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(54) Titre : ANTICORPS ANTI-IL17A HUMANISE ET SON UTILISATION
(54) Title: HUMANIZED ANTI-IL17A ANTIBODY AND USE THEREOF

(57) Abrégé/Abstract:
Provided are a humanized monoclonal antibody binding to IL 17A and a nucleic acid sequence (comprising heavy/light chain variable regions) encoding the antibody, a vector containing the nucleic acid sequence, a pharmaceutical composition and a kit. The monoclonal antibody can specifically bind to an IL 17A protein with a high affinity, has a stronger ability to block the binding of IL 17A and IL 17A/F to the receptor IL 17RA, and can be used for treating psoriasis, etc.

## ABSTRACT

Provided are a humanized monoclonal antibody binding to IL17A and a nucleic acid sequence (comprising heavy/light chain variable regions) encoding the antibody, a vector containing the nucleic acid sequence, a pharmaceutical composition and a kit. The monoclonal antibody can specifically bind to an IL17A protein with a high affinity, has a stronger ability to block the binding of IL17A and IL17A/F to the receptor IL17RA, and can be used for treating psoriasis, etc.

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# Humanized anti-IL17A antibody and use thereof

## TECHNICAL FIELD

**[0001]** The present invention relates to the field of tumor immunotherapy, and relates to a humanized anti-IL17A monoclonal antibody drug and application thereof.

## BACKGROUND

**[0002]** IL17A, also commonly referred to as IL-17, is an inflammatory cytokine consisting of 155 amino acids with a molecular weight of 35 kD. It is mainly secreted by helper T cells17, in addition to T cells17, CD4+, CD8+T, and γδ-T cells could also secrete IL-17. The IL-17 family contains six members, IL17A, IL-17B, IL-17C, IL-17D (IL-27), IL-17E (IL-25), and IL-17F (Gu, Wu et al. 2013), among which IL17A and IL-17F are the most important members. Being of 55% amino acid homology, IL17A and IL-17F can form homodimers or heterodimers connected by disulfide bonds (Dubin and Kolls 2009). Upon binding to a variety of IL-17RA-expressing cells in the IL-17 receptor family such as: macrophages, dendritic cells, hematopoietic cells, osteoblasts, fibroblasts, etc., IL17A/A or IL-17A/F dimer can activate NFκB, C/EBPs, MAPK and other signal pathways in the receptor cells, inducing these cells to secrete inflammatory factors and chemokines (IL-6, IL-8, CXCL1, etc.), recruit neutrophils, and mediate the development of inflammatory responses (Mitra, Raychaudhuri et al. 2014). The occurrence and development of many inflammation-related autoimmune diseases such as psoriasis, psoriatic arthritis, rheumatoid arthritis, and ankylosing spondylitis are closely associated with the IL-17 pathway (Wang, Suzuki et al. 2017), with significant up-regulation of IL-17 expression levels in the serum of patients (Marinoni, Ceribelli et al. 2014), leading to a persistent inflammatory response. In addition, IL-17 can also directly act on endothelial cells, epithelial cells, fibroblasts and keratinocytes in the skin,



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increasing the release of multiple inflammatory factors and creating pathological skin (Mitra, Raychaudhuri et al. 2014, Brembilla, Senra et al. 2018). Therefore, blockage of the IL-17 pathway provides feasibility to inhibit autoimmune diseases process.

**[0003]** Currently marketed antibody drugs targeting IL-17 are COSENTYX®/Secukinumab (US7807155B2) from Novartis and Taltz®/Ixekizumab (US7838638B2/CN101326195B) from Eli Lilly, the main mechanism is: through its binding to IL17A and IL17A/F, the binding of IL17A to the receptor (IL-17RA/C) is inhibited, sequentially the release of inflammatory factors and chemokines is blocked, thus autoimmune diseases (Fala 2016, Liu, Lu et al. 2016) is effectively alleviated. Secukinumab is approved for the treatment of plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis. Ixekizumab is approved for the treatment of plaque psoriasis and psoriatic arthritis. The humanized monoclonal IL17A antibody in the present invention is able to specifically bind IL17A protein with high affinity, has a strong ability to block the binding of IL17A, IL17A/F to the receptor IL17RA, and has a superior or equivalent ability to block IL17A, IL17A/F from inducing the inflammatory cytokine secretion of human epidermal fibroblasts HFF compared with comparable drugs; in the mouse psoriasis model, said antibody also shows significantly better *in vivo* pharmacodynamic activity than comparable drugs, with significantly lower PASI scores after dosing; , said humanized antibody demonstrates favorable pharmacokinetic profiles in the cynomolgus monkeys, including rapid absorption after subcutaneous injection, long half-life, and better drug exposure, laying the foundation for longer dosing cycles. The antibody of the present invention are planned to be used for, including but not limited to, the treatment of psoriasis.

## SUMMARY



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**[0004]** The present invention meets the above need by developing an IL17A binding antibody with a novel structure. The present invention discloses a humanized monoclonal antibody that binds IL17A specifically with high affinity and has a strong ability to block the binding of IL17A, IL17A/F to the receptor IL17RA. Compared with other comparable drugs, the antibody provided herein has superior or equivalent capability of blocking IL17A and IL17A/F to induce the inflammatory cytokine secretion of human epidermal fibroblasts HFF; in a mouse psoriasis model, said antibody also showed a significant advantage of *in vivo* pharmacological activity than comparable drugs, and significantly reduced PASI scores after dosing; in the pharmacokinetic study in cynomolgus monkeys, said humanized antibody demonstrated superior pharmacokinetic characteristics, including rapid absorption after subcutaneous injection, long half-life, better drug exposure, etc., laying the foundation for longer dosing cycles. The humanized monoclonal antibody of the present invention can be used for the treatment of psoriasis.

**[0005]** In one aspect, the present invention provides an isolated anti-IL17A antibody or antigen-binding fragment thereof, comprising a heavy chain variable region having a heavy chain CDR1 region having the amino acid sequence as set forth in SEQ ID NO: 13 and a heavy chain CDR2 region having the amino acid sequence as set forth in SEQ ID NO: 14 and a heavy chain CDR3 region having the amino acid sequence as set forth in SEQ ID NO: 15; and a light chain variable region having a light chain CDR1 region having the amino acid sequence as set forth in SEQ ID NO: 10, a light chain CDR2 region having the amino acid sequence as set forth in SEQ ID NO: 11, and a light chain CDR3 region having the amino acid sequence as set forth in SEQ ID NO: 12. (The 6 CDRs shared by murine antibody M069 and humanized antibody H069 are identical in mouse and human)

**[0006]** In one embodiment, said anti-IL17A antibody or antigen-binding fragment thereof has a heavy chain variable region having the amino acid



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sequence as set forth in SEQ ID NO: 22, or the amino acid sequences having at least 90%, 92%, 95%, 98% or 99% sequence identity to SEQ ID NO: 22; and a light chain variable region having the amino acid sequence as set forth in SEQ ID NO: 23, or the amino acid sequences having at least 90%, 92%, 95%, 98% or 99% sequence identity to SEQ ID NO: 23. (Amino acid sequences of the heavy chain and light chain variable regions of the humanized antibody H069)

**[0007]** In one embodiment, said anti-IL17A antibody or antigen-binding fragment thereof is a humanized antibody or a chimeric antibody.

**[0008]** In one embodiment, said anti-IL17A antibody further comprises a heavy chain constant region and a light chain constant region, preferably said heavy chain constant region is the IgG1 heavy chain constant region having the amino acid sequence as set forth in SEQ ID NO: 24, or the amino acid sequences having at least 90%, 92%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 24; and/or said light chain constant region is the human kappa light chain constant region having the amino acid sequence as set forth in SEQ ID NO: 25, or the amino acid sequences having at least 90%, 92%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 25. (Amino acid sequences of the heavy chain and light chain constant regions of the humanized antibody H069)

**[0009]** In one embodiment, said anti-IL17A antibody further comprises a signal peptide linked to the heavy chain variable region and/or a signal peptide linked to the light chain variable region, preferably said signal peptide linked to the heavy chain variable region is an amino acid sequence as set forth in SEQ ID NO: 20 or amino acid sequences having at least 90%, 92%, 95%, 98% or 99% sequence identity to SEQ ID NO: 20; and/or said signal peptide linked to the light chain variable region is an amino acid sequence as set forth in SEQ ID NO: 21 or amino acid sequences having at least 90%, 92%, 95%, 98% or 99% sequence identity to SEQ ID NO: 21. (Amino acid



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sequences of the heavy chain and light chain signal peptides of the humanized antibody H069)

**[0010]** In one embodiment, said anti-IL17A antibody or antigen-binding fragment thereof is an IgG antibody, preferably an IgG1 antibody.

**[0011]** In one embodiment, said anti-IL17A antibody or antigen-binding fragment thereof is a monoclonal antibody.

**[0012]** In one embodiment, the binding affinity KD of said anti-IL17A antibody or antigen-binding fragment thereof to the recombinant human IL17A protein is 0.1-10E-11M, preferably 0.5-5E-11M, and more preferably 2.88E-11M.

**[0013]** In one embodiment, the binding affinity KD of said anti-IL17A antibody or antigen-binding fragment thereof to the recombinant human IL17A/F protein is 0.1-10E-10M, preferably 0.5-5E-10M, and more preferably 5.37E-10M.

**[0014]** In one embodiment, said antigen-binding fragment is Fv, Fab, Fab', Fab'-SH, F(ab')2, Fd fragment, Fd' fragment, single chain antibody molecule or single domain antibody; wherein the single chain antibody molecule is preferably scFv, di-scFv, tri-scFv, diabody or scFab.

**[0015]** In another aspect, the present invention provides an antibody-drug conjugate, comprising the anti-IL17A antibody or antigen-binding fragment thereof as described herein and an additional therapeutic agent, preferably said anti-IL17A antibody or antigen-binding fragment thereof is connected with the additional therapeutic agent via a linker.

**[0016]** In yet another aspect, the present invention provides a nucleic acid encoding the anti-IL17A antibody or antigen-binding fragment thereof as described herein.

**[0017]** In one embodiment, said nucleic acid comprises a nucleotide sequence as set forth in SEQ ID NO: 30 encoding heavy chain variable region and/or a nucleotide sequence as set forth in SEQ ID NO: 31 encoding light chain variable region.



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**[0018]** In yet another aspect, the present invention provides an expression vector comprising the nucleic acid as described herein.

**[0019]** In yet another aspect, the present invention provides a host cell comprising the nucleic acid as described herein or the expression vector as described herein.

**[0020]** In yet another aspect, the present invention provides a method for producing the anti-IL17A antibody or antigen-binding fragment thereof as described herein, comprising culturing the host cell as described herein under conditions suitable for antibody expression, and recovering the expressed antibody from the culture medium.

**[0021]** In yet another aspect, the present invention provides a pharmaceutical composition comprising the anti-IL17A antibody or antigen-binding fragment thereof as described herein, or the antibody-drug conjugate as described herein, or the nucleic acid as described herein, or the expression vector as described herein, and a pharmaceutically acceptable carrier.

**[0022]** In yet another aspect, the present invention provides anti-IL17A antibodies or antigen-binding fragments thereof as described herein, or antibody-drug conjugates as described herein, or pharmaceutical compositions as described herein, for the treatment of psoriasis.

**[0023]** In yet another aspect, the present invention provides a method for treating psoriasis, comprising administering to a subject in need a therapeutically effective amount of the anti-IL17A antibody or antigen-binding fragment thereof as described herein, or the antibody-drug conjugate as described herein, or the pharmaceutical composition as described herein, thereby treating psoriasis.

**[0024]** In yet another aspect, the present invention provides the use of the anti-IL17A antibody or antigen-binding fragment thereof as described herein, or the antibody-drug conjugate as described herein or the pharmaceutical composition as described herein in the preparation of a medicament for the treatment of psoriasis.



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**[0025]** In yet another aspect, the present invention provides a pharmaceutical composition comprising the anti-IL17A antibody or antigen-binding fragment thereof as described herein, or the antibody-drug conjugate as described herein, or the pharmaceutical composition as described herein, and one or more additional therapeutic agents.

**[0026]** In yet another aspect, the present invention provides a kit comprising the anti-IL17A antibody or antigen-binding fragment thereof as described herein, or the antibody-drug conjugate as described herein, or the pharmaceutical composition as described herein, and preferably further comprising a device for administration.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0027]** Figure 1 shows that IL17A-M069 blocks IL17A-induced IL-6 secretion of HFF cells. Figure 2 shows the binding of IL17A-H069 to recombinant human IL17A protein.

**[0028]** Figure 3 shows the binding of IL17A-H069 to recombinant human IL17A/F protein.

**[0029]** Figure 4 shows the species cross-binding between IL17A-H069 and mouse IL17A protein.

**[0030]** Figure 5 shows that IL17A-H069 blocks the binding of IL17RA to IL17A protein.

**[0031]** Figure 6 shows that IL17A-H069 blocks the binding of IL17RA to IL17A/F protein.

**[0032]** Figure 7 shows that IL17A-H069 blocks IL17A-mediated IL-6 secretion of HFF cells.

**[0033]** Figure 8 shows the effect of IL17A-H069 on the Psoriasis Area and Severity Index PASI in a mouse psoriasis model.

**[0034]** Figure 9 shows the drug concentration-time curve of a single subcutaneous injection of IL17A-H069 in cynomolgus monkeys.



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## DETAILED DESCRIPTION

**[0035]** Various aspects of the present invention relate to an isolated anti-IL17A antibody or antigen-binding fragment thereof, an antibody-drug conjugate comprising said antibody or antigen-binding fragment thereof, a nucleic acid and an expression vector encoding said antibody or antigen-binding fragment thereof, and a host cell containing said nucleic acid or expression vector, a method for producing said anti-IL17A antibody or antigen-binding fragment thereof, a pharmaceutical composition comprising said anti-IL17A antibody or antigen-binding fragment thereof, and a method of using said anti-IL17A antibody or antigen-binding fragment thereof for treating psoriasis.

**[0036]** ***Definition***

**[0037]** Unless otherwise stated, all technical and scientific terms used herein have the meaning normally understood by a person skilled in the art to which the present invention belongs. For the purposes of the present invention, the following terms are defined to be consistent with the meanings commonly understood in the art.

**[0038]** When used herein and in the appended claims, the singular forms "one", "a/an", "another" and "said" include the plural designation of the object unless the context clearly indicates otherwise.

**[0039]** The term "antibody" refers to an immunoglobulin molecule and refers to any form of antibody that exhibits the desired biological activity. These include, but are not limited to, monoclonal antibodies (including full-length monoclonal antibodies), polyclonal antibodies and multispecific antibodies (e.g. bispecific antibodies), and even antibody fragments. Typically, full-length antibody structures preferably comprise four polypeptide chains, two heavy (H) chains and two light (L) chains, typically interconnected by disulfide bonds. Each heavy chain contains a heavy chain variable region and a heavy chain constant region. Each light chain contains a light chain variable



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region and a light chain constant region. In addition to this typical full-length antibody structure, the structure also includes other derivative forms.

**[0040]** Said heavy chain variable region and light chain variable region can be further subdivided into more conservative regions (called framework regions (FR)) and hypervariable regions (called complementarity determining regions (CDR)) interspersed therewith.

**[0041]** The term "complementary determining region" (CDR, e.g. CDR1, CDR2 and CDR3) refers to such amino acid residues in the variable region of an antibody whose presence is necessary for antigen binding. Each variable region typically has three CDR regions identified as CDR1, CDR2 and CDR3. Each complementary determining region may contain amino acid residues from a "complementary determining region" as defined by Kabat (Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD. 1991) and/or those residues from the "high-variable loop" (Chothia and Lesk; J MolBiol 196: 901-917 (1987)).

**[0042]** The term "framework" or "FR" residues are those residues within the variable region other than CDR residues as defined herein.

**[0043]** Each heavy chain variable region and light chain variable region typically contains 3 CDRs and up to 4 FRs, said CDRs and FRs being arranged from the amino terminus to the carboxyl terminus in the following order, for example: FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4.

**[0044]** The complementary determining region (CDR) and the framework region (FR) of a given antibody can be identified using the Kabat system (Kabat et al: Sequences of Proteins of Immunological Interest, 5th edition, US Department of Health and Human Services, PHS, NIH, NIH Publication No. 91- 3242, 1991).

**[0045]** The term "constant region" refers to such amino acid sequences in the light and heavy chains of an antibody that are not directly involved in the



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binding of the antibody to the antigen but exhibit a variety of effector functions such as antibody-dependent cytotoxicity.

