BALB/c-hIL17A

Strain Name: BALB/cJGpt-*Il17a*$^{em1Cin(hIL17A)}$/*Gpt*
Strain type: Knock-in
Strain number: T003277
Background: BALB/cJGpt

Description

Interleukin-17A (Interleukin-17, IL-17) is an inflammatory cytokine expressed mainly by activated T cells (CD4+ Th17). IL17A can regulate IL-1/6/8, GM-CSF, and G-CSF, TNF, CXCL1/2 and CCL2/7/20 and other pro-inflammatory cytokines and chemokines expression[1]. Binding of IL17A to its receptor IL17RA can induce epithelial cells, endothelial cells and fibroblasts to express inflammatory cytokines through the NF-κB signaling pathway. Therefore, high expression of IL17A will lead to autoimmune diseases and inflammatory damage.

IL17A levels in the serum of patients with autoimmune diseases such as asthma, rheumatoid arthritis, psoriasis, multiple sclerosis, and inflammatory bowel disease are higher[2, 3]. So maybe the anti-IL17A antibody could be an ideal drug for these types of disease. In January 2015, Novartis' IL17A monoclonal antibody Cosentyx (secukinumab) was approved by the European Union for the treatment of moderate to severe plaque psoriasis[4, 5]. In March 2016, Eli Lilly's IL17A monoclonal antibody Taltz (ixekizumab) is approved by the FDA for the treatment of psoriatic arthritis.

GemPharmatech independently developed a humanized IL17A mouse model using gene editing technology. In this model, the human IL17A gene was used to replace the mouse IL17A gene in situ. This strain will facilitate research on arthritis and other autoimmune disease.

Strategy

Fig.1 Schematic diagram of IL17A humanization strategy in BALB/c-hIL17A mice.

Application

1. Rheumatoid arthritis model and secondary osteoporosis model for anti-inflammatory immune drug development and pharmacodynamic evaluation
2. Medical research on IL17A related pathological mechanisms
3. Autoimmune disease research, cancer and antibody drug development

Supporting data

1. hIL17A mRNA expression analysis

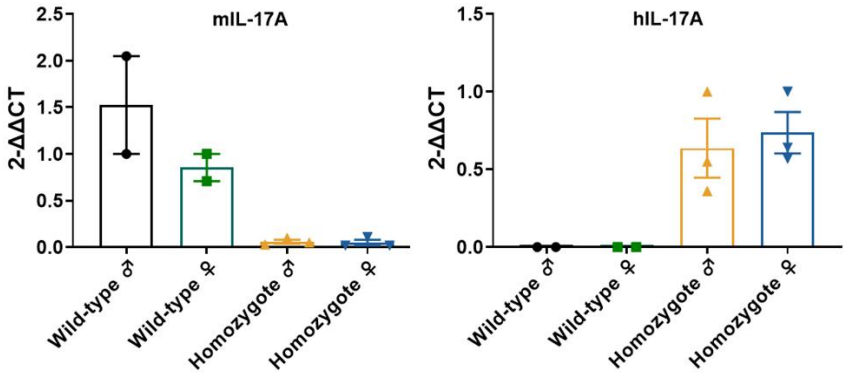

Fig.2 Quantitative PCR analysis of hIL17A mRNA expression in BALB/c-hIL-17A mice.
Wild-type BALB/c and homozygous BALB/c-hIL17A mice were treated with imiquimod (IMQ) cream daily for a total of 5 days. Back skin was collected at the endpoint, and RT-qPCR method was used to detect the mRNA expression of IL17A. The results showed that the expression of mIL17A mRNA was detectable in wild-type mice. The expression of hIL17A mRNA was only detectable in homozygous BALB/c-hIL17A.

