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(54) Title: ANTI-TIGIT ANTIBODY AND USES THEREOF

(54) 发明名称: 抗TIGIT抗体及其用途

(57) Abstract: A novel antibody and antibody fragment that specifically bind to TIGIT, and a composition comprising the antibody or the antibody fragment. A nucleic acid encoding the antibody or the antibody fragment thereof, a host cell containing same, and related uses, comprising therapeutic and diagnostic uses of the antibody and the antibody fragment.

(57) 摘要: 特异性结合TIGIT的新型抗体和抗体片段以及含有所述抗体或抗体片段的组合物。编码所述抗体或其抗体片段的核酸及包含其的宿主细胞, 以及相关用途, 包括抗体和抗体片段的治疗和诊断用途。



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ANTI-TIGIT ANTIBODY AND USE THEREOF

TECHNICAL FIELD

The present invention relates to a novel antibody and an antibody fragment thereof that specifically bind to TIGIT and a composition comprising the antibody or the antibody fragment. In addition, the present invention relates to a nucleic acid encoding the antibody or the antibody fragment thereof, a host cell comprising the nucleic acid, and related use. Furthermore, the present invention relates to therapeutic and diagnostic use of the antibody and the antibody fragment.

BACKGROUND

TIGIT (a T-cell immune receptor comprising Ig and ITIM domains, also known as WUCAM, Vstm3, or Vsig9) is originally discovered as a member of the CD28 family by comparison in bioinformatics. TIGIT is a co-inhibitory receptor expressed on the membrane surface of various immune cells (natural killer cells/activated T cells/memory T cells/regulatory T cells/follicular T-helper cells, *etc.*) and is a member of the immunoglobulin superfamily. It is believed that TIGIT molecules may exert a regulating effect on the immune system through three mechanisms: 1) TIGIT competes with a co-stimulatory receptor CD226 for binding to the shared ligand CD155/CD112 expressed on the surface of dendritic or cancer cells, and transmits inhibitory signals to cells expressing TIGIT so as to inhibit activation of such cells; 2) TIGIT interacts directly with the co-stimulatory receptor CD226 to disrupt homodimerization of CD226 and block its activation signal transmitted downstream; 3) after TIGIT binds to CD155 expressed in dendritic cells, the intracellular ITIM sequence transmits inhibitory signals so as to express immunosuppressive cytokines to inhibit the activation of the immune system. TIGIT may play a role in a variety of cells in the tumor microenvironment. These cells may be tumor-infiltrating CD8⁺ T cells, regulatory T cells, and NK cells as well. Overall, numerous studies suggest that the first mechanism is probably the most critical mechanism for TIGIT to exert its immunosuppressive effects.

An antibody binding to human TIGIT has been demonstrated to be useful for treating cancers. See, for example, WO 2006/124667. Antibody blockade of PD-L1 and TIGIT can increase the CD8⁺ T cell-mediated tumor rejection in a synergistic manner in a mouse model. Grogan *et al.* (2014) *J. Immunol.* 192(1) Suppl. 203.15; Johnston *et al.* (2014) *Cancer Cell* 26:1-15. Similar results are obtained in an animal model of melanoma. Inozume *et al.* (2014) *J. Invest. Dermatol.* 134:S121-Abstract 693.

In view of its role in immune responses, TIGIT is considered an attractive cancer immunotherapy target. Accordingly, there is a need in the art to develop new TIGIT antibodies, particularly CD155/CD112 blocking antibodies targeting TIGIT, more particularly human anti-TIGIT antibodies, and combination therapies thereof, for disease treatments, particularly cancer treatments.

Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of common general knowledge in the field.

SUMMARY OF THE INVENTION

In one aspect, the present disclosure provides an antibody or an antigen-binding fragment thereof that binds to TIGIT, comprising: (i) HCDR1, HCDR2 and HCDR3 sequences of a heavy chain variable region set forth in SEQ ID NOs: 99, and LCDR1, LCDR2 and LCDR3 sequences of a light chain variable region set forth in SEQ ID NO: 109; or (ii) HCDR1, HCDR2 and HCDR3 sequences of a heavy chain variable region set forth in SEQ ID NOs: 100, and LCDR1, LCDR2 and LCDR3 sequences of a light chain variable region set forth in SEQ ID NO: 109.

In another aspect, the present disclosure provides an antibody or an antigen-binding fragment thereof that binds to TIGIT, comprising three heavy chain complementarity determining regions (HCDRs) and three light chain complementarity determining regions (LCDRs), wherein: (i) HCDR1 comprises an amino acid sequence set forth in SEQ ID NO: 61, HCDR2 comprises an amino acid sequence set forth in SEQ ID NO: 63, HCDR3 comprises an amino acid sequence set forth in SEQ ID NO: 66, LCDR1 comprises an amino acid sequence set forth in SEQ ID NO: 69, LCDR2 comprises an amino acid sequence set forth in SEQ ID NO: 17, and LCDR3 comprises an amino acid sequence set forth in SEQ ID NO: 70; (ii) HCDR1 comprises an amino acid sequence set forth in SEQ ID NO: 61, HCDR2 comprises an amino acid sequence set forth in SEQ ID NO: 64, HCDR3 comprises an amino acid sequence set forth in SEQ ID NO: 67, LCDR1 comprises an amino acid sequence set forth in SEQ ID NO: 69, LCDR2 comprises an amino acid sequence set forth in SEQ ID NO: 17, and LCDR3 comprises an amino acid sequence set forth in SEQ ID NO: 70; (iii) HCDR1 comprises an amino acid sequence set forth in SEQ ID NO: 200, HCDR2 comprises an amino acid sequence set forth in SEQ ID NO: 63, HCDR3 comprises an amino acid sequence set forth in SEQ ID NOs: 201, LCDR1 comprises an amino acid sequence set forth in SEQ ID NO: 69, LCDR2 comprises an amino acid sequence set forth in SEQ ID NO: 17, and LCDR3 comprises an amino acid sequence set forth in SEQ ID NO: 70; or (iv) HCDR1 comprises an amino acid sequence set forth in SEQ ID NO: 200, HCDR2 comprises an amino acid sequence set forth in SEQ ID NO: 64, HCDR3 comprises an amino acid sequence set forth in SEQ ID NOs: 202, LCDR1 comprises an amino acid sequence set forth in SEQ ID NO: 69, LCDR2 comprises an amino acid sequence set forth in SEQ ID NO: 17, and LCDR3 comprises an amino acid sequence set forth in SEQ ID NO: 70.

In another aspect, the present disclosure provides an isolated nucleic acid encoding an anti-TIGIT antibody or the antigen-binding fragment thereof according to the invention.

In another aspect, the present disclosure provides a vector comprising a nucleic acid according to the invention.

In another aspect, the present disclosure provides a host cell comprising a nucleic acid according to the invention or a vector according to the invention.

In another aspect, the present disclosure provides a method for preparing an anti-TIGIT antibody or an antigen-binding fragment thereof, comprising cultivating a host cell according to the invention under conditions suitable for expressing a nucleic acid encoding an anti-TIGIT antibody or the antigen-binding fragment thereof according to the invention.

In another aspect, the present disclosure provides an immunoconjugate comprising an antibody or the antigen-binding fragment thereof according to the invention conjugated to a therapeutic or diagnostic agent.

In another aspect, the present disclosure provides a multispecific antibody comprising an antibody or the antigen-binding fragment thereof according to the invention.

In another aspect, the present disclosure provides a pharmaceutical composition comprising an antibody or the antigen-binding fragment thereof according to the invention, and optionally a pharmaceutical adjuvant.

In another aspect, the present disclosure provides a method for preventing or treating a tumor or an infectious disease in a subject, the method comprising administering to the subject in need thereof an effective amount of an anti-TIGIT antibody or the antigen-binding fragment thereof according to the invention, or a pharmaceutical composition according to the invention.

In another aspect, the present disclosure provides use of an effective amount of an anti-TIGIT antibody or the antigen-binding fragment thereof of the invention, or a pharmaceutical composition according to the invention, in the manufacture of a medicament for treating a tumor or an infectious disease.

In another aspect, the present disclosure provides a method for blocking binding of TIGIT to CD155 so as to reduce or eliminate the immunosuppressive effect of TIGIT in a subject, the method comprising administering to the subject an effective amount of an anti-TIGIT antibody or the antigen-binding fragment thereof according to the invention, or a pharmaceutical composition according to the invention.

In another aspect, the present disclosure provides a method for detecting TIGIT in a sample, comprising: (a) contacting the sample with an antibody or the antigen-binding fragment thereof according to the invention; and (b) detecting a complex formed by the antibody or the antigen-binding fragment and TIGIT, wherein, optionally, the antibody is detectably labeled.

The present invention provides an anti-TIGIT antibody, a coding gene thereof, and use thereof. Through the genetic engineering and yeast display, the inventor screened a fully humanized anti-human-TIGIT antibody from a human antibody library displayed on the surface of yeasts, and further obtained an affinity-matured high-affinity anti-human TIGIT antibody. The fully humanized

antibody molecule of the present invention can effectively block the binding of TIGIT to its ligand CD155, reduce or eliminate inhibitory signals transmitted to cells, increase the production of IL-2, and inhibit the tumor growth when administered *in vivo*, the tumor inhibition effect of which is particularly outstanding when administered in combination with an anti-PD-1 antibody. Therefore, the antibody of the present invention can be used for multiple purposes, including but not limited to enhancing immunization reactions, inhibiting tumor growths, resisting infections, and detecting TIGIT proteins.

The present invention provides a novel fully humanized antibody binding to human TIGIT, and an antigen-binding fragment thereof.

In some embodiments, the anti-TIGIT antibody of the present invention has one or more of the following properties:

- (i) capacity of binding to human TIGIT with high affinity;
- (ii) activity of cross-immunoreaction with monkey and/or murine TIGIT;
- (iii) effectively binding to TIGIT on cell surface;
- (iv) blocking the binding of TIGIT to its ligand CD155;
- (v) relieving the inhibition effect of the binding of CD155 to TIGIT on an IL-2 signaling pathway downstream of TIGIT;
- (vi) increasing IL-2 production in T cells;
- (vii) anti-tumor activity, *e.g.*, inhibiting tumor growth;
- (viii) having better tumor inhibitory effect in combination with anti-PD-1 antibody, *e.g.*, better inhibiting tumor growth.

In some embodiments, the present invention provides an antibody or antigen-binding fragment thereof that binds to TIGIT, comprising: HCDR1, HCDR2, and HCDR3 sequences of one of the heavy chain variable regions set forth in SEQ ID NOs: 84-103, and/or LCDR1, LCDR2, and LCDR3 sequences of the light chain variable regions set forth in SEQ ID NOs: 104-110, or a variant of a combination of the CDR sequences described above.

In some embodiments, the present invention also provides an anti-TIGIT antibody or an antigen-binding fragment thereof. The anti-TIGIT antibody and an exemplary antibody (*e.g.*, an antibody having a combination of the antibody VH and VL sequences of listed in Table B) of the present invention bind to the same or an overlapping epitope and/or compete for binding to TIGIT, and/or the anti-TIGIT antibody inhibits (*e.g.*, competitively inhibits) the exemplary antibody of the present invention.

In some embodiments, the present invention provides a nucleic acid encoding the antibody or the antigen-binding fragment thereof disclosed herein, a vector comprising the nucleic acid, and a host cell comprising the vector.

In some embodiments, the present invention provides a method for preparing the antibody or the antigen-binding fragment thereof disclosed herein.

In some embodiments, the present invention provides an immunoconjugate, a pharmaceutical composition, and a combination product comprising the antibody of the present invention.

The present invention also provides a method for blocking the binding of TIGIT to CD155 (*e.g.*, CD155 expressed on the surface of a dendritic cell or a cancer cell) in a subject using the antibody of the present invention. In some embodiments, TIGIT-mediated inhibitory signaling is reduced or eliminated in cells (particularly T cells, natural killer cells) expressing TIGIT by the method, so as to stimulate the activation of T cells and NK cells. In some embodiments, the production of IL-2 in T cells is increased by the method. In some embodiments, CD155-mediated inhibitory signaling is reduced in cells (*e.g.*, dendritic cells) expressing CD155 by the method, so as to reduce the expression of immunosuppressive cytokines. In some embodiments, the activation of the immune system is promoted by the method. Accordingly, the present invention also provides a method for preventing or treating a cancer or an infection using the antibody of the present invention.

The present invention also relates to a method for detecting TIGIT in a sample.

The present invention is further illustrated in the following drawings and specific embodiments. However, these drawings and specific embodiments should not be construed as limiting the scope of the invention, and modifications easily conceived by those skilled in the art will be included in the spirit of the present invention and the protection scope of the appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. 1A-F show the binding of antibodies expressed by yeasts to human TIGIT expressed on the surface of CHO cells before and after affinity maturation.

FIG. 2 shows the binding of 7 candidate antibodies expressed by CHO cells to human TIGIT expressed on the surface of CHO cells.

FIGS. 3A-F show the blocking ability of antibodies expressed by yeasts to CD155 before and after affinity maturation.

FIG. 4 shows the blocking ability of 7 candidate antibodies expressed by CHO cells to CD155.

FIGS. 5A-E show MOA biological activity assays for antibodies expressed by yeasts before and after affinity maturation.

FIG. 6 shows MOA biological activity assays of 7 candidate antibodies expressed by CHO cells.

FIG. 7 shows pharmacodynamic studies of candidate molecules ADI-30293 and ADI-30278 administered alone (10 mg/kg) in a human TIGIT knock-in MC38 mouse model.

FIGS. 8A-B show pharmacodynamic studies of candidate molecules ADI-30293 and ADI-30278 administered (10+1 mg/kg) in combination with an anti-PD1 antibody (antibody C, WO 2017133540A1) in a human TIGIT knock-in MC38 mouse model.

FIG. 9 shows an exemplary human TIGIT sequence used in examples of the present invention.

DETAILED DESCRIPTION

Definitions

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as those commonly understood by those of ordinary skill in the art. For the purposes of the present invention, the following terms are defined below.

The term "about" used in combination with a numerical value is intended to encompass the numerical values in a range from a lower limit less than the specified numerical value by 5% to an upper limit greater than the specified numerical value by 5%.

The term "and/or" should be understood to refer to any one of the options or any two or more of the options.

As used herein, the term "comprise" or "include" is intended to mean that the elements, integers or steps are included, but not to the exclusion of any other elements, integers or steps. As used herein, the term "comprise" or "include", unless indicated otherwise, also encompasses the situation where the entirety consists of the described elements, integers or steps. For example, when referring to "comprise" an antibody variable region of a particular sequence, it is also intended to encompass an antibody variable region consisting of the particular sequence.

As used herein, the term "antibody" refers to a polypeptide comprising at least an immunoglobulin light chain variable region or heavy chain variable region that specifically recognizes and binds to an antigen. The term "antibody" encompasses a variety of antibody structures, including but not limited to, monoclonal antibodies, polyclonal antibodies, single-chain or multi-chain antibodies, monospecific or multispecific antibodies (*e.g.*, bispecific antibodies), fully human or chimeric or humanized antibodies, and full-length antibodies and antibody fragments, so long as they exhibit the desired antigen-binding activity.

It will be appreciated by those skilled in the art that a "whole antibody" (used interchangeably herein with "full-length antibody", "complete antibody" and "intact antibody") comprises at least two heavy chains (Hs) and two light chains (Ls). Each heavy chain consists of a heavy chain variable region (abbreviated herein as VH) and a heavy chain constant region. The heavy chain constant region consists of 3 domains CH1, CH2 and CH3. Each light chain consists of a light chain variable region (abbreviated herein as VL) and a light chain constant region. The light chain constant region consists of a domain CL. The variable regions are domains in the heavy chains or light chains of antibodies that participate in binding of the antibodies to the antigens thereof. The constant regions are not directly involved in binding of antibodies to antigens, but exhibit a variety of effector functions. The light chains of an antibody can be assigned to one of two types, kappa (κ) and lambda (λ), based on the amino acid sequence of a constant domain thereof. Depending on the amino acid sequence of the heavy chain constant region, the heavy chains of an antibody can be divided into 5 major types, *i.e.* IgA, IgD, IgE, IgG, and IgM, several of which can be further divided into subtypes, *e.g.* IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2. The heavy chain constant regions corresponding to the 5 different antibody types are called α , δ , ϵ , γ , and μ respectively. The term "isotype" refers to an antibody type determined by the heavy chain constant region of the antibody. See, for example, *Fundamental Immunology*, Ch.7 (Paul, w. Eds., 2nd edition, Raven Press, N.Y. (1989)) which is incorporated herein by reference in its entirety for all purposes.

The term "antigen-binding portion" (used interchangeably herein with "antibody fragment" and "antigen-binding fragment") of the antibody refers to an incomplete antibody molecule that comprises a portion of an intact antibody for binding to an antigen to which the intact antibody binds. It will be understood by those skilled in the art that the antigen-binding portion of an antibody generally comprises amino acid residues from a "complementarity determining region"

or a "CDR". An antigen-binding fragment may be prepared by recombinant DNA techniques, or by enzymatic or chemical cleavage of an intact antibody. The antigen-binding fragment includes, but is not limited to, a Fab, an scFab, a Fab', an F(ab')₂, a Fab'-SH, an Fv, a single-chain Fv, a diabody, a triabody, a tetrabody, a minibody, and a single-domain antibody (sdAb). For more detailed descriptions of the antibody fragment, see: *Fundamental Immunology*, W.E. Paul eds., Raven Press, N.Y. (1993); Shao Rongguang *et al.* (eds.), *Antibody Drug Research and Application*, People's Medical Publishing House (2013); Hollinger *et al.*, *PNAS USA* 90: 6444-6448 (1993); Hudson *et al.*, *Nat. Med.* 9:129-134 (2003).

The terms "human antibody" and "fully humanized antibody" are used interchangeably herein and refer to an antibody comprising variable regions in which both framework regions and CDR regions are derived from human germline immunoglobulin sequences. Furthermore, if the antibody comprises constant regions, the constant regions are also derived from human germline immunoglobulin sequences. The human antibody disclosed herein may comprises amino acid sequences (*e.g.*, mutations introduced by *in vitro* random or site-specific mutagenesis or *in vivo* somatic mutation) that are not encoded by human germline immunoglobulin sequences, for example, in CDRs, particularly in CDR3. However, as used herein, the term "human antibody" does not include antibodies in which CDR sequences derived from the germline of other mammalian species (*e.g.*, mice) are grafted into human framework sequences.

As used herein, the term "recombinant human antibody" includes all human antibodies that are prepared, expressed, produced or isolated by recombinant means, for example, (a) antibodies isolated from transgenic or transchromosomal animals (*e.g.*, mice) using human immunoglobulin genes or from hybridomas prepared from the human immunoglobulin genes; (b) antibodies isolated from host cells (*e.g.*, transfectomas) that transform to express human antibodies; (c) antibodies isolated from recombinant and combinatorial human antibody libraries (*e.g.*, yeast display libraries); and (d) antibodies prepared, expressed, produced or isolated in any other ways including splicing of human immunoglobulin genes to other DNA sequences. These recombinant human antibodies have variable regions in which both framework regions and CDR regions are derived from human germline immunoglobulin sequences. However, in certain embodiments, the recombinant human antibodies can be subjected to *in vitro* mutagenesis (or *in vivo* somatic mutagenesis in the case of transgenic animals using human Ig sequences), and the amino acid sequences of the VH and VL regions of the resulting recombinant antibodies, although derived from and related to human germline VH and VL sequences, do not naturally occur in a human antibody germline library.

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

The term "humanized antibody" refers to an antibody in which CDR sequences derived from another mammalian species, such as mice, are linked to human framework sequences. Additional framework region modifications may be introduced in the human framework sequences.

An "isolated" antibody is an antibody which has been separated from components of its natural environment. In some embodiments, the antibody is purified to a purity greater than 95% or 99% as determined by, for example, electrophoresis (*e.g.*, SDS-PAGE, isoelectric focusing (IEF), capillary electrophoresis), or chromatography (*e.g.*, ion exchange or reverse-phase HPLC). For a review of methods for assessing antibody purity, see, *e.g.*, Flatman, S. *et al.*, *J.Chrom.B* 848 (2007) 79-87.

The term "epitope" is an antigen region to which an antibody binds. Epitopes can be formed by contiguous amino acids or noncontiguous amino acids juxtaposed by tertiary folding of a protein.

Herein, TIGIT refers to a "T-cell immune receptor comprising Ig and ITIM domains". The term also includes variants, isotypes, homologs and species homologs of TIGIT. The term "human TIGIT" refers to a human sequence TIGIT. One specific human TIGIT sequence is set forth in SEQ ID NO: 208. In some embodiments, the human TIGIT sequence has at least 95%, even at least 96%, 97%, 98%, or 99% amino acid sequence identity to the human TIGIT amino acid sequence set forth in SEQ ID NO: 208. TIGIT proteins may also include fragments of TIGIT, such as fragments comprising extracellular domains, *e.g.*, fragments that retain the ability of binding to any of the antibodies disclosed herein. Herein, CD155, also known as PVR (poliovirus receptor), PVS, HVED, CD155, NECL5, TAGE4, and Necl-5, interacts with TIGIT to induce immunosuppressive signals.

The term "specifically binds to" means that an antibody selectively or preferentially binds to an antigen. If an antibody binds to human TIGIT with a K_D of about 5×10^{-7} M or less, about 1×10^{-7} M or less, about 5×10^{-8} M or less, about 1×10^{-8} M or less, about 5×10^{-9} M or less measured by biological optical interferometry, the antibody is an antibody that "specifically binds to human TIGIT". However, the antibody that specifically binds to human TIGIT may have cross-reactivity with TIGIT proteins from other species. For example, an antibody specific to human TIGIT, in some embodiments, can cross-react with TIGIT proteins from non-human species. In other embodiments, an antibody specific to human TIGIT may be completely specific to human TIGIT without exhibiting cross-reactivity to other species, or exhibiting cross-reactivity only to TIGIT from certain species.

As used herein, the term "cross-reaction" refers to the ability of an antibody to bind to TIGIT from different species. For example, the antibody binding to human TIGIT described herein may also bind to TIGIT from other species (*e.g.*, monkey and/or mouse TIGIT). A method for determining cross-reactivity includes the method described in examples, as well as standard assays known in the art, such as biological optical interferometry, or flow cytometry.

"Affinity" or "binding affinity" refers to inherent binding affinity that reflects interactions between members of a binding pair. The affinity of a molecule X for its partner Y can be generally represented by an equilibrium dissociation constant (K_D), which is the ratio of a dissociation rate constant (k_{dis}) to an association rate constant (k_{on}). Affinity can be measured by common methods known in the art. One specific method for measuring affinity is the ForteBio kinetic binding assay described herein.

For an IgG antibody, the term "high affinity" means that the antibody binds to a target antigen with a K_D of 1×10^{-7} M or less, preferably 5×10^{-8} M or less, more preferably about 1×10^{-8} M or less, most preferably about 5×10^{-9} M or less. However, "high affinity" binding may vary with antibody isotypes. For example, for IgM isotypes, "high affinity" means that an antibody has a K_D of 1×10^{-6} M or less, preferably 1×10^{-7} M or less, more preferably about 1×10^{-8} M or less.

An "antibody that competes for binding" to antigen (*e.g.*, TIGIT) with a reference antibody is an antibody that blocks the binding of the reference antibody to the antigen (*e.g.*, TIGIT) by 50% or more in a competitive assay, and conversely, the reference antibody blocks the binding of the antibody to the antigen (*e.g.*, TIGIT) by 50% or more in the competitive assay. Exemplary competitive assays are described in: "Antibodies", Harbor and Lane (Cold Spring Harbor Press,

Cold Spring Harbor, NY). The antibody that competes for binding and the reference antibody can bind to the same epitope region, *e.g.*, the same epitope, adjacent epitopes or overlapping epitopes.

An antibody that inhibits (*e.g.*, competitively inhibits) the binding of a reference antibody to its antigen refers to an antibody that inhibits 50%, 60%, 70%, 80%, 90%, or 95% or more of the binding of the reference antibody to its antigen. Conversely, the reference antibody inhibits 50%, 60%, 70%, 80%, 90%, or 95% or more of the binding of the antibody to its antigen. The binding of an antibody to its antigen can be measured by affinity (*e.g.*, equilibrium dissociation constant). Methods for determining affinity are known in the art.

An antibody that shows the same or similar binding affinity and/or specificity as a reference antibody refers to an antibody that is capable of having at least 50%, 60%, 70%, 80%, 90%, or 95% or more of the binding affinity and/or specificity of the reference antibody. This can be determined by any method known in the art for determining binding affinity and/or specificity.

The term "Fc region" is used herein to define the C-terminus region of an immunoglobulin heavy chain comprising at least a portion of the constant region. The term includes an Fc-region of native sequence and a variant Fc-region. In one embodiment, a human IgG heavy chain Fc-region extends from Cys226 or from Pro230 of a heavy chain to a carboxyl terminus. However, the C-terminus lysine (Lys447) of the Fc region may or may not be present. Unless otherwise indicated herein, the numbering of amino acid residues in the Fc-region or constant region is based on the EU numbering system, also known as the EU index, as described in Kabat, E.A., *et.al.*, *Sequences of Proteins of Immunological Interest*, 5th edition, Public Health Service, National Institutes of Health, Bethesda, MD (1991), NIH Publication 91-3242.

The term "variant" related to an antibody herein refers to an antibody that comprises a target antibody region having amino acid alterations by virtue of at least one, for example, 1-30, 1-20 or 1-10, *e.g.*, 1, 2, 3, 4 or 5 amino acid substitutions, deletions and/or insertions, when compared to the reference antibody, wherein the variant substantially retains at least one biological property (*e.g.*, antigen binding capacity) of the antibody molecule prior to alteration. The target antibody region may be the full length of the antibody, or the heavy chain variable region or the light chain variable region or a combination thereof, or one or more heavy chain CDR regions or one or more light chain CDR regions or a combination thereof. Herein, an antibody region having amino acid alterations relative to a reference antibody region is also referred to as a "variant" of the reference antibody region.

Herein, the term "sequence identity" refers to the degree to which sequences are identical on a nucleotide-by-nucleotide or amino acid-by-amino acid basis in a comparison window. The "percent sequence identity" can be calculated by the following steps: comparing two optimally aligned sequences in a comparison window; determining the number of positions in which nucleic acid bases (*e.g.*, A, T, C, G and I) or amino acid residues (*e.g.*, Ala, Pro, Ser, Thr, Gly, Val, Leu, Ile, Phe, Tyr, Trp, Lys, Arg, His, Asp, Glu, Asn, Gln, Cys, and Met) are the same in the two sequences to yield the number of matched positions; dividing the number of matched positions by the total number of positions in the comparison window (*i.e.*, the window size); and multiplying the result by 100 to yield a percent sequence identity. Optimal alignment for determining the percent

sequence identity may be achieved in a variety of ways known in the art, for example, using publicly available computer software such as BLAST, BLAST-2, ALIGN, or Megalign (DNASTAR) software. Those skilled in the art can determine suitable parameters for alignment of the sequences, including any algorithm necessary to yield optimal alignment within a full-length sequence range or target sequence region being compared.

Herein, with respect to antibody sequences, the percent amino acid sequence identity is determined by optimally aligning a candidate antibody sequence with a reference antibody sequence, and in a preferred embodiment, optimal alignment is performed according to the Kabat numbering scheme. Herein, without specifying the comparison window (*i.e.* the target antibody region to be compared), it will be applicable to align over the full length of the reference antibody sequence. In some embodiments, with respect to antibodies, the sequence identity may be achieved throughout the heavy chain variable region and/or the light chain variable region, or the percent sequence identity may be limited to the framework regions only, while the sequences of corresponding CDR regions remain 100% identical.

Similarly, with respect to antibody sequences, a candidate antibody having amino acid alterations in the target antibody region relative to a reference antibody can be determined based on the alignment.

Herein, "conservative substitution" refers to an amino acid alteration that results in the replacement of an amino acid with a chemically similar amino acid. Amino acid modifications such as substitutions can be introduced into the antibody of the invention by standard methods known in the art, such as site-directed mutagenesis and PCR-mediated mutagenesis.

Conservative replacement tables that provide functionally similar amino acids are well known in the art. In a preferred aspect, conservatively substituted residues are from the Table A of conservative substitutions below, preferably are the preferred conservatively substituted residues shown in Table A.

25

Table A

Primitive residue	Exemplary substitution	Preferred conservative substitution
Ala (A)	Val; Leu; Ile	Val
Arg (R)	Lys; Gln; Asn	Lys
Asn (N)	Gln; His; Asp; Lys; Arg	Gln
Asp (D)	Glu; Asn	Glu
Cys (C)	Ser; Ala	Ser
Gln (Q)	Asn; Glu	Asn
Glu (E)	Asp; Gln	Asp
Gly (G)	Ala	Ala
His (H)	Asn; Gln; Lys; Arg	Arg
Ile (I)	Leu; Val; Met; Ala; Phe; Nle	Leu
Leu (L)	Nle; Ile; Val; Met; Ala; Phe	Ile
Lys (K)	Arg; Gln; Asn	Arg

Met (M)	Leu; Phe; Ile	Leu
Phe (F)	Trp; Leu; Val; Ile; Ala; Tyr	Tyr
Pro (P)	Ala	Ala
Ser (S)	Thr	Thr
Thr (T)	Val; Ser	Ser
Trp (W)	Tyr; Phe	Tyr
Tyr (Y)	Trp; Phe; Thr; Ser	Phe
Val (V)	Ile; Leu; Met; Phe; Ala; Nle	Leu

All aspects of the present invention are further detailed in the following sections.

I. Anti-TIGIT antibody of the present invention

In one aspect, the present invention provides an antibody or an antigen-binding fragment thereof, particularly a fully humanized antibody or an antigen-binding fragment thereof, that specifically binds to TIGIT, preferably a human TIGIT protein (*e.g.*, the human TIGIT sequence of SEQ ID NO: 208). In some embodiments, the antigen-binding fragment of the antibody disclosed herein is an antibody fragment selected from: a Fab, a Fab', a Fab'-SH, an Fv, a single-chain antibody such as an scFv, an (Fab')₂ fragment, a single-domain antibody, a diabody (dAbs), and a linear antibody.

Advantageous biological properties of antibodies

In some embodiments, the anti-TIGIT antibody or the antigen-binding fragment thereof disclosed herein binds to human TIGIT with high affinity, *e.g.*, with a dissociation equilibrium constant (K_D) of less than 100×10^{-9} M, less than or equal to about 50×10^{-9} M, preferably less than or equal to about $1-30 \times 10^{-9}$ M, more preferably about 1×10^{-9} M, further preferably about $1-10 \times 10^{-10}$ M. Preferably, K_D is determined by using biological optical interferometry (*e.g.*, Fortebio affinity assay). In some embodiments, the K_D is determined by measuring the monovalent affinity of a Fab (*e.g.*, a Fab expressed by yeasts) of the antibody to human TIGIT. Preferably, the monovalent K_D is $1-100 \times 10^{-10}$ M, more preferably $1-50 \times 10^{-10}$ M, further preferably $1-10 \times 10^{-10}$ M or $2-5 \times 10^{-10}$ M. In other embodiments, the K_D is determined by measuring the monovalent affinity of an intact antibody (*e.g.*, an intact antibody expressed by CHO cells) to human TIGIT. Preferably, the monovalent K_D is $1-50 \times 10^{-10}$ M, more preferably $1-30 \times 10^{-10}$ M or $1-10 \times 10^{-10}$ M.

In some embodiments, the anti-TIGIT antibody or the antigen-binding fragment thereof disclosed herein have a cross-reaction with monkey TIGIT. In some embodiments, the antibody binds to monkey TIGIT with high affinity, wherein the K_D (*e.g.*, determined by measuring the monovalent affinity of an intact antibody to monkey TIGIT) is about $0.1-100 \times 10^{-9}$ M, more preferably $0.1-50 \times 10^{-9}$ M or $1-30 \times 10^{-10}$ M. In some embodiments, the antibody has a cross-reaction with mouse TIGIT, wherein the K_D (*e.g.*, determined by measuring the monovalent affinity of an intact antibody to mouse TIGIT) is about $1-100 \times 10^{-9}$ M, *e.g.*, $1-10 \times 10^{-7}$ M or $1-10 \times 10^{-8}$ M, or $1-10 \times 10^{-9}$ M. In other embodiments, the anti-TIGIT antibody of the present invention does not have a cross-reaction with mouse TIGIT.

In some embodiments, the antibody or the antigen-binding fragment thereof disclosed herein binds to TIGIT expressed on the surface of cells with high affinity. In one embodiment, a cell expressing human TIGIT on the surface is a CHO cell. Preferably, the EC_{50} of the antibody binding to a cell expressing human TIGIT is measured by flow cytometry (*e.g.*, FACS). In some embodiments, the antibody is an intact antibody expressed by yeasts with an EC_{50} of less than about 10 nM, *e.g.*, 0.1-1

nM, preferably less than or equal to about 1 nM, more preferably about 0.2-0.9 nM, such as 0.9 nM, 0.6 nM, or 0.4 nM. In other embodiments, the antibody is an intact antibody expressed by CHO cells with an EC₅₀ of less than about 10 nM, *e.g.*, 0.1-1 nM, preferably about 0.1-0.3 nM, such as about 0.3 nM, 0.2 nM or 0.1 nM.

5 In some embodiments, the antibody or the antigen-binding fragment thereof disclosed herein inhibits relevant activities of TIGIT. In some embodiments, the antibody or the antigen-binding fragment thereof disclosed herein blocks the binding of TIGIT to its ligand CD155. Preferably, the ability of the antibody to block the binding of human TIGIT (TIGIT expressed on cells) to human CD155 (*e.g.*, IC₅₀) is measured by flow cytometry (*e.g.*, FACS). In some embodiments, the
10 antibody is an intact antibody expressed by yeasts with an IC₅₀ of less than about 10 nM, *e.g.*, 0.1-2 nM, preferably about 0.1-1.0 nM, such as 0.8 nM, 0.6 nM, 0.4 nM, or 0.2 nM. In other embodiments, the antibody is an intact antibody expressed by CHO cells with an EC₅₀ of less than about 1 nM, *e.g.*, 0.1-0.5 nM, preferably about 0.3 nM, 0.2 nM or 0.1 nM.

In some embodiments, the antibody or the antigen-binding fragment thereof disclosed herein
15 reduces or eliminates the inhibitory signaling caused by the binding of TIGIT to CD155. In some embodiments, the antibody or fragment disclosed herein reduces or eliminates TIGIT-mediated inhibitory signaling in a cell (particularly a T cell) expressing TIGIT. In some embodiments, the antibody or the antigen-binding fragment thereof disclosed herein induces the expression of genes downstream of IL-2 promoters in T cells, and in some embodiments, increases the production of
20 IL-2 in T cells. In some embodiments, the ability of the antibody to reduce or eliminate the inhibitory signaling caused by the binding of TIGIT to CD155 (*e.g.*, EC₅₀) is detected using fluorescent reporter assay (*e.g.*, the MOA assay of example 5). In some embodiments, the antibody is an intact antibody expressed by yeasts, with an EC₅₀ of preferably less than about 10 nM, *e.g.*, 0.1-5 nM, more preferably about 0.1-3.0 nM, such as about 2.0 nM, 1.5 nM, 1.0 nM, or 0.5 nM.
25 In other embodiments, the antibody is an intact antibody expressed by CHO cells, with an EC₅₀ of preferably less than 5 nM, *e.g.*, about 0.1-3.0 nM, such as about 1.6 nM, 1.2 nM, 1.0 nM, or about 0.18-0.5 nM.

In some embodiments, the antibody or the antigen-binding fragment thereof disclosed herein inhibits
30 the growth of a tumor that comprises infiltrating lymphocytes expressing human TIGIT. In one embodiment, the tumor is a gastrointestinal tumor, preferably colorectal cancer. For example, in an *in vivo* transplanted tumor model, such as in a MC38 mouse, the growth of colon cancer cells is inhibited. In some embodiments, the combination therapy of the antibody of the present invention with an anti-PD-1 antibody achieves a much better anti-tumor effect than either antibody used alone.

Preferably, the antibody or the antigen-binding fragment thereof disclosed herein exhibits at least
35 one, preferably at least two, more preferably at least three, four, or five, even more preferably all of the above properties.

CDR regions of antibodies

"Complementarity determining region", "CDR region" or "CDR" (used interchangeably herein with a hypervariable region "HVR") is an amino acid region in the variable region of an antibody that
40 is primarily responsible for binding to an epitope of an antigen. The CDRs of the heavy and light chains are generally referred to as CDR1, CDR2, and CDR3, which are numbered sequentially from N-terminus. The CDRs located in the heavy chain variable domain of the antibody are referred to

as HCDR1, HCDR2 and HCDR3, whereas the CDRs located in the light chain variable domain of the antibody are referred to as LCDR1, LCDR2 and LCDR3.

Combinations of the VH and VL sequences of some exemplary antibodies disclosed herein are listed in Table B below:

Anti body	VH, which comprises or consists of an amino acid sequence set forth in the following SEQ ID NOs	VL, which comprises or consists of an amino acid sequence set forth in the following SEQ ID NOs
1	SEQ ID NO:84	SEQ ID NO:104
2	SEQ ID NO:85	SEQ ID NO:104
3	SEQ ID NO:86	SEQ ID NO:104
4	SEQ ID NO:87	SEQ ID NO:104
5	SEQ ID NO:88	SEQ ID NO:105
6	SEQ ID NO:89	SEQ ID NO:105
7	SEQ ID NO:90	SEQ ID NO:106
8	SEQ ID NO:91	SEQ ID NO:107
9	SEQ ID NO:92	SEQ ID NO:107
10	SEQ ID NO:93	SEQ ID NO:107
11	SEQ ID NO:94	SEQ ID NO:108
12	SEQ ID NO:95	SEQ ID NO:108
13	SEQ ID NO:96	SEQ ID NO:108
14	SEQ ID NO:97	SEQ ID NO:108
15	SEQ ID NO:98	SEQ ID NO:109
16	SEQ ID NO:99	SEQ ID NO:109
17	SEQ ID NO:100	SEQ ID NO:109
18	SEQ ID NO:101	SEQ ID NO:110
19	SEQ ID NO:102	SEQ ID NO:110
20	SEQ ID NO:103	SEQ ID NO:110

5

Various schemes for determining the CDR sequence of a given VH or VL amino acid sequence are known in the art. For example, Kabat complementarity determining regions (CDRs) are determined based on sequence variability and are the most commonly used (Kabat *et al.*, *Sequences of Proteins of Immunological Interest*, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991)). Chothia scheme is based on the positions of structural loops (Chothia and Lesk, *J. mol. biol.* 196:901–917 (1987)). AbM HVRs are a compromise between Kabat HVRs and Chothia structural loops and are used by Oxford Molecular's AbM antibody modeling software. The "Contact" HVRs are based on analysis of available complex crystal structures. According to

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different CDR determination schemes, the residue of each HVR/CDR among these HVRs is described as follows.

CDR	Kabat scheme	AbM scheme	Chothia scheme	Contact scheme
LCDR1	L24-L34	L24-L34	L26-L32	L30-L36
LCDR2	L50-L56	L50-L56	L50-L52	L46-L55
LCDR3	L89-L97	L89-L97	L91-L96	L89-L96
HCDR1	H31-H35B	H26-H35B	H26-H32	H30-H35B
(Kabat numbering system)				
HCDR1	H31-H35	H26-H35	H26-H32	H30-H35
(Chothia numbering system)				
HCDR2	H50-H65	H50-H58	H53-H55	H47-H58
HCDR3	H95-H102	H95-H102	H96-H101	H93-H101
(Kabat numbering system)				

HVRs may also be HVR sequences located at following Kabat residue positions according to the Kabat numbering system:

- 5 positions 24-36 or 24-34 (LCDR1), positions 46-56 or 50-56 (LCDR2), and positions 89-97 or 89-96 (LCDR3) in the VL; and positions 26-35 or 27-35B (HCDR1), positions 50-65 or 49-65 (HCDR2), and positions 93-102, 94-102, or 95-102 (HCDR3) in the VH.

