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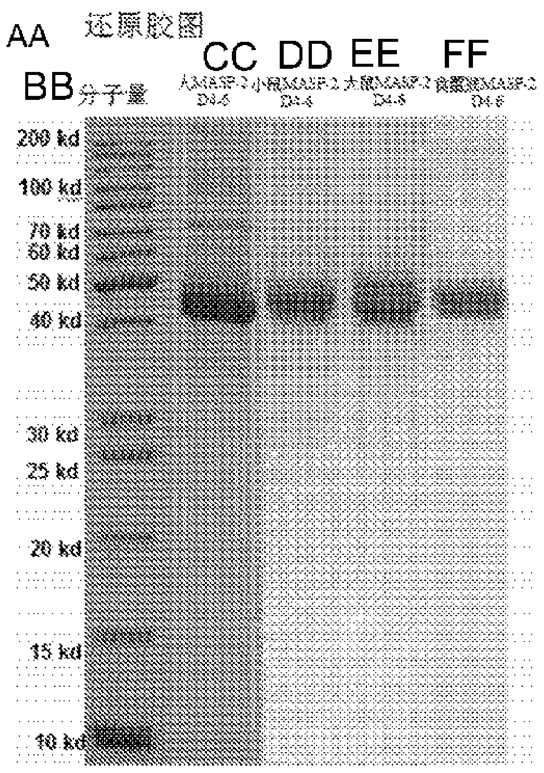


图 1

AA Reduction gel image
BB Molecular weight
CC Human MASP-2
DD Mouse MASP-2
EE Rat MASP-2
FF Cynomolgus monkey MASP-2

(57) **Abstract:** Provided are an antibody or antigen-binding portion thereof that binds MASP-2, and a use of the antibody or antigen-binding portion thereof in the preparation of a drug or kit for diagnosing, treating or preventing diseases associated with lectin pathway complement activation. The antibody can specifically recognize enzymatic activity domains CCP1-CCP2-SP of human, monkey, mouse and rat MASP-2, and effectively inhibit the production of a complement component C4b and a C3 convertase C4b2a.

(57) **摘要**: 提供了一种结合MASP-2的抗体或其抗原结合部分，以及该抗体或其抗原结合部分在制备用于诊断、治疗或预防与凝集素途径补体活化相关的疾病的药物或试剂盒中的用途。该抗体可以特异性识别人、猴、小鼠和大鼠MASP-2的酶活结构域CCP1-CCP2-SP，有效抑制补体成分C4b及C3转化酶C4b2a的生成。

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本国际公布：

— 包括国际检索报告(条约第21条(3))。

— 包括说明书序列表部分(细则5.2(a))。

Description

DEVELOPMENT AND APPLICATION OF COMPLEMENT INHIBITOR

Technical Field

The present disclosure relates to a complement inhibitor and applications thereof, in particular, to a MASP-2 inhibitory antibody and applications thereof.

Background Art

Mannose-binding lectin-associated serine protease 2 (MASP-2) belongs to the serine protease family and is a key enzyme in the complement lectin activation pathway. MASP-2 contains six domains, namely N-terminal CUB1, EGF, CUB2, CCP1, CCP2, and C-terminal SP enzymatic activity domain, with a molecular weight of about 75 kDa. MASP-2 in the blood binds the lectin pathway recognition molecules mannose-binding lectin (MBL), collectin-11 (CL-K1), and ficolin (Ficolin-1, Ficolin-2, and Ficolin-3) via N-terminal CUB1-EGF-CUB2 three domains and forms a complex. When MBL, CL-K1 or ficolin bind to pathogen-associated molecular PAMPs such as D-mannose, N-acetyl-D-glucosamine or acetyl, MASP-1 and MASP-2 are activated sequentially. The activated MASP-2 cleaves C4 and C2, and the fragment C4b formed by cleavage interacts with C2a to produce a C3 convertase (C4b2a). The C3 convertase (C4b2a) activates C3, resulting in the production of a C5 convertase (C4b2a3b) and the formation of a membrane attack complex (C5b-9) capable of causing microbial lysis. Activated forms of C3 and C4 (C3b and C4b) are covalently deposited on the surface of foreign targets, which are recognized by complement receptors on various phagocytes, resulting in phagocytosis of the corresponding pathogen. The lectin pathway plays an important role in the innate immunity of the body against pathogenic microorganisms such as bacteria, yeasts, and viruses.

Under certain pathological conditions, glycoproteins with incomplete internal glycosylation modifications (containing high mannose "precursor" glycan clusters) are released after cell injury and rupture, which can be recognized by MBL with high affinity and initiate complement activation (Maynard et al., J. Biol. Chem. 257: 3788-3794, 1982); similarly, immune complexes formed by IgA antibody with galactose modification defects are deposited on the inner wall of glomerular blood vessels, etc. and activate the complement lectin pathway through MBL-MASP-2, causing an inflammatory response. The granzyme released by overactivated inflammatory cells may cause damage to the nearby tissues and organs. In addition, activated complement components are deposited on the nearby cells, which may lead to the generation of the complement membrane attack complex and cell lysis. The complement system is associated with

the pathogenesis of a variety of acute or chronic disease conditions, such as IgA nephropathy (IgAN), ischemia-reperfusion injury, transplant rejection, rheumatoid arthritis, myocardial infarction, vascular remodeling following stroke, ARDS, septic shock, capillary leak following thermal burns, inflammation following cardiopulmonary bypass, multiple sclerosis, myasthenia gravis, and Alzheimer's disease, etc. Recent studies have shown that various tissue damage such as lung and kidney caused by novel coronavirus COVID-2019 infection is associated with the complement lectin pathway (Magro C et al., Transl Res. 2020 Jun; 220: 1-13), and inhibition of MASP-2 activity can greatly reduce mortality in severe patients with COVID-2019 (Rambaldi A et al., Immunobiology. 2020 Aug 9: 152001).

MASP-2 is a unique C4-cleaving protease in the lectin pathway, and its concentration in healthy human blood is much lower than that of MASP-1 and other complement components in the lectin pathway. Kidmose R et al. showed that MASP-2 binds to C4 via the CCP2 domain, resulting in the latter being allosteric and exposing restriction sites thereof. The mutation of the CCP2 domain can completely inhibit the activity of MASP-2 (PNAS September 18, 2012, 109 (38) 15425-15430).

Summary of the Invention

The present disclosure relates to anti-MASP-2 inhibitory antibodies for inhibiting the undesirable effects of MASP-2 dependent complement activation.

In one aspect, the present disclosure provides an antibody or antigen-binding portion thereof that binds to MASP-2.

In one aspect, the present disclosure provides a bispecific antibody or antigen-binding portion thereof.

In one aspect, the present disclosure provides a nucleic acid encoding the aforementioned antibody or antigen-binding portion thereof that binds to MASP-2, or the bispecific antibody or antigen-binding portion thereof.

In one aspect, the present disclosure provides a vector comprising the aforementioned nucleic acid.

In one aspect, the present disclosure provides a cell comprising the aforementioned vector.

In one aspect, the present disclosure provides a composition or kit comprising the aforementioned antibody or antigen-binding portion thereof, encoding nucleic acid, vector, and cell.

In one aspect, the present disclosure provides a method of treating diseases associated with MASP-2 dependent complement activation, comprising the steps of administering to the subject a therapeutically effective amount of the antibody or antigen-binding fragment thereof, nucleic acid, vector, cell and/or composition of any of the preceding aspects.

In one aspect, the present disclosure provides a use of the antibody or antigen-binding fragment thereof, nucleic acid, vector, cell and/or pharmaceutical composition of any of the preceding aspects in the preparation of a drug or kit for treating diseases associated with MASP-2 dependent complement activation in a subject.

Brief Description of the Drawings

FIG. 1 shows SDS-PAGE results for MASP-2 D4-6 recombinant proteins.

FIG. 2 shows the inhibition of C4b deposition by hybridoma supernatant.

FIG. 3 shows the inhibition of C4b deposition by hybridoma clonal chimeric antibodies.

FIG. 4 shows the inhibition of C3b deposition by hybridoma clonal chimeric antibodies.

FIG. 5 shows ELISA detection of candidate chimeric antibodies binding to different species of MASP-2 D4-6.

FIG. 6 shows the inhibition of C4b deposition by Fab candidate clones from the phage display library.

FIG. 7 shows the inhibition of C4b deposition after the purification of Fab candidate clones from the phage display library.

FIG. 8 shows the inhibition of C4b deposition after 28O14 clone mutation. Among them, Ser102 represents the wild-type antibody, with serine at position 102. Gly102, Tyr102, Ala102, Glu102, Gln102, Val102, Leu102, and His102 represent mutant antibodies in which serine is mutated at position 102 to glycine, tyrosine, alanine, glutamic acid, glutamine, valine, leucine, and histidine, respectively.

FIGs. 9A and 9B show the inhibition of C4b deposition by humanized MASP-2 antibodies.

FIGs. 10A, 10B, and 10C show the inhibition of C3b deposition by humanized MASP-2 antibodies.

FIG. 11 shows ELISA detection of humanized MASP-2 antibodies binding to different species of antigens.

FIG. 12 shows the efficacy of humanized MASP-2 antibody in a mouse hemolytic uremic syndrome model.

Detailed Description of Embodiments

I. Definitions

In the present disclosure, the scientific and technical terms used herein have the meanings commonly understood by those skilled in the art, unless otherwise specified. Also, the terms and laboratory procedures related to protein and nucleic acid chemistry, molecular biology, cell and tissue culture, microbiology, and immunology used herein are terms and routine procedures

widely used in the corresponding fields. Meanwhile, to better understand the present disclosure, definitions and explanations of related terms are provided below.

Provided herein are antibodies (e.g., monoclonal antibodies) that specifically bind to MASP-2 and antigen-binding fragments thereof. In a specific aspect, provided herein are anti-MASP-2 monoclonal antibodies that specifically bind to MASP-2, wherein the anti-MASP-2 antibodies include variants of the parent antibody. In a specific aspect, provided herein are antibodies that specifically bind to MASP-2 (e.g., human MASP-2). In a particular aspect, provided herein are anti-MASP-2 antibodies comprising modifications in one or more amino acid residues (e.g., 5-13 amino acid substitutions in the framework region of the heavy chain variable region), which retain affinity to antigens compared to the parent antibody without the modifications. The term "MASP-2" refers to any MASP-2 molecule known to those skilled in the art. For example, the MASP-2 may be from mammals, e.g., the MASP-2 may be from humans.

As used herein, the term "MASP-2 dependent complement activation" comprises MASP-2 dependent activation of the lectin pathway, which occurs under physiological conditions (i.e., in the presence of Ca^{2+}), resulting in the formation of a lectin pathway C3 convertase C4b2a, and resulting in the formation of a C5 convertase C4b2a(C3b)n after accumulation of the C3 cleavage product C3b.

As used herein, the term "MASP-2 inhibitory antibody" refers to any anti-MASP-2 antibody or MASP-2 binding fragment thereof that binds to or directly interacts with MASP-2 and effectively inhibits MASP-2 dependent complement activation. MASP-2 inhibitory antibodies used in the disclosed method may reduce MASP-2 dependent complement activation by greater than 20%, e.g., greater than 30%, greater than 40%, greater than 50%, greater than 60%, greater than 70%, greater than 80%, greater than 90%, or greater than 95%.

The term "lectin pathway" refers to complement activation by specific binding of serum and non-serum carbohydrate-binding proteins, including mannan-binding lectin (MBL) and ficolin.

As used herein, the term "about" or "approximately" refers to within plus or minus 10% of a given value or range, unless otherwise specified. Where integers are required, the term refers to integers within plus or minus 10% of a given value or range, rounded up or down to the nearest integer.

The phrase "substantially identical" with respect to an antibody chain polypeptide sequence may be construed as an antibody chain exhibiting at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more sequence identity to a reference polypeptide sequence. The term with respect to a nucleotide sequence may be construed as a nucleotide sequence exhibiting at least greater than 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more sequence identity to the reference nucleotide sequence.

Sequence "identity" has a recognized meaning in this field and the percentage of sequence identity

between two nucleic acid or polypeptide molecules or regions can be calculated using published techniques. Sequence identity can be measured along the entire length of a polynucleotide or polypeptide or a region of the molecule. While there are many methods of measuring identity between two polynucleotides or polypeptides, the term "identity" is well-known to those skilled in the art (Carrillo, H. & Lipman, D. SIAM J Applied Math 48: 1073 (1988)).

"Substitution" variants are those in which at least one amino acid residue in the native sequence has been removed and inserted by a different amino acid at the same position. The substitution may be single, with only one amino acid in the molecule being substituted; or may be multiple, with two or more amino acids being substituted in the same molecule. Multiple substitutions may be at consecutive positions. Likewise, an amino acid may be substituted with multiple residues, wherein such variants include both substitutions and insertions. "Insertion" variants are those in which one or more amino acids are inserted immediately adjacent to an amino acid at a particular position in a native sequence. By immediately adjacent amino acid is meant attached to the α-carboxy or α-amino functional group of the amino acid. "Deletion" variants are those in which one or more amino acids in the native amino acid sequence have been removed. Typically, one or two amino acids are deleted in a particular region of the molecules of deletion variants.

With respect to the variable domains of antibodies, the term "variable" refers to certain portions of related molecules that differ widely in sequence between antibodies and are used for specifically recognizing and binding to a specific target of a particular antibody. However, the variability is not uniformly distributed throughout the variable domain of the antibody. Variability is concentrated on three segments called complementarity determining regions (CDRs; i.e., CDR1, CDR2, and CDR3) or hypervariable regions, all of which are located within the variable domains of the light and heavy chains. The more conserved portions within the variable domains are referred to as framework (FR) regions or framework sequences. Each variable domain of native heavy and light chains comprises four FR regions, predominantly in a β -sheet configuration, connected by three CDRs, which form loops connecting and in some cases forming part of the β -sheet structure. The CDRs of each chain are typically joined together by adjacent FR regions and aid in the formation of antibody target binding sites (epitopes or determinants) by means of CDR from other chains. As used herein, the numbering of immunoglobulin amino acid residues is based on Kabat et al.'s immunoglobulin amino acid residues numbering scheme, unless otherwise indicated. One CDR may have the ability to specifically bind to an associated epitope.

As used herein, the "antibody fragment" or "antigen-binding fragment" of an antibody refers to any portion of the full-length antibody, which is less than full-length, but comprises at least a portion of the variable region (e.g., one or more CDRs and/or one or more antibody binding sites) of the antibody that binds to an antigen, and thus retaining binding specificity as well as at least a

portion of the specific binding capacity of the full-length antibody. Thus, an antigen-binding fragment refers to an antibody fragment that comprises an antigen-binding portion that binds the same antigen as the antibody from which the antibody fragment was derived. Antibody fragments include antibody derivatives produced by enzymatic treatment of full-length antibodies, as well as synthetically produced derivatives, e.g., recombinantly produced derivatives. Antibodies include antibody fragments. Examples of the antibody fragments include, but are not limited to, Fab, Fab', $F(ab')_2$, single chain Fv (scFv), Fv, dsFv, diabodies, Fd, and Fd' fragments and other fragments, including modified fragments (see, e.g., Methods in Molecular Biology, Vol 207: Recombinant Antibodies for Cancer Therapy Methods and Protocols (2003); Chapter 1; p 3-25, Kipriyanov). The fragments may comprise multiple chains linked together, for example, by disulfide bonds and/or by peptide linkers. Antibody fragments generally comprise at least or about 50 amino acids, and typically at least or about 200 amino acids. Antigen-binding fragments include any antibody fragment that, when inserted into an antibody framework (e.g., by displacement of the corresponding region), results in the antibody that immunospecifically binds to an antigen (i.e., exhibiting a Ka of at least or at least about 10^7-$10^8 M^{-1}$). The "functional fragment" or "analog of an anti-MASP-2 antibody" is a fragment or analog that may prevent or substantially reduce the ability of the receptor to bind a ligand or initiate signal transduction. As used herein, the functional fragments generally have the same meaning as "antibody fragments" and, in the case of antibodies, may refer to fragments that may prevent or substantially reduce the ability of the receptor to bind to a ligand or initiate signal transduction, e.g., Fv, Fab, $F(ab')_2$, and the like. The "Fv" fragment consists of a dimer (V_H-V_L dimer) formed by the non-covalent binding of a variable domain of a heavy chain and a variable domain of a light chain. In this configuration, the three CDRs of each variable domain interact to determine the target binding sites on the surface of the V_H-V_L dimer, as is the case with intact antibodies. The six CDRs together confer target binding specificity to the intact antibody. However, even a single variable domain (or half of an Fv comprising only three target-specific CDRs) may still have the ability to recognize and bind to targets.

As used herein, the term "bispecific antibody (BsAb)" refers to an antibody and/or antigen-binding molecule capable of specifically binding to two different antigenic determinants. Generally, a bispecific antibody and/or antigen-binding molecule comprises two antigen-binding sites, each of which is specific for different antigenic determinants. In some embodiments, the bispecific antibody and/or antigen-binding molecule is capable of binding to two antigenic determinants simultaneously, particularly two antigenic determinants expressed on two different cells.

As used herein, the "monoclonal antibody" refers to a population of identical antibodies, meaning that each individual antibody molecule in the population of monoclonal antibodies is identical to another antibody molecule. This property is in contrast to the property of a population of

polyclonal antibodies comprising antibodies having a plurality of different sequences. Monoclonal antibodies can be prepared by a number of well-known methods (Smith et al., (2004) J. Clin. Pathol. 57, 912-917; and Nelson et al., J Clin Pathol (2000), 53, 111-117). For example, monoclonal antibodies can be prepared by immortalizing B cells, for example, by fusing with myeloma cells to generate hybridoma cell lines or by infecting B cells with a virus such as EBV. Recombinant techniques can also be used to prepare antibodies from clonal populations of host cells in vitro by transforming host cells with plasmids carrying artificial sequences encoding the nucleotides of the antibodies.

As used herein, the term "hybridoma" or "hybridoma cell" refers to a cell or cell line (typically a myeloma or lymphoma cell) resulting from the fusion of antibody-producing lymphocytes and non-antibody-producing cancer cells. As known to those of ordinary skill in the art, the hybridoma may be propagated and continuously supplied to produce a particular monoclonal antibody. Methods for producing hybridomas are known in the art. When referring to the term "hybridoma" or "hybridoma cell", it also comprises subclones and progeny cells of the hybridoma.

As used herein, a full-length antibody is an antibody having two full-length heavy chains (e.g., VH-CH1-CH2-CH3 or VH-CH1-CH2-CH3-CH4) and two full-length light chains (VL-CL) and a hinge region, e.g., an antibody naturally produced by an antibody-secreting B cell as well as a synthetically produced antibody having the same domain.

The term "chimeric antibody" refers to an antibody in which the variable region sequences are derived from one species and the constant region sequences are derived from another species, such as an antibody in which the variable region sequences are derived from a mouse antibody and the constant region sequences are derived from a human antibody.

The "humanized" antibody refers to a form of non-human (e.g., mouse) antibody that is a chimeric immunoglobulin, immunoglobulin chain or fragment thereof (e.g., Fv, Fab, Fab', $F(ab')_2$ or other antigen-binding subsequences of the antibody), containing minimal sequence derived from non-human immunoglobulin. Preferably, the humanized antibody is a human immunoglobulin (recipient antibody) in which residues from a complementarity determining region (CDR) of the recipient antibody are replaced by CDR residues from a non-human species (donor antibody) such as mouse, rat, or rabbit having the desired specificity, affinity, and capacity.

Furthermore, in humanization it is also possible to mutate amino acid residues within the CDR1, CDR2 and/or CDR3 regions of VH and/or VL, thereby improving one or more binding properties (e.g., affinity) of the antibody. Mutations may be introduced, e.g., by PCR-mediated mutagenesis, and their effects on antibody binding or other functional properties can be assessed using the in vitro or in vivo assays described herein. Typically, conservative mutations are introduced. Such mutations may be amino acid substitutions, additions, or deletions. In addition, mutations within

CDR typically do not exceed one or two. Thus, humanized antibodies of the present disclosure also encompass antibodies comprising 1 or 2 amino acid mutations within CDR.

As used herein, the term "CDR" refers to a complementarity-determining region, where it is known that each heavy and light chain of antibody molecules has three CDRs. CDR is also known as a hypervariable region and is present in the variable region of each of the heavy and light chains of an antibody with a very high site of variability in the primary structure of CDR. In the present specification, the CDR of the heavy chain is represented by CDR1, CDR2 and CDR3 from the amino terminus of the amino-terminal sequence of the heavy chain, and the CDR of the light chain is represented by CDR1, CDR2 and CDR3 from the amino terminus of the amino-terminal sequence of the light chain. These sites are adjacent to each other in the tertiary structure and determine the specificity of the antigen to which the antibody binds.

As used herein, the term "epitope" refers to any antigenic determinant on an antigen to which the paratope of an antibody binds. Epitopic determinants usually comprise chemically active surface types of molecules, such as amino acids or sugar side chains, and usually have specific three-dimensional structural characteristics as well as specific charge characteristics.

As used herein, the "specific binding" or "immunospecifically binding" with respect to an antibody or antigen-binding fragment thereof is used interchangeably herein and refers to the ability of an antibody or antigen-binding fragment to form one or more non-covalent bonds with the same antigen through non-covalent interactions between the antibody and the antibody binding site of the antigen. The antigen may be an isolated antigen or present in a tumor cell. Typically, the antibody that immunospecifically binds (or specifically binds) to the antigen is the one that binds to the antigen with an affinity constant Ka of about or $1\times10^{7}M^{-1}$ or $1x10^{8}M^{-1}$ or more (or a dissociation constant (Kd) of $1x10^{-7}M$ or $1\times10^{-8}M$ or less). Affinity constant can be determined by standard kinetic methods for antibody reactions, e.g., immunoassays, surface plasmon resonance (SPR) (Rich and Myszka (2000) Curr. Opin. Biotechnol 11:54; Englebienne (1998) Analyst. 123:1599), isothermal titration calorimetry (ITC), or other kinetic interaction assays known in the art; see also U.S. Patent No. 7, 229, 619 describing exemplary SPR and ITC method for calculating the binding affinity of an antibody. Instruments and methods for real-time detection and monitoring of the binding rate are known and commercially available (see, Malmqvist (2000) Biochem.Soc.Trans. 27:335).

As used herein, the terms "polynucleotide" and "nucleic acid molecule" refer to an oligomer or polymer comprising at least two linked nucleotides or nucleotide derivatives, including deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), typically linked together by phosphodiester bonds. As used herein, the term "nucleic acid molecule" is intended to include DNA molecules and RNA molecules. The nucleic acid molecule may be single-stranded or

double-stranded, and may be cDNA.

As used herein, an isolated nucleic acid molecule is a nucleic acid molecule isolated from other nucleic acid molecules present in the natural source of the nucleic acid molecule. The "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material or culture medium when prepared by recombinant techniques, or substantially free of chemical precursors or other chemical components when chemically synthesized. Exemplary isolated nucleic acid molecules provided herein comprise isolated nucleic acid molecules encoding provided antibodies or antigen-binding fragments.

As used herein, the "operably linked" with respect to a nucleotide sequence, region, element or domain means that the nucleic acid regions are functionally related to one another. For example, a promoter may be operably linked to a nucleic acid encoding a polypeptide such that the promoter regulates or mediates transcription of the nucleic acid.

Also provided are "conservative sequence modifications" of the sequences set forth in the sequence listings described herein, i.e., nucleotide and amino acid sequence modifications that do not eliminate the binding ability of the antibody encoded by the nucleotide sequence or containing an amino acid sequence to an antigen. These conservative sequence modifications comprise conservative nucleotide and amino acid substitutions as well as nucleotide and amino acid additions and deletions. For example, modifications can be introduced into the sequence listings described herein by standard techniques known in the art, such as site-directed mutagenesis and PCR-mediated mutagenesis. Conservative sequence modifications comprise conservative amino acid substitutions in which an amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids containing basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine, tryptophan), non-polar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine), β-branched side chains (e.g., threonine, valine, isoleucine), and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Thus, a predicted nonessential amino acid residue in an anti-MASP-2 antibody is preferably replaced with another amino acid residue from the same side chain family. Methods for identifying conservative substitutions of nucleotides and amino acids that do not eliminate antigen binding are well-known in the art (see, e.g., Brummell et al., Biochem. 32: 1180-1187 (1993); Kobayashi et al., Protein Eng. 12(10): 879-884 (1999); Burks et al., Proc.Natl.Acad.Sci.USA 94: 412-417 (1997)).

Alternatively, in another embodiment, mutations can be randomly introduced along all or a portion of the anti-MASP-2 antibody coding sequence, e.g., by saturation mutagenesis, and the resulting

modified anti-MASP-2 antibodies can be screened for improved binding activity.

As used herein, the "expression" refers to a process of producing a polypeptide by transcription and translation of a polynucleotide. The level of expression of a polypeptide can be assessed using any method known in the art, including, for example, methods of determining the amount of polypeptide produced from a host cell. Such methods may include, but are not limited to, quantitation of polypeptides in cell lysates by ELISA, gel electrophoresis followed by Coomassie blue staining, Lowry protein assay, and Bradford protein assay.

As used herein, the "host cell" is a cell for receiving, maintaining, replicating, and expanding a vector. The host cell may also be used to express a polypeptide encoded by the vector. The nucleic acid contained in the vector replicates during the host cell division, thereby amplifying the nucleic acid. The host cell may be a eukaryotic cell or a prokaryotic cell. Suitable host cells include, but are not limited to, CHO cells, various COS cells, HeLa cells, and HEK cells such as HEK 293 cells.

As used herein, the “vector" is a replicable nucleic acid from which one or more heterologous proteins can be expressed when the vector is transformed into an appropriate host cell. References to vectors include those into which a nucleic acid encoding a polypeptide or fragment thereof may be introduced, typically by restriction digestion and ligation. References to vectors also include those comprising a nucleic acid encoding a polypeptide. Vectors are used to introduce a nucleic acid encoding a polypeptide into a host cell, to amplify the nucleic acid, or to express/display the polypeptide encoded by the nucleic acid. The vector generally remains free but can be designed to allow the integration of a gene or portion thereof into the chromosome of the genome. Also contemplated are vectors for artificial chromosomes, such as yeast artificial vectors and mammalian artificial chromosomes. The selection and use of such vehicles are well-known to those skilled in the art.

As used herein, the vector also comprises a "virus vector" or a "viral vector". The viral vector is an engineered virus that is operably linked to an exogenous gene to transfer (as a vehicle or shuttle) the exogenous gene into a cell.

As used herein, the "expression vector" comprises a vector capable of expressing a DNA operably linked to regulatory sequences, such as a promoter region, capable of affecting the expression of such DNA fragments. Such additional fragments may comprise promoter and terminator sequences, and optionally may comprise one or more origins of replication, one or more selectable markers, enhancers, polyadenylation signals, etc. Expression vectors are typically derived from plasmid or viral DNA, or may contain elements of both. Thus, the expression vector refers to a recombinant DNA or RNA construct, such as a plasmid, phage, recombinant virus, or other vectors, which results in the expression of a cloned DNA when introduced into an appropriate host

cell. Appropriate expression vectors are well-known to those skilled in the art and comprise expression vectors that are replicable in eukaryotic and/or prokaryotic cells as well as expression vectors that remain free or that are integrated into the host cell genome.

As used herein, "treating" individuals with a disease or condition means that the individual symptoms are partially or completely alleviated or remain unchanged after the treatment. Thus, the treatment comprises prevention, treatment, and/or cure. Prevention refers to preventing the underlying disease and/or preventing the worsening of symptoms or the progression of the disease. The treatment also comprises any pharmaceutical use of any antibody or antigen-binding fragment thereof provided and the composition provided herein.

As used herein, the "therapeutic effect" refers to an effect resulting from the treatment of an individual that alters, typically improves or ameliorates the symptoms of a disease or condition, or cures a disease or condition.

As used herein, the "therapeutically effective amount" or "therapeutically effective dose" refers to an amount of a substance, compound, material, or composition comprising the compound that is at least sufficient to produce a therapeutic effect after being administered to the subject. Thus, it is an amount necessary to prevent, cure, ameliorate, block, or partially block the symptoms of a disease or disorder.

As used herein, the "prophylactically effective amount" or "prophylactically effective dose" refers to an amount of a substance, compound, material, or composition comprising the compound that, when administered to a subject, has the desired prophylactic effect, e.g., preventing or delaying the occurrence or recurrence of a disease or condition, reducing the likelihood of the occurrence or recurrence of a disease or condition. A fully prophylactically effective dose need not occur by administration of one dose, and may occur only after administration of a series of doses. Thus, the prophylactically effective amount may be administered in one or more administrations.

As used herein, the term "patient" or “subject” refers to a mammal, such as a human.

II. Detailed description of specific embodiments

In one aspect, the present disclosure provides an antibody or antigen-binding portion thereof that binds to MASP-2, comprising heavy chain CDRs selected from the group consisting of amino acid sequences SEQ ID NOs: 7, 8, 9, 17, 18, 26, 27, 28, 36, 37, 38, 46, 47, 60, 65, 66, 67, 79, 85, 86, 94, 95, 96, 104, 105, 113, 114, 126, 127, 128, 136, 137, 138, 141, 149, 150, 151, 165, 183, 192 or any variant thereof, and/or light chain CDRs selected from the group consisting of amino acid sequences SEQ ID NOs: 12, 13, 14, 21, 22, 23, 31, 32, 33, 41, 42, 43, 50, 51, 52, 57, 70, 71, 72, 82, 91, 108, 109, 110, 117, 118, 123, 131, 132, 133, 144, 145, 146, 154, 155, 156, 161, 162, 168, 173, 174, 201, 202, 207, 216 or any variant thereof.

The antibody or antigen-binding portion thereof according to the previous aspect, comprising a

heavy chain CDR1 selected from the group consisting of amino acid sequences SEQ ID NOs: 7, 26, 36, 65, 94, 126, 136, 149 or any variant thereof, a heavy chain CDR2 selected from the group consisting of amino acid sequences SEQ ID NOs: 8, 17, 27, 37, 46, 66, 85, 95, 104, 113, 127, 137, 150, 165, 183, 192 or any variant thereof, and a heavy chain CDR3 selected from the group consisting of amino acid sequences SEQ ID NOs: 9, 18, 28, 38, 47, 60, 67, 79, 86, 96, 105, 114, 128, 138, 141, 151 or any variant thereof; and/or a light chain CDR1 selected from the group consisting of amino acid sequences SEQ ID NOs: 12, 21, 31, 41, 50, 70, 99, 108, 117, 123, 131, 144, 154, 161, 201, 216 or any variant thereof, a light chain CDR2 selected from the group consisting of amino acid sequences SEQ ID NOs: 13, 22, 32, 42, 51, 57, 71, 100, 109, 118, 132, 145, 155, 162, 168, 173, 202, 207 or any variant thereof, and a light chain CDR3 selected from the group consisting of amino acid sequences SEQ ID NOs: 14, 23, 33, 43, 52, 72, 82, 91, 101, 110, 133, 146, 156, 174 or any variant thereof.

The antibody or antigen-binding portion thereof according to the previous aspect, comprising a combination of heavy and light chain CDRs selected from the group consisting of:

(1) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 7, 8 and 9, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 12, 13 and 14, respectively;

(2) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 7, 17 and 18, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 21, 22 and 23, respectively;

(3) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 26, 27 and 28, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 31, 32 and 33, respectively;

(4) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 36, 37 and 38, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 41, 42 and 43, respectively;

(5) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 7, 46 and 47, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 50, 51 and 52, respectively;

(6) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 7, 17 and 18, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 21, 57 and 23, respectively;

(7) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 7, 17 and 60, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 50, 51 and 52, respectively;

(8) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 65, 66 and 67, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 70, 71 and 72, respectively;

(9) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 7, 17 and 47, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 50, 51 and 52, respectively;

(10) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 7, 17 and 79, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 50, 51 and 82, respectively;

(11) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 36, 85 and 86, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 41, 42 and 43, respectively;

(12) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 36, 85 and 86, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 41, 42 and 91, respectively;

(13) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 94, 95 and 96, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 99, 100 and 101, respectively;

(14) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 7, 104 and 105, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 108, 109 and 110, respectively;

(15) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 26, 113 and 114, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 117, 118 and 33, respectively;

(16) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 94, 95 and 96, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 123, 100 and 101, respectively;

(17) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 126, 127 and 128, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 131, 132 and 133, respectively;

(18) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 136, 137 and 138, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 131, 132 and 133, respectively;

(19) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 7, 17 and 141, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs:

144, 145 and 146, respectively;

(20) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 149, 150 and 151, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 154, 155 and 156, respectively;

(21) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 7, 17 and 9, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 161, 162 and 14, respectively;

(22) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 7, 165 and 9, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 144, 168 and 14, respectively;

(23) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 7, 17 and 9, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 144, 173 and 174, respectively;

(24) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 136, 183 and 138, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 216, 132 and 133, respectively;

(25) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 126, 192 and 128, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 216, 132 and 133, respectively;

(26) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 7, 17 and 141, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 201, 202 and 146, respectively;

(27) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 7, 17 and 141, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 201, 207 and 146, respectively.

The antibody or antigen-binding portion thereof according to the previous aspect, comprising a heavy chain variable region selected from the group consisting of amino acid sequences SEQ ID NOs: 5, 15, 24, 34, 44, 53, 58, 63, 73, 77, 83, 92, 102, 111, 119, 124, 134, 139, 147, 157, 163, 169, 175, 177, 179, 181, 184, 186, 188, 190, 193, 195, 197 or any variant thereof, and/or a light chain variable region selected from the group consisting of amino acid sequences SEQ ID NOs: 10, 19, 29, 39, 48, 55, 61, 68, 75, 80, 87, 89, 97, 106, 115, 121, 129, 142, 152, 159, 166, 171, 199, 203, 205, 208, 210, 212, 214 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 5 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 10 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 15 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 19 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 24 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 29 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 34 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 39 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 44 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 48 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 53 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 55 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 58 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 61 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 63 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 68 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 73 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 75 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 77 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 80 or any variant

thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 83 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 87 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 83 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 89 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 92 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 97 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 102 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 106 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 111 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 115 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 119 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 121 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 124 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 129 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 134 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 129 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 139 or any variant thereof,

and the light chain variable region of the amino acid sequence SEQ ID NO: 142 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 147 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 152 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 157 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 159 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 163 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 166 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 169 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 171 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 181 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 214 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 184 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 214 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 186 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 214 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 188 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 214 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the

heavy chain variable region of the amino acid sequence SEQ ID NO: 190 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 214 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 193 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 214 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 195 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 214 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 197 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 214 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 175 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 199 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 175 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 203 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 175 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 205 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 177 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 205 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 177 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 199 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 177 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 203 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 179 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 199 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 179 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 203 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 179 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 205 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 175 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 208 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 175 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 210 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 175 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 212 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 177 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 208 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 177 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 210 or any variant

thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 177 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 212 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 179 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 208 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 179 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 210 or any variant thereof;

in some preferred embodiments, the antibody or antigen-binding portion thereof comprises the heavy chain variable region of the amino acid sequence SEQ ID NO: 179 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 212 or any variant thereof.

In one aspect, the present disclosure provides a bispecific or multispecific molecule comprising the antibody or antigen-binding portion thereof of any of the preceding aspects.

In some preferred embodiments of the present disclosure, the antibody or antigen-binding portion thereof is humanized.

In one aspect, the present disclosure provides a nucleic acid molecule encoding the antibody or antigen-binding portion thereof or the bispecific or multispecific molecule according to any of the preceding aspects.

In some preferred embodiments, the nucleic acid comprises an antibody heavy chain variable region nucleotide sequence selected from the group consisting of SEQ ID NOs: 6, 16, 25, 35, 45, 54, 59, 64, 74, 78, 84, 93, 103, 112, 120, 125, 135, 140, 148, 158, 164, 170, 176, 178, 180, 182, 185, 187, 189, 191, 194, 196, 198 or any variant thereof, and/or an antibody light chain variable region nucleotide sequence selected from the group consisting of SEQ ID NOs: 11, 20, 30, 40, 49, 56, 62, 69, 76, 81, 88, 90, 98, 107, 116, 122, 130, 143, 153, 160, 167, 172, 200, 204, 206, 209, 211, 213, 215 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 6 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 11 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 16 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 20 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 25 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 30 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 35 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 40 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 45 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 49 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 54 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 56 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 59 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 62 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 64 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 69 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 74 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 76 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 78 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 81 or any

variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 84 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 88 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 84 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 90 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 93 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 98 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 103 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 107 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 112 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 116 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 120 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 122 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 125 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 130 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 135 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 130 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 140 or any variant thereof, and the

light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 143 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 148 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 153 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 158 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 160 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 164 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 167 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 170 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 172 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 182 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 215 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 185 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 215 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 187 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 215 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 189 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 215 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region

nucleotide sequence of the nucleotide sequence SEQ ID NO: 191 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 215 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 194 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 215 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 196 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 215 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 198 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 215 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 176 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 200 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 176 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 204 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 176 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 206 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 178 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 206 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 178 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 200 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 178 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 204 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 180 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 200 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 180 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 204 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 180 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 206 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 176 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 209 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 176 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 211 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 176 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 213 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 178 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 209 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 178 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 211 or

any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 178 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 213 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 180 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 209 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 180 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 211 or any variant thereof;

in some preferred embodiments, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 180 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 213 or any variant thereof.

in one aspect, the present disclosure provides an antibody or antigen-binding portion thereof that binds to MASP-2, having at least greater than 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or more sequence identity to the antibody or antigen-binding portion thereof of any of the preceding aspects.

In one aspect, the present disclosure provides a nucleic acid molecule encoding the antibody or antigen-binding portion thereof of any of the preceding aspects, or a nucleic acid molecule having at least greater than 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or more sequence identity thereto.

In one aspect, the present disclosure provides a vector comprising the nucleic acid of any of the preceding aspects.

In one aspect, the present disclosure provides a cell comprising the vector of any of the preceding aspects.

In one aspect, the present disclosure provides a composition comprising the aforementioned antibody or antigen-binding portion thereof, bispecific or multispecific molecule, nucleic acid, vector, and/or cell.

The antibodies of the present disclosure are useful as therapeutic or diagnostic tools in a variety of diseases in which MASP-2 is adversely expressed or found.

A method of treating diseases associated with MASP-2-dependent complement activation with the

MASP-2 inhibitor of the present disclosure, comprising the steps of administering a therapeutically effective amount of the antibody or antigen-binding fragment thereof or nucleic acid molecule or vector or cell or pharmaceutical composition of any of the preceding aspects to a subject.

MASP-2 dependent complement activation has been indicated to contribute to the pathogenesis of a number of acute and chronic disease states, including MASP-2 dependent complement-mediated vascular conditions, ischemia-reperfusion injury, atherosclerosis, inflammatory gastrointestinal tract disorders, lung conditions, in vitro reperfusion processes, skeletal muscle conditions, kidney conditions, skin conditions, organ or tissue transplantation, neurological disorders or injuries, blood disorders, urogenital tract conditions, diabetes, chemotherapy or radiation therapy, malignancies, endocrine disorders, coagulation disorders, or ophthalmic conditions. Thus, the MASP-2 inhibitory antibodies of the present disclosure can be used to treat the diseases and conditions described above.

The clinical condition of a preferred embodiment of the present disclosure is a chronic inflammatory disease. Chronic inflammatory disease may be, for example, an autoimmune inflammatory condition.

Autoimmune inflammatory conditions (also referred to hereby as "autoimmune disorders ") can be loosely classified into diseases that are primarily limited to specific organs or tissues and that affect the entire body. Examples of organ-specific disorders (and affected organs) comprise multiple sclerosis (myelin coated on neurites), type I diabetes (pancreas), Hashimoto's thyroiditis (thyroid), pernicious anemia (stomach), Addison's disease (adrenal gland), myasthenia gravis (acetylcholine receptors on neuromuscular junctions), rheumatoid arthritis (joint lining), uveitis (eye), psoriasis (skin), Guillain-Barre syndrome (nerve cell) and Graves' disease (thyroid). Systemic autoimmune diseases comprise systemic lupus erythematosus, glomeronephritis, and dermatomyositis.

In one embodiment of the present disclosure, the preferred clinical condition is selected from the group consisting of rheumatoid arthritis or systemic lupus erythematosus.

Other examples of autoimmune disorders comprise asthma, eczema, atopicaldermatitis, contact dermatitis, other eczematous dermatitises, seborrheic dermatitis, rhinitis, lichen planus, pemplugus, bullous pemphigoid, epidermolysis bullosa, urticaria, angioedema, vasculitis, erythema, cutaneous eosinophilia, alopecia areata, arteriosclerosis, primary biliary cirrhosis and nephrotic syndrome. Related diseases comprise enteritis, such as coeliac disease, proctitis, eosinophilic gastroenteritis, mastocytosis, inflammatory bowel disease, Chrohn's disease, ulcerative colitis, and food-related allergies.

In another embodiment of the present disclosure, the clinical condition is characterized by massive

cell loss, e.g., due to programmed cell death or necrosis. Necrosis or programmed cell death can be induced by a number of factors.

In a preferred embodiment of the present disclosure, the clinical condition is ischemic/reperfusion injury. Ischemia can be caused by a variety of causes, such as after stroke, myocardial infarction, major surgery, or organ transplantation. Thus, the clinical condition may be an ischemic/reperfusion injury caused by, for example, stroke, myocardial infarction, major surgery, or organ transplantation.