2. Analysis of blood immune cell subpopulations in BALB/c-hIL17A mice

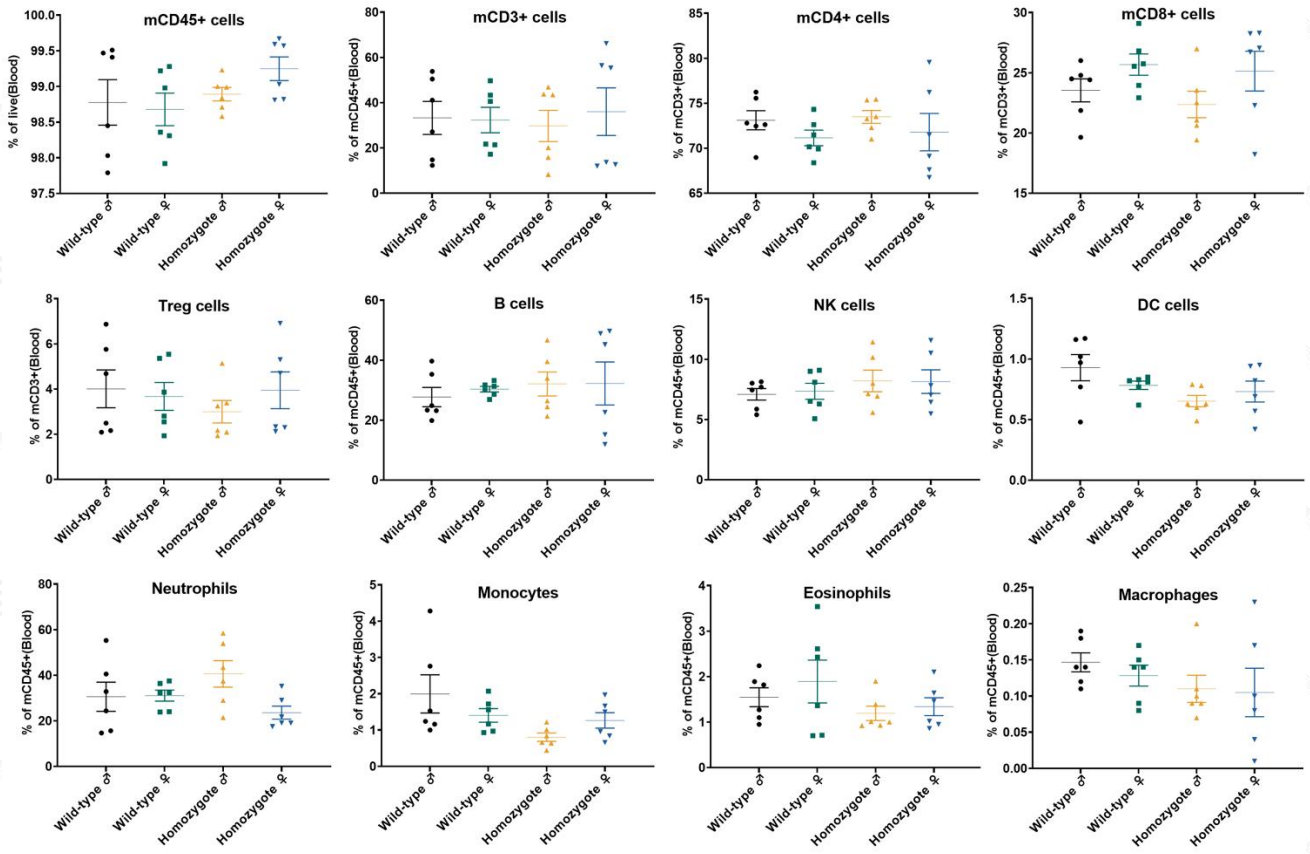

Fig.3 Analysis of blood immune cell subpopulations in BALB/c and BALB/c-hIL17A.

Blood was taken from BALB/c and BALB/c-hIL17A mice for flow cytometry analysis to assess immune cell subpopulations. As shown in Figure 3, the percentages of T cells, NK cells, neutrophils, eosinophils, monocytes, macrophages and dendritic cells in BALB/c-hIL17A mice were similar to those in BALB/c, indicating that the replacement of mIL17A by hIL17A did not alter the development, differentiation, and distribution of these cells in blood.