In one embodiment, the HVRs of the antibody disclosed herein are HVR sequences located at the following Kabat residue positions according to the Kabat numbering system:

- 10 positions 24-34 (LCDR1), 50-56 (LCDR2), and 89-97 (LCDR3) in the VL, and positions 27-35B (HCDR1), 50-65 (HCDR2), and 93-102 (HCDR3) in the VH.

In one embodiment, the HVRs of the antibody disclosed herein are HVR sequences located at the following Kabat residue positions according to the Kabat numbering system:

- 15 positions 24-34 (LCDR1), 50-56 (LCDR2), and 89-97 (LCDR3) in the VL, and positions 26-35B (HCDR1), 50-65 (HCDR2), and 95-102 (HCDR3) in the VH.

HVRs may also be determined based on the same Kabat numbering positions of a reference CDR sequence (*e.g.*, any one of the exemplary CDRs disclosed herein).

Unless otherwise stated, the term "CDR", "CDR sequence", "HVR", or "HVR sequence" used herein includes HVR or CDR sequences determined in any of the ways described above.

- 20 Unless otherwise stated, residue positions of an antibody variable region (including heavy chain variable region residues and light chain variable region residues) are numbered according to the

Kabat numbering system (Kabat *et al.*, *Sequences of Proteins of Immunological Interest*, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991)) in the present invention.

5 In one preferred embodiment, the CDR sequences disclosed herein are shown in Table 2, wherein the HCDR1 is a CDR sequence determined by the AbM scheme, and remaining CDRs are CDR sequences determined by the Kabat scheme.

In another preferred embodiment, the CDR sequences disclosed herein are shown in Table 1.

Combinations of some exemplary CDR sequences disclosed herein are listed in Table C below:

Combinations	HCDR1, which comprises or consists of an amino acid sequence set forth in the following SEQ ID NOs	HCDR2, which comprises or consists of an amino acid sequence set forth in the following SEQ ID Nos	HCDR3, which comprises or consists of an amino acid sequence set forth in the following SEQ ID Nos	LCDR1, which comprises or consists of an amino acid sequence set forth in the following SEQ ID NOs	LCDR2, which comprises or consists of an amino acid sequence set forth in the following SEQ ID Nos	LCDR3, which comprises or consists of an amino acid sequence set forth in the following SEQ ID Nos
1	SEQ ID NO:1	SEQ ID NO:6	SEQ ID NO:11	SEQ ID NO:16	SEQ ID NO:17	SEQ ID NO:18
2	SEQ ID NO:2	SEQ ID NO:7	SEQ ID NO:12	SEQ ID NO:16	SEQ ID NO:17	SEQ ID NO:18
3	SEQ ID NO:3	SEQ ID NO:8	SEQ ID NO:13	SEQ ID NO:16	SEQ ID NO:17	SEQ ID NO:18
4	SEQ ID NO:4	SEQ ID NO:9	SEQ ID NO:14	SEQ ID NO:16	SEQ ID NO:17	SEQ ID NO:18
5	SEQ ID NO:5	SEQ ID NO:10	SEQ ID NO:15	SEQ ID NO:16	SEQ ID NO:17	SEQ ID NO:18
6	SEQ ID NO:19	SEQ ID NO:22	SEQ ID NO:25	SEQ ID NO:26	SEQ ID NO:27	SEQ ID NO:28
7	SEQ ID NO:20	SEQ ID NO:23	SEQ ID NO:25	SEQ ID NO:26	SEQ ID NO:27	SEQ ID NO:28
8	SEQ ID NO:19	SEQ ID NO:22	SEQ ID NO:25	SEQ ID NO:26	SEQ ID NO:27	SEQ ID NO:29
9	SEQ ID NO:21	SEQ ID NO:24	SEQ ID NO:25	SEQ ID NO:26	SEQ ID NO:27	SEQ ID NO:30
10	SEQ ID NO:31	SEQ ID NO:34	SEQ ID NO:38	SEQ ID NO:41	SEQ ID NO:42	SEQ ID NO:43
11	SEQ ID NO:31	SEQ ID NO:35	SEQ ID NO:38	SEQ ID NO:41	SEQ ID NO:42	SEQ ID NO:43
12	SEQ ID NO:32	SEQ ID NO:36	SEQ ID NO:39	SEQ ID NO:41	SEQ ID NO:42	SEQ ID NO:43

13	SEQ ID NO:33	SEQ ID NO:37	SEQ ID NO:40	SEQ ID NO:41	SEQ ID NO:42	SEQ ID NO:43
14	SEQ ID NO:44	SEQ ID NO:48	SEQ ID NO:53	SEQ ID NO:57	SEQ ID NO:58	SEQ ID NO:59
15	SEQ ID NO:45	SEQ ID NO:49	SEQ ID NO:53	SEQ ID NO:57	SEQ ID NO:58	SEQ ID NO:59
16	SEQ ID NO:46	SEQ ID NO:50	SEQ ID NO:54	SEQ ID NO:57	SEQ ID NO:58	SEQ ID NO:59
17	SEQ ID NO:46	SEQ ID NO:51	SEQ ID NO:55	SEQ ID NO:57	SEQ ID NO:58	SEQ ID NO:59
18	SEQ ID NO:47	SEQ ID NO:52	SEQ ID NO:56	SEQ ID NO:57	SEQ ID NO:58	SEQ ID NO:59
19	SEQ ID NO:60	SEQ ID NO:6	SEQ ID NO:66	SEQ ID NO:69	SEQ ID NO:17	SEQ ID NO:70
20	SEQ ID NO:61	SEQ ID NO:63	SEQ ID NO:66	SEQ ID NO:69	SEQ ID NO:17	SEQ ID NO:70
21	SEQ ID NO:61	SEQ ID NO:64	SEQ ID NO:67	SEQ ID NO:69	SEQ ID NO:17	SEQ ID NO:70
22	SEQ ID NO:62	SEQ ID NO:65	SEQ ID NO:68	SEQ ID NO:69	SEQ ID NO:17	SEQ ID NO:70
23	SEQ ID NO:71	SEQ ID NO:22	SEQ ID NO:78	SEQ ID NO:81	SEQ ID NO:82	SEQ ID NO:83
24	SEQ ID NO:72	SEQ ID NO:75	SEQ ID NO:78	SEQ ID NO:81	SEQ ID NO:82	SEQ ID NO:83
25	SEQ ID NO:73	SEQ ID NO:76	SEQ ID NO:79	SEQ ID NO:81	SEQ ID NO:82	SEQ ID NO:83
26	SEQ ID NO:74	SEQ ID NO:77	SEQ ID NO:80	SEQ ID NO:81	SEQ ID NO:82	SEQ ID NO:83

Combinations of other exemplary CDR sequences disclosed herein are listed in Table D below:

Combinations	HCDR1, which comprises or consists of an amino acid sequence set forth in the following SEQ ID NOs	HCDR2, which comprises or consists of an amino acid sequence set forth in the following SEQ ID Nos	HCDR3, which comprises or consists of an amino acid sequence set forth in the following SEQ ID Nos	LCDR1, which comprises or consists of an amino acid sequence set forth in the following SEQ ID NOs	LCDR2, which comprises or consists of an amino acid sequence set forth in the following SEQ ID Nos	LCDR3, which comprises or consists of an amino acid sequence set forth in the following SEQ ID Nos
1	SEQ ID NO:178	SEQ ID NO:6	SEQ ID NO:182	SEQ ID NO:16	SEQ ID NO:17	SEQ ID NO:18
2	SEQ ID	SEQ ID	SEQ ID	SEQ ID	SEQ ID	SEQ ID

	NO:179	NO:7	NO:183	NO:16	NO:17	NO:18
3	SEQ ID NO:180	SEQ ID NO:8	SEQ ID NO:184	SEQ ID NO:16	SEQ ID NO:17	SEQ ID NO:18
4	SEQ ID NO:181	SEQ ID NO:9	SEQ ID NO:185	SEQ ID NO:16	SEQ ID NO:17	SEQ ID NO:18
5	SEQ ID NO:186	SEQ ID NO:22	SEQ ID NO:188	SEQ ID NO:26	SEQ ID NO:27	SEQ ID NO:28
6	SEQ ID NO:187	SEQ ID NO:23	SEQ ID NO:188	SEQ ID NO:26	SEQ ID NO:27	SEQ ID NO:28
7	SEQ ID NO:186	SEQ ID NO:22	SEQ ID NO:188	SEQ ID NO:26	SEQ ID NO:27	SEQ ID NO:29
8	SEQ ID NO:189	SEQ ID NO:34	SEQ ID NO:191	SEQ ID NO:41	SEQ ID NO:42	SEQ ID NO:43
9	SEQ ID NO:189	SEQ ID NO:35	SEQ ID NO:191	SEQ ID NO:41	SEQ ID NO:42	SEQ ID NO:43
10	SEQ ID NO:190	SEQ ID NO:36	SEQ ID NO:192	SEQ ID NO:41	SEQ ID NO:42	SEQ ID NO:43
11	SEQ ID NO:193	SEQ ID NO:48	SEQ ID NO:196	SEQ ID NO:57	SEQ ID NO:58	SEQ ID NO:59
12	SEQ ID NO:194	SEQ ID NO:49	SEQ ID NO:196	SEQ ID NO:57	SEQ ID NO:58	SEQ ID NO:59
13	SEQ ID NO:195	SEQ ID NO:50	SEQ ID NO:197	SEQ ID NO:57	SEQ ID NO:58	SEQ ID NO:59
14	SEQ ID NO:195	SEQ ID NO:51	SEQ ID NO:198	SEQ ID NO:57	SEQ ID NO:58	SEQ ID NO:59
15	SEQ ID NO:199	SEQ ID NO:6	SEQ ID NO:201	SEQ ID NO:69	SEQ ID NO:17	SEQ ID NO:70
16	SEQ ID NO:200	SEQ ID NO:63	SEQ ID NO:201	SEQ ID NO:69	SEQ ID NO:17	SEQ ID NO:70
17	SEQ ID NO:200	SEQ ID NO:64	SEQ ID NO:202	SEQ ID NO:69	SEQ ID NO:17	SEQ ID NO:70
18	SEQ ID NO:203	SEQ ID NO:22	SEQ ID NO:206	SEQ ID NO:81	SEQ ID NO:82	SEQ ID NO:83
19	SEQ ID NO:204	SEQ ID NO:75	SEQ ID NO:206	SEQ ID NO:81	SEQ ID NO:82	SEQ ID NO:83
20	SEQ ID NO:205	SEQ ID NO:76	SEQ ID NO:207	SEQ ID NO:81	SEQ ID NO:82	SEQ ID NO:83

Antibodies with different specificities (*i.e.*, different binding sites for different antigens) have different CDRs. However, although CDRs differ from antibody to antibody, only a limited number of amino acid positions within the CDRs are directly involved in antigen binding. The smallest overlapping region can be determined using at least two of the Kabat, Chothia, AbM, and Contact schemes, thereby providing a "minimal binding unit" for antigen binding. The minimal binding unit may be a sub-portion of the CDR. As will be clear to those skilled in the art, residues of the rest

CDR sequences can be determined via antibody structure and protein folding. Therefore, any variants of the CDRs given herein are also considered in the present invention. For example, in a CDR variant, the amino acid residues in the minimal binding unit may remain unchanged, while the other CDR residues defined by Kabat or Chothia may be substituted by conservative amino acid residues.

In some embodiments, the antibody of the present invention has at least one, two, three, four, five, or six CDRs that are identical to, or are variants of, corresponding CDRs in the variable region sequences of any of the antibodies listed in Table B. In some embodiments, the antibody of the present invention has at least one, two, or three HCDRs that are identical to, or are variants of, corresponding heavy chain CDRs in the variable region sequences of any of the antibodies listed in Table B. In some embodiments, the antibody of the present invention has at least one, two, or three LCDRs that are identical to, or are variants of, corresponding light chain CDRs in the variable region sequences of any of the antibodies listed in Table B. Herein, "corresponding CDRs" refer to CDRs that are located at positions in the amino acid sequences of a variable region of a candidate antibody that are most similar to where CDRs of a reference antibody locate at after optimal alignment. Herein, a CDR variant is a CDR that has been modified by at least one, for example, one or two or three amino acid substitutions, deletions, and/or insertions, wherein an antigen-binding molecule comprising the CDR variant substantially retains the biological properties of the antigen-binding molecule comprising the unmodified CDRs, *e.g.*, retains at least 60%, 70%, 80%, 90%, or 100% of the biological activity (*e.g.*, antigen-binding ability). It is understood that each CDR may be modified independently or in combination. Preferably, an amino acid modification is an amino acid substitution, in particular a conservative amino acid substitution, such as a preferred conservative amino acid replacement listed in Table A. In some embodiments, amino acid substitutions preferably occur at amino acid positions corresponding to X residues of the consensus CDR sequences (*e.g.*, SEQ ID NOs: 5, 10, 15, 21, 24, 30, 33, 37, 40, 47, 52, 56, 62, 65, 68, 74, 77, and 80) provided herein.

In addition, it is known in the art that the CDR3 region, which is independent of the CDR1 and/or CDR2 regions, alone can determine the binding specificity of an antibody to an associated antigen. Furthermore, a variety of other antibodies having the same binding specificity can be generated based on the consensus CDR3 sequence. See, *e.g.*, U.S. Patents Nos: 6,951,646; 6,914,128; 6,090,382; 6,818,216; 6,156,313; 6,827,925; 5,833,943; 5,762,905; and 5,760,185. All of these references are incorporated herein by reference.

Thus, in one embodiment, the antibody of the present invention comprises a CDR3 sequence from the heavy and/or light chain variable region sequence of any one of the antibodies shown in Table B, wherein the antibody is capable of specifically binding to human TIGIT. In yet another embodiment, the antibody may further comprise a CDR2 from the heavy and/or light chain variable region of the same antibody, or a CDR2 from the heavy and/or light chain variable region of different TIGIT antibodies. In yet another embodiment, the antibody may further comprise a CDR1 from the heavy and/or light chain variable region of the same antibody, or a CDR1 from the heavy and/or light chain variable region of different TIGIT antibodies. Activities of these antibodies, including an activity of binding to human TIGIT, an activity of blocking the binding of TIGIT to CD155 molecules, and/or an activity of inhibiting tumor growth, can be characterized by assays described herein.

In yet another aspect, given that the antigen-binding specificity is dependent primarily on the CDR1, CDR2, and CDR3 regions, in some embodiments, VH CDRs 1, 2, and 3 sequences and VL CDRs 1,

2, and 3 sequences can be "combined and paired" (*i.e.*, CDRs from different antibodies that bind to the same TIGIT antigen can be combined and paired, and each antibody preferably comprises VH CDRs 1, 2, and 3 and VL CDRs 1, 2, and 3) to produce other molecules of the present invention that bind to TIGIT. The binding of such "combined and paired" antibodies to TIGIT can be tested
5 by binding assays known in the art (*e.g.*, ELISA, SET, and Biacore) and other assays described in the examples. When VH CDR sequences are combined and paired, CDR1, CDR2, and/or CDR3 sequences from a particular VH sequence are preferably substituted with structurally similar CDR sequences. Likewise, when VL CDR sequences are combined and paired, CDR1, CDR2, and/or CDR3 sequences from a particular VL sequence are preferably substituted with structurally similar
10 CDR sequences. CDRs can be "combined and paired" among the antibodies shown in Table 3 of the present invention. In addition, It will be appreciated by those skilled in the art that other antibodies of the present invention may also be generated by substituting the structurally similar CDR sequences of the antibodies disclosed herein with one or more of VH CDR and/or VL CDR sequences from other different antibodies.

15 Thus, in some embodiments, the antibody or the antigen-binding fragment thereof disclosed herein comprises a heavy chain variable region comprising a heavy chain complementarity determining region 3 (HCDR3), the HCDR3:

- (i) is identical to an HCDR3 of the heavy chain variable region of any one of the antibodies listed in Table B;
- 20 (ii) is identical to any of the HCDR3 sequences listed in Table C or D; or
- (iii) comprises at least 1 (preferably 1-2, and more preferably 1) amino acid alteration (preferably substitution, and more preferably conservative substitution) relative to the HCDR3 of (i) or (ii).

In some embodiments, the antibody or the antigen-binding fragment thereof disclosed herein comprises a heavy chain variable region and a light chain variable region, and the heavy chain
25 complementarity determining regions 3 (HCDR3) and light chain complementarity determining regions 3 (LCDR3) of the antibody:

- (i) are identical to an HCDR3 and an LCDR3 of the heavy and light chain variable region sequences of any one of the antibodies listed in Table B;
- (ii) are identical to the HCDR3 and LCDR3 sequences in any combination listed in Table C or D; or
- 30 (iii) comprise at least 1 (preferably 1-2, and more preferably 1) amino acid alteration (preferably substitution, and more preferably conservative substitution) in total relative to the HCDR3 and LCDR3 of (i) or (ii).

In one embodiment, the antibody or the antigen-binding fragment thereof disclosed herein comprises a heavy chain variable region (VH), wherein the VH comprises:

- 35 (i) HCDR1, HCDR2 and HCDR3 sequences contained in a VH sequence of any one of the antibodies listed in Table B;
- (ii) HCDR1, HCDR2 and HCDR3 sequences in any combination listed in Table C or D; or
- (iii) sequences having at least one and no more than 5, 4, 3, 2, or 1 amino acid alteration (preferably amino acid substitution, preferably conservative substitution) in the three CDRs in total relative to
40 the sequences of (i) or (ii).

In another embodiment, the antibody or the antigen-binding fragment thereof disclosed herein comprises a light chain variable region (VL), wherein the VL comprises:

(i) LCDR1, LCDR2, and LCDR3 sequences contained in a VL sequence of any one of the antibodies listed in Table B;

5 (ii) LCDR1, LCDR2 and LCDR3 sequences in any combination listed in Table C or D; or

(iii) sequences having at least one and no more than 5, 4, 3, 2, or 1 amino acid alteration (preferably amino acid substitution, preferably conservative substitution) in the three CDRs in total relative to the sequences of (i) or (ii).

10 In another embodiment, the antibody or the antigen-binding fragment thereof disclosed herein comprises a heavy chain variable region and a light chain variable region, wherein the antibody comprises:

(i) six CDR sequences contained in VH and VL sequences of any one of the antibodies listed in Table B;

(ii) six CDR sequences in any combination listed in Table C or D; or

15 (iii) sequences having at least one and no more than 10, 5, 4, 3, 2, or 1 amino acid alteration (preferably amino acid substitution, preferably conservative substitution) in the six CDRs in total relative to the sequences of (i) or (ii).

In one embodiment, the antibody or antigen-binding fragment thereof disclosed herein comprises:

20 (i) HCDR1, HCDR2 and HCDR3 sequences of a heavy chain variable region set forth in SEQ ID NOs: 84, 85, 86, or 87, and LCDR1, LCDR2 and LCDR3 sequences of a light chain variable region set forth in SEQ ID NO: 104,

(ii) HCDR1, HCDR2 and HCDR3 sequences of a heavy chain variable region set forth in SEQ ID NOs: 88, 89, or 90, and LCDR1, LCDR2 and LCDR3 sequences of a light chain variable region set forth in SEQ ID NO: 105 or 106,

25 (iii) HCDR1, HCDR2 and HCDR3 sequences of a heavy chain variable region set forth in SEQ ID NOs: 91, 92, or 93, and LCDR1, LCDR2 and LCDR3 sequences of a light chain variable region set forth in SEQ ID NO: 107,

(iv) HCDR1, HCDR2 and HCDR3 sequences of a heavy chain variable region set forth in SEQ ID NOs: 94, 95, 96, or 97, and LCDR1, LCDR2 and LCDR3 sequences of a light chain variable region
30 set forth in SEQ ID NO: 108,

(v) HCDR1, HCDR2 and HCDR3 sequences of a heavy chain variable region set forth in SEQ ID NOs: 98, 99, or 100, and LCDR1, LCDR2 and LCDR3 sequences of a light chain variable region set forth in SEQ ID NO: 109, or

35 (vi) HCDR1, HCDR2 and HCDR3 sequences of a heavy chain variable region set forth in SEQ ID NOs: 101, 102, or 103, and LCDR1, LCDR2 and LCDR3 sequences of a light chain variable region set forth in SEQ ID NO: 110.

In a preferred embodiment, the antibody or the antigen-binding fragment thereof disclosed herein comprises three complementarity determining regions of a heavy chain variable region (HCDRs), and three complementarity determining regions of a light chain variable region (LCDRs), wherein

(i) HCDR1 comprises or consists of an amino acid sequence selected from SEQ ID NOs: 1-5 or 178-181, HCDR2 comprises or consists of an amino acid sequence selected from SEQ ID NOs: 6-10, HCDR3 comprises or consists of an amino acid sequence selected from SEQ ID NOs: 11-15 or 182-185, LCDR1 comprises or consists of an amino acid sequence of SEQ ID NO: 16, LCDR2 comprises or consists of an amino acid sequence of SEQ ID NO: 17, and LCDR3 comprises or consists of an amino acid sequence of SEQ ID NO: 18;

(ii) HCDR1 comprises or consists of an amino acid sequence selected from SEQ ID NOs: 19-21 or 186-187, HCDR2 comprises or consists of an amino acid sequence selected from SEQ ID NOs: 22-24, HCDR3 comprises or consists of an amino acid sequence of SEQ ID NOs: 25 and 188, LCDR1 comprises or consists of an amino acid sequence of SEQ ID NO: 26, LCDR2 comprises or consists of an amino acid sequence of SEQ ID NO: 27, and LCDR3 comprises or consists of an amino acid sequence selected from SEQ ID NOs: 28-30;

(iii) HCDR1 comprises or consists of an amino acid sequence selected from SEQ ID NOs: 31-33 or 189-190, HCDR2 comprises or consists of an amino acid sequence selected from SEQ ID NOs: 34-37, HCDR3 comprises or consists of an amino acid sequence selected from SEQ ID NOs: 38-40 or 191-192, LCDR1 comprises or consists of an amino acid sequence of SEQ ID NO: 41, LCDR2 comprises or consists of an amino acid sequence of SEQ ID NO: 42, and LCDR3 comprises or consists of an amino acid sequence of SEQ ID NO: 43;

(iv) HCDR1 comprises or consists of an amino acid sequence selected from SEQ ID NOs: 44-47 or 193-195, HCDR2 comprises or consists of an amino acid sequence selected from SEQ ID NOs: 48-52, HCDR3 comprises or consists of an amino acid sequence selected from SEQ ID NOs: 53-56 or 196-198, LCDR1 comprises or consists of an amino acid sequence of SEQ ID NO: 57, LCDR2 comprises or consists of an amino acid sequence of SEQ ID NO: 58, and LCDR3 comprises or consists of an amino acid sequence of SEQ ID NO: 59;

(v) HCDR1 comprises or consists of an amino acid sequence selected from SEQ ID NOs: 60-62 or 199-200, HCDR2 comprises or consists of an amino acid sequence selected from SEQ ID NOs: 63-65, HCDR3 comprises or consists of an amino acid sequence selected from SEQ ID NOs: 66-68 or 201-202, LCDR1 comprises or consists of an amino acid sequence of SEQ ID NO: 69, LCDR2 comprises or consists of an amino acid sequence of SEQ ID NO: 70, and LCDR3 comprises or consists of an amino acid sequence of SEQ ID NO: 71; or

(vi) HCDR1 comprises or consists of an amino acid sequence selected from SEQ ID NOs: 72-74 or 203-205, HCDR2 comprises or consists of an amino acid sequence selected from SEQ ID NOs: 75-77, HCDR3 comprises or consists of an amino acid sequence selected from SEQ ID NOs: 78-80 or 206-207, LCDR1 comprises or consists of an amino acid sequence of SEQ ID NO: 81, LCDR2 comprises or consists of an amino acid sequence of SEQ ID NO: 82, and LCDR3 comprises or consists of an amino acid sequence of SEQ ID NO: 83.

In one preferred embodiment, the antibody or the antigen-binding fragment thereof disclosed herein comprises 6 CDR sequences of one of the combinations listed in Table C.

In another preferred embodiment, the antibody or the antigen-binding fragment thereof disclosed herein comprises 6 CDR sequences of one of the combinations listed in Table D.

Variable regions of antibodies

A "variable region" or "variable domain" is a domain in the heavy or light chain of an antibody that participates in binding of the antibody to the antigen thereof. A heavy chain variable region (VH) and a light chain variable region (VL) can be further subdivided into hypervariable regions (HVRs, also known as complementarity determining regions (CDRs)) with more conservative regions (*i.e.*, framework regions (FRs)) inserted therebetween. Each VH or VL consists of three CDRs and four FRs, arranged from the N-terminus to C-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. In some cases, a single VH or VL domain is sufficient to provide antigen-binding specificity. Furthermore, antibodies binding to particular antigens can be isolated by screening libraries of complementarity VL or VH domains by virtue of VH or VL domains from the antibodies binding to the antigens (see, *e.g.*, Portolano, S. *et al.*, *J. Immunol.* 150 (1993) 880-887; Clackson, T. *et al.*, *Nature* 352 (1991) 624-628).

It is known in the art that one or more residues in one or both of the variable regions (*i.e.*, VH and/or VL) can be modified, for example, one or more CDRs and/or one or more framework regions undergo residue modifications, particularly conservative residue substitutions, and the modified antibody still substantially retains at least one biological property (*e.g.*, antigen-binding ability) of the antibody molecule prior to alteration. For example, residues in CDRs may be mutated to improve one or more binding properties (*e.g.*, affinity) of the antibody. The antigen-binding properties or other functional properties of the mutated antibody can be assessed in an *in vitro* or *in vivo* assay. Preferably, conservative substitutions are introduced. Preferably, no more than 1, 2, 3, 4, or 5 residue modifications are introduced in the CDRs. Furthermore, residues in framework regions can be mutated, for example, to improve the properties of the antibody. For example, one or more residues in the framework regions may be "back mutated" to corresponding residues of a germline sequence.

CDR grafting is another modification method for antibody variable region known in the art. Since CDR sequences are responsible for most of the antibody-antigen interactions, a recombinant antibody variant that simulates the properties of known antibodies can be constructed. In the antibody variant, CDR sequences from the known antibodies are grafted onto framework regions of different antibodies having different properties. Accordingly, in one embodiment, the present invention relates to an anti-TIGIT antibody or an antigen-binding fragment thereof, wherein the antibody comprises CDR sequences of the heavy and light chain variable regions from one of the antibodies of Table B, and has different framework region sequences. A framework region sequence for substitution can be obtained from a public DNA database, including germline antibody gene sequences, or from published TIGIT antibody sequences. For example, germline DNAs encoding human heavy and light chain variable region genes can be obtained from GenBank database. Antibody protein sequences can be compared to protein sequences in the database using sequence similarity search tools, such as Gapped BLAST. Preferably, the framework region sequence for substitution is structurally similar to a framework sequence of the antibody of the present invention selected for alteration, *e.g.*, a framework sequence having at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or higher sequence identity.

In yet another embodiment, VH and VL sequences from an exemplary antibody of the present

invention (one of the antibodies shown in Table B) and other different anti-TIGIT antibodies (preferably, another antibody shown in Table B) can be "combined and paired" to produce other antibodies of the present invention binding to TIGIT. When these chains are combined and paired, it is preferred that the VH sequence from a particular VH/VL pair is substituted with a structurally similar VH sequence. Likewise, the VL sequence from a particular VH/VL pair is preferably substituted with a structurally similar VL sequence. The binding of such "combined and paired" antibodies to TIGIT can be tested by binding assays known in the art (*e.g.*, ELISA, and other assays described in the examples).

Thus, in one embodiment, the antibody of the present invention comprises or consists of a heavy chain variable region (VH) sequence of any one of the antibodies listed in Table B. In yet another embodiment, the antibody of the present invention comprises a variant of the VH sequence.

In another embodiment, the antibody of the present invention comprises or consists of a light chain variable region (VL) sequence of any one of the antibodies listed in Table B. In yet another embodiment, the antibody of the present invention comprises a variant of the VL sequence.

In yet another embodiment, the antibody of the present invention comprises:

(i) a VH sequence comprising an amino acid sequence set forth in SEQ ID NOs: 84, 85, 86, or 87 or a variant thereof, and/or a VL sequence comprising an amino acid sequence set forth in SEQ ID NO: 104 or a variant thereof,

(ii) a VH sequence comprising an amino acid sequence set forth in SEQ ID NOs: 88, 89, or 90 or a variant thereof, and/or a VL sequence comprising an amino acid sequence set forth in SEQ ID NOs: 105 or 106 or a variant thereof,

(iii) a VH sequence comprising an amino acid sequence set forth in SEQ ID NOs: 91, 92, or 93 or a variant thereof, and/or a VL sequence comprising an amino acid sequence set forth in SEQ ID NO: 107 or a variant thereof,

(iv) a VH sequence comprising an amino acid sequence set forth in SEQ ID NOs: 94, 95, 96, or 97 or a variant thereof, and/or a VL sequence comprising an amino acid sequence set forth in SEQ ID NO: 108 or a variant thereof,

(v) a VH sequence comprising an amino acid sequence set forth in SEQ ID NO: 98, 99, or 100 or a variant thereof, and/or a VL sequence comprising an amino acid sequence set forth in SEQ ID NO: 109 or a variant thereof, or

(vi) a VH sequence comprising an amino acid sequence set forth in SEQ ID NOs: 101, 102, or 103 or a variant thereof, and/or a VL sequence comprising an amino acid sequence set forth in SEQ ID NO: 110 or a variant thereof.

In one embodiment, with respect to amino acid sequence, a variant of the VH sequence has at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identity relative to the reference VH sequence (preferably, in terms of the full length, or the CDR1, CDR2 and CDR3). In one embodiment, with respect to amino acid sequence, a variant of the VH sequence comprises at least one and no more than 30, 10, 5, 4, 3, 2, 1, or 0 amino acid alteration (preferably amino acid substitution, and more preferably conservative substitution) relative to the reference VH sequence (preferably, in terms of the full length, or the CDR1, CDR2 and CDR3). Preferably, sequence differences do not occur in the CDRs.

In a preferred embodiment, with respect to amino acid sequence, a variant of the VL sequence has at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identity relative to the reference VL sequence (preferably, in terms of the full length, or the CDR1, CDR2 and CDR3). In a preferred embodiment, with respect to amino acid sequence, a variant of the VL sequence comprises at least one and no more than 30, 10, 5, 4, 3, 2, 1, or 0 amino acid alteration (preferably amino acid substitution, and more preferably conservative substitution) relative to the reference VH sequence (preferably, in terms of the full length, or the CDR1, CDR2 and CDR3). Preferably, sequence differences do not occur in the CDRs.

In a preferred embodiment, the antibody of the present invention comprises or consists of a VH/VL sequence pair of the heavy and light chain variable regions of any one of the antibodies listed in Table B. The present invention also provides a variant of the antibody, *e.g.*, a variant having at least 95-99% identity or comprising no more than 10 amino acid alterations in terms of VH, VL, or VH and VL.

In any of the above embodiments, preferably, in terms of one or more CDRs (preferably all three CDRs), a heavy chain variable region of an antibody variant comprises no more than 10, preferably no more than 5 (*e.g.*, 3, 2, 1, or 0), amino acid alterations (preferably amino acid substitutions, and more preferably conservative substitutions) relative to a reference antibody.

In any of the above embodiments, preferably, in terms of one or more CDRs (preferably all three CDRs), a light chain variable region (VL) of an antibody variant comprises no more than 10, preferably no more than 5 (*e.g.*, 3, 2, 1, or 0), amino acid alterations (preferably amino acid substitutions, and more preferably conservative substitutions) relative to a reference antibody.

Heavy and light chains of antibodies

In some embodiments, the antibody of the present invention comprises a heavy chain Fc region, *e.g.*, an Fc region of the IgG1, IgG2, or IgG4 isotype. In one embodiment, the antibody of the present invention comprises an IgG4-Fc region having a serine-to-proline mutation (S228P) at amino acid residue position 228 (EU numbering). In yet another preferred embodiment, the antibody of the present invention comprises an IgG4-PAA Fc portion. The IgG4-PAA Fc portion has a serine-to-proline mutation (S228P) at position 228, a phenylalanine-to-alanine mutation at position 234 (EU numbering) and a leucine-to-alanine mutation at position 235 (EU numbering). The S228P mutation is a mutation in a hinge region of the tumor constant region that can reduce or eliminate the heterogeneity of an inter-heavy chain disulfide bridge. The F234A and L235A mutations can further reduce the effector function of the human IgG4 isotype (which already has a low effector function). In some embodiments, the antibody of the present invention comprises an IgG4-PAA Fc portion with the heavy chain C-terminus lysine (des-Lys) removed. In some embodiments, the antibody of the present invention comprises a κ light chain constant region, *e.g.*, a human κ light chain constant region.

In yet another preferred embodiment, the Fc region comprises an amino acid sequence of SEQ ID NO: 177, or an amino acid sequence comprising at least one, two, or three but no more than 20, 10 or 5 amino acid alterations relative to the amino acid sequence of SEQ ID NO: 177, or a sequence having at least 95-99% identity to the amino acid sequence of SEQ ID NO: 177.

In a preferred embodiment, the antibody of the present invention comprises a light chain constant

region. In a preferred embodiment, the light chain constant region is a human κ light chain constant region. In yet another preferred embodiment, the light chain constant region comprises an amino acid sequence of SEQ ID NO: 209, or an amino acid sequence having at least one, two, or three but no more than 20, 10, or 5 amino acid alterations relative to the amino acid sequence of SEQ ID NO: 209, or an amino acid sequence having at least 95-99% identity to the amino acid sequence of SEQ ID NO: 209.

In some preferred embodiments, the antibody of the present invention comprises a heavy chain comprising an amino acid sequence selected from SEQ ID NOs: 111-130, or an amino acid sequence having at least one, two, or three but no more than 20, 10, or 5 amino acid alterations relative thereto, or an amino acid sequence having at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99%, or more identity thereto. Preferably, the amino acid alterations do not occur in the CDRs, and more preferably, the amino acid alterations do not occur in the variable regions.

In some preferred embodiments, the antibody of the present invention comprises a light chain comprising an amino acid sequence selected from SEQ ID NOs: 137-143, or an amino acid sequence having at least one, two, or three but no more than 20, 10 or 5 amino acid alterations relative thereto, or an amino acid sequence having at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99%, or more identity thereto. Preferably, the amino acid alterations do not occur in the CDRs, and more preferably, the amino acid alterations do not occur in the variable regions.

In a preferred embodiment, the antibody of the present invention comprises a heavy chain sequence and/or a light chain sequence selected from:

(a) a heavy chain sequence comprising an amino acid sequence selected from SEQ ID NOs: 111-114 or a variant thereof, and/or a light chain sequence comprising an amino acid sequence of SEQ ID NO: 137 or a variant thereof;

(b) a heavy chain sequence comprising an amino acid sequence selected from SEQ ID NOs: 115-117 or a variant thereof, and/or a light chain sequence comprising an amino acid sequence of SEQ ID NO: 138 or 139, or a variant thereof;

(c) a heavy chain sequence comprising an amino acid sequence selected from SEQ ID NOs: 118-120 or a variant thereof, and/or a light chain sequence comprising an amino acid sequence of SEQ ID NO: 140 or a variant thereof;

(d) a heavy chain sequence comprising an amino acid sequence selected from SEQ ID NOs: 121-124 or a variant thereof, and/or a light chain sequence comprising an amino acid sequence of SEQ ID NO: 141 or a variant thereof;

(e) a heavy chain sequence comprising an amino acid sequence selected from SEQ ID NOs: 125-127 or a variant thereof, and/or a light chain sequence comprising an amino acid sequence of SEQ ID NO: 142 or a variant thereof; and

(f) a heavy chain sequence comprising an amino acid sequence selected from SEQ ID NOs: 128-130 or a variant thereof, and/or a light chain sequence comprising an amino acid sequence of SEQ ID NO: 143 or a variant thereof,

wherein the variant comprises an amino acid sequence comprising at least one, two, or three but no more than 20, 10, or 5 amino acid alterations, or having at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99%, or more identity relative to the corresponding reference sequence. Preferably, the amino

acid alterations do not occur in the CDRs, and more preferably, the amino acid alterations do not occur in the variable regions.

In one embodiment, residue modifications are made in the constant region of an antibody, for example, to alter the properties of the antibody, such as an effector function.

- 5 In some embodiments, the heavy and/or light chain of the anti-TIGIT antibody or the fragment thereof disclosed herein further comprises a signal peptide sequence, *e.g.*, METDTLLLWVLLLWVPGSTG.

Exemplary antibody sequences

- 10 The present invention provides a fully humanized antibody specifically binding to TIGIT (*e.g.*, human TIGIT) as isolated and characterized in the examples. The VH and VL sequences of variable regions of the exemplary antibodies disclosed herein are listed in Table 3 below. The exemplary CDR sequences of the antibodies are listed in Tables 1 and 2 below. The sequence listing shows the heavy and light chain amino acid sequences of the exemplary antibodies disclosed herein and the
15 coding nucleotide sequences of the variable regions (VH and VL) of the exemplary antibodies disclosed herein.

Antibody variants

- 20 In one aspect, the present invention provides any of the antibodies described herein, particularly variants of the exemplary antibodies listed in Table B. In one embodiment, the antibody variant retains at least 60%, 70%, 80%, 90% or 100% of the biological activity (*e.g.*, antigen-binding ability) of the antibody prior to alteration. In some embodiments, the alteration does not result in loss of the binding ability of an antibody variant to an antigen, and optionally may impart properties such as increased antigen affinity and different effector functions.
- 25 It will be understood that the heavy or light chain variable regions, or all CDRs of the antibody may be altered independently or in combination. In some embodiments, there are no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid alterations in one or more or all of the three heavy chain CDRs. Preferably, the amino acid alteration refers to an amino acid substitution, preferably a conservative substitution. In some embodiments, there are no more than 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid
30 alterations in one or more or all of the three light chain CDRs. In some embodiments, there are no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid alterations in one or more or all of the six CDRs. Preferably, the amino acid alteration refers to an amino acid substitution, preferably a conservative substitution. In some embodiments, an antibody variant has at least 80%, 85%, 90%, 95%, 99% or more amino acid identity to a reference antibody in terms of target antibody sequence region. For
35 example, in one embodiment, the antibody of the present invention has at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more identity to a reference antibody (*e.g.*, one of the antibodies listed in Table 3) in terms of three heavy chain CDRs. In one embodiment, the antibody of the present invention has at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more identity to a reference antibody (*e.g.*, one of the antibodies listed in Table 3) in terms of three
40 light chain CDRs. In another embodiment, the antibody of the present invention has at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more identity to a reference antibody (*e.g.*, one of the antibodies listed in Table 3) in terms of six CDRs. In yet another embodiment, the

antibody of the present invention has at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more identity to a reference antibody (*e.g.*, one of the antibodies listed in Table 3) in terms of heavy chain variable region. In yet another embodiment, the antibody of the present invention has at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more identity to a reference antibody (*e.g.*, one of the antibodies listed in Table 3) in terms of light chain variable region. In yet another embodiment, the antibody of the present invention has at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more identity to a reference antibody (*e.g.*, one of the antibodies listed in Table 3) in terms of heavy and/or light chain variable regions.

