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(xxi) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:280, (b) a LCDR2 of SEQ ID NO:281, (c) a LCDR3 of SEQ ID NO:282; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:283, (e) a HCDR2 of SEQ ID NO:284, and (f) a HCDR3 of SEQ ID NO:285;

(xxii) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:294, (b) a LCDR2 of SEQ ID NO:295, (c) a LCDR3 of SEQ ID NO:296; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:297, (e) a HCDR2 of SEQ ID NO:298, and (f) a HCDR3 of SEQ ID NO:299; or

(xxiii) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:322, (b) a LCDR2 of SEQ ID NO:323, (c) a LCDR3 of SEQ ID NO:324; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:325, (e) a HCDR2 of SEQ ID NO:326, and (f) a HCDR3 of SEQ ID NO:327.

[0008] The combination, wherein in said antibody drug conjugate said antibody or antigen binding fragment thereof comprises:

- (i) a heavy chain variable region (vH) that comprises SEQ ID NO: 230, and a light chain variable region (vL) that comprises SEQ ID NO:231;
- (ii) a heavy chain variable region (vH) that comprises SEQ ID NO: 216, and a light chain variable region (vL) that comprises SEQ ID NO:217;
- (iii) a heavy chain variable region (vH) that comprises SEQ ID NO: 272, and a light chain variable region (vL) that comprises SEQ ID NO:273;
- (iv) a heavy chain variable region (vH) that comprises SEQ ID NO:314, and a light chain variable region (vL) that comprises SEQ ID NO:315;
- (v) a heavy chain variable region (vH) that comprises SEQ ID NO:20, and a light chain variable region (vL) that comprises SEQ ID NO:21;
- (vi) a heavy chain variable region (vH) that comprises SEQ ID NO: 34, and a light chain variable region (vL) that comprises SEQ ID NO:35;
- (vii) a heavy chain variable region (vH) that comprises SEQ ID NO:48, and a light chain variable region (vL) that comprises SEQ ID NO:49;
- (viii) a heavy chain variable region (vH) that comprises SEQ ID NO:62, and a light chain variable region (vL) that comprises SEQ ID NO:63;

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- (ix) a heavy chain variable region (vH) that comprises SEQ ID NO:76, and a light chain variable region (vL) that comprises SEQ ID NO:77;
- (x) a heavy chain variable region (vH) that comprises SEQ ID NO:90, and a light chain variable region (vL) that comprises SEQ ID NO:91;
- (xi) a heavy chain variable region (vH) that comprises SEQ ID NO:104, and a light chain variable region (vL) that comprises SEQ ID NO:105;
- (xii) a heavy chain variable region (vH) that comprises SEQ ID NO: 118, and a light chain variable region (vL) that comprises SEQ ID NO:119;
- (xiii) a heavy chain variable region (vH) that comprises SEQ ID NO: 132, and a light chain variable region (vL) that comprises SEQ ID NO:133;
- (xiv) a heavy chain variable region (vH) that comprises SEQ ID NO: 146, and a light chain variable region (vL) that comprises SEQ ID NO:147;
- (xv) a heavy chain variable region (vH) that comprises SEQ ID NO:160, and a light chain variable region (vL) that comprises SEQ ID NO:161;
- (xvi) a heavy chain variable region (vH) that comprises SEQ ID NO: 174, and a light chain variable region (vL) that comprises SEQ ID NO:175;
- (xvii) a heavy chain variable region (vH) that comprises SEQ ID NO: 188, and a light chain variable region (vL) that comprises SEQ ID NO:189;
- (xviii) a heavy chain variable region (vH) that comprises SEQ ID NO: 202, and a light chain variable region (vL) that comprises SEQ ID NO:203;
- (xix) a heavy chain variable region (vH) that comprises SEQ ID NO: 244, and a light chain variable region (vL) that comprises SEQ ID NO:245;
- (xx) a heavy chain variable region (vH) that comprises SEQ ID NO:258, and a light chain variable region (vL) that comprises SEQ ID NO:259;
- (xxi) a heavy chain variable region (vH) that comprises SEQ ID NO:286, and a light chain variable region (vL) that comprises SEQ ID NO:287;
- (xxii) a heavy chain variable region (vH) that comprises SEQ ID NO:300, and a light chain variable region (vL) that comprises SEQ ID NO:301; or

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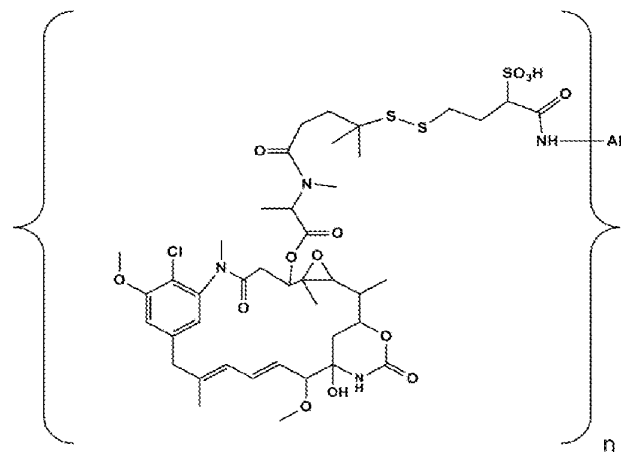
(xxiii) a heavy chain variable region (vH) that comprises SEQ ID NO:328, and a light chain variable region (vL) that comprises SEQ ID NO:329.

[0009] The combination, wherein in said antibody drug conjugate the linker (L) is selected from the group consisting of a cleavable linker, a non-cleavable linker, a hydrophilic linker, a procharged linker and a dicarboxylic acid based linker.

[0010] The combination, wherein in said antibody drug conjugate the linker is derived from a cross-linking reagent selected from the group consisting of: N-succinimidyl-4-(2-pyridyldithio)2-sulfo-butanoate (sulfo-SPDB), N-succinimidyl-3-(2-pyridyldithio)propionate (SPDP), N-succinimidyl 4-(2-pyridyldithio)pentanoate (SPP), N-succinimidyl 4-(2-pyridyldithio)butanoate (SPDB), N-succinimidyl iodoacetate (SIA), N-succinimidyl(4-iodoacetyl)aminobenzoate (SIAB), maleimide PEG NHS, N-succinimidyl 4-(maleimidomethyl) cyclohexanecarboxylate (SMCC), N-sulfosuccinimidyl 4-(maleimidomethyl) cyclohexanecarboxylate (sulfo-SMCC) or 2,5-dioxopyrrolidin-1-yl 17-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-5,8,11,14-tetraoxo-4,7,10,13-tetraazaheptadecan-1-oate (CX1-1).

[0011] The combination, wherein in said antibody drug conjugate the linker is derived from N-succinimidyl-4-(2-pyridyldithio)2-sulfo-butanoate (sulfo-SPDB).

[0012] The combination, wherein in said antibody drug conjugate D and L consist of:



Ab-sulfo-SPDB-DM4

or a pharmaceutically acceptable salt thereof.

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[0013] The combination, wherein the anti-GITR agonist antibody or antigen binding fragment thereof, specifically binds to SEQ ID NO:336.

[0014] The combination, wherein the anti-GITR agonist antibody or antigen binding fragment thereof comprises:

(i) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:422, (b) a LCDR2 of SEQ ID NO:423, (c) a LCDR3 of SEQ ID NO:424; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO: 425, (e) a HCDR2 of SEQ ID NO: 426, and (f) a HCDR3 of SEQ ID NO: 427;

(ii) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:352, (b) a LCDR2 of SEQ ID NO:353, (c) a LCDR3 of SEQ ID NO:354; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO: 355, (e) a HCDR2 of SEQ ID NO: 356, and (f) a HCDR3 of SEQ ID NO: 357;

(iii) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:366, (b) a LCDR2 of SEQ ID NO:367, (c) a LCDR3 of SEQ ID NO:368; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO: 369, (e) a HCDR2 of SEQ ID NO:370, and (f) a HCDR3 of SEQ ID NO:371;

(iv) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:380, (b) a LCDR2 of SEQ ID NO:381, (c) a LCDR3 of SEQ ID NO:382; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO: 383, (e) a HCDR2 of SEQ ID NO: 384, and (f) a HCDR3 of SEQ ID NO: 385;

(vi) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:394, (b) a LCDR2 of SEQ ID NO:395, (c) a LCDR3 of SEQ ID NO:396; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO: 397, (e) a HCDR2 of SEQ ID NO: 398, and (f) a HCDR3 of SEQ ID NO: 399;

(vii) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:408, (b) a LCDR2 of SEQ ID NO:409, (c) a LCDR3 of SEQ ID NO:410; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO: 411, (e) a HCDR2 of SEQ ID NO: 412, and (f) a HCDR3 of SEQ ID NO: 413; or

(viii) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:436, (b) a LCDR2 of SEQ ID NO:437, (c) a LCDR3 of SEQ ID NO:438; and

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a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO: 439, (e) a HCDR2 of SEQ ID NO: 440, and (f) a HCDR3 of SEQ ID NO: 441.

[0015] The combination, wherein the anti-GITR agonist antibody or antigen binding fragment thereof comprises:

- (i) a heavy chain variable region (vH) that comprises SEQ ID NO: 428, and a light chain variable region (vL) that comprises SEQ ID NO:429;
- (ii) a heavy chain variable region (vH) that comprises SEQ ID NO: 358, and a light chain variable region (vL) that comprises SEQ ID NO:359;
- (iii) a heavy chain variable region (vH) that comprises SEQ ID NO: 372, and a light chain variable region (vL) that comprises SEQ ID NO:373;
- (iv) a heavy chain variable region (vH) that comprises SEQ ID NO: 386, and a light chain variable region (vL) that comprises SEQ ID NO:387;
- (v) a heavy chain variable region (vH) that comprises SEQ ID NO: 400, and a light chain variable region (vL) that comprises SEQ ID NO:401;
- (vi) a heavy chain variable region (vH) that comprises SEQ ID NO: 414, and a light chain variable region (vL) that comprises SEQ ID NO:415; or
- (vii) a heavy chain variable region (vH) that comprises SEQ ID NO: 442, and a light chain variable region (vL) that comprises SEQ ID NO:443.

[0016] The combination, wherein the anti-GITR agonist antibody or antigen binding fragment thereof comprises:

- (i) a heavy chain that comprises SEQ ID NO: 432, and a light chain that comprises SEQ ID NO:433;
 - (ii) a heavy chain that comprises SEQ ID NO: 362, and a light chain that comprises SEQ ID NO:363;
 - (iii) a heavy chain that comprises SEQ ID NO: 376, and a light chain that comprises SEQ ID NO:377;
 - (iv) a heavy chain that comprises SEQ ID NO: 390, and a light chain that comprises SEQ ID NO:391;
 - (v) a heavy chain that comprises SEQ ID NO: 404, and a light chain that comprises SEQ ID NO:405;
 - (vi) a heavy chain that comprises SEQ ID NO: 418, and a light chain that comprises SEQ ID NO:419;
- or

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(vii) a heavy chain that comprises SEQ ID NO: 446, and a light chain that comprises SEQ ID NO:447.

[0017] The combination, wherein the anti-GITR agonist antibody or antigen binding fragment thereof consists of: (i) a light chain variable region that consists of (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:422, (b) a LCDR2 of SEQ ID NO:423, (c) a LCDR3 of SEQ ID NO:424; and a heavy chain variable region that consists of: (d) a HCDR1 of SEQ ID NO: 425, (e) a HCDR2 of SEQ ID NO: 426, and (f) a HCDR3 of SEQ ID NO: 427.

[0018] The combination, wherein the anti-GITR agonist antibody or antigen binding fragment thereof is selected from the group consisting of: BMS-986156, INCAGN01876, AMG 228, TRX518, MEDI1873, MK-4166, MK-1248 and FPA-154.

[0019] The combination, wherein the antibody drug conjugate and anti-GITR antibody or antigen binding fragment thereof are in separate forms.

[0020] The combination, wherein the antibody drug conjugate and the anti-GITR antibody or antigen binding fragment thereof are in a fixed combination.

[0021] A method of treating a CDH6 positive cancer in a patient in need thereof, comprising administering to said patient the combination of any one of the above.

[0022] The method, wherein said cancer is selected from the group consisting of: ovarian cancer, renal cancer, hepatic cancer, soft tissue cancer, CNS cancers, thyroid cancer and cholangiocarcinoma.

[0023] The method, wherein the antibody drug conjugate and the anti-GITR antibody or antigen binding fragment thereof are administered simultaneously or separately.

[0024] The method, wherein the antibody drug conjugate is administered prior to the administration of the anti-GITR antibody or antigen binding fragment thereof.

[0025] A method of decreasing Treg cells in a tumor, the method comprising:
a) administration of an antibody drug conjugate, wherein the administration of the antibody drug conjugate induces GITR expression on Treg cells;
b) administration of an anti-GITR agonist antibody or antigen binding fragment thereof, which decreases the number of Treg cells associated with the tumor.

[0026] The method, which decreases reoccurrence of the tumor in a patient.

[0027] The method, which increases progression-free survival in a patient.

[0028] Combination for use in treating cancer, wherein the combination is as in any one of the above.

[0029] Combination for use in treating cancer according to the above, wherein said cancer is selected from the group consisting of: ovarian cancer, renal cancer, hepatic cancer, soft tissue cancer, CNS cancers, thyroid cancer and cholangiocarcinoma.

[0030] Use of the combination according to any one of the above in the manufacture of a medicament for the treatment of cancer.

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[0031] Use according, wherein said cancer is selected from the group consisting of: ovarian cancer, renal cancer, hepatic cancer, soft tissue cancer, CNS cancers, thyroid cancer and cholangiocarcinoma.

Definitions

[0032] Unless stated otherwise, the following terms and phrases as used herein are intended to have the following meanings:

[0033] The term “alkyl” refers to a monovalent saturated hydrocarbon chain having the specified number of carbon atoms. For example, C₁₋₆ alkyl refers to an alkyl group having from 1 to 6 carbon atoms. Alkyl groups may be straight or branched. Representative branched alkyl groups have one, two, or three branches. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl (n-propyl and isopropyl), butyl (n-butyl, isobutyl, sec-butyl, and t-butyl), pentyl (n-pentyl, isopentyl, and neopentyl), and hexyl.

[0034] The term “antibody” as used herein refers to a polypeptide of the immunoglobulin family that is capable of binding a corresponding antigen non-covalently, reversibly, and in a specific manner. For example, a naturally occurring IgG antibody is a tetramer comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as VH) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as VL) and a light chain constant region. The light chain constant region is comprised of one domain, CL. The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FRs arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (*e.g.*, effector cells) and the first component (C1q) of the classical complement system.

[0035] The term “antibody” includes, but is not limited to, monoclonal antibodies, human antibodies, humanized antibodies, camelid antibodies, chimeric antibodies, and anti-idiotypic (anti-Id) antibodies (including, *e.g.*, anti-Id antibodies to antibodies of the present disclosure). The antibodies

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can be of any isotype/class (*e.g.*, IgG, IgE, IgM, IgD, IgA and IgY), or subclass (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2).

[0036] “Complementarity-determining domains” or “complementary-determining regions”(“CDRs”) interchangeably refer to the hypervariable regions of VL and VH. The CDRs are the target protein-binding site of the antibody chains that harbors specificity for such target protein. There are three CDRs (CDR1-3, numbered sequentially from the N-terminus) in each human VL or VH, constituting about 15-20% of the variable domains. CDRs can be referred to by their region and order. For example, “VHCDR1” or “HCDR1” both refer to the first CDR of the heavy chain variable region. The CDRs are structurally complementary to the epitope of the target protein and are thus directly responsible for the binding specificity. The remaining stretches of the VL or VH, the so-called framework regions, exhibit less variation in amino acid sequence (Kuby, Immunology, 4th ed., Chapter 4. W.H. Freeman & Co., New York, 2000).

[0037] The positions of the CDRs and framework regions can be determined using various well known definitions in the art, *e.g.*, Kabat, Chothia, and AbM (see, *e.g.*, Johnson *et al.*, Nucleic Acids Res., 29:205-206 (2001); Chothia and Lesk, J. Mol. Biol., 196:901-917 (1987); Chothia *et al.*, Nature, 342:877-883 (1989); Chothia *et al.*, J. Mol. Biol., 227:799-817 (1992); Al-Lazikani *et al.*, J.Mol.Biol., 273:927-748 (1997)). Definitions of antigen combining sites are also described in the following: Ruiz *et al.*, Nucleic Acids Res., 28:219–221 (2000); and Lefranc, M.P., Nucleic Acids Res., 29:207-209 (2001); MacCallum *et al.*, J. Mol. Biol., 262:732-745 (1996); and Martin *et al.*, Proc. Natl. Acad. Sci. USA, 86:9268–9272 (1989); Martin *et al.*, Methods Enzymol., 203:121–153 (1991); and Rees *et al.*, In Sternberg M.J.E. (ed.), Protein Structure Prediction, Oxford University Press, Oxford, 141–172 (1996).

[0038] Both the light and heavy chains are divided into regions of structural and functional homology. The terms “constant” and “variable” are used functionally. In this regard, it will be appreciated that the variable domains of both the light (VL) and heavy (VH) chain portions determine antigen recognition and specificity. Conversely, the constant domains of the light chain (CL) and the heavy chain (CH1, CH2 or CH3) confer important biological properties such as secretion, transplacental mobility, Fc receptor binding, complement binding, and the like. By convention, the numbering of the constant region domains increases as they become more distal from the antigen binding site or amino-terminus of the antibody. The N-terminus is a variable region and at the C-terminus is a constant region; the CH3 and CL domains actually comprise the carboxy-terminal domains of the heavy and light chain, respectively.

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[0039] The term “antigen binding fragment”, as used herein, refers to a polypeptide including one or more portions of an antibody that retain the ability to specifically interact with (*e.g.*, by binding, steric hindrance, stabilizing/destabilizing, spatial distribution) an epitope of an antigen. Examples of binding fragments include, but are not limited to, single-chain Fvs (scFv), disulfide-linked Fvs (sdFv), Fab fragments, F(ab') fragments, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; a F(ab)2 fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment consisting of the VH and CH1 domains; a Fv fragment consisting of the VL and VH domains of a single arm of an antibody; a dAb fragment (Ward *et al.*, Nature 341:544-546, 1989), which consists of a VH domain; and an isolated complementarity determining region (CDR), or other epitope-binding fragments of an antibody.

[0040] Furthermore, although the two domains of the Fv fragment, VL and VH, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the VL and VH regions pair to form monovalent molecules (known as single chain Fv (“scFv”); see, *e.g.*, Bird *et al.*, Science 242:423-426, 1988; and Huston *et al.*, Proc. Natl. Acad. Sci. 85:5879-5883, 1988). Such single chain antibodies are also intended to be encompassed within the term “antigen binding fragment.” These antigen binding fragments are obtained using conventional techniques known to those of skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies.

[0041] Antigen binding fragments can also be incorporated into single domain antibodies, maxibodies, minibodies, nanobodies, intrabodies, diabodies, triabodies, tetrabodies, v-NAR and bis-scFv (see, *e.g.*, Hollinger and Hudson, Nature Biotechnology 23:1126-1136, 2005). Antigen binding fragments can be grafted into scaffolds based on polypeptides such as fibronectin type III (Fn3) (see U.S. Pat. No. 6,703,199, which describes fibronectin polypeptide monobodies).

[0042] Antigen binding fragments can be incorporated into single chain molecules comprising a pair of tandem Fv segments (VH-CH1-VH-CH1) which, together with complementary light chain polypeptides, form a pair of antigen binding regions (Zapata *et al.*, Protein Eng. 8:1057-1062, 1995; and U.S. Pat. No. 5,641,870).

[0043] The term “monoclonal antibody” or “monoclonal antibody composition” as used herein refers to polypeptides, including antibodies and antigen binding fragments that have substantially identical amino acid sequence or are derived from the same genetic source. This term also includes preparations of antibody molecules of single molecular composition. A monoclonal antibody composition displays a single binding specificity and affinity for a particular epitope.

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[0044] The term “human antibody”, as used herein, includes antibodies having variable regions in which both the framework and CDR regions are derived from sequences of human origin. Furthermore, if the antibody contains a constant region, the constant region also is derived from such human sequences, *e.g.*, human germline sequences, or mutated versions of human germline sequences or antibody containing consensus framework sequences derived from human framework sequences analysis, for example, as described in Knappik *et al.*, J. Mol. Biol. 296:57-86, 2000.

[0045] The antibodies of the present disclosure can include amino acid residues not encoded by human sequences (*e.g.*, mutations introduced by random or site-specific mutagenesis in vitro or by somatic mutation in vivo, or a conservative substitution to promote stability or manufacturing).

[0046] The term “recognize” as used herein refers to an antibody or antigen binding fragment thereof that finds and interacts (*e.g.*, binds) with its epitope, whether that epitope is linear or conformational. The term “epitope” refers to a site on an antigen to which an antibody or antigen binding fragment of the disclosure specifically binds. Epitopes can be formed both from contiguous amino acids or noncontiguous amino acids juxtaposed by tertiary folding of a protein. Epitopes formed from contiguous amino acids are typically retained on exposure to denaturing solvents, whereas epitopes formed by tertiary folding are typically lost on treatment with denaturing solvents. An epitope typically includes at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 amino acids in a unique spatial conformation. Methods of determining spatial conformation of epitopes include techniques in the art, for example, x-ray crystallography and 2-dimensional nuclear magnetic resonance (see, *e.g.*, Epitope Mapping Protocols in Methods in Molecular Biology, Vol. 66, G. E. Morris, Ed. (1996)). A “paratope” is the part of the antibody which recognizes the epitope of the antigen.

[0047] The phrase “specifically binds” or “selectively binds,” when used in the context of describing the interaction between an antigen (*e.g.*, a protein) and an antibody, antibody fragment, or antibody-derived binding agent, refers to a binding reaction that is determinative of the presence of the antigen in a heterogeneous population of proteins and other biologics, *e.g.*, in a biological sample, *e.g.*, a blood, serum, plasma or tissue sample. Thus, under certain designated immunoassay conditions, the antibodies or binding agents with a particular binding specificity bind to a particular antigen at least two times the background and do not substantially bind in a significant amount to other antigens present in the sample. In one aspect, under designated immunoassay conditions, the antibody or binding agent with a particular binding specificity binds to a particular antigen at least ten (10) times the background and does not substantially bind in a significant amount to other antigens present in the sample. Specific binding to an antibody or binding agent under such conditions may require the

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antibody or agent to have been selected for its specificity for a particular protein. As desired or appropriate, this selection may be achieved by subtracting out antibodies that cross-react with molecules from other species (*e.g.*, mouse or rat) or other subtypes. Alternatively, in some aspects, antibodies or antibody fragments are selected that cross-react with certain desired molecules.

[0048] The term “affinity” as used herein refers to the strength of interaction between antibody and antigen at single antigenic sites. Within each antigenic site, the variable region of the antibody “arm” interacts through weak non-covalent forces with antigen at numerous sites; the more interactions, the stronger the affinity.

[0049] The term “isolated antibody” refers to an antibody that is substantially free of other antibodies having different antigenic specificities. An isolated antibody that specifically binds to one antigen may, however, have cross-reactivity to other antigens. Moreover, an isolated antibody may be substantially free of other cellular material and/or chemicals.

[0050] The term “corresponding human germline sequence” refers to the nucleic acid sequence encoding a human variable region amino acid sequence or subsequence that shares the highest determined amino acid sequence identity with a reference variable region amino acid sequence or subsequence in comparison to all other all other known variable region amino acid sequences encoded by human germline immunoglobulin variable region sequences. The corresponding human germline sequence can also refer to the human variable region amino acid sequence or subsequence with the highest amino acid sequence identity with a reference variable region amino acid sequence or subsequence in comparison to all other evaluated variable region amino acid sequences. The corresponding human germline sequence can be framework regions only, complementarity determining regions only, framework and complementary determining regions, a variable segment (as defined above), or other combinations of sequences or subsequences that comprise a variable region. Sequence identity can be determined using the methods described herein, for example, aligning two sequences using BLAST, ALIGN, or another alignment algorithm known in the art. The corresponding human germline nucleic acid or amino acid sequence can have at least about 90%, 91, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with the reference variable region nucleic acid or amino acid sequence.

[0051] A variety of immunoassay formats may be used to select antibodies specifically immunoreactive with a particular protein. For example, solid-phase ELISA immunoassays are routinely used to select antibodies specifically immunoreactive with a protein (see, *e.g.*, Harlow & Lane, *Using Antibodies*, A Laboratory Manual (1998), for a description of immunoassay formats and

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conditions that can be used to determine specific immunoreactivity). Typically a specific or selective binding reaction will produce a signal at least twice over the background signal and more typically at least 10 to 100 times over the background.

[0052] The term “equilibrium dissociation constant (KD, M)” refers to the dissociation rate constant (kd, time-1) divided by the association rate constant (ka, time-1, M-1). Equilibrium dissociation constants can be measured using any known method in the art. The antibodies of the present disclosure generally will have an equilibrium dissociation constant of less than about 10^{-7} or 10^{-8} M, for example, less than about 10^{-9} M or 10^{-10} M, in some aspects, less than about 10^{-11} M, 10^{-12} M or 10^{-13} M.

[0053] The term “bioavailability” refers to the systemic availability (i.e., blood/plasma levels) of a given amount of drug administered to a patient. Bioavailability is an absolute term that indicates measurement of both the time (rate) and total amount (extent) of drug that reaches the general circulation from an administered dosage form.

[0054] As used herein, the phrase “consisting essentially of” refers to the genera or species of active pharmaceutical agents included in a method or composition, as well as any excipients inactive for the intended purpose of the methods or compositions. In some aspects, the phrase “consisting essentially of” expressly excludes the inclusion of one or more additional active agents other than an antibody drug conjugate of the present disclosure. In some aspects, the phrase “consisting essentially of” expressly excludes the inclusion of one or more additional active agents other than an antibody drug conjugate of the present disclosure and a second co-administered agent.

[0055] The term “amino acid” refers to naturally occurring, synthetic, and unnatural amino acids, as well as amino acid analogs and amino acid mimetics that function in a manner similar to the naturally occurring amino acids. Naturally occurring amino acids are those encoded by the genetic code, as well as those amino acids that are later modified, *e.g.*, hydroxyproline, γ -carboxyglutamate, and O-phosphoserine. Amino acid analogs refer to compounds that have the same basic chemical structure as a naturally occurring amino acid, i.e., an α -carbon that is bound to a hydrogen, a carboxyl group, an amino group, and an R group, *e.g.*, homoserine, norleucine, methionine sulfoxide, methionine methyl sulfonium. Such analogs have modified R groups (*e.g.*, norleucine) or modified peptide backbones, but retain the same basic chemical structure as a naturally occurring amino acid. Amino acid mimetics refers to chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but that functions in a manner similar to a naturally occurring amino acid.

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[0056] The term “conservatively modified variant” applies to both amino acid and nucleic acid sequences. With respect to particular nucleic acid sequences, conservatively modified variants refers to those nucleic acids which encode identical or essentially identical amino acid sequences, or where the nucleic acid does not encode an amino acid sequence, to essentially identical sequences. Because of the degeneracy of the genetic code, a large number of functionally identical nucleic acids encode any given protein. For instance, the codons GCA, GCC, GCG and GCU all encode the amino acid alanine. Thus, at every position where an alanine is specified by a codon, the codon can be altered to any of the corresponding codons described without altering the encoded polypeptide. Such nucleic acid variations are “silent variations,” which are one species of conservatively modified variations. Every nucleic acid sequence herein which encodes a polypeptide also describes every possible silent variation of the nucleic acid. One of skill will recognize that each codon in a nucleic acid (except AUG, which is ordinarily the only codon for methionine, and TGG, which is ordinarily the only codon for tryptophan) can be modified to yield a functionally identical molecule. Accordingly, each silent variation of a nucleic acid that encodes a polypeptide is implicit in each described sequence.

[0057] For polypeptide sequences, “conservatively modified variants” include individual substitutions, deletions or additions to a polypeptide sequence which result in the substitution of an amino acid with a chemically similar amino acid. Conservative substitution tables providing functionally similar amino acids are well known in the art. Such conservatively modified variants are in addition to and do not exclude polymorphic variants, interspecies homologs, and alleles. The following eight groups contain amino acids that are conservative substitutions for one another: 1) Alanine (A), Glycine (G); 2) Aspartic acid (D), Glutamic acid (E); 3) Asparagine (N), Glutamine (Q); 4) Arginine (R), Lysine (K); 5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V); 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W); 7) Serine (S), Threonine (T); and 8) Cysteine (C), Methionine (M) (see, *e.g.*, Creighton, Proteins (1984)). In some aspects, the term “conservative sequence modifications” are used to refer to amino acid modifications that do not significantly affect or alter the binding characteristics of the antibody containing the amino acid sequence.

[0058] The term “optimized” as used herein refers to a nucleotide sequence that has been altered to encode an amino acid sequence using codons that are preferred in the production cell or organism, generally a eukaryotic cell, for example, a yeast cell, a *Pichia* cell, a fungal cell, a *Trichoderma* cell, a Chinese Hamster Ovary cell (CHO) or a human cell. The optimized nucleotide

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sequence is engineered to retain completely or as much as possible the amino acid sequence originally encoded by the starting nucleotide sequence, which is also known as the “parental” sequence.

[0059] The terms “percent identical” or “percent identity,” in the context of two or more nucleic acids or polypeptide sequences, refers to the extent to which two or more sequences or subsequences that are the same. Two sequences are “identical” if they have the same sequence of amino acids or nucleotides over the region being compared. Two sequences are “substantially identical” if two sequences have a specified percentage of amino acid residues or nucleotides that are the same (i.e., 60% identity, optionally 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% identity over a specified region, or, when not specified, over the entire sequence), when compared and aligned for maximum correspondence over a comparison window, or designated region as measured using one of the following sequence comparison algorithms or by manual alignment and visual inspection. Optionally, the identity exists over a region that is at least about 30 nucleotides (or 10 amino acids) in length, or more preferably over a region that is 100 to 500 or 1000 or more nucleotides (or 20, 50, 200 or more amino acids) in length.

[0060] For sequence comparison, typically one sequence acts as a reference sequence, to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are entered into a computer, subsequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated. Default program parameters can be used, or alternative parameters can be designated. The sequence comparison algorithm then calculates the percent sequence identities for the test sequences relative to the reference sequence, based on the program parameters.

[0061] A “comparison window”, as used herein, includes reference to a segment of any one of the number of contiguous positions selected from the group consisting of from 20 to 600, usually about 50 to about 200, more usually about 100 to about 150 in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned. Methods of alignment of sequences for comparison are well known in the art. Optimal alignment of sequences for comparison can be conducted, *e.g.*, by the local homology algorithm of Smith and Waterman, Adv. Appl. Math. 2:482c (1970), by the homology alignment algorithm of Needleman and Wunsch, J. Mol. Biol. 48:443 (1970), by the search for similarity method of Pearson and Lipman, Proc. Natl. Acad. Sci. USA 85:2444 (1988), by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package,

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Genetics Computer Group, 575 Science Dr., Madison, WI), or by manual alignment and visual inspection (see, *e.g.*, Brent *et al.*, Current Protocols in Molecular Biology, 2003).

[0062] Two examples of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul *et al.*, Nuc. Acids Res. 25:3389-3402, 1977; and Altschul *et al.*, J. Mol. Biol. 215:403-410, 1990, respectively. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul *et al.*, supra). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Cumulative scores are calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always > 0) and N (penalty score for mismatching residues; always < 0). For amino acid sequences, a scoring matrix is used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a word length (W) of 11, an expectation (E) or 10, M=5, N=-4 and a comparison of both strands. For amino acid sequences, the BLASTP program uses as defaults a word length of 3, and expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff and Henikoff, (1989) Proc. Natl. Acad. Sci. USA 89:10915) alignments (B) of 50, expectation (E) of 10, M=5, N=-4, and a comparison of both strands.