Thus, the clinical condition may be an ischemic/reperfusion injury, which is the result of PTCA (percutaneous transluminal coronary angioplasty) or CABG (coronary artery bypass grafting). Furthermore, the clinical condition may be ischemic/reperfusion injury, which is the result of acute myocardial infarction or cerebral ischemia.

The dosage of the agents comprising the MASP-2 inhibitor generally varies according to the age, body weight, height, gender, general disease condition and medical history of the subject to be treated. For example, the MASP-2 inhibitor, e.g., the MASP-2 antibody, can be administered in a dosage range of about 0.010-10.0 mg/kg, preferably 0.010-1.0 mg/kg, more preferably 0.010-0.1 mg/kg of the body weight of the subject to be treated. In certain embodiments, the composition comprises the combination of the anti-MASP-2 antibody and a MASP-2 inhibitory peptide.

Compositions and methods comprising the MASP-2 inhibitor may optionally comprise one or more additional therapeutic agents, which may enhance the activity of the MASP-2 inhibitor or provide relevant therapeutic functions in an additive or synergistic manner. For example, one or more MASP-2 inhibitors may be combined with one or more anti-inflammatory and/or analgesic agents. The amount and choice of additional agents can be determined to achieve the desired therapeutic results. Suitable anti-inflammatory and/or analgesic agents comprise: 5-hydroxytryptamine receptor antagonists; 5-hydroxytryptamine receptor agonists; histamine receptor antagonists; bradykinin receptor antagonists; kallikrein inhibitors; tachykinin receptor antagonists including neurokinin 1 and neurokinin 2 receptor subtype antagonists; calcitonin gene-related peptide (CGRP) receptor antagonists; interleukin receptor antagonists; inhibitors of active enzymes in the arachidonic acid metabolite synthesis pathway, including phospholipase inhibitors, including inhibitors of the PLA2 isoform and PLC gamma isoform, cyclooxygenase (COX) inhibitors (which may be inhibitors of COX-1, COX-2 or non-selective inhibitors of COX-1 and COX-2), lipoxygenase inhibitors; prostanoid receptor antagonists, including eicosanoid EP-I and EP-4 receptor subtype antagonists and thromboxane receptor subtype antagonists; leukotriene receptor antagonists, including leukotriene B4 receptor subtype antagonists and leukotriene D4 receptor subtype antagonists; opioid receptor agonists, including μ-opioid, δ-opioid and κ-opioid receptor subtype agonists; purine receptor agonists and

antagonists, including P2x receptor antagonists and P2Y receptor agonists; adenosine triphosphate (ATP) sensitive potassium channel openers; MAP kinase inhibitors; nicotinic acetylcholine inhibitors; and alpha adrenergic receptor agonists (including alpha-1, alpha-2 and non-selective alpha-1 and alpha-2 agonists).

When used to inhibit or treat restenosis, the MASP-2 inhibitors of the present disclosure may be co-administered in combination with one or more anti-restenosis agents. Suitable anti-restenosis agents comprise antiplatelet agents, including thrombin inhibitors and receptor antagonists, adenosine diphosphate (ADP) receptor antagonists (also known as purinergic receptor 1 receptor antagonists), thromboxane inhibitors and receptor antagonists, and platelet membrane glycoprotein receptor antagonists; inhibitors of cell adhesion molecules, including selectin inhibitors and integrin free radicals; anti-chemotactic agents; interleukin receptor antagonists; and intracellular signal transduction inhibitors, including protein kinase C (PKC) inhibitors and protein tyrosine phosphatases, modulators of intracellular protein tyrosine kinase inhibitors, inhibitors of src homology 2 (SH2) domains, and calcium channel antagonists.

The MASP-2 inhibitors of the present disclosure may also be used in combination with one or more other complement inhibitors. Complement inhibitors have not been approved for use in the human body, but some agents have been shown to block complement in vivo. Many of such agents are also toxic, or only partial inhibitors, and their use is limited to being used as research tools. K76COOH and nafamostat mesylate are two agents that have certain therapeutic effects in animal models of transplantation. Studies have shown that low molecular weight heparin also effectively modulates complement activity. We believe that these small molecule inhibitors may be used as agents in combination with the MASP-2 inhibitors of the present disclosure.

Other naturally occurring complement inhibitors may be used in combination with the MASP-2 inhibitors of the present disclosure. The biological inhibitor of complement comprises soluble complement factor 1 (sCR1). This is a naturally occurring inhibitor that may be found on the outer membrane of human cells. Other membrane inhibitors include DAF, MCP, and CD59. Recombinant forms have been assayed for anti-complement activity in vitro and in vivo. sCR1 was shown to be effective in xenografts where the complement system (both alternative and classical) causes hyperreactive rejection syndrome within a few minutes of perfusion of blood into the newly transplanted organ. The use of sCR1 protects and extends the survival time of the transplanted organ, suggesting a complement pathway in organ survival mechanisms.

Other complement inhibitors suitable for use in combination with the compositions of the present disclosure also comprise, for example, the monoclonal antibody (MoAb) being developed by Alexion Pharmaceuticals, Inc. New Haven, Connecticut, and the anti-properdin monoclonal antibody (MoAb).

When used to treat arthritis (e.g., osteoarthritis and rheumatoid arthritis), the MASP-2 inhibitors of the present disclosure may be used in combination with one or more chondroprotective agents, which may include one or more cartilage anabolism promoters and/or one or more cartilage catabolism inhibitors, suitably including both an anabolic agent and a catabolic inhibitory agent administered simultaneously. Suitable chondroprotective agents that promote anabolism comprise interleukin (IL) receptor agonists, including IL-4, IL-10, IL-13, rhIL-4, rhIL-10 and rhIL-13 as well as chimeric IL-4, IL-10 or IL-13; transforming growth factor β superfamily agonists (including TGF-β, TGF-β1, TGF-β2, TGF-β3), bone morphogenetic proteins including BMP-2, BMP-4, BMP-5, BMP-6, BMP-7 (OP-1) and OP-2/BMP-8, growth differentiation factors including GDF-5, GDF-6 and GDF-7, recombinant TGF-β and BMP, and chimeric TGF-β and BMP; insulin-like growth factors, including IGF-1; and fibroblast growth factors, including bFGF. Suitable chondroprotective agents that inhibit catabolism comprise interleukin-1 (IL-1) receptor antagonists (IL-lra), including soluble human IL-1 receptor (shuIL-IR), rshuIL-IR, rhIL-lra, anti-IL1 antibodies, AF11567 and AF12198; tumor necrosis factor (TNF) receptor antagonists (TNF-alpha), soluble receptors including sTNFRI and sTNFRII, recombinant TNF soluble receptors and chimeric TNF soluble receptors including chimeric rhTNFR: Fc, Fc fusion soluble receptors and anti-TNF antibodies; cyclooxygenase-2 (COX-2 specific) inhibitors; including DuP 697, SC-58451, celecoxib, rofecoxib, nimesulide, diclofenac, meloxicam, piroxicam, NS-398, RS-57067, SC-57666, SC-58125, flosulide, etodolac, L-745, 337 and DFU-T-614; mitogen-activated protein kinase (MAPK) inhibitors, including inhibitors of ERKi, ERK2, SAPK1, SAPK2a, SAPK2b, SAPK2d, SAPK3, including SB 203580, SB 203580 iodine, SB202190, SB 242235, SB 220025, RWJ 67657, RWJ 68354, FR 133605, L-167307, PD 98059, PD 1693 16; nuclear factor kappa B (NFκB) inhibitors, including caffeic acid phenethyl ester (CAPE), DM-CAPE, SN-50 peptide, hymenialdisine, and pyrrolidone dithiocarbamate; nitric oxide synthase (NOS) inhibitors, including NG-monomethyl-L-arginine, 1400W, diphenylene iodide, S-methylisothiourea, S-(aminoethyl) isothiourea, L-N6-(l-iminoethyl) lysine, 1,3-PBITU, 2-ethyl-2-thiopseudourea, aminoguanidine, Nω-nitro-L-arginine, methyl Nω-nitro-L-arginine, inhibitors of matrix metalloproteinases (MMP), including inhibitors of MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-10, MMP-11, MMP-12, MMP-13, MMP-14 and MMP-15, including U-24522, minocycline, 4-Abz-Gly-Pro-D-Leu-D-Ala-NHOH, Ac-Arg-Cys-Gly-Val-Pro-Asp-NH2, recombinant human TIMP1, recombinant human TIMP2 and phosphoramidon; cell adhesion molecules, including integrin agonists and antagonists, including αVβ3 MoAb LM 609 and echistatin; anti-chemotactic agents, including F-Met-Leu-Phe receptors, IL-8 receptors, MCP-1 receptors and MIP1-I/RANTES receptors; intracellular signal transduction inhibitors, including (a) protein kinase inhibitors, including (i) protein kinase C (PKC) inhibitors

(isozymes) including calphostin C, G-6203 and GF109203 X and (ii) protein tyrosine kinase inhibitors; (b) intracellular protein tyrosine phosphatase (PTP enzyme) modulators; and (c) SH2 domain inhibitors (src homology 2 domains).

For some applications, it may be advantageous to combine the MASP-2 inhibitors of the present disclosure with a spasm inhibitor. For example, for urogenital applications, it may be advantageous to comprise at least one smooth muscle spasm inhibitor and/or at least one anti-inflammatory agent, and for vascular surgery, it may be beneficial to comprise at least one vasospasm inhibitor and/or at least one anti-inflammatory agent and/or at least one anti-restenosis agent. Suitable examples of the spasm inhibitor include 5-hydroxytryptamine 2 receptor subtype antagonists; tachykinin receptor antagonists; nitric oxide donors; ATP sensitive potassium channel openers; calcium channel antagonists; and endothelin receptor antagonists.

In one embodiment of the present disclosure, the antibody is administered in a single dose or multiple doses.

If the aforementioned antibody is administered in multiple doses according to the present disclosure, the antibody is preferably administered in at least 3 doses, at least 4 doses, at least 5 doses, at least 6 doses, at least 7 doses, at least 8 doses, at least 9 doses, or at least 10 doses and preferably at most 30 doses, 25 doses, 20 doses, 15 doses, or 10 doses. The dose of the aforementioned antibody is preferably administered at intervals of at least 7 days, at least 10 days, at least 14 days, or at least 20 days. Dose of the aforementioned antibody is preferably administered at intervals of 7 to 30 days, 10 to 20 days, and preferably about 14 days.

In one aspect, the present disclosure provides a use of the antibody or antigen-binding fragment thereof, nucleic acid molecule, vector, cell or pharmaceutical composition of any of the preceding aspects in the preparation of a drug for treating diseases associated with MASP-2 dependent complement activation in a subject.

In one aspect, the present disclosure provides a kit comprising the aforementioned antibody or antigen-binding portion thereof, bispecific or multispecific molecule, nucleic acid, vector, cell, and/or composition.

The disclosed kit comprises the antibodies, fragments, homologs, derivatives thereof, etc., of the present disclosure, e.g., the labeled or cytotoxic conjugates, as well as the instructions for use of the antibodies, the conjugates to kill a particular type of cell, and the like. The instructions may comprise directions for using the antibodies, conjugates, etc. in vitro, in vivo, or ex vivo. The antibodies may be in liquid form or solid form, usually lyophilized. The kit may comprise other suitable reagents, such as buffers, reconstitution solutions, and other necessary components for the intended use. Combinations of reagents packaged in predetermined amounts with instructions for their use, e.g., for therapeutic use or for conducting diagnostic assays, are contemplated. When the

antibody is labeled, e.g., with an enzyme, then the kit may comprise a substrate and cofactors required for the enzyme (e.g., a substrate precursor providing a detectable chromophore or fluorophore). In addition, other additives, such as stabilizers, buffers (e.g., blocking buffers or lysis buffers), and the like, may also be included. The relative amounts of the various reagents can be varied to provide a concentrate of reagent solution, which provides user flexibility, and savings space and reagent. These reagents may also be provided in dry powder form, usually in lyophilized form, including excipients which, when dissolved, provide a reagent solution having the appropriate concentration.

In one aspect, the present disclosure provides a use of the aforementioned antibody or antigen-binding portion thereof, bispecific or multispecific molecule, nucleic acid molecule, vector, cell and/or composition in the preparation of a drug or kit for diagnosing, treating or preventing diseases associated with MASP-2 dependent complement activation.

In addition, the antibodies of the present disclosure may also be used in immunoassays, purification methods, and other methods using immunoglobulins or fragments thereof. Such uses are well-known in the art.

Accordingly, the present disclosure further provides a composition comprising the anti-MASP-2 antibody of the present disclosure, or fragment thereof, conveniently in combination with pharmaceutically acceptable carriers, diluents, or excipients, as is conventional in the art.

As used herein, the term "pharmaceutical composition" refers to formulations of various preparations. Formulations comprising therapeutically effective amounts of multivalent antibodies are in a sterile liquid solution, liquid suspension, or lyophilized form, optionally comprising stabilizers or excipients.

It will be appreciated that therapeutic agents according to the preceding embodiments will be administered with suitable pharmaceutically acceptable carriers, excipients, and other agents incorporated into formulations to provide improved transfer, delivery, tolerability, and the like. A large number of suitable formulations can be found in all pharmacopeias known to pharmaceutical chemists: Remington's Pharmaceutical Sciences (15th ed. Mack Publishing Company, Easton, Pa. (1975)), particularly Chapter 87: Blaug, Seymour. These formulations comprise, for example, powders, pastes, ointments, gels, waxes, oils, lipids, lipid-containing (cationic or anionic) carriers (e.g., Lipofectin^{TM}), DNA conjugates, anhydrous syrups, oil-in-water and water-in-oil emulsions, emulsion polyethylene glycols (polyethylene glycols with various molecular weights), semi-solid gels, and semi-solid mixtures containing polyethylene glycol. Any of the aforementioned mixtures may be suitable for the treatment or therapy according to the present disclosure, provided that the active ingredient in the formulation is not inactivated by the formulation and that the formulation is physiologically compatible and tolerates the route of administration.

In another embodiment, antibodies against MASP-2 may be used in methods known in the art relating to localization and/or quantitation of MASP-2 (e.g., for determining MASP-2 and/or levels of MASP-2 in an appropriate physiological sample, for diagnostic methods, for protein imaging, etc.). In a given embodiment, the antibody comprising an antibody-derived antigen-binding domain specific for MASP-2 or derivatives, fragments, analogs or homologs thereof is used as a pharmaceutically active compound (hereinafter referred to as "therapeutic agent").

In another embodiment, MASP-2 polypeptides may be isolated using antibodies specific for MASP-2 by standard techniques such as immunoaffinity, chromatography, or immunoprecipitation. The proteins in a biological sample may be detected with antibodies (or fragments thereof) against the MASP-2 protein. In some embodiments, MASP-2 may be detected in a biological sample as part of a clinical testing procedure, for example, to determine the efficacy of a given therapeutic regimen. Detection may be facilitated by coupling (i.e., physically linking) the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β-galactosidase or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazine aminofluorescein, dansyl chloride, or phycoerythrin; one example of luminescent materials includes luminol; examples of bioluminescent materials include luciferase, luciferin and aequorin, and examples of suitable radioactive materials include ^{125}I, ^{131}I, ^{35}S, or ^{3}H.

In another embodiment, the antibody according to the present disclosure may be used as reagents for detecting the presence of MASP-2 or a protein fragment thereof in a sample. In some embodiments, the antibody comprises a detectable label. The antibody is a polyclonal antibody, or more preferably a monoclonal antibody. Intact antibodies or fragments thereof (e.g., Fab, scFv, or $F(ab')_2$) are used. The term "labeling" with respect to an antibody is intended to encompass direct labeling of the antibody by coupling (i.e., physically linking) a detectable substance to the antibody, as well as indirect labeling of the antibody by reaction with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently labeled secondary antibody, and end-labeling of the antibody with biotin to enable detection with fluorescently labeled streptavidin. The term "biological sample" is intended to comprise tissues, cells, and biological fluids isolated from a subject, as well as tissues, cells, and fluids present in a subject. Thus, the term "biological sample" used comprises blood and fractions or components in blood, including serum, plasma, or lymph. In other words, the detection method

of the preceding embodiments may be used to detect the mRNA, protein, or genomic DNA analytes in a biological sample both in vitro and in vivo. For example, in vitro techniques for the detection of mRNA analytes include Northern hybridization and in situ hybridization. In vitro techniques for the detection of protein analytes include enzyme-linked immunosorbent assay (ELISA), Western blot, immunoprecipitation, and immunofluorescence. In vitro techniques for the detection of genomic DNA analytes include Southern hybridization. Procedures for performing immunoassay are described, for example, in "ELISA: Theory and Practice: Methods in Molecular Biology", vol. 42, J. R. Crowther (ed.) Human Press, Totowa, N. J. 1995; "Immunoassay", E. Diamandis and T. Christopoulus, Academic Press, Inc., San Diego, Calif., 1996; and "Practice and Theory of Enzyme Immunoassays", P. Tijssen, Elsevier Science Publishers, Amsterdam, 1985. In addition, in vivo techniques for the detection of protein analytes include introducing a labeled anti-analyte protein antibody into a subject. For example, an antibody can be labeled with a radiolabel, and the presence and location of the radiolabel in the subject can then be detected by standard imaging techniques.

The antibodies described herein and derivatives, fragments, analogs, and homologs thereof may be incorporated into pharmaceutical compositions suitable for administration. The principles and considerations involved in preparing such compositions, as well as guidance in selecting components, are well-known in the art.

Such compositions typically comprise the antibody and a pharmaceutically acceptable carrier. When the antibody fragments are used, minimal inhibitory fragments that specifically bind the target protein binding domain may be preferred. For example, based on the variable region sequence of the antibody, peptide molecules can be designed to retain the ability to bind a target protein sequence. Such peptides can be chemically synthesized and/or produced by recombinant DNA technique (see, e.g., Marasco et al., Proc. Natl. Acad. Sci. USA, 90:7889-7893 (1993)).

As used herein, the term "pharmaceutically acceptable carrier" is intended to comprise any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic agents and absorption delaying agents, etc., compatible with pharmaceutical administration. Suitable pharmaceutically acceptable carriers are described in the latest edition of Remington's Pharmaceutical Sciences, a standard bibliography in the art, which is incorporated herein by reference. Preferred examples of such carriers or diluents include, but are not limited to, water, saline, Ringer's solution, dextrose solution, and 5% human serum albumin. Liposomes and non-aqueous vehicles such as fixed oils can also be used. The use of such media and agents for pharmaceutically active substances is well-known in the art. Except insofar as any conventional media or agent is incompatible with the antibody, its use in the compositions is contemplated.

The pharmaceutical compositions of the preceding embodiments are formulated to be compatible

with their intended route of administration. Examples of routes of administration include parenteral, e.g., intravenous, intradermal, subcutaneous, oral (e.g., inhalation), transdermal (i.e., topical), transmucosal, and rectal administration. Solutions or suspensions for parenteral, intradermal or subcutaneous administration may comprise the following components: sterile diluents for injection such as water, saline solutions, fixed oils, polyethylene glycols, glycerol, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl p-hydroxybenzoate; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediamine tetraacetic acid (EDTA); buffers, such as acetates, citrates, or phosphates, and reagents to adjust the osmotic pressure, such as sodium chloride or dextrose. The pH may be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation may be packaged in an ampoule, disposable syringe, or multiple dose vials made of glass or plastic.

Pharmaceutical compositions suitable for injectable use comprise sterile aqueous solutions (where is water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solution or dispersion. For intravenous administration, suitable pharmaceutically acceptable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N. J.), or phosphate-buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against contamination from microorganisms such as bacteria and fungi. The carrier may be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol, etc.), and suitable mixtures thereof. For example, the desired particle size can be maintained in the case of dispersions by the use of coatings such as lecithin, and proper fluidity can be maintained by the use of surfactants. Prevention of the action of microorganisms may be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, etc. In many cases, it will be preferable to comprise isotonic agents, e.g., sugars, polyalcohols such as mannitol, sorbitol, and sodium chloride in the composition. The absorption of the injectable compositions can be prolonged by encompassing in the aforementioned composition an agent that delays absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the antibody in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the antibody into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of

sterile injectable solutions, the preparation method is vacuum drying and freeze-drying which yields a powder comprising the active ingredient and any additional desired ingredient from a sterile-filtered solution of those aforementioned ingredients.

For administration by inhalation, the compounds are delivered in the form of an aerosol spray from a pressurized container or dispenser or a nebulizer containing a suitable propellant, e.g., a gas such as carbon dioxide.

Systemic administration may also be carried out by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to permeate the barrier are used in the formulation. Such penetrants are generally known in the art, and include, for example, detergents, bile salts, and fusidic acid derivatives for transmucosal administration. Transmucosal administration may be accomplished through the use of nasal sprays or suppositories. For transdermal administration, one or more of the aforementioned antibodies may be formulated into pastes, ointments, gels, or creams as generally known in the art.

The compounds may also be prepared in the form of suppositories (e.g., with conventional suppository bases such as cocoa butter or other glycerides) or retention enemas for rectal delivery.

In one embodiment, the aforementioned antibodies can be prepared with carriers that prevent their rapid elimination from the body, such as sustained/controlled release formulations, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene-vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparing such formulations will be apparent to those skilled in the art.

It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form, as used herein, refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit contains a predetermined quantity of one or more of the aforementioned antibodies calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the preceding embodiments are dictated by and directly dependent on the unique characteristics of antibodies and the specific therapeutic effects to be achieved, and the limitations inherent in the art of formulating such antibodies for treating individuals.

The aforementioned pharmaceutical compositions may be placed in a container, package, or dispenser together with instructions for administration.

The formulations described herein may also comprise more than one of the aforementioned antibodies, preferably those with complementary activities but without adversely affecting each other, depending on the particular situation to be treated. Alternatively or additionally, the compositions may, for example, comprise an agent that enhances its function, such as a cytotoxic

agent, a cytokine, a chemotherapeutic agent, or a growth inhibitor. Such molecules are suitably present in combination in amounts effective for the intended purpose. For example, they may be present in combination in a kit or in combination for use.

In one embodiment, one or more of the aforementioned antibodies may be administered in combination therapy, i.e., in combination with other agents, such as therapeutic agents, which can be used to treat pathological conditions or disorders, such as various forms of autoimmune diseases, and inflammatory diseases. The term "in combination" means herein that the agents are administered substantially synchronously, simultaneously, or sequentially. If administered sequentially, the first of the two compounds is still preferably detected at an effective concentration at the treatment site when the second compound is initially administered. In one case, the "combination" can also comprise both the antibody of the present disclosure and another therapeutic agent in the kit.

For example, combination therapy may comprise coformulation and/or coadministration of one or more antibodies described herein with one or more additional therapeutic agents (e.g., one or more cytokine and growth factor inhibitors, immunosuppressants, anti-inflammatory agents, metabolic inhibitors, enzyme inhibitors, and/or cytotoxic or cytostatic agents, as described in more detail below). Such combination therapy may advantageously utilize lower dosages of the administered therapeutic agents, thus avoiding possible toxicities or complications associated with each monotherapy.

Experiments of the present disclosure demonstrate that a variety of monoclonal antibodies and variants thereof provided by the present disclosure that bind to MASP-2 with high affinity and inhibit lectin-mediated complement activation can specifically recognize enzymatic activity domains CCP1-CCP2-SP of human, monkey, mouse and rat MASP-2, and effectively inhibit the production of C4b and C3 convertase C4b2a at a low concentration with a blocking activity 50-200 fold higher than that of the known antibodies. The results of the pre-toxicological study in rhesus monkeys showed that the animals tolerated the high-dose novel MASP-2 antibodies well without any toxic reaction, and its efficacy and safety were superior to those of similar antibodies.

For purposes of clarity and conciseness, features are described herein as part of the same or separate embodiments, however, it will be understood that the scope of the present disclosure may include some embodiments having a combination of all or some of the features described.

Examples

Example 1. Lectin pathway MASP-2 activity detection

After recognition of the repeated N-galactosamine or mannose structures by MBL in plasma, serine proteases MASP-1 and MASP-2 can be sequentially activated. The activated MASP-2 cleaves complement components C4 and C2, and the formed C4b is deposited on a well plate,

which can be recognized by an anti-C4b antibody; after cleavage of complement component C3 by C3 convertase C4b2a formed by C4 and C2 cleavage products, the formed C3b is deposited on a well plate, which can be recognized by an anti-C3b antibody. Therefore, the inhibitory activity of the MASP-2 antibody against MASP-2 in serum can be demonstrated by detecting the production of C4b or C3b in the lectin-activated reaction.

C4 cleavage activity assay

20 μg/ml mannan (Sigma, M7504) was added to the ELISA plate and coated overnight at 4℃. After blocking with 2% BSA at room temperature for 60 minutes, 0.5% diluted human serum was added, and overnight at 4℃. After washing, 50 μl/well of different concentrations of MASP-2 antibodies (initial concentration of 30 μg/ml, 5-fold gradient dilution, 9 gradients in total) were added, and pre-incubated at 4℃ for 30 min, then 50 μl of 2 μg/ml human C4 protein (CompTech, # A105) was added, and reacted at 37℃ for 90 min. After washing the plate, 1:1000 diluted Biotin-labeled human C4b polyclonal antibody (ASSAYPRO, # 11223-05021) was added and incubated at room temperature for 90 min, 1:5000 peroxidase-streptavidin (Jackson ImmunoResearch 016-030-084) was added and incubated at room temperature for 60 min, and then TMB developing solution was added, developed in dark at 37℃ for about 10 min. The reaction was stopped and the OD value was read.

C3 convertase activity assay

20 μg/ml mannan was added to the ELISA plate and coated overnight at 4℃. After blocking with 2% BSA at room temperature for 60 min, MASP-2 antibody diluted with 0.5% human serum (initial concentration of 60 μg/ml, 5-fold gradient dilution, 9 gradients in total) was added and reacted at 37℃ for 90 min, 1:500 rabbit anti-human C3/C3b/C3c polyclonal antibody (Proteintech, # 21337-1-AP) was added and incubated at room temperature for 60 min, 1:5000 HRP-labeled goat anti-rabbit secondary antibody (Jackson ImmunoResearch 111-035-144) was added and incubated at room temperature for 60 min, and then TMB developing solution was added, developed in dark at 37℃ for about 10 min. The reaction was stopped, and the OD value was read.

Example 2. Preparation of MASP-2 recombinant proteins

The sequence encoding the enzymatic activity domains CCP1-CCP2-SP of human MASP-2 was cloned into the eukaryotic expression plasmid and fused with his6 tag at N-terminus to facilitate purification. After 7 days of transfection into HEK293E cells, the supernatant of the culture medium was collected and purified by nickel chelating column to obtain the human MASP-2 D4-6 recombinant protein (SEQ ID NO: 1). Similarly, Cynomolgus monkey MASP-2 D4-6 (SEQ ID NO: 2), mouse MASP-2 D4-6 (SEQ ID NO: 3) and rat MASP-2 D4-6 (SEQ ID NO: 4) recombinant proteins were obtained, respectively. FIG. 1 shows the SDS-PAGE result for human,

Cynomolgus monkey, mouse and rat MASP-2 D4-6 recombinant proteins.

Example 3. Immunization of animals and preparation of hybridoma antibodies

BALB/c female mice at 6 weeks of age were selected and immunized subcutaneously or footpad with an equal volume mixture of human or Cynomolgus monkey MASP-2 D4-6 recombinant protein and Freund's adjuvant. Two weeks after the initial immunization, a booster immunization was performed. When the serum titer of the immunized mice reached 1:100000, a shock immunization was performed. Three days later, the spleen and peripheral lymph nodes of the mice are collected and isolated to obtain B cells.

The appropriate amount of B cells and SP2/0 cells were fused and selected in DMEM complete medium containing HAT. The hybridoma cells were cultured at 5% CO_2, 37℃ for 5-7 days. Human or Cynomolgus monkey MASP-2 D4-6 recombinant protein (1 μg/mL) was coated and the hybridoma culture supernatant was detected by ELISA. A total of 778 monoclonal antibodies cross-recognized human or Cynomolgus monkey MASP-2. The supernatant was harvested and assayed by C4 lysis activity, of which 61 clones had significant MASP-2 inhibitory activity (as shown in FIG. 2).

Based on the results of hybridoma screening, RNAs of hybridoma monoclonal cell candidates were extracted by TRNzol lysis method, and then single-chain cDNAs were synthesized by reverse transcription, which was used as a template to amplify the variable region sequences of antibodies in the hybridoma monoclonal cells.

The variable region sequences of the MASP-2 antibodies are as follows:

Table 1. The variable region sequences of MASP-2 murine antibodies

MASP-2 murine antibody	HCVR		HCDR1	HCDR2	HCDR3	LCVR		LCDR1	LCDR2	LCDR3
	Amino acid sequence	Nucleotide sequence	Amino acid sequence	Amino acid sequence	Amino acid sequence	Amino acid sequence	Nucleotide sequence	Amino acid sequence	Amino acid sequence	Amino acid sequence
1B2	5	6	7	8	9	10	11	12	13	14
3B9	15	16	7	17	18	19	20	21	22	23
4F8	24	25	26	27	28	29	30	31	32	33
5J11	34	35	36	37	38	39	40	41	42	43
9P13	44	45	7	46	47	48	49	50	51	52
10H9	53	54	7	17	18	55	56	21	57	23
10L3	58	59	7	17	60	61	62	50	51	52
11F8	63	64	65	66	67	68	69	70	71	72
11G8	73	74	7	17	47	75	76	50	51	52
14K22	77	78	7	17	79	80	81	50	51	82
16A15	83	84	36	85	86	87	88	41	42	43
16A17	83	84	36	85	86	89	90	41	42	91
20J6	92	93	94	95	96	97	98	99	100	101
21E1	102	103	7	104	105	106	107	108	109	110

24G17	111	112	26	113	114	115	116	117	118	33
25L15	119	120	94	95	96	121	122	123	100	101
28O14	124	125	126	127	128	129	130	131	132	133

Clone: 1B2

The amino acid sequence of the heavy chain VH is shown in SEQ ID NO: 5, its encoding nucleic acid is shown in SEQ ID NO: 6, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NO: 7, 8 and 9, respectively.

<----------FR1----------> CDR1 <----FR2-----> CDR2
<--
DVQLQESGPGLVKPSQSLSLTCTVTGYSI**TSDYAWN**WIRQFSGDKLEWMG**YISYSGST**
SYNPSLKSRIS
----------FR3----------->CDR3 <---FR4--->
ITRDTSKNQFFLHLSSVTTEDTATYFCAR**YWGDY**WGHGTTLTVSS

Nucleotide sequence

GATGTGCAGCTTCAGGAGTCGGGACCTGGCCTGGTGAAACCTTCTCAGTCTCTGTCCC
TCACCTGCACTGTCACTGGCTACTCAATCACCAGTGATTATGCCTGGAACTGGATCCGG
CAGTTTTCAGGAGACAAACTGGAGTGGATGGGCTACATAAGCTACAGTGGTTCCACTA
GCTATAACCCATCTCTCAAAAGTCGAATCTCTATCACTCGAGACACATCCAAGAACCAG
TTCTTCCTGCACTTGAGTTCTGTGACTACTGAGGACACAGCCACATATTTCTGTGCAAG
ATATTGGGGCGACTACTGGGGCCACGGCACCACTCTCACAGTCTCCTCA

The amino acid sequence of light chain VK is shown in SEQ ID NO: 10, its encoding nucleic acid is shown in SEQ ID NO: 11, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 12, 13 and 14, respectively.

<----------FR1--------> CDR1 <-----FR2-----> CDR2
<------------
DSVMTQSQKFMSTSVGDRVSVTC**KASHNVGTNVA**WFQQKPGQSPKGLIY**SASYRSS**GV
PDRFTGSGSGT
-----FR3----------> CDR3 <---FR4--->
DFTLTISNVQSEDLAEYFC**LQYNSNPLT**FGGGTKLEVK

Nucleotide sequence

GACAGTGTGATGACCCAGTCTCAAAAATTCATGTCCACATCAGTAGGAGACAGGGTCA
GCGTCACCTGCAAGGCCAGTCACAATGTGGGTACTAATGTAGCCTGGTTTCAACAGAA
ACCAGGACAATCTCCTAAAGGACTGATTTACTCGGCATCCTACCGGTCCAGTGGAGTC
CCTGATCGCTTCACAGGCAGTGGATCTGGGACAGACTTCACTCTCACCATCAGCAATG
TGCAGTCTGAAGACTTGGCAGAGTATTTCTGTCTACAATATAACAGCAATCCTCTGACG
TTCGGTGGAGGCACCAAGCTGGAGGTCAAG

Clone: 3B9

The amino acid sequence of the heavy chain VH is shown in SEQ ID NO: 15, its encoding nucleic acid is shown in SEQ ID NO: 16, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 7, 17 and 18, respectively.

<----------FR1----------> CDR1 <----FR2-----> CDR2
<--
DVQLQESGPGLVRPSQSLSLTCTVTGYSI**TSDYAWN**WIRQFPGNKLEWMG**YISYSGRT**
SYNPSLKSRLS
------------FR3-------------> CDR3 <---FR4--->
ITRDTSKNQFFLQLNSVSSADTATYYCAI**ISTAVDFDY**WGQGTTLTVSS

Nucleotide sequence

GATGTACAACTTCAGGAGTCGGGACCTGGCCTGGTGAGACCTTCTCAGTCTCTGTCCC
TCACCTGCACTGTCACTGGCTACTCAATCACCAGTGATTATGCCTGGAACTGGATCCGG
CAGTTTCCAGGAAACAAACTGGAGTGGATGGGCTACATAAGTTACAGTGGTCGCACTA
GTTACAACCCCTCTCTCAAAAGTCGACTCTCTATCACTCGAGACACATCCAAGAACCA
GTTCTTCCTGCAGTTGAATTCTGTGAGTTCTGCGGACACAGCCACGTATTACTGTGCAA
TTATTTCTACGGCAGTAGACTTTGACTACTGGGGCCAAGGCACCACTCTCACAGTCTCC
TCA

The amino acid sequence of light chain VK is shown in SEQ ID NO: 19, its encoding nucleic acid is shown in SEQ ID NO: 20, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 21, 22 and 23, respectively.

<----------FR1--------> CDR1 <-----FR2-----> CDR2
<------------
QTVLTQSPAIMSASLGERVTMTC**TASSSVSSSYLL**WYQQKPGSSPKLWIY**STSKLAS**G
VPVRFSGSGSG
-----FR3-----------> CDR3 <---FR4--->
TSYSLTISSMEADDAATYYC**LQYNRSPLT**FGAGTKLELK

Nucleotide sequence

CAAACTGTTCTCACCCAGTCTCCAGCAATCATGTCTGCATCTCTAGGGGAACGGGTCA
CCATGACCTGCACTGCCAGCTCAAGTGTAAGTTCCAGTTACTTGCTCTGGTACCAGCA
GAAGCCAGGATCCTCCCCCAAACTCTGGATTTATAGCACATCCAAGTTGGCTTCTGGAG
TCCCAGTTCGCTTCAGTGGCAGTGGGTCTGGGACCTCTTACTCTCTCACAATCAGCAG
CATGGAGGCTGACGATGCTGCCACTTATTACTGCCTCCAGTATAATCGTTCCCCGCTCA
CGTTCGGTGCTGGGACCAAGCTGGAGCTGAAA

Clone: 4F8

The amino acid sequence of the heavy chain VH is shown in SEQ ID NO: 24, its encoding nucleic acid is shown in SEQ ID NO: 25, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 26, 27 and 28, respectively.

<----------FR1----------> CDR1 <----FR2-----> CDR2
<--
EVQLQESGPGLVKPSQSLSLACTVTGYSI**TSDYAWH**WIRQFPGNKLEWMG**FISYSGRT**
NYNPPLTSRIS
------------FR3-------------> CDR3 <---FR4--->
ITRDTSKNQFFLQLNSVTTEDTATYYCAR**SYDYWFGY**WGQGTLVTVSA

Nucleotide sequence

GAGGTCCAGCTGCAGGAGTCGGGACCTGGCCTGGTGAAACCTTCTCAGTCTCTGTCCC
TCGCCTGCACTGTCACTGGCTACTCAATCACCAGTGATTATGCCTGGCACTGGATCCGG

CAGTTTCCAGGAAACAAACTGGAGTGGATGGGCTTCATAAGCTACAGTGGTAGAACTA
ACTACAACCCACCTCTCACAAGTCGAATCTCTATCACTCGAGACACATCCAAGAACCA
GTTCTTCCTGCAGTTGAATTCTGTGACTACTGAGGACACAGCCACATATTACTGTGCAA
GATCATATGATTACTGGTTTGGTTATTGGGGCCAAGGGACTCTGGTCACTGTCTCTGCA

The amino acid sequence of light chain VK is shown in SEQ ID NO: 29, its encoding nucleic acid is shown in SEQ ID NO: 30, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 31, 32 and 33, respectively.

<----------FR1--------> CDR1 <-----FR2-----> CDR2 <-------
NVLMTQTPLSLPVSLGDQASISC**RSSQSLVHSNGNTYLE**WYMQKPGQSPKLLIY**TVSR**
RFSGVPDRFSG
-----FR3-----------> CDR3 <---FR4--->
SGSGTDFTLKISRVEAEDLGVYYC**FQGSHVPVT**FGAGTKLELK

Nucleotide sequence

AATGTTTTGATGACCCAAACTCCACTCTCCCTGCCTGTCAGTCTTGGAGATCAAGCCTC
CATCTCTTGCAGATCTAGTCAGAGTCTTGTACATAGTAATGGAAACACCTATTTAGAATG
GTACATGCAGAAACCAGGCCAGTCTCCAAAGCTCCTGATCTACACAGTTTCCAGACGA
TTTTCTGGGGTCCCAGACAGGTTCAGTGGCAGTGGATCAGGGACAGATTTCACACTCA
AGATCAGCAGAGTGGAGGCTGAGGATCTGGGAGTTTATTATTGCTTTCAAGGTTCACAT
GTTCCGGTCACGTTCGGTGCTGGGACCAAGCTGGAGCTGAAA

Clone: 5J11

The amino acid sequence of the heavy chain VH is shown in SEQ ID NO: 34, its encoding nucleic acid is shown in SEQ ID NO: 35, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 36, 37 and 38, respectively.

<-------------FR1-----------> CDR1 <----FR2-----> CDR2
<--
DVQLQESGPGLVKPSQSLSLTCTVTGYSI**TSDYAWK**WIRQFPGNKLEWMG**YISYSGST**
SYNPSLKGRIS
------------FR3-------------> CDR3 <---FR4--->
ITRDTSKNQFFLHLQSVTIEDTATYYCAI**LGYFAMDY**WGQGTPVTVSS

Nucleotide sequence

GATGTACAACTTCAGGAGTCGGGACCTGGCCTGGTGAAACCTTCTCAGTCTCTGTCCC
TCACCTGCACTGTCACTGGCTACTCAATCACCAGTGATTATGCCTGGAAGTGGATCCGG
CAGTTTCCAGGAAACAAACTGGAGTGGATGGGCTACATAAGTTACAGTGGCAGCACTA
GCTACAACCCTTCTCTCAAAGGTCGAATCTCTATCACTCGAGACACATCCAAGAACCA
GTTTTTCCTGCACTTGCAATCTGTGACTATTGAGGACACAGCCACCTATTACTGTGCAAT
ACTAGGTTACTTTGCTATGGACTACTGGGGGCAAGGAACCCCAGTCACCGTCTCCTCA

The amino acid sequence of light chain VK is shown in SEQ ID NO: 39, its encoding nucleic acid is shown in SEQ ID NO: 40, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 41, 42 and 43, respectively.

<----------FR1--------> CDR1 <-----FR2-----> CDR2

<------------
DIVMTQSQKFMSTSVGDRVSITC**KASQNVRVDVA**WYQQKSGQSPKSLIY**LASNRHT**GV
PDRFTGSGSGT
-----FR3----------> CDR3 <---FR4--->
DFTLTISNVQSEDLADYFC**LQHWSYPLT**FGGGTKLEIK

Nucleotide sequence

GACATTGTGATGACCCAGTCTCAAAAATTCATGTCCACTTCAGTAGGAGACAGGGTCA
GCATCACCTGCAAGGCCAGTCAGAATGTTCGTGTTGACGTTGCCTGGTATCAACAGAA
ATCAGGGCAGTCTCCTAAATCACTGATTTACTTGGCATCCAACCGGCACACTGGAGTCC
CTGATCGCTTCACAGGCAGTGGATCTGGGACAGATTTCACTCTCACCATTAGCAATGTG
CAATCTGAAGACCTGGCAGATTATTTCTGTCTACAACATTGGAGTTATCCTCTGACGTTC
GGTGGAGGCACCAAGCTGGAAATCAAA

Clone: 9P13

The amino acid sequence of the heavy chain VH is shown in SEQ ID NO: 44, its encoding nucleic acid is shown in SEQ ID NO: 45, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 7, 46 and 47, respectively.