In addition, alterations may be made to an Fc region of an antibody. The alterations to the Fc region may be made alone or in combination with the alterations to the framework regions and/or CDRs described above. The Fc region can be altered, for example, to alter one or more functions of the antibody, such as serum half-life, complement fixation, Fc receptor binding, and/or antigen-dependent cytotoxicity. In addition, the antibody of the present invention may be chemically modified (*e.g.*, linked to PEG), or its glycosylation pattern may be altered.

In certain embodiments, the Fc region may comprise an Fc-region having one or more amino acid replacements that improve the ADCC activity, *e.g.*, replacements at positions 298, 333 and/or 334 (EU numbering of residues) of the Fc-region. In some embodiments, the Fc-region can also be altered to result in altered (*i.e.*, increased or decreased) C1q binding and/or complement dependent cytotoxicity (CDC) (see, *e.g.*, US 6,194,551, WO 99/51642 and Idusogie, E. E. *et al.*, *J. Immunol.* 164 (2000) 4178-4184).

In other embodiments, the Fc region can be altered to increase or decrease its glycosylation degree and/or alter its glycosylation pattern. Addition or deletion of glycosylation sites of the Fc region can be conveniently achieved by producing or removing one or more glycosylation sites through amino acid sequence alteration. For example, one or more amino acid substitutions may be made to eliminate one or more glycosylation sites, thereby eliminating the glycosylation at the sites. Antibodies with altered types of glycosylation can be prepared, such as low-fucosylated or non-fucosylated antibodies with reduced amount of fucosyl residues or antibodies with increased bisecting GlcNac structures. Such altered glycosylation patterns have shown the ability to increase ADCC of antibodies. Herein, antibody variants having at least one galactose residue in the oligosaccharide linked to the Fc region are also considered. The antibody variants may have an increased CDC function.

In certain embodiments, the present invention also considers antibody variants having some but not all effector functions, which makes them a desirable candidate for some applications in which the half-life period of the antibody *in vivo* is important yet certain effector functions (such as complement and ADCC) are unnecessary or deleterious. For example, the Fc region may comprise a mutation that eliminates or reduces effector functions, such as the human IgG1 Fc region with mutations P329G and/or L234A and L235A, or the human IgG4 Fc region with mutations P329G and/or S228P and L235E.

In certain embodiments, antibodies modified by cysteine engineering may need to be produced, such as "sulfo-MAb", wherein one or more residues of the antibodies are substituted by cysteine

residues. For example, the number of cysteine residues in the hinge region of an antibody can be altered, *e.g.*, to facilitate assembly of the light and heavy chains or to increase or decrease the stability of the antibody. See, for example, U.S. Patent NO. 5677425.

In certain embodiments, the antibodies provided herein can be further modified to contain other non-protein portions. Suitable portions for antibody derivatization include, but are not limited to, water-soluble polymers. Non-limiting examples of water-soluble polymers include, but are not limited to, polyethylene glycol (PEG) to, *e.g.*, increase the (*e.g.*, serum) half-life of an antibody. Methods for protein PEGylation are known in the art and can be applied to the antibodies of the present invention. See, for example, EP 0154316 and EP 0401384.

II. Polynucleotides, vectors, and hosts

The present invention provides a nucleic acid encoding any of the above anti-TIGIT antibodies or fragments thereof, and also provides a vector comprising the nucleic acid. In one embodiment, the vector is an expression vector. In addition, a host cell comprising the nucleic acid or the vector is provided. In one embodiment, the host cell is eukaryotic. In another embodiment, the host cell is selected from a yeast cell, and a mammal cell (*e.g.*, a CHO cell or a 293 cell). In another embodiment, the host cell is prokaryotic.

In one aspect, the present invention provides a nucleic acid encoding any of the above anti-TIGIT antibodies or fragments thereof. The nucleic acid can include a nucleic acid encoding an amino acid sequence of light chain variable regions and/or heavy chain variable regions of the antibodies, or a nucleic acid encoding an amino acid sequence of light chains and/or heavy chains of the antibodies. Exemplary nucleic acid sequences encoding heavy chain variable regions of the antibodies include nucleic acid sequences having at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to nucleic acid sequences selected from SEQ ID NOs: 150-169, or include nucleic acid sequences selected from SEQ ID NOs: 150-169. Exemplary nucleic acid sequences encoding light chain variable regions of the antibodies include nucleic acid sequences having at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to nucleic acid sequences selected from SEQ ID NOs: 170-176, or include nucleic acid sequences selected from SEQ ID NOs: 170-176. Polypeptides encoded by the polynucleotides can show antigen-binding (TIGIT-binding) ability when expressed in a suitable expression vector.

The present invention also provides a polynucleotide encoding at least one CDR and typically all three CDRs from a heavy chain (VH) sequence or a light chain (VL) sequence of the antibodies binding to TIGIT described above. In some further embodiments, the polynucleotide encodes a complete or substantially complete variable region sequence of heavy chains and/or light chains of the antibodies binding to TIGIT described above.

As will be appreciated by those skilled in the art, each antibody or polypeptide amino acid sequence can be encoded by a variety of nucleic acid sequences because of codon degeneracy.

In a preferred embodiment, the nucleic acid encoding the antibodies of the present invention further comprises a nucleotide sequence encoding a heavy chain Fc region, *e.g.*, an Fc region sequence set forth in SEQ ID NO: 177 or a sequence substantially identical thereto.

In a preferred embodiment, the nucleic acid encoding the antibodies of the present invention further comprises a nucleotide sequence encoding a light chain constant region sequence, *e.g.*, a sequence set forth in SEQ ID NO: 209 or a sequence substantially identical thereto.

By virtue of methods well known in the art, the polynucleotide sequences can be produced by *de novo* solid phase DNA synthesis or by PCR mutagenesis of existing sequences (*e.g.*, a VH DNA sequence set forth in SEQ ID NOs: 150-169 and a VL DNA sequence set forth in SEQ ID NOs: 170-176) encoding antibodies binding to TIGIT or antigen-binding fragments thereof.

5 In one embodiment, one or more vectors comprising the nucleic acid of the present invention are provided. In one embodiment, the vector is an expression vector, such as a eukaryotic expression vector. The vector includes, but is not limited to, a virus, a plasmid, a cosmid, a lambda phage, or a yeast artificial chromosome (YAC). In a preferred embodiment, the expression vector of the present invention is a pTT5 expression vector.

10 In one embodiment, a host cell comprising the vector is provided. The suitable host cell for cloning or expressing the vector encoding the antibody includes a prokaryocyte or a eukaryocyte described herein. For example, antibodies may be produced in bacteria, particularly when glycosylation and Fc effector functions are not required. Expression of antibody fragments and polypeptides in bacteria is described in, for example, U.S. Pat. Nos. 5648237, 5789199 and 5840523, and also
15 described in Charlton, *Methods in Molecular Biology*, Vol. 248 (B. K. C. Lo, ed., Humana Press, Totowa, NJ, 2003), pg. 245-254, which describes expression of antibody fragments in *E. coli*. After expression, antibodies in a soluble fraction can be isolated from bacterial cell paste and can be further purified.

In one embodiment, the host cell is eukaryotic. In another embodiment, the host cell is selected
20 from a yeast cell, a mammalian cell and other cells suitable for preparing an antibody or an antigen-binding fragment thereof. For example, eukaryotic microorganisms, such as filamentous fungi or yeast, are suitable cloning or expression hosts for the vector encoding antibodies. For example, fungus and yeast strains in which a glycosylation pathway has been "humanized" result in the production of antibodies having a partial or complete human glycosylation pattern. See
25 Gerngross, *Nat. Biotech.* 22: 1409-1414 (2004), and Li *et al.*, *Nat. Biotech.* 24:210-215 (2006). Host cells suitable for expressing glycosylated antibodies may also be derived from multicellular organisms (invertebrates and vertebrates). Vertebrate cells may also be used as hosts. For example, a mammalian cell line engineered to be suitable for suspension growth may be used. Some examples of useful mammalian host cell lines are monkey kidney CV1 lines (COS-7) transformed
30 with SV40, human embryonic kidney lines (293 HEK or 293 cells, as described in, *e.g.*, Graham *et al.*, *J. Gen Virol.* 36:59 (1977)) and the like. Other useful mammalian host cell lines include Chinese hamster ovary (CHO) cells including DHFR⁻ CHO cells (Urlaub *et al.*, *Proc. Natl. Acad. Sci. USA* 77: 216 (1980)), and myeloma cell lines such as Y0, NS0, and Sp2/0. For reviews of certain mammalian host cell lines suitable for antibody production, see, *e.g.*, Yazaki and Wu,
35 *Methods in Molecular Biology*, Vol. 248 (B. K. C. Lo, ed., Humana Press, Totowa, NJ), pg. 255-268 (2003).

III. Preparation of antibodies

In one embodiment, a method for preparing an anti-TIGIT antibody is provided, wherein the method comprises culturing host cells comprising a nucleic acid encoding the antibody under
40 conditions suitable for antibody expression, as provided above, and optionally isolating the antibody from the host cells (or host cell culture media). For recombinant production of the anti-TIGIT antibody, a nucleic acid encoding the antibody (*e.g.*, the antibody described above) is isolated and inserted into one or more vectors for further cloning and/or expression in the host cells. Such a nucleic acid can be easily isolated and sequenced by using conventional procedures (*e.g.*, by

using oligonucleotide probes that are capable of specifically binding to genes encoding heavy and light chains of antibodies).

IV. Assay

The anti-TIGIT antibodies provided herein can be identified, screened, or characterized for physical/chemical properties and/or bioactivity thereof through a variety of assays known in the art.

In one aspect, the antibodies of the present invention are tested for antigen-binding activity. For example, the binding to human TIGIT can be determined by methods known in the art, such as ELISA, Western blot, and the like, or by the exemplary methods disclosed in the examples herein. For example, the assay can be performed using flow cytometry, wherein the antibodies react with a cell line expressing human TIGIT, *e.g.*, CHO cells transfected to express human TIGIT on cell surfaces. Flow cytometry is also applicable to other cells, including T cells expressing natural TIGIT. Alternatively, binding of the antibodies, including binding kinetics (*e.g.*, K_D), can be determined in a biological optical interferometry assay using recombinant TIGIT proteins. In some embodiments, for example, a Fortebio affinity assay is adopted.

In another aspect, a competition assay can be used to identify an antibody that competes for binding to TIGIT with any of the anti-TIGIT antibodies disclosed herein. In certain embodiments, such a competitive antibody binds to the same or an overlapping epitope (*e.g.*, a linear or conformational epitope) as any of the anti-TIGIT antibodies disclosed herein. A detailed exemplary method for locating an epitope to which an antibody binds is described in Morris (1996) "Epitope Mapping Protocols", *Methods in Molecular Biology* vol. 66 (Humana Press, Totowa, NJ).

The present invention also provides an assay for identifying anti-TIGIT antibodies having bioactivity. The bioactivity can include, for example, binding to TIGIT (*e.g.*, human TIGIT), blocking binding of TIGIT (*e.g.*, human TIGIT) to CD155 molecules, blocking TIGIT-mediated inhibitory signaling, increasing the production of IL2 in T cells, and/or inhibiting tumor growth. For example, the ability of antibodies in inhibiting tumor growth are tested in an *in vivo* tumor suppression model (see, *e.g.*, Example 6). Antibodies having such bioactivity *in vivo* and/or *in vitro* are also provided herein.

It will be appreciated that any of the above assays can be performed using the immunoconjugates or multispecific antibodies of the present invention to replace or supplement anti-TIGIT antibodies.

V. Multispecific antibodies

In a further aspect, the present invention provides a multispecific (including bispecific) antibody molecule that specifically binds to TIGIT, preferably human TIGIT. In one embodiment, among multispecific antibodies, the antibodies (or the antigen-binding fragments thereof) of the present invention have a first binding specificity for TIGIT. In yet another embodiment, the multispecific antibodies further have a second binding specificity, or, in yet another embodiment, have a second binding specificity and a third binding specificity. In yet another embodiment, the multispecific antibodies are bispecific antibodies.

In one embodiment, the binding specificity is dependent on a "binding site" or an "antigen-binding site" (a region of an antibody molecule that actually binds to an antigen) of the antibodies. In a preferred embodiment, the antigen-binding site is formed by a VH/VL pair consisting of a light chain variable domain (VL) and a heavy chain variable domain (VH) of the antibodies. Thus, in one embodiment, the "multispecific" antibodies have at least two antigen-binding sites, each of which

can bind to a different epitope of the same antigen or to a different epitope of a different antigen.

For multispecific antibodies and preparation thereof, see, for example, the descriptions in WO 2009/080251, WO 2009/080252, WO 2009/080253, WO 2009/080254, WO 2010/112193, WO 2010/115589, WO 2010/136172, WO 2010/145792, and WO 2010/145793.

5 VI. Immunoconjugates

In yet another aspect, the present invention provides an immunoconjugate produced by conjugating the antibodies of the present invention to a heterologous molecule. In one embodiment, in the immunoconjugate, the antibodies (or the antigen-binding fragments thereof) of the present invention are conjugated to a therapeutic or diagnostic agent. In some embodiments, the antibodies
10 of the present invention can be conjugated to a heterologous molecule in the form of full-length antibodies or antibody fragments. For example, the antibodies are conjugated in the form of Fab fragments, Fab' fragments, F(ab)'₂ fragments, single chain scFab antibodies, single chain scFvs, or other fragments.

In some embodiments, the antibodies of the present invention are conjugated to a therapeutic molecule. Linkers can be used to covalently link the antibodies to the therapeutic molecule. Suitable
15 linkers include chemical linkers or peptide linkers.

In other embodiments, the antibodies of the present invention can be conjugated to a diagnostic or detectable agent. Such conjugates can be used as part of a clinical testing method (*e.g.*, to determine the efficacy of a particular therapy) to monitor or predict the onset, formation, progression, and/or
20 severity of a disease or disorder. Such diagnosis and detection can be achieved by coupling the antibodies to a detectable agent.

VII. Pharmaceutical compositions and pharmaceutical preparations

The present invention also provides a composition (including a pharmaceutical composition or a pharmaceutical preparation) comprising the anti-TIGIT antibodies or immunoconjugates thereof
25 or multispecific antibodies, and a composition comprising a polynucleotide encoding the anti-TIGIT antibodies or immunoconjugates thereof or multispecific antibodies. Such compositions can further optionally comprise suitable pharmaceutical adjuvants, such as a pharmaceutical carrier, a pharmaceutical excipient, and the like known in the art, including buffers.

In one embodiment, the composition further comprises a second therapeutic agent. The second
30 therapeutic agent can be selected from a group including, but not limited to, such as anti-PD-1 antibodies and anti-PD-L1 antibodies. Preferably, the second therapeutic agent is a PD-1 antagonist, in particular an anti-PD-1 antibody.

The pharmaceutical carrier applicable to the present invention may be sterile liquid, such as water and oil, including those derived from petroleum, animals, plants or synthesis, such as peanut oil,
35 soybean oil, mineral oil, sesame oil, *etc.* Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions, 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,
40 propylene, glycol, water, ethanol, *etc.* For use and application of excipients, see *Handbook of Pharmaceutical Excipients*, the fifth edition, R. C. Rowe, P. J. Seskey and S. C. Owen,

Pharmaceutical Press, London, Chicago. The composition may further comprise a small quantity of wetting agents or emulsifiers, or pH buffer, if desired. The composition may take the form of a solution, a suspension, an emulsion, a tablet, a pill, a capsule, a powder, a sustained release preparation, and the like. Oral preparations may comprise a standard carrier, such as pharmaceutical grade mannitol, lactose, starch, magnesium stearate, and saccharin.

A pharmaceutical preparation comprising the present invention can be prepared by mixing the anti-TIGIT antibodies, immunoconjugates or multispecific antibodies of the present invention of a desired purity with one or more optional pharmaceutical adjuvants, preferably in the form of a lyophilized preparation or an aqueous solution (*Remington's Pharmaceutical Sciences*, 16th edition, Osol, A. eds. (1980)).

An exemplary lyophilized antibody preparation is described in U.S. Pat. No. 6,267,958. The aqueous antibody preparation includes those described in U.S. Pat. Nos. 6,171,586 and WO 2006/044908, and the latter preparation comprises a histidine-acetate buffer.

The pharmaceutical composition or preparation of the present invention can further comprise one or more other active ingredients which are required for a specific indication being treated, preferably active ingredients having complementary activities that do not adversely affect one another. For example, it may be desirable to further provide other anti-cancer active ingredients, such as PD-1 binding antagonists or PD-L1 binding antagonists, *e.g.*, an anti-PD-1 antibody or an anti-PD-L1 antibody. The active ingredients are suitably combined in an amount effective for an intended purpose.

A sustained release preparation can be prepared. Suitable examples of the sustained release preparation include a semipermeable matrix of a solid hydrophobic polymer comprising an antibody. The matrix is in the form of a shaped article, such as a film or a microcapsule.

For other components of the pharmaceutical preparation, see also those disclosed in WO 2015/153513.

VIII. Combination products

In one aspect, the present invention also provides a combination product comprising the antibodies or the antigen-binding fragments thereof, bispecific antibodies, or immunoconjugates of the present invention, and one or more other therapeutic agents (*e.g.*, a chemotherapeutic agent, other antibodies, a cytotoxic agent, a vaccine, an anti-infection active agent). The combination product of the present invention can be used in a therapeutic method disclosed herein.

In some embodiments, the combination product is provided, wherein the other therapeutic agents refer to, for example, a therapeutic agent, such as an antibody, which is effective to stimulate an immune response and thus further enhance, stimulate, or upregulate the immune response in a subject. In some embodiments, the other antibodies refer to, *e.g.*, an anti-PD-1 antibody or an anti-PD-L1 antibody.

In some embodiments, the combination product is used for preventing or treating a tumor. In some embodiments, the tumor is a cancer, *e.g.*, a gastrointestinal cancer (such as a gastric cancer, a rectal cancer, a colon cancer, and a colorectal cancer), or a skin cancer (such as malignant melanoma).

In some embodiments, the combination product is used for preventing or treating an infection, such as a bacterial infection, a viral infection, a fungal infection, a protozoan infection, and the like.

IX. Therapeutic method and use of antibodies

Herein, the terms "individual" and "subject" can be used interchangeably and refer to a mammal. Mammals include, but are not limited to, domesticated animals (*e.g.*, cows, sheep, cats, dogs, and horses), primates (*e.g.*, human and non-human primates such as monkeys), rabbits and rodents (*e.g.*, mice and rats). In particular, a subject is a human.

Herein, the term "treating" refers to a clinical intervention intending to alter the natural progress of a disease in an individual being treated. Desired therapeutic effects include, but are not limited to, preventing the occurrence or recurrence of diseases, alleviating symptoms, reducing any direct or indirect pathological outcomes of diseases, preventing metastasis, delaying disease progression, improving or alleviating conditions, and improving prognosis.

In one aspect, the present invention relates to a method for enhancing an immune response of the body of a subject, wherein the method comprises administering to the subject an effective amount of any of the anti-TIGIT antibodies fragments thereof described herein, an immunoconjugate or a multispecific antibody comprising the antibodies or fragments thereof, or a pharmaceutical composition. In some embodiments, the anti-TIGIT antibodies or antigen-binding fragments thereof of the present invention are administered to a subject carrying a tumor to stimulate an anti-tumor immune response. In other embodiments, the antibodies or the antigen-binding fragments thereof of the present invention are administered to a subject carrying an infection to stimulate an anti-infection immune response.

In another aspect, the present invention relates to a method for treating a tumor, *e.g.*, a cancer, in a subject, wherein the method comprises administering to the subject an effective amount of any of the anti-TIGIT antibodies or fragments thereof described herein, an immunoconjugate or a multispecific antibody comprising the antibodies or fragments thereof, or a pharmaceutical composition. The cancer may be at an early, intermediate, or advanced stage or a metastatic cancer.

TIGIT has been demonstrated to be highly expressed on the surface of human tumor-infiltrating CD8⁺ T cells. In some embodiments, the method of the present invention is used for treating a cancer, particularly a solid tumor infiltrated with tumor-infiltrating lymphocytes expressing TIGIT.

In one embodiment, the cancer is a gastrointestinal cancer, such as a colon cancer.

In some embodiments, the tumor or tumor cell can be selected from a colorectal neoplasm, an ovarian neoplasm, a pancreatic neoplasm, a lung neoplasm, a hepatic neoplasm, a breast neoplasm, a renal neoplasm, a prostate neoplasm, a gastrointestinal neoplasm, a melanoma, a cervical neoplasm, a bladder neoplasm, a glioblastoma, and a head and neck neoplasm. In some embodiments, the cancer can be selected from a colorectal cancer, an ovarian cancer, a pancreatic cancer, a lung cancer, a liver cancer, a breast cancer, a renal cancer, a prostate cancer, a gastrointestinal cancer, a melanoma, a cervical cancer, a bladder cancer, a glioblastoma, and a head and neck cancer.

In some embodiments, a method for treating a tumor (*e.g.*, a cancer) is provided herein, wherein the method comprises administering to a subject the anti-TIGIT antibodies of the present invention and antagonistic anti-PD-1 antibodies. In some embodiments, the method is used for treating a tumor co-expressing TIGIT and PD-1, *e.g.*, melanoma co-expressing TIGIT and PD-1 (Chauvin *et al.* (2015) *J. Clin. Invest.* 125:2046), a non-small cell lung cancer (NSCLC), and a renal cell carcinoma (RCC).

In another aspect, the present invention relates to a method for treating an infectious disease, *e.g.*, a chronic infection, in a subject, wherein the method comprises administering to the subject an

effective amount of any of the anti-TIGIT antibodies or fragments thereof described herein, an immunoconjugate or a multispecific antibody comprising the antibodies or fragments thereof, or a pharmaceutical composition. In one embodiment, the infection is a virus infection.

In one embodiment, the infectious disease results from a virus infection. Some examples of pathogenic viruses include hepatitis viruses (A, B, and C), influenza viruses (A, B, and C), HIV, herpes viruses (*e.g.*, VZV, HSV-1, HAV-6, HSV-II, CMV, and Epstein Barr virus), adenoviruses, flaviviruses, echoviruses, rhinoviruses, coxsackieviruses, coronaviruses, respiratory syncytial viruses, mumps viruses, rotaviruses, measles viruses, rubella viruses, parvoviruses, vaccinia viruses, HTLV viruses, dengue viruses, papillary carcinomas, molluscum viruses, polioviruses, rabies viruses, JC viruses, and arthropod-borne encephalitis viruses.

In some embodiments, the method described herein further comprises administering to the subject one or more therapies in combination (*e.g.*, therapeutic modality and/or other therapeutic agents). In some embodiments, the therapeutic modality includes a surgical treatment and/or a radiation therapy.

In some embodiments, a T cell response can be stimulated by a combination of the anti-TIGIT antibodies of the present invention and one or more therapeutic agents. In some embodiments, in addition to administering the antibodies of present the invention, the method of the present invention further comprises administering at least one additional immunostimulatory antibody, *e.g.*, an anti-PD-1 antibody and an anti-PD-L1 antibody, which can be, *e.g.*, fully humanized, chimeric, or humanized.

In other embodiments, other therapeutic agents that can be used in combination with the antibodies of the present invention are PD-1 binding antagonists and PD-L1 binding antagonists. Alternative names for "PD-1" include CD279 and SLEB2. Alternative names for "PD-L1" include B7-H1, B7-4, CD274, and B7-H. In some embodiments, PD-1 and PD-L1 are human PD-1 and human PD-L1, respectively. In some embodiments, the PD-1 binding antagonist is a molecule that inhibits the binding of PD-1 to a ligand/binding partner thereof. In a particular aspect, the PD-1 ligand/binding partner is PD-L1. In another embodiment, the PD-L1 binding antagonist is a molecule that inhibits the binding of PD-L1 to a binding partner thereof. In a particular aspect, the PD-L1 binding partner is PD-1. The antagonist may be an antibody, an antigen-binding fragment, an immunoadhesin, a fusion protein, or an oligopeptide. In some embodiments, the PD-1 binding antagonist is an anti-PD-1 antibody (*e.g.*, a human antibody, a humanized antibody, or a chimeric antibody). In some embodiments, the anti-PD-1 antibody is selected from: IBI308 (Sintilimab monoclonal antibody, WO2017/025016A1), MDX-1106 (nivolumab, OPDIVO), Merck 3475 (MK-3475, pembrolizumab, KEYTRUDA) and CT-011 (pidilizumab). In some embodiments, the anti-PD-1 antibody is MDX-1106. In some embodiments, the anti-PD-1 antibody is nivolumab (CAS Registry Number: 946414-94-4). In a preferred embodiment, the anti-PD-1 antibody is the "Antibody C" as described herein.

In some further embodiments, the anti-TIGIT antibodies or fragments thereof, alone or in combination with the PD-1/PD-L1 binding antagonist, can also be administered in combination with one or more other therapies, *e.g.*, therapeutic modalities and/or therapeutic agents. In some embodiments, the therapeutic modalities include a surgery (*e.g.*, a tumor resection), a radiation therapy (*e.g.*, an external beam therapy that involves a three-dimensional conformal radiation therapy in which an irradiation region is designed), a partial irradiation (*e.g.*, an irradiation directed to a preselected target or an organ), a focused irradiations, and the like.

In some embodiments, the anti-TIGIT antibodies or antigen-binding fragments thereof of the present invention can be administered in combination with a chemotherapy or a chemotherapeutic agent. In some embodiments, the anti-TIGIT antibodies or antigen-binding fragments thereof of the present invention can be administered in combination with a radiation therapy or a radiotherapeutic agent. In some embodiments, the anti-TIGIT antibodies or antigen-binding fragments thereof of the present invention can be administered in combination with a targeted therapy or a targeted therapeutic agent. In some embodiments, the anti-TIGIT antibodies or antigen-binding fragments thereof of the present invention can be administered in combination with an immunotherapy or an immunotherapeutic agent, *e.g.*, a monoclonal antibody.

The antibody of the present invention (the pharmaceutical composition or the immunoconjugate comprising the same, and any other therapeutic agents) can be administered by any suitable method, including parenteral administration, intrapulmonary administration, intranasal administration, and intralesional administration if required by local treatment. Parenteral infusion includes intramuscular, intravenous, intra-arterial, intraperitoneal, or subcutaneous administration. The medicaments may be administered by any suitable means, such as injection, *e.g.*, intravenous or subcutaneous injection, to some extent depending on short-term or long-term treatment. Various administration schedules are encompassed herein, including, but not limited to, single administration or multiple administrations, bolus injections, and pulse infusions at multiple time points.

In order to prevent or treat diseases, the appropriate dosage of the antibody of the present invention (when used alone or in combination with one or more other additional therapeutic agents) will depend on types of diseases to be treated, types of antibodies, severity and progression of the disease, purpose of administration (prophylactic or therapeutic), previous treatments, clinical histories of patients, responses to the antibody, and the discretion of an attending physician. The antibody is suitably administered to a patient through a single treatment or through a series of treatments.

In the methods described above, the composition, multispecific antibody, or immunoconjugate of the present invention can be administered in place of the antibody or the antigen-binding fragment thereof disclosed herein. Alternatively, in the methods, the composition, multispecific antibody, or immunoconjugate of the present invention can be further administered after the antibody or the antigen-binding fragment thereof disclosed herein is administered.

In yet another aspect, the present invention provides a use of the anti-TIGIT antibody, composition, immunoconjugate, and multispecific antibody of the present invention in preparation of drugs used for the methods described above (*e.g.*, used for treatment).

X. Methods and compositions for diagnosis and detection

In yet another aspect, the present invention relates to a method and a kit for detecting TIGIT in a sample, wherein the method comprises: (a) contacting the sample with the antibody or the antigen-binding fragment thereof or the immunoconjugate disclosed herein; and (b) detecting the formation of a complex of the antibody or the antigen-binding fragment thereof or the immunoconjugate with a TIGIT protein. In some embodiments, the sample is from a cancer patient, *e.g.*, a skin cancer patient. The detection may be *in vitro* or *in vivo*.

The term "detection" used herein includes quantitative or qualitative detection, and exemplary detections may involve immunohistochemistry, immunocytochemistry, flow cytometry (*e.g.*, FACS), magnetic beads complexed with antibody molecules, ELISA, and PCR techniques (*e.g.*,

RT-PCR). In certain embodiments, the biological sample is blood, serum, or other liquid samples of biological origin. In certain embodiments, the biological sample includes cells or tissues. In some embodiments, the biological sample is derived from a proliferative or cancerous lesion. In certain embodiments, the TIGIT to be detected is human TIGIT.

- 5 In one embodiment, the anti-TIGIT antibody is used to select a subject suitable for treatment with the anti-TIGIT antibody, *e.g.*, wherein TIGIT is a biomarker for selecting the subject. In one embodiment, the antibody of the present invention can be used to diagnose cancers or tumors, *e.g.*, to assess (*e.g.*, monitor) the treatment or progression, diagnosis and/or staging of a disease (*e.g.*, the hyperproliferative or cancerous disease) described herein in a subject.
- 10 In certain embodiments, a labeled anti-TIGIT antibody is provided. The label includes, but is not limited to, a label or moiety (*e.g.*, a fluorescent label, a chromophoric label, an electron-dense label, a chemiluminescent label, and a radioactive label) that is detected directly, as well as a moiety that is detected indirectly, such as an enzyme or a ligand, for example, by an enzymatic reaction or a molecular interaction. Exemplary labels include, but are not limited to, radioisotopes of ³²P, ¹⁴C, ¹²⁵I,
- 15 ³H and ¹³¹I, fluorophores (such as rare earth chelates or fluorescein) and derivatives thereof, rhodamine and derivatives thereof, dansyl, umbelliferone, luciferase (such as firefly luciferase and bacterial luciferase (U.S. Pat. No. 4,737,456)), fluorescein, 2,3-dihydrophthalazinedione, horseradish peroxidase (HR), alkaline phosphatase, β -galactosidase, glucoamylase, lysozyme, carbohydrate oxidase (such as glucose oxidase, galactose oxidase and glucose-6-phosphate
- 20 dehydrogenase), heterocyclic oxidase (such as uricase and xanthine oxidase), enzymes oxidizing dye precursors with hydrogen peroxide (such as HR, lactoperoxidase, or microperoxidase), biotin/avidin, spin labels, phage labels, stable free radicals, *etc.*

- 25 The following examples are described to assist in understanding the present invention. The examples are not intended and should not be interpreted in any way as limiting the protection scope of the present invention.

Table 1: CDR sequences of exemplary antibodies of the present invention

Antibody	HCDR1	SEQ ID NO:	HCDR2	SEQ ID NO:	HCDR3	SEQ ID NO:	LCDR1	SEQ ID NO:	LCDR ₂	SEQ ID NO:	LCDR3	SEQ ID NO:
Kabat numbering position	H27-35B		H50-65		H93-102		L24-34		L50-56		L89-97	
ADI-27238	YTFTSYMS	1	IINPSGGSTSYAQKFQG	6	ARARYPSSWPYGM _D V	11	RASQSINSYLN	16	AASSLQS	17	QQSLLTPFT	18
ADI-30263	YTFLSYMN	2	IIDPSGGRTSYAQKFQG	7	ARARYPSSWPYGM _D V	12	RASQSINSYLN	16	AASSLQS	17	QQSLLTPFT	18
ADI-30267	YTFRSYMS	3	IIDPSGGRTSFAQKFQG	8	ARARYPESWPYGM _D V	13	RASQSINSYLN	16	AASSLQS	17	QQSLLTPFT	18
ADI-30268	YTFGSYYMG	4	IIDPSGGRTSYARKFQG	9	ARARTPSSWPYGM _D V	14	RASQSINSYLN	16	AASSLQS	17	QQSLLTPFT	18
Consensus sequence	YTFX ₁ SYMX ₂ (wherein X ₁ is selected from T, L, R, G and a conservatively substituted residue thereof, and X ₂ is selected from S, N, G and a conservatively substituted residue thereof)	5	IIX ₁ PSGGX ₂ TSX ₃ AX ₄ KFQG (wherein X ₁ is selected from N, D and a conservatively substituted residue thereof, X ₂ is selected from S, R and a conservatively substituted residue thereof, X ₃ is selected from Y, F and a conservatively substituted residue thereof, and X ₄ is selected from Q, R and a conservatively substituted residue thereof)	10	ARARX ₁ PSSWPYGX ₂ D (wherein X ₁ is selected from Y, T and a conservatively substituted residue thereof, and X ₂ is selected from M, T and a conservatively substituted residue thereof)	15	RASQSINSYLN	16	AASSLQS	17	QQSLLTPFT	18
ADI-27243	GSISSRRYYWG	19	SIYYSGSTYYNPSLKS	22	ARDGLYHTPEYFQH	25	RASQSVSSYLA	26	DASN RAT	27	QQRFAF PYT	28
ADI-30302	GSIGSSQYYWG	20	SIYRSGGTYYNPSLKS	23	ARDGLYHTPEYFQH	25	RASQSVSSYLA	26	DASN RAT	27	QQRFAF PYT	28
ADI-30336	GSISSRRYYWG	19	SIYYSGSTYYNPSLKS	22	ARDGLYHTPEYFQH	25	RASQSVSSYLA	26	DASN RAT	27	QQRFA HPYT	29
Consensus sequence	GSIX ₁ SSX ₂ YYWG (wherein X ₁ is selected from S, G and a conservatively substituted residue thereof, and X ₂ is selected from R, Q and a conservatively substituted residue thereof)	21	SIYX ₁ SGX ₂ TYYNPSLKS (wherein X ₁ is selected from Y, R and a conservatively substituted residue thereof, and X ₂ is selected from S, G and a conservatively substituted residue thereof)	24	ARDGLYHTPEYFQH	25	RASQSVSSYLA	26	DASN RAT	27	QQRFA X ₁ PYT (wherein X ₁ is selected from F, H and a conservatively substituted residue thereof)	30

ADI-27278	FTFSSYSMN	31	YISGSSSTIYYADSVKG	34	ARHRIADSPSRAFDI	38	KSSQSVLFSSNN KNYLA	41	WAST RES	42	QQSYFF PT	43
ADI-30293	FTFSSYSMN	31	YI-SSSGTINYADSVKG	35	ARHRIADSPSRAFDI	38	KSSQSVLFSSNN KNYLA	41	WAST RES	42	QQSYFF PT	43
ADI-30296	FTIGGYSMN	32	YI-SSSSTIHYADSVKG	36	ARHRIGRSPSRAFDI	39	KSSQSVLFSSNN KNYLA	41	WAST RES	42	QQSYFF PT	43
Consensus sequence	FTFX ₁ X ₂ X ₃ YSMN (wherein X ₁ is selected from F, I and a conservatively substituted residue thereof, X ₂ is selected from S, G and a conservatively substituted residue thereof, and X ₃ is selected from S, G and a conservatively substituted residue thereof)	33	YIX ₁ X ₂ SSX ₃ TIX ₄ YADSVKG (wherein X ₁ is selected from deletion, S and a conservatively substituted residue thereof, X ₂ is selected from G, S and a conservatively substituted residue thereof, X ₃ is selected from S, G and a conservatively substituted residue thereof, and X ₄ is selected from Y, N, H and a conservatively substituted residue thereof)	37	ARHRIX ₁ X ₂ SPSRAFDI (wherein X ₁ is selected from A, G and a conservatively substituted residue thereof, and X ₂ is selected from D, R or a conservatively substituted residue thereof)	40	KSSQSVLFSSNN KNYLA	41	WAST RES	42	QQSYFF PT	43
ADI-27291	FTFSSYAMS	44	AISGSGSTYYADSVKG	48	AKDPGTDSSGYYIWR RY	53	RASQSVSSNLA	57	SASTR AT	58	QQYVP HPPFT	59
ADI-30283	FTFSPYGMS	45	SISGSGGRTYYADSVKG	49	AKDPGTDSSGYYIWR RY	53	RASQSVSSNLA	57	SASTR AT	58	QQYVP HPPFT	59
ADI-30286	FTFGPYGMS	46	AISGSGASTWYADSVKG	50	AKDPGTHYSGYYIWR RY	54	RASQSVSSNLA	57	SASTR AT	58	QQYVP HPPFT	59
ADI-30288	FTFGPYGMS	46	AISGSGASTWHADSVKG	51	AKDPGTDSTGYYYIWR RY	55	RASQSVSSNLA	57	SASTR AT	58	QQYVP HPPFT	59
Consensus sequence	FTFX ₁ X ₂ YX ₃ AMS (wherein X ₁ is selected from S, G and a conservatively substituted residue thereof, X ₂ is selected from S, P and a conservatively substituted residue thereof, and X ₃ is selected from A, G and a conservatively substituted residue thereof)	47	X ₁ ISGSGX ₂ X ₃ TX ₄ X ₅ ADSVKG (wherein X ₁ is selected from A, S and a conservatively substituted residue thereof, X ₂ is selected from G, A and a conservatively substituted residue thereof, X ₃ is selected from S, R and a conservatively substituted residue thereof, X ₄ is selected from Y, W and a conservatively substituted residue thereof, and X ₅ is selected from Y, H and a conservatively substituted residue thereof)	52	AKDPGTX ₁ X ₂ X ₃ GYYY IWR (wherein X ₁ is selected from D, H and a conservatively substituted residue thereof, X ₂ is selected from S, Y and a conservatively substituted residue thereof, and X ₃ is selected from S, T and a conservatively substituted residue thereof)	56	RASQSVSSNLA	57	SASTR AT	58	QQYVP HPPFT	59
ADI-27297	YTFTSYYMH	60	IINPSGSGSTSYAQKFQG	6	ARDHIDIAAAGRLADY thereof)	66	RASQGISSWLA	69	AASS LQS	17	QQAVIL PIT	70

ADI-30272	YTFTEYYMH	61	IISPSAGSTSYAQKFQG	63	ARDHIDIAAAGRLADY	66	RASQGISSWLA	69	AASS LQS	17	QQA VIL PIT	70
ADI-30278	YTFTEYYMH	61	IISPSAGSTKYAQKFQG	64	ARDHIDIRLAGRLADY	67	RASQGISSWLA	69	AASS LQS	17	QQA VIL PIT	70
Consensus sequence	YTFTX ₁ YYMH (wherein X ₁ is selected from S, E and a conservatively substituted residue thereof)	62	IIX ₁ PSX ₂ GSTX ₃ YAKFKQG (wherein X ₁ is selected from N, S and a conservatively substituted residue thereof, X ₂ is selected from G, A and a conservatively substituted residue thereof, and X ₃ is selected from S, K and a conservatively substituted residue thereof)	65	ARDHDIX ₁ X ₂ AGR LAD Y (wherein X ₁ is selected from A, R and a conservatively substituted residue thereof, and X ₂ is selected from A, L and a conservatively substituted residue thereof)	68	RASQGISSWLA	69	AASS LQS	17	QQA VIL PIT	70
ADI-27301	GSISSSSYYWG	71	SIYYSGSTYYNPSLKS	22	AREAGRGTGGLLDY	78	RASQSISSWLA	81	KASS LES	82	QQA VIL PIT	83
ADI-30306	GSISSSLYYWG	72	SIYYSGSTFYNPSFKS	75	AREAGRGTGGLLDY	78	RASQSISSWLA	81	KASS LES	82	QQA VIL PIT	83
ADI-30311	GSIASSVYYWG	73	SIYYSGSTWYNPSLKS	76	AREAGRGTGGLLDY	79	RASQSISSWLA	81	KASS LES	82	QQA VIL PIT	83
Consensus sequence	GSIX ₁ SSX ₂ YYWG (wherein X ₁ is selected from A, S and a conservatively substituted residue thereof, and X ₂ is selected from S, L, V and a conservatively substituted residue thereof)	74	SIYYSGSTX ₁ YNPSX ₂ KS (wherein X ₁ is selected from Y, F, W and a conservatively substituted residue thereof, and X ₂ is selected from L, F and a conservatively substituted residue thereof)	77	AREAGR _{X₁} X ₂ TGGLLDY Y (wherein X ₁ is selected from G, T and a conservatively substituted residue thereof, and X ₂ is selected from T, G and a conservatively substituted residue thereof)	80	RASQSISSWLA	81	KASS LES	82	QQA VIL PIT	83