[0063] The BLAST algorithm also performs a statistical analysis of the similarity between two sequences (see, *e.g.*, Karlin and Altschul, Proc. Natl. Acad. Sci. USA 90:5873-5787, 1993). One measure of similarity provided by the BLAST algorithm is the smallest sum probability (P(N)), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a nucleic acid is considered similar to a reference sequence if the smallest sum probability in a comparison of the test nucleic acid to the reference

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nucleic acid is less than about 0.2, more preferably less than about 0.01, and most preferably less than about 0.001.

[0064] The percent identity between two amino acid sequences can also be determined using the algorithm of E. Meyers and W. Miller, Comput. Appl. Biosci. 4:11-17, 1988) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. In addition, the percent identity between two amino acid sequences can be determined using the Needleman and Wunsch, J. Mol. Biol. 48:444-453, 1970) algorithm which has been incorporated into the GAP program in the GCG software package using either a Blossum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6.

[0065] Other than percentage of sequence identity noted above, another indication that two nucleic acid sequences or polypeptides are substantially identical is that the polypeptide encoded by the first nucleic acid is immunologically cross reactive with the antibodies raised against the polypeptide encoded by the second nucleic acid, as described below. Thus, a polypeptide is typically substantially identical to a second polypeptide, for example, where the two peptides differ only by conservative substitutions. Another indication that two nucleic acid sequences are substantially identical is that the two molecules or their complements hybridize to each other under stringent conditions, as described below. Yet another indication that two nucleic acid sequences are substantially identical is that the same primers can be used to amplify the sequence.

[0066] The term “nucleic acid” is used herein interchangeably with the term “polynucleotide” and refers to deoxyribonucleotides or ribonucleotides and polymers thereof in either single- or double-stranded form. The term encompasses nucleic acids containing known nucleotide analogs or modified backbone residues or linkages, which are synthetic, naturally occurring, and non-naturally occurring, which have similar binding properties as the reference nucleic acid, and which are metabolized in a manner similar to the reference nucleotides. Examples of such analogs include, without limitation, phosphorothioates, phosphoramidates, methyl phosphonates, chiral-methyl phosphonates, 2-O-methyl ribonucleotides, peptide-nucleic acids (PNAs).

[0067] Unless otherwise indicated, a particular nucleic acid sequence also implicitly encompasses conservatively modified variants thereof (*e.g.*, degenerate codon substitutions) and complementary sequences, as well as the sequence explicitly indicated. Specifically, as detailed below, degenerate codon substitutions may be achieved by generating sequences in which the third position of one or more selected (or all) codons is substituted with mixed-base and/or deoxyinosine

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residues (Batzner *et al.*, (1991) Nucleic Acid Res. 19:5081; Ohtsuka *et al.*, (1985) J. Biol. Chem. 260:2605-2608; and Rossolini *et al.*, (1994) Mol. Cell. Probes 8:91-98).

[0068] The term “operably linked” in the context of nucleic acids refers to a functional relationship between two or more polynucleotide (*e.g.*, DNA) segments. Typically, it refers to the functional relationship of a transcriptional regulatory sequence to a transcribed sequence. For example, a promoter or enhancer sequence is operably linked to a coding sequence if it stimulates or modulates the transcription of the coding sequence in an appropriate host cell or other expression system. Generally, promoter transcriptional regulatory sequences that are operably linked to a transcribed sequence are physically contiguous to the transcribed sequence, *i.e.*, they are *cis*-acting. However, some transcriptional regulatory sequences, such as enhancers, need not be physically contiguous or located in close proximity to the coding sequences whose transcription they enhance.

[0069] The terms “polypeptide” and “protein” are used interchangeably herein to refer to a polymer of amino acid residues. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymer. Unless otherwise indicated, a particular polypeptide sequence also implicitly encompasses conservatively modified variants thereof.

[0070] The term “immunoconjugate” or “antibody drug conjugate” or “ADC” as used herein refers to the linkage of an antibody or an antigen binding fragment thereof with another agent, such as a payload, drug moiety, chemotherapeutic agent, a toxin, an immunotherapeutic agent, an imaging probe, and the like. The linkage can be covalent bonds, or non-covalent interactions such as through electrostatic forces. Various linkers, known in the art, can be employed in order to form the immunoconjugate. Additionally, the immunoconjugate can be provided in the form of a fusion protein that may be expressed from a polynucleotide encoding the immunoconjugate. As used herein, “fusion protein” refers to proteins created through the joining of two or more genes or gene fragments which originally coded for separate proteins (including peptides and polypeptides). Translation of the fusion gene results in a single protein with functional properties derived from each of the original proteins.

[0071] The term “subject” includes human and non-human animals. Non-human animals include all vertebrates, *e.g.*, mammals and non-mammals, such as non-human primates, sheep, dog, cow, chickens, amphibians, and reptiles. Except when noted, the terms “patient” or “subject” are used herein interchangeably.

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[0072] The term “toxin,” “cytotoxin” or “cytotoxic agent” as used herein, refers to any agent that is detrimental to the growth and proliferation of cells and may act to reduce, inhibit, or destroy a cell or malignancy.

[0073] The term “anti-cancer agent” as used herein refers to any agent that can be used to treat a cell proliferative disorder such as cancer, including but not limited to, cytotoxic agents, chemotherapeutic agents, radiotherapy and radiotherapeutic agents, targeted anti-cancer agents, and immunotherapeutic agents.

[0074] The term “drug moiety” or “payload” as used herein refers to a chemical moiety that is conjugated to an antibody or antigen binding fragment, and can include any therapeutic or diagnostic agent, for example, an anti-cancer, anti-inflammatory, anti-infective (*e.g.*, anti-fungal, antibacterial, anti-parasitic, anti-viral), or an anesthetic agent. In certain aspects, a drug moiety is selected from a V-ATPase inhibitor, a HSP90 inhibitor, an IAP inhibitor, an mTor inhibitor, a microtubule stabilizer, a microtubule destabilizer, an auristatin, a dolastatin, a maytansinoid, a MetAP (methionine aminopeptidase), an inhibitor of nuclear export of proteins CRM1, a DPPIV inhibitor, an inhibitor of phosphoryl transfer reactions in mitochondria, a protein synthesis inhibitor, a kinase inhibitor, a CDK2 inhibitor, a CDK9 inhibitor, a proteasome inhibitor, a kinesin inhibitor, an HDAC inhibitor, a DNA damaging agent, a DNA alkylating agent, a DNA intercalator, a DNA minor groove binder and a DHFR inhibitor. Methods for attaching each of these to a linker compatible with the antibodies and method of the present disclosure are known in the art. See, *e.g.*, Singh et al., (2009) *Therapeutic Antibodies: Methods and Protocols*, vol. 525, 445-457. In addition, a payload can be a biophysical probe, a fluorophore, a spin label, an infrared probe, an affinity probe, a chelator, a spectroscopic probe, a radioactive probe, a lipid molecule, a polyethylene glycol, a polymer, a spin label, DNA, RNA, a protein, a peptide, a surface, an antibody, an antibody fragment, a nanoparticle, a quantum dot, a liposome, a PLGA particle, a saccharide or a polysaccharide.

[0075] The term “maytansinoid drug moiety” means the substructure of an antibody-drug conjugate that has the structure of a maytansinoid compound. Maytansine was first isolated from the east African shrub *Maytenus serrata* (U.S. Pat. No. 3,896,111). Subsequently, it was discovered that certain microbes also produce maytansinoids, such as maytansinol and C-3 maytansinol esters (U.S. Pat. No. 4,151,042). Synthetic maytansinol and maytansinol analogues have been reported. See U.S. Pat. Nos. 4,137,230; 4,248,870; 4,256,746; 4,260,608; 4,265,814; 4,294,757; 4,307,016; 4,308,268; 4,308,269; 4,309,428; 4,313,946; 4,315,929; 4,317,821; 4,322,348; 4,331,598; 4,361,650; 4,364,866; 4,424,219; 4,450,254; 4,362,663; and 4,371,533, and Kawai et al (1984) *Chem. Pharm. Bull.* 3441-

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3451, each of which are expressly incorporated by reference. Specific examples of maytansinoids useful for conjugation include DM1, DM3 and DM4.

[0076] “Tumor” refers to neoplastic cell growth and proliferation, whether malignant or benign, and all pre-cancerous and cancerous cells and tissues.

[0077] The term “anti-tumor activity” means a reduction in the rate of tumor cell proliferation, viability, or metastatic activity. A possible way of showing anti-tumor activity is to show a decline in growth rate of tumor cells, tumor size stasis or tumor size reduction. Such activity can be assessed using accepted in vitro or in vivo tumor models, including but not limited to xenograft models, allograft models, MMTV models, and other known models known in the art to investigate anti-tumor activity.

[0078] The term “malignancy” refers to a non-benign tumor or a cancer. As used herein, the term “cancer” includes a malignancy characterized by deregulated or uncontrolled cell growth. Exemplary cancers include: carcinomas, sarcomas, leukemias and lymphomas.

[0079] The term “cancer” includes primary malignant tumors (*e.g.*, those whose cells have not migrated to sites in the subject's body other than the site of the original tumor) and secondary malignant tumors (*e.g.*, those arising from metastasis, the migration of tumor cells to secondary sites that are different from the site of the original tumor).

[0080] “Immunogenic cell death” or “ICD” refers a process by which certain cytotoxic drugs induce apoptosis in such a way that stimulates immune cell recruitment to tumors (see Gerber et al., *supra*).

[0081] The term “Cadherin 6” or “CDH6” refers to a cell adhesion molecule that is a member of the cadherin family of cell-cell adhesion molecules. The nucleic acid and amino acid sequences of CDH6 are known, and have been published in GenBank Accession Nos. AK291290 (protein accession number BAF83979.1) See also SEQ ID NO:1 for the human CDH6 cDNA sequence and SEQ ID NO:2 for the human CDH6 protein sequence. Structurally, CDH6 receptor is a type II cadherin with five extracellular cadherin repeats and has over its full length at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with the amino acid sequence of SEQ ID NO:2. Structurally, a CDH6 nucleic acid sequence has over its full length at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with the nucleic acid sequence of SEQ ID NO 1.

[0082] The term “glucocorticoid-induced tumor necrosis factor receptor family-related protein” or “GITR” (alternatively TNFRSF18) refers to a molecule that is a member of the TNF-R superfamily. The nucleic acid and amino acid sequences of GITR are known, and have been published in GenBank Accession Nos. BC152381 (protein accession number AAI52382) See also

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SEQ ID NO: 336 for the human GITR protein sequence. GITR has over its full length at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with the amino acid sequence of SEQ ID NO: 336.

[0083] The term “P-cadherin” (also known as Pcad, PCad, or CDH3) refers to the nucleic acid and amino acid sequence of P-cadherin, which have been published in GenBank Accession Nos. NP_001784, NP_001784.2 (amino acid sequence), and NM_001793.4, GenBank Accession Nos. AA14462, NG_009096, and NG_009096.1 (nucleotide sequences). Sequence information for human P-cadherin domains 1-5 are extracellular and are published in GenBank Accession Nos. NM_001793.4 and NP_001784.

[0084] The terms “CDH6 expressing cancer” or “CDH6 positive cancer” refers to a cancer that expresses CDH6 and/or a mutant form of CDH6 on the surface of cancer cells.

[0085] As used herein, the terms “treat,” “treating,” or “treatment” of any disease or disorder refer in one aspect, to ameliorating the disease or disorder (i.e., slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another aspect, “treat,” “treating,” or “treatment” refers to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient. In yet another aspect, “treat,” “treating,” or “treatment” refers to modulating the disease or disorder, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both. In yet another aspect, “treat,” “treating,” or “treatment” refers to preventing or delaying the onset or development or progression of the disease or disorder.

[0086] The term “therapeutically acceptable amount” or “therapeutically effective dose” interchangeably refers to an amount sufficient to effect the desired result (i.e., a reduction in tumor size, inhibition of tumor growth, prevention of metastasis, inhibition or prevention of viral, bacterial, fungal or parasitic infection). In some aspects, a therapeutically acceptable amount does not induce or cause undesirable side effects. A therapeutically acceptable amount can be determined by first administering a low dose, and then incrementally increasing that dose until the desired effect is achieved. A “prophylactically effective dosage,” and a “therapeutically effective dosage,” of the molecules of the present disclosure can prevent the onset of, or result in a decrease in severity of, respectively, disease symptoms, including symptoms associated with cancer.

[0087] The term “co-administer” refers to the simultaneous presence of two active agents in the blood of an individual. Active agents that are co-administered can be concurrently or sequentially delivered.

[0088] The term “combination” or “pharmaceutical combination” is defined as the combined administration of an antibody drug conjugate and an anti-GITR antibody, or a binding fragment of

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each respective antibody thereof to a patient in need. The combination may be administered independently, at the same time or separately, or sequentially within time intervals that allow the combination partners show a cooperative, e.g., additive or synergistic, effect. The combination can be a fixed or non-fixed combination.

[0089] The term "fixed combination" means that the active ingredients or therapeutic agents, are administered to a patient simultaneously in the form of a single entity or dosage form.

[0090] The term "non-fixed combination" means that the active ingredients or therapeutic agents, are both administered to a patient as separate entities or dosage forms either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the three compounds in the body of the subject, e.g., a mammal or human, in need thereof.

[0091] The term "combination therapy" refers to the administration of two or more therapeutic agents to treat a therapeutic condition or disorder described in the present disclosure. Such administration encompasses co-administration of these therapeutic agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients. Alternatively, such administration encompasses co-administration in multiple, or in separate containers (*e.g.*, capsules, powders, and liquids) for each active ingredient. Powders and/or liquids may be reconstituted or diluted to a desired dose prior to administration. In addition, such administration also encompasses use of each type of therapeutic agent in a sequential manner, either at approximately the same time or at different times. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the conditions or disorders described herein.

[0092] The combination therapy can provide "synergy" and prove "synergistic", *i.e.*, the effect achieved when the active ingredients used together is greater than the sum of the effects that results from using the compounds separately. A synergistic effect can be attained when the active ingredients are: (1) co-formulated and administered or delivered simultaneously in a combined, unit dosage formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect can be attained when the compounds are administered or delivered sequentially, *e.g.*, by different injections in separate syringes. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, *i.e.*, serially, whereas in combination therapy, effective dosages of two or more active ingredients are administered together.

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BRIEF DESCRIPTION OF THE DRAWINGS

- [0093] Figure 1 shows in vivo efficacy of anti-CDH6 antibodies as sulfo-SPDB-DM4 conjugates as a single agent in a xenograft mouse model of ovarian cancer.
- [0094] Figure 2 shows in vivo efficacy of anti-GITR antibodies as a single agent in a mouse model of colon cancer.
- [0095] Figure 3 depicts the generation of the RENCA murine CDH6 mouse model.
- [0096] Figure 4 demonstrates the increase in Tregs following treatment with CDH6 ADC in the RENCA mouse model.
- [0097] Figure 5 shows a reduction in tumor volume of RENCAm CDH6 tumors when treated with the CDH6 ADC/GITR combination.
- [0098] Figure 6 demonstrates that the CDH6 ADC/GITR combination increases survival in a RENCAmCDH6 mouse model.
- [0099] Figure 7 is a graph of a tumor re-challenge in the RENCAmCDH6 mouse model.
- [00100] Figure 8 is a graph of individual tumor volume from control mice during the tumor re-challenge.
- [00101] Figure 9 is a graph of TEE survival data in the RENCAm CDH6 mouse model.
- [00102] Figure 10 shows the increase of IFN-gamma signal in the presence of splenocytes from re-challenged mice incubated with target cells compared to control splenocytes ($p < 0.0001$, 2 way ANOVA).
- [00103] Figure 11 depicts a colon tumor mouse xenograft model treated with CDH6 ADC as a single agent.
- [00104] Figure 12 shows the increase in expression in GITR on T_{reg} cells following CDH6ADC treatment in the colon tumor mouse model.

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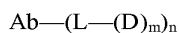
DETAILED DESCRIPTION

[00105] The present disclosure provides for CDH6 antibody drug conjugates in combination with anti-GITR antibodies. In particular, the present disclosure is directed to the combination of CDH6 antibody drug conjugates (ADC), and agonistic anti-GITR antibodies. The combination of antibodies and antibody fragments (*e.g.*, antigen binding fragments) of the present disclosure can be used in the treatment of cancer. For example, in the treatment of: ovarian cancer, renal cancer, hepatic cancer, soft tissue cancer, CNS cancers, thyroid cancer and cholangiocarcinoma. The present disclosure further provides pharmaceutical compositions comprising the combination and methods dosing of the combination for the treatment of cancer.

Antibody Drug Conjugates

[00106] The present disclosure provides antibody drug conjugates, where an antibody, antigen binding fragment or its functional equivalent that specifically binds to CDH6 is linked to a drug moiety. In one aspect, the antibodies, antigen binding fragments or their functional equivalents are linked, via covalent attachment by a linker, to a drug moiety that is an anti-cancer agent. The antibody drug conjugates can selectively deliver an effective dose of an anti-cancer agent (*e.g.*, a cytotoxic agent) to tumor tissues expressing CDH6, whereby greater selectivity (and lower efficacious dose) may be achieved.

[00107] In one aspect, the disclosure provides for an immunoconjugate of Formula (I):



Wherein Ab represents a CDH6 binding antibody or antibody fragment (*e.g.*, antigen binding fragment) described herein;

L is a linker;

D is a drug moiety;

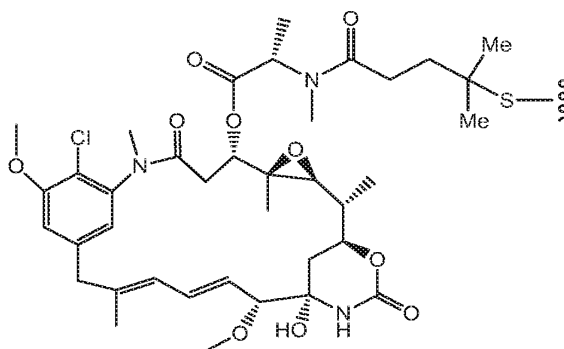
m is an integer from 1-8; and

n is an integer from 1-20. In one aspect, n is an integer from 1 to 10, 2 to 8, or 2 to 5. In a specific aspect, n is 3 to 4. In some aspects, m is 1. In some aspects, m is 2, 3 or 4.

[00108] While the drug moiety to antibody ratio has an exact integer value for a specific conjugate molecule (*e.g.*, n multiplied by m in Formula (I)), it is understood that the value will often be an average value when used to describe a sample containing many molecules, due to some degree of inhomogeneity, typically associated with the conjugation step. The average loading for a sample of an immunoconjugate is referred to herein as the drug moiety to antibody ratio, or “DAR.” In the

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[00109] The present disclosure provides immunoconjugates comprising the antibodies, antibody fragments (*e.g.*, antigen binding fragments) and their functional equivalents as disclosed herein, linked or conjugated to a drug moiety. In one aspect, the drug moiety D is a maytansinoid drug moiety, including those having the structure:



[00110] The drug moiety D can be linked to the antibody Ab through a linker L. L is any chemical moiety that is capable of linking the antibody Ab to the drug moiety D. The linker, L attaches the antibody Ab to the drug moiety D through covalent bond(s). The linker reagent is a bifunctional or multifunctional moiety which can be used to link a drug moiety D and an antibody Ab to form antibody drug conjugates. Antibody drug conjugates can be prepared using a linker having a reactive functionality for binding to the drug moiety D and to the antibody Ab. A cysteine, thiol or an amine, e.g. N-terminus or amino acid side chain such as lysine of the antibody can form a bond with a functional group of a linker reagent.

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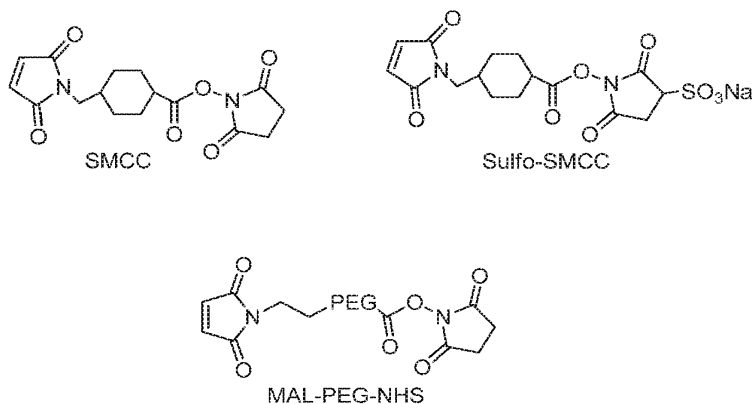
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cleavable linker, a disulfide bond reducible linker, a hydrophilic linker, a procharged linker, or a dicarboxylic acid based linker.

[00112] Suitable cross-linking reagents that form a non-cleavable linker between the drug moiety D, for example maytansinoid, and the antibody Ab are well known in the art, and can form non-cleavable linkers that comprise a sulfur atom (such as SMCC) or those that are without a sulfur atom. Preferred cross-linking reagents that form non-cleavable linkers between the drug moiety D, for example maytansinoid, and the antibody Ab comprise a maleimido- or haloacetyl-based moiety. According to the present disclosure, such non-cleavable linkers are said to be derived from maleimido- or haloacetyl-based moieties.

[00113] Cross-linking reagents comprising a maleimido-based moiety include but not limited to, *N*-succinimidyl-4-(maleimidomethyl)cyclohexanecarboxylate (SMCC), sulfosuccinimidyl 4-(*N*-maleimidomethyl) cyclohexane-1-carboxylate (sulfo-SMCC), *N*-succinimidyl-4-(maleimidomethyl)cyclohexane-1-carboxy-(6-amidocaproate), which is a “long chain” analog of SMCC (LC-SMCC), κ -maleimidoundeconoic acid *N*-succinimidyl ester (KMUA), γ -maleimidobutyric acid *N*-succinimidyl ester (GMBS), ϵ -maleimidocaproic acid *N*-succinimidyl ester (EMCS), *m*-maleimidobenzoyl-*N*-hydroxysuccinimide ester (MBS), *N*-(α -maleimidoacetoxy)-succinimide ester (AMSA), succinimidyl-6-(β -maleimidopropionamido)hexanoate (SMPH), *N*-succinimidyl-4-(*p*-maleimidophenyl)-butyrate (SMPB), *N*-(*p*-maleimidophenyl)isocyanate (PMIP) and maleimido-based cross-linking reagents containing a polyethylene glycol spacer, such as MAL-PEG-NHS. These cross-linking reagents form non-cleavable linkers derived from maleimido-based moieties. Representative structures of maleimido-based cross-linking reagents are shown below.

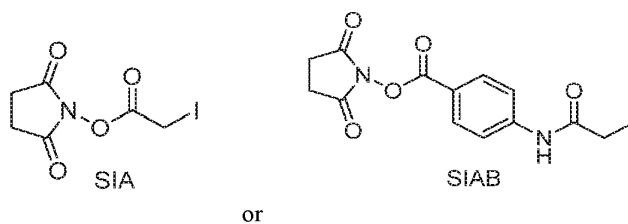


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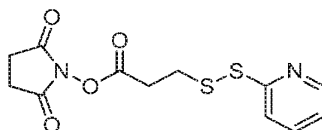
[00114] In another aspect, the linker L is derived from *N*-succinimidyl-4-(maleimidomethyl)cyclohexanecarboxylate (SMCC), sulfosuccinimidyl 4-(*N*-maleimidomethyl)cyclohexane-1-carboxylate (sulfo-SMCC) or MAL-PEG-NHS.

[00115] Cross-linking reagents comprising a haloacetyl-based moiety include *N*-succinimidyl iodoacetate (SIA), *N*-succinimidyl(4-iodoacetyl)aminobenzoate (SIAB), *N*-succinimidyl bromoacetate (SBA) and *N*-succinimidyl 3-(bromoacetamido)propionate (SBAP). These cross-linking reagents form a non-cleavable linker derived from haloacetyl-based moieties. Representative structures of haloacetyl-based cross-linking reagents are shown below.



[00116] In one aspect, the linker L is derived from *N*-succinimidyl iodoacetate (SIA) or *N*-succinimidyl(4-iodoacetyl)aminobenzoate (SIAB).

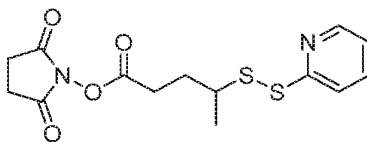
[00117] Suitable cross-linking reagents that form a cleavable linker between the drug moiety D, for example maytansinoid, and the antibody Ab are well known in the art. Disulfide containing linkers are linkers cleavable through disulfide exchange, which can occur under physiological conditions. According to the present disclosure, such cleavable linkers are said to be derived from disulfide-based moieties. Suitable disulfide cross-linking reagents include *N*-succinimidyl-3-(2-pyridyldithio)propionate (SPDP), *N*-succinimidyl-4-(2-pyridyldithio)pentanoate (SPP), *N*-succinimidyl-4-(2-pyridyldithio)butanoate (SPDB) and *N*-succinimidyl-4-(2-pyridyldithio)2-sulfo-butanoate (sulfo-SPDB), the structures of which are shown below. These disulfide cross-linking reagents form a cleavable linker derived from disulfide-based moieties.



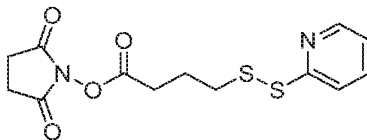
N-succinimidyl-3-(2-pyridyldithio)propionate (SPDP),

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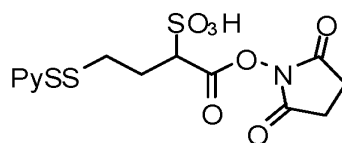
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N-succinimidyl-4-(2-pyridylthio)pentanoate (SPP),



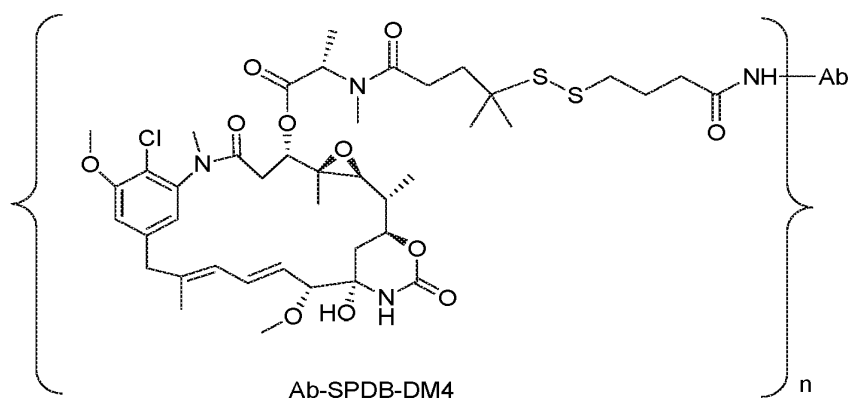
N-succinimidyl-4-(2-pyridylthio)butanoate (SPDB) and



N-succinimidyl-4-(2-pyridylthio)2-sulfo-butanoate (sulfo-SPDB)

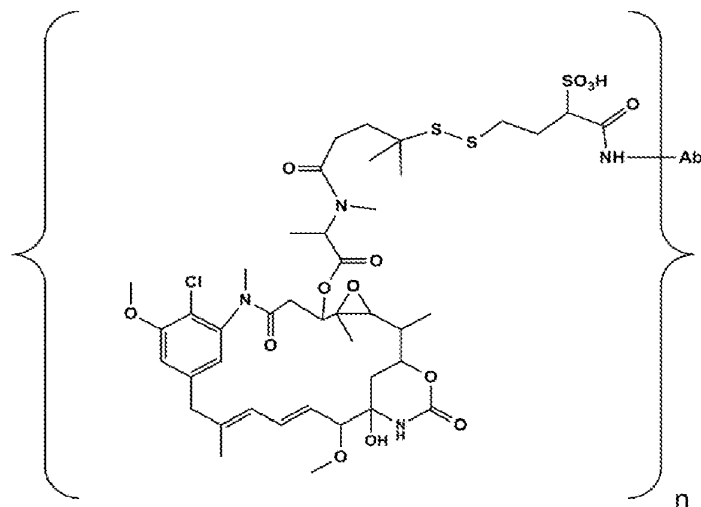
[00118] In one aspect, the linker L is derived from N-succinimidyl-4-(2-pyridylthio)2-sulfo-butanoate (sulfo-SPDB).

[00119] In one aspect provided by the disclosure, the conjugate is represented by any one of the following structural formulae:

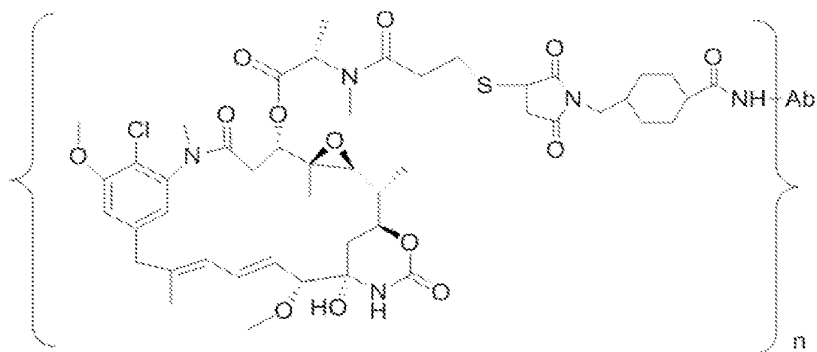


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Ab-sulfo-SPDB-DM4



Ab-MCC-DM1

[00120] wherein: Ab is an antibody or antigen binding fragment thereof that specifically binds to human CDH6; n, which indicates the number of D-L groups attached the Ab through the formation

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of an amide bond with a primary amine of the Ab, is an integer from 1 to 20. In one aspect, n is an integer from 1 to 10, 2 to 8 or 2 to 5. In a specific aspect, n is 3 or 4.

[00121] In one aspect, the average molar ratio of drug moiety (*e.g.*, DM1 or DM4) to the antibody in the conjugate (*i.e.*, average w value, also known as Maytansinoid Antibody Ratio (MAR)) is about 1 to about 10, about 2 to about 8 (*e.g.*, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, or 8.1), about 2.5 to about 7, about 3 to about 5, about 2.5 to about 4.5 (*e.g.*, about 2.5, about 2.6, about 2.7, about 2.8, about 2.9, about 3.0, about 3.1, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, about 4.0, about 4.1, about 4.2, about 4.3, about 4.4, about 4.5), about 3.0 to about 4.0, about 3.2 to about 4.2, or about 4.5 to 5.5 (*e.g.*, about 4.5, about 4.6, about 4.7, about 4.8, about 4.9, about 5.0, about 5.1, about 5.2, about 5.3, about 5.4, or about 5.5).

[00122] In one aspect provided by the disclosure, the conjugate has substantially high purity and has one or more of the following features: (a) greater than about 90% (*e.g.*, greater than or equal to about 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%), preferably greater than about 95%, of conjugate species are monomeric, (b) unconjugated linker level in the conjugate preparation is less than about 10% (*e.g.*, less than or equal to about 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or 0%) (relative to total linker), (c) less than 10% of conjugate species are crosslinked (*e.g.*, less than or equal to about 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or 0%), (d) free drug moiety (*e.g.*, DM1 or DM4) level in the conjugate preparation is less than about 2% (*e.g.*, less than or equal to about 1.5%, 1.4%, 1.3%, 1.2%, 1.1%, 1.0%, 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, or 0%) (mol/mol relative to total cytotoxic agent).

[00123] As used herein, the term “unconjugated linker” refers to the antibody that is covalently linked with a linker derived from a cross-linking reagent (*e.g.*, SMCC, Sulfo-SMCC, SPDB, Sulfo-SPDB or CX1-1), wherein the antibody is not covalently coupled to the drug moiety (*e.g.*, DM1 or DM4) through a linker (*i.e.*, the “unconjugated linker” can be represented by Ab-SMCC, Ab-SPDB, Ab-sulfo-SPDB, or Ab-CX1-1).

1. Drug Moiety

[00124] The present disclosure provides immunoconjugates that specifically bind to CDH6. The immunoconjugates of the present disclosure comprise anti-CDH6 antibodies, antibody fragments (*e.g.*, antigen binding fragments) or functional equivalents that are conjugated to a drug moiety, *e.g.*,

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an anti-cancer agent, anti-hematological disorder agent, an autoimmune treatment agent, an anti-inflammatory agent, an antifungal agent, an antibacterial agent, an anti-parasitic agent, an anti-viral agent, or an anesthetic agent. The antibodies, antibody fragments (*e.g.*, antigen binding fragments) or functional equivalents can be conjugated to several identical or different drug moieties using any methods known in the art.