3. Analysis of spleen immune cell subpopulations in BALB/c-hIL17A mice

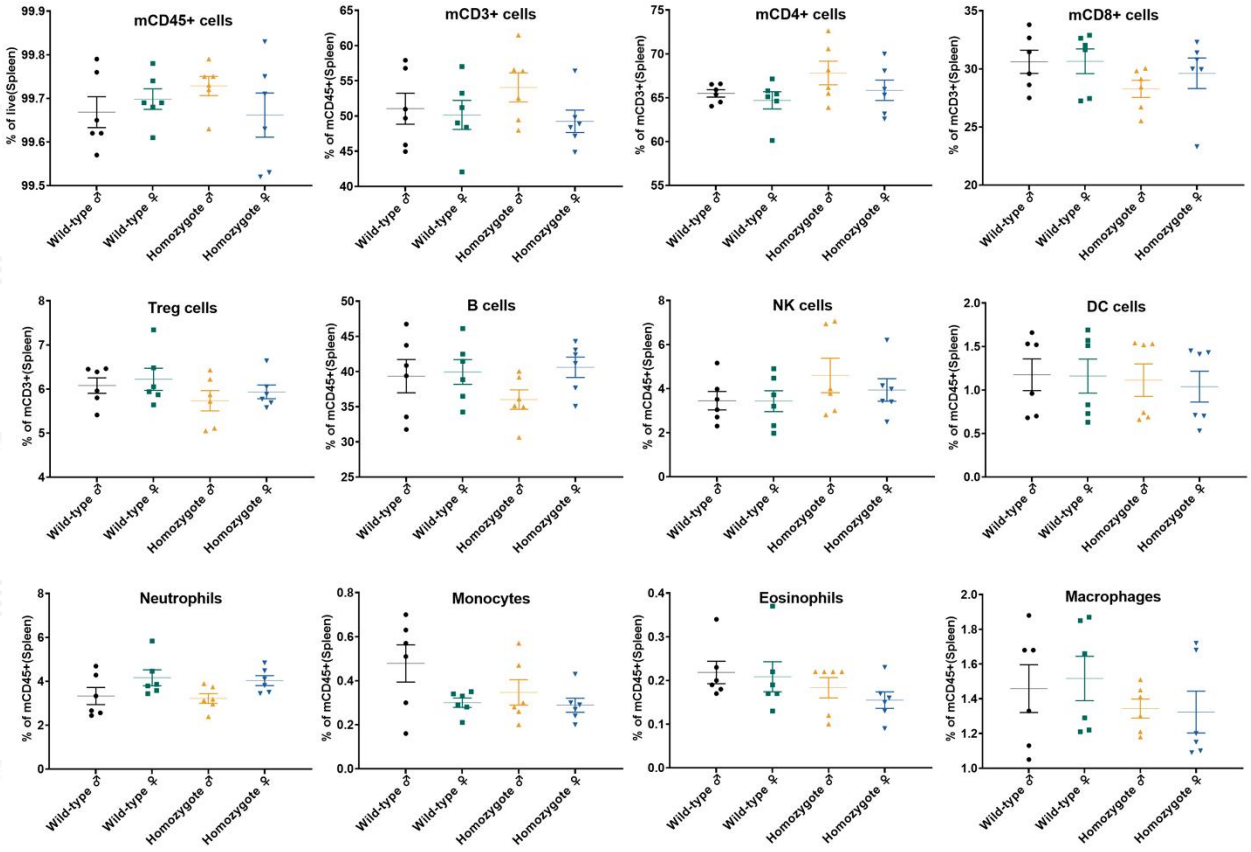

Fig.4 Analysis of spleen immune cell subpopulations in BALB/c and BALB/c-hIL17A

Splenocytes were taken from BALB/c and BALB/c-hIL17A 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, monocytes, and dendritic cells in BALB/c-hIL17A mice were similar to those in BALB/c, indicating that the replacement of mIL17A by hIL17A did not alter the development, differentiation, and distribution of these cells in spleen.

