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(54) **Title:** BINDING MOLECULE AGAINST DLL3 AND USE THEREOF

(54) 发明名称: 针对DLL3的结合分子及其应用

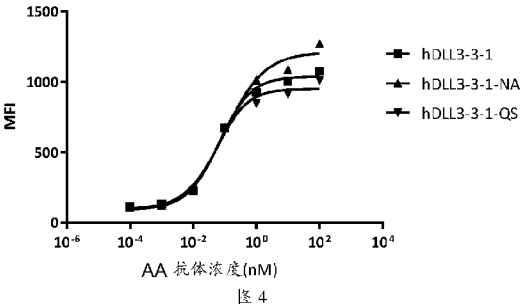

图 4

AA Antibody concentration (nM)

(57) **Abstract:** A binding molecule against DLL3 or an antigen-binding fragment thereof, a derivative containing the binding molecule or the antigen-binding fragment thereof, and a pharmaceutical composition. In addition, the present invention also relates to the related use of the binding molecule or the antigen-binding fragment thereof in the treatment of cancers and in detection and diagnosis.

(57) 摘要: 针对DLL3的结合分子或其抗原结合片段、包含结合分子或其抗原结合片段的衍生物以及药物组合物。此外，还涉及结合分子或其抗原结合片段在治疗癌症和检测诊断方面的相关应用。

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Description

BINDING MOLECULE AGAINST DLL3 AND USE THEREOF

FIELD OF THE INVENTION

The present disclosure belongs to the field of immunology, in particular, the present disclosure relates to a binding molecule against DLL3 or an antigen-binding fragment thereof, a derivative containing the binding molecule or the antigen-binding fragment thereof, and a pharmaceutical composition, and related application thereof in the treatment of cancer.

BACKGROUND TO THE INVENTION

Lung cancer is one of the malignant tumors with the fastest increase in morbidity and mortality and the greatest threat to human health and life. According to pathology, it is divided into small cell lung cancer and non-small cell lung cancer.

Non-small cell lung cancer (NSCLC) is the most important form of lung cancer, and more than 80% of lung cancer patients are of this type. Targeted therapy of lung cancer, PD-1 immunodrugs, and gene sequencing nowadays receive attention, and the following breakthrough progress is mainly focused on non-small cell lung cancer, which greatly increases the available and effective treatment of this subgroup of lung cancer, and greatly improves the five-year survival rate of non-small cell lung cancer patients.

Small cell lung cancer (SCLC) is a highly aggressive, fatal, and widely metastatic lung cancer, accounting for about 15% of lung cancers, and is very different from other lung cancers in pathology, molecular biology, biology, and clinical. It is estimated that over 234, 000 SCLC patients are diagnosed each year, resulting in approximately 250, 000 deaths worldwide each year. SCLC is characterized in rapid tumor growth, high vascularity, unstable genome, and early metastatic spread. Only modest improvements in SCLC detection, treatment, or survival have been seen over the past 30 years, leading to the classification of SCLC as a refractory cancer. Local treatment, such as surgery or radiotherapy, or a combination of both, is almost impossible to cure completely. Platinum-based combination chemotherapy remains the cornerstone of treatment. The first-line standard regimen consists of platinum (carboplatin or cisplatin) in combination with other cytotoxic drugs (such as etoposide). The response rate of chemotherapy for small cell lung cancer is very high, but it is also often accompanied by recurrence, especially in patients with the extensive stage. For patients with limited stage, the median survival period is 14-20 months, while for patients with extensive stage, it is only 9-11 months. For patients with recurrence, the survival period is shorter and there is almost no treatment option. Topotecan, the only one recommended by FDA, is limited

for its Hematology toxicity, and the treatment response rate is also unsatisfactory, only 5-24%. The median survival time is less than 25 weeks. Currently, there is no specific third-line treatment recommendation, so a new effective therapeutic drug is urgently needed.

Delta-like 3, also known as DLL3, is a protein encoded by DLL3 gene and is one of the ligands of the Notch family. DLL3 has only 36% homology with DLL1, and unlike other delta type dsl (delta/serate/lag-2) proteins, such as DLL1 and DLL4, DLL3 has the highest expression in normal tissues of a fetal brain and plays a key role in the growth and development of paraxial mesoderm. It was found that it was expressed on the surface of tumor cells in about 85% of patients with small cell lung cancer and large cell neuroendocrine cancer, and also highly expressed in glioblastoma multiforme, melanoma, pancreatic cancer, and rectal cancer. But it is not expressed in healthy tissues and non-neuroendocrine tumors. This protein is involved in influencing the Notch regulatory signaling pathway such that signaling from the Notch pathway ultimately promotes unrestricted growth of cancer. In normal tissues, mRNA expression of DLL3 is restricted to the brain, esophagus, and pancreas.

Studies have further shown that by detecting the expression of DLL3 in whole transcriptome sequencing data of primary SCLC biopsies, SCLC cell lines, and normal lung biopsies in the analysis of tumor tissue and normal tissue specimens, it was shown that the mRNA of DLL3 in SCLC is increased about 35-fold relative to a normal lung. These SCLC tumor samples were compared with transcriptome data from normal tissues and other tumor types in the cancer genome to further confirm that DLL3 expression in primary SCLC tumor samples and low-grade gliomas (LGG), glioblastoma (GBM), and melanoma (SKCM) was increased. Illumina BeadChip data of the clinical lung cancer genome project also showed elevated DLL3 in primary SCLC tumor specimens compared to NSCLC.

Data obtained from Cancer Cell Line Encyclopedia further confirmed that expression of DLL3 mRNA is particularly elevated in the SCLC cell line. Collectively, these expression data across multiple technology platforms and samples suggest that DLL3 mRNA is overexpressed in primary SCLC tumors, SCLC PDX, traditional SCLC cell lines, and LCNEC PDX, whereas mRNA expression in normal tissues is primarily restricted to the brain.

SUMMARY

The object of the present disclosure provides a binding molecule against DLL3 and an antigen-binding fragment thereof, the binding molecule or antigen-binding fragments thereof being capable of specifically binding to DLL3 without non-specifically binding to the family proteins DLL1 and DLL4.

A first aspect of the present disclosure provides a DLL3 binding molecule or an antigen binding

fragment thereof, the DLL3 binding molecule or the antigen binding fragment thereof including:

i) a heavy chain complementary determinant region 1 (HCDR1) selected from SEQ ID NOs: 6, 9, 12, 15, or 18;

ii) a heavy chain complementary determinant region 2 (HCDR2) selected from: SEQ ID NOs: 7, 10, 13, 16, or 19; and

iii) a heavy chain complementary determinant region 3 (HCDR3) selected from: SEQ ID NOs: 8, 11, 14, 17, 20, 110, or 111.

In an embodiment, the DLL3 binding molecule or the antigen binding fragment thereof comprises a heavy chain variable region (VH), the heavy chain variable region comprises HCDR1, HCDR2, and HCDR3, and the amino acid sequences of the HCDR1, HCDR2, and HCDR3 are respectively:

a) SED ID NOs: 6, 7, and 8; or

b) SED ID NOs: 9, 10, and 11; or

c) SED ID NOs: 12, 13, and 14; or

d) SED ID NOs: 15, 16, and 17; or

e) SED ID NOs: 18, 19, and 20; or

f) SED ID NOs: 6, 7, and 110; or

g) SED ID NOs: 6, 7, and 111.

In an embodiment, the heavy chain variable region comprises an amino acid sequence selected from any one of SEQ ID NOs: 1-5, 21-29, or comprises an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identity to any one of SEQ ID NOs: 1-5, 21-29.

A second aspect of the present disclosure provides another DLL3 binding molecule or an antigen binding fragment thereof, the DLL3 binding molecule or the antigen binding fragment thereof including:

i) a heavy chain complementary determinant region 1 (HCDR1) selected from: SEQ ID NOs: 57, 63, 69, 72, 78, 84, 93, or 99.

ii) a heavy chain complementary determinant region 2 (HCDR2) selected from: SEQ ID NOs: 58, 64, 70, 73, 79, 85, 94, or 100.

iii) a heavy chain complementary determinant region 3 (HCDR3) selected from: SEQ ID NOs: 59, 65, 71, 74, 80, 86, 95, or 101.

iv) a light chain complementary determinant region 1 (LCDR1) selected from: SEQ ID NOs: 60, 66, 75, 81, 87, 90, 96, or 102.

v) a light chain complementary determinant region 2 (LCDR2) selected from: SEQ ID NOs: 61, 67, 76, 82, 88, 91, 97, or 103; and

vi) a light chain complementary determinant region 3 (LCDR3) selected from: SEQ ID NOs: 62,

68, 77, 83, 89, 92, 98, 104, 112, 113, or 114.

In an embodiment, the DLL3 binding molecule or the antigen binding fragment thereof comprises a heavy chain variable region (VH) including HCDR1, HCDR2, and HCDR3 and a light chain variable region (VL) including LCDR1, LCDR2, and LCDR3, wherein the amino acid sequences of the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 are respectively:

a) SED ID NOs: 57, 58, 59, 60, 61, and 62; or

b) SED ID NOs: 63, 64, 65, 66, 67, and 68; or

c) SED ID NOs: 69, 70, 71, 66, 67, and 68; or

d) SED ID NOs: 72, 73, 74, 75, 76 and 77; or

e) SED ID NOs: 78, 79, 80, 81, 82, and 83; or

f) SED ID NOs: 84, 85, 86, 87, 88, and 89; or

g) SED ID NOs: 84, 85, 86, 90, 91 and 92; or

h) SED ID NOs: 93, 94, 95, 96, 97, and 98; or

i) SED ID NOs: 99, 100, 101, 75, 76 and 77; or

j) SED ID NOs: 72, 73, 74, 102, 103 and 104; or

k) SED ID NOs: 63, 64, 65, 66, 67, and 112; or

l) SED ID NOs: 63, 64, 65, 66, 67, and 113; or

m) SED ID NOs: 63, 64, 65, 66, 67, and 114.

In an embodiment, the heavy chain variable region comprises an amino acid sequence selected from any one of SEQ ID NOs: 30, 32, 34, 35, 37, 39, 42, 44, 46, 49, or 51, or comprises an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identity to any one of SEQ ID NOs: 30, 32, 34, 35, 37, 39, 42, 44, 46, 49, or 51.

In an embodiment, the light chain variable region comprises an amino acid sequence selected from any one of SEQ ID NOs: 31, 33, 36, 38, 40, 41, 43, 45, 47, 48, 50, 52, 53, 54, 55, or 56, or comprises an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identity to any one of SEQ ID NOs: 31, 33, 36, 38, 40, 41, 43, 45, 47, 48, 50, 52, 53, 54, 55, or 56.

In an embodiment, the heavy chain variable region and the light chain variable region each comprise sequences selected from a group consisting of:

1) SED ID NOs: 30 and 31; or

2) SED ID NOs: 32 and 33; or

3) SED ID NOs: 34 and 33; or

4) SED ID NOs: 35 and 36; or

5) SED ID NOs: 37 and 38; or

6) SED ID NOs: 39 and 40; or

7) SED ID NOs: 39 and 41; or

8) SED ID NOs: 42 and 43; or

9) SED ID NOs: 44 and 36; or

10) SED ID NOs: 35 and 45; or

11) SED ID NOs: 46 and 47; or

12) SED ID NOs: 46 and 48; or

13) SED ID NOs: 49 and 50; or

14) SED ID NOs: 51 and 52; or

15) SED ID NOs: 51 and 53; or

16) SED ID NOs: 46 and 54; or

17) SED ID NOs: 46 and 55; or

18) SED ID NOs: 46 and 56.

The DLL3 binding molecule or antigen binding fragment thereof of the present disclosure further comprises a heavy chain constant region and/or a light chain constant region; preferably, the heavy chain constant region comprises an Fc; more preferably, Fc is derived from murine or human; more preferably, the sequence of the Fc is native or modified.

The DLL3 binding molecules or antigen binding fragment thereof of the present disclosure can be a monoclonal antibody, a bispecific binding molecule, a multispecific binding molecule, a humanized antibody, a chimeric antibody, a modified antibody, a fully human antibody, a full-length antibody, a heavy chain antibody, a nanobody, an Fab, an Fv, an scFv, an F(ab')2, a linear antibody, or a single domain antibody.

The DLL3 binding molecules or antigen binding fragments thereof of the present disclosure may be in the form of IgG1, IgG2, IgG3, or IgG4.

The present disclosure also provides a conjugate formed by coupling the DLL3 binding molecule or the antigen binding fragment thereof of the present disclosure to a capture label or a detection label; preferably, the detection label comprises a radionuclide, a luminescent substance, a colored substance, or an enzyme.

The present disclosure also provides an antibody drug conjugate (ADC) formed by coupling the DLL3 binding molecule or the antigen binding fragment thereof of the present disclosure with another biologically active molecule; the other biologically active molecule is a small molecule drug; preferably, the DLL3 binding molecule or the antigen binding fragment thereof is linked to the other biologically active molecule via a linker.

The disclosure also provides a nucleic acid encoding the DLL3 binding molecule or the antigen binding fragment thereof of the present disclosure, as well as a recombinant vector including the

nucleic acid, and a host cell including the nucleic acid or vector described above. Preferably, the host cell is a prokaryotic cell, preferably E. coli, or a eukaryotic cell, preferably a mammalian cell or yeast; further preferably, the mammalian cell is a CHO cell or a HEK293 cell.

The present disclosure also provides a method for preparing the DLL3 binding molecule or the antigen binding fragment thereof of the present disclosure, the method including: culturing the host cell described above under suitable conditions and purifying an expression product from the cell.

The present disclosure also provides the use of the DLL3 binding molecule or the antigen binding fragment thereof of the present disclosure in the manufacture of a medicament for the treatment or amelioration of a tumor.

In an embodiment, the medicament targets a tumor cell aberrantly expressing DLL3.

In an embodiment, the tumor is selected from: small cell lung cancer, glioblastoma, neuroendocrine cancer, melanoma, pancreatic cancer, rectal cancer, and metastatic cancers of the aforementioned tumors.

The present disclosure also provides the use of the DLL3 binding molecule or the antigen binding fragment thereof of the present disclosure in the manufacture of a medicament for the treatment or amelioration of a tumor.

In an embodiment, the detection reagent is used for detecting expression of DLL3; the diagnostic reagent is used for diagnosing a tumor; preferably, the tumor is selected from: small cell lung cancer, glioblastoma, neuroendocrine cancer, melanoma, pancreatic cancer, rectal cancer, and metastatic cancers of the aforementioned tumors.

The present disclosure also provides a method for detecting DLL3 expression in a sample, the method including:

(1) contacting the sample with the DLL3 binding molecule or the antigen binding fragment thereof of the present disclosure; and

(2) detecting the formation of a complex of the DLL3 binding molecule or the antigen binding fragment thereof and DLL3; optionally, the DLL3 binding molecule or the antigen binding fragment thereof is detectably labeled.

The present disclosure also provides a pharmaceutical composition including an effective amount of the DLL3 binding molecules or the antigen binding fragment thereof of the present disclosure, or an effective amount of the antibody drug conjugates of the present disclosure, or an effective amount of the nucleic acid of the present disclosure, or an effective amount of the recombinant vector of the present disclosure, or an effective amount of the host cell of the present disclosure.

In an embodiment, the pharmaceutical composition also comprises a pharmaceutically acceptable carrier.

Preferably, the pharmaceutical composition further comprises one or more additional therapeutic

agents.

The present disclosure also provides a drug box or kit including a container and the pharmaceutical composition of the present disclosure in the container.

The present disclosure also provides a method for inducing death of a cell expressing DLL3, the method including contacting the cell with the pharmaceutical composition of the present disclosure, the cell expressing DLL3 being a tumor cell.

In an embodiment, the tumor cell is a cell selected from the following tumors: small cell lung cancer, glioblastoma, neuroendocrine cancer, melanoma, pancreatic cancer, rectal cancer, and metastatic cancers of the aforementioned tumors.

The present disclosure also provides a method for treating a disease associated with the expression of DLL3 in a subject, the method including administering the pharmaceutical composition of the present disclosure, or the drug box or kit of the foregoing to a subject in need thereof.

In an embodiment, the disease is a tumor; small cell lung cancer, glioblastoma, neuroendocrine cancer, melanoma, pancreatic cancer, rectal cancer, and metastatic cancer of the aforementioned tumors.

In an embodiment, the method further comprises administering an additional therapeutic agent to the subject.

The technical solutions of the present disclosure have the following advantageous effects: the DLL3 binding molecule and the antigen binding fragment thereof of the present disclosure is capable of specifically binding to DLL3 without non-specifically binding to the family proteins DLL1 and DLL4.

BRIEF DESCRIPTION OF THE FIGURES

The figures further illustrate the novel features disclosed herein. The features and advantages disclosed in this specification will be better understood with reference to the figures, but it is understood that the figures are merely for purposes of illustrating specific embodiments of the principles disclosed herein and are not intended to limit the scope of the appended claims.

FIG. 1A shows the binding of camelid-derived anti-DLL3 chimeric antibodies of the present disclosure to DLL3-expressing cells (SHP-77).

FIG. 1B shows the binding of camelid-derived anti-DLL3 chimeric antibodies of the present disclosure to DLL3-expressing cells (HEK293-cyno DLL3).

FIG. 2A shows the binding of camelid-derived humanized anti-DLL3 antibodies of the present disclosure to DLL3-expressing cells (SHP-77).

FIG. 2B shows the binding of camelid-derived humanized anti-DLL3 antibodies of the present disclosure to DLL3-expressing cells (HEK293-cyno DLL3).

FIG. 3A shows the binding of camelid-derived humanized anti-DLL3 antibodies of the present disclosure to the family protein DLL1.

FIG. 3B shows the binding of camelid-derived humanized anti-DLL3 antibodies of the present disclosure to the family protein DLL4.

FIG. 4 shows the binding of camelid-derived hDLL3-3-1 humanized antibody variants of the present disclosure to DLL3-expressing cells (SHP-77).

FIG. 5A shows binding of mouse hybridoma-derived anti-DLL3 chimeric antibodies of the present disclosure to DLL3-expressing cells (SHP-77).

FIG. 5B shows binding of mouse hybridoma-derived anti-DLL3 chimeric antibodies of the present disclosure to DLL3-expressing cells (HEK293-cyno DLL3).

FIG. 6 shows the binding of mouse hybridoma-derived humanized anti-DLL3 antibodies of the present disclosure to DLL3-expressing cells (SHP-77).

FIG. 7A shows the binding of mouse hybridoma-derived humanized anti-DLL3 antibodies of the present disclosure to the family protein DLL1.

FIG. 7B shows the binding of mouse hybridoma-derived humanized anti-DLL3 antibodies of the present disclosure to the family protein DLL4.

FIG. 8 shows the binding of mouse hybridoma-derived humanized H2-39E2D11 antibody variants of the present disclosure to DLL3-expressing cells (SHP-77).

DETAILED DESCRIPTION OF THE INVENTION

TERMS

All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

Before the present disclosure is described in detail below, it is to be understood that the present disclosure is not limited to the particular methodology, protocols, and reagents described herein, as these may vary. It should also be understood that the terms used herein are only intended to describe specific embodiments and are not intended to limit the scope of the present disclosure. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the present disclosure belongs.

Certain embodiments disclosed herein encompass numerical ranges, and certain aspects of the present disclosure may be described in terms of ranges. Unless otherwise indicated, it is to be understood that the numerical ranges or descriptions of ranges are merely for brevity and convenience and are not to be construed as strictly limiting the scope of the present disclosure. Therefore, the description using a range approach should be considered as specifically disclosing

all possible sub-ranges and all possible specific numerical points within that range, as these sub-ranges and numerical points have been clearly stated herein. The above principles apply equally regardless of the breadth of the numerical values recited. When a range description is used, the range includes the endpoints of the range.

The term "about", when referring to a measurable value such as an amount, temporal duration, and the like, is meant to encompass variations of ± 20%, or in some cases ± 10%, or in some cases ± 5%, or in some cases ± 1%, or in some cases ± 0.1% of the specified value.

The three-letter code and the one-letter code for amino acids used herein are as described in J. Biol. Chem, 243, p3558 (1968).

As used herein, the term "antibody" may include intact antibodies (e.g. full-length monoclonal antibodies) and any antigen-binding fragment (i.e. antigen-binding portion) thereof or single chain thereof, as well as a product having antigen-specific binding capability that is engineered (e.g. linked to other peptide segments, rearranged functional units, etc.) based on the intact antibody or antigen-binding fragment or the single chain thereof.

In an embodiment, an antibody typically refers to a Y-type tetrameric protein comprising two heavy (H) polypeptide chains and two light (L) polypeptide chains held together by covalent disulfide bonds and non-covalent interactions. The native IgG antibody has such a structure. Each light chain consists of a variable domain (VL) and a constant domain (CL). Each heavy chain consists of a variable domain (VH) and a constant region.

There are five main categories of antibodies known in the art: IgA, IgD, IgE, IgG, and IgM, with corresponding heavy chain constant domains called α, δ, ε, γ and μ; IgG and IgA can be further divided into different subclasses, for example, IgG can be divided into IgG1, IgG2, IgG3, IgG4; IgA can be divided into IgA1 and IgA2. The light chain of antibodies from any vertebrate species can be assigned to one of two distinct types based on their constant domain amino acid sequence, called κ and λ。

In the case of the IgG, IgA, and IgD antibodies, the constant region comprises three domains designated CH1, CH2, and CH3 (IgM and IgE have a fourth domain CH4). In the IgG, IgA, and IgD classes, the CH1 and CH2 domains are separated by a flexible hinge region that is a variable-length proline and cysteine-rich segment. Each class of antibodies further comprises inter-and intra-chain disulfide bonds formed from the paired cysteine residues.

The term "variable region" or "variable domain" shows a significant change in amino acid composition from one antibody to another and is primarily responsible for antigen recognition and binding. The variable region of each light/heavy chain pair forms the antibody binding site such that the intact IgG antibody has two binding sites (i.e. it is bivalent). The variable region (VH) of the heavy chain and the variable region (VL) of the light chain each comprise three regions of extreme

variability, referred to as HVR or, more generally, as complementary determinant region (CDR), each VH and VL having four framework regions FR, designated FR1, FR2, FR3, FR4, respectively. Thus, the CDR and FR sequences typically appear in the heavy chain variable domain (or light chain variable domain) in the following sequences: FR1-HCDR1(LCDR1)-FR2-HCDR2(LCDR2)-FR3-HCDR3(LCDR3)-FR4.

The term "Fc" is used to define the C-terminal region of an immunoglobulin heavy chain comprising at least a portion of a constant region. This term includes the natural sequence Fc region and the variant Fc region.

As used herein, "antibody" is used in the broadest sense and may include, for example, polyclonal antibodies, monoclonal antibodies, chimeric antibodies, humanized and primatized antibodies, CDR-grafted antibodies, human antibodies (including recombinant human antibodies), recombinant antibodies, intracellular antibodies, multispecific antibodies, bispecific antibodies, monovalent antibodies, multivalent antibodies, anti-idiotypic antibodies, synthetic antibodies (including muteins and variants), and the like.

The term "monoclonal antibody" (or "mAb ") refers to an antibody produced by a single cell clone that is substantially homogeneous and directed only to a particular epitope. Monoclonal antibodies can be prepared using a variety of techniques known in the art, including hybridoma techniques, recombinant techniques, phage display techniques, transgenic animals, synthetic techniques, combinations thereof, and the like.

Note that the partitioning of CDR and FR for the variable regions of the monoclonal antibodies of the present disclosure is determined according to the Kabat definition. Other naming and numbering systems, such as Chothia, IMGT, or AHo, are known to those skilled in the art. Thus, humanized antibodies comprising one or more CDR derived from any nomenclature based on the sequences of the monoclonal antibodies of the present disclosure clearly remain within the scope of the present disclosure.

The term "humanized antibody" refers to an antibody in which all or a portion of the amino acids other than CDR of a non-human antibody (e.g. a mouse antibody) have been replaced with the corresponding amino acids derived from a human immunoglobulin. Small additions, deletions, insertions, substitutions, or modifications of amino acids are permissible so long as they do not eliminate the ability of the antibody to bind a particular antigen. A "humanized" antibody retains similar antigen specificity as the original antibody.

The term "chimeric antibody" refers to an antibody in which the variable region originates from one specie and the constant region originates from another specie, e.g., an antibody in which the variable region originates from a mouse antibody and the constant region originates from a human antibody.

