 mm<sup>3</sup>, the animals were randomly assigned into a control group and a treatment group (n=8). The drug was given twice a week for a total of 4 administrations.
Humanized OX40 Mouse

Strain Name: C57BL/6J-Tnfrsf4em1(hTNFRSF4)Smoc  Strain Background: C57BL/6J

It is well known that the dual role of OX40 (also known as TNFRSF4, Tumor necrosis factor receptor superfamily, member 4) creates a tumor microenvironment that is more conducive to the initiation of anti-tumor immune responses. Our humanized mouse model of OX40 provides a powerful tool for further research on the efficacy, potency and adverse effects of OX40-related drugs. Unlike traditional immunodeficient mice, humanized OX40 mice not only carry human OX40, but also have a complete immune system and are therefore a more relevant, reliable, and accurate type of model.

Generation strategy

On the C57BL/6J genetic background, the coding sequences for the extracellular domain of human OX40 and the transmembrane and intracellular domains of murine Ox40 were inserted into the ATG position of the mouse Ox40 gene, so that the expression of endogenous Ox40 in the mouse was replaced by the expression of humanized chimeric protein.

Validation data

**Figure 6.** Expression of OX40 in the spleen lymphocytes of humanized OX40 mice is detected by FACS. The spleen lymphocytes of heterozygous humanized OX40 mice were activated by anti-CD3 and anti-CD28 for 48 hours, and then collected for staining. Along with a group undergoing no stimulation, the expression of murine and human OX40 was detected by FACS. The results showed that the active expression of human OX40 can be detected in both activated CD4+ and CD8+ T lymphocytes collected from heterozygous humanized OX40 mice, and the expression trend of human OX40 and murine Ox40 was similar.

**Figure 7.** In vivo validation of anti-tumor efficacy in a MC38 tumor-bearing model of humanized OX40 mice. Heterozygous humanized OX40 mice were inoculated with MC38 colon cancer cells. After the tumors grew to 100 mm³, the animals were randomly assigned into a control group and a treatment group (n=8). The results indicated that the antibodies targeting human OX40 showed a very significant anti-tumor effect (p<0.001).
Humanized ICOS Mouse

Strain Name: C57BL/6J-Icos^{em1(hICOS)Smoc} Strain Background: C57BL/6J

ICOS (inducible T cell co-stimulator) is a member of the CD28 family and is expressed on the surface of activated T cells. The ICOS-ICOSL costimulatory signal regulates cellular immunity and humoral immunity.

Generation strategy

Under the C57BL/6J genetic background, the coding sequences for the extracellular domain of human ICOS and the transmembrane and intracellular domains of murine Icos were inserted into the ATG position of the mouse Icos gene, so that the expression of endogenous Icos in the mouse was replaced by the expression of humanized chimeric protein.

Validation data

**Figure 8.** Expression of ICOS in the activated spleen lymphocytes of humanized ICOS mice is detected by FACS. The spleen lymphocytes of heterozygous humanized ICOS mice were stimulated by anti-CD3 and anti-CD28 for 48h, and then harvested for staining. Along with a group undergoing no stimulation, the expression of humanized ICOS was detected by FACS after antibody staining. The results showed that the active expression of humanized ICOS can be detected in both activated CD4$^+$ and CD8$^+$ T lymphocytes collected from heterozygous humanized ICOS mice.
Humanized CTLA4 Mouse

Strain Name: C57BL/6J-Ctla4em1(hCTLA4)/Smoc  
Strain Background: C57BL/6J

CTLA4 (cytotoxic T-lymphocyte antigen 4) is a transmembrane glycoprotein and an immune checkpoint receptor expressed on the surface of cytotoxic T lymphocytes. CTLA4 plays an important role in maintaining immune homeostasis and preventing the occurrence of excessive immune responses. By activating the CTLA4 signaling pathway, tumor cells can avoid the anti-tumor effects exerted by the immune system.

Generation strategy

On the C57BL/6J genetic background, the protein coding sequences for human CTLA4 were inserted into the ATG position of the mouse Ctla4 gene, so that the expression of endogenous Ctla4 in the mouse was replaced by the expression of fully humanized CTLA4 protein.