4. Blood biochemistry analysis in BALB/c- hIL17A

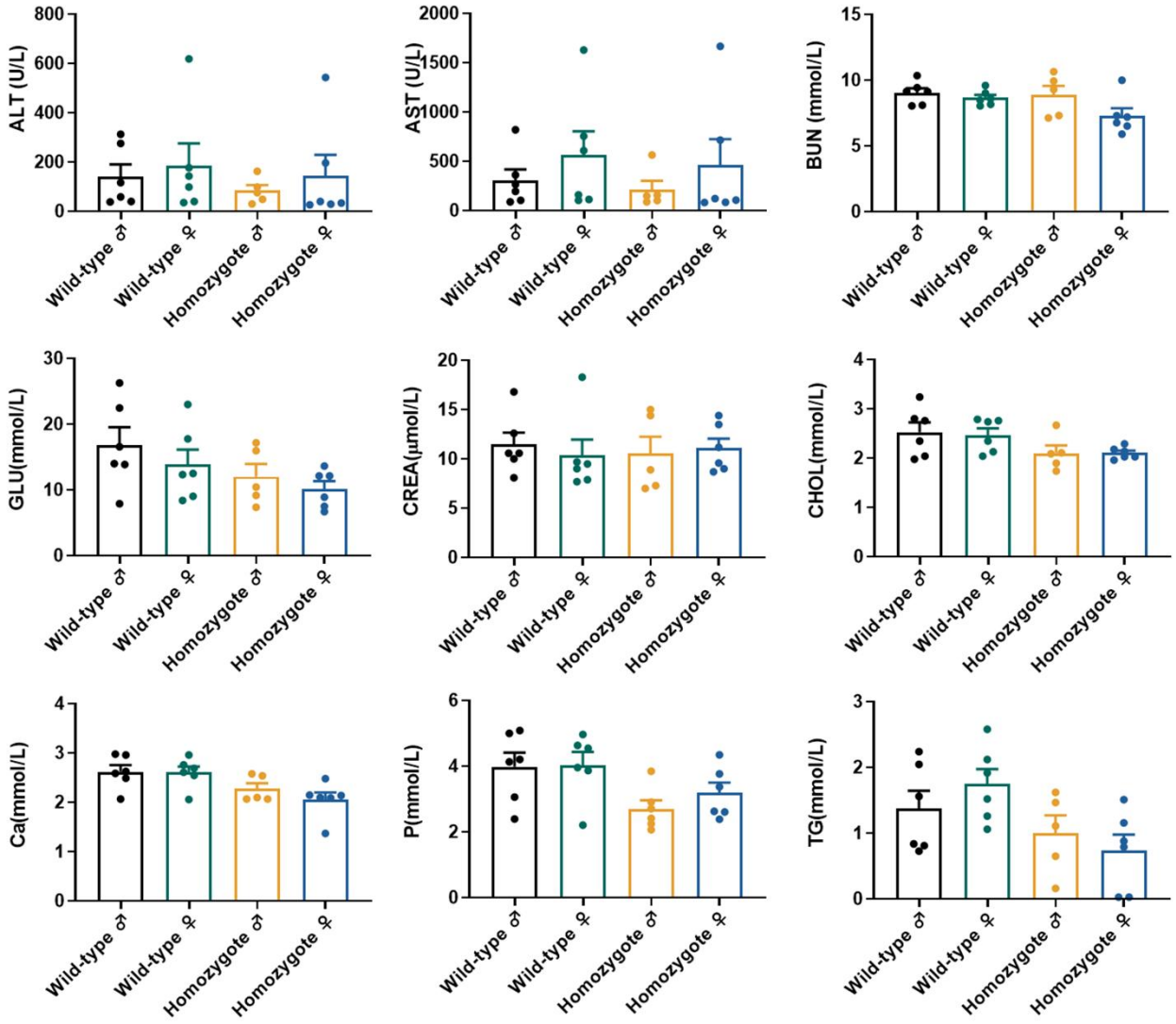

Fig.5 Blood biochemistry analysis in BALB/c and BALB/c-hIL17A

Blood biochemistry analysis was performed in wild-type BALB/c and homozygous BALB/c-hIL17A mice. As shown in Figure 5, there was no differences among any measurement between wild-type BALB/c and homozygous BALB/c-hIL17A mice.