The term "antibody fragment" encompasses at least a portion of an intact antibody. As used herein,

a "fragment" of an antibody molecule includes an "antigen-binding fragment" of an antibody, and the term "antigen-binding fragment" refers to a polypeptide fragment of an immunoglobulin or antibody that specifically binds to or reacts with a selected antigen or immunogenic determining portion thereof, or a fusion protein product further derived from the fragment, e.g. a single chain antibody, an extracellular binding region in a chimeric antigen receptor, etc. Exemplary antibody fragments or antigen-binding fragments thereof include but are not limited to variable light chain fragments, variable heavy chain fragments, Fab fragments, F(ab')2 fragments, Fd fragments, Fv fragments, single domain antibodies, linear antibodies, single chain antibodies (scFv), bispecific or multispecific antibodies formed from antibody fragments, and the like.

The term "antigen" refers to a substance that is recognized and specifically bound by an antibody or antibody binding fragment. In a broad sense, an antigen can include any immunogenic fragment or determinant of a selected target, including a single epitope, multiple epitopes, single domain, multiple domain, complete extracellular ECD, or protein. Peptides, proteins, glycoproteins, polysaccharides, lipids, portions thereof, and combinations thereof may constitute antigens. Non-limiting exemplary antigens include tumor antigens or pathogen antigens and the like. An "antigen" may also refer to a molecule that elicits an immune response. Any form of antigen or cell or preparation containing the antigen may be used to generate an antibody specific for an antigenic determinant. The antigen can be an isolated full-length protein, a cell surface protein (e.g. immunized with the cell expressing at least a portion of the antigen on its surface), or a soluble protein (e.g. immunized with only the ECD portion of the protein) or a protein construct (e.g. an Fc antigen). The antigen may be produced in a genetically modified cell. Any of the foregoing antigens may be used alone or in combination with one or more immunogenicity enhancing adjuvants known in the art. The DNA encoding the antigen may be genomic or non-genomic (e.g. cDNA) and may encode at least a portion of the ECD sufficient to elicit an immunogenic response. Any vector can be used to transform cells in which the antigen is expressed, including, but not limited to, adenoviral vectors, lentiviral vectors, plasmids, and non-viral vectors such as cationic lipids.

The term "epitope" refers to a site on an antigen to which an immunoglobulin or antibody specifically binds. Epitopes can be formed by adjacent amino acids or non-adjacent amino acids that are juxtaposed through the tertiary folding of proteins. Epitopes formed by adjacent amino acids are usually maintained after exposure to denaturing solvents, while epitopes formed through tertiary folding are typically lost after treatment with denaturing solvents. Epitopes typically exist in a unique spatial conformation and comprise at least 3-15 amino acids. Methods for determining the epitope to which a given antibody binds are well-known in the art and include immunoblotting and immunoprecipitation assays, among others. The methods for determining the spatial conformation of the epitope include techniques in this field, such as X-ray crystal analysis and two-dimensional

nuclear magnetic resonance.

The terms "bispecific binding molecule", and "multispecific binding molecule" refer to a binding molecule (e.g. an antibody or a molecule comprising an antibody fragment), preferably a bispecific antibody, having specificity for two or more different antigens (or epitopes), respectively.

When using the variable region in the present disclosure to produce antibodies, binding molecules, bispecific binding molecules, or multispecific binding molecules, the constant region is not particularly limited. It is possible to use a well-known constant region or a self-obtained constant region by those skilled in the art and to introduce amino acid mutations (such as mutations increasing or decreasing bonding to Fcγ receptor or FcRn) in the constant region part.

The method for obtaining the binding molecules, antigen-binding fragments, antibodies, bispecific binding molecules, or multispecific binding molecules of the present disclosure is not particularly limited and may be obtained by any method, e.g. Cold Spring Harbor's Using Antibodies: A Laboratory Manual, chapters 5-8 and 15. The binding molecules, antigen-binding fragments, antibodies, bispecific binding molecules, or multi-specific binding molecules invented can be prepared and purified using conventional methods. For example, cDNA sequences encoding heavy and light chains can be cloned and recombined into expression vectors. Recombinant immunoglobulin expression vectors can be stably transfected into CHO cells. As a more recommended existing technique, mammalian expression systems can lead to glycosylation of antibodies, especially in the highly conserved N-terminus of the Fc region. Stable clones are obtained by expressing antibodies that specifically bind to human antigens. Positive clones were expanded in a serum-free medium in a bioreactor to produce antibodies. The antibody-secreting medium can be purified and collected using conventional techniques. The antibodies may be concentrated by filtration using conventional methods. Soluble mixtures and multimers may also be removed by conventional methods, such as molecular sieves, and ion exchange.

The term "antibody drug conjugate" (ADC) refers to an antibody that has covalently conjugated to a therapeutic active substance or active pharmaceutical ingredient (API), so that the therapeutic active substance or active pharmaceutical ingredient (API) can target the binding target of the antibody to demonstrate its pharmacological function. The therapeutically active substance or active pharmaceutical ingredient may be a cytotoxin capable of killing cells targeted by ADC, preferably malignant or cancer cells. The covalent bonding of therapeutic active substances, active pharmaceutical ingredients, or cytotoxics can be performed in a non-site specific manner using standard chemical linkers that couple payloads to lysine or cysteine residues, or preferably, the conjugation is performed in a site-specific manner, which allows full control of the conjugation site and the ratio of drug specific antibodies to the generated ADC.

The term "affinity" or "binding affinity" refers to the strength of all non-covalent interactions

between a single binding site of a molecule (such as an antibody) and its binding partner (such as an antigen). The term "KD" refers to the dissociation constant of a particular antibody-antigen interaction. Binding affinity can be determined using various techniques known in the art, such as surface plasmon resonance, biolayer interferometry, dual polarization interferometry, static light scattering, dynamic light scattering, isothermal titration calorimetry, ELISA, analytical ultracentrifugation, and flow cytometry, among others.

The term "biological activity" refers to the ability of an antibody to bind an antigen and cause a measurable biological response, which can be measured in vitro or in vivo.

The pharmaceutical compositions of the present disclosure can be formulated in admixture with suitable pharmaceutically acceptable carriers, vehicles, and the like which are inert, as desired, for example, physiological saline, sterile water, excipients, stabilizers, antioxidants (e.g. ascorbic acid, etc.), buffers, preservatives, surfactants, chelating agents (e.g. EDTA, etc.) or binders, and the like. In addition, other low molecular weight polypeptides, proteins such as serum albumin, gelatin, and immunoglobulins, amino acids such as glycine, glutamine, asparagine, glutamic acid, aspartic acid, methionine, arginine and lysine, carbohydrates such as polysaccharides and monosaccharides or carbohydrates, sugar alcohols such as mannitol and sorbitol may be included. In the case of aqueous solutions for injection, for example, physiological saline, isotonic solutions containing glucose and other adjuvants, e.g. D-sorbitol, D-mannose, D-mannitol, sodium chloride, can be used in combination with suitable cosolvents, such as alcohols (ethanol and the like), polyols (propylene glycol, PEG and the like), non-ionic surfactants (polysorbate 80, polysorbate 20, poloxamer 188, HCO-50) and the like. In addition, by mixing hyaluronidase in the formulation, subcutaneous administration of larger amounts of fluid is also possible.

The binding molecules or antigen-binding fragments disclosed in the present disclosure can be used in combination with other drugs, and the active ingredients can be mixed together to form a single dosage unit, or they can be separately used as a dosage unit.

The term "effective amount" refers to the dosage of the drug formulation of the antibody or fragment disclosed in the present disclosure, which produces the expected effect in the treated patient after being administered in single or multiple dosages. The effective amount can be easily determined by attending physicians who are skilled in the field by considering various factors such as ethnic differences; weight, age, and health status; specific diseases involved; the severity of the disease; individual patient responses; specific antibodies administered; administration mode; the bioavailability characteristics of the administered formulation; selected medication regimen; the use of any accompanying therapy.

The term "kit" or "reagent kit" includes an effective amount of one or more of the pharmaceutical compositions of the present disclosure in unit dosage form. In some embodiments, the drug kit may

comprise a sterile container; such containers may be boxes, ampoules, bottles, vials, tubes, bags, blister packs, or other suitable container forms known in the art. Such containers may be made of plastic, glass, laminated paper, metal foil, or other materials suitable for holding medicaments. In addition, the drug kit includes instructions for administering the pharmaceutical composition of the present disclosure to an individual. Methods for treating diseases using the pharmaceutical compositions of the present disclosure are generally included in the specification.

The term "individual" or "subject" used herein refers to any animal, such as a mammal or marsupial. Individuals of the present disclosure include, but are not limited to, humans, non-human primates (e.g. cynomolgus or rhesus monkeys or other types of macaques), mice, pigs, horses, donkeys, cattle, sheep, rats, and poultry of any species.

As used herein, the terms "disease", "condition" or "disorder" and the like refer to any alteration or disorder that impairs or interferes with the normal function of a cell, tissue, or organ. For example, such "diseases" include, but are not limited to a tumor, a pathogen infection, an autoimmune disease, a T-cell dysfunction disease, or a defect in immune tolerance (e.g. transplant rejection).

As used herein, the term "tumor" refers to a disease characterized by pathological proliferation of cells or tissues, and subsequent migration or invasion of other tissues or organs. Tumor growth is generally uncontrolled and progressive and does not induce or inhibit normal cell proliferation.

As used herein, the term "treatment" refers to clinical intervention in an attempt to alter an individual or to treat a cell-caused disease process, either prophylactically or clinically pathological. Therapeutic effects include but are not limited to, preventing the onset or recurrence of the disease, alleviating symptoms, diminishing any direct or indirect pathological consequences of the disease, preventing metastasis, slowing disease progression, amelioration or palliation of the disease state, relieving or improving prognosis, and the like.

Examples

The present disclosure is further illustrated by the following specific examples. It should be understood that the examples are only used to illustrate the present disclosure and not to limit the scope of the present disclosure. Experimental procedures for which no specific conditions are indicated in the following examples are generally performed according to conventional conditions (such as those described in J. SAMBROOK et al. eds. Molecular Cloning: A Laboratory Manual, 3rd Ed. Science Press, 2002) or as recommended by the manufacturer.

Example 1. Human DLL3 and Cynomolgus monkey DLL3 antigen information

The full-length amino acid sequence of human DLL3 (SEQ ID NO: 105) (Uniprot ID: Q9 NYJ7) used in the embodiment is shown below, which was purchased from Kactus Biosystems (Cat. No:

DLL-HM103).

MVSPRMSGLLSQTVILALIFLPQTRPAGVFELQIHSFGPGPGPGAPRSPCSARLPCRLFFRVC
LKPGLSEEAAESPCALGAALSARGPVYTEQPGAPAPDLPLPDGLLQVPFRDAWPGTFSFIIE
TWREELGDQIGGPAWSLLARVAGRRRLAAGGPWARDIQRAGAWELRFSYRARCEPPAVG
TACTRLCRPRSAPSRCGPGLRPCAPLEDECEAPLVCRAGCSPEHGFCEQPGECRCLEGWTG
PLCTVPVSTSSCLSPRGPSSATTGCLVPGPGPCDGNPCANGGSCSETPRSFECTCPRGFYGL
RCEVSGVTCADGPCFNGGLCVGGADPDSAYICHCPPGFQGSNCEKRVDRCSLQPCRNGG
LCLDLGHALRCRCRAGFAGPRCEHDLDDCAGRACANGGTCVEGGGAHRCSCALGFGGR
DCRERADPCAARPCAHGGRCYAHFSGLVCACAPGYMGARCEFPVHPDGASALPAAPPGL
RPGDPQRYLLPPALGLLVAAGVAGAALLLV*HVRRRGHSQDAGSRLLAGTPEPSVHALPDALN*
NLRTQEGSGDGPSSSVDWNRPEDVDPQGIYVISAPSIYAREVATPLFPPLHTGRAGQRQHLLFPY
PSSILSVK

Note: the double underline part represents a signal peptide (1-26); the underline part represents an extracellular domain of DLL3 (27-492); the dotted line represents a transmembrane region (493-513); the italic part represents an intracellular region (514-618).

The full-length amino acid sequence (SEQ ID NO: 106) (Uniprot ID: A0A2K5WSR4) of the Cynomolgus monkey DLL3 (cyno DLL3) used in the embodiment is shown below, which was purchased from Kactus Biosystems (Cat. No: CM103).

MVSPRMSRLLSQTVILALIFIPQARPAGVFELQIHSFGPGPGPGAPRSPCSARGPCRLFFRVC
LKPGLSEEAAESPCALGAALSARGPVYTEQPEAPAPDLPLPNGLLQVPFRDAWPGTFSLIIE
TWREELGDQIGGPAWSLLARVTRRRRLAAGGPWARDIQRAGAWELRFSYRARCELPAVG
TACTRLCRPRSAPSRCGPGLRPCAPLEDECEAPPVCRAGCSLEHGFCEQPGECRCLEGWT
GPLCMVPVSTSSCLGLRGPSSTTTGCLVPGPGPCDGNPCANGGSCSETPGSFECTCPRGFY
GLRCEVSGVTCADGPCFNGGLCVGGADPDSAYICHCPPGFQGSNCEKRVDRCSLQPCRN
GGLCLDLGHALRCRCRAGFAGPRCEHDLDDCAGRACANGGTCVEGGGAHRCSCALGFG
GRNCRERADPCAARPCAHGGRCYAHFSGLVCACAPGYMGARCEFPVHPDGVSALPAAPP
GLRPGDPQRYLLPPALGLLVAAGVAGAALLLV*HVRRRGHAQDAGSRLLAGTPEPSVHALPD*
ALNNLRTQEGPGDVPSSSVDWNRPEDVDSRGIYVISAPSIYAREVAMPLFPPLHTGRAGQRQNL
LFPFPSSILSVK

Note: the double underline part represents a signal peptide (1-26); the underline part represents an extracellular domain of DLL3 (27-490); the dotted line represents a transmembrane region (491-513); the italic part represents an intracellular region (514-618).

Example 2. Family member DLL1 and DLL4 antigen information

The full-length amino acid sequence (SEQ ID NO: 107) (Uniprot ID: O00548) of human DLL1

used in the embodiment is shown below, which was purchased from Sino Biological (Cat. No: 11635-H08H).

MGSRCALALAVLSALLCQVWSSGVFELKLQEFVNKKGLLGNRNCCRGGAGPPPCACRTF
FRVCLKHYQASVSPEPPCTYGSAVTPVLGVDSFSLPDGGGADSAFSNPIRFPFGFTWPGTFS
LIIEALHTDSPDDLATENPERLISRLATQRHLTVGEEWSQDLHSSGRTDLKYSYRFVCDEHY
YGEGCSVFCRPRDDAFGHFTCGERGEKVCNPGWKGPYCTEPICLPGCDEQHGFCDKPGE
CKCRVGWQGRYCDECIRYPGCLHGTCQQPWQCNCQEGWGGLFCNQDLNYCTHHKPCK
NGATCTNTGQGSYTCSCRPGYTGATCELGIDECDPSPCKNGGSCTDLENSYSCTCPPGFYG
KICELSAMTCADGPCFNGGRCSDSPDGGYSCRCPVGYSGFNCEKKIDYCSSSPCSNGAKC
VDLGDAYLCRCQAGFSGRHCDDNVDDCASSPCANGGTCRDGVNDFSCTCPPGYTGRNC
SAPVSRCEHAPCHNGATCHERGHRYVCECARGYGGPNCQFLLPELPPGPAVVDLTEKLEG
QGGPFPWVAVCAGVILVLMLLLGCAAVVVC*VRLRLQKHRPPADPCRGETETMNNLANCQR*
EKDISVSIIGATQIKNTNKKADFHGDHSADKNGFKARYPAVDYNLVQDLKGDDTAVRDAHSKRD
TKCQPQGSSGEEKGTPTTLRGGEASERKRPDSGCSTSKDTKYQSVYVISEEKDECVIATEV

Note: the double underline part represents a signal peptide (1-17); the underline part represents an extracellular domain of DLL3 (18-545); the dotted line represents a transmembrane region (546-568); the italic part represents an intracellular region (569-723).

The full-length amino acid sequence (SEQ ID NO: 108) (Uniprot ID: Q9NR61) of human DLL4 in the embodiment is shown below, which was purchased from Sino Biological (Cat. No: 10171-H08H).

MAAASRSASGWALLLLVALWQQRAAGSGVFQLQLQEFINERGVLASGRPCEPGCRTFFRV
CLKHFQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSSGGGRNPLQLPFNFTWPGTFSLIIEAW
HAPGDDLRPEALPPDALISKIAIQGSLAVGQNWLLDEQTSTLTRLRYSYRVICSDNYYGDN
CSRLCKKRNDHFGHYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNGYCSKPAECLCR
PGWQGRLCNECIPHNGCRHGTCSTPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGVDCELELSECDSNPCRNGGSCKDQEDGYHCLCPPGYYGLHC
EHSTLSCADSPCFNGGSCRERNQGANYACECPPNFTGSNCEKKVDRCTSNPCANGGQCL
NRGPSRMCRCRPGFTGTYCELHVSDCARNPCAHGGTCHDLENGLMCTCPAGFSGRRCEV
RTSIDACASSPCFNRATCYTDLSTDTFVCNCPYGFVGSRCEFPVGLPPSFPWVAVSLGVGL
AVLLVLLGMVAV*AVRQLRLRRPDDGSREAMNNLSDFQKDNLIPAAQLKNTNQKKELEVDCGL*
DKSNCGKQQNHTLDYNLAPGPLGRGTMPGKFPHSDKSLGEKAPLRLHSEKPECRISAICSPRD
SMYQSVCLISEERNECVIATEV

Note: the double underline part represents a signal peptide (1-26); the underline part represents an extracellular domain of DLL3 (27-529); the dotted line represents a transmembrane region (530-550); the italic part represents an intracellular region (551-685).

Example 3. Construction of heavy chain antibody immune library for camel immunity

Camels were immunized with the human DLL3 antigen (described in Example 1). The days of immunization were Day 0, Day 21, Day 35, and Day 49, respectively, for a total of 4 immunizations. Blood samples were collected on Day 28, 42, and 73, respectively, and the immune response was detected by ELISA. The titer of serum was detected to be greater than 1: 128000. After the completion of immunization, 100 mL of blood sample was collected again from immunized camels, and PBMC of camels were separated using the lymphocyte separation solution of Solarbio according to the manufacturer's instructions. After total RNA was extracted (OMEGA cell total RNA extraction kit), cDNA was synthesized using Takara PrimeScript™ II reverse transcription kit as a template, and a VHH gene fragment was amplified by nested PCR using designed specific primers. After recovery of the VHH fragment, the fragment was ligated into a pADL-23c phagemid vector by Sfi I digestion, and TG1 electroporation competent cells were used to build immune library of DLL3 camels (capacity: 1.12E8).

Example 4. Screening of camelid-derived anti-DLL3 positive clones

In order to obtain a positive antibody that can cross-bind to human DLL3 and Cynomolgus monkey DLL3, the above library was amplified and added to the M13K07 helper phage to assemble phage. 1×10^{12} pfu camel immune library phage was added and incubated with biotinylated human DLL3 proteins (8 μg/mL) bound to magnetic beads for 1 h at room temperature. After washing with 0.05% PBST to remove unbound phage, the phage specifically bound to DLL3 was eluted with 100 mM triethylamine. After gradient dilution, log-phase growth of E. coli SS320 was infected and spread on an ampicillin plate overnight at 37°C. A single clone was picked for IPTG-induced expression and the supernatant was used for ELISA detection. The ELISA plate was coated with 2 μg/ml human DLL3 or Cynomolgus monkey DLL3 antigen respectively overnight at 4°C. The plate was washed with 0.05% PBST 3 times, then blocked with 5% skimmed milk for 1 h at room temperature, and washed with 0.05% PBST 3 times. Then 30 μL of induced supernatant was added to each well, and a culture medium was added to a negative control well. The plate was incubated for 1 h at room tempature. Finally, anti-Myc HRP detection was performed (VHH expressed by IPTG induction has his and c-Myc labels). The amino acid sequences of the five heavy chain antibody variable regions of the present disclosure were obtained by sequencing clones from the ELISA assay that bound human and Cynomolgus monkey DLL3 with OD450 values greater than 1.0 and ELISA OD450 ratios greater than 3 to the medium as negative control, with the results shown in Table 1:

Table 1 Amino acid sequences of five camelid-derived anti-DLL3 heavy chain antibody variable region

Clone No.	SEQ ID NO	Variable Heavy Chain (VHH)
DLL3-3	1	DVQLVESGGGSVQAGGSLKLSCKSPTYTISSGYMGWFRQAPGKEREGVAAIYIGGSTTLYADSVKGRFTISADNAEKTVYLQMNTLKPEDSAMYYCAAQLRPNSAYHPLDGRKYNYWGQGTQVTVSS
DLL3-12	2	QVQLVESGGGLVQPGESLRLSCAGSGFAFSSYDMHWVRQAPGKDFEWVSSISRDGRGPRYADFVKGRFTISKDNGRNMLYLQLNSLEIEDTAMYYCSKGYPIMGGTTQGTQVTVSS
DLL3-26	3	QVQLVESGGGSVQAGGSLRLSCAASGDIYSSSYVGWFRQAPGKEREGVAIIYTSGDSTYYANSVKGRFTISQDKAKKTLYLQMNSLKPEDTAMYYCAARFAIDNSNYWGQGTQVTVSS
DLL3-122	4	QVQLVESGGGSVQAGGSLRLSCTASGDTYRSYCMGWFRKAPGKEREGVADIVSDGSTSYADSVKGRFTISKDNAKNTLYLQMNSLKPEDTAMYYCAVDRGGSGGYCYTGRYDYWGQGTQVTVSS
DLL3-276	5	QVQLVESGGGSVQAGGSLNLSCATSGSTASTTYMGWFRQAPGKGREGVAIIYTARDNPWYANSVKGRFIISQDNAKKTLYLQMNTLKPEDTATYYCAATLANPTRTAWGQGTLVTVSS

On the basis of the above amino acid sequences, the CDR and FR of antibody variable regions were divided using the Kabat numbering rule, and the composition of 3 CDR sequences of each antibody is shown in Table 2 below.

Table 2 CDR sequences of five camelid-derived anti-DLL3 heavy chain antibodies

Clone No.		HCDR1	HCDR2	HCDR3
DLL3-3	SEQ ID NO	6	7	8
	Amino Acid Sequence	SGYMG	AAIYIGGSTTLYADSVKG	QLRPNSAYHPLDGRKYNY
DLL3-12	SEQ ID NO	9	10	11
	Amino Acid Sequence	SYDMH	SSISRDGRGPRYADFVKG	GYPIMGG
DLL3-26	SEQ ID NO	12	13	14
	Amino Acid Sequence	SSYVG	AIIYTSGDSTYYANSVKG	RFAIDNSNY
DLL3-122	SEQ ID NO	15	16	17

	Amino Acid Sequence	RSYCMG	ADIVSDGSTSYADSVKG	DRGGSGGYCYTGRYDY
DLL3-276	SEQ ID NO	18	19	20
	Amino Acid Sequence	TTYMG	IIYTARDNPWYANSVKG	TLANPTRTA

Example 5. Construction of camelid-derived anti-DLL3 chimeric antibodies and their transient transfection expression in eukaryotic cells

The gene fragment of interest generated after splicing the sequenced heavy chain antibody variable region of the present disclosure with the human IgG1 constant region was cloned into a pTT5 expression vector to prepare a transfection-grade expression plasmid. The heavy chain antibody variable region can be linked to the human IgG1 constant region by a linking short peptide, i.e. to form: heavy chain antibody variable region-linking short peptide-human IgG1 constant region. The linking short peptide sequence used in this example was GGGGS.

The introduced human IgG1 constant region sequence (SEQ ID NO: 109) is as follows:

DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA
KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS
DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

Expi293F™ cells (Thermo Fisher Scientific) were cultured in a serum-free medium, seeded in a shake flask (Corning Inc.), and cultured on a 37°C, 8% CO_2 shaker. After adjusting the cell density, the recombinant expression vector containing the gene fragment of interest and PEI transfection reagent were mixed in an appropriate ratio and added into a cell culture flask. After 6 days of cell culture, the expression supernatant was collected, centrifuged at high speed to remove cell debris, and subjected to affinity purification using a Protein A column. The column was rinsed with PBS until the A280 reading dropped to baseline. The protein of interest was eluted with an acidic eluent at pH 3.0-pH 3.5 and neutralized with 1M Tris-HCl, pH 8.0-9.0. After the eluted sample was appropriately concentrated, the solution was changed to PBS and aliquoted for later use. Final purified chimeric antibodies were subjected to SDS-PAGE and HPLC purity analysis and A280 concentration determination.

Example 6. Binding of camelid-derived anti-DLL3 chimeric antibodies to DLL3-expressing cells

HEK293 cells (from the Chinese Academy of Sciences) were transfected with the full-length gene of cyno-DLL3 antigen (see Example 1 for the sequence), for cell culture and passage. Monoclonal

selection was performed, and the expression level of DLL3 protein in the monoclonal cells were identified by flow cytometry. The culture was expanded and stored in storage for later use.