Validation data

Figure 9. Expression of CTLA4 in the activated spleen lymphocytes of humanized CTLA4 mice is detected by FACS. The spleen lymphocytes of homozygous humanized CTLA4 mice were activated by anti-CD3 and anti-CD28 for 72 hours, and then collected for staining. The expression of humanized CTLA4 was detected by FACS. The results showed that the active expression of humanized CTLA4 can be detected in both activated CD4+ and CD8+ T lymphocytes collected from homozygous humanized CTLA4 mice. (Completed in collaboration with CrownBio)

Figure 10. In vivo validation of anti-tumor efficacy in a MC38 tumor-bearing model of humanized CTLA4 mice. Homozygous humanized CTLA4 mice were inoculated with MC38 colon cancer cells. After the tumors grew to 100 mm³, the animals were randomly assigned into a control group and a treatment group (n=9). The results showed: Yervoy, a drug targeting human CTLA4, showed a very significant anti-tumor effect (p<0.001), demonstrating that the humanized CTLA4 mice are a good in vivo model for validating the efficacy of antibodies targeting human CTLA4. (Completed in collaboration with PharmaLegacy)
Humanized LAG3 Mouse

**Strain Name: B6.129-Lag3tm1(hLAG3)/SMOC**  
**Strain Background: B6.129**

LAG3 (lymphocyte activating 3, also known as CD223) has been shown to act as a co-inhibitory molecule expressed on activated T cells, NK cells, B cells, and plasmacytoid dendritic cells. LAG3 is an immune checkpoint receptor that binds to the antigen-MHC complex to present antigen to T cells. Experiments have shown that LAG3 exerts a negative regulatory effect on the proliferation and long-lasting memory of T cells.

**Generation strategy**

Using homologous recombination, the sequence for the extracellular domain of endogenous mouse Lag3 gene was completely replaced with the human LAG3 sequence to express a humanized chimeric LAG3 protein.

**Validation data**

Figure 11. FACS detection of LAG3 expression in tumor infiltrating lymphocytes collected from humanized LAG3 mice. Homozygous humanized LAG3 mice were inoculated with MC38 colon cancer cells. After the tumors grew to 1000 mm$^3$, tumor infiltrating lymphocytes were isolated and detected by FACS to measure the expression of humanized LAG3 in CD4$^+$ and CD8$^+$ T cells. The results showed that the active expression of humanized LAG3 was detected in the tumor infiltrating lymphocytes collected from humanized LAG3 mice. (Completed in collaboration with CrownBio)

Figure 12. Expression of LAG3 in the activated spleen lymphocytes of humanized LAG3 mice is detected by FACS. Stimulated spleen lymphocytes of homozygous humanized LAG3 mice. The results showed that the active expression of humanized LAG3 can be detected in both activated CD4$^+$ and CD8$^+$ T lymphocytes collected from homozygous humanized LAG3 mice. (Completed in collaboration with CrownBio)

Figure 13. In vivo validation of anti-tumor efficacy in a MC38 tumor-bearing model of humanized LAG3 mouse. Homozygous humanized LAG3 mice were inoculated with MC38 colon cancer cell lines. After the tumors grew to 50 mm$^3$, the animals were randomly assigned into different groups (n=5). The results showed that the anti-tumor effect was not observed when the antibody targeting human LAG3 was administered alone. However, a significant anti-tumor effect was observed when the antibody targeting human LAG3 was administered together with the anti-PD-1 antibody.

Figure 14. In vivo validation of anti-tumor efficacy in a MC38 tumor-bearing model of humanized LAG3 mouse. Homozygous humanized LAG3 mice were inoculated with MC38 colon cancer cell lines. After the tumors grew to 70-80 mm$^3$, the animals were randomly assigned into different groups (n=8). The results showed a significant anti-tumor effect was observed when the antibody targeting human LAG3 was administered together with Tecentriq.
Humanized TIM3 Mouse

**Strain Name:** C57BL/6J-Havcr2\textsuperscript{em1(HAVCR2)/Smoc}

**Strain Background:** C57BL/6J

As an inhibitory receptor of T cells, TIM3 (T-cell immunoglobulin and mucin-domain containing-3, also known as HAVCR2) is expressed on Th1, Th17, and CD8\(^+\) T cells. TIM3 is induced in Th1 cells and inhibits Th1-mediated immune responses by directly triggering apoptosis. TIM3 is an intriguing candidate for new treatments due to its demonstrated success in multiple preclinical cancer models.