5. The blood routine examination in BALB/c- hIL17A

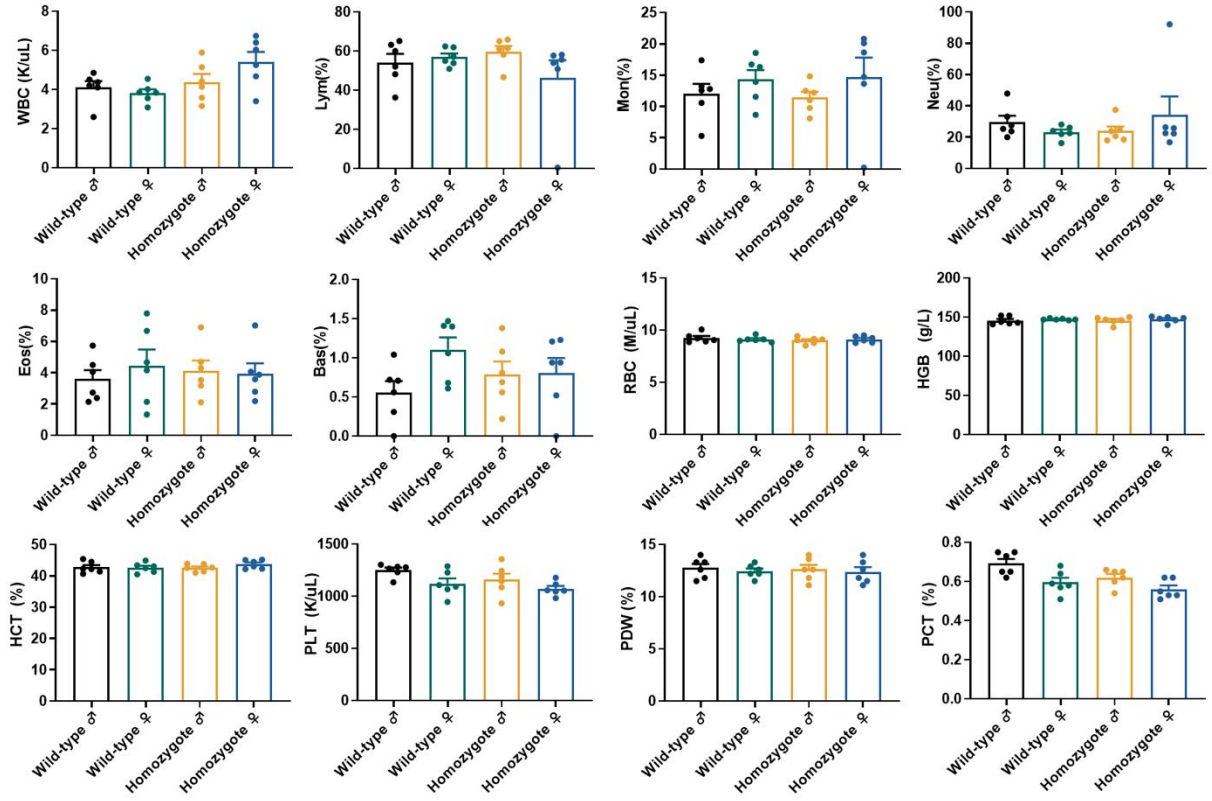

Fig.6 Complete blood count analysis in BALB/c and BALB/c-hIL17A

Blood routine examination was performed in wild-type BALB/c and homozygous BALB/c-hIL17A mice. As shown in Figure 6, there was no differences among any measurement between wild-type BALB/c and homozygous BALB/c-hIL17A mice.