<----------FR1----------> CDR1 <----FR2-----> CDR2
<--
DVQLQESGPGLVKPSQSLSLTCTVTGYSI**TSDYAWN**WIRQFPGNTLEWMG**YISYSGRT**
SYNPSLIGRIS
----------FR3----------> CDR3 <---FR4--->
ITRDTTKNQFFLQLNSVSTEDTATYYCAK**LAGGHGMDY**WGQGTSVTVSS

Nucleotide sequence

GATGTGCAGCTTCAGGAGTCGGGACCTGGCCTGGTGAAACCTTCTCAGTCTCTGTCCC
TCACCTGCACTGTCACTGGCTACTCAATCACCAGTGATTATGCCTGGAACTGGATCCGG
CAGTTTCCAGGAAACACATTGGAGTGGATGGGCTATATAAGTTATAGTGGTAGGACTAG
CTACAACCCATCTCTGATAGGTCGAATCTCAATCACTCGAGACACAACCAAGAACCAG
TTCTTTCTGCAGTTGAATTCTGTGTCTACTGAGGACACAGCCACATATTACTGTGCAAA
ATTGGCCGGAGGACATGGGATGGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCC
TCA

The amino acid sequence of light chain VK is shown in SEQ ID NO: 48, its encoding nucleic acid is shown in SEQ ID NO: 49, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 50, 51 and 52, respectively.

<----------FR1--------> CDR1 <-----FR2-----> CDR2
<------------
NIVMTQSQQFMSTSVGDRVSVTC**KASQNVDTNVA**WYQQKPGQSPKALIY**SASYRYS**GV
PDRFTGSGSGT
-----FR3----------> CDR3 <---FR4--->
DFTLTISNVQSEDLAEYFC**LQYNSYLT**FGSGTKLELK

Nucleotide sequence

AACATTGTGATGACCCAGTCTCAACAATTCATGTCCACATCAGTAGGAGACAGGGTCA
GCGTCACCTGCAAGGCCAGTCAGAATGTGGATACTAATGTAGCCTGGTATCAACAGAA
ACCAGGACAATCTCCTAAAGCACTGATTTACTCGGCATCCTACCGGTACAGTGGAGTCC

CTGATCGCTTCACAGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAATGTG
CAGTCTGAAGACTTGGCAGAATATTTCTGTCTGCAATATAATAGTTACCTCACGTTCGGT
TCTGGGACCAAGCTGGAGCTGAAA

Clone: 10H9

The amino acid sequence of the heavy chain VH is shown in SEQ ID NO: 53, its encoding nucleic acid is shown in SEQ ID NO: 54, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 7, 17 and 18, respectively.

<----------FR1----------> CDR1 <----FR2-----> CDR2
<--
DVQLQESGPGLVRPSQSLSLTCTVTGYSI**TSDYAWN**WIRQFPGNKLEWMG**YISYSGRT**
SYNPSLKSRLS
----------FR3----------> CDR3 <---FR4--->
VTRDTSKNQFFLQLNSVNAADTATYYCAI**ISTAVDFDY**WGQGTTLTVSS

Nucleotide sequence

GATGTACAACTTCAGGAGTCGGGACCTGGCCTGGTGAGACCTTCTCAGTCTCTGTCCC
TCACCTGCACTGTCACTGGCTACTCAATCACCAGTGATTATGCCTGGAACTGGATCCGG
CAGTTTCCAGGAAACAAACTGGAGTGGATGGGCTACATAAGTTACAGTGGTCGCACTA
GCTACAACCCCTCTCTCAAGAGTCGACTCTCTGTCACTCGAGACACATCCAAGAACCA
GTTCTTCCTGCAGTTGAATTCTGTGAATGCTGCGGACACAGCCACGTATTACTGTGCAA
TTATTTCTACGGCAGTAGACTTTGACTACTGGGGCCAAGGCACCACTCTCACAGTCTCC
TCA

The amino acid sequence of light chain VK is shown in SEQ ID NO: 55, its encoding nucleic acid is shown in SEQ ID NO: 56, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 21, 57 and 23, respectively.

<----------FR1--------> CDR1 <-----FR2-----> CDR2
<------------
QIVLTQSPAIMSASLGERVTMTC**TASSSVSSSYLL**WYQQKPGSSPKLWIY**SSSKLAS**G
VPVRFSGSGSG
-----FR3----------> CDR3 <---FR4-->
TSYSLTISSMEAEDAATYYC**LQYNRSPLT**FGAGTKLELK

Nucleotide sequence

CAAATTGTTCTCACCCAGTCTCCAGCAATCATGTCTGCATCTCTAGGGGAACGGGTCAC
CATGACCTGCACTGCCAGCTCAAGTGTAAGTTCCAGTTACTTGCTCTGGTACCAGCAG
AAGCCAGGATCCTCCCCCAAACTCTGGATTTATAGCTCATCCAAGTTGGCTTCTGGAGT
CCCAGTTCGCTTCAGTGGCAGTGGGTCTGGGACCTCTTACTCTCTCACAATCAGCAGC
ATGGAGGCTGAAGATGCTGCCACTTATTACTGCCTCCAGTATAATCGTTCCCCGCTCAC
GTTCGGTGCTGGGACCAAGCTGGAGCTGAAA

Clone: 10L3

The amino acid sequence of the heavy chain VH is shown in SEQ ID NO: 58, its encoding nucleic acid is shown in SEQ ID NO: 59, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 7, 17 and 60, respectively.

<-------------FR1-----------> CDR1 <----FR2-----> CDR2
<--
DVQLQESGPGLVKPSQSLSLTCTVTGYSI**TSDYAWN**WIRQFPGNKLEWMG**YISYSGRT**
SYNPSLKSRIS
------------FR3-------------> CDR3 <---FR4--->
ITRDTSKNQFFLQLNSVTTEDTATYYCAK**LGGGHGMDY**WGQGTSVTVSS

Nucleotide sequence

GATGTGCAGCTTCAGGAGTCGGGACCTGGCCTGGTGAAACCTTCTCAGTCTCTGTCCC
TCACCTGCACTGTCACTGGCTACTCAATCACCAGTGATTATGCCTGGAACTGGATCCGG
CAGTTTCCAGGAAACAAATTGGAGTGGATGGGCTACATAAGTTATAGTGGTAGGACTA
GCTACAACCCATCTCTGAAAAGTCGAATCTCAATCACTCGAGACACATCCAAGAACCA
GTTCTTCCTGCAGTTGAATTCTGTGACTACTGAGGACACAGCCACATATTACTGTGCAA
AATTGGGCGGAGGACATGGGATGGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTC
CTCA

The amino acid sequence of light chain VK is shown in SEQ ID NO: 61, its encoding nucleic acid is shown in SEQ ID NO: 62, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 50, 51 and 52, respectively.

<----------FR1--------> CDR1 <-----FR2-----> CDR2
<-------------
IVMTQSQKFMSTSVGDRVSVTC**KASQNVDTNVA**WYQQKPGQSPKALIY**SASYRYS**GVP
DRFTGSGSGTD
----FR3----------> CDR3 <---FR4--->
FTLTISNVQSEDLAEYFC**LQYNSYLT**FGSGTKLELK

Nucleotide sequence

ACATTGTGATGACCCAGTCTCAAAAATTCATGTCCACATCAGTAGGAGACAGGGTCAG
CGTCACCTGCAAGGCCAGTCAGAATGTGGATACTAATGTAGCCTGGTATCAACAGAAA
CCAGGGCAATCTCCTAAAGCGCTGATTTACTCGGCATCCTACCGTTACAGTGGAGTCCC
TGATCGCTTCACAGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAATGTGC
AGTCTGAAGACTTGGCAGAGTATTTCTGTCTGCAATATAACAGCTACCTCACGTTCGGT
TCTGGGACCAAGCTGGAGCTGAAA

Clone: 11F8

The amino acid sequence of the heavy chain VH is shown in SEQ ID NO: 63, its encoding nucleic acid is shown in SEQ ID NO: 64, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 65, 66 and 67, respectively.

<-------------FR1-----------> CDR1 <----FR2-----> CDR2 <-
QVTLKESGPGILKPSQTLILTCSFSGFSL**NTSGMGVG**WIRQPSGKGLEWLA**HIWWDDD**
KDYNPSLKSQV
------------FR3--------------> CDR3 <---FR4--->
TISKDTSTNQVFLKITSVDTADGATYYCVR**DTTFLDAMDY**WGQGTSVTVSS

Nucleotide sequence

CAAGTTACTCTAAAAGAGTCTGGCCCTGGGATATTGAAGCCCTCACAGACCCTCATTCT
GACTTGTTCTTTCTCTGGGTTTTCACTGAACACTTCTGGTATGGGTGTAGGCTGGATTC

GTCAGCCTTCAGGGAAGGGTCTGGAGTGGCTGGCACACATTTGGTGGGATGATGATAA
GGACTATAACCCATCCCTGAAGAGCCAAGTCACAATCTCCAAGGATACCTCCACAAAC
CAGGTGTTCCTCAAGATCACCAGTGTGGACACTGCAGATGGTGCCACTTACTACTGTG
TTCGAGATACTACGTTTTTAGATGCTATGGACTACTGGGGTCAAGGAACCTCAGTCACC
GTCTCCTCA

The amino acid sequence of light chain VK is shown in SEQ ID NO: 68, its encoding nucleic acid is shown in SEQ ID NO: 69, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 70, 71 and 72, respectively.

<----------FR1--------> CDR1 <-----FR2-----> CDR2 <-------
DVLMTQTPLSLPVSLGDQASISC**RSSQSIVHRNGNTFLE**WYLQKPGQSPKLLIY**RVSN RFS**GVPDRFSG
-----FR3--------------> CDR3 <---FR4-->
SGSGTDFTLKISRVEAEDLGVYYC**FQGSHVPFT**FGSGTKLEIK

Nucleotide sequence

GATGTTTTGATGACCCAAACTCCACTCTCCCTGCCTGTCAGTCTTGGAGATCAAGCCTC
CATCTCTTGCAGGTCTAGTCAGAGCATTGTACATCGTAATGGAAACACCTTTTTAGAAT
GGTACCTGCAGAAACCAGGCCAGTCTCCAAAGCTCCTGATCTACAGGGTTTCCAACCG
ATTTTCTGGGGTCCCAGACAGGTTCAGTGGCAGTGGATCAGGGACAGATTTCACACTC
AAGATCAGCAGAGTGGAGGCTGAGGATCTGGGAGTTTATTACTGCTTTCAAGGTTCAC
ATGTTCCATTCACGTTCGGCTCGGGGACAAAGTTGGAAATAAAA

Clone: 11G8

The amino acid sequence of the heavy chain VH is shown in SEQ ID NO: 73, its encoding nucleic acid is shown in SEQ ID NO: 74, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 7, 17 and 47, respectively.

<----------FR1----------> CDR1 <----FR2-----> CDR2 <--
DVQLQESGPGLVKPSQSLSLTCTVTGYSI**TSDYAWN**WIRQLPGNKLEWVG**YISYSGRT SYNPSLKS**RIS
----------FR3----------> CDR3 <---FR4--->
ITRDTTKNQFFLQLNSVTTEDTATYYCAK**LAGGHGMDY**WGQGTSVTVSS

Nucleotide sequence

GATGTGCAGCTTCAGGAGTCGGGACCTGGCCTGGTGAAACCTTCTCAGTCTCTGTCCC
TCACCTGCACTGTCACTGGCTACTCAATCACCAGTGATTATGCCTGGAACTGGATCCGG
CAGTTACCAGGAAACAAATTGGAGTGGGTGGGCTATATAAGTTATAGTGGTAGGACTAG
CTACAACCCATCTCTGAAAAGTCGAATCTCAATCACTCGAGACACAACCAAGAACCAG
TTCTTCCTGCAGTTGAATTCTGTGACTACTGAGGACACAGCCACATATTACTGTGCAAA
GTTGGCCGGGGGACATGGGATGGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCC
TCA

The amino acid sequence of light chain VK is shown in SEQ ID NO: 75, its encoding nucleic acid is shown in SEQ ID NO: 76, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 50, 51

and 52, respectively.

<----------FR1--------> CDR1 <-----FR2-----> CDR2
<-------------
NIVMTQSQKFMSTSVGDRVSVTC**KASQNVDTNVA**WYQQKPGQSPKALIH**SASYRYS**GV
PDRFTGSGSGT
----FR3-----------> CDR3 <---FR4--->
DFILTISNVQSEDLAEYFC**LQYNSYLT**FGSGTKLELK

Nucleotide sequence

AACATTGTGATGACCCAGTCTCAAAAATTCATGTCCACATCAGTAGGAGACAGGGTCA
GCGTCACCTGCAAGGCCAGTCAGAATGTGGATACTAATGTAGCCTGGTATCAACAGAA
ACCAGGGCAATCTCCTAAAGCACTGATTCACTCGGCATCCTACCGGTACAGTGGAGTC
CCTGATCGCTTCACAGGCAGTGGATCTGGGACAGATTTCATTCTCACCATCAGTAATGT
GCAGTCTGAAGACTTGGCAGAGTATTTCTGTCTGCAATATAACAGCTACCTCACGTTCG
GTTCTGGGACCAAGCTGGAGCTGAAA

Clone: 14K22

The amino acid sequence of the heavy chain VH is shown in SEQ ID NO: 77, its encoding nucleic acid is shown in SEQ ID NO: 78, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 7, 17 and 79, respectively.

<-------------FR1-----------> CDR1 <----FR2-----> CDR2
<--
DVQLQESGPGLVKPSQSLSLTCTVTGYSI**TSDYAWN**WIRQFPGNKLEWMG**YISYSGRT**
SYNPSLKSRIS
------------FR3-------------> CDR3 <---FR4--->
ITRDTSKNQFFLHLNSVTTEDTATYFCAV**LGLYFDY**WGQGTPLTVSS

Nucleotide sequence

GATGTGCAGCTTCAGGAGTCGGGACCTGGCCTGGTGAAACCTTCTCAGTCTCTGTCCC
TCACCTGCACTGTCACTGGCTACTCAATCACCAGTGATTATGCCTGGAACTGGATCCGG
CAGTTTCCAGGAAACAAACTGGAGTGGATGGGCTACATAAGCTACAGTGGTAGAACTA
GCTACAACCCATCTCTCAAAAGTCGAATCTCTATCACTCGAGACACATCCAAGAACCA
GTTCTTCCTGCACTTGAATTCTGTGACTACTGAGGACACAGCCACATATTTCTGTGCAG
TACTGGGACTCTACTTTGACTACTGGGGCCAAGGCACCCCTCTCACAGTCTCCTCA

The amino acid sequence of light chain VK is shown in SEQ ID NO: 80, its encoding nucleic acid is shown in SEQ ID NO: 81, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 50, 51 and 82, respectively.

<----------FR1--------> CDR1 <-----FR2-----> CDR2
<------------
DIVMTQSQKFMSTSVGDRVSVTC**KASQNVDTNVA**WYQQKPGQSPKALIY**SASYRYS**GV
PDRFTGSGSGT
----FR3-----------> CDR3 <---FR4--->
DFTLTISNVQSEDLAEYFC**HQFNSNPLT**FGAGTKLELK

Nucleotide sequence

GACATTGTGATGACCCAGTCTCAAAAATTCATGTCCACATCAGTAGGAGACAGGGTCA
GCGTCACCTGCAAAGCCAGTCAGAATGTGGATACTAATGTAGCCTGGTATCAACAGAA

ACCAGGGCAATCTCCTAAAGCACTGATTTACTCGGCATCCTACCGGTACAGTGGAGTCC
CTGATCGCTTCACAGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAATGTG
CAGTCTGAAGACTTGGCAGAATATTTCTGTCACCAATTTAACAGCAATCCTCTCACGTT
CGGTGCTGGGACCAAGCTGGAGCTGAAA

Clone: 16A15

The amino acid sequence of the heavy chain VH is shown in SEQ ID NO: 83, its encoding nucleic acid is shown in SEQ ID NO: 84, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 36, 85 and 86, respectively.

```
<-------------FR1-----------> CDR1 <----FR2----->     CDR2
<--
DVQLQESGPGLVKPSQSLSLTCTVTGYSITSDYAWKWIRQFPGNKLEWMGYISYSGST
SYHPSLKGRIS
------------FR3-------------> CDR3 <---FR4--->
ITRDTSKNQFFLQLNSVTADDTATYYCAILGYYAMDYWGQGTSVTVSS
```

Nucleotide sequence

GATGTGCAGCTTCAGGAGTCGGGACCTGGCCTGGTGAAACCTTCTCAGTCTCTGTCCC
TCACCTGCACTGTCACTGGCTACTCAATCACCAGTGATTATGCCTGGAAATGGATCCGG
CAGTTTCCAGGAAACAAACTGGAATGGATGGGCTACATAAGCTACAGTGGTTCCACTA
GCTATCACCCATCTCTCAAAGGTCGAATCTCCATCACTCGAGACACATCCAAGAACCA
GTTCTTCCTGCAGTTGAATTCTGTGACTGCTGACGACACAGCCACATATTACTGTGCAA
TATTAGGTTACTATGCTATGGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCTCA

The amino acid sequence of light chain VK is shown in SEQ ID NO: 87, its encoding nucleic acid is shown in SEQ ID NO: 88, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 41, 42 and 43, respectively.

```
<----------FR1-------->     CDR1     <-----FR2-----> CDR2
<------------
DIVMTQSQKFMSTSVGDRVSITCKASQNVRVDVAWYQQKSGQSPRALIYLASNRHTGV
PDRFTGSGSGT
----FR3----------->  CDR3  <---FR4--->
DFTLTITNVQSEDLADYFCLQHWSYPLTFGGGTKLEIK
```

Nucleotide sequence

GACATTGTGATGACCCAGTCTCAAAAATTCATGTCCACATCAGTAGGAGACAGGGTCA
GTATCACCTGCAAGGCCAGTCAGAATGTTCGTGTTGACGTAGCCTGGTATCAACAGAA
ATCAGGGCAGTCTCCTAGAGCACTGATTTACTTGGCATCCAACCGGCACACTGGAGTC
CCTGATCGCTTCACAGGCAGTGGATCTGGGACAGATTTCACTCTCACCATTACCAATGT
GCAATCTGAGGACCTGGCAGATTATTTCTGTCTACAACATTGGAGTTATCCTCTGACGT
TCGGTGGAGGCACCAAGCTGGAAATCAAA

Clone: 16A17

The amino acid sequence of the heavy chain VH is shown in SEQ ID NO: 83, its encoding nucleic acid is shown in SEQ ID NO: 84, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 36, 85 and 86, respectively.

<----------FR1----------> CDR1 <----FR2-----> CDR2 <--

DVQLQESGPGLVKPSQSLSLTCTVTGYSI**TSDYAWK**WIRQFPGNKLEWMG**YISYSGST**

SYHPSLKGRIS

----------FR3----------> CDR3 <---FR4--->

ITRDTSKNQFFLQLNSVTADDTATYYCAI**LGYYAMDY**WGQGTSVTVSS

Nucleotide sequence

GATGTGCAGCTTCAGGAGTCGGGACCTGGCCTGGTGAAACCTTCTCAGTCTCTGTCCC

TCACCTGCACTGTCACTGGCTACTCAATCACCAGTGATTATGCCTGGAAATGGATCCGG

CAGTTTCCAGGAAACAAACTGGAATGGATGGGCTACATAAGCTACAGTGGTTCCACTA

GCTATCACCCATCTCTCAAAGGTCGAATCTCCATCACTCGAGACACATCCAAGAACCA

GTTCTTCCTGCAGTTGAATTCTGTGACTGCTGACGACACAGCCACATATTACTGTGCAA

TATTAGGTTACTATGCTATGGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCTCA

The amino acid sequence of light chain VK is shown in SEQ ID NO: 89, its encoding nucleic acid is shown in SEQ ID NO: 90, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 41, 42 and 91, respectively.

<----------FR1--------> CDR1 <-----FR2-----> CDR2 <------------

DIVMTQSQKFMSTSVGDRVSITC**KASQNVRVDVA**WYQQKSGQSPRALIY**LASNRHT**GV

PDRFTGSGSGT

----FR3-----------> CDR3 <---FR4--->

DFTLTITNVQSEDLADYFC**PQHWSYPLT**FGGGTKLEIK

Nucleotide sequence

GACATTGTGATGACCCAGTCTCAAAAATTCATGTCCACATCAGTAGGAGACAGGGTCA

GTATCACCTGCAAGGCCAGTCAGAATGTTCGTGTTGACGTAGCCTGGTATCAACAGAA

ATCAGGGCAGTCTCCTAGAGCACTGATTTACTTGGCATCCAACCGGCACACTGGAGTC

CCTGATCGCTTCACAGGCAGTGGATCTGGGACAGATTTCACTCTCACCATTACCAATGT

GCAATCTGAGGACCTGGCAGATTATTTCTGTCCACAACATTGGAGTTATCCTCTGACGT

TCGGTGGAGGCACCAAGCTGGAAATCAAA

Clone: 20J6

The amino acid sequence of the heavy chain VH is shown in SEQ ID NO: 92, its encoding nucleic acid is shown in SEQ ID NO: 93, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 94, 95 and 96, respectively.

<----------FR1----------> CDR1 <----FR2-----> CDR2 <--

KVKLVESGGDLVKPGGSLKISCTASGFTF**SNYAMS**WIRQTPDKRLEWVA**TVSSGGPYT**

YYPDSVKGRFT

----------FR3----------> CDR3 <---FR4--->

ISRDNAENTLYLQMSSLRSDDTAIYYCAR**QIYSDYDVTY**WGQGTLVTVSA

Nucleotide sequence

AAAGTGAAGCTGGTGGAGTCTGGGGGAGACTTAGTGAAGCCTGGAGGGTCCCTGAAA

ATCTCCTGTACAGCCTCTGGATTCACTTTCAGTAACTATGCCATGTCTTGGATTCGCCAG

ACTCCGGACAAGAGGCTGGAGTGGGTCGCAACCGTTAGTAGTGGTGGTCCTTACACCT

ACTATCCAGACAGTGTGAAGGGGCGATTCACCATCTCCAGAGACAATGCCGAAAACAC
CCTGTACCTGCAAATGAGCAGTCTGAGGTCTGATGACACGGCCATATATTACTGTGCAA
GGCAGATCTACTCTGATTACGACGTCACTTACTGGGGCCAAGGGACTCTGGTCACTGT
CTCTGCA

The amino acid sequence of light chain VK is shown in SEQ ID NO: 97, its encoding nucleic acid is shown in SEQ ID NO: 98, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 99, 100 and 101, respectively.

<----------FR1--------> CDR1 <-----FR2-----> CDR2
<-------------
QIVLSQSPAILSASPGETVTMTC**RASSSVSFMY**WLQQKPGSSPQPWIY**ATSNLAS**GVP
ARFSGSGSGTS
----FR3----------> CDR3 <---FR4--->
YSLTITRVEAEDAATYYC**QQWSFRPWT**FGGGTKLEIK

Nucleotide sequence

CAAATTGTTCTCTCCCAGTCTCCAGCAATCCTGTCTGCATCTCCAGGGGAGACGGTCAC
AATGACTTGCAGGGCCAGTTCAAGTGTAAGTTTCATGTACTGGCTCCAGCAGAAGCCA
GGTTCCTCCCCCCAACCCTGGATTTATGCCACATCCAACCTGGCTTCTGGAGTCCCTGC
TCGCTTCAGTGGCAGTGGGTCTGGGACCTCTTACTCCCTCACAATCACCAGAGTGGAG
GCTGAAGATGCTGCCACTTATTACTGTCAACAGTGGAGTTTTAGACCGTGGACGTTCG
GTGGAGGCACCAAGCTGGAAATCAAA

Clone: 21E1

The amino acid sequence of the heavy chain VH is shown in SEQ ID NO: 102, its encoding nucleic acid is shown in SEQ ID NO: 103, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 7, 104 and 105, respectively.

<-------------FR1-----------> CDR1 <----FR2-----> CDR2
<--
DVQLQESGPGLVKPSQSLSLTCTVTGFSI**TSDYAWN**WIRQFPGNKLEWMG**YISYSGRT**
NYNPSLKSRFS
------------FR3-------------> CDR3 <---FR4--->
ITRDTSKNQFFLQLNSVTTEDTATYYCAR**SYDYWFPY**WGQGTLVTVSA

Nucleotide sequence

GATGTGCAGCTTCAGGAGTCGGGACCTGGCCTGGTGAAACCTTCTCAGTCTCTGTCCC
TCACCTGCACTGTCACTGGCTTCTCAATCACCAGTGATTATGCCTGGAACTGGATCCGG
CAGTTTCCAGGAAACAAACTGGAGTGGATGGGCTACATAAGCTACAGTGGTAGAACTA
ACTACAACCCATCTCTCAAAAGTCGATTCTCTATCACTCGAGACACATCCAAGAACCA
GTTCTTCCTGCAGTTGAATTCTGTGACTACTGAGGACACAGCCACATATTACTGTGCAA
GATCATATGATTACTGGTTTCCTTACTGGGGCCAAGGGACTCTGGTCACTGTCTCTGCA

The amino acid sequence of light chain VK is shown in SEQ ID NO: 106, its encoding nucleic acid is shown in SEQ ID NO: 107, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 108, 109 and 110, respectively.

<----------FR1--------> CDR1 <-----FR2----->

CDR2 <-------
DVLMTQTPLSLPVSLGDQASISC**RSSQSIVHSNGNTFLE**WYLQKPGQSPKLLIY**KVSN**
RFSGVPDRFSG
----FR3-----------------> CDR3 <---FR4--->
SGSGTDFTLKISRVEAEDLGVYYC**FQGSHIPVT**FGAGTKLELK

Nucleotide sequence

GATGTTTTGATGACCCAAACTCCACTCTCCCTGCCTGTCAGTCTTGGAGATCAAGCCTC
CATCTCTTGCAGATCTAGTCAGAGCATTGTACATAGTAATGGAAACACCTTTTTGGAAT
GGTACCTGCAGAAACCAGGCCAGTCTCCAAAGCTCCTGATCTACAAAGTTTCCAACCG
ATTTTCTGGGGTCCCAGACAGGTTCAGTGGCAGTGGATCAGGGACAGATTTCACACTC
AAGATCAGCAGAGTGGAGGCTGAGGATCTGGGAGTTTATTACTGCTTTCAAGGTTCAC
ATATTCCGGTCACGTTCGGTGCTGGGACCAAGCTGGAGCTGAAA

Clone: 24G17

The amino acid sequence of the heavy chain VH is shown in SEQ ID NO: 111, its encoding nucleic acid is shown in SEQ ID NO: 112, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 26, 113 and 114, respectively.

<-------------FR1-----------> CDR1 <----FR2-----> CDR2
<--
EVQLQESGPGLVKPSQSLSLTCTVTGFSI**TSDYAWH**WIRQFPGNKLEWMG**FINYSGRT**
NYNPSLTSRIS
------------FR3-------------> CDR3 <---FR4--->
IIRDTSKNQFFLQLNSVTTEDTATYYCAR**SYDFWFGY**WGQGTLVTVSA

Nucleotide sequence

GAGGTCCAGCTGCAGGAGTCGGGACCTGGCCTGGTGAAACCTTCTCAGTCTCTGTCCC
TCACCTGCACTGTCACTGGCTTCTCAATCACCAGTGATTATGCCTGGCACTGGATCCGG
CAGTTTCCAGGAAACAAACTGGAGTGGATGGGCTTCATAAACTACAGTGGTAGAACTA
ACTACAACCCATCTCTCACAAGTCGAATCTCTATCATTCGGGACACATCCAAGAACCAG
TTCTTCCTGCAGTTGAATTCTGTGACTACTGAGGACACAGCCACATATTACTGTGCAAG
ATCATATGATTTCTGGTTTGGTTATTGGGGCCAAGGGACTCTGGTCACTGTCTCTGCA

The amino acid sequence of light chain VK is shown in SEQ ID NO: 115, its encoding nucleic acid is shown in SEQ ID NO: 116, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 117, 118 and 33, respectively.

<----------FR1--------> CDR1 <-----FR2----->
CDR2 <-------
NVLMTQSPLSLPVSLGDQASISC**RSSQSIVHSNGNTYLE**WYMQKPGQSPKLLIY**TVSK**
RFSGVPDRFSG
----FR3-----------------> CDR3 <---FR4--->
SGSGTDFTLKISRVEAEDLGVYYC**FQGSHVPVT**FGAGTKLELK

Nucleotide sequence

AATGTTTTGATGACCCAAAGTCCACTCTCCCTGCCTGTCAGTCTTGGAGATCAAGCCTC
CATCTCTTGCAGATCTAGTCAGAGTATTGTACATAGTAATGGAAACACCTATTTAGAATG
GTATATGCAGAAACCAGGCCAGTCTCCAAAGCTCCTGATCTACACAGTTTCCAAACGAT
TTTCTGGGGTCCCAGACAGGTTCAGTGGCAGTGGATCAGGGACAGATTTCACACTCAA

GATCAGCAGAGTGGAGGCTGAGGATCTGGGAGTTTATTATTGCTTTCAAGGTTCACATG
TTCCGGTCACGTTCGGTGCTGGGACCAAGCTGGAGCTGAAA

Clone: 25L15

The amino acid sequence of the heavy chain VH is shown in SEQ ID NO: 119, its encoding nucleic acid is shown in SEQ ID NO: 120, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 94, 95 and 96, respectively.

<----------FR1----------> CDR1 <----FR2-----> CDR2
<--
KVKLVESGGDLVKPGGSLKISCAASGFTF**SNYAMS**WIRQTPDKRLEWVA**TVSSGGPYT**
YYPDSVKGRFT
----------FR3----------> CDR3 <---FR4--->
ISRDNAENTLYLQMSSLRSDDTAIYYCAR**QIYSDYDVTY**WGQGTLVTVSA

Nucleotide sequence

AAAGTGAAGCTGGTGGAGTCTGGGGGAGACTTAGTGAAGCCTGGAGGGTCCCTGAAA
ATCTCCTGTGCAGCCTCTGGATTCACTTTCAGTAACTATGCCATGTCTTGGATTCGCCAG
ACTCCGGACAAGAGGCTGGAGTGGGTCGCAACCGTTAGTAGTGGTGGTCCTTACACCT
ACTATCCAGACAGTGTGAAGGGGCGATTCACCATCTCCAGAGACAATGCCGAAAACAC
CCTGTACCTGCAAATGAGCAGTCTGAGGTCTGATGACACGGCCATTTATTACTGTGCAA
GGCAGATCTACTCTGATTACGACGTCACTTACTGGGGCCAAGGGACTCTGGTCACTGT
CTCTGCA

The amino acid sequence of light chain VK is shown in SEQ ID NO: 121, its encoding nucleic acid is shown in SEQ ID NO: 122, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 123, 100 and 101, respectively.

<----------FR1--------> CDR1 <-----FR2-----> CDR2
<-------------
QIVLSQSPAILSASPGETVTMTC**RVSSSVSYMY**WLQQKPGSSPKPWIY**ATSNLAS**GVP
ARFSGSGSGTS
----FR3----------> CDR3 <---FR4--->
YSLTITRVEAEDAATYYC**QQWSFRPWT**FGGGTKLEIK

Nucleotide sequence

CAAATTGTTCTCTCCCAGTCTCCAGCAATCCTGTCTGCATCTCCAGGGGAGACGGTCAC
AATGACTTGCAGGGTCAGTTCAAGTGTAAGTTACATGTACTGGCTCCAACAGAAGCCA
GGATCCTCCCCCAAACCCTGGATTTATGCCACATCCAACCTGGCTTCTGGAGTCCCTGC
TCGCTTCAGTGGCAGTGGGTCTGGGACCTCTTACTCCCTCACAATCACCAGAGTGGAG
GCTGAAGATGCTGCCACTTATTACTGTCAGCAGTGGAGTTTTAGACCGTGGACGTTCG
GTGGAGGCACCAAGCTGGAAATCAAA

Clone: 28O14

The amino acid sequence of the heavy chain VH is shown in SEQ ID NO: 124, its encoding nucleic acid is shown in SEQ ID NO: 125, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 126, 127 and 128, respectively.

<----------FR1----------> CDR1 <----FR2----> CDR2 <--

QVQLQQSGTELARPGASVRMSCKASGYTFR**SHTMH**WVKQRPGQGLEWIG**YINPSTGYINYNQKFKD**KAT
----------FR3----------> CDR3 <---FR4--->
LTADKSSSTAYMQLSSLTSEDSAVYYCAR**SNYSYYYGMDY**WGQGTSVTVSS

Nucleotide sequence

CAGGTCCAGCTGCAGCAGTCTGGGACTGAACTGGCAAGACCTGGGGCCTCAGTGAGG
ATGTCCTGCAAGGCTTCTGGCTACACCTTTAGGAGTCACACGATGCACTGGGTAAAAC
AGAGGCCTGGACAGGGTCTGGAATGGATTGGATACATTAATCCTAGCACTGGTTATATT
AATTACAATCAGAAGTTCAAGGACAAGGCCACATTGACTGCAGACAAATCCTCCAGCA
CAGCCTACATGCAACTGAGCAGCCTGACATCTGAGGACTCTGCAGTCTATTACTGTGCA
AGAAGTAACTACTCTTATTACTATGGTATGGACTACTGGGGTCAAGGAACCTCAGTCAC
CGTCTCCTCA

The amino acid sequence of light chain VK is shown in SEQ ID NO: 129, its encoding nucleic acid is shown in SEQ ID NO: 130, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 131, 132 and 133, respectively.

<----------FR1--------> CDR1 <-----FR2-----> CDR2 <----------
DIVMTQSHKFMSTSVGDRVTITCKASQDVNTAVAWYQQKPGQSPKLLIYSASYRYTGVPDRFTGSGSGT
----FR3-----------> CDR3 <---FR4--->
DFTFTISSLQAEDLAVYYCQQHYNIPLTFGAGTKLELK

Nucleotide sequence

GACATTGTGATGACCCAGTCTCACAAATTCATGTCCACATCAGTGGGAGACAGGGTCA
CCATCACCTGCAAGGCCAGTCAGGATGTAAATACTGCTGTAGCCTGGTATCAACAGAA
ACCAGGACAATCTCCTAAACTACTGATTTACTCGGCATCCTACCGGTACACTGGGGTCC
CTGATCGCTTCACTGGCAGTGGATCTGGGACGGATTTCACTTTCACCATCAGCAGTTTA
CAGGCTGAAGACCTGGCAGTTTATTACTGTCAGCAACATTATAATATTCCGCTCACGTTC
GGTGCTGGGACCAAGCTGGAGCTGAAA

The light chain variable region of the antibody described above was cloned into the vector containing the human light chain constant region, and the heavy chain variable region was cloned into the vector containing the human heavy chain constant region. The plasmid was co-transfected into CHO-S cells. The entire IgG antibody was expressed and secreted into the culture medium. After expression for 7 days at 37℃, 5% CO_2 and 125 rpm, the supernatant was collected and purified by Protein A chromatography to obtain chimeric IgG. The concentration of IgG was determined by spectrophotometry. The control antibody 17D20_3521N11 (OMS646) was synthesized according to the literature US20120282263.

Each chimeric antibody was tested for inhibitory activity against the cleaved C4 response as described in Example 1, and the OD450 nm value was read. After collecting data, the results were calculated using GraphPad Prism 5 software. The results are shown in FIG. 3, in which the chimeric antibodies 10L3, 3B9, 16A17, 4F18, 25L15, 28O14 and 1B2 showed significantly greater inhibitory activity against MASP-2 than the control antibody in the C4 cleavage activity

assay.

The selected dominant chimeric antibodies were tested for inhibition of C3 convertase activity as described in Example 1. After collecting data, the results were calculated using GraphPad Prism 5 software. The results are shown in FIG. 4, in which the dominant chimeric antibodies 10L3, 3B9, 16A17, 4F18, 25L15, 28O14 and 1B2 showed significantly greater inhibitory activity than the control antibody in the C3 convertase activity assay.

Affinity assessment

Human MASP-2 D4-6 recombinant protein was coated at 1 μg/mL in a 96-well ELISA plate and incubated overnight at 4°C. After blocking with 2% skim milk at room temperature for 1 hour, gradient-diluted MASP-2 antibodies, i.e. chimeric antibodies 10L3, 3B9, 16A17, 4F18, 25L15, 28O14 and 1B2 (initial concentration of 30 μg/ml, 1:4 gradient dilution), were added and incubated at room temperature for 60 min. Goat anti-human Fc-HRP diluted 1:4000 was added and incubated at room temperature for 60 min. The color was developed with TMB for 10 min, then the reaction was stopped by adding concentrated sulfuric acid. The OD450 nm was determined, and the results were calculated using Graph Pad Prism 5 software.

The results are shown in FIG. 5, in which the chimeric antibodies bind to human, Cynomolgus monkey, rat and mouse MASP-2 (Table 2).

Table 2. Binding of MASP-2 antibodies to each species protein.

EC50 (nM)	Human MASP-2	Cynomolgus monkey MASP-2	Rat MASP-2	Mouse MASP-2
1B2	0.015	0.014	1.439	0.947
3B9	0.025	0.038	1.624	4.393
4F18	0.004	0.003	0.127	0.287
10L3	0.022	0.016	30.19	30.90
16A17	0.014	0.014	4.296	1.973
25L15	0.012	0.008	0.021	0.023
28O14	0.033	0.043	-	-

Surface plasmon resonance technology (SPR/Biacore T200) was used to capture 0.1 μg/ml of the antibody on the surface of the Protein A chip, with a capture time of 40 seconds and a flow rate of 10 μl/min. The chip was washed with buffer until the baseline leveled off, then gradient-diluted antigen was flowed through the chip at the flow rate of 30 μl/min, with a binding time of 120 sec and a dissociation time of 600 sec. The equilibrium dissociation constant (KD) was obtained by fitting in Langmuir 1:1 kinetics mode. The affinity of the candidate antibodies with each species of MASP-2 antigen is shown in Table 3.

Table 3. The affinity of MASP-2 antibodies with each species protein.

KD (nM)	Human MASP-2	Cynomolgus monkey MASP-2	Rat MASP-2	Mouse MASP-2
1B2	0.002	0.078	Weak	632
3B9	0.067	0.051	1043	476
4F18	0.108	24.76	2471	218
10L3	0.070	1.290	Weak	214
16A17	0.008	0.063	Weak	487
25L15	0.120	0.920	167	499
28O14	0.090	0.010	162	767
Control antibody	21.1	8.750	88.5	225

Example 4. Construction and screening of phage antibody library

Total RNA was extracted from the partially immunized mouse B cells obtained in Example 3, and reverse transcribed using light and heavy chain specific primers, respectively, to generate an antibody cDNA library. The variable region fragments of antibody were amplified using variable region primers, and cloned into phage plasmid by enzyme digestion. The phage display library of antibody Fab based on M13 phage was constructed, with the capacity of 1×10^{10}.

Conventional phage panning was used for library screening. MASP-2 D4-6 recombinant protein was coated onto an Immuno tube, and about 1×10^{12} phages were added per screening reaction for incubation and panning. After 2 rounds of panning, single clones were picked and inoculated into a 96-well U-shaped plate for culture and inducible expression. The culture supernatant was taken for ELISA detection of MASP-2 recombinant protein. A total of 494 monoclonal Fab antibodies cross-recognizing human, Cynomolgus monkey, rat and mouse MASP-2 were obtained, of which 34 clones can inhibit C4b deposition catalyzed by MASP-2 (FIG. 6).

After re-inducing the expression of the Fab clone with the inhibitory activity described above, the Fab antibody was purified and the inhibitory activity of the MASP-2 antibody was determined by C4 cleavage activity assay. The results are shown in FIG. 7, in which the monoclonal antibodies 3H6, 14F11, 16B11, 20C8, 21A3 and 21B1 showed the most significant inhibitory activity against C4b deposition catalyzed by MASP-2 at concentrations greater than 0.01 μg/ml.

The surface plasmon resonance (SPR/Biacore T200) technique was used to capture the anti-Flag antibody with Protein A chip. 10 μg/ml purified Fab antibody containing Flag tag was captured on the chip surface, with a capture time of 40 sec and a flow rate of 10 μl/min. The chip was washed with buffer until the baseline leveled off, then gradient-diluted MASP-2 antigens were injected as the analytes successively to determine the affinity between Fab and different species antigens. The data were fitted by Biacore T200 Evaluation software 3.1 software in Langmuir 1:1 kinetics mode. Table 4 shows the affinity of mAbs 16B11 and 14F11 with each species of MASP-2 antigens.

Table 4. The affinity of MASP-2 antibodies with the antigens.

MASP-2	16B11			14F11		
	ka (1/Ms)	kd (1/s)	KD (M)	ka (1/Ms)	kd (1/s)	KD (M)
Human	2.15E+06	8.75E-05	4.07E-11	9.48E+05	1.63E-04	1.72E-10
Cynomolgus	1.66E+06	1.81E-04	1.09E-10	2.46E+10	1.14E+02	4.66E-09
Mouse	4.61E+06	8.11E-03	1.76E-09	6.44E+07	1.16E+00	1.80E-08
Rat	1.84E+06	9.31E-03	5.06E-09	3.34E+06	1.82E-03	5.46E-10

The variable region sequences of the Fab antibodies were obtained by Sanger sequencing as follows:

Table 5. The variable region sequences of MASP-2 murine antibodies

MASP-2 murine antibody	HCVR		HCDR1	HCDR2	HCDR3	LCVR		LCDR1	LCDR2	LCDR3
	Amino acid sequence	Nucleotide sequence	Amino acid sequence	Amino acid sequence	Amino acid sequence	Amino acid sequence	Nucleotide sequence	Amino acid sequence	Amino acid sequence	Amino acid sequence
3H6	134	135	136	137	138	129	130	131	132	133
16B11	139	140	7	17	141	142	143	144	145	146
14F11	147	148	149	150	151	152	153	154	155	156
20C8	157	158	7	17	9	159	160	161	162	14
21A3	163	164	7	165	9	166	167	144	168	14
21B1	169	170	7	17	9	171	172	144	173	174

Clone: 3H6

The amino acid sequence of the heavy chain VH is shown in SEQ ID NO: 134, its encoding nucleic acid is shown in SEQ ID NO: 135, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 136, 137 and 138, respectively.