Table 2: CDR sequences of exemplary antibodies of the present invention

Antibody	HCDR1-AbM	SE Q	HCDR2-Kabat	SE Q	HCDR3-Kabat	SE Q	LCDR1-Kabat	SE Q	LCDR2-Kabat	SE Q	LCDR3-Kabat	SE Q
ADI-27238	GYTFTSYYS	178	IINPSGGSTSYAQKFQG	6	ARYPSSWPYGM DV	182	RASQSINSYLN	16	AASSLQS	17	QQSLLTPFT	18
ADI-30263	GYTFLSYMN	179	IIDPSGGRTSYAQKFQG	7	ARYPSSWPYGT DV	183	RASQSINSYLN	16	AASSLQS	17	QQSLLTPFT	18
ADI-30267	GYTFSYYMS	180	IIDPSGGRTSFAQKFQG	8	ARYPESWPYGM DV	184	RASQSINSYLN	16	AASSLQS	17	QQSLLTPFT	18
ADI-30268	GYTFGSYYMG	181	IIDPSGGRTSYARKFQG	9	ARTPSSWPYGM DV	185	RASQSINSYLN	16	AASSLQS	17	QQSLLTPFT	18
ADI-27243	GGSISSRRYYW G	186	SIYSGSTYYNPSLKS	22	DGLYHTPEYFQH	188	RASQSVSSYLA	26	DASNRAT	27	QQRFAFPYT	28
ADI-30302	GGSIGSSQYYW G	187	SIYRSGGTYYNPSLKS	23	DGLYHTPEYFQH	188	RASQSVSSYLA	26	DASNRAT	27	QQRFAFPYT	28
ADI-30336	GGSISSRRYYW G	186	SIYSGSTYYNPSLKS	22	DGLYHTPEYFQH	188	RASQSVSSYLA	26	DASNRAT	27	QQRFAFPYT	29
ADI-27278	GFTFSSYSMN	189	YISGSSSTIYYADSVKG	34	HRIADSPSRAFDI	191	KSSQSVLFSSNNKNYL A	41	WASTRES	42	QQSYFFPT	43
ADI-30293	GFTFSSYSMN	189	YI-SSSGTINYADSVKG	35	HRIADSPSRAFDI	191	KSSQSVLFSSNNKNYL A	41	WASTRES	42	QQSYFFPT	43
ADI-30296	GFTIGGYSMN	190	YI-SSSSTIHYADSVKG	36	HRIGRSPSRAFDI	192	KSSQSVLFSSNNKNYL A	41	WASTRES	42	QQSYFFPT	43
ADI-27291	GFTFSSYAMIS	193	AISGSGGSTYYADSVK G	48	DPGTDSSGYYIWR Y	196	RASQSVSSNLA	57	SASTRAT	58	QQYVPHPPF T	59
ADI-30283	GFTFSPYGMS	194	SISGSGGRTYYADSVK G	49	DPGTDSSGYYIWR Y	196	RASQSVSSNLA	57	SASTRAT	58	QQYVPHPPF T	59
ADI-30286	GFTFGPYGMS	195	AISGSGASTWYADSVK G	50	DPGTHYSGYYIWR Y	197	RASQSVSSNLA	57	SASTRAT	58	QQYVPHPPF T	59
ADI-30288	GFTFGPYGMS	195	AISGSGASTWHADSVK G	51	DPGTDSTGYIWR Y	198	RASQSVSSNLA	57	SASTRAT	58	QQYVPHPPF T	59
ADI-27297	GYTFTSYMH	199	IINPSGGSTSYAQKFQG	6	DHDIAAAGRLADY	201	RASQGISSWLA	69	AASSLQS	17	QQAVILPIT	70
ADI-30272	GYTFTEYYMH	200	IISPSAGSTSYAQKFQG	63	DHDIAAAGRLADY	201	RASQGISSWLA	69	AASSLQS	17	QQAVILPIT	70
ADI-30278	GYTFTEYYMH	200	IISPSAGSTKYAQKFQG	64	DHDIRLAGRLADY	202	RASQGISSWLA	69	AASSLQS	17	QQAVILPIT	70
ADI-27301	GGSISSSSYYW	203	SIYSGSTYYNPSLKS	22	EAGRGTGGLFDY	206	RASQSISSWLA	81	KASSLES	82	QQYGILPRT	83

91	VYYCAKDPGTDSSGYYIWRYYWGQGLTVTVSS	
ADI-302 83	EVQLLESGGGLVQPGGSLRLSCAASGFTFSPYGMWVRQAPGKGLEWVSSISGSGGRYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTA VYYCAKDPGTDSSGYYIWRYYWGQGLTVTVSS	95
ADI-302 86	EVQLLESGGGLVQPGGSLRLSCAASGFTFSPYGMWVRQAPGKGLEWVSAISGSGASTWYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTA VYYCAKDPGTHYSGYYIWRYYWGQGLTVTVSS	96
ADI-302 88	EVQLLESGGGLVQPGGSLRLSCAASGFTFSPYGMWVRQAPGKGLEWVSAISGSGASTWHDADSVKGRFTISRDN SKNTLYLQMNSLRAEDTA VYYCAKDPGTDSTGYYIWRYYWGQGLTVTVSS	97
ADI-272 97	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYMHWVRQAPGQGLEWMGIINPSGGSTSYAQKFQGRVTMTTRDTSTSTVYMEISSLRSEDT AVYYCARDHDAAGRLADYWGQGLTVTVSS	98
ADI-302 72	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYMHWVRQAPGQGLEWMGIISPSAGSTSYAQKFQGRVTMTTRDTSTSTVYMEISSLRSEDT AVYYCARDHDAAGRLADYWGQGLTVTVSS	99
ADI-302 78	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYMHWVRQAPGQGLEWMGIISPSAGSTKYAQKFQGRVTMTTRDTSTSTVYMEISSLRSEDT AVYYCARDHDIRLAGRLADYWGQGLTVTVSS	10 0
ADI-273 01	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIROPQPGKGLEWIGISYYSGSTYYNPSLKS RVTISVDTSKNQFSLKLSSTVAADTAVY YCAREAGRTGTLFDYWGQGLTVTVSS	10 1
ADI-303 06	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSLYYWGWIROPQPGKGLEWIGISYYSGSTFYNPSFKSRVTISVDTSKNQFSLKLSSTVAADTAVY YCAREAGRTGTLFDYWGQGLTVTVSS	10 2
ADI-303 11	QLQLQESGPGLVKPSETLSLTCTVSGGSIASSVYYWGWIROPQPGKGLEWIGISYYSGSTWYNPSLKS RVTISVDTSKNQFSLKLSSTVAADTAVY YCAREAGRTGTLFDYWGQGLTVTVSS	10 3
VL sequences of exemplary antibodies		
Antibody	VL	SEQ ID NO:
ADI-27 238	DIQMTQSPSSLSASVGD RVTITCRASQINSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFLTITISSLPEDFATYYCQQSLLTP FTFGGGTKVEIK	104
ADI-30 263	DIQMTQSPSSLSASVGD RVTITCRASQINSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFLTITISSLPEDFATYYCQQSLLTP FTFGGGTKVEIK	104
ADI-30 267	DIQMTQSPSSLSASVGD RVTITCRASQINSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFLTITISSLPEDFATYYCQQSLLTP FTFGGGTKVEIK	104
ADI-30 268	DIQMTQSPSSLSASVGD RVTITCRASQINSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFLTITISSLPEDFATYYCQQSLLTP FTFGGGTKVEIK	104
ADI-27	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASN RATGIPARFSGSGSGTDFLTITISSLEPEDFAVYYCQQRFAPF	105

243	YTFGGGTKVEIK		
ADI-30 302	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRTGIPARFSGSGSGTDFTLTISLSEPEDEFAVYYCQQRFAFP YTFGGGTKVEIK		105
ADI-30 336	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRTGIPARFSGSGSGTDFTLTISLSEPEDEFAVYYCQQRFAHP YTFGGGTKVEIK		106
ADI-27 278	DIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNNKNYLAWYQQKPGQPPKLLIYWASTRESGVPDPRFSGSGSGTDFTLTISLQAEDVAVYY CQQSYFFPTFGGGTKVEIK		107
ADI-30 293	DIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNNKNYLAWYQQKPGQPPKLLIYWASTRESGVPDPRFSGSGSGTDFTLTISLQAEDVAVYY CQQSYFFPTFGGGTKVEIK		107
ADI-30 296	DIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNNKNYLAWYQQKPGQPPKLLIYWASTRESGVPDPRFSGSGSGTDFTLTISLQAEDVAVYY CQQSYFFPTFGGGTKVEIK		107
ADI-27 291	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLLIYSASTRATGIPARFSGSGSGTEFTLTISLQSEDEFAVYYCQQYVPH PFTFGGGTKVEIK		108
ADI-30 283	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLLIYSASTRATGIPARFSGSGSGTEFTLTISLQSEDEFAVYYCQQYVPH PFTFGGGTKVEIK		108
ADI-30 286	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLLIYSASTRATGIPARFSGSGSGTEFTLTISLQSEDEFAVYYCQQYVPH PFTFGGGTKVEIK		108
ADI-30 288	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLLIYSASTRATGIPARFSGSGSGTEFTLTISLQSEDEFAVYYCQQYVPH PFTFGGGTKVEIK		108
ADI-27 297	DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLISAASSLQSGVPSRFSFGSGSGTDFTLTISLQPEDFATYYCQQA VILP ITFGGGTKVEIK		109
ADI-30 272	DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLISAASSLQSGVPSRFSFGSGSGTDFTLTISLQPEDFATYYCQQA VILP ITFGGGTKVEIK		109
ADI-30 278	DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLISAASSLQSGVPSRFSFGSGSGTDFTLTISLQPEDFATYYCQQA VILP ITFGGGTKVEIK		109
ADI-27 301	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYKASSLESQVPSRFSFGSGSGTEFTLTISLQPDDEFATYYCQQY GILP RTFGGGTKVEIK		110
ADI-30 306	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYKASSLESQVPSRFSFGSGSGTEFTLTISLQPDDEFATYYCQQY GILP RTFGGGTKVEIK		110
ADI-30 311	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYKASSLESQVPSRFSFGSGSGTEFTLTISLQPDDEFATYYCQQY GILP RTFGGGTKVEIK		110

Table 4: SEQ ID numbers of related sequences of all antibodies involved in the present invention

Antibody	HCDR1	HCDR2	HCDR3	VH	HC	VH DNA	LCDR1	LCDR2	LCDR3	VL	LC	VL DNA
ADI-27238	1	6	11	84	111	150	16	17	18	104	137	170
ADI-30263	2	7	12	85	112	151	16	17	18	104	137	170
ADI-30267	3	8	13	86	113	152	16	17	18	104	137	170
ADI-30268	4	9	14	87	114	153	16	17	18	104	137	170
Consensus sequence	5	10	15									
ADI-27243	19	22	25	88	115	154	26	27	28	105	138	171
ADI-30302	20	23	25	89	116	155	26	27	28	105	138	171
ADI-30336	19	22	25	90	117	156	26	27	29	106	139	172
Consensus sequence	21	24	25						30			
ADI-27278	31	34	38	91	118	157	41	42	43	107	140	173
ADI-30293	31	35	38	92	119	158	41	42	43	107	140	173
ADI-30296	32	36	39	93	120	159	41	42	43	107	140	173
Consensus sequence	33	37	40									
ADI-27291	44	48	53	94	121	160	57	58	59	108	141	174
ADI-30283	45	49	53	95	122	161	57	58	59	108	141	174
ADI-30286	46	50	54	96	123	162	57	58	59	108	141	174
ADI-30288	46	51	55	97	124	163	57	58	59	108	141	174
Consensus sequence	47	52	56									
ADI-27297	60	6	66	98	125	164	69	17	70	109	142	175
ADI-30272	61	63	66	99	126	165	69	17	70	109	142	175
ADI-30278	61	64	67	100	127	166	69	17	70	109	142	175

The 20 exemplary antibodies (ADI-27238, ADI-30263, ADI-30267, ADI-30268, ADI-27243, ADI-30302, ADI-30336, ADI-27278, ADI-30293, ADI-30296, ADI-27291, ADI-30283, ADI-30286, ADI-30288, ADI-27297, ADI-30272, ADI-30278, ADI-27301, ADI-30306, and ADI-30311) involved in the examples of the present invention described below, the amino acid sequences of the CDRs, the light and heavy chain variable regions, and the light and heavy chains of these antibodies, as well as the corresponding nucleotide sequences, are listed in Tables 1-3 and sequence listing of the present application. The corresponding sequence numbers are summarized in **Table 4**.

Examples

Example 1: Preparation of antibodies

Screening for anti-TIGIT fully humanized antibodies by yeast display

Yeast-based antibody presentation libraries (Adimab) were amplified according to prior art (described in WO 2009036379, WO 2010105256, and WO 2012009568), with a diversity of 1×10^9 in each library. Briefly, the first two rounds of screening employed magnetic bead cell sorting using the MACS system available from Miltenyi. First, yeast cells (about 1×10^{10} cells/library) from the libraries were incubated in FACS buffer (phosphate buffer, containing 0.1% bovine serum albumin and 100 nM biotin-labeled human TIGIT antigens (Acro Biosystems, TIT-H52H3)) for 15 min at room temperature. The cells were washed once with 50 mL of pre-cooled FACS buffer and resuspended with 40 mL of the same buffer, followed by addition of 500 μ L of streptavidin microbeads (Miltenyi LS) and incubation at 4 °C for 15 min. The mixture was centrifuged at 1000 rpm for 5 min. After discarding the supernatant, the cells were resuspended with 5 mL of FACS buffer. The resulting cell suspension was loaded on a Miltenyi LS column. After loading, the column was washed three times, with 3 mL of FACS buffer each time. The Miltenyi LS column was removed from the magnetic field and eluted with 5 mL of growth medium. The eluted yeast cells were collected and incubated overnight at 37 °C.

The next round of sorting was performed using a flow cytometer, wherein approximately 1×10^8 yeast cells screened by the MACS system were washed three times with FACS buffer and co-incubated with TIGIT antigens labeled by a low concentration of biotin (100-1 nM) at room temperature. The supernatant was discarded. The cells were washed twice with FACS buffer and mixed with LC-FITC (FITC-labeled anti-human immunoglobulin kappa light chain antibody, Southern Biotech) (1:100 dilution) and SA-633 (streptavidin-633, Molecular Probes) (1:500 dilution) or SA-PE (streptavidin-PE, Sigma) (1:50 dilution) reagents, and the mixture was incubated at 4 °C for 15 min. The cells were eluted twice with pre-cooled FACS buffer, resuspended in 0.4 mL of buffer and transferred into a separator tube with a filter. The cells were sorted using FACS ARIA (BD Biosciences).

The yeast cells expressing the anti-TIGIT antibody obtained by screening were induced by shaking at 30 °C for 48 h to express the anti-TIGIT antibody. After the induction, the yeast cells were removed by centrifugation at 1300 rpm for 10 min, and the supernatant was collected. The anti-TIGIT antibodies in the supernatant were purified using Protein A and eluted using acetic acid buffer at pH 2.0 prior to harvest. The purity of the antibodies was more than 95%. The antibodies were digested by papain and purified by KappaSelect (GE Healthcare) to produce the corresponding Fab fragments. The anti-TIGIT antibodies (ADI-27301, ADI-27238, ADI-27278, ADI-27243, ADI-27297, and ADI-27291) were obtained from this screening.

Affinity optimization for anti-human TIGIT antibodies

To obtain anti-human TIGIT antibodies with higher affinity, antibodies (ADI-27301, ADI-27238, ADI-27278, ADI-27243, ADI-27297, and ADI-27291) were optimized by the following methods.

5 *VHmut screening*

This method was to introduce mutations into antibody heavy chain regions by conventional mismatch PCR. In the PCR process, the probability of base pair mismatch raised to about 0.01 bp by adding 1 μ M highly mutated base analogs dPTP and 8-oxo-dGTP.

10 The resulting mismatch PCR products were constructed into a vector containing the heavy chain constant region by homologous recombination. By this method, a secondary library with the capacity of 1×10^7 was obtained under screening pressure including TIGIT antigen titers, unlabeled antigen competition, and competition with the parent antibodies. Three rounds of screening were successfully performed by FACS.

CDRH1/CDRH2 screening

15 CDRH3 genes of progeny antibodies obtained by VHmut were constructed into a CDRH1/CDRH2 gene pool with the diversity of 1×10^8 , and 3 rounds of screening were carried out for the genes. The first round of screening adopted MACS, while the second and third rounds adopted FACS. Antibody-antigen conjugates were subjected to pressurized screening for screening out antibodies with the highest affinity.

20 Through the above affinity maturation process of 6 parent antibodies, 14 anti-human TIGIT monoclonal antibodies ADI-30263/ADI-30267/ADI-30268 (ADI-27238 progeny), ADI-30302/ADI-30336 (ADI-27243 progeny), ADI-30293/ADI-30296 (ADI-27278 progeny), ADI-30283/ADI-30286/ADI-30288 (ADI-27291 progeny), ADI-30272/ADI-30278 (ADI-27297 progeny), and ADI-30306/ADI-30311 (ADI-27301 progeny) with improved affinity were obtained.

25 The yeast cells expressing the anti-TIGIT antibody obtained by screening were induced by shaking at 30 °C for 48 h to express the anti-TIGIT antibody. After the induction, the yeast cells were removed by centrifugation at 1300 rpm for 10 min, and the supernatant was collected. The anti-TIGIT antibodies in the supernatant were purified using Protein A and eluted using acetic acid buffer at pH 2.0 prior to harvest. The purity of the antibodies was more than 95%. The antibodies
30 were digested by papain and purified by KappaSelect (GE Healthcare) to produce the corresponding Fab fragments.

Expression and purification of antibodies

35 The sequence information and numbers of the anti-human TIGIT antibodies involved in the present invention are shown in Tables 1-9, wherein the parent antibodies and the affinity-matured progeny antibodies were all expressed and purified by yeasts with the method described above.

The following reference antibodies used in examples were expressed and purified in HEK293 cells: 22G2 is an anti-human TIGIT antibody from BMS that was transiently expressed in HEK293 cells, with the light and heavy chain variable region sequences identical to those of antibody "22G2" in
40 Patent Application No. WO 2016/106302A1; 31C6 is an anti-human TIGIT antibody from Merck that was transiently expressed in HEK293 cells, with the light and heavy chain variable region sequences identical to those of antibody "31C6" in Patent Application No. WO 2016/028656A1; both 10A7 and 1F4 were anti-human TIGIT antibodies from Genentech that were transiently

expressed in HEK293 cells, with light and heavy chain variable region sequences identical to those of antibodies "10A7" and "1F4" in Patent Application No. WO2015009856A2, respectively. The constant regions of the 4 reference antibodies all adopted wild-type IgG4 sequences.

For a transient expression of an antibody in HEK293 cells, the vector pTT5 was used. The heavy and light chains of the antibody were first cloned into separate pTT5 vectors. The pTT5 vectors carrying the heavy and light chains of the antibody molecule were transferred into the HEK293 cells by a chemical transfection method. The cultivated HEK293 cells were transiently transfected using a chemical transfection reagent PEI (purchased from Polysciences) according to a scheme provided by the manufacturer. Plasmid DNAs and transfection reagent were prepared in a laminar flow hood, and then F17 medium (Gibco) (the volume was 1/5 of transfection volume) was aliquoted into two 50-mL centrifuge tubes. The filtered plasmids (130 µg/100 mL) were added to one tube, and the filtered PEI (1 g/L, Polysciences) (mass ratio (plasmid:PEI) = 1:3) was added to another. The two mixtures were each mixed well for 5 min, and then the two were mixed well and gently together for 20 times, followed by letting stand for 15-30 min (no more than 30 min). The DNA/PEI mixture was gently poured into the HEK293 cells and mixed well. The cells were cultivated at 37 °C, 8% CO₂ for 7 days, with fresh medium fed every 48 h. Seven days later, or when the cells were continuously cultivated to cell viability was ≤ 60%, the mixture was centrifuged at 13000 rpm for 20 min. The supernatant was taken and purified with Protein A to achieve an antibody purity of greater than 95%.

Furthermore, the intact antibodies (ADI-30268, ADI-30278, ADI-30286, ADI-30288, ADI-30293, ADI-30306, and ADI-30336) were expressed and purified in CHO cells.

Expression and purification in CHO cells: CHO cell lines expressing the antibodies were produced using HD-BIOP1(GS Null CHO-K1) from Horizon according to the manufacturer's instructions. The DNA sequences of the heavy and light chains of the antibody molecule were first inserted into pD2531 plasmids from ATUM. The constructed plasmids were then transferred into CHO cell lines by electrotransfection, and the antibody production was detected by ForteBio to determine the transfection efficiency after transfection for 24 h. The transfected cells were subjected to pressurized screening to obtain a cell pool of highly-expressed antibodies. The cell pool was then amplified to express large quantities of antibodies. The cell supernatant was collected and purified by Protein A and gel filtration to achieve an antibody purity of more than 95%.

Example 2. Affinity assay of antibodies

The equilibrium dissociation constant (K_D) for binding of the above 20 exemplary antibodies of the present invention to human TIGIT was measured by biological optical interferometry (ForteBio).

An ForteBio affinity assay was performed according to the prior art (Estep, P, *et al.*, High throughput solution based measurement of antibody-antigen affinity and epitope binning. *MAbs*, 2013.5(2); p. 270-8).

Measurement of monovalent affinity of the candidate antibody Fab to TIGIT-FC: a sensor was equilibrated off-line in an assay buffer for 20 min, followed by detecting online for 120 s to establish a baseline. Human TIGIT-FC was loaded on an AHQ sensor (ForteBio) for ForteBio affinity assay. The sensor with the loaded antigens was exposed to a solution containing 100 nM Fab until to a plateau, and then transferred to an assay buffer for dissociation for at least 2 min to measure the dissociation rate. Kinetic analysis was performed using a 1:1 binding model.

Measurement of monovalent affinity of intact candidate antibodies to human (ACRO, TIT-H52H3), mouse (ACRO, TIT-M52E6), and monkey TIGIT-his (ACRO, TIT-C5223): the sensor was equilibrated off-line in an assay buffer for 20 min, followed by detecting online for 120 s to establish a baseline. The purified antibodies were loaded on an AHQ sensor (ForteBio) to a thickness of 1 nanometer for ForteBio affinity assay. The sensor with loaded antibodies was exposed to 100 nM TIGIT-his antigens until to a plateau, and then transferred to an assay buffer for dissociation for at least 2 min to measure the dissociation rate. Kinetic analysis was performed using a 1:1 binding model.

In experiments performed as described in the above assays, the K_D values of 20 yeast-expressed candidate antibodies (Fab) are shown in Table 5.

Table 5. Monovalent K_D values of 20 yeast-expressed candidate antibodies (Fab) to human TIGIT-FC

Parent	Progeny		
ADI-27238 1.38E-08	ADI-30263 7.95E-10	ADI-30267 1.66E-09	ADI-30268 5.71E-10
ADI-27243 9.47E-09	ADI-30302 3.29E-10	ADI-30336 5.66E-10	
ADI-27278 1.09E-08	ADI-30293 3.49E-09	ADI-30296 2.43E-09	
ADI-27291 6.48E-09	ADI-30283 5.53E-10	ADI-30286 4.36E-10	ADI-30288 5.47E-10
ADI-27297 3.21E-08	ADI-30272 1.19E-09	ADI-30278 2.43E-10	
ADI-27301 8.01E-09	ADI-30306 7.29E-10	ADI-30311 8.07E-10	

In experiments performed as described in the above assays, the monovalent K_D values of 7 intact candidate antibodies expressed by CHO cells to human, mouse and monkey TIGIT are shown in Table 6.

Table 6. Monovalent K_D values of 7 candidate antibodies expressed by CHO cells and reference antibodies to human, mouse and monkey TIGIT

No.	KD (human)	KD (monkey)	KD (mouse)
ADI-30268	3.29E-09	6.23E-08	4.64E-08
ADI-30278	1.75E-09	4.53E-09	N.B.
ADI-30286	1.76E-09	1.06E-08	1.34E-07
ADI-30288	1.31E-09	7.19E-09	5.70E-09
ADI-30293	7.89E-10	3.49E-08	1.30E-08
ADI-30306	2.70E-09	3.44E-09	N.B.
ADI-30336	1.46E-09	5.56E-10	N.B.
22G2(BMS)	3.50E-09	4.20E-09	N.B.
31C6(MSD)	2.34E-09	4.72E-10	N.B.

It can be seen from the above Tables that: (1) after affinity maturation, each progeny antibody has significantly improved affinity to human TIGIT compared with its parent antibody; (2) after affinity maturation, the affinity of the selected 7 antibodies expressed by CHO cells to human TIGIT was similar to or higher than that of the reference antibodies; all of the 7 candidate antibodies can cross-react with monkey TIGIT; and 4 (ADI-30268/ADI-30286/ADI-30288/ADI-30293) of the 7 candidate antibodies can cross-react with mice.

Example 3. Binding of anti-TIGIT antibodies to human TIGIT expressed on cells

The binding ability of the above 20 exemplary antibodies of the present invention to human TIGIT expressed on the surface of CHO cells was measured in a flow cytometry-based assay. The binding ability of the different antibodies was determined by comparing the binding curves thereof to human TIGIT expressed on the surface of CHO cells.

Specifically, after affinity maturation, yeasts were used to express both parent and progeny antibodies. After harvest (with the antibody purity of about 70%), the binding experiments of these antibodies to human TIGIT expressed on the surface of CHO cells were performed. The specific experimental process was as follows: (1) CHOS cells were transfected with human TIGIT plasmids constructed in pCHO1.0, and then screened for a stable cell pool using methotrexate and puromycin. (2) Candidate antibodies at different concentrations were incubated with the stable cell pool at 4 °C for 30 min. After three washes with PBS, the cells were incubated with PE-labeled mouse anti-human secondary antibodies for 30 min at 4 °C. After three more washes with PBS, the cells were resuspended with 100 μ L of PBS. (3) Flow cytometry was used to determine median fluorescence values in two channels for the cells. The EC₅₀ and the peak values of the curves were compared by plotting the base-10 logs of the antibody concentrations on the abscissa and the median fluorescence values in two channels on the ordinate. The results are shown in the following table and in FIG. 1 (EC₅₀: nM).

Antibody	IgG1	10A7	1F4	22G2	31C6	
EC50	~1.388e+007	0.2690	0.7096	0.5106	0.4358	
Antibody	ADI-27238	ADI-30267	ADI-30268	ADI-27243	ADI-30302	ADI-30336
EC50	0.7512	0.7402	0.3293	0.5873	0.3262	0.6291
Antibody	ADI-27278	ADI-30293	ADI-30296	ADI-27291	ADI-30286	ADI-30288
EC50	0.9682	0.9003	0.3714	0.8522	0.4459	0.4755
Antibody	ADI-27297	ADI-30272	ADI-30278	ADI-27301	ADI-30306	ADI-30311
EC50	0.4958	0.6098	0.4086	0.8990	0.7634	0.7566

From the above experimental results, the following conclusions can be drawn: (1) after affinity maturation, each progeny antibody has enhanced binding ability to human TIGIT expressed on the surface of CHO cells compared to its parent antibody (as indicated by a higher plateau in the binding curve); (2) The binding ability of the affinity matured progeny antibodies to human TIGIT expressed on the surface of CHO cells is superior than that of the two molecules 10A7 and 1F4 from Genetech, and is comparable to that of the molecule 22G2 from BMS and the molecule 31C6 from Merck.

Furthermore, after affinity maturation, the selected 7 molecules were expressed and purified using a CHO system to obtain antibodies with high purity. The binding experiment of the antibodies with high purity to human TIGIT expressed on the surface of CHO cells was performed. In experiments

performed as described in the above assays, ADI-30268, ADI-30336, ADI-30293, ADI-30286, ADI-30288, ADI-30278, and ADI-30306 bind to human TIGIT overexpressed on CHO cells with EC₅₀ values of 0.1392 nM, 0.1300 nM, 0.2288 nM, 0.1758 nM, 0.1860 nM, 0.1321 nM and 0.1999 nM, respectively, and the binding ability thereof is superior to that of reference antibodies 22G2 and 1F4 (EC₅₀ values of 0.7249 nM and 0.6073 nM, respectively) to human TIGIT overexpressed on CHO cells, and similar to that (an EC₅₀ value of 0.1846 nM) of reference antibody 31C6 to human TIGIT overexpressed on CHO cells. Although the reference antibody 10A7 has an EC₅₀ value (0.1949 nM) similar to that of the 7 candidate antibodies, it can be revealed from the binding curve of this antibody that the plateau of the curve thereof is lower than that of the 7 candidate antibodies. This is generally believed to be attributed to its faster dissociation characteristics (see FIG. 2). Therefore, the binding ability of 7 candidate antibodies to human TIGIT expressed on the surface of CHO cells is considered to be superior to that of 10A7.

Example 4. Blocking of anti-TIGIT antibody to its ligand CD155

The ability of the candidate antibodies to block the ligands was determined by flow cytometry. The method is specifically as follows: a CHOS cell pool stably overexpressing human TIGIT was constructed, and 50 nM human CD155 protein (ACRO, TIT-H5253-1MG) with a mouse IgG2aFC fragment and antibodies at different concentrations were incubated with the cells for 30 min at 4 °C. After three washes with PBS, ligands CD155 remaining on the cells were strained using goat anti-mouse FC (at a concentration of 1%) and secondary antibodies labeled with APC fluorescein (Biolegend, 405308). After three more washes with PBS, the median fluorescence values in a corresponding channel (C6, channel 4) were measured by a flow cytometer. The base-10 logs of the antibody concentrations (nM) were plotted on the abscissa and the median fluorescence value corresponding to each antibody concentration point was plotted on the ordinate. The blocking ability of different antibodies to CD155 was distinguished by analyzing the IC₅₀ values of the curves.

IgG1 was used as a negative control, and 10A7, 22G2, and 31C6 were used as positive controls to test the blocking ability of candidate molecules to CD155 before and after affinity maturation. FIG. 3 and the following table show the blocking ability of yeast-expressed antibodies to CD155 (IC₅₀: nM) before and after affinity maturation.

Antibody	IgG1	10A7	22G2	31C6		
IC50	~0.03904	0.7408	0.1786	0.1536		
Antibody	ADI-27238	ADI-30267	ADI-30268	ADI-27243	ADI-30302	ADI-30336
IC50	0.4181	0.2775	0.2209	0.8188	0.2808	0.4093
Antibody	ADI-27278	ADI-30293	ADI-30296	ADI-27291	ADI-30286	ADI-30288
IC50	0.5859	0.8586	0.2781	1.614	0.2965	0.6677
Antibody	ADI-27297	ADI-30272	ADI-30278	ADI-27301	ADI-30306	ADI-30311
IC50	0.6029	0.4036	0.2175	0.6411	0.5281	0.5313

It can be concluded from the experimental results that most of the affinity matured progeny antibodies have improved blocking abilities to CD155 as compared to parent antibodies thereof, similar to the blocking abilities of reference antibodies 22G2 and 31C6 and stronger than that of reference antibody 10A7.

7 high-purity antibodies expressed by CHO cells were adopted for blocking the binding of CD155 to TIGIT. In the experiments performed as described in the above assays, IgG4 was used as a

negative control, and 22G2, 31C6, and 10A7 were used as positive controls. It can be concluded from the experimental results that IC₅₀ of antibodies ADI-30268, ADI-30336, and ADI-30278 are 0.1402 nM, 0.1219 nM and 0.1164 nM, respectively, which are lower than those of reference antibodies 22G2 (0.6069 nM), 31C6 (0.1659 nM) and 10A7 (0.3252 nM), indicating that the three antibodies have stronger ligand (CD155) blocking ability than the reference antibodies; the other 4 candidate antibodies (ADI-30293, ADI-30286, ADI-30288, and ADI-30306) have IC₅₀ of 0.2510 nM, 0.1893 nM, 0.2238 nM, and 0.2420 nM, respectively, which are all lower than those of reference antibodies 22G2 and 10A7 but greater than that of reference antibody 31C6, indicating that these four antibodies have stronger ligand (CD155) blocking ability than reference antibodies 22G2 and 10A7 but weaker ligand (CD155) blocking ability than 31C6. The results are shown in the following table and in FIG. 4 (IC₅₀: nM).

Antibody	IgG1	22G2	31C6	10A7
IC ₅₀	~1.152	0.6069	0.1659	0.3252
Antibody	ADI-30268	ADI-30336	ADI-30293	ADI-30286
IC ₅₀	0.1402	0.1219	0.2510	0.1893
Antibody	ADI-30288	ADI-30278	ADI-30306	
IC ₅₀	0.2238	0.1164	0.2420	

Example 5. MOA-based biological activity assay of candidate antibodies

Anti-TIGIT antibodies can relieve the inhibitory effect of CD155 on the downstream IL2 signaling pathway by blocking the binding of TIGIT to CD155. In this example, MOA-based assay cell lines (J2201) provided by Promega were used to detect the expression of fluorescent reporter genes and reflect the activation of IL2 signaling, thereby detecting the inhibitory effect of the antibodies on binding of TIGIT to CD155. The assay was performed in accordance with standard methods of Promega. The procedures were as follows: Jurkat cells stably expressing human TIGIT and luciferase reporter genes under the control of IL2 promoters, CHO-K1 cells stably expressing human CD155 and T cell activating elements, and anti-human TIGIT antibodies with different concentration gradients were co-incubated in a carbon dioxide incubator at 37 °C for 6 h, and then fluorescence signals were detected.

The experimental results showed that the affinity-matured progeny molecules (directly expressed by yeast, with the purity of about 70%) have significantly improved *in vitro* biological activity as compared to their parent molecules, and mostly reached the level similar to the two reference antibodies 22G2 and 31C6. The results are shown in the following table and in FIG. 5 (EC₅₀: nM).

Antibody	IgG1	10A7	22G2	31C6
EC ₅₀	~272.8	~77.84	2.113	0.8383
Antibody	ADI-27238	ADI-30267	ADI-30268	
EC ₅₀	68.70	2.064	1.224	
Antibody	ADI-27243	ADI-30302	ADI-30336	
EC ₅₀	297.1	0.9831	3.334	
Antibody	ADI-27278	ADI-30293	ADI-30296	
EC ₅₀	~1.405e+008	1.559	1.088	
Antibody	ADI-27297	ADI-30272	ADI-30278	
EC ₅₀	~25059	1.489	0.5228	
Antibody	ADI-27301	ADI-30306	ADI-30311	

EC50	~1.085e+012	1.645	1.824	
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MOA-based biological activity assay were performed using 7 high-purity antibodies expressed by CHO cells. In the assay described above, IgG4 were used as negative controls, and 31C6 were used as positive controls. It can be concluded from the experimental results that the candidate antibody ADI-30278 have an EC₅₀ of 0.1856 nM in the experiments, which was lower than those of other candidate antibodies and the reference antibody 31C6 (0.3424 nM), showing stronger *in vitro* biological activity; antibodies ADI-30268, ADI-30286, ADI-30288, and ADI-30306 have EC₅₀ of 0.5065 nM, 0.3963 nM, 0.3844 nM, and 0.3984 nM, respectively, showing similar biological activity to reference antibody 31C6; and antibodies ADI-30336 and ADI-30293 have EC₅₀ of 1.274 nM and 1.624 nM, respectively, showing weaker biological activity. The results are shown in the following table and in FIG. 6 (EC₅₀: nM).

Antibody			
Antibody			
Antibody			

Example 6. *In vivo* efficacy assay in animals

In this assay, the anti-tumor activity of the anti-TIGIT antibodies was investigated in a human TIGIT knock-in MC38 mouse tumor model.

The pharmacodynamics of candidate molecules ADI-30293 and ADI-30278 administered alone (10 mg/kg) to a human TIGIT knock-in MC38 mouse model were investigated. Mouse colon cancer MC38 cells (OBiO Technology (Shanghai) Co., Ltd., HYC0116) were grafted into female TIGIT transgenic mice (Biocytogen Beijing Co., Ltd.). Mice of each group were injected with antibodies subcutaneously on days 6, 10, 13 and 17 after grafting. Tumor volume was measured on days 6, 10, 13, 17, 21 and 25 after grafting, after which the mice were euthanized. The results are shown in FIG. 7.

It can be seen from the results in FIG. 7 that the anti-TIGIT monoclonal antibodies ADI-30293 and ADI-30278 of the present invention have a certain inhibitory effect on the growth of tumor when used alone, compared to the negative control Ig4. The tumor inhibitory effect of the two candidate antibodies used alone was not significantly different from that of the positive control 31C6.

The pharmacodynamics of candidate molecules ADI-30293 and ADI-30278 administered (10 + 1 mg/kg) in combination with an anti-PD1 antibody (antibody C, WO2017133540A1) to the human TIGIT knock-in MC38 mouse model was further studied.

Mouse colon cancer cells MC38 (OBiO Technology (Shanghai) Co., Ltd., HYC0116) were cultivated in a DMEM medium. 1×10^6 MC38 cells in 0.2 mL of DMEM basal medium suspension were grafted to the right side of female TIGIT transgenic mice (SHANGHAI MODEL ORGANISMS). Tumor volume and body weight were measured twice a week throughout the study. Tumor length and width were measured using a vernier caliper on day 8 after tumor cell transplantation. The tumor volume was calculated according to the following formula: $\text{width}^2 \times \text{length} / 2$ (mm³). Mice with an average tumor volume of about 71 mm³ were randomly grouped with 6 mice per group and were euthanized when the tumor volume reached the detection endpoint or when the mice lost more than 20% of body weight. Mice of each group were injected subcutaneously with h-IgG (10 mg/kg), antibody C (1 mg/kg), and anti-TIGIT antibodies or isotype antibodies thereof (10 mg/kg), respectively, on days 8, 12, 15 and 19 after cell transplantation. The

mean tumor volume at the endpoint was determined on day 29 after cell transplantation, after which the mice were euthanized. The results are shown in FIG. 8.

It can be seen from the results in FIG. 8 that the anti-TIGIT antibody (ADI-30293) used in combination with the anti-PD1 antibody (antibody C) shows a stronger tumor inhibitory effect than either of them used alone; and the combined effect of the ADI-30293 and the anti-PD1 antibody is better than that of the 31C6 and the anti-PD1 antibody. Likewise, the combined effect of the ADI-30278 and the anti-PD1 antibody was better than that of 31C6 and the anti-PD1 antibody (antibody C).

In this study, there was no significant change in body weight for mice of all groups on day 29 after grafting.

CLAIMS

1. An antibody or an antigen-binding fragment thereof that binds to TIGIT, comprising

(i) HCDR1, HCDR2 and HCDR3 sequences of a heavy chain variable region set forth in SEQ ID NOs: 99, and LCDR1, LCDR2 and LCDR3 sequences of a light chain variable region set forth in SEQ ID NO: 109, or

(ii) HCDR1, HCDR2 and HCDR3 sequences of a heavy chain variable region set forth in SEQ ID NOs: 100, and LCDR1, LCDR2 and LCDR3 sequences of a light chain variable region set forth in SEQ ID NO: 109.

