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(54) Title: ANTI-CLAUDIN 18.2 ANTIBODIES AND USES THEREOF

(57) Abstract: Provided are antibodies or fragment thereof having binding specificity to the wild-type human claudin 18.2 (CLDN18.2) protein and also capable of binding the M149L mutant. By contrast, such antibodies and fragments do not or weakly bind to claudin 18.1 (CLDN18.1).



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ANTI-CLAUDIN 18.2 ANTIBODIES AND USES THEREOF

BACKGROUND

[0001] Claudins are a family of proteins that form the important components of the tight cell junctions. They establish a paracellular barrier which controls the flow of molecules between the cells. The proteins have N-terminus and a C-terminus in the cytoplasm. Different claudins are expressed on different tissues, their altered function has linked to formation of cancers of respective tissues. Claudin-1 is expressed in colon cancer, claudin-18 is expressed in gastric cancer, and claudin-10 is expressed in hepatocellular carcinoma.

[0002] Claudin-18 has two isoforms, isoform 1 and isoform 2. Isoform 2 (Claudin 18.2 or CLDN18.2) is a highly selective cell lineage marker. Claudin 18.2's expression in normal tissues is strictly confined to differentiated epithelial cells of the gastric mucosa, but it was absent from the gastric stem cell zone. Claudin 18.2 was retained on malignant transformation and was expressed in a significant proportion of primary gastric cancers and its metastases. Frequently ectopic activation of claudin 18.2 was also found in pancreatic, esophageal, ovarian, and lung tumors. These data suggested that CLDN18.2 has highly restricted expression pattern in normal tissues, with frequent ectopic activation in a diversity of human cancers.

SUMMARY

[0003] Anti-claudin 18.2 antibodies are discovered herein that have high affinity to both the wild-type claudin 18.2 and a common mutant, M149L. Such antibodies, therefore, have the unique advantage of being capable of targeting both the wild-type and the M149L mutant claudin 18.2 protein. This advantage is important because a significant portion of cancer patients harbor this common mutation. Moreover, the antibodies of the present disclosure do not bind to the other claudin 18 isoform, claudin 18.1 and thus are highly selective.

[0004] In accordance with one embodiment of the present disclosure, provided is an antibody or fragment thereof having binding specificity to a wild-type human claudin 18.2 (CLDN18.2) protein, wherein the antibody or fragment further binds to a M149L mutant of the CLDN18.2 protein at an affinity that is at least about 1% of the affinity to the wild-type CLDN18.2 protein, and wherein the antibody or fragment further does not bind to a human wild-type claudin 18.1 (CLDN18.1) protein at an affinity that is greater than about 1% of the

affinity to the wild-type CLDN18.2 protein. In some embodiments, the antibody or fragment thereof does not bind to the CLDN18.1 protein.

[0005] Also provided, in one embodiment, is an antibody or fragment thereof having binding specificity to a wild-type human claudin 18.2 (CLDN18.2) protein, wherein the binding between the antibody or fragment thereof and the wild-type CLDN18.2 protein involves amino acid residues comprising: at least an amino acid residue selected from the group consisting of Y46, G48, L49, W50, C53, V54, R55, E56 and S58; and at least an amino acid residue selected from the group consisting of Y169 and G172, of the wild-type CLDN18.2 protein. In some embodiments, the binding further involves W30 of the CLDN18.2 protein.

[0006] In some embodiments, the binding involves amino acid residues comprising: W30; two or more amino acid residues selected from the group consisting of G48, L49, W50, C53, and E56; and at least an amino acid residue selected from the group consisting of Y169 and G172, of the wild-type CLDN18.2 protein. In some embodiments, the binding involves amino acid residues comprising W30, G48, L49, W50, C53, E56 and Y169 of the wild-type CLDN18.2 protein.

[0007] Methods and uses for the treatment of diseases and conditions are also provided. In one embodiment, provided is a method of treating cancer in a patient in need thereof, comprising administering to the patient the antibody or fragment thereof of the present disclosure. In another embodiment, a method of treating cancer in a patient in need thereof is provided, comprising: (a) treating a cell, in vitro, with the antibody or fragment thereof of the present disclosure; and (b) administering the treated cell to the patient.

BRIEF DESCRIPTION OF THE DRAWINGS

[0008] FIG. 1 shows that the mouse sera from all mice after DNA immunisation have high titration reacted with HEK293 cells transfected with CLD 18A2 by flow cytometry, CLD 18A1 as negative control.

[0009] FIG. 2 shows that the hybridoma supernatants can bind to HEK293 cells transfected with human CLD18A2 by cell ELISA or flow cytometry.

[0010] FIG. 3 shows that the purified murine antibodies can bind to MKN45 cells transfected with human CLD18A2 by flow cytometry with high EC50, compared with positive reference antibody.

[0011] FIG. 4 shows that the purified murine antibodies can bind to SU620 cells endogenously expressing human CLD18A2 bearing M149L mutation by flow cytometry with high EC50, while the reference antibody did not.

[0012] FIG. 5 shows that the purified murine antibodies can bind to HEK293 cells transfected with mouse CLD18A2 by flow cytometry with high EC50.

[0013] FIG. 6 shows that the purified murine antibodies can bind to HEK293 cells transfected with cyno CLD18A2 by flow cytometry with high EC50.

[0014] FIG. 7 shows that the purified murine antibodies can bind to HEK293 cells transfected with human CLD18A2 by flow cytometry with high EC50.

[0015] FIG. 8 shows that the chimeric antibodies can bind to MKN45 cells transfected with human CLD18A2 by flow cytometry with high EC50, compared with positive reference antibody.

[0016] FIG. 9 shows that the chimeric antibodies can not bind to MKN45 cells transfected with human CLD18A1 by flow cytometry.

[0017] FIG. 10 shows that humanized antibodies can bind to MKN45 cells transfected with human CLD18A2 by flow cytometry with high EC50, compared with positive reference antibody.

[0018] FIG. 11 shows that the humanized antibodies cannot bind to MKN45 cells transfected with human CLD18A1 by flow cytometry.

[0019] FIG. 12 shows that humanized antibodies with CDR mutation can bind to MKN45 cells transfected with human CLD18A2 by flow cytometry with high EC50, compared with positive reference antibody.

[0020] FIG. 13 shows that the humanized antibodies with CDR mutation cannot bind to MKN45 cells transfected with human CLD18A1 by flow cytometry.

[0021] FIG. 14 shows that the de-risked variants had potent binding to cell surface CLD18A2.

[0022] FIG. 15 shows that certain mutations of CLD18A2 have significant effect on the indicated antibodies binding to HEK293 cells transfected these mutants, suggesting that these amino acid residues constitute at least part of the epitope.

[0023] FIG. 16 shows that antibodies 4F11E2, 72C1B6A3 and 120B7B2 had superior binding in both claudin 18.2 high and low CHO-K1 cells, as compared to 175D10.

[0024] FIG. 17 shows the potent ADCC testing results of 4F11E2, 72C1B6A3 and 120B7B2 using 175D10 antibody as a reference.

[0025] FIG. 18 shows that the S239D/I332E versions of the 4F11E2, 72C1B6A3 and 120B7B2 outperformed the 175D10 counterpart in the ADCC assays.

[0026] FIG. 19 shows that 4F11E2, 72C1B6A3 and 120B7B2 also had better ADCP effects than 175D10.

DETAILED DESCRIPTION

Definitions

[0027] It is to be noted that the term “a” or “an” entity refers to one or more of that entity; for example, “an antibody,” is understood to represent one or more antibodies. As such, the terms “a” (or “an”), “one or more,” and “at least one” can be used interchangeably herein.

[0028] As used herein, the term “polypeptide” is intended to encompass a singular “polypeptide” as well as plural “polypeptides,” and refers to a molecule composed of monomers (amino acids) linearly linked by amide bonds (also known as peptide bonds). The term “polypeptide” refers to any chain or chains of two or more amino acids, and does not refer to a specific length of the product. Thus, peptides, dipeptides, tripeptides, oligopeptides, “protein,” “amino acid chain,” or any other term used to refer to a chain or chains of two or more amino acids, are included within the definition of “polypeptide,” and the term “polypeptide” may be used instead of, or interchangeably with any of these terms. The term “polypeptide” is also intended to refer to the products of post-expression modifications of the polypeptide, including without limitation glycosylation, acetylation, phosphorylation,

amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, or modification by non- naturally occurring amino acids. A polypeptide may be derived from a natural biological source or produced by recombinant technology, but is not necessarily translated from a designated nucleic acid sequence. It may be generated in any manner, including by chemical synthesis.

[0029] The term “isolated” as used herein with respect to cells, nucleic acids, such as DNA or RNA, refers to molecules separated from other DNAs or RNAs, respectively, that are present in the natural source of the macromolecule. The term “isolated” as used herein also refers to a nucleic acid or peptide that is substantially free of cellular material, viral material, or culture medium when produced by recombinant DNA techniques, or chemical precursors or other chemicals when chemically synthesized. Moreover, an “isolated nucleic acid” is meant to include nucleic acid fragments which are not naturally occurring as fragments and would not be found in the natural state. The term “isolated” is also used herein to refer to cells or polypeptides which are isolated from other cellular proteins or tissues. Isolated polypeptides is meant to encompass both purified and recombinant polypeptides.

[0030] As used herein, the term “recombinant” as it pertains to polypeptides or polynucleotides intends a form of the polypeptide or polynucleotide that does not exist naturally, a non-limiting example of which can be created by combining polynucleotides or polypeptides that would not normally occur together.

[0031] “Homology” or “identity” or “similarity” refers to sequence similarity between two peptides or between two nucleic acid molecules. Homology can be determined by comparing a position in each sequence which may be aligned for purposes of comparison. When a position in the compared sequence is occupied by the same base or amino acid, then the molecules are homologous at that position. A degree of homology between sequences is a function of the number of matching or homologous positions shared by the sequences. An “unrelated” or “non-homologous” sequence shares less than 40% identity, though preferably less than 25% identity, with one of the sequences of the present disclosure.

[0032] A polynucleotide or polynucleotide region (or a polypeptide or polypeptide region) has a certain percentage (for example, 60 %, 65 %, 70 %, 75 %, 80 %, 85 %, 90 %, 95 %, 98 % or 99 %) of “sequence identity” to another sequence means that, when aligned, that percentage of bases (or amino acids) are the same in comparing the two sequences. This

alignment and the percent homology or sequence identity can be determined using software programs known in the art, for example those described in Ausubel *et al.* eds. (2007) Current Protocols in Molecular Biology. Preferably, default parameters are used for alignment. One alignment program is BLAST, using default parameters. In particular, programs are BLASTN and BLASTP, using the following default parameters: Genetic code = standard; filter = none; strand = both; cutoff = 60; expect = 10; Matrix = BLOSUM62; Descriptions = 50 sequences; sort by = HIGH SCORE; Databases = non-redundant, GenBank + EMBL + DDBJ + PDB + GenBank CDS translations + SwissProtein + SPupdate + PIR. Biologically equivalent polynucleotides are those having the above-noted specified percent homology and encoding a polypeptide having the same or similar biological activity.

[0033] The term “an equivalent nucleic acid or polynucleotide” refers to a nucleic acid having a nucleotide sequence having a certain degree of homology, or sequence identity, with the nucleotide sequence of the nucleic acid or complement thereof. A homolog of a double stranded nucleic acid is intended to include nucleic acids having a nucleotide sequence which has a certain degree of homology with or with the complement thereof. In one aspect, homologs of nucleic acids are capable of hybridizing to the nucleic acid or complement thereof. Likewise, “an equivalent polypeptide” refers to a polypeptide having a certain degree of homology, or sequence identity, with the amino acid sequence of a reference polypeptide. In some aspects, the sequence identity is at least about 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99%. In some aspects, the equivalent polypeptide or polynucleotide has one, two, three, four or five addition, deletion, substitution and their combinations thereof as compared to the reference polypeptide or polynucleotide. In some aspects, the equivalent sequence retains the activity (*e.g.*, epitope-binding) or structure (*e.g.*, salt-bridge) of the reference sequence.

[0034] Hybridization reactions can be performed under conditions of different “stringency”. In general, a low stringency hybridization reaction is carried out at about 40°C in about 10 x SSC or a solution of equivalent ionic strength/temperature. A moderate stringency hybridization is typically performed at about 50°C in about 6 x SSC, and a high stringency hybridization reaction is generally performed at about 60°C in about 1 x SSC. Hybridization reactions can also be performed under “physiological conditions” which is well known to one of skill in the art. A non-limiting example of a physiological condition is the temperature, ionic strength, pH and concentration of Mg²⁺ normally found in a cell.

[0035] A polynucleotide is composed of a specific sequence of four nucleotide bases: adenine (A); cytosine (C); guanine (G); thymine (T); and uracil (U) for thymine when the polynucleotide is RNA. Thus, the term “polynucleotide sequence” is the alphabetical representation of a polynucleotide molecule. This alphabetical representation can be input into databases in a computer having a central processing unit and used for bioinformatics applications such as functional genomics and homology searching. The term “polymorphism” refers to the coexistence of more than one form of a gene or portion thereof. A portion of a gene of which there are at least two different forms, i.e., two different nucleotide sequences, is referred to as a “polymorphic region of a gene”. A polymorphic region can be a single nucleotide, the identity of which differs in different alleles.

[0036] The terms “polynucleotide” and “oligonucleotide” are used interchangeably and refer to a polymeric form of nucleotides of any length, either deoxyribonucleotides or ribonucleotides or analogs thereof. Polynucleotides can have any three-dimensional structure and may perform any function, known or unknown. The following are non-limiting examples of polynucleotides: a gene or gene fragment (for example, a probe, primer, EST or SAGE tag), exons, introns, messenger RNA (mRNA), transfer RNA, ribosomal RNA, ribozymes, cDNA, dsRNA, siRNA, miRNA, recombinant polynucleotides, branched polynucleotides, plasmids, vectors, isolated DNA of any sequence, isolated RNA of any sequence, nucleic acid probes and primers. A polynucleotide can comprise modified nucleotides, such as methylated nucleotides and nucleotide analogs. If present, modifications to the nucleotide structure can be imparted before or after assembly of the polynucleotide. The sequence of nucleotides can be interrupted by non-nucleotide components. A polynucleotide can be further modified after polymerization, such as by conjugation with a labeling component. The term also refers to both double- and single-stranded molecules. Unless otherwise specified or required, any embodiment of this disclosure that is a polynucleotide encompasses both the double-stranded form and each of two complementary single-stranded forms known or predicted to make up the double-stranded form.

[0037] The term “encode” as it is applied to polynucleotides refers to a polynucleotide which is said to “encode” a polypeptide if, in its native state or when manipulated by methods well known to those skilled in the art, it can be transcribed and/or translated to produce the mRNA for the polypeptide and/or a fragment thereof. The antisense strand is the complement of such a nucleic acid, and the encoding sequence can be deduced therefrom.

[0038] As used herein, an “antibody” or “antigen-binding polypeptide” refers to a polypeptide or a polypeptide complex that specifically recognizes and binds to an antigen. An antibody can be a whole antibody and any antigen binding fragment or a single chain thereof. Thus the term “antibody” includes any protein or peptide containing molecule that comprises at least a portion of an immunoglobulin molecule having biological activity of binding to the antigen. Examples of such include, but are not limited to a complementarity determining region (CDR) of a heavy or light chain or a ligand binding portion thereof, a heavy chain or light chain variable region, a heavy chain or light chain constant region, a framework (FR) region, or any portion thereof, or at least one portion of a binding protein.

[0039] The terms “antibody fragment” or “antigen-binding fragment”, as used herein, is a portion of an antibody such as F(ab')₂, F(ab)₂, Fab', Fab, Fv, scFv and the like. Regardless of structure, an antibody fragment binds with the same antigen that is recognized by the intact antibody. The term “antibody fragment” includes aptamers, spiegelmers, and diabodies. The term “antibody fragment” also includes any synthetic or genetically engineered protein that acts like an antibody by binding to a specific antigen to form a complex.

[0040] A “single-chain variable fragment” or “scFv” refers to a fusion protein of the variable regions of the heavy (V_H) and light chains (V_L) of immunoglobulins. In some aspects, the regions are connected with a short linker peptide of ten to about 25 amino acids. The linker can be rich in glycine for flexibility, as well as serine or threonine for solubility, and can either connect the N-terminus of the V_H with the C-terminus of the V_L, or vice versa. This protein retains the specificity of the original immunoglobulin, despite removal of the constant regions and the introduction of the linker. ScFv molecules are known in the art and are described, *e.g.*, in US patent 5,892,019.

[0041] The term antibody encompasses various broad classes of polypeptides that can be distinguished biochemically. Those skilled in the art will appreciate that heavy chains are classified as gamma, mu, alpha, delta, or epsilon (γ , μ , α , δ , ϵ) with some subclasses among them (*e.g.*, γ 1- γ 4). It is the nature of this chain that determines the “class” of the antibody as IgG, IgM, IgA, IgG, or IgE, respectively. The immunoglobulin subclasses (isotypes) *e.g.*, IgG₁, IgG₂, IgG₃, IgG₄, IgG₅, etc. are well characterized and are known to confer functional specialization. Modified versions of each of these classes and isotypes are readily discernable to the skilled artisan in view of the instant disclosure and, accordingly, are within the scope of the instant disclosure. All immunoglobulin classes are clearly within the scope

of the present disclosure, the following discussion will generally be directed to the IgG class of immunoglobulin molecules. With regard to IgG, a standard immunoglobulin molecule comprises two identical light chain polypeptides of molecular weight approximately 23,000 Daltons, and two identical heavy chain polypeptides of molecular weight 53,000-70,000. The four chains are typically joined by disulfide bonds in a “Y” configuration wherein the light chains bracket the heavy chains starting at the mouth of the “Y” and continuing through the variable region.

[0042] Antibodies, antigen-binding polypeptides, variants, or derivatives thereof of the disclosure include, but are not limited to, polyclonal, monoclonal, multispecific, human, humanized, primatized, or chimeric antibodies, single chain antibodies, epitope-binding fragments, *e.g.*, Fab, Fab' and F(ab')₂, Fd, Fvs, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv), fragments comprising either a VK or VH domain, fragments produced by a Fab expression library, and anti- idiotypic (anti-Id) antibodies (including, *e.g.*, anti-Id antibodies to LIGHT antibodies disclosed herein). Immunoglobulin or antibody molecules of the disclosure can be of any type (*e.g.*, IgG, IgE, IgM, IgD, IgA, and IgY), class (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule.

[0043] Light chains are classified as either kappa or lambda (K, λ). Each heavy chain class may be bound with either a kappa or lambda light chain. In general, the light and heavy chains are covalently bonded to each other, and the “tail” portions of the two heavy chains are bonded to each other by covalent disulfide linkages or non-covalent linkages when the immunoglobulins are generated either by hybridomas, B cells or genetically engineered host cells. In the heavy chain, the amino acid sequences run from an N-terminus at the forked ends of the Y configuration to the C-terminus at the bottom of each chain.

[0044] Both the light and heavy chains are divided into regions of structural and functional homology. The terms “constant” and “variable” are used functionally. In this regard, it will be appreciated that the variable domains of both the light (VK) and heavy (VH) chain portions determine antigen recognition and specificity. Conversely, the constant domains of the light chain (CK) and the heavy chain (CH1, CH2 or CH3) confer important biological properties such as secretion, transplacental mobility, Fc receptor binding, complement binding, and the like. By convention the numbering of the constant region domains increases as they become more distal from the antigen-binding site or amino- terminus of the antibody.

The N-terminal portion is a variable region and at the C-terminal portion is a constant region; the CH3 and CK domains actually comprise the carboxy-terminus of the heavy and light chain, respectively.

[0045] As indicated above, the variable region allows the antibody to selectively recognize and specifically bind epitopes on antigens. That is, the VK domain and VH domain, or subset of the complementarity determining regions (CDRs), of an antibody combine to form the variable region that defines a three dimensional antigen-binding site. This quaternary antibody structure forms the antigen-binding site present at the end of each arm of the Y. More specifically, the antigen-binding site is defined by three CDRs on each of the VH and VK chains (*i.e.* CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2 and CDR-L3). In some instances, *e.g.*, certain immunoglobulin molecules derived from camelid species or engineered based on camelid immunoglobulins, a complete immunoglobulin molecule may consist of heavy chains only, with no light chains. *See, e.g.*, Hamers-Casterman *et al.*, *Nature* 363:446-448 (1993).

[0046] In naturally occurring antibodies, the six “complementarity determining regions” or “CDRs” present in each antigen-binding domain are short, non-contiguous sequences of amino acids that are specifically positioned to form the antigen-binding domain as the antibody assumes its three dimensional configuration in an aqueous environment. The remainder of the amino acids in the antigen-binding domains, referred to as “framework” regions, show less inter-molecular variability. The framework regions largely adopt a β -sheet conformation and the CDRs form loops which connect, and in some cases form part of, the β -sheet structure. Thus, framework regions act to form a scaffold that provides for positioning the CDRs in correct orientation by inter-chain, non-covalent interactions. The antigen-binding domain formed by the positioned CDRs defines a surface complementary to the epitope on the immunoreactive antigen. This complementary surface promotes the non-covalent binding of the antibody to its cognate epitope. The amino acids comprising the CDRs and the framework regions, respectively, can be readily identified for any given heavy or light chain variable region by one of ordinary skill in the art, since they have been precisely defined (*see* “Sequences of Proteins of Immunological Interest,” Kabat, E., *et al.*, U.S. Department of Health and Human Services, (1983); and Chothia and Lesk, *J. Mol. Biol.*, 196:901-917 (1987)).

[0047] In the case where there are two or more definitions of a term which is used and/or accepted within the art, the definition of the term as used herein is intended to include all such meanings unless explicitly stated to the contrary. A specific example is the use of the term “complementarity determining region” (“CDR”) to describe the non-contiguous antigen combining sites found within the variable region of both heavy and light chain polypeptides. This particular region has been described by Kabat *et al.*, U.S. Dept. of Health and Human Services, “Sequences of Proteins of Immunological Interest” (1983) and by Chothia *et al.*, *J. Mol. Biol.* 196:901-917 (1987), which are incorporated herein by reference in their entireties. The CDR definitions according to Kabat and Chothia include overlapping or subsets of amino acid residues when compared against each other. Nevertheless, application of either definition to refer to a CDR of an antibody or variants thereof is intended to be within the scope of the term as defined and used herein. The appropriate amino acid residues which encompass the CDRs as defined by each of the above cited references are set forth in the table below as a comparison. The exact residue numbers which encompass a particular CDR will vary depending on the sequence and size of the CDR. Those skilled in the art can routinely determine which residues comprise a particular CDR given the variable region amino acid sequence of the antibody.

	Kabat	Chothia
CDR-H1	31-35	26-32
CDR-H2	50-65	52-58
CDR-H3	95-102	95-102
CDR-L1	24-34	26-32
CDR-L2	50-56	50-52
CDR-L3	89-97	91-96

[0048] Kabat *et al.* also defined a numbering system for variable domain sequences that is applicable to any antibody. One of ordinary skill in the art can unambiguously assign this system of “Kabat numbering” to any variable domain sequence, without reliance on any experimental data beyond the sequence itself. As used herein, “Kabat numbering” refers to the numbering system set forth by Kabat *et al.*, U.S. Dept. of Health and Human Services, “Sequence of Proteins of Immunological Interest” (1983).

[0049] In addition to table above, the Kabat number system describes the CDR regions as follows: CDR-H1 begins at approximately amino acid 31 (*i.e.*, approximately 9 residues after the first cysteine residue), includes approximately 5-7 amino acids, and ends at the next tryptophan residue. CDR-H2 begins at the fifteenth residue after the end of CDR-H1,

includes approximately 16-19 amino acids, and ends at the next arginine or lysine residue. CDR-H3 begins at approximately the thirty third amino acid residue after the end of CDR-H2; includes 3-25 amino acids; and ends at the sequence W-G-X-G, where X is any amino acid. CDR-L1 begins at approximately residue 24 (*i.e.*, following a cysteine residue); includes approximately 10-17 residues; and ends at the next tryptophan residue. CDR-L2 begins at approximately the sixteenth residue after the end of CDR-L1 and includes approximately 7 residues. CDR-L3 begins at approximately the thirty third residue after the end of CDR-L2 (*i.e.*, following a cysteine residue); includes approximately 7-11 residues and ends at the sequence F or W-G-X-G, where X is any amino acid.

[0050] Antibodies disclosed herein may be from any animal origin including birds and mammals. Preferably, the antibodies are human, murine, donkey, rabbit, goat, guinea pig, camel, llama, horse, or chicken antibodies. In another embodiment, the variable region may be chondrichthoid in origin (*e.g.*, from sharks).

[0051] As used herein, the term “heavy chain constant region” includes amino acid sequences derived from an immunoglobulin heavy chain. A polypeptide comprising a heavy chain constant region comprises at least one of: a CH1 domain, a hinge (*e.g.*, upper, middle, and/or lower hinge region) domain, a CH2 domain, a CH3 domain, or a variant or fragment thereof. For example, an antigen-binding polypeptide for use in the disclosure may comprise a polypeptide chain comprising a CH1 domain; a polypeptide chain comprising a CH1 domain, at least a portion of a hinge domain, and a CH2 domain; a polypeptide chain comprising a CH1 domain and a CH3 domain; a polypeptide chain comprising a CH1 domain, at least a portion of a hinge domain, and a CH3 domain, or a polypeptide chain comprising a CH1 domain, at least a portion of a hinge domain, a CH2 domain, and a CH3 domain. In another embodiment, a polypeptide of the disclosure comprises a polypeptide chain comprising a CH3 domain. Further, an antibody for use in the disclosure may lack at least a portion of a CH2 domain (*e.g.*, all or part of a CH2 domain). As set forth above, it will be understood by one of ordinary skill in the art that the heavy chain constant region may be modified such that they vary in amino acid sequence from the naturally occurring immunoglobulin molecule.

[0052] The heavy chain constant region of an antibody disclosed herein may be derived from different immunoglobulin molecules. For example, a heavy chain constant region of a polypeptide may comprise a CH1 domain derived from an IgG1 molecule and a hinge region

derived from an IgG₃ molecule. In another example, a heavy chain constant region can comprise a hinge region derived, in part, from an IgG₁ molecule and, in part, from an IgG₃ molecule. In another example, a heavy chain portion can comprise a chimeric hinge derived, in part, from an IgG₁ molecule and, in part, from an IgG₄ molecule.

[0053] As used herein, the term “light chain constant region” includes amino acid sequences derived from antibody light chain. Preferably, the light chain constant region comprises at least one of a constant kappa domain or constant lambda domain.

[0054] A “light chain-heavy chain pair” refers to the collection of a light chain and heavy chain that can form a dimer through a disulfide bond between the CL domain of the light chain and the CH1 domain of the heavy chain.

[0055] As previously indicated, the subunit structures and three dimensional configuration of the constant regions of the various immunoglobulin classes are well known. As used herein, the term “VH domain” includes the amino terminal variable domain of an immunoglobulin heavy chain and the term “CH1 domain” includes the first (most amino terminal) constant region domain of an immunoglobulin heavy chain. The CH1 domain is adjacent to the VH domain and is amino terminal to the hinge region of an immunoglobulin heavy chain molecule.

[0056] As used herein the term “CH2 domain” includes the portion of a heavy chain molecule that extends, *e.g.*, from about residue 244 to residue 360 of an antibody using conventional numbering schemes (residues 244 to 360, Kabat numbering system; and residues 231-340, EU numbering system; *see* Kabat *et al.*, U.S. Dept. of Health and Human Services, “Sequences of Proteins of Immunological Interest” (1983). The CH2 domain is unique in that it is not closely paired with another domain. Rather, two N-linked branched carbohydrate chains are interposed between the two CH2 domains of an intact native IgG molecule. It is also well documented that the CH3 domain extends from the CH2 domain to the C-terminal of the IgG molecule and comprises approximately 108 residues.

[0057] As used herein, the term “hinge region” includes the portion of a heavy chain molecule that joins the CH1 domain to the CH2 domain. This hinge region comprises approximately 25 residues and is flexible, thus allowing the two N-terminal antigen-binding regions to move independently. Hinge regions can be subdivided into three distinct domains: upper, middle, and lower hinge domains (Roux *et al.*, *J. Immunol* 161:4083 (1998)).

[0058] As used herein the term “disulfide bond” includes the covalent bond formed between two sulfur atoms. The amino acid cysteine comprises a thiol group that can form a disulfide bond or bridge with a second thiol group. In most naturally occurring IgG molecules, the CH1 and CK regions are linked by a disulfide bond and the two heavy chains are linked by two disulfide bonds at positions corresponding to 239 and 242 using the Kabat numbering system (position 226 or 229, EU numbering system).

[0059] As used herein, the term “chimeric antibody” will be held to mean any antibody wherein the immunoreactive region or site is obtained or derived from a first species and the constant region (which may be intact, partial or modified in accordance with the instant disclosure) is obtained from a second species. In certain embodiments the target binding region or site will be from a non-human source (*e.g.* mouse or primate) and the constant region is human.

[0060] As used herein, “percent humanization” is calculated by determining the number of framework amino acid differences (*i.e.*, non-CDR difference) between the humanized domain and the germline domain, subtracting that number from the total number of amino acids, and then dividing that by the total number of amino acids and multiplying by 100.

[0061] By “specifically binds” or “has specificity to,” it is generally meant that an antibody binds to an epitope via its antigen-binding domain, and that the binding entails some complementarity between the antigen-binding domain and the epitope. According to this definition, an antibody is said to “specifically bind” to an epitope when it binds to that epitope, via its antigen-binding domain more readily than it would bind to a random, unrelated epitope. The term “specificity” is used herein to qualify the relative affinity by which a certain antibody binds to a certain epitope. For example, antibody “A” may be deemed to have a higher specificity for a given epitope than antibody “B,” or antibody “A” may be said to bind to epitope “C” with a higher specificity than it has for related epitope “D.”

[0062] As used herein, the terms “treat” or “treatment” refer to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) an undesired physiological change or disorder, such as the progression of cancer. Beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of disease, stabilized (*i.e.*, not worsening) state of disease, delay or

slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment. Those in need of treatment include those already with the condition or disorder as well as those prone to have the condition or disorder or those in which the condition or disorder is to be prevented.

[0063] By "subject" or "individual" or "animal" or "patient" or "mammal," is meant any subject, particularly a mammalian subject, for whom diagnosis, prognosis, or therapy is desired. Mammalian subjects include humans, domestic animals, farm animals, and zoo, sport, or pet animals such as dogs, cats, guinea pigs, rabbits, rats, mice, horses, cattle, cows, and so on.

[0064] As used herein, phrases such as "to a patient in need of treatment" or "a subject in need of treatment" includes subjects, such as mammalian subjects, that would benefit from administration of an antibody or composition of the present disclosure used, *e.g.*, for detection, for a diagnostic procedure and/or for treatment.

Anti-Claudin 18.2 Antibodies

[0065] The present disclosure provides anti-claudin 18.2 antibodies with high affinity to both the wild-type claudin 18.2 and a common mutant, M149L (the SU620 cell endogenously expressing this mutation). To the best knowledge of the inventors, all currently known anti-claudin 18.2 proteins do not bind to this mutant. The antibodies of the present disclosure, therefore, have the unique advantage of being capable of targeting both the wild-type and the M149L mutant claudin 18.2 protein. This advantage is important because a significant portion of cancer patients harbor this common mutation. It is also worth noting that the antibodies of the present disclosure do not bind to the other claudin 18 isoform, claudin 18.1 (or binds claudin 18.1 at a much lower affinity).

[0066] Experiments presented in the Examples revealed that certain amino acids in the first and second extracellular fragments of the claudin 18.2 protein are involved in or otherwise impact the binding of the presently disclosed antibodies to the protein. More specifically, three clusters of amino acid residues are shown to represent the epitope of the antibodies. The first cluster includes W30, which is in the first part of the first extracellular domain of the

claudin 18.2 protein. The second cluster, including N45, Y46, G48, L49, W50, C53, V54, R55, E56, S58, F60, E62, and C63, is also located in the first extracellular domain. The third cluster, including Y169 and G172, on the other hand, are located at or close to the second extracellular domain.

[0067] The antibodies and fragments of the present disclosure exhibited superior properties even when using a clinical candidate as a reference. 175D10 (IMAB362) is currently undergoing phase III clinical trials for treating gastric and gastroesophageal junction adenocarcinoma. The instant antibodies and fragment not only showed stronger binding activities, they also exhibited higher ADCC and ADCP activities under various different conditions, as compared to 175D10.

[0068] The improved properties of these new antibodies and fragments, it is contemplated, are attributed to the higher binding specificity of these antibodies and fragments as compared to those under development, such as 175D10. For instance, 175D10's interaction with claudin 18.2 is strong across the spectrum in FIG. 15, which includes strong binding to D28, Q33, N38 and V43, and then G59 and V79. The new antibodies, 4F11E2, 72C1B6A3 and 120B7B2, by contrast, have higher specificity to W30 within the first half of the first extracellular domain, and higher specificity to G48 through E56 within the second half of the first extracellular domain. The new antibodies also have slightly stronger binding to Y46 and S58, which are also in the second half. Their binding to D28, Q33, N38, V43, G59 and V79 is considerably weaker (or not functional), which likely contributed to the improved ADCC and ADCP of the new antibodies.

Human claudin 18.2 sequence

Name	Sequence (SEQ ID NO:30)
Human Claudin 18.2 (NP_001002026)	1 MAVTACQGLG FVVSLLIGIAG IIAATC MDQW STQDLYNNPV TAVF NYQGLW 51 RSC CVRES SGF TE CRGYFTLL GLPAMLQAVR ALMIVGIVLG AIGLLVSIFA 101 LKCIRIGSME DSAKANMTLT SGIMFIVSGL CAIAGVSVFA NMLVTNFWMS 151 TANMYTGMGG MVQTVQTRY I F G AALFVGWV AGGLTLIGGV MMCIACRGLA 201 PEETNYKAVS YHASGHSVAY KPGGFKASTG FGSNTKNKKI YDGGARTEDE 251 VQSYPSKHDY V

[0069] In accordance with one embodiment of the present disclosure, provided is an antibody or fragment thereof having binding specificity to a wild-type human claudin 18.2 (CLDN18.2) protein, wherein the antibody or fragment further binds to a M149L mutant of the CLDN18.2 protein. In some embodiments, the antibody or fragment does not bind to a

human wild-type claudin 18.1 (CLDN18.1) protein, or does not bind CLDN18.1 at an affinity that is greater than about 1% of the affinity to the wild-type CLDN18.2 protein.

[0070] The binding affinity of an antibody or fragment to a protein can be measured with many methods known in the art. For examples, it can be measured cell-free assays with standalone CLDN18.1 or CLDN18.2 proteins. Preferably, however, the measurement is done with the CLDN18.1 or CLDN18.2 protein on a cell surface mimicking the actual binding environment. Such binding assays are adequately exemplified in the experimental examples.

[0071] In some embodiments, the antibodies or fragments thereof have a binding affinity to the M149L mutant that is at least 1%, or alternatively at least 0.001%, 0.01%, 0.1%, 0.5%, 2%, 3%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, 80%, 90%, 95%, 98%, or 99% of the affinity to the wild-type CLDN18.2 protein.

[0072] In some embodiments, the antibodies or fragments thereof do not bind human CLDN18.1. In some embodiments, the antibodies or fragments thereof, as compared to binding to CLDN18.2, have a much weaker binding to human CLDN18.1, e.g., not greater than 10%, 5%, 2%, 1%, 0.5%, 0.1%, 0.05%, 0.01%, 0.005%, or 0.001%, without limitation.