SHP-77 and HEK293-cyno DLL3 cells were cultured. The culture medium for SHP-77 cells were RPMI1640+10% FBS, and the culture medium for HEK293 cyno DLL3 cells were DMEM+10% FBS+200 μg/ml Hygromycin. The cells were cultured in a T75 cell culture flask at a 37°C in a 5% CO_2 incubator. When using cells, they are washed with sterile DPBS, digested with 0.25% trypsin EDTA for about 5 minutes, and then stopped with a complete medium.

The digested cells were centrifuged at 1000 rpm for 5 min at room temperature. The supernatant was discarded and the cells were resuspended in 100 μL of 1% BSA (in PBS). The cells were counted and adjusted to a cell density of 1E6/m. The dilute cells were seeded in a 96-well round-bottom culture plate (corning 3799), and centrifuged at 1500 rpm for 5 min at 4°C. The supernatant was discarded and the cells were stored at 4°C until use. Antibody samples to be tested were diluted with 1% BSA (in PBS) at a starting concentration of 100 nM, downwards by a 10-fold gradient for 7 concentrations. The cells were resuspended with the diluted antibody at 100 μL/well and incubated for 1 hour at 4°C. The cells were centrifuged at 1500 rpm for 5 minutes at 4°C and the supernatant was discarded. The cells were resuspended and washed with 160 μL of 1%BSA (in PBS), centrifuged at 1500 rpm for 5 minutes at 4°C. The supernatant was discarded. The secondary antibody (goat anti human IgG Fc PE) was diluted 1: 200 with 1% BSA (in PBS) according to the manufacturer's instructions and the cells were resuspended with the diluted secondary antibody, 100 μL/well, and incubated for 0.5 h at 4°C. The cells were centrifuged at 1500 rpm for 5 minutes at 4°C and the supernatant was discarded. The cells were resuspended and washed with 160 μL of 1%BSA (in PBS), centrifuged at 1500 rpm for 5 minutes at 4°C. The supernatant was discarded. The cells were resuspended in 100 μL of 1% BSA (in PBS), and filtered across a 300 mesh gauze. The mean fluorescence intensity of the PE channels was measured by flow cytometry.

The FCS file was exported from the flow cytometer. The mean fluorescence intensity of the PE channel (hereinafter referred to as MFI) of each sample was analyzed with the Flowjo software. The analyzed mean fluorescence intensity was imported into Graphpad to analyze the median-binding concentration (hereinafter referred to as EC50) of antibody and cell and the top mean fluorescence intensity (Top MFI). The results are shown in Table 3 and FIG. 1.

Table 3 Binding of anti-DLL3 chimeric antibodies to DLL3-expressing cells

Clone No.	SHP-77		HEK293 - cyno DLL3	
	EC_{50} (nM)	Top Mean Fluorescence Intensity (Top MFI))	EC_{50} (nM)	Top Mean Fluorescence Intensity (Top MFI))
Negative control antibody	Unfitted	92	Unfitted	104
DLL3-3	0.047	874	0.025	438
DLL3-12	0.092	886	0.073	220
DLL3-26	0.519	821	0.439	450
DLL3-122	0.427	846	0.415	460
DLL3-276	0.374	763	0.897	175

Example 7. Humanization Design of Camel Derived Anti-DLL3 Heavy Chain Antibodies

The germline gene sequences with high homology to the candidate heavy chain antibody were selected as the VHH transplantation framework template through sequence alignment. After grafting the CDR region of the candidate antibody to the framework of the variable region of the selected human antibody, reverse mutation of individual amino acids was performed to obtain a humanized antibody. The amino acid sequence of the humanized variable region is shown in Table 4.

Table 4 Amino acid sequence of variable region of 7 camelid-derived humanized anti-DLL3 antibodies

Clone No.	SEQ ID NO	Variable Heavy Chain (VHH)
hDLL3-3 -1	21	EVQLVESGGGLVQPGGSLRLSCAASTYTISSGYMGWFRQAPGKEREGV AAIYIGGSTTLYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCA AQLRPNSAYHPLDGRKYNYWGQGTLVTVSS
hDLL3-3 -2	22	EVQLVESGGGLVQPGGSLRLSCKSPTYTISSGYMGWFRQAPGKEREGV AAIYIGGSTTLYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCA AQLRPNSAYHPLDGRKYNYWGQGTLVTVSS
hDLL3-12 -1	23	QVQLVESGGGVVQPGRSLRLSCAASGFAFSSYDMHWVRQAPGKGLEW VSSISRDGRGPRYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC SKGYPIMGGTTQGTLVTVSS
hDLL3-12 -2	24	QVQLVESGGGVVQPGRSLRLSCAASGFAFSSYDMHWVRQAPGKDFEW VSSISRDGRGPRYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC SKGYPIMGGTTQGTLVTVSS

hDLL3-26	25	EVQLVESGGGLVQPGGSLRLSCAASGDIYSSSYVGWFRQAPGKEREGV AIIYTSGDSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCA ARFAIDNSNYWGQGTLVTVSS
hDLL3-122	26	EVQLVESGGGLVQPGGSLRLSCAASGDTYRSYCMGWFRQAPGKEREG VADIVSDGSTSYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCA VDRGGSGGYCYTGRYDYWGQGTLVTVSS
hDLL3-276	27	QVQLVESGGGVVQPGGSLRLSCAASGSTASTTYMGWFRQAPGKGREG VAIIYTARDNPWYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC AATLANPTRTAWGQGTLVTVSS

Example 8. Preparation of camelid-derived humanized anti-DLL3 antibodies

As described in Example 5, the gene fragment of interest generated after splicing the variable region of the humanized antibody with the constant region of human IgG1 was cloned into the pTT5 expression vector to prepare a transfection-grade expression plasmid.

Expi293F™ cells (Thermo Fisher Scientific) were cultured in a serum-free medium, seeded in a shake flask (Corning Inc.), and cultured on a 37°C, 8% CO_2 shaker. After adjusting the cell density, the recombinant expression vector containing the gene fragment of interest and PEI transfection reagent were mixed in an appropriate ratio and added into a cell culture flask. After 6 days of cell culture, the expression supernatant was collected, centrifuged at high speed to remove cell debris, and subjected to affinity purification using a Protein A column. The column was rinsed with PBS until the A280 reading dropped to baseline. The protein of interest was eluted with an acidic eluent at pH 3.0-pH 3.5 and neutralized with 1M Tris-HCl, pH 8.0-9.0. After the eluted sample was appropriately concentrated, the solution was changed to PBS and aliquoted for later use. The final purified humanized antibody was subjected to SDS-PAGE and HPLC purity analysis and A280 concentration determination.

Example 9. In vitro cell binding validation of camelid-derived humanized anti-DLL3 antibodies

SHP-77 and HEK293-cyno DLL3 cells were cultured. The culture medium for SHP-77 cells were RPMI1640+10% FBS, and the culture medium for HEK293 cyno DLL3 cells were DMEM+10% FBS+200 μg/ml Hygromycin. The cells were cultured in a T75 cell culture flask at a 37°C 5% CO_2 incubator. When using cells, they are washed with sterile DPBS, digested with 0.25% trypsin EDTA for about 5 minutes, and then stopped with a complete medium.

The digested cells were centrifuged at 1000 rpm for 5 min at room temperature. The supernatant was discarded and the cells were resuspended in 100 μL of 1% BSA (in PBS). The cells were counted

and adjusted to a cell density of 1E6/m. The dilute cells were seeded in a 96-well round-bottom culture plate (corning 3799), and centrifuged at 1500 rpm for 5 min at 4°C. The supernatant was discarded and the cells were stored at 4°C until use. Antibody samples to be tested were diluted with 1% BSA (in PBS) at a starting concentration of 100 nM, downwards by a 10-fold gradient for 7 concentrations. The cells were resuspended with the diluted antibody at 100 μL/well and incubated for 1 hour at 4°C. The cells were centrifuged at 1500 rpm for 5 minutes at 4°C and the supernatant was discarded. The cells were resuspended and washed with 160 μL of 1%BSA (in PBS), centrifuged at 1500 rpm for 5 minutes at 4°C. The supernatant was discarded. The secondary antibody (goat anti human IgG Fc PE) was diluted 1: 200 with 1% BSA (in PBS) according to the manufacturer's instructions and the cells were resuspended with the diluted secondary antibody, 100 μL/well, and incubated for 0.5 h at 4°C. The cells were centrifuged at 1500 rpm for 5 minutes at 4°C and the supernatant was discarded. The cells were resuspended and washed with 160 μL of 1%BSA (in PBS), centrifuged at 1500 rpm for 5 minutes at 4°C. The supernatant was discarded. The cells were resuspended in 100 μL of 1% BSA (in PBS), and filtered across a 300 mesh gauze. The mean fluorescence intensity of the PE channels was measured by flow cytometry.

The FCS file was exported from the flow cytometer. The mean fluorescence intensity of the PE channel (hereinafter referred to as MFI) of each sample was analyzed with the Flowjo software. The analyzed mean fluorescence intensity was imported into Graphpad to analyze the median-binding concentration (hereinafter referred to as EC50) of antibody and cell and the top mean fluorescence intensity (Top MFI). The results are shown in Table 5 and Figure 2.

Table 5 Binding of humanized anti-DLL3 antibodies to DLL3-expressing cells

Clone No.	SHP-77		HEK293 - cyno DLL3	
	EC_{50} (nM)	Top Mean Fluorescence Intensity (Top MFI))	EC_{50} (nM)	Top Mean Fluorescence Intensity (Top MFI))
DLL3-3	0.061	864	0.08	379
hDLL3-3 -1	0.086	702	0.22	346
hDLL3-3 -2	0.049	691	0.15	344
DLL3-12	0.114	935	1.38	232
hDLL3-12 -1	0.052	690	2.36	178
hDLL3-12 -2	0.081	804	1.35	190
DLL3-26	0.499	841	0.54	336
hDLL3-26	0.786	696	2.24	301
DLL3-122	0.478	877	0.58	351
hDLL3-122	0.589	778	0.99	351
DLL3-276	0.396	782	2.08	179

hDLL3-276	0.389	622	1.01	148

Example 10. Biacore Affinity Experiment of a camelid-derived humanized anti-DLL3 antibody

The affinity and kinetic properties of the humanized anti-DLL3 antibody to human DLL3 were analyzed using a Biacore 8K instrument. CM5 chips were activated with EDC and NHS, followed by immobilization of anti-human Fc murine mAb and blocked with ethanolamine.

To determine the affinity to human DLL3 and kinetic properties, the DLL3 humanized antibody was diluted to 0.2 μg/mL with HBS-EP + (10 mM HEPES, pH 7.4, 150 mM NaCl, 3 mM EDTA, 0.05% P20) buffer and captured at a flow rate of 10 μL/min for 45 s. Human DLL3 was diluted two-fold serially to serial concentrations (100 nM-0.39 nM) and associated for 90 s and dissociated for 600 s at a flow rate of 50 μL/min.

After completion of each cycle of the experiment, the captured antibody was removed together with the antigen by washing with a 3M $MgCl_2$ solution at a flow rate of 30 μL/min for 30 s to complete the regeneration of the chip. The raw data were analyzed using Biacore Insight Evaluation Software (3.0.12.15655) software and fitted with a (1: 1) Langmuir model. The results were shown in Table 6.

Table 6. Affinity test results of humanized anti-DLL3 antibodies with human DLL3 antigen proteins

Clone No.	ka (1/Ms)	kd(1/s)	KD(M)
DLL3-3	2.15E+06	2.74E-04	1.27E-10
hDLL3-3 -1	1.91E+06	5.80E-04	3.04E-10
hDLL3-3 -2	1.95E+06	7.76E-04	3.99E-10
DLL3-26	3.82E+05	1.23E-05	3.22E-11
hDLL3-26	2.10E+05	3.55E-04	1.69E-09
DLL3-122	9.32E+04	3.92E-04	4.21E-09
hDLL3-122	9.85E+04	4.66E-04	4.73E-09

Example 11. Binding experiments of camelid-derived humanized anti-DLL3 antibodies to the family proteins DLL1 and DLL4

The antigenic proteins human DLL1 (SinoBiological, cat. No. 11635-H08H) or human DLL4 (SinoBiological, cat. No. 10171-H08H) were dissolved in 1 × PBS at a concentration of 1 μg/mL. The antigen was then added to a high-affinity ELISA plate (Biolegend, cat. No. 423501) at 100 μL/well and left overnight at 4°C. The antigen was washed three times with PBST, 300 μL/well. The antigen was blocked with 1% BSA (in PBST), 200 μL/well, and incubated at 37°C for 1.5 hours. Antibodies to be tested were diluted with 1% BSA (in PBS) at a starting concentration of 100 nM,

downwards by a 10-fold gradient for 7 concentrations. The plates were washed three times with PBST, 300 μL/well. The diluted antibody was added to an ELISA plate at 100 μL/well and incubated at room temperature for 2 hours. The antibodies were washed three times with PBST, 300 μL/well. The secondary antibodies (goat anti-human IgG Fc for DLL4 (HRP), 1: 20000 dilution; HRP goat anti-mouse IgG (H + L) for DLL1, 1: 10000 dilution) were diluted with 1% BSA in PBST. The diluted secondary antibodies were added to the ELISA plate at 100 μL/well and incubated at room temperature for 1 hour. The plates were washed 6 times with PBST, 300 μL/well. The developing solution (TMA and TMB 1:1 mixed) was prepared. The developing solution was added to the plate, 100 μL/well, and incubated in the dark for 5 min. 50 μL of ELISA stop solution was added to the plate and shaken well.

OD450s were read on the envision and plotted on the GraphPad for EC_{50} values. The results are shown in FIG. 3, which show that the antibodies tested did not non-specifically bind to either of the family proteins DLL1 and DLL4.

Example 12. Preparation of variants of Camelid-derived humanized anti-DLL3 antibodies

After post-translational modification (PTM) analysis of the heavy chain antibody of the present disclosure, it was found that there was one deamidation site in the variable region of hDLL3-3-1; and site-directed mutation for a single site was performed on amino acid 103 to prepare two mutants of hDLL3-3-1: hDLL3-3-1-NA and hDLL3-3-1-QS, respectively. The variable region amino acid sequences of the two variants are shown in Table 7.

Table 7 Amino acid sequences of hDLL3-3-1 humanized antibody variants

Clone No.	SEQ ID NO	Variable Heavy Chain (VHH)	SEQ ID NO	Heavy Chain CDR3
hDLL3-3-1-NA	28	EVQLVESGGGLVQPGGSLRLSCAASTYTISSGYMGWFRQAPGKEREGVAAIYIGGSTTLYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAAQLRPNAAYHPLDGRKYNYWGQGTLVTVSS	110	QLRPNAAYHPLDGRKYNY
hDLL3-3-1-QS	29	EVQLVESGGGLVQPGGSLRLSCAASTYTISSGYMGWFRQAPGKEREGVAAIYIGGSTTLYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAAQLRPQ	111	QLRPQSAYHPLDGRKYNY

		SAYHPLDGRKYNYWGQGTL VTVSS		

The two variants were prepared as described in Example 5. After transient expression in mammalian cell lines, affinity assays were performed using SHP-77 cells. The results shown in Table 8 and FIG. 4 show that the two variants were able to eliminate the risk of post-translational modification without significant changes in binding at the cellular level. See Table 9 for affinity assay results using human DLL3 antigen proteins.

Table 8 Binding of hDLL3-3-1 humanized antibody variants to DLL3-expressing cells (SHP-77)

Clone No.	SHP-77	
	EC_{50} (nM)	Top Mean Fluorescence Intensity (Top MFI))
hDLL3-3 -1	0.068	1076
hDLL3-3-1-NA	0.104	1271
hDLL3-3-1-QS	0.055	1009

Table 9 Affinity test results of hDLL3-3-1 humanized antibody variants with human DLL3 antigen protein

Clone No.	ka (1/Ms)	kd(1/s)	KD(M)
hDLL3-3 -1	1.36E+06	6.14E-04	4.50E-10
hDLL3-3-1-NA	1.29E+06	1.35E-04	1.05E-10
hDLL3-3-1-QS	1.22E+06	6.11E-03	5.02E-09

Example 13. Obtaining mouse hybridoma-derived anti-DLL3 antibodies

Anti-DLL3 monoclonal antibodies were generated by immunizing mice. The experiment used Swiss Webster white mice, female, 6 weeks old (Charles River). Housing: SPF grade. After the mice were purchased, they were kept in a laboratory environment for 1 week. The light/dark cycle was 12/12 hours, the temperature was 20-25°C; humidity was 40-60%. The immunizing antigen was His-tagged human DLL3 recombinant protein (huDLL3-His). Titermax (sigma Lot Num: T2684) was an adjuvant. The antigen to adjuvant (titermax) ratio was 1: 1, the antigen was emulsified and inoculated on days 0, 14, 35, and 56, and boosted 3 days before splenocyte fusion. During this period, the ELISA and FACS methods were used to detect mouse serum and determine the antibody titer in

the mouse serum. After the fifth immunization, mice with high and plateau antibody titer in serum were selected for splenocyte fusion. Splenic lymphocytes were fused with myeloma cells Sp2/0 cells (ATCC® CRL-8287™) using an optimized electrofusion procedure to obtain hybridoma cells. After the fused hybridoma cells are cultured for 7-14 days, the culture medium supernatant was taken. The hybridoma supernatant was subjected to antibody screening using DLL3 recombinant proteins and an ELISA experiment. The obtained positive antibody strain was further screened with stably transfected CHO-K1 cells expressing DLL3 to exclude non-specific antibody-binding hybridoma strains by comparing with blank CHO-K1 cells and subjected to screening using flow sorting method, thereby selecting hybridomas that bind to the recombinant protein and also bind to the antigen expressed by the cells. Hybridoma cells were harvested in the log phase and RNA was extracted with Trizol (Invitrogen, 15596-018) and reverse transcribed (PrimeScript™ Reverse Transcriptase, Takara # 2680A). The reverse transcribed cDNA was subjected to PCR amplification using a mouse Ig-Primer Set (Novagen, TB326 Rev. B 0503) and sequenced to obtain the amino acid sequences of the variable regions of the 10 monoclonal antibodies of the present disclosure, as shown in Table 10A.

Table 10A Amino acid sequences of 10 mouse hybridomas-derived anti-dll3 monoclonal antibody variable regions

Clone No.		Variable Heavy Chain (VH)	Variable Light Chain (VL)
26C4D2	SEQ ID NO	30	31
	Amino Acid Sequence	QVQLQQPGAELVKPGASVKLSCK ASGYSFTSYWMHWVKQRPGQGL EWIGMIHPTLGDTNYNEKFKSKAT LTVDKSSSTAYMELSSLTSEDSAVY YCARLGSLSMMDYWGQGTSVTV SS	DIQMTQTTSSLSASLGDRVTISCS ASQGISNYLNWYQQKPDGTVKL LIYYTSSLHSGVPARFSGSGSGT DYSLTISNLEPEDIAIYYCQQYSK FPYTFGGGTKLEIK
39E2D11-1	SEQ ID NO	32	33
	Amino Acid Sequence	QVQLQQSGAELVKPGASVKMSCK ASGYTFISYWITWVKQRPGQGLE WIGDIYPGSGSTTNYNEKFKSKAT LTVDTSSSTAYMQLSSLTSEDSAVY YCARETTVGGAYAMDYWGQGTS VTVSS	DIVLTQSPATLSVTPGDSVSLSCR ASQSINNNLHWYQQKSHESPRL LIKYVSQSISGIPSRFSGSGSGTDF TLTINSVETEDFGMYFCQQTNS WPLTFGAGTKLELK
39E2D11-2	SEQ ID NO	34	33
	Amino Acid Sequence	QVQLKQSGPGLVQPSQSLSITCTVS GFSLTSYGVHWVRQSPGKGLEWL	DIVLTQSPATLSVTPGDSVSLSCR ASQSINNNLHWYQQKSHESPRL

		GVIWSGGSTDYNAAFISRLSISKDN PKSQVFFKMNSLQADDTAIYYCA RENYYGNSLWFFDVWGTGTTVTV SS	LIKYVSQSISGIPSRFSGSGSGTDF TLTINSVETEDFGMYFCQQTNS WPLTFGAGTKLELK
40G3D1	SEQ ID NO	35	36
	Amino Acid Sequence	QVQLQQSGAELVKPGASVKISCKA SGYAFSSQWMNWVKQRPGKGLE WIGQIYPGNGDTNYNGKFKGKAT LTADKSSSTAYIQLSSLTSEDSAVYF CARWFAYWGQGTLVTVSA	DIVLTQSPVTLSVTPGDSVSLSCR ASQSVRNNLHWYQQKSHESPRL LIKYVSQSISGIPSRFSGSGSGTDF TLSINSVETEDFGVYFCQQSNSW PLTFGAGTKLELK
46A5A4	SEQ ID NO	37	38
	Amino Acid Sequence	QVQLQQSDAELVKPGASVKISCKV SGYTFTDHTIHWMKQRPEQGLEW IGYIYPRDGYTMYNEKFKGKATLT ADKSSSTAYMQLNSLTSEDSAVHF CARAFHALDYWGQGTSVTVSS	DIQMTQTTSSLSASLGDRVTFTC SASQGISNYLNWYQQKPDGTIK LLIYYTSSLHSGVPSRFSGSGSGT DYSLTISNLEPEDIATYYCQQYSK LPYTFGGGTKLEIK
47E12D12-1	SEQ ID NO	39	40
	Amino Acid Sequence	EVQLVESGGGLVKPGGSLKLSCAA SGFTFSDYGMHWVRQAPEKGLE WVAYISSGSSTIYYADTVKGRFTIS RDNAKNTLFLQMTSLRSEDTAMY YCARNSRGFAYWGQGTLVTVSA	DIVLTQSPAIMSASPGEKVTMTC SASSSVSYMYWYQQKPGSSPRL LIYDTSNLASGVPVRFSGSGSGT SYSLTISRMEAEDAATYYCQQW SSYPRTFGGGTKLEIK
47E12D12-2	SEQ ID NO	39	41
	Amino Acid Sequence	EVQLVESGGGLVKPGGSLKLSCAA SGFTFSDYGMHWVRQAPEKGLE WVAYISSGSSTIYYADTVKGRFTIS RDNAKNTLFLQMTSLRSEDTAMY YCARNSRGFAYWGQGTLVTVSA	DIVLIQSPTIMSASPGEKVTMTCS ASSSVSSMHWYQQKSGTSPKRW IYDTSKLASGVPARFSGSGSGTS YSLTISTMEAEDAATYYCQQWN SYHLTFGAGTKLELK
48B6D7	SEQ ID NO	42	43
	Amino Acid Sequence	QVQLQQPGAELVKPGTSVKLSCE ASGYTFSNYWMQWVRQRPGQGL EWIGMILPNSDITNYNENFQTKAT LTVDKSSSTAYMQLSSLTSEDSAVY YCARQARYSAMDYWGQGTSVTV SS	DIQMTQTTSSLSVSLGDRVTINC SASQGISNYLNWYQQKPDGTVK LLIYYTSNLHSGVPSRFSGSGSG TDYSLTISNLEPEDIATYYCQHYS KFPYTFGGGTKLEIK

45E4D7	SEQ ID NO	44	36
	Amino Acid Sequence	QVQLQQPGAELVKPGTSVKLSCKASGYTFTSHWITWVKQRPGQGLEWIGDIYPISGSTNNNEKFRNKATLTVDTSSSTAYMQLSSLTSEDSAVYFCAKIITVGGAYVMDYWGQGTSVTVSS	DIVLTQSPVTLSVTPGDSVSLSCRASQSVRNNLHWYQQKSHESPRLLIKYVSQSISGIPSRFSGSGSGTDFTLSINSVETEDFGVYFCQQSNSWPLTFGAGTKLELK
27E10C5	SEQ ID NO	35	45
	Amino Acid Sequence	QVQLQQSGAELVKPGASVKISCKASGYAFSSQWMNWVKQRPGKGLEWIGQIYPGNGDTNYNGKFKGKATLTADKSSSTAYIQLSSLTSEDSAVYFCARWFAYWGQGTLVTVSA	DIVMTQSPSSLAMSVGQKVTMNCKSSQSLLNSSHQKNYLAWYQQKPGQSPKLLVYFASTRESGVPDRFIGSGSGTDFTLTISSVQAEDLADYFCQQHYSTPWTFGGGTKLEIK

On the basis of the above amino acid sequences, the CDR and FR of antibody variable regions were divided using the Kabat numbering rule, and the composition of 6 CDR sequences of each antibody is shown in Table 10B below.