2. An antibody or an antigen-binding fragment thereof that binds to TIGIT, comprising three heavy chain complementarity determining regions (HCDRs) and three light chain complementarity determining regions (LCDRs), wherein

(i) HCDR1 comprises an amino acid sequence set forth in SEQ ID NO: 61, HCDR2 comprises an amino acid sequence set forth in SEQ ID NO: 63, HCDR3 comprises an amino acid sequence set forth in SEQ ID NO: 66, LCDR1 comprises an amino acid sequence set forth in SEQ ID NO: 69, LCDR2 comprises an amino acid sequence set forth in SEQ ID NO: 17, and LCDR3 comprises an amino acid sequence set forth in SEQ ID NO: 70;

(ii) HCDR1 comprises an amino acid sequence set forth in SEQ ID NO: 61, HCDR2 comprises an amino acid sequence set forth in SEQ ID NO: 64, HCDR3 comprises an amino acid sequence set forth in SEQ ID NO: 67, LCDR1 comprises an amino acid sequence set forth in SEQ ID NO: 69, LCDR2 comprises an amino acid sequence set forth in SEQ ID NO: 17, and LCDR3 comprises an amino acid sequence set forth in SEQ ID NO: 70;

(iii) HCDR1 comprises an amino acid sequence set forth in SEQ ID NO: 200, HCDR2 comprises an amino acid sequence set forth in SEQ ID NO: 63, HCDR3 comprises an amino acid sequence set forth in SEQ ID NOs: 201, LCDR1 comprises an amino acid sequence set forth in SEQ ID NO: 69, LCDR2 comprises an amino acid sequence set forth in SEQ ID NO: 17, and LCDR3 comprises an amino acid sequence set forth in SEQ ID NO: 70; or

(iv) HCDR1 comprises an amino acid sequence set forth in SEQ ID NO: 200, HCDR2 comprises an amino acid sequence set forth in SEQ ID NO: 64, HCDR3 comprises an amino acid sequence set forth in SEQ ID NOs: 202, LCDR1 comprises an amino acid sequence set forth in SEQ ID NO: 69, LCDR2 comprises an amino acid sequence set forth in SEQ ID NO: 17, and LCDR3 comprises an amino acid sequence set forth in SEQ ID NO: 70.

3. The antibody or the antigen-binding fragment thereof according to claim 1 or claim 2, comprising

(i) a heavy chain variable region comprising an amino acid sequence having at least 80%, 85%, or 90% sequence identity to an amino acid sequence set forth in SEQ ID NO: 99, and/or a light chain variable region comprising an amino acid sequence having at least 80%, 85%, or 90% sequence identity to an amino acid sequence set forth in SEQ ID NO: 109, or

(ii) a heavy chain variable region comprising an amino acid sequence having at least 80%, 85%, or 90% sequence identity to an amino acid sequence set forth in SEQ ID NO: 100, and/or a light chain variable region comprising an amino acid sequence having at least 80%, 85%, or 90% sequence identity to an amino acid sequence set forth in SEQ ID NO: 109.

4. The antibody or the antigen-binding fragment thereof according to any one of claims 1 to 3, comprising a heavy chain variable region and a light chain variable region selected from:
- (i) a heavy chain variable region comprising an amino acid sequence set forth in SEQ ID NO: 99, and a light chain variable region comprising an amino acid sequence set forth in SEQ ID NO: 109, or
 - (ii) a heavy chain variable region comprising an amino acid sequence set forth in SEQ ID NO: 100, and a light chain variable region comprising an amino acid sequence set forth in SEQ ID NO: 109.
5. The antibody or the antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody is an antibody in the form of IgG1, IgG2, or IgG4, or an antigen-binding fragment thereof.
6. The antibody or the antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody comprises an IgG4 Fc region comprising S228P, F234A, and L235A mutations.
7. The antibody or the antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody is a fully humanized antibody, a humanized antibody, or a chimeric antibody.
8. The antibody or the antigen-binding fragment thereof according to any one of the preceding claims, wherein the antigen-binding fragment is an antibody fragment selected from: Fab, Fab', Fab'-SH, Fv, scFv, and (Fab')₂.
9. The antibody or the antigen-binding fragment thereof according to any one of the preceding claims, wherein the antibody has one or more of the following properties:
- (i) capacity of binding to human TIGIT with high affinity;
 - (ii) activity of cross-immunoreaction with monkey and/or murine TIGIT;
 - (iii) effectively binding to TIGIT on cell surface;
 - (iv) blocking the binding of TIGIT to its ligand CD155;
 - (v) relieving the inhibitory effect of binding of TIGIT to CD155 on a downstream IL-2 signaling pathway;
 - (vi) increasing IL-2 production in T cells; and
 - (vii) anti-tumor activity.
10. An isolated nucleic acid encoding the anti-TIGIT antibody or the antigen-binding fragment thereof according to any one of the preceding claims.
11. A vector comprising the nucleic acid according to claim 10.
12. A host cell comprising the nucleic acid according to claim 10 or the vector according to claim 11.
13. A method for preparing an anti-TIGIT antibody or an antigen-binding fragment thereof, comprising cultivating the host cell according to claim 12 under conditions suitable for expressing a nucleic acid encoding the anti-TIGIT antibody or the antigen-binding fragment thereof according to any one of claims 1-9.

14. An immunoconjugate comprising the antibody or the antigen-binding fragment thereof according to any one of claims 1-9 conjugated to a therapeutic or diagnostic agent.
15. A multispecific antibody comprising the antibody or the antigen-binding fragment thereof according to any one of claims 1-9.
- 5 16. A pharmaceutical composition comprising the antibody or the antigen-binding fragment thereof according to any one of claims 1-9, and optionally a pharmaceutical adjuvant.
17. The pharmaceutical composition according to claim 16, comprising a second therapeutic agent, wherein the second therapeutic agent is selected from an anti-PD-1 antibody or an anti-PD-L1 antibody.
- 0 18. A method for preventing or treating a tumor or an infectious disease in a subject, the method comprising administering to the subject in need thereof an effective amount of the anti-TIGIT antibody or the antigen-binding fragment thereof according to any one of claims 1-9, or the pharmaceutical composition according to claim 16 or claim 17.
- 5 19. Use of an effective amount of the anti-TIGIT antibody or the antigen-binding fragment thereof of any one of claims 1 to 9, or the pharmaceutical composition according to claim 16 or claim 17, in the manufacture of a medicament for treating a tumor or an infectious disease.
20. The method of claim 18 or the use of claim 19, wherein the tumor is a gastrointestinal cancer.
21. The method or the use of claim 20, wherein the tumor is colon cancer.
- 0 22. A method for blocking binding of TIGIT to CD155 so as to reduce or eliminate the immunosuppressive effect of TIGIT in a subject, the method comprising administering to the subject an effective amount of the anti-TIGIT antibody or the antigen-binding fragment thereof according to any one of claims 1-9, or the pharmaceutical composition according to claim 16 or claim 17.
23. A method for detecting TIGIT in a sample, comprising:
25 (a) contacting the sample with the antibody or the antigen-binding fragment thereof according to any one of claims 1-9; and
(b) detecting a complex formed by the antibody or the antigen-binding fragment and TIGIT, wherein, optionally, the antibody is detectably labeled.