[0073] As described above, the antibodies and fragments thereof of the present disclosure bind to the claudin 18.2 protein at an epitope that is different from known antibodies (see FIG. 4; at least the reference antibody interacts with M149 whereas the presently disclosed ones do not). In one embodiment, therefore, provided is an antibody or fragment thereof having binding specificity to a wild-type human claudin 18.2 (CLDN18.2) protein, wherein the binding between the antibody or fragment thereof and the wild-type CLDN18.2 protein involves amino acid residues comprising at least an amino acid residue selected from the group consisting of Y46, G48, L49, W50, C53, V54, R55, E56 and S58; and at least an amino acid residue selected from the group consisting of Y169 and G172, of the wild-type CLDN18.2 protein. In some embodiments, the binding further involves one or more of W30 of the CLDN18.2 protein.

[0074] In some embodiments, the antibody or fragment thereof binds to N45 of CLDN18.2. In some embodiments, the antibody or fragment thereof binds to Y46 of CLDN18.2. In some embodiments, the antibody or fragment thereof binds to G48 of CLDN18.2. In some embodiments, the antibody or fragment thereof binds to L49 of CLDN18.2. In some embodiments, the antibody or fragment thereof binds to W50 of CLDN18.2. In some

embodiments, the antibody or fragment thereof binds to C53 of CLDN18.2. In some embodiments, the antibody or fragment thereof binds to V54 of CLDN18.2. In some embodiments, the antibody or fragment thereof binds to R55 of CLDN18.2. In some embodiments, the antibody or fragment thereof binds to E56 of CLDN18.2. In some embodiments, the antibody or fragment thereof binds to E58 of CLDN18.2. In some embodiments, the antibody or fragment thereof binds to F60 of CLDN18.2. In some embodiments, the antibody or fragment thereof binds to E62 of CLDN18.2. In some embodiments, the antibody or fragment thereof binds to C63 of CLDN18.2.

[0075] In some embodiments, the antibody or fragment thereof binds to at least two amino acid residues selected from G48, L49, W50, C53, V54, R55, and E56. In some embodiments, the antibody or fragment thereof binds to at least three amino acid residues selected from G48, L49, W50, C53, V54, R55, and E56. In some embodiments, the antibody or fragment thereof binds to at least four amino acid residues selected from G48, L49, W50, C53, V54, R55, and E56. In some embodiments, the antibody or fragment thereof binds to at least five amino acid residues selected from G48, L49, W50, C53, V54, R55, and E56.

[0076] In some embodiments, the antibody or fragment thereof binds to at least two amino acid residues selected from Y46, G48, L49, W50, C53, V54, R55, E56 and S58. In some embodiments, the antibody or fragment thereof binds to at least three amino acid residues selected from Y46, G48, L49, W50, C53, V54, R55, E56 and S58. In some embodiments, the antibody or fragment thereof binds to at least four amino acid residues selected from Y46, G48, L49, W50, C53, V54, R55, E56 and S58. In some embodiments, the antibody or fragment thereof binds to at least five amino acid residues selected from Y46, G48, L49, W50, C53, V54, R55, E56 and S58.

[0077] In some embodiments, the antibody or fragment thereof binds to at least Y169 of CLDN18.2. In some embodiments, the antibody or fragment thereof binds to at least G172 of CLDN18.2. In some embodiments, the antibody or fragment thereof binds to at least two amino acid residues selected from Y169 and G172 of CLDN18.2.

[0078] In some embodiments, the binding involves amino acid residues comprising W30; two, three, four, five or more amino acid residues selected from the group consisting of G48, L49, W50, C53, and E56; and at least an amino acid residue selected from the group consisting of Y169 and G172, of the wild-type CLDN18.2 protein. In some embodiments, the

binding involves amino acid residues comprising W30, G48, L49, W50, C53, E56 and Y169 of the wild-type CLDN18.2 protein.

[0079] In some embodiments, the binding between the antibody or fragment thereof and the wild-type CLDN18.2 protein involves at least Y46 and/or S58. In some embodiments, the binding between the antibody or fragment thereof and the wild-type CLDN18.2 protein does not involve N38 or V43. In some embodiments, the binding between the antibody or fragment thereof and the wild-type CLDN18.2 protein does not involve D28, Q33, N38, V43, G59 and V79, or have weaker bindings to one, two, three, four or all of D28, Q33, N38, V43, G59 and V79.

[0080] The weaker bindings to these amino acids on CLDN18.2 may be as compared to the other amino acids, such as G48, L49, W50, C53, V54, R55, E56. In some embodiments, the comparison is to the binding at the same amino acid to 175D10. For instance, the binding of the antibody or fragment of the present disclosure is weaker than that of 175D10 (IMGT/2Dstructure-DB card No: 10473) to at least one, two, three, four, five or all of D28, Q33, N38, V43, G59 and V79.

[0081] In some embodiments, the antibody or fragment thereof does not bind M149L of the CLDN18.2 protein. In some embodiments, the antibody or fragment thereof binds to a M149L mutant of the CLDN18.2 protein.

[0082] In accordance with one embodiment of the present disclosure, provided is an antibody or fragment thereof that includes the heavy chain and light chain variable domains with the CDR regions as shown in the CDR combinations of **Table A and Table A'**.

Table A. CDR combinations of tested antibodies

Comb No.	Antibody	CDRL1 (SEQ ID NO:)	CDRL2 (SEQ ID NO:)	CDRL3 (SEQ ID NO:)	CDRH1 (SEQ ID NO:)	CDRH2 (SEQ ID NO:)	CDRH3 (SEQ ID NO:)
1	64G11B4	QSLFNSGNQKNY (31)	WAS (2)	QNDYFYPPFT (42)	GYAFTNYL (59)	INPGNGS (77)	ARIYYGNSFAY (96)
2	65G888	QSLFNSGNLKNY (32)	WAS (2)	QNVYIYPPFT (43)	GFSLTSGY (60)	IWGDGNT (78)	AKQGLYGHAMDY (97)
3	56F8F10F4	QSLFNSGNQKNY (1)	WAS (2)	QNDYFYPPFT (44)	GFTFNSFG (61)	ISGGSNTI (79)	TRLALGNAMDY (98)
4	54A2C4	QSLFNSGNQKNY (33)	GAS (39)	QNDLYYPPWT (45)	GFTFTNTA (62)	IRSKSNNYAT (80)	VSGAYYGNASKAFDY (99)
5	54A2C4'	QSLFNSGNQKNY (33)	GAS (39)	QNDLYYPPWT (45)	GYAFTNYL (59)	INPGNGGSN (81)	ARIYYGNSFAY (96)
6	54A2C4''	QSLFNSGNQKNY (33)	GAS (39)	QNDLYYPPWT (45)	GYTFPTYS (63)	INPSTIYT (82)	AREGYGRGNAMDY (100)
7	44F6B11	QSLFNSGNQKNY (34)	WAS (2)	QNGYSYPPFT (46)	GFTFSNYG (64)	FSYGDSHN (83)	ARFGRGNIMDY (101)
8	15C2B7	QSLFNSGNQKNY (1)	WAS (2)	QNNYFYPLT (47)	GYFTNYG (65)	INANTGEP (84)	ARLTGRNSFDY (102)
9	20F1E10	QSLFNSGNQKNY (35)	WAS (2)	QNVYSYPLT (48)	GYFTTKYG (66)	ISTNTGEP (85)	ARLVGRNSFDF (103)
10	72C1B6A3	QSLFNSGNQKNY (1)	PAS (7)	QNDYIYPPY (8)	GYFTTTP (9)	FHPYNDT (10)	ARRAYGYPIYAMDY (11)
11	58G2C2	QSLFNSGNQKNY (1)	WAF (40)	QNSYSYPPFT (49)	GYAFTNYL (59)	INPGRSGT (86)	ARTRYGNAMDY (104)
12	101C4F12	QSLFNSGNQKNY (31)	WSS (41)	QNNFYPLT (50)	GFSLSY (67)	IWAGGST (87)	ARSLYGNSLDS (105)
13	103A10B2	MSLFNSGNQKSY (36)	WAS (2)	HNDYIYPLT (51)	GLSLTSFG (68)	IWAGGST (87)	ARSLYGNISFDY (106)
14	78F8G9G6	QSLFNSGNQKNY (1)	WAS (2)	QNSYSYPPFT (49)	GFSLSY (69)	IWAGGST (88)	ARDRYGNISLDY (107)
15	4F11E2	QSLFNSGNRKNY (12)	WAS (2)	QNAYSYPPFT (13)	GFTFSFG (14)	ITSGNSPI (15)	ARSSYYGNISMDY (16)
16	10G7G11	QSLFNSGNQKNY (35)	WAS (2)	QNAYSYPPFT (19)	GFSLNTYG (70)	MLSDGNT (89)	ARHKAYGNAMDY (108)
17	12F1F4	QSLFNSGNQKNY (35)	WSS (41)	QNNYFYPPFT (52)	GFSLNTYG (71)	IWGDGNT (78)	AKVGRGNAMDH (109)
18	78C10B6G4	QSLFNSGNQKNY (1)	PAS (7)	QNDYIYPPY (8)	GFSLNTYG (71)	IRGDGNT (90)	AKVGRGNAMDH (109)
19	119G11D9	QSLFNSGNQKNY (37)	WAS (2)	QNAYSYPLT (53)	GYFTTGFL (72)	INPYNDGT (5)	ARLDYGNAMDY (110)
20	113G12F5E6	QSLFNSGNQKNY (1)	WAS (2)	QNAFYPPCT (54)	DFSLTKYG (73)	IWTGGNT (91)	ARNGYYGNAMDY (111)
21	116A8B7	QSLFNSGNQKNY (35)	WAS (2)	QNAYSYPLT (53)	GYFTTGFL (72)	INPYNDGT (5)	GRLDYGNAMDY (112)
22	105F7G12	QSLFNSGNQKNY (1)	WAS (2)	QNAFYPPCT (54)	DFSLTKYG (73)	IWTGGNT (91)	ARNGYYGNAMDY (111)
23	84F9E12	QSVFNSGNQKNY (38)	WAS (2)	QNDYFYPLT (55)	GYSTISGYF (74)	ISYDGSN (92)	ASFRFFAY (113)
24	103F4D4	QSLFNSGNQKNY (33)	WAS (2)	QNAFYPPFT (56)	GYTFPTYS (63)	INPSTIYT (82)	AREGYGRGNAMDY (100)
25	110C12B6	QSLFNSGNQKNY (35)	WAS (2)	QNAYSYPLT (53)	GYFTTGFL (72)	INPYNDGT (5)	GRLDYGNAMDY (112)
26	85H12E8	QSLFNSGNQKNY (31)	WAS (2)	QNAFYPPFT (56)	GFSLSNYG (75)	IWAGGST (93)	ARHGYGKGNAMDN (114)
27	103H2B4	QSLFNSGNQKNY (1)	WAS (2)	QNNYFYPLT (57)	GYSTNTFL (76)	INPTNGRT (94)	ARIYYGNISMDY (115)
28	103F6D3	QSLFNSGNQKNY (33)	WAS (2)	QNAFYPPFT (56)	GYTFPTYS (63)	INPNTIYT (95)	AREGYGRGNAMDY (100)

29	113E12F7	QSLFNSGNQKNY (37)	WAS (2)	QNNIYIPLA (58)	GFSLSYG (67)	IWAGGST (87)	ARSLYGNISFDH (116)
30	120B7B2	QSLFNSGNQKNY (1)	WAS (2)	QNGYFFPT (3)	GYFTGYI (4)	INPYNDGT (5)	ARAYFGNSFAY (6)
31	111B12D11	QSLFNSGNQKNY (35)	WAS (2)	QNNIYIPLA (58)	GFSLTSYG (60)	IWAGGST (87)	ARSLYGNISFDH (116)
32	111E7E2	QSLFNSGNQKNY (37)	WAS (2)	QNNIYIPLA (58)	GFSLTSYG (60)	IWAGGST (87)	ARSLYGNISFDH (116)
33	100F4G12	QSLFNSGNQKNY (31)	WAS (2)	QNAIYIPLT (53)	GYFTGFL (72)	INPYNDGT (5)	ARLDYGNAMDY (110)

Table A': CDR combinations of tested antibodies (Kabat numbering)

Comb No.	Antibody	CDRL1 (SEQ ID NO:)	CDRL2 (SEQ ID NO:)	CDRL3 (SEQ ID NO:)	CDRH1 (SEQ ID NO:)	CDRH2 (SEQ ID NO:)	CDRH3 (SEQ ID NO:)
1	64G11B4	KSSQSLFNSGNQKNYLT (208)	WASTRES (227)	QNDYFYFPT (42)	NYLLE (234)	EINPNGGSGNYNEKFKG (255)	IYYGNSFAY (281)
2	65G8B8	KSSQSLFNSGNQKNYLT (209)	WASTRES (227)	QNVYIYFPT (43)	SYGVS (235)	VIWGDGNTIYHSALKS (256)	QGLYGHAMDY (282)
3	56E8F10F4	KSSQSLFNSGNQKNYLT (210)	WASTRES (227)	QNDYFYFPT (44)	SFGVN (236)	FISGGNTIHYLDITVKG (257)	LALGNAMDY (283)
4	54A2C4	KSSQSLFNSGNQKNYLA (211)	GASTRES (228)	QNDLYYPWT (45)	TNAMN (237)	RIRSKNNYATYYADSVKD (258)	GAYYGNISKAFDY (284)
5	54A2C4'	KSSQSLFNSGNQKNYLA (211)	GASTRES (228)	QNDLYYPWT (45)	NYLLE (234)	EINPNGGSGNYNEKFKG (255)	IYYGNSFAY (281)
6	54A2C4''	KSSQSLFNSGNQKNYLA (211)	GASTRES (228)	QNDLYYPWT (45)	TYSTH (238)	YINPSTIYTNYNQFKY (259)	EGYGRGNAMDY (285)
7	44F6B11	KSNQSLFNSGNQKNYLT (212)	WASTRES (227)	QNGYSYFPT (46)	NYGMS (239)	TFSYGDGSHNYSDSVKG (260)	FGRGNTMDY (286)
8	15C2B7	KSSQSLFNSGNQKNYLT (210)	WASTRES (227)	QNNYFYFPT (47)	NYGMN (240)	WINANTGEPTYAAEEFKG (261)	LTRGNSFDY (287)
9	20F1E10	KSSQSLFNSGNQKNYLT (213)	WASTRES (227)	QNVYSYFPT (48)	KYGMN (241)	WISTINTGEPTYAAEEFKG (262)	LVRGNSFDF (288)
10	72C1B6A3	KSSQSLFNSGNQKNYLT (210)	RASSRES (229)	QNDYIYFPT (8)	TYPIE (242)	NFHPYNDDTKYNEKFKG (263)	RAYGYPYAMDY (289)
11	58G2C2	KSSQSLFNSGNQKNYLT (210)	WAFTRRES (230)	QNSYSYFPT (49)	NYLIE (243)	VINPGRSGTNYNEKFKG (264)	TRYGNGAMDY (290)
12	101C4F12	KSSQSLFNSGNQKNYLT (208)	WSSTRDS (231)	QNNFYFPT (50)	SYGVH (244)	VIWAGGSTNYDSALMS (265)	SLYGNISLDS (291)
13	103A10B2	RSSMSLFNSGNQKSYLS (214)	WASTRDS (232)	HNDYIYFPT (51)	SFGVH (245)	VIWAGGSTNYNSALMS (266)	SLYGNISFDY (292)
14	78E8G9G6	RSIQSLFNSGNQKNYLS (215)	WASTRES (227)	QNSYSYFPT (49)	SYGVH (244)	VIWAGGSTNYNSALMS (267)	DRYGGNSLDY (293)
15	4F11E2	RSSQSLFNSGNQKNYLT (216)	WASTRES (227)	QNAYSYFPT (13)	TFGMH (246)	YITSGNSPIYFTDITVKG (268)	SSYYGNISMDY (294)
16	10G7G11	KSSQSLFNSGNQKNYLT (213)	WASTRES (227)	QNAIYFPT (19)	TYGVH (247)	VMLSDGNTVYNSLKS (269)	HKAYGNAMDY (295)
17	12F1F4	KSSQSLFNSGNQKNYLT (213)	WSSTRRES (233)	QNNYFYFPT (52)	NYGVS (248)	VIWGDGNTNYQSALRS (270)	VGRGNAMDH (296)
18	78C10B6G4	KSSQSLFNSGNQKNYLT (210)	RASSRES (229)	QNDYIYFPT (8)	NYGVS (248)	VIRGDGNTNYQSALRS (271)	VGRGNAMDH (296)
19	119G11D9	RSTQSLFNSGNQKNYLT (217)	WASTRES (227)	QNAIYFPT (53)	GFLMH (249)	YINPYNDGTKYSEKFKG (272)	LDYGNAMDY (297)
20	113G12E5E6	KPSQSLFNSGNQKNYLA (218)	WASTRES (227)	QNAIYFPT (54)	KYGVH (250)	VIWGTGNTDYNPALIP (273)	NGYYGNAMDY (298)

21	116A8B7	RSTQSLFNSGNQNRNYLT (219)	WASTRES (227)	QNAYYYPLT (53)	GFLMH (249)	YINPYNDGTKEYSEKFKG (272)	LDYGNAMDY (297)
22	105F7G12	KSSQSLLLNSGNQKNYLA (220)	WASTRES (227)	QNAYFYPCI (54)	KYGVH (250)	VIWTGGNTDYNPALIP (273)	NGYYGNAMDY (298)
23	84E9E12	KSSQSVFNSGNQKNYLT (221)	WASTRES (227)	QNDYYFPLT (55)	SGYEW (251)	YISYDGSNNYNPSLKN (274)	FRFFAY (299)
24	103F4D4	RSSQSLLLNGGNQKNYLT (222)	WASTRES (227)	QNAYFYPT (56)	TYSIH (238)	YINPSTIYTNNQKFKY (259)	EGYGRGNAMDY (285)
25	110C12B6	RSTQSLFNSGNQNRNYLT (219)	WASTRES (227)	QNAYYYPLT (53)	GFLMH (249)	YINPYNDGTKEYSEKFKG (272)	LDYGNAMDY (297)
26	85H12E8	KSSQSLLLNSGNQNRNYLS (223)	WASTRES (227)	QNAYFYPT (56)	NYGVS (248)	VIWAGGNTNNNSALMS (275)	HGYGKGNAMD (300)
27	103H2B4	KSSQSLLLNSGNQKNYLT (210)	WASTRES (227)	QNNYFYPLT (57)	NFLTH (252)	EINPINTGRTYTNEKFKR (276)	IYYGNSMDY (301)
28	103F6D3	RSSQSLLLNGGNQKNYLT (222)	WASTRES (227)	QNAYFYPT (56)	TYSIH (238)	YINPNTIYTNNQKFKY (277)	EGYGRGNAMDY (285)
29	113E12F7	KSSQSLFNSGNQKNYLT (224)	WASTRES (227)	QNNYIYPLA (58)	SYGVH (244)	VIWAGGSTNYDSALMS (265)	SLYGNSFDH (302)
30	120B7B2	KSSQSLLLNSGNQKNYLT (210)	WASTRES (227)	QNGYFFPT (3)	GYIIQ (253)	FINPYNDGTKEYEQFKG (278)	AYFGNSFAY (303)
31	111B12D11	RSSQSLFNSGNQNRNYLT (225)	WASTRES (227)	QNNYIYPLA (58)	SYGVH (244)	VIWAGGSTNYDSTLMS (279)	SLYGNSFDH (302)
32	111E7E2	KSSQSLFNSGNQKNYLT (224)	WASTRES (227)	QNNYIYPLA (58)	SYGAH (254)	VIWAGGSTNYDSALMS (265)	SLYGNSFDH (302)
33	100F4G12	KSTQSLLLNSGNQNRNYLT (226)	WASTRES (227)	QNAYYYPLT (53)	GFLMH (249)	YINPYNDGTKEYSERFKG (280)	LDYGNAMDY (297)

Table B. CDRs of 120B7B2

CDR	Sequence (SEQ ID NO:)	De-Risked Versions (SEQ ID NO:)
CDRL1	QSLNLSGNQKNY (1)	QSLNLSGNQKNY (17) QSLNLSGNQKNY (18)
CDRL2	WAS (2)	
CDRL3	QNGYYFPFT (3)	QNAYYFPFT (19) QEGYYFPFT (20)
CDRH1	GYTFTGYI (4)	
CDRH2	INPYNDGT (5)	INPYNDT (21)
CDRH3	ARAYFGNSFAY (6)	ARAYFGNAFAY (22)

Table C. CDRs of 72C1B6A3

CDR	Sequence (SEQ ID NO:)	De-Risked Versions (SEQ ID NO:)
CDRL1	QSLNLSGNQKNY (1)	QSLNLSGNQKNY (17) QSLNLSGNQKNY (18)
CDRL2	RAS (7)	
CDRL3	QNDYIYPYT (8)	
CDRH1	GYTFTTYP (9)	
CDRH2	FHPYNDDT (10)	
CDRH3	ARRAYGYPYAMDY (11)	

Table D. CDRs of 4F11E2

CDR	Sequence (SEQ ID NO:)	De-Risked Versions (SEQ ID NO:)
CDRL1	QSLNLSGNRKNY (12)	QSLNLSGNRKNY (23) QSLNLSGNRKNY (24)
CDRL2	WAS (2)	
CDRL3	QNAYSYPFT (13)	
CDRH1	GFTFSTFG (14)	
CDRH2	ITSGNSPI (15)	ITSGSPI (25) ITSGSPI (26)
CDRH3	ARSSYYGNSMDY (16)	ARSSYYGQSMY (27) ARSSYYGESMDY (28) ARSSYYGNAAMDY (29)

Table B'. CDRs of 120B7B2 (Kabat numbering)

CDR	Sequence (SEQ ID NO:)	De-Risked Versions (SEQ ID NO:)
CDRL1	KSSQSLNLSGNQKNYLT (210)	KSSQSLNLSGNQKNYLT (304) KSSQSLNLSGNQKNYLT (305)
CDRL2	WASTRES (227)	
CDRL3	QNGYYFPFT (3)	QNAYYFPFT (19) QEGYYFPFT (20)

CDRH1	GYIIQ (253)	
CDRH2	FINPYNDGTYNEQFKG (278)	FINPYND <u>D</u> TKYNEQFKG (306)
CDRH3	AYFGNSFAY (303)	AYFGN <u>A</u> FAY (307)

Table C'. CDRs of 72C1B6A3 (Kabat numbering)

CDR	Sequence (SEQ ID NO:)	De-Risked Versions (SEQ ID NO:)
CDRL1	KSSQSLLNSGNQKNYLT (210)	KSSQSLLN <u>A</u> GNQKNYLT (304) KSSQSLL <u>E</u> SGNQKNYLT (305)
CDRL2	RASSRES (229)	
CDRL3	QNDYIYPYT (8)	
CDRH1	TYPIE (242)	
CDRH2	NFHPYNDDTKYNEKFKG (263)	
CDRH3	RAYGYPYAMDY (289)	

Table D'. CDRs of 4F11E2 (Kabat numbering)

CDR	Sequence (SEQ ID NO:)	De-Risked Versions (SEQ ID NO:)
CDRL1	RSSQSLLNSGNRKNYLT (216)	RSSQSLL <u>E</u> SGNRKNYLT (308) RSSQSLLN <u>A</u> GNRKNYLT (309)
CDRL2	WASTRES (227)	
CDRL3	QNAYSYPFT (13)	
CDRH1	TFGMH (246)	
CDRH2	YITSGNSPIYFTDTVKG (268)	YITSG <u>Q</u> SPIYFTDTVKG (310) YITSG <u>E</u> SPIYFTDTVKG (311)
CDRH3	SSYYGNSMDY (294)	SSYYG <u>Q</u> SMDY (312) SSYYG <u>E</u> SMDY (313) SSYYGN <u>A</u> MDY (314)

[0083] The antibodies that contained these CDR regions, whether mouse, humanized or chimeric, had potent claudin 18.2 binding and inhibitory activities. As shown in Examples 11 and 12, certain residues within the CDR can be modified to retain or improve the property or reduce their potential to have post-translational modifications (PTMs). Such modified CDR can be referred to as affinity matured or de-risked CDRs.

[0084] Non-limiting examples of de-risked CDRs are provided in **Tables B-D and B'-D'**, in the third columns. Affinity matured ones can include those having one, two or three amino acid addition, deletion and/or substitutions. In some embodiments, the substitutions can be conservative substitutions.

[0085] A “conservative amino acid substitution” is one in which the 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, including 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), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Thus, a nonessential amino acid residue in an immunoglobulin polypeptide is preferably replaced with another amino acid residue from the same side chain family. In another embodiment, a string of amino acids can be replaced with a structurally similar string that differs in order and/or composition of side chain family members.

[0086] Non-limiting examples of conservative amino acid substitutions are provided in the table below, where a similarity score of 0 or higher indicates conservative substitution between the two amino acids.

Table E. Amino Acid Similarity Matrix

	C	G	P	S	A	T	D	E	N	Q	H	K	R	V	M	I	L	F	Y	W
W	-8	-7	-6	-2	-6	-5	-7	-7	-4	-5	-3	-3	2	-6	-4	-5	-2	0	0	17
Y	0	-5	-5	-3	-3	-3	-4	-4	-2	-4	0	-4	-5	-2	-2	-1	-1	7	10	
F	-4	-5	-5	-3	-4	-3	-6	-5	-4	-5	-2	-5	-4	-1	0	1	2	9		
L	-6	-4	-3	-3	-2	-2	-4	-3	-3	-2	-2	-3	-3	2	4	2	6			
I	-2	-3	-2	-1	-1	0	-2	-2	-2	-2	-2	-2	-2	4	2	5				
M	-5	-3	-2	-2	-1	-1	-3	-2	0	-1	-2	0	0	2	6					
V	-2	-1	-1	-1	0	0	-2	-2	-2	-2	-2	-2	-2	4						
R	-4	-3	0	0	-2	-1	-1	-1	0	1	2	3	6							
K	-5	-2	-1	0	-1	0	0	0	1	1	0	5								
H	-3	-2	0	-1	-1	-1	1	1	2	3	6									
Q	-5	-1	0	-1	0	-1	2	2	1	4										
N	-4	0	-1	1	0	0	2	1	2											
E	-5	0	-1	0	0	0	3	4												
D	-5	1	-1	0	0	0	4													
T	-2	0	0	1	1	3														
A	-2	1	1	1	2															
S	0	1	1	1																
P	-3	-1	6																	
G	-3	5																		
C	12																			

Table F. Conservative Amino Acid Substitutions

For Amino Acid	Substitution With
Alanine	D-Ala, Gly, Aib, β -Ala, L-Cys, D-Cys
Arginine	D-Arg, Lys, D-Lys, Orn D-Orn
Asparagine	D-Asn, Asp, D-Asp, Glu, D-Glu Gln, D-Gln
Aspartic Acid	D-Asp, D-Asn, Asn, Glu, D-Glu, Gln, D-Gln
Cysteine	D-Cys, S-Me-Cys, Met, D-Met, Thr, D-Thr, L-Ser, D-Ser
Glutamine	D-Gln, Asn, D-Asn, Glu, D-Glu, Asp, D-Asp
Glutamic Acid	D-Glu, D-Asp, Asp, Asn, D-Asn, Gln, D-Gln
Glycine	Ala, D-Ala, Pro, D-Pro, Aib, β -Ala
Isoleucine	D-Ile, Val, D-Val, Leu, D-Leu, Met, D-Met
Leucine	Val, D-Val, Met, D-Met, D-Ile, D-Leu, Ile
Lysine	D-Lys, Arg, D-Arg, Orn, D-Orn
Methionine	D-Met, S-Me-Cys, Ile, D-Ile, Leu, D-Leu, Val, D-Val
Phenylalanine	D-Phe, Tyr, D-Tyr, His, D-His, Trp, D-Trp
Proline	D-Pro
Serine	D-Ser, Thr, D-Thr, allo-Thr, L-Cys, D-Cys
Threonine	D-Thr, Ser, D-Ser, allo-Thr, Met, D-Met, Val, D-Val
Tyrosine	D-Tyr, Phe, D-Phe, His, D-His, Trp, D-Trp
Valine	D-Val, Leu, D-Leu, Ile, D-Ile, Met, D-Met

[0087] In one embodiment, therefore, provided is an antibody or fragment thereof having binding specificity to a wild-type human claudin 18.2 (CLDN18.2) protein, wherein the antibody or fragment thereof comprises a light chain variable region comprising light chain complementarity determining regions CDRL1, CDRL2, and CDRL3 and a heavy chain variable region comprising heavy chain complementarity determining regions CDRH1, CDRH2, and CDRH3, and wherein the CDRL1, CDRL2, CDRL3, CDRH1, CDRH2, and CDRH3 are selected from combinations 1-33 of **Table A or Table A'** or each of the combinations 1-33 in which one or more of the CDRL1, CDRL2, CDRL3, CDRH1, CDRH2, and CDRH3 each includes one, two, or three amino acid addition, deletion, conservative amino acid substitution or the combinations thereof.

[0088] In some embodiments, an anti-CLDN18.2 antibody or fragment is provided that includes CDRL1, CDRL2, CDRL3, CDRH1, CDRH2, and CDRH3, each of which is selected from Table A or Tables B-D. For instance, provided is an antibody or fragment thereof

having binding specificity to a wild-type human claudin 18.2 (CLDN18.2) protein, wherein the antibody or fragment thereof comprises a light chain variable region comprising light chain complementarity determining regions CDRL1, CDRL2, and CDRL3 and a heavy chain variable region comprising heavy chain complementarity determining regions CDRH1, CDRH2, and CDRH3, and wherein: the CDRL1 comprises an amino acid sequence selected from the group of SEQ ID NO:1, 12 and 31-38, or comprises an amino acid sequence derived anyone of SEQ ID NO:1, 12 and 31-38 by one, two, or three amino acid addition, deletion, amino acid substitution; the CDRL2 comprises an amino acid sequence selected from the group of SEQ ID NO:2, 7 and 39-41, or comprises an amino acid sequence derived anyone of SEQ ID NO:2, 7 and 39-41 by an amino acid addition, deletion, amino acid substitution; the CDRL3 comprises an amino acid sequence selected from the group of SEQ ID NO:3, 8, 13, 19 and 42-58, or comprises an amino acid sequence derived anyone of SEQ ID NO: 3, 8, 13, 19 and 42-58 by one, two, or three amino acid addition, deletion, amino acid substitution; the CDRH1 comprises an amino acid sequence selected from the group of SEQ ID NO:4, 9, 14 and 59-76, or comprises an amino acid sequence derived anyone of SEQ ID NO:4, 9, 14 and 59-76 by one, two, or three amino acid addition, deletion, amino acid substitution; the CDRH2 comprises an amino acid sequence selected from the group of SEQ ID NO:5, 10, 15 and 77-95, or comprises an amino acid sequence derived anyone of SEQ ID NO:5, 10, 15 and 77-95 by one, two, or three amino acid addition, deletion, amino acid substitution; and the CDRH3 comprises an amino acid sequence selected from the group of SEQ ID NO:6, 11, 16 and 96-116, or comprises an amino acid sequence derived anyone of SEQ ID NO:6, 11, 16 and 96-116 by one, two, or three amino acid addition, deletion, amino acid substitution.

[0089] In some embodiments, the CDRL1 comprises an amino acid sequence selected from the group of SEQ ID NO:1, 12, 17-18, 23-24 and 31-38; the CDRL2 comprises an amino acid sequence selected from the group of SEQ ID NO:2, 7 and 39-41; the CDRL3 comprises an amino acid sequence selected from the group of SEQ ID NO:3, 8, 13, 19-20 and 42-58; the CDRH1 comprises an amino acid sequence selected from the group of SEQ ID NO:4, 9, 14 and 59-76; the CDRH2 comprises an amino acid sequence selected from the group of SEQ ID NO:5, 10, 15, 21, 25-26 and 77-95; and the CDRH3 comprises an amino acid sequence selected from the group of SEQ ID NO:6, 11, 16, 22, 27-29 and 96-116.

[0090] In some embodiments, an anti-CLDN18.2 antibody or fragment is provided that includes CDRL1, CDRL2, CDRL3, CDRH1, CDRH2, and CDRH3, each of which is selected

from Table A' or Tables B'-D'. For instance, provided is an antibody or fragment thereof having binding specificity to a wild-type human claudin 18.2 (CLDN18.2) protein, wherein the antibody or fragment thereof comprises a light chain variable region comprising light chain complementarity determining regions CDRL1, CDRL2, and CDRL3 and a heavy chain variable region comprising heavy chain complementarity determining regions CDRH1, CDRH2, and CDRH3, and wherein: the CDRL1 comprises an amino acid sequence selected from the group of SEQ ID NO:208-226, or comprises an amino acid sequence derived anyone of SEQ ID NO:208-226 by one, two, or three amino acid addition, deletion, amino acid substitution; the CDRL2 comprises an amino acid sequence selected from the group of SEQ ID NO:227-233, or comprises an amino acid sequence derived anyone of SEQ ID NO:227-233 by an amino acid addition, deletion, amino acid substitution; the CDRL3 comprises an amino acid sequence selected from the group of SEQ ID NO:3, 8, 13, 19 and 42-58, or comprises an amino acid sequence derived anyone of SEQ ID NO: 3, 8, 13, 19 and 42-58 by one, two, or three amino acid addition, deletion, amino acid substitution; the CDRH1 comprises an amino acid sequence selected from the group of SEQ ID NO:234-254, or comprises an amino acid sequence derived anyone of SEQ ID NO:234-254 by one, two, or three amino acid addition, deletion, amino acid substitution; the CDRH2 comprises an amino acid sequence selected from the group of SEQ ID NO:255-280, or comprises an amino acid sequence derived anyone of SEQ ID NO:255-280 by one, two, or three amino acid addition, deletion, amino acid substitution; and the CDRH3 comprises an amino acid sequence selected from the group of SEQ ID NO:281-303, or comprises an amino acid sequence derived anyone of SEQ ID NO:281-303 by one, two, or three amino acid addition, deletion, amino acid substitution.

[0091] In some embodiments, the CDRL1 comprises an amino acid sequence selected from the group of SEQ ID NO:208-226, 304-305 and 308-309; the CDRL2 comprises an amino acid sequence selected from the group of SEQ ID NO:227-233; the CDRL3 comprises an amino acid sequence selected from the group of SEQ ID NO:3, 8, 13, 19, 20 and 42-58; the CDRH1 comprises an amino acid sequence selected from the group of SEQ ID NO:234-254; the CDRH2 comprises an amino acid sequence selected from the group of SEQ ID NO:255-280, 306, 310 and 311; and the CDRH3 comprises an amino acid sequence selected from the group of SEQ ID NO:281-303, 307, and 312-314.

[0092] The antibody 120B7B2 has been demonstrated to be potent inhibitor of claudin 18.2. Its CDR sequences, along with a few de-risked versions, are provided in Table B. In one embodiment, the present disclosure provides an antibody or fragment thereof having binding specificity to a wild-type human claudin 18.2 (CLDN18.2) protein, wherein the antibody or fragment thereof comprises a light chain variable region comprising light chain complementarity determining regions CDRL1, CDRL2, and CDRL3 and a heavy chain variable region comprising heavy chain complementarity determining regions CDRH1, CDRH2, and CDRH3, and wherein: the CDRL1 comprises the amino acid sequence of QSLNLSGNQKNY (SEQ ID NO:1), QSLNLSGNQKNY (SEQ ID NO:17) or QSLLESNLSGNQKNY (SEQ ID NO:18) or an amino acid sequence having one, two or three amino acid substitution from SEQ ID NO:1, 17 or 18, the CDRL2 comprises the amino acid sequence of WAS (SEQ ID NO:2) or an amino acid sequence having one or two amino acid substitution from SEQ ID NO:2, the CDRL3 comprises the amino acid sequence of CQNGYYFPFT (SEQ ID NO:3), QNAYYYFPFT (SEQ ID NO:19) or QEGYYFPFT (SEQ ID NO:20) or an amino acid sequence having one, two or three amino acid substitution from SEQ ID NO:3, 19 or 20, the CDRH1 comprises the amino acid sequence of GYTFTGYI (SEQ ID NO:4) or an amino acid sequence having one, two or three amino acid substitution from SEQ ID NO:4, the CDRH2 comprises the amino acid sequence of INPYNDGT (SEQ ID NO:5) or INPYNDDT (SEQ ID NO:21) or an amino acid sequence having one, two or three amino acid substitution from SEQ ID NO:5 or 21, and the CDRH3 comprises the amino acid sequence of ARAYFGNSFAY (SEQ ID NO:6) or ARAYFGNAFAY (SEQ ID NO:22) or an amino acid sequence having one, two or three amino acid substitution from SEQ ID NO:6 or 22.