**[0046]** According to the antigenic differences of the amino acid sequence of its constant region, the heavy chain of an antibody can be classified into five classes: α, δ, ε, γ, and μ. When it forms a complete antibody with the light chain, it can be classified into five classes: IgA , IgD, IgE, IgG and IgM, of which can be further classified into subclasses (isotypes), such as IgG1, IgG2, IgG3, IgG4, IgA and IgA2. Based on the amino acid sequence of its constant domain, the light chain of an antibody can be classified into κ and λ.

**[0047]** An "antigen-binding fragment of an antibody" comprises a portion of an intact antibody molecule that retains at least some of the binding specificity of the parent antibody and typically includes at least a portion of the antigen-binding region or variable region (e.g. one or more CDRs) of the parent antibody. Examples of antigen-binding fragments include, but are not limited to, Fv, Fab, Fab', Fab'-SH, F(ab')2, Fd fragment, Fd' fragment, single chain antibody molecules (e.g. scFv, di-scFv or tri-scFv, diabody or scFab), single domain antibodies.

**[0048]** The term "antibody fragment" refers to a non-intact antibody molecule that retains at least some of the biological properties of the parent antibody, including, but not limited to, an Fc fragment, in addition to those described above as "antigen-binding fragments".

**[0049]** The term "antibody-drug conjugate" or "ADC" refers to a binding protein, such as an antibody or antigen-binding fragment thereof, that chemically linked to one or more of chemical drugs (also referred to as agents herein), which may optionally be a therapeutic agent or a cytotoxic agent. In a preferred embodiment, an ADC includes an antibody, a cytotoxic or therapeutic drug, and a linker that enables the drug to be linked or conjugated to the antibody. ADCs usually have any value of 1 to 8 drugs conjugated to the antibody, including 2, 4, 6, or 8 drug-loading substances. Non-limiting examples of drugs that can be included in the ADCs are mitotic inhibitors,



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anti-tumor antibiotics, immunomodulators, vectors for gene therapy, alkylating agents, anti-IL17A agents, antimetabolites, boron-containing agents, chemotherapeutic protective agents, hormones, antihormonal agents, corticosteroids, photoactive therapeutic agents, oligonucleotides, radionuclide agents, topoisomerase inhibitors, tyrosine kinase inhibitors and radiosensitizers.

**[0050]** The term "chimeric antibody" refers to an antibody in which a part of the heavy chain and/or light chain is derived from a specific source or species, and the remaining part is derived from a different source or species. The "chimeric antibody" may also be a functional fragment as defined above. "Humanized antibodies" are a subset of "chimeric antibodies."

**[0051]** The term "humanized antibody" or "humanized antigen-binding fragment" is defined herein as an antibody or antibody fragment that is: (i) derived from a non-human source (e.g., a transgenic mouse carrying a heterologous immune system) and based on a human germline sequence; or (ii) a chimeric antibody where the variable region is of non-human origin and the constant region is of human origin; or (iii) a CDR transplant where the CDR of the variable region is of non-human origin and one or more frame work regions of the variable region are of human origin and the constant region, if any, is of human origin. The aim of "humanization" is to eliminate the immunogenicity of antibodies of non-human origin in the human body, while retaining the greatest possible affinity. It is advantageous to select the human framework sequence that is most similar to the framework sequence of the non-human source antibody as the template for humanization. In some cases, it may be necessary to replace one or more amino acids in the human framework sequence with corresponding residues in the non-human construct to avoid loss of affinity.

**[0052]** The term "monoclonal antibody" refers to an antibody derived from a substantially homogeneous population of antibodies, i.e. every single antibody comprised in the population is identical except for possible



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mutations (e.g. natural mutations) which may be present in very small quantities. The term "monoclonal" therefore indicates the nature of the antibody in question, i.e. not a mixture of unrelated antibodies. In contrast to polyclonal antibody preparations, which usually comprise different antibodies against different epitopes, each monoclonal antibody in a monoclonal antibody preparation is directed against a single epitope on the antigen. In addition to their specificity, monoclonal antibody preparations have the advantage that they are usually not contaminated by other antibodies. The term "monoclonal" should not be understood as requiring the production of said antibodies by any particular method.

**[0053]** The antibody "specifically binds" to a target antigen such as a tumor-associated peptide antigen target (in this case, PD-1), i.e. binds said antigen with sufficient affinity to enable said antibody to be used as a therapeutic agent, targeting a cell or tissue expressing said antigen, and does not significantly cross-react with other proteins, or does not significantly cross-react with proteins other than the homologues and variants of the target proteins mentioned above (e.g. mutant forms, splice variants, or protein hydrolysis truncated forms).

**[0054]** The term "binding affinity" refers to the strength of the sum of the non-covalent interactions between a molecule's individual binding sites and its binding partners. Unless otherwise stated, "binding affinity", when used herein, refers to the intrinsic binding affinity, which reflects a 1:1 interaction between members of a binding pair (e.g. antibody and antigen). As used herein, the term "KD" refers to the equilibrium dissociation constant of the antibody-antigen interaction. As used herein, the term "$k_{on}$" refers to the rate constant at which an antibody binds to an antigen. As used herein, the term "$k_{off}$" refers to the rate constant at which an antibody dissociates from an antibody/antigen complex. "KD", "binding rate constant $k_{on}$" and "dissociation rate constant $k_{off}$" are commonly used to describe the affinity between a molecule (e.g. an antibody) and its binding partner (e.g. an



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antigen). Affinity, i.e. the tight degree at which a receptor binds a particular protein. Binding affinity is influenced by non-covalent intermolecular interactions such as hydrogen bonding, electrostatic interactions, hydrophobic and van der Waals forces between two molecules. In addition, the binding affinity between a ligand and its target molecule may be influenced by the presence of other molecules. Affinity can be analyzed by conventional methods known in the art, including the ELISA described herein.

**[0055]** The term "epitope" includes any protein determinant cluster that specifically binds to an antibody or T-cell receptor. Epitope determinant clusters typically consist of a molecule's chemically active surface groups (e.g. amino acid or sugar side chains, or a combination thereof) and often have specific three-dimensional structural features as well as specific charge characteristics.

**[0056]** The term "isolated" antibody is an antibody that has been identified and isolated from the components of the cell where the antibody expressed. Isolated antibodies include in situ antibodies inside of recombinant cells, where at least one component in natural environment of said antibody is absent. However, usually, the isolated antibody is prepared through at least one purification step.

**[0057]** "sequence identity" between two polypeptides or nucleic acid sequences indicates the number of residues that are identical between said sequences as a percentage of the total number of residues, and is calculated based on the size of the smaller of the compared molecules. When calculating the percentage identity, the sequences being aligned are matched in such a way as to produce a maximum match between the sequences, with the gaps in the match (if present) being resolved by a specific algorithm. Preferred computer program methods for determining identity between two sequences include, but are not limited to, GCG program packages including GAP, BLASTP, BLASTN and FASTA (Altschul et al., 1990, J. Mol. Biol. 215: 403-



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410). The above procedures are publicly available from the International Center for Biotechnology Information (NCBI) and other sources. The well-known Smith Waterman algorithm can also be used to determine identity.

**[0058]** The term "Fc receptor" or "FcR" refers to a receptor that binds to the Fc region of an antibody. Human FcRs of natural sequence are preferred, and preferably receptors that bind to IgG antibodies (gamma receptors), which include the FcγRI, FcγRII and FcγRIII isoforms, as well as variants of these receptors. All other FcRs are included in the term "FcR". The term also includes the neonatal receptor (FcRn), which is responsible for the transport of maternal IgG to the fetus (Guyer et al, Journal of Immunology 117: 587 (1976) and Kim et al, Journal of Immunology 24: 249 (1994)).

**[0059]** The term "neonatal Fc receptor", abbreviated as "FcRn", binds to the Fc region of IgG antibodies. The neonatal Fc receptor (FcRn) plays an important role in the metabolic fate of IgG-like antibodies in vivo. FcRn functions to rescue IgG from the lysosomal degradation pathway, thereby reducing its clearance in serum and lengthening its half-life. Therefore, the in vitro FcRn binding properties/characteristics of IgG are indicative of its in vivo pharmacokinetic properties in the circulation.

**[0060]** The term "effector function" refers to those biological activities attributable to the Fc region of an antibody, which vary from isotype to isotype. Examples of antibody effector functions include C1q binding and complement-dependent cytotoxicity (CDC), Fc receptor binding, antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), cytokine secretion, immune complex-mediated uptake of antigen by antigen-presenting cells, cell surface receptors down-regulation (e.g. B-cell receptors) and B-cell activation.

**[0061]** The term "effector cell" refers to a leukocyte that expresses one or more FcRs and performs effector functions. In one aspect, said effector cells express at least FcγRIII and perform ADCC effector functions. Examples of human leukocytes that mediate ADCC include peripheral blood mononuclear



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cells (PBMCs), natural killer (NK) cells, monocytes, cytotoxic T cells and neutrophils. Effector cells can be isolated from natural sources, for example, blood. Effector cells are usually lymphocytes associated with effector phase and function to produce cytokines (helper T cells), kill cells infected by pathogens (cytotoxic T cells) or secrete antibodies (differentiated B cells).

**[0062]** "Immune cells" include cells that have a haematopoietic origin and play a role in the immune response. Immune cells include: lymphocytes, such as B cells and T cells; natural killer cells; and myeloid cells, such as monocytes, macrophages, eosinophils, mast cells, basophils and granulocytes.

**[0063]** "Antibody-dependent cell-mediated cytotoxicity" or "ADCC" refers to a form of cytotoxicity in which secreted Ig binds to Fcγ receptors presented on certain cytotoxic cells (e.g. NK cells, neutrophils and macrophages) allows these cytotoxic effector cells to specifically bind to target cells bearing antigens and subsequently kill said target cells using, for example, a cytotoxin. To assess the ADCC activity of the target antibody, in vitro ADCC assays can be performed, such as the in vitro ADCC assays documented in US Patent No. 5,500,362 or 5,821,337 or US Patent No. 6,737,056 (Presta). Useful effector cells for use in such assays include PBMCs and NK cells.

**[0064]** "Complement-dependent cytotoxicity" or "CDC" refers to the lysis of target cells in the presence of complement. The classic pathway for complement activation is initiated by binding the first component of the complement system (C1q) to an antibody (of the appropriate subclass) that binds to its corresponding antigen. To assess complement activation, a CDC assay can be performed, such as the CDC assay recited in Gazzano-Santoro et al., J. Immunol Methods 202: 163 (1996). For example in US Patent No. 6,194,551 Bl and WO1999/51642, there described polypeptide variants having altered amino acid sequences of the Fc region (polypeptides having a variant Fc region) and polypeptide variants having enhanced or reduced C1q binding.



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**[0065]** The terms "COSENTYX biosimilar" and "Taltz biosimilar" refer to antibodies prepared according to the structures of COSENTYX and Taltz, respectively.

**[0066]** ***Amino acid sequence of the antibody of the present invention***

**[0067]** The present invention used recombinant human IL17A protein to immunize mice, and then obtained the antibody clone IL17A-M069 that specifically bind to recombinant human IL17A protein by phage display library screening. The nucleotide sequences encoding the heavy and light chain variable regions of the IL17A-M069 scFv antibody were then inserted by PCR into pSTEP2 vectors harboring nucleotide sequence encoding the mouse IgG1 constant region or the mouse kappa light chain constant region respectively, and cultured for expression. The high purity antibodies were purified using a protein A purification column. ELISA showed that said murine antibody was able to block the binding of IL17A induced IL-6 secretion of HFF cells.

**[0068]** Then, using the classic method for humanized CDR transplantation, the human antibody light chain or heavy chain variable region whose sequence is closer to the sequence of mouse light chain or heavy chain variable region was elected as the template, the humanized light chain variable region (VL) and heavy chain variable region (VH) sequences were obtained by inserting each of the three CDRs (Table 1) of the murine antibody light chain or heavy chain into the variable regions of said human antibody. As the key sites of the mouse framework region are essential for maintaining the stability of the CDR activity, the key sites were reverse-mutated to the corresponding sequence of murine antibody. IL17A-H069 light chain/heavy chain expression vectors were obtained by whole gene synthesis, transfected into CHO-K1-GS deficient cells and cultured for expression, and the clones having high antibody expression were selected for further culture to obtain IL17A-H069 antibodies with high purity and high quality.



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**[0069]** ***Nucleic acids of the present invention***

**[0070]** The present invention also relates to nucleic acid molecules encoding antibodies or portions thereof of the present invention. The sequences of these nucleic acid molecules include, but are not limited to, SEQ ID NOs: 2-7, 26-33, 36-37, 40-41 and 43.

**[0071]** The nucleic acid molecules of the present invention are not limited to the sequences disclosed herein, but also include variants thereof. Variants in the present invention may be described with reference to their physical properties in hybridization. It will be recognized by those of skill in the art that using nucleic acid hybridization techniques, nucleic acids can be used to identify their complements as well as their equivalents or homologues. It will also be recognized that hybridization can occur at less than 100% complementarity. However, given the appropriate choice of conditions, hybridization techniques can be used to distinguish said DNA sequences based on the structural relevance of the DNA sequence to a particular probe. For guidance on such conditions see Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd Ed. Cold Spring Harbor Press, Cold Spring Harbor, N. Y., 1989 and Ausubel, F. M., Brent, R., Kingston, R. E., Moore, D. D., Sedman, J. G., Smith, J. A., &Struhl, K. eds. (1995). Current Protocols in Molecular Biology. New York: John Wiley and Sons.

**[0072]** ***Recombinant vectors and expression***

**[0073]** The present invention also provides recombinant constructs comprising one or more nucleotide sequences of the present invention. The recombinant construct of the present invention is constructed by inserting the nucleic acid molecule encoding the antibody of the present invention into a vector such as a plasmid, phagemid, phage or viral vector.

**[0074]** The antibodies provided herein can be prepared by recombinantly expressing nucleotide sequences encoding light and heavy chains or portions thereof in a host cell. In order to recombinantly express the antibody, the host cell may be transfected with one or more recombinant expression vectors



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carrying nucleotide sequences encoding the light and/or heavy chains or portions thereof, so that said light and heavy chains are expressed in said host cell. Standard recombinant DNA methodologies are used to prepare and/or obtain nucleic acids encoding heavy and light chains, to incorporate these nucleic acids into recombinant expression vectors and to introduce said vectors into host cells, e.g. Sambrook, Fritsch and Maniatis (eds.), Molecular Cloning; A Laboratory Manual, Second Edition, Cold Spring Harbor, N.Y., (1989), Ausubel, F. M. et al. (eds.) Current Protocols in Molecular Biology, Greene Publishing Associates, (1989) and those documented in U.S. Patent No. 4,816,397 by Boss et al.

**[0075]** Suitable host cells are prokaryotic and eukaryotic cells. Examples of prokaryotic host cells are bacteria and examples of eukaryotic host cells are yeast, insect or mammalian cells. It should be understood that the design of an expression vector including the selection of a regulatory sequence is determined by a number of factors, such as the choice of host cell, the level of expression of the desired protein and whether the expression is constitutive or inducible.

**[0076]** ***Bacterial expression***

**[0077]** By inserting a structural DNA sequence encoding the desired antibody together with appropriate translation initiation and termination signals and a functional promoters into an operable reading frame, an expression vector for use in bacteria is constructed. The vector will contain one or more phenotypic selection markers and an origin of replication to ensure the maintenance of the vector and provide amplification in the host as needed. Suitable prokaryotic hosts for transformation include multiple species of *E. coli*, *Bacillus subtilis*, *Salmonella typhimurium*, as well as *Pseudomonas*, *Streptomyces* and *Staphylococcus*.

**[0078]** The bacterial vector may be, for example, phage-, plasmid- or phagemid-based. These vectors may contain selection markers and bacterial replication origins, which are derived from commercially available plasmids



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that usually contain elements of the well-known cloning vector pBR322 (ATCC 37017). After transforming an appropriate host strain and growing the host strain to an appropriate cell density, the selected promoter is de-repressed/induced by an appropriate method (for example, temperature change or chemical induction), and the cells are cultured for an additional time. The cells are usually harvested by centrifugation, disrupted by physical or chemical methods, and the resulting crude extract is retained for further purification.

**[0079]** In a bacterial system, a variety of expression vectors can be advantageously selected according to the intended use of the expressed protein. For example, when a large number of such proteins are to be produced for antibody production or for peptide library screening, for example, a vector that directs high-level expression of a fusion protein product to be easily purified may be required.