[00125] In certain aspects, the drug moiety of the immunoconjugates of the present disclosure is selected from a group consisting of: a maytansinoid, a V-ATPase inhibitor, a pro-apoptotic agent, a Bcl2 inhibitor, an MCL1 inhibitor, a HSP90 inhibitor, an IAP inhibitor, an mTor inhibitor, a microtubule stabilizer, a microtubule destabilizer, an auristatin, a dolastatin, a MetAP (methionine aminopeptidase), an inhibitor of nuclear export of proteins CRM1, a DPPIV inhibitor, proteasome inhibitors, an inhibitor of phosphoryl transfer reactions in mitochondria, a protein synthesis inhibitor, a kinase inhibitor, a CDK2 inhibitor, a CDK9 inhibitor, a kinesin inhibitor, an HDAC inhibitor, a DNA damaging agent, a DNA alkylating agent, a DNA intercalator, a DNA minor groove binder and a DHFR inhibitor.

[00126] In one aspect, the drug moiety of the immunoconjugates of the present disclosure is a maytansinoid drug moiety, such as but not limited to, DM1, DM3, or DM4.

[00127] Further, the antibodies, antibody fragments (*e.g.*, antigen binding fragments) or functional equivalents of the present disclosure may be conjugated to a drug moiety that modifies a given biological response. Drug moieties are not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein, peptide, or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, cholera toxin, or diphtheria toxin, a protein such as tumor necrosis factor, α -interferon, β -interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, a cytokine, an apoptotic agent, an anti-angiogenic agent, or, a biological response modifier such as, for example, a lymphokine.

[00128] In one aspect, the antibodies, antibody fragments (*e.g.*, antigen binding fragments) or functional equivalents of the present disclosure are conjugated to a drug moiety, such as a cytotoxin, a drug (*e.g.*, an immunosuppressant) or a radiotoxin. Examples of cytotoxin include but are not limited to, taxanes (see, *e.g.*, International (PCT) Patent Application Nos. WO 01/38318 and PCT/US03/02675), DNA-alkylating agents (*e.g.*, CC-1065 analogs), anthracyclines, tubulysin analogs, duocarmycin analogs, auristatin E, auristatin F, maytansinoids, and cytotoxic agents comprising a reactive polyethylene glycol moiety (see, *e.g.*, Sasse *et al.*, J. Antibiot. (Tokyo), 53, 879-85 (2000),

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Suzawa *et al.*, Bioorg. Med. Chem., 8, 2175-84 (2000), Ichimura *et al.*, J. Antibiot. (Tokyo), 44, 1045-53 (1991), Francisco *et al.*, Blood 2003 15;102(4):1458-65), U.S. Pat. Nos. 5,475,092, 6,340,701, 6,372,738, and 6,436,931, U.S. Patent Application Publication No. 2001/0036923 A1, Pending U.S. patent application Ser. Nos. 10/024,290 and 10/116,053, and International (PCT) Patent Application No. WO 01/49698), taxon, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicine, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1 -dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents also include, for example, anti-metabolites (*e.g.*, methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), ablating agents (*e.g.*, mechlorethamine, thiotepa chlorambucil, meiphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin, anthracyclines (*e.g.*, daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (*e.g.*, dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (*e.g.*, vincristine and vinblastine). (See *e.g.*, Seattle Genetics US20090304721).

[00129] Other examples of cytotoxins that can be conjugated to the antibodies, antibody fragments (antigen binding fragments) or functional equivalents of the present disclosure include duocarmycins, calicheamicins, maytansines and auristatins, and derivatives thereof.

[00130] Various types of cytotoxins, linkers and methods for conjugating therapeutic agents to antibodies are known in the art, see, *e.g.*, Saito *et al.*, (2003) Adv. Drug Deliv. Rev. 55:199-215; Trail *et al.*, (2003) Cancer Immunol. Immunother. 52:328-337; Payne, (2003) Cancer Cell 3:207-212; Allen, (2002) Nat. Rev. Cancer 2:750-763; Pastan and Kreitman, (2002) Curr. Opin. Investig. Drugs 3:1089-1091; Senter and Springer, (2001) Adv. Drug Deliv. Rev. 53:247-264.

[00131] The antibodies, antibody fragments (*e.g.*, antigen binding fragments) or functional equivalents of the present disclosure can also be conjugated to a radioactive isotope to generate cytotoxic radiopharmaceuticals, referred to as radioimmunoconjugates. Examples of radioactive isotopes that can be conjugated to antibodies for use diagnostically or therapeutically include, but are not limited to, iodine-131, indium-111, yttrium-90, and lutetium-177. Methods for preparing radioimmunoconjugates are established in the art. Examples of radioimmunoconjugates are commercially available, including ZevalinTM (IDEC Pharmaceuticals) and BexxarTM (Corixa Pharmaceuticals), and similar methods can be used to prepare radioimmunoconjugates using the

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antibodies disclosed herein. In certain aspects, the macrocyclic chelator is 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA) which can be attached to the antibody via a linker molecule. Such linker molecules are commonly known in the art and described in Denardo *et al.*, (1998) Clin Cancer Res. 4(10):2483-90; Peterson *et al.*, (1999) Bioconjug. Chem. 10(4):553-7; and Zimmerman *et al.*, (1999) Nucl. Med. Biol. 26(8):943-50, each incorporated by reference in their entireties.

[00132] The antibodies, antibody fragments (*e.g.*, antigen binding fragments) or functional equivalents of the present disclosure can also conjugated to a heterologous protein or polypeptide (or fragment thereof, preferably to a polypeptide of at least 10, at least 20, at least 30, at least 40, at least 50, at least 60, at least 70, at least 80, at least 90 or at least 100 amino acids) to generate fusion proteins. In particular, the present disclosure provides fusion proteins comprising an antibody fragment (*e.g.*, antigen binding fragment) described herein (*e.g.*, a Fab fragment, Fd fragment, Fv fragment, F(ab)₂ fragment, a VH domain, a VH CDR, a VL domain or a VL CDR) and a heterologous protein, polypeptide, or peptide.

[00133] Additional fusion proteins may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to alter the activities of antibodies of the present disclosure or fragments thereof (*e.g.*, antibodies or fragments thereof with higher affinities and lower dissociation rates). See, generally, U.S. Patent Nos. 5,605,793, 5,811,238, 5,830,721, 5,834,252, and 5,837,458; Patten *et al.*, (1997) Curr. Opin Biotechnol. 8:724-33; Harayama, (1998) Trends Biotechnol. 16(2):76-82; Hansson *et al.*, (1999) J. Mol. Biol. 287:265-76; and Lorenzo and Blasco, (1998) Biotechniques 24(2):308-313 (each of these patents and publications are hereby incorporated by reference in its entirety). Antibodies or fragments thereof, or the encoded antibodies or fragments thereof, may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. A polynucleotide encoding an antibody or fragment thereof that specifically binds to an antigen may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

2. Linker

[00134] As used herein, a "linker" is any chemical moiety that is capable of linking an antibody, antibody fragment (*e.g.*, antigen binding fragments) or functional equivalent to another moiety, such as a drug moiety. Linkers can be susceptible to cleavage (cleavable linker), such as,

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acid-induced cleavage, photo-induced cleavage, peptidase-induced cleavage, esterase-induced cleavage, and disulfide bond cleavage, at conditions under which the compound or the antibody remains active. Alternatively, linkers can be substantially resistant to cleavage (*e.g.*, stable linker or noncleavable linker). In some aspects, the linker is a procharged linker, a hydrophilic linker, or a dicarboxylic acid based linker.

[00135] In one aspect, the linker used is derived from a crosslinking reagent such as N-succinimidyl-3-(2-pyridyldithio)propionate (SPDP), N-succinimidyl 4-(2-pyridyldithio)pentanoate (SPP), N-succinimidyl 4-(2-pyridyldithio)butanoate (SPDB), *N*-succinimidyl-4-(2-pyridyldithio)-2-sulfo-butanoate (sulfo-SPDB), N-succinimidyl iodoacetate (SIA), N-succinimidyl(4-iodoacetyl)aminobenzoate (SIAB), maleimide PEG NHS, N-succinimidyl 4-(maleimidomethyl) cyclohexanecarboxylate (SMCC), N-sulfosuccinimidyl 4-(maleimidomethyl) cyclohexanecarboxylate (sulfo-SMCC) or 2,5-dioxopyrrolidin-1-yl 17-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-5,8,11,14-tetraoxo-4,7,10,13-tetraazaheptadecan-1-oate (CX1-1). In another aspect, the linker used is derived from a cross-linking agent such as N-succinimidyl-3-(2-pyridyldithio)propionate (SPDP), N-succinimidyl 4-(maleimidomethyl) cyclohexanecarboxylate (SMCC), N-sulfosuccinimidyl 4-(maleimidomethyl) cyclohexanecarboxylate (sulfo-SMCC), *N*-succinimidyl-4-(2-pyridyldithio)-2-sulfo-butanoate (sulfo-SPDB) or 2,5-dioxopyrrolidin-1-yl 17-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-5,8,11,14-tetraoxo-4,7,10,13-tetraazaheptadecan-1-oate (CX1-1).

[00136] Non-cleavable linkers are any chemical moiety capable of linking a drug moiety, such as a maytansinoid, to an antibody in a stable, covalent manner and does not fall off under the categories listed above for cleavable linkers. Thus, non-cleavable linkers are substantially resistant to acid-induced cleavage, photo-induced cleavage, peptidase-induced cleavage, esterase-induced cleavage and disulfide bond cleavage. Furthermore, non-cleavable refers to the ability of the chemical bond in the linker or adjoining to the linker to withstand cleavage induced by an acid, photolabile-cleaving agent, a peptidase, an esterase, or a chemical or physiological compound that cleaves a disulfide bond, at conditions under which the drug moiety, such as maytansinoid or the antibody does not lose its activity.

[00137] Acid-labile linkers are linkers cleavable at acidic pH. For example, certain intracellular compartments, such as endosomes and lysosomes, have an acidic pH (pH 4-5), and provide conditions suitable to cleave acid-labile linkers.

[00138] Photo-labile linkers are linkers that are useful at the body surface and in many body cavities that are accessible to light. Furthermore, infrared light can penetrate tissue.

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[00139] Some linkers can be cleaved by peptidases, i.e. peptidase cleavable linkers. Only certain peptides are readily cleaved inside or outside cells, see e.g. Trout et al., 79 Proc. Natl. Acad. Sci. USA, 626-629 (1982) and Umemoto et al. 43 Int. J. Cancer, 677-684 (1989). Furthermore, peptides are composed of α -amino acids and peptidic bonds, which chemically are amide bonds between the carboxylate of one amino acid and the amino group of a second amino acid. Other amide bonds, such as the bond between a carboxylate and the ϵ -amino group of lysine, are understood not to be peptidic bonds and are considered non-cleavable.

[00140] Some linkers can be cleaved by esterases, i.e. esterase cleavable linkers. Again, only certain esters can be cleaved by esterases present inside or outside of cells. Esters are formed by the condensation of a carboxylic acid and an alcohol. Simple esters are esters produced with simple alcohols, such as aliphatic alcohols, and small cyclic and small aromatic alcohols.

[00141] Procharged linkers are derived from charged cross-linking reagents that retain their charge after incorporation into an antibody drug conjugate. Examples of procharged linkers can be found in US 2009/0274713.

3. Conjugation and Preparation of ADCs

[00142] The conjugates of the present disclosure can be prepared by any methods known in the art, such as those described in US Patent Nos. 7,811,572, 6,411,163, 7,368,565, and 8,163,888, and US application publications 2011/0003969, 2011/0166319, 2012/0253021 and 2012/0259100. The entire teachings of these patents and patent application publications are herein incorporated by reference.

One-Step Process

[00143] In one aspect, the conjugates of the present disclosure can be prepared by a one-step process. The process comprises combining the antibody, drug and cross-linking agent in a substantially aqueous medium, optionally containing one or more co-solvents, at a suitable pH. In one aspect, the process comprises the step of contacting the antibody of the present disclosure with a drug (e.g., DM1 or DM4) to form a first mixture comprising the antibody and the drug, and then contacting the first mixture comprising the antibody and the drug with a cross-linking agent (e.g., SMCC, Sulfo-SMCC, SPDB, Sulfo-SPDB or CX1-1) in a solution having a pH of about 4 to about 9 to provide a mixture comprising (i) the conjugate (e.g., Ab-MCC-DM1, Ab-SPDB-DM4, Sulfo-SPDB-DM4, or Ab-CX1-1-DM1), (ii) free drug (e.g., DM1 or DM4), and (iii) reaction by-products.

[00144] In one aspect, the one-step process comprises contacting the antibody with the drug (e.g., DM1 or DM4) and then the cross-linking agent (e.g., SMCC, Sulfo-SMCC, SPDB, Sulfo-SPDB or CX1-1) in a solution having a pH of about 6 or greater (e.g., about 6 to about 9, about 6 to about 7,

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about 7 to about 9, about 7 to about 8.5, about 7.5 to about 8.5, about 7.5 to about 8.0, about 8.0 to about 9.0, or about 8.5 to about 9.0). For example, the process comprises contacting a cell-binding agent with the drug (DM1 or DM4) and then the cross-linking agent (*e.g.*, SMCC, Sulfo-SMCC, SPDB, Sulfo-SPDB or CX1-1) in a solution having a pH of about 6.0, about 6.1, about 6.2, about 6.3, about 6.4, about 6.5, about 6.6, about 6.7, about 6.8, about 6.9, about 7.0, about 7.1, about 7.2, about 7.3, about 7.4, about 7.5, about 7.6, about 7.7, about 7.8, about 7.9, about 8.0, about 8.1, about 8.2, about 8.3, about 8.4, about 8.5, about 8.6, about 8.7, about 8.8, about 8.9, or about 9.0. In another aspect, the process comprises contacting a cell-binding agent with the drug (*e.g.*, DM1 or DM4) and then the cross-linking agent (*e.g.*, SMCC, Sulfo-SMCC, SPDB, Sulfo-SPDB or CX1-1) in a solution having a pH of about 7.8 (*e.g.*, a pH of 7.6 to 8.0 or a pH of 7.7 to 7.9).

[00145] The one-step process (*i.e.*, contacting the antibody with the drug (*e.g.*, DM1 or DM4) and then the cross-linking agent (*e.g.*, SMCC, Sulfo-SMCC, SPDB, Sulfo-SPDB or CX1-1)) can be carried out at any suitable temperature known in the art. For example, the one-step process can occur at about 20°C or less (*e.g.*, about -10°C (provided that the solution is prevented from freezing, *e.g.*, by the presence of organic solvent used to dissolve the cytotoxic agent and the bifunctional crosslinking reagent) to about 20°C, about 0°C to about 18°C, about 4°C to about 16°C), at room temperature (*e.g.*, about 20°C to about 30°C or about 20°C to about 25°C), or at an elevated temperature (*e.g.*, about 30°C to about 37°C). In one aspect, the one-step process occurs at a temperature of about 16°C to about 24°C (*e.g.*, about 16°C, about 17°C, about 18°C, about 19°C, about 20°C, about 21°C, about 22°C, about 23°C, about 24°C, or about 25°C). In another aspect, the one-step process is carried out at a temperature of about 15°C or less (*e.g.*, about -10°C to about 15°C, or about 0°C to about 15°C). For example, the process comprises contacting the antibody with the drug (*e.g.*, DM1 or DM4) and then the cross-linking agent (*e.g.*, SMCC, Sulfo-SMCC, SPDB, Sulfo-SPDB or CX1-1) at a temperature of about 15°C, about 14°C, about 13°C, about 12°C, about 11°C, about 10°C, about 9°C, about 8°C, about 7°C, about 6°C, about 5°C, about 4°C, about 3°C, about 2°C, about 1°C, about 0°C, about -1°C, about -2°C, about -3°C, about -4°C, about -5°C, about -6°C, about -7°C, about -8°C, about -9°C, or about -10°C, provided that the solution is prevented from freezing, *e.g.*, by the presence of organic solvent(s) used to dissolve the cross-linking agent (*e.g.*, SMCC, Sulfo-SMCC, Sulfo-SPDB, SPDB, or CX1-1). In one aspect, the process comprises contacting the antibody with the drug (*e.g.*, DM1 or DM4) and then the cross-linking agent (*e.g.*, SMCC, Sulfo-SMCC, SPDB, Sulfo-SPDB or CX1-1) at a temperature of about -10°C to about 15°C, about 0°C to about 15°C, about 0°C to about 10°C, about 0°C to about 5°C, about 5°C to about 15°C, about 10°C to about 15°C, or about 5°C to about 10°C. In another aspect, the process comprises contacting the antibody with the drug (*e.g.*, DM1 or DM4) and then the cross-linking agent (*e.g.*, SMCC, Sulfo-SMCC, SPDB, Sulfo-SPDB or CX1-1) at a temperature of about 10°C (*e.g.*, a temperature of 8°C to 12°C or a temperature of 9°C to 11°C).

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[00146] In one aspect, the contacting described above is effected by providing the antibody, then contacting the antibody with the drug (*e.g.*, DM1 or DM4) to form a first mixture comprising the antibody and the drug (*e.g.*, DM1 or DM4), and then contacting the first mixture comprising the antibody and the drug (*e.g.*, DM1 or DM4) with the cross-linking agent (*e.g.*, SMCC, Sulfo-SMCC, SPDB, Sulfo-SPDB or CX1-1). For example, in one aspect, the antibody is provided in a reaction vessel, the drug (*e.g.*, DM1 or DM4) is added to the reaction vessel (thereby contacting the antibody), and then the cross-linking agent (*e.g.*, SMCC, Sulfo-SMCC, SPDB, Sulfo-SPDB or CX1-1) is added to the mixture comprising the antibody and the drug (*e.g.*, DM1 or DM4) (thereby contacting the mixture comprising the antibody and the drug). In one aspect, the antibody is provided in a reaction vessel, and the drug (*e.g.*, DM1 or DM4) is added to the reaction vessel immediately following providing the antibody to the vessel. In another aspect, the antibody is provided in a reaction vessel, and the drug (*e.g.*, DM1 or DM4) is added to the reaction vessel after a time interval following providing the antibody to the vessel (*e.g.*, about 5 minutes, about 10 minutes, about 20 minutes, about 30 minutes, about 40 minutes, about 50 minutes, about 1 hour, about 1 day or longer after providing the cell-binding agent to the space). The drug (*e.g.*, DM1 or DM4) can be added quickly (*i.e.*, within a short time interval, such as about 5 minutes, about 10 minutes) or slowly (such as by using a pump).

[00147] The mixture comprising the antibody and the drug (*e.g.*, DM1 or DM4) can then be contacted with the cross-linking agent (*e.g.*, SMCC, Sulfo-SMCC, SPDB, Sulfo-SPDB or CX1-1) either immediately after contacting the antibody with the drug (*e.g.*, DM1 or DM4) or at some later point (*e.g.*, about 5 minutes to about 8 hours or longer) after contacting the antibody with the drug (*e.g.*, DM1 or DM4). For example, in one aspect, the cross-linking agent (*e.g.*, SMCC, Sulfo-SMCC, SPDB, Sulfo-SPDB or CX1-1) is added to the mixture comprising the antibody and the drug (*e.g.*, DM1 or DM4) immediately after the addition of the drug (*e.g.*, DM1 or DM4) to the reaction vessel comprising the antibody. Alternatively, the mixture comprising the antibody and the drug (*e.g.*, DM1 or DM4) can be contacted with the cross-linking agent (*e.g.*, SMCC, Sulfo-SMCC, SPDB, Sulfo-SPDB or CX1-1) at about 5 minutes, about 10 minutes, about 20 minutes, about 30 minutes, about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, or longer after contacting the antibody with the drug (*e.g.*, DM1 or DM4).

[00148] After the mixture comprising the antibody and the drug (*e.g.*, DM1 or DM4) is contacted with the cross-linking agent (*e.g.*, SMCC, Sulfo-SMCC, SPDB, Sulfo-SPDB or CX1-1) the reaction is allowed to proceed for about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 11 hours, about 12 hours, about 13 hours, about 14 hours, about 15 hours, about 16 hours, about 17 hours, about 18 hours, about 19 hours, about 20 hours, about 21 hours, about 22 hours, about 23 hours, about 24 hours, or longer (*e.g.*, about 30 hours, about 35 hours, about 40 hours, about 45 hours, or about 48 hrs).

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[00149] In one aspect, the one-step process further comprises a quenching step to quench any unreacted drug (*e.g.*, DM1 or DM4) and/or unreacted cross-linking agent (*e.g.*, SMCC, Sulfo-SMCC, SPDB, Sulfo-SPDB or CX1-1). The quenching step is typically performed prior to purification of the conjugate. In one aspect, the mixture is quenched by contacting the mixture with a quenching reagent. As used herein, the “quenching reagent” refers to a reagent that reacts with the free drug (*e.g.*, DM1 or DM4) and/or cross-linking agent (*e.g.*, SMCC, Sulfo-SMCC, SPDB, Sulfo-SPDB or CX1-1). In one aspect, maleimide or haloacetamide quenching reagents, such as 4-maleimidobutyric acid, 3-maleimidopropionic acid, N-ethylmaleimide, iodoacetamide, or iodoacetamidopropionic acid, can be used to ensure that any unreacted group (such as thiol) in the drug (*e.g.*, DM1 or DM4) is quenched. The quenching step can help prevent the dimerization of the drug (*e.g.*, DM1). The dimerized DM1 can be difficult to remove. Upon quenching with polar, charged thiol-quenching reagents (such as 4-maleimidobutyric acid or 3-maleimidopropionic acid), the excess, unreacted DM1 is converted into a polar, charged, water-soluble adduct that can be easily separated from the covalently-linked conjugate during the purification step. Quenching with non-polar and neutral thiol-quenching reagents can also be used. In one aspect, the mixture is quenched by contacting the mixture with a quenching reagent that reacts with the unreacted cross-linking agent (*e.g.*, SMCC, Sulfo-SMCC, SPDB, Sulfo-SPDB or CX1-1). For example, nucleophiles can be added to the mixture in order to quench any unreacted SMCC. The nucleophile preferably is an amino group containing nucleophile, such as lysine, taurine and hydroxylamine.

[00150] In another aspect, the reaction (*i.e.*, contacting the antibody with the drug (*e.g.*, DM1 or DM4) and then cross-linking agent (*e.g.*, SMCC, Sulfo-SMCC, SPDB, Sulfo-SPDB or CX1-1)) is allowed to proceed to completion prior to contacting the mixture with a quenching reagent. In this regard, the quenching reagent is added to the mixture about 1 hour to about 48 hours (*e.g.*, about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 11 hours, about 12 hours, about 13 hours, about 14 hours, about 15 hours, about 16 hours, about 17 hours, about 18 hours, about 19 hours, about 20 hours, about 21 hours, about 22 hours, about 23 hours, about 24 hours, or about 25 hours to about 48 hours) after the mixture comprising the antibody and the drug (*e.g.*, DM1 or DM4) is contacted with the cross-linking agent (*e.g.*, SMCC, Sulfo-SMCC, SPDB, Sulfo-SPDB or CX1-1).

[00151] Alternatively, the mixture is quenched by lowering the pH of the mixture to about 5.0 (*e.g.*, 4.8, 4.9, 5.0, 5.1 or 5.2). In another aspect, the mixture is quenched by lowering the pH to less than 6.0, less than 5.5, less than 5.0, less than 4.8, less than 4.6, less than 4.4, less than 4.2, less than 4.0. Alternatively, the pH is lowered to about 4.0 (*e.g.*, 3.8, 3.9, 4.0, 4.1 or 4.2) to about 6.0 (*e.g.*, 5.8, 5.9, 6.0, 6.1 or 6.2), about 4.0 to about 5.0, about 4.5 (*e.g.*, 4.3, 4.4, 4.5, 4.6 or 4.7) to about 5.0. In one aspect, the mixture is quenched by lowering the pH of the mixture to 4.8. In another aspect, the mixture is quenched by lowering the pH of the mixture to 5.5.

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[00152] In one aspect, the one-step process further comprises a holding step to release the unstably bound linkers from the antibody. The holding step comprises holding the mixture prior to purification of the conjugate (*e.g.*, after the reaction step, between the reaction step and the quenching step, or after the quenching step). For example, the process comprises (a) contacting the antibody with the drug (*e.g.*, DM1 or DM4) to form a mixture comprising the antibody and the drug (*e.g.*, DM1 or DM4); and then contacting the mixture comprising the antibody and drug (*e.g.*, DM1 or DM4) with the cross-linking agent (*e.g.*, SMCC, Sulfo-SMCC, SPDB, Sulfo-SPDB or CX1-1), in a solution having a pH of about 4 to about 9 to provide a mixture comprising (i) the conjugate (*e.g.*, Ab-MCC-DM1, Ab-SPDB-DM4, Sulfo-SPDB-DM4 or Ab-CX1-1-DM1), (ii) free drug (*e.g.*, DM1 or DM4), and (iii) reaction by-products, (b) holding the mixture prepared in step (a) to release the unstably bound linkers from the cell-binding agent, and (c) purifying the mixture to provide a purified conjugate.

[00153] In another aspect, the process comprises (a) contacting the antibody with the drug (*e.g.*, DM1 or DM4) to form a mixture comprising the antibody and the drug (*e.g.*, DM1 or DM4); and then contacting the mixture comprising the antibody and the drug (*e.g.*, DM1 or DM4) with the cross-linking agent (*e.g.*, SMCC, Sulfo-SMCC, SPDB, Sulfo-SPDB or CX1-1), in a solution having a pH of about 4 to about 9 to provide a mixture comprising (i) the conjugate, (ii) free drug (*e.g.*, DM1 or DM4), and (iii) reaction by-products, (b) quenching the mixture prepared in step (a) to quench any unreacted drug (*e.g.*, DM1 or DM4) and/or unreacted cross-linking agent (*e.g.*, SMCC, Sulfo-SMCC, SPDB, Sulfo-SPDB or CX1-1), (c) holding the mixture prepared in step (b) to release the unstably bound linkers from the cell-binding agent, and (d) purifying the mixture to provide a purified conjugate (*e.g.*, Ab-MCC-DM1, Ab-SPDB-DM4, Ab-Sulfo-SPDB-DM4 or Ab-CX1-1-DM1).

[00154] Alternatively, the holding step can be performed after purification of the conjugate, followed by an additional purification step.

[00155] In another aspect, the reaction is allowed to proceed to completion prior to the holding step. In this regard, the holding step can be performed about 1 hour to about 48 hours (*e.g.*, about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 11 hours, about 12 hours, about 13 hours, about 14 hours, about 15 hours, about 16 hours, about 17 hours, about 18 hours, about 19 hours, about 20 hours, about 21 hours, about 22 hours, about 23 hours, about 24 hours, or about 24 hours to about 48 hours) after the mixture comprising the antibody and the drug (*e.g.*, DM1 or DM4) is contacted with the cross-linking agent (*e.g.*, SMCC, Sulfo-SMCC, SPDB, Sulfo-SPDB or CX1-1).

[00156] The holding step comprises maintaining the solution at a suitable temperature (*e.g.*, about 0°C to about 37°C) for a suitable period of time (*e.g.*, about 1 hour to about 1 week, about 1 hour to about 24 hours, about 1 hour to about 8 hours, or about 1 hour to about 4 hours) to release the unstably bound linkers from the antibody while not substantially releasing the stably bound linkers

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from the antibody. In one aspect, the holding step comprises maintaining the solution at about 20 °C or less (*e.g.*, about 0°C to about 18°C, about 4°C to about 16°C), at room temperature (*e.g.*, about 20°C to about 30°C or about 20°C to about 25°C), or at an elevated temperature (*e.g.*, about 30°C to about 37°C). In one aspect, the holding step comprises maintaining the solution at a temperature of about 16°C to about 24°C (*e.g.*, about 15°C, about 16°C, about 17°C, about 18°C, about 19°C, about 20°C, about 21°C, about 22°C, about 23°C, about 24°C, or about 25°C). In another aspect, the holding step comprises maintaining the solution at a temperature of about 2°C to about 8°C (*e.g.*, about 0°C, about 1°C, about 2°C, about 3°C, about 4°C, about 5°C, about 6°C, about 7°C, about 8°C, about 9°C, or about 10°C). In another aspect, the holding step comprises maintaining the solution at a temperature of about 37°C (*e.g.*, about 34°C, about 35°C, about 36°C, about 37°C, about 38°C, about 39°C, or about 40°C).

[00157] The duration of the holding step depends on the temperature and the pH at which the holding step is performed. For example, the duration of the holding step can be substantially reduced by performing the holding step at elevated temperature, with the maximum temperature limited by the stability of the cell-binding agent-cytotoxic agent conjugate. The holding step can comprise maintaining the solution for about 1 hour to about 1 day (*e.g.*, about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, or about 24 hours), about 10 hours to about 24 hours, about 12 hours to about 24 hours, about 14 hours to about 24 hours, about 16 hours to about 24 hours, about 18 hours to about 24 hours, about 20 hours to about 24 hours, about 5 hours to about 1 week, about 20 hours to about 1 week, about 12 hours to about 1 week (*e.g.*, about 12 hours, about 16 hours, about 20 hours, about 24 hours, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, or about 7 days), or about 1 day to about 1 week.

[00158] In one aspect, the holding step comprises maintaining the solution at a temperature of about 2 °C to about 8 °C for a period of at least about 12 hours for up to a week. In another aspect, the holding step comprises maintaining the solution at a temperature of about 2 °C to about 8 °C overnight (*e.g.*, about 12 to about 24 hours, preferably about 20 hours).

[00159] The pH value for the holding step preferably is about 4 to about 10. In one aspect, the pH value for the holding step is about 4 or more, but less than about 6 (*e.g.*, 4 to 5.9) or about 5 or more, but less than about 6 (*e.g.*, 5 to 5.9). In another aspect, the pH values for the holding step range from about 6 to about 10 (*e.g.*, about 6.5 to about 9, about 6 to about 8). For example, pH values for the holding step can be about 6, about 6.5, about 7, about 7.5, about 8, about 8.5, about 9, about 9.5, or about 10.

[00160] In other aspects, the holding step can comprise incubating the mixture at 25°C at a pH of about 6-7.5 for about 12 hours to about 1 week, incubating the mixture at 4°C at a pH of about 4.5-

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5.9 for about 5 hours to about 5 days, or incubating the mixture at 25°C at a pH of about 4.5-5.9 for about 5 hours to about 1 day.

[00161] The one-step process can optionally include the addition of sucrose to the reaction step to increase solubility and recovery of the conjugates. Desirably, sucrose is added at a concentration of about 0.1% (w/v) to about 20% (w/v) (*e.g.*, about 0.1% (w/v), 1% (w/v), 5% (w/v), 10% (w/v), 15% (w/v), or 20% (w/v)). Preferably, sucrose is added at a concentration of about 1% (w/v) to about 10% (w/v) (*e.g.*, about 0.5% (w/v), about 1% (w/v), about 1.5% (w/v), about 2% (w/v), about 3% (w/v), about 4% (w/v), about 5% (w/v), about 6% (w/v), about 7% (w/v), about 8% (w/v), about 9% (w/v), about 10% (w/v), or about 11% (w/v)). In addition, the reaction step also can comprise the addition of a buffering agent. Any suitable buffering agent known in the art can be used. Suitable buffering agents include, for example, a citrate buffer, an acetate buffer, a succinate buffer, and a phosphate buffer. In one aspect, the buffering agent is selected from the group consisting of HEPPSO (N-(2-hydroxyethyl)piperazine-N'-(2-hydroxypropanesulfonic acid)), POPSO (piperazine-1,4-bis-(2-hydroxy-propane-sulfonic acid) dehydrate), HEPES (4-(2-hydroxyethyl)piperazine-1-ethanesulfonic acid), HEPPS (EPPS) (4-(2-hydroxyethyl)piperazine-1-propanesulfonic acid), TES (N-[tris(hydroxymethyl)methyl]-2-aminoethanesulfonic acid), and a combination thereof.