<----------FR1----------> CDR1 <----FR2-----> CDR2 <--
QVQLQQSGTELARPGASVKMSCKASGYTF**ATYSIH**WVKQRPGQGLEWIG**YINPSSGYTNYNQKFRD**KAT
----------FR3----------> CDR3 <---FR4--->
LTADRSSNTAYMQLSSLTSEDSAVYYCAR**VYYTFYHAMDY**WGQGTSVTVSS

Nucleotide sequence

CAGGTCCAGCTGCAGCAGTCTGGGACTGAACTGGCAAGACCTGGGGCCTCAGTGAAG
ATGTCCTGCAAGGCTTCTGGCTACACCTTTGCTACCTACTCGATACACTGGGTAAAACA
GAGGCCTGGGCAGGGTCTGGAATGGATTGGATACATTAATCCTAGCAGTGGTTATACTA
ATTACAATCAGAAGTTCAGGGACAAGGCCACATTGACTGCAGACAGATCCTCCAACAC
AGCCTACATGCAACTGAGCAGCCTGACATCTGAGGACTCTGCAGTCTATTACTGTGCA
AGAGTCTACTATACTTTTTACCATGCTATGGACTACTGGGGTCAAGGAACCTCAGTCAC
CGTCTCCTCA

The amino acid sequence of light chain VK is shown in SEQ ID NO: 129, its encoding nucleic acid is shown in SEQ ID NO: 130, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 131, 132 and 133, respectively.

<----------FR1--------> CDR1 <-----FR2-----> CDR2 <------------
DIVMTQSHKFMSTSVGDRVTITC**KASQDVNTAVA**WYQQKPGQSPKLLIY**SASYRYT**GVPDRFTGSGSGT

----FR3-----------> CDR3 <---FR4--->
DFTFTISSLQAEDLAVYYC**QQHYNIPLT**FGAGTKLELK

Nucleotide sequence

GACATTGTGATGACCCAGTCTCACAAATTCATGTCCACATCAGTGGGAGACAGGGTCA

CCATCACCTGCAAGGCCAGTCAGGATGTAAATACTGCTGTAGCCTGGTATCAACAGAA

ACCAGGACAATCTCCTAAACTACTGATTTACTCGGCATCCTACCGGTACACTGGGGTCC

CTGATCGCTTCACTGGCAGTGGATCTGGGACGGATTTCACTTTCACCATCAGCAGTTTA

CAGGCTGAAGACCTGGCAGTTTATTACTGTCAGCAACATTATAATATTCCGCTCACGTTC

GGTGCTGGGACCAAGCTGGAGCTGAAA

Clone: 16B11

The amino acid sequence of the heavy chain VH is shown in SEQ ID NO: 139, its encoding nucleic acid is shown in SEQ ID NO: 140, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 7, 17 and 141, respectively.

<-------------FR1-----------> CDR1 <----FR2-----> CDR2 <--
QMQLQESGPGLVKPSQSLSLTCTVTGYSI**TSDYAWN**WIRQFPGNKLEWMG**YISYSGRTSYNPSLKS**RIS
-----------FR3--------------> CDR3<---FR4--->
ITRDTSKNQFFLQLNSVTTEDTATYYCAR**HYGDY**WGQGTTLTVSS

Nucleotide sequence

CAGATGCAGCTTCAGGAGTCGGGACCTGGCCTGGTGAAACCTTCTCAGTCTCTGTCCC

TCACCTGCACTGTCACTGGCTACTCAATCACCAGTGATTATGCCTGGAACTGGATCCGG

CAGTTTCCAGGAAACAAACTGGAGTGGATGGGCTACATAAGCTACAGTGGTAGGACTA

GCTACAACCCATCTCTCAAAAGTCGAATCTCTATCACTCGAGACACATCCAAGAACCA

GTTCTTCCTGCAGTTGAATTCTGTGACTACTGAGGACACAGCCACATATTACTGTGCAA

GACACTACGGAGACTACTGGGGCCAAGGCACCACTCTCACAGTCTCCTCA

The amino acid sequence of light chain VK is shown in SEQ ID NO: 142, its encoding nucleic acid is shown in SEQ ID NO: 143, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 144, 145 and 146, respectively.

<----------FR1--------> CDR1 <-----FR2-----> CDR2 <------------
DIVMTQSQKLMSTSVGDRVSVTC**KASQNVGTNVA**WYQQKPGQSPKALIY**SASYRNS**GVPDRFTGSGSGT
----FR3-----------> CDR3 <---FR4--->
DFTLTISNVQSEDLAEYFC**QQFNTNPLT**FGSGTKLEIK

Nucleotide sequence

GACATTGTGATGACTCAGTCTCAAAAACTCATGTCCACATCAGTAGGAGACAGGGTCA

GCGTCACCTGCAAGGCCAGTCAGAATGTGGGTACTAATGTAGCCTGGTATCAACAGAA

ACCAGGGCAATCTCCTAAAGCACTGATTTACTCGGCATCCTACCGGAACAGTGGAGTC

CCTGATCGCTTCACAGGCAGTGGTTCTGGGACAGATTTCACTCTCACCATCAGCAATGT

GCAGTCTGAAGACTTGGCAGAGTATTTCTGTCAGCAATTTAACACCAATCCTCTCACGT

TCGGCTCGGGGACAAAGTTGGAAATAAAA

Clone: 14F11

The amino acid sequence of the heavy chain VH is shown in SEQ ID NO: 147, its encoding

nucleic acid is shown in SEQ ID NO: 148, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 149, 150 and 151, respectively.

<----------FR1----------> CDR1 <----FR2-----> CDR2 <--
QVQLQQSGPQLLRPGASVKISCKASGFSF**TNHWIH**WVKQRPGQGLEWIG**MIDPSDSETGLNQKFRD**KAT
----------FR3----------> CDR3 <---FR4--->
LTVDKSSSTAYMHLNSPTSEDSAVYYCAR**LGIHDGYYIYAMDF**WGQGTSVTVSS

Nucleotide sequence

CAGGTTCAGCTGCAGCAGTCTGGGCCTCAGCTACTTAGGCCTGGGGCTTCAGTGAAGA
TATCCTGCAAGGCTTCTGGTTTCTCATTCACCAACCACTGGATACACTGGGTGAAACAG
AGGCCTGGACAAGGTCTTGAGTGGATTGGCATGATTGATCCTTCCGATAGTGAAACTG
GCCTCAATCAGAAGTTCAGGGACAAGGCCACATTGACTGTAGACAAGTCCTCCAGCAC
AGCCTACATGCACCTCAACAGCCCGACATCTGAGGACTCTGCGGTCTATTACTGTGCAA
GATTGGGAATCCATGATGGTTACTACATCTATGCTATGGACTTTTGGGGTCAAGGAACC
TCAGTCACCGTCTCCTCA

The amino acid sequence of light chain VK is shown in SEQ ID NO: 152, its encoding nucleic acid is shown in SEQ ID NO: 153, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 154, 155 and 156, respectively.

<----------FR1--------> CDR1 <-----FR2-----> CDR2 <------------
NIVMTQSPKSMSMSVGERVTLSC**KASENVGTYVS**WYQQKPEQSPKLLIY**GASNRYT**GVPDRFTGSGSAT
----FR3----------> CDR3 <---FR4--->
DFTLTISSVQAEDLADYHC**GQSYSYPLT**FGAGTKLELK

Nucleotide sequence

AACATTGTAATGACCCAATCTCCCAAATCCATGTCCATGTCAGTAGGAGAGAGGGTCAC
CTTGAGCTGCAAGGCCAGTGAGAATGTGGGTACTTATGTATCCTGGTATCAACAGAAA
CCAGAGCAGTCTCCTAAACTGCTGATATACGGGGCATCCAACCGGTACACTGGGGTCC
CCGATCGCTTCACAGGCAGTGGATCTGCAACAGATTTCACTCTGACCATCAGCAGTGT
GCAGGCTGAAGACCTTGCAGATTATCACTGTGGACAGAGTTACAGCTATCCGCTCACG
TTCGGTGCTGGGACCAAGCTGGAGCTGAAA

Clone: 20C8

The amino acid sequence of the heavy chain VH is shown in SEQ ID NO: 157, its encoding nucleic acid is shown in SEQ ID NO: 158, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 7, 17 and 9, respectively.

<----------FR1----------> CDR1 <----FR2-----> CDR2 <--
EVQLQESGPGLVKPSQSLSLTCSVTGYSI**TSDYAWN**WIRQFPGNKLEWMG**YISYSGRTSYNPSLKS**RIS
----------FR3----------> CDR3<---FR4--->
ITRDTSKNQFFLQLISVTTEDTATYYCAR**YWGDY**WGQGTTLTVSS

Nucleotide sequence

GAGGTGCAGCTTCAGGAGTCGGGACCTGGCCTGGTGAAACCTTCTCAGTCTCTGTCCC
TCACCTGCTCTGTCACTGGCTACTCAATCACCAGTGATTATGCCTGGAACTGGATCCGG
CAGTTTCCAGGAAACAAGCTGGAGTGGATGGGCTACATAAGTTACAGTGGTAGAACTA
GCTACAACCCATCTCTCAAAAGTCGAATCTCTATCACTCGAGACACATCCAAGAACCA

GTTCTTCCTGCAGTTGATTTCTGTGACTACTGAGGACACAGCCACATATTATTGTGCAA

GATATTGGGGCGACTACTGGGGCCAAGGCACCACTCTCACAGTCTCCTCA

The amino acid sequence of light chain VK is shown in SEQ ID NO: 159, its encoding nucleic acid is shown in SEQ ID NO: 160, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 161, 162 and 14, respectively.

<----------FR1--------> CDR1 <-----FR2-----> CDR2 <------------
DIVMTQSQKFISTSIGDRVSVTC**KASQDVGGHVA**WFQQRPGQSPKPLIY**SATFRHS**GVPDRFTGSGSGT
----FR3-----------> CDR3 <---FR4--->
DFTLTISNLQSEDLAEYVC**LQYNSNPLT**FGPGTKLELK

Nucleotide sequence

GACATTGTGATGACCCAGTCTCAAAAATTCATCTCCACATCAATAGGAGACAGGGTCA

GCGTCACCTGCAAGGCCAGTCAGGATGTGGGTGGACATGTGGCCTGGTTTCAACAGA

GACCCGGGCAATCTCCTAAACCTCTGATTTATTCGGCAACCTTCCGGCACAGTGGAGTC

CCTGATCGCTTCACGGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGTAATCT

ACAGTCTGAGGACTTGGCAGAATATGTCTGTCTGCAATATAACAGTAATCCACTCACGT

TCGGTCCTGGGACCAAGCTGGAGCTGAAA

Clone: 21A3

The amino acid sequence of the heavy chain VH is shown in SEQ ID NO: 163, its encoding nucleic acid is shown in SEQ ID NO: 164, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 7, 165 and 9, respectively.

<-------------FR1-----------> CDR1 <----FR2-----> CDR2 <--
DVQLQESGPGLVKPSQSLSLTCTVTGYSI**TSDYAWN**WIRQFPGNKLEWMG**YISYSGRTSYNPYLKS**RIS
------------FR3-------------> CDR3<---FR4--->
ITRDTSKNQFFLQLNSVTTEDTATYYCAR**YWGDY**WGQGTTLTVSS

Nucleotide sequence

GATGTGCAGCTTCAGGAGTCGGGACCTGGCCTGGTGAAACCTTCTCAGTCTCTGTCCC

TCACCTGCACTGTCACTGGCTACTCAATCACCAGTGATTATGCCTGGAACTGGATCCGG

CAGTTTCCAGGAAACAAACTGGAGTGGATGGGCTACATAAGCTACAGTGGTCGCACTA

GCTACAACCCATATCTCAAAAGTCGAATTTCTATCACTCGAGACACATCCAAGAACCAG

TTCTTCCTGCAGTTGAATTCTGTGACTACTGAGGACACAGCCACATATTACTGTGCAAG

ATATTGGGGCGACTACTGGGGCCAAGGCACCACTCTCACAGTCTCCTCA

The amino acid sequence of light chain VK is shown in SEQ ID NO: 166, its encoding nucleic acid is shown in SEQ ID NO: 167, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 144, 168 and 14, respectively.

<----------FR1--------> CDR1 <-----FR2-----> CDR2 <------------
DIVMTQSQKFMSTSVGDRVSVTC**KASQNVGTNVA**WYKQKPGQSPKALIY**SASYRHS**GVPDRFTGSGSGT
----FR3-----------> CDR3 <---FR4--->
DFTLTISNVQSEDLAEYFC**LQYNSNPLT**FGAGTKLELK

Nucleotide sequence

GACATTGTGATGACCCAGTCTCAAAAATTCATGTCCACATCAGTAGGAGACAGGGTCA

GCGTCACCTGCAAGGCCAGTCAGAATGTGGGTACTAATGTAGCCTGGTATAAACAGAA

ACCAGGGCAATCTCCTAAAGCACTGATTTACTCGGCATCCTACCGGCACAGTGGAGTC
CCTGATCGCTTCACAGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAATGT
GCAGTCTGAAGACTTGGCAGAGTATTTCTGTCTGCAATATAACAGCAATCCTCTCACGT
TCGGTGCTGGGACCAAGCTGGAGCTGAAA

Clone: 21B1

The amino acid sequence of the heavy chain VH is shown in SEQ ID NO: 169, its encoding nucleic acid is shown in SEQ ID NO: 170, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 7, 17 and 9, respectively.

<----------FR1----------> CDR1 <----FR2-----> CDR2 <--
DVQLQESGPGLVKPSQSLSLTCTVTGYSI**TSDYAWN**WIRQFPGNKLEWMG**YISYSGRTSYNPSLKS**RIS
----------FR3----------> CDR3<---FR4--->
ITRDTSKNQFFLQLNSVTAEDTATYYCAR**YWGDY**WGQGTTLTVSS

Nucleotide sequence

GATGTGCAGCTTCAGGAGTCGGGACCTGGCCTGGTGAAACCTTCTCAGTCTCTGTCCC
TCACCTGCACTGTCACTGGCTACTCAATCACCAGTGATTATGCCTGGAACTGGATCCGG
CAGTTTCCAGGAAACAAACTGGAGTGGATGGGCTACATAAGCTACAGTGGTCGCACTA
GCTACAACCCATCTCTCAAAAGTCGAATCTCTATCACTCGAGACACATCCAAGAACCA
GTTCTTCCTGCAGTTGAATTCTGTGACTGCTGAGGACACAGCCACATATTACTGTGCAA
GATATTGGGGCGACTACTGGGGCCAAGGCACCACTCTCACAGTCTCCTCA

The amino acid sequence of light chain VK is shown in SEQ ID NO: 171, its encoding nucleic acid is shown in SEQ ID NO: 172, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 144, 173 and 174, respectively.

<----------FR1--------> CDR1 <-----FR2-----> CDR2 <----------
DIVMTQSQKFMSTSVGDRVSVTC**KASQNVGTNVA**WFQQKPGQSPKALIY**STSYRSS**GVPDRFTGSGSGT
----FR3----------> CDR3 <---FR4--->
DFTLTISNVQSEDLAEYFC**QQFNSNPLT**FGGGTKLELK

Nucleotide sequence

GACATTGTGATGACACAGTCTCAAAAATTCATGTCCACATCAGTAGGAGACAGGGTCA
GCGTCACCTGCAAGGCCAGTCAGAATGTGGGTACTAATGTAGCCTGGTTTCAACAGAA
ACCAGGGCAATCTCCTAAAGCACTGATTTACTCGACATCCTACCGGTCCAGTGGAGTCC
CTGATCGCTTCACAGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAATGTG
CAGTCTGAAGACTTGGCAGAGTACTTCTGTCAGCAATTTAACAGCAATCCTCTCACGTT
CGGAGGGGGGACCAAGCTGGAGCTGAAA

Example 5. Humanization of MASP-2 antibodies

Murine antibodies 28O14, 3H6 and 16B11 with high affinity and activity were selected for humanization of variable region sequences. The glycosylation site NYS of clone 28O14 heavy chain CDR3 was first subjected to site-directed mutagenesis, and the mutant was expressed as Fab in E. coli. The affinity assay showed that the S-A mutant (Ala102) with a serine to alanine mutation at position 102 did not affect MASP-2 binding activity after the removal of the

glycosylation site of 28O14 heavy chain CDR3 (as shown in FIG. 8).

The sequence of murine antibody was aligned with that of human antibody germline to find out the human germline light chain genes which have good homology, are completely identical with the key amino acid sequences maintaining the antibody structure core and have a high frequency of occurrence in the human body, and murine antibody CDR grafting was conducted; the CDR region and its surrounding framework amino acid sequences were analyzed by computer homology modeling to avoid the concentrated distribution of molecular surface charges or hydrophobic regions. Humanization design yielded a total of three heavy and six light chain 16B11 variants, four heavy and one light chain 3H6 variants, four heavy and one light chain 28O14 variants, and three heavy and six light chain 16B11 variants.

The humanized sequences are as follows:

Table 6. The Heavy chain variable region sequences of MASP-2 humanized antibodies

MASP-2 humanized antibody	HCVR		HCDR1	HCDR2	HCDR3
	Amino acid sequence	Nucleotide sequence	Amino acid sequence	Amino acid sequence	Amino acid sequence
h16B11 H1	175	176	7	17	141
h16B11 H2	177	178	7	17	141
h16B11 H3	179	180	7	17	141
h3H6 H1	181	182	136	183	138
h3H6 H2	184	185	136	183	138
h3H6 H3	186	187	136	183	138
h3H6 H4	188	189	136	183	138
h28O14 H1	190	191	126	192	128
h28O14 H2	193	194	126	192	128
h28O14 H3	195	196	126	192	128
h28O14 H4	197	198	126	192	128

Table 7. The light chain variable region sequences of MASP-2 humanized antibodies

MASP-2 humanized antibody	LCVR		LCDR1	LCDR2	LCDR3
	Amino acid sequence	Nucleotide sequence	Amino acid sequence	Amino acid sequence	Amino acid sequence
h16B11 K1	199	200	201	202	146
h16B11 K2	203	204	201	202	146
h16B11 K3	205	206	201	207	146
h16B11 K4	208	209	201	202	146
h16B11 K5	210	211	201	202	146
h16B11 K6	212	213	201	207	146
h28O14 K1	214	215	216	132	133
h3H6 K1	214	215	216	132	133

h16B11:

h16B11 H1

The amino acid sequence of h16B11 H1 is shown in SEQ ID NO: 175, its encoding nucleic acid is shown in SEQ ID NO: 176, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 7, 17 and 141, respectively.

<----------FR1----------> CDR1 <-----FR2-----> CDR2

<-------
QMQLQESGPGLVKPSETLSLTCTVSGYSI**TSDYAWN**WIRQPPGKGLEWIG**YISYSGRTSYNPSLK**
SRVTISRD
----------FR3------------> CDR3 <----FR4--->
TSKNQFSLKLSSVTAADTAVYYCAR**HYGDY**WGQGTLVTVSS

Nucleotide sequence

CAGATGCAGCTGCAAGAGTCTGGACCTGGACTGGTCAAGCCCAGCGAGACACTGAGC

CTGACCTGTACCGTGTCCGGCTACAGCATCACAAGCGACTACGCCTGGAACTGGATCA

GACAGCCTCCTGGCAAAGGCCTCGAGTGGATCGGCTACATCAGCTACAGCGGCAGAA

CCAGCTACAACCCCAGCCTGAAGTCCAGAGTGACCATCAGCAGAGACACCAGCAAGA

ACCAGTTCTCCCTGAAGCTGAGCAGCGTGACAGCCGCCGATACAGCCGTGTACTACTG

CGCTAGACACTACGGCGATTACTGGGGCCAGGGAACCCTGGTCACAGTGTCATCT

h16B11 H2

The amino acid sequence of h16B11 H2 is shown in SEQ ID NO: 177, its encoding nucleic acid is shown in SEQ ID NO: 178, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 7, 17 and 141, respectively.

<--------------FR1-------------> CDR1 <-----FR2-----> CDR2
<-------
QLQLQESGPGLVKPSETLSLTCTVSGYSI**TSDYAWN**WIRQPPGKGLEWIG**YISYSGRTSYNPSLKS**RVT
ISRD
----------FR3-------------->CDR3<----FR4--->
TSKNQFSLKLSSVTAADTAVYYCAR**HYGDY**WGQGTLVTVSS

Nucleotide sequence

CAGCTCCAGCTGCAAGAGTCTGGACCTGGACTGGTCAAGCCCAGCGAGACACTGAGC

CTGACCTGTACCGTGTCCGGCTACAGCATCACAAGCGACTACGCCTGGAACTGGATCA

GACAGCCTCCTGGCAAAGGCCTCGAGTGGATCGGCTACATCAGCTACAGCGGCAGAA

CCAGCTACAACCCCAGCCTGAAGTCCAGAGTGACCATCAGCAGAGACACCAGCAAGA

ACCAGTTCTCCCTGAAGCTGAGCAGCGTGACAGCCGCCGATACAGCCGTGTACTACTG

CGCTAGACACTACGGCGATTACTGGGGCCAGGGAACCCTGGTCACAGTGTCATCT

h16B11 H3

The amino acid sequence of h16B11 H3 is shown in SEQ ID NO: 179, its encoding nucleic acid is shown in SEQ ID NO: 180, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 7, 17 and 141, respectively.

<--------------FR1-------------> CDR1 <-----FR2-----> CDR2
<-------
QLQLQESGPGLVKPSETLSLTCTVSGYSI**TSDYAWN**WIRQPPGKGLEWIG**YISYSGRTSYNPSLKS**RVT
ISVD
----------FR3-------------->CDR3<----FR4--->
TSKNQFSLKLSSVTAADTAVYYCAR**HYGDY**WGQGTLVTVSS

Nucleotide sequence

CAGCTCCAGCTGCAAGAGTCTGGACCTGGACTGGTCAAGCCCAGCGAGACACTGAGC

CTGACCTGTACCGTGTCCGGCTACAGCATCACAAGCGACTACGCCTGGAACTGGATCA

GACAGCCTCCTGGCAAAGGCCTCGAGTGGATCGGCTACATCAGCTACAGCGGCAGAA

CCAGCTACAACCCCAGCCTGAAGTCCAGAGTGACCATCAGCGTAGACACCAGCAAGA
ACCAGTTCTCCCTGAAGCTGAGCAGCGTGACAGCCGCCGATACAGCCGTGTACTACTG
CGCTAGACACTACGGCGATTACTGGGGCCAGGGAACCCTGGTCACAGTGTCATCT

h3H6:

h3H6 H1

The amino acid sequence of h3H6 H1 is shown in SEQ ID NO: 181, its encoding nucleic acid is shown in SEQ ID NO: 182, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 136, 183 and 138, respectively.

<----------FR1----------> CDR1 <-----FR2-----> CDR2
<-------
QVQLVQSGAEVKKPGSSVKVSCKASGYTF**ATYSIH**WVRQAPGQGLEWMG**YINPSSGYTNYNQKFQG**RVT
LTAD
--------FR3--------------> CDR3 <----FR4--->
KSTSTAYMELSSLRSEDTAVYYCAR**VYYTFYHAMDY**WGQGTTVTVSS

Nucleotide sequence

CAGGTTCAGCTGGTTCAGTCTGGCGCCGAAGTGAAGAAACCTGGCAGCAGCGTGAAG
GTGTCCTGCAAGGCTAGCGGCTACACCTTCGCCACCTACAGCATCCACTGGGTCCGAC
AGGCTCCAGGACAGGGACTTGAGTGGATGGGCTACATCAACCCCAGCTCTGGCTACAC
CAACTACAACCAGAAATTCCAGGGCCGCGTGACCCTCACAGCCGACAAGTCTACAAG
CACCGCCTACATGGAACTGAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTG
CGCCAGAGTGTACTACACATTCTACCACGCCATGGACTACTGGGGCCAGGGCACAACA
GTGACCGTTAGCTCT

h3H6 H2

The amino acid sequence of h3H6 H2 is shown in SEQ ID NO: 184, its encoding nucleic acid is shown in SEQ ID NO: 185, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 136, 183 and 138, respectively.

<----------FR1----------> CDR1<-----FR2-----> CDR2
<-------
QVQLVQSGAEVKKPGSSVKVSCKASGYTF**ATYSIH**WVRQAPGQGLEWMG**YINPSSGYTNYNQKFQG**RVT
LTAD
--------FR3--------------> CDR3 <----FR4--->
ESTSTAYMELSSLRSEDTAVYYCAR**VYYTFYHAMDY**WGQGTTVTVSS

Nucleotide sequence

CAGGTTCAGCTGGTTCAGTCTGGCGCCGAAGTGAAGAAACCTGGCAGCAGCGTGAAG
GTGTCCTGCAAGGCTAGCGGCTACACCTTCGCCACCTACAGCATCCACTGGGTCCGAC
AGGCTCCAGGACAGGGACTTGAGTGGATGGGCTACATCAACCCCAGCTCTGGCTACAC
CAACTACAACCAGAAATTCCAGGGCCGCGTGACCCTCACAGCCGACGAGTCTACAAG
CACCGCCTACATGGAACTGAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTG
CGCCAGAGTGTACTACACATTCTACCACGCCATGGACTACTGGGGCCAGGGCACAACA
GTGACCGTTAGCTCT

h3H6 H3

The amino acid sequence of h3H6 H3 is shown in SEQ ID NO: 186, its encoding nucleic acid is shown in SEQ ID NO: 187, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 136, 183 and 138, respectively.

<----------FR1----------> CDR1<-----FR2-----> CDR2
<-------
QVQLVQSGAEVKKPGSSVKVSCKASGYTF**ATYSIH**WVRQAPGQGLEWMG**YINPSSGYTNYNQKFQG**RVT
ITAD
--------FR3--------------> CDR3 <----FR4--->
KSTSTAYMELSSLRSEDTAVYYCAR**VYYTFYHAMDY**WGQGTTVTVSS

Nucleotide sequence

CAGGTTCAGCTGGTTCAGTCTGGCGCCGAAGTGAAGAAACCTGGCAGCAGCGTGAAG
GTGTCCTGCAAGGCTAGCGGCTACACCTTCGCCACCTACAGCATCCACTGGGTCCGAC
AGGCTCCAGGACAGGGACTTGAGTGGATGGGCTACATCAACCCCAGCTCTGGCTACAC
CAACTACAACCAGAAATTCCAGGGCCGCGTGACCATCACAGCCGACAAGTCTACAAG
CACCGCCTACATGGAACTGAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTG
CGCCAGAGTGTACTACACATTCTACCACGCCATGGACTACTGGGGCCAGGGCACAACA
GTGACCGTTAGCTCT

h3H6 H4

The amino acid sequence of h3H6 H4 is shown in SEQ ID NO: 188, its encoding nucleic acid is shown in SEQ ID NO: 189, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 136, 183 and 138, respectively.

<----------FR1----------> CDR1<-----FR2-----> CDR2
<-------
QVQLVQSGAEVKKPGSSVKVSCKASGYTF**ATYSIH**WVRQAPGQGLEWMG**YINPSSGYTNYNQKFQG**RVT
ITAD
--------FR3--------------> CDR3 <----FR4--->
ESTSTAYMELSSLRSEDTAVYYCAR**VYYTFYHAMDY**WGQGTTVTVSS

Nucleotide sequence

CAGGTTCAGCTGGTTCAGTCTGGCGCCGAAGTGAAGAAACCTGGCAGCAGCGTGAAG
GTGTCCTGCAAGGCTAGCGGCTACACCTTCGCCACCTACAGCATCCACTGGGTCCGAC
AGGCTCCAGGACAGGGACTTGAGTGGATGGGCTACATCAACCCCAGCTCTGGCTACAC
CAACTACAACCAGAAATTCCAGGGCCGCGTGACCATCACAGCCGACGAGTCTACAAG
CACCGCCTACATGGAACTGAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTG
CGCCAGAGTGTACTACACATTCTACCACGCCATGGACTACTGGGGCCAGGGCACAACA
GTGACCGTTAGCTCT

h28O14:

h28O14 H1

The amino acid sequence of h28O14 H1 is shown in SEQ ID NO: 190, its encoding nucleic acid is shown in SEQ ID NO: 191, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 126, 192 and 128, respectively.

<----------FR1----------> CDR1<-----FR2-----> CDR2

<-------
QVQLVQSGAEVKKPGSSVKVSCKASGYTF**RSHTMH**WVRQAPGQGLEWMG**YINPSTGYINYNQKFQG**RVT
LTAD
--------FR3--------------> CDR3 <----FR4--->
KSTSTAYMELSSLRSEDTAVYYCAR**SNYAYYYGMDY**WGQGTTVTVSS

Nucleotide sequence

CAGGTTCAGCTGGTTCAGTCTGGCGCCGAAGTGAAGAAACCTGGCAGCAGCGTGAAG
GTGTCCTGCAAGGCTAGCGGCTACACCTTCAGATCCCACACCATGCACTGGGTCCGAC
AGGCTCCAGGACAGGGACTTGAGTGGATGGGCTACATCAACCCCAGCACCGGCTATAT
CAACTACAACCAGAAATTCCAGGGCCGCGTGACCCTCACAGCCGACAAGTCTACAAG
CACCGCCTACATGGAACTGAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTG
CGCCAGAAGCAACTACGCCTACTACTACGGCATGGACTACTGGGGCCAGGGCACCACA
GTGACAGTCTCTTCT

h28O14 H2

The amino acid sequence of h28O14 H2 is shown in SEQ ID NO: 193, its encoding nucleic acid is shown in SEQ ID NO: 194, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 126, 192 and 128, respectively.

<-------------FR1-------------> CDR1<-----FR2-----> CDR2
<-------
QVQLVQSGAEVKKPGSSVKVSCKASGYTF**RSHTMH**WVRQAPGQGLEWMG**YINPSTGYINYNQKFQG**RVT
LTAD
--------FR3--------------> CDR3 <----FR4--->
ESTSTAYMELSSLRSEDTAVYYCAR**SNYAYYYGMDY**WGQGTTVTVSS

Nucleotide sequence

CAGGTTCAGCTGGTTCAGTCTGGCGCCGAAGTGAAGAAACCTGGCAGCAGCGTGAAG
GTGTCCTGCAAGGCTAGCGGCTACACCTTCAGATCCCACACCATGCACTGGGTCCGAC
AGGCTCCAGGACAGGGACTTGAGTGGATGGGCTACATCAACCCCAGCACCGGCTATAT
CAACTACAACCAGAAATTCCAGGGCCGCGTGACCCTCACAGCCGACGAGTCTACAAG
CACCGCCTACATGGAACTGAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTG
CGCCAGAAGCAACTACGCCTACTACTACGGCATGGACTACTGGGGCCAGGGCACCACA
GTGACAGTCTCTTCT

h28O14 H3

The amino acid sequence of h28O14 H3 is shown in SEQ ID NO: 195, its encoding nucleic acid is shown in SEQ ID NO: 196, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 126, 192 and 128, respectively.

<-------------FR1-------------> CDR1<-----FR2-----> CDR2
<-------
QVQLVQSGAEVKKPGSSVKVSCKASGYTF**RSHTMH**WVRQAPGQGLEWMG**YINPSTGYINYNQKFQG**RVT
ITAD
--------FR3--------------> CDR3 <----FR4--->
KSTSTAYMELSSLRSEDTAVYYCAR**SNYAYYYGMDY**WGQGTTVTVSS

Nucleotide sequence

CAGGTTCAGCTGGTTCAGTCTGGCGCCGAAGTGAAGAAACCTGGCAGCAGCGTGAAG

GTGTCCTGCAAGGCTAGCGGCTACACCTTCAGATCCCACACCATGCACTGGGTCCGAC
AGGCTCCAGGACAGGGACTTGAGTGGATGGGCTACATCAACCCCAGCACCGGCTATAT
CAACTACAACCAGAAATTCCAGGGCCGCGTGACCATCACAGCCGACAAGTCTACAAG
CACCGCCTACATGGAACTGAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTG
CGCCAGAAGCAACTACGCCTACTACTACGGCATGGACTACTGGGGCCAGGGCACCACA
GTGACAGTCTCTTCT

h28O14 H4

The amino acid sequence of h28O14 H4 is shown in SEQ ID NO: 197, its encoding nucleic acid is shown in SEQ ID NO: 198, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 126, 192 and 128, respectively.

<-------------FR1-------------> CDR1<-----FR2-----> CDR2
<-------
QVQLVQSGAEVKKPGSSVKVSCKASGYTF**RSHTMH**WVRQAPGQGLEWMG**YINPSTGYINYNQKFQG**RVT
ITAD
--------FR3--------------> CDR3 <----FR4--->
ESTSTAYMELSSLRSEDTAVYYCAR**SNYAYYYGMDY**WGQGTTVTVSS

Nucleotide sequence

CAGGTTCAGCTGGTTCAGTCTGGCGCCGAAGTGAAGAAACCTGGCAGCAGCGTGAAG
GTGTCCTGCAAGGCTAGCGGCTACACCTTCAGATCCCACACCATGCACTGGGTCCGAC
AGGCTCCAGGACAGGGACTTGAGTGGATGGGCTACATCAACCCCAGCACCGGCTATAT
CAACTACAACCAGAAATTCCAGGGCCGCGTGACCATCACAGCCGACGAGTCTACAAG
CACCGCCTACATGGAACTGAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTG
CGCCAGAAGCAACTACGCCTACTACTACGGCATGGACTACTGGGGCCAGGGCACCACA
GTGACAGTCTCTTCT

h16B11:

h16B11 K1

The amino acid sequence of h16B11 K1 is shown in SEQ ID NO: 199, its encoding nucleic acid is shown in SEQ ID NO: 200, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 201, 202 and 146, respectively.

<----------FR1---------> CDR1 <-----FR2------> CDR2
<----------------
DIQMTQSPSSLSASVGDRVTITC**RASQNVGTNVA**WYQQKPGKAPKALIY**SASYRES**GVPSRFSGSGSGT
DFTL
--FR3----------> CDR3 <---FR4--->
TISSLQPEDFATYFC**QQFNTNPLT**FGGGTKVEIK

Nucleotide sequence

GACATCCAGATGACACAGAGCCCTAGCAGCCTGTCTGCCAGCGTGGGAGACAGAGTG
ACCATCACCTGTAGAGCCAGCCAGAACGTGGGCACAAACGTGGCCTGGTATCAGCAG
AAGCCTGGCAAGGCTCCCAAGGCGCTGATCTACAGCGCCAGCTACAGAGAGAGCGGC
GTGCCATCTAGATTCAGCGGCTCTGGCTCTGGCACCGACTTCACCCTGACAATCTCTAG

CCTGCAGCCTGAGGACTTCGCTACCTACTTCTGCCAGCAGTTCAACACAAACCCTCTG

ACCTTCGGCGGAGGCACCAAGGTGGAAATCAAG

h16B11 K2

The amino acid sequence of h16B11 K2 is shown in SEQ ID NO: 203, its encoding nucleic acid is shown in SEQ ID NO: 204, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 201, 202 and 146, respectively.

<----------FR1---------> CDR1 <-----FR2------> CDR2
<----------------
DIQMTQSPSSLSASVGDRVTITC**RASQNVGTNVA**WYQQKPGKAPKLLIY**SASYRES**GVPSRFSGSGSGT
DFTL
--FR3----------> CDR3 <---FR4--->
TISSLQPEDFATYFC**QQFNTNPLT**FGGGTKVEIK

Nucleotide sequence

GACATCCAGATGACACAGAGCCCTAGCAGCCTGTCTGCCAGCGTGGGAGACAGAGTG

ACCATCACCTGTAGAGCCAGCCAGAACGTGGGCACAAACGTGGCCTGGTATCAGCAG

AAGCCTGGCAAGGCTCCCAAGCTGCTGATCTACAGCGCCAGCTACAGAGAGAGCGGC

GTGCCATCTAGATTCAGCGGCTCTGGCTCTGGCACCGACTTCACCCTGACAATCTCTAG

CCTGCAGCCTGAGGACTTCGCTACCTACTTCTGCCAGCAGTTCAACACAAACCCTCTG

ACCTTCGGCGGAGGCACCAAGGTGGAAATCAAG

h16B11 K3

The amino acid sequence of h16B11 K3 is shown in SEQ ID NO: 205, its encoding nucleic acid is shown in SEQ ID NO: 206, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 201, 207 and 146, respectively.

<----------FR1---------> CDR1 <-----FR2------> CDR2
<----------------
DIQMTQSPSSLSASVGDRVTITC**RASQNVGTNVA**WYQQKPGKAPKALIY**SASYRQS**GVPSRFSGSGSGT
DFTL
--FR3----------> CDR3 <---FR4--->
TISSLQPEDFATYFC**QQFNTNPLT**FGGGTKVEIK

Nucleotide sequence

GACATCCAGATGACACAGAGCCCTAGCAGCCTGTCTGCCAGCGTGGGAGACAGAGTG

ACCATCACCTGTAGAGCCAGCCAGAACGTGGGCACAAACGTGGCCTGGTATCAGCAG

AAGCCTGGCAAGGCTCCCAAGGCGCTGATCTACAGCGCCAGCTACAGACAGAGCGGC

GTGCCATCTAGATTCAGCGGCTCTGGCTCTGGCACCGACTTCACCCTGACAATCTCTAG

CCTGCAGCCTGAGGACTTCGCTACCTACTTCTGCCAGCAGTTCAACACAAACCCTCTG

ACCTTCGGCGGAGGCACCAAGGTGGAAATCAAG

h16B11 K4

The amino acid sequence of h16B11 K4 is shown in SEQ ID NO: 208, its encoding nucleic acid is shown in SEQ ID NO: 209, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 201, 202 and 146, respectively.

<----------FR1---------> CDR1 <-----FR2------> CDR2

<----------
EIVMTQSPATLSVSPGERATLSC**RASQNVGTNVA**WYQQKPGQAPRALIY**SASYRES**GIPARFSGSGSGT
EFTL
--FR3----------> CDR3 <---FR4--->
TISSLQSEDFAVYFC**QQFNTNPLT**FGGGTKVEIK

Nucleotide sequence

GAGATCGTGATGACACAGAGCCCCGCCACACTGAGTGTGTCTCCAGGCGAAAGAGCT

ACCCTGAGCTGTAGAGCCTCTCAGAACGTGGGCACAAACGTGGCCTGGTATCAGCAG

AAGCCTGGACAGGCTCCCAGAGCGCTGATCTACAGCGCCAGCTACAGAGAGTCTGGC

ATCCCTGCTAGATTCAGCGGCTCTGGCTCTGGCACCGAGTTCACCCTGACAATCAGCA

GCCTGCAGAGCGAGGACTTCGCCGTGTACTTCTGCCAGCAGTTCAACACAAACCCTCT

GACCTTCGGCGGAGGCACCAAGGTGGAAATCAAG

h16B11 K5

The amino acid sequence of h16B11 K5 is shown in SEQ ID NO: 210, its encoding nucleic acid is shown in SEQ ID NO: 211, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 201, 202 and 146, respectively.

<----------FR1---------> CDR1 <-----FR2------> CDR2
<----------
EIVMTQSPATLSVSPGERATLSC**RASQNVGTNVA**WYQQKPGQAPRLLIY**SASYRES**GIPARFSGSGSGT
EFTL
--FR3----------> CDR3 <---FR4--->
TISSLQSEDFAVYFC**QQFNTNPLT**FGGGTKVEIK

Nucleotide sequence

GAGATCGTGATGACACAGAGCCCCGCCACACTGAGTGTGTCTCCAGGCGAAAGAGCT

ACCCTGAGCTGTAGAGCCTCTCAGAACGTGGGCACAAACGTGGCCTGGTATCAGCAG

AAGCCTGGACAGGCTCCCAGACTGCTGATCTACAGCGCCAGCTACAGAGAGTCTGGCA

TCCCTGCTAGATTCAGCGGCTCTGGCTCTGGCACCGAGTTCACCCTGACAATCAGCAG

CCTGCAGAGCGAGGACTTCGCCGTGTACTTCTGCCAGCAGTTCAACACAAACCCTCTG

ACCTTCGGCGGAGGCACCAAGGTGGAAATCAAG

h16B11 K6

The amino acid sequence of h16B11 K6 is shown in SEQ ID NO: 212, its encoding nucleic acid is shown in SEQ ID NO: 213, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 201, 207 and 146, respectively.