Table 10B CDR Sequences of 10 mouse hybridomas-derived anti-DLL3 monoclonal antibodies

Clone No.		CDR1		CDR2		CDR3	
		SEQ ID NO	Amino Acid Sequence	SEQ ID NO	Amino Acid Sequence	SEQ ID NO	Amino Acid Sequence
26C4D2	Heavy Chain	57	SYWMH	58	MIHPTLGDTNYNEKFKS	59	LGSLSMMDY
	Light chain	60	SASQGISNYLN	61	YTSSLHS	62	QQYSKFPYT
39E2D11-1	Heavy Chain	63	SYWIT	64	DIYPGSGSTTNYNEKFKS	65	ETTVGGAYAMDY
	Light Chain	66	RASQSINNNLH	67	YVSQSIS	68	QQTNSWPLT
39E2D11-2	Heavy Chain	69	SYGVH	70	VIWSGGSTDYNAAFIS	71	ENYYGNSLWFFDV
	Light Chain	66	RASQSINNNLH	67	YVSQSIS	68	QQTNSWPLT
40G3D1	Heavy	72	SQWMN	73	QIYPGNGDTNYNGK	74	WFAY

	Chain				FKG		
	Light Chain	75	RASQSVRNNLH	76	YVSQSIS	77	QQSNSWPLT
46A5A4	Heavy Chain	78	DHTIH	79	YIYPRDGYTMYNEKFKG	80	AFHALDY
	Light chain	81	SASQGISNYLN	82	YTSSLHS	83	QQYSKLPYT
47E12D12-1	Heavy Chain	84	DYGMH	85	YISSGSSTIYYADTVKG	86	NSRGFAY
	Light Chain	87	SASSSVSYMY	88	DTSNLAS	89	QQWSSYPRT
47E12D12-2	Heavy Chain	84	DYGMH	85	YISSGSSTIYYADTVKG	86	NSRGFAY
	Light Chain	90	SASSSVSSMH	91	DTSKLAS	92	QQWNSYHLT
48B6D7	Heavy Chain	93	NYWMQ	94	MILPNSDITNYNENFQT	95	QARYSAMDY
	Light Chain	96	SASQGISNYLN	97	YTSNLHS	98	QHYSKFPYT
45E4D7	Heavy Chain	99	SHWIT	100	DIYPISGSTNNNEKFRN	101	IITVGGAYVMDY
	Light Chain	75	RASQSVRNNLH	76	YVSQSIS	77	QQSNSWPLT
27E10C5	Heavy Chain	72	SQWMN	73	QIYPGNGDTNYNGKFKG	74	WFAY
	Light Chain	102	KSSQSLLNSSHQKNYLA	103	FASTRES	104	QQHYSTPWT

Example 14. Construction of mouse hybridoma-derived anti-DLL3 chimeric antibodies and their transient transfection expression in eukaryotic cells

The gene fragment of interest generated after splicing the sequenced heavy and light chain variable region of the monoclonal antibody of the present disclosure with the IgG1 heavy chain constant region and kappa light chain constant region was cloned into the pTT5 expression vector to prepare a transfection-grade expression plasmid.

Expi293F™ cells (Thermo Fisher Scientific) were cultured in a serum-free medium, seeded in a

shake flask (Corning Inc.), and cultured in a 37°C, 8% CO_2 shaker. After adjusting the cell density, the recombinant expression vector containing the gene fragment of interest and PEI transfection reagent were mixed in an appropriate ratio and added into a cell culture flask. After 6 days of cell culture, the expression supernatant was collected, centrifuged at high speed to remove cell debris, and subjected to affinity purification using a Protein A column. The column was rinsed with PBS until the A280 reading dropped to baseline. The protein of interest was eluted with an acidic eluent at pH 3.0-pH 3.5 and neutralized with 1M Tris-HCl, pH 8.0-9.0. After the eluted sample was appropriately concentrated, the solution was changed to PBS and aliquoted for later use. Final purified chimeric antibodies were subjected to SDS-PAGE and HPLC purity analysis and A280 concentration determination.

Example 15. In vitro, cell binding verification of mouse hybridoma-derived anti-DLL3 chimeric antibodies

SHP-77 and HEK293-cyno DLL3 cells were cultured. The culture medium for SHP-77 cells were RPMI1640+10% FBS, and the culture medium for HEK293 cyno DLL3 cells was DMEM+10% FBS+200 μg/ml Hygromycin. The cells were cultured in a T75 cell culture flask at a 37°C 5% CO_2 incubator. When using cells, they are washed with sterile DPBS, digested with 0.25% trypsin EDTA for about 5 minutes, and then stopped with a complete medium.

The digested cells were centrifuged at 1000 rpm for 5 min at room temperature. The supernatant was discarded and the cells were resuspended in 100 μL of 1% BSA (in PBS). The cells were counted and adjusted to a cell density of 1E6/m. The dilute cells were seeded in a 96-well round-bottom culture plate (corning 3799), and centrifuged at 1500 rpm for 5 min at 4°C. The supernatant was discarded and the cells were stored at 4°C until use. Antibody samples to be tested were diluted with 1% BSA (in PBS) at a starting concentration of 100 nM, downwards by a 10-fold gradient for 7 concentrations. The cells were resuspended with the diluted antibody at 100 μL/well and incubated for 1 hour at 4°C. The cells were centrifuged at 1500 rpm for 5 minutes at 4°C and the supernatant was discarded. The cells were resuspended and washed with 160 μL of 1%BSA (in PBS), centrifuged at 1500 rpm for 5 minutes at 4°C. The supernatant was discarded. The secondary antibody (goat anti human IgG Fc PE) was diluted 1: 200 with 1% BSA (in PBS) according to the manufacturer's instructions and the cells were resuspended with the diluted secondary antibody, 100 μL/well, and incubated for 0.5 h at 4°C. The cells were centrifuged at 1500 rpm for 5 minutes at 4°C and the supernatant was discarded. The cells were resuspended and washed with 160 μL of 1%BSA (in PBS), centrifuged at 1500 rpm for 5 minutes at 4°C. The supernatant was discarded. The cells were resuspended in 100 μL of 1% BSA (in PBS), and filtered across a 300 mesh gauze. The mean fluorescence intensity of the PE channels was measured by flow cytometry.

The FCS file was exported from the flow cytometer. The mean fluorescence intensity of PE channel (hereinafter referred to as MFI) of each sample was analyzed with the Flowjo software. The analyzed mean fluorescence intensity was imported into Graphpad to analyze the median-binding concentration (hereinafter referred to as EC50) of antibody and cell and the top mean fluorescence intensity (Top MFI). The results are shown in Table 11 and Figure 5.

Table 11 Binding of mouse hybridoma-derived anti-DLL3 chimeric antibodies to DLL3-expressing cells

Clone No.	SHP-77		HEK293 - cyno DLL3	
	EC_{50} (nM)	Top Mean Fluorescence Intensity (Top MFI))	EC_{50} (nM)	Top Mean Fluorescence Intensity (Top MFI))
26C4D2	0.60	1053	0.43	421
39E2D11-1	0.85	999	1.03	445
39E2D11-2	8.63	193	not detected	not detected
40G3D1	Unfitted	369	not detected	not detected
46A5A4	1.18	1013	0.67	475
47E12D12-1	1.45	178	not detected	not detected
47E12D12-2	69.28	455	not detected	not detected
48B6D7	0.65	990	0.53	480
45E4D7	0.68	965	0.71	454
27E10C5	1.20	813	1.39	396

Example 16. Humanization of mouse hybridoma-derived anti-DLL3 antibodies

10 chimeric antibodies were subjected to an expression purification test and cell-level binding test, and 3 clones were further selected for humanization design.

Humanization of murine anti-human DLL3 monoclonal antibodies was performed as disclosed in many references in the art. Briefly, a human constant domain was used in place of a parental (murine antibody) constant domain, and the human antibody sequence was selected based on the homology between murine and human antibodies. Based on the obtained VH/VL CDR typical structure of a murine antibody, the heavy and light chain variable region sequences were compared with the human antibody germline database to obtain human germline templates with high homology.

The CDR region of the murine antibody was grafted onto a selected corresponding humanized

template to replace the humanized variable region and recombined with the IgG constant region (preferably IgG1 for heavy chain and kappa for light chain). Then, based on the three-dimensional structure of mouse-derived antibodies, reverse mutations were performed on embedded residues, residues that directly interact with the CDR region, and residues that have a significant impact on the conformation of VL and VH. Antibodies were designed by combining the following humanized light and heavy chain variable region sequences, as shown in Table 12.

Table 12 Amino acid sequences of three mouse hybridomas-derived humanized antibody variable regions

Clone No.		Variable Heavy Chain (VH)	Variable Light Chain (VL)
H1-39E2D11	SEQ ID NO	46	47
	Amino Acid Sequence	QVQLVQSGAEVKKPGASVKVSCKA SGYTFISYWITWVRQAPGQGLEWM GDIYPGSGSTTNYNEKFKSRVTMTR DTSTSTVYMELSSLRSEDTAVYYCA RETTVGGAYAMDYWGQGTLVTVSS	EIVLTQSPATLSLSPGERATLSC RASQSINNNLHWYQQKPGQAP RLLIYYVSQSISGIPARFSGSGS GTDFTLTISSLEPEDFAVYYCQQ TNSWPLTFGGGTKLEIK
H2-39E2D11	SEQ ID NO	46	48
	Amino Acid Sequence	QVQLVQSGAEVKKPGASVKVSCKA SGYTFISYWITWVRQAPGQGLEWM GDIYPGSGSTTNYNEKFKSRVTMTR DTSTSTVYMELSSLRSEDTAVYYCA RETTVGGAYAMDYWGQGTLVTVSS	EIVLTQSPATLSLSPGERATLSC RASQSINNNLHWYQQKPGQAP RLLIKYVSQSISGIPARFSGSGS GTDFTLTISSLEPEDFAVYYCQQ TNSWPLTFGGGTKLEIK
H-46A5A4	SEQ ID NO	49	50
	Amino Acid Sequence	QVQLVQSGAEVKKPGASVKVSCKA SGYTFTDHTIHWVRQAPGQGLEWM GYIYPRDGYTMYNEKFKGRVTMTR DTSTSTVYMELSSLRSEDTAVYYCA RAFHALDYWGQGTLVTVSS	DIQMTQSPSSLSASVGDRVTIT CSASQGISNYLNWYQQKPGKA PKLLIYYTSSLHSGVPSRFSGSG SGTDFTFTISSLQPEDIATYYCQ QYSKLPYTFGGGTKLEIK
H1-45E4D7	SEQ ID NO	51	52
	Amino Acid Sequence	QVQLVQSGAEVKKPGASVKVSCKA SGYTFTSHWITWVRQAPGQGLEWM GDIYPISGSTNNNEKFRNRVTMTRD TSTSTVYMELSSLRSEDTAVYYCAKI ITVGGAYVMDYWGQGTLVTVSS	EIVMTQSPATLSVSPGERATLSC RASQSVRNNLHWYQQKPGQA PRLLIYYVSQSISGIPARFSGSGS GTEFTLTISSLQSEDFAVYYCQQ SNSWPLTFGGGTKLEIK
H2-45E4D7	SEQ ID NO	51	53
	Amino Acid	QVQLVQSGAEVKKPGASVKVSCKA	EIVMTQSPATLSVSPGERATLSC

	Sequence	SGYTFTSHWITWVRQAPGQGLEWM GDIYPISGSTNNNEKFRNRVTMTRD TSTSTVYMELSSLRSEDTAVYYCAKI ITVGGAYVMDYWGQGTLVTVSS	RASQSVRNNLHWYQQKPGQA PRLLIKYVSQSISGIPARFSGSGS GTEFTLTISSLQSEDFAVYYCQQ SNSWPLTFGGGTKLEIK

Example 17. In vitro, cell binding verification of mouse hybridoma-derived humanized anti-DLL3 antibodies

SHP-77 cells were cultured. The culture medium for SHP-77 cells was RPMI1640+10% FBS. The cells were cultured in a T75 cell culture flask at a 37°C 5% CO_2 incubator. When using cells, they are washed with sterile DPBS, digested with 0.25% trypsin EDTA for about 5 minutes, and then stopped with a complete medium.

The digested cells were centrifuged at 1000 rpm for 5 min at room temperature. The supernatant was discarded and the cells were resuspended in 100 μL of 1% BSA (in PBS). The cells were counted and adjusted to a cell density of 1E6/m. The dilute cells were plated in a 96-well round-bottom culture plate (corning 3799), and centrifuged at 1500 rpm for 5 min at 4°C. The supernatant was discarded and the cells were stored at 4°C until use. Antibody samples to be tested were diluted with 1% BSA (in PBS) at a starting concentration of 100 nM, downwards by a 10-fold gradient for 7 concentrations. The cells were resuspended with the diluted antibody at 100 μL/well and incubated for 1 hour at 4°C. The cells were centrifuged at 1500 rpm for 5 minutes at 4°C and the supernatant was discarded. The cells were resuspended and washed with 160 μL of 1%BSA (in PBS), centrifuged at 1500 rpm for 5 minutes at 4°C. The supernatant was discarded. The secondary antibody (goat anti human IgG Fc PE) was diluted 1: 200 with 1% BSA (in PBS) according to the manufacturer's instructions and the cells were resuspended with the diluted secondary antibody, 100 μL/well, and incubated for 0.5 h at 4°C. The cells were centrifuged at 1500 rpm for 5 minutes at 4°C and the supernatant was discarded. The cells were resuspended and washed with 160 μL of 1%BSA (in PBS), centrifuged at 1500 rpm for 5 minutes at 4°C. The supernatant was discarded. The cells were resuspended in 100 μL of 1% BSA (in PBS), and filtered across a 300 mesh gauze. The mean fluorescence intensity of the PE channels was measured by flow cytometry.

The FCS file was exported from the flow cytometer. The mean fluorescence intensity of the PE channel (hereinafter referred to as MFI) of each sample was analyzed with the Flowjo software. The analyzed mean fluorescence intensity was imported into Graphpad to analyze the median-binding concentration (hereinafter referred to as EC50) of antibody and cell and the top mean fluorescence intensity (Top MFI). The results are shown in Table 13 and Figure 6.

Table 13. Binding of mouse hybridoma-derived humanized anti-DLL3 antibodies to DLL3-expressing cells (SHP-77)

Clone No.	SHP-77	
	EC_{50} (nM)	Top Mean Fluorescence Intensity (Top MFI))
39E2D11-1	1.491	1647
H1-39E2D11	2.128	1426
H2-39E2D11	1.125	1574
46A5A4	1.204	1574
H-46A5A4	1.348	1525
45E4D7	0.894	1561
H1-45E4D7	5.163	1588
H2-45E4D7	2.228	1614

Example 18. Biacore affinity experiment of hybridoma-derived humanized anti-dll3 antibodies

The affinity and kinetic properties of the humanized anti-DLL3 antibody to human DLL3 were analyzed using a Biacore 8K instrument. CM5 chips were activated with EDC and NHS, followed by immobilization of anti-human Fc murine mAb and blocked with ethanolamine.

To determine the affinity to human DLL3 and kinetic properties, the DLL3 humanized antibody was diluted to 0.2 μg/mL with HBS-EP + (10 mM HEPES, pH 7.4, 150 mM NaCl, 3 mM EDTA, 0.05% P20) buffer and captured at a flow rate of 10 μL/min for 45 s. Human DLL3 was diluted two-fold serially to serial concentrations (100 nM-0.39 nM) and associated for 90 s and dissociated for 600 s at a flow rate of 50 μL/min.

After completion of each round of the experiment, the captured antibody was removed together with the antigen by washing with a 3M $MgCl_2$ solution at a flow rate of 30 μL/min for 30 s to complete the regeneration of the chip. The raw data were analyzed using Biacore Insight Evaluation Software (3.0.12.15655) software and fitted with a (1: 1) Langmuir model with. The results were shown in Table 14.

Table 14. Affinity test results of hybridoma-derived humanized anti-DLL3 antibodies with human DLL3 antigen proteins

Clone No.	ka (1/Ms)	kd(1/s)	KD(M)
H2-39E2D11	3.13E+05	1.80E-04	5.76E-10
H-46A5A4	2.19E+05	1.78E-04	8.11E-10
H2-45E4D7	2.35E+05	5.78E-	2.46E-

		05	10

Example 19. Binding experiments of hybridoma-derived humanized anti-DLL3 antibodies with the family proteins DLL1 and DLL4

The antigenic proteins human DLL1 (SinoBiological, cat. No. 11635-H08H) or human DLL4 (SinoBiological, cat. No. 10171-H08H) were dissolved in 1 × PBS at a concentration of 1 μg/mL. The antigen was then added to a high-affinity ELISA plate (Biolegend, cat. No. 423501) at 100 μL/well and left overnight at 4°C. The antigen was washed three times with PBST, 300 μL/well. The antigen was blocked with 1% BSA (in PBST), 200 μL/well, and incubated at 37°C for 1.5 hours. Antibodies to be tested were diluted with 1% BSA (in PBS) at a starting concentration of 100 nM, downwards by a 10-fold gradient for 7 concentrations. The plates were washed three times with PBST, 300 μL/well. The diluted antibody was added to an ELISA plate at 100 μL/well and incubated at room temperature for 2 hours. The antibodies were washed three times with PBST, 300 μL/well. The secondary antibodies (goat anti-human IgG Fc for DLL4 (HRP), 1: 20000 dilution; HRP goat anti-mouse IgG (H + L) for DLL1, 1: 10000 dilution) were diluted with 1% BSA in PBST. The diluted secondary antibodies were added to the ELISA plate at 100 μL/well and incubated at room temperature for 1 hour. The plates were washed 6 times with PBST, 300 μL/well. The developing solution (TMA and TMB 1:1 mixed) was prepared. The developing solution was added to the plate, 100 μL/well, and incubated in the dark for 5 min. 50 μL of ELISA stop solution was added to the plate and shaken well.

OD450s were read on the envision and plotted on the GraphPad for EC_{50} values. The results are shown in FIG. 7, which show that the antibodies tested did not non-specifically bind to either of the family proteins DLL1 and DLL4.

Example 20. Preparation of hybridoma-derived humanized anti-DLL3 antibody variants

After post-translational modification (PTM) analysis of the antibodies of the present disclosure, it was found that there was one deamidation site in the light chain variable region of H2-39E2D11, and site-directed mutation for a single site was performed on amino acid 99 to prepare three mutants of H2-39E2D11: H2-39E2D11-NA, H2-39E2D11-QS, and H2-39E2D11-AS, respectively. The variable region amino acid sequences of the three variants are shown in Table 15.

Table 15 Amino acid sequences of H2-39E2D11 humanized antibody

Clone No.		Variable Heavy Chain (VH)	Variable Light Chain (VL)	LCDR3
H2-39E2D11-NA	SEQ ID NO	46	54	112
	Amino Acid Sequence	QVQLVQSGAEVKKPGASVKVSCKASGYTFISYWITWVRQAPGQG	EIVLTQSPATLSLSPGERATLSCRASQSINNNLHWYQQKPG	QQTNAWPLT

		LEWMGDIYPGSGSTTNYNEKFK SRVTMTRDTSTSTVYMELSSLRS EDTAVYYCARETTVGGAYAMDY WGQGTLVTVSS	QAPRLLIKYVSQSISGIPARFS GSGSGTDFTLTISSLEPEDFA VYYCQQTNAWPLTFGGGTK LEIK	
H2-39E2D11-QS	SEQ ID NO	46	55	113
	Amino Acid Sequence	QVQLVQSGAEVKKPGASVKVSC KASGYTFISYWITWVRQAPGQG LEWMGDIYPGSGSTTNYNEKFK SRVTMTRDTSTSTVYMELSSLRS EDTAVYYCARETTVGGAYAMDY WGQGTLVTVSS	EIVLTQSPATLSLSPGERATLS CRASQSINNNLHWYQQKPG QAPRLLIKYVSQSISGIPARFS GSGSGTDFTLTISSLEPEDFA VYYCQQTQSWPLTFGGGTK LEIK	QQTQSWPLT
H2-39E2D11-AS	SEQ ID NO	46	56	114
	Amino Acid Sequence	QVQLVQSGAEVKKPGASVKVSC KASGYTFISYWITWVRQAPGQG LEWMGDIYPGSGSTTNYNEKFK SRVTMTRDTSTSTVYMELSSLRS EDTAVYYCARETTVGGAYAMDY WGQGTLVTVSS	EIVLTQSPATLSLSPGERATLS CRASQSINNNLHWYQQKPG QAPRLLIKYVSQSISGIPARFS GSGSGTDFTLTISSLEPEDFA VYYCQQTASWPLTFGGGTK LEIK	QQTASWPLT

The three variants were prepared as described in Example 5. After transient expression in mammalian cell lines, affinity assays were performed using SHP-77 cells. The results shown in Table 8 show that the variants were able to eliminate the risk of post-translational modification without significant changes in binding at the cellular level. Affinity assay results using human DLL3 antigen proteins are shown in Table 16.

Table 16A Affinity test results of H2-39E2D11 humanized antibody variant with human DLL3 antigen protein

Clone No.	ka (1/Ms)	kd(1/s)	KD(M)
H2-39E2D11	1.81E+05	1.34E-04	7.39E-10
H2-39E2D11-NA	2.47E+05	1.20E-04	4.84E-10
H2-39E2D11-QS	1.71E+05	3.91E-05	2.29E-10
H2-39E2D11-AS	2.06E+05	3.62E-04	1.76E-09

Table 16B Affinity test results of H2-39E2D11 humanized antibody variant with Cynomolgus monkey DLL3 antigen protein

Clone No.	ka (1/Ms)	kd(1/s)	KD(M)
H2-39E2D11	2.21E+05	3.16E-05	1.43E-10
H2-39E2D11-NA	2.33E+05	8.09E-05	3.46E-10
H2-39E2D11-QS	1.98E+05	8.59E-05	4.34E-10
H2-39E2D11-AS	2.62E+05	4.27E-04	1.63E-09

The embodiments of the present disclosure described above are merely exemplary, and any person skilled in the art will recognize, or determine the equivalence of numerous specific compounds, materials, and operations without the need for unconventional experiments. All of these equivalents are within the scope of the present disclosure and are included in the claims.

Claims

1. A DLL3 binding molecule or an antigen binding fragment thereof, comprising a heavy chain variable region (VH) , wherein the heavy chain variable region comprises HCDR1, HCDR2, and HCDR3, the amino acid sequences of the HCDR1, HCDR2, and HCDR3 are respectively:

a) SED ID NOs: 6, 7, and 8; or

b) SED ID NOs: 9, 10, and 11; or

c) SED ID NOs: 12, 13, and 14; or

d) SED ID NOs: 15, 16, and 17; or

e) SED ID NOs: 18, 19, and 20; or

f) SED ID NOs: 6, 7, and 110; or

g) SED ID NOs: 6, 7, and 111;

preferably, the heavy chain variable region comprises an amino acid sequence selected from any one of SEQ ID NOs: 1-5, 21-29, or comprises an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identity to any one of SEQ ID NOs: 1-5, 21-29.

2. A DLL3 binding molecule or antigen binding fragment thereof, comprising a heavy chain variable region (VH), wherein the heavy chain variable region comprises HCDR1, HCDR2, and HCDR3 and a light chain variable region (VL) , wherein the light chain variable region comprises LCDR1, LCDR2, and LCDR3, the amino acid sequences of the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 are respectively:

a) SED ID NOs: 57, 58, 59, 60, 61, and 62; or

b) SED ID NOs: 63, 64, 65, 66, 67, and 68; or

c) SED ID NOs: 69, 70, 71, 66, 67, and 68; or

d) SED ID NOs: 72, 73, 74, 75, 76 and 77; or

e) SED ID NOs: 78, 79, 80, 81, 82, and 83; or

f) SED ID NOs: 84, 85, 86, 87, 88, and 89; or

g) SED ID NOs: 84, 85, 86, 90, 91 and 92; or

h) SED ID NOs: 93, 94, 95, 96, 97, and 98; or

i) SED ID NOs: 99, 100, 101, 75, 76 and 77; or

j) SED ID NOs: 72, 73, 74, 102, 103 and 104; or

k) SED ID NOs: 63, 64, 65, 66, 67, and 112; or

l) SED ID NOs: 63, 64, 65, 66, 67, and 113; or

m) SED ID NOs: 63, 64, 65, 66, 67, and 114; or

preferably, the heavy chain variable region comprises an amino acid sequence selected from any

one of SEQ ID NOs: 30, 32, 34, 35, 37, 39, 42, 44, 46, 49, or 51, or comprises an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identity to any one of SEQ ID NOs: 30, 32, 34, 35, 37, 39, 42, 44, 46, 49, or 51; and/or

the light chain variable region comprises an amino acid sequence selected from any one of SEQ ID NOs: 31, 33, 36, 38, 40, 41, 43, 45, 47, 48, 50, 52, 53, 54, 55, or 56, or comprises an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identity to any one of SEQ ID NOs: 31, 33, 36, 38, 40, 41, 43, 45, 47, 48, 50, 52, 53, 54, 55, or 56;

more preferably, the heavy chain variable region and the light chain variable region each comprise sequences selected from a group consisting of:

1) SED ID NOs: 30 and 31; or

2) SED ID NOs: 32 and 33; or

3) SED ID NOs: 34 and 33; or

4) SED ID NOs: 35 and 36; or

5) SED ID NOs: 37 and 38; or

6) SED ID NOs: 39 and 40; or

7) SED ID NOs: 39 and 41; or

8) SED ID NOs: 42 and 43; or

9) SED ID NOs: 44 and 36; or

10) SED ID NOs: 35 and 45; or

11) SED ID NOs: 46 and 47; or

12) SED ID NOs: 46 and 48; or

13) SED ID NOs: 49 and 50; or

14) SED ID NOs: 51 and 52; or

15) SED ID NOs: 51 and 53; or

16) SED ID NOs: 46 and 54; or

17) SED ID NOs: 46 and 55; or

18) SED ID NOs: 46 and 56.