[00162] The one-step process can further comprise the step of purifying the mixture to provide purified conjugate (*e.g.*, Ab-MCC-DM1, Ab-SPDB-DM4, Ab-Sulfo-SPDB-DM4 or Ab-CX1-1-DM1). Any purification methods known in the art can be used to purify the conjugates of the present disclosure. In one aspect, the conjugates of the present disclosure use tangential flow filtration (TFF), non-adsorptive chromatography, adsorptive chromatography, adsorptive filtration, selective precipitation, or any other suitable purification process, as well as combinations thereof. In another aspect, prior to subjecting the conjugates to purification process described above, the conjugates are first filtered through one or more PVDF membranes. Alternatively, the conjugates are filtered through one or more PVDF membranes after subjecting the conjugates to the purification process described above. For example, in one aspect, the conjugates are filtered through one or more PVDF membranes and then purified using tangential flow filtration. Alternatively, the conjugates are purified using tangential flow filtration and then filtered through one or more PVDF membranes.

[00163] Any suitable TFF systems may be utilized for purification, including a Pellicon® type system (Millipore, Billerica, MA), a Sartocan® Cassette system (Sartorius AG, Edgewood, NY), and a Centrasette® type system (Pall Corp., East Hills, NY).

[00164] Any suitable adsorptive chromatography resin may be utilized for purification. Preferred adsorptive chromatography resins include hydroxyapatite chromatography, hydrophobic charge induction chromatography (HCIC), hydrophobic interaction chromatography (HIC), ion exchange chromatography, mixed mode ion exchange chromatography, immobilized metal affinity chromatography (IMAC), dye ligand chromatography, affinity chromatography, reversed phase

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chromatography, and combinations thereof. Examples of suitable hydroxyapatite resins include ceramic hydroxyapatite (CHT Type I and Type II, Bio-Rad Laboratories, Hercules, CA), HA Ultrogel® hydroxyapatite (Pall Corp., East Hills, NY), and ceramic fluoroapatite (CFT Type I and Type II, Bio-Rad Laboratories, Hercules, CA). An example of a suitable HCIC resin is MEP Hypercel® resin (Pall Corp., East Hills, NY). Examples of suitable HIC resins include Butyl-Sepharose, Hexyl-Sepharose, Phenyl-Sepharose, and Octyl Sepharose resins (all from GE Healthcare, Piscataway, NJ), as well as Macro-prep® Methyl and Macro-Prep® t-Butyl resins (Biorad Laboratories, Hercules, CA). Examples of suitable ion exchange resins include SP-Sepharose®, CM-Sepharose®, and Q-Sepharose® resins (all from GE Healthcare, Piscataway, NJ), and Unosphere® S resin (Bio-Rad Laboratories, Hercules, CA). Examples of suitable mixed mode ion exchangers include Bakerbond® ABx resin (JT Baker, Phillipsburg NJ). Examples of suitable IMAC resins include Chelating Sepharose® resin (GE Healthcare, Piscataway, NJ) and Profinity® IMAC resin (Bio-Rad Laboratories, Hercules, CA). Examples of suitable dye ligand resins include Blue Sepharose resin (GE Healthcare, Piscataway, NJ) and Affi-gel Blue resin (Bio-Rad Laboratories, Hercules, CA). Examples of suitable affinity resins include Protein A Sepharose resin (*e.g.*, MabSelect, GE Healthcare, Piscataway, NJ) and lectin affinity resins, *e.g.* Lentil Lectin Sepharose® resin (GE Healthcare, Piscataway, NJ), where the antibody bears appropriate lectin binding sites. Examples of suitable reversed phase resins include C4, C8, and C18 resins (Grace Vydac, Hesperia, CA).

[00165] Any suitable non-adsorptive chromatography resin may be utilized for purification. Examples of suitable non-adsorptive chromatography resins include, but are not limited to, SEPHADEX™ G-25, G-50, G-100, SEPHACRYL™ resins (*e.g.*, S-200 and S-300), SUPERDEX™ resins (*e.g.*, SUPERDEX™ 75 and SUPERDEX™ 200), BIO-GEL® resins (*e.g.*, P-6, P-10, P-30, P-60, and P-100), and others known to those of ordinary skill in the art.

Two-Step Process and One-Pot Process

[00166] In one aspect, the conjugates of the present disclosure can be prepared as described in the U.S. Patent 7,811,572 and U.S. Patent Application Publication No. 2006/0182750. The process comprises the steps of (a) contacting the antibody of the present disclosure with the cross-linking agent (*e.g.*, SMCC, Sulfo-SMCC, SPDB, Sulfo-SPDB or CX1-1) to covalently attach the linker (*i.e.*, Ab-SMCC, Ab-SPDB or Ab-CX1-1) to the antibody and thereby prepare a first mixture comprising the antibody having the linker bound thereto; (b) optionally subjecting the first mixture to a purification process to prepare a purified first mixture of the antibody having the linker bound thereto; (c) conjugating the drug (*e.g.*, DM1 or DM4) to the antibody having the linker bound thereto in the first mixture by reacting the antibody having the linker bound thereto with the drug (*e.g.*, DM1 or DM4) in a solution having a pH of about 4 to about 9 to prepare a second mixture comprising (i) conjugate (*e.g.*, Ab-MCC-DM1, Ab-SPDB-DM4, Ab-Sulfo-SPDB-DM4 or Ab-CX1-1-DM1), (ii) free drug (*e.g.*, DM1 or DM4); and (iii) reaction by-products; and (d) subjecting the second mixture to a

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purification process to purify the conjugate from the other components of the second mixture.

Alternatively, the purification step (b) can be omitted. Any purification methods described herein can be used for steps (b) and (d). In one embodiment, TFF is used for both steps (b) and (d). In another embodiment, TFF is used for step (b) and absorptive chromatography (*e.g.*, CHT) is used for step (d).

One-Step Reagent and In-situ Process

[00167] In one aspect, the conjugates of the present disclosure can be prepared by conjugating pre-formed drug-linker compound (*e.g.*, SMCC-DM1, Sulfo-SMCC-DM1, SPDB-DM4, Sulfo-SPDB-DM4 or CX1-1-DM1) to the antibody of the present disclosure, as described in U.S. Patent 6,441,163 and U.S. Patent Application Publication Nos. 2011/0003969 and 2008/0145374, followed by a purification step. Any purification methods described herein can be used. The drug-linker compound is prepared by reacting the drug (*e.g.*, DM1 or DM4) with the cross-linking agent (*e.g.*, SMCC, Sulfo-SMCC, SPDB, Sulfo-SPDB or CX1-1). The drug-linker compound (*e.g.*, SMCC-DM1, Sulfo-SMCC-DM1, SPDB-DM4, Sulfo-SPDB-DM4 or CX1-1-DM1) is optionally subjected to purification before being conjugated to the antibody.

4. Characterization and Selection of Desirable Antibodies and Antibody Drug Conjugates

[00168] The antibodies, antibody fragments (*e.g.*, antigen binding fragments) or antibody drug conjugates of the present disclosure can be characterized and selected for their physical/chemical properties and/or biological activities by various assays known in the art.

[00169] For example, an antibody of the present disclosure can be tested for its antigen binding activity by known methods such as ELISA, FACS, Biacore or Western blot.

[00170] Transgenic animals and cell lines are particularly useful in screening antibody drug conjugates (ADCs) that have potential as prophylactic or therapeutic treatments of cancer overexpression of tumor-associated antigens and cell surface receptors. Screening for a useful ADC may involve administering a candidate ADC over a range of doses to the transgenic animal, and assaying at various time points for the effect(s) of the ADC on the disease or disorder being evaluated. Alternatively, or additionally, the drug can be administered prior to or simultaneously with exposure to an inducer of the disease, if applicable. The candidate ADC may be screened serially and individually, or in parallel under medium or high-throughput screening format.

[00171] One aspect is a screening method comprising (a) transplanting cells from a stable cancer cell line or human patient tumor expressing CDH6 (*e.g.*, an ovarian cell line or tumor fragment, a renal cell line or tumor fragment, a hepatic cell line or tumor fragment, a thyroid cell line or tumor fragment, a CNS cancer cell line or tumor fragment, a cholangiocarcinoma cancer cell line or tumor fragment, ovarian, renal, hepatic, soft tissue, CNS, thyroid, or cholangiocarcinoma primary cells) into

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a non-human animal, (b) administering an ADC drug candidate to the non-human animal and (c) determining the ability of the candidate to inhibit the growth of tumors from the transplanted cell line. The present disclosure also encompasses a method of screening ADC candidates for the treatment of a disease or disorder characterized by the overexpression of CDH6 comprising (a) contacting cells from a stable cancer cell line expressing CDH6 with a drug candidate, and (b) evaluating the ability of the ADC candidate to inhibit the growth of the stable cell line.

[00172] A further aspect is a screening method comprising (a) contacting cells from a stable cancer cell line expressing CDH6 with an ADC drug candidate and (b) evaluating the ability of the ADC candidate to induce immunogenic cell death. In one aspect the ability of the ADC candidate to induce apoptosis is evaluated.

[00173] Candidate ADC can be screened by being administered to the transgenic animal over a range of doses, and evaluating the animal's physiological response to the compounds over time. In some cases, it can be appropriate to administer the compound in conjunction with co-factors that would enhance the efficacy of the compound. If cell lines derived from the subject transgenic animals are used to screen for ADCs useful in treating various disorders associated with overexpression of CDH6, the test ADCs are added to the cell culture medium at an appropriate time, and the cellular response to the ADCs is evaluated over time using the appropriate biochemical and/or histological assays.

CDH6 Antibodies

[00174] The present disclosure provides for antibodies or antibody fragments (*e.g.*, antigen binding fragments) that specifically bind to human CDH6. Antibodies or antibody fragments (*e.g.*, antigen binding fragments) of the present disclosure include, but are not limited to, the human monoclonal antibodies or fragments thereof, isolated as described, in the Examples below.

[00175] The present disclosure in certain aspects provides antibodies or antibody fragments (*e.g.*, antigen binding fragments) that specifically bind CDH6, said antibodies or antibody fragments (*e.g.*, antigen binding fragments) comprise a VH domain having an amino acid sequence of SEQ ID NO: 20, 34, 48, 62, 76, 90, 104, 118, 132, 146, 160, 174, 188, 202, 216, 230, 244, 258, 272, 286, 300, 314 or 328 (Table 5). The present disclosure also provides antibodies or antibody fragments (*e.g.*, antigen binding fragments) that specifically bind to CDH6, said antibodies or antibody fragments (*e.g.*, antigen binding fragments) comprise a VH CDR having an amino acid sequence of any one of the VH CDRs listed in Table 5. In particular aspects, the present disclosure provides antibodies or antibody

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fragments (*e.g.*, antigen binding fragments) that specifically bind to CDH6, said antibodies comprising (or alternatively, consist of) one, two, three, four, five or more VH CDRs having an amino acid sequence of any of the VH CDRs listed in Table 5.

[00176] The present disclosure provides antibodies or antibody fragments (*e.g.*, antigen binding fragments) that specifically bind to CDH6, said antibodies or antibody fragments (*e.g.*, antigen binding fragments) comprise a VL domain having an amino acid sequence of SEQ ID NO: 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, 175, 189, 203, 217, 231, 245, 259, 273, 287, 301, 315 or 329 (Table 5). The present disclosure also provides antibodies or antibody fragments (*e.g.*, antigen binding fragments) that specifically bind to CDH6, said antibodies or antibody fragments (*e.g.*, antigen binding fragments) comprise a VL CDR having an amino acid sequence of any one of the VL CDRs listed in Table 5, *infra*. In particular, the disclosure provides antibodies or antibody fragments (*e.g.*, antigen binding fragments) that specifically bind to CDH6, said antibodies or antibody fragments (*e.g.*, antigen binding fragments) comprise (or alternatively, consist of) one, two, three or more VL CDRs having an amino acid sequence of any of the VL CDRs listed in Table 5.

[00177] Other antibodies or antibody fragments (*e.g.*, antigen binding fragments) of the present disclosure include amino acids that have been mutated, yet have at least 60, 70, 80, 90 or 95 percent identity in the CDR regions with the CDR regions depicted in the sequences described in Table 5. In some aspects, it includes mutant amino acid sequences wherein no more than 1, 2, 3, 4 or 5 amino acids have been mutated in the CDR regions when compared with the CDR regions depicted in the sequence described in Table 5.

[00178] The present disclosure also provides nucleic acid sequences that encode VH, VL, the full length heavy chain, and the full length light chain of the antibodies that specifically bind to CDH6. Such nucleic acid sequences can be optimized for expression in mammalian cells.

[00179] Other antibodies of the present disclosure include those where the amino acids or nucleic acids encoding the amino acids have been mutated, yet have at least 60, 70, 80, 90 or 95 percent identity to the sequences described in Table 5. In some aspects, it includes mutant amino acid sequences wherein no more than 1, 2, 3, 4 or 5 amino acids have been mutated in the variable regions when compared with the variable regions depicted in the sequence described in Table 5, while retaining substantially the same therapeutic activity.

[00180] Since each of these antibodies can bind to CDH6, the VH, VL, full length light chain, and full length heavy chain sequences (amino acid sequences and the nucleotide sequences encoding the amino acid sequences) can be "mixed and matched" to create other CDH6-binding antibodies.

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Such "mixed and matched" CDH6 -binding antibodies can be tested using the binding assays known in the art (*e.g.*, ELISAs, and other assays described in the Example section). When these chains are mixed and matched, a VH sequence from a particular VH/VL pairing should be replaced with a structurally similar VH sequence. Likewise a full length heavy chain sequence from a particular full length heavy chain / full length light chain pairing should be replaced with a structurally similar full length heavy chain sequence. Likewise, a VL sequence from a particular VH/VL pairing should be replaced with a structurally similar VL sequence. Likewise, a full length light chain sequence from a particular full length heavy chain / full length light chain pairing should be replaced with a structurally similar full length light chain sequence. Accordingly, in one aspect, the disclosure provides for an isolated monoclonal antibody or antigen binding region thereof having: a heavy chain variable region (vH) comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 20, 34, 48, 62, 76, 90, 104, 118, 132, 146, 160, 174, 188, 202, 216, 230, 244, 258, 272, 286, 300, 314 or 328 (Table 5); and a light chain variable region (vL) comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, 175, 189, 203, 217, 231, 245, 259, 273, 287, 301, 315 or 329 (Table 5); wherein the antibody specifically binds to CDH6.

[00181] In another aspect, the disclosure provides (i) an isolated monoclonal antibody having: a full length heavy chain comprising an amino acid sequence that has been optimized for expression in the cell of a mammalian selected from the group consisting of SEQ ID NO: 24, 38, 52, 66, 80, 94, 108, 122, 136, 150, 164, 178, 192, 206, 220, 234, 248, 262, 276, 290, 304, 318 or 332; and a full length light chain comprising an amino acid sequence that has been optimized for expression in the cell of a mammalian selected from the group consisting of SEQ ID NO: 25, 39, 53, 67, 81, 95, 109, 123, 137, 151, 165, 179, 193, 207, 221, 235, 249, 263, 277, 291, 305, 319 or 333 ; or (ii) a functional protein comprising an antigen binding portion thereof.

[00182] In another aspect, the present disclosure provides CDH6 -binding antibodies that comprise the heavy chain and light chain CDR1s, CDR2s and CDR3s as described in Table 5, or combinations thereof. The amino acid sequences of the VH CDR1s of the antibodies are shown in SEQ ID NOs: 17, 31, 45, 59, 73, 87, 101, 115, 129, 143, 157, 171, 185, 199, 213, 227, 241, 255, 269, 283, 297, 311 and 325. The amino acid sequences of the VH CDR2s of the antibodies and are shown in SEQ ID NOs: 18, 32, 46, 60, 74, 88, 102, 116, 130, 144, 158, 172, 186, 200, 214, 228, 242, 256, 270, 284, 298, 312 and 326. The amino acid sequences of the VH CDR3s of the antibodies are shown in SEQ ID NOs: 19, 33, 47, 61, 75, 89, 103, 117, 131, 145, 159, 173, 187, 201, 215, 229, 243, 257, 271, 285, 299, 313 and 327. The amino acid sequences of the VL CDR1s of the antibodies are shown in

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SEQ ID NOs: 14, 28, 42, 56, 70, 84, 98, 112, 126, 140, 154, 168, 182, 196, 210, 224, 238, 252, 266, 280, 294, 308 and 322. The amino acid sequences of the VL CDR2s of the antibodies are shown in SEQ ID NOs: 15, 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, 169, 183, 197, 211, 225, 239, 253, 267, 281, 295, 309 and 323. The amino acid sequences of the VL CDR3s of the antibodies are shown in SEQ ID NOs: 16, 30, 44, 58, 72, 86, 100, 114, 128, 142, 156, 170, 184, 198, 212, 226, 240, 254, 268, 282, 296, 310 and 324.

[00183] Given that each of these antibodies can bind to CDH6 and that antigen-binding specificity is provided primarily by the CDR1, 2 and 3 regions, the VH CDR1, 2 and 3 sequences and VL CDR1, 2 and 3 sequences can be "mixed and matched" (i.e., CDRs from different antibodies can be mixed and match, although each antibody must contain a VH CDR1, 2 and 3 and a VL CDR1, 2 and 3 to create other CDH6-binding binding molecules. Such "mixed and matched" CDH6-binding antibodies can be tested using the binding assays known in the art and those described in the Examples (e.g., ELISAs). When VH CDR sequences are mixed and matched, the CDR1, CDR2 and/or CDR3 sequence from a particular VH sequence should be replaced with a structurally similar CDR sequence(s). Likewise, when VL CDR sequences are mixed and matched, the CDR1, CDR2 and/or CDR3 sequence from a particular VL sequence should be replaced with a structurally similar CDR sequence(s). It will be readily apparent to the ordinarily skilled artisan that novel VH and VL sequences can be created by substituting one or more VH and/or VL CDR region sequences with structurally similar sequences from the CDR sequences shown herein for monoclonal antibodies of the present disclosure.

[00184] Accordingly, the present disclosure provides an isolated monoclonal antibody or antigen binding region thereof comprising a heavy chain CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 17, 31, 45, 59, 73, 87, 101, 115, 129, 143, 157, 171, 185, 199, 213, 227, 241, 255, 269, 283, 297, 311 and 325; a heavy chain CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 18, 32, 46, 60, 74, 88, 102, 116, 130, 144, 158, 172, 186, 200, 214, 228, 242, 256, 270, 284, 298, 312 and 326; a heavy chain CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 19, 33, 47, 61, 75, 89, 103, 117, 131, 145, 159, 173, 187, 201, 215, 229, 243, 257, 271, 285, 299, 313 and 327; a light chain CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 28, 42, 56, 70, 84, 98, 112, 126, 140, 154, 168, 182, 196, 210, 224, 238, 252, 266, 280, 294, 308 and 322; a light chain CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 15, 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, 169, 183, 197, 211, 225, 239, 253, 267, 281, 295, 309 and 323; and a light chain CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 16, 30, 44, 58, 72, 86, 100, 114, 128, 142, 156, 170, 184, 198, 212, 226, 240, 254, 268, 282, 296, 310 and 324; wherein the antibody specifically binds CDH6.

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[00185] In a specific aspect, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to CDH6 comprising:

- (i) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:224, (b) a LCDR2 of SEQ ID NO:225, (c) a LCDR3 of SEQ ID NO:226; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO: 227, (e) a HCDR2 of SEQ ID NO: 228, and (f) a HCDR3 of SEQ ID NO:229;
- (ii) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:210, (b) a LCDR2 of SEQ ID NO:211, (c) a LCDR3 of SEQ ID NO:212; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:213, (e) a HCDR2 of SEQ ID NO: 214, and (f) a HCDR3 of SEQ ID NO:215;
- (iii) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:266, (b) a LCDR2 of SEQ ID NO:267, (c) a LCDR3 of SEQ ID NO:268; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO: 269, (e) a HCDR2 of SEQ ID NO:270, and (f) a HCDR3 of SEQ ID NO: 271;
- (iv) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:308, (b) a LCDR2 of SEQ ID NO:309, (c) a LCDR3 of SEQ ID NO:310; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:311, (e) a HCDR2 of SEQ ID NO:312, and (f) a HCDR3 of SEQ ID NO:313;
- (v) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:14, (b) a LCDR2 of SEQ ID NO:15, (c) a LCDR3 of SEQ ID NO:16; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:17, (e) a HCDR2 of SEQ ID NO:18, and (f) a HCDR3 of SEQ ID NO:19;
- (vi) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:28, (b) a LCDR2 of SEQ ID NO:29, (c) a LCDR3 of SEQ ID NO:30; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:31, (e) a HCDR2 of SEQ ID NO:32, and (f) a HCDR3 of SEQ ID NO:33;
- (vii) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:42, (b) a LCDR2 of SEQ ID NO:43, (c) a LCDR3 of SEQ ID NO:44; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:45, (e) a HCDR2 of SEQ ID NO:46, and (f) a HCDR3 of SEQ ID NO:47;
- (viii) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:56, (b) a LCDR2 of SEQ ID NO:57, (c) a LCDR3 of SEQ ID NO:58; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:59, (e) a HCDR2 of SEQ ID NO:60, and (f) a HCDR3 of SEQ ID NO:61;
- (ix) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:70, (b) a LCDR2 of SEQ ID NO:71, (c) a LCDR3 of SEQ ID NO:72; and a

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heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:73, (e) a HCDR2 of SEQ ID NO:74, and (f) a HCDR3 of SEQ ID NO:75;

(x) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:84, (b) a LCDR2 of SEQ ID NO:85, (c) a LCDR3 of SEQ ID NO:86; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:87, (e) a HCDR2 of SEQ ID NO: 88, and (f) a HCDR3 of SEQ ID NO: 89;

(xi) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:98, (b) a LCDR2 of SEQ ID NO:99, (c) a LCDR3 of SEQ ID NO:100; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:101, (e) a HCDR2 of SEQ ID NO:102, and (f) a HCDR3 of SEQ ID NO:103;

(xii) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:112, (b) a LCDR2 of SEQ ID NO:113, (c) a LCDR3 of SEQ ID NO:114; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:115, (e) a HCDR2 of SEQ ID NO:116, and (f) a HCDR3 of SEQ ID NO:117;

(xiii) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:126, (b) a LCDR2 of SEQ ID NO:127, (c) a LCDR3 of SEQ ID NO:128; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:129, (e) a HCDR2 of SEQ ID NO:130, and (f) a HCDR3 of SEQ ID NO:131;

(xiv) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:140, (b) a LCDR2 of SEQ ID NO:141, (c) a LCDR3 of SEQ ID NO:142; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:143, (e) a HCDR2 of SEQ ID NO:144, and (f) a HCDR3 of SEQ ID NO:145;

(xv) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:154, (b) a LCDR2 of SEQ ID NO:155, (c) a LCDR3 of SEQ ID NO:156; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:157, (e) a HCDR2 of SEQ ID NO:158, and (f) a HCDR3 of SEQ ID NO:159;

(xvi) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:168, (b) a LCDR2 of SEQ ID NO:169, (c) a LCDR3 of SEQ ID NO:170; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:171, (e) a HCDR2 of SEQ ID NO:172, and (f) a HCDR3 of SEQ ID NO:173;

(xvii) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:182, (b) a LCDR2 of SEQ ID NO:183, (c) a LCDR3 of SEQ ID NO:184; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:185, (e) a HCDR2 of SEQ ID NO:186, and (f) a HCDR3 of SEQ ID NO:187;

(xviii) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:196, (b) a LCDR2 of SEQ ID NO:197, (c) a LCDR3 of SEQ ID NO:198; and

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a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:199, (e) a HCDR2 of SEQ ID NO:200, and (f) a HCDR3 of SEQ ID NO:201;

(xix) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:238, (b) a LCDR2 of SEQ ID NO:239, (c) a LCDR3 of SEQ ID NO:240; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:241, (e) a HCDR2 of SEQ ID NO:242, and (f) a HCDR3 of SEQ ID NO:243;

(xx) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:252, (b) a LCDR2 of SEQ ID NO:253, (c) a LCDR3 of SEQ ID NO:254; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:255, (e) a HCDR2 of SEQ ID NO:256, and (f) a HCDR3 of SEQ ID NO:257;

(xxi) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:280, (b) a LCDR2 of SEQ ID NO:281, (c) a LCDR3 of SEQ ID NO:282; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:283, (e) a HCDR2 of SEQ ID NO:284, and (f) a HCDR3 of SEQ ID NO:285;

(xxii) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:294, (b) a LCDR2 of SEQ ID NO:295, (c) a LCDR3 of SEQ ID NO:296; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:297, (e) a HCDR2 of SEQ ID NO:298, and (f) a HCDR3 of SEQ ID NO:299; or

(xxiii) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:322, (b) a LCDR2 of SEQ ID NO:323, (c) a LCDR3 of SEQ ID NO:324; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:325, (e) a HCDR2 of SEQ ID NO:326, and (f) a HCDR3 of SEQ ID NO:327.

GITR antibodies

[00186] The present disclosure provides for antibodies or antibody fragments (*e.g.*, antigen binding fragments) that specifically bind to human GITR. Antibodies or antibody fragments (*e.g.*, antigen binding fragments) of the present disclosure include, but are not limited to, the human monoclonal antibodies or fragments thereof, isolated as described in the Examples below.

[00187] The present disclosure in certain aspects provides antibodies or antibody fragments (*e.g.*, antigen binding fragments) that specifically bind GITR, said antibodies or antibody fragments (*e.g.*, antigen binding fragments) comprise a VH domain having an amino acid sequence of SEQ ID NO: 348, 358, 372, 386, 400, 414, 428 or 442 (Table 6). The present disclosure also provides antibodies or antibody fragments (*e.g.*, antigen binding fragments) that specifically bind to GITR, said antibodies or antibody fragments (*e.g.*, antigen binding fragments) comprise a VH CDR having an amino acid sequence of any one of the VH CDRs listed in Table 6. In particular aspects, the present

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disclosure provides antibodies or antibody fragments (*e.g.*, antigen binding fragments) that specifically bind to GITR, said antibodies comprising (or alternatively, consist of) one, two, three, four, five or more VH CDRs having an amino acid sequence of any of the VH CDRs listed in Table 6.

[00188] The present disclosure provides antibodies or antibody fragments (*e.g.*, antigen binding fragments) that specifically bind to GITR, said antibodies or antibody fragments (*e.g.*, antigen binding fragments) comprise a VL domain having an amino acid sequence of SEQ ID NO: 349, 359, 373, 387, 401, 415, 429 or 443 (Table 6). The present disclosure also provides antibodies or antibody fragments (*e.g.*, antigen binding fragments) that specifically bind to GITR, said antibodies or antibody fragments (*e.g.*, antigen binding fragments) comprise a VL CDR having an amino acid sequence of any one of the VL CDRs listed in Table 6, *infra*. In particular, the disclosure provides antibodies or antibody fragments (*e.g.*, antigen binding fragments) that specifically bind to GITR, said antibodies or antibody fragments (*e.g.*, antigen binding fragments) comprise (or alternatively, consist of) one, two, three or more VL CDRs having an amino acid sequence of any of the VL CDRs listed in Table 6.

[00189] Other antibodies or antibody fragments (*e.g.*, antigen binding fragments) of the present disclosure include amino acids that have been mutated, yet have at least 60, 70, 80, 90 or 95 percent identity in the CDR regions with the CDR regions depicted in the sequences described in Table 6. In some aspects, it includes mutant amino acid sequences wherein no more than 1, 2, 3, 4 or 5 amino acids have been mutated in the CDR regions when compared with the CDR regions depicted in the sequence described in Table 6.

[00190] The present disclosure also provides nucleic acid sequences that encode VH, VL, the full length heavy chain, and the full length light chain of the antibodies that specifically bind to GITR. Such nucleic acid sequences can be optimized for expression in mammalian cells.

[00191] Other antibodies of the present disclosure include those where the amino acids or nucleic acids encoding the amino acids have been mutated, yet have at least 60, 70, 80, 90 or 95 percent identity to the sequences described in Table 6. In some aspects, it includes mutant amino acid sequences wherein no more than 1, 2, 3, 4 or 5 amino acids have been mutated in the variable regions when compared with the variable regions depicted in the sequence described in Table 6, while retaining substantially the same therapeutic activity.

[00192] Since each of these antibodies can bind to GITR, the VH, VL, full length light chain, and full length heavy chain sequences (amino acid sequences and the nucleotide sequences encoding the amino acid sequences) can be "mixed and matched" to create other GITR binding antibodies. Such "mixed and matched" GITR binding antibodies can be tested using the binding assays known in the art (*e.g.*, ELISAs, and other assays described in the Example section). When these chains are mixed and

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matched, a VH sequence from a particular VH/VL pairing should be replaced with a structurally similar VH sequence. Likewise a full length heavy chain sequence from a particular full length heavy chain / full length light chain pairing should be replaced with a structurally similar full length heavy chain sequence. Likewise, a VL sequence from a particular VH/VL pairing should be replaced with a structurally similar VL sequence. Likewise, a full length light chain sequence from a particular full length heavy chain / full length light chain pairing should be replaced with a structurally similar full length light chain sequence. Accordingly, in one aspect, the disclosure provides for an isolated monoclonal antibody or antigen binding region thereof having: a heavy chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 348, 358, 372, 386, 400, 414, 428 or 442 (Table 6); and a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 349, 359, 373, 387, 401, 415, 429 or 443 (Table 6); wherein the antibody specifically binds to GITR.

[00193] In another aspect, the disclosure provides (i) an isolated monoclonal antibody having: a full length heavy chain comprising an amino acid sequence that has been optimized for expression in the cell of a mammalian selected from the group consisting of SEQ ID NO: 362, 376, 390, 404, 418, 432 or 446; and a full length light chain comprising an amino acid sequence that has been optimized for expression in the cell of a mammalian selected from the group consisting of SEQ ID NO: 363, 377, 391, 405, 419, 433 or 447; or (ii) a functional protein comprising an antigen binding portion thereof.

[00194] In another aspect, the present disclosure provides anti-GITR antibodies that comprise the heavy chain and light chains.

[00195] In another aspect, the present disclosure provides anti-GITR antibodies that comprise the heavy chain and light chain CDR1s, CDR2s and CDR3s as described in Table 6, or combinations thereof. In some embodiments, the combination comprises GITR.MAB7.

[00196] In a specific aspect, an antibody or antibody fragment (*e.g.*, antigen binding fragments) that specifically binds to GITR comprising:

(i) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:422, (b) a LCDR2 of SEQ ID NO:423, (c) a LCDR3 of SEQ ID NO:424; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO: 425, (e) a HCDR2 of SEQ ID NO: 426, and (f) a HCDR3 of SEQ ID NO: 427;

(ii) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:352, (b) a LCDR2 of SEQ ID NO:353, (c) a LCDR3 of SEQ ID NO:354; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO: 355, (e) a HCDR2 of SEQ ID NO: 356, and (f) a HCDR3 of SEQ ID NO: 357;

(iii) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:366, (b) a LCDR2 of SEQ ID NO:367, (c) a LCDR3 of SEQ ID

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NO:368; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO: 369, (e) a HCDR2 of SEQ ID NO:370, and (f) a HCDR3 of SEQ ID NO:371;

(iv) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:380, (b) a LCDR2 of SEQ ID NO:381, (c) a LCDR3 of SEQ ID NO:382; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO: 383, (e) a HCDR2 of SEQ ID NO: 384, and (f) a HCDR3 of SEQ ID NO: 385;

(vi) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:394, (b) a LCDR2 of SEQ ID NO:395, (c) a LCDR3 of SEQ ID NO:396; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO: 397, (e) a HCDR2 of SEQ ID NO: 398, and (f) a HCDR3 of SEQ ID NO: 399;

(vii) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:408, (b) a LCDR2 of SEQ ID NO:409, (c) a LCDR3 of SEQ ID NO:410; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO: 411, (e) a HCDR2 of SEQ ID NO: 412, and (f) a HCDR3 of SEQ ID NO: 413; and

(viii) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:436, (b) a LCDR2 of SEQ ID NO:437, (c) a LCDR3 of SEQ ID NO:438; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO: 439, (e) a HCDR2 of SEQ ID NO: 440, and (f) a HCDR3 of SEQ ID NO: 441.