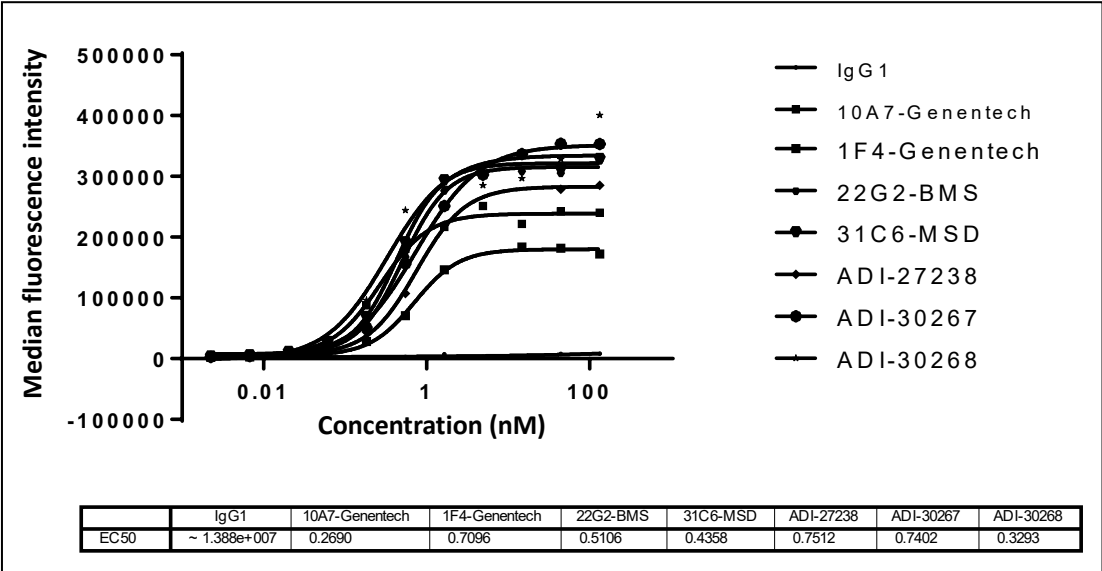


FIG. 1A

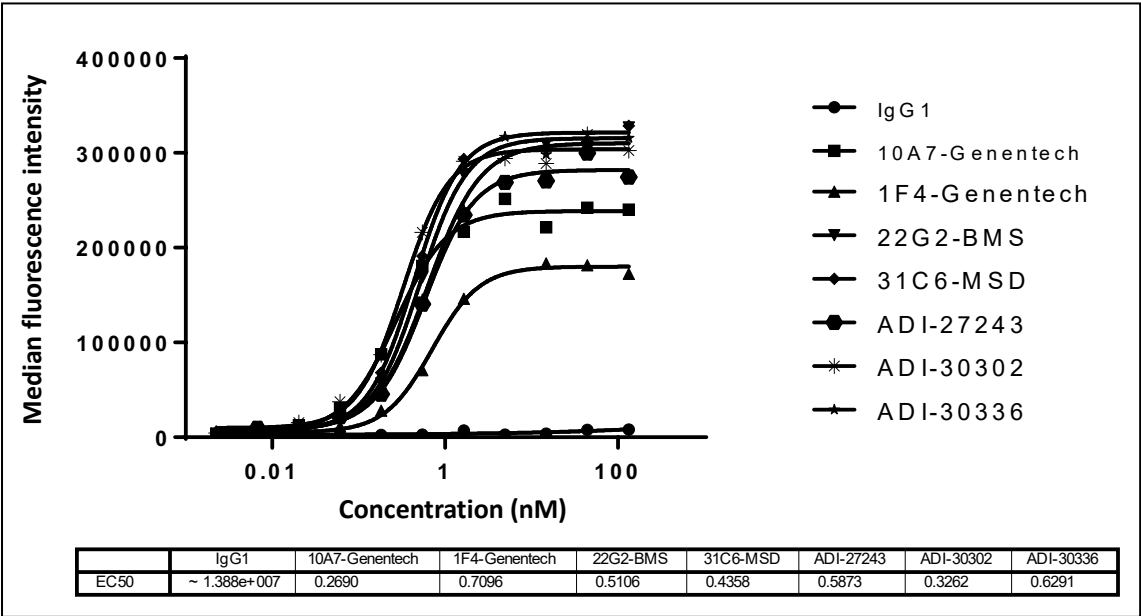


FIG. 1B

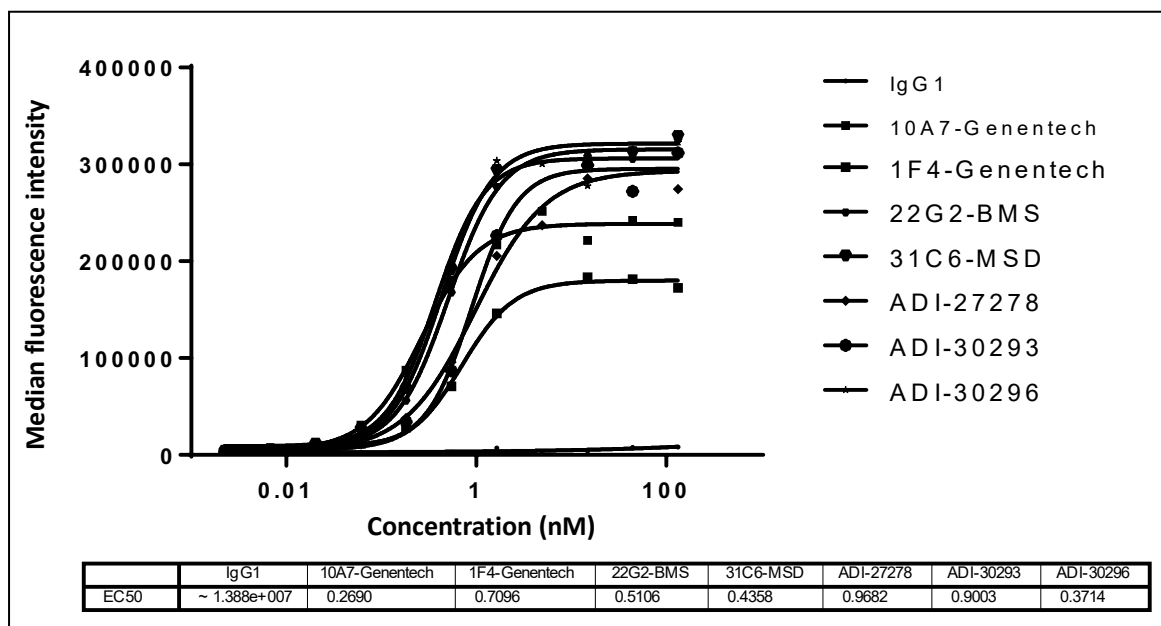


FIG. 1C

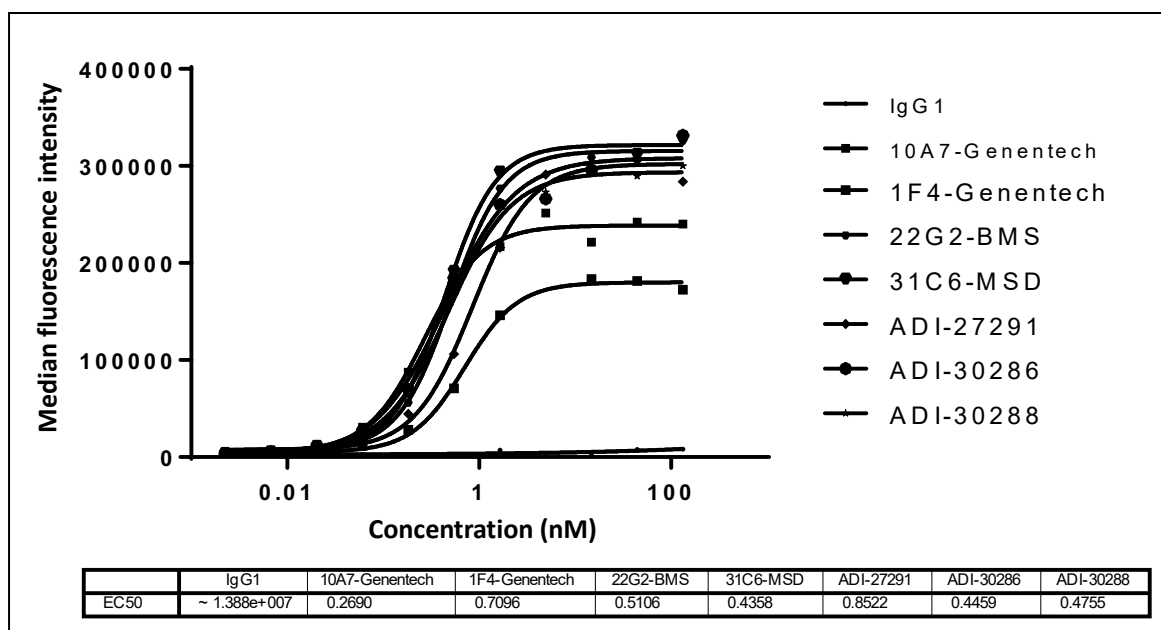


FIG. 1D

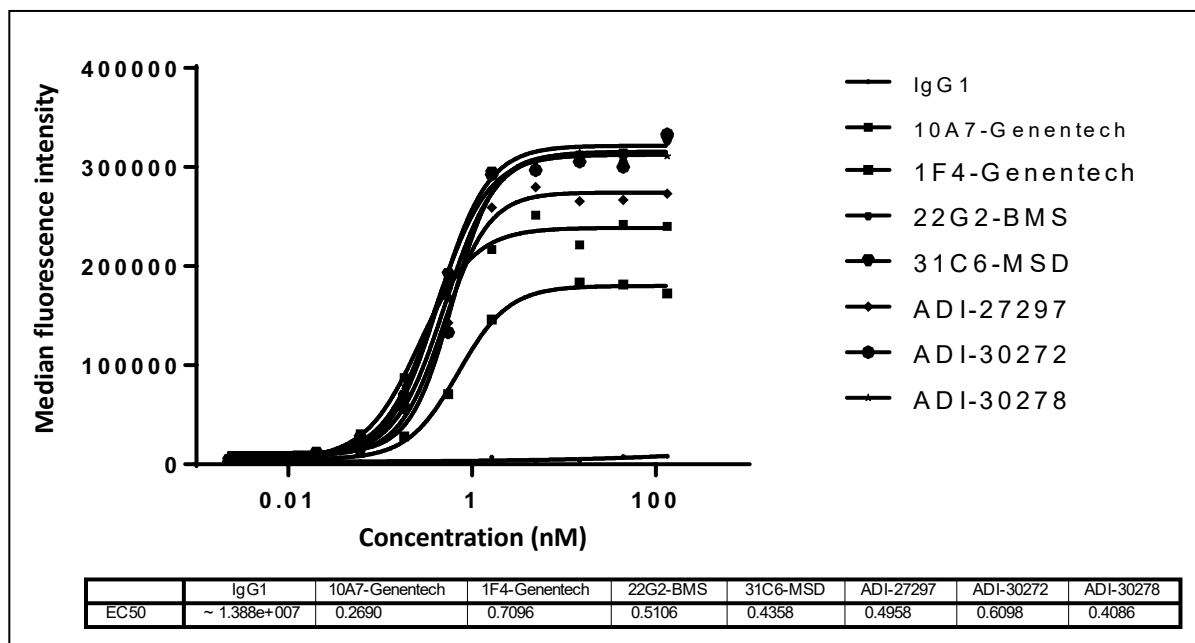


FIG. 1E

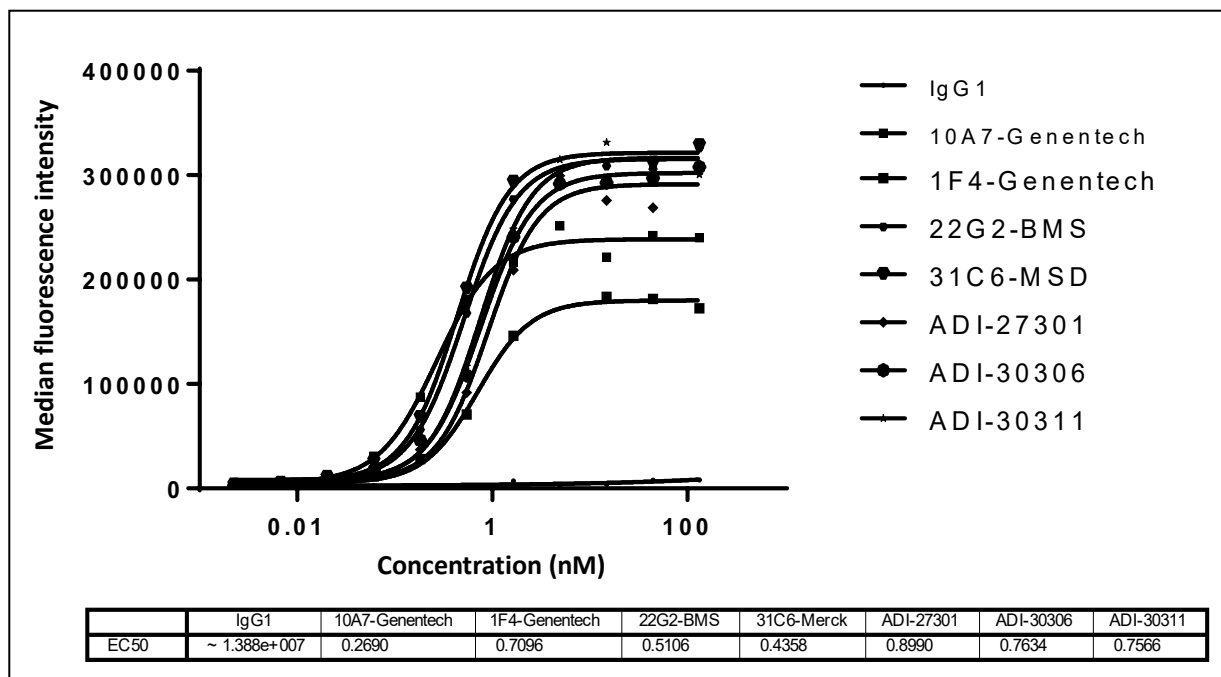


FIG. 1F

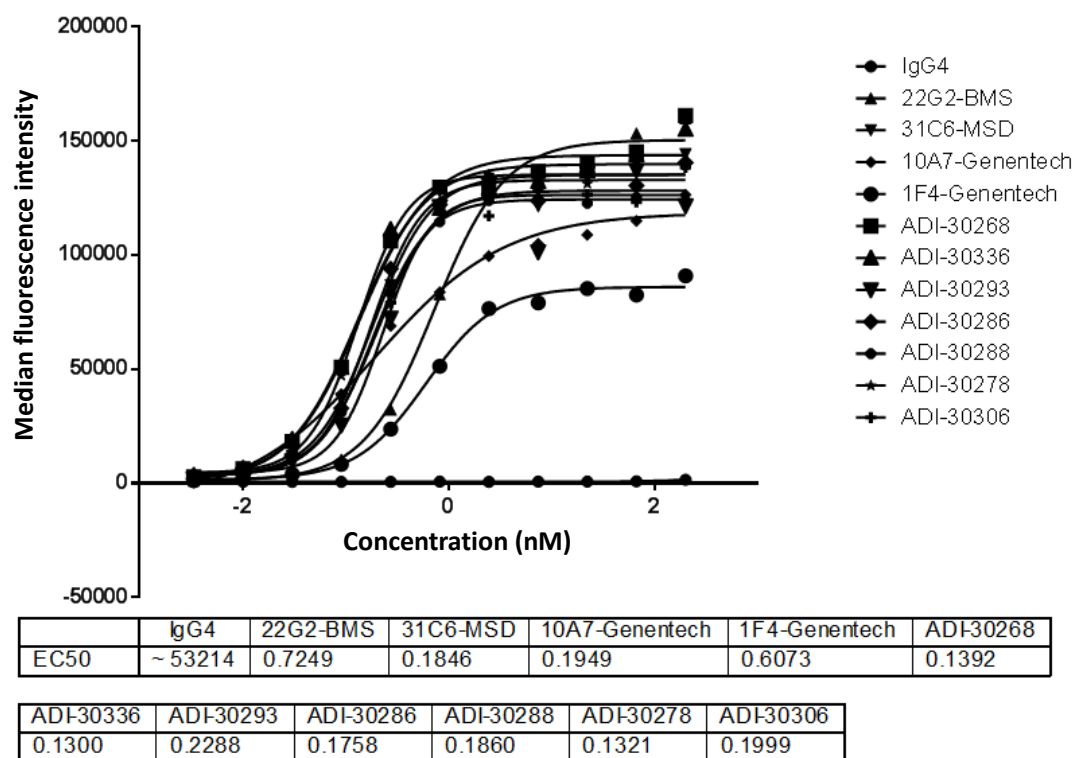


FIG. 2

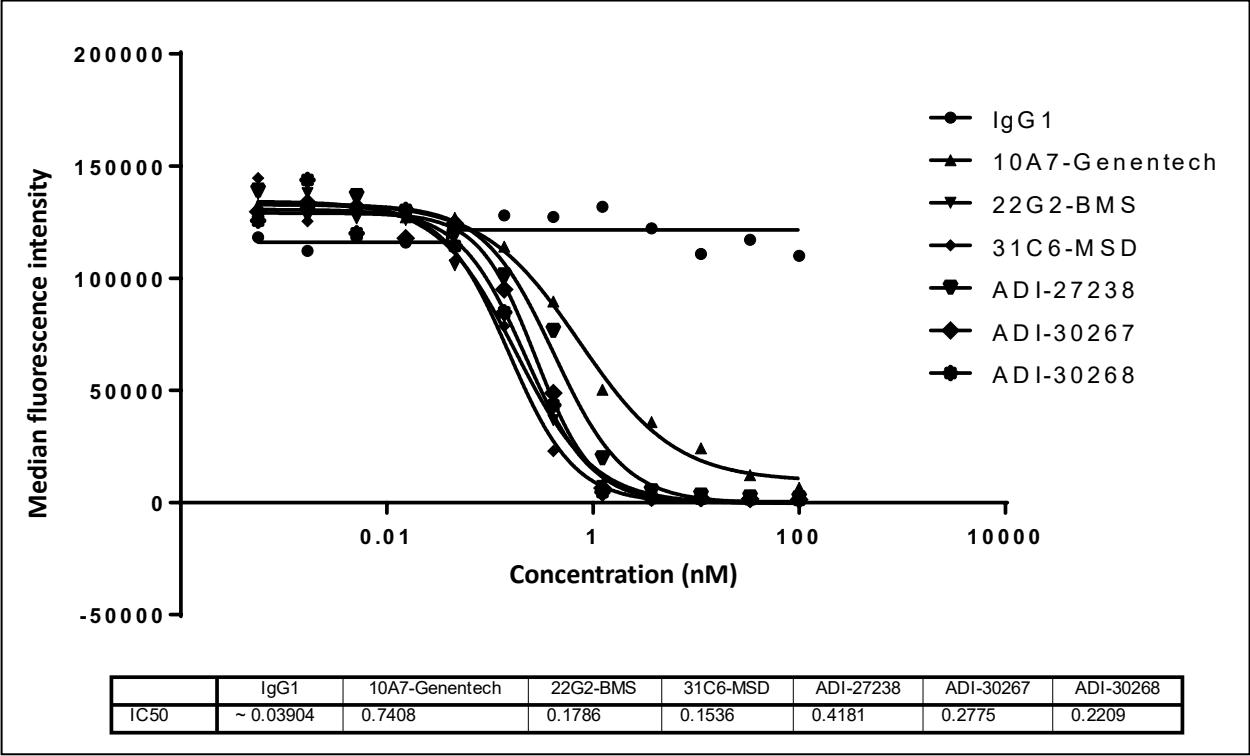


FIG. 3A

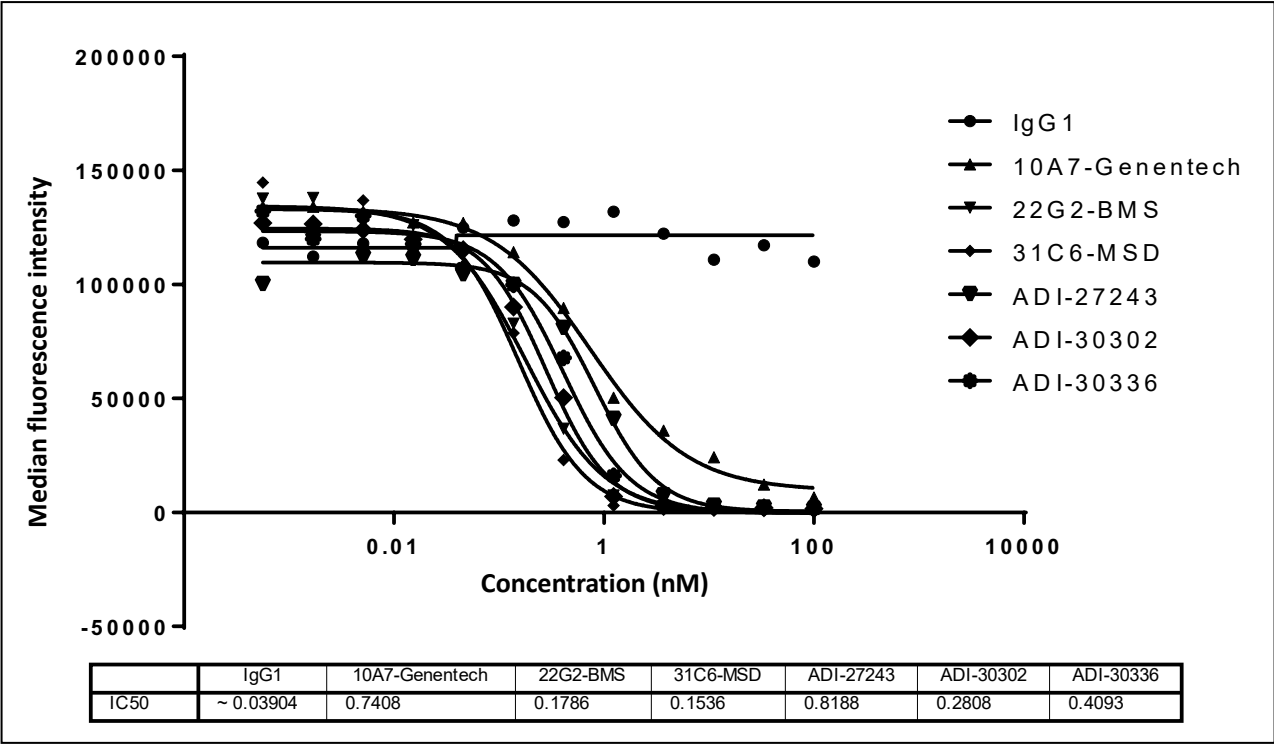


FIG. 3B

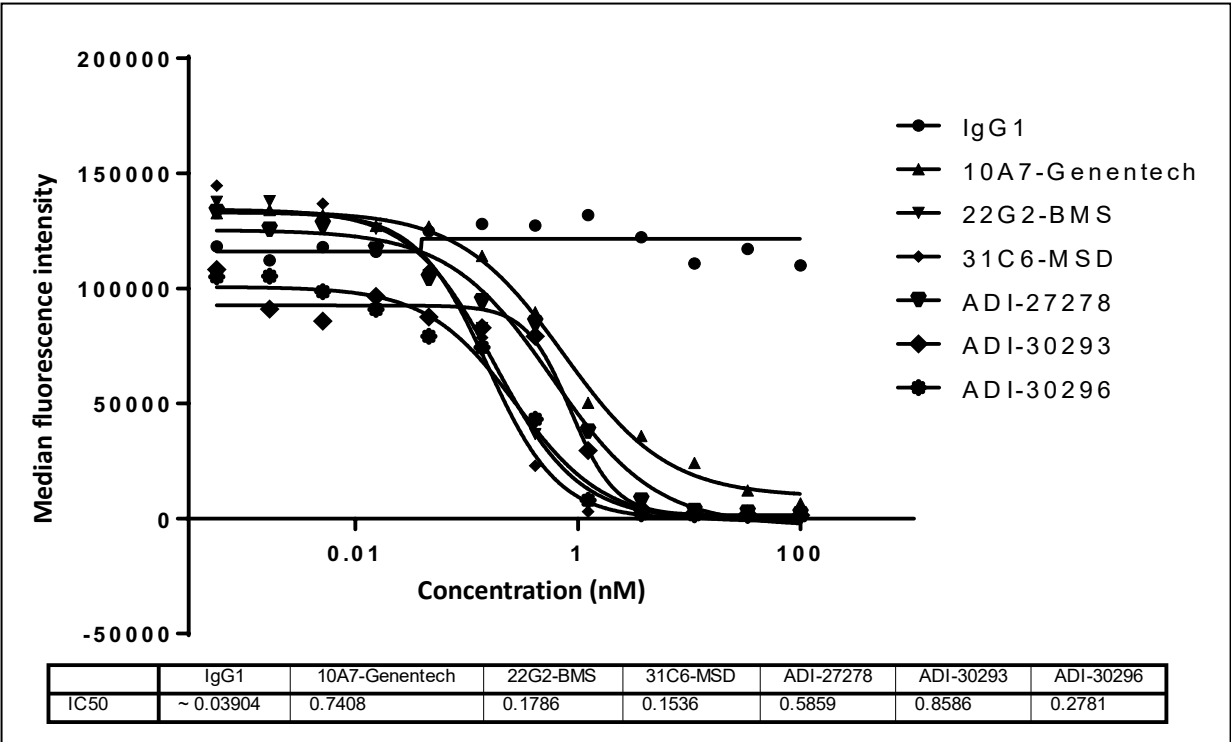


FIG. 3C

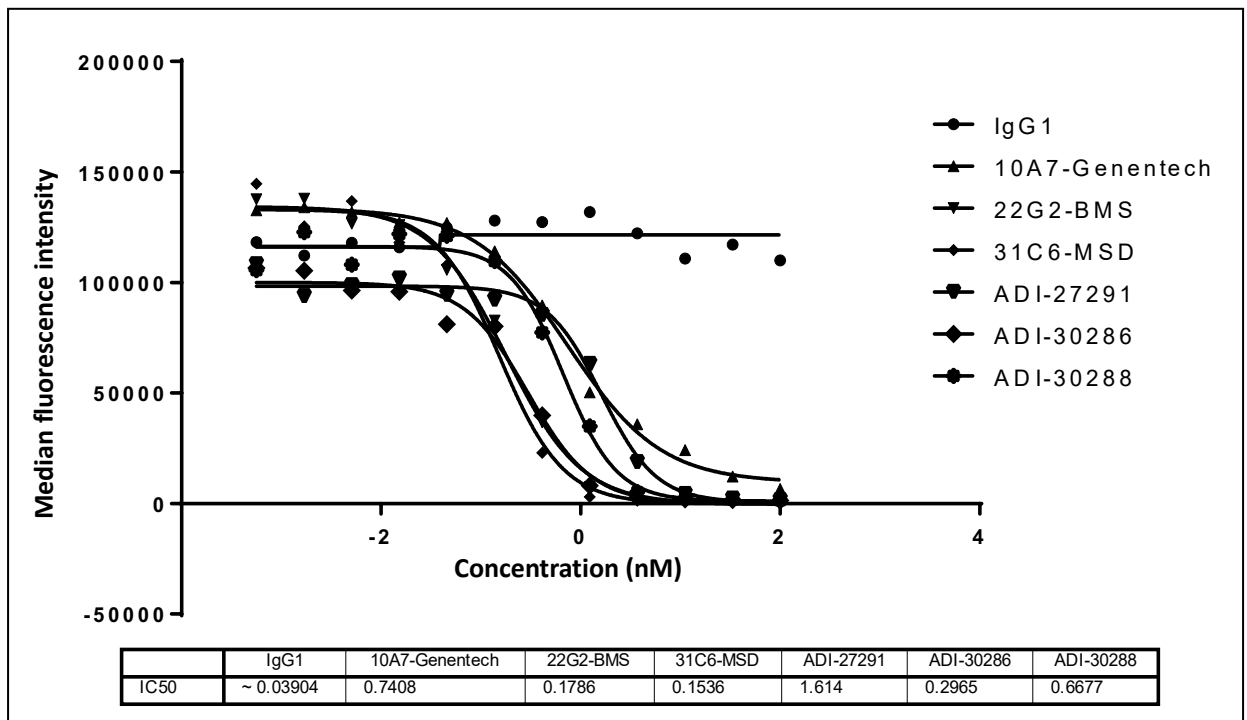


FIG. 3D

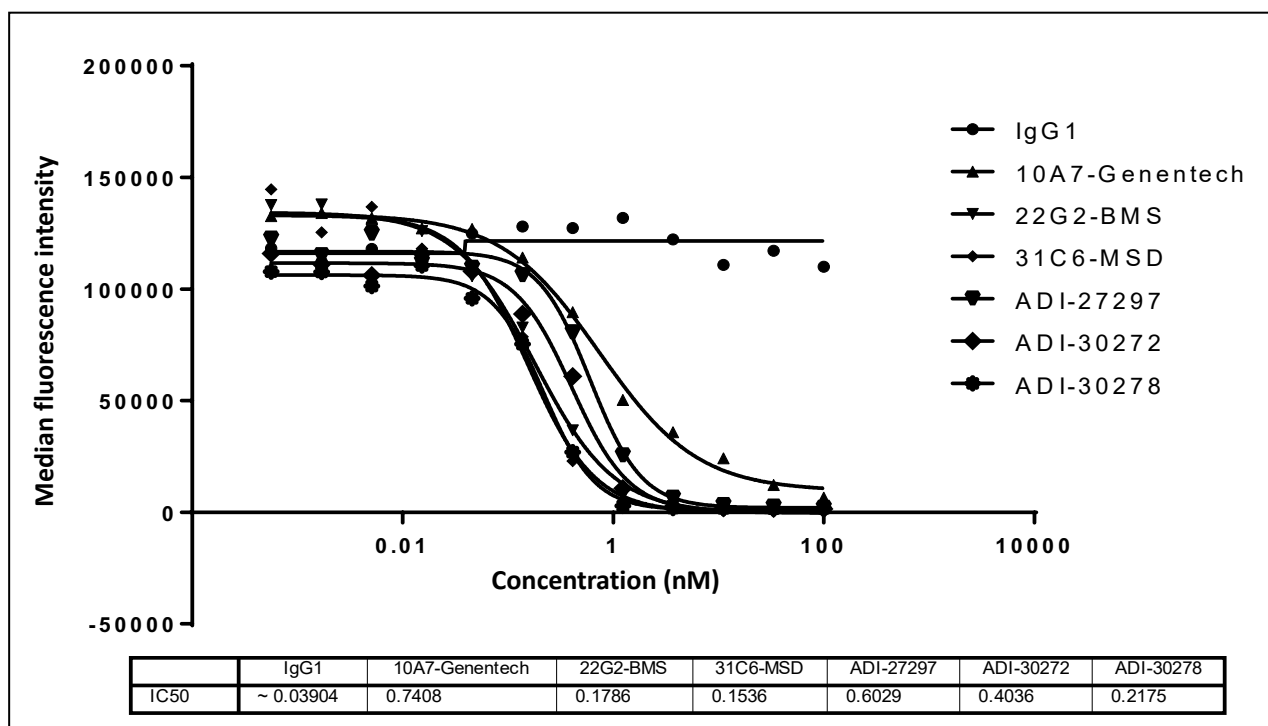


FIG. 3E

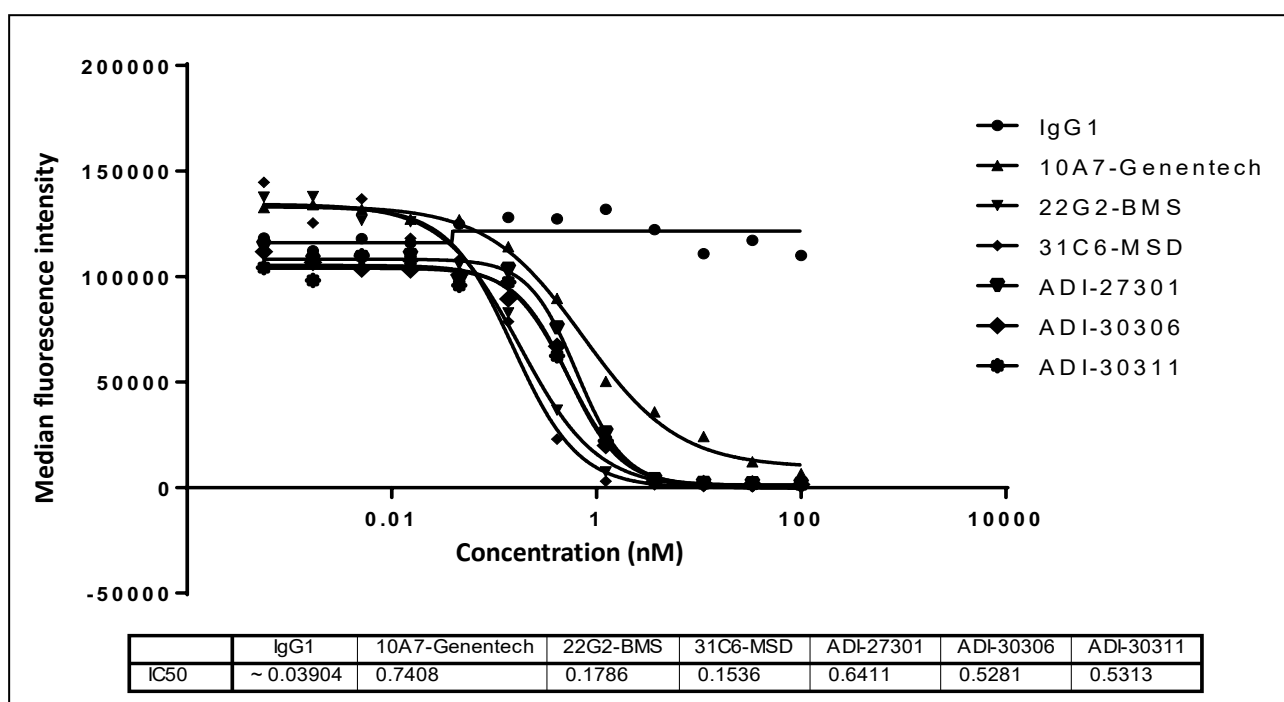


FIG. 3F

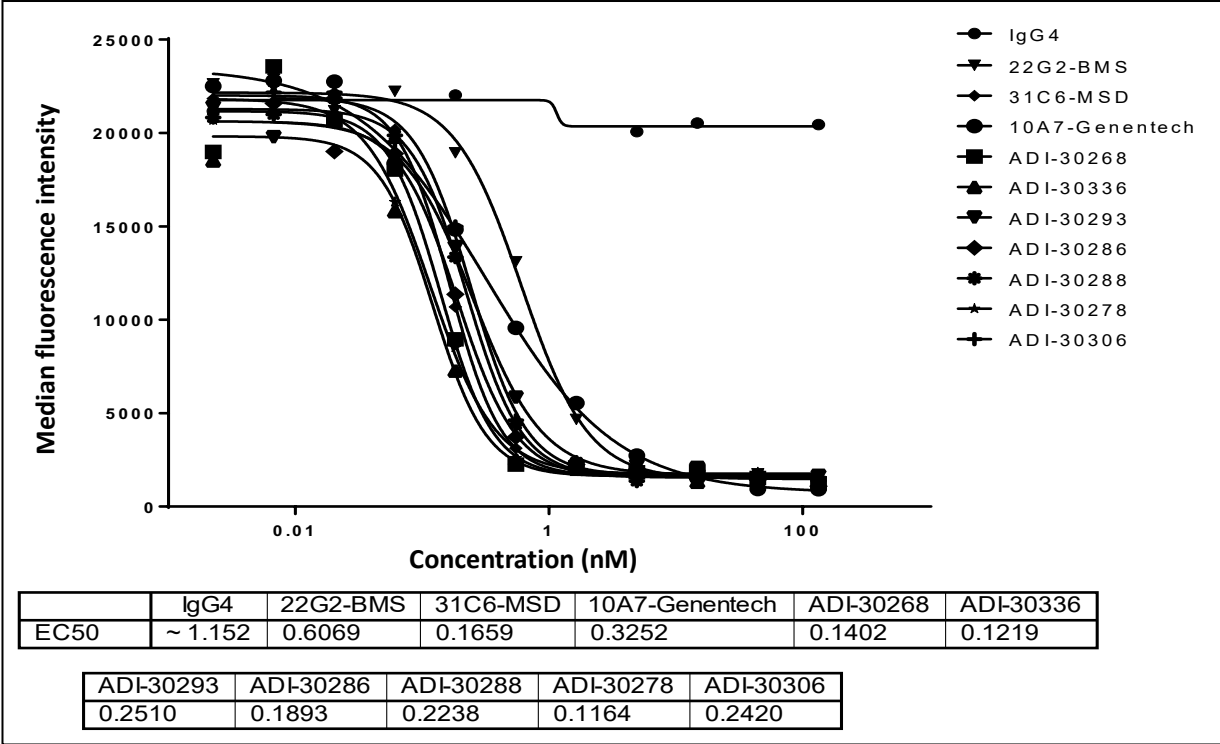


FIG. 4

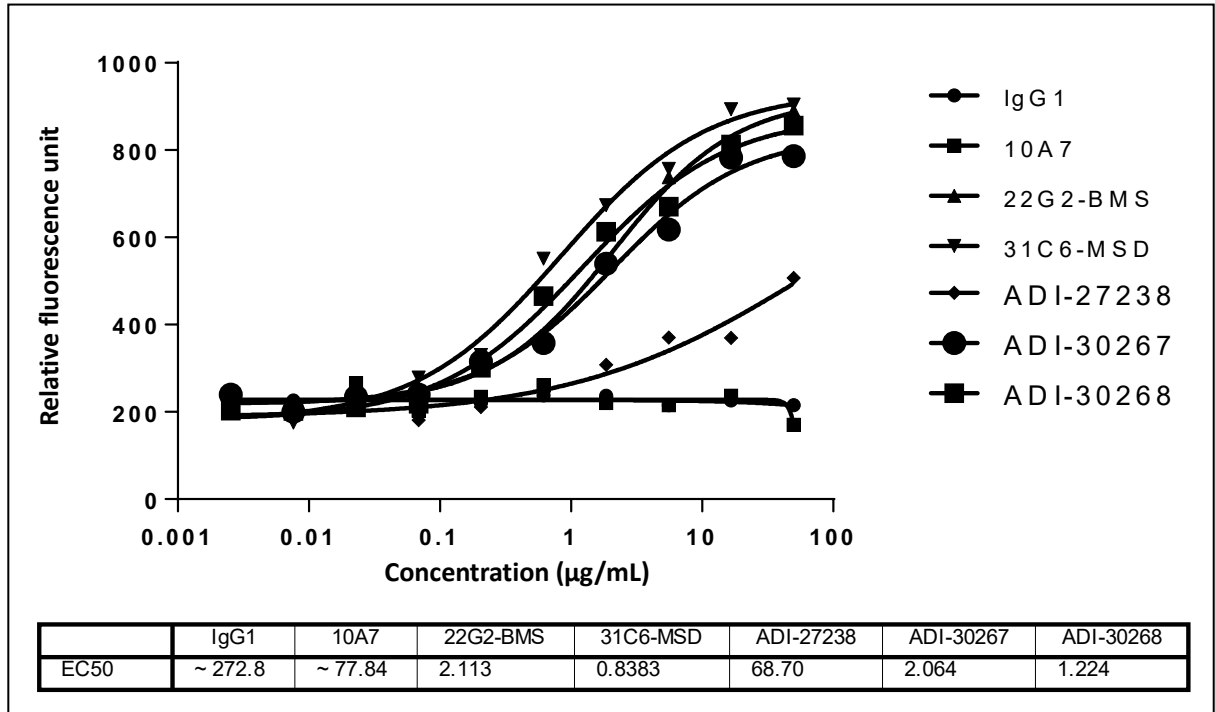


FIG. 5A

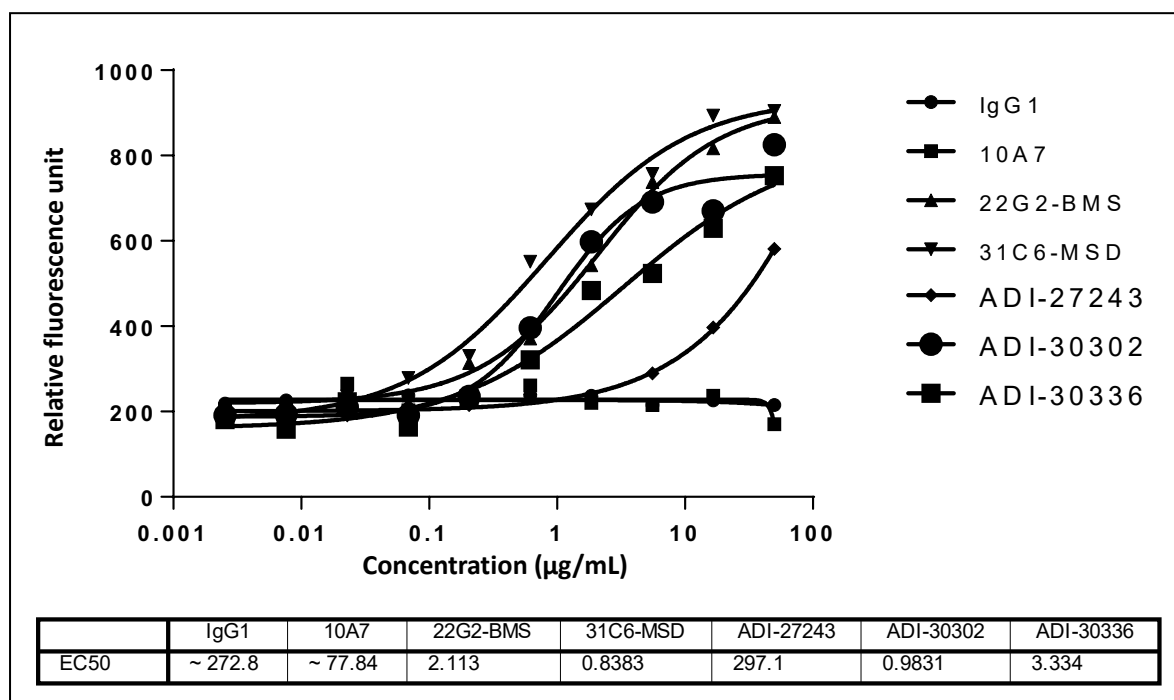


FIG. 5B

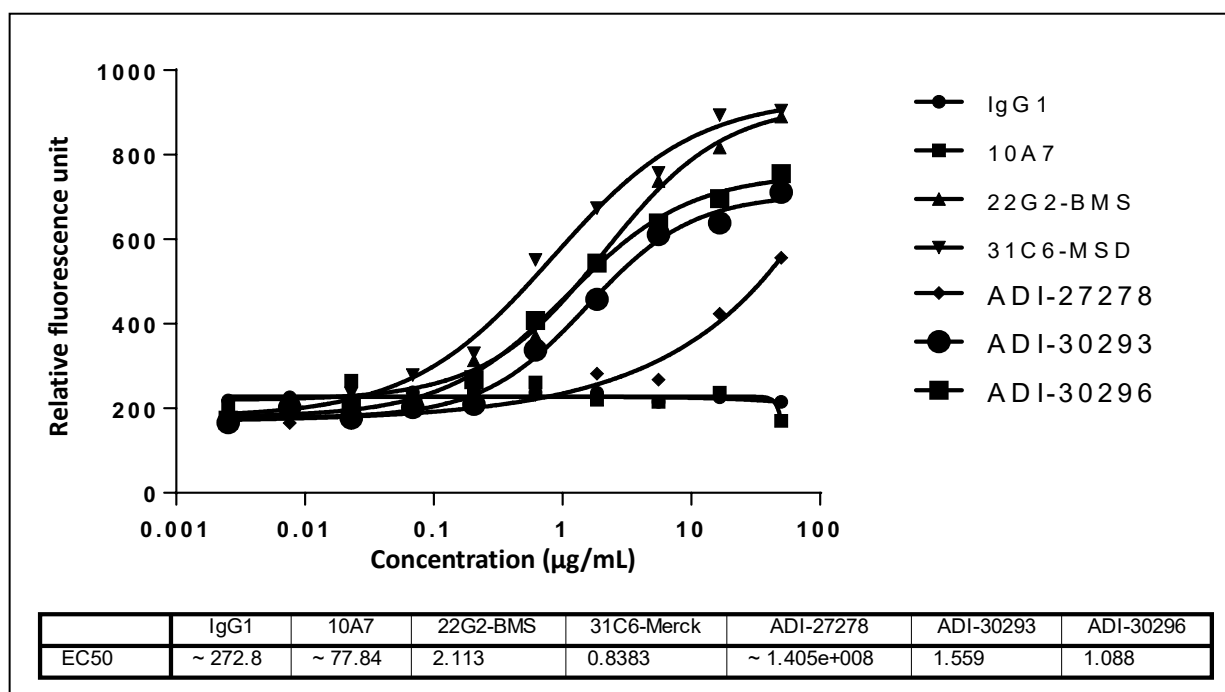


FIG. 5C

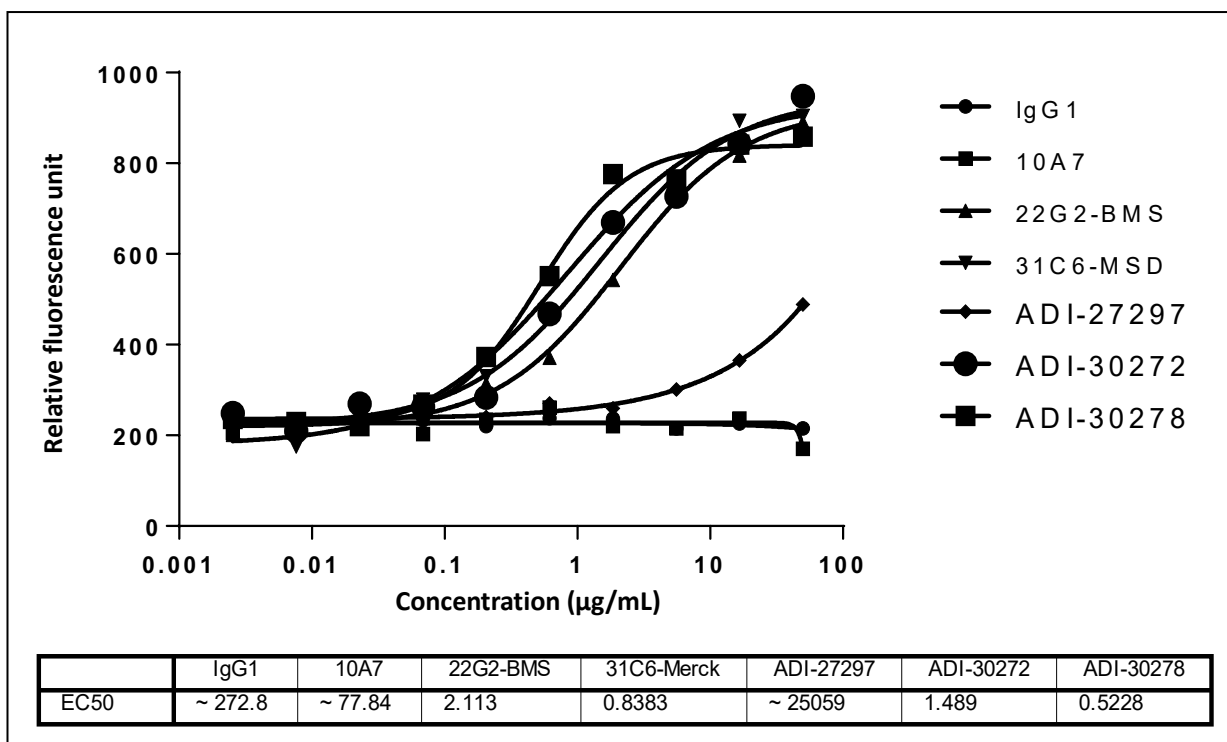


FIG. 5D

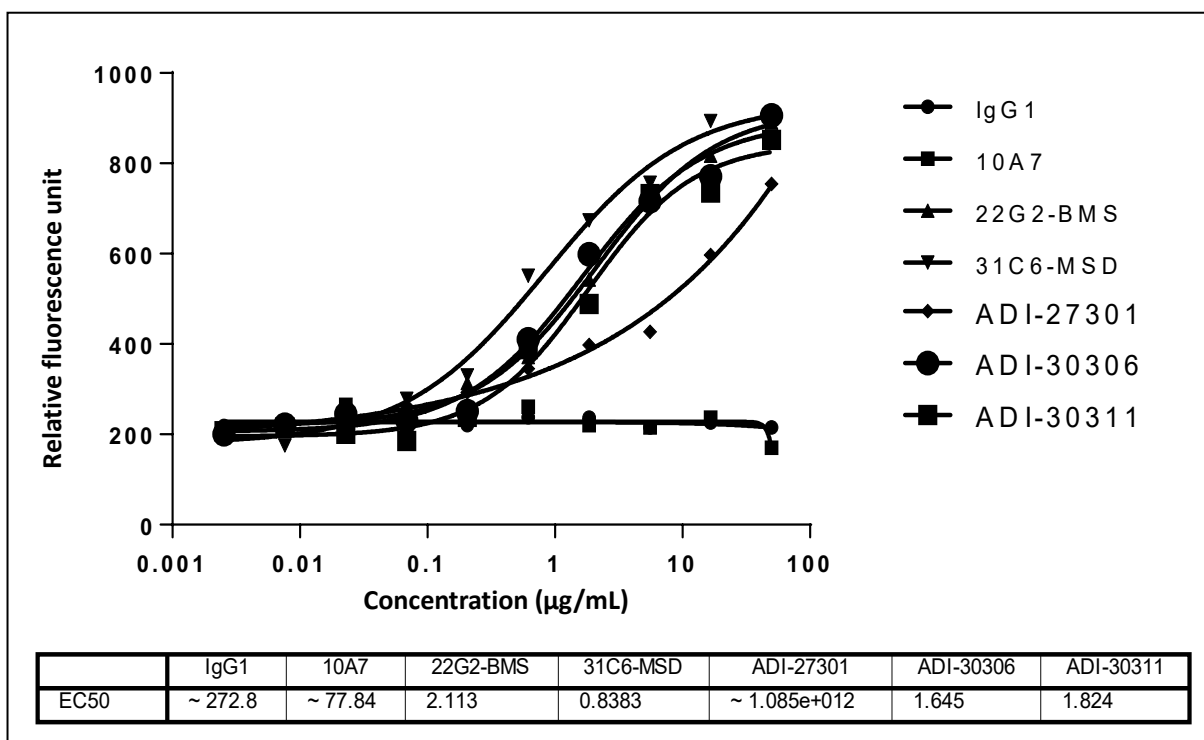


FIG. 5E

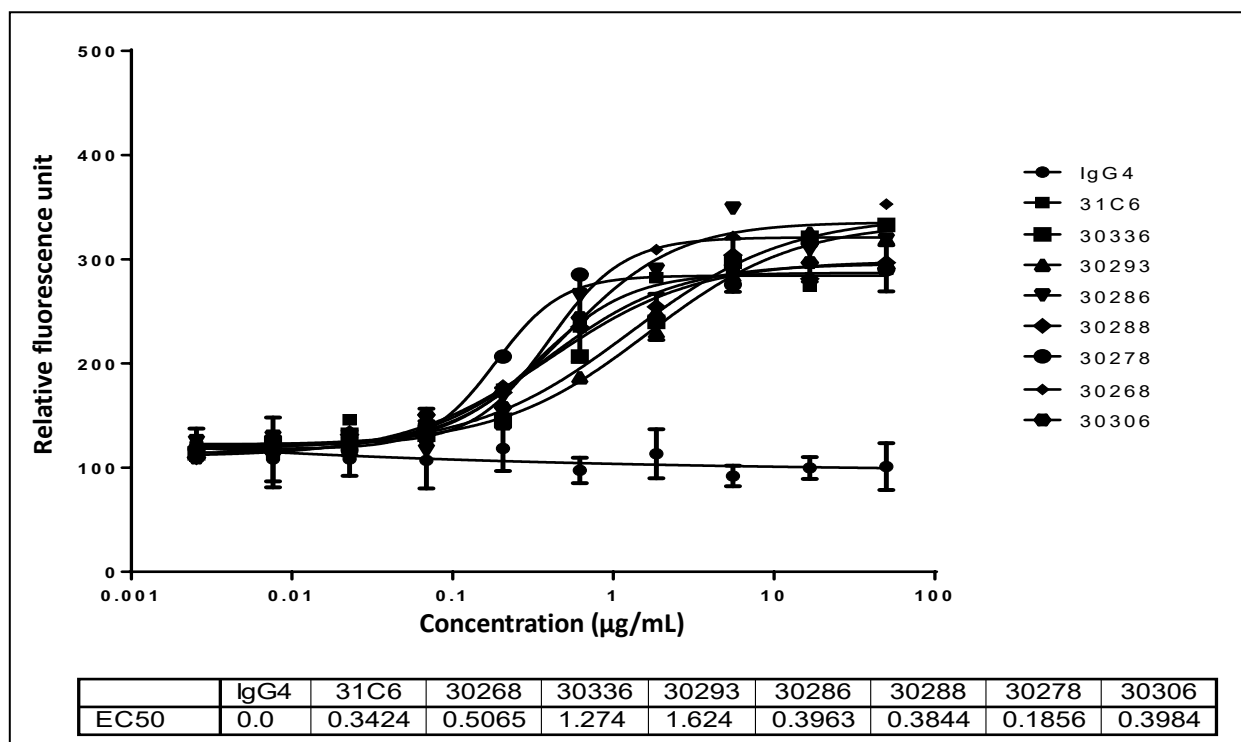


FIG. 6

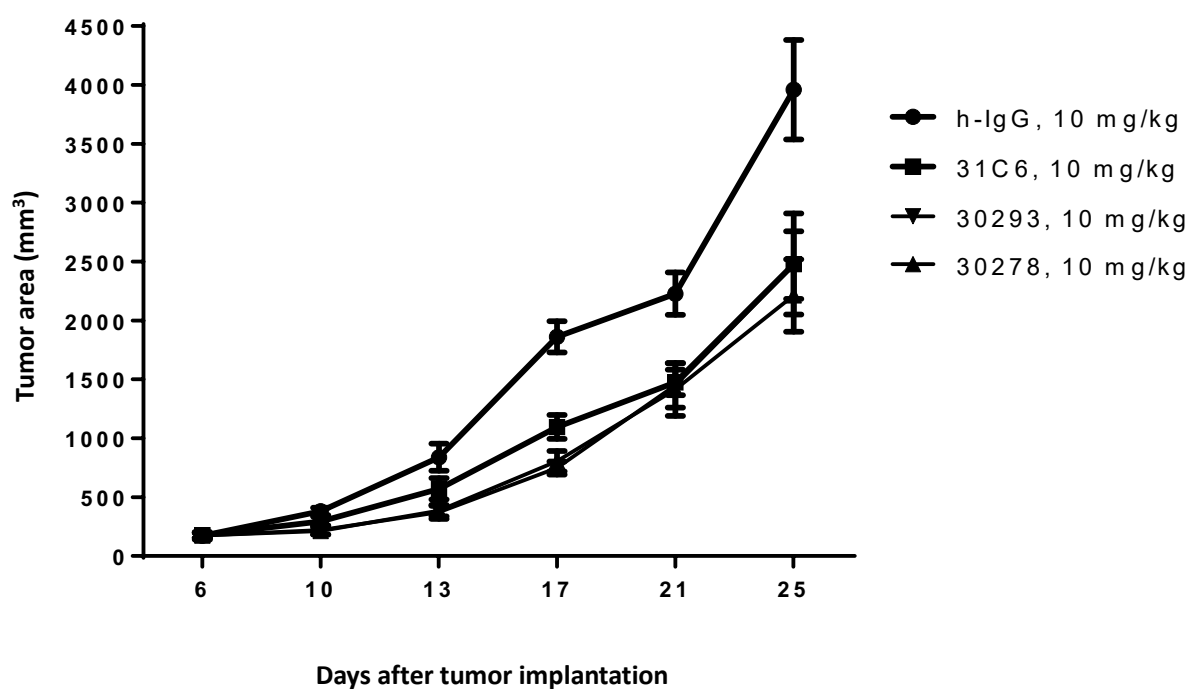


FIG. 7

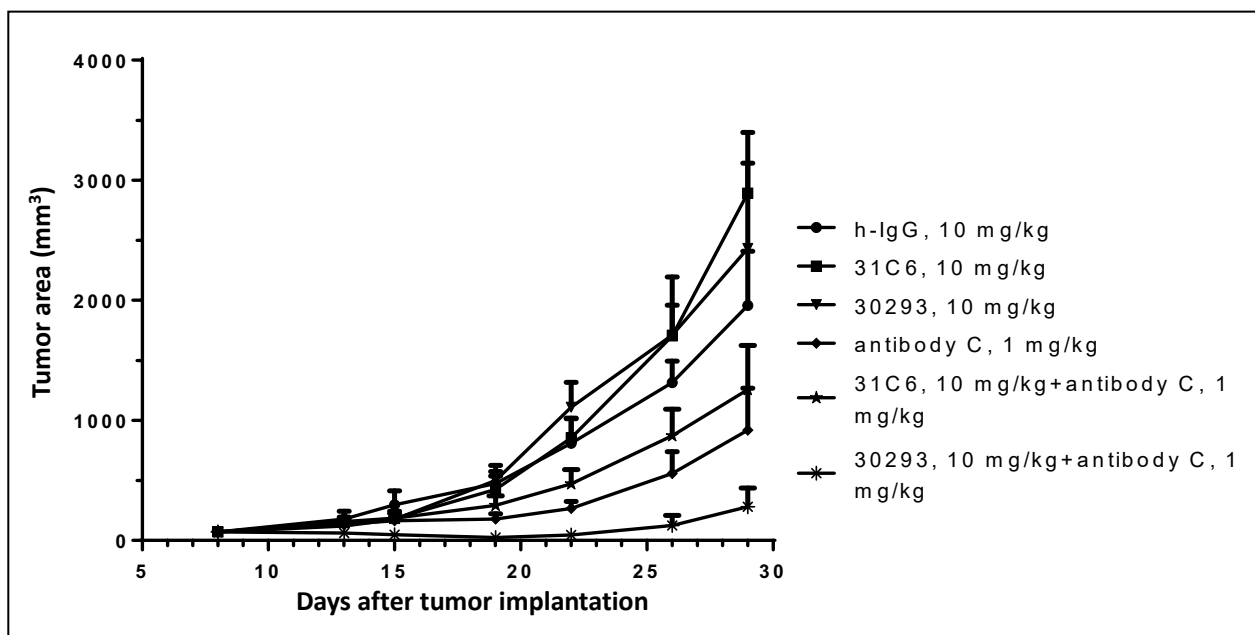


FIG. 8A

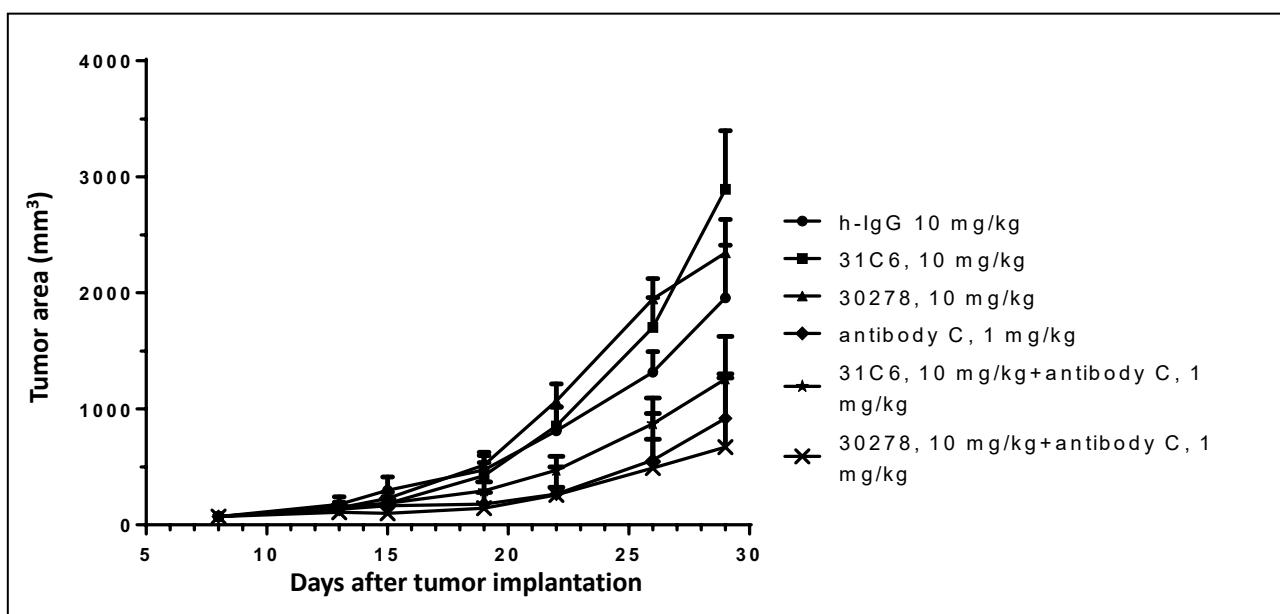


FIG. 8B

Human TIGIT sequence

MRWCLLLIWAQGLRQAPLASGMMTGTIETTGNISAEKGGSIILQCHLSSTTAQVTQVNWEQQDQLLAICNADLGWHISPSFKDR
VAPGPGLGLTLQSLTVNDTGEYFCIYHTYPDGTYTGRIFLEVLESSVAEHGARFQIPLLGAMAATLVVICTAVIVVVVALTRKKKALRIHS
VEGDLRRKSAGQEEWSPSAPSPPGSCVQAEAAPAGLCGEQRGEDCAELHDYFNVLSYRSLGNCSTFTETG (SEQ ID NO: 208)

FIG. 9

509513181_1.txt
SEQUENCE LISITNG

<110> Innovent Biologics (Suzhou) Co., Ltd.

<120> Anti-TIGIT Antibody and Use thereof

<130> PF190269PCT

<160> 209

<170> PatentIn version 3.3

<210> 1

<211> 9

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 1 ADI-27238 HCDR1 KABAT numbering positions H27-35B

<400> 1

Tyr Thr Phe Thr Ser Tyr Tyr Met Ser
1 5

<210> 2

<211> 9

<212> PRT

<213> artificial sequence

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<400> 2

Tyr Thr Phe Leu Ser Tyr Tyr Met Asn
1 5

<210> 3

<211> 9

<212> PRT

<213> artificial sequence

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<223> Antibody Sequence 3 ADI-30267 HCDR1 KABAT numbering positions H27-35B

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Tyr Thr Phe Arg Ser Tyr Tyr Met Ser
1 5

<210> 4
 <211> 9
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 4 ADI-30268 HCDR1 KABAT numbering positions H27-35B

<400> 4

Tyr Thr Phe Gly Ser Tyr Tyr Met Gly
 1 5

<210> 5
 <211> 9
 <212> PRT
 <213> artificial sequence

<220>
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<220>
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 <223> Xaa may be any natural amino acid, preferably selected from T, L, R, G and a conservatively substituted residue thereof

<220>
 <221> misc_feature
 <222> (9)..(9)
 <223> Xaa may be any natural amino acid, preferably selected from S, N, G and a conservatively substituted residue thereof

<400> 5

Tyr Thr Phe Xaa Ser Tyr Tyr Met Xaa
 1 5

<210> 6
 <211> 17
 <212> PRT
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<220>
 <223> Antibody Sequence 6 ADI-27238, ADI-27297 HCDR2 KABAT numbering positions H50-65

<400> 6

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Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 7
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> Antibody Sequence 7 ADI-30263 HCDR2 KABAT H50-65

<400> 7

Ile Ile Asp Pro Ser Gly Gly Arg Thr Ser Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 8
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> Antibody Sequence 8 ADI-30267 HCDR2 KABAT H50-65

<400> 8

Ile Ile Asp Pro Ser Gly Gly Arg Thr Ser Phe Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 9
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> Antibody Sequence 9 ADI-30268 HCDR2 KABAT H50-65

<400> 9

Ile	Ile	Asp	Pro	Ser	Gly	Gly	Arg	Thr	Ser	Tyr	Ala	Arg	Lys	Phe	Gln
1				5					10					15	

Gly

<210> 10

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 10 Consensus sequence

<220>

<221> misc_feature

<222> (3)..(3)

<223> Xaa may be any natural amino acid, preferably selected from N, D and a conservatively substituted residue thereof

<220>

<221> misc_feature

<222> (8)..(8)

<223> Xaa may be any natural amino acid, preferably selected from S, R and a conservatively substituted residue thereof

<220>

<221> misc_feature

<222> (11)..(11)

<223> Xaa may be any natural amino acid, preferably selected from Y, F and a conservatively substituted residue thereof

<220>

<221> misc_feature

<222> (13)..(13)

<223> Xaa may be any natural amino acid, preferably selected from Q, R and a conservatively substituted residue thereof

<400> 10

Ile	Ile	Xaa	Pro	Ser	Gly	Gly	Xaa	Thr	Ser	Xaa	Ala	Xaa	Lys	Phe	Gln
1				5					10					15	

Gly

<210> 11
 <211> 15
 <212> PRT
 <213> artificial sequence

<220>
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<400> 11

Ala	Arg	Ala	Arg	Tyr	Pro	Ser	Ser	Trp	Pro	Tyr	Gly	Met	Asp	Val
1				5				10						15

<210> 12
 <211> 15
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 12 ADI-30263 HCDR3 Kabat H93-102

<400> 12

Ala	Arg	Ala	Arg	Tyr	Pro	Ser	Ser	Trp	Pro	Tyr	Gly	Thr	Asp	Val
1				5				10						15

<210> 13
 <211> 15
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 13 ADI-30267 HCDR3 Kabat H93-102

<400> 13

Ala	Arg	Ala	Arg	Tyr	Pro	Glu	Ser	Trp	Pro	Tyr	Gly	Met	Asp	Val
1				5				10						15

<210> 14
 <211> 15
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 14 ADI-30268 HCDR3 Kabat H93-102

<400> 14

Ala	Arg	Ala	Arg	Thr	Pro	Ser	Ser	Trp	Pro	Tyr	Gly	Met	Asp	Val
1				5					10					15

<210> 15

<211> 15

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 15 Consensus sequence

<220>

<221> misc_feature

<222> (5)..(5)

<223> Xaa may be any natural amino acid, preferably selected from Y, T and a conservatively substituted residue thereof

<220>

<221> misc_feature

<222> (13)..(13)

<223> Xaa may be any natural amino acid, preferably selected from M, T and a conservatively substituted residue thereof

<400> 15

Ala	Arg	Ala	Arg	Xaa	Pro	Ser	Ser	Trp	Pro	Tyr	Gly	Xaa	Asp	Val
1				5					10					15

<210> 16

<211> 11

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 16 ADI-27238, ADI-30263, ADI-30267, ADI-30268 LCDR1 Kabat L24-34

<400> 16

Arg	Ala	Ser	Gln	Ser	Ile	Asn	Ser	Tyr	Leu	Asn
1				5					10	

<210> 17

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 17 ADI-27238, ADI-30263, ADI-30267, ADI-30268, ADI-27297, ADI-30272, ADI-30272 LCDR2 Kabat L50-56

<400> 17

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> 18

<211> 9

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 18 ADI-27238, ADI-30263, ADI-30267, ADI-30268 LCDR3 Kabat L89-97

<400> 18

Gln Gln Ser Leu Leu Thr Pro Phe Thr
1 5

<210> 19

<211> 11

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 19 ADI-27243, ADI-30336 HCDR1 KABAT numbering positions H27-35B

<400> 19

Gly Ser Ile Ser Ser Ser Arg Tyr Tyr Trp Gly
1 5 10

<210> 20

<211> 11

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 20 ADI-30302 HCDR1 KABAT numbering positions H27-35B

<400> 20

Gly Ser Ile Gly Ser Ser Gln Tyr Tyr Trp Gly
 1 5 10

<210> 21
 <211> 11
 <212> PRT
 <213> artificial sequence

<220>
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<220>
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 <222> (4)..(4)
 <223> Xaa may be any natural amino acid, preferably selected from S, G and a conservatively substituted residue thereof

<220>
 <221> misc_feature
 <222> (7)..(7)
 <223> Xaa may be any natural amino acid, preferably selected from R, Q and a conservatively substituted residue thereof

<400> 21

Gly Ser Ile Xaa Ser Ser Xaa Tyr Tyr Trp Gly
 1 5 10

<210> 22
 <211> 16
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 22 ADI-27243, ADI-30336, ADI-27301 HCDR2 KABAT H50-65

<400> 22

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

<210> 23
 <211> 16
 <212> PRT
 <213> artificial sequence

<220>
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<400> 23

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

<210> 24

<211> 16

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<220>

<223> Antibody Sequence 24 Consensus sequence

<220>

<221> misc_feature

<222> (4)..(4)

<223> Xaa may be any natural amino acid, preferably selected from Y, R and a conservatively substituted residue thereof

<220>

<221> misc_feature

<222> (7)..(7)

<223> Xaa may be any natural amino acid, preferably selected from S, G and a conservatively substituted residue thereof

<400> 24

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

<210> 25

<211> 14

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 25 ADI-27243, ADI-30302, ADI-30336 HCDR3 Kabat H93-102

<400> 25

Ala Arg Asp Gly Leu Tyr His Thr Pro Glu Tyr Phe Gln His
1 5 10

<210> 26

<211> 11

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 26 ADI-27243, ADI-30302, ADI-30336 LCDR1 Kabat L24-34

<400> 26

Arg	Ala	Ser	Gln	Ser	Val	Ser	Ser	Tyr	Leu	Ala
1				5					10	

<210> 27

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 27 ADI-27243, ADI-30302, ADI-30336 LCDR2 Kabat L50-56

<400> 27

Asp	Ala	Ser	Asn	Arg	Ala	Thr
1			5			

<210> 28

<211> 9

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 28 ADI-27243, ADI-30302 LCDR3 Kabat L89-97

<400> 28

Gln	Gln	Arg	Phe	Ala	Phe	Pro	Tyr	Thr
1			5					

<210> 29

<211> 9

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 29 ADI-30336 LCDR3 Kabat L89-97

<400> 29

Gln	Gln	Arg	Phe	Ala	His	Pro	Tyr	Thr
1			5					

<210> 30

<211> 9
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 30 Consensus sequence

<220>
 <221> misc_feature
 <222> (6)..(6)
 <223> Xaa may be any natural amino acid, preferably selected from F, H and a conservatively substituted residue thereof

<400> 30

Gln Gln Arg Phe Ala Xaa Pro Tyr Thr
 1 5

<210> 31
 <211> 9
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 31 ADI-27278, ADI-30293 HCDR1 KABAT numbering positions H27-35B

<400> 31

Phe Thr Phe Ser Ser Tyr Ser Met Asn
 1 5

<210> 32
 <211> 9
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 32 ADI-30296 HCDR1 KABAT numbering positions H27-35B

<400> 32

Phe Thr Ile Gly Gly Tyr Ser Met Asn
 1 5

<210> 33
 <211> 9
 <212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 33 Consensus sequence

<220>

<221> misc_feature

<222> (3)..(5)

<223> Xaa may be any natural amino acid, and preferably, Xaa at position 3 is selected from F, I and a conservatively substituted residue thereof, Xaa at position 4 is selected from S, G and a conservatively substituted residue thereof, and Xaa at position 5 is selected from S, G and a conservatively substituted residue thereof