3. The DLL3 binding molecule or the antigen binding fragment thereof according to any one of the preceding claims further having one or more of the following characteristics:

i) further comprising a heavy chain constant region and/or a light chain constant region; preferably, the heavy chain constant region comprises an Fc; more preferably, Fc is derived from murine or human; more preferably, the sequence of the Fc is native or modified;

ii) the DLL3 binding molecule or the antigen binding fragment thereof is a monoclonal antibody, a

bispecific binding molecule, a multispecific binding molecule, a humanized antibody, a chimeric antibody, a modified antibody, a fully human antibody, a full-length antibody, a heavy chain antibody, a nanobody, an Fab, an Fv, an scFv, an $F(ab')_2$, a linear antibody, or a single domain antibody; and/or

iii) in the form of IgG1, IgG2, IgG3 or IgG4.

4. A conjugate formed by coupling the DLL3 binding molecule or the antigen binding fragment thereof according to any one of the preceding claims to a capture label or a detection label; preferably, the detection label comprises a radionuclide, a luminescent substance, a colored substance, or an enzyme.

5. An antibody drug conjugate formed by coupling the DLL3 binding molecule or the antigen binding fragment thereof according to any one of the preceding claims with another biologically active molecule; preferably, the other biologically active molecule is a small molecule drug; preferably, the DLL3 binding molecule or the antigen binding fragment thereof is linked to the other biologically active molecule via a linker.

6. A nucleic acid encoding the DLL3 binding molecule or the antigen binding fragment thereof according to any one of the preceding claims, or a recombinant vector comprising the nucleic acid, or a host cell comprising the nucleic acid or the recombinant vector; preferably, the host cell is a prokaryotic cell, preferably E. coli, or a eukaryotic cell, preferably a mammalian cell or yeast; further preferably, the mammalian cell is a CHO cell or a HEK293 cell.

7. A method for preparing the DLL3 binding molecule or the antigen binding fragment thereof according to any one of the preceding claims, the method comprising culturing the host cell according to claim 6 under suitable conditions and purifying the expression product from the cell.

8. Use of the DLL3 binding molecule or the antigen binding fragment thereof according to any one of the preceding claims in the manufacture of a medicament for the treatment or amelioration of a tumor;

preferably, the drug targets tumor cells aberrantly expressing DLL3; preferably, the tumor is selected from small cell lung cancer, glioblastoma, neuroendocrine cancer, melanoma, pancreatic cancer, rectal cancer, and metastatic cancers of the aforementioned tumors.

9. Use of the DLL3 binding molecule or the antigen binding fragment thereof according to any one of the preceding claims in the manufacture of a detection or diagnostic reagent;

preferably, the detection reagent is used for detecting expression of DLL3; the diagnostic reagent is used for diagnosing a tumor; preferably, the tumor is selected from small cell lung cancer, glioblastoma, neuroendocrine cancer, melanoma, pancreatic cancer, rectal cancer, and metastatic cancers of the aforementioned tumors.

10. A method for detecting DLL3 expression in a sample, comprising:

(1) contacting the sample with the DLL3 binding molecule or the antigen binding fragment thereof according to any one of the preceding claims;

(2) detecting the formation of a complex of the DLL3 binding molecule or the antigen binding fragment thereof and DLL3; optionally, the DLL3 binding molecule or the antigen binding fragment thereof is detectably labeled.

11. A pharmaceutical composition comprising an effective amount of the DLL3 binding molecule or the antigen binding fragment thereof according to any one of the preceding claims, an effective amount of the antibody drug conjugate according to claim 5, or an effective amount of the nucleic acid or recombinant vector or host cell according to claim 6;

preferably, it further comprises a pharmaceutically acceptable carrier; preferably, it further comprises one or more additional therapeutic agents.

12. A drug box or kit comprising a container and the pharmaceutical composition according to claim 11 in the container.

13. A method for inducing death of a cell expressing DLL3, the method comprising contacting the cell with the pharmaceutical composition according to claim 11, wherein the cell expressing DLL3 is a tumor cell;

preferably, the tumor cell is a cell selected from the following tumors: small cell lung cancer, glioblastoma, neuroendocrine cancer, melanoma, pancreatic cancer, rectal cancer, and metastatic cancers of the aforementioned tumors.

14. A method for treating a disease related to DLL3 expression in a subject, comprising administering the pharmaceutical composition according to claim 11 and/or the drug box or kit according to claim 12 to the subject in need;

preferably, the disease is a tumor; small cell lung cancer, glioblastoma, neuroendocrine cancer, melanoma, pancreatic cancer, rectal cancer, and metastatic cancers of the aforementioned tumors;

more preferably, the method further comprises administering an additional therapeutic agent to the subject.

Drawings

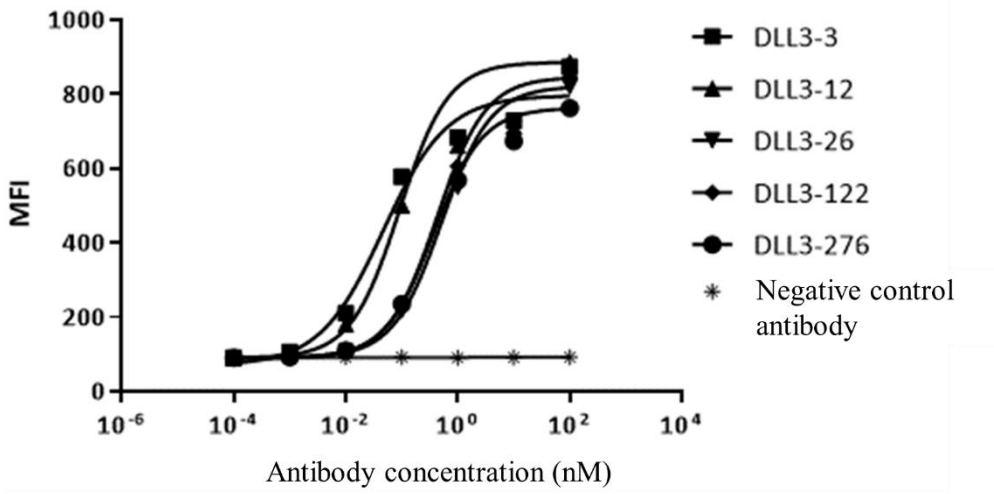


FIG. 1A

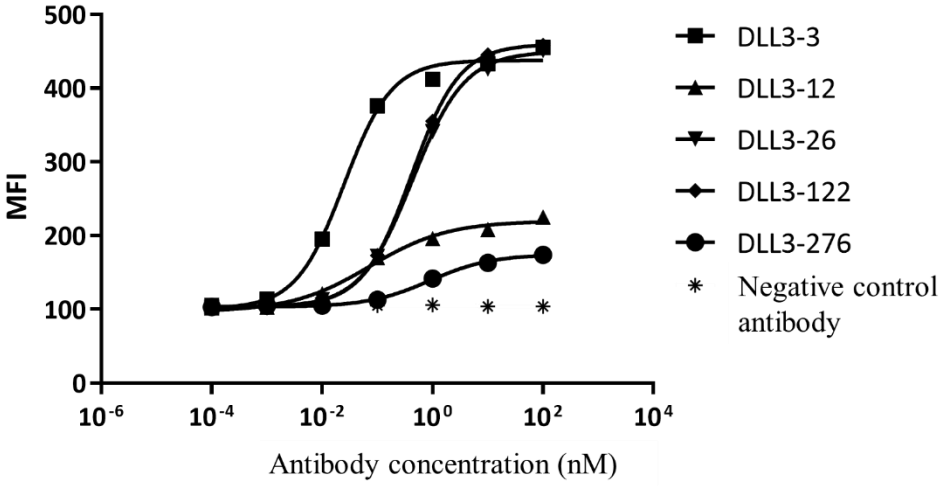
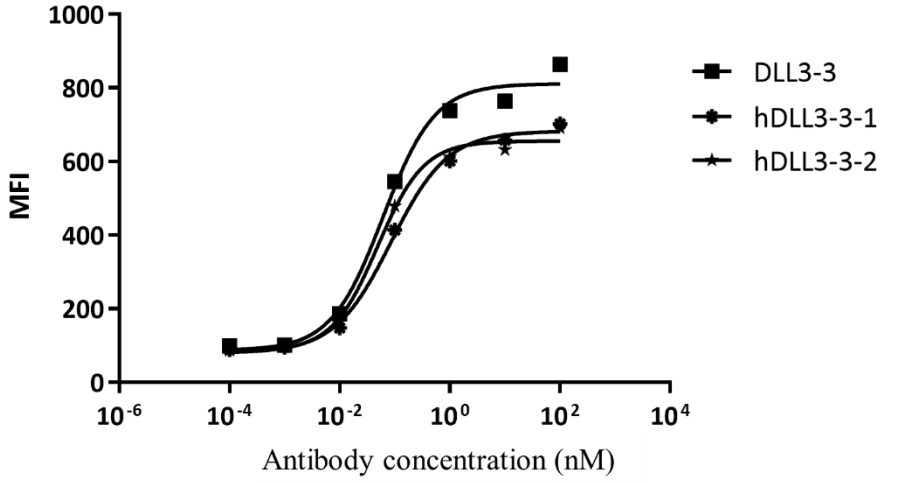


FIG. 1B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MFI
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10-2
100
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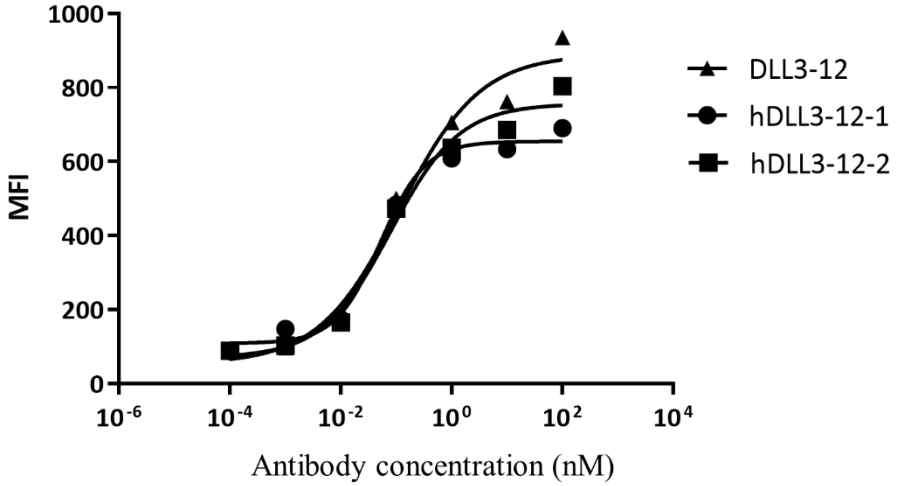
Antibody concentration (nM)
DLL3-3
hDLL3-3-1
hDLL3-3-2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Antibody concentration (nM)
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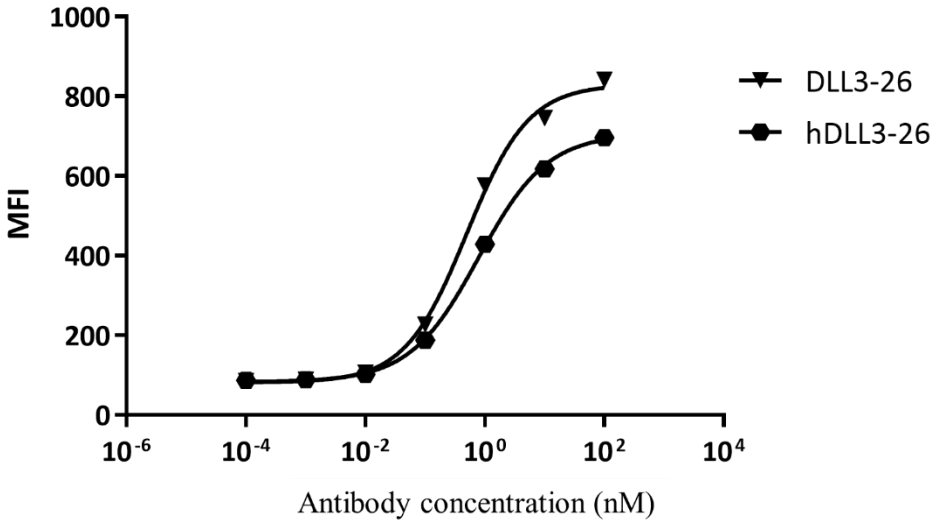
hDLL3-12-2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MFI
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Antibody concentration (nM)
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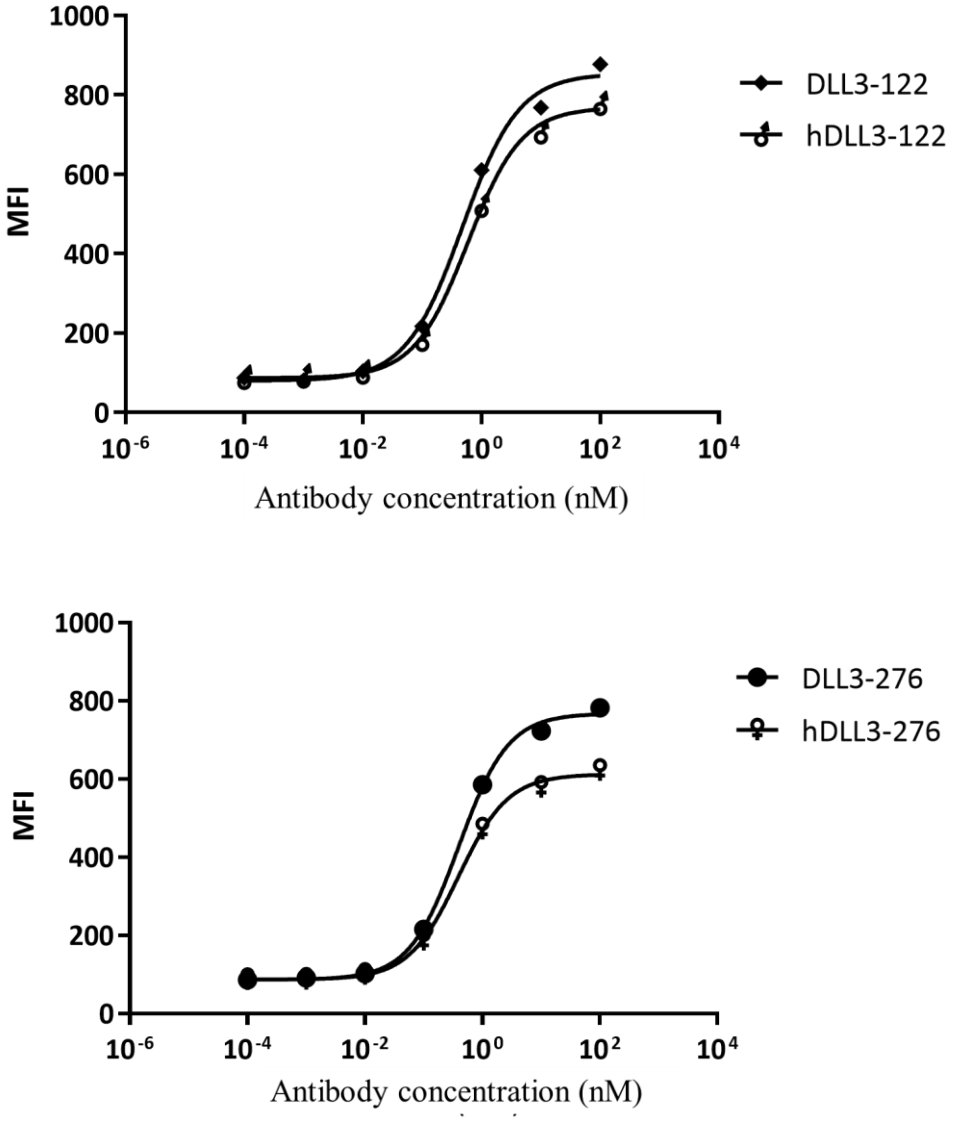
hDLL3-26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hDLL3-122
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800
600
400
200
0
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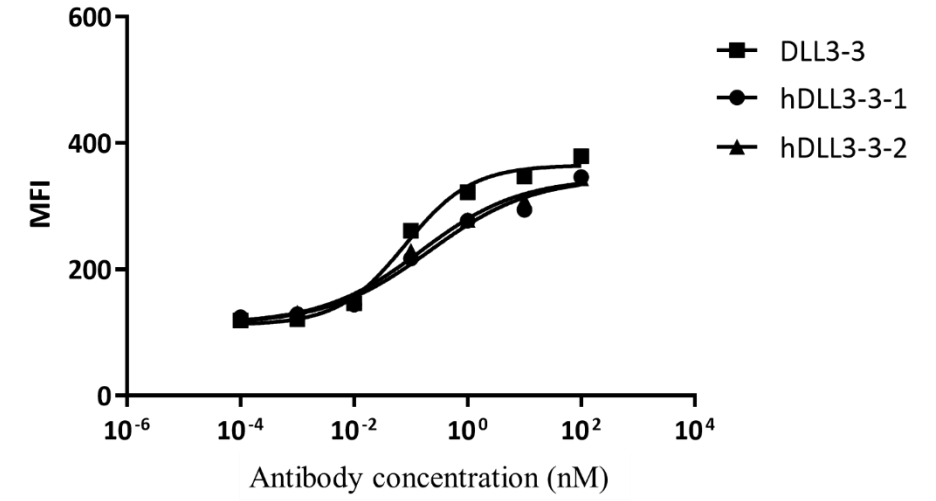
FIG. 2A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MFI
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102
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Antibody concentration (nM)
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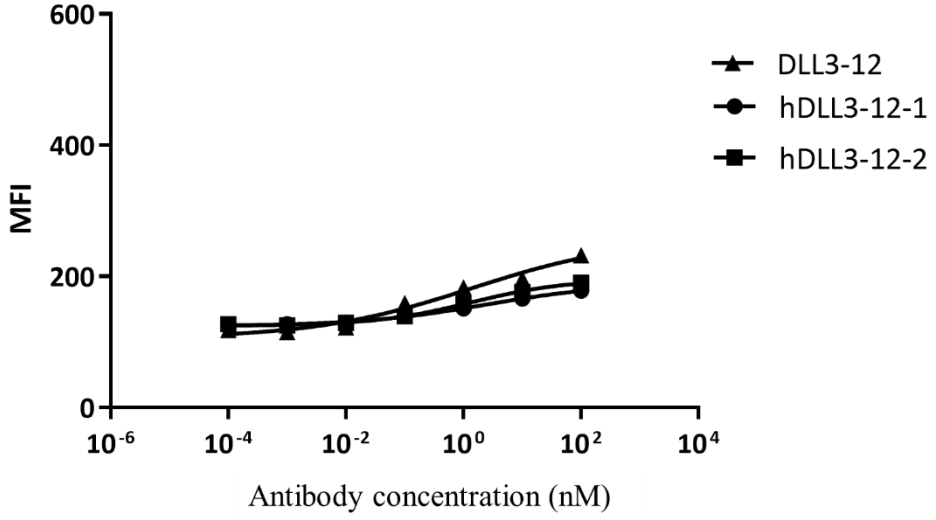
hDLL3-3-2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MFI
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Antibody concentration (nM)
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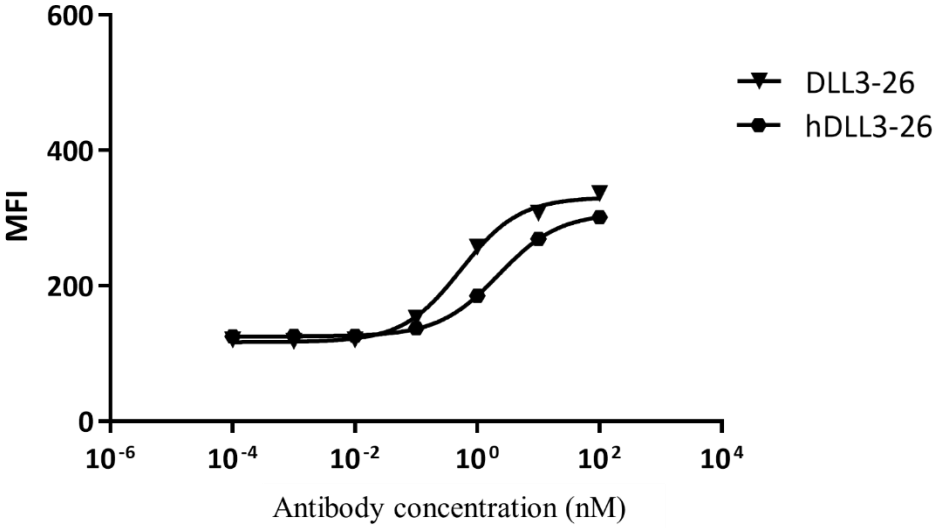
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MFI
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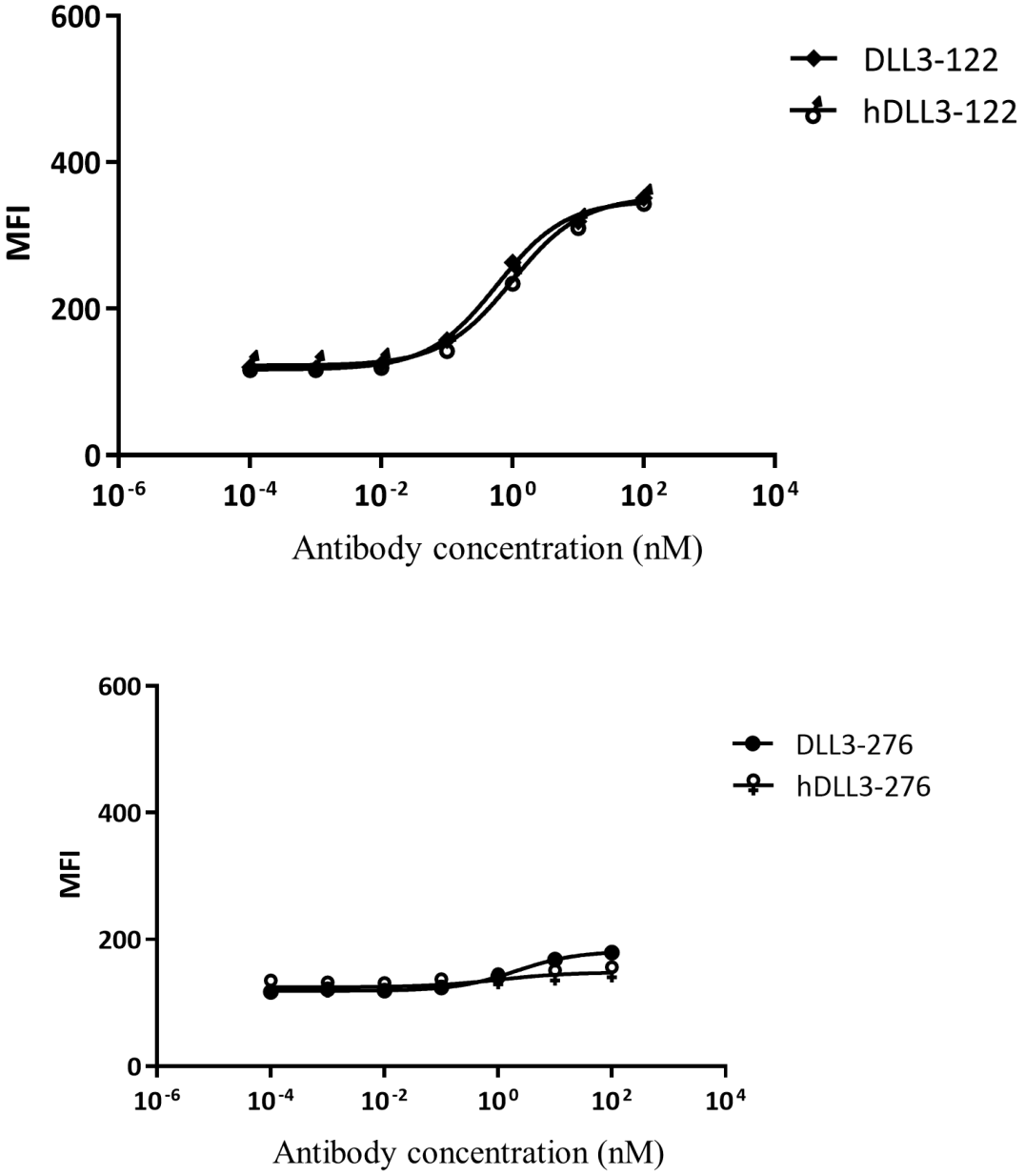
10-4
10-2
100
102
104
Antibody concentration (nM)
DLL3-26
hDLL3-26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400
200
0
MFI
DLL3-122
hDLL3-122
10-6
10-4
10-2
100
102
104
Antibody concentration (nM)
600
400
200
0
MFI
DLL3-276
hDLL3-276
10-6
10-4
10-2
100
102
104
Antibody concentration (nM)