1. Identification of Epitopes and Antibodies That Bind to the Same Epitope

[00197] The present disclosure provides antibodies and antibody fragments (*e.g.*, antigen binding fragments) that bind to an epitope of the extracellular domain of CDH6 or the extracellular domain of GITR.

[00198] The present disclosure also provides antibodies and antibody fragments (*e.g.*, antigen binding fragments) that bind to the same epitope as do the CDH6 antibodies described in Table 5 and the GITR antibodies described in Table 6. Additional antibodies and antibody fragments (*e.g.*, antigen binding fragments) can therefore be identified based on their ability to cross-compete (*e.g.*, to competitively inhibit the binding of, in a statistically significant manner) with other antibodies in antibody binding assays. The ability of a test antibody to inhibit the binding of antibodies and antibody fragments (*e.g.*, antigen binding fragments) of the present disclosure to a protein (*e.g.*, human CDH6 or human GITR) demonstrates that the test antibody can compete with that antibody or antibody fragment (*e.g.*, antigen binding fragments) for binding to CDH6 or GITR; such an antibody

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may, according to non-limiting theory, bind to the same or a related (*e.g.*, a structurally similar or spatially proximal) epitope on the respective extracellular domain as the antibody or antibody fragment (*e.g.*, antigen binding fragments) with which it competes. In a certain aspect, the antibody that binds to the same epitope on CDH6 or GITR as the antibodies or antibody fragments (*e.g.*, antigen binding fragments) of the present disclosure is a human or humanized monoclonal antibody. Such human or humanized monoclonal antibodies can be prepared and isolated as described herein.

2. Further Alteration of the Framework of Fc Region

[00199] The present disclosure provides site-specific labeled immunoconjugates. These immunoconjugates can comprise modified antibodies or antigen binding fragments thereof that further comprise modifications to framework residues within VH and/or VL, *e.g.* to improve the properties of the antibody. Typically such framework modifications are made to decrease the immunogenicity of the antibody. For example, one approach is to "back-mutate" one or more framework residues to the corresponding germline sequence. More specifically, an antibody that has undergone somatic mutation may contain framework residues that differ from the germline sequence from which the antibody is derived. Such residues can be identified by comparing the antibody framework sequences to the germline sequences from which the antibody is derived. To return the framework region sequences to their germline configuration, the somatic mutations can be "back-mutated" to the germline sequence by, for example, site-directed mutagenesis. Such "back-mutated" antibodies are also intended to be encompassed.

[00200] Another type of framework modification involves mutating one or more residues within the framework region, or even within one or more CDR regions, to remove T-cell epitopes to thereby reduce the potential immunogenicity of the antibody. This approach is also referred to as "deimmunization" and is described in further detail in U.S. Patent Publication No. 2003/0153043 by Carr *et al.*

[00201] In addition or alternative to modifications made within the framework or CDR regions, antibodies can be engineered to include modifications within the Fc region, typically to alter one or more functional properties of the antibody, such as serum half-life, complement fixation, Fc receptor binding, and/or antigen-dependent cellular cytotoxicity. Furthermore, an antibody can be chemically modified (*e.g.*, one or more chemical moieties can be attached to the antibody) or be modified to alter its glycosylation, again to alter one or more functional properties of the antibody. Each of these aspects is described in further detail below.

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[00202] In one aspect, the hinge region of CH1 is modified such that the number of cysteine residues in the hinge region is altered, *e.g.*, increased or decreased. This approach is described further in U.S. Patent No. 5,677,425 by Bodmer *et al.* The number of cysteine residues in the hinge region of CH1 is altered to, for example, facilitate assembly of the light and heavy chains or to increase or decrease the stability of the antibody.

[00203] In another aspect, the Fc hinge region of an antibody is mutated to decrease the biological half-life of the antibody. More specifically, one or more amino acid mutations are introduced into the CH2-CH3 domain interface region of the Fc-hinge fragment such that the antibody has impaired Staphylococcal protein A (SpA) binding relative to native Fc-hinge domain SpA binding. This approach is described in further detail in U.S. Patent No. 6,165,745 by Ward *et al.*

[00204] In yet other aspects, the Fc region is altered by replacing at least one amino acid residue with a different amino acid residue to alter the effector functions of the antibody. For example, one or more amino acids can be replaced with a different amino acid residue such that the antibody has an altered affinity for an effector ligand but retains the antigen-binding ability of the parent antibody. The effector ligand to which affinity is altered can be, for example, an Fc receptor or the C1 component of complement. This approach is described in, *e.g.*, U.S. Patent Nos. 5,624,821 and 5,648,260, both by Winter *et al.*

[00205] In another aspect, one or more amino acids selected from amino acid residues can be replaced with a different amino acid residue such that the antibody has altered C1q binding and/or reduced or abolished complement dependent cytotoxicity (CDC). This approach is described in, *e.g.*, U.S. Patent Nos. 6,194,551 by Idusogie *et al.*

[00206] In another aspect, one or more amino acid residues are altered to thereby alter the ability of the antibody to fix complement. This approach is described in, *e.g.*, the PCT Publication WO 94/29351 by Bodmer *et al.* In a specific aspect, one or more amino acids of an antibody or antigen binding fragment thereof of the present disclosure are replaced by one or more allotypic amino acid residues, for the IgG1 subclass and the kappa isotype. Allotypic amino acid residues also include, but are not limited to, the constant region of the heavy chain of the IgG1, IgG2, and IgG3 subclasses as well as the constant region of the light chain of the kappa isotype as described by Jefferis *et al.*, MAbs. 1:332-338 (2009).

[00207] In yet another aspect, the Fc region is modified to increase the ability of the antibody to mediate antibody dependent cellular cytotoxicity (ADCC) and/or to increase the affinity of the antibody for an Fcγ receptor by modifying one or more amino acids. This approach is described in,

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e.g., the PCT Publication WO 00/42072 by Presta. Moreover, the binding sites on human IgG1 for FcγRI, FcγRII, FcγRIII and FcRn have been mapped and variants with improved binding have been described (see Shields *et al.*, J. Biol. Chem. 276:6591-6604, 2001).

[00208] In still another aspect, the glycosylation of an antibody is modified. For example, an aglycosylated antibody can be made (*i.e.*, the antibody lacks glycosylation). Glycosylation can be altered to, for example, increase the affinity of the antibody for "antigen." Such carbohydrate modifications can be accomplished by, for example, altering one or more sites of glycosylation within the antibody sequence. For example, one or more amino acid substitutions can be made that result in elimination of one or more variable region framework glycosylation sites to thereby eliminate glycosylation at that site. Such aglycosylation may increase the affinity of the antibody for antigen. Such an approach is described in, *e.g.*, U.S. Patent Nos. 5,714,350 and 6,350,861 by Co *et al.*

[00209] Additionally or alternatively, an antibody can be made that has an altered type of glycosylation, such as a hypofucosylated antibody having reduced amounts of fucosyl residues or an antibody having increased bisecting GlcNac structures. Such altered glycosylation patterns have been demonstrated to increase the ADCC ability of antibodies. Such carbohydrate modifications can be accomplished by, for example, expressing the antibody in a host cell with altered glycosylation machinery. Cells with altered glycosylation machinery have been described in the art and can be used as host cells in which to express recombinant antibodies to thereby produce an antibody with altered glycosylation. For example, EP 1,176,195 by Hang *et al.* describes a cell line with a functionally disrupted FUT8 gene, which encodes a fucosyl transferase, such that antibodies expressed in such a cell line exhibit hypofucosylation. PCT Publication WO 03/035835 by Presta describes a variant CHO cell line, Lec13 cells, with reduced ability to attach fucose to Asn(297)-linked carbohydrates, also resulting in hypofucosylation of antibodies expressed in that host cell (see also Shields *et al.*, (2002) J. Biol. Chem. 277:26733-26740). PCT Publication WO 99/54342 by Umana *et al.* describes cell lines engineered to express glycoprotein-modifying glycosyl transferases (*e.g.*, beta(1,4)-N acetylglucosaminyltransferase III (GnTIII)) such that antibodies expressed in the engineered cell lines exhibit increased bisecting GlcNac structures which results in increased ADCC activity of the antibodies (see also Umana *et al.*, Nat. Biotech. 17:176-180, 1999).

[00210] In another aspect, the antibody is modified to increase its biological half-life. Various approaches are possible. For example, one or more of the following mutations can be introduced: T252L, T254S, T256F, as described in U.S. Patent No. 6,277,375 to Ward. Alternatively, to increase the biological half-life, the antibody can be altered within the CH1 or CL region to contain a salvage

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receptor binding epitope taken from two loops of a CH2 domain of an Fc region of an IgG, as described in U.S. Patent Nos. 5,869,046 and 6,121,022 by Presta *et al.*

[00211] In order to minimize the ADCC activity of an antibody, specific mutations in the Fc region result in "Fc silent" antibodies that have minimal interaction with effector cells. In general, the "IgG Fc region" is used to define the C-terminal region of an immunoglobulin heavy chain, including native sequence Fc region and variant Fc regions. The human IgG heavy chain Fc region is generally defined as comprising the amino acid residue from position C226 or from P230 to the carboxyl-terminus of the IgG antibody. The numbering of residues in the Fc region is that of the EU index of Kabat. The C-terminal lysine (residue K447) of the Fc region may be removed, for example, during production or purification of the antibody.

[00212] Silenced effector functions can be obtained by mutation in the Fc region of the antibodies and have been described in the art: LALA and N297A (Strohl, W., 2009, Curr. Opin. Biotechnol. vol. 20(6):685-691); and D265A (Baudino et al., 2008, J. Immunol. 181 : 6664-69) see also Heusser et al., WO2012065950. Examples of silent Fc IgG1 antibodies are the LALA mutant comprising L234A and L235A mutation in the IgG1 Fc amino acid sequence. Another example of a silent IgG1 antibody is the DAPA (D265A, P329A) mutation (US 6,737,056). Another silent IgG1 antibody comprises the N297A mutation, which results in aglycosylated/non-glycosylated antibodies.

[00213] Fc silent antibodies result in no or low ADCC activity, meaning that an Fc silent antibody exhibits an ADCC activity that is below 50% specific cell lysis. No ADCC activity means that the Fc silent antibody exhibits an ADCC activity (specific cell lysis) that is below 1 %.

3. Production of the Antibodies

[00214] The CDH6 or GITR antibodies and antibody fragments (*e.g.*, antigen binding fragments) thereof can be produced by any means known in the art, including but not limited to, recombinant expression, chemical synthesis, and enzymatic digestion of antibody tetramers, whereas full-length monoclonal antibodies can be obtained by, *e.g.*, hybridoma or recombinant production. Recombinant expression can be from any appropriate host cells known in the art, for example, mammalian host cells, bacterial host cells, yeast host cells, insect host cells, etc.

[00215] The disclosure further provides polynucleotides encoding the antibodies described herein, *e.g.*, polynucleotides encoding heavy or light chain variable regions or segments comprising the complementarity determining regions as described herein. In some aspects, the polynucleotide encoding the CDH6 antibody heavy chain variable regions has at least 85%, 89%, 90%, 91%, 92%,

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93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% nucleic acid sequence identity with a polynucleotide selected from the group consisting of SEQ ID NOs: 22, 36, 50, 64, 78, 92, 106, 120, 134, 148, 162, 176, 190, 204, 218, 232, 246, 260, 274, 288, 302, 316, and 330. In some aspects, the polynucleotide encoding the CDH6 antibody light chain variable regions has at least 85%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% nucleic acid sequence identity with a polynucleotide selected from the group consisting of SEQ ID NOs: 23, 37, 51, 65, 79, 93, 107, 121, 135, 149, 163, 177, 191, 205, 219, 233, 247, 261, 275, 289, 303, 317, and 331.

[00216] In some aspects, the polynucleotide encoding the CDH6 antibody heavy chain has at least 85%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% nucleic acid sequence identity with a polynucleotide of SEQ ID NO: 26, 40, 54, 68, 82, 96, 110, 124, 138, 152, 166, 180, 194, 208, 222, 236, 250, 264, 278, 292, 306, 320, and 334. In some aspects, the polynucleotide encoding the CDH6 antibody light chain has at least 85%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% nucleic acid sequence identity with a polynucleotide of SEQ ID NO: 27, 41, 55, 69, 83, 97, 111, 125, 139, 153, 167, 181, 195, 209, 223, 237, 251, 265, 279, 293, 307, 321, and 335.

[00217] In some aspects, the polynucleotide encoding the GITR antibody heavy chain has at least 85%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% nucleic acid sequence identity with a polynucleotide of SEQ ID NO: 364, 378, 392, 406, 420, 434 or 448. In some aspects, the polynucleotide encoding the GITR antibody light chain has at least 85%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% nucleic acid sequence identity with a polynucleotide of SEQ ID NO: 365, 379, 393, 407, 421, 435 or 449.

[00218] In some aspects, the polynucleotide encoding the GITR antibody heavy chain variable regions has at least 85%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% nucleic acid sequence identity with a polynucleotide selected from the group consisting of SEQ ID NOs: 350, 360, 374, 388, 402, 416, 430 and 444. In some aspects, the polynucleotide encoding the GITR antibody light chain variable regions has at least 85%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% nucleic acid sequence identity with a polynucleotide selected from the group consisting of SEQ ID NOs: 351, 361, 375, 389, 403, 417, 431 and 445.

[00219] The polynucleotide sequences can be produced by de novo solid-phase DNA synthesis or by PCR mutagenesis of an existing sequence (*e.g.*, sequences as described in the Examples below) encoding an anti-CDH6 antibody or its binding fragment. Direct chemical synthesis of nucleic acids can be accomplished by methods known in the art, such as the phosphotriester method of Narang *et al.*,

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Meth. Enzymol. 68:90, 1979; the phosphodiester method of Brown *et al.*, Meth. Enzymol. 68:109, 1979; the diethylphosphoramidite method of Beaucage *et al.*, Tetra. Lett., 22:1859, 1981; and the solid support method of U.S. Patent No. 4,458,066. Introducing mutations to a polynucleotide sequence by PCR can be performed as described in, *e.g.*, PCR Technology: Principles and Applications for DNA Amplification, H.A. Erlich (Ed.), Freeman Press, NY, NY, 1992; PCR Protocols: A Guide to Methods and Applications, Innis *et al.* (Ed.), Academic Press, San Diego, CA, 1990; Mattila *et al.*, Nucleic Acids Res. 19:967, 1991; and Eckert *et al.*, PCR Methods and Applications 1:17, 1991.

[00220] Also provided in the present disclosure are expression vectors and host cells for producing the anti-CDH6 or anti-GITR antibodies described above. Various expression vectors can be employed to express the polynucleotides encoding the antibody chains or binding fragments. Both viral-based and nonviral expression vectors can be used to produce the antibodies in a mammalian host cell. Nonviral vectors and systems include plasmids, episomal vectors, typically with an expression cassette for expressing a protein or RNA, and human artificial chromosomes (see, *e.g.*, Harrington *et al.*, Nat Genet 15:345, 1997). For example, nonviral vectors useful for expression of the antibody polynucleotides and polypeptides in mammalian (*e.g.*, human) cells include pThioHis A, B & C, pcDNA3.1/His, pEBVHis A, B & C (Invitrogen, San Diego, CA), MPSV vectors, and numerous other vectors known in the art for expressing other proteins. Useful viral vectors include vectors based on retroviruses, adenoviruses, adenoassociated viruses, herpes viruses, vectors based on SV40, papilloma virus, HBP Epstein Barr virus, vaccinia virus vectors and Semliki Forest virus (SFV). See, Brent *et al.*, *supra*; Smith, Annu. Rev. Microbiol. 49:807, 1995; and Rosenfeld *et al.*, Cell 68:143, 1992.

[00221] The choice of expression vector depends on the intended host cells in which the vector is to be expressed. Typically, the expression vectors contain a promoter and other regulatory sequences (*e.g.*, enhancers) that are operably linked to the polynucleotides encoding an antibody chain or fragment. In some aspects, an inducible promoter is employed to prevent expression of inserted sequences except under inducing conditions. Inducible promoters include, *e.g.*, arabinose, lacZ, metallothionein promoter or a heat shock promoter. Cultures of transformed organisms can be expanded under noninducing conditions without biasing the population for coding sequences whose expression products are better tolerated by the host cells. In addition to promoters, other regulatory elements may also be required or desired for efficient expression of an antibody chain or fragment. These elements typically include an ATG initiation codon and adjacent ribosome binding site or other sequences. In addition, the efficiency of expression may be enhanced by the inclusion of enhancers

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appropriate to the cell system in use (see, *e.g.*, Scharf *et al.*, Results Probl. Cell Differ. 20:125, 1994; and Bittner *et al.*, Meth. Enzymol., 153:516, 1987). For example, the SV40 enhancer or CMV enhancer may be used to increase expression in mammalian host cells.

[00222] The expression vectors may also provide a secretion signal sequence position to form a fusion protein with polypeptides encoded by inserted anti-CDH6 or anti-GITR antibody sequences. More often, the inserted anti-CDH6 or anti-GITR antibody sequences are linked to a signal sequences before inclusion in the vector. Vectors to be used to receive sequences encoding antibody light and heavy chain variable domains sometimes also encode constant regions or parts thereof. Such vectors allow expression of the variable regions as fusion proteins with the constant regions thereby leading to production of intact antibodies or fragments thereof. Typically, such constant regions are human.

[00223] The host cells for harboring and expressing the anti-CDH6 or anti-GITR antibody chains can be either prokaryotic or eukaryotic. *E. coli* is one prokaryotic host useful for cloning and expressing the polynucleotides of the present disclosure. Other microbial hosts suitable for use include bacilli, such as *Bacillus subtilis*, and other enterobacteriaceae, such as *Salmonella*, *Serratia*, and various *Pseudomonas* species. In these prokaryotic hosts, one can also make expression vectors, which typically contain expression control sequences compatible with the host cell (*e.g.*, an origin of replication). In addition, any number of a variety of well-known promoters will be present, such as the lactose promoter system, a tryptophan (*trp*) promoter system, a beta-lactamase promoter system, or a promoter system from phage lambda. The promoters typically control expression, optionally with an operator sequence, and have ribosome binding site sequences and the like, for initiating and completing transcription and translation. Other microbes, such as yeast, can also be employed to express anti-CDH6 or anti-GITR polypeptides. Insect cells in combination with baculovirus vectors can also be used.

[00224] In other aspects, mammalian host cells are used to express and produce the anti-CDH6 or anti-GITR polypeptides of the present disclosure. For example, they can be either a hybridoma cell line expressing endogenous immunoglobulin genes (*e.g.*, a myeloma hybridoma clone) or a mammalian cell line harboring an exogenous expression vector (*e.g.*, SP2/0 myeloma cells). These include any normal mortal or normal or abnormal immortal animal or human cell. For example, a number of suitable host cell lines capable of secreting intact immunoglobulins have been developed, including the CHO cell lines, various COS cell lines, HeLa cells, myeloma cell lines, transformed B-cells and hybridomas. The use of mammalian tissue cell culture to express polypeptides is discussed generally in, *e.g.*, Winnacker, From Genes to Clones, VCH Publishers, N.Y., N.Y., 1987. Expression

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vectors for mammalian host cells can include expression control sequences, such as an origin of replication, a promoter, and an enhancer (see, *e.g.*, Queen *et al.*, Immunol. Rev. 89:49-68, 1986), and necessary processing information sites, such as ribosome binding sites, RNA splice sites, polyadenylation sites, and transcriptional terminator sequences. These expression vectors usually contain promoters derived from mammalian genes or from mammalian viruses. Suitable promoters may be constitutive, cell type-specific, stage-specific, and/or modulatable or regulatable. Useful promoters include, but are not limited to, the metallothionein promoter, the constitutive adenovirus major late promoter, the dexamethasone-inducible MMTV promoter, the SV40 promoter, the MRP polIII promoter, the constitutive MPSV promoter, the tetracycline-inducible CMV promoter (such as the human immediate-early CMV promoter), the constitutive CMV promoter, and promoter-enhancer combinations known in the art.

[00225] Methods for introducing expression vectors containing the polynucleotide sequences of interest vary depending on the type of cellular host. For example, calcium chloride transfection is commonly utilized for prokaryotic cells, whereas calcium phosphate treatment or electroporation may be used for other cellular hosts (see generally Sambrook *et al.*, *supra*). Other methods include, *e.g.*, electroporation, calcium phosphate treatment, liposome-mediated transformation, injection and microinjection, ballistic methods, virosomes, immunoliposomes, polycation:nucleic acid conjugates, naked DNA, artificial virions, fusion to the herpes virus structural protein VP22 (Elliot and O'Hare, Cell 88:223, 1997), agent-enhanced uptake of DNA, and *ex vivo* transduction. For long-term, high-yield production of recombinant proteins, stable expression will often be desired. For example, cell lines which stably express anti-CDH6 or anti-GITR antibody chains or binding fragments can be prepared using expression vectors which contain viral origins of replication or endogenous expression elements and a selectable marker gene. Following introduction of the vector, cells may be allowed to grow for 1-2 days in an enriched media before they are switched to selective media. The purpose of the selectable marker is to confer resistance to selection, and its presence allows growth of cells which successfully express the introduced sequences in selective media. Resistant, stably transfected cells can be proliferated using tissue culture techniques appropriate to the cell type.

Therapeutic Uses

[00226] The antibodies, antibody fragments (*e.g.*, antigen binding fragments), and antibody drug conjugates of the present disclosure are useful in a variety of applications including, but not limited to, treatment of cancer, such as solid cancers. In certain aspects, the antibodies, antibody

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fragments (*e.g.*, antigen binding fragments), and antibody drug conjugates are useful for inhibiting tumor growth, inducing differentiation, reducing tumor volume, and/or reducing the tumorigenicity of a tumor. The methods of use can be *in vitro*, *ex vivo*, or *in vivo* methods.

[00227] In one aspect, the disclosure provides for a method of treating, preventing or ameliorating a disease comprising administering the antibodies, antibody fragments (*e.g.*, antigen binding fragments), and antibody drug conjugates to a patient, thereby treating the disease. In certain aspects, the disease treated with the antibodies, antibody fragments (*e.g.*, antigen binding fragments), and antibody drug conjugates is a cancer. Examples of diseases which can be treated and/or prevented include, but are not limited to, ovarian cancer, renal cancer, hepatic cancer, soft tissue cancer, CNS cancers, thyroid cancer and cholangiocarcinoma. In certain aspects, the cancer is characterized by CDH6 expressing cells to which the antibodies, antibody fragments (*e.g.*, antigen binding fragments), and antibody drug conjugates can specifically bind.

[00228] The present disclosure provides for methods of treating cancer comprising administering a therapeutically effective amount of the CDH6 ADC and GITR antibody in combination. In certain aspects, the cancer is a solid cancer. In certain aspects, the subject is a human.

[00229] In certain aspects, the method of inhibiting tumor growth comprises administering to a subject a therapeutically effective amount of the CDH6 ADC and GITR antibody. In certain aspects, the subject is a human. In certain aspects, the subject has a tumor or has had a tumor removed. In another aspect, the subject has a reoccurrence of the tumor.

[00230] In certain aspects, the tumor expresses the CDH6 to which the anti-CDH6 ADC binds. In certain aspects, the tumor overexpresses the human CDH6. In other aspects, the administration of the anti-CDH6 ADC results in an increase of GITR expression on Treg cells.

[00231] For the treatment of the disease, the appropriate dosage of the CDH6 ADC and GITR antibody combination depends on various factors, such as the type of disease to be treated, the severity and course of the disease, the responsiveness of the disease, previous therapy, patient's clinical history, and so on. The CDH6 ADC and GITR antibody combination can be administered one time or over a series of treatments lasting from several days to several months, or until a cure is effected or a diminution of the disease state is achieved (*e.g.*, reduction in tumor size). Optimal dosing schedules can be calculated from measurements of drug accumulation in the body of the patient and will vary depending on the relative potency of an individual antibody, antibody fragment (*e.g.*, antigen binding fragment), or antibody drug conjugates. In certain aspects, dosage is from 0.01mg to 10 mg (*e.g.*, 0.01 mg, 0.05mg, 0.1mg, 0.5mg, 1mg, 2mg, 3mg, 4mg, 5mg, 7mg, 8mg, 9mg, or 10mg) per kg of body

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weight, and can be given once or more daily, weekly, monthly or yearly. In certain aspects, the CDH6 ADC and GITR antibody combination of the present disclosure is given once every two weeks or once every three weeks. In another aspect, the CDH6 ADC is given as a single agent, and the anti-GTIR antibody is administered a certain time afterward. The treating physician can estimate repetition rates for dosing based on measured residence times and concentrations of the drug in bodily fluids or tissues.

Additional Combination Therapy

[00232] In certain instances, the CDH6 ADC/anti-GITR combination of the present disclosure is combined with other therapeutic agents, such as other anti-cancer agents, anti-allergic agents, anti-nausea agents (or anti-emetics), pain relievers, cytoprotective agents, and combinations thereof.

[00233] General chemotherapeutic agents considered for use in combination therapies include anastrozole (Arimidex[®]), bicalutamide (Casodex[®]), bleomycin sulfate (Blenoxane[®]), busulfan (Myleran[®]), busulfan injection (Busulfex[®]), capecitabine (Xeloda[®]), N4-pentoxycarbonyl-5-deoxy-5-fluorocytidine, carboplatin (Paraplatin[®]), carmustine (BiCNU[®]), chlorambucil (Leukeran[®]), cisplatin (Platinol[®]), cladribine (Leustatin[®]), cyclophosphamide (Cytosan[®] or Neosar[®]), cytarabine, cytosine arabinoside (Cytosar-U[®]), cytarabine liposome injection (DepoCyt[®]), dacarbazine (DTIC-Dome[®]), dactinomycin (Actinomycin D, Cosmegen[®]), daunorubicin hydrochloride (Cerubidine[®]), daunorubicin citrate liposome injection (DaunoXome[®]), dexamethasone, docetaxel (Taxotere[®]), doxorubicin hydrochloride (Adriamycin[®], Rubex[®]), etoposide (Vepesid[®]), fludarabine phosphate (Fludara[®]), 5-fluorouracil (Adrucil[®], Efudex[®]), flutamide (Eulexin[®]), tezacitibine, Gemcitabine (difluorodeoxycytidine), hydroxyurea (Hydrea[®]), Idarubicin (Idamycin[®]), ifosfamide (IFEX[®]), irinotecan (Camptosar[®]), L-asparaginase (ELSPAR[®]), leucovorin calcium, melphalan (Alkeran[®]), 6-mercaptopurine (Purinethol[®]), methotrexate (Folex[®]), mitoxantrone (Novantrone[®]), mylotarg, paclitaxel (Taxol[®]), phoenix (Yttrium90/MX-DTPA), pentostatin, polifeprosan 20 with carmustine implant (Gliadel[®]), tamoxifen citrate (Nolvadex[®]), teniposide (Vumon[®]), 6-thioguanine, thiotepe, tirapazamine (Tirazone[®]), topotecan hydrochloride for injection (Hycamptin[®]), vinblastine (Velban[®]), vincristine (Oncovin[®]), and vinorelbine (Navelbine[®]).

[00234] In one aspect, an antibody, antibody fragment (*e.g.*, antigen binding fragment), or antibody drug conjugate of the present disclosure is combined in a pharmaceutical combination formulation, or dosing regimen as combination therapy, with a second compound having anti-cancer properties. The second compound of the pharmaceutical combination formulation or dosing regimen can have complementary activities to the antibody or immunoconjugate of the combination such that they do not adversely affect each other. For example, an antibody, antibody fragment (*e.g.*, antigen

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binding fragment), or antibody drug conjugate of the present disclosure can be administered in combination with, but not limited to, a chemotherapeutic agent, a tyrosine kinase inhibitor, for example, Imatinib.

[00235] In one aspect, the present disclosure provides a method of treating cancer by administering to a subject in need thereof an antibody drug conjugate in combination with one or more tyrosine kinase inhibitors, including but not limited to, EGFR inhibitors, Her2 inhibitors, Her3 inhibitors, IGFR inhibitors, and Met inhibitors.

[00236] For example, tyrosine kinase inhibitors include but are not limited to, Erlotinib hydrochloride (Tarceva®); Linifanib (N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-(2-fluoro-5-methylphenyl)urea, also known as ABT 869, available from Genentech); Sunitinib malate (Sutent®); Bosutinib (4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline-3-carbonitrile, also known as SKI-606, and described in US Patent No. 6,780,996); Dasatinib (Sprycel®); Pazopanib (Votrient®); Sorafenib (Nexavar®); Zactima (ZD6474); nilotinib (Tasigna®); Regorafenib (Stivarga®) and Imatinib or Imatinib mesylate (Gilevec® and Gleevec®).

[00237] Epidermal growth factor receptor (EGFR) inhibitors include but are not limited to, Erlotinib hydrochloride (Tarceva®), Gefitinib (Iressa®); N-[4-[(3-Chloro-4-fluorophenyl)amino]-7-[[3-(3"-tetrahydro-3-furanyl)oxy]-6-quinazolinyl]-4(dimethylamino)-2-butenamide, Tovok®); Vandetanib (Caprelsa®); Lapatinib (Tykerb®); (3R,4R)-4-Amino-1-((4-((3-methoxyphenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-5-yl)methyl)piperidin-3-ol (BMS690514); Canertinib dihydrochloride (CI-1033); 6-[4-[(4-Ethyl-1-piperazinyl)methyl]phenyl]-N-[(1R)-1-phenylethyl]-7H-Pyrrolo[2,3-d]pyrimidin-4-amine (AEE788, CAS 497839-62-0); Mubritinib (TAK165); Pelitinib (EKB569); Afatinib (BIBW2992); Neratinib (HKI-272); N-[4-[[1-(3-Fluorophenyl)methyl]-1H-indazol-5-yl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3S)-3-morpholinylmethyl ester (BMS599626); N-(3,4-Dichloro-2-fluorophenyl)-6-methoxy-7-[[3(α,5β,6α)-octahydro-2-methylcyclopenta[c]pyrrol-5-yl]methoxy]-4-quinazolinamine (XL647, CAS 781613-23-8); and 4-[4-[(1R)-1-Phenylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-phenol (PKI166, CAS 187724-61-4).

[00238] EGFR antibodies include but are not limited to, Cetuximab (Erbitux®); Panitumumab (Vectibix®); Matuzumab (EMD-72000); Nimotuzumab (hR3); Zalutumumab; TheraCIM h-R3; MDX0447 (CAS 339151-96-1); and ch806 (mAb-806, CAS 946414-09-1).

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[00239] Human Epidermal Growth Factor Receptor 2 (HER2 receptor) (also known as Neu, ErbB-2, CD340, or p185) inhibitors include but are not limited to, Trastuzumab (Herceptin®); Pertuzumab (Omnitarg®); Neratinib (HKI-272, (2E)-N-[4-[[3-chloro-4-[(pyridin-2-yl)methoxy]phenyl]amino]-3-cyano-7-ethoxyquinolin-6-yl]-4-(dimethylamino)but-2-enamide, and described PCT Publication No. WO 05/028443); Lapatinib or Lapatinib ditosylate (Tykerb®); (3R,4R)-4-amino-1-((4-((3-methoxyphenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-5-yl)methyl)piperidin-3-ol (BMS690514); (2E)-N-[4-[(3-Chloro-4-fluorophenyl)amino]-7-[(3S)-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]-4-(dimethylamino)-2-butenamide (BIBW-2992, CAS 850140-72-6); N-[4-[[1-[(3-Fluorophenyl)methyl]-1H-indazol-5-yl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3S)-3-morpholinylmethyl ester (BMS 599626, CAS 714971-09-2); Canertinib dihydrochloride (PD183805 or CI-1033); and N-(3,4-Dichloro-2-fluorophenyl)-6-methoxy-7-[(3 α ,5 β ,6 α)-octahydro-2-methylcyclopenta[c]pyrrol-5-yl]methoxy]-4-quinazolinamine (XL647, CAS 781613-23-8).

[00240] HER3 inhibitors include but are not limited to, LJM716, MM-121, AMG-888, RG7116, REGN-1400, AV-203, MP-RM-1, MM-111, and MEHD-7945A.