**Generation strategy**

Under the C57BL/6J genetic background, the coding sequences for the extracellular domain of human TIM3 and the transmembrane and intracellular domains of murine Tim3 (Havcr2) were inserted into the ATG position of the mouse Tim3 gene, so that the expression of endogenous Tim3 in the mouse was replaced by the expression of humanized chimeric protein.

**Validation data**

![FACS detection of TIM3 expression in tumor infiltrating lymphocytes collected from humanized TIM3 mice.](image)

After the tumors grew to 1000 mm\(^3\), tumor infiltrating lymphocytes were isolated and detected by FACS to measure the expression of humanized TIM3 in CD4\(^+\) and CD8\(^+\) T cells. The results showed that the cells with positive TIM3 expression could be detected in the tumor infiltrating lymphocytes collected from humanized TIM3 mice. (Completed in cooperation with GenScript)
Humanized TIGIT Mouse

**Strain Name:** C57BL/6J-Tigit^{em1[hTIGIT]Smoc}  **Strain Background:** C57BL/6J

TIGIT (T-cell immunoreceptor with Ig and ITIM domains) belongs to the PVR family of immunoglobulin (Ig) proteins. TIGIT can inhibit the effect of NK cells by preventing the initial death of tumor cells and the release of tumor antigens.

**Generation strategy**

Under the C57BL/6J genetic background, the coding sequences for the extracellular domain of human TIGIT and the transmembrane and intracellular domains of murine Tigit were inserted into the ATG position of the mouse Tigit gene, so that the expression of endogenous Tigit in the mouse was replaced by the expression of humanized chimeric protein.

**Validation data**

![Image of flow cytometry plots showing expression of human TIGIT in humanized TIGIT mice compared to WT mice.](image)

**Figure 16.** Expression of human TIGIT in the polarized CD4^+ T cells of humanized TIGIT mice is detected by FACS. Spleen Naive CD4^+ T cells were isolated from heterozygous humanized TIGIT mice. After in vitro stimulation, activation and expansion by cytokines and antibodies, the CD4^+ T cells were re-stimulated with PMA/ionomycin before the expression of human TIGIT in polarized CD4^+ T cells was detected by FACS. The results showed that the active expression of human TIGIT could be detected in polarized CD4^+ T cells collected from humanized TIGIT mice, and the expression trend of human TIGIT was similar to that of murine Tigit.
Humanized 4-1BB Mouse

Strain Name: C57BL/6J-4-Tnfrsf9<sup>em1(hTNFRSF9)Smoc</sup> Strain Background: C57BL/6J

4-1BB (also known as TNFRSF9 and CD137), a member of the tumor necrosis factor (TNF) receptor family, is mainly expressed on activated T cells. Its ligand is 4-1BBL, and the combination of the two can stimulate the activation and proliferation of T cells (and B cells).

Generation strategy

On the C57BL/6J genetic background, the coding sequences for the extracellular domain of human 4-1BB and the transmembrane and intracellular domains of murine 4-1bb(Tnfrsf9) were inserted into the ATG position of the mouse 4-1bb gene, so that the expression of endogenous 4-1bb in the mouse was replaced by the expression of humanized chimeric protein.

Validation data

Figure 17. Expression of humanized 4-1BB in the activated spleen lymphocytes of humanized 4-1BB mice is detected by FACS. The spleen lymphocytes of heterozygous humanized 4-1BB mice were activated by anti-CD3 and anti-CD28 for 48 hours, and then collected for staining. Along with a group undergoing no stimulation, the expression of humanized 4-1BB was detected by FACS. The results showed that the active expression of humanized 4-1BB can be detected in both activated CD8<sup>+</sup> and CD8<sup>-</sup> T lymphocytes collected from heterozygous humanized 4-1BB mice.