6. Psoriasis model induced in BALB/c- hIL17A

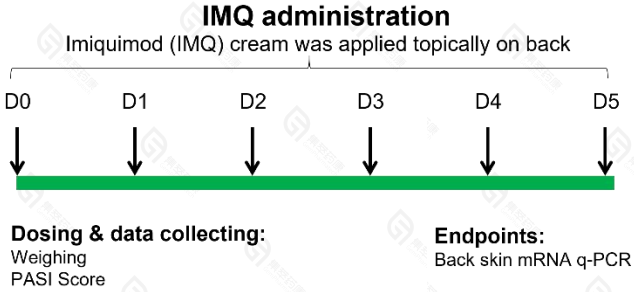

Fig. 7 Experimental schedule for induction of psoriasis in BALB/c-hIL17A mice

6.1 PASI score of back skin

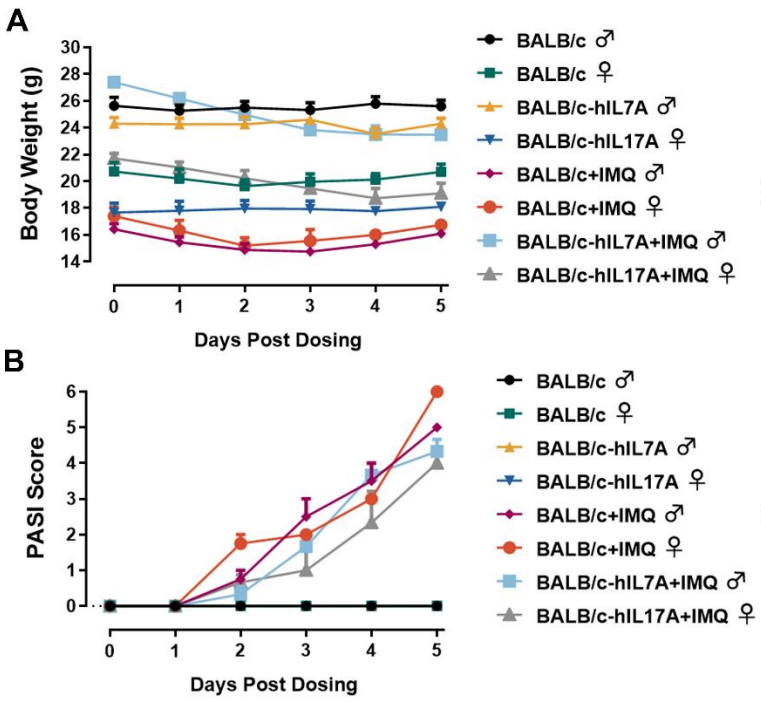

Fig.8 PASI score of back skin

Wild-type BALB/c and homozygous BALB/c-hIL17A mice were scored daily for up to 5 days for body weight and PASI score following treatment with imiquimod (IMQ) cream. (A) Body weight changes. (B) PASI score of the back skin. Results indicated the psoriasis model could be successfully induced with IMQ on our homozygous BALB/c-hIL17A mice.