[00241] MET inhibitors include but are not limited to, Cabozantinib (XL184, CAS 849217-68-1); Foretinib (GSK1363089, formerly XL880, CAS 849217-64-7); Tivantinib (ARQ197, CAS 1000873-98-2); 1-(2-Hydroxy-2-methylpropyl)-N-(5-(7-methoxyquinolin-4-yloxy)pyridin-2-yl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (AMG 458); Cryzotinib (Xalkori®, PF-02341066); (3Z)-5-(2,3-Dihydro-1H-indol-1-ylsulfonyl)-3-({3,5-dimethyl-4-[(4-methylpiperazin-1-yl)carbonyl]-1H-pyrrol-2-yl}methylene)-1,3-dihydro-2H-indol-2-one (SU11271); (3Z)-N-(3-Chlorophenyl)-3-({3,5-dimethyl-4-[(4-methylpiperazin-1-yl)carbonyl]-1H-pyrrol-2-yl}methylene)-N-methyl-2-oxoindoline-5-sulfonamide (SU11274); (3Z)-N-(3-Chlorophenyl)-3-{{3,5-dimethyl-4-(3-morpholin-4-ylpropyl)-1H-pyrrol-2-yl}methylene}-N-methyl-2-oxoindoline-5-sulfonamide (SU11606); 6-[Difluoro[6-(1-methyl-1H-pyrazol-4-yl)-1,2,4-triazolo[4,3-b]pyridazin-3-yl]methyl]-quinoline (JNJ38877605, CAS 943540-75-8); 2-[4-[1-(Quinolin-6-ylmethyl)-1H-[1,2,3]triazolo[4,5-b]pyrazin-6-yl]-1H-pyrazol-1-yl]ethanol (PF04217903, CAS 956905-27-4); N-((2R)-1,4-Dioxan-2-ylmethyl)-N-methyl-N'-[3-(1-methyl-1H-pyrazol-4-yl)-5-oxo-5H-benzo[4,5]cyclohepta[1,2-b]pyridin-7-yl]sulfamide (MK2461, CAS 917879-39-1); 6-[[6-(1-Methyl-1H-pyrazol-4-yl)-1,2,4-triazolo[4,3-b]pyridazin-3-yl]thio]-quinoline (SGX523, CAS 1022150-57-7); and (3Z)-5-[[2,6-Dichlorophenyl)methyl]sulfonyl]-3-[[3,5-dimethyl-4-[(2R)-2-(1-pyrrolidinyl)methyl]-1-

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pyrrolidinyllcarbonyl]-1*H*-pyrrol-2-yl)methylene]-1,3-dihydro-2*H*-indol-2-one (PHA665752, CAS 477575-56-7).

[00242] IGF1R inhibitors include but are not limited to, BMS-754807, XL-228, OSI-906, GSK0904529A, A-928605, AXL1717, KW-2450, MK0646, AMG479, IMCA12, MEDI-573, and BI836845. See *e.g.*, Yee, JNCI, 104; 975 (2012) for review.

[00243] In another aspect, the present disclosure provides a method of treating cancer by administering to a subject in need thereof an antibody drug conjugate in combination with one or more FGF downstream signaling pathway inhibitors, including but not limited to, MEK inhibitors, Braf inhibitors, PI3K/Akt inhibitors, SHP2 inhibitors, and also mTor inhibitors.

[00244] For example, mitogen-activated protein kinase (MEK) inhibitors include but are not limited to, XL-518 (also known as GDC-0973, Cas No. 1029872-29-4, available from ACC Corp.); 2-[(2-Chloro-4-iodophenyl)amino]-N-(cyclopropylmethoxy)-3,4-difluoro-benzamide (also known as CI-1040 or PD184352 and described in PCT Publication No. WO2000035436); N-[(2*R*)-2,3-Dihydroxypropoxy]-3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]-benzamide (also known as PD0325901 and described in PCT Publication No. WO2002006213); 2,3-Bis[amino[(2-aminophenyl)thio]methylene]-butanedinitrile (also known as U0126 and described in US Patent No. 2,779,780); N-[3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]-6-methoxyphenyl]-1-[(2*R*)-2,3-dihydroxypropyl]-cyclopropanesulfonamide (also known as RDEA119 or BAY869766 and described in PCT Publication No. WO2007014011); (3*S*,4*R*,5*Z*,8*S*,9*S*,11*E*)-14-(Ethylamino)-8,9,16-trihydroxy-3,4-dimethyl-3,4,9,19-tetrahydro-1*H*-2-benzoxacyclotetradecine-1,7(8*H*)-dione] (also known as E6201 and described in PCT Publication No. WO2003076424); 2'-Amino-3'-methoxyflavone (also known as PD98059 available from Biaffin GmbH & Co., KG, Germany); Vemurafenib (PLX-4032, CAS 918504-65-1); (R)-3-(2,3-Dihydroxypropyl)-6-fluoro-5-(2-fluoro-4-iodophenylamino)-8-methylpyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (TAK-733, CAS 1035555-63-5); Pimasertib (AS-703026, CAS 1204531-26-9); and Trametinib dimethyl sulfoxide (GSK-1120212, CAS 1204531-25-80).

[00245] Phosphoinositide 3-kinase (PI3K) inhibitors include but are not limited to, 4-[2-(1*H*-Indazol-4-yl)-6-[[4-(methylsulfonyl)piperazin-1-yl]methyl]thieno[3,2-*d*]pyrimidin-4-yl]morpholine (also known as GDC 0941 and described in PCT Publication Nos. WO 09/036082 and WO 09/055730); 2-Methyl-2-[4-[3-methyl-2-oxo-8-(quinolin-3-yl)-2,3-dihydroimidazo[4,5-*c*]quinolin-1-yl]phenyl]propionitrile (also known as BEZ 235 or NVP-BEZ 235, and described in PCT Publication No. WO 06/122806); 4-(trifluoromethyl)-5-(2,6-dimorpholinopyrimidin-4-yl)pyridin-2-amine (also

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known as BKM120 or NVP-BKM120, and described in PCT Publication No. WO2007/084786); Tozasertib (VX680 or MK-0457, CAS 639089-54-6); (5Z)-5-[[4-(4-Pyridinyl)-6-quinolinyl]methylene]-2,4-thiazolidinedione (GSK1059615, CAS 958852-01-2); (1E,4S,4aR,5R,6aS,9aR)-5-(Acetyloxy)-1-[(di-2-propenylamino)methylene]-4,4a,5,6,6a,8,9,9a-octahydro-11-hydroxy-4-(methoxymethyl)-4a,6a-dimethyl-cyclopenta[5,6]naphtho[1,2-c]pyran-2,7,10(1H)-trione (PX866, CAS 502632-66-8); and 8-Phenyl-2-(morpholin-4-yl)-chromen-4-one (LY294002, CAS 154447-36-6).

[00246] mTor inhibitors include but are not limited to, Temsirolimus (Torisel®); Ridaforolimus (formally known as deferolimus, (1R,2R,4S)-4-[(2R)-2-[(1R,9S,12S,15R,16E,18R,19R,21R, 23S,24E,26E,28Z,30S,32S,35R)-1,18-dihydroxy-19,30-dimethoxy-15,17,21,23, 29,35-hexamethyl-2,3,10,14,20-pentaoxo-11,36-dioxo-4-azatricyclo[30.3.1.0^{4,9}] hexatriaconta-16,24,26,28-tetraen-12-yl]propyl]-2-methoxycyclohexyl dimethylphosphinate, also known as AP23573 and MK8669, and described in PCT Publication No. WO 03/064383); Everolimus (Afinitor® or RAD001); Rapamycin (AY22989, Sirolimus®); Simapimod (CAS 164301-51-3); (5-{2,4-Bis[(3S)-3-methylmorpholin-4-yl]pyrido[2,3-d]pyrimidin-7-yl}-2-methoxyphenyl)methanol (AZD8055); 2-Amino-8-[*trans*-4-(2-hydroxyethoxy)cyclohexyl]-6-(6-methoxy-3-pyridinyl)-4-methyl-pyrido[2,3-d]pyrimidin-7(8H)-one (PF04691502, CAS 1013101-36-4); and *N*²-[1,4-dioxo-4-[[4-(4-oxo-8-phenyl-4*H*-1-benzopyran-2-yl)morpholinium-4-yl]methoxy]butyl]-L-arginylglycyl-L- α -aspartyl-L-serine-, inner salt (SF1126, CAS 936487-67-1).

[00247] In yet another aspect, the present disclosure provides a method of treating cancer by administering to a subject in need thereof a CDH6 ADC and anti-GITR combination with one or more pro-apoptotics, including but not limited to, IAP inhibitors, Bcl2 inhibitors, Mcl1 inhibitors, Trail agents, Chk inhibitors.

[00248] For examples, IAP inhibitors include but are not limited to, NVP-LCL161, GDC-0917, AEG-35156, AT406, and TL32711. Other examples of IAP inhibitors include but are not limited to those disclosed in WO04/005284, WO 04/007529, WO05/097791, WO 05/069894, WO 05/069888, WO 05/094818, US2006/0014700, US2006/0025347, WO 06/069063, WO 06/010118, WO 06/017295, and WO08/134679, all of which are incorporated herein by reference.

[00249] BCL-2 inhibitors include but are not limited to, 4-[4-[[2-(4-Chlorophenyl)-5,5-dimethyl-1-cyclohexen-1-yl]methyl]-1-piperazinyl]-N-[[4-[[[(1R)-3-(4-morpholinyl)-1-[(phenylthio)methyl]propyl]amino]-3-[(trifluoromethyl)sulfonyl]phenyl]sulfonyl]benzamide (also known as ABT-263 and described in PCT Publication No. WO 09/155386); Tetrocarcin A;

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Antimycin; Gossypol ((-)-BL-193); Obatoclax; Ethyl-2-amino-6-cyclopentyl-4-(1-cyano-2-ethoxy-2-oxoethyl)-4Hchromone-3-carboxylate (HA14 – 1); Oblimersen (G3139, Genasense®); Bak BH3 peptide; (-)-Gossypol acetic acid (AT-101); 4-[4-[(4'-Chloro[1,1'-biphenyl]-2-yl)methyl]-1-piperazinyl]-N-[[4-[(1R)-3-(dimethylamino)-1-[(phenylthio)methyl]propyl]amino]-3-nitrophenyl]sulfonyl]-benzamide (ABT-737, CAS 852808-04-9); and Navitoclax (ABT-263, CAS 923564-51-6).

[00250] Proapoptotic receptor agonists (PARAs) including DR4 (TRAILR1) and DR5 (TRAILR2), including but are not limited to, Dulanermin (AMG-951, RhApo2L/TRAIL); Mapatumumab (HRS-ETR1, CAS 658052-09-6); Lexatumumab (HGS-ETR2, CAS 845816-02-6); Apomab (Apomab®); Conatumumab (AMG655, CAS 896731-82-1); and Tigatuzumab (CS1008, CAS 946415-34-5, available from Daiichi Sankyo).

[00251] Checkpoint Kinase (CHK) inhibitors include but are not limited to, 7-Hydroxystaurosporine (UCN-01); 6-Bromo-3-(1-methyl-1*H*-pyrazol-4-yl)-5-(3*R*)-3-piperidinyl-pyrazolo[1,5-*a*]pyrimidin-7-amine (SCH900776, CAS 891494-63-6); 5-(3-Fluorophenyl)-3-ureidothiophene-2-carboxylic acid N-[(S)-piperidin-3-yl]amide (AZD7762, CAS 860352-01-8); 4-[[[(3*S*)-1-Azabicyclo[2.2.2]oct-3-yl]amino]-3-(1*H*-benzimidazol-2-yl)-6-chloroquinolin-2(1*H*)-one (CHIR 124, CAS 405168-58-3); 7-Aminodactinomycin (7-AAD), Isogranulatimide, debromohymenialdisine; N-[5-Bromo-4-methyl-2-[(2*S*)-2-morpholinylmethoxy]-phenyl]-N'-(5-methyl-2-pyrazinyl)urea (LY2603618, CAS 911222-45-2); Sulforaphane (CAS 4478-93-7, 4-Methylsulfinylbutyl isothiocyanate); 9,10,11,12-Tetrahydro-9,12-epoxy-1*H*-diindolo[1,2,3-*fg*:3',2',1'-*kl*]pyrrolo[3,4-*i*][1,6]benzodiazocine-1,3(2*H*)-dione (SB-218078, CAS 135897-06-2); and TAT-S216A (Sha et al., Mol. Cancer. Ther 2007; 6(1):147-153), and CBP501.

[00252] In one aspect, the present disclosure provides a method of treating cancer by administering to a subject in need thereof an antibody drug conjugate in combination with one or more FGFR inhibitors. For example, FGFR inhibitors include but are not limited to, Brivanib alaninate (BMS-582664, (S)-((R)-1-(4-(4-Fluoro-2-methyl-1*H*-indol-5-yloxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yloxy)propan-2-yl)2-aminopropanoate); Vargatef (BIBF1120, CAS 928326-83-4); Dovitinib dilactate (TKI258, CAS 852433-84-2); 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-yl}-1-methyl-urea (BGJ398, CAS 872511-34-7); Danusertib (PHA-739358); and (PD173074, CAS 219580-11-7). In a specific aspect, the present disclosure provides a method of treating cancer by administering to a subject in need thereof a CDH6 ADC and anti-GITR antibody combination with an FGFR2 inhibitor, such as 3-(2,6-dichloro-3,5-

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dimethoxyphenyl)-1-(6((4-(4-ethylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)-1-methylurea (also known as BGJ-398); or 4-amino-5-fluoro-3-(5-(4-methylpiperazin-1-yl)-1*H*-benzo[*d*]imidazole-2-yl)quinolin-2(1*H*)-one (also known as dovitinib or TKI-258). AZD4547 (Gavine *et al.*, 2012, Cancer Research 72, 2045-56, N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-2*H*-pyrazol-3-yl]-4-(3*R*,5*S*)-diethylpiperazin-1-yl)benzamide), Ponatinib (AP24534; Gozgit *et al.*, 2012, Mol Cancer Ther., 11; 690-99; 3-[2-(imidazo[1,2-*b*]pyridazin-3-yl)ethynyl]-4-methyl-N-{4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl}benzamide, CAS 943319-70-8)

[00253] In one embodiment, a CDH6 ADC and anti-GITR antibody combination is used with a PD-1 inhibitor, e.g., as described in WO2015/026684 or WO2016/057846. WO2016/057846 in particular discloses that treatment with an anti-GITR antagonist antibody causes an increase in PD-1 expression on CD8+ T cells in a mouse colon tumor model. In some embodiments, the PD-1 inhibitor is an anti-PD-1 antibody chosen from Nivolumab, Pembrolizumab or Pidilizumab.

[00254] In some embodiments, the anti-PD-1 antibody is Nivolumab. Alternative names for Nivolumab include MDX-1106, MDX-1106-04, ONO-4538, or BMS-936558. In some embodiments, the anti-PD-1 antibody is Nivolumab (CAS Registry Number: 946414-94-4). Nivolumab is a fully human IgG4 monoclonal antibody which specifically blocks PD1. Nivolumab (clone 5C4) and other human monoclonal antibodies that specifically bind to PD1 are disclosed in US 8,008,449 and WO2006/121168. In one embodiment, the inhibitor of PD-1 is Nivolumab, and having a sequence disclosed therein (or a sequence substantially identical or similar thereto, e.g., a sequence at least 85%, 90%, 95% identical or higher to the sequence specified).

[00255] In some embodiments, the anti-PD-1 antibody is Pembrolizumab. Pembrolizumab (also referred to as Lambrolizumab, MK-3475, MK03475, SCH-900475 or KEYTRUDA®; Merck) is a humanized IgG4 monoclonal antibody that binds to PD-1. Pembrolizumab and other humanized anti-PD-1 antibodies are disclosed in Hamid, O. *et al.* (2013) New England Journal of Medicine 369 (2): 134-44, US 8,354,509 and WO2009/114335.

[00256] In one embodiment, the inhibitor of PD-1 is Pembrolizumab disclosed in, e.g., US 8,354,509 and WO 2009/114335, and having a sequence disclosed therein (or a sequence substantially identical or similar thereto, e.g., a sequence at least 85%, 90%, 95% identical or higher to the sequence specified).

[00257] In some embodiments, the anti-PD-1 antibody is Pidilizumab. Pidilizumab (CT-011; Cure Tech) is a humanized IgG1k monoclonal antibody that binds to PD1. Pidilizumab and other humanized anti-PD-1 monoclonal antibodies are disclosed in WO2009/101611. Other anti-PD1

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antibodies include AMP 514 (Amplimmune), among others, e.g., anti-PD1 antibodies disclosed in US 8,609,089, US 2010028330, and/or US 20120114649.

[00258] In some embodiments, the PD-1 inhibitor is an immunoadhesin (e.g., an immunoadhesin comprising an extracellular or PD-1 binding portion of PD-L1 or PD-L2 fused to a constant region (e.g., an Fc region of an immunoglobulin sequence). In some embodiments, the PD-1 inhibitor is AMP-224 (B7-DCIg; Amplimmune; e.g., disclosed in WO2010/027827 and WO2011/066342), is a PD-L2 Fc fusion soluble receptor that blocks the interaction between PD-1 and B7-H1.

[00259] In certain embodiments the CDH6 ADC is in combination with an anti-GITR antibody, wherein the anti-GITR antibody is BMS-986156, INCAGN01876, AMG 228, TRX518, MEDI1873, MK-4166, MK-1248 or FPA-154. In some embodiments, the combination comprises an anti-GITR antibody or agonist described in any of the following publications: WO2015187835, WO2015031667, WO2015026684, WO2015184099, WO2016196792, WO2016126781, WO17015623, WO2017025610, WO2013039954, WO2011028683, WO2009009116, WO2006105021, WO2005007190, US20070098719, US20050014224, or US20140072566.

[00260] In other embodiments, the anti-GITR antibody is in combination with an ADC. For example, the ADC NOV169N31Q-MCC-DM1 is a P-cadherin antibody conjugated to DM1, and is disclosed in US 2016/0137730. DM1 as well as DM4 can induce immunogenic cell death, and the combination of NOV169N31Q-MCC-DM1 and anti-GITR antibody can be used for the treatment of P-cadherin positive cancers.

Pharmaceutical Compositions

[00261] To prepare pharmaceutical or sterile compositions the CDH6 ADC and GITR antibody of the present disclosure are mixed with a pharmaceutically acceptable carrier or excipient. The CDH6 ADC and GITR antibody can be prepared separately or as an admixture. The compositions can additionally contain one or more other therapeutic agents that are suitable for treating or preventing cancer, for example, ovarian cancer, renal cancer, hepatic cancer, soft tissue cancer, CNS cancers, thyroid cancer and cholangiocarcinoma.

[00262] Formulations of therapeutic and diagnostic agents can be prepared by mixing with physiologically acceptable carriers, excipients, or stabilizers in the form of, e.g., lyophilized powders, slurries, aqueous solutions, lotions, or suspensions (see, e.g., Hardman *et al.*, Goodman and Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, N.Y., 2001; Gennaro,

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Remington: The Science and Practice of Pharmacy, Lippincott, Williams, and Wilkins, New York, N.Y., 2000; Avis, *et al.* (eds.), Pharmaceutical Dosage Forms: Parenteral Medications, Marcel Dekker, NY, 1993; Lieberman, *et al.* (eds.), Pharmaceutical Dosage Forms: Tablets, Marcel Dekker, NY, 1990; Lieberman, *et al.* (eds.) Pharmaceutical Dosage Forms: Disperse Systems, Marcel Dekker, NY, 1990; Weiner and Kotkoskie, Excipient Toxicity and Safety, Marcel Dekker, Inc., New York, N.Y., 2000).

[00263] Selecting an administration regimen for a therapeutic depends on several factors, including the serum or tissue turnover rate of the entity, the level of symptoms, the immunogenicity of the entity, and the accessibility of the target cells in the biological matrix. In certain aspects, an administration regimen maximizes the amount of therapeutic delivered to the patient consistent with an acceptable level of side effects. Accordingly, the amount of biologic delivered depends in part on the particular entity and the severity of the condition being treated. Guidance in selecting appropriate doses of antibodies, cytokines, and small molecules are available (see, *e.g.*, Wawrzynczak, Antibody Therapy, Bios Scientific Pub. Ltd, Oxfordshire, UK, 1996; Kresina (ed.), Monoclonal Antibodies, Cytokines and Arthritis, Marcel Dekker, New York, N.Y., 1991; Bach (ed.), Monoclonal Antibodies and Peptide Therapy in Autoimmune Diseases, Marcel Dekker, New York, N.Y., 1993; Baert *et al.*, New Engl. J. Med. 348:601-608, 2003; Milgrom *et al.*, New Engl. J. Med. 341:1966-1973, 1999; Slamon *et al.*, New Engl. J. Med. 344:783-792, 2001; Beniaminovitz *et al.*, New Engl. J. Med. 342:613-619, 2000; Ghosh *et al.*, New Engl. J. Med. 348:24-32, 2003; Lipsky *et al.*, New Engl. J. Med. 343:1594-1602, 2000).

[00264] Actual dosage levels of the CDH6 ADC and GITR antibody in pharmaceutical compositions can be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient. The selected dosage level will depend upon a variety of pharmacokinetic factors including the activity of the particular compositions of the present disclosure employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compositions employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors known in the medical arts.

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[00265] Compositions comprising the CDH6 ADC and GITR antibody combination can be provided by continuous infusion, or by doses at intervals of, *e.g.*, one day, one week, or 1-7 times per week. Doses can be provided intravenously, subcutaneously, topically, orally, nasally, rectally, intramuscular, intracerebrally, or by inhalation. A specific dose protocol is one involving the maximal dose or dose frequency that avoids significant undesirable side effects.

[00266] The dosage of each respective CDH6 ADC and GITR antibody administered to a patient can be 0.0001 mg/kg to 100 mg/kg of the patient's body weight. The dosage can be between 0.0001 mg/kg and 20 mg/kg, 0.0001 mg/kg and 10 mg/kg, 0.0001 mg/kg and 5 mg/kg, 0.0001 and 2 mg/kg, 0.0001 and 1 mg/kg, 0.0001 mg/kg and 0.75 mg/kg, 0.0001 mg/kg and 0.5 mg/kg, 0.0001 mg/kg to 0.25 mg/kg, 0.0001 to 0.15 mg/kg, 0.0001 to 0.10 mg/kg, 0.001 to 0.5 mg/kg, 0.01 to 0.25 mg/kg or 0.01 to 0.10 mg/kg of the patient's body weight. The dosage of each CDH6 ADC and GITR antibody of the combination can thereof be calculated using the patient's weight in kilograms (kg) multiplied by the dose to be administered in mg/kg.

[00267] Doses of the CDH6 ADC and GITR antibody combination can be repeated and the administrations may be separated by at least 1 day, 2 days, 3 days, 5 days, 10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, or at least 6 months. In a specific aspect, doses of the CDH6 ADC and GITR antibody combination of the present disclosure are repeated every 3 weeks.

[00268] An effective amount for a particular patient may vary depending on factors such as the condition being treated, the overall health of the patient, the method, route and dose of administration and the severity of side effects (see, *e.g.*, Maynard *et al.*, A Handbook of SOPs for Good Clinical Practice, Interpharm Press, Boca Raton, Fla., 1996; Dent, Good Laboratory and Good Clinical Practice, Urch Publ., London, UK, 2001).

[00269] The route of administration may be by, *e.g.*, topical or cutaneous application, injection or infusion by intravenous, intraperitoneal, intracerebral, intramuscular, intraocular, intraarterial, intracerebrospinal, intralesional, or by sustained release systems or an implant (see, *e.g.*, Sidman *et al.*, Biopolymers 22:547-556, 1983; Langer *et al.*, J. Biomed. Mater. Res. 15:167-277, 1981; Langer, Chem. Tech. 12:98-105, 1982; Epstein *et al.*, Proc. Natl. Acad. Sci. USA 82:3688-3692, 1985; Hwang *et al.*, Proc. Natl. Acad. Sci. USA 77:4030-4034, 1980; U.S. Pat. Nos. 6,350,466 and 6,316,024). Where necessary, the composition may also include a solubilizing agent or a local anesthetic such as lidocaine to ease pain at the site of the injection, or both. In addition, pulmonary administration can also be employed, *e.g.*, by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

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See, *e.g.*, U.S. Pat. Nos. 6,019,968, 5,985,320, 5,985,309, 5,934,272, 5,874,064, 5,855,913, 5,290,540, and 4,880,078; and PCT Publication Nos. WO 92/19244, WO 97/32572, WO 97/44013, WO 98/31346, and WO 99/66903, each of which is incorporated herein by reference their entirety.

[00270] A composition of the present disclosure can also be administered via one or more routes of administration using one or more of a variety of methods known in the art. As will be appreciated by the skilled artisan, the route and/or mode of administration will vary depending upon the desired results. Selected routes of administration for the immunoconjugates include intravenous, intramuscular, intradermal, intraperitoneal, subcutaneous, spinal or other parenteral routes of administration, for example by injection or infusion. Parenteral administration may represent modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection and infusion. Alternatively, a composition of the present disclosure can be administered via a non-parenteral route, such as a topical, epidermal or mucosal route of administration, for example, intranasally, orally, vaginally, rectally, sublingually or topically. In one aspect, the CDH6 ADC and GITR antibody combination of the present disclosure is administered by infusion. In another aspect, the CDH6 ADC and GITR antibody combination is administered subcutaneously.

[00271] If the CDH6 ADC and anti-GITR combination of the present disclosure are administered in a controlled release or sustained release system, a pump may be used to achieve controlled or sustained release (see Langer, *supra*; Sefton, *CRC Crit. Ref Biomed. Eng.* 14:20, 1987; Buchwald *et al.*, *Surgery* 88:507, 1980; Saudek *et al.*, *N. Engl. J. Med.* 321:574, 1989). Polymeric materials can be used to achieve controlled or sustained release of the therapies of the immunoconjugates (see *e.g.*, *Medical Applications of Controlled Release*, Langer and Wise (eds.), CRC Pres., Boca Raton, Fla., 1974; *Controlled Drug Bioavailability, Drug Product Design and Performance*, Smolen and Ball (eds.), Wiley, New York, 1984; Ranger and Peppas, *J. Macromol. Sci. Rev. Macromol. Chem.* 23:61, 1983; see also Levy *et al.*, *Science* 228:190, 1985; During *et al.*, *Ann. Neurol.* 25:351, 1989; Howard *et al.*, *J. Neurosurg.* 71:105, 1989; U.S. Pat. No. 5,679,377; U.S. Pat. No. 5,916,597; U.S. Pat. No. 5,912,015; U.S. Pat. No. 5,989,463; U.S. Pat. No. 5,128,326; PCT Publication No. WO 99/15154; and PCT Publication No. WO 99/20253. Examples of polymers used in sustained release formulations include, but are not limited to, poly(2-hydroxy ethyl methacrylate),

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poly(methyl methacrylate), poly(acrylic acid), poly(ethylene-co-vinyl acetate), poly(methacrylic acid), polyglycolides (PLG), polyanhydrides, poly(N-vinyl pyrrolidone), poly(vinyl alcohol), polyacrylamide, poly(ethylene glycol), polylactides (PLA), poly(lactide-co-glycolides) (PLGA), and polyorthoesters. In one aspect, the polymer used in a sustained release formulation is inert, free of leachable impurities, stable on storage, sterile, and biodegradable. A controlled or sustained release system can be placed in proximity of the prophylactic or therapeutic target, thus requiring only a fraction of the systemic dose (see, *e.g.*, Goodson, in *Medical Applications of Controlled Release*, supra, vol. 2, pp. 115-138, 1984).

[00272] Controlled release systems are discussed in the review by Langer, *Science* 249:1527-1533, 1990). Any technique known to one of skill in the art can be used to produce sustained release formulations comprising the CDH6 ADC and anti-GITR combination of the present disclosure. See, *e.g.*, U.S. Pat. No. 4,526,938, PCT publication WO 91/05548, PCT publication WO 96/20698, Ning *et al.*, *Radiotherapy & Oncology* 39:179-189, 1996; Song *et al.*, *PDA Journal of Pharmaceutical Science & Technology* 50:372-397, 1995; Cleek *et al.*, *Pro. Int'l. Symp. Control. Rel. Bioact. Mater.* 24:853-854, 1997; and Lam *et al.*, *Proc. Int'l. Symp. Control Rel. Bioact. Mater.* 24:759-760, 1997, each of which is incorporated herein by reference in their entirety.

[00273] If the CDH6 ADC and anti-GITR combination of the disclosure is administered topically, they can be formulated in the form of an ointment, cream, transdermal patch, lotion, gel, shampoo, spray, aerosol, solution, emulsion, or other form well-known to one of skill in the art. See, *e.g.*, Remington's *Pharmaceutical Sciences and Introduction to Pharmaceutical Dosage Forms*, 19th ed., Mack Pub. Co., Easton, Pa. (1995). For non-sprayable topical dosage forms, viscous to semi-solid or solid forms comprising a carrier or one or more excipients compatible with topical application and having a dynamic viscosity, in some instances, greater than water are typically employed. Suitable formulations include, without limitation, solutions, suspensions, emulsions, creams, ointments, powders, liniments, salves, and the like, which are, if desired, sterilized or mixed with auxiliary agents (*e.g.*, preservatives, stabilizers, wetting agents, buffers, or salts) for influencing various properties, such as, for example, osmotic pressure. Other suitable topical dosage forms include sprayable aerosol preparations wherein the active ingredient, in some instances, in combination with a solid or liquid inert carrier, is packaged in a mixture with a pressurized volatile (*e.g.*, a gaseous propellant, such as freon) or in a squeeze bottle. Moisturizers or humectants can also be added to pharmaceutical

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compositions and dosage forms if desired. Examples of such additional ingredients are well-known in the art.

[00274] If the compositions comprising the immunoconjugates are administered intranasally, it can be formulated in an aerosol form, spray, mist or in the form of drops. In particular, prophylactic or therapeutic agents for use according to the present disclosure can be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant (*e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas). In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges (composed of, *e.g.*, gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[00275] The CDH6 ADC and GITR antibody combination as disclosed herein can be administered together or separately. The CDH6 ADC and GITR antibody can be administered separately less than 5 minutes apart, less than 30 minutes apart, 1 hour apart, at about 1 hour apart, at about 1 to about 2 hours apart, at about 2 hours to about 3 hours apart, at about 3 hours to about 4 hours apart, at about 4 hours to about 5 hours apart, at about 5 hours to about 6 hours apart, at about 6 hours to about 7 hours apart, at about 7 hours to about 8 hours apart, at about 8 hours to about 9 hours apart, at about 9 hours to about 10 hours apart, at about 10 hours to about 11 hours apart, at about 11 hours to about 12 hours apart, at about 12 hours to 18 hours apart, 18 hours to 24 hours apart, 24 hours to 36 hours apart, 36 hours to 48 hours apart, 48 hours to 52 hours apart, 52 hours to 60 hours apart, 60 hours to 72 hours apart, 72 hours to 84 hours apart, 84 hours to 96 hours apart, or 96 hours to 120 hours apart. The CDH6 ADC and GITR antibody combination can be administered within one same patient visit.

[00276] In certain aspects, the CDH6 ADC and GITR antibody combination can be formulated to ensure proper distribution in vivo. For example, the blood-brain barrier (BBB) excludes many highly hydrophilic compounds. To ensure that the therapeutic compounds of the disclosure cross the BBB (if desired), they can be formulated, for example, in liposomes. For methods of manufacturing liposomes, see, *e.g.*, U.S. Pat. Nos. 4,522,811; 5,374,548; and 5,399,331. The liposomes may comprise one or more moieties which are selectively transported into specific cells or organs, thus enhance targeted drug delivery (see, *e.g.*, Ranade, (1989) J. Clin. Pharmacol. 29:685). Exemplary targeting moieties include folate or biotin (see, *e.g.*, U.S. Pat. No. 5,416,016 to Low *et al.*);

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mannosides (Umezawa *et al.*, (1988) Biochem. Biophys. Res. Commun. 153:1038); antibodies (Bloeman *et al.*, (1995) FEBS Lett. 357:140; Owais *et al.*, (1995) Antimicrob. Agents Chemother. 39:180); surfactant protein A receptor (Briscoe *et al.*, (1995) Am. J. Physiol. 1233:134); p 120 (Schreier *et al.*, (1994) J. Biol. Chem. 269:9090); see also K. Keinänen; M. L. Laukkanen (1994) FEBS Lett. 346:123; J. J. Killian; I. J. Fidler (1994) Immunomethods 4:273.