<----------FR1---------> CDR1 <-----FR2------> CDR2
<----------
EIVMTQSPATLSVSPGERATLSC**RASQNVGTNVA**WYQQKPGQAPRALIY**SASYRQS**GIPARFSGSGSGT
EFTL
--FR3----------> CDR3 <---FR4--->
TISSLQSEDFAVYFC**QQFNTNPLT**FGGGTKVEIK

Nucleotide sequence

GAGATCGTGATGACACAGAGCCCCGCCACACTGAGTGTGTCTCCAGGCGAAAGAGCT

ACCCTGAGCTGTAGAGCCTCTCAGAACGTGGGCACAAACGTGGCCTGGTATCAGCAG

AAGCCTGGACAGGCTCCCAGAGCGCTGATCTACAGCGCCAGCTACAGACAGTCTGGC

ATCCCTGCTAGATTCAGCGGCTCTGGCTCTGGCACCGAGTTCACCCTGACAATCAGCA
GCCTGCAGAGCGAGGACTTCGCCGTGTACTTCTGCCAGCAGTTCAACACAAACCCTCT
GACCTTCGGCGGAGGCACCAAGGTGGAAATCAAG

h28O14:

h28O14 K1

The amino acid sequence of h28O14 K1 is shown in SEQ ID NO: 214, its encoding nucleic acid is shown in SEQ ID NO: 215, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 216, 132 and 133, respectively.

<----------FR1---------> CDR1 <-----FR2------> CDR2
<----------------
DIQMTQSPSSLSASVGDRVTITC**RASQDVNTAVA**WYQQKPGKAPKLLIY**SASYRYT**GVPSRFSGSGSGT
DFTL
--FR3----------> CDR3 <---FR4--->
TISSLQPEDFATYYC**QQHYNIPLT**FGGGTKVEIK

Nucleotide sequence

GACATCCAGATGACACAGAGCCCTAGCAGCCTGTCTGCCAGCGTGGGAGACAGAGTG
ACCATCACCTGTAGAGCCAGCCAGGACGTGAACACAGCCGTGGCTTGGTATCAGCAG
AAGCCTGGCAAGGCCCCTAAGCTGCTGATCTACAGCGCCAGCTACAGATACACCGGCG
TGCCCTCTAGATTCAGCGGCTCTGGCTCTGGCACCGACTTCACCCTGACAATCTCTAGC
CTGCAGCCTGAGGACTTCGCCACCTACTACTGCCAGCAGCACTACAACATCCCTCTGA
CCTTCGGCGGAGGCACCAAGGTGGAAATCAAG

h3H6 K:

h3H6 K1

The amino acid sequence of h3H6 K1 is shown in SEQ ID NO: 214, its encoding nucleic acid is shown in SEQ ID NO: 215, and its CDR1, CDR2 and CDR3 are shown in SEQ ID NOs: 216, 132 and 133, respectively.

<----------FR1---------> CDR1 <-----FR2------> CDR2
<----------------
DIQMTQSPSSLSASVGDRVTITC**RASQDVNTAVA**WYQQKPGKAPKLLIY**SASYRYT**GVPSRFSGSGSGT
DFTL
--FR3----------> CDR3 <---FR4--->
TISSLQPEDFATYYC**QQHYNIPLT**FGGGTKVEIK

Nucleotide sequence

GACATCCAGATGACACAGAGCCCTAGCAGCCTGTCTGCCAGCGTGGGAGACAGAGTG
ACCATCACCTGTAGAGCCAGCCAGGACGTGAACACAGCCGTGGCTTGGTATCAGCAG
AAGCCTGGCAAGGCCCCTAAGCTGCTGATCTACAGCGCCAGCTACAGATACACCGGCG
TGCCCTCTAGATTCAGCGGCTCTGGCTCTGGCACCGACTTCACCCTGACAATCTCTAGC
CTGCAGCCTGAGGACTTCGCCACCTACTACTGCCAGCAGCACTACAACATCCCTCTGA
CCTTCGGCGGAGGCACCAAGGTGGAAATCAAG

After full-sequence synthesis of the light and heavy chains, respectively, they were cloned into eukaryotic expression vectors containing antibody kappa chain constant region Ckappa or human

IgG4 constant region CH1-CH3. The light and heavy chain plasmids were pair-matched, then transfected into CHO-S cells and expressed at 37°C for 5-6 days. The culture supernatant was collected and purified by the Protein A column.

Example 6. MASP-2 inhibitory activity of humanized antibodies

C4 cleavage activity assay

According to the C4 cleavage assay in Example 1, different concentrations of MASP-2 antibodies (initial concentration of 30 μg/ml, 5-fold gradient dilution, 9 gradients in total) were added to the reaction wells at 50 μl per well and allowed to react at 4℃ for 30 min. 50 μl of 2 μg/ml C4 pure protein (CompTech) was added, and reacted in a constant temperature incubator at 37℃ for 90 min, then C4b antibody was added to detect C4b deposition. As can be seen from Figures 9A, 9B and Table 8, the humanized antibodies can significantly inhibit MASP-2 activity.

Table 8. Inhibitory activity of C4b deposition by MASP-2 humanized antibodies

Humanized antibody	Heavy chain variable region	Light chain variable region	IC50 (nM)
h3H6 H1K1	h3H6 H1	h3H6 K1	0.014
h3H6 H2K1	h3H6 H2	h3H6 K1	0.086
h3H6 H3K1	h3H6 H3	h3H6 K1	0.017
h3H6 H4K1	h3H6 H4	h3H6 K1	0.090
h28O14 H1K1	h28O14 H1	h28O14 K1	0.083
h28O14 H2K1	h28O14 H2	h28O14 K1	0.324
h28O14 H3K1	h28O14 H3	h28O14 K1	0.064
h28O14 H4K1	h28O14 H4	h28O14 K1	0.338
h16B11 H1K1	h16B11 H1	h16B11 K1	0.020
h16B11 H1K2	h16B11 H1	h16B11 K2	0.051
h16B11 H1K3	h16B11 H1	h16B11 K3	0.021
h16B11 H2K1	h16B11 H2	h16B11 K1	0.020
h16B11 H2K2	h16B11 H2	h16B11 K2	0.032
h16B11 H2K3	h16B11 H2	h16B11 K3	0.012
h16B11 H3K1	h16B11 H3	h16B11 K1	0.098
h16B11 H3K2	h16B11 H3	h16B11 K2	1.691
h16B11 H3K3	h16B11 H3	h16B11 K3	0.440
Control antibody			0.909

C3 convertase activity assay

According to the C3 convertase activity assay in Example 1, different concentrations of MASP-2 antibodies (initial concentration of 30 μg/ml, 5-fold gradient dilution, 9 gradients in total) were added to the reaction wells at 50 μl per well and reacted at 37℃ for 90 min. C3b antibody was added at 1:500 to detect C3b deposition. As can be seen in Figures 10A, 10B, 10C and Table 9, each humanized antibody can inhibit the deposition of C3b.

Table 9. Inhibitory activity of C3b deposition by MASP-2 humanized antibodies

Humanized antibody	Heavy chain variable region	Light chain variable region	IC50 (nM)
h3H6 H1K1	h3H6 H1	h3H6 K1	0.030
h3H6 H2K1	h3H6 H2	h3H6 K1	0.151

h3H6 H3K1	h3H6 H3	h3H6 K1	0.034
h3H6 H4K1	h3H6 H4	h3H6 K1	0.151
h28O14 H1K1	h28O14 H1	h28O14 K1	0.146
h28O14 H2K1	h28O14 H2	h28O14 K1	0.483
h28O14 H3K1	h28O14 H3	h28O14 K1	0.161
h28O14 H4K1	h28O14 H4	h28O14 K1	0.506
h16B11 H1K1	h16B11 H1	h16B11 K1	0.014
h16B11 H1K2	h16B11 H1	h16B11 K2	0.040
h16B11 H1K3	h16B11 H1	h16B11 K3	0.023
h16B11 H2K3	h16B11 H2	h16B11 K3	0.018
h16B11 H2K1	h16B11 H2	h16B11 K1	0.017
h16B11 H2K2	h16B11 H2	h16B11 K2	0.028
h16B11 H3K1	h16B11 H3	h16B11 K1	0.060
h16B11 H3K2	h16B11 H3	h16B11 K2	0.399
h16B11 H3K3	h16B11 H3	h16B11 K3	0.112
h16B11 H1K4	h16B11 H1	h16B11 K4	0.015
h16B11 H1K5	h16B11 H1	h16B11 K5	0.024
h16B11 H1K6	h16B11 H1	h16B11 K6	0.018
h16B11 H2K4	h16B11 H2	h16B11 K4	0.015
h16B11 H2K5	h16B11 H2	h16B11 K5	0.032
h16B11 H2K6	h16B11 H2	h16B11 K6	0.018
h16B11 H3K4	h16B11 H3	h16B11 K4	0.052
h16B11 H3K5	h16B11 H3	h16B11 K5	0.440
h16B11 H3K6	h16B11 H3	h16B11 K6	0.071
Control antibody			3.692

Example 7. Affinity of MASP-2 humanized antibodies

(1) ELISA detection of the affinity of humanized MASP-2 antibodies with each species antigen

Human MASP-2 D4-6 recombinant protein was coated at 1 μg/mL in a 96-well ELISA plate and incubated overnight at 4°C. After blocking with 2% skim milk at room temperature for 1 h, gradient-diluted MASP-2 antibodies (initial concentration of 30 μg/ml, 1:4 gradient dilution) were added and incubated at room temperature for 60 min. Goat anti-human Fc-HRP diluted 1:4000 was added and incubated at room temperature for 60 min. The color was developed with TMB for 10 min, then the reaction was stopped by adding concentrated sulfuric acid. The OD450 nm was determined, and the results were calculated using Graph Pad Prism 5 software.

The results are shown in FIG. 11, in which the MASP-2 humanized antibodies bind to human, Cynomolgus monkey, rat and mouse MASP-2 with comparable affinity.

(2) BIAcore detection of the affinity of humanized antibodies with mouse MASP-2

The antibody of 0.1 μg/ml was captured on the surface of the Protein A chip, with a capture time of 40 sec and a flow rate of 10 μl/min. The chip was washed with buffer until the baseline leveled off, then gradient diluted antigen was flowed through the chip at the flow rate of 30 μl/min, with a binding time of 120 sec and a dissociation time of 600 sec. The equilibrium dissociation constant (KD) was obtained by fitting. The affinity measurements are shown in Table 10.

Table 10. The affinity of MASP-2 antibodies with MASP-2

MASP-	Human MASP-2-D4-6	Mouse MASP-2-D4-6

2	ka (1/Ms)	kd (1/s)	KD (M)	ka (1/Ms)	kd (1/s)	KD (M)
h16B11	3.26E+0	3.77E-0	1.16E-1	4.66E+0	1.38E-02	2.95E-0
h16B11	5.00E+0	1.46E-0	2.92E-1	9.36E+0	1.18E-01	1.26E-0
h16B11	6.35E+0	1.91E-0	3.01E-1	6.88E+0	3.71E-02	5.39E-0
h16B11	4.33E+0	4.97E-0	1.15E-11	5.00E+0	8.47E-03	1.69E-0
h16B11	3.81E+0	1.40E-0	3.69E-11	6.24E+0	6.42E-02	1.03E-0
h16B11	4.60E+0	5.74E-0	1.25E-11	5.88E+0	2.16E-02	3.68E-0
h16B11	4.91E+0	3.35E-0	6.83E-1	4.75E+0	1.44E-02	3.04E-0
h16B11	4.66E+0	1.41E-0	3.02E-11	6.91E+0	8.71E-02	1.26E-0
h16B11	5.23E+0	5.04E-0	9.63E-1	5.54E+0	3.42E-02	6.18E-0
h16B11	4.23E+0	5.14E-0	1.22E-11	4.78E+0	8.63E-03	1.81E-0
h16B11	3.88E+0	1.34E-0	3.46E-11	6.10E+0	5.95E-02	9.76E-0
h16B11	4.67E+0	6.30E-0	1.35E-11	5.44E+0	2.25E-02	4.13E-0
h16B11	3.61E+0	1.21E-0	3.34E-11	6.97E+0	6.73E-02	9.65E-0
h16B11	3.51E+0	6.77E-0	1.93E-1	1.43E+0	2.76E+0	1.93E-0
h16B11	3.63E+0	1.66E-0	4.57E-11	1.23E+0	1.90E-01	1.54E-0
h16B11	2.97E+0	1.20E-0	4.03E-11	5.26E+0	6.06E-02	1.15E-0
h16B11	3.04E+0	5.66E-0	1.87E-1	2.76E+0	9.55E-02	3.47E-0
h16B11	3.07E+0	1.74E-0	5.66E-11	8.07E+0	1.80E-01	2.22E-0

Example 8. Shiga toxin 2 induced hemolytic uremic syndrome model in mice

cDNA plasmid with STX2 (Sino Biological, cat. No: EG40019-G) was used as a template for PCR amplification of the STX2A (Arg23-Lys319) and STX2B (Ala20-Asp89) gene fragments of E. coli O157:H7, and cloned into a prokaryotic expression plasmid, in which the N-terminus of STX2A protein was fused with twin strep tag to facilitate purification, and an enterokinase cleavage site, DDDDK, was added between them. The constructed STX2 expression plasmid was transformed into TG1 E. coli competent cells, then a single clone was picked into bacterial culture medium and added IPTG to induce and cultured overnight. The bacteria were collected, and PPB and 5 mM MgSO4 solution were added successively. The bacterial cell wall was lysed, and the protein expression solution in the periplasmic cavity was collected by centrifugation. Shiga toxin STX2 protein was purified by Strep-TactinX (Sino HaiGene, cat. No: C0402), and EK enterokinase was added to the protein collection solution and incubated overnight at 25℃ to cleave the twin strep tag.

About 18 g C57BL/6 female mice were selected and divided into 4 dose groups of MASP-2 antibodies 0 mg/kg, 3 mg/kg, 10 mg/kg and 30 mg/kg, with 7 mice in each group. The anti-MASP-2 antibody h16B11 H2K4 (100 μl) was injected via tail vein 2 hours in advance, followed by intraperitoneal injection of LPS (5 μg/animal, L6136-Sigma) and STX2 (10 ng/animal). Mice were monitored for survival rate beginning 60 hours after dosing and sacrificed upon reaching the lethargic phase of the HUS pathology. The results are shown in FIG. 12, in

which anti-MASP-2 antibodies significantly prolonged the survival time of mice in a dose-dependent manner.

Claims

1. An antibody or antigen-binding portion thereof that binds to MASP-2, comprising heavy chain CDRs selected from the group consisting of amino acid sequences SEQ ID NOs: 7, 8, 9, 17, 18, 26, 27, 28, 36, 37, 38, 46, 47, 60, 65, 66, 67, 79, 85, 86, 94, 95, 96, 104, 105, 113, 114, 126, 127, 128, 136, 137, 138, 141, 149, 150, 151, 165, 183, 192 or any variant thereof, and/or light chain CDRs selected from the group consisting of amino acid sequences SEQ ID NOs: 12, 13, 14, 21, 22, 23, 31, 32, 33, 41, 42, 43, 50, 51, 52, 57, 70, 71, 72, 82, 91, 108, 109, 110, 117, 118, 123, 131, 132, 133, 144, 145, 146, 154, 155, 156, 161, 162, 168, 173, 174, 201, 202, 207, 216 or any variant thereof.

2. The antibody or antigen-binding portion thereof of claim 1, comprising a heavy chain CDR1 selected from the group consisting of amino acid sequences SEQ ID NOs: 7, 26, 36, 65, 94, 126, 136, 149 or any variant thereof, a heavy chain CDR2 selected from the group consisting of amino acid sequences SEQ ID NOs: 8, 17, 27, 37, 46, 66, 85, 95, 104, 113, 127, 137, 150, 165, 183, 192 or any variant thereof, and a heavy chain CDR3 selected from the group consisting of amino acid sequences SEQ ID NOs: 9, 18, 28, 38, 47, 60, 67, 79, 86, 96, 105, 114, 128, 138, 141, 151 or any variant thereof; and/or a light chain CDR1 selected from the group consisting of amino acid sequences SEQ ID NOs: 12, 21, 31, 41, 50, 70, 99, 108, 117, 123, 131, 144, 154, 161, 201, 216 or any variant thereof, a light chain CDR2 selected from the group consisting of amino acid sequences SEQ ID NOs: 13, 22, 32, 42, 51, 57, 71, 100, 109, 118, 132, 145, 155, 162, 168, 173, 202, 207 or any variant thereof, and a light chain CDR3 selected from the group consisting of amino acid sequences SEQ ID NOs: 14, 23, 33, 43, 52, 72, 82, 91, 101, 110, 133, 146, 156, 174 or any variant thereof.

3. The antibody or antigen-binding portion thereof of claim 1 or 2, comprising a combination of heavy and light chain CDRs selected from the group consisting of:

(1) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 7, 8 and 9, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 12, 13 and 14, respectively;

(2) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 7, 17 and 18, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 21, 22 and 23, respectively;

(3) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 26, 27 and 28, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 31, 32 and 33, respectively;

(4) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 36, 37 and 38,

respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 41, 42 and 43, respectively;

(5) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 7, 46 and 47, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 50, 51 and 52, respectively;

(6) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 7, 17 and 18, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 21, 57 and 23, respectively;

(7) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 7, 17 and 60, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 50, 51 and 52, respectively;

(8) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 65, 66 and 67, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 70, 71 and 72, respectively;

(9) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 7, 17 and 47, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 50, 51 and 52, respectively;

(10) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NO: 7, 17 and 79, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NO: 50, 51 and 82, respectively;

(11) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 36, 85 and 86, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 41, 42 and 43, respectively;

(12) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 36, 85 and 86, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 41, 42 and 91, respectively;

(13) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NO: 94, 95 and 96, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NO: 99, 100 and 101, respectively;

(14) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 7, 104 and 105, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 108, 109 and 110, respectively;

(15) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 26, 113 and 114, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 117, 118 and 33, respectively;

(16) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 94, 95 and 96, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 123, 100 and 101, respectively;

(17) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 126, 127 and 128, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 131, 132 and 133, respectively;

(18) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 136, 137 and 138, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 131, 132 and 133, respectively;

(19) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 7, 17 and 141, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 144, 145 and 146, respectively;

(20) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 149, 150 and 151, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 154, 155 and 156, respectively;

(21) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 7, 17 and 9, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 161, 162 and 14, respectively;

(22) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 7, 165 and 9, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 144, 168 and 14, respectively;

(23) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 7, 17 and 9, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 144, 173 and 174, respectively;

(24) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 136, 183 and 138, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 216, 132 and 133, respectively;

(25) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 126, 192 and 128, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 216, 132 and 133, respectively;

(26) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 7, 17 and 141, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 201, 202 and 146, respectively;

(27) the heavy chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs: 7, 17 and 141, respectively, and/or the light chain CDR1, CDR2 and CDR3 sequences comprising SEQ ID NOs:

201, 207 and 146, respectively.

4. The antibody or antigen-binding portion thereof of claim 1 or 2, comprising a heavy chain variable region selected from the group consisting of amino acid sequences SEQ ID NOs: 5, 15, 24, 34, 44, 53, 58, 63, 73, 77, 83, 92, 102, 111, 119, 124, 134, 139, 147, 157, 163, 169, 175, 177, 179, 181, 184, 186, 188, 190, 193, 195, 197 or any variant thereof, and/or a light chain variable region selected from the group consisting of amino acid sequences SEQ ID NOs: 10, 19, 29, 39, 48, 55, 61, 68, 75, 80, 87, 89, 97, 106, 115, 121, 129, 142, 152, 159, 166, 171, 199, 203, 205, 208, 210, 212, 214 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 5 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 10 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 15 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 19 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 24 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 29 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 34 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 39 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 44 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 48 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 53 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 55 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 58 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 61 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 63 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 68 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 73 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 75 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 77 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 80 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 83 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 87 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 83 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 89 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 92 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 97 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 102 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 106 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 111 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 115 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 119 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 121 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 124 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 129 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 134 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 129 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 139 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 142 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 147 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 152 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 157 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID

NO: 159 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 163 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 166 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 169 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 171 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 181 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 214 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 184 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 214 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 186 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 214 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 188 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 214 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 190 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 214 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 193 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 214 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 195 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 214 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 197 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 214 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 175 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 199 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO:

175 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 203 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 175 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 205 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 177 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 205 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 177 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 199 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 177 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 203 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 179 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 199 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 179 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 203 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 179 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 205 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 175 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 208 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 175 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 210 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 175 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 212 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 177 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 208 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 177 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 210 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 177 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 212 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 179 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 208 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 179 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 210 or any variant thereof;

preferably, comprising the heavy chain variable region of the amino acid sequence SEQ ID NO: 179 or any variant thereof, and the light chain variable region of the amino acid sequence SEQ ID NO: 212 or any variant thereof.

5. A bispecific or multispecific molecule, comprising the antibody or antigen-binding portion thereof that binds to MASP-2 of any one of claims 1-4.

6. The antibody or antigen-binding portion thereof of any one of claims 1-4 or the bispecific or multispecific molecule of claim 5, wherein the antibody or antigen-binding portion thereof is humanized.

7. A nucleic acid encoding the antibody or antigen-binding portion thereof of any one of claims 1-4, the bispecific or multispecific molecule of claim 5, or the antibody or antigen-binding portion thereof or the bispecific or multispecific molecule of claim 6;

preferably, the nucleic acid comprises an antibody heavy chain variable region nucleotide sequence selected from the group consisting of SEQ ID NOs: 6, 16, 25, 35, 45, 54, 59, 64, 74, 78, 84, 93, 103, 112, 120, 125, 135, 140, 148, 158, 164, 170, 176, 178, 180, 182, 185, 187, 189, 191, 194, 196, 198 or any variant thereof, and/or an antibody light chain variable region nucleotide sequence selected from the group consisting of SEQ ID NOs: 11, 20, 30, 40, 49, 56, 62, 69, 76, 81, 88, 90, 98, 107, 116, 122, 130, 143, 153, 160, 167, 172, 200, 204, 206, 209, 211, 213, 215 or any variant thereof;

more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 6 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 11 or any variant thereof;

more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 16 or any variant thereof, and the light chain variable

region nucleotide sequence of the nucleotide sequence SEQ ID NO: 20 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 25 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 30 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 35 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 40 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 45 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 49 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 54 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 56 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 59 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 62 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 64 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 69 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 74 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 76 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 78 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 81 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 84 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 88 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 84 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 90 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 93 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 98 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence

of the nucleotide sequence SEQ ID NO: 103 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 107 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 112 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 116 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 120 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 122 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 125 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 130 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 135 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 130 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 140 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 143 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 148 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 153 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 158 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 160 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 164 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 167 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 170 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 172 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 182 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 215 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 185 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 215 or any variant thereof;

more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 187 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 215 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 189 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 215 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 191 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 215 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 194 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 215 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 196 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 215 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 198 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 215 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 176 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 200 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 176 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 204 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 176 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 206 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 178 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 206 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 178 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 200 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 178 or any variant thereof, and the light chain variable

region nucleotide sequence of the nucleotide sequence SEQ ID NO: 204 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 180 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 200 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 180 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 204 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 180 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 206 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 176 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 209 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 176 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 211 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 176 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 213 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 178 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 209 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 178 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 211 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 178 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 213 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 180 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 209 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 180 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 211 or any variant thereof; more preferably, the nucleic acid comprises the heavy chain variable region nucleotide sequence

of the nucleotide sequence SEQ ID NO: 180 or any variant thereof, and the light chain variable region nucleotide sequence of the nucleotide sequence SEQ ID NO: 213 or any variant thereof.

8. A vector, comprising the nucleic acid of claim 7.

9. A cell, comprising the nucleic acid of claim 7 or the vector of claim 8.

10. A composition, comprising the antibody or antigen-binding portion thereof of any one of claims 1-4, the bispecific or multispecific molecule of claim 5, the antibody or antigen-binding portion thereof or the bispecific or multispecific molecule of claim 6, the nucleic acid of claim 7, the vector of claim 8 and/or the cell of claim 9.

11. The composition of claim 10, further comprising one or more additional therapeutic agents; the additional therapeutic agents being selected from the group consisting of anti-inflammatory and/or analgesic agents, anti-restenosis agents, other complement inhibitors, chondroprotective agents, and/or spasm inhibitors.

12. A kit, comprising the antibody or antigen-binding portion thereof of any one of claims 1-4, the bispecific or multispecific molecule of claim 5, the antibody or antigen-binding portion thereof or the bispecific or multispecific molecule of claim 6, the nucleic acid molecule of claim 7, the vector of claim 8, the cell of claim 9 and/or the composition of claim 10 or 11.

13. Use of the antibody or antigen-binding portion thereof of any one of claims 1-4, the bispecific or multispecific molecule of claim 5, the antibody or antigen-binding portion thereof or the bispecific or multispecific molecule of claim 6, the nucleic acid of claim 7, the vector of claim 8, the cell of claim 9 and/or the composition of claim 10 or 11 in the preparation of a drug or kit for diagnosing, treating or preventing diseases associated with lectin pathway of complement activation;

preferably, the diseases associated with MASP-2 dependent complement activation are selected from the group consisting of MASP-2 dependent complement-mediated vascular conditions, ischemia-reperfusion injury, atherosclerosis, inflammatory gastrointestinal tract disorders, lung conditions, in vitro reperfusion processes, skeletal muscle conditions, kidney conditions, skin conditions, organ or tissue transplantation, neurological disorders or injuries, blood disorders, urogenital tract conditions, diabetes, chemotherapy or radiation therapy, malignancies, endocrine disorders, coagulation disorders, or ophthalmic conditions; injuries and diseases related to complement activation caused by bacterial, fungal or viral infections;

preferably, the diseases associated with MASP-2 dependent complement activation are autoimmune inflammatory conditions or autoimmune diseases; preferably, the autoimmune inflammatory conditions are selected from the group consisting of multiple sclerosis (myelin coated on neurites), type I diabetes (pancreas), Hashimoto's thyroiditis (thyroid), pernicious anemia (stomach), Addison' s disease (adrenal gland), myasthenia gravis (acetylcholine receptors

on neuromuscular junctions), rheumatoid arthritis, uveitis (eye), psoriasis (skin), Guillain-Barre syndrome (nerve cells), Grave's disease (thyroid), systemic lupus erythematosus, glomeronephritis, dermatomyositis, asthma, eczema, atopicaldermatitis, contact dermatitis, other eczematous dermatitises, seborrheic dermatitis, rhinitis, lichen planus, pemplugus, bullous pemphigoid, epidermolysis bullosa, urticaria, angioedema, vasculitis, erythema, cutaneous eosinophilia, alopecia areata, arteriosclerosis, primary biliary cirrhosis and nephrotic syndrome,

preferably, the diseases associated with MASP-2 dependent complement activation are selected from the group consisting of enteritis, such as coeliac disease, proctitis, eosinophilic gastroenteritis, mastocytosis, inflammatory bowel disease, Chrohn's disease, ulcerative colitis, and food-related allergies.

Drawings

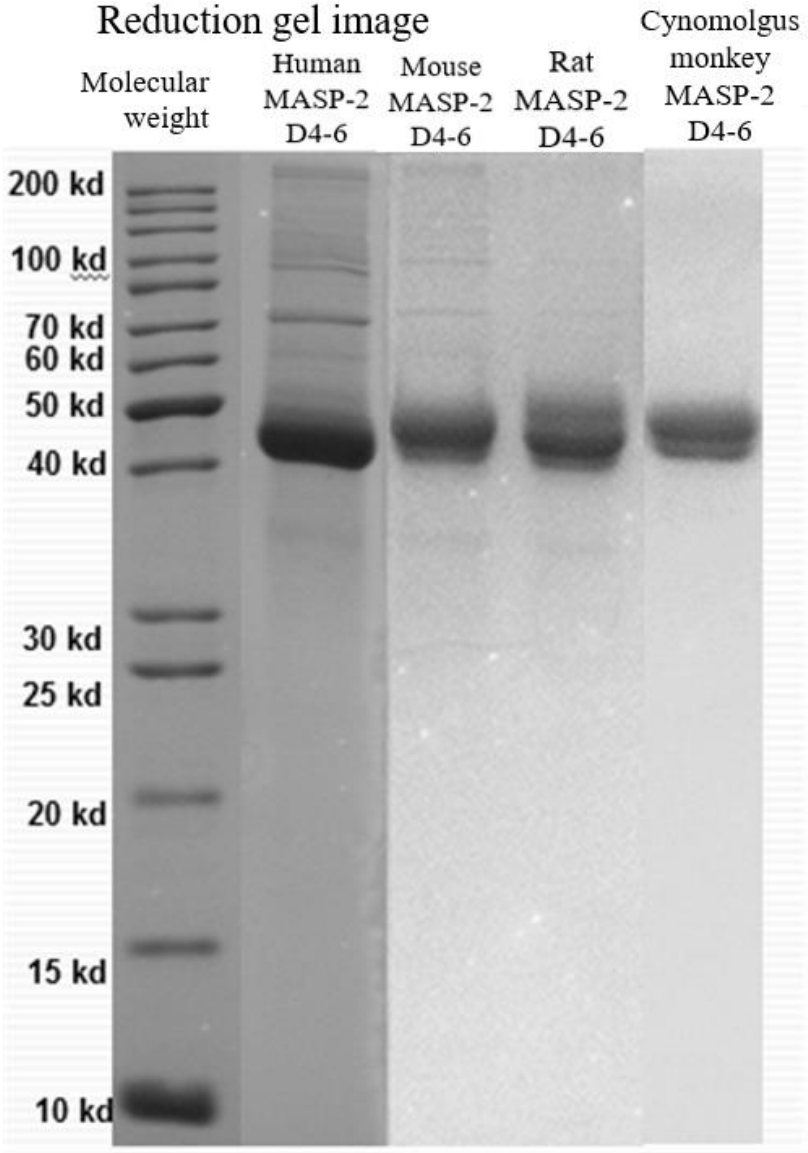


FIG. 1

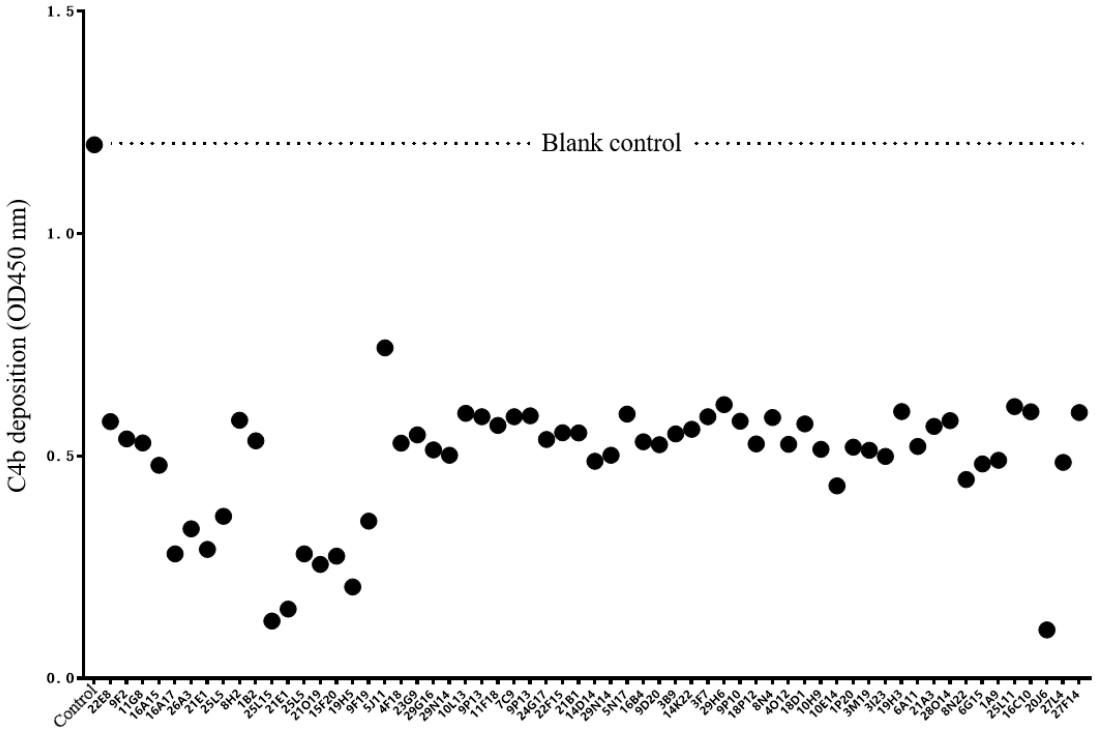

Blank control
C4b deposition (OD450 nm)
1.5
1.0
0.5
0.0
Control
2E8
9F2
11G8
16A15
16A17
26A3
21E1
25L5
8H2
1B2
25L15
21E1
25L5
21O19
15F20
19H5
9F19
5J11
4F18
23G9
29G16
29N14
10L13
9P13
11F18
7C9
9P13
24G17
22F15
21B1
14D14
29N14
5N17
16B4
9D20
3B9
14K22
3F7
29H6
9P10
18P12
8N4
4D12
18D1
10H9
10E14
1P20
3M19
3I23
19H3
6A11
21A3
28O14
8N22
6G15
1A9
25L11
16C10
20J6
27L1
27F14

FIG. 2

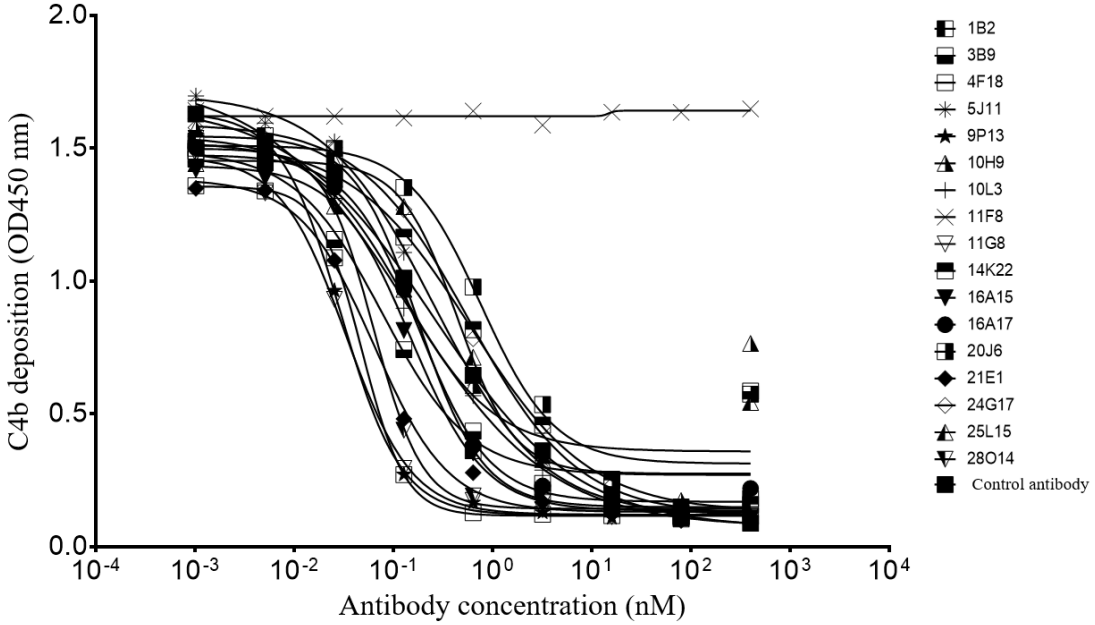

C4b deposition (OD450 nm)
2.0
1.5
1.0
0.5
0.0
10-4
10-3
10-2
10-1
100
101
102
103
104
Antibody concentration (nM)
1B2
3B9
4F18
5J11
9P13
10H9
10L3
11F8
11G8
14K22
16A15
16A17
20J6
21E1
24G17
25L15
28O14
Control antibody

FIG. 3

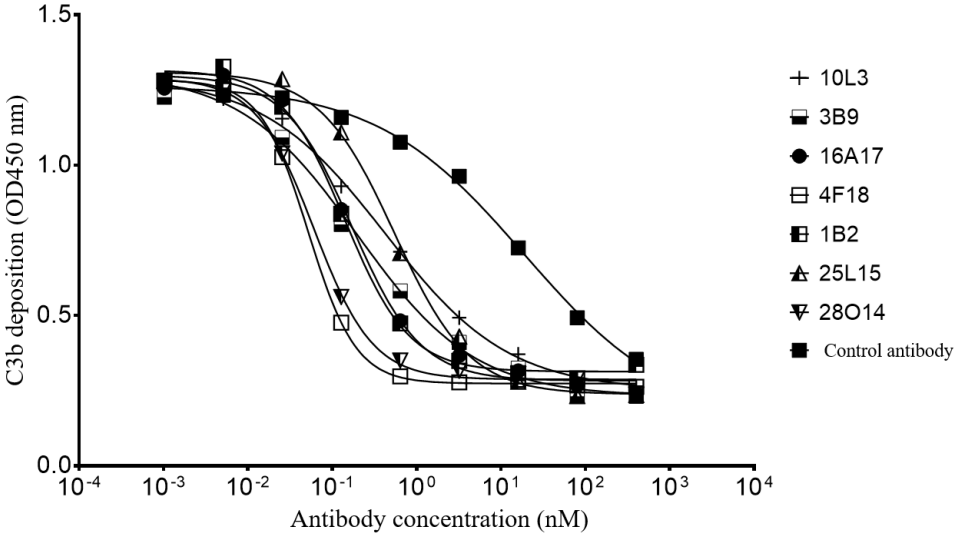

C3b deposition (OD450 nm)
1.5
1.0
0.5
0.0
10-4
10-3
10-2
10-1
100
101
102
103
104
Antibody concentration (nM)
10L3
3B9
16A17
4F18
1B2
25L15
28O14
Control antibody

FIG. 4

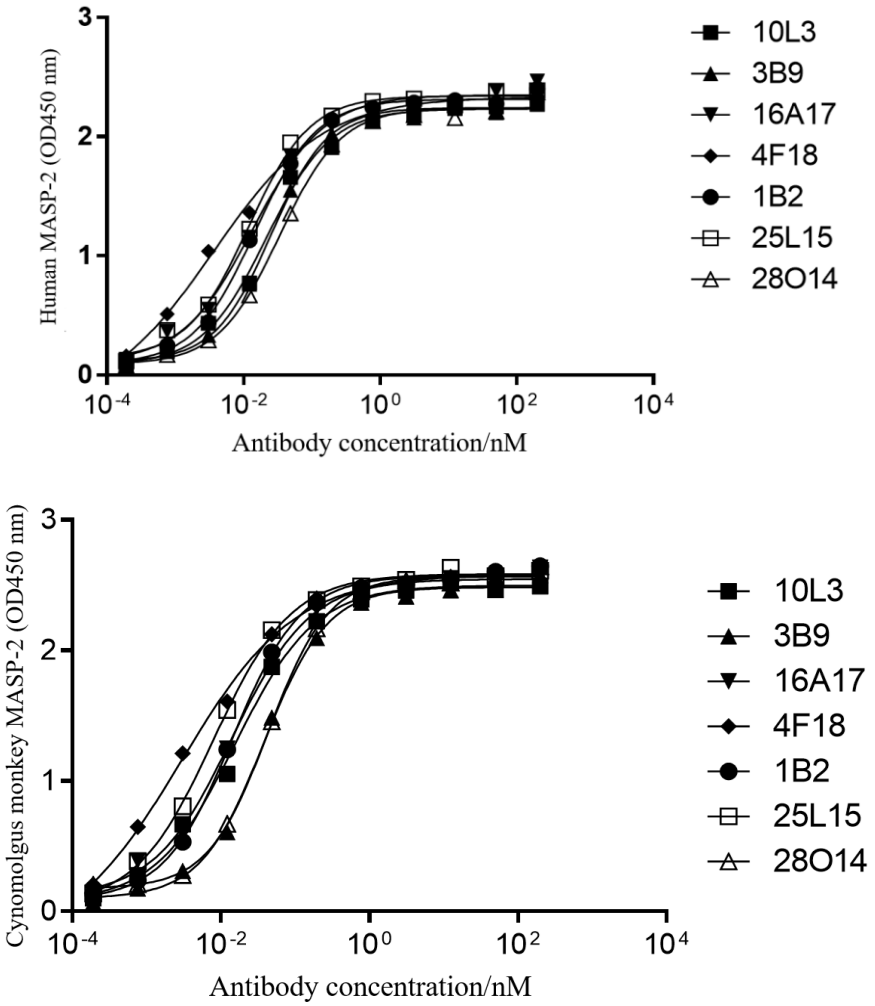
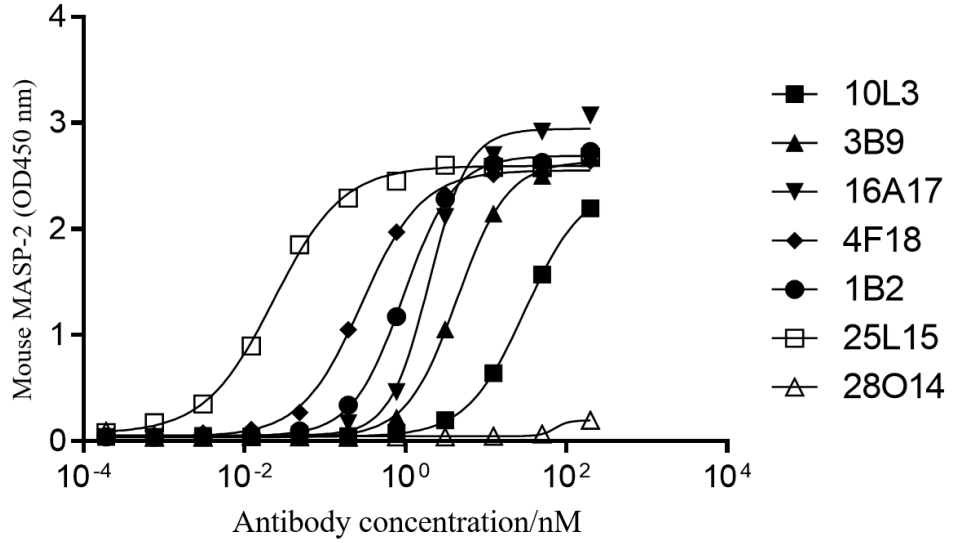

Human MASP-2 (OD450 nm)
3
2
1
0
10-4
10-2
100
102
104
Antibody concentration/nM
10L3
3B9
16A17
4F18
1B2
25L15
28O14
Cynomolgus monkey MASP-2 (OD450 nm)
3
2
1
0
10-4
10-2
100
102
104
Antibody concentration/nM
10L3
3B9
16A17
4F18
1B2
25L15
28O14

FIG. 5


Mouse MASP-2 (OD450 nm)
4
3
2
1
0
10-4
10-2
100
102
104
Antibody concentration/nM
10L3
3B9
16A17
4F18
1B2
25L15
28O14

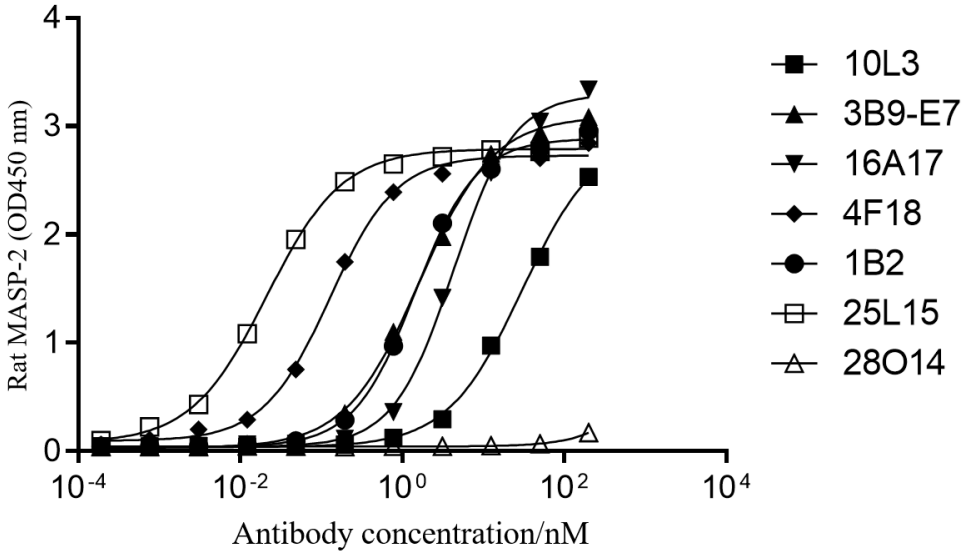

Rat MASP-2 (OD450 nm)
4
3
2
1
0
10-4
10-2
100
102
104
Antibody concentration/nM
10L3
3B9-E7
16A17
4F18
1B2
25L15
28O14

FIG. 5 cont.