<400> 33

Phe Thr Xaa Xaa Xaa Tyr Ser Met Asn
1 5

<210> 34

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 34 ADI-27278 HCDR2 KABAT H50-65

<400> 34

Tyr Ile Ser Gly Ser Ser Ser Thr Ile Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 35

<211> 16

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 35 ADI-30293 HCDR2 KABAT H50-65

<400> 35

Tyr Ile Ser Ser Ser Gly Thr Ile Asn Tyr Ala Asp Ser Val Lys Gly
1 5 10 15

<210> 36
 <211> 16
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 36 ADI-30296 HCDR2 KABAT H50-65

<400> 36

Tyr	Ile	Ser	Ser	Ser	Ser	Thr	Ile	His	Tyr	Ala	Asp	Ser	Val	Lys	Gly
1				5					10					15	

<210> 37
 <211> 17
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 37 Consensus sequence

<220>
 <221> misc_feature
 <222> (3)..(4)
 <223> Xaa may be any natural amino acid, and preferably, Xaa at position 3 is selected from deletion, S and a conservatively substituted residue thereof, and Xaa at position 4 is selected from G, S and a conservatively substituted residue thereof

<220>
 <221> misc_feature
 <222> (7)..(7)
 <223> Xaa may be any natural amino acid, preferably selected from S, G and a conservatively substituted residue thereof

<220>
 <221> misc_feature
 <222> (10)..(10)
 <223> Xaa may be any natural amino acid, preferably selected from Y, N, H and a conservatively substituted residue thereof

<400> 37

Tyr	Ile	Xaa	Xaa	Ser	Ser	Xaa	Thr	Ile	Xaa	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 38
 <211> 15
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 38 ADI-27278, ADI-30293 HCDR3 Kabat H93-102

<400> 38

Ala	Arg	His	Arg	Ile	Ala	Asp	Ser	Pro	Ser	Arg	Ala	Phe	Asp	Ile
1				5					10				15	

<210> 39
 <211> 15
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 39 ADI-30296 HCDR3 Kabat H93-102

<400> 39

Ala	Arg	His	Arg	Ile	Gly	Arg	Ser	Pro	Ser	Arg	Ala	Phe	Asp	Ile
1				5					10				15	

<210> 40
 <211> 15
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 40 Consensus sequence

<220>
 <221> misc_feature
 <222> (6)..(7)
 <223> Xaa may be any natural amino acid, and preferably, Xaa at position 6 is selected from A, G and a conservatively substituted residue thereof, and Xaa at position 7 is selected from D, R and a conservatively substituted residue thereof

<400> 40

Ala	Arg	His	Arg	Ile	Xaa	Xaa	Ser	Pro	Ser	Arg	Ala	Phe	Asp	Ile
1				5					10				15	

<210> 41
 <211> 17
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 41 ADI-27278, ADI-30293, ADI-30296 LCDR1-Kabat L24-34

<400> 41

Lys Ser Ser Gln Ser Val Leu Phe Ser Ser Asn Asn Lys Asn Tyr Leu
 1 5 10 15

Ala

<210> 42
 <211> 7
 <212> PRT
 <213> artificial sequence

<220>
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<400> 42

Trp Ala Ser Thr Arg Glu Ser
 1 5

<210> 43
 <211> 8
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 43 ADI-27278, ADI-30293, ADI-30296 LCDR3 Kabat L89-97

<400> 43

Gln Gln Ser Tyr Phe Phe Pro Thr
 1 5

<210> 44
 <211> 9
 <212> PRT
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<220>

<223> Antibody Sequence 44 ADI-27291 HCDR1 KABAT numbering positions H27-35B

<400> 44

Phe Thr Phe Ser Ser Tyr Ala Met Ser
1 5

<210> 45

<211> 9

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 45 ADI-30283 HCDR1 KABAT numbering positions H27-35B

<400> 45

Phe Thr Phe Ser Pro Tyr Gly Met Ser
1 5

<210> 46

<211> 9

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 46 ADI-30286, ADI-30288 HCDR1 KABAT numbering positions H27-35B

<400> 46

Phe Thr Phe Gly Pro Tyr Gly Met Ser
1 5

<210> 47

<211> 9

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 47 Consensus sequence

<220>

<221> misc_feature

<222> (4)..(5)

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<223> Xaa may be any natural amino acid, and preferably, Xaa at position 4 is selected from S, G and a conservatively substituted residue thereof, and Xaa at position 5 is selected from S, P and a conservatively substituted residue thereof

<220>

<221> misc_feature

<222> (7)..(7)

<223> Xaa may be any natural amino acid, preferably selected from A, G and a conservatively substituted residue thereof

<400> 47

Phe Thr Phe Xaa Xaa Tyr Xaa Met Ser
1 5

<210> 48

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 48 ADI-27291 HCDR2 KABAT H50-65

<400> 48

Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 49

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 49 ADI-30283 HCDR2 KABAT H50-65

<400> 49

Ser Ile Ser Gly Ser Gly Gly Arg Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 50
 <211> 17
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 50 ADI-30286 HCDR2 KABAT H50-65

<400> 50

Ala	Ile	Ser	Gly	Ser	Gly	Ala	Ser	Thr	Trp	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 51
 <211> 17
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 51 ADI-30288 HCDR2 KABAT H50-65

<400> 51

Ala	Ile	Ser	Gly	Ser	Gly	Ala	Ser	Thr	Trp	His	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 52
 <211> 17
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 52 Consensus sequence

<220>
 <221> misc_feature
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 <223> Xaa may be any natural amino acid, preferably selected from A, S and a conservatively substituted residue thereof

<220>

<221> misc_feature

<222> (7)..(8)

<223> Xaa may be any natural amino acid, and preferably, Xaa at position 7 is selected from G, A and a conservatively substituted residue thereof, and Xaa at position 8 is selected from S, R and a conservatively substituted residue thereof

<220>

<221> misc_feature

<222> (10)..(11)

<223> Xaa may be any natural amino acid, and preferably, Xaa at position 10 is selected from Y, W and a conservatively substituted residue thereof, and Xaa at position 11 is selected from Y, H and a conservatively substituted residue thereof

<400> 52

Xaa	Ile	Ser	Gly	Ser	Gly	Xaa	Xaa	Thr	Xaa	Xaa	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 53

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 53 ADI-27291, ADI-30283 HCDR3 Kabat H93-102

<400> 53

Ala	Lys	Asp	Pro	Gly	Thr	Asp	Ser	Ser	Gly	Tyr	Tyr	Tyr	Ile	Trp	Arg
1				5					10					15	

Tyr

<210> 54

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 54 ADI-30286 HCDR3 Kabat H93-102

<400> 54

Ala Lys Asp Pro Gly Thr His Tyr Ser Gly Tyr Tyr Tyr Ile Trp Arg
1 5 10 15

Tyr

<210> 55

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 55 ADI-30288 HCDR3 Kabat H93-102

<400> 55

Ala Lys Asp Pro Gly Thr Asp Ser Thr Gly Tyr Tyr Tyr Ile Trp Arg
1 5 10 15

Tyr

<210> 56

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 56 Consensus sequence

<220>

<221> misc_feature

<222> (7)..(9)

<223> Xaa may be any natural amino acid, and preferably, Xaa at position 7 is selected from D, H and a conservatively substituted residue thereof, Xaa at position 8 is selected from S, Y and a conservatively substituted residue thereof, and Xaa at position 9 is selected from S, T and a conservatively substituted residue thereof

<400> 56

Ala Lys Asp Pro Gly Thr Xaa Xaa Xaa Gly Tyr Tyr Tyr Ile Trp Arg
1 5 10 15

Tyr

<210> 57
 <211> 11
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 57 ADI-27291, ADI-30296, ADI-30286, ADI-30288 LCDR1
 Kabat L24-34

<400> 57

Arg Ala Ser Gln Ser Val Ser Ser Asn Leu Ala
 1 5 10

<210> 58
 <211> 7
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 58 ADI-27291, ADI-30283, ADI-30286, ADI-30288 LCDR2
 Kabat L50-56

<400> 58

Ser Ala Ser Thr Arg Ala Thr
 1 5

<210> 59
 <211> 10
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 59 ADI-27291, ADI-30283, ADI-30286, ADI-30288 LCDR3
 Kabat L89-97

<400> 59

Gln Gln Tyr Val Pro His Pro Pro Phe Thr
 1 5 10

<210> 60
 <211> 9
 <212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 60 ADI-27297 HCDR1 KABAT numbering positions H27-35B

<400> 60

Tyr Thr Phe Thr Ser Tyr Tyr Met His
1 5

<210> 61

<211> 9

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 61 ADI-30272, ADI-30278 HCDR1 KABAT numbering positions H27-35B

<400> 61

Tyr Thr Phe Thr Glu Tyr Tyr Met His
1 5

<210> 62

<211> 9

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 62 Consensus sequence

<220>

<221> misc_feature

<222> (5)..(5)

<223> Xaa may be any natural amino acid, preferably selected from S, E and a conservatively substituted residue thereof

<400> 62

Tyr Thr Phe Thr Xaa Tyr Tyr Met His
1 5

<210> 63

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 63 ADI-30272 HCDR2 KABAT H50-65

<400> 63

Ile	Ile	Ser	Pro	Ser	Ala	Gly	Ser	Thr	Ser	Tyr	Ala	Gln	Lys	Phe	Gln
1				5					10					15	

Gly

<210> 64

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 64 ADI-30278 HCDR2 KABAT H50-65

<400> 64

Ile	Ile	Ser	Pro	Ser	Ala	Gly	Ser	Thr	Lys	Tyr	Ala	Gln	Lys	Phe	Gln
1				5					10					15	

Gly

<210> 65

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 65 Consensus sequence

<220>

<221> misc_feature

<222> (3)..(3)

<223> Xaa may be any natural amino acid, preferably selected from N, S and a conservatively substituted residue thereof

<220>

<221> misc_feature

<222> (6)..(6)

<223> Xaa may be any natural amino acid, preferably selected from G, A and a conservatively substituted residue thereof

<220>

<221> misc_feature

<222> (10)..(10)

<223> Xaa may be any natural amino acid, preferably selected from S, K and a conservatively substituted residue thereof

<400> 65

Ile	Ile	Xaa	Pro	Ser	Xaa	Gly	Ser	Thr	Xaa	Tyr	Ala	Gln	Lys	Phe	Gln
1				5					10					15	

Gly

<210> 66

<211> 15

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 66 ADI-27297, ADI-30272 HCDR3 Kabat H93-102

<400> 66

Ala	Arg	Asp	His	Asp	Ile	Ala	Ala	Ala	Gly	Arg	Leu	Ala	Asp	Tyr
1				5					10					15

<210> 67

<211> 15

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 67 ADI-30278 HCDR3 Kabat H93-102

<400> 67

Ala	Arg	Asp	His	Asp	Ile	Arg	Leu	Ala	Gly	Arg	Leu	Ala	Asp	Tyr
1				5					10					15

<210> 68

<211> 15

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 68 Consensus sequence

<220>
 <221> misc_feature
 <222> (7)..(8)
 <223> Xaa may be any natural amino acid, and preferably, Xaa at position 7 is selected from A, R and a conservatively substituted residue thereof, and Xaa at position 8 is selected from A, L and a conservatively substituted residue thereof

<400> 68

Ala	Arg	Asp	His	Asp	Ile	Xaa	Xaa	Ala	Gly	Arg	Leu	Ala	Asp	Tyr
1				5					10				15	

<210> 69
 <211> 11
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 69 ADI-27297, ADI-30272, ADI-30278 LCDR1-Kabat L24-34

<400> 69

Arg	Ala	Ser	Gln	Gly	Ile	Ser	Ser	Trp	Leu	Ala
1				5					10	

<210> 70
 <211> 9
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 70 ADI-27297, ADI-30272, ADI-30278 LCDR3 Kabat L89-97

<400> 70

Gln	Gln	Ala	Val	Ile	Leu	Pro	Ile	Thr
1				5				

<210> 71
 <211> 11
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 71 ADI-27301 HCDR1 KABAT numbering positions H27-35B

<400> 71

Gly Ser Ile Ser Ser Ser Ser Tyr Tyr Trp Gly
1 5 10

<210> 72
<211> 11
<212> PRT
<213> artificial sequence

<220>
<223> Antibody Sequence 72 ADI-30306 HCDR1 KABAT numbering positions H27-35B

<400> 72

Gly Ser Ile Ser Ser Ser Leu Tyr Tyr Trp Gly
1 5 10

<210> 73
<211> 11
<212> PRT
<213> artificial sequence

<220>
<223> Antibody Sequence 73 ADI-30311 HCDR1 KABAT numbering positions H27-35B

<400> 73

Gly Ser Ile Ala Ser Ser Val Tyr Tyr Trp Gly
1 5 10

<210> 74
<211> 11
<212> PRT
<213> artificial sequence

<220>
<223> Antibody Sequence 74 Consensus sequence

<220>
<221> misc_feature
<222> (4)..(4)
<223> Xaa may be any natural amino acid, preferably selected from A, S and a conservatively substituted residue thereof

<220>
<221> misc_feature
<222> (7)..(7)
<223> Xaa may be any natural amino acid, preferably selected from S, L, V and a

conservatively substituted residue thereof

<400> 74

Gly	Ser	Ile	Xaa	Ser	Ser	Xaa	Tyr	Tyr	Trp	Gly
1				5					10	

<210> 75

<211> 16

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 75 ADI-30306 HCDR2 KABAT H50-65

<400> 75

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

<210> 76

<211> 16

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 76 ADI-30311 HCDR2 KABAT H50-65

<400> 76

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

<210> 77

<211> 16

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 77 Consensus sequence

<220>

<221> misc_feature

<222> (9)..(9)

<223> Xaa may be any natural amino acid, preferably selected from Y, F, W and a conservatively substituted residue thereof

<220>

<221> misc_feature

<222> (14)..(14)

<223> Xaa may be any natural amino acid, preferably selected from L, F and a conservatively substituted residue thereof

<400> 77

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

<210> 78

<211> 15

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 78 ADI-27301, ADI-30306 HCDR3 Kabat H93-102

<400> 78

Ala	Arg	Glu	Ala	Gly	Arg	Gly	Thr	Thr	Gly	Leu	Leu	Phe	Asp	Tyr
1				5					10					15

<210> 79

<211> 15

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 79 ADI-30311 HCDR3 Kabat H93-102

<400> 79

Ala	Arg	Glu	Ala	Gly	Arg	Thr	Gly	Thr	Gly	Leu	Leu	Phe	Asp	Tyr
1				5					10					15

<210> 80

<211> 15

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 80 Consensus sequence

<220>

<221> misc_feature

<222> (7)..(8)

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<223> Xaa may be any natural amino acid, and preferably, Xaa at position 7 is selected from G, T and a conservatively substituted residue thereof, and Xaa at position 8 is selected from T, G and a conservatively substituted residue thereof

<400> 80

Ala	Arg	Glu	Ala	Gly	Arg	Xaa	Xaa	Thr	Gly	Leu	Leu	Phe	Asp	Tyr
1				5					10					15

<210> 81

<211> 11

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 81 ADI-27301, ADI-30306, ADI-30311 LCDR1 Kabat L24-34

<400> 81

Arg	Ala	Ser	Gln	Ser	Ile	Ser	Ser	Trp	Leu	Ala
1				5					10	

<210> 82

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 82 ADI-27301, ADI-30306, ADI-30311 LCDR2-Kabat L50-56

<400> 82

Lys	Ala	Ser	Ser	Leu	Glu	Ser
1				5		

<210> 83

<211> 9

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 83 ADI-27301, ADI-30306, ADI-30311 LCDR3 Kabat L89-97

<400> 83

Gln	Gln	Tyr	Gly	Ile	Leu	Pro	Arg	Thr
1				5				

<210> 84
 <211> 122
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 84 ADI-27238 VH

<400> 84

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

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

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
 65 70 75 80

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

Ala Arg Ala Arg Tyr Pro Ser Ser Trp Pro Tyr Gly Met Asp Val Trp
 100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120

<210> 85
 <211> 122
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 85 ADI-30263 VH

<400> 85

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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 Leu Ser Tyr
20 25 30

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

Gly Ile Ile Asp Pro Ser Gly Gly Arg Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

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

Ala Arg Ala Arg Tyr Pro Ser Ser Trp Pro Tyr Gly Thr Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 86
<211> 122
<212> PRT
<213> artificial sequence

<220>
<223> Antibody Sequence 86 ADI-30267 VH

<400> 86

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 Arg Ser Tyr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met

35

40

45

Gly Ile Ile Asp Pro Ser Gly Gly Arg Thr Ser Phe Ala Gln Lys Phe
 50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
 65 70 75 80

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

Ala Arg Ala Arg Tyr Pro Glu Ser Trp Pro Tyr Gly Met Asp Val Trp
 100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120

<210> 87

<211> 122

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 87 ADI-30268 VH

<400> 87

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 Gly Ser Tyr
 20 25 30

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
 65 70 75 80

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

Ala Arg Ala Arg Thr Pro Ser Ser Trp Pro Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 88

<211> 122

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 88 ADI-27243 VH

<400> 88

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

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

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

Trp Ile Gly Ser Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
50 55 60

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

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Arg Asp Gly Leu Tyr His Thr Pro Glu Tyr Phe Gln His Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser

115

120

<210> 89
 <211> 122
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 89 ADI-30302 VH

<400> 89

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

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

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

Trp Ile Gly Ser Ile Tyr Arg Ser Gly Gly Thr Tyr Tyr Asn Pro Ser
 50 55 60

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

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
 85 90 95

Cys Ala Arg Asp Gly Leu Tyr His Thr Pro Glu Tyr Phe Gln His Trp
 100 105 110

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

<210> 90
 <211> 122
 <212> PRT
 <213> artificial sequence

<220>

<223> Antibody Sequence 90 ADI-30336 VH

<400> 90

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

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

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

Trp Ile Gly Ser Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
50 55 60

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

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Arg Asp Gly Leu Tyr His Thr Pro Glu Tyr Phe Gln His Trp
100 105 110

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

<210> 91

<211> 122

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 91 ADI-27278 VH

<400> 91

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 Ser Tyr
20 25 30

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

Ser Tyr Ile Ser Gly Ser Ser Ser Thr Ile Tyr Tyr Ala Asp Ser 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 His Arg Ile Ala Asp Ser Pro Ser Arg Ala Phe Asp Ile Trp
100 105 110

Gly Gln Gly Thr Met Val Thr Val Ser Ser
115 120

<210> 92

<211> 121

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 92 ADI-30293 VH

<400> 92

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 Ser Tyr
20 25 30

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

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

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

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

Arg His Arg Ile Ala Asp Ser Pro Ser Arg Ala Phe Asp Ile Trp Gly
100 105 110

Gln Gly Thr Met Val Thr Val Ser Ser
115 120

<210> 93
<211> 121
<212> PRT
<213> artificial sequence

<220>
<223> Antibody Sequence 93 ADI-30296 VH

<400> 93

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 Ile Gly Gly Tyr
20 25 30

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

Ser Tyr Ile Ser Ser Ser Ser Thr Ile His Tyr Ala Asp Ser Val Lys
50 55 60

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

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

Arg His Arg Ile Gly Arg Ser Pro Ser Arg Ala Phe Asp Ile Trp Gly
100 105 110

Gln Gly Thr Met Val Thr Val Ser Ser
115 120

<210> 94
<211> 124
<212> PRT
<213> artificial sequence

<220>
<223> Antibody Sequence 94 ADI-27291 VH

<400> 94

Glu Val Gln Leu Leu 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 Ser Tyr
20 25 30

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

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

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

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

Ala Lys Asp Pro Gly Thr Asp Ser Ser Gly Tyr Tyr Tyr Ile Trp Arg
100 105 110

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

<210> 95
<211> 124
<212> PRT
<213> artificial sequence

<220>

<223> Antibody Sequence 95 ADI-30283 VH

<400> 95

Glu Val Gln Leu Leu 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 Pro Tyr
20 25 30

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

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

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

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

Ala Lys Asp Pro Gly Thr Asp Ser Ser Gly Tyr Tyr Tyr Ile Trp Arg
100 105 110

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

<210> 96

<211> 124

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 96 ADI-30286 VH

<400> 96

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

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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Gly Pro Tyr
20 25 30

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

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

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

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

Ala Lys Asp Pro Gly Thr His Tyr Ser Gly Tyr Tyr Tyr Ile Trp Arg
100 105 110

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

<210> 97

<211> 124

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 97 ADI-30288 VH

<400> 97

Glu Val Gln Leu Leu 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 Gly Pro Tyr
20 25 30

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

Ser Ala Ile Ser Gly Ser Gly Ala Ser Thr Trp His Ala Asp Ser Val
50 55 60

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

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

Ala Lys Asp Pro Gly Thr Asp Ser Thr Gly Tyr Tyr Tyr Ile Trp Arg
100 105 110

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

<210> 98
<211> 122
<212> PRT
<213> artificial sequence

<220>
<223> Antibody Sequence 98 ADI-27297 VH

<400> 98

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

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

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

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

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Ala Arg Asp His Asp Ile Ala Ala Ala Gly Arg Leu Ala Asp Tyr Trp
 100 105 110

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

<210> 99
 <211> 122
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 99 ADI-30272 VH

<400> 99

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 Glu Tyr
 20 25 30

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
 65 70 75 80

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

Ala Arg Asp His Asp Ile Ala Ala Ala Gly Arg Leu Ala Asp Tyr Trp
 100 105 110

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

<210> 100
 <211> 122

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 100 ADI-30278 VH

<400> 100

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 Glu Tyr
 20 25 30

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
 65 70 75 80

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

Ala Arg Asp His Asp Ile Arg Leu Ala Gly Arg Leu Ala Asp Tyr Trp
 100 105 110

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

<210> 101

<211> 123

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 101 ADI-27301 VH

<400> 101

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

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

<210> 102
 <211> 123
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 102 ADI-30306 VH

<400> 102

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

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

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

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

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

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

<210> 103
<211> 123
<212> PRT
<213> artificial sequence

<220>
<223> Antibody Sequence 103 ADI-30311 VH

<400> 103

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

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

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

Trp Ile Gly Ser Ile Tyr Tyr Ser Gly Ser Thr Trp Tyr Asn Pro Ser
50 55 60

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

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr

85

90

95

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

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

<210> 104
 <211> 107
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 104 ADI-27238, ADI-30263, ADI-30267, ADI-30268 VL

<400> 104

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

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

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

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

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

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

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

<210> 105
 <211> 107
 <212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 105 ADI-27243, ADI-30302 VL

<400> 105

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

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

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

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

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Phe Ala Phe Pro Tyr
85 90 95

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

<210> 106

<211> 107

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 106 ADI-30336 VL

<400> 106

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

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

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

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

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Phe Ala His Pro Tyr
85 90 95

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

<210> 107

<211> 112

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 107 ADI-27278, ADI-30293, ADI-30296 VL

<400> 107

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 Val Leu Phe Ser
20 25 30

Ser Asn Asn Lys Asn Tyr Leu Ala 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 Gln

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

<210> 108

<211> 108

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 108 ADI-27291, ADI-30283, ADI-30286, ADI-30288 VL

<400> 108

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

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

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

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

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
 65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Val Pro His Pro Pro
 85 90 95

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

<210> 109

<211> 107

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 109 ADI-27297, ADI-30272, ADI-30278 VL

<400> 109

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30

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

Ser Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Val Ile Leu Pro Ile
85 90 95

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

<210> 110

<211> 107

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 110 ADI-27301, ADI-30306, ADI-30311 VL

<400> 110

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

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

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

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

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Gly Ile Leu Pro Arg
85 90 95

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

<210> 111
<211> 448
<212> PRT
<213> artificial sequence

<220>
<223> Antibody Sequence 111 ADI-27238 HC

<400> 111

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

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

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

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

Ala Arg Ala Arg Tyr Pro Ser Ser Trp Pro Tyr Gly Met Asp Val Trp

100

105

110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
 115 120 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
 130 135 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
 145 150 155 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
 165 170 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
 180 185 190

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
 195 200 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
 210 215 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
 225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
 245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
 260 265 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
 275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val
 290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu

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305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
435 440 445

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<210> 112
<211> 448
<212> PRT
<213> artificial sequence
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<220>
<223> Antibody Sequence 112 ADI-30263 HC

$\langle 400 \rangle$ 112

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 Leu Ser Tyr
20 25 30

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

Gly Ile Ile Asp Pro Ser Gly Gly Arg Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

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

Ala Arg Ala Arg Tyr Pro Ser Ser Trp Pro Tyr Gly Thr Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
115 120 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
130 135 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145 150 155 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
165 170 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
180 185 190

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
195 200 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
210 215 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225 230 235 240

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Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
260 265 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
435 440 445

<210> 113
 <211> 448
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 113 ADI-30267 HC

<400> 113

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 Arg Ser Tyr
 20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

Gly Ile Ile Asp Pro Ser Gly Gly Arg Thr Ser Phe Ala Gln Lys Phe
 50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
 65 70 75 80

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

Ala Arg Ala Arg Tyr Pro Glu Ser Trp Pro Tyr Gly Met Asp Val Trp
 100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
 115 120 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
 130 135 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
 145 150 155 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro

165

170

175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
 180 185 190

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
 195 200 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
 210 215 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
 225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
 245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
 260 265 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
 275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val
 290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
 305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
 325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
 340 345 350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
 355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu

370

375

380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
 385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
 405 410 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
 420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
 435 440 445

<210> 114

<211> 448

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 114 ADI-30268 HC

<400> 114

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 Gly Ser Tyr
 20 25 30

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
 65 70 75 80

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

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Ala Arg Ala Arg Thr Pro Ser Ser Trp Pro Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
115 120 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
130 135 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145 150 155 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
165 170 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
180 185 190

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
195 200 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
210 215 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
260 265 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val
290 295 300

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Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
435 440 445

<210> 115
<211> 448
<212> PRT
<213> artificial sequence

<220>
<223> Antibody Sequence 115 ADI-27243 HC

<400> 115

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Ser

20

25

30

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

Trp Ile Gly Ser Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
 50 55 60

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

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
 85 90 95

Cys Ala Arg Asp Gly Leu Tyr His Thr Pro Glu Tyr Phe Gln His Trp
 100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
 115 120 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
 130 135 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
 145 150 155 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
 165 170 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
 180 185 190

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
 195 200 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
 210 215 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro

225		230		235		240
Ser	Val	Phe	Leu	Phe	Pro	Pro
			245			
				Lys	Pro	Lys
				250		
				Asp	Thr	Leu
						Met
						Ile
						255
Arg	Thr	Pro	Glu	Val	Thr	Cys
			260			
				Val	Val	Val
				265		
				Asp	Val	Ser
						Gln
						270
Pro	Glu	Val	Gln	Phe	Asn	Trp
			275			
				Tyr	Val	Asp
				280		
				Gly	Val	Glu
						285
						Val
						His
						Asn
Ala	Lys	Thr	Lys	Pro	Arg	Glu
			290			
				Glu	Gln	Phe
				295		
				Asn	Ser	Thr
						300
						Tyr
						Arg
						Val
Val	Ser	Val	Leu	Thr	Val	Leu
				310		
				His	Gln	Asp
						315
						Trp
						Leu
						Asn
						Gly
						Lys
						320
Tyr	Lys	Cys	Lys	Val	Ser	Asn
				325		
				Lys	Gly	Leu
						330
						Pro
						Ser
						Ser
						Ile
						Glu
						335
						Lys
Thr	Ile	Ser	Lys	Ala	Lys	Gly
				340		
				Gln	Pro	Arg
						345
						Glu
						Pro
						Gln
						Val
						Tyr
						350
						Thr
Leu	Pro	Pro	Ser	Gln	Glu	Glu
				355		
						Met
						360
						Thr
						Lys
						Asn
						Gln
						Val
						Ser
						Leu
						365
						Thr
Cys	Leu	Val	Lys	Gly	Phe	Tyr
				370		
						Pro
						375
						Ser
						Asp
						Ile
						Ala
						380
						Val
						Glu
						Trp
						Glu
Ser	Asn	Gly	Gln	Pro	Glu	Asn
				385		
						Asn
						390
						Tyr
						Lys
						Thr
						395
						Thr
						Pro
						Pro
						Val
						Leu
						400
Asp	Ser	Asp	Gly	Ser	Phe	Phe
				405		
						Leu
						Tyr
						Ser
						410
						Arg
						Leu
						Thr
						Val
						Asp
						415
						Lys
Ser	Arg	Trp	Gln	Glu	Gly	Asn
				420		
						Val
						Phe
						425
						Ser
						Cys
						Ser
						Val
						Met
						430
						His
						Glu
Ala	Leu	His	Asn	His	Tyr	Thr
						Gln
						Lys
						Ser
						Leu
						Ser
						Leu
						Ser
						Leu
						Gly

435

440

445

<210> 116
 <211> 448
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 116 ADI-30302 HC

<400> 116

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

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

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

Trp Ile Gly Ser Ile Tyr Arg Ser Gly Gly Thr Tyr Tyr Asn Pro Ser
 50 55 60

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

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
 85 90 95

Cys Ala Arg Asp Gly Leu Tyr His Thr Pro Glu Tyr Phe Gln His Trp
 100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
 115 120 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
 130 135 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
 145 150 155 160

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Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
165 170 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
180 185 190

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
195 200 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
210 215 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
260 265 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
355 360 365

509513181_1.txt

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
435 440 445

<210> 117
<211> 448
<212> PRT
<213> artificial sequence

<220>
<223> Antibody Sequence 117 ADI-30336 HC

<400> 117

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

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

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

Trp Ile Gly Ser Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
50 55 60

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

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr

Cys Ala Arg Asp Gly Leu Tyr His Thr Pro Glu Tyr Phe Gln His Trp
 100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
 115 120 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
 130 135 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
 145 150 155 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
 165 170 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
 180 185 190

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
 195 200 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
 210 215 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
 225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
 245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
 260 265 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
 275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val

290

295

300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
 305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
 325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
 340 345 350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
 355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
 370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
 385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
 405 410 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
 420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
 435 440 445

<210> 118

<211> 448

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 118 ADI-27278 HC

<400> 118

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

509513181_1.txt

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

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

Ser Tyr Ile Ser Gly Ser Ser Ser Thr Ile Tyr Tyr Ala Asp Ser 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 His Arg Ile Ala Asp Ser Pro Ser Arg Ala Phe Asp Ile Trp
100 105 110

Gly Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
115 120 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
130 135 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145 150 155 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
165 170 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
180 185 190

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
195 200 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
210 215 220

509513181_1.txt

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
260 265 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

509513181_1.txt

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
435 440 445

<210> 119
<211> 447
<212> PRT
<213> artificial sequence

<220>
<223> Antibody Sequence 119 ADI-30293 HC

<400> 119

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 Ser Tyr
20 25 30

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

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

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

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

Arg His Arg Ile Ala Asp Ser Pro Ser Arg Ala Phe Asp Ile Trp Gly
100 105 110

Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125

Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala
130 135 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val

145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190

Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His
195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly
210 215 220

Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
245 250 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro
260 265 270

Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val
290 295 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
340 345 350

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

355

360

365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
 370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
 385 390 395 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser
 405 410 415

Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
 420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
 435 440 445

<210> 120

<211> 447

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 120 ADI-30296 HC

<400> 120

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 Ile Gly Gly Tyr
 20 25 30

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

Ser Tyr Ile Ser Ser Ser Ser Thr Ile His Tyr Ala Asp Ser Val Lys
 50 55 60

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

509513181_1.txt

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

Arg His Arg Ile Gly Arg Ser Pro Ser Arg Ala Phe Asp Ile Trp Gly
100 105 110

Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125

Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala
130 135 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190

Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His
195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly
210 215 220

Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
245 250 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro
260 265 270

Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

509513181_1.txt

Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val
290 295 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
340 345 350

Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
435 440 445

<210> 121
<211> 450
<212> PRT
<213> artificial sequence

<220>
<223> Antibody Sequence 121 ADI-27291 HC

<400> 121

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

210

215

220

Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
 225 230 235 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
 245 250 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln
 260 265 270

Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
 275 280 285

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr
 290 295 300

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
 305 310 315 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
 325 330 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
 340 345 350

Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser
 355 360 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
 370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
 385 390 395 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val
 405 410 415

Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met

420

425

430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
 435 440 445

Leu Gly
 450

<210> 122
 <211> 450
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 122 ADI-30283 HC

<400> 122

Glu Val Gln Leu Leu 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 Pro Tyr
 20 25 30

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

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

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

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

Ala Lys Asp Pro Gly Thr Asp Ser Ser Gly Tyr Tyr Tyr Ile Trp Arg
 100 105 110

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

509513181_1.txt

Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu
130 135 140

Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
145 150 155 160

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
165 170 175

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
180 185 190

Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn
195 200 205

Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser
210 215 220

Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
225 230 235 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
245 250 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln
260 265 270

Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
275 280 285

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr
290 295 300

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305 310 315 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
325 330 335

509513181_1.txt

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
340 345 350

Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser
355 360 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val
405 410 415

Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445

Leu Gly
450

<210> 123
<211> 450
<212> PRT
<213> artificial sequence

<220>
<223> Antibody Sequence 123 ADI-30286 HC

<400> 123

Glu Val Gln Leu Leu 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 Gly Pro Tyr
20 25 30

Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

35

40

45

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

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

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

Ala Lys Asp Pro Gly Thr His Tyr Ser Gly Tyr Tyr Tyr Ile Trp Arg
 100 105 110

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

Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu
 130 135 140

Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
 145 150 155 160

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
 165 170 175

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
 180 185 190

Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn
 195 200 205

Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser
 210 215 220

Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
 225 230 235 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met

245

250

255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln
 260 265 270

Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
 275 280 285

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr
 290 295 300

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
 305 310 315 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
 325 330 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
 340 345 350

Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser
 355 360 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
 370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
 385 390 395 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val
 405 410 415

Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met
 420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
 435 440 445

Leu Gly

450

<210> 124
 <211> 450
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 124 ADI-30288 HC

<400> 124

Glu Val Gln Leu Leu 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 Gly Pro Tyr
 20 25 30

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

Ser Ala Ile Ser Gly Ser Gly Ala Ser Thr Trp His Ala Asp Ser Val
 50 55 60

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

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

Ala Lys Asp Pro Gly Thr Asp Ser Thr Gly Tyr Tyr Tyr Ile Trp Arg
 100 105 110

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

Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu
 130 135 140

Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
 145 150 155 160

509513181_1.txt

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
165 170 175

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
180 185 190

Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn
195 200 205

Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser
210 215 220

Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
225 230 235 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
245 250 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln
260 265 270

Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
275 280 285

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr
290 295 300

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305 310 315 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
325 330 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
340 345 350

Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser
355 360 365

509513181_1.txt

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val
405 410 415

Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445

Leu Gly
450

<210> 125
<211> 448
<212> PRT
<213> artificial sequence

<220>
<223> Antibody Sequence 125 ADI-27297 HC

<400> 125

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

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

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr

65		70		75		80
Met	Glu	Leu	Ser	Ser	Leu	Arg
			85			
				Glu	Asp	Thr
				90		
				Ala	Val	Tyr
						Tyr
						Cys
						95
Ala	Arg	Asp	His	Asp	Ile	Ala
			100			
				Ala	Ala	Ala
				105		
				Gly	Arg	Leu
						Ala
						Asp
						Tyr
						Trp
						110
Gly	Gln	Gly	Thr	Leu	Val	Thr
				Val	Ser	Ser
				120		
				Ala	Ser	Thr
						Lys
						Gly
						Pro
						125
Ser	Val	Phe	Pro	Leu	Ala	Pro
				Pro	Cys	Ser
				135		
				Arg	Ser	Thr
						Ser
						Glu
						Ser
						Thr
						140
Ala	Ala	Leu	Gly	Cys	Leu	Val
				Leu	Lys	Asp
				150		
				Tyr	Phe	Pro
						Glu
						Pro
						Val
						Thr
						160
Val	Ser	Trp	Asn	Ser	Gly	Ala
				Leu	Thr	Ser
				165		
				Gly	Val	His
						Thr
						Phe
						Pro
						175
Ala	Val	Leu	Gln	Ser	Ser	Gly
				Leu	Tyr	Ser
				180		
				Leu	Ser	Ser
						Val
						Val
						Thr
						190
Val	Pro	Ser	Ser	Ser	Leu	Gly
				Thr	Lys	Thr
				195		
				Tyr	Thr	Cys
						Asn
						Val
						Asp
						205
His	Lys	Pro	Ser	Asn	Thr	Lys
				Val	Asp	Lys
				210		
				Arg	Val	Glu
						Ser
						Lys
						Tyr
						220
Gly	Pro	Pro	Cys	Pro	Pro	Cys
				Pro	Ala	Pro
				225		
				Glu	Ala	Ala
				235		
				Gly	Gly	Pro
						240
Ser	Val	Phe	Leu	Phe	Pro	Pro
				Lys	Pro	Lys
				245		
				Asp	Thr	Leu
						Met
						Ile
						Ser
						255
Arg	Thr	Pro	Glu	Val	Thr	Cys
				Val	Val	Val
				260		
				Asp	Val	Ser
						Gln
						Glu
						Asp
						270
Pro	Glu	Val	Gln	Phe	Asn	Trp
				Tyr	Val	Asp
						Gly
						Val
						Glu
						Val
						His
						Asn

275

280

285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val
 290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
 305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
 325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
 340 345 350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
 355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
 370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
 385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
 405 410 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
 420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
 435 440 445

<210> 126

<211> 448

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 126 ADI-30272 HC

<400> 126

509513181_1.txt

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 Glu Tyr
20 25 30

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

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

Ala Arg Asp His Asp Ile Ala Ala Ala Gly Arg Leu Ala Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
115 120 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
130 135 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145 150 155 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
165 170 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
180 185 190

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
195 200 205

509513181_1.txt

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
210 215 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
260 265 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
405 410 415

509513181_1.txt

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
435 440 445

<210> 127
<211> 448
<212> PRT
<213> artificial sequence

<220>
<223> Antibody Sequence 127 ADI-30278 HC

<400> 127

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 Glu Tyr
20 25 30

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

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

Ala Arg Asp His Asp Ile Arg Leu Ala Gly Arg Leu Ala Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
115 120 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr

130

135

140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
 145 150 155 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
 165 170 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
 180 185 190

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
 195 200 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
 210 215 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
 225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
 245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
 260 265 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
 275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val
 290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
 305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
 325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr

340

345

350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
 355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
 370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
 385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
 405 410 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
 420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
 435 440 445

<210> 128

<211> 449

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 128 ADI-27301 HC

<400> 128

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

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

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

Trp Ile Gly Ser Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
 50 55 60

509513181_1.txt

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

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

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

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
115 120 125

Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser
130 135 140

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
145 150 155 160

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
165 170 175

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
180 185 190

Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val
195 200 205

Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys
210 215 220

Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu
260 265 270

509513181_1.txt

Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg
290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu
435 440 445

Gly

<210> 129

<211> 449

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 129 ADI-30306 HC

<400> 129

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

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

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

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

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

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

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

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
115 120 125

Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser
130 135 140

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
145 150 155 160

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
165 170 175

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val

180

185

190

Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val
 195 200 205

Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys
 210 215 220

Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
 225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
 245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu
 260 265 270

Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
 275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg
 290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
 305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu
 325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
 340 345 350

Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu
 355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
 370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu
435 440 445

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<210> 130
<211> 449
<212> PRT
<213> artificial sequence
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<220>
<223> Antibody Sequence 130 ADI-30311 HC