[00277] The present disclosure provides protocols for the administration of a CDH6 ADC and GITR antibody combination to a subject in need thereof. The CDH6 ADC and GITR antibody combination can be administered concomitantly or sequentially to a subject. The CDH6 ADC and GITR antibody combination can also be cyclically administered. Cycling therapy involves the administration of a first therapy (*e.g.*, CDH6 ADC) for a period of time, followed by the administration of a second therapy (*e.g.*, anti-GITR antibody) for a period of time and repeating this sequential administration, *i.e.*, the cycle, in order to reduce the development of resistance to one of the therapies to avoid or reduce the side effects of one of the therapies, and/or to improve the efficacy of the therapies.

[00278] The CDH6 ADC and GITR antibody combination of the disclosure can be administered to a subject concurrently. The term "concurrently" is not limited to the administration of the combination at exactly the same time, but rather it is meant that a pharmaceutical composition comprising the combination is administered to a subject in a sequence and within a time interval such that the combination can act together to provide an increased benefit than if they were administered otherwise. For example, each therapy may be administered to a subject at the same time or sequentially in any order at different points in time; however, if not administered at the same time, they should be administered sufficiently close in time so as to provide the desired therapeutic or prophylactic effect. Each therapy can be administered to a subject separately, in any appropriate form and by any suitable route.

[00279] The CDH6 ADC and GITR antibody combination can be administered to a subject in the same pharmaceutical composition. Alternatively, the CDH6 ADC and GITR antibody combination can be administered concurrently to a subject in separate pharmaceutical compositions.

EXAMPLES

Example 1: Identification of CDH6 antibodies by phage-display technology

HuCAL PLATINUM[®] Pannings

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[00280] Antibodies were identified by the selection of clones that bound to CDH6-ECD. As a source of antibody variants a commercially available phage display library, the Morphosys HuCAL PLATINUM® library, was used. The phagemid library is based on the HuCAL® concept (Knappik et al., J Mol Biol. 2000; 296(1):57-86; Prassler et al., J Mol Biol. 2011; 413(1):261-78 2011) and employs the CysDisplay™ technology for displaying the Fab on the phage surface (Rothe et al., J Mol Biol. 2008; 376(4):1182-200). For isolation of anti-CDH6 antibodies, standard panning strategies were performed using solid phase and solution panning approaches.

[00281] Pannings were done on various forms of CDH6 antigens. An overview of recombinant CDH6 proteins and CDH6-expressing cell lines used as antigens for pannings and subsequent screening and characterization is given in Table 1.

[00282] Human, mouse and rat CDH6 extracellular domains were gene synthesized based on amino acid sequences from the GenBank or Uniprot databases (see Table 1). Cynomolgus CDH6 cDNA template was gene synthesized based on amino acid sequences and homology information generated using mRNA from various cyno tissues (*e.g.* Zyagen Laboratories, San Diego, CA). All synthesized DNA fragments were cloned into appropriate expression vectors listed affinity tags to allow for purification or expression vectors Zyagen Laboratories for mammalian cell surface expression.

[00283] For the generation of a stable CHO cell line exogenously expressing human CDH6 the TREX expression system (Invitrogen, Carlsbad, CA) was used according to the manufacturer's instructions. Briefly, CHO-TREx cells (Invitrogen, R718-07, Carlsbad, CA) were grown in DMEM media (Invitrogen 11995-085) with 10% FBS (Invitrogen, 10082-147, Carlsbad, CA), and 10 µg/ml Blasticidin (Invitrogen A11139-02, Carlsbad, CA). Transfection was performed in 6 well plates when cell reach 90% confluence. 4 µg of linearized CDH6 plasmid DNA was mixed with 100 µl DMEM media (no FBS) in a sterile Eppendorf tube, 12 µl of Lipofectamine® 2000 (Invitrogen 11668-019, Carlsbad, CA) were mixed with 100 µl DMEM media in another sterile Eppendorf tube. DNA and Lipofectamine® were mixed together, and incubated in room temperature for 15 min. The culture media of CHO-TREx cells was changed to 1 ml DMEM media without FBS for each well; half above DNA/Lipofectamine® mix were added into each well, incubated for 2 hours. Then 2 ml growth media (with FBS) were added into each well, and the cells were incubated overnight. The transfected cells were split from 6 well plate to T175 flask next day and grew in selection DMEM media with 10% FBS, 10 µg/ml Blasticidin, 800-1000 µg/ml Geneticin (Invitrogen 10131-027). CDH6 expression was induced with final 1 µg/ml Tetracycline in selection media for 20-24 hours. Positive cells were labeled with final 5 µg/ml anti-CDH6 primary monoclonal antibody (MAB2715 from R&D Systems, Minneapolis, MN), and then labeled with PE conjugated anti-mouse secondary antibody (cat #12-4010-87, eBioscience, San Diego, CA) and sorted by FACS.

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[00284] Stable CHO cell lines featuring exogenous expression of CDH6 from mouse, rat and cynomolgus origin were generated by transfection of CHO-K1 cells (Invitrogen, Carlsbad, CA) with the respective cDNAs cloned into a mammalian expression vector (pcDNA6.1, Invitrogen, Carlsbad, CA). Transfection was performed in 6 well plates when cell reach 90% confluence. 4 µg of linearized CDH6 plasmid DNA were mixed with 100 µl DMEM media without FBS in a sterile Eppendorf tube, 12 µl of Lipofectamine® 2000 (Invitrogen 11668-019, Carlsbad, CA) were mixed with 100 µl DMEM media in another sterile Eppendorf tube. The DNA and Lipofectamine® solution were mixed together, and incubated at room temperature for 15 min. The culture media of CHO cells was changed to 1 ml DMEM media without FBS for each well; half above DNA/Lipofectamine® mix were added into each well, incubated for 2 hours. Then 2 ml growth media (with FBS) were added into each well, and the cells were incubated overnight. The transfected cells were split from 6 well plate to T175 flask next day and grew in selection DMEM media with 10% FBS, 10 µg/ml Blasticidin, 800-1000 µg/ml Geneticin (Invitrogen 10131-027 Carlsbad, CA). CDH6 expression was induced with final 1 µg/ml Tetracycline in selection media for 20-24 hours. Positive cells were labeled with final 5 µg/ml anti-CDH6 primary monoclonal antibody (MAB2715 from R&D Systems, Minneapolis, MN), and then labeled with PE conjugated anti-mouse secondary antibody (cat #12-4010-87, eBioscience, San Diego, CA) and sorted by FACS. An alternative commercially available anti-CDH6 antibody is the 2B6 antibody (#GWB-E8FDF3 - Genway, San Diego, CA). This antibody was also used to confirm CDH6 expression in cells.

Table 1*Overview of antigen, antibody and cell line reagents for pannings and screenings*

Antigen/Antibody	Accession	Description	Sequence
Human CDH6	AK291290	Full length human cDNA (SEQ ID NO:2)	MRTYRYFLLLFWVGQPYPTLSTPLSKRTS GFP AKKRALELSGNSKNEINRSKR SWM WNQFFLLLEEYTGSDYQYVVGKLHSDQDR GDGSLKYILSGDGAGDLFIINENTGDIQA TKRLDREEKPVYILRAQAINRRRTGRPVEP ESEFIKIHDINDNEPIFTKEVYTATVPMS DVGTFFVQVTATDADDPTYGNSAKVVY SILQGQPYFSVESETGHIKTALLNMDREN EQYQVVIQAKDMGGMGGLSGTTTNI TLTDVNDNPPRFPQSTYQFKTPESP PGTP IGRIKASDADVGENAEIEYSITDGEGLDM FDVITDQETQEGITVKKLLDFEKKKVYT LKVEASNPYVEPRFLYLGPFKDSATVRIV VEDVDEPPVFSKLAYILQIREDAQINTTIG SVTAQDPDAARNPVKYSVDRHTDMDRIF NIDSGNGSIFTSKLLDRETLNWHNITVIAT EINNPKQSSRVPLYIKVLDVNDNAPEFAE FYETFVCEKAKADQLIQT LHAVDKDDPY SGHQFSFSLAPEAASGSNFTIQDNKDNTA GILTRKNGYNRHEMSTYLLPVVISDNDY PVQSSTGTVTVRVCACDHHGNMQSCHA

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			EALIHPTGLSTGALVAILLCIVILLVTVVLF FAALRRQRKKEPLISKEDIRDNIVSYNDE GGGEEDTQAFDIGTLRNPEAIEDNKLRRD IVPEALFLPRRTPTARDNTDVRDFINQRL KENDTDPTAPPYDSLATYAYEGTGSVAD SLSSLESVTTDADQDYDYLSDWGPRFKK LADMYGGVDSKDS
His6-SUMO- CDH6 aa54-260- APP-Avi	NM_004932.3	human EC 1/2 domain variant (SEQ ID NO:3)	SWMWNQFFLLEEYTGSDYQYVGKLHSD QDRGDGSLKYILSGDGAGDLFIINENTGD IQATKRLDREEKPVYILRAQAINRRTGRP VEPESEFIKIHDINDNEPIFTKEVYTATVP EMSDVGTFVVQVTATDADDPTYGNSAK VVYSILQGQPYFSVESETGIIKTALLNMD RENREQYQVVIQAKDMGGQMGGLSGTT TVNITLTDGGGGSEFRHDSGLNDIFEAQK IEWHE
hCDH6aa54-615 APPavi	NM_004932.3	human full- length ECD (SEQ ID NO:4)	SWMWNQFFLLEEYTGSDYQYVGKLHSD QDRGDGSLKYILSGDGAGDLFIINENTGD IQATKRLDREEKPVYILRAQAINRRTGRP VEPESEFIKIHDINDNEPIFTKEVYTATVP EMSDVGTFVVQVTATDADDPTYGNSAK VVYSILQGQPYFSVESETGIIKTALLNMD RENREQYQVVIQAKDMGGQMGGLSGTT TVNITLTDVNDNPPRFPQSTYQFKTPESSP PGTPIGRIKASDADVGENAEIEYSITDGE LDMFDVITDQETQEGIITVKKLLDFEKKK VYTLKVEASNPYVEPRFLYLGPFKDSAT VRIVVEDVDEPPVFSKLAYILQIREDAQIN TTIGSVTAQDPDAARNPVKYSVDRHTDM DRIFNIDSGNGSIFTSKLLDRETLWHNIT VIATEINNPKQSSRVPLYIKVLDVNDNAP EFAEFYETFVCEKAKADQLIOTLHAVDK DDPYSGHQFSFSLAPEAASGSNFTIQDNK DNTAGILTRKNGYNRHEMSTYLLPVVIS DNDYPVQSSTGTVTVRVCACDHHGNMQ SCHAEALIHPTGLSTGA
hCDH6aa54-615 APPavi-biotin	NM_004932.3	human full- length ECD, biotinylated (SEQ ID NO:5)	SWMWNQFFLLEEYTGSDYQYVGKLHSD QDRGDGSLKYILSGDGAGDLFIINENTGD IQATKRLDREEKPVYILRAQAINRRTGRP VEPESEFIKIHDINDNEPIFTKEVYTATVP EMSDVGTFVVQVTATDADDPTYGNSAK VVYSILQGQPYFSVESETGIIKTALLNMD RENREQYQVVIQAKDMGGQMGGLSGTT TVNITLTDVNDNPPRFPQSTYQFKTPESSP PGTPIGRIKASDADVGENAEIEYSITDGE LDMFDVITDQETQEGIITVKKLLDFEKKK VYTLKVEASNPYVEPRFLYLGPFKDSAT VRIVVEDVDEPPVFSKLAYILQIREDAQIN TTIGSVTAQDPDAARNPVKYSVDRHTDM DRIFNIDSGNGSIFTSKLLDRETLWHNIT VIATEINNPKQSSRVPLYIKVLDVNDNAP EFAEFYETFVCEKAKADQLIOTLHAVDK

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			DDPYSGHQFSFLAPEAASGSNFTIQDNK DNTAGILTRKNGYNRHEMSTYLLPVVIS DNDYPVQSSTGTVTVRVCACDHHGNMQ SCHAEALIHPTGLSTGAGSEFRHDSGLND IFEAQK(BIOTIN)IEWHE
hCDH6aa54-615 Fc	NM_004932.3	human full-length ECD, dimerized (SEQ ID NO:6)	SWMWNQFFLLEEYTGSDYQYVGKLHSD QDRGDGSLKYILSGDGAGDLFIINENTGD IQATKRLDREEKPVYILRAQAINRRTGRP VEPESEFIKIHDINDNEPIFTKEVYTATVP EMSDVGTFVVQVTATDADDPTYGNSAK VVYSILQGQPYFSVESETGIIKTALLNMD RENREQYQVVIQAKDMGGQMGGLSGTT TVNITLTDVNDNPPRFPQSTYQFKTPESSP PGTPIGRIKASDADVGENAEIEYSITDGEG LDMFDVITDQETQEGIIIVKLLDFEKKK VYTLKVEASNPHYVEPRFLYLGPFKDSAT VRIVVEDVDEPPVFSKLAYILQIREDAQIN TTIGSVTAQDPDAARNPVKYSVDRHTDM DRIFNIDSGNGSIFTSKLLDRETLLWHNIT VIATEINNPKQSSRVPLYIKVLDVNDNAP EFAEFYETFVCEKAKADQLIQTILHAVDK DDPYSGHQFSFLAPEAASGSNFTIQDNK DNTAGILTRKNGYNRHEMSTYLLPVVIS DNDYPVQSSTGTVTVRVCACDHHGNMQ SCHAEALIHPTGLSTGAGSDKTHTCPPCP APELLGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVSVLTVLHQDWL NGKEYKCKVSNKALPAPIEKTISKAKGQP REPQVYTLPPSREEMTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTPPVLDS DGSFFLYSKLTVDKSRWQQGNVFCFSVM HEALHNHYTQKSLSLSPGK
cynoCDH6 FL	See above description on cynomolgus sequence derivation	Cynomolgus (<i>Macaca fascicularis</i>) full-length CDH6 (SEQ ID NO:7)	SWMWNQFFLLEEYTGSDYQYVGKLHSD QDRGDGSLKYILSGDGAGDLFIINENTGD IQATKRLDREEKPVYILRAQAINRRTGRP VEPESEFIKIHDINDNEPIFTKEVYTATVP EMSDVGTFVVQVTATDADDPTYGNSAK VVYSILQGQPYFSVESETGIIKTALLNMD RENREQYQVVIQAKDMGGQMGGLSGTT TVNITLTDVNDNPPRFPQSTYQFKTPESSP PGTPIGRIKASDADVGENAEIEYSITDGEG LDMFDVITDQETQEGIIIVKLLDFEKKK VYTLKVEASNPHYVEPRFLYLGPFKDSAT VRIVVEDVDEPPVFSKLAYILQIREDAQIN TTIGSVTAQDPDAARNPVKYSVDRHTDM DRIFNIDSGNGSIFTSKLLDRETLLWHNIT VIATEINNPKQSSRVPLYIKVLDVNDNAP EFAEFYETFVCEKAKADQLIQTILRAVDK DDPYSGHQFSFLAPEAASGSNFTIQDNK DNTAGILTRKNGYNRHEMSTYLLPVVIS DNDYPVQSSTGTVTVRVCACDHHGNMQ SCHAEALIHPTGLSTGAGSEFRHDSGLND IFEAQKIEWHE

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moCDH6 FL	NM_007666.3	Mouse (<i>Mus musculus</i>) full-length CDH6 (SEQ ID NO:8)	SWMWNQFFLLEEYTGSDYQYVGKLHSD QDRGDGSLKYILSGDGAGDLFIINENTGD IQATKRLDREEKPVYILRAQAVNRRRTGRP VEPESEFIIKIHINDNEPIFTKDVYTATVP EMADVGTFFVQVTATDADDPTYGNSAK VVYSILQGQPYFSVESETGIIKTALLNMD RENREQYQVVIQAKDMGGQMGGLSGTT TVNITLTDVNDNPPRFPQSTYQFKTPESSP PGTPIGRIKASDADVGNAEIEYSITDGE HEMFVDITDQETQEGIIIVKKLLDFEKKK VYTLKVEASNPHVEPRFLYLGPFKDSAT VRIVVDDVDEPPVFSKLAYILQIREDARIN TTIGSVAAQDPDAARNPVKYSVDRHTD MDRIFNIDSGNGSIFTSKLLDRETLWHNI TVIATEINNPKQSSRVPLIYKVLVDVNDNA PEFAEFYETFFVCEKAKADQLIQTALRAVD KDDPYSGHQFSFSLAPEAASSNFTIQDN KDNTAGILTRKNGYNRHEMSTYLLPVVI SDNDYPVQSSTGTVTVRVCADHHGNNM QSCHAEALIHPTGLSTGAGSEFRHDSGLN DIFEAQKIEWHE
ratCDH6 FL	NM_012927.1	Rat (<i>Rattus norvegicus</i>) full-length CDH6 (SEQ ID NO:9)	SWMWNQFFLLEEYTGSDYQYVGKLHSD QDRGDGSLKYILSGDGAGDLFIINENTGD IQATKRLDREEKPVYILRAQAINRRRTGRP VEPESEFIIKIHINDNEPIFTKDVYTATVP EMADVGTFFVQVTATDADDPTYGNSAK VVYSILQGQPYFSVESETGIIKTALLNMD RENREQYQVVIQAKDMGGQMGGLSGTT TVNITLTDVNDNPPRFPQSTYQFKTPESSP PGTPIGRIKASDADVGNAEIEYSITDGE HDMFVDITDQETQEGIIIVKKLLDFEKKR VYTLKVEASNPHIEPRFLYLGPFKDSATV RIVVDDVDEPPVFSKLAYILQIRED AQINT TIGSVAAQDPDAARNPVKYSVDRHTDM DRIFNIDSGNGSIFTSKLLDRETLWHNIT VIATEINNPKQSSRVPLIYKVLVDVNDNAP EFAEFYETFFVCEKAKADQLIQTALHAVDK DDPYSGHQFSFSLAPEAASGSNFTIQDNK DNTAGILTRKNGYNRHEMSTYLLPVVIS DNDYPVQSSTGTVTVRVCADHHGNNMQ SCHAEALIHPTGLSTGAGSEFRHDSGLND IFEAQKIEWHE

Recombinant protein expression and purification:*His6-SUMO-CDH6 aa54-260-APP-Avi*

[00285] Protein was expressed in Rosetta® 2 De3 pLysS cells (Millipore, Billerica, MA) in pET vector using 2xYT + 50 µg/ml Kanamycin and 30 µg/ml chloramphenicol. Cells were induced with 0.1 mM IPTG at 30°C. The pellet resuspended in 400 ml 20mM Tris-Cl, pH 8.0, 150 mM NaCl, 3mM CaCl₂, 20 mM Imidazole, + PI tabs (1 per 50 ml) + 1mg/ml lysozyme added fresh, homogenized to break up clumps and passed through microfluidizer 3 times. Following centrifugation at 20K x g for

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30 min the soluble fraction of supernatant was used for purification over a 2 ml Ni-NTA (Qiagen superflow resin, Qiagen, Venlo, Netherlands). The lysate was passed over the column at 2.0 ml/min, washed with 10 CV (column volume) 20mM Tris-Cl, pH 8.0, 150 mM NaCl, 3mM CaCl₂, 20 mM Imidazole and protein was eluted with 4 x 3.0 ml elution fractions using 20mM Tris-Cl, pH 8.0, 500 mM NaCl, 3mM CaCl₂, 250 mM Imidazole. Fractions were pooled. 200 units of SUMO Protease (Invitrogen) were added with ~15ml protein (~20mgs) and dialyzed into 5L of 20 mM Tris-Cl, pH 8.0, 150 mM NaCl, 3 mM CaCl₂ overnight at 4°C using Snakeskin® pleated tubing with 10K cutoff (Thermo Scientific, Rockford, IL). Dialyzed material was collected and re-purified over 2.0 ml Ni-NTA resin to remove uncleaved protein and SUMO Protease. Cleaved protein was collected from flow through and wash fractions. Concentrated flow through and wash from reverse Ni-NTA to 5 ml volume, added NaCl to final concentration of 500mM and injected onto S200 column, buffer = 20mM Tris-Cl, pH 8.0, 150 mM NaCl, 3mM CaCl₂.

hCDH6aa54-615 APPavi, hCDH6aa54-615 Fc, cynoCDH6 FL, moCDH6 FL, ratCDH6 FL

[00286] The protein was expressed in HEK293 (ATCC CRL-1573) derived cell lines previously adapted to suspension culture and grown in a Novartis proprietary serum-free medium. Small scale expression verification was undertaken in transient 6-well-plate transfection assays on the basis of lipofection. Large-scale protein production via transient transfection and was performed at the 10-20 L scale in the Wave™ bioreactor system (GE Healthcare, Pittsburgh, PA). DNA Polyethylenimine (Polysciences, Warrington, PA) was used as a plasmid carrier at a ratio of 1:3 (w:w). The cell culture supernatants were harvested 7-10 days post transfection and concentrated by cross-flow filtration and diafiltration prior to purification.

[00287] For purification, clarified and filtered conditioned supernatant from the transient transfection was passed over a 20 ml affinity column at 5ml/min. Wash 20 CV PBS, 1% TX100, 0.3% t-n-butylphosphate buffer, 20CV PBS. Elute using 100 mM sodium citrate, 150 mM NaCl pH3.0, protein collecting 2 ml fractions. Pooled fractions were neutralized and then dialyzed overnight at 4°C with 5L 50 mM Tris, 150 mM NaCl pH 7.4, 3 mM CaCl₂. Sample was then subjected to size exclusion chromatography on a Superdex® S200 16/60 column (GE Healthcare, Pittsburgh, PA) equilibrated with dialysis buffer.

[00288] An overview of the various panning strategies is indicated in Table 2

Table 2

Overview of panning strategies

Pancode	Phage subpool	Target and conditions
1038.1	VH1A/B/5 λ +κ	SP on hCDH6aa54-615 APPavi, without CaCl ₂
1038.2	VH3 λ +κ	

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Pancode	Phage subpool	Target and conditions
1038.3	VH2/6 $\lambda+\kappa$	
1038.4	VH6, κ	
1038.5	VH1A/B/5 $\lambda+\kappa$	SP on hCDH6aa54-615 APPavi, with CaCl_2
1038.6	VH3 $\lambda+\kappa$	
1038.7	VH2/6 $\lambda+\kappa$	
1038.8	VH6, κ	
1038.9	VH1A/B/5 $\lambda+\kappa$	SP on His6-SUMO-CDH6 aa54-260-APP-Avi, with 1mM CaCl_2
1038.10	VH3 $\lambda+\kappa$	
1038.11	VH2/6 $\lambda+\kappa$	
1038.12	VH6, κ	
1038.13	VH1A/B/5 $\lambda+\kappa$	SP on His6-SUMO-CDH6 aa54-260-APP-Avi, with 1mM CaCl_2
1038.14	VH3 $\lambda+\kappa$	Binding competition using tool antibody MAB2715
1038.15	VH2/6 $\lambda+\kappa$	
1038.16	VH6, κ	
1038.17	VH1A/B/5 $\lambda+\kappa$	LP on biotinylated hCDH6aa54-615 APPavi
1038.18	VH3 $\lambda+\kappa$	
1038.19	VH2/6 $\lambda+\kappa$	
1038.20	VH1A/B/5 $\lambda+\kappa$	LP on hCDH6aa54-615 APPavi
1038.21	VH3 $\lambda+\kappa$	Pull-down panning using biotinylated tool antibody 2B6
1038.22	VH2/6 $\lambda+\kappa$	
1038.23	VH1A/B/5 $\lambda+\kappa$	LP on Biotinylated hCDH6aa54-615-Fc
1038.24	VH3 $\lambda+\kappa$	
1038.25	VH2/6 $\lambda+\kappa$	
1038.26	VH1A/B/5 $\lambda+\kappa$	SP on hCDH6aa54-615-Fc
1038.27	VH3 $\lambda+\kappa$	
1038.28	VH2/6 $\lambda+\kappa$	

Biotinylation of proteins

[00289] Avi-tagged proteins were biotinylated using BirA enzyme following manufacture (Avidity, Aurora, CO) standard protocol for protein biotinylation on an Avi-tagged protein. After biotinylation the protein was subjected to size exclusion chromatography on a Superdex® S200 16/60 column into 50 mM Tris, 150 mM NaCl pH 7.4, 3 mM CaCl_2 .

[00290] Non-Avi-tagged proteins were dialyzed using Slide-A-Lyzer Mini Dialysis units, 10000 MWCO (#69576 Thermo Scientific, Rockford, IL) twice for 2h against 5L of 1x PBS under

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stirring at room temperature prior to biotinylation. EZ-link Sulfo-NHS-LC-biotin (#21327 Thermo Scientific, Rockford, IL) was reconstituted according to the manufacturer's protocol. The proteins were incubated with a 20-fold molar excess of biotin reagent for 30 min at room temperature. To remove non-reacted biotin reagent the sample was again dialyzed twice for 2h against 5L of 1x PBS under stirring at room temperature. Protein concentrations were determined by means of the Nanodrop® device (Thermo Scientific, Rockford, IL). Samples were stored at 4°C until usage.

Solid phase panning

[00291] In solid phase pannings the Fab fragment displaying phages are incubated with antigen that has been bound to a surface support by direct immobilization.

[00292] Prior to the antigen selection process, a coating check ELISA was performed to determine the optimal antigen coating concentration. For this purpose a 2 fold dilution series of hCDH6aa54-615 APPavi (see Table 1) covering 24 to 0.19 µg/mL was generated. The individual dilutions were used to coat wells on a 96-well Maxisorp™ plate (#442404 Nunc, Rochester, NY) via direct immobilization. After coating the plate was washed thrice with 300 µL PBS and subsequently blocked with 1x blocking buffer (2.5% milk, 2.5% BSA, 0.05% Tween 20) for 2h at room temperature.

[00293] To detect bound antigen, an anti-APP antibody (generated in-house) was added to 1 µM, 0.18 µM or 0.04 µM. Secondary detection was done using AP-labeled anti-mouse IgG-F(ab)2 specific antibody in a 1:5000 dilution Ref. 115-056-006 Jackson-ImmunoResearch, West Grove, PA). The antigen concentration at which signal saturation was observed was chosen as coating concentrations for SP pannings.

Pancodes 1038.1-8

[00294] For SP pannings 1038.1-8 (see Table 2) hCDH6aa54-615 APPavi (see Table 1, SEQ ID NO:4) was coated on a 96-well Maxisorp™ plate (Nunc) via direct immobilization. Two wells were coated with 300 µL antigen solution (10 µg/mL in PBS) per phage subpool combination. Coating was done at 4°C overnight with (pannings 1038.1-4) or without (pannings 1038.4-8) the presence of 1 mM CaCl₂. The wells were subsequently washed twice with 400 µL PBS and blocked with 400 µL blocking buffer for 2h at room temperature at 400 rpm. After blocking the cells were washed twice with 400 µL PBS.

[00295] Prior to binding phage subpools were blocked and depleted with unrelated FLT2-APPavi at 10 µg/mL for 1h at room temperature to eliminate unspecific and tag binders. 300 µL of blocked and depleted phage pools were transferred per coated well and incubated for 2h at room temperature and 400 rpm. Non-specific bound phages were removed by the washing steps listed below in Table 3.

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Table 3

First Round	Second Round	Third round (only pancodes 1038.9-16)
3x PBST (quick)	1x PBST (quick)	10x PBST (quick)
2x PBST / 5min	4x PBST / 5min	5x PBST / 5min
3x PBS (quick)	1x PBS (quick)	10x PBS (quick)
2x PBS / 5min	4x PBS / 5min	5x PBS / 5min

[00296] The specifically bound phages were eluted with 300 μ L elution buffer for 10 min at room temperature. Eluted phages were used to reinfect 14 mL of *E. coli* TG1F+ (Stratagene/Agilent, Santa Clara, CA), at an optical density of OD₆₀₀ = 0.6-0.8. The mix of *E. coli* TG1F+ and phage eluate was incubated for 45 min in a water bath at 37°C for phage infection. The bacterial pellets were re-suspended in 2xYT medium, plated on LB agar plates supplemented with 34 μ g/mL chloramphenicol and incubated overnight at 37°C. Colonies were scraped off the plates and were used for polyclonal amplification of enriched clones and phage production. With purified phage the next panning round was started. The second round of pannings was performed according to the protocol of the first round except for a more stringent washing condition. A third panning round was omitted due to the low second round output titers of $\sim 10^4$ cfu/mL.

Pancodes 1038.9-16

[00297] For SP pannings 1038.9-16 (Table 2) His6-SUMO-CDH6 aa54-260-APP-Avi (see Table 1) was coated on a 96-well Maxisorp™ plate (Nunc) via direct immobilization as described for pancodes 1038.1-8. For pannings 1038.13-16 300 μ L of a 100 nM solution of tool antibody MAB2715 was added per well and incubated for 1 h at room temperature to avoid selection of binders recognizing the same epitope as MAB2715. Besides the antigen coated and a third panning round the pannings were done as described for pancodes 1038.1-8.

Pancodes 1038.26-28

[00298] For SP pannings 1038.26-28 (see Table 2) hCDH6aa54-615-Fc (see Table 1, SEQ ID NO:6) was coated on a 96-well Maxisorp™ plate (Nunc) via direct immobilization as described for pancodes 1038.1-8. Besides the antigen coated and the washing stringencies the pannings were done as described for pancodes 1038.1-8.

Liquid phase panning

[00299] During solution panning, the Fab fragment displaying phage and biotinylated antigens are incubated in solution which is expected to increase accessibility of the antigen by the phage. Antigen biotinylation was done as described above.

Pancodes 1038.17-22

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[00300] Each phage library subpool was blocked with an equal volume of 2x Chemiblocker for 2h at room temperature on a turning wheel. To avoid selection of antibodies against the APPavi and biotin tag unrelated FLT3-APPavi and biotinylated anti-Cyclosporin mIgG was added to 7.5 and 18 µg/mL in the blocking step, respectively. For removal of phage particles binding to Streptavidin-beads, pre-adsorption of blocked phage particles was performed using blocked Streptavidin beads (# 112.06D Invitrogen, Carlsbad, CA). Blocked and pre-adsorbed phages were incubated with biotinylated hCDH6aa54-615 APPavi (see Table 1, SEQ ID NO:4) for 1h at room temperature on a turning wheel. Phage-antigen complexes were captured either with washed beads (Pancodes 1038.17-19) or with beads precoated with biotinylated anti-CDH6 antibody 2B6 (Genway, San Diego, CA) to enrich binders for non-2B6 epitopes (Pancodes 1038.20-22). Non-specific phage particles were removed by several washing steps (see below). Elution of specifically bound phage particles, infection, and amplification were done as described for pancodes 1038.1-8.

Table 4*Washing conditions Pancodes 1038.17-25*

First Round	Second Round	Third round (only pancodes 1038.9-16)
5x PBST (quick)	10x PBST (quick)	10x PBST (quick)
2x PBST / 5min	3x PBST / 5min	5x PBST / 5min
3x PBS (quick)	5x PBS (quick)	5x PBS (quick)

Pancodes 1038.23-25

[00301] Pannings were done as described for pancodes 1038.1-8 but using biotinylated hCDH6aa54-615-Fc (see Table 1, SEQ ID NO:6) as antigen.