[0093] It is interesting to note (see Table A) that the CDRs from different antibody share great homology. It is then contemplated that each corresponding CDR can be interchanged without greatly impacting the antibody or fragment's binding affinity or activity. Alternatively, each particular amino acid in a CDR can be substituted with another amino acid present in a corresponding CDR from a different antibody. In some embodiments, therefore, the following tables summarize some feasible substitutions based on sequence alignments.

Table G1. Example substitutions of amino acid residues in SEQ ID NO:1

Kabat numbering	Residue	Substitution
27	Q	M

29	L	V
30	L	F
30B	S	G
30E	Q	L or R
30F	K	R
31	N	K or S

Table G2. Example substitutions of amino acid residues in SEQ ID NO:2

Kabat numbering	Residue	Substitution
50	W	G or R
51	A	S
52	S	F

Table G3. Example substitutions of amino acid residues in SEQ ID NO:3

Kabat numbering	Residue	Substitution
89	Q	H
91	G	A, D, N, S or V
92	Y	F or L
93	Y	F, I or S
94	F	Y
96	F	C, L, W, or Y
97	T	A

Table G4. Example substitutions of amino acid residues in SEQ ID NO:4

Kabat numbering	Residue	Substitution
26	G	D
27	Y	F or L
28	T	A or S
29	F	I or L
30	T	I, N, P or S
31	G	K, N, S or T
32	Y	F, G or N
33	I	A, G, L, P, S or Y

Table G5. Example substitutions of amino acid residues in SEQ ID NO:5

Kabat numbering	Residue	Substitution
51	I	F or M
52	N	H, I, L, R, S, T or W
52A	P	A, G, S, T or Y
53	Y	D, G, K, N, S or T
54	N	D, G, R, S or T
55	D	G, R, S or T

56	G	D, R, S, Y or deletion
57	T	E, H, I, N, P or S

Table G6. Example substitutions of amino acid residues in SEQ ID NO:6

Kabat numbering	Residue	Substitution
93	A	G, I, N, P or Y
94	R	A, K, N, S or T
95	A	F, R, T, E, I, L, S, V, H, Q, D, N or deletion
96	Y	A, R, I, G, D, S, L, K or deletion
97	F	A, Y, W, L, S or R
98	G	P
99	N	H or Y
100	S	A, T or V
100A	F	L or M
101	A	D
102	Y	F, H, N or S

[0094] In some embodiments of the antibody or fragment thereof, the CDRL1 comprises the amino acid sequence of SEQ ID NO:1, 17 or 18, the CDRL2 comprises the amino acid sequence of SEQ ID NO:2, the CDRL3 comprises the amino acid sequence of SEQ ID NO:3, 19 or 20, the CDRH1 comprises the amino acid sequence of SEQ ID NO:4, the CDRH2 comprises the amino acid sequence of SEQ ID NO:5 or 21, and the CDRH3 comprises the amino acid sequence of SEQ ID NO:6 or 22.

[0095] Non-limiting examples of a light chain variable region includes an amino acid sequence selected from the group consisting of SEQ ID NO:141, 192-195 and 206-207, or a biological equivalent, e.g., a peptide having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:141, 192-195 and 206-207.

[0096] Non-limiting examples of a heavy chain variable region includes an amino acid sequence selected from the group consisting of SEQ ID NO:171, 188-191 and 205, or a biological equivalent, e.g., a peptide having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:171, 188-191 and 205.

[0097] In some embodiments, the CDRL1 comprises the amino acid sequence of SEQ ID NO:17, the CDRL2 comprises the amino acid sequence of SEQ ID NO:2, the CDRL3 comprises the amino acid sequence of SEQ ID NO:19, the CDRH1 comprises the amino acid

sequence of SEQ ID NO:4, the CDRH2 comprises the amino acid sequence of SEQ ID NO:21, and the CDRH3 comprises the amino acid sequence of SEQ ID NO:22.

[0098] In some embodiments, the antibody or fragment thereof include a light chain variable region comprising an amino acid sequence of SEQ ID NO:206 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:205, or their biological equivalents thereof.

[0099] Tables A'-D' provide the CDR sequences according to Kabat numbering. It is apparent to the skilled artisan that the substitutions disclosed above can be readily translated to the CDR according to a different numbering scheme.

[0100] In some embodiments, an antibody or fragment thereof is provided having binding specificity to a wild-type human claudin 18.2 (CLDN18.2) protein. In some embodiments, the antibody or fragment thereof comprises a light chain variable region comprising light chain complementarity determining regions CDRL1, CDRL2, and CDRL3 and a heavy chain variable region comprising heavy chain complementarity determining regions CDRH1, CDRH2, and CDRH3, and wherein: the CDRL1 comprises the amino acid sequence of SEQ ID NO:210, 304 or 305 or an amino acid sequence having one, two or three amino acid substitution from SEQ ID NO:210, 304 or 305, the CDRL2 comprises the amino acid sequence of SEQ ID NO:227 or an amino acid sequence having one or two amino acid substitution from SEQ ID NO:227, the CDRL3 comprises the amino acid sequence of SEQ ID NO:3, 19 or 20 or an amino acid sequence having one, two or three amino acid substitution from SEQ ID NO:3, 19 or 20, the CDRH1 comprises the amino acid sequence of SEQ ID NO:253 or an amino acid sequence having one, two or three amino acid substitution from SEQ ID NO: 253, the CDRH2 comprises the amino acid sequence of SEQ ID NO:278 or 306 or an amino acid sequence having one, two or three amino acid substitution from SEQ ID NO:278 or 306, and the CDRH3 comprises the amino acid sequence of SEQ ID NO:303 or 307 or an amino acid sequence having one, two or three amino acid substitution from SEQ ID NO:303 or 307.

[0101] In some embodiments, the CDRL1 comprises the amino acid sequence of SEQ ID NO:210, 304 or 305, the CDRL2 comprises the amino acid sequence of SEQ ID NO:227, the CDRL3 comprises the amino acid sequence of SEQ ID NO:3, 19 or 20, the CDRH1 comprises the amino acid sequence of SEQ ID NO:253, the CDRH2 comprises the amino

acid sequence of SEQ ID NO:278 or 306, and the CDRH3 comprises the amino acid sequence of SEQ ID NO:303 or 307.

[0102] Non-limiting examples of a light chain variable region includes an amino acid sequence selected from the group consisting of SEQ ID NO:141, 192-195 and 206-207, or a biological equivalent, such as a peptide having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:141, 192-195 and 206-207.

[0103] Non-limiting examples of a heavy chain variable region include an amino acid sequence selected from the group consisting of SEQ ID NO:171, 188-191 and 205, or a biological equivalent, such as a peptide having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:171, 188-191 and 205.

[0104] In some embodiments, the CDRL1 comprises the amino acid sequence of SEQ ID NO:304, the CDRL2 comprises the amino acid sequence of SEQ ID NO:227, the CDRL3 comprises the amino acid sequence of SEQ ID NO:19, the CDRH1 comprises the amino acid sequence of SEQ ID NO:253, the CDRH2 comprises the amino acid sequence of SEQ ID NO:306, and the CDRH3 comprises the amino acid sequence of SEQ ID NO:307. A non-limiting example of the antibody or fragment includes a light chain variable region comprising an amino acid sequence of SEQ ID NO:206 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:205.

[0105] Likewise, 72C1B6A3 has been shown to be a good antibody. In another embodiment, therefore, provided is an antibody or fragment thereof having binding specificity to a wild-type human claudin 18.2 (CLDN18.2) protein, wherein the antibody or fragment thereof comprises a light chain variable region comprising light chain complementarity determining regions CDRL1, CDRL2, and CDRL3 and a heavy chain variable region comprising heavy chain complementarity determining regions CDRH1, CDRH2, and CDRH3, and wherein: the CDRL1 comprises the amino acid sequence of QSLNLSGNQKNY (SEQ ID NO:1), QSLNAGNQKNY (SEQ ID NO:17) or QSLLESGNQKNY (SEQ ID NO:18) or an amino acid sequence having one, two or three amino acid substitution from SEQ ID NO:1, 17 or 18, the CDRL2 comprises the amino acid sequence of RAS (SEQ ID NO:7) or an amino acid sequence having one or two amino acid substitution from SEQ ID NO:7, the CDRL3 comprises the amino acid sequence of QNDYIYPYT (SEQ ID NO:8) or an amino acid sequence having one, two or three amino acid substitution from SEQ ID NO:8, the CDRH1

comprises the amino acid sequence of GYTFTTYP (SEQ ID NO:9) or an amino acid sequence having one, two or three amino acid substitution from SEQ ID NO:9, the CDRH2 comprises the amino acid sequence of FHPYNDDT (SEQ ID NO:10) or an amino acid sequence having one, two or three amino acid substitution from SEQ ID NO:10, and the CDRH3 comprises the amino acid sequence of ARRAYGYPYAMDY (SEQ ID NO:11) or an amino acid sequence having one, two or three amino acid substitution from SEQ ID NO:11.

[0106] Likewise, each particular amino acid in a CDR can be substituted with another amino acid present in a corresponding CDR from a different antibody. In some embodiments, therefore, the following tables summarize some feasible substitutions based on sequence alignments.

Table H1. Example substitutions of amino acid residues in SEQ ID NO:1

Kabat numbering	Residue	Substitution
27	Q	M
29	L	V
30	L	F
30B	S	G
30E	Q	L or R
30F	K	R
31	N	K or S

Table H2. Example substitutions of amino acid residues in SEQ ID NO:7

Kabat numbering	Residue	Substitution
50	R	G or W
51	A	S
52	S	F

Table H3. Example substitutions of amino acid residues in SEQ ID NO:8

Kabat numbering	Residue	Substitution
89	Q	H
91	D	A, G, N, S or V
92	Y	F or L
93	I	F, Y or S
94	Y	F
96	Y	C, L, W, or F
97	T	A

Table H4. Example substitutions of amino acid residues in SEQ ID NO:9

Kabat numbering	Residue	Substitution
26	G	D
27	Y	F or L
28	T	A or S
29	F	I or L
30	T	I, N, P or S
31	T	K, N, S or G
32	Y	F, G or N
33	P	A, G, L, I, S or Y

Table H5. Example substitutions of amino acid residues in SEQ ID NO:10

Kabat numbering	Residue	Substitution
51	F	I or M
52	H	N, I, L, R, S, T or W
52A	P	A, G, S, T or Y
53	Y	D, G, K, N, S or T
54	N	D, G, R, S or T
55	D	G, R, S or T
56	D	G, R, S, Y or deletion
57	T	E, H, I, N, P or S

Table H6. Example substitutions of amino acid residues in SEQ ID NO:11

Kabat numbering	Residue	Substitution
93	A	G, I, N, P or Y
94	R	A, K, N, S or T
95	R	F, A, T, E, I, L, S, V, H, Q, D, N or deletion
96	A	Y, R, I, G, D, S, L, K or deletion
97	Y	A, F, W, L, S or R
98	G	P
99	Y	H or N
100	P	S, A, T or V
100A	Y	F, L or M
101	A	D
102	M	Y, F, H, N or S

[0107] In some embodiments of the antibody or fragment thereof of 23, the CDRL1 comprises the amino acid sequence of SEQ ID NO:1, 17 or 18, the CDRL2 comprises the amino acid sequence of SEQ ID NO:7, the CDRL3 comprises the amino acid sequence of SEQ ID NO:8, the CDRH1 comprises the amino acid sequence of SEQ ID NO:9, the CDRH2

comprises the amino acid sequence of SEQ ID NO:10, and the CDRH3 comprises the amino acid sequence of SEQ ID NO:11.

[0108] Non-limiting examples of a light chain variable region includes an amino acid sequence selected from the group consisting of SEQ ID NO:124, 185-187 and 203-204, or a biological equivalents, e.g., a peptide having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:124, 185-187 and 203-204.

[0109] Non-limiting examples of a heavy chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NO:153 and 181-184, or a biological equivalent, e.g., a peptide having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:153 and 181-184.

[0110] In some embodiments, in the antibody or fragment thereof, the CDRL1 comprises the amino acid sequence of SEQ ID NO:17, the CDRL2 comprises the amino acid sequence of SEQ ID NO:7, the CDRL3 comprises the amino acid sequence of SEQ ID NO:8, the CDRH1 comprises the amino acid sequence of SEQ ID NO:9, the CDRH2 comprises the amino acid sequence of SEQ ID NO:10, and the CDRH3 comprises the amino acid sequence of SEQ ID NO:11.

[0111] The antibody or fragment thereof, in some embodiments, includes a light chain variable region comprising an amino acid sequence of SEQ ID NO:203 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:181, or their corresponding biological equivalents.

[0112] Tables A'-D' provide the CDR sequences according to Kabat numbering. It is apparent to the skilled artisan that the substitutions disclosed above can be readily translated to the CDR according to a different numbering scheme.

[0113] In some embodiments, provided is an antibody or fragment thereof having binding specificity to a wild-type human claudin 18.2 (CLDN18.2) protein, wherein the antibody or fragment thereof comprises a light chain variable region comprising light chain complementarity determining regions CDRL1, CDRL2, and CDRL3 and a heavy chain variable region comprising heavy chain complementarity determining regions CDRH1, CDRH2, and CDRH3, and wherein: the CDRL1 comprises the amino acid sequence of SEQ ID NO:210, 304 or 305 or an amino acid sequence having one, two or three amino acid

substitution from SEQ ID NO:210, 304 or 305, the CDRL2 comprises the amino acid sequence of SEQ ID NO:229 or an amino acid sequence having one or two amino acid substitution from SEQ ID NO:229, the CDRL3 comprises the amino acid sequence of SEQ ID NO:8 or an amino acid sequence having one, two or three amino acid substitution from SEQ ID NO:8, the CDRH1 comprises the amino acid sequence of SEQ ID NO:242 or an amino acid sequence having one, two or three amino acid substitution from SEQ ID NO:242, the CDRH2 comprises the amino acid sequence of SEQ ID NO:263 or an amino acid sequence having one, two or three amino acid substitution from SEQ ID NO:263, and the CDRH3 comprises the amino acid sequence of SEQ ID NO:289 or an amino acid sequence having one, two or three amino acid substitution from SEQ ID NO:289.

[0114] In some embodiments, the CDRL1 comprises the amino acid sequence of SEQ ID NO:210, 304 or 305, the CDRL2 comprises the amino acid sequence of SEQ ID NO:229, the CDRL3 comprises the amino acid sequence of SEQ ID NO:8, the CDRH1 comprises the amino acid sequence of SEQ ID NO:242, the CDRH2 comprises the amino acid sequence of SEQ ID NO:263, and the CDRH3 comprises the amino acid sequence of SEQ ID NO:289.

[0115] Non-limiting examples of a light chain variable region include an amino acid sequence selected from the group consisting of SEQ ID NO:124, 185-187 and 203-204, or a biological equivalent, such as a peptide having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:124, 185-187 and 203-204.

[0116] Non-limiting examples of a heavy chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NO:153 and 181-184, or a biological equivalent, such as a peptide having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:153 and 181-184.

[0117] In some embodiments, the CDRL1 comprises the amino acid sequence of SEQ ID NO:304, the CDRL2 comprises the amino acid sequence of SEQ ID NO:229, the CDRL3 comprises the amino acid sequence of SEQ ID NO:8, the CDRH1 comprises the amino acid sequence of SEQ ID NO:242, the CDRH2 comprises the amino acid sequence of SEQ ID NO:263, and the CDRH3 comprises the amino acid sequence of SEQ ID NO:289. A non-limiting example antibody or fragment thereof includes a light chain variable region comprising an amino acid sequence of SEQ ID NO:203 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:181.

[0118] Also, 4F11E2 has been shown to be a good antibody. In another embodiment, therefore, provided is an antibody or fragment thereof having binding specificity to a wild-type human claudin 18.2 (CLDN18.2) protein, wherein the antibody or fragment thereof comprises a light chain variable region comprising light chain complementarity determining regions CDRL1, CDRL2, and CDRL3 and a heavy chain variable region comprising heavy chain complementarity determining regions CDRH1, CDRH2, and CDRH3, and wherein: the CDRL1 comprises the amino acid sequence of QSLNLSGNRKNY (SEQ ID NO:12), QSLLESNGNRKNY (SEQ ID NO:23) or QSLNAGNRKNY (SEQ ID NO:24) or an amino acid sequence having one, two or three amino acid substitution from SEQ ID NO:12, 23 or 24, the CDRL2 comprises the amino acid sequence of WAS (SEQ ID NO:2) or an amino acid sequence having one or two amino acid substitution from SEQ ID NO:2, the CDRL3 comprises the amino acid sequence of QNAYSYPFT (SEQ ID NO:13) or an amino acid sequence having one, two or three amino acid substitution from SEQ ID NO:13, the CDRH1 comprises the amino acid sequence of GFTFSTFG (SEQ ID NO:14) or an amino acid sequence having one, two or three amino acid substitution from SEQ ID NO:14, the CDRH2 comprises the amino acid sequence of ITSGNSPI (SEQ ID NO:15), ITSGQSPI (SEQ ID NO:25), or ITSGESPI (SEQ ID NO:26) or an amino acid sequence having one, two or three amino acid substitution from SEQ ID NO:15, 25 or 26, and the CDRH3 comprises the amino acid sequence of ARSSYYGNSMDY (SEQ ID NO:16), ARSSYYGQSMDY (SEQ ID NO:27), ARSSYYGESMDY (SEQ ID NO:28), or ARSSYYGNAMDY (SEQ ID NO:29) or an amino acid sequence having one, two or three amino acid substitution from SEQ ID NO:16, 27, 28 or 29.

[0119] Likewise, each particular amino acid in a CDR can be substituted with another amino acid present in a corresponding CDR from a different antibody. In some embodiments, therefore, the following tables summarize some feasible substitutions based on sequence alignments.

Table II. Example substitutions of amino acid residues in SEQ ID NO:12

Kabat numbering	Residue	Substitution
27	Q	M
29	L	V
30	L	F
30B	S	G
30E	R	L or Q

30F	K	R
31	N	K or S

Table I2. Example substitutions of amino acid residues in SEQ ID NO:2

Kabat numbering	Residue	Substitution
50	W	G or R
51	A	S
52	S	F

Table I3. Example substitutions of amino acid residues in SEQ ID NO:13

Kabat numbering	Residue	Substitution
89	Q	H
91	A	G, D, N, S or V
92	Y	F or L
93	S	F, I or Y
94	Y	F
96	F	C, L, W, or Y
97	T	A

Table I4. Example substitutions of amino acid residues in SEQ ID NO:14

Kabat numbering	Residue	Substitution
26	G	D
27	F	Y or L
28	T	A or S
29	F	I or L
30	S	I, N, P or T
31	T	K, N, S or G
32	F	Y, G or N
33	G	A, I, L, P, S or Y

Table I5. Example substitutions of amino acid residues in SEQ ID NO:15

Kabat numbering	Residue	Substitution
51	I	F or M
52	T	H, I, L, R, S, N or W
52A	S	A, G, P, T or Y

53	G	D, Y, K, N, S or T
54	N	D, G, R, S or T
55	S	G, R, D or T
56	P	G, D, R, S, Y or deletion
57	I	E, H, T, N, P or S

Table 16. Example substitutions of amino acid residues in SEQ ID NO:16

Kabat numbering	Residue	Substitution
93	A	G, I, N, P or Y
94	R	A, K, N, S or T
95	S	F, R, T, E, I, L, A, V, H, Q, D, N or deletion
96	S	A, R, I, G, D, Y, L, K or deletion
97	Y	F, A, Y, W, L, S or R
98	Y	G or P
99	N	H or Y
100	S	A, T or V
100A	M	L or F
101	D	A
102	Y	F, H, N or S

[0120] In some embodiments, in the antibody or fragment thereof, the CDRL1 comprises the amino acid sequence of SEQ ID NO:12, 23 or 24, the CDRL2 comprises the amino acid sequence of SEQ ID NO:2, the CDRL3 comprises the amino acid sequence of SEQ ID NO:13, the CDRH1 comprises the amino acid sequence of SEQ ID NO:14, the CDRH2 comprises the amino acid sequence of SEQ ID NO:15, 25 or 26, and the CDRH3 comprises the amino acid sequence of SEQ ID NO:16, 27, 28 or 29.

[0121] Non-limiting examples of a light chain variable region includes an amino acid sequence selected from the group consisting of SEQ ID NO:129, 178-180 and 201-202, or their biological equivalents, e.g., a peptide having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:129, 178-180 and 201-202.

[0122] Non-limiting examples of a heavy chain variable region includes an amino acid sequence selected from the group consisting of SEQ ID NO:159, 175-177 and 196-200, or their biological equivalents, e.g., a peptide having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:159, 175-177 and 196-200.

[0123] In some embodiments, the CDRL1 comprises the amino acid sequence of SEQ ID NO:24, the CDRL2 comprises the amino acid sequence of SEQ ID NO:2, the CDRL3 comprises the amino acid sequence of SEQ ID NO:13, the CDRH1 comprises the amino acid sequence of SEQ ID NO:14, the CDRH2 comprises the amino acid sequence of SEQ ID NO:26, and the CDRH3 comprises the amino acid sequence of SEQ ID NO:16.

[0124] In some embodiments, the antibody or fragment thereof includes a light chain variable region comprising an amino acid sequence of SEQ ID NO:202 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:197, or their corresponding biological equivalents.

[0125] Tables A'-D' provide the CDR sequences according to Kabat numbering. It is apparent to the skilled artisan that the substitutions disclosed above can be readily translated to the CDR according to a different numbering scheme.

[0126] Some embodiments of the present disclosure provide an antibody or fragment thereof having binding specificity to a wild-type human claudin 18.2 (CLDN18.2) protein, wherein the antibody or fragment thereof comprises a light chain variable region comprising light chain complementarity determining regions CDRL1, CDRL2, and CDRL3 and a heavy chain variable region comprising heavy chain complementarity determining regions CDRH1, CDRH2, and CDRH3, and wherein: the CDRL1 comprises the amino acid sequence of SEQ ID NO:216, 308 or 309 or an amino acid sequence having one, two or three amino acid substitution from SEQ ID NO:216, 308 or 309, the CDRL2 comprises the amino acid sequence of SEQ ID NO:227 or an amino acid sequence having one or two amino acid substitution from SEQ ID NO:227, the CDRL3 comprises the amino acid sequence of SEQ ID NO:13 or an amino acid sequence having one, two or three amino acid substitution from SEQ ID NO:13, the CDRH1 comprises the amino acid sequence of SEQ ID NO:246 or an amino acid sequence having one, two or three amino acid substitution from SEQ ID NO:246, the CDRH2 comprises the amino acid sequence of SEQ ID NO:268, 310 or 311 or an amino acid sequence having one, two or three amino acid substitution from SEQ ID NO:268, 310 or 311, and the CDRH3 comprises the amino acid sequence of SEQ ID NO:294, 312, 313 or 314, or an amino acid sequence having one, two or three amino acid substitution from SEQ ID NO:294, 312, 313 or 314.

[0127] In some embodiments, the CDRL1 comprises the amino acid sequence of SEQ ID NO:216, 308 or 309, the CDRL2 comprises the amino acid sequence of SEQ ID NO:227, the CDRL3 comprises the amino acid sequence of SEQ ID NO:13, the CDRH1 comprises the amino acid sequence of SEQ ID NO:246, the CDRH2 comprises the amino acid sequence of SEQ ID NO:268, 310 or 311, and the CDRH3 comprises the amino acid sequence of SEQ ID NO:294, 312, 313 or 314.

[0128] Non-limiting examples of a light chain variable region include an amino acid sequence selected from the group consisting of SEQ ID NO:129, 178-180 and 201-202, or a biological equivalent, such as a peptide having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:129, 178-180 and 201-202.

[0129] Non-limiting examples of a heavy chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NO:159, 175-177 and 196-200, or a biological equivalents, such as a peptide having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:159, 175-177 and 196-200.

[0130] In some embodiments, the CDRL1 comprises the amino acid sequence of SEQ ID NO:309, the CDRL2 comprises the amino acid sequence of SEQ ID NO:227, the CDRL3 comprises the amino acid sequence of SEQ ID NO:13, the CDRH1 comprises the amino acid sequence of SEQ ID NO:246, the CDRH2 comprises the amino acid sequence of SEQ ID NO:311, and the CDRH3 comprises the amino acid sequence of SEQ ID NO:294. A non-limiting example of the antibody or fragment includes a light chain variable region comprising an amino acid sequence of SEQ ID NO:202 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:197.

[0131] In some embodiments, the antibodies are humanized antibodies. Humanized antibodies, as shown in Example 9, can include one or more back mutations to the mouse counterpart. Examples of such back mutations are shown in Table 3. In some embodiments, the antibody or fragment can include one, two, three, four, five or more of the back mutations.

[0132] In some embodiments, the anti-claudin 18.2 antibody of the present disclosure includes a VL of any one of SEQ ID NO: 117-144, 178-180, 185-187, 192-195, 201-202, 203-204 or 206-207, and a VH of any one of SEQ ID NO: 145-174, 175-177, 181-184, 188-191, 196-200, or 205 or their respective biological equivalents. A biological equivalent of a

VH or VL is a sequence that includes the designated amino acids while having an overall 80%, 85%, 90%, 95%, 98% or 99% sequence identity. A biological equivalent of SEQ ID NO:145, therefore, can be a VH that has an overall 80%, 85%, 90%, 95%, 98% or 99% sequence identity to SEQ ID NO:145 but retains the CDRs, and optionally retains one or more, or all of the back-mutations.

[0133] It will also be understood by one of ordinary skill in the art that antibodies as disclosed herein may be modified such that they vary in amino acid sequence from the naturally occurring binding polypeptide from which they were derived. For example, a polypeptide or amino acid sequence derived from a designated protein may be similar, *e.g.*, have a certain percent identity to the starting sequence, *e.g.*, it may be 60%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% identical to the starting sequence.

[0134] In certain embodiments, the antibody comprises an amino acid sequence or one or more moieties not normally associated with an antibody. Exemplary modifications are described in more detail below. For example, an antibody of the disclosure may comprise a flexible linker sequence, or may be modified to add a functional moiety (*e.g.*, PEG, a drug, a toxin, or a label).

[0135] Antibodies, variants, or derivatives thereof of the disclosure include derivatives that are modified, *i.e.*, by the covalent attachment of any type of molecule to the antibody such that covalent attachment does not prevent the antibody from binding to the epitope. For example, but not by way of limitation, the antibodies can be modified, *e.g.*, by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the antibodies may contain one or more non-classical amino acids.

[0136] In some embodiments, the antibodies may be conjugated to therapeutic agents, prodrugs, peptides, proteins, enzymes, viruses, lipids, biological response modifiers, pharmaceutical agents, or PEG.

[0137] The antibodies may be conjugated or fused to a therapeutic agent, which may include detectable labels such as radioactive labels, an immunomodulator, a hormone, an enzyme, an

oligonucleotide, a photoactive therapeutic or diagnostic agent, a cytotoxic agent, which may be a drug or a toxin, an ultrasound enhancing agent, a non-radioactive label, a combination thereof and other such agents known in the art.

[0138] The antibodies can be detectably labeled by coupling it to a chemiluminescent compound. The presence of the chemiluminescent-tagged antigen-binding polypeptide is then determined by detecting the presence of luminescence that arises during the course of a chemical reaction. Examples of particularly useful chemiluminescent labeling compounds are luminol, isoluminol, thionin acridinium ester, imidazole, acridinium salt and oxalate ester.

[0139] The antibodies can also be detectably labeled using fluorescence emitting metals such as ^{152}Eu , or others of the lanthanide series. These metals can be attached to the antibody using such metal chelating groups as diethylenetriaminepentaacetic acid (DTPA) or ethylenediaminetetraacetic acid (EDTA). Techniques for conjugating various moieties to an antibody are well known, *see, e.g.*, Arnon *et al.*, "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in *Monoclonal Antibodies And Cancer Therapy*, Reisfeld *et al.* (eds.), pp. 243-56 (Alan R. Liss, Inc. (1985); Hellstrom *et al.*, "Antibodies For Drug Delivery", in *Controlled Drug Delivery* (2nd Ed.), Robinson *et al.*, (eds.), Marcel Dekker, Inc., pp. 623- 53 (1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in *Monoclonal Antibodies '84: Biological And Clinical Applications*, Pinchera *et al.* (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in *Monoclonal Antibodies For Cancer Detection And Therapy*, Baldwin *et al.* (eds.), Academic Press pp. 303-16 (1985), and Thorpe *et al.*, "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", *Immunol. Rev.* (52:119-58 (1982)).

Bi-functional Molecules

[0140] As a tumor antigen targeting molecule, an antibody or antigen-binding fragment specific to claudin 18.2 can be combined with a second fragment specific to an immune cell to generate a bispecific antibody.

[0141] In some embodiments, the immune cell is selected from the group consisting of a T cell, a B cell, a monocyte, a macrophage, a neutrophil, a dendritic cell, a phagocyte, a natural killer cell, an eosinophil, a basophil, and a mast cell.

[0142] In some embodiment, the second specificity is to CD3, CD47, PD1, PD-L1, LAG3, TIM3, CTLA4, VISTA, CSFR1, A2AR, CD73, CD39, CD40, CEA, HER2, CMET, 4-1BB, OX40, SIRPA CD16, CD28, ICOS, CTLA4, BTLA, TIGIT, HVEM, CD27, VEGFR, or VEGF.

[0143] Different format of bispecific antibodies are also provided. In some embodiments, each of the anti-claudin 18.2 fragment and the second fragment each is independently selected from a Fab fragment, a single-chain variable fragment (scFv), or a single-domain antibody. In some embodiments, the bispecific antibody further includes a Fc fragment.

[0144] Bifunctional molecules that include not just antibody or antigen binding fragment are also provided. As a tumor antigen targeting molecule, an antibody or antigen-binding fragment specific to claudin 18.2, such as those described here, can be combined with an immune cytokine or ligand optionally through a peptide linker. The linked immune cytokines or ligands include, but not limited to, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-10, IL-12, IL-13, IL-15, GM-CSF, TNF- α , CD40L, OX40L, CD27L, CD30L, 4-1BBL, LIGHT and GITRL. Such bi-functional molecules can combine the immune checkpoint blocking effect with tumor site local immune modulation.

Polynucleotides Encoding the Antibodies and Methods of Preparing the Antibodies

[0145] The present disclosure also provides isolated polynucleotides or nucleic acid molecules encoding the antibodies, variants or derivatives thereof of the disclosure. The polynucleotides of the present disclosure may encode the entire heavy and light chain variable regions of the antigen-binding polypeptides, variants or derivatives thereof on the same polynucleotide molecule or on separate polynucleotide molecules. Additionally, the polynucleotides of the present disclosure may encode portions of the heavy and light chain variable regions of the antigen-binding polypeptides, variants or derivatives thereof on the same polynucleotide molecule or on separate polynucleotide molecules.

[0146] Methods of making antibodies are well known in the art and described herein. In certain embodiments, both the variable and constant regions of the antigen-binding

polypeptides of the present disclosure are fully human. Fully human antibodies can be made using techniques described in the art and as described herein. For example, fully human antibodies against a specific antigen can be prepared by administering the antigen to a transgenic animal which has been modified to produce such antibodies in response to antigenic challenge, but whose endogenous loci have been disabled. Exemplary techniques that can be used to make such antibodies are described in U.S. patents: 6,150,584; 6,458,592; 6,420,140 which are incorporated by reference in their entireties.

Treatment Methods

[0147] As described herein, the antibodies, variants or derivatives of the present disclosure may be used in certain treatment and diagnostic methods.

[0148] The present disclosure is further directed to antibody-based therapies which involve administering the antibodies of the disclosure to a patient such as an animal, a mammal, and a human for treating one or more of the disorders or conditions described herein. Therapeutic compounds of the disclosure include, but are not limited to, antibodies of the disclosure (including variants and derivatives thereof as described herein) and nucleic acids or polynucleotides encoding antibodies of the disclosure (including variants and derivatives thereof as described herein).

[0149] The antibodies of the disclosure can also be used to treat or inhibit cancer. As provided above, claudin 18.2 can be overexpressed in tumor cells, in particular gastric, pancreatic, esophageal, ovarian, and lung tumors. Inhibition of claudin 18.2 has been shown to be useful for treating the tumors.

[0150] Accordingly, in some embodiments, provided are methods for treating a cancer in a patient in need thereof. The method, in one embodiment, entails administering to the patient an effective amount of an antibody of the present disclosure. In some embodiments, at least one of the cancer cells (e.g., stromal cells) in the patient over-express claudin 18.2.

[0151] Cellular therapies, such as chimeric antigen receptor (CAR) T-cell therapies, are also provided in the present disclosure. A suitable cell can be used, that is put in contact with an anti-claudin 18.2 antibody of the present disclosure (or alternatively engineered to express an anti-claudin 18.2 antibody of the present disclosure). Upon such contact or engineering, the cell can then be introduced to a cancer patient in need of a treatment. The cancer patient may

have a cancer of any of the types as disclosed herein. The cell (e.g., T cell) can be, for instance, a tumor-infiltrating T lymphocyte, a CD4⁺ T cell, a CD8⁺ T cell, or the combination thereof, without limitation.

[0152] In some embodiments, the cell was isolated from the cancer patient him- or her-self. In some embodiments, the cell was provided by a donor or from a cell bank. When the cell is isolated from the cancer patient, undesired immune reactions can be minimized.

[0153] Non-limiting examples of cancers include bladder cancer, breast cancer, colorectal cancer, endometrial cancer, esophageal cancer, head and neck cancer, kidney cancer, leukemia, liver cancer, lung cancer, lymphoma, melanoma, pancreatic cancer, prostate cancer, and thyroid cancer. In some embodiments, the cancer is one or more of gastric, pancreatic, esophageal, ovarian, and lung cancers.

[0154] Additional diseases or conditions associated with increased cell survival, that may be treated, prevented, diagnosed and/or prognosed with the antibodies or variants, or derivatives thereof of the disclosure include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (*e.g.*, acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (*e.g.*, chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (*e.g.*, Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyo sarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma,

hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma and retinoblastoma.

[0155] A specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the particular antibodies, variant or derivative thereof used, the patient's age, body weight, general health, sex, and diet, and the time of administration, rate of excretion, drug combination, and the severity of the particular disease being treated. Judgment of such factors by medical caregivers is within the ordinary skill in the art. The amount will also depend on the individual patient to be treated, the route of administration, the type of formulation, the characteristics of the compound used, the severity of the disease, and the desired effect. The amount used can be determined by pharmacological and pharmacokinetic principles well known in the art.

[0156] Methods of administration of the antibodies, variants or include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The antigen-binding polypeptides or compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Thus, pharmaceutical compositions containing the antigen-binding polypeptides of the disclosure may be administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, drops or transdermal patch), buccally, or as an oral or nasal spray.

[0157] The term “parenteral” as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intra-articular injection and infusion.

[0158] Administration can be systemic or local. In addition, it may be desirable to introduce the antibodies of the disclosure into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, *e.g.*, by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

[0159] It may be desirable to administer the antigen-binding polypeptides or compositions of the disclosure locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, *e.g.*, in conjunction, with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering a protein, including an antibody, of the disclosure, care must be taken to use materials to which the protein does not absorb.