6.2 Cytokine mRNA level in back skin

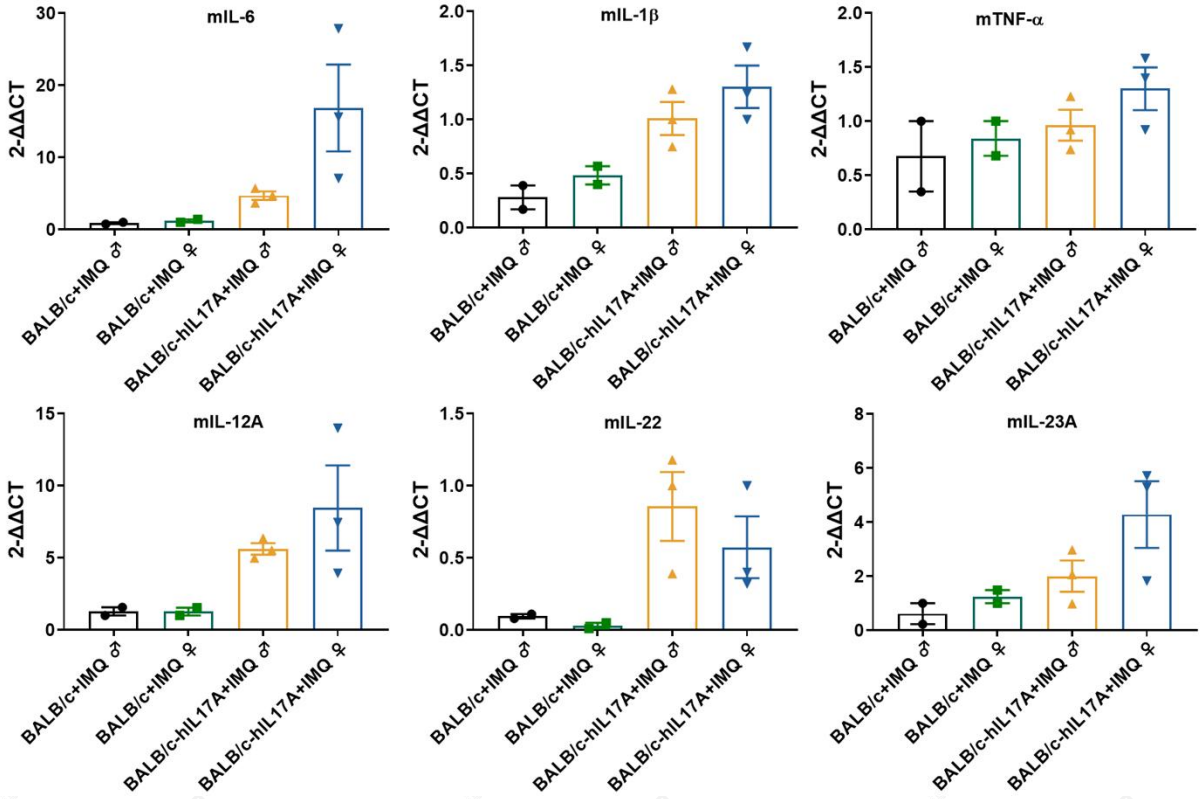

Fig.9 Quantitative PCR analysis of cytokine mRNA expression.

Back skin was collected at the endpoint, and RT-qPCR method was used to detect the mRNA expression of inflammatory cytokines. Results showed homozygous BALB/c-hIL17A mice had higher expression of inflammatory cytokines after IMQ stimulation