**[0080]** ***Mammalian Expression and Purification***

**[0081]** Preferred regulatory sequences for expression in mammalian host cells include viral elements that direct high-level protein expression in mammalian cells, such as promoters and/or enhancers derived from cytomegalovirus (CMV) (e.g., CMV promoter/enhancer), promoters and/or enhancers of simian virus 40 (SV40) (e.g. SV40 promoter/enhancer), promoters and/or enhancers of adenovirus (e.g. adenovirus major late promoter (AdMLP) ) and promoters and/or enhancers of polyoma virus. For a further description of viral regulatory elements and their sequences, see, for example, U.S. 5,168,062 by Stinski, U.S. 4,510,245 by Bell et al., and U.S. 4,968,615 by Schaffner et al. The recombinant expression vector may also include an origin of replication and a selection marker (see, for example, U.S. 4,399,216, U.S. 4,634,665 and U.S. 5,179,017 by Axel et al). Suitable selection markers include genes that confer resistance to drugs such as G418, hygromycin, or methotrexate to host cells into which the vector has been



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introduced. For example, the dihydrofolate reductase (DHFR) gene confers resistance to methotrexate, while the neo gene confers resistance to G418.

**[0082]** The transfection of the expression vector into host cells can be performed using standard techniques such as electroporation, calcium phosphate precipitation, and DEAE-dextran transfection.

**[0083]** Suitable mammalian host cells for expressing the antibodies provided herein include Chinese Hamster Ovary (CHO cells) [including dhfr-CHO cells, as described in Urlaub and Chasin, (1980) Proc. Natl. Acad. Sci. USA 77:4216-4220, DHFR selection markers are employed, as described in, for example, R.J. Kaufman and P.A. Sharp (1982) Mol. Biol. 159:601-621], NSO myeloma cells, COS cells, and SP2 cells.

**[0084]** The antibodies of the present invention can be recovered and purified from recombinant cell culture by known methods, including but not limited to, ammonium sulfate or ethanol precipitation, acid extraction, protein A affinity chromatography, protein G affinity chromatography, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxyapatite chromatography, and lectin chromatography. High performance liquid chromatography ("HPLC") can be used for purification as well. See, for example, Colligan, Current Protocols in Immunology, or Current Protocols in Protein Science, John Wiley & Sons, NY, N.Y., (1997-2001), for example, Chapters 1, 4, 6, 8, 9, and 10.

**[0085]** ***Characteristics and functions of the antibody of the present invention***

**[0086]** Characteristic analysis and function analysis of the humanized IL17A-H069 antibody of the present invention were performed. The analyses showed that the antibody of the present invention has the following advantages:



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**[0087]** (1) A better specific binding to recombinant human IL17A protein than COSENTYX biosimilar (the $EC_{50}$ of the humanized IL17A-H069 antibody is 46 ng/mL, whereas the EC50 of COSENTYX biosimilar is 74.8 ng/mL) (Example 4.1.1).

**[0088]** (2) A better specific binding to recombinant human IL17A/F dimer protein than COSENTYX biosimilar (the EC50 of the humanized IL17A-H069 antibody is 36.3 ng/mL; while the EC50 of COSENTYX biosimilar is 63.9 ng/mL) (Example 4.1.2).

**[0089]** (3) A good binding affinity (much higher than COSENTYX biosimilar; 2.88E-11M vs. 9.55-11M) and a favorable association rate (much faster than COSENTYX; 6.71E+05 $M^{-1}s^{-1}$ vs. 1.78E+05 $M^{-1}s^{-1}$) with recombinant human IL17A protein, a good binding affinity (higher than COSENTYX biosimilar; 5.37E-10M vs. 1.10-09M) and a favorable association rate (faster than COSENTYX biosimilar; 1.44E+05 $M^{-1}s^{-1}$ vs. 8.00E+04 $M^{-1}s^{-1}$) (Example 4.1.3).

**[0090]** (4) No species cross-binding activity to mouse mIL17A protein (Example 4.1.4).

**[0091]** (5) Effectively binds recombinant human IL17A protein and effectively inhibits IL17A protein from binding to receptor IL17RA significantly better than COSENTYX biosimilar, but close to Taltz biosimilar ($IC_{50}$: 0.50 μg/mL vs. 2.99 μg/mL vs. 0.50 μg/mL; maximum inhibition rate: 85.4% vs. 73.5% vs. 89.5% (Example 4.2.1).

**[0092]** (6) Effectively binds recombinant human IL17A/F dimer protein and effectively inhibits IL17A protein from binding to receptor IL17RA, better than COSENTYX biosimilar and Taltz biosimilar ($IC_{50}$: 1.02 μg/mL vs. 1.2 μg/mL vs. 1.35 μg/mL; maximum inhibition rate: 92.3%, 87.9%, and 75%) (Example 4.2.2).

**[0093]** (7) Blocks IL17A, IL17A/F induced-IL-6 secretion of HFF cells; the activity of neutralizing IL17A is much higher than that of COSENTYX biosimilar ($EC_{50}$ 0.19 μg/mL vs. 0.22 μg/mL, maximum neutralization rate



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94.6% vs. 51.6%) and the activity of neutralizing IL17A is close to that of Taltz biosimilar ($EC_{50}$ 0.20 μg/mL vs. 0.19 μg/mL, maximum neutralization rate 90.3% vs. 95.9%); the activity of neutralizing IL17A/F is also higher than that of COSENTYX biosimilar ($EC_{50}$ 1.19 μg/mL vs. 2.25 μg/mL, maximum neutralization rate 85.0% vs. 79.5%); and, the activity of neutralizing IL17A/F is better than Taltz biosimilar at low concentrations but close to Taltz biosimilar at high concentrations ($EC_{50}$: 0.83 μg/mL vs. 1.10 μg/mL, maximum neutralization rate: 72.90% vs. 76.3%) (Example 5.1).

**[0094]** (8) Being validated in the mouse psoriasis model, the antibody of the present invention effectively alleviates the progression of psoriasis and reduces symptoms with significantly better efficacy than Taltz biosimilar (Example 6).

**[0095]** (9) Pharmacokinetically, the antibody of the present invention has a faster absorption after subcutaneous injection and a longer half-life (Example 7).

**[0096]** ***Uses***

**[0097]** The antibodies of the present invention can be used to treat colorectal cancer. The antibody of the present invention can also be used to prepare medicines for the treatment of said disorders.

**[0098]** ***Pharmaceutical compositions***

**[0099]** Antibodies of the present invention may be prepared with at least one other agent (e.g. a stable compound) to form pharmaceutical compositions comprising an antibody of the present invention and one or more pharmaceutically acceptable carriers, diluents or excipients. Optionally, the pharmaceutical compositions may contain additional therapeutic agents.

**[00100]** ***Kits***

**[00101]** The present invention also relates to a pharmaceutical package and a kit comprising one or more containers, said containers contains the foregoing pharmaceutical compositions of the present invention.



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Accompanied with such containers may be specifications in the form prescribed by the governmental agency governing the manufacture, use or distribution of the drug or biological product, which reflect approval for human administration by the agency in which said product is manufactured, used or distributed.

**[00102]** ***Preparation and storage***

**[00103]** The pharmaceutical compositions of the present invention can be prepared in a manner known in the art, for example by conventional mixing, dissolution, granulation, pastille preparation, grinding, emulsification, encapsulation, embedding or lyophilization methods.

**[00104]** Having already prepared pharmaceutical compositions comprising compounds of the present invention formulated in an acceptable carrier, they may be placed in appropriate containers and labeled for the treatment of the condition indicated. Such labeling would include the amount, frequency and administration routes of the drug.

**[00105]** ***Combinations***

**[00106]** The pharmaceutical compositions comprising the antibodies of the present invention described above are also combined with one or more other therapeutic agents, such as antineoplastic agents, wherein the resulting combination does not cause unacceptable adverse effects.

## EXAMPLES

**[00107]** The present invention will be further understood with reference to the following non-limiting experimental examples. The experimental methods in the following examples, unless otherwise specified, are all conventional methods. The experimental materials used in the following examples, unless otherwise specified, were purchased from conventional biochemical reagent distributors.



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**[00108] Example 1: Screening of IL17A antibodies**

**[00109] 1.1 Immunization of mice**

**[00110]** Mice were immunized with IL17A according to the method described by StGroth et al. (de StGroth and Scheidegger 1980) with appropriate modifications. Recombinant human IL17A protein (from SinoBiological, Inc, Cat.10247-H07B) was used to immunize mice. The amino acid sequence of the IL17A protein (UniprotKB Q16552) is Met1-Ala155 (SEQ ID NO: 1). The recombinant human IL17A protein was mixed with aluminum phosphate adjuvant (where the first and fourth immunizations were performed with additional complete Freund's adjuvant CFA emulsified PBS, and the mouse was immunized subcutaneously in multiple sites at a dose of 50 μg/dose with the mixture for 4 times at intervals of 2 weeks, 3 weeks, and 3 weeks, respectively, Since the third immunization, blood was collected seven days after each immunization via the medial canthal plexus of the eyes. The serum titer of mouse anti-IL17A was measured by ELISA using coated recombinant human IL17A protein. The titer of the serum from the fourth immunization reached the target (ELISA, OD>1.0) after being diluted to 1:8000, and the mice were boosted intravenously with 25 μg recombinant human IL17A protein 75 days after the fourth immunization. 4 days later, the mice were executed and the spleen tissue was removed and frozen in liquid nitrogen.

**[00111] 1.2 Construction and screening of antibody phage-display library**

**[00112]** RNA was extracted from mouse spleen tissue using TriPure™ Isolation Reagent (from Roche, Cat. No.11 667 165 001), and cDNAs were obtained by reverse transcription of RNA using a reverse transcription kit (from Invitrogen Cat.No.18080-051). 2 pairs of primers were designed to amplify the sequence of the light chain variable region of the murine antibody and 1 pair of primers was designed to amplify the sequence of the heavy chain



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variable region, according to the method described in (Jones and Bendig 1991). The sequences encoding the light and heavy chain variable regions of the murine antibody were assembled into the nucleotide sequence encoding scFv by overlap extension PCR, then these two nucleotide sequence were linked by a linker (SEQ ID NO: 2) to assembled into a nucleotide sequence encoding scFv; then enzymatically ligated into the phage vector pComb3x(Sino Biological, Inc.) by restriction endonuclease *Sfi* I (Fermentas), and was electrotransformed into the competent X-Blue to construct the mouse scFv antibody phage-display library; the size of the library is (sic). The phage library enriched for positive anti-IL17A antibodies were obtained by screening with ELISA assay according to the process of phage antibody panning (Aitken 2002). The scFv antibodies that specifically bind the recombinant human IL17A protein were expressed by individual colony phages from the enriched library, and tested for their binding to recombinant human IL17A protein by ELISA. The nucleotide sequence of the scFv antibody of one colony was sequenced as SEQ ID NO: 3, and an antibody named as IL17A-M069 would derived from this colony after the steps in **Example 1.3**.

**[00113] 1.3 Production of murine IL17A monoclonal antibodies**

**[00114]** The nucleotide sequence encoding the scFv antibody heavy chain variable region (SEQ ID NO: 4) the heavy chain signal peptide sequence (SEQ ID NO: 43) and murine IgG1 heavy chain constant region sequence (SEQ ID NO: 6), was amplified and assembled with overlap extension PCR , was inserted into the *Hind* III + *Xba* I (Fermentas) digested pSTEP2 vector, thus the complete heavy chain (SEQ ID NO: 36) expression vector was obtained; similarly, the nucleotide sequence encoding the scFv antibody light chain variable region (SEQ ID NO: 5) the light chain signal peptide sequence (SEQ ID NO: 29) and murine kappa light chain constant region sequence (SEQ ID NO: 7) was amplified and assembled with overlap extension PCR, and was inserted into the *Hind* III + *Xba* I (Fermentas) digested pSTEP2



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vector, thus the complete light chain (SEQ ID NO: 37) expression vector was obtained. The primers for assembling the heavy chain signal peptide, the heavy chain variable region and murine IgG1 heavy chain constant region were:

| | |
|---|---|
| F1 | AAGCTTGCCGCCACCATGGGCTGGTCCCTGATTCTGC |
| F2 | GCTGGTCCCTGATTCTGCTGTTCCTGGTGGCTGTGGCT |
| F3 | TTCCTGGTGGCTGTGGCTACCAGGGTGCTGAGCCA |
| F4 | ACCAGGGTGCTGAGCCAGGCCCACCTTCAACAG |
| R1 | TCGTTTTGGCTGAGGAGACTGTGAGAGTGGT |
| F5 | TCTCCTCAGCCAAAACGACACCCCCATC |
| R2 | CACTATAGAATAGGGCCCTCTA |

**[00115]** The primers for assembling the light chain signal peptide, the light chain variable region and murine kappa light chain constant region were:

| | |
|---|---|
| F6 | CTGAAGCTTGCCGCCACCATGGGCTGGTCCTGTATCATCCTG |
| F7 | GCTGGTCCTGTATCATCCTGTTCCTGGTGGCTACAGCC |
| F8 | TTCCTGGTGGCTACAGCCACAGGAGTGCATAGCGACA |
| F9 | ACAGGAGTGCATAGCGACATTGTGATGTCACAGTC |
| R3 | CATCAGCCCGTTTTATTTCCAGCTTGGTCCC |
| F10 | AAATAAAACGGGCTGATGCTGCACCAAC |
| R4 | CACTATAGAATAGGGCCCTCTAGA |

**[00116]** 293E cells (ATCC) were passaged with SCD4-4-TC2 medium (SinoBiological, Inc.) in a flask in a volume of 200 mL/flask with an initial inoculation density of 0.3~0.4*$10^6$ cells/mL, and the flask was cultured in a $CO_2$ shaker with a rotation speed of 175 rpm at 37°C, until the cell density reached 1.5~3*$10^6$ cells/mL. Then, the plasmids encoding the light chain and the heavy chain were mixed at a ratio of 1:1, and 100μg of the mixed plasmid DNA and 800μL of TF2 transfection reagent were added into the culture flask, which was then cultured in a shaker with a rotation speed of 175 rpm at 37°C until the 7th day for collection. The culture medium was centrifuged at 4000rpm for 25min, the supernatant was collected and 1/5 supernatant



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volume of Stock buffer was added. After equilibrating the protein A chromatography column with a 5-10 time column volume of PBS buffer, the filtered culture supernatant was added to the chromatography column and again equilibrated for 5-10 times the column volume, then the column was eluted with sodium acetate buffer for collecting the sample. The sample was neutralized with Tris to obtain high purity murine monoclonal antibodies in a neutral solution.

**[00117] Example 2: Function analysis of murine IL17A monoclonal antibodies**

**[00118] 2.1 Murine antibody IL17A-M069 blocks IL17A-induced IL-6 secretion of HFF cells**

**[00119]** As described by Beerli, Bauer et al. 2014, IL17A stimulates the cytokine IL-6 secretion of human foreskin fibroblasts HFF under *in vitro* conditions. Anti-IL17A antibody was added to this system to verify the neutralizing effect of IL17A antibody to IL17A by detecting the secretion of IL-6 from the HFF cells. HFF cells (ATCC, SCRC-1041) were inoculated in a 96-well plate in a cell density of $1\times10^4$/well and cultured overnight in DMEM medium containing 15% FBS. Different concentrations of IL17A-M069 antibodies and positive control Taltz biosimilar were added respectively in 10 μL/well the next day, then IL17A proteins at a final concentration of 50 ng/mL was added in 10 μL/well. The 96-well plate was incubated in a 37°C, 5% $CO_2$ cell incubator for 48 h, and the blank well B (no cells), negative control M' (cells inoculated, no antibody sample, IL17A added) and M (cells inoculated, no antibody sample and no IL17A) were used. After incubation, the supernatant was collected and the IL-6 secretion was measured by ELISA. The IL-6 secretion of the sample well and M' group well will minus the Il-6 secretion of M group well respectively to calculate the inhibition rate. the inhibition rate% = (1 – IL-6 secretion of the sample wells) / IL-6 secretion of the M' group wells × 100%. The standard curve was calculated using a statistical software, taking the antibody sample



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concentration as the horizontal coordinate and the IL-6 secretion as the vertical coordinate. The results are shown in Figure 1, the murine antibody IL17A-M069 can block IL17A-induced IL-6 secretion of HFF cells, and the maximum inhibition rate and median inhibition concentration of IL17A-M069 on IL17A were similar to those of the positive control Taltz biosimilar, the maximum inhibition rate of the murine antibody IL17A-M069 and Taltz biosimilar were 96.33% and 97.35% respectively, and the $EC_{50}$ were 243.3 ng/mL and 246.6 ng/mL respectively. Therefore, IL17A-M069 is a favorable antibody with good *in vitro* activity, subsequent humanization modification and function analyses were performed on IL17A-M069.