[0160] The amount of the antibodies of the disclosure which will be effective in the treatment, inhibition and prevention of an inflammatory, immune or malignant disease, disorder or condition can be determined by standard clinical techniques. In addition, *in vitro* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease, disorder or condition, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

[0161] As a general proposition, the dosage administered to a patient of the antigen-binding polypeptides of the present disclosure is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight, between 0.1 mg/kg and 20 mg/kg of the patient's body weight, or 1 mg/kg to 10 mg/kg of the patient's body weight. Generally, human antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage and frequency of administration of antibodies of the disclosure may be reduced by enhancing uptake and tissue penetration (*e.g.*, into the brain) of the antibodies by modifications such as, for example, lipidation.

[0162] In an additional embodiment, the compositions of the disclosure are administered in combination with cytokines. Cytokines that may be administered with the compositions of the disclosure include, but are not limited to, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-10, IL-12, IL-13, IL-15, anti-CD40, CD40L, and TNF- α .

[0163] In additional embodiments, the compositions of the disclosure are administered in combination with other therapeutic or prophylactic regimens, such as, for example, radiation therapy.

Combination Therapies and Antibody-Drug Conjugates

[0164] Combination therapies are also provided, which includes the use of one or more of the anti-claudin 18.2 antibodies or fragments thereof of the present disclosure along with a second anticancer (chemotherapeutic) agent. In some embodiment, the chemotherapeutic agent is conjugated to the antibody or fragment.

[0165] Chemotherapeutic agents may be categorized by their mechanism of action into, for example, the following groups:

- anti-metabolites/anti-cancer agents such as pyrimidine analogs floxuridine, capecitabine, and cytarabine;
- purine analogs, folate antagonists, and related inhibitors;
- antiproliferative/antimitotic agents including natural products such as vinca alkaloid (vinblastine, vincristine) and microtubule such as taxane (paclitaxel, docetaxel), vinblastin, nocodazole, epothilones, vinorelbine (NAVELBINE[®]), and epipodophyllotoxins (etoposide, teniposide);
- DNA damaging agents such as actinomycin, amsacrine, busulfan, carboplatin, chlorambucil, cisplatin, cyclophosphamide (CYTOXAN[®]), dactinomycin, daunorubicin, doxorubicin, epirubicin, ifosfamide, melphalan, merchlorethamine, mitomycin, mitoxantrone, nitrosourea, procarbazine, taxol, taxotere, teniposide, etoposide, and triethylenethiophosphoramide;
- antibiotics such as dactinomycin, daunorubicin, doxorubicin, idarubicin, anthracyclines, mitoxantrone, bleomycins, plicamycin (mithramycin), and mitomycin;
- enzymes such as L-asparaginase which systemically metabolizes L-asparagine and deprives cells which do not have the capacity to synthesize their own asparagine;
- antiplatelet agents;

- antiproliferative/antimitotic alkylating agents such as nitrogen mustards cyclophosphamide and analogs (melphalan, chlorambucil, hexamethylmelamine, and thiotepa), alkyl nitrosoureas (carmustine) and analogs, streptozocin, and triazenes (dacarbazine);
- antiproliferative/antimitotic antimetabolites such as folic acid analogs (methotrexate);
- platinum coordination complexes (cisplatin, oxiloplatinim, and carboplatin), procarbazine, hydroxyurea, mitotane, and aminoglutethimide;
- hormones, hormone analogs (estrogen, tamoxifen, goserelin, bicalutamide, and nilutamide), and aromatase inhibitors (letrozole and anastrozole);
- anticoagulants such as heparin, synthetic heparin salts, and other inhibitors of thrombin;
- fibrinolytic agents such as tissue plasminogen activator, streptokinase, urokinase, aspirin, dipyridamole, ticlopidine, and clopidogrel;
- antimigratory agents;
- antisecretory agents (breveldin);
- immunosuppressives tacrolimus, sirolimus, azathioprine, and mycophenolate;
- compounds (TNP-470, genistein) and growth factor inhibitors (vascular endothelial growth factor inhibitors and fibroblast growth factor inhibitors);
- angiotensin receptor blockers, nitric oxide donors;
- anti-sense oligonucleotides;
- antibodies such as trastuzumab and rituximab;
- cell cycle inhibitors and differentiation inducers such as tretinoin;
- inhibitors, topoisomerase inhibitors (doxorubicin, daunorubicin, dactinomycin, eniposide, epirubicin, etoposide, idarubicin, irinotecan, mitoxantrone, topotecan, and irinotecan), and corticosteroids (cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisone, and prednisolone);
- growth factor signal transduction kinase inhibitors;
- dysfunction inducers;

- toxins such as Cholera toxin, ricin, Pseudomonas exotoxin, Bordetella pertussis adenylate cyclase toxin, diphtheria toxin, and caspase activators;
- and chromatin.

[0001] Further examples of chemotherapeutic agents include:

- alkylating agents such as thiotepa and cyclophosphamide (CYTOXAN®);
- alkyl sulfonates such as busulfan, improsulfan, and piposulfan;
- aziridines such as benzodopa, carboquone, meturedopa, and uredopa;
- emylerumines and memylamelamines including alfretamine, triemylenemelumine, triethylenephosphoramidate, triethylenethiophosphoramidate, and trimemylolomelumine;
- acetogenins, especially bullatacin and bullatacinone;
- a camptothecin, including synthetic analog topotecan;
- bryostatin;
- callistatin;
- CC-1065, including its adozelesin, carzelesin, and bizelesin synthetic analogs;
- cryptophycins, particularly cryptophycin 1 and cryptophycin 8;
- dolastatin;
- duocarmycin, including the synthetic analogs KW-2189 and CBI-TMI;
- eleutherobin;
- pancratistatin;
- a sarcodictyin;
- spongistatin;
- nitrogen mustards such as chlorambucil, chlornaphazine, cyclophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, and uracil mustard;
- nitrosoureas such as carmustine, chlorozotocin, foremustine, lomustine, nimustine, and ranimustine;
- antibiotics such as the enediyne antibiotics (*e.g.*, calicheamicin, especially calicheamicin gammaII and calicheamicin phiII), dynemicin including dynemicin A,

bisphosphonates such as clodronate, an esperamicin, neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromomophores, aclacinomycins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabycin, carminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin (including morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin, and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, porfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, and zorubicin;

- anti-metabolites such as methotrexate and 5-fluorouracil (5-FU);
- folic acid analogs such as demopterin, methotrexate, pteropterin, and trimetrexate;
- purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, and thioguanine;
- pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, and floxuridine;
- androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiothane, and testolactone;
- anti-adrenals such as aminoglutethimide, mitotane, and trilostane;
- folic acid replinishers such as frolinic acid;
- trichothecenes, especially T-2 toxin, verracurin A, roridin A, and anguidine;
- taxoids such as paclitaxel (TAXOL[®]) and docetaxel (TAXOTERE[®]);
- platinum analogs such as cisplatin and carboplatin;
- aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; hestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elformthine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; leucovorin; lonidamine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; losoxantrone; fluoropyrimidine; folinic acid; podophyllinic acid; 2-ethylhydrazide; procarbazine; polysaccharide-K (PSK); razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid;

triaziquone; 2,2',2''-trichloro-2,2',2''-triethylamine; urethane; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiopeta; chlorambucil; gemcitabine (GEMZAR®); 6-thioguanine; mercaptopurine; methotrexate; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitroxantrone; vancristine; vinorelbine (NAVELBINE®); novantrone; teniposide; edatrexate; daunomycin; aminopterin; xeoloda; ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DFMO); retinoids such as retinoic acid; capecitabine; FOLFIRI (fluorouracil, leucovorin, and irinotecan);

- and pharmaceutically acceptable salts, acids, or derivatives of any of the above.

[0002] Also included in the definition of "chemotherapeutic agent" are anti-hormonal agents such as anti-estrogens and selective estrogen receptor modulators (SERMs), inhibitors of the enzyme aromatase, anti-androgens, and pharmaceutically acceptable salts, acids or derivatives of any of the above that act to regulate or inhibit hormone action on tumors.

[0003] Examples of anti-estrogens and SERMs include, for example, tamoxifen (including NOLVADEX™), raloxifene, droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and toremifene (FARESTON®).

[0004] Inhibitors of the enzyme aromatase regulate estrogen production in the adrenal glands. Examples include 4(5)-imidazoles, aminoglutethimide, megestrol acetate (MEGACE®), exemestane, formestane, fadrozole, vorozole (RIVISOR®), letrozole (FEMARA®), and anastrozole (ARIMIDEX®).

[0005] Examples of anti-androgens include flutamide, nilutamide, bicalutamide, leuprorelin, and goserelin.

[0006] Examples of chemotherapeutic agents also include anti-angiogenic agents including, but are not limited to, retinoid acid and derivatives thereof, 2-methoxyestradiol, ANGIOSTATIN®, ENDOSTATIN®, suramin, squalamine, tissue inhibitor of metalloproteinase-1, tissue inhibitor of metalloproteinase-2, plasminogen activator inhibitor-1, plasminogen activator inhibitor-2, cartilage-derived inhibitor, paclitaxel (nab-paclitaxel),

platelet factor 4, protamine sulphate (clupeine), sulphated chitin derivatives (prepared from queen crab shells), sulphated polysaccharide peptidoglycan complex (sp-pg), staurosporine, modulators of matrix metabolism including proline analogs ((1-azetidine-2-carboxylic acid (LACA)), cishydroxyproline, d,I-3,4-dehydroproline, thiaproline, α,α' -dipyridyl, beta-aminopropionitrile fumarate, 4-propyl-5-(4-pyridinyl)-2(3h)-oxazolone, methotrexate, mitoxantrone, heparin, interferons, 2 macroglobulin-serum, chicken inhibitor of metalloproteinase-3 (ChIMP-3), chymostatin, beta-cyclodextrin tetradecasulfate, eponemycin, fumagillin, gold sodium thiomalate, d-penicillamine, beta-1-anticollagenase-serum, alpha-2-antiplasmin, bisantrene, lobenzarit disodium, n-2-carboxyphenyl-4-chloroanthronilic acid disodium or "CCA", thalidomide, angiostatic steroid, carboxy aminoimidazole, and metalloproteinase inhibitors such as BB-94. Other anti-angiogenesis agents include antibodies, preferably monoclonal antibodies against these angiogenic growth factors: beta-FGF, alpha-FGF, FGF-5, VEGF isoforms, VEGF-C, HGF/SF, and Ang-1/Ang-2.

[0007] Examples of chemotherapeutic agents also include anti-fibrotic agents including, but are not limited to, the compounds such as beta-aminopropionitrile (BAPN), as well as the compounds disclosed in U.S. Patent No.: 4,965,288 (Palfreyman, *et al.*) relating to inhibitors of lysyl oxidase and their use in the treatment of diseases and conditions associated with the abnormal deposition of collagen and U.S. Patent No.: 4,997,854 (Kagan *et al.*) relating to compounds which inhibit LOX for the treatment of various pathological fibrotic states, which are herein incorporated by reference. Further exemplary inhibitors are described in U.S. Patent No.: 4,943,593 (Palfreyman *et al.*) relating to compounds such as 2-isobutyl-3-fluoro-, chloro-, or bromo-allylamine, U.S. Patent Nos.: 5,021,456 (Palfreyman *et al.*), 5,059,714 (Palfreyman *et al.*), 5,120,764 (Mccarthy *et al.*), 5,182,297 (Palfreyman *et al.*), 5,252,608 (Palfreyman *et al.*) relating to 2-(1-naphthyloxymethyl)-3-fluoroallylamine, and U.S. Pub. No.: 2004/0248871 (Farjanel *et al.*), which are herein incorporated by reference.

[0008] Exemplary anti-fibrotic agents also include the primary amines reacting with the carbonyl group of the active site of the lysyl oxidases, and more particularly those which

produce, after binding with the carbonyl, a product stabilized by resonance, such as the following primary amines: emylenemamine, hydrazine, phenylhydrazine, and their derivatives; semicarbazide and urea derivatives; aminonitriles such as BAPN or 2-nitroethylamine; unsaturated or saturated haloamines such as 2-bromo-ethylamine, 2-chloroethylamine, 2-trifluoroethylamine, 3-bromopropylamine, and p-halobenzylamines; and selenohomocysteine lactone.

[0009] Other anti-fibrotic agents are copper chelating agents penetrating or not penetrating the cells. Exemplary compounds include indirect inhibitors which block the aldehyde derivatives originating from the oxidative deamination of the lysyl and hydroxyllysyl residues by the lysyl oxidases. Examples include the thiolamines, particularly D-penicillamine, and its analogs such as 2-amino-5-mercapto-5-methylhexanoic acid, D-2-amino-3-methyl-3-((2-acetamidoethyl)dithio)butanoic acid, p-2-amino-3-methyl-3-((2-aminoethyl)dithio)butanoic acid, sodium-4-((p-1-dimethyl-2-amino-2-carboxyethyl)dithio)butane sulphurate, 2-acetamidoethyl-2-acetamidoethanethiol sulphanate, and sodium-4-mercaptobutanesulphinate trihydrate.

[0010] Examples of chemotherapeutic agents also include immunotherapeutic agents including and are not limited to therapeutic antibodies suitable for treating patients. Some examples of therapeutic antibodies include simtuzumab, abagovomab, adecatumumab, afutuzumab, alemtuzumab, altumomab, amatuximab, anatumomab, arcitumomab, bavituximab, bectumomab, bevacizumab, bivatumumab, blinatumomab, brentuximab, cantuzumab, catumaxomab, cetuximab, citatuzumab, cixutumumab, clivatuzumab, conatumumab, daratumumab, drozitumab, duligotumab, dusigitumab, detumomab, dacetuzumab, dalotuzumab, ecromeximab, elotuzumab, ensituximab, ertumaxomab, etaracizumab, farletuzumab, ficlatuzumab, figitumumab, flanvotumab, futuximab, ganitumab, gemtuzumab, girentuximab, glembatumumab, ibritumomab, igovomab, imgatuzumab, indatuximab, inotuzumab, intetumumab, ipilimumab, iratumumab, labetuzumab, lexatumumab, lintuzumab, lorvotuzumab, lucatumumab, mapatumumab, matuzumab, milatuzumab, minretumomab, mitumomab, moxetumomab, narnatumab,

napatumomab, necitumumab, , nimotuzumab, nofetumomab, ocaratuzumab, ofatumumab, olaratumab, onartuzumab, oportuzumab, oregovomab, panitumumab, parsatuzumab, patritumab, pentumomab, pertuzumab, pintumomab, pritimomab, racotumomab, radretumab, rilotumumab, rituximab, robatumumab, satumomab, sibrotuzumab, siltuximab, solitomab, tacatuzumab, taplitumomab, tenatumomab, teprotumumab, tigatuzumab, tositumomab, trastuzumab, tucotuzumab, ublituximab, veltuzumab, vorsetuzumab, votumumab, zalutumumab, CC49, and 3F8. Rituximab can be used for treating indolent B-cell cancers, including marginal-zone lymphoma, WM, CLL and small lymphocytic lymphoma. A combination of Rituximab and chemotherapy agents is especially effective.

[0011] The exemplified therapeutic antibodies may be further labeled or combined with a radioisotope particle such as indium-111, yttrium-90, or iodine-131.

[0012] In a one embodiment, the additional therapeutic agent is a nitrogen mustard alkylating agent. Nonlimiting examples of nitrogen mustard alkylating agents include chlorambucil.

[0013] In one embodiment, the compounds and compositions described herein may be used or combined with one or more additional therapeutic agents. The one or more therapeutic agents include, but are not limited to, an inhibitor of Abl, activated CDC kinase (ACK), adenosine A2B receptor (A2B), apoptosis signal-regulating kinase (ASK), Auroa kinase, Bruton's tyrosine kinase (BTK), BET-bromodomain (BRD) such as BRD4, c-Kit, c-Met, CDK-activating kinase (CAK), calmodulin-dependent protein kinase (CaMK), cyclin-dependent kinase (CDK), casein kinase (CK), discoidin domain receptor (DDR), epidermal growth factor receptors (EGFR), focal adhesion kinase (FAK), Flt-3, FYN, glycogen synthase kinase (GSK), HCK, histone deacetylase (HDAC), IKK such as IKK β ϵ , isocitrate dehydrogenase (IDH) such as IDH1, Janus kinase (JAK), KDR, lymphocyte-specific protein tyrosine kinase (LCK), lysyl oxidase protein, lysyl oxidase-like protein (LOXL), LYN, matrix metalloprotease (MMP), MEK, mitogen-activated protein kinase (MAPK), NEK9, NPM-ALK, p38 kinase, platelet-derived growth factor (PDGF), phosphorylase kinase (PK), polo-like kinase (PLK), phosphatidylinositol 3-kinase (PI3K), protein kinase (PK) such as protein kinase A, B, and/or C, PYK, spleen tyrosine kinase (SYK), serine/threonine kinase

TPL2, serine/threonine kinase STK, signal transduction and transcription (STAT), SRC, serine/threonine-protein kinase (TBK) such as TBK1, TIE, tyrosine kinase (TK), vascular endothelial growth factor receptor (VEGFR), YES, or any combination thereof.

[0014] ASK inhibitors include ASK1 inhibitors. Examples of ASK1 inhibitors include, but are not limited to, those described in WO 2011/008709 (Gilead Sciences) and WO 2013/112741 (Gilead Sciences).

[0015] Examples of BTK inhibitors include, but are not limited to, ibrutinib, HM71224, ONO-4059, and CC-292.

[0016] DDR inhibitors include inhibitors of DDR1 and/or DDR2. Examples of DDR inhibitors include, but are not limited to, those disclosed in WO 2014/047624 (Gilead Sciences), US 2009/0142345 (Takeda Pharmaceutical), US 2011/0287011 (Oncomed Pharmaceuticals), WO 2013/027802 (Chugai Pharmaceutical), and WO 2013/034933 (Imperial Innovations).

[0017] Examples of HDAC inhibitors include, but are not limited to, pracinostat and panobinostat.

[0018] JAK inhibitors inhibit JAK1, JAK2, and/or JAK3. Examples of JAK inhibitors include, but are not limited to, filgotinib, ruxolitinib, fedratinib, tofacitinib, baricitinib, lestaurtinib, pacritinib, XL019, AZD1480, INCB039110, LY2784544, BMS911543, and NS018.

[0019] LOXL inhibitors include inhibitors of LOXL1, LOXL2, LOXL3, LOXL4, and/or LOXL5. Examples of LOXL inhibitors include, but are not limited to, the antibodies described in WO 2009/017833 (Arresto Biosciences).

[0020] Examples of LOXL2 inhibitors include, but are not limited to, the antibodies described in WO 2009/017833 (Arresto Biosciences), WO 2009/035791 (Arresto Biosciences), and WO 2011/097513 (Gilead Biologics).

[0021] MMP inhibitors include inhibitors of MMP1 through 10. Examples of MMP9 inhibitors include, but are not limited to, marimastat (BB-2516), cipemastat (Ro 32-3555), and those described in WO 2012/027721 (Gilead Biologics).

[0022] PI3K inhibitors include inhibitors of PI3K γ , PI3K δ , PI3K β , PI3K α , and/or pan-PI3K. Examples of PI3K inhibitors include, but are not limited to, wortmannin, BKM120, CH5132799, XL756, and GDC-0980.

[0023] Examples of PI3K γ inhibitors include, but are not limited to, ZSTK474, AS252424, LY294002, and TG100115.

[0024] Examples of PI3K δ inhibitors include, but are not limited to, PI3K II, TGR-1202, AMG-319, GSK2269557, X-339, X-414, RP5090, KAR4141, XL499, OXY111A, IPI-145, IPI-443, and the compounds described in WO 2005/113556 (ICOS), WO 2013/052699 (Gilead Calistoga), WO 2013/116562 (Gilead Calistoga), WO 2014/100765 (Gilead Calistoga), WO 2014/100767 (Gilead Calistoga), and WO 2014/201409 (Gilead Sciences).

[0025] Examples of PI3K β inhibitors include, but are not limited to, GSK2636771, BAY 10824391, and TGX221.

[0026] Examples of PI3K α inhibitors include, but are not limited to, buparlisib, BAY 80-6946, BYL719, PX-866, RG7604, MLN1117, WX-037, AEZA-129, and PA799.

[0027] Examples of pan-PI3K inhibitors include, but are not limited to, LY294002, BEZ235, XL147 (SAR245408), and GDC-0941.

[0028] Examples of SYK inhibitors include, but are not limited to, tamatinib (R406), fostamatinib (R788), PRT062607, BAY-61-3606, NVP-QAB 205 AA, R112, R343, and those described in US Patent No.: 8,450,321 (Gilead Connecticut).

[0029] TKIs may target epidermal growth factor receptors (EGFRs) and receptors for fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF). Examples of TKIs that target EGFR include, but are not

limited to, gefitinib and erlotinib. Sunitinib is a non-limiting example of a TKI that targets receptors for FGF, PDGF, and VEGF.

Diagnostic Methods

[0166] Over-expression of claudin 18.2 is observed in certain tumor samples, and patients having claudin 18.2-over-expressing cells are likely responsive to treatments with the anti-claudin 18.2 antibodies of the present disclosure. Accordingly, the antibodies of the present disclosure can also be used for diagnostic and prognostic purposes.

[0167] A sample that preferably includes a cell can be obtained from a patient, which can be a cancer patient or a patient desiring diagnosis. The cell be a cell of a tumor tissue or a tumor block, a blood sample, a urine sample or any sample from the patient. Upon optional pre-treatment of the sample, the sample can be incubated with an antibody of the present disclosure under conditions allowing the antibody to interact with a claudin 18.2 protein potentially present in the sample. Methods such as ELISA can be used, taking advantage of the anti-claudin 18.2 antibody, to detect the presence of the claudin 18.2 protein in the sample.

[0168] Presence of the claudin 18.2 protein in the sample (optionally with the amount or concentration) can be used for diagnosis of cancer, as an indication that the patient is suitable for a treatment with the antibody, or as an indication that the patient has (or has not) responded to a cancer treatment. For a prognostic method, the detection can be done at once, twice or more, at certain stages, upon initiation of a cancer treatment to indicate the progress of the treatment.

Compositions

[0169] The present disclosure also provides pharmaceutical compositions. Such compositions comprise an effective amount of an antibody, and an acceptable carrier. In some embodiments, the composition further includes a second anticancer agent (e.g., an immune checkpoint inhibitor).

[0170] In a specific embodiment, the term “pharmaceutically acceptable” means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in

humans. Further, a “pharmaceutically acceptable carrier” will generally be a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type.

[0171] The term “carrier” refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents such as acetates, citrates or phosphates. Antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; and agents for the adjustment of tonicity such as sodium chloride or dextrose are also envisioned. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences by E. W. Martin, incorporated herein by reference. Such compositions will contain a therapeutically effective amount of the antigen-binding polypeptide, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration. The parental preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[0172] In an embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing

agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

[0173] The compounds of the disclosure can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

EXAMPLES

Example 1: Generation of murine monoclonal antibodies against human claudin 18 isoform 2 (CLD 18A2)

a. Immunizations:

[0174] Balb/c and C57/BL6 mice were immunized with eukaryotic expression vectors, encoding human claudin 18.2 (CLD 18A2) fragments. 50 µg of plasmid DNA was injected into the quadriceps (intramuscular, i.m.) on day 1 and 10. The presence of antibodies directed against human CLD 18A2 in the serum of the mice was monitored on day 20 by flow cytometry, using HEK293 cells transiently transfected with a nucleic acid encoding human CLD 18A2. Mice with detectable immune responses (**FIG. 1**) were boosted three and two days prior to fusion by intraperitoneal injection of 5×10^7 HEK293 cells transiently transfected with a nucleic acid encoding human CLD 18A2.

b. Generation of hybridomas producing human monoclonal antibodies to CLD18A2:

[0175] Mouse splenocytes were isolated and fused with PEG to a mouse myeloma cell line based on standard protocols. The resulting hybridomas were then screened for production of

immunoglobulins with CLD 18A2 specificity using HEK293 cells transfected with a nucleic acid encoding human CLD18 by cell ELISA.

[0176] Single cell suspensions of splenic lymphocytes from immunized mice were fused with P3X63Ag8U.1 non-secreting mouse myeloma cells (ATCC, CRL 1597) in a 2:1 ratio using 50% PEG (Roche Diagnostics, CRL 738641). Cells were plated at approximately 3×10^4 /well in flat bottom microtiter plates, followed by about two weeks incubation in selective medium containing 10% fetal bovine serum, 2% hybridoma fusion and cloning supplement (HFCS, Roche Diagnostics, CRL 1 363 735) plus 10 mM HEPES, 0.055 mM 2-mercaptoethanol, 50 µg/ml gentamycin and 1x HAT (Sigma, CRL H0262). After 10 to 14 days individual wells were screened by Cell ELISA for anti-CLD 18A2 monoclonal antibodies (FIG. 2). The antibody secreting hybridomas were re-plated, screened again with HEK293 expressing CLD 18A2 or CLD 18A1 by FACS and, if still positive for CLD18A2 and negative for CLD18A1, were subcloned by limiting dilution. The stable subclones were then cultured in vitro to generate small amounts of antibody in tissue culture medium for characterization. At least one clone from each hybridoma, which retained the reactivity of parent cells (by FACS), was chosen. Three vial cell banks were generated for each clone and stored in liquid nitrogen.

c. Selection of monoclonal antibodies binding to CLD 18A2 not to for CLD18A1:

[0177] To determine the isotype of antibodies, an isotype ELISA was performed. The mouse monoAB ID Kit (Zymed, CRL 90-6550) was used to determine Ig subclasses of the identified CLD18A2 reactive monoclonal antibodies. Thirty-two hybridoma cell lines were generated: 64G11B4, 65G8B8, 56E8F10F4, 54A2C4, 44F6B11, 15C2B7, 20F1E10, 72C1B6A3, 58G2C2, 101C4F12, 103A10B2, 40C10E3, 78E8G9G6, 4F11E2, 10G7G11, 12F1F4, 78C10B6G4, 119G11D9, 113G12E5E6, 116A8B7, 105F7G12, 84E9E12, 103F4D4, 110C12B6, 85H12E8, 103H2B4, 103F6D3, 113E12F7, 120B7B2, 111B12D11, 111E7E2, and 100F4G12, with further details as shown below:

64G11B4, mouse monoclonal IgG1, κ antibody
 65G8B8, mouse monoclonal IgG1, κ antibody
 56E8F10F4, mouse monoclonal IgG1, κ antibody
 54A2C4, mouse monoclonal IgG1, κ antibody
 44F6B11, mouse monoclonal IgG1, κ antibody
 15C2B7, mouse monoclonal IgG1, κ antibody

20F1E10, mouse monoclonal IgG1, κ antibody
72C1B6A3, mouse monoclonal IgG1, κ antibody
58G2C2, mouse monoclonal IgG2a, κ antibody
101C4F12, mouse monoclonal IgG2b, κ antibody
103A10B2, mouse monoclonal IgG2b, κ antibody
40C10E3, mouse monoclonal IgG1, λ antibody
78E8G9G6, mouse monoclonal IgG1, κ antibody
4F11E2, mouse monoclonal IgG1, κ antibody
10G7G11, mouse monoclonal IgG1, κ antibody
12F1F4, mouse monoclonal IgG1, κ antibody
78C10B6G4, mouse monoclonal IgG1, κ antibody
119G11D9, mouse monoclonal IgG1, κ antibody
113G12E5E6, mouse monoclonal IgG1, κ antibody
116A8B7, mouse monoclonal IgG1, κ antibody
105F7G12, mouse monoclonal IgG1, κ antibody
84E9E12, mouse monoclonal IgG1, κ antibody
103F4D4, mouse monoclonal IgG1, κ antibody
110C12B6, mouse monoclonal IgG1, κ antibody
85H12E8, mouse monoclonal IgG1, κ antibody
103H2B4, mouse monoclonal IgG1, κ antibody
103F6D3, mouse monoclonal IgG1, κ antibody
113E12F7, mouse monoclonal IgG2a, κ antibody
120B7B2, mouse monoclonal IgG2a, κ antibody
111B12D11, mouse monoclonal IgG2a, κ antibody
111E7E2, mouse monoclonal IgG2a, κ antibody
100F4G12, mouse monoclonal IgG3, κ antibody.

Example 2. Hybridoma Sequencing

[0178] Hybridoma cells (1×10^7) were harvested and total RNA was extracted using Tri Reagent as described above for spleen tissue. cDNA was prepared using SuperScript III kit according to the manufacturer's instruction, described above. The resulting cDNA product was used as template for PCR with primers VhRevU and VhForU, the resulting 300 bp PCR product was cleaned up using a PCR clean-up kit and sequenced with the same primer. PCR

reaction was also performed with light chain V-region specific primer VkRev7 and VkFor (for variable region only) or KappaFor primers (for entire kappa light chain). Sequencing reactions were performed on cleaned PCR product to obtain DNA sequences for the antibodies, 64G11B4, 65G8B8, 56E8F10F4, 54A2C4, 44F6B11, 15C2B7, 20F1E10, 72C1B6A3, 58G2C2, 101C4F12, 103A10B2, 40C10E3, 78E8G9G6, 4F11E2, 10G7G11, 12F1F4, 78C10B6G4, 119G11D9, 113G12E5E6, 116A8B7, 105F7G12, 84E9E12, 103F4D4, 110C12B6, 85H12E8, 103H2B4, 103F6D3, 113E12F7, 120B7B2, 111B12D11, 111E7E2, and 100F4G12. Their variable (VH and VL) sequences are shown in Table 1 below.

Table 1. Sequences of the variable regions of the antibodies

Antibody chain	Sequence	SEQ ID NO:
Light chains		
64G11B4	DIVMTQSPSSLTVTAGEKVTMNCSSQSLNLSGNQKNYLTWYQQKPGQPP KLLIYWASTRESGVPDRFTGSGSGTDFTLTISVQAEDLAVYYCQNDYFY PFTFGAGTNLELK	117
65G8B8	DIMMTQSPSSLTVTGTEKVTLTCKSSQSLNLSGNLKNYLTWYQQKPGHPP KLLIYWASTRESGVPVRFTGSGSGTDFTLTISVQAEDLTVYYCQNVYIY PFTFGSGTKLEMR	118
56E8F10F4	DIVMTQSPSSLTVTAGEKVTMSCKSSQSLNLSGNQKNYLTWYQQKPGQPP KLLIYWASTRESGVPDRFTGSGSGTYFTLTISVQAEDLAVYYCQNDYFY PFTFGSGTKLEIK	119
54A2C4	DTVMTQFPSSLSVSAGEKVTMSCKSSQSLNLSGNQKNYLAWYQQKPGQPP KLLIYGASTRESGVPDRFTGSGSGTDFTLTISVQAEDLAVYYCQNDLYY PWTFGGGTKLEFK	120
44F6B11	DIVMTQSPSSLTVTAGEKVTMSCKSNQSLNLSGNQKKYLTWYQQKPGQSP KLLIYWASTRESGVPDRFTGSESGTDFTLTISVRAEDLAVYYCQNGYSY PFTFGSGTKLEMK	121
15C2B7	DIVMTQSPSSLTVTAGGKVTVSCSSQSLNLSGNQKNYLTWYQQKPGQPP KLLIYWASTRESGVPDRFTGSGSGTDFTLTISVQTEDLAVYYCQNNYFY PLTFGAGTKLELK	122
20F1E10	DIVMTQSPSSLTVTAGEKVTMSCKSSQSLFNSGNQKNYLTWYQQKPGQPP KLLIYWASTRESGVPDRFTGSGSGTDFTLTITKVQAEDLAVYYCQNVYSY PLTFGAGTKLELK	123
72C1B6A3	DIVMTQSPSSLTVTAGEKVTMSCKSSQSLNLSGNQKNYLTWYQQRPQPP KLLIYRASSRESGVPVRFTGSGSGTDFTLTISVQAEDLAVYYCQNDYIY PYTFGGGKLEMN	124
58G2C2	DIVMTQSPSSLTVTAGEKVTMSCKSSQSLNLSGNQKNYLTWYQQKPGQPP TLLIFWASTRESGVPDRFTGSGSGTDFTLTINSVQAEDLAVYYCQNSYSY PFTFGSGTKLEIK	125
101C4F12	DIVMTQSPSSLTVTAGEKVTMSCKSSQSLNLSGNQKNYLTWYQQKPGQPP RLLIYWSSTRDSGVPDRFTGSGSRTDFTLTISVQAEDLAVYYCQNNFIY PLTFGAGTKLELK	126
103B2	DIVMTQSPSSLTVTGPEKVTMSCRSSMSLFNSGNQKSYLSWYHQKPGQPP KLLIYWASTRDSGVPVRFTGSGSGTDFTLTISVQAEDLAVYYCHNDYIY PLTFGAGTKLELK	127
78E8G9G6	DIVMTQSPSSLTVTAGEKVTMNCRSIQSLNLSGNQKNYLSWYQQKPGQPP	128

	KLLIYWASTRESGVPDRFTGSGSGTDFTLTIRSVLDEDLAVYYCQNSYSY PFTFGSGTKLEMK	
4F11E2	DIVMTQSPSSSLTVTAGEKVTLCRSSQSLNLSGNRKNYLTWYQQIPGQPP KLLIYWASTRESGVPDRFTGSGSGTYFTLTISSVQAEDLAVYYCQNAYSY PFTFGSGTKLEKK	129
10G7G11	DIVMTQSPSSSLTVTAGEKVTMTCKSSQSLFNSGNQQRNYLTWYQRKPGQPP KLLIYWASTRESGVPDRFTGSGSGTYFTLTVSSVQAEDLAVYYCQNAYYF PFTFGSGTKLEKK	130
12F1F4	DIVMTQSPSSSLTVTARERVSMTCSSQSLFNSGNQQRNYLTWYQQKPGQPP KLLIYWASTRESGVPDRFTGSGSGTDFTLTISSVQAEDLAIYFCQNNYYY PFTFGSGTKLEIK	131
78C10B6G4	DIVMTQSPSSSLTVTAGEKVTMSCKSSQSLNLSGNQKNYLTWYQQRPQGPP KLLIYRASSRESGVPVRFTGSGSGTDFTLTISSVQAEDLAVYYCQNDYIY PYTFGGGKLEMN	124
119G11D9	DIVMTQSPSSSLTVTAGERVMTMCRSTQSLFNSGNQKNYLTWYQQKPGQPP KLLIYWASTRESGVPDRFTGGSGTDFTLTISSVQAEDLAVYYCQNAYYY PLTFGAGTKLERK	132
113G12E5E6	DIVMTQSPSSSLTVTAGERVMTSCKPSQSLNLSGNQKNYLAWYQQKPGQPP KLLIYWASTRESGVPDRFKGSGSGTDFTLTISSVQAEDLAVYYCQNAYFY PCTFGGGKLEMK	133
116A8B7	DIVMTQSPSSSLTVTAGEKVTMCRSTQSLFNSGNQQRNYLTWYQQKPGQPP KLLIYWASTRESGVPDRFTGSGSGTDFTLTISSVQAEDLAVYYCQNAYYY PLTFGVGKLERK	134
105F7G12	DIVMTQSPSSSLTVTAGERVMTSCKSSQSLNLSGNQKNYLAWYQQKPGQPP KLLIYWASTRESGVPDRFKGSGSGTDFTLTISSVQAEDLAVYYCQNAYFY PCTFGGGKLEMK	135
84E9E12	DIVMTQSPSSSLTVTTGEKVTMSCKSSQSVFNSGNQKNYLTWYQQKPGQPP KLLVYWASTRESGVPARFTGSGSGTVFTLTISSVQAEDLAVYYCQNDYFY PLTFGAGTRLELK	136
103F4D4	DIVMTQSPSSQTVTAGEKVTLSRSSQSLNLSGNQKNYLTWYQQKPGQPP KLLIYWASTRESGVPDRFTGSGSGTYFTFTISSVQAEDLAVYYCQNAYFY PFTFGAGTKLELK	137
110C12B6	DIVMTQSPSSSLTVTAGEKVTMCRSTQSLFNSGNQQRNYLTWYQQKPGQPP KLLIYWASTRESGVPDRFTGSGSGTDFTLTISSVQAEDLAVYYCQNAYYY PLTFGVGKLERK	134
85H12E8	DIVMTQSPSSSLTVTAGEKVTMNCKSSQSLNLSGNQQRNYLSWYQQEPGQPP KLLIYWASTRESGVPDRFTGSGSGTDFTLTISNIQAEDLALYFCQNAYFY PFTFGSGTKLEIK	138
103H2B4	DIIMTQSPSSSLTVTAGEKVTMSCKSSQSLNLSGNQKNYLTWYQQKPGQSP KLLIYWASTRESGVPDRFTGSGSGTDFTLTISSVQAEDLAVYYCQNNYFY PLTFGVGKLELK	139
103F6D3	DIVMTQSPSSQTVTAGEKVTLSRSSQSLNLSGNQKNYLTWYQQKPGQPP KLLIYWASTRESGVPDRFTGSGSGTYFTFTISSVQAEDLAVYYCQNAYFY PFTFGAGTKLELK	137
113E12F7	DIVMTQSPSSSLTVTTGEKVTMSCKSSQSLFNSGNQKNYLTWYQQKPGQPP KLLIYWASTRESGVPDRFTGSGSGTYFTLTISSVQAEDLAVYYCQNNYIY PLAFGTGKLELK	140
120B7B2	DIVMTQSPSSSLTVTAGEKVTMSCKSSQSLNLSGNQKNYLTWYQQRPQGPP KLLMYWASTRESGVPDRFTGSGSGTDFTLTISGQAEDLAIYFCQNGYFY PFTFGSGTKLETK	141
111B12D11	DIVMTQSPSSSLTVTAGEKVTMCRSSQSLFNSGNQQRNYLTWYQQKPGQPP KLLIYWASTRESGVPDRFTGSGSGTDFTLTISSVQAEDLAVYYCQNNYIY PLAFGAGTKLELK	142