FIG. 2B

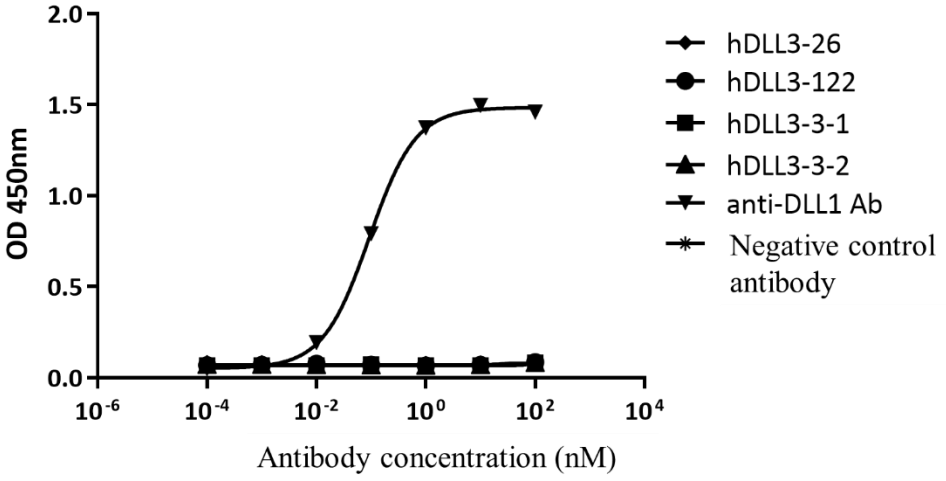


FIG. 3A

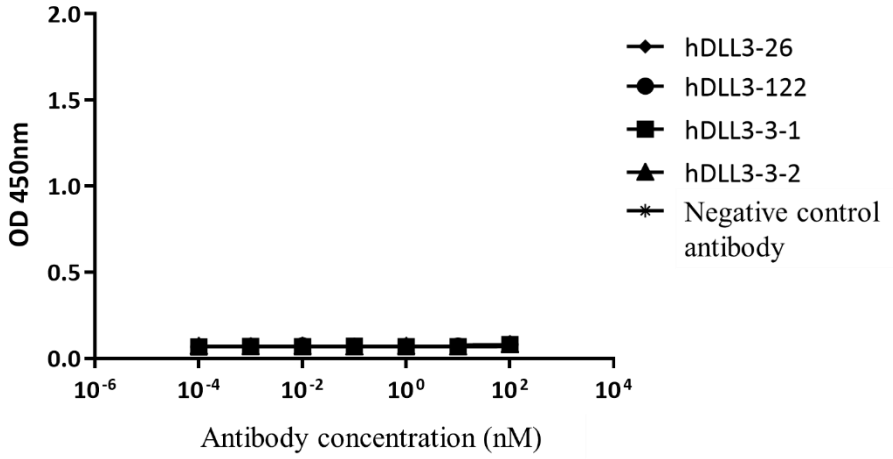


FIG. 3B

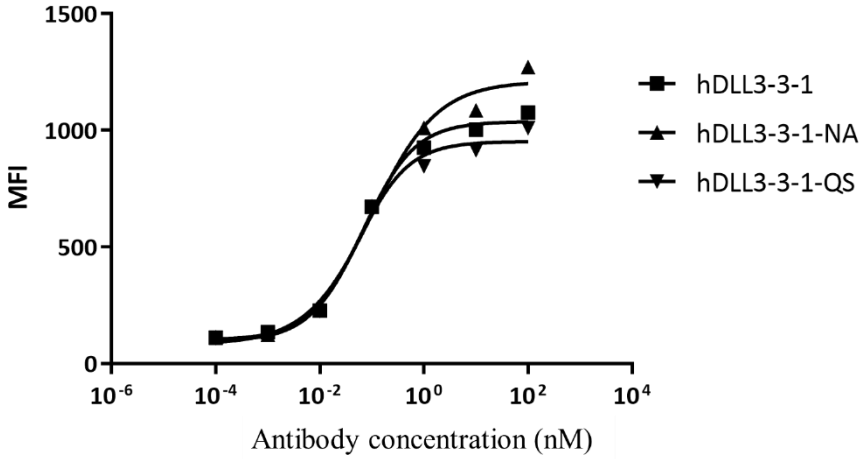


FIG. 4

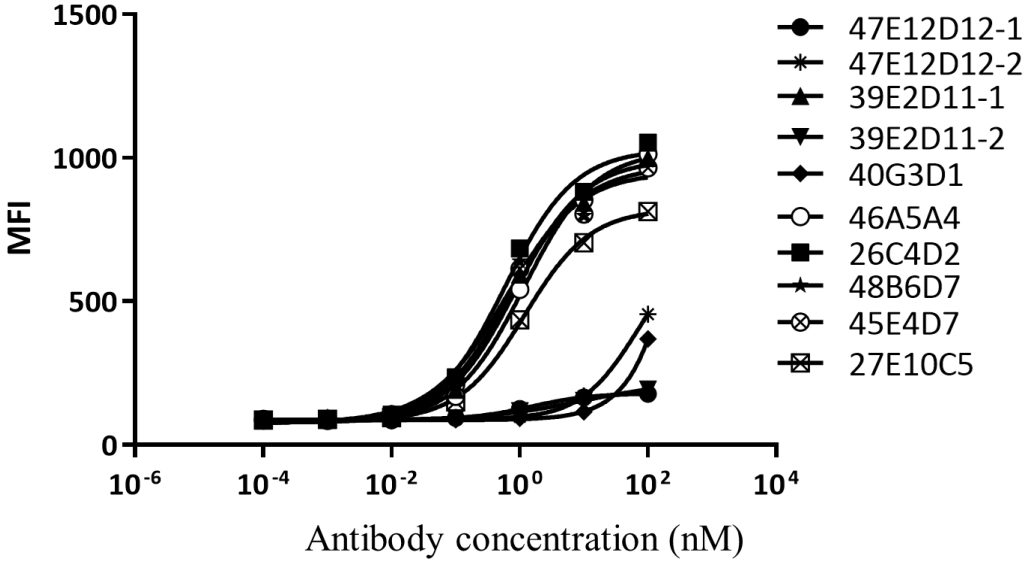

1500
1000
500
0
MFI
10^{-6}
10^{-4}
10^{-2}
10^{0}
10^{2}
10^{4}
Antibody concentration (nM)
47E12D12-1
47E12D12-2
39E2D11-1
39E2D11-2
40G3D1
46A5A4
26C4D2
48B6D7
45E4D7
27E10C5

FIG. 5A

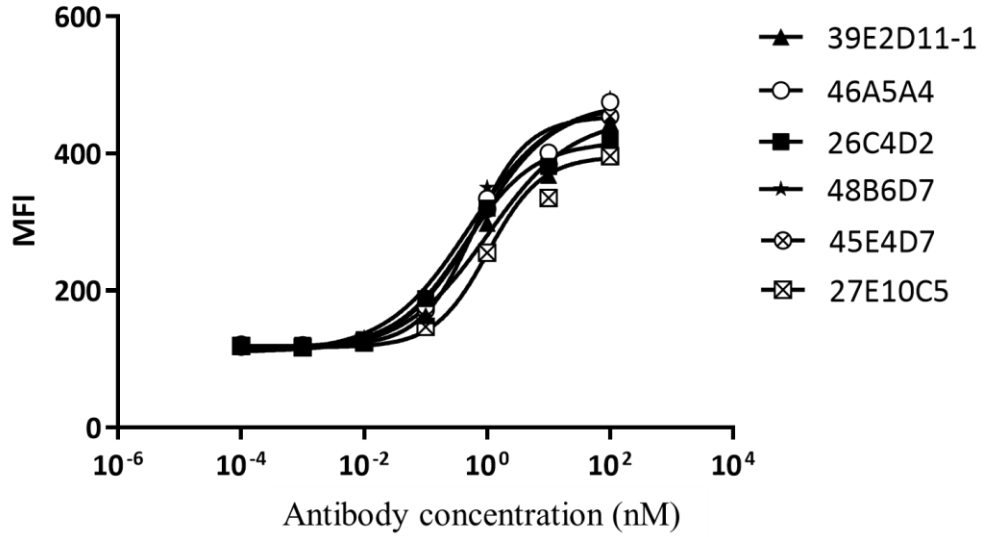
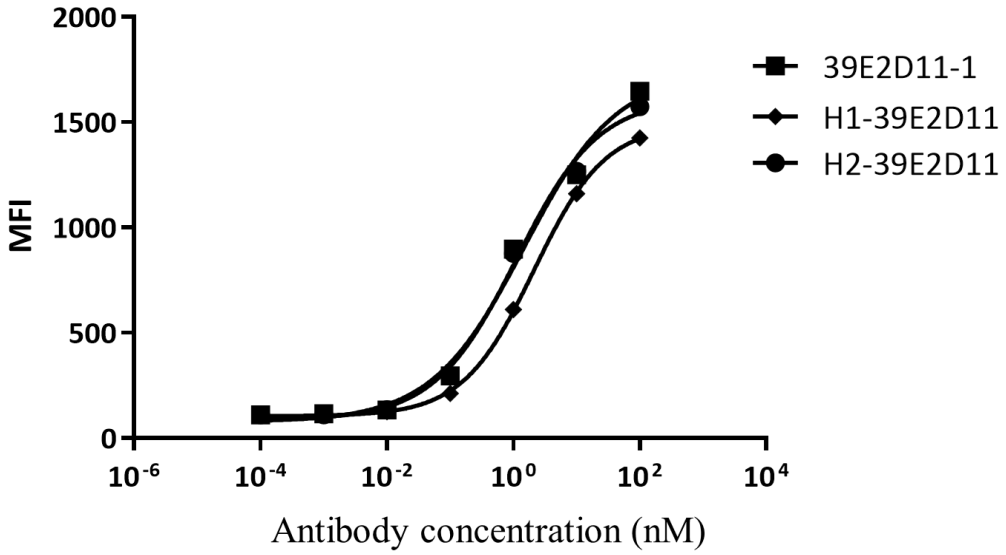
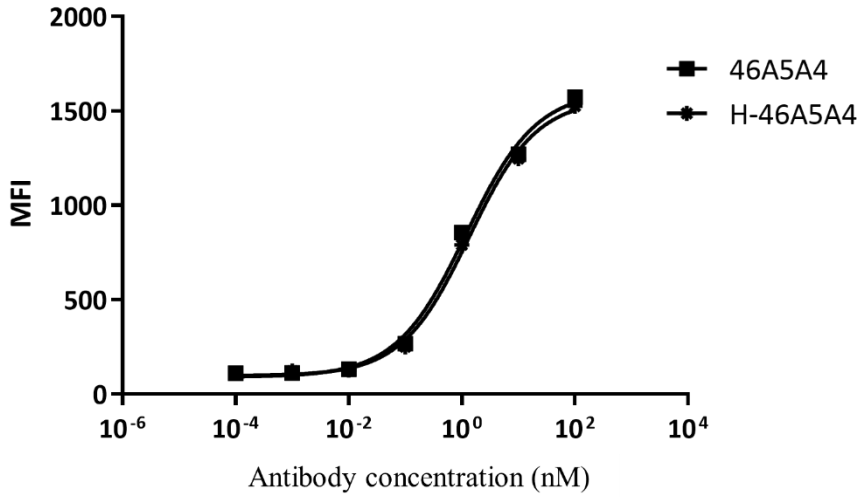

600
400
200
0
MFI
10^{-6}
10^{-4}
10^{-2}
10^{0}
10^{2}
10^{4}
Antibody concentration (nM)
39E2D11-1
46A5A4
26C4D2
48B6D7
45E4D7
27E10C5

FIG. 5B


2000
1500
1000
500
0
MFI
39E2D11-1
H1-39E2D11
H2-39E2D11
10-6
10-4
10-2
100
102
104
Antibody concentration (nM)


2000
1500
1000
500
0
MFI
46A5A4
H-46A5A4
10-6
10-4
10-2
100
102
104
Antibody concentration (nM)

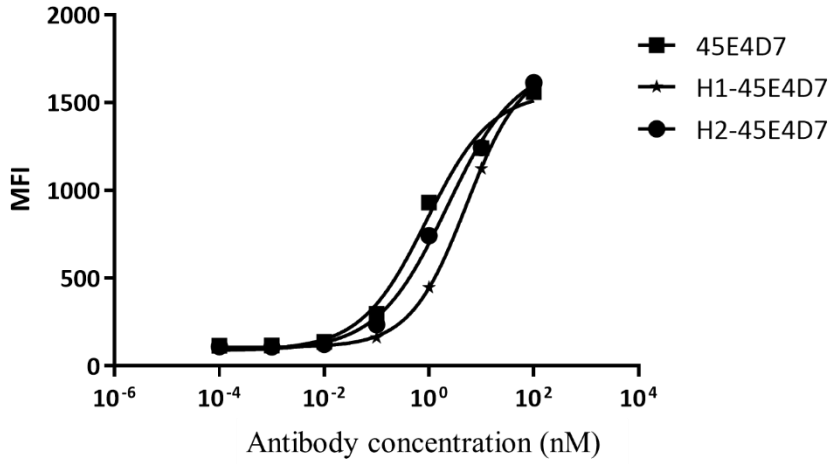

2000
1500
1000
500
0
MFI
45E4D7
H1-45E4D7
H2-45E4D7
10-6
10-4
10-2
100
102
104
Antibody concentration (nM)

FIG. 6

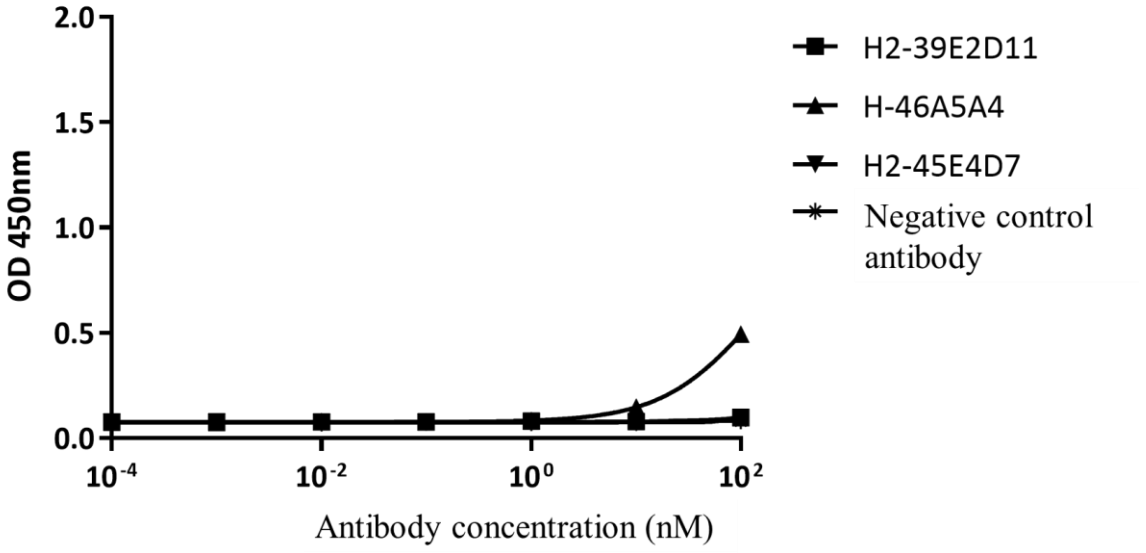

2.0
1.5
1.0
0.5
0.0
OD 450nm
10-4
10-2
100
102
Antibody concentration (nM)
H2-39E2D11
H-46A5A4
H2-45E4D7
Negative control antibody

FIG. 7A

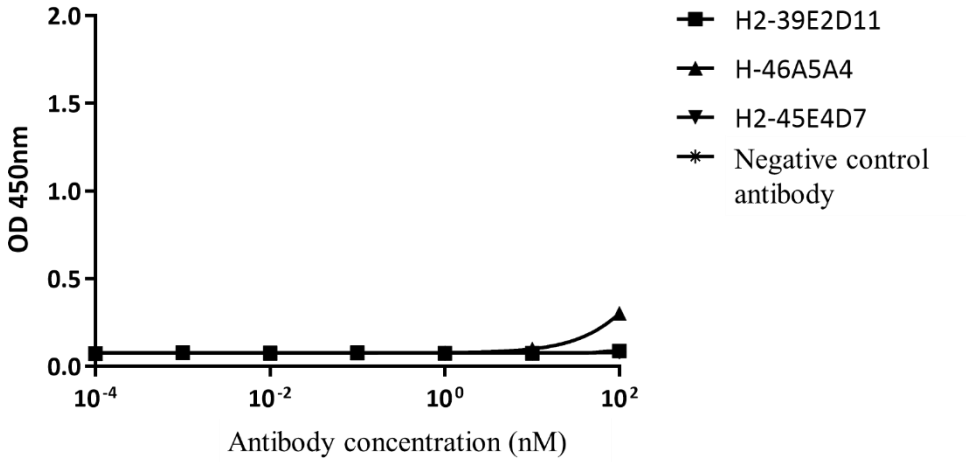

2.0
1.5
1.0
0.5
0.0
OD 450nm
10-4
10-2
100
102
Antibody concentration (nM)
H2-39E2D11
H-46A5A4
H2-45E4D7
Negative control antibody

FIG. 7B

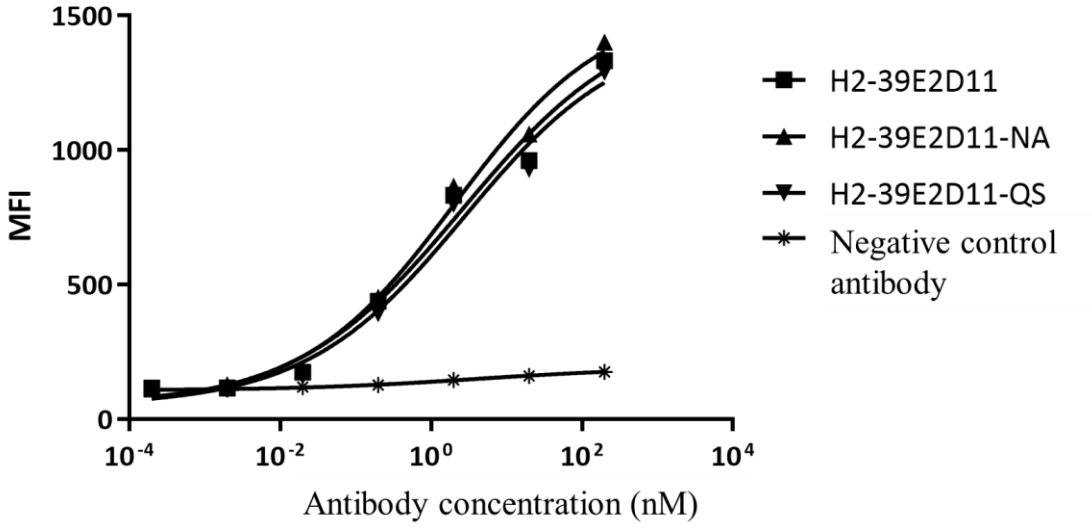

1500
1000
500
0
MFI
10^{-4}
10^{-2}
10^{0}
10^{2}
10^{4}
Antibody concentration (nM)
H2-39E2D11
H2-39E2D11-NA
H2-39E2D11-QS
Negative control antibody

FIG. 8

ÐòÁÐ±í

<110> ÉÏº£ÆëÂ³ÖÆÒ©ÑÐ¾¿ÖÐÐÄÓÐÏÞ¹«Ë¾

<120> Õë¶ÔDLL3µÄ¼áºÏ·Ö×Ó¼°ÆäÓ¦ÓÃ

<130> MTP220167

<150> CN202110499247.2
<151> 2021-05-08

<150> CN202210460557.8
<151> 2022-04-24

<160> 114

<170> SIPOSequenceListing 1.0

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<211> 127
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 1
Asp Val Gln Leu Val Glu Ser Gly Gly Gly Ser Val Gln Ala Gly Gly
1   5   10   15
Ser Leu Lys Leu Ser Cys Lys Ser Pro Thr Tyr Thr Ile Ser Ser Gly
            20   25   30
Tyr Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
        35   40   45
Ala Ala Ile Tyr Ile Gly Gly Ser Thr Thr Leu Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Ala Asp Asn Ala Glu Lys Thr Val Tyr
65   70   75   80
Leu Gln Met Asn Thr Leu Lys Pro Glu Asp Ser Ala Met Tyr Tyr Cys
                85   90   95
Ala Ala Gln Leu Arg Pro Asn Ser Ala Tyr His Pro Leu Asp Gly Arg
            100   105   110
Lys Tyr Asn Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
        115   120   125

<210> 2
<211> 116
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄµ°°×

<400> 2
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Glu
1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Gly Ser Gly Phe Ala Phe Ser Ser Tyr
            20   25   30
Asp Met His Trp Val Arg Gln Ala Pro Gly Lys Asp Phe Glu Trp Val
        35   40   45
Ser Ser Ile Ser Arg Asp Gly Arg Gly Pro Arg Tyr Ala Asp Phe Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Lys Asp Asn Gly Arg Asn Met Leu Tyr
65   70   75   80
Leu Gln Leu Asn Ser Leu Glu Ile Glu Asp Thr Ala Met Tyr Tyr Cys
                85   90   95
Ser Lys Gly Tyr Pro Ile Met Gly Gly Thr Thr Gln Gly Thr Gln Val
            100   105   110
Thr Val Ser Ser
        115

<210> 3
<211> 118
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄµ°°×

<400> 3
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Ser Val Gln Ala Gly Gly
1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Asp Ile Tyr Ser Ser Ser
            20   25   30
Tyr Val Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
        35   40   45
Ala Ile Ile Tyr Thr Ser Gly Asp Ser Thr Tyr Tyr Ala Asn Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Gln Asp Lys Ala Lys Lys Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Met Tyr Tyr Cys
                85   90   95
Ala Ala Arg Phe Ala Ile Asp Asn Ser Asn Tyr Trp Gly Gln Gly Thr
            100   105   110
Gln Val Thr Val Ser Ser
        115

<210> 4

<211> 124
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 4
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Ser Val Gln Ala Gly Gly
1   5   10   15
Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Asp Thr Tyr Arg Ser Tyr
            20   25   30
Cys Met Gly Trp Phe Arg Lys Ala Pro Gly Lys Glu Arg Glu Gly Val
        35   40   45
Ala Asp Ile Val Ser Asp Gly Ser Thr Ser Tyr Ala Asp Ser Val Lys
    50   55   60
Gly Arg Phe Thr Ile Ser Lys Asp Asn Ala Lys Asn Thr Leu Tyr Leu
65   70   75   80
Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Met Tyr Tyr Cys Ala
                85   90   95
Val Asp Arg Gly Gly Ser Gly Gly Tyr Cys Tyr Thr Gly Arg Tyr Asp
            100   105   110
Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
        115   120

<210> 5
<211> 118
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 5
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Ser Val Gln Ala Gly Gly
1   5   10   15
Ser Leu Asn Leu Ser Cys Ala Thr Ser Gly Ser Thr Ala Ser Thr Thr
            20   25   30
Tyr Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Gly Arg Glu Gly Val
        35   40   45
Ala Ile Ile Tyr Thr Ala Arg Asp Asn Pro Trp Tyr Ala Asn Ser Val
    50   55   60
Lys Gly Arg Phe Ile Ile Ser Gln Asp Asn Ala Lys Lys Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Thr Leu Lys Pro Glu Asp Thr Ala Thr Tyr Tyr Cys
                85   90   95
Ala Ala Thr Leu Ala Asn Pro Thr Arg Thr Ala Trp Gly Gln Gly Thr
            100   105   110