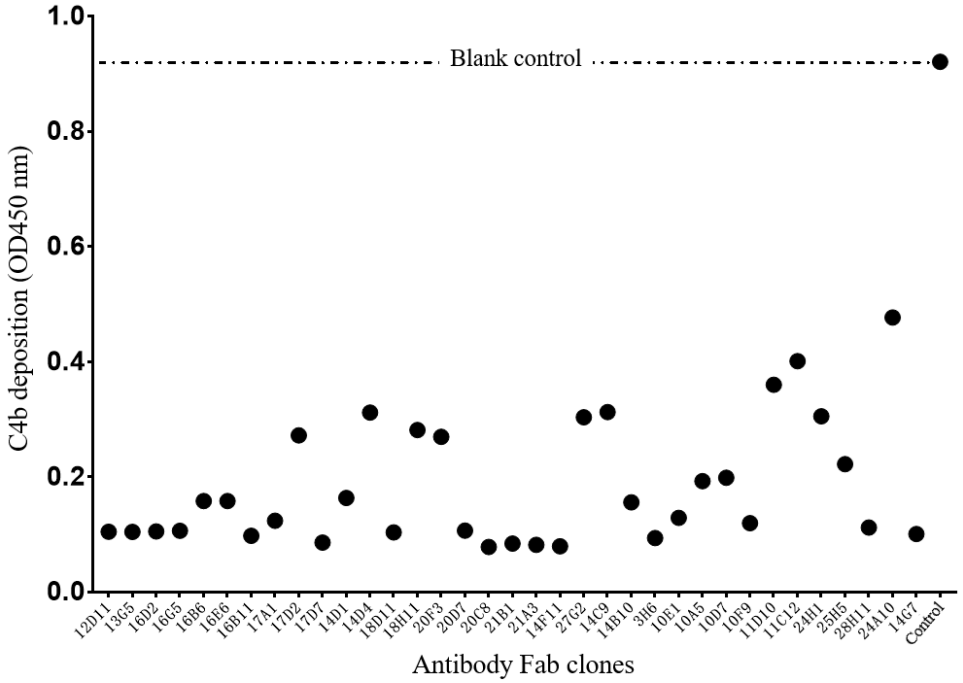


FIG. 6

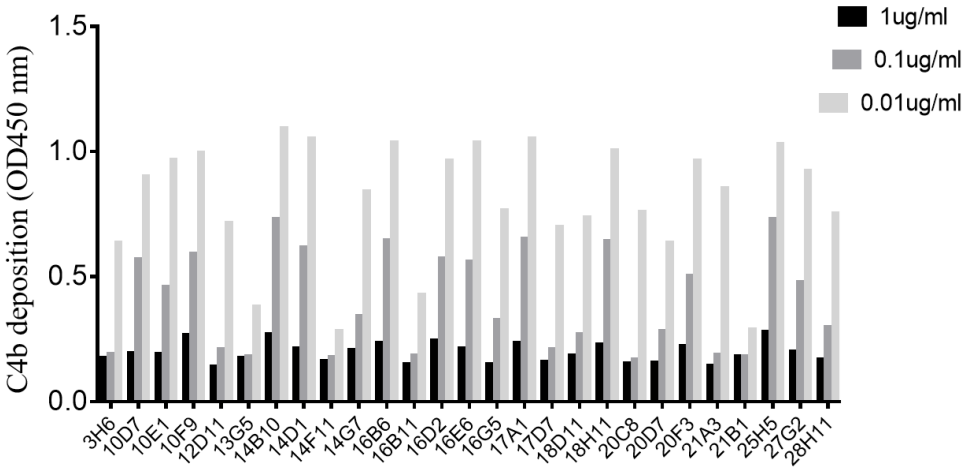
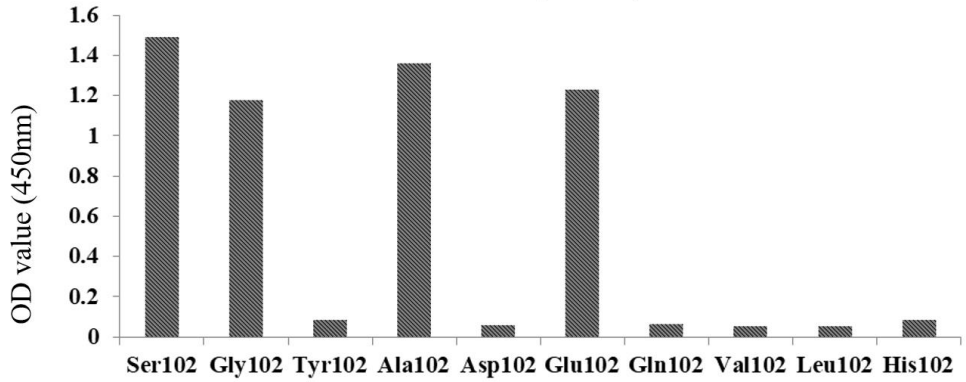


FIG. 7

MASP-2 binding activity



mAb 28O14 variants

FIG. 8

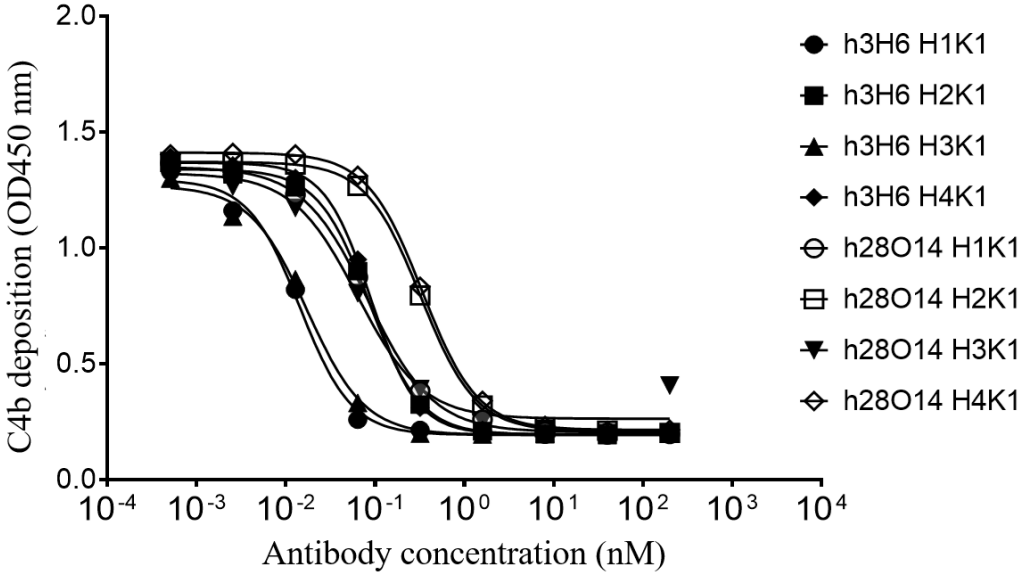


FIG. 9A

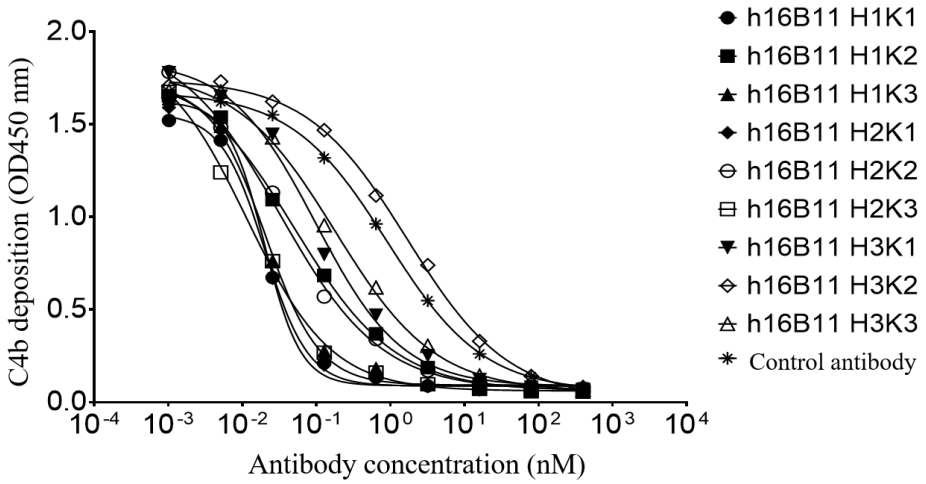


FIG. 9B

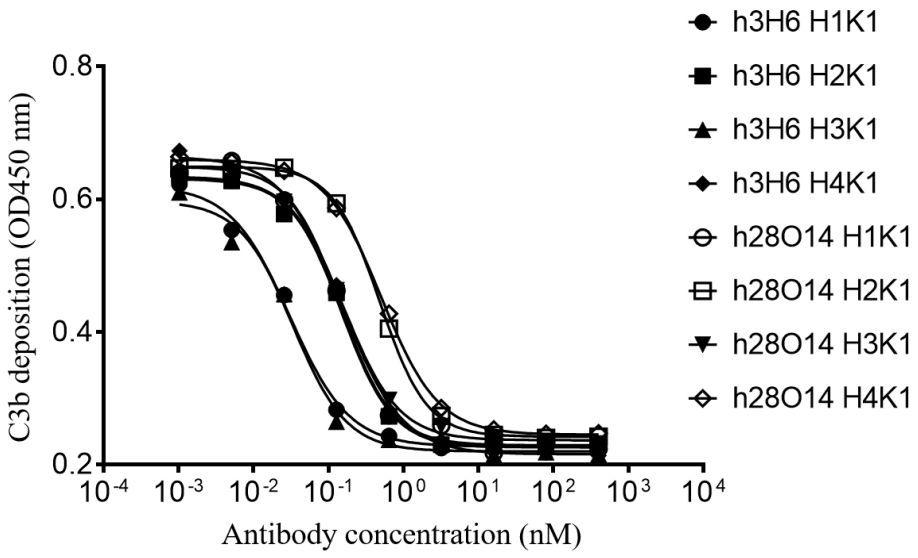


FIG. 10A

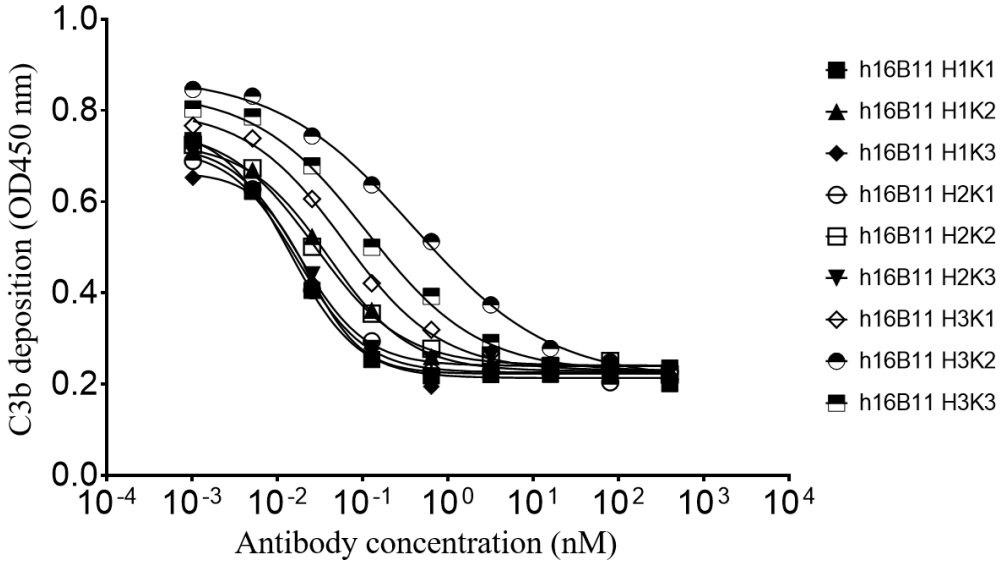


FIG. 10B

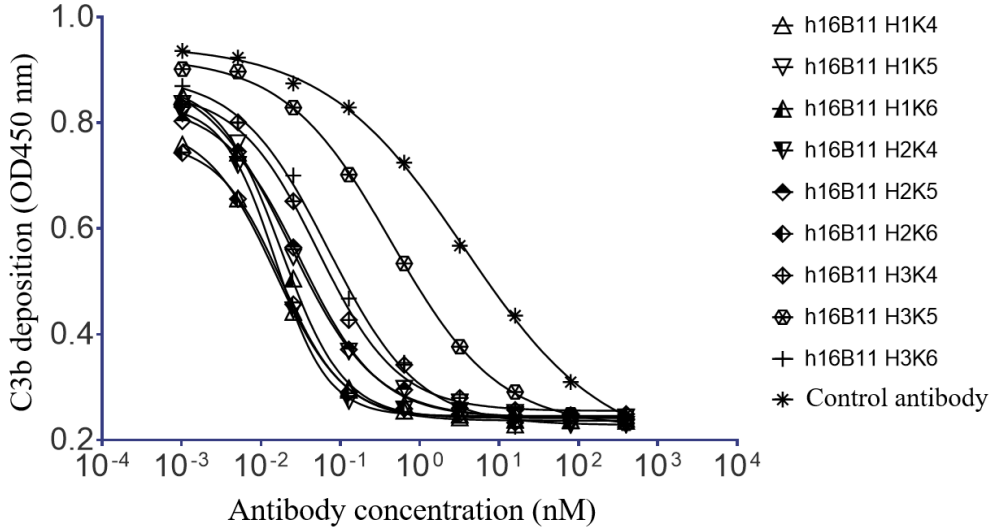


FIG. 10C

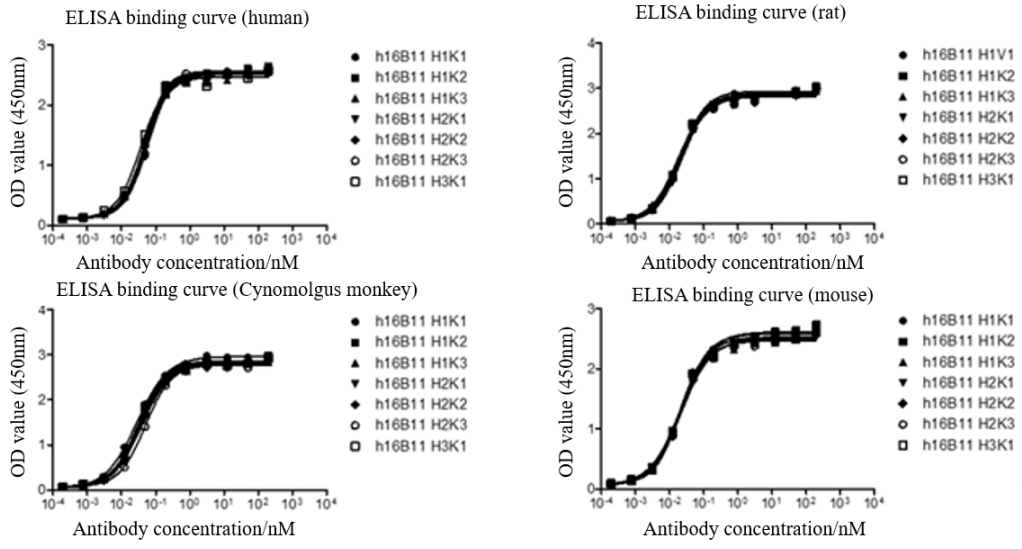


FIG. 11

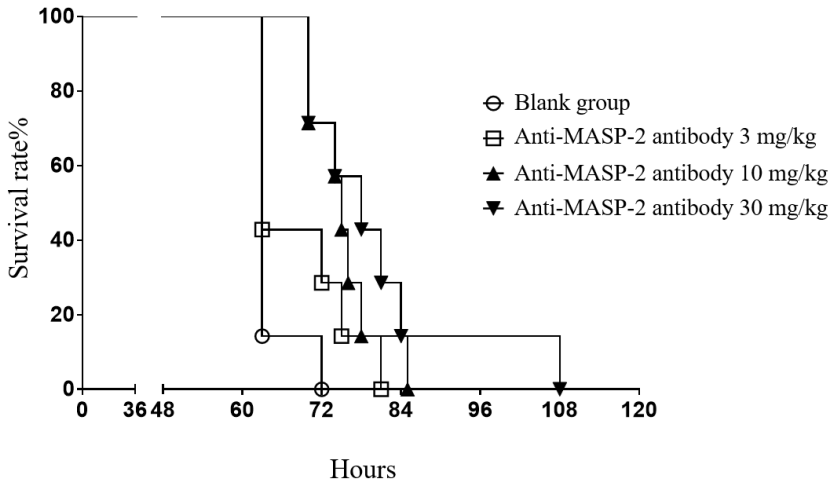

100
80
60
40
20
0
Survival rate%
0
36
48
60
72
84
96
108
120
Hours
Blank group
Anti-MASP-2 antibody 3 mg/kg
Anti-MASP-2 antibody 10 mg/kg
Anti-MASP-2 antibody 30 mg/kg

FIG. 12

ÐòÁÐ±í

<110> ¿µÅµÑÇÉúÎïÒ½Ò©¿Æ¼¼£¨³É¶¼£©ÓÐÏÞ¹«Ë¾

<120> Ò»ÖÖ²¹ÌåÒÖÖÆ¼ÁµÄ¿ª·¢ºÍ¦ÓÃ

<130> MTP20213

<160> 216

<170> PatentIn version 3.5

<210> 1
<211> 397
<212> PRT
<213> Homo sapiens

<400> 1

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            20   25   30

Asp Ser Phe Ser Ile Phe Cys Glu Thr Gly Tyr Glu Leu Leu Gln Gly
        35   40   45

His Leu Pro Leu Lys Ser Phe Thr Ala Val Cys Gln Lys Asp Gly Ser
    50   55   60

Trp Asp Arg Pro Met Pro Ala Cys Ser Ile Val Asp Cys Gly Pro Pro
65   70   75   80

Asp Asp Leu Pro Ser Gly Arg Val Glu Tyr Ile Thr Gly Pro Gly Val
                85   90   95

Thr Thr Tyr Lys Ala Val Ile Gln Tyr Ser Cys Glu Glu Thr Phe Tyr
            100   105   110

Thr Met Lys Val Asn Asp Gly Lys Tyr Val Cys Glu Ala Asp Gly Phe
        115   120   125

```
Trp Thr Ser Ser Lys Gly Glu Lys Ser Leu Pro Val Cys Glu Pro Val
    130                 135                 140

Cys Gly Leu Ser Ala Arg Thr Thr Gly Gly Arg Ile Tyr Gly Gly Gln
145                 150                 155                 160

Lys Ala Lys Pro Gly Asp Phe Pro Trp Gln Val Leu Ile Leu Gly Gly
                165                 170                 175

Thr Thr Ala Ala Gly Ala Leu Leu Tyr Asp Asn Trp Val Leu Thr Ala
            180                 185                 190

Ala His Ala Val Tyr Glu Gln Lys His Asp Ala Ser Ala Leu Asp Ile
        195                 200                 205

Arg Met Gly Thr Leu Lys Arg Leu Ser Pro His Tyr Thr Gln Ala Trp
    210                 215                 220

Ser Glu Ala Val Phe Ile His Glu Gly Tyr Thr His Asp Ala Gly Phe
225                 230                 235                 240

Asp Asn Asp Ile Ala Leu Ile Lys Leu Asn Asn Lys Val Val Ile Asn
                245                 250                 255

Ser Asn Ile Thr Pro Ile Cys Leu Pro Arg Lys Glu Ala Glu Ser Phe
            260                 265                 270

Met Arg Thr Asp Asp Ile Gly Thr Ala Ser Gly Trp Gly Leu Thr Gln
        275                 280                 285

Arg Gly Phe Leu Ala Arg Asn Leu Met Tyr Val Asp Ile Pro Ile Val
    290                 295                 300

Asp His Gln Lys Cys Thr Ala Ala Tyr Glu Lys Pro Pro Tyr Pro Arg
305                 310                 315                 320

Gly Ser Val Thr Ala Asn Met Leu Cys Ala Gly Leu Glu Ser Gly Gly
```

```
                325                 330                 335

Lys Asp Ser Cys Arg Gly Asp Ala Gly Gly Ala Leu Val Phe Leu Asp
            340                 345                 350

Ser Glu Thr Glu Arg Trp Phe Val Gly Gly Ile Val Ser Trp Gly Ser
        355                 360                 365

Met Asn Cys Gly Glu Ala Gly Gln Tyr Gly Val Tyr Thr Lys Val Ile
    370                 375                 380

Asn Tyr Ile Pro Trp Ile Glu Asn Ile Ile Ser Asp Phe
385                 390                 395
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<210> 2
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<212> PRT
<213> Macaca fascicularis

<400> 2

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Pro Pro Asn Gly His Leu Ser Pro Val Gln Ala Lys Tyr Ile Leu Lys
            20                  25                  30

Asp Ser Phe Ser Ile Phe Cys Glu Pro Gly Tyr Glu Leu Leu Gln Gly
        35                  40                  45

His Leu Pro Leu Lys Ser Phe Ala Ala Val Cys Gln Lys Asp Gly Ser
    50                  55                  60

Trp Asp Gln Pro Met Pro Ser Cys Ser Ile Val Asp Cys Gly Pro Pro
65                  70                  75                  80

Asp Asp Leu Pro Ser Gly Arg Val Glu Tyr Ile Thr Gly Pro Glu Val
                85                  90                  95
```

```
Thr Thr Tyr Lys Ala Val Ile Gln Tyr Ser Cys Glu Glu Thr Phe Tyr
            100                 105                 110

Thr Met Lys Val Asn Asp Gly Lys Tyr Val Cys Glu Ala Asp Gly Phe
        115                 120                 125

Trp Thr Ser Ser Lys Gly Glu Arg Ser Pro Pro Val Cys Glu Pro Val
    130                 135                 140

Cys Gly Leu Ser Ala Arg Thr Thr Gly Gly Arg Ile Tyr Gly Gly Gln
145                 150                 155                 160

Lys Ala Lys Pro Gly Asp Phe Pro Trp Gln Val Leu Ile Leu Gly Gly
                165                 170                 175

Ser Thr Ala Ala Gly Ala Leu Leu Tyr Asp Asn Trp Val Leu Thr Ala
            180                 185                 190

Ala His Ala Ile Tyr Glu Gln Lys His Asp Ala Ser Ser Leu Asp Ile
        195                 200                 205

Arg Leu Gly Ala Leu Lys Arg Leu Ser Pro His Tyr Thr Gln Ala Trp
    210                 215                 220

Ala Glu Ala Val Phe Ile His Glu Gly Tyr Thr His Asp Ala Gly Phe
225                 230                 235                 240

Asp Asn Asp Ile Ala Leu Ile Lys Leu Asn Asn Lys Val Val Ile Asn
                245                 250                 255

Ser Asn Ile Thr Pro Ile Cys Leu Pro Arg Lys Glu Ala Glu Ser Phe
            260                 265                 270

Met Arg Thr Asp Asp Ile Gly Thr Ala Ser Gly Trp Gly Leu Thr Gln
        275                 280                 285

Arg Gly Leu Leu Ala Arg Asn Leu Met Tyr Val Asp Ile Pro Ile Val
    290                 295                 300
```

```
Asp His Gln Lys Cys Thr Ala Ala Tyr Glu Lys Pro Pro Tyr Ser Gly
305                 310                 315                 320


Gly Ser Val Thr Ala Asn Met Leu Cys Ala Gly Leu Glu Ser Gly Gly
                325                 330                 335


Lys Asp Ser Cys Arg Gly Asp Ala Gly Gly Ala Leu Val Phe Leu Asp
            340                 345                 350


Asn Glu Thr Gln Arg Trp Phe Val Gly Gly Ile Val Ser Trp Gly Ser
        355                 360                 365


Met Asn Cys Gly Glu Ala Gly Gln Tyr Gly Val Tyr Thr Lys Val Ile
    370                 375                 380


Asn Tyr Ile Pro Trp Ile Lys Asn Ile Ile Ser Asn Phe
385                 390                 395


<210>  3
<211>  396
<212>  PRT
<213>  Mus musculus

<400>  3

His His His His His His Ala Ser Arg Pro Cys Pro Asp Pro Thr Ala
1               5                   10                  15


Pro Pro Asn Gly Ser Ile Ser Pro Val Gln Ala Ile Tyr Val Leu Lys
            20                  25                  30


Asp Arg Phe Ser Val Phe Cys Lys Thr Gly Phe Glu Leu Leu Gln Gly
        35                  40                  45


Ser Val Pro Leu Lys Ser Phe Thr Ala Val Cys Gln Lys Asp Gly Ser
    50                  55                  60


Trp Asp Arg Pro Met Pro Glu Cys Ser Ile Ile Asp Cys Gly Pro Pro
```

```
65                  70                  75                  80

Asp Asp Leu Pro Asn Gly His Val Asp Tyr Ile Thr Gly Pro Glu Val
                85                  90                  95

Thr Thr Tyr Lys Ala Val Ile Gln Tyr Ser Cys Glu Glu Thr Phe Tyr
            100                 105                 110

Thr Met Ser Ser Asn Gly Lys Tyr Val Cys Glu Ala Asp Gly Phe Trp
        115                 120                 125

Thr Ser Ser Lys Gly Glu Lys Leu Pro Pro Val Cys Glu Pro Val Cys
    130                 135                 140

Gly Leu Ser Thr His Thr Ile Gly Gly Arg Ile Val Gly Gly Gln Pro
145                 150                 155                 160

Ala Lys Pro Gly Asp Phe Pro Trp Gln Val Leu Leu Leu Gly Gln Thr
                165                 170                 175

Thr Ala Ala Ala Gly Ala Leu Ile His Asp Asn Trp Val Leu Thr Ala
            180                 185                 190

Ala His Ala Val Tyr Glu Lys Arg Met Ala Ala Ser Ser Leu Asn Ile
        195                 200                 205

Arg Met Gly Ile Leu Lys Arg Leu Ser Pro His Tyr Thr Gln Ala Trp
    210                 215                 220

Pro Glu Glu Ile Phe Ile His Glu Gly Tyr Thr His Gly Ala Gly Phe
225                 230                 235                 240

Asp Asn Asp Ile Ala Leu Ile Lys Leu Lys Asn Lys Val Thr Ile Asn
                245                 250                 255

Gly Ser Ile Met Pro Val Cys Leu Pro Arg Lys Glu Ala Ala Ser Leu
            260                 265                 270
```

```
Met Arg Thr Asp Phe Thr Gly Thr Val Ala Gly Trp Gly Leu Thr Gln
        275                 280                 285

Lys Gly Leu Leu Ala Arg Asn Leu Met Phe Val Asp Ile Pro Ile Ala
    290                 295                 300

Asp His Gln Lys Cys Thr Ala Val Tyr Glu Lys Leu Tyr Pro Gly Val
305                 310                 315                 320

Arg Val Ser Ala Asn Met Leu Cys Ala Gly Leu Glu Thr Gly Gly Lys
                325                 330                 335

Asp Ser Cys Arg Gly Asp Ala Gly Gly Ala Leu Val Phe Leu Asp Asn
            340                 345                 350

Glu Thr Gln Arg Trp Phe Val Gly Gly Ile Val Ser Trp Gly Ser Ile
        355                 360                 365

Asn Cys Gly Ala Ala Asp Gln Tyr Gly Val Tyr Thr Lys Val Ile Asn
    370                 375                 380

Tyr Ile Pro Trp Ile Glu Asn Ile Ile Ser Asn Phe
385                 390                 395
```

<210> 4
<211> 396
<212> PRT
<213> Rattus norvegicus

<400> 4

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His His His His His His Ala Ser Gln Pro Cys Pro Asp Pro Thr Ala
1               5                   10                  15

Pro Pro Asn Gly His Ile Ser Pro Val Gln Ala Thr Tyr Val Leu Lys
            20                  25                  30

Asp Ser Phe Ser Val Phe Cys Lys Thr Gly Phe Glu Leu Leu Gln Gly
        35                  40                  45
```

```
Ser Val Pro Leu Lys Ser Phe Thr Ala Val Cys Gln Lys Asp Gly Ser
    50                  55                  60

Trp Asp Arg Pro Ile Pro Glu Cys Ser Ile Ile Asp Cys Gly Pro Pro
65                  70                  75                  80

Asp Asp Leu Pro Asn Gly His Val Asp Tyr Ile Thr Gly Pro Glu Val
                85                  90                  95

Thr Thr Tyr Lys Ala Val Ile Gln Tyr Ser Cys Glu Glu Thr Phe Tyr
            100                 105                 110

Thr Met Ser Ser Asn Gly Lys Tyr Val Cys Glu Ala Asp Gly Phe Trp
        115                 120                 125

Thr Ser Ser Lys Gly Glu Lys Ser Leu Pro Val Cys Lys Pro Val Cys
    130                 135                 140

Gly Leu Ser Thr His Thr Ser Gly Gly Arg Ile Ile Gly Gly Gln Pro
145                 150                 155                 160

Ala Lys Pro Gly Asp Phe Pro Trp Gln Val Leu Leu Leu Gly Glu Thr
                165                 170                 175

Thr Ala Ala Gly Ala Leu Ile His Asp Asp Trp Val Leu Thr Ala Ala
            180                 185                 190

His Ala Val Tyr Gly Lys Thr Glu Ala Met Ser Ser Leu Asp Ile Arg
        195                 200                 205

Met Gly Ile Leu Lys Arg Leu Ser Leu Ile Tyr Thr Gln Ala Trp Pro
    210                 215                 220

Glu Ala Val Phe Ile His Glu Gly Tyr Thr His Gly Ala Gly Phe Asp
225                 230                 235                 240
```

```
Asn Asp Ile Ala Leu Ile Lys Leu Lys Asn Lys Val Thr Ile Asn Arg
                245                 250                 255

Asn Ile Met Pro Ile Cys Leu Pro Arg Lys Glu Ala Ala Ser Leu Met
            260                 265                 270

Lys Thr Asp Phe Val Gly Thr Val Ala Gly Trp Gly Leu Thr Gln Lys
        275                 280                 285

Gly Phe Leu Ala Arg Asn Leu Met Phe Val Asp Ile Pro Ile Val Asp
    290                 295                 300

His Gln Lys Cys Ala Thr Ala Tyr Thr Lys Gln Pro Tyr Pro Gly Ala
305                 310                 315                 320

Lys Val Thr Val Asn Met Leu Cys Ala Gly Leu Asp Arg Gly Gly Lys
                325                 330                 335

Asp Ser Cys Arg Gly Asp Ala Gly Gly Ala Leu Val Phe Leu Asp Asn
            340                 345                 350

Glu Thr Gln Arg Trp Phe Val Gly Gly Ile Val Ser Trp Gly Ser Ile
        355                 360                 365

Asn Cys Gly Gly Ser Glu Gln Tyr Gly Val Tyr Thr Lys Val Thr Asn
    370                 375                 380

Tyr Ile Pro Trp Ile Glu Asn Ile Ile Asn Asn Phe
385                 390                 395
```

<210> 5
<211> 114
<212> PRT
<213> Mus musculus

<400> 5

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

```
Ser Leu Ser Leu Thr Cys Thr Val Thr Gly Tyr Ser Ile Thr Ser Asp
            20                  25                  30

Tyr Ala Trp Asn Trp Ile Arg Gln Phe Ser Gly Asp Lys Leu Glu Trp
        35                  40                  45

Met Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Ser Tyr Asn Pro Ser Leu
    50                  55                  60

Lys Ser Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Phe Phe
65                  70                  75                  80

Leu His Leu Ser Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys
                85                  90                  95

Ala Arg Tyr Trp Gly Asp Tyr Trp Gly His Gly Thr Thr Leu Thr Val
            100                 105                 110

Ser Ser
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<210> 6
<211> 342
<212> DNA
<213> Mus musculus

<400> 6
gatgtgcagc ttcaggagtc gggacctggc ctggtgaaac cttctcagtc tctgtccctc 60

acctgcactg tcactggcta ctcaatcacc agtgattatg cctggaactg gatccggcag 120

ttttcaggag acaaactgga gtggatgggc tacataagct acagtggttc cactagctat 180

aacccatctc tcaaaagtcg aatctctatc actcgagaca catccaagaa ccagttcttc 240

ctgcacttga gttctgtgac tactgaggac acagccacat atttctgtgc aagatattgg 300

ggcgactact ggggccacgg caccactctc acagtctcct ca 342

<210> 7
<211> 7

<212> PRT
<213> Mus musculus

<400> 7

Thr Ser Asp Tyr Ala Trp Asn
1   5

<210> 8
<211> 16
<212> PRT
<213> Mus musculus

<400> 8

Tyr Ile Ser Tyr Ser Gly Ser Thr Ser Tyr Asn Pro Ser Leu Lys Ser
1   5   10   15

<210> 9
<211> 5
<212> PRT
<213> Mus musculus

<400> 9

Tyr Trp Gly Asp Tyr
1   5

<210> 10
<211> 107
<212> PRT
<213> Mus musculus

<400> 10

Asp Ser Val Met Thr Gln Ser Gln Lys Phe Met Ser Thr Ser Val Gly
1   5   10   15

Asp Arg Val Ser Val Thr Cys Lys Ala Ser His Asn Val Gly Thr Asn
            20   25   30

Val Ala Trp Phe Gln Gln Lys Pro Gly Gln Ser Pro Lys Gly Leu Ile
        35   40   45

```
Tyr Ser Ala Ser Tyr Arg Ser Ser Gly Val Pro Asp Arg Phe Thr Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Val Gln Ser
65                  70                  75                  80

Glu Asp Leu Ala Glu Tyr Phe Cys Leu Gln Tyr Asn Ser Asn Pro Leu
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Val Lys
            100                 105
```

<210> 11
<211> 321
<212> DNA
<213> Mus musculus

<400> 11
gacagtgtga tgacccagtc tcaaaaattc atgtccacat cagtaggaga cagggtcagc 60

gtcacctgca aggccagtca caatgtgggt actaatgtag cctggtttca acagaaacca 120

ggacaatctc ctaaaggact gatttactcg gcatcctacc ggtccagtgg agtccctgat 180

cgcttcacag gcagtggatc tgggacagac ttcactctca ccatcagcaa tgtgcagtct 240

gaagacttgg cagagtattt ctgtctacaa tataacagca atcctctgac gttcggtgga 300

ggcaccaagc tggaggtcaa g 321

<210> 12
<211> 11
<212> PRT
<213> Mus musculus

<400> 12

```
Lys Ala Ser His Asn Val Gly Thr Asn Val Ala
1               5                   10
```

<210> 13
<211> 7
<212> PRT
<213> Mus musculus

<400> 13

Ser Ala Ser Tyr Arg Ser Ser
1 5

<210> 14
<211> 9
<212> PRT
<213> Mus musculus

<400> 14

Leu Gln Tyr Asn Ser Asn Pro Leu Thr
1 5

<210> 15
<211> 118
<212> PRT
<213> Mus musculus

<400> 15

Asp Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Arg Pro Ser Gln
1 5 10 15

Ser Leu Ser Leu Thr Cys Thr Val Thr Gly Tyr Ser Ile Thr Ser Asp
20 25 30

Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Glu Trp
35 40 45

Met Gly Tyr Ile Ser Tyr Ser Gly Arg Thr Ser Tyr Asn Pro Ser Leu
50 55 60

Lys Ser Arg Leu Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Phe Phe
65 70 75 80

Leu Gln Leu Asn Ser Val Ser Ser Ala Asp Thr Ala Thr Tyr Tyr Cys
85 90 95

Ala Ile Ile Ser Thr Ala Val Asp Phe Asp Tyr Trp Gly Gln Gly Thr

100 105 110

Thr Leu Thr Val Ser Ser
115

<210> 16
<211> 354
<212> DNA
<213> Mus musculus

<400> 16
gatgtacaac ttcaggagtc gggacctggc ctggtgagac cttctcagtc tctgtccctc 60

acctgcactg tcactggcta ctcaatcacc agtgattatg cctggaactg gatccggcag 120

tttccaggaa acaaactgga gtggatgggc tacataagtt acagtggtcg cactagttac 180

aacccctctc tcaaaagtcg actctctatc actcgagaca catccaagaa ccagttcttc 240

ctgcagttga attctgtgag ttctgcggac acagccacgt attactgtgc aattatttct 300

acggcagtag actttgacta ctggggccaa ggcaccactc tcacagtctc ctca 354

<210> 17
<211> 16
<212> PRT
<213> Mus musculus

<400> 17

Tyr Ile Ser Tyr Ser Gly Arg Thr Ser Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> 18
<211> 9
<212> PRT
<213> Mus musculus

<400> 18

Ile Ser Thr Ala Val Asp Phe Asp Tyr
1 5

<210> 19
<211> 108

<212> PRT
<213> Mus musculus

<400> 19

Gln Thr Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Leu Gly
1   5   10   15

Glu Arg Val Thr Met Thr Cys Thr Ala Ser Ser Ser Val Ser Ser Ser
            20   25   30

Tyr Leu Leu Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Leu Trp
        35   40   45

Ile Tyr Ser Thr Ser Lys Leu Ala Ser Gly Val Pro Val Arg Phe Ser
    50   55   60

Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu
65   70   75   80

Ala Asp Asp Ala Ala Thr Tyr Tyr Cys Leu Gln Tyr Asn Arg Ser Pro
                85   90   95

Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
            100   105

<210> 20
<211> 324
<212> DNA
<213> Mus musculus

<400> 20
caaactgttc tcacccagtc tccagcaatc atgtctgcat ctctagggga acgggtcacc   60

atgacctgca ctgccagctc aagtgtaagt tccagttact tgctctggta ccagcagaag   120

ccaggatcct cccccaaact ctggatttat agcacatcca agttggcttc tggagtccca   180

gttcgcttca gtggcagtgg gtctgggacc tcttactctc tcacaatcag cagcatggag   240

gctgacgatg ctgccactta ttactgcctc cagtataatc gttccccgct cacgttcggt   300

gctgggacca agctggagct gaaa   324

<210> 21
<211> 12
<212> PRT
<213> Mus musculus

<400> 21

Thr Ala Ser Ser Ser Val Ser Ser Ser Tyr Leu Leu
1   5   10

<210> 22
<211> 7
<212> PRT
<213> Mus musculus

<400> 22

Ser Thr Ser Lys Leu Ala Ser
1   5

<210> 23
<211> 9
<212> PRT
<213> Mus musculus

<400> 23

Leu Gln Tyr Asn Arg Ser Pro Leu Thr
1   5

<210> 24
<211> 117
<212> PRT
<213> Mus musculus

<400> 24

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

Ser Leu Ser Leu Ala Cys Thr Val Thr Gly Tyr Ser Ile Thr Ser Asp
            20   25   30