**[00120] Example 3: Humanization and production of IL17A antibody IL17A-M069**

**[00121]** On the ground of the function analysis results of the murine antibody IL17A-M069 in **Example 2**, humanization and production were performed accordingly.

**[00122] 3.1 Determination of CDR sequences of the light and heavy chains of IL17A antibody IL17A-M069**

**[00123]** The amino acid sequences of the heavy chain and light chain variable regions of the antibody IL17A-M069-scFv were deduced from the nucleotide sequence of the antibody IL17A-M069-scFv determined in **Example 1.3**, see SEQ ID NOs: 8/9.

**[00124]** The amino acid sequences of each of the three CDRs of the light and heavy chains of the murine antibody IL17A-M069-scFv were determined with reference to Kabat index (Abhinandan and Martin 2008, Dondelinger, Filée et al. 2018) and IMGT numbering (Lefranc 2014) systems, see **Table 1** and SEQ ID NOs: 10-15. The aforementioned respective three CDRs of the light chain and the heavy chain were transplanted in the subsequent steps and retained in the finally obtained humanized antibody IL17A-H069, see **Examples 3.2** and **3.3**.

**Table 1. CDR sequences of IL17A-M069 light chain and heavy chain**



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| Name | Sequence |
|---|---|
| LCDR1 | QSLLNRSNQKNYLA（SEQ ID NO:10） |
| LCDR2 | FASTRES（SEQ ID NO:11） |
| LCDR3 | QQHYTTPFT（SEQ ID NO:12） |
| HCDR1 | GYTFTDYEMH（SEQ ID NO:13） |
| HCDR2 | VIHPGGGGTAYNQKFKG（SEQ ID NO:14） |
| HCDR3 | TRGDHDGRTDY（SEQ ID NO:15） |

**[00125] 3.2 CDR transplantation of the murine antibody**

**[00126]** The humanization of the murine antibody was performed using the classic humanization method of CDR transplantation (Kettleborough, Saldanha et al. 1991). The human antibody light or heavy chain variable region, which is closer to the mouse light or heavy chain variable region (similarity > 50%), was elected as the template, and each of three CDR sequences (SEQ ID NOs: 10-15) from the mouse light or heavy chain was inserted into the variable region of the human antibody to obtain the humanized light chain variable region (VL) or heavy chain variable region (VH) amino acid sequences respectively. The human template for the light chain variable region of IL17A-M069 is IGKV4-1*01, which is 75.2% homologous to the light chain of IL17A-M069, and the human template for the heavy chain variable region is IGHV1-69-2*01, which is 65.3% homologous to the heavy chain of IL17A-M069.

**[00127] 3.3 Reverse-mutations at the framework region of the humanized variable region**

**[00128]** As some key amino acids in the murine-derived framework region are essential to maintain the CDR spatial structure stability and the antibody binding activity, the key amino acids were reverse-mutated to the corresponding murine antibody amino acids until the antibody having stable spatial structure was obtained, the following sites were reversely mutated: according to the Kabat index system, in the light chain, Position 48 was



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reversely mutated to V, Position 49 was reversely mutated to D, and Position 87 was reversely mutated to F; while in the heavy chain, Position 24 was reversely mutated to A, and Position 43 was reversely mutated to H. The humanized antibody IL17A-H069 was obtained by CDR humanized transplantation and framework region reverse-mutations, and its heavy and light chain amino acid sequences are shown in SEQ ID NOs:16/17, respectively; its heavy and light chain amino acid sequences in the form containing the signal peptides are respectively shown in SEQ ID NOs:18/19, comprising sequentially linked heavy/light chain signal peptide sequences (SEQ ID NOs:20/21); humanized antibody heavy chain/light chain variable region sequences (SEQ ID NOs:22/23); humanized antibody IgG1 heavy chain constant region/human kappa light chain constant region sequences (SEQ ID NOs: 24/25), respectively.

**[00129] 3.4 Production of humanized monoclonal antibody IL17A-H069**

**[00130]** The nucleotide sequence (SEQ ID NO: 27) encoding the antibody IL17A-H069 light chain and the signal peptide, which contains the following nucleotide sequences encoding light chain signal peptide (SEQ ID NO: 29), the humanized antibody light chain variable region (SEQ ID NO: 31) and the human antibody kappa light chain constant region (SEQ ID NO: 33) connected in order, was PCR amplified and inserted into the self-developed pGS vector (*Kpn* I+*Xba* I) by in-fusion method, and the correct plasmids were verified by sequencing. Similarly, the nucleotide sequence (SEQ ID NO: 26) encoding the antibody IL17A-H069 heavy chain containing the signal peptide, which contains the following nucleotide sequences encoding heavy chain signal peptide (SEQ ID NO: 28), the humanized antibody heavy chain variable region (SEQ ID NO: 30) and the human IgG1 antibody heavy chain constant region (SEQ ID NO: 32) connected in order, was PCR amplified and inserted into the pGS vector (*Nhe* I+*Not* I) which had been verified to contain the light chain gene correctly by in-fusion method, and the correct vectors expressing both light and heavy chains of IL17A-H069 were verified by



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sequencing. These expression vectors are eukaryotic expression vectors containing the GS genes as the selection marker and the expression elements of the antibody light and heavy chains. These expression vectors were transfected into CHO-K1-GS-deficient cells and IL17A-H069 high expression cell lines were obtained by MSX screening. The clones with high antibody expression were selected by ELISA assay, and the high expression cell lines were selected by taking into account both the cell growth status and the key quality characteristics for antibody drugs. A serum-free suspension culture was used to culture the IL17A-H069 producing CHO cell line to obtain high purity and high quality IL17A-H069 antibodies.

**[00131] Example 4: Analyses of antigen binding affinity of the humanized antibody IL17A-H069**

**[00132] 4.1 Analysis of binding affinity of humanized antibody to IL17A protein**

**[00133] 4.1.1 Binding of IL17A-H069 to recombinant human IL17A protein**

**[00134]** Recombinant human IL17A protein (SinoBiological, Inc.) in different concentrations was coated on a 96-well plate overnight at 4°C in 100μL/well. The plate was washed the next day and blocked at room temperature for 1 h. After incubation with 100 μL of 2 μg/mL of COSENTYX biosimilar (SinoCelltech Co., Ltd.) and IL17A-H069 (SinoCelltech Co., Ltd.) respectively, the plate was washed to remove unbound antibodies, then incubated with goat anti-human IgG Fc/HRP and washed repeatedly, and the chromogenic substrate solution was added for color development. $OD_{450}$ was measured after the color development was stabilized. Taking the concentration of recombinant human IL17A protein as the horizontal coordinate and the $OD_{450}$ value as the vertical coordinate, the graphPad Prism™ 6.0 software was used for data analysis and generating a dose-efficacy curve, the median effective concentration $EC_{50}$ values were calculated.

**[00135]** The results shown in Figure 2 demonstrate that the $EC_{50}$ value of COSENTYX biosimilar binding to recombinant human IL17A protein is 74.8



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ng/mL, $R^2$ = 0.9993; the $EC_{50}$ value of IL17A-H069 binding to recombinant human IL17A protein is 46 ng/mL, $R^2$ = 0.9958. This indicates that the ability of IL17A-H069 binding to recombinant human IL17A protein is slightly better than that of COSENTYX biosimilar.

**[00136] 4.1.2 Binding of IL17A-H069 to recombinant human IL17A/IL17F protein**

**[00137]** Recombinant human IL17A/F dimer protein (SinoBiological, Inc., CT047-HNAE) in different concentrations was coated on a 96-well plate overnight at 4°C in 100μL/well. The plate was washed the next day and blocked at room temperature for 1 h. After incubation with 100 μL of 2 μg/mL of COSENTYX biosimilar (SinoCelltech Co., Ltd.) and IL17A-H069 (SinoCelltech Co., Ltd.) respectively, the plate was washed to remove unbound antibodies, then incubated with goat anti-human IgG Fc/HRP and washed repeatedly, and the chromogenic substrate solution was added for color development. $OD_{450}$ was measured after the color development was stabilized. Taking the concentration of recombinant human IL17A/F protein as the horizontal coordinate and the $OD_{450}$ value as the vertical coordinate, the graphPad Prism 6.0 software was used for data analysis and generating a dose-efficacy curve, the median effective concentration $EC_{50}$ values were calculated.

**[00138]** The results shown in Figure 3 demonstrate that the $EC_{50}$ value of COSENTYX biosimilar binding to recombinant human IL17A/F protein is 63.9 ng/mL, $R^2$ = 0.9999; the $EC_{50}$ value of IL17A-H069 binding to recombinant human IL17A/F protein is 36.3 ng/mL, $R^2$ = 1.0. This indicates that the ability of IL17A-H069 binding to recombinant human IL17A/F dimer protein is slightly better than that of COSENTYX biosimilar.

**[00139] 4.1.3 Assay of the binding affinities of IL17A-H069 to recombinant human IL17A protein and recombinant human IL17A/IL17F protein**

**[00140]** The affinities of IL17A-H069 at different concentrations (0.42 nM, 0.90 nM, 1.74 nM, and 3.47nM) and positive control COSENTYX (Norvatis,



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SHM12) at different concentrations (0.90 nM, 1.74 nM, 3.47nM, 6.94 nM, and 13.9nM) to biotinylated IL7A or IL17A/F proteins were determined respectively using the Octet Biomolecular Interaction Assay System. The results in **Table 2** showed that the binding affinity KD value of IL17A-H069 to recombinant human IL17A protein was 2.88E-11M, the association rate constant $k_{on}$ was 6.71E+05$M^{-1}s^{-1}$ and the dissociation rate constant $k_{off}$ was 1.93E-05 $s^{-1}$;while the binding affinity KD value of COSENTYX to IL17A protein was 9.55E-11M, with an association rate constant $k_{on}$ of 1.78E+05 $M^{-1}s^{-1}$ and a dissociation rate constant $k_{off}$ of 1.70E-05 $s^{-1}$. The binding affinity KD value of IL17A-H069 to recombinant human IL17A/F protein was 5.37E-10M, the association rate constant $k_{on}$ was 1.44E+05$M^{-1}s^{-1}$ and the dissociation rate constant $k_{off}$ was 7.72E-05 $s^{-1}$; while the binding affinity KD value of COSENTYX to IL17A/F protein was 1.10E-09M, with an association rate constant $k_{on}$ of 8.00E+04 $M^{-1}s^{-1}$ and a dissociation rate constant $k_{off}$ of 8.79E-05 $s^{-1}$. The results showed that IL17A-H069 binds IL17A protein with stronger affinity than that of COSENTYX, the affinity of IL17A-H069 is about 3.32 times that of COSENTYX, and IL17A-H069 has a faster association rate, so IL17A-H069 has a stronger binding ability to IL17A protein than COSENTYX; IL17A-H069 binds IL17A/F protein with stronger affinity than that of COSENTYX, the affinity of IL17A-H069 is about 2.05 times the affinity of COSENTYX, and IL17A-H069 has a faster association rate, thus IL17A-H069 has a stronger binding ability to IL17A/F protein than COSENTYX.

**Table 2. Octet assay of the binding of IL17A-H069 to IL17A, IL17A/F**

| Protein | Sample | KD (M) | $k_{on}$(1/Ms) | $k_{dis}$(1/s) |
|---|---|---|---|---|
| IL17A | IL17A-H069 | 2.88E-11 | 6.71E+05 | 1.93E-05 |
| | COSENTYX | 9.55E-11 | 1.78E+05 | 1.70E-05 |
| IL17A/F | IL17A-H069 | 5.37E-10 | 1.44E+05 | 7.72E-05 |
| | COSENTYX | 1.10E-09 | 8.00E+04 | 8.79E-05 |



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**[00141] 4.1.4 Determination of Species Cross Reactivity of IL17A-H069 to mouse IL17A protein**

**[00142]** The recombinant human IL17A protein (Sino Biological, Inc.) and mouse mIL17A protein (Sino Biological, Inc.) at different concentrations was respectively coated on a 96-well plate in 100 μL per well overnight at 4°C. The plate was washed the next day, blocked at room temperature for 1 h. 100 μL of 2 μg/mL of IL17A-H069 (Sino Biological, Inc.), positive control COSENTYX (Norvatis, SHM12) and negative control antibody H7N9-R1 (SinoCelltech Co., Ltd.) were added respectively and incubated. The plate was washed to remove unbound antibodies. The plate was incubated with goat anti-human IgG Fc/HRP (Sino Biological, Inc.) and then repeatedly washed, and the chromogenic substrate solution was added for color development. $OD_{450}$ was measured after the color development was stabilized. The results shown in Figure 4 demonstrate that IL17A-H069 has no cross-binding with mouse mIL17A protein.

**[00143] 4.2 IL17A-H069 blocks the binding of IL17A protein and IL17A/F protein to the receptor IL17RA**

**[00144] 4.2.1 IL17A-H069 blocks the binding of IL17A protein to the receptor IL17RA**

**[00145]** IL17A protein at a concentration of 0.4 μg/mL was coated on a 96-well plate in 100 μL per well overnight at 4°C. The plate was washed the next day, blocked at room temperature for 1 h. 100 μL of 2 μg/mL of biotinylated protein IL17RA-His-biotin (Sino Biological, Inc.) was added in each well, then different concentrations of IL17A-H069 (SinoCelltech Co., Ltd.), positive control COSENTYX (Norvatis, SHM12), positive control Taltz (Eli Lilly) and negative control antibody H7N9-R1 (SinoCelltech Co., Ltd.) were added respectively and incubated. The plate was washed to remove unbound antibodies. The plate was incubated with Streptavidin/HRP (Beijing ZSGB-Bio Co., Ltd., SA-5004) and then repeatedly washed, and the chromogenic



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substrate solution was added for color development. $OD_{450}$ was measured after the color development was stabilized, with each group tested in duplicate.

**[00146]** Taking the antibody concentration as the horizontal coordinate and the inhibition rate% as the vertical coordinate, the graphPad Prism 6.0 software was used for data analysis and generating a chart, the $IC_{50}$ values were calculated. Inhibition rate % = $(OD_{blank} - OD_{sample}) / OD_{blank} \times 100\%$, where $OD_{blank}$ represents the OD value of the samples with only IL17RA-His-biotin protein but no antibody added, $OD_{sample}$ represents the OD value of the samples with both IL17RA-His-biotin protein and antibody added.

**[00147]** The results shown in Figure 5 demonstrate that the biotinylated IL17RA protein could effectively bind the coated recombinant human IL17A protein, and the antibody IL17A-H069 could inhibit the binding of IL17A protein to the receptor IL17RA in a significantly better profile, presented by its inhibition curve, than positive control COSENTYX but the profile of IL17A-H069 inhibiting the binding of IL17A protein to the receptor IL17RA was close to that of positive control Taltz. The $IC_{50}$ values of IL17A-H069, COSENTYX and Taltz were 0.50 μg/mL, 2.99 μg/mL, and 0.50 μg/mL respectively, and the maximum inhibition rates were 85.4%, 73.5%, and 89.5%, respectively.

**[00148] 4.2.2 IL17A-H069 blocks the binding of IL17A/F protein to the receptor IL17RA**

**[00149]** The IL17RA-Fc protein (Sino Biological, Inc.) at a concentration of 5 μg/mL was coated on a 96-well plate in 100 μL per well overnight at 4°C. The plate was washed the next day, blocked at room temperature for 1 h. 100 μL of 0.8 μg/mL of IL17A/F-Biotin protein (Sino Biological, Inc.) was added in each well, then different concentrations of IL17A-H069 (SinoCelltech Co., Ltd.), positive control COSENTYX biosimilar (SinoCelltech Co., Ltd.), positive control Taltz biosimilar (SinoCelltech Co., Ltd.) and negative control antibody H7N9-R1 (SinoCelltech Co., Ltd.) were added respectively and



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incubated. The plate was washed to remove unbound antibodies. The plate was incubated with Streptavidin/HRP (Beijing ZSGB-Bio Co., Ltd., SA-5004) and then repeatedly washed, and the chromogenic substrate solution was added for color development. $OD_{450}$ was measured after the color development was stabilized.

**[00150]** Taking the antibody concentration as the horizontal coordinate and the inhibition rate% as the vertical coordinate, the graphPad Prism 6.0 software was used for data analysis and generating a chart, the $IC_{50}$ values were calculated. Inhibition rate % = $(OD_{blank} - OD_{sample}) / OD_{blank} \times 100\%$, where $OD_{blank}$ represents the OD value of the samples with only IL17A/F-biotin protein but no antibody added, $OD_{sample}$ represents the OD value of the samples with both IL17A/F-biotin protein and antibody added.