111E7E2	DIVMTQSPSSSLTVTAGEKVTMSCKSSQSLFNSGNQKNYLTWYQQKPGQPP KLLIYWASTRESGVDRFTGSGSGTDFTLTISVQAEDLAVYYCQNNYIY PLAFGAGTKLELK	143
100F4G12	DIVMTQSPSSSLTVTAGEKVTMRCKSTQSLNLSGNQKNYLTWYQQKPGQSP KLLIYWASTRESGVPERFTGSGSGTDFTLTISVQAEDLAVYYCQNAYYY PLTFGPGTKLERK	144
Heavy Chain		
64G11B4	QVQLHQSGTELVRPGTSVKVSCASGYAFTNYLLEWVKQRPQGQLEWIGE INPNGGGSNYNEKFKGKATLTADKSSSTAYMQLSSSLTSVDSAVYFCARIY YGNSFAYWGQGTTLTVSA	145
65G8B8	QVQLKESGPGVLVAPSQSLISITCTVSGFSLTSYGVSQVVRQPPGKLEWLG IWGDGNTIYHSALKSRLSISRDNKRQVFLKVNLSLQIDDTATYYCAKQGL YGHAMDYWGQGTSTVIVSS	146
56E8F10F4	DVQLVESGGGLVQPGGSRKLSCTASGFTFNSFGMNWVRQAPKQLEWVAF ISGGNTIHYLDTVKGRTISRDNPKNTLFLQMTSLRSEDATAMYYCTRLA LGNAMDYWGQGTSTVIVSS	147
54A2C4	EVQHVEITGGGLVQPKGSLKLSAASGFTFNTNAMNWRQAPGKLEWVAR IRSKSNYATYYADSVKDRFTISRDDSQSMYVQMNNLKTEDTAMYYCVS GAYYGNSKAFDYWGQGTTLTVSA	148
54A2C4'	QVQLHQSGTELVRPGTSVKVSCASGYAFTNYLLEWVKQRPQGQLEWIGE INPNGGGSNYNEKFKGKATLTADKSSSTAYMQLSSSLTSVDSAVYFCARIY YGNSFAYWGQGTTLTVSA	145
54A2C4''	QVQLQQSGAELARPGASVKMSCKASGYTFTYSIHWLQKQPGQLEWIGY INPSTIYTNYNQFKYKATLTADKSSSTAYIQLSSSLTSDDSAVYYCAREG YGRGNAMDYWGQGTSTVTVSS	149
44F6B11	EVQLVESGGDLVQPGGSLKLSAASGFTFSNYGMSWVRQTPDKRLEWVAT FSYGDShNYSDSVKGRFTISRDIADALYLQMSLRSDDTAIYYCARFG RGNTMDYWGQGTSTVTVSL	150
15C2B7	QIQLVQSGPELRRKPGETVKISCKASGYTFTNYGMNWRQAPGKGLKMMAW INANTGEPTYAEFFKGRFAFSLETSARSAYLQINSLKNEDTATYFCARLT RGNSTFDYWGQGTTLTVSS	151
20F1E10	QIQLVQSGPELKKPGETVKISCKASGYTFTKYGMNWRQAPGKGLKMMGW ISTNTGEPTYAEFFKGRFAFSLETSASTAFQINNLLKNEDTATYFCARLV RGNSTFDYWGQGTTLTVSS	152
72C1B6A3	QVQLQQSGGELVQPGASVKMSCKAFGYTFTTPIEWMQNHGKSLWIGN FHPYNDDTKYNEKFKGAKLTVEKSSSTVYLEVSRSLTSDDSAVYYCARRA YGYPYAMDYWGQGTSTVTVSS	153
58G2C2	QVHLQQSGAEVVRPGTSVKVSCASGYAFTNYLIEWIKRPGQGLEWVGV INPGRSGTNYNEKFKGKATLTADKSSSTAYMQLSSSLTSDDSAVYFCARTR YGGNAMDYWGQGTSTVTVSS	154
101C4F12	QVQLKESGPGQVAPSQSLSIACITVSGFSLSSYGVHWVRQPPGKLEWLG IWAGGSTNYDSALMSRLTISKDNSRTRVFLKMNSLQTDATAMYYCARSLY GNSLDSWGPQTTLTVSS	155
103B2	QVQLKESGPGVLVAPSQSLISITCTVSGLSLTSFSGVHWIRQPPGKLEWLG IWAGGSTNYNSALMSRLSISKDNSKQVFLKMNSLQTDATAMYYCARSLY GNSFDYWGQGTALTIVSS	156
40C10E3	QVQLKESGPGVLVAPSQSLISITCTVSGFSLSSYGVNWRQPPGKLEWLAA IRSDGIITYNVLSRLRISKDNSKQVFLKMNSLQTDATAMFYCARWFR GNVLDYWGQGTSTVTVSS	157
78E8G9G6	QVQLKESGPGVLVAPSQSLISITCTVSGFSLISYGVHWVRQPPGKLEWLG IWAGGRITNYNSALMSRLSISKDNSKQVFLKMNSLQTYDTAMYYCARDRY GGNSLDYWGQGTSTVTVSS	158

4F11E2	DVQLVESGGGLVQPGGSRKLSAASGFTFSTFGMHWVRQAPEKGLEWVAY ITSGNSPIYFTDTVKGRFTISRDNPKNTLFLQMTSLGSEDATAVYYCARSS YYGNSMDYWGQGTSTVTVSS	159
10G7G11	QVQLKESGPGLVAPSQSLSITCTISGFSLNITYGVHWVRQPPGKLEWLTV MLSDGNTVYNSSLSKRLSLTKDNSKSQLLLKMNSLQTDDTAIYYCARHKA YGNAMDYWGQGTSTVTVSS	160
12F1F4	QVQLKESGPGLVAPSQSLSITCTVSGFSLINYGVSWSVRQPPGKLEWLGV IWGDGNTNYQSALRSRLSIRKDTSKSQVFLKLSNVHTDGTATYYCAKVGR GNAMDHWGQGISTVIVSS	161
78C10B6G4	QVQLKESGPGLVAPSQSLSITCTVSGFSLINYGVSWSVRQPPGKLEWLGV IRGDGNTNYQSALRSRLSIRKDTSKSQVFLKLSNVHTDGTATYYCAKVGR GNAMDHWGQGISTVIVSS	162
119G11D9	EVQLQQSGPELVKPGASVKMSCKASGYTFTGFLMHWVKQKPGQGLEWIGY INPYNDGTKYSEKFKGKATLTSDKSSSTAFMELSSLTSDDSAVYYCARLD YGNAMDYWGQGTSTVTVSS	163
113G12E5E6	QVQLKQSGPGLVQPSQSLSITCTVSDFSLTKEYGVHWFRQSPGKLEWLGV IWTGGNTDYNPALIPRLSFRKDNSKSQLVFFKMNSLQSSDTAVYYCARNGY YGNAMDYWGQGTSTVTVSS	164
116A8B7	EVQLQQSGPELVKPGASVKMSCKSSGYTFTGFLMHWVKQKPGQGLEWIGY INPYNDGTKYSEKFKGKATLTSDKSSSTAYMELSSLTSDDSAVYYCGRLD YGNAMDYWGQGTSTVTVSS	165
105F7G12	QVQLKQSGPGLVQPSQSLSITCTVSDFSLTKEYGVHWFRQSPGKLEWLGV IWTGGNTDYNPALIPRLSFRKDNSKSQLVFFKMNSLQSSDTAVYYCARNGY YGNAMDYWGQGTSTVTVSS	164
84E9E12	DVQLQESGPGLVKPSQSLSLSCSVTGYSTISGYFWTWFRQFPGNKLEWMG YISYDGSNNYNPSLKNRISITRDTSKNFFLKLNSVTTEDATYYCASFR FFAYWGQGTTLTVSA	166
103F4D4	QVQLQQSGAELARPGASVKMSCKASGYTFTYSIHWLQKPGQGLEWIGY INPSTIYTNYNQKFYKATLTADKSSSTAYIQLSSLTSDDSAVYYCAREG YGRGNAMDYWGQGTSTVTVSS	149
110C12B6	EVQLQQSGPELVKPGASVKMSCKSSGYTFTGFLMHWVKQKPGQGLEWIGY INPYNDGTKYSEKFKGKATLTSDKSSSTAYMELSSLTSDDSAVYYCGRLD YGNAMDYWGQGTSTVTVSS	165
85H12E8	QVQLKESGPGLVAPSQSLSITCTVSGFSLSNYGVSWSVRQPPGKLEWLGV IWAGGNTNYSALMSRLRISKDNSKSQLVFLKMNSLQTDDTARYYCARHGY GKGNAMDNWGQGTSTVTVSS	167
103H2B4	QVQLQQPGAEPVKPGASVKLSCKASGYSTNFLTTHWVRQRPQGQGLEWIGE INPTNGRTYYNEKFKRKATLTVDKSSSTVYMQLSNLTPEDSAVFYCARIY YGNAMDYWGQGTTLTVSA	168
103F6D3	QVQLQQSGAELARPGASVKMSCKASGYTFTYSIHWLQKPGQGLEWIGY INPNTIYTNYNQKFYKTTLTADKSSSTAYIQLSSLTSDDSAVYYCAREG YGRGNAMDYWGQGTSTVTVSS	169
113E12F7	QVQLKESGPGLVAPSQSLSITCTVTGFSLSYGVHWVRQPPGKLEWLGV IWAGGSTNYDSALMSRLSISKDRSKSQVFLKMTSLQTDDTAMYYCARSLY GNSFDHWGQGTTLTVSS	170
120B7B2	EVQLQQSGPELVKPGASVKMSCKASGYTFTGYIIQWMKQKPGLEWIGF INPYNDGTKYNEQFKGKATLTSDKSSNAAVMELSSLTSEDSAVYYCARAY FGNSFAYWGQGTTLTVSA	171
111B12D11	QVQLKESGPGLVAPSQSLSITCTVSGFSLTSYGVHWVRQPPGKLEWLGV IWAGGSTNYDSTLMSRLSISKDRSKSQVFLKMTSLQTDDTAMYYCARSLY GNSFDHWGQGTTLTVSS	172
111E7E2	QVQLKESGPGLVAPSQSLSITCTVSGFSLTSYGAHWVRQPPGKLEWLGV IWAGGSTNYDSALMSRLSISKDRSKSQVFLKMTSLQTDDTAMYYCARSLY	173

	GNSFDHWGQGTTTLTVSS	
100F4G12	EVQLQQSGPELVKPGASVKMSCKASGYTFTGFLMHWVKQKPGQGLEWIGY INPYNDGTKYSERFKGKATLTSDKSSSTAYMELSSLTSDDSAVYYCARLD YGNAMDYWGQGTSTVTVSS	174

Example 3. Production and purification of monoclonal antibodies reactive to CLD18A2

[0179] To produce mg amounts of antibody for functional characterization, hybridoma cells were seeded in dialysis based bioreactors (CELLine CL1000, Integra, Chur, CH) at 2×10^6 cells / ml. Antibody containing supernatant was harvested once weekly. Mouse monoclonal antibody was purified using Melon Gel (Pierce, Rockford, USA) and concentrated by ammonium sulphate precipitation. Antibody concentration and purity was estimated by sodium dodecylsulphate gel electrophoresis and coomassie staining.

Example 4. Binding of murine monoclonal antibodies reactive to CLD18A2

[0180] MKN45 cells over-expressed CLD18A2 were harvested from flasks. 100 μ l of 1×10^6 cells/ml of cells were incubated with primary antibodies indicated as **FIG. 3** in 3-fold serial dilutions starting from 100 nM to 0.003 nM for 30 minutes on ice. After being washed with 200 μ l of FACS buffer twice, cells were incubated with secondary antibody for 30 minutes on ice. Cells were washed with 200 μ l of FACS buffer twice and transferred to BD Falcon 5 ml tube and analyzed by FACS. The results of the study showed that the purified murine antibody could bind to MKN45 cells transfected with human CLD18A2 by flow cytometry with high EC50, compared with positive reference antibody.

Example 5. Binding of murine monoclonal antibodies reactive to CLD18A2 mutant

[0181] SU620 cells that endogenously expressed CLD18A2 bearing M149L mutation were harvested from flasks. 100 μ l of 1×10^6 cells/ml of cells were incubated with primary antibodies indicated as **FIG. 4** in 3-fold serial dilutions starting from 100 nM to 0.003 nM for 30 minutes on ice. After being washed with 200 μ l of FACS buffer twice, cells were incubated with secondary antibody for 30 minutes on ice. Cells were washed with 200 μ l of FACS buffer twice and transferred to BD Falcon 5 ml tube and analyzed by FACS. The results of the study showed that the purified murine antibody could bind to SU620 cells endogenously expressing human CLD18A2 bearing M149L mutation by flow cytometry with high EC50, while the reference antibody did not (**FIG. 4**).

Example 6. Binding of murine monoclonal antibodies reactive to mouse and cyno CLD18A2

[0182] To evaluate these antibodies cross-reactivities with mouse and cyno CLD18A2, HEK293 cells over-expressed mouse, cyno or human CLD18A2 were harvested from flasks. 100 μ l of 1×10^6 cells/ml of cells were incubated with primary antibodies indicated as fig. 3a in 3-fold serial dilutions starting from 100 nM to 0.003 nM for 30 minutes on ice. After being washed with 200 μ l of FACS buffer twice, cells were incubated with secondary antibody for 30 minutes on ice. Cells were washed with 200 μ l of FACS buffer twice and transferred to BD Falcon 5 ml tube and analyzed by FACS. The results of the study showed that the purified murine antibodies can bind to mouse and cyno CLD18A2 by flow cytometry with high EC50, at least like the reference antibodies (FIG. 5, 6 and 7).

Example 7 Binding of chimeric antibodies reactive to CLD18A2

[0183] The murine VH and VK genes were produced synthetically and then respectively cloned into vectors containing the human gamma 1 and human kappa constant domains. The purified chimeric antibodies were produced from transfected CHO cells.

[0184] MKN45 cells that stably expressed human CLD18A2 or CLD18A1, were harvested from flasks. 100 μ l of 1×10^6 cells/ml of cells were incubated with primary chimeric antibodies indicated as FIG. 4 in 3-fold serial dilutions starting from 100 nM to 0.003 nM for 30 minutes on ice. After being washed with 200 μ l of FACS buffer twice, cells were incubated with secondary antibody for 30 minutes on ice. Cells were washed with 200 μ l of FACS buffer twice and transferred to BD Falcon 5 ml tube and analyzed by FACS. The results of the study showed that the chimeric antibodies can bind to human CLD18A2 with high EC50, while not CLD18A1 (FIG. 8 and 9).

Example 8. Antibody-Dependent Cellular Cytotoxicity (ADCC) of Chimeric antibodies

[0185] The ADCC Reporter Bioassay uses an alternative readout at an earlier point in ADCC MOA pathway activation: the activation of gene transcription through the NFAT (nuclear factor of activated T-cells) pathway in the effector cell. In addition, the ADCC Reporter Bioassay uses engineered Jurkat cells stably expressing the Fc γ RIIIa receptor, V158 (high affinity) variant, and an NFAT response element driving expression of firefly luciferase as

effector cells. Antibody biological activity in ADCC MOA is quantified through the luciferase produced as a result of NFAT pathway activation; luciferase activity in the effector cell is quantified with luminescence readout (**FIG. 1**). Signal is high, and assay background is low.

[0186] Serial dilutions of claudin 18.2 chimeric monoclonal antibody or Ref. Ab were incubated for 6 hours of induction at 37°C with engineered Jurkat effector cells (ADCC Bioassay Effector Cells), with or without ADCC Bioassay Target Cells (expressing claudin 18.2). Luciferase activity was quantified using Bio-Glo™ Reagent (**Table 2**). The results show that these chimeric antibodies have very strong ADCC activities.

Table 2. EC50 of the tested antibodies

Antibody	EC50 (pM)
4F11E2	22.18
12F1F4	36.77
64G11B4	125.7
72C186A3	46.32
78E8G9G6	15.86
103F6D3	79.53
120B7B2	5.806
Ref. Ab	458.5

Example 9. Humanization of the 4F11E2, 72C1B6A3 and 120B7B2 mouse mAbs

[0187] The mAb 4F11E2, 72C1B6A3 and 120B7B2 variable region genes were employed to create humanized MAb. In the first step of this process, the amino acid sequences of the VH and VL of MAb were compared against the available database of human Ig gene sequences to find the overall best-matching human germline Ig gene sequences.

[0188] The amino acid sequences of the humanized antibodies are listed in **Table 3** below.

Table 3. Humanized sequences

Name	Sequence	SEQ ID NO:
4F11VH_1 (grafted VH)	EVQLVESGGGLVQPGGSLRLSCAASGFTFTFGMHWVRQAPGKGLEWVSY ITSGNSPIYFTDTVKGRFTISRDNKNSLYLQMNSLRAEDTAVYYCARSS YYGNSMDYWGQGTLLVTVSS	175

4F11VH_2	EVQLVESGGGLVQPGGSLRLSCAASGFTFTFGMHWVRQAPGKGLEWVAY ITSGNSPIYFTDITVKGRFTISRDNANKNSLYLQMNSLRAEDTAVYYCARSS YYGNSMDYWGQGTLLTVSS	176
4F11VH_3	EVQLVESGGGLVQPGGSLRLSCAASGFTFTFGMHWVRQAPGKGLEWVAY ITSGNSPIYFTDITVKGRFTISRDNANKNTLYLQMNSLRAEDTAVYYCARSS YYGNSMDYWGQGTLLTVSS	177
4F11VL_1 (grafted VL)	DIVMTQSPDSLAVSLGERATINCRSSQSLNLSGNRKNYLTWYQQKPGQPP KLLIYWASTRESGVPDRFSGSGSGTDFTLTISLQAEDVAVYYCQNAYSY PFTFGGGTKLEIK	178
4F11VL_2	DTVMTQSPDSLAVSLGERATINCRSSQSLNLSGNRKNYLTWYQQKPGQPP KLLIYWASTRESGVPDRFSGSGSGTDFTLTISSVQAEDVAVYYCQNAYSY PFTFGGGTKLEIK	179
4F11VL_3	DTVMTQSPDSLAVSLGERVTLNCRSSQSLNLSGNRKNYLTWYQQKPGQPP KLLIYWASTRESGVPDRFSGSGSGTDFTLTISSVQAEDVAVYYCQNAYSY PFTFGGGTKLEIK	180
72C1VH_1 (grafted VH)	QVQLVQSGAEVKKPGASVKVSCKASGYFTTYPIEWVRQAPGQRLEWMGN FHPYNDGTKYNEKFGRVTITRDTSASTAYMELSSLRSEDVAVYYCARRA YGYPYAMDYWGQGTLLTVSS	181
72C1VH_2	QVQLVQSGAEVKKPGASVKVSCKASGYFTTYPIEWMRQAPGQRLEWMGN FHPYNDGTKYNEKFGRVTITVDTSASTAYMELSSLRSEDVAVYYCARRA YGYPYAMDYWGQGTLLTVSS	182
72C1VH_3	QVQLVQSGAEVKKPGASVKVSCKASGYFTTYPIEWMKQAPGQRLEWMGN FHPYNDGTKYNEKFGRVTITVDTSASTAYMEVSSLRSEDVAVYYCARRA YGYPYAMDYWGQGTLLTVSS	183
72C1VH_4	QVQLVQSGAEVKKPGASVKMSCKASGYFTTYPIEWMKQAPGQRLEWMGN FHPYNDGTKYNEKFGRVTLTVDTSASTVYLEVSSLRSEDVAVYYCARRA YGYPYAMDYWGQGTLLTVSS	184
72C1VL_1 (grafted VL)	DIVMTQSPDSLAVSLGERATINCKSSQSLNLSGNQKNYLTWYQQKPGQPP KLLIYRASSRESGVPDRFSGSGSGTDFTLTISLQAEDVAVYYCQNDYIY PYTFGGGTKLEIK	185
72C1VL_2	DIVMTQSPDSLAVSLGERATISCKSSQSLNLSGNQKNYLTWYQQKPGQPP KLLIYRASSRESGVPDRFSGSGSGTDFTLTISLQAEDVAVYYCQNDYIY PYTFGGGTKLEIK	186
72C1VL_3	DIVMTQSPDSLAVSLGERVTMSCKSSQSLNLSGNQKNYLTWYQQKPGQPP KLLIYRASSRESGVPDRFSGSGSGTDFTLTISSVQAEDVAVYYCQNDYIY PYTFGGGTKLEIK	187
120B7VH_1 (grafted VH)	QVQLVQSGAEVKKPGASVKVSCKASGYFTGYIIQWVRQAPGQRLEWMGF INPYNDGTKYNEQFKGRVTITRDTSASTAYMELSSLRSEDVAVYYCARAY FGNSFAYWGQGTLLTVSS	188
120B7VH_2	QVQLVQSGAEVKKPGASVKVSCKASGYFTGYIIQWMRQAPGQRLEWMGF INPYNDGTKYNEQFKGRVTITSDTSASAAYMELSSLRSEDVAVYYCARAY FGNSFAYWGQGTLLTVSS	189
120B7VH_3	QVQLVQSGAEVKKPGASVKVSCKASGYFTGYIIQWMKQAPGQRLEWIGF INPYNDGTKYNEQFKGRATITSDTSASAAYMELSSLRSEDVAVYYCARAY FGNSFAYWGQGTLLTVSS	190
120B7VH_4	EVQLVQSGAEVKKPGASVKMSCKASGYFTGYIIQWMKQAPGQRLEWIGF INPYNDGTKYNEQFKGRATLTSDTSASAAYMELSSLRSEDVAVYYCARAY FGNSFAYWGQGTLLTVSS	191
120B7VL_1 (grafted VL)	DIVMTQSPDSLAVSLGERATINCKSSQSLNLSGNQKNYLTWYQQKPGQPP KLLIYWASTRESGVPDRFSGSGSGTDFTLTISLQAEDVAVYYCQNGYYF PFTFGGGTKLEIK	192
120B7VL_2	DIVMTQSPDSLAVSLGERATISCKSSQSLNLSGNQKNYLTWYQQKPGQPP KLLMYWASTRESGVPDRFSGSGSGTDFTLTISLQAEDVAVYYCQNGYYF	193

	PFTFGGGTKLEIK	
120B7VL_3	DIVMTQSPDSLAVSLGERATISCKSSQSLNLSGNQKNYLTWYQQKPGQPP KLLMYWASTRESGVDRFSGSGSGTDFTLTISGQAEDVAVYFCQNGYYF PFTFGGGTKLEIK	194
120B7VL_4	DIVMTQSPDSLAVSLGERVTMSCKSSQSLNLSGNQKNYLTWYQQKPGQPP KLLMYWASTRESGVDRFSGSGSGTDFTLTISGQAEDVAVYFCQNGYYF PFTFGGGTKLEIK	195

[0189] The humanized VH and VL genes were produced synthetically and then respectively cloned into vectors containing the human gamma 1 and human kappa constant domains. The pairing of the human VH and the human VL created the humanized antibodies (see **Table 4**).

Table 4. Humanized antibodies with their VH and VL regions

4F11E2

VH	4F11VH_1	4F11VH_2	4F11VH_3
VL			
4F11VL_1	hu4F11.1	hu4F11.4	hu4F11.7
4F11VL_2	hu4F11.2	hu4F11.5	hu4F11.8
4F11VL_3	hu4F11.3	hu4F11.6	hu4F11.9

72C1B6A3

VH	72C1VH_1	72C1VH_2	72C1VH_3	72C1VH_4
VL				
72C1VL_1	hu72C1.10	hu72C1.13	hu72C1.16	hu72C1.19
72C1VL_2	hu72C1.11	hu72C1.14	hu72C1.17	hu72C1.20
72C1VL_3	hu72C1.12	hu72C1.15	hu72C1.18	hu72C1.21

120B7B2

VH	120B7VH_1	120B7VH_2	120B7VH_3	120B7VH_4
VL				
120B7VL_1	hu120B7.22	hu120B7.26	hu120B7.30	hu120B7.34
120B7VL_2	hu120B7.23	hu120B7.27	hu120B7.31	hu120B7.35
120B7VL_3	hu120B7.24	hu120B7.28	hu120B7.32	hu120B7.36
120B7VL_4	hu120B7.25	hu120B7.29	hu120B7.33	hu120B7.37

Example 10. Binding of humanized antibodies reactive to CLD18A2

[0190] MKN45 cells that stably expressed human CLD18A2 or CLD18A1, were harvested from flasks. 100 μ l of 1×10^6 cells/ml of cells were incubated with primary humanized antibodies indicated as FIG. 4 in 3-fold serial dilutions starting from 100 nM to 0.003 nM for 30 minutes on ice. After being washed with 200 μ l of FACS buffer twice, cells were incubated with secondary antibody for 30 minutes on ice. Cells were washed with 200 μ l of FACS buffer twice and transferred to BD Falcon 5 ml tube and analyzed by FACS. The

results of the study showed that the indicated humanized antibodies can bind to human CLD18A2 with high EC50, while not CLD18A1 (FIG. 10 and 11).

Example 11. Binding of PTM (post-translational modification) de-risk humanized antibodies reactive to CLD18A2

[0191] Post-translational modifications (PTMs) can cause problems during the development of a therapeutic protein such as increased heterogeneity, reduced bioactivity, reduced stability, immunogenicity, fragmentation and aggregation. The potential impact of PTMs depends on their location and in some cases on solvent exposure. The CDRs of sequence were analyzed for the following potential PTMs: Asparagine deamidation, Aspartate isomerization, free Cysteine thiol groups, N-glycosylation, oxidation, fragmentation by potential hydrolysis site etc..

[0192] To reduce the risk of developing PTM in 4F11E2, 72C1B6A3 and 120B7B2, some concerned amino acids in the VH and VL were mutated. And then nine antibodies were generated:

Clones	HC:LC*	No.
4F11E2	HC N55Q-LC N31E	1
	HC N55Q-LC S32A	2
	HC N55E-LC S32A	3
	HC N55E&N104Q-LC S32A	8
	HC N55E&N104E-LC S32A	9
	HC N55E&S105A-LC S32A	10
72C1B6A3	HC WT-LC N31E	4
	HC WT-LC S32A	5
120B7B2	HC G57D&S104A-LC-N96E&N31E	6
	HC G57D&S104A-LC-S32A&G97A	7

*The amino acid location (e.g., N55) is according to the amino acid residue number in the corresponding VH or VL amino acid sequence, not Kabat or Chothia.

Antibody	Mutant	Sequence (mutation highlighted)	SEQ ID NO:
4F11E2	HC N55Q	EVQLVESGGGLVQPGGSLRLSCAASGFTFTFGMHWRQAPGKGLEWVS YITSGQSPIYFTDTVKGRFTISRDNKNSLYLQMNSLRAEDTAVYYCARSS YYGNSMDYWGQGTLVTVSS	196
	HC N55E	EVQLVESGGGLVQPGGSLRLSCAASGFTFTFGMHWRQAPGKGLEWVS YITSGE ~~E~~ SPIYFTDTVKGRFTISRDNKNSLYLQMNSLRAEDTAVYYCARSS YYGNSMDYWGQGTLVTVSS	197
	HC N55E & N104Q	EVQLVESGGGLVQPGGSLRLSCAASGFTFTFGMHWRQAPGKGLEWVS YITSGE ~~E~~ SPIYFTDTVKGRFTISRDNKNSLYLQMNSLRAEDTAVYYCARSS YYGQ ~~Q~~ SMDYWGQGTLVTVSS	198
	HC N55E & N104E	EVQLVESGGGLVQPGGSLRLSCAASGFTFTFGMHWRQAPGKGLEWVS YITSGE ~~E~~ SPIYFTDTVKGRFTISRDNKNSLYLQMNSLRAEDTAVYYCARSS	199

		YYG E SMDYWGQGTILVTVSS	
	HC N55E & S105A	EVQLVESGGGLVQPGGSLRLSCAASGFTFTFGMHWRQAPGKGLEWVS YITSG E SPFIYFTDTVKGRFTISRDNKNSLYLQMNSLRAEDTAVYYCARSS YYGN A MDYWGQGTILVTVSS	200
	LC N31E	DIVMTQSPDSLAVSLGERATINCRSSQSLL E SGNRKNYLTWYQQKPGQPP KLLIYWASTRESGVPDFRSGSGSGTDFTLTIS S LQAEDVAVYYCQNAYSY PFTFGGGTKLEIK	201
	LC S32A	DIVMTQSPDSLAVSLGERATINCRSSQSLL N AGNRKNYLTWYQQKPGQPP KLLIYWASTRESGVPDFRSGSGSGTDFTLTIS S LQAEDVAVYYCQNAYSY PFTFGGGTKLEIK	202
72C1B6A3	HC WT	QVQLVQSGAEVKKPGASVKVSCASGYTFTTYPIEWVRQAPGQRLEWMGN FHPYND D TKYNEKFKGRVTITRDTASATAYMELSSLRSEDTAVYYCARRA YGYPYAMDYWGQGTILVTVSS	181
	LC S32A	DIVMTQSPDSLAVSLGERATINCKSSQSLL N AGNQKNYLTWYQQKPGQPP KLLIYRASSRESGVPDFRSGSGSGTDFTLTIS S LQAEDVAVYYCQNDYIY PYTFGGGTKLEIK	203
	LC N31E	DIVMTQSPDSLAVSLGERATINCKSSQSLL E SGNQKNYLTWYQQKPGQPP KLLIYRASSRESGVPDFRSGSGSGTDFTLTIS S LQAEDVAVYYCQNDYIY PYTFGGGTKLEIK	204
120B7B2	HC G57D & S104A	QVQLVQSGAEVKKPGASVKVSCASGYTFTGYIIQWVRQAPGQRLEWMGF INPYND D TKYNEQFKGRVTITRDTASATAYMELSSLRSEDTAVYYCARAY FGN A FAYWGQGTILVTVSS	205
	LC-S32A & G97A	DIVMTQSPDSLAVSLGERATINCKSSQSLL N AGNQKNYLTWYQQKPGQPP KLLIYWASTRESGVPDFRSGSGSGTDFTLTIS S LQAEDVAVYYCQNA A YYF PFTFGGGTKLEIK	206
	LC-N96E & N31E	DIVMTQSPDSLAVSLGERATINCKSSQSLL E SGNQKNYLTWYQQKPGQPP KLLIYWASTRESGVPDFRSGSGSGTDFTLTIS S LQAEDVAVYYCQ E GYFF PFTFGGGTKLEIK	207

[0193] MKN45 cells that stably expressed human CLD18A2 or CLD18A1 were harvested from flasks. 100 μ l of 1×10^6 cells/ml of cells were incubated with primary mutated humanized antibodies indicated as fig. 4 in 3-fold serial dilutions starting from 100 nM to 0.003 nM for 30 minutes on ice. After being washed with 200 μ l of FACS buffer twice, cells were incubated with secondary antibody for 30 minutes on ice. Cells were washed with 200 μ l of FACS buffer twice and transferred to BD Falcon 5 ml tube and analyzed by FACS. The results of the study showed that the indicated antibodies can bind to human CLD18A2 with high EC50, while not CLD18A1 (FIG. 12 and 13).

[0194] To evaluate the de-risked variants of 4F11E2d (HC N55E/LC S32A) and 4F11E2d (H N55E N104Q/LC S32A) antigen binding potency, the variants were tested in a cell-based binding assay. Serially diluted anti-CLDN18.2 antibodies, starting from 100nM, were incubated with 10^5 cells for 30 minutes on ice. After being washed with FACS buffer, cells were then incubated with APC labeled secondary antibody for another 30 minutes on ice. Cells bound with antibodies were analyzed by FACS. The variants showed potent binding to cell surface claudin 18.2 (FIG. 14).

Example 12. Antibody-Dependent Cellular Cytotoxicity (ADCC) of PTM de-risked humanized antibodies

[0195] Serial dilutions of claudin 18.2 PTM de-risked humanized antibodies or Ref. Ab were incubated for 6 hours of induction at 37°C with engineered Jurkat effector cells (ADCC Bioassay Effector Cells), with or without ADCC Bioassay Target Cells (expressing claudin 18.2). Luciferase activity was quantified using Bio-Glo™ Reagent (Table 5). The results show that these humanized antibodies have very strong ADCC activities.

No.	Tested antibody	EC50 (pM)
1	4F11E2 -HC N55Q-LC N31E	238.1
2	4F11E2 -HC N55Q-LC S32A	413.9
3	4F11E2 -HC N55E-LCS32A	148.1
4	72C1B6A3-HC WT-LC N31E	1651
5	72C1B6A3-HC WT- LCS32A	190.5
6	120B7B2-HC G57D&104A- LC-N96E&N31E	492.6
7	120B7B2-HC G57D&10 4A- LC-S32A&G97A	113.9
Ref. Ab	Ref. Ab	158.3

Example 13. Epitope mapping

[0196] All amino acids of extracellular domain of claudin 18.2 were single mutated to A. The each mutated or wildtype claudin 18.2 was transfected into Hek293 cells. The expression of claudin 18.2 was evaluated by indicated antibodies. The results are shown in FIG. 14 (only amino acid residues at which the mutation reduced bindings are shown).

[0197] As shown in FIG. 15, amino acids W30, N45, Y46, G48, L49, W50, C53, V54, R55, E56, S58, F60, E62, C63, R80, Y169, and G172 are involved in the binding of the three tested antibodies, 4F11E2 (H4F), 72C186A3 (H72C1) and 120B7B2 (120), or the reference antibody 175D10 (IMAB362). W30 appeared to form a cluster of residues at the first half of the first extracellular domain of the claudin 18.2 protein. N45, Y46, G48, L49, W50, C53, V54, R55, E56, S58, F60, E62 and C63 appeared to be a second cluster of residues within the same extracellular domain. Y169 and G172, on the other hand, are located at or close to the second extracellular domain.