Tyr Ala Trp His Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Glu Trp
35 40 45

Met Gly Phe Ile Ser Tyr Ser Gly Arg Thr Asn Tyr Asn Pro Pro Leu
50 55 60

Thr Ser Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Phe Phe
65 70 75 80

Leu Gln Leu Asn Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr Cys
85 90 95

Ala Arg Ser Tyr Asp Tyr Trp Phe Gly Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ala
115

<210> 25
<211> 351
<212> DNA
<213> Mus musculus

<400> 25
gaggtccagc tgcaggagtc gggacctggc ctggtgaaac cttctcagtc tctgtccctc 60

gcctgcactg tcactggcta ctcaatcacc agtgattatg cctggcactg gatccggcag 120

tttccaggaa acaaactgga gtggatgggc ttcataagct acagtggtag aactaactac 180

aacccacctc tcacaagtcg aatctctatc actcgagaca catccaagaa ccagttcttc 240

ctgcagttga attctgtgac tactgaggac acagccacat attactgtgc aagatcatat 300

gattactggt ttggttattg gggccaaggg actctggtca ctgtctctgc a 351

<210> 26
<211> 7
<212> PRT
<213> Mus musculus

<400> 26

Thr Ser Asp Tyr Ala Trp His
1   5

<210> 27
<211> 16
<212> PRT
<213> Mus musculus

<400> 27

Phe Ile Ser Tyr Ser Gly Arg Thr Asn Tyr Asn Pro Pro Leu Thr Ser
1   5   10   15

<210> 28
<211> 8
<212> PRT
<213> Mus musculus

<400> 28

Ser Tyr Asp Tyr Trp Phe Gly Tyr
1   5

<210> 29
<211> 112
<212> PRT
<213> Mus musculus

<400> 29

Asn Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1   5   10   15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
            20   25   30

Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Met Gln Lys Pro Gly Gln Ser
        35   40   45

Pro Lys Leu Leu Ile Tyr Thr Val Ser Arg Arg Phe Ser Gly Val Pro
    50   55   60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile

65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Phe Gln Gly
85 90 95

Ser His Val Pro Val Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105 110

<210> 30
<211> 336
<212> DNA
<213> Mus musculus

<400> 30
aatgttttga tgacccaaac tccactctcc ctgcctgtca gtcttggaga tcaagcctcc 60

atctcttgca gatctagtca gagtcttgta catagtaatg gaaacaccta tttagaatgg 120

tacatgcaga aaccaggcca gtctccaaag ctcctgatct acacagtttc cagacgattt 180

tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc 240

agcagagtgg aggctgagga tctgggagtt tattattgct ttcaaggttc acatgttccg 300

gtcacgttcg gtgctgggac caagctggag ctgaaa 336

<210> 31
<211> 16
<212> PRT
<213> Mus musculus

<400> 31

Arg Ser Ser Gln Ser Leu Val His Ser Asn Gly Asn Thr Tyr Leu Glu
1 5 10 15

<210> 32
<211> 7
<212> PRT
<213> Mus musculus

<400> 32

Thr Val Ser Arg Arg Phe Ser
1 5

<210> 33
<211> 9
<212> PRT
<213> Mus musculus

<400> 33

Phe Gln Gly Ser His Val Pro Val Thr
1   5

<210> 34
<211> 117
<212> PRT
<213> Mus musculus

<400> 34

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

Ser Leu Ser Leu Thr Cys Thr Val Thr Gly Tyr Ser Ile Thr Ser Asp
            20   25   30

Tyr Ala Trp Lys Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Glu Trp
        35   40   45

Met Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Ser Tyr Asn Pro Ser Leu
    50   55   60

Lys Gly Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Phe Phe
65   70   75   80

Leu His Leu Gln Ser Val Thr Ile Glu Asp Thr Ala Thr Tyr Tyr Cys
                85   90   95

Ala Ile Leu Gly Tyr Phe Ala Met Asp Tyr Trp Gly Gln Gly Thr Pro
            100   105   110

Val Thr Val Ser Ser
        115

<210> 35
<211> 351
<212> DNA
<213> Mus musculus

<400> 35
gatgtacaac ttcaggagtc gggacctggc ctggtgaaac cttctcagtc tctgtccctc 60

acctgcactg tcactggcta ctcaatcacc agtgattatg cctggaagtg gatccggcag 120

tttccaggaa acaaactgga gtggatgggc tacataagtt acagtggcag cactagctac 180

aacccttctc tcaaaggtcg aatctctatc actcgagaca catccaagaa ccagtttttc 240

ctgcacttgc aatctgtgac tattgaggac acagccacct attactgtgc aatactaggt 300

tactttgcta tggactactg ggggcaagga accccagtca ccgtctcctc a 351

<210> 36
<211> 7
<212> PRT
<213> Mus musculus

<400> 36

Thr Ser Asp Tyr Ala Trp Lys
1 5

<210> 37
<211> 16
<212> PRT
<213> Mus musculus

<400> 37

Tyr Ile Ser Tyr Ser Gly Ser Thr Ser Tyr Asn Pro Ser Leu Lys Gly
1 5 10 15

<210> 38
<211> 8
<212> PRT
<213> Mus musculus

<400> 38

Leu Gly Tyr Phe Ala Met Asp Tyr
1 5

<210> 39
<211> 107
<212> PRT
<213> Mus musculus

<400> 39

Asp Ile Val Met Thr Gln Ser Gln Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15

Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asn Val Arg Val Asp
20 25 30

Val Ala Trp Tyr Gln Gln Lys Ser Gly Gln Ser Pro Lys Ser Leu Ile
35 40 45

Tyr Leu Ala Ser Asn Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Val Gln Ser
65 70 75 80

Glu Asp Leu Ala Asp Tyr Phe Cys Leu Gln His Trp Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 40
<211> 321
<212> DNA
<213> Mus musculus

<400> 40
gacattgtga tgacccagtc tcaaaaattc atgtccactt cagtaggaga cagggtcagc 60

atcacctgca aggccagtca gaatgttcgt gttgacgttg cctggtatca acagaaatca 120

gggcagtctc ctaaatcact gatttacttg gcatccaacc ggcacactgg agtccctgat 180

cgcttcacag gcagtggatc tgggacagat ttcactctca ccattagcaa tgtgcaatct 240

gaagacctgg cagattattt ctgtctacaa cattggagtt atcctctgac gttcggtgga 300

ggcaccaagc tggaaatcaa a 321

<210> 41
<211> 11
<212> PRT
<213> Mus musculus

<400> 41

Lys Ala Ser Gln Asn Val Arg Val Asp Val Ala
1 5 10

<210> 42
<211> 7
<212> PRT
<213> Mus musculus

<400> 42

Leu Ala Ser Asn Arg His Thr
1 5

<210> 43
<211> 9
<212> PRT
<213> Mus musculus

<400> 43

Leu Gln His Trp Ser Tyr Pro Leu Thr
1 5

<210> 44
<211> 118
<212> PRT
<213> Mus musculus

<400> 44

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

```
Ser Leu Ser Leu Thr Cys Thr Val Thr Gly Tyr Ser Ile Thr Ser Asp
            20                  25                  30

Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Asn Thr Leu Glu Trp
        35                  40                  45

Met Gly Tyr Ile Ser Tyr Ser Gly Arg Thr Ser Tyr Asn Pro Ser Leu
    50                  55                  60

Ile Gly Arg Ile Ser Ile Thr Arg Asp Thr Thr Lys Asn Gln Phe Phe
65                  70                  75                  80

Leu Gln Leu Asn Ser Val Ser Thr Glu Asp Thr Ala Thr Tyr Tyr Cys
                85                  90                  95

Ala Lys Leu Ala Gly Gly His Gly Met Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Ser Val Thr Val Ser Ser
        115
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<210> 45
<211> 354
<212> DNA
<213> Mus musculus

<400> 45
gatgtgcagc ttcaggagtc gggacctggc ctggtgaaac cttctcagtc tctgtccctc 60

acctgcactg tcactggcta ctcaatcacc agtgattatg cctggaactg gatccggcag 120

tttccaggaa acacattgga gtggatgggc tatataagtt atagtggtag gactagctac 180

aacccatctc tgataggtcg aatctcaatc actcgagaca caaccaagaa ccagttcttt 240

ctgcagttga attctgtgtc tactgaggac acagccacat attactgtgc aaaattggcc 300

ggaggacatg ggatggacta ctggggtcaa ggaacctcag tcaccgtctc ctca 354

<210> 46

<211> 16
<212> PRT
<213> Mus musculus

<400> 46

Tyr Ile Ser Tyr Ser Gly Arg Thr Ser Tyr Asn Pro Ser Leu Ile Gly
1 5 10 15

<210> 47
<211> 9
<212> PRT
<213> Mus musculus

<400> 47

Leu Ala Gly Gly His Gly Met Asp Tyr
1 5

<210> 48
<211> 106
<212> PRT
<213> Mus musculus

<400> 48

Asn Ile Val Met Thr Gln Ser Gln Gln Phe Met Ser Thr Ser Val Gly
1 5 10 15

Asp Arg Val Ser Val Thr Cys Lys Ala Ser Gln Asn Val Asp Thr Asn
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Ala Leu Ile
35 40 45

Tyr Ser Ala Ser Tyr Arg Tyr Ser Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Val Gln Ser
65 70 75 80

Glu Asp Leu Ala Glu Tyr Phe Cys Leu Gln Tyr Asn Ser Tyr Leu Thr
85 90 95

Phe Gly Ser Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 49
<211> 318
<212> DNA
<213> Mus musculus

<400> 49
aacattgtga tgacccagtc tcaacaattc atgtccacat cagtaggaga cagggtcagc 60

gtcacctgca aggccagtca gaatgtggat actaatgtag cctggtatca acagaaacca 120

ggacaatctc ctaaagcact gatttactcg gcatcctacc ggtacagtgg agtccctgat 180

cgcttcacag gcagtggatc tgggacagat ttcactctca ccatcagcaa tgtgcagtct 240

gaagacttgg cagaatattt ctgtctgcaa tataatagtt acctcacgtt cggttctggg 300

accaagctgg agctgaaa 318

<210> 50
<211> 11
<212> PRT
<213> Mus musculus

<400> 50

Lys Ala Ser Gln Asn Val Asp Thr Asn Val Ala
1 5 10

<210> 51
<211> 7
<212> PRT
<213> Mus musculus

<400> 51

Ser Ala Ser Tyr Arg Tyr Ser
1 5

<210> 52
<211> 8
<212> PRT

<213> Mus musculus

<400> 52

Leu Gln Tyr Asn Ser Tyr Leu Thr
1   5

<210> 53
<211> 118
<212> PRT
<213> Mus musculus

<400> 53

Asp Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Arg Pro Ser Gln
1   5   10   15

Ser Leu Ser Leu Thr Cys Thr Val Thr Gly Tyr Ser Ile Thr Ser Asp
            20   25   30

Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Glu Trp
        35   40   45

Met Gly Tyr Ile Ser Tyr Ser Gly Arg Thr Ser Tyr Asn Pro Ser Leu
    50   55   60

Lys Ser Arg Leu Ser Val Thr Arg Asp Thr Ser Lys Asn Gln Phe Phe
65   70   75   80

Leu Gln Leu Asn Ser Val Asn Ala Ala Asp Thr Ala Thr Tyr Tyr Cys
                85   90   95

Ala Ile Ile Ser Thr Ala Val Asp Phe Asp Tyr Trp Gly Gln Gly Thr
            100   105   110

Thr Leu Thr Val Ser Ser
        115

<210> 54
<211> 354
<212> DNA

<213> Mus musculus

<400> 54
gatgtacaac ttcaggagtc gggacctggc ctggtgagac cttctcagtc tctgtccctc 60

acctgcactg tcactggcta ctcaatcacc agtgattatg cctggaactg gatccggcag 120

tttccaggaa acaaactgga gtggatgggc tacataagtt acagtggtcg cactagctac 180

aacccctctc tcaagagtcg actctctgtc actcgagaca catccaagaa ccagttcttc 240

ctgcagttga attctgtgaa tgctgcggac acagccacgt attactgtgc aattatttct 300

acggcagtag actttgacta ctggggccaa ggcaccactc tcacagtctc ctca 354

<210> 55
<211> 108
<212> PRT
<213> Mus musculus

<400> 55

Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Leu Gly
1 5 10 15

Glu Arg Val Thr Met Thr Cys Thr Ala Ser Ser Ser Val Ser Ser Ser
20 25 30

Tyr Leu Leu Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Leu Trp
35 40 45

Ile Tyr Ser Ser Ser Lys Leu Ala Ser Gly Val Pro Val Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu
65 70 75 80

Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Leu Gln Tyr Asn Arg Ser Pro
85 90 95

Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 56
<211> 324
<212> DNA
<213> Mus musculus

<400> 56
caaattgttc tcacccagtc tccagcaatc atgtctgcat ctctagggga acgggtcacc 60

atgacctgca ctgccagctc aagtgtaagt tccagttact tgctctggta ccagcagaag 120

ccaggatcct cccccaaact ctggatttat agctcatcca agttggcttc tggagtccca 180

gttcgcttca gtggcagtgg gtctgggacc tcttactctc tcacaatcag cagcatggag 240

gctgaagatg ctgccactta ttactgcctc cagtataatc gttccccgct cacgttcggt 300

gctgggacca agctggagct gaaa 324

<210> 57
<211> 7
<212> PRT
<213> Mus musculus

<400> 57

Ser Ser Ser Lys Leu Ala Ser
1 5

<210> 58
<211> 118
<212> PRT
<213> Mus musculus

<400> 58

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

Ser Leu Ser Leu Thr Cys Thr Val Thr Gly Tyr Ser Ile Thr Ser Asp
20 25 30

Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Glu Trp
35 40 45

```
Met Gly Tyr Ile Ser Tyr Ser Gly Arg Thr Ser Tyr Asn Pro Ser Leu
    50                  55                  60

Lys Ser Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Phe Phe
65                  70                  75                  80

Leu Gln Leu Asn Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr Cys
                85                  90                  95

Ala Lys Leu Gly Gly Gly His Gly Met Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Ser Val Thr Val Ser Ser
        115
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<210> 59
<211> 354
<212> DNA
<213> Mus musculus

<400> 59

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gatgtgcagc ttcaggagtc gggacctggc ctggtgaaac cttctcagtc tctgtccctc       60

acctgcactg tcactggcta ctcaatcacc agtgattatg cctggaactg gatccggcag      120

tttccaggaa acaaattgga gtggatgggc tacataagtt atagtggtag gactagctac      180

aacccatctc tgaaaagtcg aatctcaatc actcgagaca catccaagaa ccagttcttc      240

ctgcagttga attctgtgac tactgaggac acagccacat attactgtgc aaaattgggc      300

ggaggacatg ggatggacta ctggggtcaa ggaacctcag tcaccgtctc ctca            354
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<210> 60
<211> 9
<212> PRT
<213> Mus musculus

<400> 60

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Leu Gly Gly Gly His Gly Met Asp Tyr
1               5
```

<210> 61
<211> 105
<212> PRT
<213> Mus musculus

<400> 61

Ile Val Met Thr Gln Ser Gln Lys Phe Met Ser Thr Ser Val Gly Asp
1 5 10 15

Arg Val Ser Val Thr Cys Lys Ala Ser Gln Asn Val Asp Thr Asn Val
20 25 30

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Ala Leu Ile Tyr
35 40 45

Ser Ala Ser Tyr Arg Tyr Ser Gly Val Pro Asp Arg Phe Thr Gly Ser
50 55 60

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Val Gln Ser Glu
65 70 75 80

Asp Leu Ala Glu Tyr Phe Cys Leu Gln Tyr Asn Ser Tyr Leu Thr Phe
85 90 95

Gly Ser Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 62
<211> 317
<212> DNA
<213> Mus musculus

<400> 62
acattgtgat gacccagtct caaaaattca tgtccacatc agtaggagac agggtcagcg 60

tcacctgcaa ggccagtcag aatgtggata ctaatgtagc ctggtatcaa cagaaaccag 120

ggcaatctcc taaagcgctg atttactcgg catcctaccg ttacagtgga gtccctgatc 180

gcttcacagg cagtggatct gggacagatt tcactctcac catcagcaat gtgcagtctg 240

aagacttggc agagtatttc tgtctgcaat ataacagcta cctcacgttc ggttctggga 300

ccaagctgga gctgaaa 317

<210> 63
<211> 120
<212> PRT
<213> Mus musculus

<400> 63

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

Thr Leu Ile Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Asn Thr Ser
20 25 30

Gly Met Gly Val Gly Trp Ile Arg Gln Pro Ser Gly Lys Gly Leu Glu
35 40 45

Trp Leu Ala His Ile Trp Trp Asp Asp Asp Lys Asp Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Gln Val Thr Ile Ser Lys Asp Thr Ser Thr Asn Gln Val
65 70 75 80

Phe Leu Lys Ile Thr Ser Val Asp Thr Ala Asp Gly Ala Thr Tyr Tyr
85 90 95

Cys Val Arg Asp Thr Thr Phe Leu Asp Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 64
<211> 360
<212> DNA
<213> Mus musculus

<400> 64
caagttactc taaaagagtc tggccctggg atattgaagc cctcacagac cctcattctg 60

acttgttctt tctctgggtt ttcactgaac acttctggta tgggtgtagg ctggattcgt 120

cagccttcag ggaagggtct ggagtggctg gcacacattt ggtgggatga tgataaggac 180

tataacccat ccctgaagag ccaagtcaca atctccaagg atacctccac aaaccaggtg 240

ttcctcaaga tcaccagtgt ggacactgca gatggtgcca cttactactg tgttcgagat 300

actacgtttt tagatgctat ggactactgg ggtcaaggaa cctcagtcac cgtctcctca 360

<210> 65
<211> 8
<212> PRT
<213> Mus musculus

<400> 65

Asn Thr Ser Gly Met Gly Val Gly
1 5

<210> 66
<211> 16
<212> PRT
<213> Mus musculus

<400> 66

His Ile Trp Trp Asp Asp Asp Lys Asp Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> 67
<211> 10
<212> PRT
<213> Mus musculus

<400> 67

Asp Thr Thr Phe Leu Asp Ala Met Asp Tyr
1 5 10

<210> 68
<211> 112
<212> PRT
<213> Mus musculus

<400> 68

Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Arg
20 25 30

Asn Gly Asn Thr Phe Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Lys Leu Leu Ile Tyr Arg Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Phe Gln Gly
85 90 95

Ser His Val Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 69
<211> 336
<212> DNA
<213> Mus musculus

<400> 69
gatgttttga tgacccaaac tccactctcc ctgcctgtca gtcttggaga tcaagcctcc 60

atctcttgca ggtctagtca gagcattgta catcgtaatg gaaacacctt tttagaatgg 120

tacctgcaga aaccaggcca gtctccaaag ctcctgatct acagggtttc caaccgattt 180

tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc 240

agcagagtgg aggctgagga tctgggagtt tattactgct ttcaaggttc acatgttcca 300

ttcacgttcg gctcggggac aaagttggaa ataaaa 336

<210> 70

<211> 16
<212> PRT
<213> Mus musculus

<400> 70

Arg Ser Ser Gln Ser Ile Val His Arg Asn Gly Asn Thr Phe Leu Glu
1 5 10 15

<210> 71
<211> 7
<212> PRT
<213> Mus musculus

<400> 71

Arg Val Ser Asn Arg Phe Ser
1 5

<210> 72
<211> 9
<212> PRT
<213> Mus musculus

<400> 72

Phe Gln Gly Ser His Val Pro Phe Thr
1 5

<210> 73
<211> 118
<212> PRT
<213> Mus musculus

<400> 73

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

Ser Leu Ser Leu Thr Cys Thr Val Thr Gly Tyr Ser Ile Thr Ser Asp
20 25 30

Tyr Ala Trp Asn Trp Ile Arg Gln Leu Pro Gly Asn Lys Leu Glu Trp
35 40 45

```
Val Gly Tyr Ile Ser Tyr Ser Gly Arg Thr Ser Tyr Asn Pro Ser Leu
    50                  55                  60

Lys Ser Arg Ile Ser Ile Thr Arg Asp Thr Thr Lys Asn Gln Phe Phe
65                  70                  75                  80

Leu Gln Leu Asn Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr Cys
                85                  90                  95

Ala Lys Leu Ala Gly Gly His Gly Met Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Ser Val Thr Val Ser Ser
        115
```

<210> 74
<211> 354
<212> DNA
<213> Mus musculus

<400> 74

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gatgtgcagc ttcaggagtc gggacctggc ctggtgaaac cttctcagtc tctgtccctc       60

acctgcactg tcactggcta ctcaatcacc agtgattatg cctggaactg gatccggcag      120

ttaccaggaa acaaattgga gtgggtgggc tatataagtt atagtggtag gactagctac      180

aacccatctc tgaaaagtcg aatctcaatc actcgagaca caaccaagaa ccagttcttc      240

ctgcagttga attctgtgac tactgaggac acagccacat attactgtgc aaagttggcc      300

gggggacatg ggatggacta ctggggtcaa ggaacctcag tcaccgtctc ctca            354
```

<210> 75
<211> 106
<212> PRT
<213> Mus musculus

<400> 75

```
Asn Ile Val Met Thr Gln Ser Gln Lys Phe Met Ser Thr Ser Val Gly
1               5                   10                  15
```

```
Asp Arg Val Ser Val Thr Cys Lys Ala Ser Gln Asn Val Asp Thr Asn
            20                  25                  30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Ala Leu Ile
        35                  40                  45

His Ser Ala Ser Tyr Arg Tyr Ser Gly Val Pro Asp Arg Phe Thr Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Ile Leu Thr Ile Ser Asn Val Gln Ser
65                  70                  75                  80

Glu Asp Leu Ala Glu Tyr Phe Cys Leu Gln Tyr Asn Ser Tyr Leu Thr
                85                  90                  95

Phe Gly Ser Gly Thr Lys Leu Glu Leu Lys
            100                 105
```

<210> 76
<211> 318
<212> DNA
<213> Mus musculus

<400> 76
aacattgtga tgacccagtc tcaaaaattc atgtccacat cagtaggaga cagggtcagc 60

gtcacctgca aggccagtca gaatgtggat actaatgtag cctggtatca acagaaacca 120

gggcaatctc ctaaagcact gattcactcg gcatcctacc ggtacagtgg agtccctgat 180

cgcttcacag gcagtggatc tgggacagat ttcattctca ccatcagtaa tgtgcagtct 240

gaagacttgg cagagtattt ctgtctgcaa tataacagct acctcacgtt cggttctggg 300

accaagctgg agctgaaa 318

<210> 77
<211> 116
<212> PRT
<213> Mus musculus

<400> 77

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

Ser Leu Ser Leu Thr Cys Thr Val Thr Gly Tyr Ser Ile Thr Ser Asp
            20                  25                  30

Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Glu Trp
        35                  40                  45

Met Gly Tyr Ile Ser Tyr Ser Gly Arg Thr Ser Tyr Asn Pro Ser Leu
    50                  55                  60

Lys Ser Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Phe Phe
65                  70                  75                  80

Leu His Leu Asn Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys
                85                  90                  95

Ala Val Leu Gly Leu Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Pro Leu
            100                 105                 110

Thr Val Ser Ser
        115
```

<210> 78
<211> 348
<212> DNA
<213> Mus musculus

<400> 78

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gatgtgcagc ttcaggagtc gggacctggc ctggtgaaac cttctcagtc tctgtccctc       60

acctgcactg tcactggcta ctcaatcacc agtgattatg cctggaactg gatccggcag      120

tttccaggaa acaaactgga gtggatgggc tacataagct acagtggtag aactagctac      180

aacccatctc tcaaaagtcg aatctctatc actcgagaca catccaagaa ccagttcttc      240

ctgcacttga attctgtgac tactgaggac acagccacat atttctgtgc agtactggga      300

ctctactttg actactgggg ccaaggcacc cctctcacag tctcctca                  348
```

<210> 79
<211> 7
<212> PRT
<213> Mus musculus

<400> 79

Leu Gly Leu Tyr Phe Asp Tyr
1   5

<210> 80
<211> 107
<212> PRT
<213> Mus musculus

<400> 80

Asp Ile Val Met Thr Gln Ser Gln Lys Phe Met Ser Thr Ser Val Gly
1   5   10   15

Asp Arg Val Ser Val Thr Cys Lys Ala Ser Gln Asn Val Asp Thr Asn
            20   25   30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Ala Leu Ile
        35   40   45

Tyr Ser Ala Ser Tyr Arg Tyr Ser Gly Val Pro Asp Arg Phe Thr Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Val Gln Ser
65   70   75   80

Glu Asp Leu Ala Glu Tyr Phe Cys His Gln Phe Asn Ser Asn Pro Leu
                85   90   95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
            100   105

<210> 81
<211> 321

<212> DNA
<213> Mus musculus

<400> 81
gacattgtga tgacccagtc tcaaaaattc atgtccacat cagtaggaga cagggtcagc 60

gtcacctgca aagccagtca gaatgtggat actaatgtag cctggtatca acagaaacca 120

gggcaatctc ctaaagcact gatttactcg gcatcctacc ggtacagtgg agtccctgat 180

cgcttcacag gcagtggatc tgggacagat ttcactctca ccatcagcaa tgtgcagtct 240

gaagacttgg cagaatattt ctgtcaccaa tttaacagca atcctctcac gttcggtgct 300

gggaccaagc tggagctgaa a 321

<210> 82
<211> 9
<212> PRT
<213> Mus musculus

<400> 82

His Gln Phe Asn Ser Asn Pro Leu Thr
1 5

<210> 83
<211> 117
<212> PRT
<213> Mus musculus

<400> 83

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

Ser Leu Ser Leu Thr Cys Thr Val Thr Gly Tyr Ser Ile Thr Ser Asp
20 25 30

Tyr Ala Trp Lys Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Glu Trp
35 40 45

Met Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Ser Tyr His Pro Ser Leu
50 55 60

```
Lys Gly Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Phe Phe
65                  70                  75                  80


Leu Gln Leu Asn Ser Val Thr Ala Asp Asp Thr Ala Thr Tyr Tyr Cys
                85                  90                  95


Ala Ile Leu Gly Tyr Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser
            100                 105                 110


Val Thr Val Ser Ser
        115


<210>  84
<211>  351
<212>  DNA
<213>  Mus musculus

<400>  84
gatgtgcagc ttcaggagtc gggacctggc ctggtgaaac cttctcagtc tctgtccctc       60

acctgcactg tcactggcta ctcaatcacc agtgattatg cctggaaatg gatccggcag      120

tttccaggaa acaaactgga atggatgggc tacataagct acagtggttc cactagctat      180

cacccatctc tcaaaggtcg aatctccatc actcgagaca catccaagaa ccagttcttc      240

ctgcagttga attctgtgac tgctgacgac acagccacat attactgtgc aatattaggt      300

tactatgcta tggactactg gggtcaagga acctcagtca ccgtctcctc a               351


<210>  85
<211>  16
<212>  PRT
<213>  Mus musculus

<400>  85

Tyr Ile Ser Tyr Ser Gly Ser Thr Ser Tyr His Pro Ser Leu Lys Gly
1               5                   10                  15


<210>  86
<211>  8
<212>  PRT
```

<213> Mus musculus

<400> 86

Leu Gly Tyr Tyr Ala Met Asp Tyr
1   5

<210> 87
<211> 107
<212> PRT
<213> Mus musculus

<400> 87

Asp Ile Val Met Thr Gln Ser Gln Lys Phe Met Ser Thr Ser Val Gly
1   5   10   15

Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asn Val Arg Val Asp
            20   25   30

Val Ala Trp Tyr Gln Gln Lys Ser Gly Gln Ser Pro Arg Ala Leu Ile
        35   40   45

Tyr Leu Ala Ser Asn Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Thr Asn Val Gln Ser
65   70   75   80

Glu Asp Leu Ala Asp Tyr Phe Cys Leu Gln His Trp Ser Tyr Pro Leu
                85   90   95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100   105

<210> 88
<211> 321
<212> DNA
<213> Mus musculus

<400> 88
gacattgtga tgacccagtc tcaaaaattc atgtccacat cagtaggaga cagggtcagt   60

atcacctgca aggccagtca gaatgttcgt gttgacgtag cctggtatca acagaaatca 120

gggcagtctc ctagagcact gatttacttg gcatccaacc ggcacactgg agtccctgat 180

cgcttcacag gcagtggatc tgggacagat ttcactctca ccattaccaa tgtgcaatct 240

gaggacctgg cagattattt ctgtctacaa cattggagtt atcctctgac gttcggtgga 300

ggcaccaagc tggaaatcaa a 321

<210> 89
<211> 107
<212> PRT
<213> Mus musculus

<400> 89

Asp Ile Val Met Thr Gln Ser Gln Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15

Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asn Val Arg Val Asp
20 25 30

Val Ala Trp Tyr Gln Gln Lys Ser Gly Gln Ser Pro Arg Ala Leu Ile
35 40 45

Tyr Leu Ala Ser Asn Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Thr Asn Val Gln Ser
65 70 75 80

Glu Asp Leu Ala Asp Tyr Phe Cys Pro Gln His Trp Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 90
<211> 321
<212> DNA

<213> Mus musculus

<400> 90
gacattgtga tgacccagtc tcaaaaattc atgtccacat cagtaggaga cagggtcagt 60

atcacctgca aggccagtca gaatgttcgt gttgacgtag cctggtatca acagaaatca 120

gggcagtctc ctagagcact gatttacttg gcatccaacc ggcacactgg agtccctgat 180

cgcttcacag gcagtggatc tgggacagat ttcactctca ccattaccaa tgtgcaatct 240

gaggacctgg cagattattt ctgtccacaa cattggagtt atcctctgac gttcggtgga 300

ggcaccaagc tggaaatcaa a 321

<210> 91
<211> 9
<212> PRT
<213> Mus musculus

<400> 91

Pro Gln His Trp Ser Tyr Pro Leu Thr
1 5

<210> 92
<211> 119
<212> PRT
<213> Mus musculus

<400> 92

Lys Val Lys Leu Val Glu Ser Gly Gly Asp Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Ile Ser Cys Thr Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Ala Met Ser Trp Ile Arg Gln Thr Pro Asp Lys Arg Leu Glu Trp Val
35 40 45

Ala Thr Val Ser Ser Gly Gly Pro Tyr Thr Tyr Tyr Pro Asp Ser Val
50 55 60

```
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Glu Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Ser Ser Leu Arg Ser Asp Asp Thr Ala Ile Tyr Tyr Cys
                85                  90                  95


Ala Arg Gln Ile Tyr Ser Asp Tyr Asp Val Thr Tyr Trp Gly Gln Gly
            100                 105                 110


Thr Leu Val Thr Val Ser Ala
        115


<210>  93
<211>  357
<212>  DNA
<213>  Mus musculus

<400>  93
aaagtgaagc tggtggagtc tgggggagac ttagtgaagc ctggagggtc cctgaaaatc       60

tcctgtacag cctctggatt cactttcagt aactatgcca tgtcttggat tcgccagact      120

ccggacaaga ggctggagtg ggtcgcaacc gttagtagtg gtggtcctta cacctactat      180

ccagacagtg tgaaggggcg attcaccatc tccagagaca atgccgaaaa caccctgtac      240

ctgcaaatga gcagtctgag gtctgatgac acggccatat attactgtgc aaggcagatc      300

tactctgatt acgacgtcac ttactggggc caagggactc tggtcactgt ctctgca         357


<210>  94
<211>  6
<212>  PRT
<213>  Mus musculus

<400>  94

Ser Asn Tyr Ala Met Ser
1               5


<210>  95
<211>  17
<212>  PRT
<213>  Mus musculus
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<400> 95

Thr Val Ser Ser Gly Gly Pro Tyr Thr Tyr Tyr Pro Asp Ser Val Lys
1   5   10   15

Gly

<210> 96
<211> 10
<212> PRT
<213> Mus musculus

<400> 96

Gln Ile Tyr Ser Asp Tyr Asp Val Thr Tyr
1   5   10

<210> 97
<211> 106
<212> PRT
<213> Mus musculus

<400> 97

Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser Pro Gly
1   5   10   15

Glu Thr Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Ser Phe Met
            20   25   30

Tyr Trp Leu Gln Gln Lys Pro Gly Ser Ser Pro Gln Pro Trp Ile Tyr
        35   40   45

Ala Thr Ser Asn 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 Thr Arg Val Glu Ala Glu
65   70   75   80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Phe Arg Pro Trp Thr

85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 98
<211> 318
<212> DNA
<213> Mus musculus

<400> 98
caaattgttc tctcccagtc tccagcaatc ctgtctgcat ctccagggga gacggtcaca 60

atgacttgca gggccagttc aagtgtaagt ttcatgtact ggctccagca gaagccaggt 120

tcctcccccc aaccctggat ttatgccaca tccaacctgg cttctggagt ccctgctcgc 180

ttcagtggca gtgggtctgg gacctcttac tccctcacaa tcaccagagt ggaggctgaa 240

gatgctgcca cttattactg tcaacagtgg agttttagac cgtggacgtt cggtggaggc 300

accaagctgg aaatcaaa 318

<210> 99
<211> 10
<212> PRT
<213> Mus musculus

<400> 99

Arg Ala Ser Ser Ser Val Ser Phe Met Tyr
1 5 10

<210> 100
<211> 7
<212> PRT
<213> Mus musculus

<400> 100

Ala Thr Ser Asn Leu Ala Ser
1 5

<210> 101
<211> 9

<212> PRT
<213> Mus musculus

<400> 101

Gln Gln Trp Ser Phe Arg Pro Trp Thr
1   5

<210> 102
<211> 117
<212> PRT
<213> Mus musculus

<400> 102

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

Ser Leu Ser Leu Thr Cys Thr Val Thr Gly Phe Ser Ile Thr Ser Asp
            20   25   30

Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Glu Trp
        35   40   45

Met Gly Tyr Ile Ser Tyr Ser Gly Arg Thr Asn Tyr Asn Pro Ser Leu
    50   55   60

Lys Ser Arg Phe Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Phe Phe
65   70   75   80

Leu Gln Leu Asn Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr Cys
                85   90   95

Ala Arg Ser Tyr Asp Tyr Trp Phe Pro Tyr Trp Gly Gln Gly Thr Leu
            100   105   110

Val Thr Val Ser Ala
        115

<210> 103
<211> 351

<212> DNA
<213> Mus musculus

<400> 103
gatgtgcagc ttcaggagtc gggacctggc ctggtgaaac cttctcagtc tctgtccctc 60

acctgcactg tcactggctt ctcaatcacc agtgattatg cctggaactg gatccggcag 120

tttccaggaa acaaactgga gtggatgggc tacataagct acagtggtag aactaactac 180

aacccatctc tcaaaagtcg attctctatc actcgagaca catccaagaa ccagttcttc 240

ctgcagttga attctgtgac tactgaggac acagccacat attactgtgc aagatcatat 300

gattactggt ttccttactg gggccaaggg actctggtca ctgtctctgc a 351

<210> 104
<211> 16
<212> PRT
<213> Mus musculus

<400> 104

Tyr Ile Ser Tyr Ser Gly Arg Thr Asn Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> 105
<211> 8
<212> PRT
<213> Mus musculus

<400> 105

Ser Tyr Asp Tyr Trp Phe Pro Tyr
1 5

<210> 106
<211> 112
<212> PRT
<213> Mus musculus

<400> 106

Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1 5 10 15

```
Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Ser
            20                  25                  30

Asn Gly Asn Thr Phe Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
    50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Phe Gln Gly
                85                  90                  95

Ser His Ile Pro Val Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
            100                 105                 110
```

<210> 107
<211> 336
<212> DNA
<213> Mus musculus

<400> 107
gatgttttga tgacccaaac tccactctcc ctgcctgtca gtcttggaga tcaagcctcc 60

atctcttgca gatctagtca gagcattgta catagtaatg gaaacacctt tttggaatgg 120

tacctgcaga aaccaggcca gtctccaaag ctcctgatct acaaagtttc caaccgattt 180

tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc 240

agcagagtgg aggctgagga tctgggagtt tattactgct ttcaaggttc acatattccg 300

gtcacgttcg gtgctgggac caagctggag ctgaaa 336

<210> 108
<211> 16
<212> PRT
<213> Mus musculus

<400> 108

Arg Ser Ser Gln Ser Ile Val His Ser Asn Gly Asn Thr Phe Leu Glu
1   5   10   15

<210> 109
<211> 7
<212> PRT
<213> Mus musculus

<400> 109

Lys Val Ser Asn Arg Phe Ser
1   5

<210> 110
<211> 9
<212> PRT
<213> Mus musculus

<400> 110

Phe Gln Gly Ser His Ile Pro Val Thr
1   5

<210> 111
<211> 117
<212> PRT
<213> Mus musculus

<400> 111

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

Ser Leu Ser Leu Thr Cys Thr Val Thr Gly Phe Ser Ile Thr Ser Asp
            20   25   30

Tyr Ala Trp His Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Glu Trp
        35   40   45

Met Gly Phe Ile Asn Tyr Ser Gly Arg Thr Asn Tyr Asn Pro Ser Leu
    50   55   60

Thr Ser Arg Ile Ser Ile Ile Arg Asp Thr Ser Lys Asn Gln Phe Phe

65 70 75 80

Leu Gln Leu Asn Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr Cys
85 90 95

Ala Arg Ser Tyr Asp Phe Trp Phe Gly Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ala
115

<210> 112
<211> 351
<212> DNA
<213> Mus musculus

<400> 112
gaggtccagc tgcaggagtc gggacctggc ctggtgaaac cttctcagtc tctgtccctc 60

acctgcactg tcactggctt ctcaatcacc agtgattatg cctggcactg gatccggcag 120

tttccaggaa acaaactgga gtggatgggc ttcataaact acagtggtag aactaactac 180

aacccatctc tcacaagtcg aatctctatc attcgggaca catccaagaa ccagttcttc 240

ctgcagttga attctgtgac tactgaggac acagccacat attactgtgc aagatcatat 300

gatttctggt ttggttattg gggccaaggg actctggtca ctgtctctgc a 351

<210> 113
<211> 16
<212> PRT
<213> Mus musculus

<400> 113

Phe Ile Asn Tyr Ser Gly Arg Thr Asn Tyr Asn Pro Ser Leu Thr Ser
1 5 10 15

<210> 114
<211> 8
<212> PRT
<213> Mus musculus

<400> 114

Ser Tyr Asp Phe Trp Phe Gly Tyr
1 5

<210> 115
<211> 112
<212> PRT
<213> Mus musculus

<400> 115

Asn Val Leu Met Thr Gln Ser Pro Leu Ser Leu Pro Val Ser Leu Gly
1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Ser
20 25 30

Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Met Gln Lys Pro Gly Gln Ser
35 40 45

Pro Lys Leu Leu Ile Tyr Thr Val Ser Lys Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Phe Gln Gly
85 90 95

Ser His Val Pro Val Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105 110

<210> 116
<211> 336
<212> DNA
<213> Mus musculus

<400> 116
aatgttttga tgacccaaag tccactctcc ctgcctgtca gtcttggaga tcaagcctcc 60

atctcttgca gatctagtca gagtattgta catagtaatg gaaacaccta tttagaatgg 120

tatatgcaga aaccaggcca gtctccaaag ctcctgatct acacagtttc caaacgattt 180

tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc 240

agcagagtgg aggctgagga tctgggagtt tattattgct ttcaaggttc acatgttccg 300

gtcacgttcg gtgctgggac caagctggag ctgaaa 336

<210> 117
<211> 16
<212> PRT
<213> Mus musculus

<400> 117

Arg Ser Ser Gln Ser Ile Val His Ser Asn Gly Asn Thr Tyr Leu Glu
1 5 10 15

<210> 118
<211> 7
<212> PRT
<213> Mus musculus

<400> 118

Thr Val Ser Lys Arg Phe Ser
1 5

<210> 119
<211> 119
<212> PRT
<213> Mus musculus

<400> 119

Lys Val Lys Leu Val Glu Ser Gly Gly Asp Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Ile Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Ala Met Ser Trp Ile Arg Gln Thr Pro Asp Lys Arg Leu Glu Trp Val
35 40 45

```
Ala Thr Val Ser Ser Gly Gly Pro Tyr Thr Tyr Tyr Pro Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Glu Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Ser Ser Leu Arg Ser Asp Asp Thr Ala Ile Tyr Tyr Cys
                85                  90                  95

Ala Arg Gln Ile Tyr Ser Asp Tyr Asp Val Thr Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ala
        115
```

<210> 120
<211> 357
<212> DNA
<213> Mus musculus

<400> 120

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aaagtgaagc tggtggagtc tgggggagac ttagtgaagc ctggagggtc cctgaaaatc       60

tcctgtgcag cctctggatt cactttcagt aactatgcca tgtcttggat tcgccagact      120

ccggacaaga ggctggagtg ggtcgcaacc gttagtagtg gtggtcctta cacctactat      180

ccagacagtg tgaaggggcg attcaccatc tccagagaca atgccgaaaa caccctgtac      240

ctgcaaatga gcagtctgag gtctgatgac acggccattt attactgtgc aaggcagatc      300

tactctgatt acgacgtcac ttactggggc caagggactc tggtcactgt ctctgca         357
```