**[00151]** The results shown in Figure 6 demonstrate that IL17A/F-biotin protein could effectively bind the coated recombinant human IL17RA-Fc protein, and the addition of the antibody IL17A-H069 could effectively inhibit the IL17A/F protein from binding its receptor IL17RA-Fc. IL17A-H069 has a better inhibitory effect on the binding of IL17A/F protein to its receptor IL17RA-Fc than positive control COSENTYX biosimilar and positive control Taltz biosimilar. The $IC_{50}$ values of IL17A-H069, COSENTYX biosimilar and Taltz biosimilar were 1.02 μg/mL, 1.20 μg/mL and 1.35 μg/mL, respectively, and the maximum inhibition rates were 92.3%, 87.9% and 75%, respectively.

**[00152] Example 5: Function analysis of the humanized antibody IL17A-H069**

**[00153] 5.1 IL17A-H069 blocks the IL17A-induced or IL17A/F-induced IL-6 secretion of HFF cells**

**[00154]** HFF cells were inoculated in a 96-well plate in a cell density of $1\times10^4$/well and cultured overnight in DMEM medium containing 15% FBS. Different concentrations of IL17A-H069 (SinoCelltech Co., Ltd.) and positive control COSENTYX (Norvatis) or positive control Taltz (Eli Lilly)



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were added respectively in 10 μL/well the next day, Subsequently, 10 μL of IL17A protein (Sino Biological, Inc. 12047-HNAS) at a final concentration of 50 ng/mL or IL17A/F protein (Sino Biological, Inc. CT047-HNAE) at a final concentration of 1μg /mL was added to each well, respectively. The 96-well plate was incubated in a 37°C, 5% $CO_2$ cell incubator for 48 h, and the blank well B (no cells), negative control M' (cells inoculated, no antibody sample, IL17A or IL17A/F added) and M (cells inoculated, no antibody sample and no IL17A or IL17A/F) were used. After incubation, the supernatant was collected and the IL-6 secretion was measured by ELISA. The IL-6 secretion of the sample well and M' group well will minus the Il-6 secretion of M group well respectively to calculate the inhibition rate. the inhibition rate% = (1 – IL-6 secretion of the sample wells) / IL-6 secretion of the M' group wells × 100%.. The standard curve was calculated using a statistical software, taking the antibody sample concentration as the horizontal coordinate and the IL-6 secretion as the vertical coordinate, and the 4-parameter logistic regression equation was used to fit the standard "S" curve to calculate the median effective concentration ($EC_{50}$) of the antibody sample.

**[00155]** In the above-described measurement, as shown in Figure 7 and **Table 3**, the activity of IL17A-H069 in neutralizing IL17A ($EC_{50}$: 0.19 μg/mL, maximum neutralization rate: 94.6%) was much higher than the positive control COSENTYX ($EC_{50}$: 0.22 μg/mL, maximum neutralization rate: 51.6%) (Figure 6A); in comparison with the positive control Taltz, the activity of IL17A-H069 in neutralizing IL17A ($EC_{50}$: 0.20 μg/mL, maximum neutralization rate: 90.3 %) was close to the neutralization activity of Taltz ($EC_{50}$: 0.19 μg/mL, maximum neutralization rate: 95.9%) (Figure 6C); the activity of IL17A-H069 in neutralizing IL17A/F ($EC_{50}$: 1.19 μg/mL, maximum neutralization rate: 85.0%) was also slightly higher than that of COSENTYX ($EC_{50}$: 2.25 μg/mL, maximum neutralization rate: 79.5%) (Figure 6B). In comparison with the positive control Taltz, the activity of



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IL17A-H069 in neutralizing IL17A/F at high concentration ($EC_{50}$: 0.83 μg/mL, maximum neutralization rate: 72.90%) was close to that of Taltz ($EC_{50}$: 1.10 μg/mL, maximum neutralization rate: 76.3%), and superior to the positive control Taltz at low concentrations (Figure 6D). In conclusion, IL17A-H069 has better biological activity of neutralizing IL17A and IL17A/F.

**Table 3. $EC_{50}$ and maximum neutralization rate of IL17A-H069 blocking IL17A-induced IL6 secretion of HFF cells**

| Group | Antibody | $EC_{50}$(μg/mL) | Maximum neutralization rate (%) |
|---|---|---|---|
| Neutralization of IL17A | COSENTYX | 0.22 | 51.6 |
| | IL17A-H069 | 0.19 | 94.6 |
| | Taltz | 0.19 | 95.9 |
| | IL17A-H069 | 0.20 | 90.3 |
| Neutralization of IL17A/F | COSENTYX | 2.25 | 79.5 |
| | IL17A-H069 | 1.19 | 85.0 |
| | Taltz | 1.10 | 76.3 |
| | IL17A-H069 | 0.83 | 72.9 |

**[00156] Example 6: *In vivo* efficacy of the humanized antibody in mice**

**[00157] 6.1 *In vivo* efficacy of IL17A-H069 in hPBMC immune-reconstituted mouse psoriasis (PsO) model**

**[00158]** Using hPBMC from 3 donors, a total of 60 B-NDG mice (Biocytogen Pharmaceuticals (Beijing) Co., Ltd.) with humanized immune system were obtained (20 mice per donor's hPBMC). Peripheral blood was collected one week later and the percentage of human-derived cells was measured by flow cytometry. 20 mice had a percentage of human-derived cells between 0.04-1.5%, 31 mice had a percentage of 1.5-7%, and 8 mice had a percentage of >7%. Mice with the percentage of 1.5-7% were selected



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to establish IMQ (imiquimod)-induced mouse psoriasis model, based on which the efficacy of IL17A-H069 was evaluated.

**[00159]** The mice enrolled were grouped according to the following strategy: 5 unmodeled mice were grouped into the normal control group G1; 5 psoriasis modeled mice which were not administered with drug were grouped in G2 group, i.e. psoriasis model group; 7 psoriasis modeled mice which were administered with IL17A-H069 were grouped in G3 group; and 7 psoriasis modeled mice which were administered with positive control Taltz were grouped in G4 group. All mice backs were shaved to form an exposed area of about 2 cm × 3 cm in size, and 100 mg IMQ cream was applied to the back of each mouse in G2, G3 and G4 groups and 10 mg IMQ cream was applied to ears of each mouse in G2, G3 and G4 groups every day for 10 days. The PASI scores of mice were recorded daily. According to the PASI scoring criteria, as shown in **Table 4,** the mice were given scores of 0-4 for the degree of erythema, scaling and dorsal skin thickening on the back of the lesion respectively, and the three scores were summed to obtain the total scores. For the G3 and G4 groups, the antibody administration was started on Day 1 of IMQ cream application, with the dose of 10 mpk, twice weekly.

**Table 4. Criteria of PASI scoring (Severity index)**

| **Area** | **Erythema (E)** | **Induration（I）** | **Desquamation（D）** | **Area score (A) Actual area %** |
|---|---|---|---|---|
| Head & neck (H) | 0: Absent<br>1: Mild<br>2: Moderate<br>3: Severe<br>4: Very Severe | | | 0:0%<br>1:1%-9%<br>2:10%-29%<br>3:30%-49%<br>4:50%-69%<br>5:70%-89%<br>6:90%-100% |
| Upper extremity (U) | | | | |
| Trunk, armpits, groin (T) | | | | |



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|---|---|---|
| Lower extremity and buttocks (L) | | |
| PASI=0.1(EH+IH+DH)AH+0.2(EU+IU+DU)AU+0.3(ET+IT+DT)AT+0.4(EL+IL+DL)AL<br>PASI75: 75% improvement in severity index<br>PASI50: 50% improvement in severity index | | |

**[00160]** The results are shown in Figure 8. Compared with the mice in normal control group, the PASI score was significantly higher in the mice in psoriasis model group, reflecting that this mouse model can characterize psoriasis to some extent; from Day 5, the PASI scores were significantly lower in the IL17A-H069 administered group compared with the psoriasis model group; and compared with the Taltz control group, IL17A-H069 had stronger *in vivo* efficacy in reducing psoriasis scores in mice, thus IL17A-H069 is effective in alleviating the onset of psoriasis (PsO) and reducing psoriasis symptoms in psoriasis model mice.

**[00161] Example 7: *In vivo* pharmacokinetics of the humanized antibodies**

**[00162] 7.1 Pharmacokinetics of single subcutaneous injection of IL17A-H069 in cynomolgus monkeys**

**[00163]** In this example, single subcutaneous injections of IL17A-H069 antibodies were administered to cynomolgus monkeys at a dose of 1 mg/kg. Serum was collected before administration, and 1 h, 2 h, 4 h, 6 h, 8 h, 24 h, 48 h, 3 days, 4 days, 7 days, 10 days, 14 days, 17 days, 21 days, 24 days, 28 days, 31 days, and 35 days after administration, respectively. The established ELISA method was used to measure the drug concentration of IL17A-H069 in monkey serum, the pharmacokinetic parameters were calculated using the Non-compartmental Analysis (NCA)Phoenix-WinNonlin (Pharsight) 6.4 software. The dynamic pattern of *in vivo* drug changes profile after a single



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subcutaneous injection of IL17A-H069 was examined. Investigate the dynamic changes of the drug in the body after a single subcutaneous injection of IL17A-H069.

**[00164]** IL17A-H069 drug concentration changes over time are shown in **Table 6** and Figure 9. There was no significant gender difference in $C_{max}$ and $AUC_{last}$ between female and male mice (results not shown), and the half-life $t_{1/2}$ of IL17A-H069 was 353.66 h, the $T_{max}$ value was 34h. In terms of *in vivo* exposure, $AUC_{last}$ of IL17A-H069 was 3846.86 h*μg/mL.

**[00165]** At the dose of 1 mg/kg, IL17A-H069 has a shorter $T_{max}$ and a longer $t_{1/2}$, so IL17A-H06 exhibits superior pharmacokinetics, including fast absorption after subcutaneous injection, long half-life, and better drug exposure, etc., thus laying the foundation for a longer dosing cycle.

**Table 6. Pharmacokinetic parameters of a single subcutaneous injection in cynomolgus monkeys**

| Antibody | Parameter | $t_{1/2}$ (h) | $T_{max}$ (h) | $C_{max}$ (μg/mL) | $C_{max}$ (μg/mL) | $AUC_{all}$ (h*μg/mL) |
|---|---|---|---|---|---|---|
| IL17A-H069 | Mean | 353.66 | 34.00 | 13.40 | 3846.86 | 3846.86 |
| | SD | 116.09 | 24.25 | 0.77 | 629.88 | 629.88 |



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| SEQ ID NO | Identity | Sequence |
|---|---|---|
| SEQ ID NO：1 | Amino acid sequence of Met1-Ala155 of the human IL17A protein (UniProtKB Q16552) | MTPGKTSLVSLLLLLSLEAIVKAGITIPRNPGCPNSE<br>DKNFPRTVMVNLNIHNRNTNTNPKRSSDYYNRSTS<br>PWNLHRNEDPERYPSVIWEAKCRHLGCINADGNVD<br>YHMNSVPIQQEILVLRREPPHCPNSFRLEKILVSVGC<br>TCVTPIVHHVA |
| SEQ ID NO：2 | Nucleotide sequence of the linker used in the construction of the phage antibody library for the linkage of the murine antibody scFv | TCTAGTGGTGGCGGTGGTTCGGGCGGTGGTGGAG<br>GTGGTAGTTCTAGATCTTCC |
| SEQ ID NO：3 | Nucleotide sequence of murine antibody scFv which is used in the construction of antibody IL17A-M069 | Nucleotide sequence of light chain variable region of IL17A-M069 (SEQ ID NO:5):<br>GACATTGTGATGTCACAGTCTCCATCCTCCCTGGC<br>TATGTCAGTAGGACAGAAGGTCACTATGAACTGC<br>AAGTCCAATCAGAGCCTTTTAAATAGAAGCAATC<br>AAAAGAACTATTTGGCCTGGTACCAGCAGAAACC<br>AGGACAGTCTCCTAAACTTCTGGTAGACTTTGCAT<br>CCACTAGGGAATCTGGGGTCCCTGATCGCTTCATA<br>GGCAGTGGATCTGGGACAGATTTCAGTCTTACCAT<br>CAGCAGTGTGCAGGCTGAGGACCTGGCAGATTAC<br>TTCTGTCAGCAACATTATACCACTCCATTCACGTT<br>CGGCTCGGGGACCAAGCTGGAAATAAAA<br>Linker(SEQ ID NO:2):<br>TCTAGTGGTGGCGGTGGTTCGGGCGGTGGTGGAG<br>GTGGTAGTTCTAGATCTTCC<br>Nucleotide sequence of heavy chain variable region of IL17A-M069 (SEQ ID NO:4):<br>CAGGCCCACCTTCAACAGTCTGGGGCTGAGCTGG<br>TGAGGCCTGGGGCTTCAGTGAAGCTGTCCTGCAA<br>GGCTTTGGGCTACACATTTACTGACTATGAAATGC<br>ACTGGGTGAAACAGACACCTGTGCATGGCCTGGA<br>ATGGATTGGAGTTATTCATCCAGGAGGTGGTGGTA<br>CGGCCTACAATCAGAAGTTCAAGGGCAAGGCCAC<br>ACTGACTGCAGACAAGTCCTCCAGTACAGCCTAC<br>ATGGAGCTCAGCAGCCTGACATCTGAGGACTCTG<br>CTGTCTATTACTGTACAAGAGGGGATCACGACGG<br>AAGGACTGACTACTGGGGCCAAGGCACCACTCTC<br>ACAGTCTCCTCA |
| SEQ ID NO:4 | Nucleotide sequence of heavy chain variable region of the murine | CAGGCCCACCTTCAACAGTCTGGGGCTGAGCTGG<br>TGAGGCCTGGGGCTTCAGTGAAGCTGTCCTGCAA<br>GGCTTTGGGCTACACATTTACTGACTATGAAATGC<br>ACTGGGTGAAACAGACACCTGTGCATGGCCTGGA |



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|---|---|---|
| | antibody IL17A-M069 | ATGGATTGGAGTTATTCATCCAGGAGGTGGTGGTA<br>CGGCCTACAATCAGAAGTTCAAGGGCAAGGCCAC<br>ACTGACTGCAGACAAGTCCTCCAGTACAGCCTAC<br>ATGGAGCTCAGCAGCCTGACATCTGAGGACTCTG<br>CTGTCTATTACTGTACAAGAGGGGATCACGACGG<br>AAGGACTGACTACTGGGGCCAAGGCACCACTCTC<br>ACAGTCTCCTCA |
| SEQ ID NO:5 | Nucleotide sequence of light chain variable region of the murine antibody IL17A-M069 | GACATTGTGATGTCACAGTCTCCATCCTCCCTGGC<br>TATGTCAGTAGGACAGAAGGTCACTATGAACTGC<br>AAGTCCAATCAGAGCCTTTTAAATAGAAGCAATC<br>AAAAGAACTATTTGGCCTGGTACCAGCAGAAACC<br>AGGACAGTCTCCTAAACTTCTGGTAGACTTTGCAT<br>CCACTAGGGAATCTGGGGTCCCTGATCGCTTCATA<br>GGCAGTGGATCTGGGACAGATTTCAGTCTTACCAT<br>CAGCAGTGTGCAGGCTGAGGACCTGGCAGATTAC<br>TTCTGTCAGCAACATTATACCACTCCATTCACGTT<br>CGGCTCGGGGACCAAGCTGGAAATAAAA |
| SEQ ID NO:6 | Nucleotide sequence of the mouse IgG1 heavy chain constant region | GCCAAAACGACACCCCCATCTGTCTATCCACTGG<br>CCCCTGGATCTGCTGCCCAAACTAACTCCATGGTG<br>ACCCTGGGATGCCTGGTCAAGGGCTATTTCCCTGA<br>GCCAGTGACAGTGACCTGGAACTCTGGATCCCTG<br>TCCAGCGGTGTGCACACCTTCCCAGCTGTCCTGC<br>AGTCTGACCTCTACACTCTGAGCAGCTCAGTGAC<br>TGTCCCCTCCAGCACCTGGCCCAGCGAGACCGTC<br>ACCTGCAACGTTGCCCACCCGGCCAGCAGCACCA<br>AGGTGGACAAGAAAATTGTGCCCAGGGATTGTGG<br>TTGTAAGCCTTGCATATGTACAGTCCCAGAAGTAT<br>CATCTGTCTTCATCTTCCCCCCAAAGCCCAAGGAT<br>GTGCTCACCATTACTCTGACTCCTAAGGTCACGTG<br>TGTTGTGGTAGACATCAGCAAGGATGATCCCGAG<br>GTCCAGTTCAGCTGGTTTGTAGATGATGTGGAGGT<br>GCACACAGCTCAGACGCAACCCCGGGAGGAGCA<br>GTTCAACAGCACTTTCCGCTCAGTCAGTGAACTT<br>CCCATCATGCACCAGGACTGGCTCAATGGCAAGG<br>AGTTCAAATGCAGGGTCAACAGTGCAGCTTTCCC<br>TGCCCCCATCGAGAAAACCATCTCCAAAACCAAA<br>GGCAGACCGAAGGCTCCACAGGTGTACACCATTC<br>CACCTCCCAAGGAGCAGATGGCCAAGGATAAAGT<br>CAGTCTGACCTGCATGATAACAGACTTCTTCCCTG<br>AAGACATTACTGTGGAGTGGCAGTGGAATGGGCA<br>GCCAGCGGAGAACTACAAGAACACTCAGCCCATC<br>ATGGACACAGATGGCTCTTACTTCGTCTACAGCAA<br>GCTCAATGTGCAGAAGAGCAACTGGGAGGCAGG<br>AAATACTTTCACCTGCTCTGTGTTACATGAGGGCC<br>TGCACAACCACCATACTGAGAAGAGCCTCTCCCA<br>CTCTCCTGGTAAATAA |
| SEQ ID NO:7 | Nucleotide sequence of the mouse kappa light chain constant | CGGGCTGATGCTGCACCAACTGTATCCATCTTCCC<br>ACCATCCAGTGAGCAGTTAACATCTGGAGGTGCC<br>TCAGTCGTGTGCTTCTTGAACAACTTCTACCCCAA<br>AGACATCAATGTCAAGTGGAAGATTGATGGCAGT |