Figure 18. In vivo validation in a MC38 tumor-bearing model of humanized 4-1BB mice. Humanized 4-1BB mice were inoculated with MC38 colon cancer cells. After the tumors grew to 100 mm<sup>3</sup>, the animals were randomly assigned into different groups (n=8). The drug was given twice a week for a total of 4 administrations. The results showed that drug targeting human 4-1BB exerted a significant anti-tumor effect (p<0.05), demonstrating that the humanized 4-1BB mice are a good in vivo model for validating the efficacy of antibodies targeting human 4-1BB.
Humanized GITR Mouse

Strain Name: C57BL/6J-4-Tnfrsf18\textsuperscript{em1 (hTNFRSF18) Smoc}

Strain Background: C57BL/6J

GITR (also known as TNFRSF18 and CD357), a member of the tumor necrosis factor (TNF) receptor family, is mainly expressed on regulating T cells, CD4\(^+\) and CD8\(^+\) T cells. GITR plays an important role in the regulation of immune function by providing costimulatory signals in T cell activation.

**Generation strategy**

On the C57BL/6J genetic background, the coding sequences for the extracellular domain of human GITR and the transmembrane and intracellular domains of murine Gitr (Tnfrsf18) were inserted into the ATG position of the mouse Gitr gene, so that the expression of endogenous Gitr in the mouse was replaced by the expression of humanized chimeric protein.

**Validation data**

![Graphs showing FACS analysis results for different cell types and conditions.

Figure 19. Expression of humanized GITR in the spleen lymphocytes of humanized GITR mice is detected by FACS. Staining of spleen lymphocytes collected from heterozygous humanized GITR mice, while the expression of humanized GITR is detected by FACS. The results showed that the active expression of humanized GITR can be detected in the spleen lymphocytes collected from heterozygous humanized GITR mice.
Humanized CD40 Mouse

Strain Name: C57BL/6J-4-Cd40<sup>em1(hCD40)Smoc</sup> Strain Background: C57BL/6J

CD40 is a member of the tumor necrosis factor (TNF) receptor family and is also known as TNFRSF5. CD40 is expressed in antigen presenting cells (APC) such as B cells, dendritic cells (DC), and monocytes as well as many non-immune cells and various types of cancer cells. CD40L, a trimeric ligand for CD40, is expressed on the surface of CD4<sup>+</sup> T cells. After binding to CD40 expressed on the surface of antigen-presenting cells (APCs), the CD40-CD40L complex plays a crucial role in T cell functions.

**Generation strategy**

On the C57BL/6J genetic background, the sequence for the extracellular domain of endogenous mouse Cd40 gene was completely replaced with the human CD40 sequence to express a humanized chimeric CD40 protein.

**Validation data**

![CD40 expression in peripheral blood cells of humanized CD40 mice. The FACS results of peripheral blood cells collected from homozygous humanized CD40 mice and wild-type mice showed that the active expression of humanized CD40 was detected in CD19 positive cells collected from homozygous humanized CD40 mice, and its expression level was similar to that of murine Cd40 expression in wild-type mice. (Completed in collaboration with CrownBio)](image)

![In vivo validation of anti-tumor efficacy in a MC38 tumor-bearing model of humanized CD40 mice. Humanized CD40 mice were inoculated with MC38 colon cancer cells. After the tumors grew to 100 mm<sup>3</sup>, the animals were randomly assigned into different group (n=8). The results indicated that the antibodies targeting human CD40 showed a very significant anti-tumor effect (p<0.001). Combination of anti-CD40 and anti-PD-1 is shown more significant anti-tumor effect. (Cooperation with CrownBio)](image)
Humanized CD3E Mouse

Strain Name: C57BL/6J-4-Cd3eem1(hCD3E)Smoc  Strain Background: C57BL/6J

The protein encoded by CD3E is the CD3-epsilon polypeptide, which together with CD3-gamma, -delta and -zeta, and the T-cell receptor alpha/beta and gamma/delta heterodimers, forms the T-cell receptor-CD3 complex. This complex plays an important role in coupling antigen recognition to several intracellular signal-transduction pathways. The epsilon polypeptide plays an essential role in T cell development. Defects in this gene cause immunodeficiency.

Generation strategy

On the C57BL/6J genetic background, the sequence for the extracellular domain of endogenous mouse Cd3e gene was completely replaced with the human CD3E sequence to express a humanized chimeric CD3E protein.

Validation data

Figure 22. Expression of CD3E in the PBMC of heterozygous humanized CD3E mice is detected by FACS.
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