7. Dexamethasone efficacy evaluation in psoriasis model induced in BALB/c- hIL17A

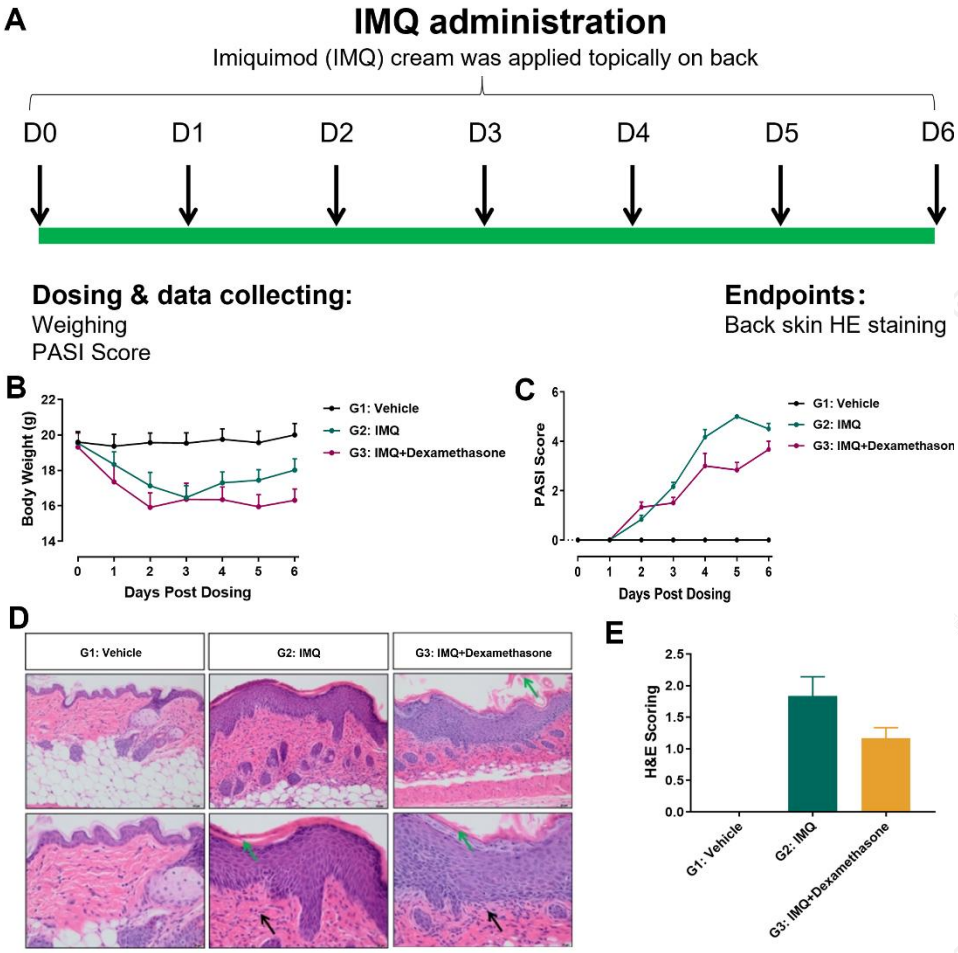

Fig.10 In vivo efficacy of dexamethasone in psoriasis model induced in BALB/c- hIL17A
Psoriasis model induced by IMQ in BALB/c- hIL17A mice. The body weight, PASI score and H&E staining of the back skin were collected after the treatment of dexamethasone. (A) Experimental schedule for induction of psoriasis in BALB/c-hIL17A mice. (B) Body weight changes during treatment. (C) PASI score of the back skin. (D) H&E staining of the back skin. (E) Histological changes were scored. Results indicated that dexamethasone had a good therapeutic effect on psoriasis-like skin lesions in our BALB/c-hIL17A mice.

References

1. Yao Z, Fanslow WC, Seldin MF, Rousseau AM, Painter SL, Comeau MR, Cohen JI, Spriggs MK: Herpesvirus Saimiri encodes a new cytokine, IL-17, which binds to a novel cytokine receptor. *Immunity* 1995, **3**, 811-821.

2. Lock C, Hermans G, Pedotti R, Brendolan A, Schadt E, Garren H, Langer-Gould A, Strober S, Cannella B, Allard J et al: Gene-microarray analysis of multiple sclerosis lesions yields new targets validated in autoimmune encephalomyelitis. *Nat. Med*. 2002,

8, 500-508.

3. Matusevicius D, Kivisakk P, He B, Kostulas N, Ozenci V, Fredrikson S, Link H: Interleukin-17 mRNA expression in blood and CSF mononuclear cells is augmented in multiple sclerosis. *Mult. Scler*. 1999, **5**, 101-104.

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5. Beringer A, Noack M, Miossec P: IL-17 in Chronic Inflammation: From Discovery to Targeting. *Trends Mol. Med*. 2016, **22**, 230-241.