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| | | |
|---|---|---|
| | region | GAACGACAAAATGGCGTCCTGAACAGTTGGACTG ATCAGGACAGCAAAGACAGCACCTACAGCATGAG CAGCACCCTCACGTTGACCAAGGACGAGTATGAA CGACATAACAGCTATACCTGTGAGGCCACTCACA AGACATCAACTTCACCCATTGTCAAGAGCTTCAA CAGGAATGAGTGTTAAA |
| SEQ ID NO:8 | Amino acid sequence of the heavy chain variable region of murine antibody IL17A-M069 | QAHLQQSGAELVRPGASVKLSCKALGYTFTDYEM HWVKQTPVHGLEWIGVIHPGGGGTAYNQKFKGKA TLTADKSSSTAYMELSSLTSEDSAVYYCTRGDHDGR TDYWGQGTTLTVSS |
| SEQ ID NO:9 | Amino acid sequence of the light chain variable region of murine antibody IL17A-M069 | DIVMSQSPSSLAMSVGQKVTMNCKSNQSLLNRSNQ KNYLAWYQQKPGQSPKLLVDFASTRESGVPDRFIGS GSGTDFSLTISSVQAEDLADYFCQQHYTTPFTFGSG TKLEIK |
| SEQ ID NO:10 | Amino acid sequence of light chain CDR1 of the murine antibody IL17A-M069/humanized antibody IL17A-H069 | QSLLNRSNQKNYLA |
| SEQ ID NO:11 | Amino acid sequence of light chain CDR2 of the murine antibody IL17A-M069/humanized antibody IL17A-H069 | FASTRES |
| SEQ ID NO:12 | Amino acid sequence of light chain CDR3 of the murine antibody IL17A-M069/humanized antibody IL17A-H069 | QQHYTTPFT |
| SEQ ID NO:13 | Amino acid sequence of heavy chain CDR1 of the murine antibody IL17A-M069/humanized antibody IL17A- | GYTFTDYEMH |



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| | H069 | |
| SEQ ID NO:14 | Amino acid sequence of heavy chain CDR2 of the murine antibody IL17A-M069/humanized antibody IL17A-H069 | VIHPGGGGTAYNQKFKG |
| SEQ ID NO:15 | Amino acid sequence of heavy chain CDR3 of the murine antibody IL17A-M069/humanized antibody IL17A-H069 | TRGDHDGRTDY |
| SEQ ID NO:16 | Amino acid sequence of the heavy chain of humanized antibody IL17A-H069 | Amino acid sequence of the heavy chain variable region (SEQ ID NO:22):<br>EVQLVQSGAEVKKPGATVKISCKASGYTFTDYEMH<br>WVQQAPGHGLEWMGVIHPGGGGTAYNQKFKGRV<br>TITADTSTDTAYMELSSLRSEDTAVYYCTRGDHDGR<br>TDYWGQGTLVTVSS<br>Amino acid sequence of the heavy chain constant region (SEQ ID NO:24):<br>ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP<br>VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP<br>SSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTH<br>TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC<br>VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ<br>YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP<br>APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLT<br>CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG<br>SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT<br>QKSLSLSPG |
| SEQ ID NO:17 | Amino acid sequence of the light chain of humanized antibody IL17A-H069 | Amino acid sequence of the light chain variable region (SEQ ID NO:23):<br>DIVMTQSPDSLAVSLGERATINCKSSQSLLNRSNQK<br>NYLAWYQQKPGQPPKLLVDFASTRESGVPDRFSGS<br>GSGTDFTLTISSLQAEDVAVYFCQQHYTTPFTFGPGT<br>KVDIK<br>Amino acid sequence of the light chain constant region (SEQ ID NO:25):<br>RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA<br>KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL<br>TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC |
| SEQ ID NO:18 | Amino acid sequence of the heavy chain of the | Amino acid sequence of the heavy chain signal peptide (SEQ ID NO:20):<br>MELGLSWIFLLAILKGVQC |



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| | humanized antibody IL17A-H069 containing the signal peptide | Amino acid sequence of the heavy chain variable region (SEQ ID NO:22):<br>EVQLVQSGAEVKKPGATVKISCKASGYTFTDYEMH<br>WVQQAPGHGLEWMGVIHPGGGGTAYNQKFKGRV<br>TITADTSTDTAYMELSSLRSEDTAVYYCTRGDHDGR<br>TDYWGQGTLVTVSS<br>Amino acid sequence of the heavy chain constant region (SEQ ID NO:24):<br>ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP<br>VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP<br>SSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTH<br>TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC<br>VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ<br>YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP<br>APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLT<br>CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG<br>SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT<br>QKSLSLSPG |
| SEQ ID NO:19 | Amino acid sequence of the light chain of the humanized antibody IL17A-H069 containing the signal peptide | Amino acid sequence of the light chain signal peptide (SEQ ID NO:21):<br>MGWSCIILFLVATATGVHS<br>Amino acid sequence of the light chain variable region (SEQ ID NO:23):<br>DIVMTQSPDSLAVSLGERATINCKSSQSLLNRSNQK<br>NYLAWYQQKPGQPPKLLVDFASTRESGVPDRFSGS<br>GSGTDFTLTISSLQAEDVAVYFCQQHYTTPFTFGPGT<br>KVDIK<br>Amino acid sequence of the light chain constant region (SEQ ID NO:25):<br>RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA<br>KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL<br>TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC |
| SEQ ID NO:20 | Amino acid sequence of the heavy chain signal peptide of the humanized antibody IL17A-H069 | MELGLSWIFLLAILKGVQC |
| SEQ ID NO:21 | Amino acid sequence of the light chain signal peptide of the humanized antibody IL17A-H069/murine antibody IL17A-M069 | MGWSCIILFLVATATGVHS |
| SEQ ID NO:22 | Amino acid sequence of the | EVQLVQSGAEVKKPGATVKISCKASGYTFTDYEMH<br>WVQQAPGHGLEWMGVIHPGGGGTAYNQKFKGRV |



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| | heavy chain variable region of the humanized antibody IL17A-H069 | TITADTSTDTAYMELSSLRSEDTAVYYCTRGDHDGR TDYWGQGTLVTVSS |
| SEQ ID NO:23 | Amino acid sequence of the light chain variable region of the humanized antibody IL17A-H069 | DIVMTQSPDSLAVSLGERATINCKSSQSLLNRSNQK NYLAWYQQKPGQPPKLLVDFASTRESGVPDRFSGS GSGTDFTLTISSLQAEDVAVYFCQQHYTTPFTFGPGT KVDIK |
| SEQ ID NO:24 | Amino acid sequence of the humanized antibody IL17A-H069 heavy chain constant region | ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTH TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPG |
| SEQ ID NO:25 | Amino acid sequence of the humanized antibody IL17A-H069 light chain constant region | RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC |
| SEQ ID NO:26 | Nucleotide sequence of the humanized antibody IL17A-H069 heavy chain containing the signal peptide | Nucleotide sequence of heavy chain signal peptide (SEQ ID NO:28):<br>ATGGAGTTGGGACTGAGCTGGATTTTCCTTTTGGC TATTTTAAAAGGTGTCCAGTGT<br>Nucleotide sequence of heavy chain variable region (SEQ ID NO:30):<br>GAGGTCCAACTTGTCCAGTCTGGAGCAGAGGTGA AGAAGCCTGGAGCCACAGTGAAGATTTCCTGTAA GGCATCTGGCTACACCTTCACAGACTATGAGATGC ACTGGGTCCAACAGGCTCCTGGCCATGGATTGGA GTGGATGGGAGTGATTCACCCTGGAGGAGGAGGC ACAGCCTACAACCAGAAGTTCAAGGGCAGGGTG ACCATCACAGCAGACACCAGCACAGACACAGCCT ATATGGAACTGTCCTCCCTGAGGTCTGAGGACAC AGCAGTCTACTACTGTACCAGGGGAGACCATGAT GGCAGGACAGACTACTGGGGACAAGGCACCCTG GTGACAGTGTCCTCT<br>Nucleotide sequence of the heavy chain constant region (SEQ ID NO:32):<br>GCAAGCACCAAGGGCCCATCGGTCTTCCCCCTGG CACCCTCCTCCAAGAGCACCTCTGGGGGCACAGC GGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCC |



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| | | GAACCGGTGACGGTGTCGTGGAACTCAGGCGCCC<br>TGACCAGCGGCGTGCACACCTTCCCGGCTGTCCT<br>ACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTG<br>GTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGA<br>CCTACATCTGCAACGTGAATCACAAGCCCAGCAA<br>CACCAAGGTGGACAAGAAAGTTGAGCCCAAATCT<br>TGTGACAAAACTCACACATGCCCACCGTGCCCAG<br>CACCTGAACTCCTGGGGGGACCGTCAGTCTTCCT<br>CTTCCCCCCAAAACCCAAGGACACCCTCATGATC<br>TCCCGGACCCCTGAGGTCACgTGCGTGGTGGTGG<br>ACGTGAGCCACGAAGACCCcGAGGTCAAGTTCAA<br>CTGGTACGTGGACGGCGTGGAGGTGCATAATGCC<br>AAGACAAAGCCGCGGGAGGAGCAGTACAACAGC<br>ACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGC<br>ACCAGGACTGGCTGAATGGCAAGGAGTACAAGT<br>GCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCAT<br>CGAGAAAACCATCTCCAAAGCCAAAGGGCAGCC<br>CCGAGAACCACAGGTGTACACCCTGCCCCCATCC<br>CGGGATGAGCTGACCAAGAACCAGGTCAGCCTG<br>ACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACAT<br>CGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGA<br>GAACAACTACAAGACCACGCCTCCCGTGCTGGAC<br>TCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCAC<br>CGTGGACAAGAGCAGGTGGCAGCAGGGGAACGT<br>CTTCTCATGCTCCGTGATGCATGAGGCTCTGCACA<br>ACCACTACACCCAGAAGTCCCTGTCTCTGAGCCC<br>TGGCTAATAGTGA |
| SEQ ID NO:27 | Nucleotide sequence of humanized antibody IL17A-H069 light chain containing signal peptide | Nucleotide sequence of the light chain signal peptide (SEQ ID NO:29):<br>ATGGGCTGGTCCTGTATCATCCTGTTCCTGGTGGC<br>TACAGCCACAGGAGTGCATTCT<br>Nucleotide sequence of the light chain variable region (SEQ ID NO:31):<br>GACATTGTGATGACCCAGAGCCCTGACTCCCTGG<br>CTGTGTCCCTGGGAGAGAGGGCTACCATCAACTG<br>TAAGTCCAGCCAGTCCCTGCTGAACAGGAGCAAC<br>CAGAAGAACTACCTGGCTTGGTATCAACAGAAGC<br>CTGGACAACCTCCAAAACTGCTGGTGGACTTTGC<br>CAGCACCAGGGAGTCTGGAGTGCCTGACAGGTTC<br>TCTGGCTCTGGCTCTGGCACAGACTTCACCCTGA<br>CCATCTCCTCCCTCCAAGCAGAGGATGTGGCTGTC<br>TACTTCTGTCAACAACACTACACCACACCATTCAC<br>CTTTGGACCTGGCACCAAGGTGGACATCAAG<br>Nucleotide sequence of the light chain constant region (SEQ ID NO:33):<br>CGTACGGTGGCTGCACCATCTGTCTTCATCTTCCC<br>GCCATCTGATGAGCAGTTGAAATCTGGAACTGCC<br>TCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAG<br>AGAGGCCAAAGTACAGTGGAAGGTGGATAACGC<br>CCTCCAATCGGGTAACTCCCAGGAGAGTGTCACA |



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| | | GAGCAGGACAGCAAGGACAGCACCTACAGCCTC AGCAGCACCCTGACGCTGAGCAAAGCAGACTAC GAGAAACACAAAGTCTACGCCTGCGAAGTCACCC ATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTT CAACAGGGGAGAGTGTTAA |
| SEQ ID NO:28 | Nucleotide sequence of heavy chain signal peptide of humanized antibody IL17A-H069 | ATGGAGTTGGGACTGAGCTGGATTTTCCTTTTGGC TATTTTAAAAGGTGTCCAGTGT |
| SEQ ID NO:29 | Nucleotide sequence of light chain signal peptide of humanized antibody IL17A-H069 | ATGGGCTGGTCCTGTATCATCCTGTTCCTGGTGGC TACAGCCACAGGAGTGCATTCT |
| SEQ ID NO:30 | Nucleotide sequence of the heavy chain variable region of the humanized antibody IL17A-H069 | GAGGTCCAACTTGTCCAGTCTGGAGCAGAGGTGA AGAAGCCTGGAGCCACAGTGAAGATTTCCTGTAA GGCATCTGGCTACACCTTCACAGACTATGAGATGC ACTGGGTCCAACAGGCTCCTGGCCATGGATTGGA GTGGATGGGAGTGATTCACCCTGGAGGAGGAGGC ACAGCCTACAACCAGAAGTTCAAGGGCAGGGTG ACCATCACAGCAGACACCAGCACAGACACAGCCT ATATGGAACTGTCCTCCCTGAGGTCTGAGGACAC AGCAGTCTACTACTGTACCAGGGGAGACCATGAT GGCAGGACAGACTACTGGGGACAAGGCACCCTG GTGACAGTGTCCTCT |
| SEQ ID NO:31 | Nucleotide sequence of the light chain variable region of the humanized antibody IL17A-H069 | GACATTGTGATGACCCAGAGCCCTGACTCCCTGG CTGTGTCCCTGGGAGAGAGGGCTACCATCAACTG TAAGTCCAGCCAGTCCCTGCTGAACAGGAGCAAC CAGAAGAACTACCTGGCTTGGTATCAACAGAAGC CTGGACAACCTCCAAAACTGCTGGTGGACTTTGC CAGCACCAGGGAGTCTGGAGTGCCTGACAGGTTC TCTGGCTCTGGCTCTGGCACAGACTTCACCCTGA CCATCTCCTCCCTCCAAGCAGAGGATGTGGCTGTC TACTTCTGTCAACAACACTACACCACACCATTCAC CTTTGGACCTGGCACCAAGGTGGACATCAAG |
| SEQ ID NO:32 | Nucleotide sequence of the heavy chain constant region of the humanized antibody IL17A-H069 | GCAAGCACCAAGGGCCCATCGGTCTTCCCCCTGG CACCCTCCTCCAAGAGCACCTCTGGGGGCACAGC GGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCC GAACCGGTGACGGTGTCGTGGAACTCAGGCGCCC TGACCAGCGGCGTGCACACCTTCCCGGCTGTCCT ACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTG GTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGA CCTACATCTGCAACGTGAATCACAAGCCCAGCAA CACCAAGGTGGACAAGAAAGTTGAGCCCAAATCT TGTGACAAAACTCACACATGCCCACCGTGCCCAG CACCTGAACTCCTGGGGGGACCGTCAGTCTTCCT CTTCCCCCCAAAACCCAAGGACACCCTCATGATC |