<210> 121
<211> 106
<212> PRT
<213> Mus musculus

<400> 121

```
Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser Pro Gly
1               5                   10                  15
```

```
Glu Thr Val Thr Met Thr Cys Arg Val Ser Ser Ser Val Ser Tyr Met
            20                  25                  30

Tyr Trp Leu Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
        35                  40                  45

Ala Thr Ser Asn 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 Thr Arg Val Glu Ala Glu
65                  70                  75                  80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Phe Arg Pro Trp Thr
                85                  90                  95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105
```

<210> 122
<211> 318
<212> DNA
<213> Mus musculus

<400> 122
caaattgttc tctcccagtc tccagcaatc ctgtctgcat ctccagggga gacggtcaca 60

atgacttgca gggtcagttc aagtgtaagt tacatgtact ggctccaaca gaagccagga 120

tcctccccca aaccctggat ttatgccaca tccaacctgg cttctggagt ccctgctcgc 180

ttcagtggca gtgggtctgg gacctcttac tccctcacaa tcaccagagt ggaggctgaa 240

gatgctgcca cttattactg tcagcagtgg agttttagac cgtggacgtt cggtggaggc 300

accaagctgg aaatcaaa 318

<210> 123
<211> 10
<212> PRT
<213> Mus musculus

<400> 123

```
Arg Val Ser Ser Ser Val Ser Tyr Met Tyr
1               5                   10


<210>  124
<211>  120
<212>  PRT
<213>  Mus musculus

<400>  124

Gln Val Gln Leu Gln Gln Ser Gly Thr Glu Leu Ala Arg Pro Gly Ala
1               5                   10                  15


Ser Val Arg Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Arg Ser His
            20                  25                  30


Thr Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45


Gly Tyr Ile Asn Pro Ser Thr Gly Tyr Ile Asn Tyr Asn Gln Lys Phe
    50                  55                  60


Lys Asp Lys Ala Thr Leu Thr Ala 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 Ser Asn Tyr Ser Tyr Tyr Tyr Gly Met Asp Tyr Trp Gly Gln
            100                 105                 110


Gly Thr Ser Val Thr Val Ser Ser
        115                 120


<210>  125
<211>  360
<212>  DNA
<213>  Mus musculus

<400>  125
```

caggtccagc tgcagcagtc tgggactgaa ctggcaagac ctggggcctc agtgaggatg 60

tcctgcaagg cttctggcta cacctttagg agtcacacga tgcactgggt aaaacagagg 120

cctggacagg gtctggaatg gattggatac attaatccta gcactggtta tattaattac 180

aatcagaagt tcaaggacaa ggccacattg actgcagaca aatcctccag cacagcctac 240

atgcaactga gcagcctgac atctgaggac tctgcagtct attactgtgc aagaagtaac 300

tactcttatt actatggtat ggactactgg ggtcaaggaa cctcagtcac cgtctcctca 360

<210> 126
<211> 5
<212> PRT
<213> Mus musculus

<400> 126

Ser His Thr Met His
1 5

<210> 127
<211> 17
<212> PRT
<213> Mus musculus

<400> 127

Tyr Ile Asn Pro Ser Thr Gly Tyr Ile Asn Tyr Asn Gln Lys Phe Lys
1 5 10 15

Asp

<210> 128
<211> 11
<212> PRT
<213> Mus musculus

<400> 128

Ser Asn Tyr Ser Tyr Tyr Tyr Gly Met Asp Tyr
1 5 10

<210> 129
<211> 107
<212> PRT
<213> Mus musculus

<400> 129

Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Asn Thr Ala
            20   25   30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
        35   40   45

Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Ala
65   70   75   80

Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln His Tyr Asn Ile Pro Leu
                85   90   95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
            100   105

<210> 130
<211> 321
<212> DNA
<213> Mus musculus

<400> 130
gacattgtga tgacccagtc tcacaaattc atgtccacat cagtgggaga cagggtcacc   60

atcacctgca aggccagtca ggatgtaaat actgctgtag cctggtatca acagaaacca   120

ggacaatctc ctaaactact gatttactcg gcatcctacc ggtacactgg ggtccctgat   180

cgcttcactg gcagtggatc tgggacggat ttcactttca ccatcagcag tttacaggct   240

gaagacctgg cagtttatta ctgtcagcaa cattataata ttccgctcac gttcggtgct   300

gggaccaagc tggagctgaa a 321

<210> 131
<211> 11
<212> PRT
<213> Mus musculus

<400> 131

Lys Ala Ser Gln Asp Val Asn Thr Ala Val Ala
1 5 10

<210> 132
<211> 7
<212> PRT
<213> Mus musculus

<400> 132

Ser Ala Ser Tyr Arg Tyr Thr
1 5

<210> 133
<211> 9
<212> PRT
<213> Mus musculus

<400> 133

Gln Gln His Tyr Asn Ile Pro Leu Thr
1 5

<210> 134
<211> 120
<212> PRT
<213> Mus musculus

<400> 134

Gln Val Gln Leu Gln Gln Ser Gly Thr Glu Leu Ala Arg Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ala Thr Tyr
20 25 30

```
Ser Ile His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Tyr Ile Asn Pro Ser Ser Gly Tyr Thr Asn Tyr Asn Gln Lys Phe
    50                  55                  60

Arg Asp Lys Ala Thr Leu Thr Ala Asp Arg Ser Ser Asn 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 Val Tyr Tyr Thr Phe Tyr His Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Ser Val Thr Val Ser Ser
        115                 120
```

<210> 135
<211> 360
<212> DNA
<213> Mus musculus

<400> 135
caggtccagc tgcagcagtc tgggactgaa ctggcaagac ctggggcctc agtgaagatg 60

tcctgcaagg cttctggcta cacctttgct acctactcga tacactgggt aaaacagagg 120

cctgggcagg gtctggaatg gattggatac attaatccta gcagtggtta tactaattac 180

aatcagaagt tcagggacaa ggccacattg actgcagaca gatcctccaa cacagcctac 240

atgcaactga gcagcctgac atctgaggac tctgcagtct attactgtgc aagagtctac 300

tatacttttt accatgctat ggactactgg ggtcaaggaa cctcagtcac cgtctcctca 360

<210> 136
<211> 6
<212> PRT
<213> Mus musculus

<400> 136

Ala Thr Tyr Ser Ile His
1   5

<210> 137
<211> 17
<212> PRT
<213> Mus musculus

<400> 137

Tyr Ile Asn Pro Ser Ser Gly Tyr Thr Asn Tyr Asn Gln Lys Phe Arg
1   5   10   15

Asp

<210> 138
<211> 11
<212> PRT
<213> Mus musculus

<400> 138

Val Tyr Tyr Thr Phe Tyr His Ala Met Asp Tyr
1   5   10

<210> 139
<211> 114
<212> PRT
<213> Mus musculus

<400> 139

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

Ser Leu Ser Leu Thr Cys Thr Val Thr Gly Tyr Ser Ile Thr Ser Asp
            20   25   30

Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Glu Trp
        35   40   45

```
Met Gly Tyr Ile Ser Tyr Ser Gly Arg Thr Ser Tyr Asn Pro Ser Leu
    50                  55                  60

Lys Ser Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Phe Phe
65                  70                  75                  80

Leu Gln Leu Asn Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr Cys
                85                  90                  95

Ala Arg His Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
            100                 105                 110

Ser Ser
```

<210> 140
<211> 342
<212> DNA
<213> Mus musculus

<400> 140

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cagatgcagc ttcaggagtc gggacctggc ctggtgaaac cttctcagtc tctgtccctc       60

acctgcactg tcactggcta ctcaatcacc agtgattatg cctggaactg gatccggcag      120

tttccaggaa acaaactgga gtggatgggc tacataagct acagtggtag gactagctac      180

aacccatctc tcaaaagtcg aatctctatc actcgagaca catccaagaa ccagttcttc      240

ctgcagttga attctgtgac tactgaggac acagccacat attactgtgc aagacactac      300

ggagactact ggggccaagg caccactctc acagtctcct ca                         342
```

<210> 141
<211> 5
<212> PRT
<213> Mus musculus

<400> 141

```
His Tyr Gly Asp Tyr
1               5
```

<210> 142
<211> 107
<212> PRT
<213> Mus musculus

<400> 142

Asp Ile Val Met Thr Gln Ser Gln Lys Leu Met Ser Thr Ser Val Gly
1   5   10   15

Asp Arg Val Ser Val Thr Cys Lys Ala Ser Gln Asn Val Gly Thr Asn
            20   25   30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Ala Leu Ile
        35   40   45

Tyr Ser Ala Ser Tyr Arg Asn Ser Gly Val Pro Asp Arg Phe Thr Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Val Gln Ser
65   70   75   80

Glu Asp Leu Ala Glu Tyr Phe Cys Gln Gln Phe Asn Thr Asn Pro Leu
                85   90   95

Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
            100   105

<210> 143
<211> 321
<212> DNA
<213> Mus musculus

<400> 143
gacattgtga tgactcagtc tcaaaaactc atgtccacat cagtaggaga cagggtcagc   60

gtcacctgca aggccagtca gaatgtgggt actaatgtag cctggtatca acagaaacca   120

gggcaatctc ctaaagcact gatttactcg gcatcctacc ggaacagtgg agtccctgat   180

cgcttcacag gcagtggttc tgggacagat ttcactctca ccatcagcaa tgtgcagtct   240

gaagacttgg cagagtattt ctgtcagcaa tttaacacca atcctctcac gttcggctcg 300

gggacaaagt tggaaataaa a 321

<210> 144
<211> 11
<212> PRT
<213> Mus musculus

<400> 144

Lys Ala Ser Gln Asn Val Gly Thr Asn Val Ala
1 5 10

<210> 145
<211> 7
<212> PRT
<213> Mus musculus

<400> 145

Ser Ala Ser Tyr Arg Asn Ser
1 5

<210> 146
<211> 9
<212> PRT
<213> Mus musculus

<400> 146

Gln Gln Phe Asn Thr Asn Pro Leu Thr
1 5

<210> 147
<211> 123
<212> PRT
<213> Mus musculus

<400> 147

Gln Val Gln Leu Gln Gln Ser Gly Pro Gln Leu Leu Arg Pro Gly Ala
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Phe Ser Phe Thr Asn His

```
            20                  25                  30

Trp Ile His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Met Ile Asp Pro Ser Asp Ser Glu Thr Gly Leu Asn Gln Lys Phe
    50                  55                  60

Arg Asp Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80

Met His Leu Asn Ser Pro Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Leu Gly Ile His Asp Gly Tyr Tyr Ile Tyr Ala Met Asp Phe
            100                 105                 110

Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
        115                 120


<210>  148
<211>  369
<212>  DNA
<213>  Mus musculus

<400>  148
caggttcagc tgcagcagtc tgggcctcag ctacttaggc ctggggcttc agtgaagata       60

tcctgcaagg cttctggttt ctcattcacc aaccactgga tacactgggt gaaacagagg      120

cctggacaag gtcttgagtg gattggcatg attgatcctt ccgatagtga aactggcctc      180

aatcagaagt tcagggacaa ggccacattg actgtagaca agtcctccag cacagcctac      240

atgcacctca acagcccgac atctgaggac tctgcggtct attactgtgc aagattggga      300

atccatgatg gttactacat ctatgctatg gacttttggg gtcaaggaac ctcagtcacc      360

gtctcctca                                                              369


<210>  149
<211>  6
```

<212> PRT
<213> Mus musculus

<400> 149

Thr Asn His Trp Ile His
1   5

<210> 150
<211> 17
<212> PRT
<213> Mus musculus

<400> 150

Met Ile Asp Pro Ser Asp Ser Glu Thr Gly Leu Asn Gln Lys Phe Arg
1   5   10   15

Asp

<210> 151
<211> 14
<212> PRT
<213> Mus musculus

<400> 151

Leu Gly Ile His Asp Gly Tyr Tyr Ile Tyr Ala Met Asp Phe
1   5   10

<210> 152
<211> 107
<212> PRT
<213> Mus musculus

<400> 152

Asn Ile Val Met Thr Gln Ser Pro Lys Ser Met Ser Met Ser Val Gly
1   5   10   15

Glu Arg Val Thr Leu Ser Cys Lys Ala Ser Glu Asn Val Gly Thr Tyr
            20   25   30

```
Val Ser Trp Tyr Gln Gln Lys Pro Glu Gln Ser Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Gly Ala Ser Asn Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly
    50                  55                  60

Ser Gly Ser Ala Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala
65                  70                  75                  80

Glu Asp Leu Ala Asp Tyr His Cys Gly Gln Ser Tyr Ser Tyr Pro Leu
                85                  90                  95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
            100                 105
```

<210> 153
<211> 321
<212> DNA
<213> Mus musculus

<400> 153

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aacattgtaa tgacccaatc tcccaaatcc atgtccatgt cagtaggaga gagggtcacc       60

ttgagctgca aggccagtga gaatgtgggt acttatgtat cctggtatca acagaaacca      120

gagcagtctc ctaaactgct gatatacggg gcatccaacc ggtacactgg ggtccccgat      180

cgcttcacag gcagtggatc tgcaacagat ttcactctga ccatcagcag tgtgcaggct      240

gaagaccttg cagattatca ctgtggacag agttacagct atccgctcac gttcggtgct      300

gggaccaagc tggagctgaa a                                                321
```

<210> 154
<211> 11
<212> PRT
<213> Mus musculus

<400> 154

```
Lys Ala Ser Glu Asn Val Gly Thr Tyr Val Ser
1               5                   10
```

<210> 155
<211> 7
<212> PRT
<213> Mus musculus

<400> 155

Gly Ala Ser Asn Arg Tyr Thr
1   5

<210> 156
<211> 9
<212> PRT
<213> Mus musculus

<400> 156

Gly Gln Ser Tyr Ser Tyr Pro Leu Thr
1   5

<210> 157
<211> 114
<212> PRT
<213> Mus musculus

<400> 157

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

Ser Leu Ser Leu Thr Cys Ser Val Thr Gly Tyr Ser Ile Thr Ser Asp
            20   25   30

Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Glu Trp
        35   40   45

Met Gly Tyr Ile Ser Tyr Ser Gly Arg Thr Ser Tyr Asn Pro Ser Leu
    50   55   60

Lys Ser Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Phe Phe
65   70   75   80

Leu Gln Leu Ile Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr Cys

85 90 95

Ala Arg Tyr Trp Gly Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
100 105 110

Ser Ser

<210> 158
<211> 342
<212> DNA
<213> Mus musculus

<400> 158
gaggtgcagc ttcaggagtc gggacctggc ctggtgaaac cttctcagtc tctgtccctc 60

acctgctctg tcactggcta ctcaatcacc agtgattatg cctggaactg gatccggcag 120

tttccaggaa acaagctgga gtggatgggc tacataagtt acagtggtag aactagctac 180

aacccatctc tcaaaagtcg aatctctatc actcgagaca catccaagaa ccagttcttc 240

ctgcagttga tttctgtgac tactgaggac acagccacat attattgtgc aagatattgg 300

ggcgactact ggggccaagg caccactctc acagtctcct ca 342

<210> 159
<211> 107
<212> PRT
<213> Mus musculus

<400> 159

Asp Ile Val Met Thr Gln Ser Gln Lys Phe Ile Ser Thr Ser Ile Gly
1 5 10 15

Asp Arg Val Ser Val Thr Cys Lys Ala Ser Gln Asp Val Gly Gly His
20 25 30

Val Ala Trp Phe Gln Gln Arg Pro Gly Gln Ser Pro Lys Pro Leu Ile
35 40 45

Tyr Ser Ala Thr Phe Arg His Ser Gly Val Pro Asp Arg Phe Thr Gly

```
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Leu Gln Ser
65                  70                  75                  80

Glu Asp Leu Ala Glu Tyr Val Cys Leu Gln Tyr Asn Ser Asn Pro Leu
                85                  90                  95

Thr Phe Gly Pro Gly Thr Lys Leu Glu Leu Lys
            100                 105
```

<210> 160
<211> 321
<212> DNA
<213> Mus musculus

<400> 160
gacattgtga tgacccagtc tcaaaaattc atctccacat caataggaga cagggtcagc 60

gtcacctgca aggccagtca ggatgtgggt ggacatgtgg cctggtttca acagagaccc 120

gggcaatctc ctaaacctct gatttattcg gcaaccttcc ggcacagtgg agtccctgat 180

cgcttcacgg gcagtggatc tgggacagat ttcactctca ccatcagtaa tctacagtct 240

gaggacttgg cagaatatgt ctgtctgcaa tataacagta atccactcac gttcggtcct 300

gggaccaagc tggagctgaa a 321

<210> 161
<211> 11
<212> PRT
<213> Mus musculus

<400> 161

```
Lys Ala Ser Gln Asp Val Gly Gly His Val Ala
1               5                   10
```

<210> 162
<211> 7
<212> PRT
<213> Mus musculus

<400> 162

Ser Ala Thr Phe Arg His Ser
1   5

<210> 163
<211> 114
<212> PRT
<213> Mus musculus

<400> 163

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

Ser Leu Ser Leu Thr Cys Thr Val Thr Gly Tyr Ser Ile Thr Ser Asp
            20   25   30

Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Glu Trp
        35   40   45

Met Gly Tyr Ile Ser Tyr Ser Gly Arg Thr Ser Tyr Asn Pro Tyr Leu
    50   55   60

Lys Ser Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Phe Phe
65   70   75   80

Leu Gln Leu Asn Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr Cys
                85   90   95

Ala Arg Tyr Trp Gly Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
            100   105   110

Ser Ser

<210> 164
<211> 342
<212> DNA
<213> Mus musculus

<400> 164
gatgtgcagc ttcaggagtc gggacctggc ctggtgaaac cttctcagtc tctgtccctc 60

acctgcactg tcactggcta ctcaatcacc agtgattatg cctggaactg gatccggcag 120

tttccaggaa acaaactgga gtggatgggc tacataagct acagtggtcg cactagctac 180

aacccatatc tcaaaagtcg aatttctatc actcgagaca catccaagaa ccagttcttc 240

ctgcagttga attctgtgac tactgaggac acagccacat attactgtgc aagatattgg 300

ggcgactact ggggccaagg caccactctc acagtctcct ca 342

<210> 165
<211> 16
<212> PRT
<213> Mus musculus

<400> 165

Tyr Ile Ser Tyr Ser Gly Arg Thr Ser Tyr Asn Pro Tyr Leu Lys Ser
1 5 10 15

<210> 166
<211> 107
<212> PRT
<213> Mus musculus

<400> 166

Asp Ile Val Met Thr Gln Ser Gln Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15

Asp Arg Val Ser Val Thr Cys Lys Ala Ser Gln Asn Val Gly Thr Asn
20 25 30

Val Ala Trp Tyr Lys Gln Lys Pro Gly Gln Ser Pro Lys Ala Leu Ile
35 40 45

Tyr Ser Ala Ser Tyr Arg His Ser Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Val Gln Ser
65 70 75 80

```
Glu Asp Leu Ala Glu Tyr Phe Cys Leu Gln Tyr Asn Ser Asn Pro Leu
                85                  90                  95


Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
            100                 105


<210>  167
<211>  321
<212>  DNA
<213>  Mus musculus

<400>  167
gacattgtga tgacccagtc tcaaaaattc atgtccacat cagtaggaga cagggtcagc       60

gtcacctgca aggccagtca gaatgtgggt actaatgtag cctggtataa acagaaacca      120

gggcaatctc ctaaagcact gatttactcg gcatcctacc ggcacagtgg agtccctgat      180

cgcttcacag gcagtggatc tgggacagat ttcactctca ccatcagcaa tgtgcagtct      240

gaagacttgg cagagtattt ctgtctgcaa tataacagca atcctctcac gttcggtgct      300

gggaccaagc tggagctgaa a                                                321


<210>  168
<211>  7
<212>  PRT
<213>  Mus musculus

<400>  168

Ser Ala Ser Tyr Arg His Ser
1               5


<210>  169
<211>  114
<212>  PRT
<213>  Mus musculus

<400>  169

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

```
Ser Leu Ser Leu Thr Cys Thr Val Thr Gly Tyr Ser Ile Thr Ser Asp
            20                  25                  30

Tyr Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Glu Trp
        35                  40                  45

Met Gly Tyr Ile Ser Tyr Ser Gly Arg Thr Ser Tyr Asn Pro Ser Leu
    50                  55                  60

Lys Ser Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Phe Phe
65                  70                  75                  80

Leu Gln Leu Asn Ser Val Thr Ala Glu Asp Thr Ala Thr Tyr Tyr Cys
                85                  90                  95

Ala Arg Tyr Trp Gly Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
            100                 105                 110

Ser Ser
```

<210> 170
<211> 342
<212> DNA
<213> Mus musculus

<400> 170

```
gatgtgcagc ttcaggagtc gggacctggc ctggtgaaac cttctcagtc tctgtccctc       60

acctgcactg tcactggcta ctcaatcacc agtgattatg cctggaactg gatccggcag      120

tttccaggaa acaaactgga gtggatgggc tacataagct acagtggtcg cactagctac      180

aacccatctc tcaaaagtcg aatctctatc actcgagaca catccaagaa ccagttcttc      240

ctgcagttga attctgtgac tgctgaggac acagccacat attactgtgc aagatattgg      300

ggcgactact ggggccaagg caccactctc acagtctcct ca                         342
```

<210> 171
<211> 107

<212> PRT
<213> Mus musculus

<400> 171

Asp Ile Val Met Thr Gln Ser Gln Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15

Asp Arg Val Ser Val Thr Cys Lys Ala Ser Gln Asn Val Gly Thr Asn
20 25 30

Val Ala Trp Phe Gln Gln Lys Pro Gly Gln Ser Pro Lys Ala Leu Ile
35 40 45

Tyr Ser Thr Ser Tyr Arg Ser Ser Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Val Gln Ser
65 70 75 80

Glu Asp Leu Ala Glu Tyr Phe Cys Gln Gln Phe Asn Ser Asn Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 172
<211> 321
<212> DNA
<213> Mus musculus

<400> 172
gacattgtga tgacacagtc tcaaaaattc atgtccacat cagtaggaga cagggtcagc 60

gtcacctgca aggccagtca gaatgtgggt actaatgtag cctggtttca acagaaacca 120

gggcaatctc ctaaagcact gatttactcg acatcctacc ggtccagtgg agtccctgat 180

cgcttcacag gcagtggatc tgggacagat ttcactctca ccatcagcaa tgtgcagtct 240

gaagacttgg cagagtactt ctgtcagcaa tttaacagca atcctctcac gttcggaggg 300

gggaccaagc tggagctgaa a 321

<210> 173
<211> 7
<212> PRT
<213> Mus musculus

<400> 173

Ser Thr Ser Tyr Arg Ser Ser
1   5

<210> 174
<211> 9
<212> PRT
<213> Mus musculus

<400> 174

Gln Gln Phe Asn Ser Asn Pro Leu Thr
1   5

<210> 175
<211> 114
<212> PRT
<213> Homo sapiens

<400> 175

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Tyr Ser Ile Thr Ser Asp
            20   25   30

Tyr Ala Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35   40   45

Ile Gly Tyr Ile Ser Tyr Ser Gly Arg Thr Ser Tyr Asn Pro Ser Leu
    50   55   60

Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65   70   75   80

```
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg His Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
            100                 105                 110


Ser Ser



<210>  176
<211>  342
<212>  DNA
<213>  Homo sapiens

<400>  176
cagatgcagc tgcaagagtc tggacctgga ctggtcaagc ccagcgagac actgagcctg       60

acctgtaccg tgtccggcta cagcatcaca agcgactacg cctggaactg gatcagacag      120

cctcctggca aaggcctcga gtggatcggc tacatcagct acagcggcag aaccagctac      180

aaccccagcc tgaagtccag agtgaccatc agcagagaca ccagcaagaa ccagttctcc      240

ctgaagctga gcagcgtgac agccgccgat acagccgtgt actactgcgc tagacactac      300

ggcgattact ggggccaggg aaccctggtc acagtgtcat ct                         342


<210>  177
<211>  114
<212>  PRT
<213>  Homo sapiens

<400>  177

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


Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Tyr Ser Ile Thr Ser Asp
            20                  25                  30


Tyr Ala Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45
```

```
Ile Gly Tyr Ile Ser Tyr Ser Gly Arg Thr Ser Tyr Asn Pro Ser Leu
    50                  55                  60

Lys Ser Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65                  70                  75                  80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg His Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
            100                 105                 110

Ser Ser
```

<210> 178
<211> 342
<212> DNA
<213> Homo sapiens

<400> 178

```
cagctccagc tgcaagagtc tggacctgga ctggtcaagc ccagcgagac actgagcctg       60

acctgtaccg tgtccggcta cagcatcaca agcgactacg cctggaactg gatcagacag      120

cctcctggca aaggcctcga gtggatcggc tacatcagct acagcggcag aaccagctac      180

aaccccagcc tgaagtccag agtgaccatc agcagagaca ccagcaagaa ccagttctcc      240

ctgaagctga gcagcgtgac agccgccgat acagccgtgt actactgcgc tagacactac      300

ggcgattact ggggccaggg aaccctggtc acagtgtcat ct                         342
```

<210> 179
<211> 114
<212> PRT
<213> Homo sapiens

<400> 179

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

```
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Tyr Ser Ile Thr Ser Asp
            20                  25                  30

Tyr Ala Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45

Ile Gly Tyr Ile Ser Tyr Ser Gly Arg Thr Ser Tyr Asn Pro Ser Leu
    50                  55                  60

Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser
65                  70                  75                  80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg His Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
            100                 105                 110

Ser Ser
```

<210> 180
<211> 342
<212> DNA
<213> Homo sapiens

<400> 180
cagctccagc tgcaagagtc tggacctgga ctggtcaagc ccagcgagac actgagcctg 60

acctgtaccg tgtccggcta cagcatcaca agcgactacg cctggaactg gatcagacag 120

cctcctggca aaggcctcga gtggatcggc tacatcagct acagcggcag aaccagctac 180

aaccccagcc tgaagtccag agtgaccatc agcgtagaca ccagcaagaa ccagttctcc 240

ctgaagctga gcagcgtgac agccgccgat acagccgtgt actactgcgc tagacactac 300

ggcgattact ggggccaggg aaccctggtc acagtgtcat ct 342

<210> 181
<211> 120

<212> PRT
<213> Homo sapiens

<400> 181

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ala Thr Tyr
            20   25   30

Ser Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45

Gly Tyr Ile Asn Pro Ser Ser Gly Tyr Thr Asn Tyr Asn Gln Lys Phe
    50   55   60

Gln Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala 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 Val Tyr Tyr Thr Phe Tyr His Ala Met Asp Tyr Trp Gly Gln
            100   105   110

Gly Thr Thr Val Thr Val Ser Ser
        115   120

<210> 182
<211> 360
<212> DNA
<213> Homo sapiens

<400> 182
caggttcagc tggttcagtc tggcgccgaa gtgaagaaac ctggcagcag cgtgaaggtg   60

tcctgcaagg ctagcggcta caccttcgcc acctacagca tccactgggt ccgacaggct   120

ccaggacagg gacttgagtg gatgggctac atcaacccca gctctggcta caccaactac   180

aaccagaaat tccagggccg cgtgaccctc acagccgaca agtctacaag caccgcctac   240

atggaactga gcagcctgag aagcgaggac accgccgtgt actactgcgc cagagtgtac 300

tacacattct accacgccat ggactactgg ggccagggca caacagtgac cgttagctct 360

<210> 183
<211> 17
<212> PRT
<213> Homo sapiens

<400> 183

Tyr Ile Asn Pro Ser Ser Gly Tyr Thr Asn Tyr Asn Gln Lys Phe Gln
1 5 10 15

Gly

<210> 184
<211> 120
<212> PRT
<213> Homo sapiens

<400> 184

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ala Thr Tyr
20 25 30

Ser Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Tyr Ile Asn Pro Ser Ser Gly Tyr Thr Asn Tyr Asn Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Leu Thr Ala Asp Glu Ser Thr Ser Thr Ala 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 Val Tyr Tyr Thr Phe Tyr His Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 185
<211> 360
<212> DNA
<213> Homo sapiens

<400> 185
caggttcagc tggttcagtc tggcgccgaa gtgaagaaac ctggcagcag cgtgaaggtg 60

tcctgcaagg ctagcggcta caccttcgcc acctacagca tccactgggt ccgacaggct 120

ccaggacagg gacttgagtg gatgggctac atcaacccca gctctggcta caccaactac 180

aaccagaaat tccagggccg cgtgaccctc acagccgacg agtctacaag caccgcctac 240

atggaactga gcagcctgag aagcgaggac accgccgtgt actactgcgc cagagtgtac 300

tacacattct accacgccat ggactactgg ggccagggca caacagtgac cgttagctct 360

<210> 186
<211> 120
<212> PRT
<213> Homo sapiens

<400> 186

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ala Thr Tyr
20 25 30

Ser Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Tyr Ile Asn Pro Ser Ser Gly Tyr Thr Asn Tyr Asn Gln Lys Phe
50 55 60

```
Gln Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala 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 Val Tyr Tyr Thr Phe Tyr His Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110


Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210>  187
<211>  360
<212>  DNA
<213>  Homo sapiens

<400>  187
caggttcagc tggttcagtc tggcgccgaa gtgaagaaac ctggcagcag cgtgaaggtg       60

tcctgcaagg ctagcggcta caccttcgcc acctacagca tccactgggt ccgacaggct      120

ccaggacagg gacttgagtg gatgggctac atcaacccca gctctggcta caccaactac      180

aaccagaaat tccagggccg cgtgaccatc acagccgaca agtctacaag caccgcctac      240

atggaactga gcagcctgag aagcgaggac accgccgtgt actactgcgc cagagtgtac      300

tacacattct accacgccat ggactactgg ggccagggca caacagtgac cgttagctct      360


<210>  188
<211>  120
<212>  PRT
<213>  Homo sapiens

<400>  188

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


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ala Thr Tyr
            20                  25                  30
```

```
Ser Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Tyr Ile Asn Pro Ser Ser Gly Tyr Thr Asn Tyr Asn Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala 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 Val Tyr Tyr Thr Phe Tyr His Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Thr Val Thr Val Ser Ser
        115                 120
```

<210> 189
<211> 360
<212> DNA
<213> Homo sapiens

<400> 189

```
caggttcagc tggttcagtc tggcgccgaa gtgaagaaac ctggcagcag cgtgaaggtg       60

tcctgcaagg ctagcggcta caccttcgcc acctacagca tccactgggt ccgacaggct      120

ccaggacagg gacttgagtg gatgggctac atcaacccca gctctggcta caccaactac      180

aaccagaaat tccagggccg cgtgaccatc acagccgacg agtctacaag caccgcctac      240

atggaactga gcagcctgag aagcgaggac accgccgtgt actactgcgc cagagtgtac      300

tacacattct accacgccat ggactactgg ggccagggca caacagtgac cgttagctct      360
```

<210> 190
<211> 120
<212> PRT
<213> Homo sapiens

<400> 190

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Arg Ser His
20 25 30

Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Tyr Ile Asn Pro Ser Thr Gly Tyr Ile Asn Tyr Asn Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala 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 Ser Asn Tyr Ala Tyr Tyr Tyr Gly Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 191
<211> 360
<212> DNA
<213> Homo sapiens

<400> 191
caggttcagc tggttcagtc tggcgccgaa gtgaagaaac ctggcagcag cgtgaaggtg 60

tcctgcaagg ctagcggcta caccttcaga tcccacacca tgcactgggt ccgacaggct 120

ccaggacagg gacttgagtg gatgggctac atcaacccca gcaccggcta tatcaactac 180

aaccagaaat tccagggccg cgtgaccctc acagccgaca agtctacaag caccgcctac 240

atggaactga gcagcctgag aagcgaggac accgccgtgt actactgcgc cagaagcaac 300

tacgcctact actacggcat ggactactgg ggccagggca ccacagtgac agtctcttct 360

<210> 192
<211> 17
<212> PRT
<213> Homo sapiens

<400> 192

Tyr Ile Asn Pro Ser Thr Gly Tyr Ile Asn Tyr Asn Gln Lys Phe Gln
1 5 10 15

Gly

<210> 193
<211> 120
<212> PRT
<213> Homo sapiens

<400> 193

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Arg Ser His
20 25 30

Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Tyr Ile Asn Pro Ser Thr Gly Tyr Ile Asn Tyr Asn Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Leu Thr Ala Asp Glu Ser Thr Ser Thr Ala 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 Ser Asn Tyr Ala Tyr Tyr Tyr Gly Met Asp Tyr Trp Gly Gln

100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 194
<211> 360
<212> DNA
<213> Homo sapiens

<400> 194
caggttcagc tggttcagtc tggcgccgaa gtgaagaaac ctggcagcag cgtgaaggtg 60

tcctgcaagg ctagcggcta caccttcaga tcccacacca tgcactgggt ccgacaggct 120

ccaggacagg gacttgagtg gatgggctac atcaacccca gcaccggcta tatcaactac 180

aaccagaaat tccagggccg cgtgaccctc acagccgacg agtctacaag caccgcctac 240

atggaactga gcagcctgag aagcgaggac accgccgtgt actactgcgc cagaagcaac 300

tacgcctact actacggcat ggactactgg ggccagggca ccacagtgac agtctcttct 360

<210> 195
<211> 120
<212> PRT
<213> Homo sapiens

<400> 195

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Arg Ser His
20 25 30

Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Tyr Ile Asn Pro Ser Thr Gly Tyr Ile Asn Tyr Asn Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala 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 Ser Asn Tyr Ala Tyr Tyr Tyr Gly Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 196
<211> 360
<212> DNA
<213> Homo sapiens

<400> 196
caggttcagc tggttcagtc tggcgccgaa gtgaagaaac ctggcagcag cgtgaaggtg 60

tcctgcaagg ctagcggcta caccttcaga tcccacacca tgcactgggt ccgacaggct 120

ccaggacagg gacttgagtg gatgggctac atcaacccca gcaccggcta tatcaactac 180

aaccagaaat tccagggccg cgtgaccatc acagccgaca agtctacaag caccgcctac 240

atggaactga gcagcctgag aagcgaggac accgccgtgt actactgcgc cagaagcaac 300

tacgcctact actacggcat ggactactgg ggccagggca ccacagtgac agtctcttct 360

<210> 197
<211> 120
<212> PRT
<213> Homo sapiens

<400> 197

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Arg Ser His
20 25 30

Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met

```
        35                  40                  45

Gly Tyr Ile Asn Pro Ser Thr Gly Tyr Ile Asn Tyr Asn Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala 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 Ser Asn Tyr Ala Tyr Tyr Tyr Gly Met Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Thr Val Thr Val Ser Ser
        115                 120
```

<210> 198
<211> 360
<212> DNA
<213> Homo sapiens

<400> 198

```
caggttcagc tggttcagtc tggcgccgaa gtgaagaaac ctggcagcag cgtgaaggtg       60

tcctgcaagg ctagcggcta caccttcaga tcccacacca tgcactgggt ccgacaggct      120

ccaggacagg gacttgagtg gatgggctac atcaacccca gcaccggcta tatcaactac      180

aaccagaaat tccagggccg cgtgaccatc acagccgacg agtctacaag caccgcctac      240

atggaactga gcagcctgag aagcgaggac accgccgtgt actactgcgc cagaagcaac      300

tacgcctact actacggcat ggactactgg ggccagggca ccacagtgac agtctcttct      360
```

<210> 199
<211> 107
<212> PRT
<213> Homo sapiens

<400> 199

```
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 Arg Ala Ser Gln Asn Val Gly Thr Asn
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Ala Leu Ile
35 40 45

Tyr Ser Ala Ser Tyr Arg Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Phe Asn Thr Asn Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 200
<211> 321
<212> DNA
<213> Homo sapiens

<400> 200
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ggcaaggctc ccaaggcgct gatctacagc gccagctaca gagagagcgg cgtgccatct 180

agattcagcg gctctggctc tggcaccgac ttcaccctga caatctctag cctgcagcct 240

gaggacttcg ctacctactt ctgccagcag ttcaacacaa accctctgac cttcggcgga 300

ggcaccaagg tggaaatcaa g 321

<210> 201
<211> 11
<212> PRT
<213> Homo sapiens

<400> 201

Arg Ala Ser Gln Asn Val Gly Thr Asn Val Ala
1 5 10

<210> 202
<211> 7
<212> PRT
<213> Homo sapiens

<400> 202

Ser Ala Ser Tyr Arg Glu Ser
1 5

<210> 203
<211> 107
<212> PRT
<213> Homo sapiens

<400> 203

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 Arg Ala Ser Gln Asn Val Gly Thr Asn
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Tyr Arg Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Phe Asn Thr Asn Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys

100 105

<210> 204
<211> 321
<212> DNA
<213> Homo sapiens

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atcacctgta gagccagcca gaacgtgggc acaaacgtgg cctggtatca gcagaagcct 120

ggcaaggctc ccaagctgct gatctacagc gccagctaca gagagagcgg cgtgccatct 180

agattcagcg gctctggctc tggcaccgac ttcaccctga caatctctag cctgcagcct 240

gaggacttcg ctacctactt ctgccagcag ttcaacacaa accctctgac cttcggcgga 300

ggcaccaagg tggaaatcaa g 321

<210> 205
<211> 107
<212> PRT
<213> Homo sapiens

<400> 205

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 Arg Ala Ser Gln Asn Val Gly Thr Asn
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Ala Leu Ile
35 40 45

Tyr Ser Ala Ser Tyr Arg Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Phe Asn Thr Asn Pro Leu

85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 206
<211> 321
<212> DNA
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atcacctgta gagccagcca gaacgtgggc acaaacgtgg cctggtatca gcagaagcct 120

ggcaaggctc ccaaggcgct gatctacagc gccagctaca gacagagcgg cgtgccatct 180

agattcagcg gctctggctc tggcaccgac ttcaccctga caatctctag cctgcagcct 240

gaggacttcg ctacctactt ctgccagcag ttcaacacaa accctctgac cttcggcgga 300

ggcaccaagg tggaaatcaa g 321

<210> 207
<211> 7
<212> PRT
<213> Homo sapiens

<400> 207

Ser Ala Ser Tyr Arg Gln Ser
1 5

<210> 208
<211> 107
<212> PRT
<213> Homo sapiens

<400> 208

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 Asn Val Gly Thr Asn
20 25 30

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Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Ala Leu Ile
        35                  40                  45

Tyr Ser Ala Ser Tyr Arg Glu 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 Phe Cys Gln Gln Phe Asn Thr Asn Pro Leu
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105
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<210> 209
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<212> DNA
<213> Homo sapiens

<400> 209

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ggacaggctc ccagagcgct gatctacagc gccagctaca gagagtctgg catccctgct      180

agattcagcg gctctggctc tggcaccgag ttcaccctga caatcagcag cctgcagagc      240

gaggacttcg ccgtgtactt ctgccagcag ttcaacacaa accctctgac cttcggcgga      300

ggcaccaagg tggaaatcaa g                                                321
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<210> 210
<211> 107
<212> PRT
<213> Homo sapiens

<400> 210

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Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1               5                   10                  15
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Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asn Val Gly Thr Asn
            20                  25                  30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45

Tyr Ser Ala Ser Tyr Arg Glu 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 Phe Cys Gln Gln Phe Asn Thr Asn Pro Leu
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105
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<210> 211
<211> 321
<212> DNA
<213> Homo sapiens

<400> 211

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ctgagctgta gagcctctca gaacgtgggc acaaacgtgg cctggtatca gcagaagcct      120

ggacaggctc ccagactgct gatctacagc gccagctaca gagagtctgg catccctgct      180

agattcagcg gctctggctc tggcaccgag ttcaccctga caatcagcag cctgcagagc      240

gaggacttcg ccgtgtactt ctgccagcag ttcaacacaa accctctgac cttcggcgga      300

ggcaccaagg tggaaatcaa g                                                321
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<210> 212
<211> 107
<212> PRT
<213> Homo sapiens

<400> 212

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 Asn Val Gly Thr Asn
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Ala Leu Ile
35 40 45

Tyr Ser Ala Ser Tyr Arg Gln 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 Phe Cys Gln Gln Phe Asn Thr Asn Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 213
<211> 321
<212> DNA
<213> Homo sapiens

<400> 213
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ctgagctgta gagcctctca gaacgtgggc acaaacgtgg cctggtatca gcagaagcct 120

ggacaggctc ccagagcgct gatctacagc gccagctaca gacagtctgg catccctgct 180

agattcagcg gctctggctc tggcaccgag ttcaccctga caatcagcag cctgcagagc 240

gaggacttcg ccgtgtactt ctgccagcag ttcaacacaa accctctgac cttcggcgga 300

ggcaccaagg tggaaatcaa g 321

<210> 214

<211> 107
<212> PRT
<213> Homo sapiens

<400> 214

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 Arg Ala Ser Gln Asp Val Asn Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Asn Ile Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 215
<211> 321
<212> DNA
<213> Homo sapiens

<400> 215
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atcacctgta gagccagcca ggacgtgaac acagccgtgg cttggtatca gcagaagcct 120

ggcaaggccc ctaagctgct gatctacagc gccagctaca gatacaccgg cgtgccctct 180

agattcagcg gctctggctc tggcaccgac ttcaccctga caatctctag cctgcagcct 240

gaggacttcg ccacctacta ctgccagcag cactacaaca tccctctgac cttcggcgga 300

ggcaccaagg tggaaatcaa g 321

<210> 216
<211> 11
<212> PRT
<213> Homo sapiens

<400> 216

Arg Ala Ser Gln Asp Val Asn Thr Ala Val Ala
1 5 10