**Example 14 . Comparison of humanized 4F11E2, 72C1B6A3 and 120B7B2 antibodies
with benchmark 175D10 claudin 18.2 antibody**

Cell based binding

[0198] To compare the humanized anti-claudin18.2 antibodies: 4F11E2 (HC N55E/LC S32A), 72C1B6A3(HC WT/ LC S32A) and 120B7B2 (HC G57D S104A/LC S32A G97A) to benchmark antibody 175D10 (IMAB362), this example determined the cell-based binding in human claudin 18.2 expressed cells. CHO-K1 cells that stably expressed human CLDN18A2 were sorted for high expressor and low expressor based on the level of human CLDN18.2 expression. Serially diluted anti-CLDN18.2 antibodies, starting from 100nM, were incubated with 10^5 cells for 30 minutes on ice. After being washed with FACS buffer, cells were then incubated with APC labeled secondary antibody for another 30 minutes on ice. Cells bound with antibodies were analyzed by FACS.

[0199] As shown in the FIG 16, 4F11E2, 72C1B6A3 and 120B7B2 showed superior binding to 175D10 in both claudin 18.2 high and low CHO-K1 cells.

ADCC assay

[0200] To further compare the ADCC effect of humanized anti-claudin18.2 antibodies: 4F11E2 (HC N55E/LC S32A), 72C1B6A3(HC WT/ LC S32A) and 120B7B2 (HC G57D S104A/LC S32A G97A) to benchmark antibody 175D10 (IMAB362), this example performed a cell based ADCC assay. Briefly, NK92 cells were cocultured with claudin18.2 overexpressed 293 cells in the presence of different dose anti-claudin 18.2 antibodies. As shown in FIG. 17, 4F11E2, 72C1B6A3 and 120B7B2 showed superior ADCC potency to the 175D10 antibody.

[0201] For certain therapeutic antibodies, enhanced ADCC may increase the therapeutic window to antibody-based target therapy. Enhanced ADCC may be achieved through engineering the Fc region such as with the S239D/I332E mutations. In a NK92 cell based ADCC assay, the 4F11E2, 72C1B6A3 and 120B7B2 antibodies with S239D/I332E mutations in the Fc region mediated stronger NK92-mediated cell killing of claudin 18.2 overexpressed 293 cells as compared to the control antibody 175D10 with the same S239D/I332E mutations (FIG. 18).

Antibody-dependent cellular phagocytosis (ADCP)

[0202] The effect of anti-CLDN 18.2 mAbs on the tumor cell phagocytosis by macrophages was evaluated in an *in vitro* assay in which CLDN18.2 positive NUG-C4 cells were co-cultured with human differentiated macrophages in the presence of different concentration of anti-CLDN18.2 mAbs. In short, CD14⁺ monocytes were purified from human peripheral blood mononuclear cells (PBMCs) and *in vitro* differentiated into mature macrophages for 6 days. The monocyte derived macrophages (MDMs) were collected and re-plated in 24-well dishes overnight as effector cells. NUG-C4 expressing CLDN 18.2-eGFP as target cells were added to MDMs at a ratio of 5 tumor cells per phagocyte in the presence of different concentrations of anti-CLDN18.2 mAbs. After 3 hours' incubation, non-phagocytosed target cells were washed away with PBS and the remaining phagocytes were collected and stained with macrophage marker CD14 followed by flow cytometry analysis. Phagocytosis index was calculated by quantitating the percent of GFP⁺ cells in CD14⁺ cells, normalized to that of IgG control.

[0203] As shown in **FIG. 19**, all C18.2 mAbs significantly enhanced the phagocytosis of NUG-C4 cells in a concentration-dependent manner. In both wildtype IgG1 and S239D/I332E mutated IgG1 formats, 4H11E2, 72C1B6A3 and 120B7B2 antibodies showed stronger ADCP effect than the reference antibody 175D10.

[0204] Taken together, this example demonstrates that the newly developed 4F11E2, 72C1B6A3 and 120B7B2 antibodies had stronger cell-based binding and ADCC/ADCP potency than the reference antibody 175D10. It is contemplated that the improved properties of these new antibodies can be attributed to the higher binding specificity of these antibodies as compared to that of the reference antibody 175D10. For instance, 175D10's interaction with claudin 18.2 is strong across the spectrum in **FIG. 15**, which includes strong binding to D28, Q33, N38 and V43, and then G59 and V79. The new antibodies, 4F11E2, 72C1B6A3 and 120B7B2, by contrast, have higher specificity to W30 within the first half of the first extracellular domain, and higher specificity to G48 through E56 within the second half of the first extracellular domain. The new antibodies also have slightly stronger binding to Y46 which is also in the second half. Their binding to D28, Q33, N38, V43, G59 and V79 is considerably weaker, which likely contributed to the improved ADCC and ADCP of the new antibodies.

[0205] The present disclosure is not to be limited in scope by the specific embodiments described which are intended as single illustrations of individual aspects of the disclosure, and any compositions or methods which are functionally equivalent are within the scope of this disclosure. It will be apparent to those skilled in the art that various modifications and variations can be made in the methods and compositions of the present disclosure without departing from the spirit or scope of the disclosure. Thus, it is intended that the present disclosure cover the modifications and variations of this disclosure provided they come within the scope of the appended claims and their equivalents.

[0206] All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

[0207] Reference to any prior art in the specification is not an acknowledgement or suggestion that this prior art forms part of the common general knowledge in any jurisdiction or that this prior art could reasonably be expected to be combined with any other piece of prior art by a skilled person in the art.

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CLAIMS

What is claimed is:

1. An antibody or fragment thereof having binding specificity to human claudin 18.2 (CLDN18.2) protein, comprising a light chain variable region comprising light chain complementarity determining regions CDRL1, CDRL2, and CDRL3 and a heavy chain variable region comprising heavy chain complementarity determining regions CDRH1, CDRH2, and CDRH3, and wherein:
 - the CDRL1 comprises the amino acid sequence of SEQ ID NO:210, or 304,
 - the CDRL2 comprises the amino acid sequence of SEQ ID NO:229,
 - the CDRL3 comprises the amino acid sequence of SEQ ID NO:8,
 - the CDRH1 comprises the amino acid sequence of SEQ ID NO:242,
 - the CDRH2 comprises the amino acid sequence of SEQ ID NO:263, and
 - the CDRH3 comprises the amino acid sequence of SEQ ID NO:289.
2. The antibody or fragment thereof of claim 1, wherein the light chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NO:124, 185-187 and 203-204.
3. The antibody or fragment thereof of claim 1 or 2, wherein the heavy chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NO:153 and 181-184.
4. The antibody or fragment thereof of claim 1, wherein:
 - the CDRL1 comprises the amino acid sequence of SEQ ID NO:304,
 - the CDRL2 comprises the amino acid sequence of SEQ ID NO:229,
 - the CDRL3 comprises the amino acid sequence of SEQ ID NO:8,
 - the CDRH1 comprises the amino acid sequence of SEQ ID NO:242,
 - the CDRH2 comprises the amino acid sequence of SEQ ID NO:263, and

the CDRH3 comprises the amino acid sequence of SEQ ID NO:289.

5. The antibody or fragment thereof of claim 4, wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO:203 and the heavy chain variable region comprises an amino acid sequence of SEQ ID NO:181.

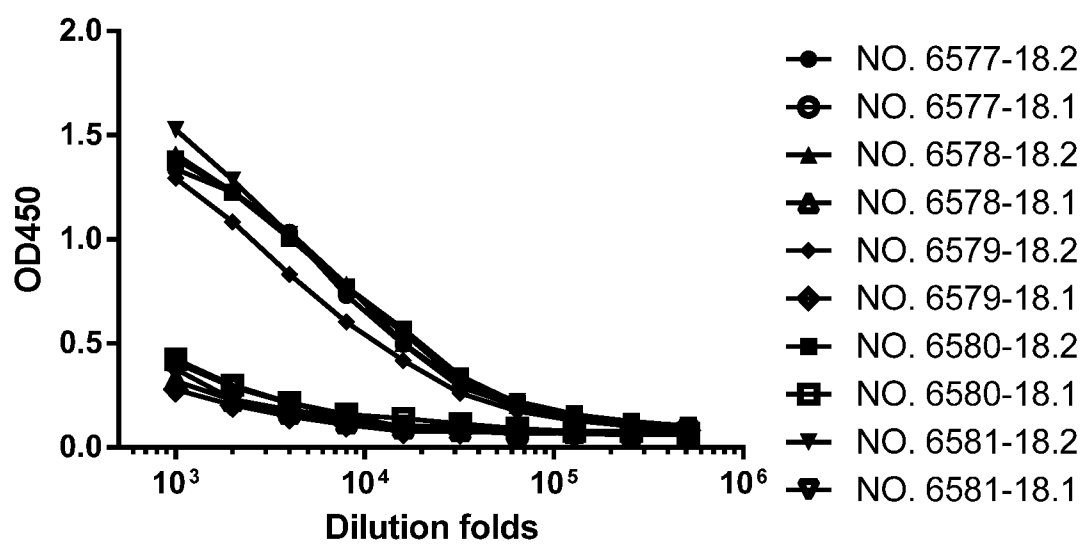
6. An antibody or fragment thereof having binding specificity to human claudin 18.2 (CLDN18.2) protein, comprising a light chain variable region comprising light chain complementarity determining regions CDRL1, CDRL2, and CDRL3 and a heavy chain variable region comprising heavy chain complementarity determining regions CDRH1, CDRH2, and CDRH3, and wherein:

- (i) the CDRL1 comprises the amino acid sequence of SEQ ID NO:216,
the CDRL2 comprises the amino acid sequence of SEQ ID NO:227,
the CDRL3 comprises the amino acid sequence of SEQ ID NO:13,
the CDRH1 comprises the amino acid sequence of SEQ ID NO:246,
the CDRH2 comprises the amino acid sequence of SEQ ID NO:268, and
the CDRH3 comprises the amino acid sequence of SEQ ID NO:294; or
- (ii) the CDRL1 comprises the amino acid sequence of SEQ ID NO:309,
the CDRL2 comprises the amino acid sequence of SEQ ID NO:227,
the CDRL3 comprises the amino acid sequence of SEQ ID NO:13,
the CDRH1 comprises the amino acid sequence of SEQ ID NO:246,
the CDRH2 comprises the amino acid sequence of SEQ ID NO:311, and
the CDRH3 comprises the amino acid sequence of SEQ ID NO:294.

7. The antibody or fragment thereof of claim 6, wherein:
the CDRL1 comprises the amino acid sequence of SEQ ID NO:309,
the CDRL2 comprises the amino acid sequence of SEQ ID NO:227,
the CDRL3 comprises the amino acid sequence of SEQ ID NO:13,

the CDRH1 comprises the amino acid sequence of SEQ ID NO:246,
the CDRH2 comprises the amino acid sequence of SEQ ID NO:311, and
the CDRH3 comprises the amino acid sequence of SEQ ID NO:294.

8. The antibody or fragment thereof of claim 7, comprising a light chain variable region comprising an amino acid sequence of SEQ ID NO:202 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:197.
9. A composition comprising the antibody or fragment thereof of any one of claims 1-8 and a pharmaceutically acceptable carrier.
10. A method of treating cancer, the method comprising administering the antibody or fragment thereof according to any one of claims 1-8, or the composition according to claim 9, wherein the cancer overexpresses claudin 18.2.
11. Use of the antibody or fragment thereof according to any one of claims 1-8, or the composition according to claim 9, in the manufacture of a medicament for treating cancer, wherein the cancer overexpresses claudin 18.2.
12. The method of claim 10 or the use of claim 11, wherein the cancer is selected from the group consisting of: bladder cancer, liver cancer, colon cancer, rectal cancer, endometrial cancer, leukemia, lymphoma, pancreatic cancer, small cell lung cancer, non-small cell lung cancer, breast cancer, urethral cancer, head and neck cancer, gastrointestinal cancer, stomach cancer, oesophageal cancer, ovarian cancer, renal cancer, melanoma, prostate cancer and thyroid cancer.

**FIG. 1**

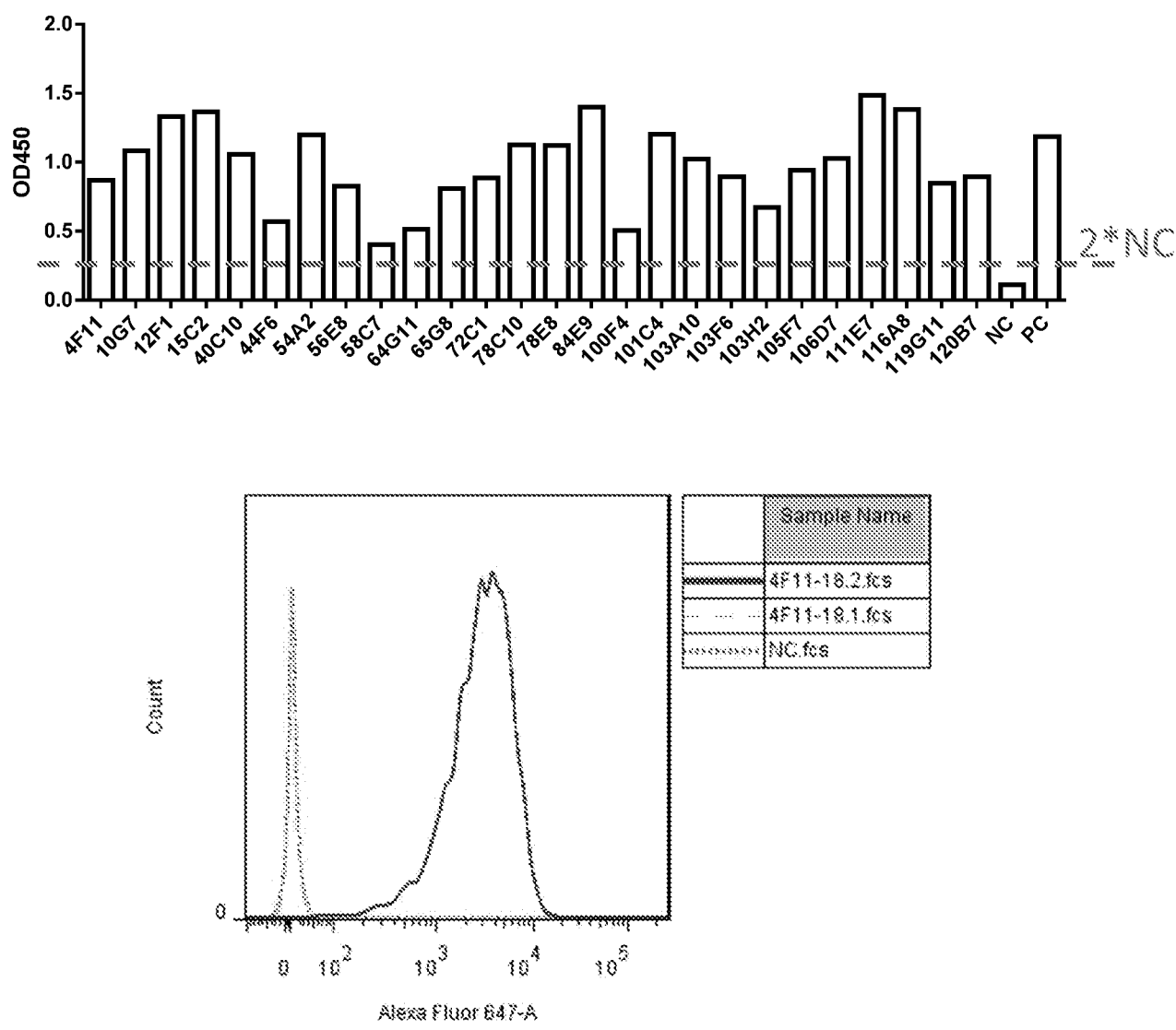


FIG. 2

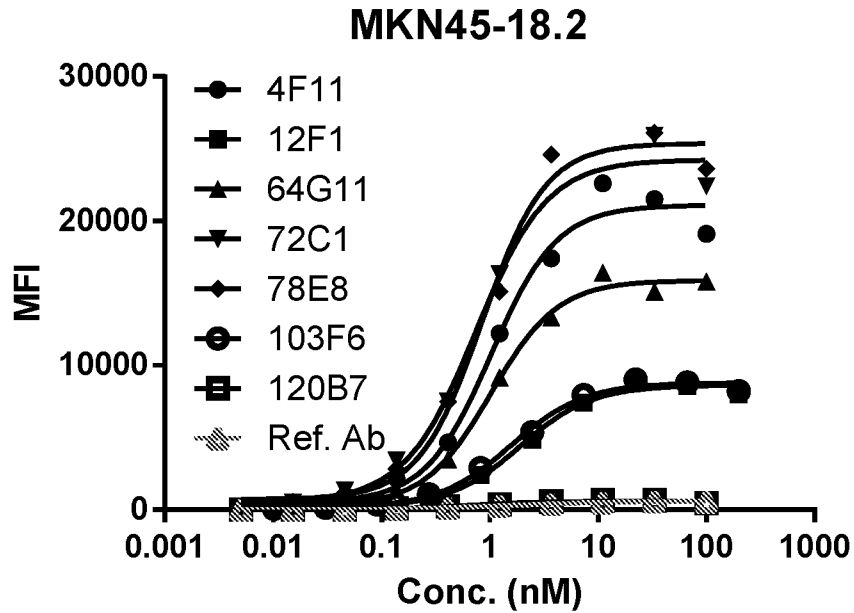


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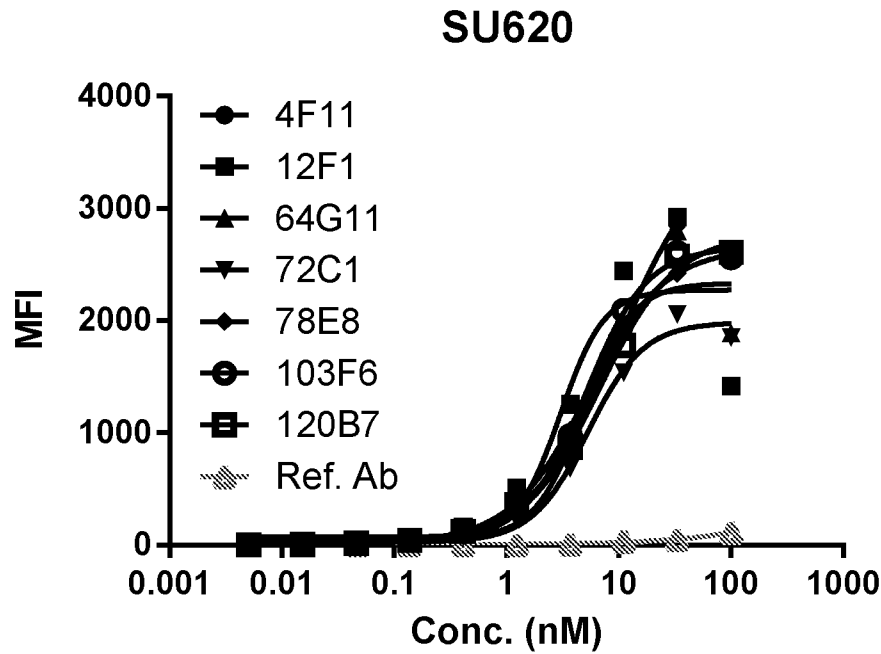


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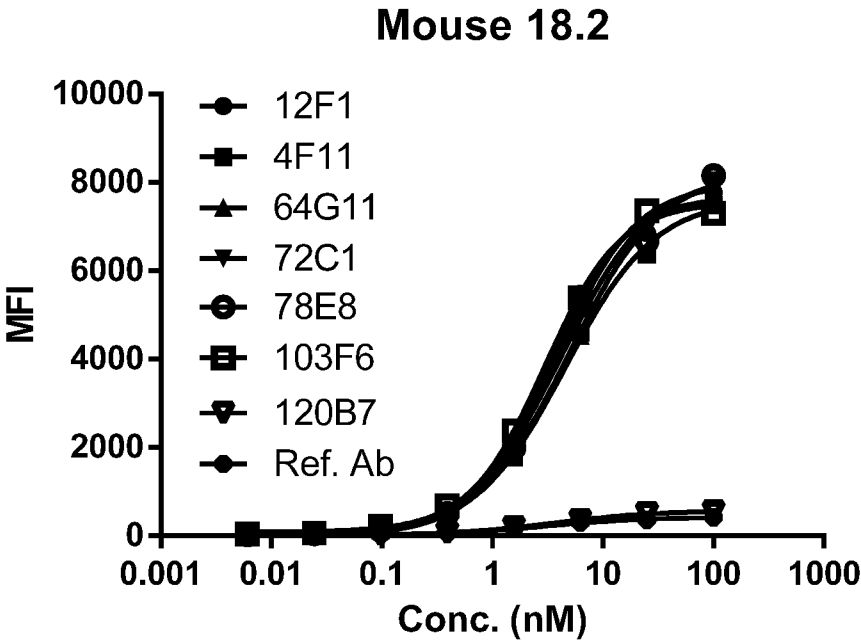


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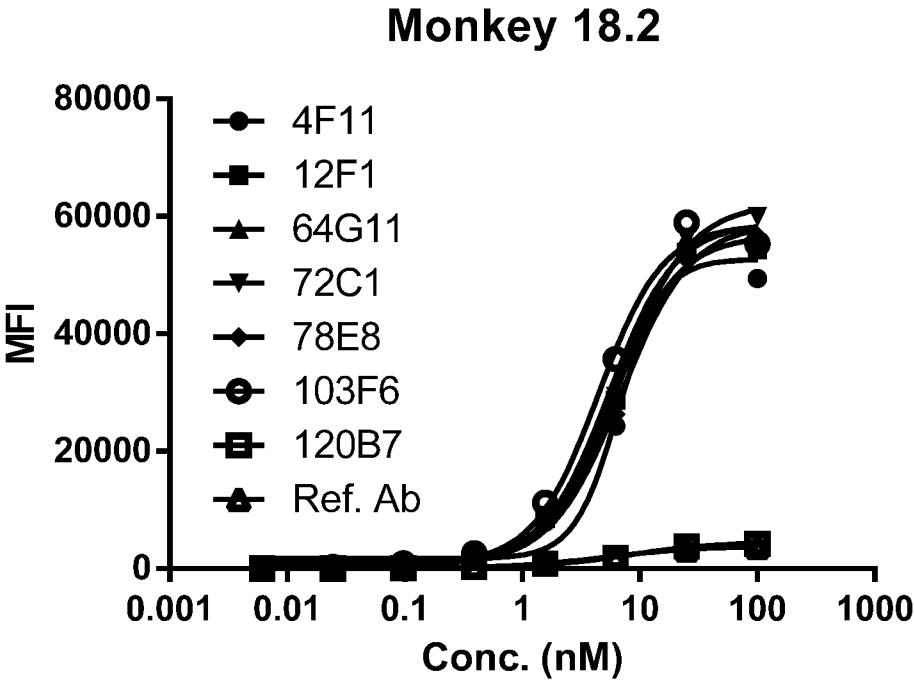
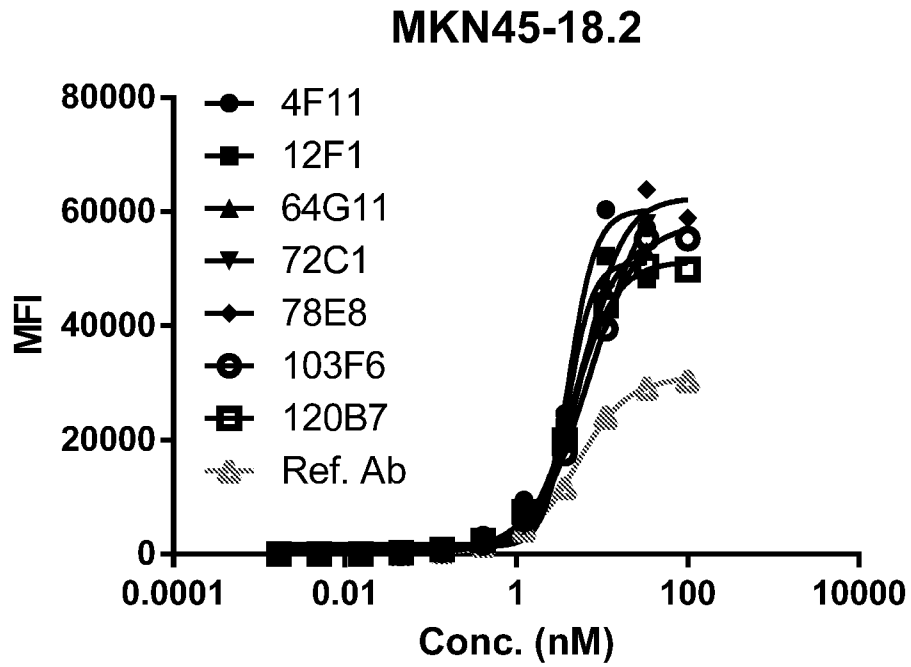
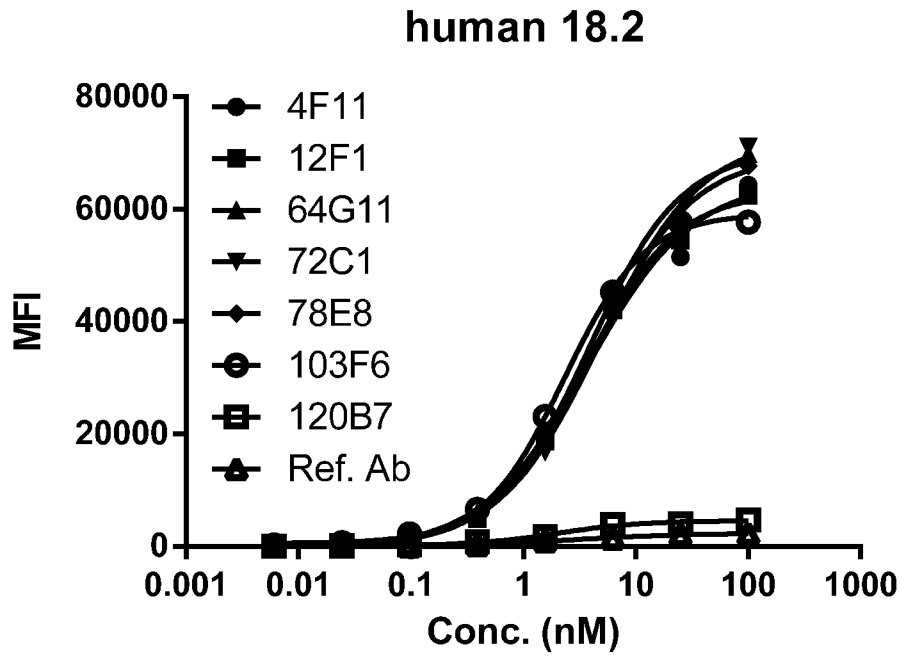


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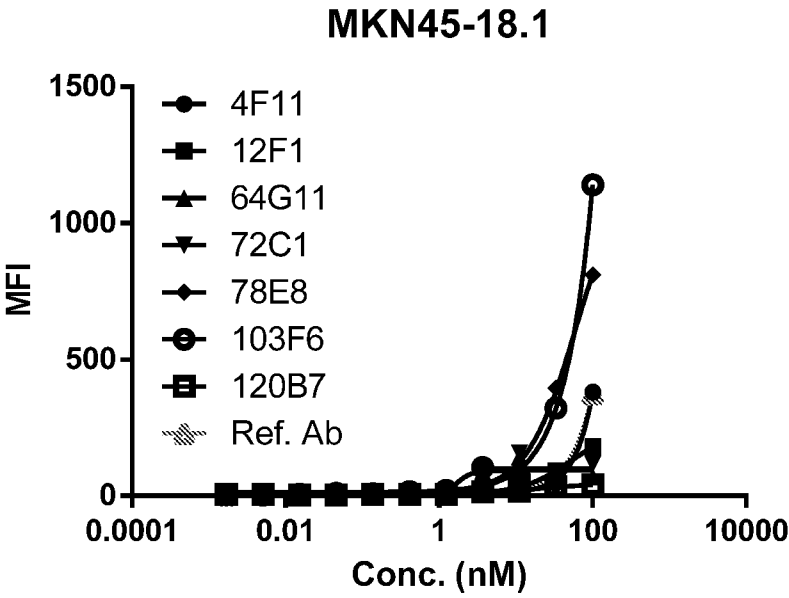


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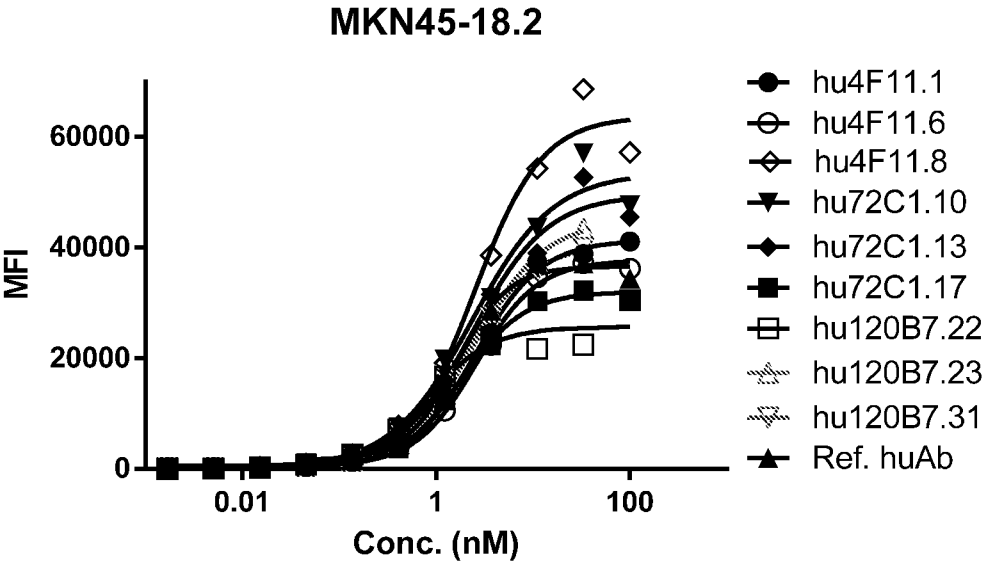
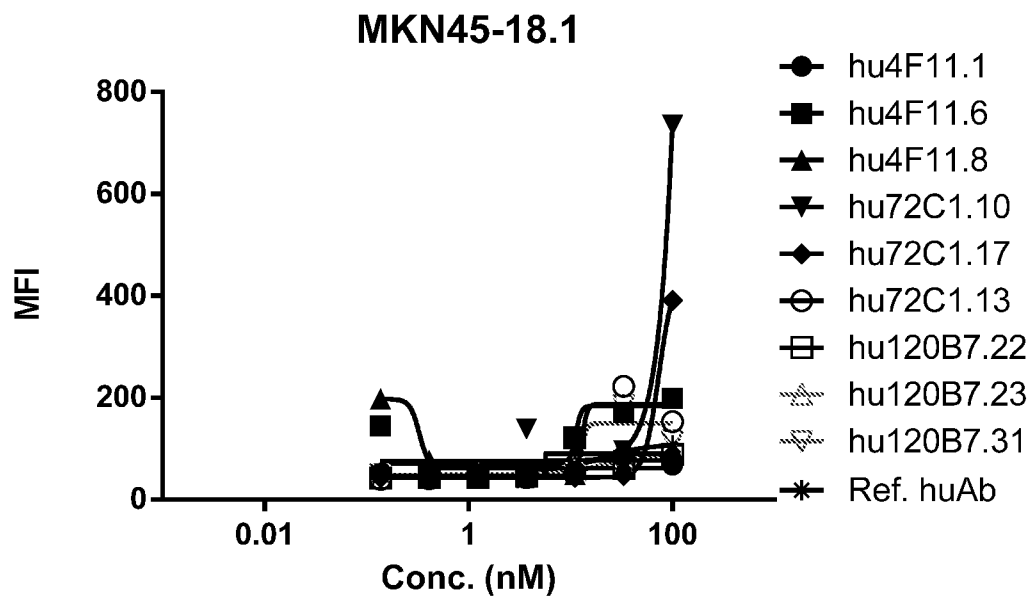
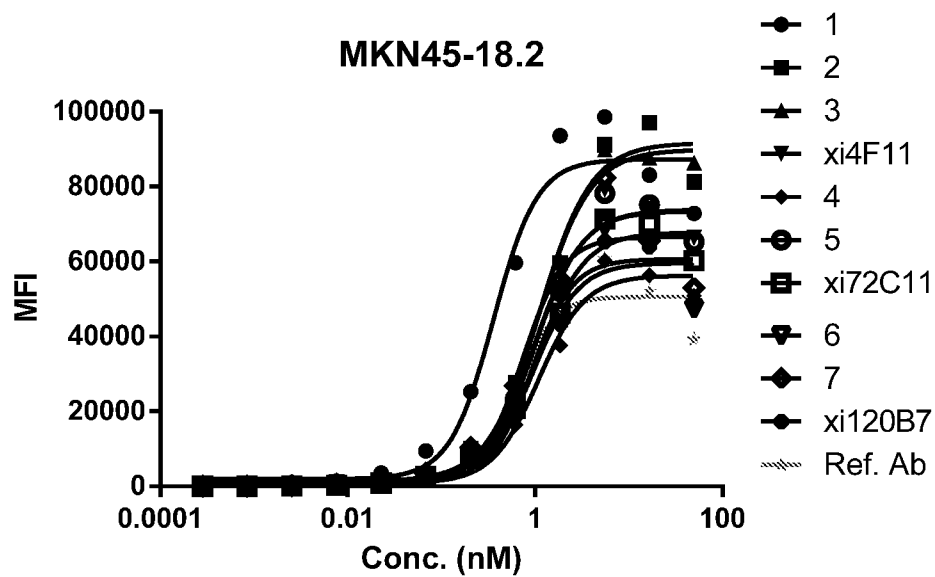