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| | | TCCCGGACCCCTGAGGTCACgTGCGTGGTGGTGG<br>ACGTGAGCCACGAAGACCCcGAGGTCAAGTTCAA<br>CTGGTACGTGGACGGCGTGGAGGTGCATAATGCC<br>AAGACAAAGCCGCGGGAGGAGCAGTACAACAGC<br>ACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGC<br>ACCAGGACTGGCTGAATGGCAAGGAGTACAAGT<br>GCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCAT<br>CGAGAAAACCATCTCCAAAGCCAAAGGGCAGCC<br>CCGAGAACCACAGGTGTACACCCTGCCCCCATCC<br>CGGGATGAGCTGACCAAGAACCAGGTCAGCCTG<br>ACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACAT<br>CGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGA<br>GAACAACTACAAGACCACGCCTCCCGTGCTGGAC<br>TCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCAC<br>CGTGGACAAGAGCAGGTGGCAGCAGGGGAACGT<br>CTTCTCATGCTCCGTGATGCATGAGGCTCTGCACA<br>ACCACTACACCCAGAAGTCCCTGTCTCTGAGCCC<br>TGGCTAATAGTGA |
| SEQ ID NO:33 | Nucleotide sequence of the light chain constant region of the humanized antibody IL17A-H069 | CGTACGGTGGCTGCACCATCTGTCTTCATCTTCCC<br>GCCATCTGATGAGCAGTTGAAATCTGGAACTGCC<br>TCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAG<br>AGAGGCCAAAGTACAGTGGAAGGTGGATAACGC<br>CCTCCAATCGGGTAACTCCCAGGAGAGTGTCACA<br>GAGCAGGACAGCAAGGACAGCACCTACAGCCTC<br>AGCAGCACCCTGACGCTGAGCAAAGCAGACTAC<br>GAGAAACACAAAGTCTACGCCTGCGAAGTCACCC<br>ATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTT<br>CAACAGGGGAGAGTGTTAA |
| SEQ ID NO:34 | Amino acid sequence of murine antibody scFv which is used in the construction of antibody IL17A-M069 | Amino acid sequence of light chain variable region of IL17A-M069 (SEQ ID NO:9):<br>DIVMSQSPSSLAMSVGQKVTMNCKSNQSLLNRSNQ<br>KNYLAWYQQKPGQSPKLLVDFASTRESGVPDRFIGS<br>GSGTDFSLTISSVQAEDLADYFCQQHYTTPFTFGSG<br>TKLEIK<br>Linker(SEQ ID NO:35):<br>SSGGGGSGGGGGGSSRSS<br>Amino acid sequence of heavy chain variable region of IL17A-M069 (SEQ ID NO:8):<br>QAHLQQSGAELVRPGASVKLSCKALGYTFTDYEM<br>HWVKQTPVHGLEWIGVIHPGGGGTAYNQKFKGKA<br>TLTADKSSSTAYMELSSLTSEDSAVYYCTRGDHDGR<br>TDYWGQGTTLTVSS |
| SEQ ID NO：35 | Amino acid sequence of the linker used in the construction of the phage antibody library for the linkage of the | SSGGGGSGGGGGGSSRSS |



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| | murine antibody scFv | |
| SEQ ID NO：36 | Nucleotide sequence of the murine antibody IL17A-M069 heavy chain containing the signal peptide | Nucleotide sequence of heavy chain signal peptide (SEQ ID NO:43):<br>ATGGGCTGGTCCCTGATTCTGCTGTTCCTGGTGGC<br>TGTGGCTACCAGGGTGCTGAGC<br>Nucleotide sequence of heavy chain variable region (SEQ ID NO:4):<br>CAGGCCCACCTTCAACAGTCTGGGGCTGAGCTGG<br>TGAGGCCTGGGGCTTCAGTGAAGCTGTCCTGCAA<br>GGCTTTGGGCTACACATTTACTGACTATGAAATGC<br>ACTGGGTGAAACAGACACCTGTGCATGGCCTGGA<br>ATGGATTGGAGTTATTCATCCAGGAGGTGGTGGTA<br>CGGCCTACAATCAGAAGTTCAAGGGCAAGGCCAC<br>ACTGACTGCAGACAAGTCCTCCAGTACAGCCTAC<br>ATGGAGCTCAGCAGCCTGACATCTGAGGACTCTG<br>CTGTCTATTACTGTACAAGAGGGGATCACGACGG<br>AAGGACTGACTACTGGGGCCAAGGCACCACTCTC<br>ACAGTCTCCTCA<br>Nucleotide sequence of the heavy chain constant region (SEQ ID NO:6):<br>GCCAAAACGACACCCCCATCTGTCTATCCACTGG<br>CCCCTGGATCTGCTGCCCAAACTAACTCCATGGTG<br>ACCCTGGGATGCCTGGTCAAGGGCTATTTCCCTGA<br>GCCAGTGACAGTGACCTGGAACTCTGGATCCCTG<br>TCCAGCGGTGTGCACACCTTCCCAGCTGTCCTGC<br>AGTCTGACCTCTACACTCTGAGCAGCTCAGTGAC<br>TGTCCCCTCCAGCACCTGGCCCAGCGAGACCGTC<br>ACCTGCAACGTTGCCCACCCGGCCAGCAGCACCA<br>AGGTGGACAAGAAAATTGTGCCCAGGGATTGTGG<br>TTGTAAGCCTTGCATATGTACAGTCCCAGAAGTAT<br>CATCTGTCTTCATCTTCCCCCCAAAGCCCAAGGAT<br>GTGCTCACCATTACTCTGACTCCTAAGGTCACGTG<br>TGTTGTGGTAGACATCAGCAAGGATGATCCCGAG<br>GTCCAGTTCAGCTGGTTTGTAGATGATGTGGAGGT<br>GCACACAGCTCAGACGCAACCCCGGGAGGAGCA<br>GTTCAACAGCACTTTCCGCTCAGTCAGTGAACTT<br>CCCATCATGCACCAGGACTGGCTCAATGGCAAGG<br>AGTTCAAATGCAGGGTCAACAGTGCAGCTTTCCC<br>TGCCCCCATCGAGAAAACCATCTCCAAAACCAAA<br>GGCAGACCGAAGGCTCCACAGGTGTACACCATTC<br>CACCTCCCAAGGAGCAGATGGCCAAGGATAAAGT<br>CAGTCTGACCTGCATGATAACAGACTTCTTCCCTG<br>AAGACATTACTGTGGAGTGGCAGTGGAATGGGCA<br>GCCAGCGGAGAACTACAAGAACACTCAGCCCATC<br>ATGGACACAGATGGCTCTTACTTCGTCTACAGCAA<br>GCTCAATGTGCAGAAGAGCAACTGGGAGGCAGG<br>AAATACTTTCACCTGCTCTGTGTTACATGAGGGCC<br>TGCACAACCACCATACTGAGAAGAGCCTCTCCCA<br>CTCTCCTGGTAAATAA |



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| SEQ ID NO：37 | Nucleotide sequence of the murine antibody IL17A-M069 light chain containing the signal peptide | Nucleotide sequence of the light chain signal peptide (SEQ ID NO:29):<br>ATGGGCTGGTCCTGTATCATCCTGTTCCTGGTGGC<br>TACAGCCACAGGAGTGCATAGC<br>Nucleotide sequence of the light chain variable region (SEQ ID NO:5):<br>GACATTGTGATGTCACAGTCTCCATCCTCCCTGGC<br>TATGTCAGTAGGACAGAAGGTCACTATGAACTGC<br>AAGTCCAATCAGAGCCTTTTAAATAGAAGCAATC<br>AAAAGAACTATTTGGCCTGGTACCAGCAGAAACC<br>AGGACAGTCTCCTAAACTTCTGGTAGACTTTGCAT<br>CCACTAGGGAATCTGGGGTCCCTGATCGCTTCATA<br>GGCAGTGGATCTGGGACAGATTTCAGTCTTACCAT<br>CAGCAGTGTGCAGGCTGAGGACCTGGCAGATTAC<br>TTCTGTCAGCAACATTATACCACTCCATTCACGTT<br>CGGCTCGGGGACCAAGCTGGAAATAAAA<br>Nucleotide sequence of the light chain constant region (SEQ ID NO:7):<br>CGGGCTGATGCTGCACCAACTGTATCCATCTTCCC<br>ACCATCCAGTGAGCAGTTAACATCTGGAGGTGCC<br>TCAGTCGTGTGCTTCTTGAACAACTTCTACCCCAA<br>AGACATCAATGTCAAGTGGAAGATTGATGGCAGT<br>GAACGACAAAATGGCGTCCTGAACAGTTGGACTG<br>ATCAGGACAGCAAAGACAGCACCTACAGCATGAG<br>CAGCACCCTCACGTTGACCAAGGACGAGTATGAA<br>CGACATAACAGCTATACCTGTGAGGCCACTCACA<br>AGACATCAACTTCACCCATTGTCAAGAGCTTCAA<br>CAGGAATGAGTGTTAAA |
| SEQ ID NO：38 | Amino acid sequence of the heavy chain of the murine antibody IL17A-M069 containing the signal peptide | Amino acid sequence of the heavy chain signal peptide (SEQ ID NO:42):<br>MGWSLILLFLVAVATRVLS<br>Amino acid sequence of the heavy chain variable region (SEQ ID NO:8):<br>QAHLQQSGAELVRPGASVKLSCKALGYTFTDYEM<br>HWVKQTPVHGLEWIGVIHPGGGGTAYNQKFKGKA<br>TLTADKSSSTAYMELSSLTSEDSAVYYCTRGDHDGR<br>TDYWGQGTTLTVSS<br>Amino acid sequence of the heavy chain constant region (SEQ ID NO:40):<br>AKTTPPSVYPLAPGSAAQTNSMVTLGCLVKGYFPE<br>PVTVTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVP<br>SSTWPSETVTCNVAHPASSTKVDKKIVPRDCGCKPC<br>ICTVPEVSSVFIFPPKPKDVLTITLTPKVTCVVVDISK<br>DDPEVQFSWFVDDVEVHTAQTQPREEQFNSTFRSV<br>SELPIMHQDWLNGKEFKCRVNSAAFPAPIEKTISKT<br>KGRPKAPQVYTIPPPKEQMAKDKVSLTCMITDFFPE<br>DITVEWQWNGQPAENYKNTQPIMDTDGSYFVYSK<br>LNVQKSNWEAGNTFTCSVLHEGLHNHHTEKSLSHS<br>PGK |
| SEQ ID | Amino acid | Amino acid sequence of the light chain signal peptide (SEQ |



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| NO：39 | sequence of the light chain of the murine antibody IL17A-M069 containing the signal peptide | ID NO:21):<br>MGWSCIILFLVATATGVHS<br>Amino acid sequence of the light chain variable region (SEQ ID NO:9):<br>DIVMSQSPSSLAMSVGQKVTMNCKSNQSLLNRSNQ<br>KNYLAWYQQKPGQSPKLLVDFASTRESGVPDRFIGS<br>GSGTDFSLTISSVQAEDLADYFCQQHYTTPFTFGSG<br>TKLEIK<br>Amino acid sequence of the light chain constant region (SEQ ID NO:41)<br>RADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDI<br>NVKWKIDGSERQNGVLNSWTDQDSKDSTYSMSST<br>LTLTKDEYERHNSYTCEATHKTSTSPIVKSFNRNEC |
| SEQ ID NO：40 | Amino acid sequence of the heavy chain constant region of the murine antibody IL17A-M069 | AKTTPPSVYPLAPGSAAQTNSMVTLGCLVKGYFPE<br>PVTVTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVP<br>SSTWPSETVTCNVAHPASSTKVDKKIVPRDCGCKPC<br>ICTVPEVSSVFIFPPKPKDVLTITLTPKVTCVVVDISK<br>DDPEVQFSWFVDDVEVHTAQTQPREEQFNSTFRSV<br>SELPIMHQDWLNGKEFKCRVNSAAFPAPIEKTISKT<br>KGRPKAPQVYTIPPPKEQMAKDKVSLTCMITDFFPE<br>DITVEWQWNGQPAENYKNTQPIMDTDGSYFVYSK<br>LNVQKSNWEAGNTFTCSVLHEGLHNHHTEKSLSHS<br>PGK |
| SEQ ID NO：41 | Amino acid sequence of the light chain constant region of the murine antibody IL17A-M069 | RADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDI<br>NVKWKIDGSERQNGVLNSWTDQDSKDSTYSMSST<br>LTLTKDEYERHNSYTCEATHKTSTSPIVKSFNRNEC |
| SEQ ID NO：42 | Amino acid sequence of the heavy chain signal peptide of the murine antibody IL17A-M069 | MGWSLILLFLVAVATRVLS |
| SEQ ID NO：43 | Nucleotide sequence of the heavy chain signal peptide of the murine antibody IL17A-M069 | ATGGGCTGGTCCCTGATTCTGCTGTTCCTGGTGGC<br>TGTGGCTACCAGGGTGCTGAGC |



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What is claimed are:

1. An isolated anti-IL17A antibody or antigen-binding fragment thereof, comprising
a heavy chain variable region having a heavy chain CDR1 region having the amino acid sequence as set forth in SEQ ID NO: 13 and a heavy chain CDR2 region having the amino acid sequence as set forth in SEQ ID NO: 14 and a heavy chain CDR3 region having the amino acid sequence as set forth in SEQ ID NO: 15; and
a light chain variable region having a light chain CDR1 region having the amino acid sequence as set forth in SEQ ID NO: 10, a light chain CDR2 region having the amino acid sequence as set forth in SEQ ID NO: 11, and a light chain CDR3 region having the amino acid sequence as set forth in SEQ ID NO: 12.

2. The anti-IL17A antibody or antigen-binding fragment thereof according to claim 1, comprising
a heavy chain variable region having the amino acid sequence as set forth in SEQ ID NO: 22, or the amino acid sequences having at least 90%, 92%, 95%, 98% or 99% sequence identity to SEQ ID NO: 22; and
a light chain variable region having the amino acid sequence as set forth in SEQ ID NO: 23, or the amino acid sequences having at least 90%, 92%, 95%, 98% or 99% sequence identity to SEQ ID NO: 23.

3. The anti-IL17A antibody or antigen-binding fragment thereof according to claim 1, wherein the anti-IL17A antibody or antigen-binding fragment thereof is a humanized antibody or a chimeric antibody.

4. The anti-IL17A antibody or antigen-binding fragment thereof according to any one of claims 1 to 3, further comprising
a heavy chain constant region and a light chain constant region.



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5. The anti-IL17A antibody or antigen-binding fragment thereof according to claim 4, wherein the heavy chain constant region is the IgG1 heavy chain constant region having the amino acid sequence as set forth in SEQ ID NO: 24, or the amino acid sequences having at least 90%, 92%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 24; and/or

the light chain constant region is the human kappa light chain constant region having the amino acid sequence as set forth in SEQ ID NO: 25, or the amino acid sequences having at least 90%, 92%, 95%, 98%, or 99% sequence identity to SEQ ID NO: 25.

6. The anti-IL17A antibody or antigen-binding fragment thereof according to any one of claims 1 to 5, further comprising

a signal peptide linked to the heavy chain variable region and/or a signal peptide linked to the light chain variable region.

7. The anti-IL17A antibody or antigen-binding fragment thereof according to claim 6, wherein the signal peptide linked to the heavy chain variable region is the amino acid sequence as set forth in SEQ ID NO: 20 or amino acid sequences having at least 90%, 92%, 95%, 98% or 99% sequence identity to SEQ ID NO: 20; and/or

the signal peptide linked to the light chain variable region is the amino acid sequence as set forth in SEQ ID NO: 21 or amino acid sequences having at least 90%, 92%, 95%, 98% or 99% sequence identity to SEQ ID NO: 21.

8. The anti-IL17A antibody or antigen-binding fragment thereof according to any one of claims 1 to 7, wherein the anti-IL17A antibody or antigen-binding fragment thereof is an IgG antibody.

9. The anti-IL17A antibody or antigen-binding fragment thereof according to claim 8, wherein the anti-IL 17A antibody or antigen-binding fragment thereof is an IgG1 antibody.



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10. The anti-IL17A antibody or antigen-binding fragment thereof according to any one of claims 1 to 9, wherein the anti-IL17A antibody or antigen-binding fragment thereof is a monoclonal antibody.

11. The anti-IL17A antibody or antigen-binding fragment thereof according to any one of claims 1 to 10, wherein the binding affinity KD of the anti-IL17A antibody or antigen-binding fragment thereof to the recombinant human IL17A protein is 0.1-10E-11M.

12. The anti-IL17A antibody or antigen-binding fragment thereof according to claim 11, wherein the binding affinity KD of the anti-IL17A antibody or antigen-binding fragment thereof to the recombinant human IL17A protein is 0.5-5E-11M.