Leu Val Thr Val Ser Ser
        115

<210> 6
<211> 5
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 6
Ser Gly Tyr Met Gly
1   5

<210> 7
<211> 18
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 7
Ala Ala Ile Tyr Ile Gly Gly Ser Thr Thr Leu Tyr Ala Asp Ser Val
1   5   10   15
Lys Gly

<210> 8
<211> 18
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 8
Gln Leu Arg Pro Asn Ser Ala Tyr His Pro Leu Asp Gly Arg Lys Tyr
1   5   10   15
Asn Tyr

<210> 9
<211> 5
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄµ°°×

<400> 9
Ser Tyr Asp Met His
1   5

<210> 10
<211> 18
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄµ°°×

<400> 10
Ser Ser Ile Ser Arg Asp Gly Arg Gly Pro Arg Tyr Ala Asp Phe Val
1   5   10   15
Lys Gly

<210> 11
<211> 7
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄµ°°×

<400> 11
Gly Tyr Pro Ile Met Gly Gly
1   5

<210> 12
<211> 5
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄµ°°×

<400> 12
Ser Ser Tyr Val Gly
1   5

<210> 13
<211> 18
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 13
Ala Ile Ile Tyr Thr Ser Gly Asp Ser Thr Tyr Tyr Ala Asn Ser Val
1   5   10   15
Lys Gly

<210> 14
<211> 9
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 14
Arg Phe Ala Ile Asp Asn Ser Asn Tyr
1   5

<210> 15
<211> 6
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 15
Arg Ser Tyr Cys Met Gly
1   5

<210> 16
<211> 17
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 16
Ala Asp Ile Val Ser Asp Gly Ser Thr Ser Tyr Ala Asp Ser Val Lys
1 5 10 15
Gly

<210> 17
<211> 16
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 17
Asp Arg Gly Gly Ser Gly Gly Tyr Cys Tyr Thr Gly Arg Tyr Asp Tyr
1 5 10 15

<210> 18
<211> 5
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 18
Thr Thr Tyr Met Gly
1 5

<210> 19
<211> 17
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 19
Ile Ile Tyr Thr Ala Arg Asp Asn Pro Trp Tyr Ala Asn Ser Val Lys
1 5 10 15
Gly

<210> 20
<211> 9
<212> PRT

<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 20
Thr Leu Ala Asn Pro Thr Arg Thr Ala
1   5

<210> 21
<211> 127
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 21
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Thr Tyr Thr Ile Ser Ser Gly
            20   25   30
Tyr Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
        35   40   45
Ala Ala Ile Tyr Ile Gly Gly Ser Thr Thr Leu Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ala Gln Leu Arg Pro Asn Ser Ala Tyr His Pro Leu Asp Gly Arg
            100   105   110
Lys Tyr Asn Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115   120   125

<210> 22
<211> 127
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 22
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1   5   10   15
Ser Leu Arg Leu Ser Cys Lys Ser Pro Thr Tyr Thr Ile Ser Ser Gly

```
            20                  25                  30
Tyr Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
        35                  40                  45
Ala Ala Ile Tyr Ile Gly Gly Ser Thr Thr Leu Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Ala Gln Leu Arg Pro Asn Ser Ala Tyr His Pro Leu Asp Gly Arg
            100                 105                 110
Lys Tyr Asn Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120                 125

<210>  23
<211>  116
<212>  PRT
<213>  ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223>  ºÏ³ÉµÄµ°°×


<400>  23
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ala Phe Ser Ser Tyr
            20                  25                  30
Asp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Ser Ile Ser Arg Asp Gly Arg Gly Pro Arg Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ser Lys Gly Tyr Pro Ile Met Gly Gly Thr Thr Gln Gly Thr Leu Val
            100                 105                 110
Thr Val Ser Ser
        115

<210>  24
<211>  116
<212>  PRT
<213>  ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223>  ºÏ³ÉµÄµ°°×
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<400> 24
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ala Phe Ser Ser Tyr
            20   25   30
Asp Met His Trp Val Arg Gln Ala Pro Gly Lys Asp Phe Glu Trp Val
        35   40   45
Ser Ser Ile Ser Arg Asp Gly Arg Gly Pro Arg Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ser Lys Gly Tyr Pro Ile Met Gly Gly Thr Thr Gln Gly Thr Leu Val
            100   105   110
Thr Val Ser Ser
        115

<210> 25
<211> 118
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄµ°°×

<400> 25
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Asp Ile Tyr Ser Ser Ser
            20   25   30
Tyr Val Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
        35   40   45
Ala Ile Ile Tyr Thr Ser Gly Asp Ser Thr Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ala Arg Phe Ala Ile Asp Asn Ser Asn Tyr Trp Gly Gln Gly Thr
            100   105   110
Leu Val Thr Val Ser Ser
        115

<210> 26
<211> 124
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄµ°°×

<400> 26
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Asp Thr Tyr Arg Ser Tyr
            20   25   30
Cys Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
        35   40   45
Ala Asp Ile Val Ser Asp Gly Ser Thr Ser Tyr Ala Asp Ser Val Lys
    50   55   60
Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65   70   75   80
Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                85   90   95
Val Asp Arg Gly Gly Ser Gly Gly Tyr Cys Tyr Thr Gly Arg Tyr Asp
            100   105   110
Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 27
<211> 118
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄµ°°×

<400> 27
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly
1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Thr Ala Ser Thr Thr
            20   25   30
Tyr Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Gly Arg Glu Gly Val
        35   40   45
Ala Ile Ile Tyr Thr Ala Arg Asp Asn Pro Trp Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ala Thr Leu Ala Asn Pro Thr Arg Thr Ala Trp Gly Gln Gly Thr
            100   105   110
Leu Val Thr Val Ser Ser
        115

<210> 28

<211> 127
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 28
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Thr Tyr Thr Ile Ser Ser Gly
            20   25   30
Tyr Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
        35   40   45
Ala Ala Ile Tyr Ile Gly Gly Ser Thr Thr Leu Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ala Gln Leu Arg Pro Asn Ala Ala Tyr His Pro Leu Asp Gly Arg
            100   105   110
Lys Tyr Asn Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115   120   125

<210> 29
<211> 127
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 29
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Thr Tyr Thr Ile Ser Ser Gly
            20   25   30
Tyr Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
        35   40   45
Ala Ala Ile Tyr Ile Gly Gly Ser Thr Thr Leu Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ala Gln Leu Arg Pro Gln Ser Ala Tyr His Pro Leu Asp Gly Arg
            100   105   110

Lys Tyr Asn Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115   120   125

<210> 30
<211> 118
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 30
Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala
1   5   10   15
Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Ser Tyr
            20   25   30
Trp Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
        35   40   45
Gly Met Ile His Pro Thr Leu Gly Asp Thr Asn Tyr Asn Glu Lys Phe
    50   55   60
Lys Ser Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65   70   75   80
Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85   90   95
Ala Arg Leu Gly Ser Leu Ser Met Met Asp Tyr Trp Gly Gln Gly Thr
            100   105   110
Ser Val Thr Val Ser Ser
        115

<210> 31
<211> 107
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 31
Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
1   5   10   15
Asp Arg Val Thr Ile Ser Cys Ser Ala Ser Gln Gly Ile Ser Asn Tyr
            20   25   30
Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
        35   40   45
Tyr Tyr Thr Ser Ser Leu His Ser Gly Val Pro Ala Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Pro
65   70   75   80

Glu Asp Ile Ala Ile Tyr Tyr Cys Gln Gln Tyr Ser Lys Phe Pro Tyr
                85   90   95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100   105

<210> 32
<211> 122
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 32
Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Lys Pro Gly Ala
1   5   10   15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ile Ser Tyr
            20   25   30
Trp Ile Thr Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
        35   40   45
Gly Asp Ile Tyr Pro Gly Ser Gly Ser Thr Thr Asn Tyr Asn Glu Lys
    50   55   60
Phe Lys Ser Lys Ala Thr Leu Thr Val Asp Thr Ser Ser Ser Thr Ala
65   70   75   80
Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
                85   90   95
Cys Ala Arg Glu Thr Thr Val Gly Gly Ala Tyr Ala Met Asp Tyr Trp
            100   105   110
Gly Gln Gly Thr Ser Val Thr Val Ser Ser
        115   120

<210> 33
<211> 107
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 33
Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Val Thr Pro Gly
1   5   10   15
Asp Ser Val Ser Leu Ser Cys Arg Ala Ser Gln Ser Ile Asn Asn Asn
            20   25   30
Leu His Trp Tyr Gln Gln Lys Ser His Glu Ser Pro Arg Leu Leu Ile
        35   40   45
Lys Tyr Val Ser Gln Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
    50   55   60

```
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Val Glu Thr
65                  70                  75                  80
Glu Asp Phe Gly Met Tyr Phe Cys Gln Gln Thr Asn Ser Trp Pro Leu
                85                  90                  95
Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
            100                 105
```

<210> 34
<211> 121
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 34

```
Gln Val Gln Leu Lys Gln Ser Gly Pro Gly Leu Val Gln Pro Ser Gln
1               5                   10                  15
Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Ser Tyr
            20                  25                  30
Gly Val His Trp Val Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp Leu
        35                  40                  45
Gly Val Ile Trp Ser Gly Gly Ser Thr Asp Tyr Asn Ala Ala Phe Ile
    50                  55                  60
Ser Arg Leu Ser Ile Ser Lys Asp Asn Pro Lys Ser Gln Val Phe Phe
65                  70                  75                  80
Lys Met Asn Ser Leu Gln Ala Asp Asp Thr Ala Ile Tyr Tyr Cys Ala
                85                  90                  95
Arg Glu Asn Tyr Tyr Gly Asn Ser Leu Trp Phe Phe Asp Val Trp Gly
            100                 105                 110
Thr Gly Thr Thr Val Thr Val Ser Ser
        115                 120
```

<210> 35
<211> 113
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 35

```
Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Lys Pro Gly Ala
1               5                   10                  15
Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Gln
            20                  25                  30
Trp Met Asn Trp Val Lys Gln Arg Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45
```

```
Gly Gln Ile Tyr Pro Gly Asn Gly Asp Thr Asn Tyr Asn Gly Lys Phe
    50                  55                  60
Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80
Ile Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
                85                  90                  95
Ala Arg Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
            100                 105                 110
Ala
```

<210> 36
<211> 107
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 36

```
Asp Ile Val Leu Thr Gln Ser Pro Val Thr Leu Ser Val Thr Pro Gly
1               5                   10                  15
Asp Ser Val Ser Leu Ser Cys Arg Ala Ser Gln Ser Val Arg Asn Asn
            20                  25                  30
Leu His Trp Tyr Gln Gln Lys Ser His Glu Ser Pro Arg Leu Leu Ile
        35                  40                  45
Lys Tyr Val Ser Gln Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Ser Ile Asn Ser Val Glu Thr
65                  70                  75                  80
Glu Asp Phe Gly Val Tyr Phe Cys Gln Gln Ser Asn Ser Trp Pro Leu
                85                  90                  95
Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
            100                 105
```

<210> 37
<211> 116
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 37

```
Gln Val Gln Leu Gln Gln Ser Asp Ala Glu Leu Val Lys Pro Gly Ala
1               5                   10                  15
Ser Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Asp His
            20                  25                  30
```

```
Thr Ile His Trp Met Lys Gln Arg Pro Glu Gln Gly Leu Glu Trp Ile
        35                  40                  45
Gly Tyr Ile Tyr Pro Arg Asp Gly Tyr Thr Met Tyr Asn Glu Lys Phe
    50                  55                  60
Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80
Met Gln Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val His Phe Cys
                85                  90                  95
Ala Arg Ala Phe His Ala Leu Asp Tyr Trp Gly Gln Gly Thr Ser Val
            100                 105                 110
Thr Val Ser Ser
        115
```

<210> 38
<211> 107
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 38

```
Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
1               5                   10                  15
Asp Arg Val Thr Phe Thr Cys Ser Ala Ser Gln Gly Ile Ser Asn Tyr
            20                  25                  30
Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Ile Lys Leu Leu Ile
        35                  40                  45
Tyr Tyr Thr Ser Ser Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Pro
65                  70                  75                  80
Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Lys Leu Pro Tyr
                85                  90                  95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105
```

<210> 39
<211> 116
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 39

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15
```

```
Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20                  25                  30
Gly Met His Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
        35                  40                  45
Ala Tyr Ile Ser Ser Gly Ser Ser Thr Ile Tyr Tyr Ala Asp Thr Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Phe
65                  70                  75                  80
Leu Gln Met Thr Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95
Ala Arg Asn Ser Arg Gly Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val
            100                 105                 110
Thr Val Ser Ala
        115
```

<210> 40
<211> 106
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 40

```
Asp Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
1               5                   10                  15
Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
            20                  25                  30
Tyr Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Arg Leu Leu Ile Tyr
        35                  40                  45
Asp Thr Ser Asn Leu Ala Ser Gly Val Pro Val Arg Phe Ser Gly Ser
    50                  55                  60
Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Met Glu Ala Glu
65                  70                  75                  80
Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Tyr Pro Arg Thr
                85                  90                  95
Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105
```

<210> 41
<211> 106
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 41

```
Asp Ile Val Leu Ile Gln Ser Pro Thr Ile Met Ser Ala Ser Pro Gly
1               5                  10                  15
Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Ser Met
            20                  25                  30
His Trp Tyr Gln Gln Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile Tyr
        35                  40                  45
Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
    50                  55                  60
Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Thr Met Glu Ala Glu
65                  70                  75                  80
Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Asn Ser Tyr His Leu Thr
                85                  90                  95
Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
            100                 105
```

<210> 42
<211> 118
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 42

```
Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Thr
1               5                  10                  15
Ser Val Lys Leu Ser Cys Glu Ala Ser Gly Tyr Thr Phe Ser Asn Tyr
            20                  25                  30
Trp Met Gln Trp Val Arg Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45
Gly Met Ile Leu Pro Asn Ser Asp Ile Thr Asn Tyr Asn Glu Asn Phe
    50                  55                  60
Gln Thr Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80
Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Gln Ala Arg Tyr Ser Ala Met Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110
Ser Val Thr Val Ser Ser
        115
```

<210> 43
<211> 107
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 43
Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Val Ser Leu Gly
1   5   10   15
Asp Arg Val Thr Ile Asn Cys Ser Ala Ser Gln Gly Ile Ser Asn Tyr
            20   25   30
Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
        35   40   45
Tyr Tyr Thr Ser Asn Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Pro
65   70   75   80
Glu Asp Ile Ala Thr Tyr Tyr Cys Gln His Tyr Ser Lys Phe Pro Tyr
                85   90   95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100   105

<210> 44
<211> 121
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄµ°°×

<400> 44
Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Thr
1   5   10   15
Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser His
            20   25   30
Trp Ile Thr Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
        35   40   45
Gly Asp Ile Tyr Pro Ile Ser Gly Ser Thr Asn Asn Asn Glu Lys Phe
    50   55   60
Arg Asn Lys Ala Thr Leu Thr Val Asp Thr Ser Ser Ser Thr Ala Tyr
65   70   75   80
Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
                85   90   95
Ala Lys Ile Ile Thr Val Gly Gly Ala Tyr Val Met Asp Tyr Trp Gly
            100   105   110
Gln Gly Thr Ser Val Thr Val Ser Ser
        115   120

<210> 45
<211> 113
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>

<223> ºÏ³ÉµÄµ°°×

<400> 45
Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ala Met Ser Val Gly
1   5   10   15
Gln Lys Val Thr Met Asn Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
            20   25   30
Ser His Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
        35   40   45
Ser Pro Lys Leu Leu Val Tyr Phe Ala Ser Thr Arg Glu Ser Gly Val
    50   55   60
Pro Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65   70   75   80
Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln
                85   90   95
His Tyr Ser Thr Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
            100   105   110
Lys

<210> 46
<211> 122
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄµ°°×

<400> 46
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ile Ser Tyr
            20   25   30
Trp Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45
Gly Asp Ile Tyr Pro Gly Ser Gly Ser Thr Thr Asn Tyr Asn Glu Lys
    50   55   60
Phe Lys Ser Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val
65   70   75   80
Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr
                85   90   95
Cys Ala Arg Glu Thr Thr Val Gly Gly Ala Tyr Ala Met Asp Tyr Trp
            100   105   110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 47
<211> 107

<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 47
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1   5   10   15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Asn Asn Asn
            20   25   30
Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35   40   45
Tyr Tyr Val Ser Gln Ser Ile Ser Gly Ile Pro Ala Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65   70   75   80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Thr Asn Ser Trp Pro Leu
                85   90   95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100   105

<210> 48
<211> 107
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 48
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1   5   10   15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Asn Asn Asn
            20   25   30
Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35   40   45
Lys Tyr Val Ser Gln Ser Ile Ser Gly Ile Pro Ala Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65   70   75   80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Thr Asn Ser Trp Pro Leu
                85   90   95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100   105

<210> 49
<211> 116

<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 49
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp His
            20   25   30
Thr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45
Gly Tyr Ile Tyr Pro Arg Asp Gly Tyr Thr Met Tyr Asn Glu Lys Phe
    50   55   60
Lys Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65   70   75   80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Arg Ala Phe His Ala Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val
            100   105   110
Thr Val Ser Ser
        115

<210> 50
<211> 107
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 50
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15
Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Gln Gly Ile Ser Asn Tyr
            20   25   30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45
Tyr Tyr Thr Ser Ser Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65   70   75   80
Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Lys Leu Pro Tyr
                85   90   95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100   105

<210> 51
<211> 121
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 51
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser His
            20   25   30
Trp Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45
Gly Asp Ile Tyr Pro Ile Ser Gly Ser Thr Asn Asn Asn Glu Lys Phe
    50   55   60
Arg Asn Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65   70   75   80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Lys Ile Ile Thr Val Gly Gly Ala Tyr Val Met Asp Tyr Trp Gly
            100   105   110
Gln Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 52
<211> 107
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 52
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1   5   10   15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Arg Asn Asn
            20   25   30
Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35   40   45
Tyr Tyr Val Ser Gln Ser Ile Ser Gly Ile Pro Ala Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65   70   75   80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ser Asn Ser Trp Pro Leu
                85   90   95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys

100 105

<210> 53
<211> 107
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄµ°×

<400> 53
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Arg Asn Asn
20 25 30
Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Lys Tyr Val Ser Gln Ser Ile Ser Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ser Asn Ser Trp Pro Leu
85 90 95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 54
<211> 107
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄµ°×

<400> 54
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Asn Asn Asn
20 25 30
Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Lys Tyr Val Ser Gln Ser Ile Ser Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Thr Asn Ala Trp Pro Leu
85 90 95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys

100 105

<210> 55
<211> 107
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄµ°×

<400> 55
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Asn Asn Asn
20 25 30
Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Lys Tyr Val Ser Gln Ser Ile Ser Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Thr Gln Ser Trp Pro Leu
85 90 95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 56
<211> 107
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄµ°×

<400> 56
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Asn Asn Asn
20 25 30
Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Lys Tyr Val Ser Gln Ser Ile Ser Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Thr Ala Ser Trp Pro Leu
85 90 95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys

100 105

<210> 57
<211> 5
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 57
Ser Tyr Trp Met His
1 5

<210> 58
<211> 17
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 58
Met Ile His Pro Thr Leu Gly Asp Thr Asn Tyr Asn Glu Lys Phe Lys
1 5 10 15
Ser

<210> 59
<211> 9
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 59
Leu Gly Ser Leu Ser Met Met Asp Tyr
1 5

<210> 60
<211> 11
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 60
Ser Ala Ser Gln Gly Ile Ser Asn Tyr Leu Asn
1   5   10

<210> 61
<211> 7
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 61
Tyr Thr Ser Ser Leu His Ser
1   5

<210> 62
<211> 9
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 62
Gln Gln Tyr Ser Lys Phe Pro Tyr Thr
1   5

<210> 63
<211> 5
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 63
Ser Tyr Trp Ile Thr
1   5

<210> 64
<211> 18
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄµ°°×

<400> 64
Asp Ile Tyr Pro Gly Ser Gly Ser Thr Thr Asn Tyr Asn Glu Lys Phe
1   5   10   15
Lys Ser

<210> 65
<211> 12
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄµ°°×

<400> 65
Glu Thr Thr Val Gly Gly Ala Tyr Ala Met Asp Tyr
1   5   10

<210> 66
<211> 11
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄµ°°×

<400> 66
Arg Ala Ser Gln Ser Ile Asn Asn Asn Leu His
1   5   10

<210> 67
<211> 7
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄµ°°×

<400> 67
Tyr Val Ser Gln Ser Ile Ser
1   5

<210> 68

<211> 9
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 68
Gln Gln Thr Asn Ser Trp Pro Leu Thr
1   5

<210> 69
<211> 5
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 69
Ser Tyr Gly Val His
1   5

<210> 70
<211> 16
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 70
Val Ile Trp Ser Gly Gly Ser Thr Asp Tyr Asn Ala Ala Phe Ile Ser
1   5   10   15

<210> 71
<211> 13
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 71
Glu Asn Tyr Tyr Gly Asn Ser Leu Trp Phe Phe Asp Val
1   5   10

<210> 72
<211> 5
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 72
Ser Gln Trp Met Asn
1   5

<210> 73
<211> 17
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 73
Gln Ile Tyr Pro Gly Asn Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys
1   5   10   15
Gly

<210> 74
<211> 4
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 74
Trp Phe Ala Tyr
1

<210> 75
<211> 11
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 75
Arg Ala Ser Gln Ser Val Arg Asn Asn Leu His
1   5   10

<210> 76
<211> 7
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 76
Tyr Val Ser Gln Ser Ile Ser
1   5

<210> 77
<211> 9
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 77
Gln Gln Ser Asn Ser Trp Pro Leu Thr
1   5

<210> 78
<211> 5
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 78
Asp His Thr Ile His
1   5

<210> 79
<211> 17
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>

<223> ºÏ³ÉµÄµ°°×

<400> 79
Tyr Ile Tyr Pro Arg Asp Gly Tyr Thr Met Tyr Asn Glu Lys Phe Lys
1 5 10 15
Gly

<210> 80
<211> 7
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄµ°°×

<400> 80
Ala Phe His Ala Leu Asp Tyr
1 5

<210> 81
<211> 11
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄµ°°×

<400> 81
Ser Ala Ser Gln Gly Ile Ser Asn Tyr Leu Asn
1 5 10

<210> 82
<211> 7
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄµ°°×

<400> 82
Tyr Thr Ser Ser Leu His Ser
1 5

<210> 83
<211> 9

<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 83
Gln Gln Tyr Ser Lys Leu Pro Tyr Thr
1   5

<210> 84
<211> 5
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 84
Asp Tyr Gly Met His
1   5

<210> 85
<211> 17
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 85
Tyr Ile Ser Ser Gly Ser Ser Thr Ile Tyr Tyr Ala Asp Thr Val Lys
1   5   10   15
Gly

<210> 86
<211> 7
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 86
Asn Ser Arg Gly Phe Ala Tyr

1 5

<210> 87
<211> 10
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 87
Ser Ala Ser Ser Ser Val Ser Tyr Met Tyr
1 5 10

<210> 88
<211> 7
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 88
Asp Thr Ser Asn Leu Ala Ser
1 5

<210> 89
<211> 9
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 89
Gln Gln Trp Ser Ser Tyr Pro Arg Thr
1 5

<210> 90
<211> 10
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 90
Ser Ala Ser Ser Ser Val Ser Ser Met His
1   5   10

<210> 91
<211> 7
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 91
Asp Thr Ser Lys Leu Ala Ser
1   5

<210> 92
<211> 9
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 92
Gln Gln Trp Asn Ser Tyr His Leu Thr
1   5

<210> 93
<211> 5
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 93
Asn Tyr Trp Met Gln
1   5

<210> 94
<211> 17
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 94
Met Ile Leu Pro Asn Ser Asp Ile Thr Asn Tyr Asn Glu Asn Phe Gln
1 5 10 15
Thr

<210> 95
<211> 9
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 95
Gln Ala Arg Tyr Ser Ala Met Asp Tyr
1 5

<210> 96
<211> 11
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 96
Ser Ala Ser Gln Gly Ile Ser Asn Tyr Leu Asn
1 5 10

<210> 97
<211> 7
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 97
Tyr Thr Ser Asn Leu His Ser
1 5

<210> 98
<211> 9
<212> PRT

<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 98
Gln His Tyr Ser Lys Phe Pro Tyr Thr
1 5

<210> 99
<211> 5
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 99
Ser His Trp Ile Thr
1 5

<210> 100
<211> 17
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 100
Asp Ile Tyr Pro Ile Ser Gly Ser Thr Asn Asn Asn Glu Lys Phe Arg
1 5 10 15
Asn