FIG. 10

**FIG. 11****FIG. 12**

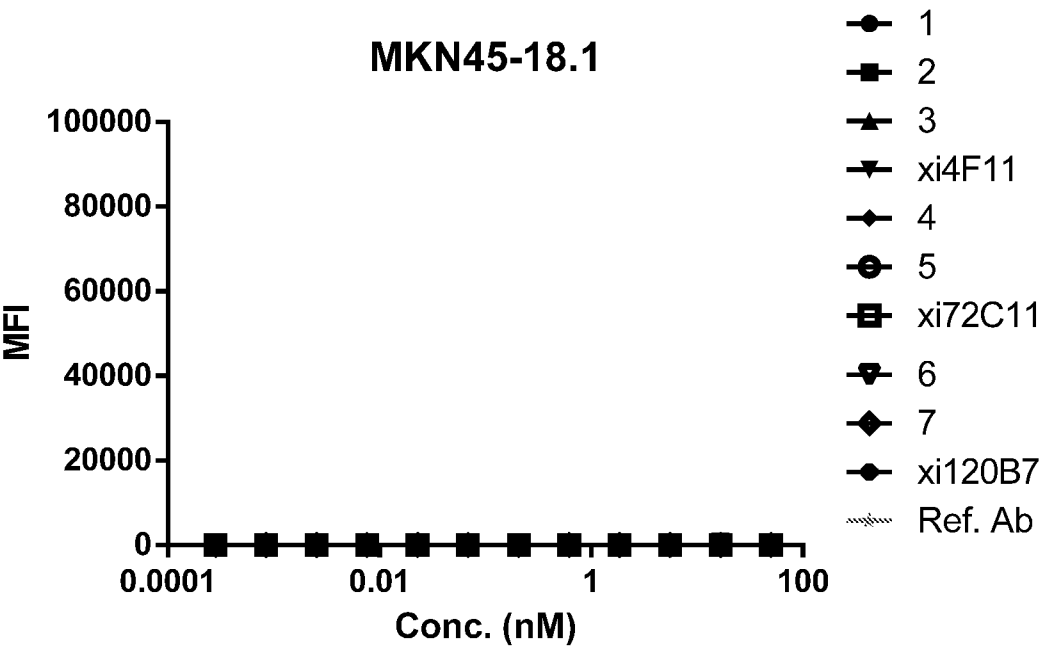


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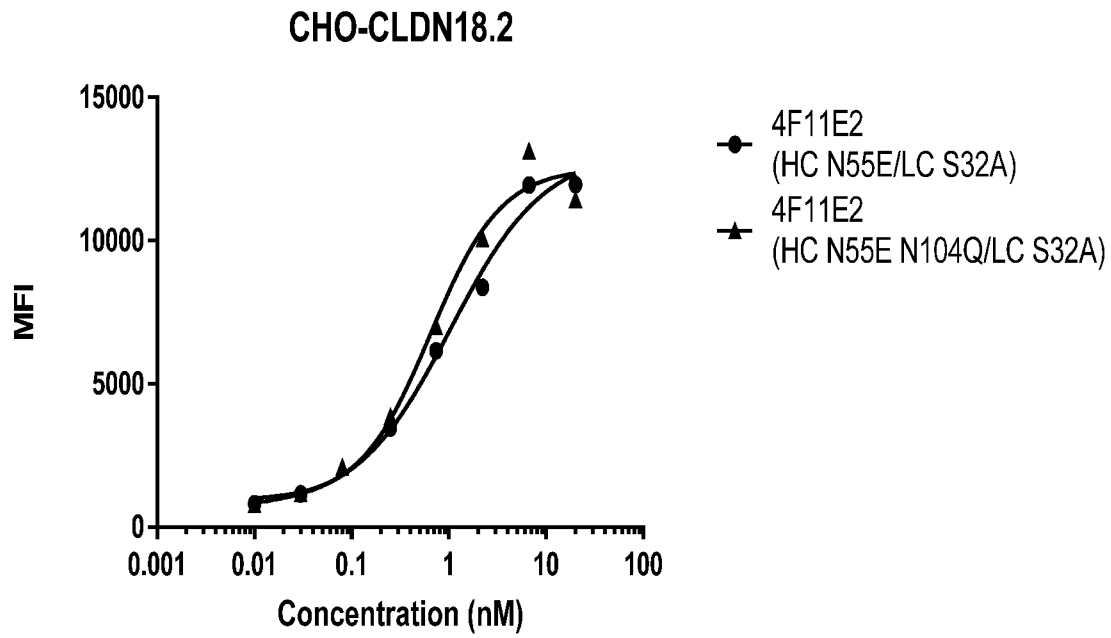


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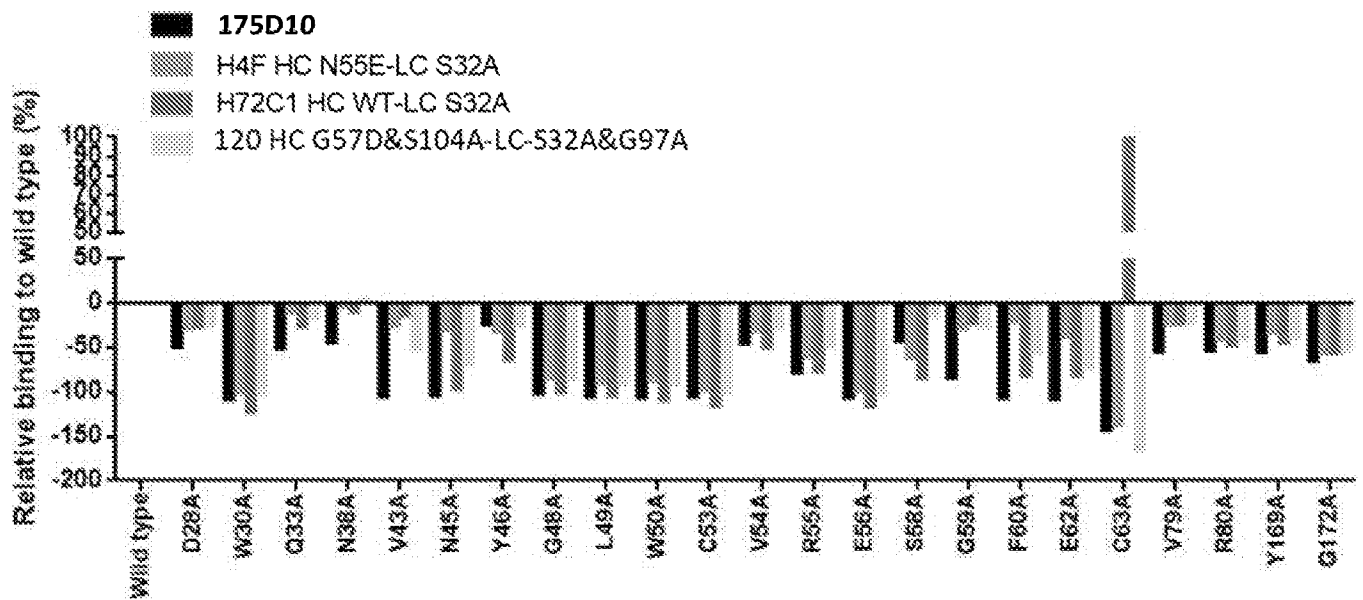
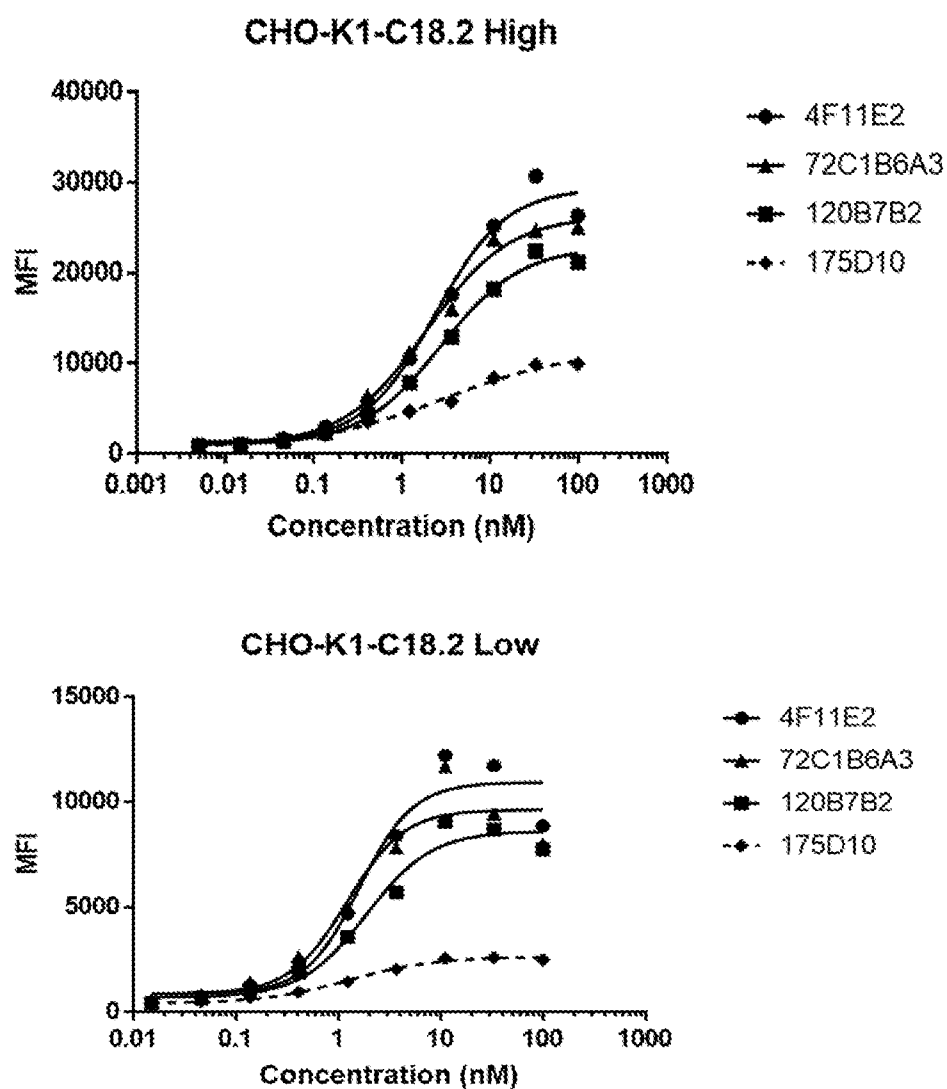


FIG. 15

**FIG. 16**

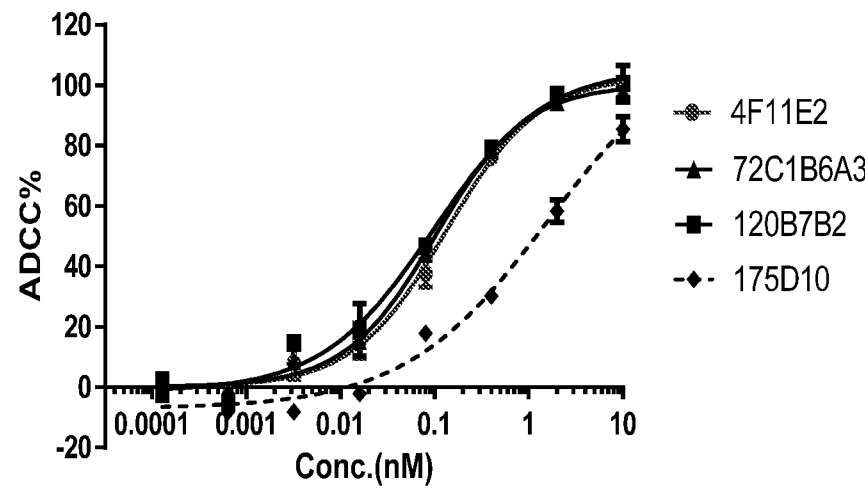


FIG. 17

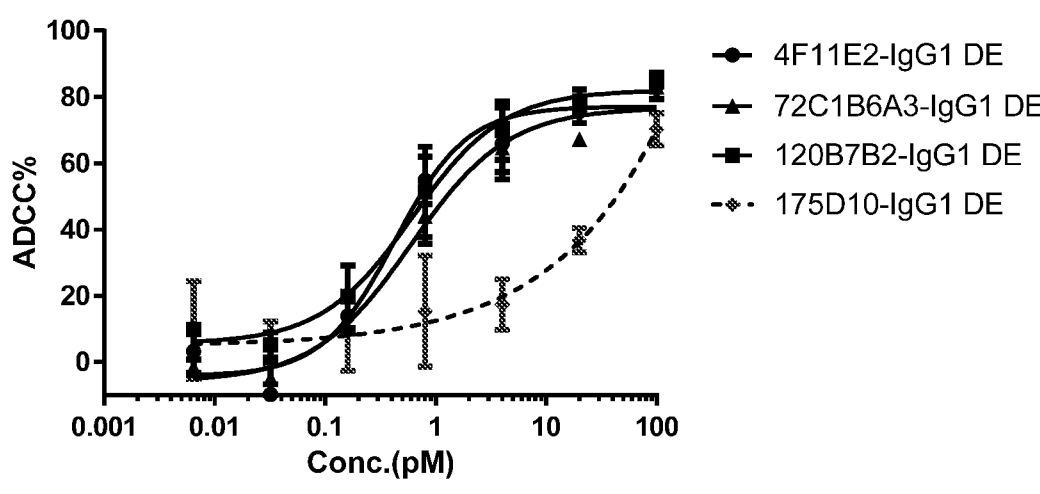


FIG. 18

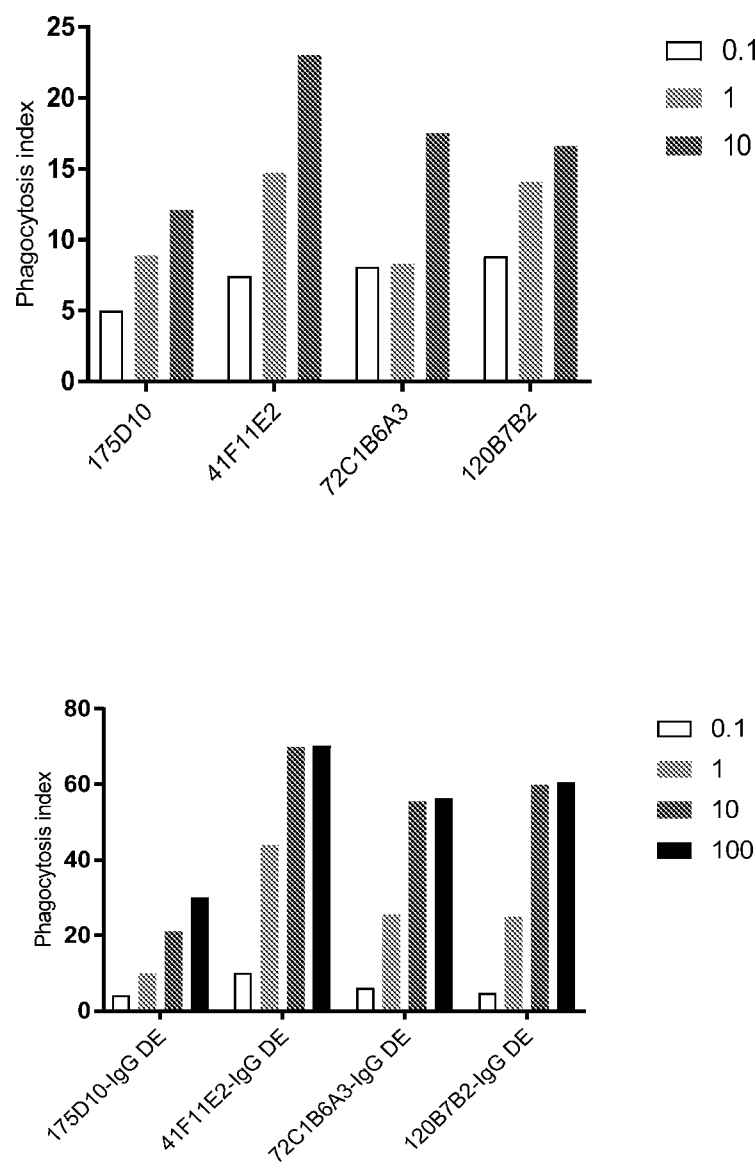


FIG. 19

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40

45

Leu Trp Arg Ser Cys Val Arg Glu Ser Ser Gly Phe Thr Glu Cys Arg

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55

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Gly Tyr Phe Thr Leu Leu Gly Leu Pro Ala Met Leu Gln Ala Val Arg

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70

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<400> 70

Gly Phe Ser Leu Asn Thr Tyr Gly
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<400> 71

Gly Phe Ser Leu Ile Asn Tyr Gly
1 5

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<400> 72

Gly Tyr Thr Phe Thr Gly Phe Leu
1 5

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<211> 8

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<223> Synthetic

<400> 73

Asp Phe Ser Leu Thr Lys Tyr Gly
1 5

<210> 74

<211> 9

<212> PRT

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<400> 74

Gly Tyr Ser Ile Thr Ser Gly Tyr Phe
1 5

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<400> 75

Gly Phe Ser Leu Ser Asn Tyr Gly
 1 5

<210> 76
 <211> 8
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<400> 76

Gly Tyr Ser Phe Thr Asn Phe Leu
 1 5

<210> 77
 <211> 8
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<400> 77

Ile Asn Pro Gly Asn Gly Gly Ser
 1 5

<210> 78
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<400> 78

Ile Trp Gly Asp Gly Asn Thr
1 5

<210> 79
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<400> 79

Ile Ser Gly Gly Ser Asn Thr Ile
1 5

<210> 80
<211> 10
<212> PRT
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<220>
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<400> 80

Ile Arg Ser Lys Ser Asn Asn Tyr Ala Thr
1 5 10

<210> 81
<211> 9
<212> PRT
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<400> 81

Ile Asn Pro Gly Asn Gly Gly Ser Asn
1 5

<210> 82
<211> 8
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<400> 82

Ile Asn Pro Ser Thr Ile Tyr Thr
1 5

<210> 83

<211> 8

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<400> 83

Phe Ser Tyr Gly Asp Ser His Asn
1 5

<210> 84

<211> 8

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<213> Artificial Sequence

<220>

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<400> 84

Ile Asn Ala Asn Thr Gly Glu Pro
1 5

<210> 85

<211> 8

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<400> 85

Ile Ser Thr Asn Thr Gly Glu Pro
1 5

<210> 86

<211> 8
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<400> 86

Ile Asn Pro Gly Arg Ser Gly Thr
 1 5

<210> 87
 <211> 7
 <212> PRT
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<220>
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<400> 87

Ile Trp Ala Gly Gly Ser Thr
 1 5

<210> 88
 <211> 7
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<220>
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<400> 88

Ile Trp Ala Gly Gly Arg Thr
 1 5

<210> 89
 <211> 7
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<220>
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<400> 89

Met Leu Ser Asp Gly Asn Thr

1 5

<210> 90
<211> 7
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<400> 90

Ile Arg Gly Asp Gly Asn Thr
1 5

<210> 91
<211> 7
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<220>
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<400> 91

Ile Trp Thr Gly Gly Asn Thr
1 5

<210> 92
<211> 7
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<220>
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<400> 92

Ile Ser Tyr Asp Gly Ser Asn
1 5

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<400> 93

Ile Trp Ala Gly Gly Asn Thr
1 5

<210> 94

<211> 8

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<213> Artificial Sequence

<220>

<223> Synthetic

<400> 94

Ile Asn Pro Thr Asn Gly Arg Thr
1 5

<210> 95

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 95

Ile Asn Pro Asn Thr Ile Tyr Thr
1 5

<210> 96

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 96

Ala Arg Ile Tyr Tyr Gly Asn Ser Phe Ala Tyr
1 5 10

<210> 97

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 97

Ala	Lys	Gln	Gly	Leu	Tyr	Gly	His	Ala	Met	Asp	Tyr
1				5					10		

<210> 98

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 98

Thr	Arg	Leu	Ala	Leu	Gly	Asn	Ala	Met	Asp	Tyr
1				5					10	

<210> 99

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 99

Val	Ser	Gly	Ala	Tyr	Tyr	Gly	Asn	Ser	Lys	Ala	Phe	Asp	Tyr
1				5					10				

<210> 100

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 100

Ala	Arg	Glu	Gly	Tyr	Gly	Arg	Gly	Asn	Ala	Met	Asp	Tyr
1				5					10			

<210> 101
 <211> 11
 <212> PRT
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<220>
 <223> Synthetic

<400> 101

Ala	Arg	Phe	Gly	Arg	Gly	Asn	Thr	Met	Asp	Tyr
1				5					10	

<210> 102
 <211> 11
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 102

Ala	Arg	Leu	Thr	Arg	Gly	Asn	Ser	Phe	Asp	Tyr
1				5					10	

<210> 103
 <211> 11
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 103

Ala	Arg	Leu	Val	Arg	Gly	Asn	Ser	Phe	Asp	Phe
1				5					10	

<210> 104
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 104

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Ala Arg Thr Arg Tyr Gly Gly Asn Ala Met Asp Tyr
1 5 10

<210> 105
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 105

Ala Arg Ser Leu Tyr Gly Asn Ser Leu Asp Ser
1 5 10

<210> 106
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 106

Ala Arg Ser Leu Tyr Gly Asn Ser Phe Asp Tyr
1 5 10

<210> 107
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 107

Ala Arg Asp Arg Tyr Gly Gly Asn Ser Leu Asp Tyr
1 5 10

<210> 108
<211> 12
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 108

Ala	Arg	His	Lys	Ala	Tyr	Gly	Asn	Ala	Met	Asp	Tyr
1				5					10		

<210> 109

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 109

Ala	Lys	Val	Gly	Arg	Gly	Asn	Ala	Met	Asp	His
1				5					10	

<210> 110

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 110

Ala	Arg	Leu	Asp	Tyr	Gly	Asn	Ala	Met	Asp	Tyr
1				5					10	

<210> 111

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 111

Ala	Arg	Asn	Gly	Tyr	Tyr	Gly	Asn	Ala	Met	Asp	Tyr
1				5					10		

<210> 112

<211> 11
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 112

Gly	Arg	Leu	Asp	Tyr	Gly	Asn	Ala	Met	Asp	Tyr
1				5					10	

<210> 113
 <211> 8
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 113

Ala	Ser	Phe	Arg	Phe	Phe	Ala	Tyr
1				5			

<210> 114
 <211> 13
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 114

Ala	Arg	His	Gly	Tyr	Gly	Lys	Gly	Asn	Ala	Met	Asp	Asn
1				5					10			

<210> 115
 <211> 11
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 115

Ala	Arg	Ile	Tyr	Tyr	Gly	Asn	Ser	Met	Asp	Tyr
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

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1

5

10

<210> 116
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 116

Ala Arg Ser Leu Tyr Gly Asn Ser Phe Asp His
1 5 10

<210> 117
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 117

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

Glu Lys Val Thr Met Asn Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

Gly Asn Gln Arg Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

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

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

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

Asp Tyr Phe Tyr Pro Phe Thr Phe Gly Ala Gly Thr Asn Leu Glu Leu

100

105

110

Lys

<210> 118
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 118

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

Glu Lys Val Thr Leu Thr Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
 20 25 30

Gly Asn Leu Lys Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly His
 35 40 45

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

Pro Val Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
 65 70 75 80

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

Val Tyr Ile Tyr Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Met
 100 105 110

Arg

<210> 119
 <211> 113
 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 119

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

Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

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

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

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Tyr Phe Thr Leu Thr
65 70 75 80

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

Asp Tyr Tyr Phe Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile
100 105 110

Lys

<210> 120

<211> 113

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 120

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

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Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Gly
20 25 30

Gly Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

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

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

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

Asp Leu Tyr Tyr Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Phe
100 105 110

Lys

<210> 121
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 121

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

Glu Lys Val Ile Met Ser Cys Lys Ser Asn Gln Ser Leu Leu Asn Ser
20 25 30

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

Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val

FSP1P180889-seq1.txt

50

55

60

Pro Asp Arg Phe Thr Gly Ser Glu Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

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

Gly Tyr Ser Tyr Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Met
100 105 110

Lys

<210> 122
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 122

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

Gly Lys Val Thr Val Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

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

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

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

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

FSP1P180889-seq1.txt

Asn Tyr Tyr Phe Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
100 105 110

Lys

<210> 123
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 123

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

Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Phe Asn Ser
20 25 30

Gly Asn Gln Arg Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

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

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Ile Leu Thr
65 70 75 80

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

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

Lys

<210> 124

FSP1P180889-seq1.txt

<211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 124

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

Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
 20 25 30

Gly Asn Gln Lys Asn Tyr Leu Thr Trp Tyr Gln Gln Arg Pro Gly Gln
 35 40 45

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

Pro Val Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
 65 70 75 80

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

Asp Tyr Ile Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Met
 100 105 110

Asn

<210> 125
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 125

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Thr Val Thr Ala Gly

FSP1P180889-seq1.txt

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

Lys

<210> 126
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 126

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

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Pro Pro Arg Leu Leu Ile Tyr Trp Ser Ser Thr Arg Asp Ser Gly Val
50 55 60

Pro Asp Arg Phe Thr Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr
65 70 75 80

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

Asn Phe Ile Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
100 105 110

Lys

<210> 127
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 127

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

Glu Lys Val Thr Met Ser Cys Arg Ser Ser Met Ser Leu Phe Asn Ser
20 25 30

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

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

Pro Val Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys His Asn

FSP1P180889-seq1.txt

85

90

95

Asp Tyr Ile Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
100 105 110

Lys

<210> 128
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 128

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

Glu Lys Val Thr Met Asn Cys Arg Ser Ile Gln Ser Leu Leu Asn Ser
20 25 30

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

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

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

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

Ser Tyr Ser Tyr Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Met
100 105 110

Lys

FSP1P180889-seq1.txt

<210> 129
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 129

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

Glu Lys Val Thr Leu Thr Cys Arg Ser Ser Gln Ser Leu Leu Asn Ser
 20 25 30

Gly Asn Arg Lys Asn Tyr Leu Thr Trp Tyr Gln Gln Ile Pro Gly Gln
 35 40 45

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

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Tyr Phe Thr Leu Thr
 65 70 75 80

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

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

Lys

<210> 130
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
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<400> 130

FSP1P180889-seq1.txt

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

Glu Lys Val Thr Met Thr Cys Lys Ser Ser Gln Ser Leu Phe Asn Ser
20 25 30

Gly Asn Gln Arg Asn Tyr Leu Thr Trp Tyr Gln Arg Lys Pro Gly Gln
35 40 45

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

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Tyr Phe Thr Leu Thr
65 70 75 80

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

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

Lys

<210> 131
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 131

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

Glu Arg Val Ser Met Thr Cys Lys Ser Ser Gln Ser Leu Phe Asn Ser
20 25 30

Gly Asn Gln Arg Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln

35

40

45

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

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
 65 70 75 80

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

Asn Tyr Tyr Tyr Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile
 100 105 110

Lys

<210> 132
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 132

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

Glu Arg Val Thr Met Arg Cys Arg Ser Thr Gln Ser Leu Phe Asn Ser
 20 25 30

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

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

Pro Asp Arg Phe Thr Gly Gly Gly Ser Gly Thr Asp Phe Thr Leu Thr
 65 70 75 80

FSP1P180889-seq1.txt

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

Ala Tyr Tyr Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Arg
100 105 110

Lys

<210> 133
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 133

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

Glu Arg Val Thr Met Ser Cys Lys Pro Ser Gln Ser Leu Leu Asn Ser
20 25 30

Gly Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Leu Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Lys Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

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

Ala Tyr Phe Tyr Pro Cys Thr Phe Gly Gly Gly Thr Lys Leu Glu Met
100 105 110

Lys

<210> 134
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 134

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

Glu Lys Val Thr Met Arg Cys Arg Ser Thr Gln Ser Leu Phe Asn Ser
 20 25 30

Gly Asn Gln Arg Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
 35 40 45

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

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
 65 70 75 80

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

Ala Tyr Tyr Tyr Pro Leu Thr Phe Gly Val Gly Thr Lys Leu Glu Arg
 100 105 110

Lys

<210> 135
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

FSP1P180889-seq1.txt

<400> 135

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

Glu Arg Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

Gly Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Leu Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Lys Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

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

Ala Tyr Phe Tyr Pro Cys Thr Phe Gly Gly Gly Thr Lys Leu Glu Met
100 105 110

Lys

<210> 136

<211> 113

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 136

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

Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Val Phe Asn Ser
20 25 30

FSP1P180889-seq1.txt

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

Pro Pro Lys Leu Leu Val Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
 50 55 60

Pro Ala Arg Phe Thr Gly Ser Gly Ser Gly Thr Val Phe Thr Leu Thr
 65 70 75 80

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

Asp Tyr Tyr Phe Pro Leu Thr Phe Gly Ala Gly Thr Arg Leu Glu Leu
 100 105 110

Lys

<210> 137
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 137

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

Glu Lys Val Thr Leu Ser Cys Arg Ser Ser Gln Ser Leu Leu Asn Gly
 20 25 30

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

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

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Tyr Phe Thr Phe Thr

FSP1P180889-seq1.txt

65		70		75		80									
Ile	Ser	Ser	Val	Gln	Ala	Glu	Asp	Leu	Ala	Val	Tyr	Tyr	Cys	Gln	Asn
			85						90					95	
Ala	Tyr	Phe	Tyr	Pro	Phe	Thr	Phe	Gly	Ala	Gly	Thr	Lys	Leu	Glu	Leu
			100					105					110		
Lys															
<210> 138															
<211> 113															
<212> PRT															
<213> Artificial Sequence															
<220>															
<223> Synthetic															
<400> 138															
Asp	Ile	Val	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Thr	Val	Thr	Ala	Gly
1				5					10					15	
Glu	Lys	Val	Thr	Met	Asn	Cys	Lys	Ser	Ser	Gln	Ser	Leu	Leu	Asn	Ser
			20					25					30		
Gly	Asn	Gln	Arg	Asn	Tyr	Leu	Ser	Trp	Tyr	Gln	Gln	Glu	Pro	Gly	Gln
		35					40					45			
Pro	Pro	Lys	Leu	Leu	Ile	Tyr	Trp	Ala	Ser	Thr	Ang	Glu	Ser	Gly	Val
	50					55					60				
Pro	Asp	Arg	Phe	Thr	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr
65					70					75				80	
Ile	Ser	Asn	Ile	Gln	Ala	Glu	Asp	Leu	Ala	Leu	Tyr	Phe	Cys	Gln	Asn
			85						90					95	
Ala	Tyr	Phe	Tyr	Pro	Phe	Thr	Phe	Gly	Ser	Gly	Thr	Lys	Leu	Glu	Ile
			100					105					110		

Lys

<210> 139
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 139

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

Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
 20 25 30

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

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

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
 65 70 75 80

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

Asn Tyr Phe Tyr Pro Leu Thr Phe Gly Val Gly Thr Lys Leu Glu Leu
 100 105 110

Lys

<210> 140
 <211> 113
 <212> PRT
 <213> Artificial Sequence

FSP1P180889-seq1.txt

<220>

<223> Synthetic

<400> 140

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

Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Phe Asn Ser
20 25 30

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

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

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Tyr Phe Thr Leu Thr
65 70 75 80

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

Asn Tyr Ile Tyr Pro Leu Ala Phe Gly Thr Gly Thr Lys Leu Glu Leu
100 105 110

Lys

<210> 141

<211> 113

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 141

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

Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser

FSP1P180889-seq1.txt

20

25

30

Gly Asn Gln Lys Asn Tyr Leu Thr Trp Tyr Gln Gln Arg Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Met Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

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

Gly Tyr Tyr Phe Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Thr
100 105 110

Lys

<210> 142
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 142

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

Glu Lys Val Thr Met Arg Cys Arg Ser Ser Gln Ser Leu Phe Asn Ser
20 25 30

Gly Asn Gln Arg Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

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

FSP1P180889-seq1.txt

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

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

Asn Tyr Ile Tyr Pro Leu Ala Phe Gly Ala Gly Thr Lys Leu Glu Leu
100 105 110

Lys

<210> 143
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 143

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

Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Phe Asn Ser
20 25 30

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

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

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

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

Asn Tyr Ile Tyr Pro Leu Ala Phe Gly Ala Gly Thr Lys Leu Glu Leu

100

105

110

Lys

<210> 144
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 144

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

Glu Lys Val Thr Met Arg Cys Lys Ser Thr Gln Ser Leu Leu Asn Ser
 20 25 30

Gly Asn Gln Arg Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
 35 40 45

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

Pro Glu Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
 65 70 75 80

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

Ala Tyr Tyr Tyr Pro Leu Thr Phe Gly Pro Gly Thr Lys Leu Glu Arg
 100 105 110

Lys

<210> 145
 <211> 118
 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 145

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Asn Tyr
20 25 30

Leu Leu Glu Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Asn Pro Gly Asn Gly Gly Ser Asn Tyr Asn Glu Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Ile Tyr Tyr Gly Asn Ser Phe Ala Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ala
115

<210> 146

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 146

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

FSP1P180889-seq1.txt

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

Gly Val Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45

Gly Val Ile Trp Gly Asp Gly Asn Thr Ile Tyr His Ser Ala Leu Lys
50 55 60

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

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

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

Ser Val Ile Val Ser Ser
115

<210> 147
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 147

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

Ser Arg Lys Leu Ser Cys Thr Ala Ser Gly Phe Thr Phe Asn Ser Phe
20 25 30

Gly Met Asn Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
35 40 45

Ala Phe Ile Ser Gly Gly Ser Asn Thr Ile His Tyr Leu Asp Thr Val

FSP1P180889-seq1.txt

50

55

60

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

Leu Gln Met Thr Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Thr Arg Leu Ala Leu Gly Asn Ala Met Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Ser Val Ile Val Ser Ser
115

<210> 148
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 148

Glu Val Gln His Val Glu Thr Gly Gly Gly Leu Val Gln Pro Lys Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Thr Asn
20 25 30

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Arg Ile Arg Ser Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
50 55 60

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

Leu Tyr Val Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Met Tyr
85 90 95

FSP1P180889-seq1.txt

Tyr Cys Val Ser Gly Ala Tyr Tyr Gly Asn Ser Lys Ala Phe Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala
115 120

<210> 149
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 149

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

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Pro Thr Tyr
20 25 30

Ser Ile His Trp Leu Lys Gln Gly Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Asn Pro Ser Thr Ile Tyr Thr Asn Tyr Asn Gln Lys Phe
50 55 60

Lys Tyr Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Glu Gly Tyr Gly Arg Gly Asn Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 150

FSP1P180889-seq1.txt

<211> 118
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 150

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

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
 20 25 30

Gly Met Ser Trp Val Arg Gln Thr Pro Asp Lys Arg Leu Glu Trp Val
 35 40 45

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

Lys Gly Arg Phe Thr Ile Ser Arg Asp Ile Ala Lys Asp Ala Leu Tyr
 65 70 75 80

Leu Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Ile Tyr Tyr Cys
 85 90 95

Ala Arg Phe Gly Arg Gly Asn Thr Met Asp Tyr Trp Gly Gln Gly Thr
 100 105 110

Ser Val Thr Val Ser Leu
 115

<210> 151
 <211> 118
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 151

Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Arg Lys Pro Gly Glu

FSP1P180889-seq1.txt

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

<210> 152
 <211> 118
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 152

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

FSP1P180889-seq1.txt

Gly Trp Ile Ser Thr Asn Thr Gly Glu Pro Thr Tyr Ala Glu Glu Phe
50 55 60

Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Phe
65 70 75 80

Leu Gln Ile Asn Asn Leu Lys Asn Glu Asp Thr Ala Thr Tyr Phe Cys
85 90 95

Ala Arg Leu Val Arg Gly Asn Ser Phe Asp Phe Trp Gly Gln Gly Ile
100 105 110

Thr Leu Thr Val Ser Ser
115

<210> 153
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 153

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

Ser Val Lys Met Ser Cys Lys Ala Phe Gly Tyr Thr Phe Thr Thr Tyr
20 25 30

Pro Ile Glu Trp Met Lys Gln Asn His Gly Lys Ser Leu Glu Trp Ile
35 40 45

Gly Asn Phe His Pro Tyr Asn Asp Asp Thr Lys Tyr Asn Glu Lys Phe
50 55 60

Lys Gly Lys Ala Lys Leu Thr Val Glu Lys Ser Ser Ser Thr Val Tyr
65 70 75 80

Leu Glu Val Ser Arg Leu Thr Ser Asp Asp Ser Ala Val Tyr Tyr Cys

FSP1P180889-seq1.txt

85

90

95

Ala Arg Arg Ala Tyr Gly Tyr Pro Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 154
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 154

Gln Val His Leu Gln Gln Ser Gly Ala Glu Val Val Arg Pro Gly Thr
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Asn Tyr
20 25 30

Leu Ile Glu Trp Ile Lys Lys Arg Pro Gly Gln Gly Leu Glu Trp Val
35 40 45

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

Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Thr Arg Tyr Gly Gly Asn Ala Met Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Ser Val Thr Val Ser Ser
115

FSP1P180889-seq1.txt

<210> 155
 <211> 117
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 155

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

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

Gly Val His Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
 35 40 45

Gly Val Ile Trp Ala Gly Gly Ser Thr Asn Tyr Asp Ser Ala Leu Met
 50 55 60

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

Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala
 85 90 95

Arg Ser Leu Tyr Gly Asn Ser Leu Asp Ser Trp Gly Pro Gly Thr Thr
 100 105 110

Leu Thr Val Ser Ser
 115

<210> 156
 <211> 117
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 156

FSP1P180889-seq1.txt

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

Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Leu Ser Leu Thr Ser Phe
20 25 30

Gly Val His Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45

Gly Val Ile Trp Ala Gly Gly Ser Thr Asn Tyr Asn Ser Ala Leu Met
50 55 60

Ser Arg Leu Ser Ile Ser Lys Asp Asn Ser Lys Ser Gln Val Tyr Leu
65 70 75 80

Lys Met His Ser Leu Gln Thr Asp Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