13. The anti-IL17A antibody or antigen-binding fragment thereof according to claim 11, wherein the binding affinity KD of the anti-IL17A antibody or antigen-binding fragment thereof to the recombinant human IL17A protein is 2.88E-11M.

14. The anti-IL17A antibody or antigen-binding fragment thereof according to any one of claims 1 to 13, wherein the binding affinity KD of the anti-IL17A antibody or antigen-binding fragment thereof to the recombinant human IL17A/F protein is 0.1-10E-10M.

15. The anti-IL17A antibody or antigen-binding fragment thereof according to claim 14, wherein the binding affinity KD of the anti-IL17A antibody or antigen-binding fragment thereof to the recombinant human IL17A protein is 0.5-5E-10M.

16. The anti-IL17A antibody or antigen-binding fragment thereof according to claim 14, wherein the binding affinity KD of the anti-IL17A antibody or antigen-binding fragment thereof to the recombinant human IL17A protein is 5.37E-10M.



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17. The anti-IL17A antibody or antigen-binding fragment thereof according to any one of claims 1-16, wherein the antigen-binding fragment is Fv, Fab, Fab', Fab'-SH, F(ab')2, or single chain antibody molecule.

18. The anti-IL17A antibody or antigen-binding fragment thereof according to claim 17, wherein the single chain antibody molecule is scFv, di-scFv, tri-scFv, diabody or scFab.

19. An antibody-drug conjugate, comprising the anti-IL17A antibody or antigen-binding fragment thereof according to any one of claims 1-18 and an additional therapeutic agent.

20. The antibody-drug conjugate according to claim 19, wherein the anti-IL17A antibody or antigen-binding fragment thereof is connected with the additional therapeutic agent via a linker.

21. A nucleic acid encoding the anti-IL17A antibody or antigen-binding fragment thereof according to any one of claims 1-18.

22. The nucleic acid according to claim 21, comprising a nucleotide sequence as set forth in SEQ ID NO: 30 encoding heavy chain variable region and/or a nucleotide sequence as set forth in SEQ ID NO: 31 encoding light chain variable region.

23. An expression vector, comprising the nucleic acid according to claim 21 or 22.

24. A host cell, comprising the nucleic acid according to claim 21 or 22, or the expression vector according to claim 23.

25. A method for producing the anti-IL17A antibody or antigen-binding fragment thereof according to any one of claims 1-18, comprising culturing the host cells according to claim 24 under conditions suitable



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for antibody expression, and harvesting the expressed antibodies from the culture medium.

26. A pharmaceutical composition, comprising the anti-IL17A antibody or antigen-binding fragment thereof according to any one of claims 1-18, or the antibody-drug conjugate according to claim 19 or 20, or the nucleic acid according to claim 21 or 22, or the expression vector according to claim 23, and a pharmaceutically acceptable carrier.

27. The anti-IL17A antibody or antigen-binding fragment thereof according to any one of claims 1-18 or the antibody-drug conjugate according to claim 19 or 20 or the pharmaceutical composition according to claim 26, for use in the treatment of psoriasis.

28. A use of the anti-IL17A antibody or antigen-binding fragment thereof according to any one of claims 1-18 or the antibody-drug conjugate according to claim 19 or 20 or the pharmaceutical composition according to claim 26 in the preparation of a medicament for the treatment of psoriasis.

29. A pharmaceutical combination, comprising the anti-IL17A antibody or antigen-binding fragment thereof according to any one of claims 1-18 or the antibody-drug conjugate according to claim 19 or 20 or the pharmaceutical composition according to claim 26, and one or more additional therapeutic agents.

30. A kit, comprising the anti-IL17A antibody or antigen-binding fragment according to any one of claims 1-18 or the antibody-drug conjugate according to claim 19 or 20 or the pharmaceutical composition according to claim 26, further comprising a device for administration.



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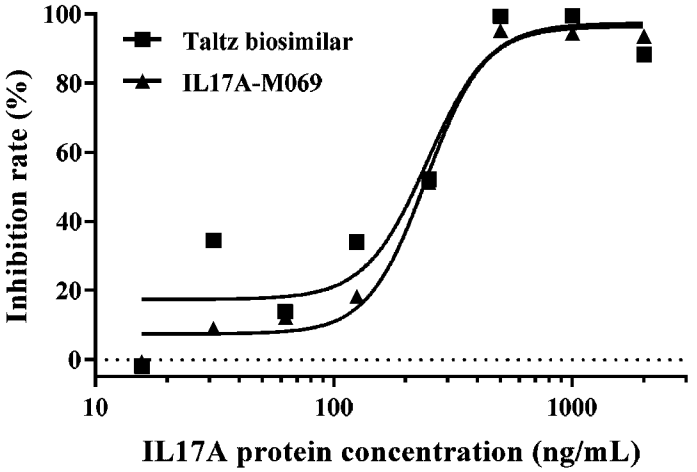


Figure 1





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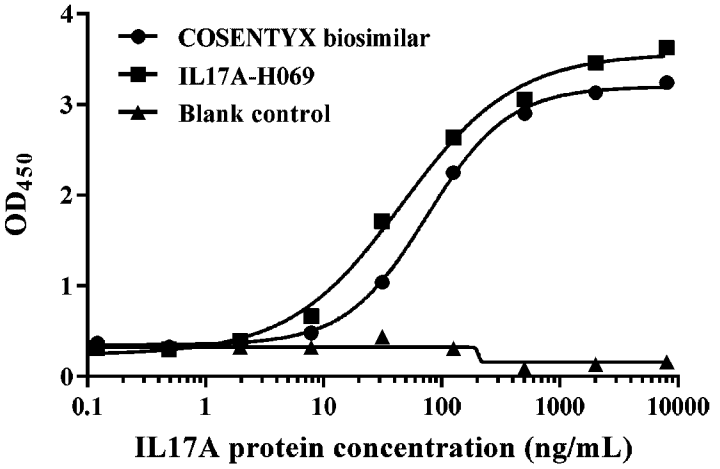


Figure 2



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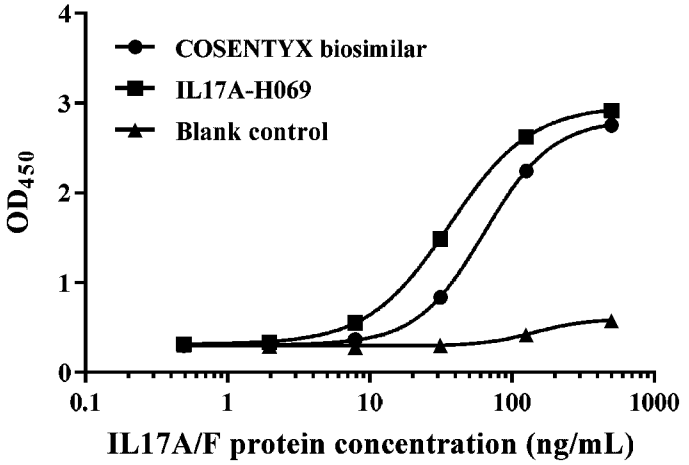


Figure 3

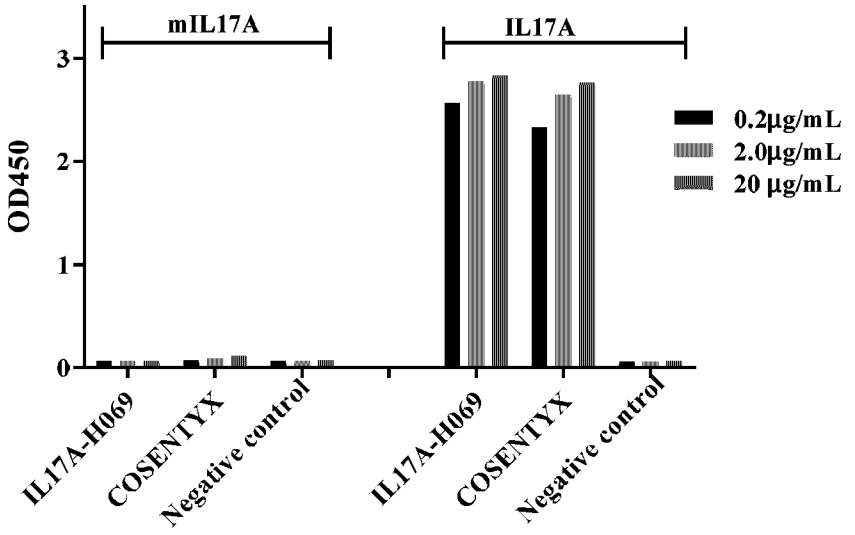


Figure 4



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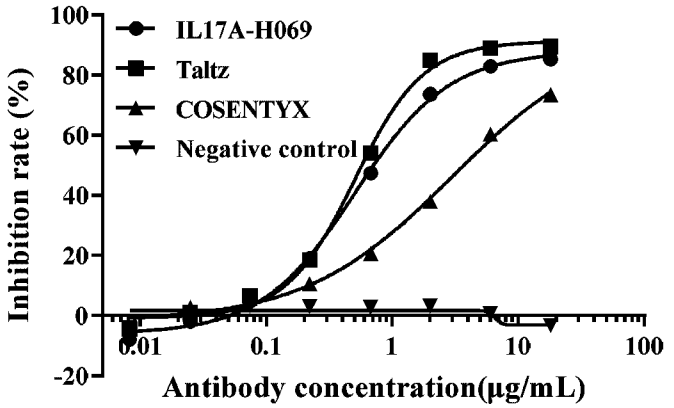


Figure 5

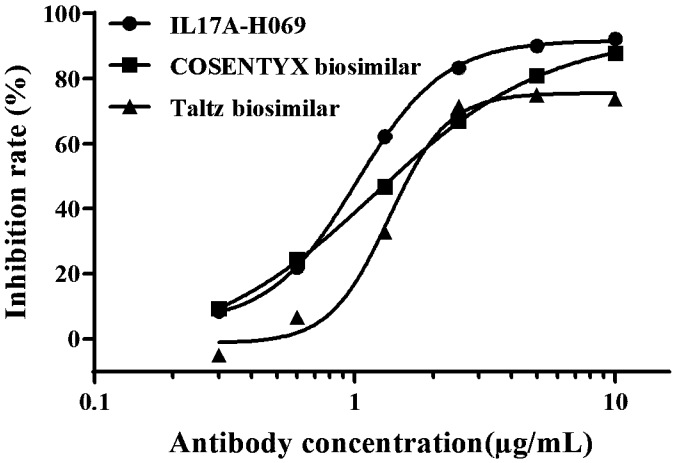


Figure 6



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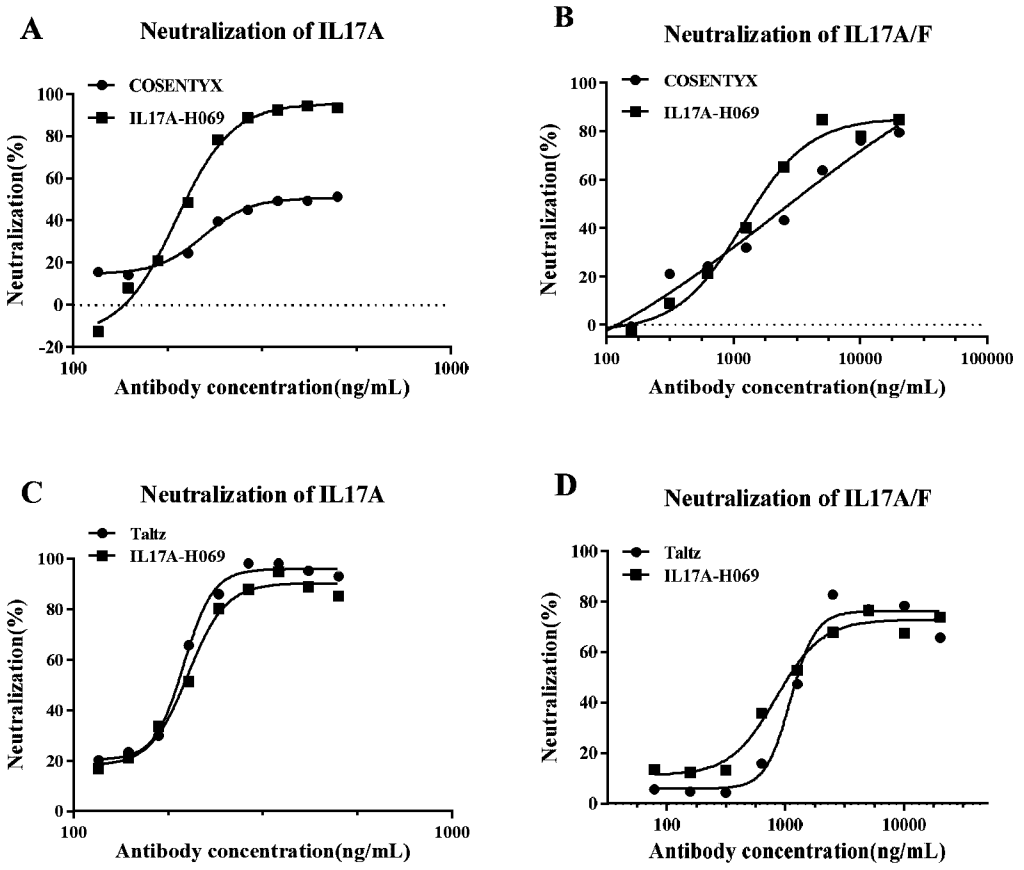


**Figure 7**



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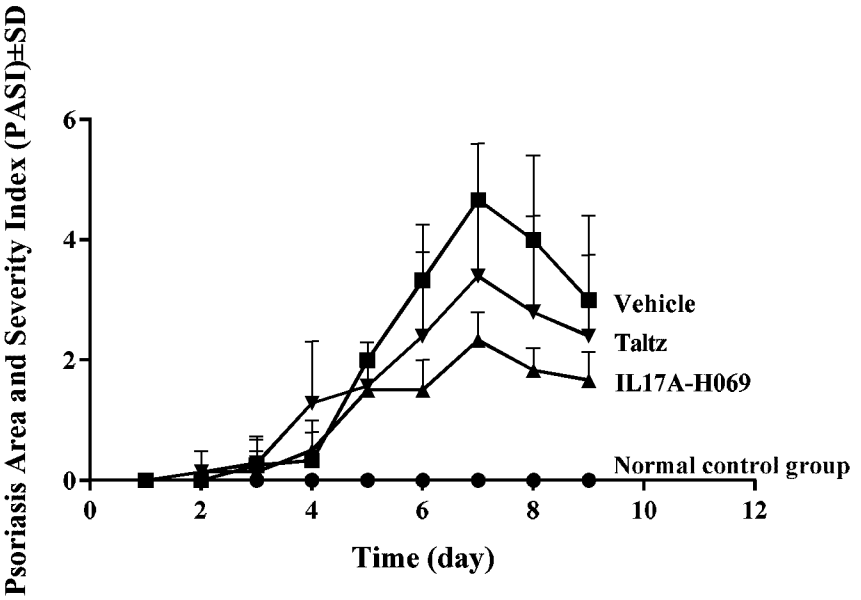


Figure 8

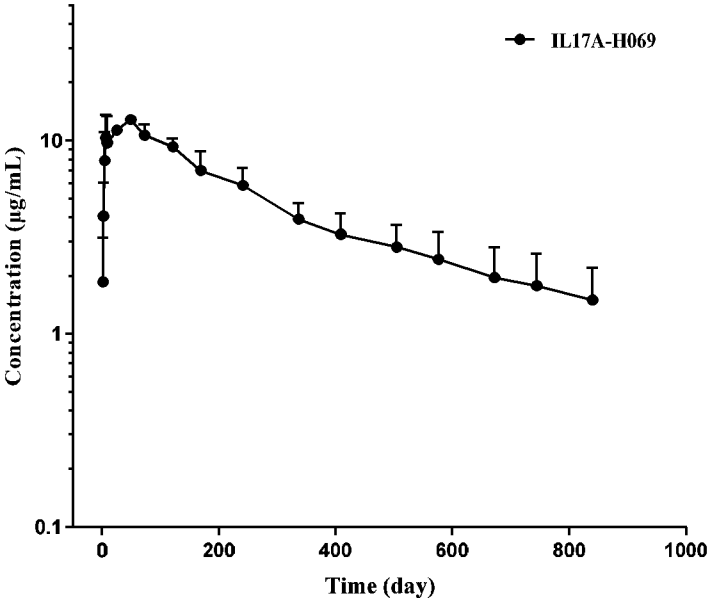


Figure 9



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