<400> 130

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

Trp Ile Gly Ser Ile Tyr Tyr Ser Gly Ser Thr Trp Tyr Asn Pro Ser
50 55 60

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

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

509513181_1.txt

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

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
115 120 125

Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser
130 135 140

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
145 150 155 160

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
165 170 175

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
180 185 190

Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val
195 200 205

Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys
210 215 220

Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu
260 265 270

Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg
290 295 300

509513181_1.txt

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu
435 440 445

Gly

<210> 131

<211> 441

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 131 Positive control antibody 10A7-IgG4 (Genentech)
HC

<400> 131

509513181_1.txt

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

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

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

Ala Phe Ile Arg Ser Gly Ser Gly Ile Val Phe Tyr Ala Asp Ala Val
 50 55 60

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

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

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

Thr Leu Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys
 115 120 125

Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys
 130 135 140

Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu
 145 150 155 160

Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu
 165 170 175

Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr
 180 185 190

Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val
 195 200 205

509513181_1.txt

Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro
 210 215 220

Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
 225 230 235 240

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
 245 250 255

Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
 260 265 270

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
 275 280 285

Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
 290 295 300

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
 305 310 315 320

Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
 325 330 335

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met
 340 345 350

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
 355 360 365

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
 370 375 380

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
 385 390 395 400

Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val
 405 410 415

509513181_1.txt

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
420 425 430

Lys Ser Leu Ser Leu Ser Leu Gly Lys
435 440

<210> 132
<211> 457
<212> PRT
<213> artificial sequence

<220>
<223> Antibody Sequence 132 Positive control antibody 22G2-IgG4(BMS)
HC

<400> 132

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

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

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

Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Asn Tyr Asn Pro Ser
50 55 60

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

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Arg Asp Tyr Tyr Val Ser Gly Asn Tyr Tyr Asn Val Asp Tyr
100 105 110

Tyr Phe Phe Gly Val Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val
115 120 125

Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys

130

135

140

Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys
 145 150 155 160

Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu
 165 170 175

Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu
 180 185 190

Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr
 195 200 205

Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val
 210 215 220

Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro
 225 230 235 240

Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
 245 250 255

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
 260 265 270

Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
 275 280 285

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
 290 295 300

Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
 305 310 315 320

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
 325 330 335

Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln

340

345

350

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met
 355 360 365

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
 370 375 380

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
 385 390 395 400

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
 405 410 415

Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val
 420 425 430

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
 435 440 445

Lys Ser Leu Ser Leu Ser Leu Gly Lys
 450 455

<210> 133
 <211> 446
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 133 Positive control antibody 31C6--IgG4(MSD)
 HC

<400> 133

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

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

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

509513181_1.txt

Gly Tyr Ile Asp Pro Tyr Asn Asp Gly Ala Lys Tyr Asn 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 Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Gly Pro Tyr Gly Trp Tyr Phe Asp Val Trp Gly Ala Gly
100 105 110

Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

509513181_1.txt

Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val
260 265 270

Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
435 440 445

<210> 134

<211> 446

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 134 Positive control antibody 1F4 HC

<400> 134

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

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

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

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

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

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

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

Thr Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
 115 120 125

Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
 130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
 145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
 165 170 175

509513181_1.txt

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
 180 185 190

Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro
 195 200 205

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro
 210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe
 225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
 245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val
 260 265 270

Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
 275 280 285

Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val
 290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
 305 310 315 320

Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser
 325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
 340 345 350

Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
 355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
 370 375 380

509513181_1.txt

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
435 440 445

<210> 135
<211> 467
<212> PRT
<213> artificial sequence

<220>
<223> Antibody Sequence 135 Negative control IgG1 HC

<400> 135

Met Gly Trp Ser Leu Ile Leu Leu Phe Leu Val Ala Val Ala Thr Arg
1 5 10 15

Val Leu Ser Glu Val Arg Leu Leu Glu Ser Gly Gly Gly Leu Val Gln
20 25 30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
35 40 45

Ser Asn Tyr Ala Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala
65 70 75 80

Asp Ser Val Lys Gly Arg Phe Thr Thr Ser Arg Asp Asp Ser Lys Asn
85 90 95

Ala Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
100 105 110

509513181_1.txt

Tyr Tyr Cys Ala Arg Gly Gly Pro Gly Trp Tyr Ala Ala Asp Val Trp
115 120 125

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
130 135 140

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
145 150 155 160

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
165 170 175

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
180 185 190

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
195 200 205

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
210 215 220

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
225 230 235 240

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
245 250 255

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
260 265 270

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
275 280 285

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
290 295 300

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
305 310 315 320

509513181_1.txt

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
325 330 335

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
340 345 350

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
355 360 365

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
370 375 380

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
385 390 395 400

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
405 410 415

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
420 425 430

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
435 440 445

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
450 455 460

Ser Pro Gly
465

<210> 136
<211> 465
<212> PRT
<213> artificial sequence

<220>
<223> Antibody Sequence 136 Negative control IgG4 HC

<400> 136

509513181_1.txt

Met Gly Trp Ser Leu Ile Leu Leu Phe Leu Val Ala Val Ala Thr Arg
 1 5 10 15

Val Leu Ser Glu Val Arg Leu Leu Glu Ser Gly Gly Gly Leu Val Gln
 20 25 30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
 35 40 45

Ser Asn Tyr Ala Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
 50 55 60

Glu Trp Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala
 65 70 75 80

Asp Ser Val Lys Gly Arg Phe Thr Thr Ser Arg Asp Asp Ser Lys Asn
 85 90 95

Ala Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
 100 105 110

Tyr Tyr Cys Ala Arg Gly Gly Pro Gly Trp Tyr Ala Ala Asp Val Trp
 115 120 125

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
 130 135 140

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
 145 150 155 160

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
 165 170 175

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
 180 185 190

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
 195 200 205

509513181_1.txt

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
 210 215 220

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
 225 230 235 240

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro
 245 250 255

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
 260 265 270

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
 275 280 285

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
 290 295 300

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val
 305 310 315 320

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
 325 330 335

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
 340 345 350

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
 355 360 365

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
 370 375 380

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
 385 390 395 400

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
 405 410 415

509513181_1.txt

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
420 425 430

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
435 440 445

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
450 455 460

Lys
465

<210> 137
<211> 214
<212> PRT
<213> artificial sequence

<220>
<223> Antibody Sequence 137 ADI-27238, ADI-30263, ADI-30267, ADI-30268 LC

<400> 137

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

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

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

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

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

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

509513181_1.txt

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 138
<211> 214
<212> PRT
<213> artificial sequence

<220>
<223> Antibody Sequence 138 ADI-27243, ADI-30302 LC

<400> 138

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

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

509513181_1.txt

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

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

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Phe Ala Phe Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 139
<211> 214
<212> PRT
<213> artificial sequence

<220>
<223> Antibody Sequence 139 ADI-30336 LC

<400> 139

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
 20 25 30

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

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

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

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Phe Ala His Pro Tyr
 85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
 100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
 115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
 130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
 145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
 165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
 180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser

195

200

205

Phe Asn Arg Gly Glu Cys
210

<210> 140

<211> 219

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 140 ADI-27278, ADI-30293, ADI-30296 LC

<400> 140

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 Val Leu Phe Ser
20 25 30

Ser Asn Asn Lys Asn Tyr Leu Ala 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 Gln
85 90 95

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

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

509513181_1.txt

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 141
<211> 215
<212> PRT
<213> artificial sequence

<220>
<223> Antibody Sequence 141 ADI-27291, ADI-30283, ADI-30286, ADI-30288 LC
<400> 141

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

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

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

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

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Val Pro His Pro Pro

Phe Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
 100 105 110

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
 115 120 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
 130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
 145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
 165 170 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
 180 185 190

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
 195 200 205

Ser Phe Asn Arg Gly Glu Cys
 210 215

<210> 142
 <211> 214
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 142 ADI-27297, ADI-30272, ADI-30278 LC

<400> 142

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
 20 25 30

509513181_1.txt

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

Ser Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Val Ile Leu Pro Ile
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 143

<211> 214

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 143 ADI-27301, ADI-30306, ADI-30311 LC

<400> 143

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

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

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

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

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Gly Ile Leu Pro Arg
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr

180

185

190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
 195 200 205

Phe Asn Arg Gly Glu Cys
 210

<210> 144
 <211> 220
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 144 Positive control antibody 10A7-IgG4 LC

<400> 144

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

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

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

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

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

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

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

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
 115 120 125

509513181_1.txt

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
130 135 140

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
145 150 155 160

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
165 170 175

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
180 185 190

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
195 200 205

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215 220

<210> 145

<211> 214

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 145 Positive control antibody 22G2-IgG4(BMS)
LC

<400> 145

Gly 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 Ala Ser Gln Asp Val Ile Asn Tyr
20 25 30

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

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

509513181_1.txt

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

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

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 146
<211> 214
<212> PRT
<213> artificial sequence

<220>
<223> Antibody Sequence 146 Positive control antibody 31C6-IgG4(MSD)
LC

<400> 146

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

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

<400> 147

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

509513181_1.txt

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 148
<211> 236
<212> PRT
<213> artificial sequence

<220>
<223> Antibody Sequence 148 Negative control IgG1 LC

<400> 148

Met Asp Phe Gln Val Gln Ile Ile Ser Phe Leu Leu Ile Ser Ala Ser
1 5 10 15

Val Ile Met Ser Arg Gly Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
35 40 45

Gln Ser Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys
50 55 60

Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln

100

105

110

Ala Asp Leu Pro Ala Phe Ala Phe Gly Gly Gly Thr Lys Val Glu Ile
 115 120 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
 130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
 145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
 165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
 180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
 195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
 210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
 225 230 235

<210> 149
 <211> 236
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 149 Negative control IgG4 LC

<400> 149

Met Asp Phe Gln Val Gln Ile Ile Ser Phe Leu Leu Ile Ser Ala Ser
 1 5 10 15

Val Ile Met Ser Arg Gly Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
 20 25 30

509513181_1.txt

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
35 40 45

Gln Ser Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys
50 55 60

Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
100 105 110

Ala Asp Leu Pro Ala Phe Ala Phe Gly Gly Gly Thr Lys Val Glu Ile
115 120 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

509513181_1.txt

<210> 150
 <211> 366
 <212> DNA
 <213> artificial sequence

<220>
 <223> Antibody Sequence 150 ADI-27238 VH DNA

<400> 150
 caggtgcagc tgggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaagggtt 60
 tcctgcaagg catctggata caccttcacc agctactata tgtcatgggt gcgacaggcc 120
 cctggacaag ggcttgagt gatgggaata atcaacccta gtggtggtag cacaagctac 180
 gcacagaagt tccagggcag agtcacatg accagggaca cgtccacgag cacagtctac 240
 atggagctga gcagcctgag atctgaggac acggcgggtgt actactgcgc aagggctaga 300
 tacccatcaa gctggccata cggaatggac gtatggggcc agggaacaac tgtcaccgtc 360
 tcctca 366

<210> 151
 <211> 366
 <212> DNA
 <213> artificial sequence

<220>
 <223> Antibody Sequence 151 ADI-30263 VH DNA

<400> 151
 caggtgcagc tgggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaagggtt 60
 tcctgcaagg catctggata cacattcctg agctactata tgaattgggt gcgacaggcc 120
 cctggacaag ggcttgagt gatgggaata atcgatccta gtggtggtag gacaagctac 180
 gcacagaagt tccagggcag agtcacatg accagggaca cgtccacgag cacagtctac 240
 atggagctga gcagcctgag atctgaggac acggcgggtgt actactgcgc aagggctaga 300
 tacccatcaa gctggccata cggaacggat gtatggggcc agggaacaac tgtcaccgtc 360
 tcctca 366

<210> 152
 <211> 366
 <212> DNA

<213> artificial sequence

<220>

<223> Antibody Sequence 152 ADI-30267 VH DNA

<400> 152

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caggtgcagc tgggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt    60
tcctgcaagg catctggata caccttcagg agctactata tgagttgggt gcgacaggcc    120
cctggacaag ggcttgagtg gatgggaata atcgatccta gtggtgggtc tacaagcttc    180
gcacaaaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac    240
atggagctga gcagcctgag atctgaggac acggcggtgt actactgcgc aagggctaga    300
taccagagt cttggccata cggaatggac gtatggggcc agggaacaac tgtcaccgtc    360
tcctca                                         366
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<210> 153

<211> 366

<212> DNA

<213> artificial sequence

<220>

<223> Antibody Sequence 153 ADI-30268 VH DNA

<400> 153

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caggtgcagc tgggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt    60
tcctgcaagg catctggata caccttcagg agctactata tggggtgggt gcgacaggcc    120
cctggacaag ggcttgagtg gatgggaata atcgacccta gtggtggtag gacaagttac    180
gcacggaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac    240
atggagctga gcagcctgag atctgaggac acggcggtgt actactgcgc aagggctcgt    300
acgccatcaa gctggccata cggaatggac gtatggggcc agggaacaac tgtcaccgtc    360
tcctca                                         366
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<210> 154

<211> 366

<212> DNA

<213> artificial sequence

<220>

<223> Antibody Sequence 154 ADI-27243 VH DNA

<400> 154

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cagctgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc    60
acctgcactg tctctggtgg ctccatcagc agtagtcgct actactgggg ctggatccgc    120
cagccccag ggaaggggct ggagtggatt gggagtatct attatagtgg gagcacctac    180
tacaacccgt ccctcaagag tcgagtcacc atatccgtag acacgtccaa gaaccagttc    240
tccctgaagc tgagttctgt gaccgccgca gacacggcgg tgtactactg cgccagagat    300
gggttgtagc acaccccaga atacttccaa cactggggac aggttacatt ggtcaccgtc    360
tcctca                                         366
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<210> 155

<211> 366

<212> DNA

<213> artificial sequence

<220>

<223> Antibody Sequence 155 ADI-30302 VH DNA

<400> 155

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cagctgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc    60
acctgcactg tctctggtgg ctccatcggg agtagtcagt actactgggg ctggatccgc    120
cagccccag ggaaggggct ggagtggatt gggagtatct atcgtagtgg ggggacctac    180
tacaacccgt ccctcaagag tcgagtcacc atatccgtag acacgtccaa gaaccagttc    240
tccctgaagc tgagttctgt gaccgccgca gacacggcgg tgtactactg cgccagagat    300
gggttgtagc acaccccaga atacttccaa cactggggac aggttacatt ggtcaccgtc    360
tcctca                                         366
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<210> 156

<211> 366

<212> DNA

<213> artificial sequence

<220>

<223> Antibody Sequence 156 ADI-30336 VH DNA

<400> 156

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cagctgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc    60
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509513181_1.txt

acctgcactg tctctgggtg ctccatcagc agtagtcgct actactgggg ctggatccgc	120
cagccccag ggaaggggct ggagtggatt gggagtatct attatagtgg gagcacctac	180
tacaacccgt ccctcaagag tcgagtcacc atatccgtag acacgtccaa gaaccagttc	240
tccctgaagc tgagttctgt gaccgccgca gacacggcgg tgtactactg cgccagagat	300
gggttgtacc acaccccaga atacttccaa cactggggac aggttacatt ggtcaccgtc	360
tcctca	366

<210> 157
 <211> 366
 <212> DNA
 <213> artificial sequence

<220>
 <223> Antibody Sequence 157 ADI-27278 VH DNA

<400> 157	
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tcctgtgcag cctctggatt caccttcagt agctatagca tgaactgggt ccgccaggct	120
ccaggaagg ggctggagtg ggtttcatac attagtggaa gtagtagtac catatactac	180
gcagactctg tgaagggccg attcaccatc tccagagaca atgccaagaa ctactgtat	240
ctgcaaatga acagcctgag agccgaggac acggcggtgt actactgcgc cagacaccgc	300
atagcagact caccaagcag agccttcgat atatggggtc aggtacaat ggtcaccgtc	360
tcctca	366

<210> 158
 <211> 363
 <212> DNA
 <213> artificial sequence

<220>
 <223> Antibody Sequence 158 ADI-30293 VH DNA

<400> 158	
gaggtgcagc tgggtggagtc tgggggaggc ttggtacagc ctggggggtc cctgagactc	60
tcctgtgcag cctctggatt caccttcagt agctatagca tgaactgggt ccgccaggct	120

509513181_1.txt

ccaggggaagg gactggagtg ggtttcatac attagtagta gtgggacat aaattacgca 180
gactctgtga agggccgatt caccatctcc agagacaatg ccaagaactc actgtatctg 240
caaatgaaca gcctgagagc cgaggacacg gcggtgtact actgcgccag acaccgcata 300
gcagactcac caagcagagc cttcgatata tggggtcagg gtacaatggg caccgtctcc 360
tca 363

<210> 159
<211> 363
<212> DNA
<213> artificial sequence

<220>
<223> Antibody Sequence 159 ADI-30296 VH DNA

<400> 159
gaggtgcagc tggtggagtc tgggggaggc ttggtacagc ctgggggggtc cctgagactc 60
tcctgtgcag cctctggatt caccatcggg ggttatagca tgaactgggt ccgccaggct 120
ccaggggaagg ggctggagtg ggtttcatac attagtagta gtagtaccat acattacgca 180
gactctgtga agggccgatt caccatctcc agagacaatg ccaagaactc actgtatctg 240
caaatgaaca gcctgagagc tgaggacacg gcggtgtact actgcgccag acaccgcata 300
gggcgttcac caagcagagc cttcgatata tggggtcagg gtacaatggg caccgtctcc 360
tca 363

<210> 160
<211> 372
<212> DNA
<213> artificial sequence

<220>
<223> Antibody Sequence 160 ADI-27291 VH DNA

<400> 160
gaggtgcagc tggtggagtc tgggggaggc ttggtacagc ctgggggggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttagc agctatgcc a tgagctgggt ccgccaggct 120
ccaggggaagg ggctggagtg ggtctcagct attagtggta gtggtggtag cacatactac 180
gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cagctgttat 240

509513181_1.txt

ctgcaaatga acagcctgag agccgaggac acggcggtgt actactgcgc caaggacccc 300
ggaacagaca gcagcggcta ctactacata tggcgatact ggggacaggg tacattggtc 360
accgtctcct ca 372

<210> 161
<211> 372
<212> DNA
<213> artificial sequence

<220>
<223> Antibody Sequence 161 ADI-30283 VH DNA

<400> 161
gaggtgcagc tggtggagtc tgggggaggc ttggtacagc ctgggggggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttagc ccgtatggga tgagctgggt ccgccaggct 120
ccagggaagg ggctggagt ggtctcaagt attagtggaa gtggtggtag gacatactac 180
gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggcggtgt actactgcgc caaggacccc 300
ggaacagaca gcagcggcta ctactacata tggcgatact ggggacaggg tacattggtc 360
accgtctcct ca 372

<210> 162
<211> 372
<212> DNA
<213> artificial sequence

<220>
<223> Antibody Sequence 162 ADI-30286 VH DNA

<400> 162
gaggtgcagc tggtggagtc tgggggaggc ttggtacagc ctgggggggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttggc ccgtatggta tgagctgggt ccgccaggct 120
ccagggaagg ggctggagt ggtctcagct attagtggaa gtggtgagc cacatggtac 180
gcagactccg tgaagggccg gttcaccatc tccagagaca actccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggcggtgt actactgcgc caaggacccc 300
ggaacacatt atagcggcta ctactacata tggcgatact ggggacaggg tacattggtc 360

accgtctcct ca 372

<210> 163
 <211> 372
 <212> DNA
 <213> artificial sequence

<220>
 <223> Antibody Sequence 163 ADI-30288 VH DNA

<400> 163
 gaggtgcagc tgttgagtc tgggggaggc ttggtacagc ctggggggtc cctgagactc 60
 tcctgtgcag cctctggatt cacctttggc ccgtatggta tgagctgggt ccgccaggct 120
 ccagggaagg ggctggagtg ggtctcagct attagtggaa gtggtgagc cacatggcac 180
 gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240
 ctgcaaatga acagcctgag agccgaggac acggcggtgt actactgcgc caaggacccc 300
 ggaacagaca gcactgggta ctactacata tggcgatact ggggacaggg tacattggtc 360
 accgtctcct ca 372

<210> 164
 <211> 366
 <212> DNA
 <213> artificial sequence

<220>
 <223> Antibody Sequence 164 ADI-27297 VH DNA

<400> 164
 caggtgcagc tgggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60
 tcctgcaagg catctggata caccttcacc agctactata tgcactgggt gcgacaggcc 120
 cctggacaag ggcttgagtg gatgggaata atcaacccta gtggtggtag cacaagctac 180
 gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240
 atggagctga gcagcctgag atctgaggac acggcggtgt actactgcgc aagagaccac 300
 gacatagcag cagcaggaag attggctgat tactggggac aggggtacatt ggtcaccgtc 360
 tcctca 366

509513181_1.txt

<210> 165
<211> 366
<212> DNA
<213> artificial sequence

<220>
<223> Antibody Sequence 165 ADI-30272 VH DNA

<400> 165
caggtgcagc tgggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaagggtt 60
tcctgcaagg catctggata caccttcacg gagtactata tgcactgggt gcgacaggcc 120
cctggacaag ggcttgagt gatgggaata atctcgcta gtgcgggtag cacaagctac 180
gcacagaagt tccagggcag agtcacatg accagggaca cgtccacgag cacagtctac 240
atggagctga gcagcctgag atctgaggac acggcggtgt actactgcgc aagagaccac 300
gacatagcag cagcaggaag attggctgat tactggggac agggtagatt ggtagcagtc 360
tcctca 366

<210> 166
<211> 366
<212> DNA
<213> artificial sequence

<220>
<223> Antibody Sequence 166 ADI-30278 VH DNA

<400> 166
caggtgcagc tgggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaagggtt 60
tcctgcaagg catctggata caccttcacg gagtactata tgcactgggt gcgacaggcc 120
cctggacaag ggcttgagt gatgggaata atctcgcta gtgcgggtag cacaagctac 180
gcacagaagt tccagggcag agtcacatg accagggaca cgtccacgag cacagtctac 240
atggagctga gcagcctgag atctgaggac acggcggtgt actactgcgc aagagaccac 300
gacatagcag cagcaggaag attggctgat tactggggac agggtagatt ggtagcagtc 360
tcctca 366

<210> 167
<211> 369
<212> DNA
<213> artificial sequence

509513181_1.txt

<220>

<223> Antibody Sequence 167 ADI-27301 VH DNA

<400> 167

cagctgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc	60
acctgcactg tctctggtgg ctccatcagc agtagtagtt actactgggg ctggatccgc	120
cagccccag ggaaggggct ggagtggatt gggagtatct attatagtgg gagcacctac	180
tacaaccgt ccctcaagag tcgagtcacc atatccgtag acacgtcaa gaaccagttc	240
tccctgaagc tgagttctgt gaccgccgca gacacggcgg tgtactactg cgccagagaa	300
gccggacgcg gcaccactgg tctcttggtc gactactggg gacagggtag attggtcacc	360
gtctcctca	369

<210> 168

<211> 369

<212> DNA

<213> artificial sequence

<220>

<223> Antibody Sequence 168 ADI-30306 VH DNA

<400> 168

cagctgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc	60
acctgcactg tctctggtgg ctccatcagc agtagtcttt actactgggg ctggatccgc	120
cagccccag ggaaggggct ggagtggatt ggggtctatct attatagtgg gagcaccttt	180
tacaaccgt ccttcaagag tcgagtcacc atatccgtag acacgtcaa gaaccagttc	240
tccctgaagc tgagttctgt gaccgccgca gacacggcgg tgtactactg cgccagagaa	300
gccggacgcg gcaccactgg tctcttggtc gactactggg gacagggtag attggtcacc	360
gtctcctca	369

<210> 169

<211> 369

<212> DNA

<213> artificial sequence

<220>

<223> Antibody Sequence 169 ADI-30311 VH DNA

509513181_1.txt

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<400> 169
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acctgcactg tctctggtgg ctccatcgcg agtagtgttt actactgggg ctggatccgc    120
cagccccag ggaaggggct ggagtggatt gggagtatct attatagtgg gagcacctgg    180
tacaacccgt ccctcaagag tcgagtcacc atatccgtag acacgtccaa gaaccagttc    240
tccctgaagc tgagttctgt gaccgccgca gacacggcgg tgtactactg cgccagagaa    300
gccggacgca ctgggactgg tctcttgttc gactactggg gacagggtac attggtcacc    360
gtctcctca                                                                    369
```

```
<210> 170
<211> 321
<212> DNA
<213> artificial sequence
```

```
<220>
<223> Antibody Sequence 170 ADI-27238, ADI-30263, ADI-30267, ADI-30268 VL DNA
```

```
<400> 170
gacatccaga tgaccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc    60
atcacttgcc gggcaagtca gagcattaac agctatttaa attggtatca gcagaaacca    120
gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca    180
aggttcagtg gcagtggatc tgggacagat ttactctca ccatcagcag tctgcaacct    240
gaagattttg caacttacta ctgtcagcaa agcctcctca ctcctttcac ttttggcgga    300
gggaccaagg ttgagatcaa a                                                                    321
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```
<210> 171
<211> 321
<212> DNA
<213> artificial sequence
```

```
<220>
<223> Antibody Sequence 171 ADI-27243, ADI-30302 VL DNA
```

```
<400> 171
gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc    60
ctctcctgca gggccagtca gagtgttagc agctacttag cctggtacca acagaaacct    120
ggccaggctc ccaggctcct catctatgat gcatccaaca gggccactgg catcccagcc    180
```

509513181_1.txt

aggttcagtgc gcagtgggtc tgggacagac ttcactctca ccatcagcag cctagagcct 240
gaagattttg cagtttatta ctgtcagcag agattcgccct tcccttacac ttttggcgga 300
gggaccaagg ttgagatcaa a 321

<210> 172
<211> 321
<212> DNA
<213> artificial sequence

<220>
<223> Antibody Sequence 172 ADI-30336 VL DNA

<400> 172
gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60
ctctcctgca gggccagtca gagggttagc agctacttag cctggtacca acagaaacct 120
ggccaggctc ccaggctcct catctatgat gcatccaaca gggccactgg catcccagcc 180
aggttcagtgc gcagtgggtc tgggacagac ttcactctca ccatcagcag cctagagcct 240
gaagattttg cagtttatta ctgtcagcag agattcgccc atccttacac ttttggcgga 300
gggaccaagg ttgagatcaa a 321

<210> 173
<211> 336
<212> DNA
<213> artificial sequence

<220>
<223> Antibody Sequence 173 ADI-27278, ADI-30293, ADI-30296 VL DNA

<400> 173
gacatcgtga tgaccagtc tccagactcc ctggctgtgt ctctgggcga gagggccacc 60
atcaactgca agtccagcca gagggtttta ttcagctcca acaataagaa ctacttagct 120
tggtaccagc agaaaccagg acagcctcct aagctgctca tttactgggc atctaccgg 180
gaatccggggg tccctgaccg attcagtggc agcgggtctg ggacagattt cactctcacc 240
atcagcagcc tgcaggctga agatgtggca gtttattact gtcagcagtc ctacttcttc 300
cctacttttg gcggaggag caaggttgag atcaaa 336

<210> 174
 <211> 324
 <212> DNA
 <213> artificial sequence

<220>

<223> Antibody Sequence 174 ADI-27291, ADI-30283, ADI-30286, ADI-30288 VL DNA

<400> 174
 gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60
 ctctcctgca gggccagtca gagtgttagc agcaacttag cctggtacca gcagaaacct 120
 ggccaggctc ccaggctcct catctatagc gcatccacca gggccactgg tatcccagcc 180
 aggttcagtg gcagtgggtc tgggacagag ttactctca ccatcagcag cctgcagtct 240
 gaagattttg cagtttatta ctgtcagcag tacgtcccc accctccttt cacttttggc 300
 ggagggacca aggttgagat caaa 324

<210> 175
 <211> 321
 <212> DNA
 <213> artificial sequence

<220>

<223> Antibody Sequence 175 ADI-27297, ADI-30272, ADI-30278 VL DNA

<400> 175
 gacatccaga tgaccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc 60
 atcacttgtc gggcgagtca ggggtattagc agctggtttag cctggtatca gcagaaacca 120
 gggaaagccc ctaagctcct gatctccgct gcatccagtt tgcaaagtgg ggtcccatca 180
 aggttcagcg gcagtggatc tgggacagat ttactctca ccatcagcag cctgcagcct 240
 gaagattttg caacttatta ctgtcagcag gcagtcatcc tccctatcac ttttggcgga 300
 gggaaccaagg ttgagatcaa a 321

<210> 176
 <211> 321
 <212> DNA
 <213> artificial sequence

<220>

<223> Antibody Sequence 176 ADI-27301, ADI-30306, ADI-30311 VL DNA

<400> 176

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gacatccaga tgaccagtc tccttcacc ctgtctgcat ctgtaggaga cagagtcacc      60
atcacttgcc gggccagtca gagtattagt agctggttgg cctggtatca gcagaaacca    120
gggaaagccc ctaagctcct gatctataaa gcctccagtt tggaaagtgg ggtcccatca    180
aggttcagcg gcagtggatc tgggacagaa ttcactctca ccatcagcag cctgcagcct    240
gatgattttg caacttatta ctgccagcag tacggcatcc tccctaggac ttttggcgga    300
gggaccaagg ttgagatcaa a                                              321
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<210> 177

<211> 327

<212> PRT

<213> artificial sequence

<220>

<223> Antibody 177 Heavy chain constant region (IgG4_PAA)

<220>

<221> misc_feature

<222> (327)..(327)

<223> Xaa may be any natural amino acid, and preferably Xaa is lysine or is deleted

<400> 177

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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1           5           10          15
```

```
Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
          20          25          30
```

```
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
          35          40          45
```

```
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
          50          55          60
```

```
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65          70          75          80
```

509513181_1.txt

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
100 105 110

Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
115 120 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
130 135 140

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145 150 155 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
165 170 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
180 185 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
195 200 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
210 215 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225 230 235 240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
245 250 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
260 265 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
275 280 285

509513181_1.txt

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
290 295 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305 310 315 320

Leu Ser Leu Ser Leu Gly Xaa
325

<210> 178
<211> 10
<212> PRT
<213> artificial sequence

<220>
<223> Antibody Sequence 178 ADI-27238 HCDR1-AbM

<400> 178

Gly Tyr Thr Phe Thr Ser Tyr Tyr Met Ser
1 5 10

<210> 179
<211> 10
<212> PRT
<213> artificial sequence

<220>
<223> Antibody Sequence 179 ADI-30263 HCDR1-AbM

<400> 179

Gly Tyr Thr Phe Leu Ser Tyr Tyr Met Asn
1 5 10

<210> 180
<211> 10
<212> PRT
<213> artificial sequence

<220>
<223> Antibody Sequence 180 ADI-30267 HCDR1-AbM

<400> 180

Gly Tyr Thr Phe Arg Ser Tyr Tyr Met Ser

1

5

10

<210> 181
<211> 10
<212> PRT
<213> artificial sequence

<220>
<223> Antibody Sequence 181 ADI-30268 HCDR1-AbM

<400> 181

Gly Tyr Thr Phe Gly Ser Tyr Tyr Met Gly
1 5 10

<210> 182
<211> 13
<212> PRT
<213> artificial sequence

<220>
<223> Antibody Sequence 182 ADI-27238 HCDR3-Kabat

<400> 182

Ala Arg Tyr Pro Ser Ser Trp Pro Tyr Gly Met Asp Val
1 5 10

<210> 183
<211> 13
<212> PRT
<213> artificial sequence

<220>
<223> Antibody Sequence 183 ADI-30263 HCDR3-Kabat

<400> 183

Ala Arg Tyr Pro Ser Ser Trp Pro Tyr Gly Thr Asp Val
1 5 10

<210> 184
<211> 13
<212> PRT
<213> artificial sequence

<220>
<223> Antibody Sequence 184 ADI-30267 HCDR3-Kabat

<400> 184

Ala Arg Tyr Pro Glu Ser Trp Pro Tyr Gly Met Asp Val
1 5 10

<210> 185

<211> 13

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 185 ADI-30268 HCDR3-Kabat

<400> 185

Ala Arg Thr Pro Ser Ser Trp Pro Tyr Gly Met Asp Val
1 5 10

<210> 186

<211> 12

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 186 ADI-27243, ADI-30336 HCDR1-AbM

<400> 186

Gly Gly Ser Ile Ser Ser Ser Arg Tyr Tyr Trp Gly
1 5 10

<210> 187

<211> 12

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 187 ADI-30302 HCDR1-AbM

<400> 187

Gly Gly Ser Ile Gly Ser Ser Gln Tyr Tyr Trp Gly
1 5 10

<210> 188

<211> 12

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 188 ADI-27243, ADI-30302, ADI-30336 HCDR3-Kabat

<400> 188

Asp	Gly	Leu	Tyr	His	Thr	Pro	Glu	Tyr	Phe	Gln	His
1				5					10		

<210> 189

<211> 10

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 189 ADI-27278, ADI-30293 HCDR1-AbM

<400> 189

Gly	Phe	Thr	Phe	Ser	Ser	Tyr	Ser	Met	Asn
1				5					10

<210> 190

<211> 10

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 190 ADI-30296 HCDR1-AbM

<400> 190

Gly	Phe	Thr	Ile	Gly	Gly	Tyr	Ser	Met	Asn
1				5					10

<210> 191

<211> 13

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 191 ADI-27278, ADI-30293 HCDR3-Kabat

<400> 191

His	Arg	Ile	Ala	Asp	Ser	Pro	Ser	Arg	Ala	Phe	Asp	Ile
1				5					10			

<210> 192
 <211> 13
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 192 ADI-30296 HCDR3-Kabat

<400> 192

His	Arg	Ile	Gly	Arg	Ser	Pro	Ser	Arg	Ala	Phe	Asp	Ile
1				5					10			

<210> 193
 <211> 10
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 193 ADI-27291 HCDR1-AbM

<400> 193

Gly	Phe	Thr	Phe	Ser	Ser	Tyr	Ala	Met	Ser
1				5				10	

<210> 194
 <211> 10
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 194 ADI-30283 HCDR1-AbM

<400> 194

Gly	Phe	Thr	Phe	Ser	Pro	Tyr	Gly	Met	Ser
1				5				10	

<210> 195
 <211> 10
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 195 ADI-30286, ADI-30288 HCDR1-AbM

<400> 195

Gly Phe Thr Phe Gly Pro Tyr Gly Met Ser
1 5 10

<210> 196
<211> 15
<212> PRT
<213> artificial sequence

<220>
<223> Antibody Sequence 196 ADI-27291, ADI-30283 HCDR3-Kabat

<400> 196

Asp Pro Gly Thr Asp Ser Ser Gly Tyr Tyr Tyr Ile Trp Arg Tyr
1 5 10 15

<210> 197
<211> 15
<212> PRT
<213> artificial sequence

<220>
<223> Antibody Sequence 197 ADI-30286 HCDR3-Kabat

<400> 197

Asp Pro Gly Thr His Tyr Ser Gly Tyr Tyr Tyr Ile Trp Arg Tyr
1 5 10 15

<210> 198
<211> 15
<212> PRT
<213> artificial sequence

<220>
<223> Antibody Sequence 198 ADI-30288 HCDR3-Kabat

<400> 198

Asp Pro Gly Thr Asp Ser Thr Gly Tyr Tyr Tyr Ile Trp Arg Tyr
1 5 10 15

<210> 199
<211> 10
<212> PRT
<213> artificial sequence

<220>

<223> Antibody Sequence 199 ADI-27297 HCDR1-AbM

<400> 199

Gly	Tyr	Thr	Phe	Thr	Ser	Tyr	Tyr	Met	His
1				5					10

<210> 200

<211> 10

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 200 ADI-30272, ADI-30278 HCDR1-AbM

<400> 200

Gly	Tyr	Thr	Phe	Thr	Glu	Tyr	Tyr	Met	His
1				5					10

<210> 201

<211> 13

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 201 ADI-27297, ADI-30272 HCDR3-Kabat

<400> 201

Asp	His	Asp	Ile	Ala	Ala	Ala	Gly	Arg	Leu	Ala	Asp	Tyr
1				5						10		

<210> 202

<211> 13

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 202 ADI-30278 HCDR3-Kabat

<400> 202

Asp	His	Asp	Ile	Arg	Leu	Ala	Gly	Arg	Leu	Ala	Asp	Tyr
1				5						10		

<210> 203

<211> 12
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 203 ADI-27301 HCDR1-AbM
 <400> 203

Gly Gly Ser Ile Ser Ser Ser Ser Tyr Tyr Trp Gly
 1 5 10

<210> 204
 <211> 12
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 204 ADI-30306 HCDR1-AbM
 <400> 204

Gly Gly Ser Ile Ser Ser Ser Leu Tyr Tyr Trp Gly
 1 5 10

<210> 205
 <211> 12
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 205 ADI-30311 HCDR1-AbM
 <400> 205

Gly Gly Ser Ile Ala Ser Ser Val Tyr Tyr Trp Gly
 1 5 10

<210> 206
 <211> 13
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 206 ADI-27301, ADI-30306 HCDR3-Kabat
 <400> 206

Glu Ala Gly Arg Gly Thr Thr Gly Leu Leu Phe Asp Tyr

1

5

10

<210> 207
 <211> 13
 <212> PRT
 <213> artificial sequence

<220>
 <223> Antibody Sequence 207 ADI-30311 HCDR3-Kabat

<400> 207

Glu Ala Gly Arg Thr Gly Thr Gly Leu Leu Phe Asp Tyr
 1 5 10

<210> 208
 <211> 244
 <212> PRT
 <213> artificial sequence

<220>
 <223> Sequence 208 Human TIGIT sequence

<400> 208

Met Arg Trp Cys Leu Leu Leu Ile Trp Ala Gln Gly Leu Arg Gln Ala
 1 5 10 15

Pro Leu Ala Ser Gly Met Met Thr Gly Thr Ile Glu Thr Thr Gly Asn
 20 25 30

Ile Ser Ala Glu Lys Gly Gly Ser Ile Ile Leu Gln Cys His Leu Ser
 35 40 45

Ser Thr Thr Ala Gln Val Thr Gln Val Asn Trp Glu Gln Gln Asp Gln
 50 55 60

Leu Leu Ala Ile Cys Asn Ala Asp Leu Gly Trp His Ile Ser Pro Ser
 65 70 75 80

Phe Lys Asp Arg Val Ala Pro Gly Pro Gly Leu Gly Leu Thr Leu Gln
 85 90 95

Ser Leu Thr Val Asn Asp Thr Gly Glu Tyr Phe Cys Ile Tyr His Thr

100

105

110

Tyr Pro Asp Gly Thr Tyr Thr Gly Arg Ile Phe Leu Glu Val Leu Glu
 115 120 125

Ser Ser Val Ala Glu His Gly Ala Arg Phe Gln Ile Pro Leu Leu Gly
 130 135 140

Ala Met Ala Ala Thr Leu Val Val Ile Cys Thr Ala Val Ile Val Val
 145 150 155 160

Val Ala Leu Thr Arg Lys Lys Lys Ala Leu Arg Ile His Ser Val Glu
 165 170 175

Gly Asp Leu Arg Arg Lys Ser Ala Gly Gln Glu Glu Trp Ser Pro Ser
 180 185 190

Ala Pro Ser Pro Pro Gly Ser Cys Val Gln Ala Glu Ala Ala Pro Ala
 195 200 205

Gly Leu Cys Gly Glu Gln Arg Gly Glu Asp Cys Ala Glu Leu His Asp
 210 215 220

Tyr Phe Asn Val Leu Ser Tyr Arg Ser Leu Gly Asn Cys Ser Phe Phe
 225 230 235 240

Thr Glu Thr Gly

<210> 209

<211> 107

<212> PRT

<213> artificial sequence

<220>

<223> Antibody Sequence 209 Light chain constant region (? light chain)

<400> 209

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
 1 5 10 15

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

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
 35 40 45

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
 50 55 60

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

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
 85 90 95

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
 100 105