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

Leu Thr Val Ser Ser
115

<210> 157
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 157

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

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

Gly Val Asn Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu

FSP1P180889-seq1.txt

35

40

45

Ala Ala Ile Arg Ser Asp Gly Ile Ile Thr Tyr Asn Ser Val Leu Lys
 50 55 60

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

Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Met Phe Tyr Cys Ala
 85 90 95

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

Val Thr Val Ser Ser
 115

<210> 158
 <211> 118
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 158

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

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

Gly Val His Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
 35 40 45

Gly Val Ile Trp Ala Gly Gly Arg Thr Asn Tyr Asn Ser Ala Leu Met
 50 55 60

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

FSP1P180889-seq1.txt

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

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

Ser Val Thr Val Ser Ser
115

<210> 159
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 159

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

Ser Arg Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Phe
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
35 40 45

Ala Tyr Ile Thr Ser Gly Asn Ser Pro Ile Tyr Phe Thr Asp Thr Val
50 55 60

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

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

Ala Arg Ser Ser Tyr Tyr Gly Asn Ser Met Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Ser Val Thr Val Ser Ser

115

<210> 160
 <211> 118
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 160

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

Ser Leu Ser Ile Thr Cys Thr Ile Ser Gly Phe Ser Leu Asn Thr Tyr
 20 25 30

Gly Val His Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
 35 40 45

Val Val Met Leu Ser Asp Gly Asn Thr Val Tyr Asn Ser Ser Leu Lys
 50 55 60

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

Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala
 85 90 95

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

Ser Val Thr Val Ser Ser
 115

<210> 161
 <211> 117
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

FSP1P180889-seq1.txt

<400> 161

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

Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Ile Asn Tyr
20 25 30

Gly Val Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45

Gly Val Ile Trp Gly Asp Gly Asn Thr Asn Tyr Gln Ser Ala Leu Arg
50 55 60

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

Lys Leu Asn Ser Val His Thr Asp Gly Thr Ala Thr Tyr Tyr Cys Ala
85 90 95

Lys Val Gly Arg Gly Asn Ala Met Asp His Trp Gly Gln Gly Ile Ser
100 105 110

Val Ile Val Ser Ser
115

<210> 162

<211> 117

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 162

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

Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Ile Asn Tyr
20 25 30

FSP1P180889-seq1.txt

Gly Val Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45

Gly Val Ile Arg Gly Asp Gly Asn Thr Asn Tyr Gln Ser Ala Leu Arg
50 55 60

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

Lys Leu Asn Ser Val His Thr Asp Gly Thr Ala Thr Tyr Tyr Cys Ala
85 90 95

Lys Val Gly Arg Gly Asn Ala Met Asp His Trp Gly Gln Gly Ile Ser
100 105 110

Val Ile Val Ser Ser
115

<210> 163
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 163

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

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Phe
20 25 30

Leu Met His Trp Val Lys Gln Lys Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Ser Glu Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser Thr Ala Phe

FSP1P180889-seq1.txt

65		70		75		80
Met	Glu	Leu	Ser	Ser	Leu	Thr
			85			
				Asp	Asp	Ser
				90		
					Ala	Val
						Tyr
						Tyr
						95
						Cys
Ala	Arg	Leu	Asp	Tyr	Gly	Asn
			100			Ala
						105
						Met
						Asp
						Tyr
						Trp
						Gly
						Gln
						110
						Gly
						Thr
Ser	Val	Thr	Val	Ser	Ser	
						115
<210>	164					
<211>	118					
<212>	PRT					
<213>	Artificial Sequence					
<220>						
<223>	Synthetic					
<400>	164					
Gln	Val	Gln	Leu	Lys	Gln	Ser
1			5			
						Gly
						Pro
						Gly
						10
						Leu
						Val
						Gln
						Pro
						Ser
						15
						Gln
Ser	Leu	Ser	Ile	Thr	Cys	Thr
			20			Val
						Ser
						25
						Asp
						Phe
						Ser
						Leu
						Thr
						30
						Lys
						Tyr
Gly	Val	His	Trp	Phe	Arg	Gln
						Ser
						40
						Pro
						Gly
						Lys
						Gly
						45
						Leu
						Glu
						Trp
						Leu
Gly	Val	Ile	Trp	Thr	Gly	Gly
						55
						Asn
						Thr
						Asp
						Tyr
						60
						Asn
						Pro
						Ala
						Leu
						Ile
Pro	Arg	Leu	Ser	Phe	Arg	Lys
65						70
						Asp
						Asn
						Ser
						Lys
						75
						Ser
						Gln
						Val
						Phe
						80
						Phe
Lys	Met	Asn	Ser	Leu	Gln	Ser
						85
						Ser
						Asp
						Thr
						90
						Ala
						Val
						Tyr
						Tyr
						95
						Cys
						Ala
Arg	Asn	Gly	Tyr	Tyr	Gly	Asn
						100
						Ala
						Met
						105
						Asp
						Tyr
						Trp
						Gly
						Gln
						110
						Gly
						Thr

FSP1P180889-seq1.txt

Ser Val Thr Val Ser Ser
115

<210> 165
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 165

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

Ser Val Lys Met Ser Cys Lys Ser Ser Gly Tyr Thr Phe Thr Gly Phe
20 25 30

Leu Met His Trp Val Lys Gln Lys Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Ser Glu Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

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

Gly Arg Leu Asp Tyr Gly Asn Ala Met Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Ser Val Thr Val Ser Ser
115

<210> 166
<211> 115
<212> PRT
<213> Artificial Sequence

FSP1P180889-seq1.txt

<220>

<223> Synthetic

<400> 166

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

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

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

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

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

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

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

Val Ser Ala
115

<210> 167

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 167

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

Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Ser Asn Tyr

FSP1P180889-seq1.txt

20

25

30

Gly Val Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45

Gly Val Ile Trp Ala Gly Gly Asn Thr Asn Tyr Asn Ser Ala Leu Met
50 55 60

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

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

Arg His Gly Tyr Gly Lys Gly Asn Ala Met Asp Asn Trp Gly Gln Gly
100 105 110

Thr Ser Val Thr Val Ser Ser
115

<210> 168
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 168

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

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Asn Phe
20 25 30

Leu Thr His Trp Val Arg Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Asn Pro Thr Asn Gly Arg Thr Tyr Tyr Asn Glu Lys Phe
50 55 60

FSP1P180889-seq1.txt

Lys Arg Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Thr Thr Val Tyr
65 70 75 80

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

Ala Arg Ile Tyr Tyr Gly Asn Ser Met Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ala
115

<210> 169
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 169

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

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Pro Thr Tyr
20 25 30

Ser Ile His Trp Leu Lys Gln Gly Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Asn Pro Asn Thr Ile Tyr Thr Asn Tyr Asn Gln Lys Phe
50 55 60

Lys Tyr Lys Thr Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Glu Gly Tyr Gly Arg Gly Asn Ala Met Asp Tyr Trp Gly Gln

100

105

110

Gly Thr Ser Val Thr Val Ser Ser
 115 120

<210> 170
 <211> 117
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 170

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

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

Gly Val His Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
 35 40 45

Gly Val Ile Trp Ala Gly Gly Ser Thr Asn Tyr Asp Ser Ala Leu Met
 50 55 60

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

Lys Met Thr Ser Leu Gln Thr Asp Asp Thr Ala Met Tyr Tyr Cys Ala
 85 90 95

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

Leu Thr Val Ser Ser
 115

<210> 171
 <211> 118
 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 171

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

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
20 25 30

Ile Ile Gln Trp Met Lys Gln Lys Pro Gly Leu Gly Leu Glu Trp Ile
35 40 45

Gly Phe Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn Glu Gln Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Asn Ala Ala Tyr
65 70 75 80

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

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

Leu Val Thr Val Ser Ala
115

<210> 172

<211> 117

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 172

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

FSP1P180889-seq1.txt

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

Gly Val His Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45

Gly Val Ile Trp Ala Gly Gly Ser Thr Asn Tyr Asp Ser Thr Leu Met
50 55 60

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

Lys Met Thr Ser Leu Gln Thr Asp Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

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

Leu Thr Val Ser Ser
115

<210> 173
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 173

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

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

Gly Ala His Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45

Gly Val Ile Trp Ala Gly Gly Ser Thr Asn Tyr Asp Ser Ala Leu Met

FSP1P180889-seq1.txt

50

55

60

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

Lys Met Thr Ser Leu Gln Thr Asp Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

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

Leu Thr Val Ser Ser
115

<210> 174
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 174

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

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Phe
20 25 30

Leu Met His Trp Val Lys Gln Lys Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Ser Glu Arg Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

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

FSP1P180889-seq1.txt

Ala Arg Leu Asp Tyr Gly Asn Ala Met Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Ser Val Thr Val Ser Ser
115

<210> 175
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 175

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Phe
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Thr Ser Gly Asn Ser Pro Ile Tyr Phe Thr Asp Thr Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

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

Ala Arg Ser Ser Tyr Tyr Gly Asn Ser Met Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 176

FSP1P180889-seql.txt

<211> 119
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 176

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Phe
 20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ala Tyr Ile Thr Ser Gly Asn Ser Pro Ile Tyr Phe Thr Asp Thr Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
 65 70 75 80

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

Ala Arg Ser Ser Tyr Tyr Gly Asn Ser Met Asp Tyr Trp Gly Gln Gly
 100 105 110

Thr Leu Val Thr Val Ser Ser
 115

<210> 177
 <211> 119
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 177

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

FSP1P180889-seq1.txt

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

<210> 178
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 178

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

FSP1P180889-seq1.txt

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

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

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

Ala Tyr Ser Tyr Pro Phe Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
100 105 110

Lys

<210> 179
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 179

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

Glu Arg Ala Thr Ile Asn Cys Arg Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

Gly Asn Arg Lys Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

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

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Val Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Asn

FSP1P180889-seq1.txt

85

90

95

Ala Tyr Ser Tyr Pro Phe Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
100 105 110

Lys

<210> 180
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 180

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

Glu Arg Val Thr Leu Asn Cys Arg Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

Gly Asn Arg Lys Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

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

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

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

Ala Tyr Ser Tyr Pro Phe Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
100 105 110

Lys

FSP1P180889-seq1.txt

<210> 181
 <211> 120
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 181

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Thr Tyr
 20 25 30

Pro Ile Glu Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
 35 40 45

Gly Asn Phe His Pro Tyr Asn Asp Asp Thr Lys Tyr Asn Glu Lys Phe
 50 55 60

Lys Gly Arg Val Thr Ile Thr Arg Asp Thr Ser Ala 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 Arg Ala Tyr Gly Tyr Pro Tyr Ala Met Asp Tyr Trp Gly Gln
 100 105 110

Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 182
 <211> 120
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 182

FSP1P180889-seq1.txt

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Thr Tyr
20 25 30

Pro Ile Glu Trp Met Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
35 40 45

Gly Asn Phe His Pro Tyr Asn Asp Asp Thr Lys Tyr Asn Glu Lys Phe
50 55 60

Lys Gly Arg Val Thr Ile Thr Val Asp Thr Ser Ala 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 Arg Ala Tyr Gly Tyr Pro Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 183
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 183

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Thr Tyr
20 25 30

Pro Ile Glu Trp Met Lys Gln Ala Pro Gly Gln Arg Leu Glu Trp Met

FSP1P180889-seq1.txt

35

40

45

Gly Asn Phe His Pro Tyr Asn Asp Asp Thr Lys Tyr Asn Glu Lys Phe
50 55 60

Lys Gly Arg Val Thr Ile Thr Val Asp Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80

Met Glu Val Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Ala Tyr Gly Tyr Pro Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 184

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 184

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

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Thr Tyr
20 25 30

Pro Ile Glu Trp Met Lys Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
35 40 45

Gly Asn Phe His Pro Tyr Asn Asp Asp Thr Lys Tyr Asn Glu Lys Phe
50 55 60

Lys Gly Arg Val Thr Leu Thr Val Asp Thr Ser Ala Ser Thr Val Tyr
65 70 75 80

FSP1P180889-seq1.txt

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

Ala Arg Arg Ala Tyr Gly Tyr Pro Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 185
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 185

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

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

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

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

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

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

Asp Tyr Ile Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
100 105 110

Lys

FSP1P180889-seq1.txt

<210> 186
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 186

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

Glu Arg Ala Thr Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
 20 25 30

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

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

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
 65 70 75 80

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

Asp Tyr Ile Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
 100 105 110

Lys

<210> 187
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

FSP1P180889-seq1.txt

<400> 187

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

Glu Arg Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

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

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

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

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

Asp Tyr Ile Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
100 105 110

Lys

<210> 188

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 188

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
20 25 30

FSP1P180889-seq1.txt

Ile Ile Gln Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
35 40 45

Gly Phe Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn Glu Gln Phe
50 55 60

Lys Gly Arg Val Thr Ile Thr Arg Asp Thr Ser Ala 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 Ala Tyr Phe Gly Asn Ser Phe Ala Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 189
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 189

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
20 25 30

Ile Ile Gln Trp Met Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
35 40 45

Gly Phe Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn Glu Gln Phe
50 55 60

Lys Gly Arg Val Thr Ile Thr Ser Asp Thr Ser Ala Ser Ala Ala Tyr

FSP1P180889-seq1.txt

65		70		75		80
Met	Glu	Leu	Ser	Ser	Leu	Arg
			85			
				Glu	Asp	Thr
				90		
					Ala	Val
						Tyr
						95
						Tyr
						Cys
Ala	Arg	Ala	Tyr	Phe	Gly	Asn
			100			
				Ser	Phe	Ala
				105		
					Tyr	Trp
						Gly
						110
						Gln
						Gly
						Thr
Leu	Val	Thr	Val	Ser	Ser	
						115
<210>	190					
<211>	118					
<212>	PRT					
<213>	Artificial Sequence					
<220>						
<223>	Synthetic					
<400>	190					
Gln	Val	Gln	Leu	Val	Gln	Ser
1			5			
				Gly	Ala	Glu
				10		
					Val	Val
						Lys
						Pro
						Gly
						15
						Ala
Ser	Val	Lys	Val	Ser	Cys	Lys
			20			
				Ala	Ser	Gly
				25		
					Tyr	Thr
						Phe
						Thr
						30
						Gly
						Tyr
Ile	Ile	Gln	Trp	Met	Lys	Gln
						35
						Ala
						40
						Pro
						Gly
						Gln
						Arg
						45
						Leu
						Glu
						Trp
						Ile
Gly	Phe	Ile	Asn	Pro	Tyr	Asn
						50
						Asp
						55
						Gly
						Thr
						Lys
						Tyr
						60
						Asn
						Glu
						Gln
						Phe
Lys	Gly	Arg	Ala	Thr	Ile	Thr
65						70
						Ser
						Asp
						75
						Thr
						Ser
						Ala
						Ser
						Ala
						Ala
						80
						Tyr
Met	Glu	Leu	Ser	Ser	Leu	Arg
				85		
						Glu
						90
						Asp
						Thr
						Ala
						Val
						Tyr
						95
						Tyr
						Cys
Ala	Arg	Ala	Tyr	Phe	Gly	Asn
						100
						Ser
						105
						Phe
						Ala
						Tyr
						Trp
						Gly
						110
						Gln
						Gly
						Thr

FSP1P180889-seq1.txt

Leu Val Thr Val Ser Ser
115

<210> 191
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 191

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

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
20 25 30

Ile Ile Gln Trp Met Lys Gln Ala Pro Gly Gln Arg Leu Glu Trp Ile
35 40 45

Gly Phe Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn Glu Gln Phe
50 55 60

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

Leu Val Thr Val Ser Ser
115

<210> 192
<211> 113
<212> PRT
<213> Artificial Sequence

FSP1P180889-seq1.txt

<220>

<223> Synthetic

<400> 192

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

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

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

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

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

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

Gly Tyr Tyr Phe Pro Phe Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
100 105 110

Lys

<210> 193

<211> 113

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 193

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

Glu Arg Ala Thr Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser

FSP1P180889-seq1.txt

20

25

30

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

Pro Pro Lys Leu Leu Met Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

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

Gly Tyr Tyr Phe Pro Phe Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
100 105 110

Lys

<210> 194
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 194

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

Glu Arg Ala Thr Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

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

Pro Pro Lys Leu Leu Met Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

FSP1P180889-seq1.txt

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Gly Gln Ala Glu Asp Val Ala Val Tyr Phe Cys Gln Asn
85 90 95

Gly Tyr Tyr Phe Pro Phe Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
100 105 110

Lys

<210> 195
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 195

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

Glu Arg Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

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

Pro Pro Lys Leu Leu Met Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Gly Gln Ala Glu Asp Val Ala Val Tyr Phe Cys Gln Asn
85 90 95

Gly Tyr Tyr Phe Pro Phe Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile

100

105

110

Lys

<210> 196
 <211> 119
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 196

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Phe
 20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Tyr Ile Thr Ser Gly Gln Ser Pro Ile Tyr Phe Thr Asp Thr Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
 65 70 75 80

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

Ala Arg Ser Ser Tyr Tyr Gly Asn Ser Met Asp Tyr Trp Gly Gln Gly
 100 105 110

Thr Leu Val Thr Val Ser Ser
 115

<210> 197
 <211> 119
 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 197

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Phe
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Thr Ser Gly Glu Ser Pro Ile Tyr Phe Thr Asp Thr Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

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

Ala Arg Ser Ser Tyr Tyr Gly Asn Ser Met Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 198

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 198

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

FSP1P180889-seq1.txt

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Phe
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Thr Ser Gly Glu Ser Pro Ile Tyr Phe Thr Asp Thr Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

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

Ala Arg Ser Ser Tyr Tyr Gly Gln Ser Met Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 199
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 199

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Phe
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Thr Ser Gly Glu Ser Pro Ile Tyr Phe Thr Asp Thr Val

FSP1P180889-seq1.txt

50

55

60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

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

Ala Arg Ser Ser Tyr Tyr Gly Glu Ser Met Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 200
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 200

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Phe
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Thr Ser Gly Glu Ser Pro Ile Tyr Phe Thr Asp Thr Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

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

FSP1P180889-seq1.txt

Ala Arg Ser Ser Tyr Tyr Gly Asn Ala Met Asp Tyr Trp Gly Gln Gly
 100 105 110

Thr Leu Val Thr Val Ser Ser
 115

<210> 201
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 201

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

Glu Arg Ala Thr Ile Asn Cys Arg Ser Ser Gln Ser Leu Leu Glu Ser
 20 25 30

Gly Asn Arg Lys Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
 35 40 45

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

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
 65 70 75 80

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

Ala Tyr Ser Tyr Pro Phe Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
 100 105 110

Lys

<210> 202

FSP1P180889-seq1.txt

<211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 202

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

Glu Arg Ala Thr Ile Asn Cys Arg Ser Ser Gln Ser Leu Leu Asn Ala
 20 25 30

Gly Asn Arg Lys Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
 35 40 45

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

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
 65 70 75 80

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

Ala Tyr Ser Tyr Pro Phe Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
 100 105 110

Lys

<210> 203
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 203

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly

FSP1P180889-seq1.txt

```

1             5             10             15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu Leu Asn Ala
      20                      25                      30

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

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

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65                      70                      75                      80

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

Asp Tyr Ile Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
      100                      105                      110

```

Lys

<210> 204
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 204

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

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu Leu Glu Ser
      20                      25                      30

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

```

FSP1P180889-seq1.txt

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

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

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

Asp Tyr Ile Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
100 105 110

Lys

<210> 205
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 205

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
20 25 30

Ile Ile Gln Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
35 40 45

Gly Phe Ile Asn Pro Tyr Asn Asp Asp Thr Lys Tyr Asn Glu Gln Phe
50 55 60

Lys Gly Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys

FSP1P180889-seq1.txt

85

90

95

Ala Arg Ala Tyr Phe Gly Asn Ala Phe Ala Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 206
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 206

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

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu Leu Asn Ala
20 25 30

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

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

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

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

Ala Tyr Tyr Phe Pro Phe Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
100 105 110

Lys

FSP1P180889-seq1.txt

<210> 207
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 207

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

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu Leu Glu Ser
 20 25 30

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

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

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
 65 70 75 80

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

Gly Tyr Tyr Phe Pro Phe Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
 100 105 110

Lys

<210> 208
 <211> 17
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 208

FSP1P180889-seq1.txt

Lys Ser Ser Gln Ser Leu Leu Asn Ser Gly Asn Gln Arg Asn Tyr Leu
1 5 10 15

Thr

<210> 209
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 209

Lys Ser Ser Gln Ser Leu Leu Asn Ser Gly Asn Leu Lys Asn Tyr Leu
1 5 10 15

Thr

<210> 210
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 210

Lys Ser Ser Gln Ser Leu Leu Asn Ser Gly Asn Gln Lys Asn Tyr Leu
1 5 10 15

Thr

<210> 211
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

FSP1P180889-seq1.txt

<400> 211

Lys	Ser	Ser	Gln	Ser	Leu	Leu	Asn	Gly	Gly	Asn	Gln	Lys	Asn	Tyr	Leu
1				5					10					15	

Ala

<210> 212

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 212

Lys	Ser	Asn	Gln	Ser	Leu	Leu	Asn	Ser	Gly	Asn	Gln	Lys	Lys	Tyr	Leu
1				5					10					15	

Thr

<210> 213

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 213

Lys	Ser	Ser	Gln	Ser	Leu	Phe	Asn	Ser	Gly	Asn	Gln	Arg	Asn	Tyr	Leu
1				5					10					15	

Thr

<210> 214

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 214

Arg	Ser	Ser	Met	Ser	Leu	Phe	Asn	Ser	Gly	Asn	Gln	Lys	Ser	Tyr	Leu
1				5					10					15	

Ser

<210> 215

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 215

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

Ser

<210> 216

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 216

Arg	Ser	Ser	Gln	Ser	Leu	Leu	Asn	Ser	Gly	Asn	Arg	Lys	Asn	Tyr	Leu
1				5					10					15	

Thr

<210> 217

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 217

Arg	Ser	Thr	Gln	Ser	Leu	Phe	Asn	Ser	Gly	Asn	Gln	Lys	Asn	Tyr	Leu
1				5					10					15	

Thr

<210> 218

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 218

Lys	Pro	Ser	Gln	Ser	Leu	Leu	Asn	Ser	Gly	Asn	Gln	Lys	Asn	Tyr	Leu
1				5					10					15	

Ala

<210> 219

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 219

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

Thr

<210> 220

FSP1P180889-seq1.txt

<211> 17
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 220

Lys	Ser	Ser	Gln	Ser	Leu	Leu	Asn	Ser	Gly	Asn	Gln	Lys	Asn	Tyr	Leu
1				5					10					15	

Ala

<210> 221
 <211> 17
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 221

Lys	Ser	Ser	Gln	Ser	Val	Phe	Asn	Ser	Gly	Asn	Gln	Lys	Asn	Tyr	Leu
1				5					10					15	

Thr

<210> 222
 <211> 17
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 222

Arg	Ser	Ser	Gln	Ser	Leu	Leu	Asn	Gly	Gly	Asn	Gln	Lys	Asn	Tyr	Leu
1				5					10					15	

Thr

FSP1P180889-seq1.txt

<210> 223
 <211> 17
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 223

Lys	Ser	Ser	Gln	Ser	Leu	Leu	Asn	Ser	Gly	Asn	Gln	Arg	Asn	Tyr	Leu
1				5					10					15	

Ser

<210> 224
 <211> 17
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 224

Lys	Ser	Ser	Gln	Ser	Leu	Phe	Asn	Ser	Gly	Asn	Gln	Lys	Asn	Tyr	Leu
1				5					10					15	

Thr

<210> 225
 <211> 17
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 225

Arg	Ser	Ser	Gln	Ser	Leu	Phe	Asn	Ser	Gly	Asn	Gln	Arg	Asn	Tyr	Leu
1				5					10					15	

Thr

<210> 226
 <211> 17
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 226

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

Thr

<210> 227
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 227

Trp Ala Ser Thr Arg Glu Ser
 1 5

<210> 228
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 228

Gly Ala Ser Thr Arg Glu Ser
 1 5

<210> 229
 <211> 7
 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 229

Arg Ala Ser Ser Arg Glu Ser
1 5

<210> 230

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 230

Trp Ala Phe Thr Arg Glu Ser
1 5

<210> 231

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 231

Trp Ser Ser Thr Arg Asp Ser
1 5

<210> 232

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 232

Trp Ala Ser Thr Arg Asp Ser
1 5

<210> 233
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 233

Trp Ser Ser Thr Arg Glu Ser
 1 5

<210> 234
 <211> 5
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 234

Asn Tyr Leu Leu Glu
 1 5

<210> 235
 <211> 5
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 235

Ser Tyr Gly Val Ser
 1 5

<210> 236
 <211> 5
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 236

Ser Phe Gly Met Asn
1 5

<210> 237
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 237

Thr Asn Ala Met Asn
1 5

<210> 238
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 238

Thr Tyr Ser Ile His
1 5

<210> 239
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 239

Asn Tyr Gly Met Ser
1 5

<210> 240
<211> 5
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 240

Asn	Tyr	Gly	Met	Asn
1				5

<210> 241

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 241

Lys	Tyr	Gly	Met	Asn
1				5

<210> 242

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 242

Thr	Tyr	Pro	Ile	Glu
1				5

<210> 243

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 243

Asn	Tyr	Leu	Ile	Glu
1				5

<210> 244

<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 244

Ser Tyr Gly Val His
1 5

<210> 245
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 245

Ser Phe Gly Val His
1 5

<210> 246
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 246

Thr Phe Gly Met His
1 5

<210> 247
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 247

Thr Tyr Gly Val His

1 5

<210> 248
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 248

Asn Tyr Gly Val Ser
1 5

<210> 249
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 249

Gly Phe Leu Met His
1 5

<210> 250
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 250

Lys Tyr Gly Val His
1 5

<210> 251
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 251

Ser Gly Tyr Phe Trp
1 5

<210> 252

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 252

Asn Phe Leu Thr His
1 5

<210> 253

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 253

Gly Tyr Ile Ile Gln
1 5

<210> 254

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 254

Ser Tyr Gly Ala His
1 5

<210> 255

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 255

Glu	Ile	Asn	Pro	Gly	Asn	Gly	Gly	Ser	Asn	Tyr	Asn	Glu	Lys	Phe	Lys
1				5				10						15	

Gly

<210> 256

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 256

Val	Ile	Trp	Gly	Asp	Gly	Asn	Thr	Ile	Tyr	His	Ser	Ala	Leu	Lys	Ser
1				5				10						15	

<210> 257

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 257

Phe	Ile	Ser	Gly	Gly	Ser	Asn	Thr	Ile	His	Tyr	Leu	Asp	Thr	Val	Lys
1				5				10						15	

Gly

<210> 258

<211> 19

<212> PRT

<213> Artificial Sequence

FSP1P180889-seq1.txt

<220>

<223> Synthetic

<400> 258

Arg	Ile	Arg	Ser	Lys	Ser	Asn	Asn	Tyr	Ala	Thr	Tyr	Tyr	Ala	Asp	Ser
1				5					10					15	

Val Lys Asp

<210> 259

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 259

Tyr	Ile	Asn	Pro	Ser	Thr	Ile	Tyr	Thr	Asn	Tyr	Asn	Gln	Lys	Phe	Lys
1				5					10					15	

Tyr

<210> 260

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 260

Thr	Phe	Ser	Tyr	Gly	Asp	Ser	His	Asn	Tyr	Tyr	Ser	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 261

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 261

Trp	Ile	Asn	Ala	Asn	Thr	Gly	Glu	Pro	Thr	Tyr	Ala	Glu	Glu	Phe	Lys
1				5					10					15	

Gly

<210> 262

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 262

Trp	Ile	Ser	Thr	Asn	Thr	Gly	Glu	Pro	Thr	Tyr	Ala	Glu	Glu	Phe	Lys
1				5					10					15	

Gly

<210> 263

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 263

Asn	Phe	His	Pro	Tyr	Asn	Asp	Asp	Thr	Lys	Tyr	Asn	Glu	Lys	Phe	Lys
1				5					10					15	

Gly

<210> 264

FSP1P180889-seq1.txt

<211> 17
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 264

Val	Ile	Asn	Pro	Gly	Arg	Ser	Gly	Thr	Asn	Tyr	Asn	Glu	Lys	Phe	Lys
1				5					10					15	

Gly

<210> 265
 <211> 16
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 265

Val	Ile	Trp	Ala	Gly	Gly	Ser	Thr	Asn	Tyr	Asp	Ser	Ala	Leu	Met	Ser
1				5					10					15	

<210> 266
 <211> 16
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 266

Val	Ile	Trp	Ala	Gly	Gly	Ser	Thr	Asn	Tyr	Asn	Ser	Ala	Leu	Met	Ser
1				5					10					15	

<210> 267
 <211> 16
 <212> PRT
 <213> Artificial Sequence

<220>
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FSP1P180889-seq1.txt

<400> 267

Val	Ile	Trp	Ala	Gly	Gly	Arg	Thr	Asn	Tyr	Asn	Ser	Ala	Leu	Met	Ser
1				5					10					15	

<210> 268

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 268

Tyr	Ile	Thr	Ser	Gly	Asn	Ser	Pro	Ile	Tyr	Phe	Thr	Asp	Thr	Val	Lys
1				5					10					15	

Gly

<210> 269

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 269

Val	Met	Leu	Ser	Asp	Gly	Asn	Thr	Val	Tyr	Asn	Ser	Ser	Leu	Lys	Ser
1				5					10					15	

<210> 270

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 270

Val	Ile	Trp	Gly	Asp	Gly	Asn	Thr	Asn	Tyr	Gln	Ser	Ala	Leu	Arg	Ser
1				5					10					15	

FSP1P180889-seq1.txt

<210> 271
 <211> 16
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 271

Val	Ile	Arg	Gly	Asp	Gly	Asn	Thr	Asn	Tyr	Gln	Ser	Ala	Leu	Arg	Ser
1				5				10						15	

<210> 272
 <211> 17
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 272

Tyr	Ile	Asn	Pro	Tyr	Asn	Asp	Gly	Thr	Lys	Tyr	Ser	Glu	Lys	Phe	Lys
1				5					10					15	

Gly

<210> 273
 <211> 16
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 273

Val	Ile	Trp	Thr	Gly	Gly	Asn	Thr	Asp	Tyr	Asn	Pro	Ala	Leu	Ile	Pro
1				5					10					15	

<210> 274
 <211> 16
 <212> PRT
 <213> Artificial Sequence

FSP1P180889-seq1.txt

<220>

<223> Synthetic

<400> 274

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

<210> 275

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 275

Val	Ile	Trp	Ala	Gly	Gly	Asn	Thr	Asn	Tyr	Asn	Ser	Ala	Leu	Met	Ser
1				5					10					15	

<210> 276

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 276

Glu	Ile	Asn	Pro	Thr	Asn	Gly	Arg	Thr	Tyr	Tyr	Asn	Glu	Lys	Phe	Lys
1				5					10					15	

Arg

<210> 277

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 277

Tyr	Ile	Asn	Pro	Asn	Thr	Ile	Tyr	Thr	Asn	Tyr	Asn	Gln	Lys	Phe	Lys
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

1 5 10 15

Tyr

<210> 278
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 278

Phe Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn Glu Gln Phe Lys
1 5 10 15

Gly

<210> 279
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 279

Val Ile Trp Ala Gly Gly Ser Thr Asn Tyr Asp Ser Thr Leu Met Ser
1 5 10 15

<210> 280
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 280

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

Gly

<210> 281
 <211> 9
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 281

Ile Tyr Tyr Gly Asn Ser Phe Ala Tyr
 1 5

<210> 282
 <211> 10
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 282

Gln Gly Leu Tyr Gly His Ala Met Asp Tyr
 1 5 10

<210> 283
 <211> 9
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 283

Leu Ala Leu Gly Asn Ala Met Asp Tyr
 1 5

<210> 284
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Synthetic

<400> 284

Gly	Ala	Tyr	Tyr	Gly	Asn	Ser	Lys	Ala	Phe	Asp	Tyr
1				5					10		

<210> 285

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 285

Glu	Gly	Tyr	Gly	Arg	Gly	Asn	Ala	Met	Asp	Tyr
1				5					10	

<210> 286

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 286

Phe	Gly	Arg	Gly	Asn	Thr	Met	Asp	Tyr
1				5				

<210> 287

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 287

Leu	Thr	Arg	Gly	Asn	Ser	Phe	Asp	Tyr
1				5				

<210> 288

<211> 9
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 288

Leu Val Arg Gly Asn Ser Phe Asp Phe
 1 5

<210> 289
 <211> 11
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 289

Arg Ala Tyr Gly Tyr Pro Tyr Ala Met Asp Tyr
 1 5 10

<210> 290
 <211> 10
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 290

Thr Arg Tyr Gly Gly Asn Ala Met Asp Tyr
 1 5 10

<210> 291
 <211> 9
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 291

Ser Leu Tyr Gly Asn Ser Leu Asp Ser

1 5

<210> 292
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 292

Ser Leu Tyr Gly Asn Ser Phe Asp Tyr
1 5

<210> 293
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 293

Asp Arg Tyr Gly Gly Asn Ser Leu Asp Tyr
1 5 10

<210> 294
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 294

Ser Ser Tyr Tyr Gly Asn Ser Met Asp Tyr
1 5 10

<210> 295
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 295

His Lys Ala Tyr Gly Asn Ala Met Asp Tyr
1 5 10

<210> 296

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 296

Val Gly Arg Gly Asn Ala Met Asp His
1 5

<210> 297

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 297

Leu Asp Tyr Gly Asn Ala Met Asp Tyr
1 5

<210> 298

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 298

Asn Gly Tyr Tyr Gly Asn Ala Met Asp Tyr
1 5 10

<210> 299

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 299

Phe Arg Phe Phe Ala Tyr
1 5

<210> 300

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 300

His Gly Tyr Gly Lys Gly Asn Ala Met Asp Asn
1 5 10

<210> 301

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 301

Ile Tyr Tyr Gly Asn Ser Met Asp Tyr
1 5

<210> 302

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 302

Ser Leu Tyr Gly Asn Ser Phe Asp His
1 5

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<210> 303
 <211> 9
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 303

Ala Tyr Phe Gly Asn Ser Phe Ala Tyr
 1 5

<210> 304
 <211> 17
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 304

Lys Ser Ser Gln Ser Leu Leu Asn Ala Gly Asn Gln Lys Asn Tyr Leu
 1 5 10 15

Thr

<210> 305
 <211> 17
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 305

Lys Ser Ser Gln Ser Leu Leu Glu Ser Gly Asn Gln Lys Asn Tyr Leu
 1 5 10 15

Thr

<210> 306

FSP1P180889-seq1.txt

<211> 17
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 306

Phe	Ile	Asn	Pro	Tyr	Asn	Asp	Asp	Thr	Lys	Tyr	Asn	Glu	Gln	Phe	Lys
1				5					10					15	

Gly

<210> 307
 <211> 9
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 307

Ala	Tyr	Phe	Gly	Asn	Ala	Phe	Ala	Tyr
1				5				

<210> 308
 <211> 17
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 308

Arg	Ser	Ser	Gln	Ser	Leu	Leu	Glu	Ser	Gly	Asn	Arg	Lys	Asn	Tyr	Leu
1				5					10					15	

Thr

<210> 309
 <211> 17
 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 309

Arg	Ser	Ser	Gln	Ser	Leu	Leu	Asn	Ala	Gly	Asn	Arg	Lys	Asn	Tyr	Leu
1				5					10					15	

Thr

<210> 310

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 310

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

Gly

<210> 311

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 311

Tyr	Ile	Thr	Ser	Gly	Glu	Ser	Pro	Ile	Tyr	Phe	Thr	Asp	Thr	Val	Lys
1				5					10					15	

Gly

<210> 312

<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 312

Ser	Ser	Tyr	Tyr	Gly	Gln	Ser	Met	Asp	Tyr
1				5					10

<210> 313
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 313

Ser	Ser	Tyr	Tyr	Gly	Glu	Ser	Met	Asp	Tyr
1				5					10

<210> 314
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 314

Ser	Ser	Tyr	Tyr	Gly	Asn	Ala	Met	Asp	Tyr
1				5					10