<210> 101
<211> 12
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 101
Ile Ile Thr Val Gly Gly Ala Tyr Val Met Asp Tyr
1 5 10

<210> 102
<211> 17
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 102
Lys Ser Ser Gln Ser Leu Leu Asn Ser Ser His Gln Lys Asn Tyr Leu
1   5   10   15
Ala

<210> 103
<211> 7
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 103
Phe Ala Ser Thr Arg Glu Ser
1   5

<210> 104
<211> 9
<212> PRT
<213> ÈË¹¤ÐòÁÐ(Artificial Sequence)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 104
Gln Gln His Tyr Ser Thr Pro Trp Thr
1   5

<210> 105
<211> 618
<212> PRT
<213> ÈËÀà(Homo sapiens)

<220>
<223> ºÏ³ÉµÄ°°×

<400> 105
Met Val Ser Pro Arg Met Ser Gly Leu Leu Ser Gln Thr Val Ile Leu
1   5   10   15
Ala Leu Ile Phe Leu Pro Gln Thr Arg Pro Ala Gly Val Phe Glu Leu
            20   25   30
Gln Ile His Ser Phe Gly Pro Gly Pro Gly Pro Gly Ala Pro Arg Ser
        35   40   45
Pro Cys Ser Ala Arg Leu Pro Cys Arg Leu Phe Phe Arg Val Cys Leu
    50   55   60
Lys Pro Gly Leu Ser Glu Glu Ala Ala Glu Ser Pro Cys Ala Leu Gly
65   70   75   80
Ala Ala Leu Ser Ala Arg Gly Pro Val Tyr Thr Glu Gln Pro Gly Ala
                85   90   95
Pro Ala Pro Asp Leu Pro Leu Pro Asp Gly Leu Leu Gln Val Pro Phe
            100   105   110
Arg Asp Ala Trp Pro Gly Thr Phe Ser Phe Ile Ile Glu Thr Trp Arg
        115   120   125
Glu Glu Leu Gly Asp Gln Ile Gly Gly Pro Ala Trp Ser Leu Leu Ala
    130   135   140
Arg Val Ala Gly Arg Arg Arg Leu Ala Ala Gly Gly Pro Trp Ala Arg
145   150   155   160
Asp Ile Gln Arg Ala Gly Ala Trp Glu Leu Arg Phe Ser Tyr Arg Ala
                165   170   175
Arg Cys Glu Pro Pro Ala Val Gly Thr Ala Cys Thr Arg Leu Cys Arg
            180   185   190
Pro Arg Ser Ala Pro Ser Arg Cys Gly Pro Gly Leu Arg Pro Cys Ala
        195   200   205
Pro Leu Glu Asp Glu Cys Glu Ala Pro Leu Val Cys Arg Ala Gly Cys
    210   215   220
Ser Pro Glu His Gly Phe Cys Glu Gln Pro Gly Glu Cys Arg Cys Leu
225   230   235   240
Glu Gly Trp Thr Gly Pro Leu Cys Thr Val Pro Val Ser Thr Ser Ser
                245   250   255
Cys Leu Ser Pro Arg Gly Pro Ser Ser Ala Thr Thr Gly Cys Leu Val
            260   265   270
Pro Gly Pro Gly Pro Cys Asp Gly Asn Pro Cys Ala Asn Gly Gly Ser
        275   280   285
Cys Ser Glu Thr Pro Arg Ser Phe Glu Cys Thr Cys Pro Arg Gly Phe
    290   295   300
Tyr Gly Leu Arg Cys Glu Val Ser Gly Val Thr Cys Ala Asp Gly Pro
305   310   315   320
Cys Phe Asn Gly Gly Leu Cys Val Gly Gly Ala Asp Pro Asp Ser Ala
                325   330   335
Tyr Ile Cys His Cys Pro Pro Gly Phe Gln Gly Ser Asn Cys Glu Lys
            340   345   350
Arg Val Asp Arg Cys Ser Leu Gln Pro Cys Arg Asn Gly Gly Leu Cys
        355   360   365
Leu Asp Leu Gly His Ala Leu Arg Cys Arg Cys Arg Ala Gly Phe Ala
    370   375   380

```
Gly Pro Arg Cys Glu His Asp Leu Asp Asp Cys Ala Gly Arg Ala Cys
385                 390                 395                 400
Ala Asn Gly Gly Thr Cys Val Glu Gly Gly Gly Ala His Arg Cys Ser
                405                 410                 415
Cys Ala Leu Gly Phe Gly Gly Arg Asp Cys Arg Glu Arg Ala Asp Pro
            420                 425                 430
Cys Ala Ala Arg Pro Cys Ala His Gly Gly Arg Cys Tyr Ala His Phe
        435                 440                 445
Ser Gly Leu Val Cys Ala Cys Ala Pro Gly Tyr Met Gly Ala Arg Cys
    450                 455                 460
Glu Phe Pro Val His Pro Asp Gly Ala Ser Ala Leu Pro Ala Ala Pro
465                 470                 475                 480
Pro Gly Leu Arg Pro Gly Asp Pro Gln Arg Tyr Leu Leu Pro Pro Ala
                485                 490                 495
Leu Gly Leu Leu Val Ala Ala Gly Val Ala Gly Ala Ala Leu Leu Leu
            500                 505                 510
Val His Val Arg Arg Arg Gly His Ser Gln Asp Ala Gly Ser Arg Leu
        515                 520                 525
Leu Ala Gly Thr Pro Glu Pro Ser Val His Ala Leu Pro Asp Ala Leu
    530                 535                 540
Asn Asn Leu Arg Thr Gln Glu Gly Ser Gly Asp Gly Pro Ser Ser Ser
545                 550                 555                 560
Val Asp Trp Asn Arg Pro Glu Asp Val Asp Pro Gln Gly Ile Tyr Val
                565                 570                 575
Ile Ser Ala Pro Ser Ile Tyr Ala Arg Glu Val Ala Thr Pro Leu Phe
            580                 585                 590
Pro Pro Leu His Thr Gly Arg Ala Gly Gln Arg Gln His Leu Leu Phe
        595                 600                 605
Pro Tyr Pro Ser Ser Ile Leu Ser Val Lys
    610                 615
```

<210> 106
<211> 618
<212> PRT
<213> Ê³Ð·ºï(Macaca fascicularis)

<220>
<223> ºÏ³ÉµÄµ°°×

<400> 106

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Met Val Ser Pro Arg Met Ser Arg Leu Leu Ser Gln Thr Val Ile Leu
1               5                   10                  15
Ala Leu Ile Phe Ile Pro Gln Ala Arg Pro Ala Gly Val Phe Glu Leu
            20                  25                  30
Gln Ile His Ser Phe Gly Pro Gly Pro Gly Pro Gly Ala Pro Arg Ser
        35                  40                  45
Pro Cys Ser Ala Arg Gly Pro Cys Arg Leu Phe Phe Arg Val Cys Leu
    50                  55                  60
Lys Pro Gly Leu Ser Glu Glu Ala Ala Glu Ser Pro Cys Ala Leu Gly
```

```
65                  70                  75                  80
Ala Ala Leu Ser Ala Arg Gly Pro Val Tyr Thr Glu Gln Pro Glu Ala
                85                  90                  95
Pro Ala Pro Asp Leu Pro Leu Pro Asn Gly Leu Leu Gln Val Pro Phe
            100                 105                 110
Arg Asp Ala Trp Pro Gly Thr Phe Ser Leu Ile Ile Glu Thr Trp Arg
        115                 120                 125
Glu Glu Leu Gly Asp Gln Ile Gly Gly Pro Ala Trp Ser Leu Leu Ala
    130                 135                 140
Arg Val Thr Arg Arg Arg Arg Leu Ala Ala Gly Gly Pro Trp Ala Arg
145                 150                 155                 160
Asp Ile Gln Arg Ala Gly Ala Trp Glu Leu Arg Phe Ser Tyr Arg Ala
                165                 170                 175
Arg Cys Glu Leu Pro Ala Val Gly Thr Ala Cys Thr Arg Leu Cys Arg
            180                 185                 190
Pro Arg Ser Ala Pro Ser Arg Cys Gly Pro Gly Leu Arg Pro Cys Ala
        195                 200                 205
Pro Leu Glu Asp Glu Cys Glu Ala Pro Pro Val Cys Arg Ala Gly Cys
    210                 215                 220
Ser Leu Glu His Gly Phe Cys Glu Gln Pro Gly Glu Cys Arg Cys Leu
225                 230                 235                 240
Glu Gly Trp Thr Gly Pro Leu Cys Met Val Pro Val Ser Thr Ser Ser
                245                 250                 255
Cys Leu Gly Leu Arg Gly Pro Ser Ser Thr Thr Thr Gly Cys Leu Val
            260                 265                 270
Pro Gly Pro Gly Pro Cys Asp Gly Asn Pro Cys Ala Asn Gly Gly Ser
        275                 280                 285
Cys Ser Glu Thr Pro Gly Ser Phe Glu Cys Thr Cys Pro Arg Gly Phe
    290                 295                 300
Tyr Gly Leu Arg Cys Glu Val Ser Gly Val Thr Cys Ala Asp Gly Pro
305                 310                 315                 320
Cys Phe Asn Gly Gly Leu Cys Val Gly Gly Ala Asp Pro Asp Ser Ala
                325                 330                 335
Tyr Ile Cys His Cys Pro Pro Gly Phe Gln Gly Ser Asn Cys Glu Lys
            340                 345                 350
Arg Val Asp Arg Cys Ser Leu Gln Pro Cys Arg Asn Gly Gly Leu Cys
        355                 360                 365
Leu Asp Leu Gly His Ala Leu Arg Cys Arg Cys Arg Ala Gly Phe Ala
    370                 375                 380
Gly Pro Arg Cys Glu His Asp Leu Asp Asp Cys Ala Gly Arg Ala Cys
385                 390                 395                 400
Ala Asn Gly Gly Thr Cys Val Glu Gly Gly Gly Ala His Arg Cys Ser
                405                 410                 415
Cys Ala Leu Gly Phe Gly Gly Arg Asn Cys Arg Glu Arg Ala Asp Pro
            420                 425                 430
Cys Ala Ala Arg Pro Cys Ala His Gly Gly Arg Cys Tyr Ala His Phe
        435                 440                 445
Ser Gly Leu Val Cys Ala Cys Ala Pro Gly Tyr Met Gly Ala Arg Cys
    450                 455                 460
Glu Phe Pro Val His Pro Asp Gly Val Ser Ala Leu Pro Ala Ala Pro
```

```
465                 470                 475                 480
Pro Gly Leu Arg Pro Gly Asp Pro Gln Arg Tyr Leu Leu Pro Pro Ala
                485                 490                 495
Leu Gly Leu Leu Val Ala Ala Gly Val Ala Gly Ala Ala Leu Leu Leu
            500                 505                 510
Val His Val Arg Arg Arg Gly His Ala Gln Asp Ala Gly Ser Arg Leu
        515                 520                 525
Leu Ala Gly Thr Pro Glu Pro Ser Val His Ala Leu Pro Asp Ala Leu
    530                 535                 540
Asn Asn Leu Arg Thr Gln Glu Gly Pro Gly Asp Val Pro Ser Ser Ser
545                 550                 555                 560
Val Asp Trp Asn Arg Pro Glu Asp Val Asp Ser Arg Gly Ile Tyr Val
                565                 570                 575
Ile Ser Ala Pro Ser Ile Tyr Ala Arg Glu Val Ala Met Pro Leu Phe
            580                 585                 590
Pro Pro Leu His Thr Gly Arg Ala Gly Gln Arg Gln Asn Leu Leu Phe
        595                 600                 605
Pro Phe Pro Ser Ser Ile Leu Ser Val Lys
    610                 615

<210>  107
<211>  723
<212>  PRT
<213>  ÈËÀà(Homo sapiens)

<220>
<223>  ºÏ³ÉµÄµ°°×


<400>  107
Met Gly Ser Arg Cys Ala Leu Ala Leu Ala Val Leu Ser Ala Leu Leu
1               5                   10                  15
Cys Gln Val Trp Ser Ser Gly Val Phe Glu Leu Lys Leu Gln Glu Phe
            20                  25                  30
Val Asn Lys Lys Gly Leu Leu Gly Asn Arg Asn Cys Cys Arg Gly Gly
        35                  40                  45
Ala Gly Pro Pro Pro Cys Ala Cys Arg Thr Phe Phe Arg Val Cys Leu
    50                  55                  60
Lys His Tyr Gln Ala Ser Val Ser Pro Glu Pro Pro Cys Thr Tyr Gly
65                  70                  75                  80
Ser Ala Val Thr Pro Val Leu Gly Val Asp Ser Phe Ser Leu Pro Asp
                85                  90                  95
Gly Gly Gly Ala Asp Ser Ala Phe Ser Asn Pro Ile Arg Phe Pro Phe
            100                 105                 110
Gly Phe Thr Trp Pro Gly Thr Phe Ser Leu Ile Ile Glu Ala Leu His
        115                 120                 125
Thr Asp Ser Pro Asp Asp Leu Ala Thr Glu Asn Pro Glu Arg Leu Ile
    130                 135                 140
Ser Arg Leu Ala Thr Gln Arg His Leu Thr Val Gly Glu Glu Trp Ser
145                 150                 155                 160
```

```
Gln Asp Leu His Ser Ser Gly Arg Thr Asp Leu Lys Tyr Ser Tyr Arg
                165                 170                 175
Phe Val Cys Asp Glu His Tyr Tyr Gly Glu Gly Cys Ser Val Phe Cys
            180                 185                 190
Arg Pro Arg Asp Asp Ala Phe Gly His Phe Thr Cys Gly Glu Arg Gly
        195                 200                 205
Glu Lys Val Cys Asn Pro Gly Trp Lys Gly Pro Tyr Cys Thr Glu Pro
    210                 215                 220
Ile Cys Leu Pro Gly Cys Asp Glu Gln His Gly Phe Cys Asp Lys Pro
225                 230                 235                 240
Gly Glu Cys Lys Cys Arg Val Gly Trp Gln Gly Arg Tyr Cys Asp Glu
                245                 250                 255
Cys Ile Arg Tyr Pro Gly Cys Leu His Gly Thr Cys Gln Gln Pro Trp
            260                 265                 270
Gln Cys Asn Cys Gln Glu Gly Trp Gly Gly Leu Phe Cys Asn Gln Asp
        275                 280                 285
Leu Asn Tyr Cys Thr His His Lys Pro Cys Lys Asn Gly Ala Thr Cys
    290                 295                 300
Thr Asn Thr Gly Gln Gly Ser Tyr Thr Cys Ser Cys Arg Pro Gly Tyr
305                 310                 315                 320
Thr Gly Ala Thr Cys Glu Leu Gly Ile Asp Glu Cys Asp Pro Ser Pro
                325                 330                 335
Cys Lys Asn Gly Gly Ser Cys Thr Asp Leu Glu Asn Ser Tyr Ser Cys
            340                 345                 350
Thr Cys Pro Pro Gly Phe Tyr Gly Lys Ile Cys Glu Leu Ser Ala Met
        355                 360                 365
Thr Cys Ala Asp Gly Pro Cys Phe Asn Gly Gly Arg Cys Ser Asp Ser
    370                 375                 380
Pro Asp Gly Gly Tyr Ser Cys Arg Cys Pro Val Gly Tyr Ser Gly Phe
385                 390                 395                 400
Asn Cys Glu Lys Lys Ile Asp Tyr Cys Ser Ser Ser Pro Cys Ser Asn
                405                 410                 415
Gly Ala Lys Cys Val Asp Leu Gly Asp Ala Tyr Leu Cys Arg Cys Gln
            420                 425                 430
Ala Gly Phe Ser Gly Arg His Cys Asp Asp Asn Val Asp Asp Cys Ala
        435                 440                 445
Ser Ser Pro Cys Ala Asn Gly Gly Thr Cys Arg Asp Gly Val Asn Asp
    450                 455                 460
Phe Ser Cys Thr Cys Pro Pro Gly Tyr Thr Gly Arg Asn Cys Ser Ala
465                 470                 475                 480
Pro Val Ser Arg Cys Glu His Ala Pro Cys His Asn Gly Ala Thr Cys
                485                 490                 495
His Glu Arg Gly His Arg Tyr Val Cys Glu Cys Ala Arg Gly Tyr Gly
            500                 505                 510
Gly Pro Asn Cys Gln Phe Leu Leu Pro Glu Leu Pro Pro Gly Pro Ala
        515                 520                 525
Val Val Asp Leu Thr Glu Lys Leu Glu Gly Gln Gly Gly Pro Phe Pro
    530                 535                 540
Trp Val Ala Val Cys Ala Gly Val Ile Leu Val Leu Met Leu Leu Leu
545                 550                 555                 560
```

```
Gly Cys Ala Ala Val Val Val Cys Val Arg Leu Arg Leu Gln Lys His
                565                 570                 575
Arg Pro Pro Ala Asp Pro Cys Arg Gly Glu Thr Glu Thr Met Asn Asn
            580                 585                 590
Leu Ala Asn Cys Gln Arg Glu Lys Asp Ile Ser Val Ser Ile Ile Gly
        595                 600                 605
Ala Thr Gln Ile Lys Asn Thr Asn Lys Lys Ala Asp Phe His Gly Asp
    610                 615                 620
His Ser Ala Asp Lys Asn Gly Phe Lys Ala Arg Tyr Pro Ala Val Asp
625                 630                 635                 640
Tyr Asn Leu Val Gln Asp Leu Lys Gly Asp Asp Thr Ala Val Arg Asp
                645                 650                 655
Ala His Ser Lys Arg Asp Thr Lys Cys Gln Pro Gln Gly Ser Ser Gly
            660                 665                 670
Glu Glu Lys Gly Thr Pro Thr Thr Leu Arg Gly Gly Glu Ala Ser Glu
        675                 680                 685
Arg Lys Arg Pro Asp Ser Gly Cys Ser Thr Ser Lys Asp Thr Lys Tyr
    690                 695                 700
Gln Ser Val Tyr Val Ile Ser Glu Glu Lys Asp Glu Cys Val Ile Ala
705                 710                 715                 720
Thr Glu Val
```

<210> 108
<211> 685
<212> PRT
<213> ÈËÀà(Homo sapiens)

<220>
<223> ºÏ³ÉµÄµ°°×

<400> 108

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Met Ala Ala Ala Ser Arg Ser Ala Ser Gly Trp Ala Leu Leu Leu Leu
1               5                   10                  15
Val Ala Leu Trp Gln Gln Arg Ala Ala Gly Ser Gly Val Phe Gln Leu
            20                  25                  30
Gln Leu Gln Glu Phe Ile Asn Glu Arg Gly Val Leu Ala Ser Gly Arg
        35                  40                  45
Pro Cys Glu Pro Gly Cys Arg Thr Phe Phe Arg Val Cys Leu Lys His
    50                  55                  60
Phe Gln Ala Val Val Ser Pro Gly Pro Cys Thr Phe Gly Thr Val Ser
65                  70                  75                  80
Thr Pro Val Leu Gly Thr Asn Ser Phe Ala Val Arg Asp Asp Ser Ser
                85                  90                  95
Gly Gly Gly Arg Asn Pro Leu Gln Leu Pro Phe Asn Phe Thr Trp Pro
            100                 105                 110
Gly Thr Phe Ser Leu Ile Ile Glu Ala Trp His Ala Pro Gly Asp Asp
        115                 120                 125
Leu Arg Pro Glu Ala Leu Pro Pro Asp Ala Leu Ile Ser Lys Ile Ala
```

```
    130                 135                 140
Ile Gln Gly Ser Leu Ala Val Gly Gln Asn Trp Leu Leu Asp Glu Gln
145                 150                 155                 160
Thr Ser Thr Leu Thr Arg Leu Arg Tyr Ser Tyr Arg Val Ile Cys Ser
                165                 170                 175
Asp Asn Tyr Tyr Gly Asp Asn Cys Ser Arg Leu Cys Lys Lys Arg Asn
            180                 185                 190
Asp His Phe Gly His Tyr Val Cys Gln Pro Asp Gly Asn Leu Ser Cys
        195                 200                 205
Leu Pro Gly Trp Thr Gly Glu Tyr Cys Gln Gln Pro Ile Cys Leu Ser
    210                 215                 220
Gly Cys His Glu Gln Asn Gly Tyr Cys Ser Lys Pro Ala Glu Cys Leu
225                 230                 235                 240
Cys Arg Pro Gly Trp Gln Gly Arg Leu Cys Asn Glu Cys Ile Pro His
                245                 250                 255
Asn Gly Cys Arg His Gly Thr Cys Ser Thr Pro Trp Gln Cys Thr Cys
            260                 265                 270
Asp Glu Gly Trp Gly Gly Leu Phe Cys Asp Gln Asp Leu Asn Tyr Cys
        275                 280                 285
Thr His His Ser Pro Cys Lys Asn Gly Ala Thr Cys Ser Asn Ser Gly
    290                 295                 300
Gln Arg Ser Tyr Thr Cys Thr Cys Arg Pro Gly Tyr Thr Gly Val Asp
305                 310                 315                 320
Cys Glu Leu Glu Leu Ser Glu Cys Asp Ser Asn Pro Cys Arg Asn Gly
                325                 330                 335
Gly Ser Cys Lys Asp Gln Glu Asp Gly Tyr His Cys Leu Cys Pro Pro
            340                 345                 350
Gly Tyr Tyr Gly Leu His Cys Glu His Ser Thr Leu Ser Cys Ala Asp
        355                 360                 365
Ser Pro Cys Phe Asn Gly Gly Ser Cys Arg Glu Arg Asn Gln Gly Ala
    370                 375                 380
Asn Tyr Ala Cys Glu Cys Pro Pro Asn Phe Thr Gly Ser Asn Cys Glu
385                 390                 395                 400
Lys Lys Val Asp Arg Cys Thr Ser Asn Pro Cys Ala Asn Gly Gly Gln
                405                 410                 415
Cys Leu Asn Arg Gly Pro Ser Arg Met Cys Arg Cys Arg Pro Gly Phe
            420                 425                 430
Thr Gly Thr Tyr Cys Glu Leu His Val Ser Asp Cys Ala Arg Asn Pro
        435                 440                 445
Cys Ala His Gly Gly Thr Cys His Asp Leu Glu Asn Gly Leu Met Cys
    450                 455                 460
Thr Cys Pro Ala Gly Phe Ser Gly Arg Arg Cys Glu Val Arg Thr Ser
465                 470                 475                 480
Ile Asp Ala Cys Ala Ser Ser Pro Cys Phe Asn Arg Ala Thr Cys Tyr
                485                 490                 495
Thr Asp Leu Ser Thr Asp Thr Phe Val Cys Asn Cys Pro Tyr Gly Phe
            500                 505                 510
Val Gly Ser Arg Cys Glu Phe Pro Val Gly Leu Pro Pro Ser Phe Pro
        515                 520                 525
Trp Val Ala Val Ser Leu Gly Val Gly Leu Ala Val Leu Leu Val Leu
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    530                 535                 540
Leu Gly Met Val Ala Val Ala Val Arg Gln Leu Arg Leu Arg Arg Pro
545                 550                 555                 560
Asp Asp Gly Ser Arg Glu Ala Met Asn Asn Leu Ser Asp Phe Gln Lys
                565                 570                 575
Asp Asn Leu Ile Pro Ala Ala Gln Leu Lys Asn Thr Asn Gln Lys Lys
            580                 585                 590
Glu Leu Glu Val Asp Cys Gly Leu Asp Lys Ser Asn Cys Gly Lys Gln
        595                 600                 605
Gln Asn His Thr Leu Asp Tyr Asn Leu Ala Pro Gly Pro Leu Gly Arg
    610                 615                 620
Gly Thr Met Pro Gly Lys Phe Pro His Ser Asp Lys Ser Leu Gly Glu
625                 630                 635                 640
Lys Ala Pro Leu Arg Leu His Ser Glu Lys Pro Glu Cys Arg Ile Ser
                645                 650                 655
Ala Ile Cys Ser Pro Arg Asp Ser Met Tyr Gln Ser Val Cys Leu Ile
            660                 665                 670
Ser Glu Glu Arg Asn Glu Cys Val Ile Ala Thr Glu Val
        675                 680                 685

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<212>  PRT
<213>  ÈËÀà(Homo sapiens)

<220>
<223>  ºÏ³ÉµÄµ°°×


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Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1               5                   10                  15
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125
Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160
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Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165   170   175
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180   185   190
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195   200   205
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210   215   220
Pro Gly
225

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Gln Leu Arg Pro Asn Ala Ala Tyr His Pro Leu Asp Gly Arg Lys Tyr
1   5   10   15
Asn Tyr

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1   5   10   15
Asn Tyr

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1   5

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1   5