Subcloning*Conversion for FAB-FH expression*

[00302] To facilitate rapid expression of soluble Fab fragments, the Fab encoding inserts of the selected HuCAL® PLATINUM phage particles were subcloned from the pMORPH®30 display vector into the pMORPH®11_FH expression vector. Glycerol stocks containing E. coli that were infected with the final panning round output phages were used to inoculate cultures for pMORPH®30 DNA purification using the Nucleobond® Xtra Midi Plus kit according to the manufacturers manual (#740.412.50 Machery Nagel, Bethlehem, PA). 5 µg of each pMORPH®30 DNA output pool was triple digested via EcoRI/XbaI/BmtI (all restriction enzymes were purchased from New England Biolabs, Ipswich, MA). The resulting EcoRI/XbaI Fab encoding 1485 bp fragment was gel purified

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using the Wizard SV Gel/PCR clean-up kit according to the manufacturers manual (A9282, Promega, Madison, WI) and ligated into the EcoRI/XbaI cut pMORPH®11_FH vector backbone.

Conversion for IgG expression

[00303] In order to express full length IgG, variable domain fragments of VH and VL were subcloned from Fab expression vectors into pMORPH®4_hIgG1f vectors following the RapCLONE® protocol (Morphosys, Martinsried/Planegg, Germany). RapCLONE® is a two-step cloning method for the batch conversion of a large amount of Fab expression vectors into IgG expression vectors. In a first cloning step, a eukaryotic expression cassette was introduced into the pMORPH®11 expression vectors via BsiWI/MfeI (for κ pools) or HpaI/MfeI (for λ pools) digestion and subsequent ligation. This was followed by a second cloning step, in which the Fab pools containing the expression cassette were digested using EcoRV/BlpI (both κ and λ pools) and subsequently cloned into the pMORPH®4_IgG1f acceptor vector for expression in mammalian cells.

Expression and Purification of Fab Fragments

Transformation of E. coli TG1F

[00304] Electroporation-competent E. coli TG1F- aliquots of 50 μ L were thawed on ice, mixed with 50 pg/ μ l pMORPH®11_FH plasmid DNA and transferred into pre-cooled electroporation cuvettes. The cells were electroporated (Bio-Rad Gene Pulser; settings: 1.75 kV, 200 Ω , and 25 μ F (Bio-Rad, Hercules, CA), transferred into 950 μ l pre-warmed SOB medium and incubated for 1 h at 37 °C shaking at 220 rpm. An appropriate volume of the transformation samples were plated onto LB agar plates supplemented with 34 μ g/mL Chloramphenicol and incubated overnight at 37°C to obtain single colonies.

Generation of Master plates

[00305] Chloramphenicol resistant single clones were picked into the wells of a sterile 384-well microtiter plate (Nunc) pre-filled with 60 μ l 2xYT medium supplemented with 34 μ g/ml of Chloramphenicol and 1 % glucose and grown overnight at 37°C. Next morning, 20 μ l sterile 2xYT media containing 60 % glycerol and 1 % glucose were added into each well of the master plates. Plates were sealed with aluminum foil and stored at -8 °C.

Generation of Fab-Containing Bacterial Lysates for ELISA Screening

[00306] 5 μ l of each well of a Master plate was transferred to a sterile 384-well microtiter plate pre-filled with 40 μ l 2xYT medium per well supplemented with 34 μ g/ml of Chloramphenicol and 0.1 % glucose. Plates were incubated at 37°C at 480 rpm and 80% humidity until the cultures were slightly turbid. 10 μ l of 2xYT medium supplemented with 34 μ g/ml Chloramphenicol and 5 mM IPTG were added per well for induction of Fab fragment expression. Plates were sealed with a gas-

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permeable tape and incubated overnight at 22°C at 500 rpm and 80% humidity. The next day 15 µl BEL lysis buffer (2.5 mg/ml lysozyme (#10837059001, Roche, Nutley, NJ), 4 mM EDTA, 10 U/µl Benzonase (# 1.01654.0001 Merck, White House Station, NJ) was added to each well and plates were incubated for 1 h at 500 rpm and 80% humidity. Resulting Fab lysates were blocked by adding 15 µL of 2x Chemiblocker per well followed by incubation for 30 min at 22°C, 500 rpm and 80% humidity.

Generation of Fab-Containing Bacterial Lysates for FACS Screening

[00307] 5 µl of each well of a compression plate was transferred to a sterile 96-well round bottom microtiter plate pre-filled with 100 µl 2xYT medium per well supplemented with 34 µg/ml of Chloramphenicol. Plates were incubated at 37°C at 500 rpm and 80% humidity until the cultures were slightly turbid. 10 µl of 2xYT medium supplemented with 34 µg/ml Chloramphenicol and 5 mM IPTG were added per well for induction of Fab fragment expression. Plates were sealed with a gas-permeable tape and incubated overnight at 22°C at 500 rpm and 80% humidity. The next day the plate was centrifuged for 10 min at 1200g and the supernatant discarded. The bacterial pellets were frozen overnight at -20°C to facilitate the lysis step. The thawed pellets were re-suspended in 200 µL of BEL lysis buffer (see above) and incubated for 1 h at 22°C and 250 rpm. Resulting Fab lysates were centrifuged to remove cellular debris for 10 min at 1200 g. Fab containing supernatants were used for screening purposes.

Expression and Purification of His6-tagged Fab Fragments in E. coli

[00308] E. coli TG1F- transformants containing pMORPH®11 Fab FH DNA were singled out on 2xYT supplemented with 34 µg/mL Chloramphenicol and 1% glucose. Individual clones were picked and transferred into 3 mL 2xYT seed cultures supplemented with 34 µg/mL Chloramphenicol and 1% glucose and incubated at 37°C, 220 rpm for 4h. The seed culture was used to inoculate 50 mL main cultures with 2xYT supplemented with 34 µg/mL Chloramphenicol and 1% glucose and incubated in 250 mL shake flasks at 30°C until the OD600 reached a value of 0.6. Fab expression was induced by addition of IPTG to a final concentration of 0.75 mM and cultures were further incubated overnight at 25°C and 220 rpm. The next day cells were harvested and the cell pellets frozen overnight at -20°C. Cells pellets were disrupted by re-suspending and incubating in lysis buffer ((25 mM TRIS/pH=8, 500 mM NaCl, 2 mM MgCl₂, 10 U/µl Benzonase (# 1.01654.0001 Merck), 0.1% Lysozyme (# 10837059001, Roche), Protease Inhibitor Complete w/o EDTA 1 tablet/ 50 mL of buffer (#11873580001 Roche)) for 1h at room temperature on a rocking table. Lysates were clarified by centrifugation for 30 min at 15000 g and filtration of the supernatant through a 200 nm pore sized filter. His6-tagged Fab fragments were isolated via immobilized metal ion affinity chromatography (Ni-NTA Superflow® beads, #30430 Qiagen, Venlo, Netherlands) and eluted using imidazole. Buffer exchange to 1x PBS was performed using PD-10 columns (# 17-0851-01 GE Healthcare, Pittsburgh, PA). Samples were sterile-filtered and the protein concentrations were determined by UV-

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spectrophotometry. The purity of the samples was analyzed in denaturing, reducing 15% SDS-PAGE. The identity of the samples was confirmed by MS.

Expression and purification of IgGs

Expression of IgGs at screening scale

[00309] Eukaryotic HEK293c18 cells (ATCC CRL-10852) were used in a 96-well expression system for the generation of conditioned cell culture supernatants containing full-length IgG for the subsequent use in specificity and/or functional assays. Eukaryotic HEK293 c18 cells were re-suspended in transfection medium (D-MEM supplemented with 2% L-glutamine (#25030-024 Gibco, Grand Island, NY) 10 % FCS (#3302 PAN Biotech, Aidenbach, Germany) and 1 % penicillin/streptomycin (#15140-122 Gibco, Grand Island, NY)) and seeded in 96-well F-bottom plates to a density of approximately 4×10^4 cells in 50 μ l per well the day before. A transfection master mix was prepared by mixing 0.6 μ l Lipofectamine® 2000 (#11668 Invitrogen, Carlsbad, CA) per well with 25 μ l Opti-MEM® I medium. (#31985-047 Invitrogen, Carlsbad, CA). The master mix was incubated for 15 min at room temperature. On a new plate 20 μ l of Opti-MEM® I medium was added to wells containing 300 ng DNA and gently mixed. After that, the DNA was combined with the pre-incubated Lipofectamine® 2000, mixed gently and incubated for 20 min at room temperature. 100 μ l of the pre-incubated Lipofectamine® 2000/DNA complexes were then transferred to each well of the plates with the cells and gently mixed. Plates were incubated for 40 h at 37°C and 6 % CO₂ for transient expression. The culture supernatants were transferred to 96-well V-bottom plates and cleared by centrifugation. The resulting IgG-containing supernatants were tested by an anti-Fd capture ELISA for assessment of IgG protein concentration in reference to a known standard and stored at -80°C for later use.

IgG expression check by anti-Fd ELISA

[00310] To assess IgG levels in screening scale derived supernatants Maxisorp® 96-well plates (#437111 Nunc) were coated with 50 μ l/well Fd-fragment-specific sheep anti-human IgG (#PC075 The Binding Site, San Diego, CA) diluted 1:1000 in PBS. After coating, the plates were washed twice with TBST and blocked for 1h with 5 % skim milk powder in TBST. In the meantime the IgG containing supernatants were diluted 1:50 in 2.5% skim milk powder in TBST. After washing the ELISA plates three times with TBST, 100 μ l of the diluted supernatants were transferred per well and plates were incubated for 1 h at room temperature. Subsequently, the plates were washed five times with TBST and the captured IgGs were detected by incubation with 50 μ l F(ab')₂-specific goat anti-human IgG (#109-055-097 Dianova, Hamburg, Germany) (diluted 1:5000) in 0.5 % skim milk powder in TBST for 1h. After washing the plates five times with TBST the AttoPhos fluorescence substrate (#1484281 Roche, Nutley, NJ) was added according to the manufacturer's instructions and the fluorescence emission at 535 nm was recorded with excitation at 430 nm with an ELISA reader.

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Expression and Purification of IgGs in Microscale

[00311] CAP-T® cells (CEVEC Pharmaceuticals, Cologne, Germany) were transiently transfected with pMORPH®4 IgG expression plasmid in FreeStyle293® expression medium (#12338 Invitrogen, Carlsbad, CA) using 40 kDa linear PEI ((PEI Max (#24765-2 Polysciences Warrington, PA)) as gene delivery vehicle.

[00312] One day prior to the transfection cells were diluted to $\sim 0.8 \times 10^6$ cells/ml to ensure exponential growth. At the day of transfection cells were diluted in 9 mL pre-warmed Freestyle® (Invitrogen, Carlsbad, CA) medium to $\sim 0.5 \times 10^7$ cells/ml and transferred into a 125ml shake flask. 30 µg DNA was diluted in 500 µl OptiMEM. 1200 µg PEI Max (#24765-2 Polysciences Warrington, PA) was diluted in 8.80 mL OptiMEM medium. The DNA solution was added drop wise to the cells and gently mixed. After that, 500 µL PEI Max solution was added to the cells and gently mixed.

[00313] The cells were incubated at 37°C, 6 % CO₂, 85 % humidity with agitation at 100 rpm. After 4 h 10 mL pre-warmed PEM supplemented with 4 mM L-Glutamine and 5 µg/ml blasticidin (#R21001 Invitrogen, Carlsbad, CA) was added. Simultaneously, 400 µL valproic acid (#P4543-25G Sigma Aldrich, St. Louis, MO) was added to a final concentration of 4 mM. Cells were incubated for 6 days at 37°C, 6 % CO₂, 85 % humidity with agitation at 100 rpm.

[00314] After centrifugation for 5 min at 1200 g at 4°C the supernatant was sterile-filtered (0.2 µm pore size) and subjected to a Protein A affinity chromatography (MabSelect® SURE, GE Healthcare, Pittsburgh, PA) using a liquid handling station. Buffer exchange was performed to 1x PBS and samples were sterile filtered (0.2 µm pore size). Protein concentrations were determined by UV spectrophotometry and purity of IgGs was analyzed under denaturing, reducing conditions in SDS-PAGE.

Screening of Fab-containing raw bacterial lysates*ELISA screening*

[00315] Using ELISA screening, single Fab clones were identified from panning outputs for binding to the target antigen. Fab fragments were tested using Fab containing crude E. coli lysates.

ELISA screening on directly coated antigen

[00316] Maxisorp® (#442404 Nunc, Rochester, NY) 384-well plates were coated overnight at 4°C with huCDH6 proteins at a concentration of 3 µg/ml in PBS. After washing plates were blocked for 2 h with 5% skimmed milk in 1xPBST. Fab-containing E. coli lysates were added and binding allowed for 1 h at room temperature.

[00317] To detect bound Fab fragments plates were washed 5x with TBST and AP-anti human IgG F(ab')₂ (#109-055-097 Jackson ImmunoResearch, West Grove, PA) was added in a 1/2500

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dilution. After 1h at room temperature plates were washed 5x with TBST and AttoPhos substrate was added according to the manufacturer's specifications. Plates were read in an ELISA reader 5 minutes after adding the substrate.

ELISA Screening on Biotinylated Antigen using NeutrAvidin® Plates

[00318] Maxisorp® (#442404 Nunc, Rochester, NY) 384-well plates were coated overnight at 4°C with NeutrAvidin® (#31000 Thermo Scientific, Rockford, IL) at a concentration of 10 µg/ml in PBS. After washing, plates were blocked for 2 h with 1x Chemiblocker. Fab-containing E. coli lysates were dispensed into a fresh 384-well microtiter plate and biotinylated CDH6 antigens added at a concentration of 2.5 µg/mL. Fab-antigen complexes were then transferred to the NeutrAvidin® coated plates and capturing allowed for 1h at room temperature and detected as described above.

FACS screening

[00319] In FACS screening, Fab fragments binding to cell surface expressed CDH6 antigen were identified from the panning output. 1×10^5 cells/well were transferred into U bottom 96 well plates and mixed with 40 µl/well of the Fab-containing bacterial lysates. Plates were incubated shaking at 4°C for 1 h. After the incubation, 100 µl/well ice-cold FACS buffer (3% FCS, 0.02% NaN_3 , 2 mM EDTA in PBS) was added, cells were spun down at 4°C for 5 min at 250 g and washed twice with 180 µl/well ice-cold FACS buffer. After each washing step, cells were centrifuged and carefully re-suspended. After the last washing step cells were re-suspended in 50 µL of 1/200 diluted secondary detection antibody (PE-conjugated goat anti-human IgG (#109-116-088, Jackson ImmunoResearch, West Grove, PA). After 1h incubation at 4°C cells were again washed twice in 180 µL/well ice-cold FACS buffer. Finally, cell pellets were re-suspended in 120 µl/well FACS buffer with 0.4 % paraformaldehyde and analyzed in a FACSCalibur® (BD Biosciences, San Jose, CA) equipped with an HTS plate reader.

Clone sequencing

Fab clone sequencing

[00320] Confirmed cell binding Fab hits were subjected to VL and VH sequencing. 1.2 mL 2xYT supplemented with 34 µg/mL Chloramphenicol and 1% glucose were inoculated with 5 µL of bacterial glycerol stock deriving from the compression plates and grown in 96-well deep well microtiter plates overnight at 37°C and 500 rpm. The next day the bacteria were harvested and the pMORPH®11 FH plasmids purified using a 96-well DNA purification kit (Nucleospin® 96 Plasmid Purification Kit #740625.24, Machery Nagel, Bethlehem, PA) according to the manufacturers protocol. To sequence the VL and VH primers M13rev (5' CAGGAAACAGCTATGAC 3' (SEQ ID NO:10) and HuCAL_VH_for ((5' GATAAGCATGCGTAGGAGAAA 3 (SEQ ID NO:11)) were used, respectively.

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IgG clone sequencing

[00321] Unique cell binding Fab clones were converted in the IgG1 format in a polyclonal manner and afterwards retrieved by VL and VH sequencing. 1.5 mL 2xYT medium supplemented with 100 µg/mL Amp and 1% glucose were inoculated with single clones and grown in 96-well deep well microtiter plates overnight at 37°C, 450 rpm and 80% humidity. The next day the bacteria were harvested and the IgG encoding pMORPH®4 plasmids purified using a 96-well DNA purification kit according to the manufacturer's protocol (Nucleospin® 96 Plasmid Purification Kit #740625.24, Machery Nagel, Bethlehem, PA). To sequence the VL and VH primers ((T7 5' TAATACGACTCACTATAGGG 3' (SEQ ID NO:12) and CMV HC for (5' CTCTAGCGCCACCATGAAACA 3' (SEQ ID NO:13)) were used, respectively.

[00322] *In vitro* assays*Affinity assessment using Octet® QK*

[00323] Affinity assessments by determining kinetic parameters were performed via Bio-Layer Interferometry technology. All Fab samples were measured using Streptavidin Dip and Read biosensors (#18-0009 ForteBio, Menlo Park, CA). The plate was placed in an Octet® QK instrument (ForteBio, Menlo Park, CA) and allowed to equilibrate to 27°C in the chamber. The run was initiated by placing the sensors in the wells containing 150 nM of biotinylated CDH6 protein for 300s. After that the sensors were placed in the wells containing 250 nM Fab sample. Fab association and dissociation were each recorded for 600s by measuring the change in layer thickness (in nanometers, nm) with time, all under computer control. Data were processed automatically using the Octet® User Software version 3.0.

Assessment of antibody cellular internalization propensity

[00324] Cell Internalization of IgGs by target mediated endocytosis was assessed by microscopy using a VTI ArrayScan® HC reader (ThermoFischer, Waltham, MA) as described below. The underlying analysis protocol was the Spot Detector V4 algorithm (ThermoScientific Cellomics®, Thermo Scientific, Rockford, IL). In brief, this analysis protocol provides a fast and generic spot analysis that identifies intracellular punctuate objects, such as IgG containing lysosomal vesicles after immunofluorescent staining. The total punctuate fluorescent intensity can then be averaged over the number of cells analyzed.

[00325] OVCAR3 cells (ATCC HTB-161) were grown in T150 tissue culture flasks to approximately 90% confluency. Media was discarded and cells flushed with 10 mL PBS. Cells were detached by incubation with 4 mL cell dissociation buffer for 5 min at 37°C. Detached cells were re-suspended thoroughly in growth medium and transferred to a 50 mL tube. After counting the cells on a Vi-Cell® analyzer (Beckman Coulter, Brea, CA) the suspension was adjusted to 10⁵ cells/mL in

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growth medium. 100 μ L of the cell suspension was seeded per well of a 96-well microtiter plate with transparent bottom. Plates were incubated for 24 h at 37°C in 5% CO₂ to allow the cells to adhere and to expand.

[00326] IgG containing cell culture supernatants were generated as described and diluted in PBS in a fourfold dilution series covering dilutions ranging from 1:4 to 1:128. 100 μ l of each sample dilution was dispensed per well of the cell containing microtiter plate and incubated for 2h at 37°C to permit IgG internalization. Subsequently, cells were fixed by adding 100 μ l 1x CellFix® reagent (#340181 BD Biosciences, San Jose, CA) per well. After 10 minutes plates were washed twice with PBS and cells then permeabilized by adding 100 μ l 0.1% Triton X-100 per well. After 10 min plates were washed again twice with PBS and blocked with 100 μ l 1x Odyssey blocking buffer (#927-40000 LiCor, Lincoln, NE) for 2 hours at room temperature. To detect internalized IgGs 100 μ l of a 1:1000 dilution of secondary antibody Alexa Fluor® 488 goat anti-human IgG (#11001 Molecular Probes, Grand Island, NY) supplemented with a 1:10000 dilution of Hoechst nucleus staining reagent (#B2261 Sigma, St. Louis, Mo) were added per well and incubated for 1 hours at room temperature in the dark. Cells were then washed twice with PBS without final aspiration. Plates were then loaded into the Cellomics® VTI Array Scan HC reader (ThermoFischer, Waltham, MA) and analyzed. The extent of IgG internalization was assessed by the mean average spot intensity (MSAI) per cell.

Surrogate ADC assay using anti-human FAB-DM1 conjugate

[00327] To test the ability of CDH6 antibodies to internalize after receptor binding and deliver cytotoxic payload, a surrogate ADC assay was performed mixing anti-human Fab-DM1 reagent (AffiniPure® Fab Fragment Goat Anti-Human IgG H+L conjugated with SMCC-DM1) with purified IgGs at a fixed 1:2 ratio. Cytotoxic potential was tested on the cancer cell line OVCAR3 (ovarian serous carcinoma, cultured in McCoy's + 20% FCS) as these cells show high expression of CDH6.

[00328] Cells in culture were counted and diluted in medium to a concentration of 1×10^5 cells/ml. 1000 cells/well were transferred to 384-well plates (Corning Costar#3707, Corning, Tewksbury, MA). Primary antibody/Fab-DM1 solution was prepared in 1.4ml Matrix tubes (Thermo, # 3790, Rockford, IL) by combining 666nM Fab-DM1 with 333nM primary human IgG diluted in cell culture media and incubated at 37°C for 30 minutes. A 10-point, 1:3 serial dilution was prepared in a 384-well deep-well plate (Brandtech Scientific Inc #701355, Essex, CT) and 25 μ l were transferred per assay plate (triplicates) to yield a highest starting concentration of FAB-DM1/human IgG of 66nM and 33nM, respectively. For controls, wells with cells only (=100% viability control) and cells only incubated with Fab-DM1 (to check for unspecific killing of the secondary reagent) were prepared. Plates were incubated for 120 h at 37°C and 5% CO₂. Cellular activity of the primary antibody/Fab-

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DM1 complexes was determined using CellTiter-Glo® reagent (#G7571 Promega, Madison, WI) according to the manufacturer's instructions. Viability was normalized to the cells only control.

Antibody screening summary

[00329] The HuCAL® PLATINUM phagemid library was used to select specific Fab fragments against human CDH6-ECD antigens. Recombinant human APPAvi and Fc fusion as well as truncated domain APPAvi fusion proteins were used for the pannings. HuCAL® PLATINUM antibody-phage particles were subjected in different subpool combinations to a total of 8 different panning strategies resulting in 28 panning output pools. In summary, six out of eight strategies have been productive and resulted in 771 ELISA positive screening hits.

[00330] FACS screening on CHO cells expressing human CDH6 as well as OVCAR3 cells resulted in 271 confirmed cell binding hits. To consolidate these cell binding hits VL and VH sequencing was performed leading to the identification of 53 unique Fab antibody clones.

[00331] To allow for the functional characterization, the Fab antibody clones were converted into the IgG format, yielding 47 unique IgG clones of which 44 were successfully expressed at screening scale. The purified, unique IgGs were subjected to a series of characterization assays including human/cyno/rat/mouse cross-reactivity by FACS, affinity ranking by Octet, cellular internalization assays as well as surrogate ADC assays using an anti-human IgG Fab-SMCC-DM1 secondary reagent. Based on these assays, human IgGs were selected for scaled up production, subsequent direct conjugation to ADC linker/payloads and testing as ADCs in *in vitro* and *in vivo* experiments.

[00332] The sequence information for the anti-CDH6 IgGs selected for further in-depth characterization are shown in Table 5.

Table 5

Sequence information of the IgGs selected for in-depth characterization.

NOV ID	Category	Value
NOV0670	LCDR1 (Kabat) (SEQ ID NO:14)	SGSSSNIGSQYVY
	LCDR2 (Kabat) (SEQ ID NO:15)	YNSERPS
	LCDR3 (Kabat)	QTWDASSQSFV

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(SEQ ID NO:16)	
HCDR1 (Kabat) (SEQ ID NO:17)	SYAIS
HCDR2 (Kabat) (SEQ ID NO:18)	GIIPIFGTANYAQKFQG
HCDR3 (Kabat) (SEQ ID NO:19)	KFPGRGPFAY
vH full sequence (SEQ ID NO:20)	QVQLVQSGAEVKKPGSSVKVSKASGGTFSSYAIWVRQAPGQGLEWMGGIIPFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARKFPGRGPFAYWGQGLVTVSS
vL full sequence (SEQ ID NO:21)	DIVLTQPPSVSGAPGQRVTISCSGSSSNIGSQYVYWYQQLPGTAPKLLIYYNSERPSGMPDRFSGSKSGTSASLAITGLQAEDEADYYCQTDWASSQSFVFGGGTKLTVL
vH DNA sequence (SEQ ID NO:22)	CAGGTGCAATTGGTGCAGAGCGGTGCCGAAGTGAAAAAACCGGGCAGCAGCGTGAAAGTTAGCTGCAAAGCATCCGGAGGACGTTTTCTTCTTACGCTATCTCTTGGGTGCGCCAGGCCCCGGGCCAGGGCCTCGAGTGGATGGGCGGTATCATCCCGATCTTCGGCACTGCGAACTACGCCCAGAAATTCAGGGCCGGGTGACCATACCGCCGATGAAAGCACCAGCACC GCCTATATGGA ACTGAGCAGCCTGCGCAGCGAAGATACGGCCGTGTATTATTGCGCGCGTAAATTCGCGGGTCGTGGTCCGTTCTGCTTACTGGG GCCAAGGCACCCTGGTGACTGTTAGCTCA
vL DNA sequence (SEQ ID NO:23)	GATATCGTGCTGACCCAGCCGCCGAGCGTGAGCGGTGCACCGGGCCAGCGCGTGACCATTAGCTGTAGCGGCAGCAGCAGCAACATTGGTTCTCAGTACGTGTACTGGTACCAGCAGCTGCCGGCACGGCGCCGAAACTGCTGATCTACTACAACCTGGAACGCCGAGCGGCATGCCGGATCGCTTTAGCGGATCCAAAAGCGGCACCAGCGCCAGCCTGGCGATTACCGGCCTGCAAGCAGAA GACGAAGCGGATTATTACTGCCAGACTTGGGACGCTTCTTCTCAGTCTTTCGTGTTTGGCGGCGGCACGAAGTTAACCGTCCTA
HC full sequence (SEQ ID NO:24)	QVQLVQSGAEVKKPGSSVKVSKASGGTFSSYAIWVRQAPGQGLEWMGGIIPFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARKFPGRGPFAYWGQGLVTVSSASTKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRV VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK
LC full sequence (SEQ ID NO:25)	DIVLTQPPSVSGAPGQRVTISCSGSSSNIGSQYVYWYQQLPGTAPKLLIYYNSERPSGMPDRFSGSKSGTSASLAITGLQAEDEADYYCQTDWASSQSFVFGGGTKLTVLGPKAAPSVTLPSPSEELQA

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	NO:25)	NKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSN KYAASSYLSLTPEQWKSHRYSYSCQVTHEGSTVEKTVAPTECS
	HC DNA sequence (SEQ ID NO:26)	CAGGTGCAATTGGTGCAGAGCGGTGCCGAAGTGAAAAAAC CGGGCAGCAGCGTGAAAGTTAGCTGCAAAGCATCCGGAGG GACGTTTTCTTCTTACGCTATCTCTTGGGTGCGCCAGGCCCC GGGCCAGGGCCTCGAGTGGATGGGCGGTATCATCCCGATCT TCGGCACTGCGAACTACGCCCAGAAATTTTCAGGGCCGGGTG ACCATTACCGCCGATGAAAGCACCAGCACC GCCTATATGGA ACTGAGCAGCCTGCGCAGCGAAGATACGGCCGTGTATTATT GCGCGCGTAAATTTCCCGGGTCTGTGGTCCGTTTCGCTTACTGGG GCCAAGGCACCCTGGTGACTGTTAGCTCAGCCTCCACCAAG GGTCCATCGGTCTTCCCCCTGGCACCCCTCCTCCAAGAGCACC TCTGGGGGACAGCGGCCCTGGGCTGCCTGGTCAAGGACTA CTTCCCCGAACCGGTGACGGTGTCTGTGAACTCAGGCGCCC TGACCAGCGGCGTGCACACCTTCCCGGCTGTCTACAGTCTT CAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCC AGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCA CAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCC AAATCTTGTGACAAAACCTCACACATGCCCCACCGTGCCAGC ACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCC AAAACCCAAGGACACCCCTCATGATCTCCCGGACCCCTGAGG TCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCGTAG GTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAA TGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACG TACCGGGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTG GCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAA GCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAGCCAA AGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCAT CCCGGGAGGAGATGACCAAGAACCAGGTACAGCTGACCTGC CTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTG GGAGAGCAATGGGCAGCCGAGAACAACTACAAGACCACG CCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTACAGC AAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACG TCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACT ACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA
	LC DNA sequence (SEQ ID NO:27)	GATATCGTGCTGACCCAGCCGCCGAGCGTGAGCGGTGCACC GGGCCAGCGCGTGACCATTAGCTGTAGCGGCAGCAGCAGCA ACATTGGTTCTCAGTACGTGTACTGGTACCAGCAGCTGCCG GGCACGGCGCCGAAACTGCTGATCTACTACAACCTCTGAACG CCCGAGCGGCATGCCGATCGCTTTAGCGGATCCAAAAGCG GCACCAGCGCCAGCCTGGCGATTACCGGCCTGCAAGACGAA GACGAAGCGGATTATTACTGCCAGACTTGGGACGCTTCTTCT CAGTCTTTCGTGTTTGGCGGCGGCACGAAGTTAACCGTCCTA GGTCAGCCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCC TCCTCTGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTG TCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCCT GGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGAGAC CACCACACCCTCCAAACAAGCAACAACAAGTACGCGGCCA GCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCAC AGAAGCTACAGCTGCCAGGTACGCATGAAGGGAGCACCGT GGAGAAGACAGTGGCCCCCTACAGAATGTTCA
NOV0672	LCDR1 (Kabat) (SEQ ID	TGTSSDVGAYNYVS

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	NO:28)	
	LCDR2 (Kabat) (SEQ ID NO:29)	GVSKRPS
	LCDR3 (Kabat) (SEQ ID NO:30)	QSYDHLLHV
	HCDR1 (SEQ ID NO:31)	TYGIH
	HCDR2 (Kabat) (SEQ ID NO:32)	YIHYSGSSTYYADSVKG
	HCDR3 (Kabat) (SEQ ID NO:33)	HAYGYMDF
	vH full sequence (SEQ ID NO:34)	QVQLLES G G G L V Q P G G S L R L S C A A S G F T F N T Y G I H W V R Q A P G K G L E W V S Y I H Y S G S S T Y Y A D S V K G R F T I S R D N S K N T L Y L Q M N S L R A E D T A V Y Y C A R H A Y G Y M D F W G Q G T L V T V S S
	vL full sequence (SEQ ID NO:35)	D I A L T Q P A S V S G S P G Q S I T I S C T G T S S D V G A Y N Y V S W Y Q Q H P G K A P K L M I Y G V S K R P S G V S N R F S G S K S G N T A S L T I S G L Q A E D E A D Y Y C Q S Y D H L L H V V F G G G T K L T V L
	vH DNA sequence (SEQ ID NO:36)	C A G G T G C A A T T G C T G G A A A G C G G C G G T G G C C T G G T G C A G C C G G G T G G C A G C C T G C G T C T G A G C T G C G C G G C G T C C G G A T T C A C C T T T A A C A C T T A C G G T A T C C A T T G G G T G C G C C A G G C C C C G G G C A A A G G T C T C G A G T G G G T T T C C T A C A T C C A T T A C T C T G G T T C T T C T A C C T A C T A T G C G G A T A G C G T G A A A G G C C G C T T T A C C A T C A G C C G C G A T A T T C G A A A A A C A C C C T G T A T C T G C A A A T G A A C A G C C T G C G T G C G G A A G A T A C G G C C G T G T A T T A T T G C G C G C G T C A T G C T T A C G G T T A C A T G G A T T T C T G G G G C C A A G G C A C C C T G G T G A C T G T T A G C T C A
	vL DNA sequence (SEQ ID NO:37)	G A T A T C G C G C T G A C C C A G C C G G C G A G C G T G A G C G G T A G C C C G G G C C A G A G C A T T A C C A T T A G C T G C A C C G G C A C C A G C A G C G A T G T G G G C G C T T A C A A C T A C G T G T C T T G G T A C C A G C A G C A T C C G G G C A A G G C G C C G A A A C T G A T G A T C T A C G G T G T T T C T A A A C G T C C G A G C G G C G T G A G C A A C C G T T T T A G C G G A T C C A A A A G C G G C A A C A C C G C G A G C C T G A C C A T T A G C G G C C T G C A A G C G G A A G A C G A A G C G G A T T A T T A C T G C C A G T C T T A C G A C C A T C T G C T G C A T G T T G T G T T T G G C G G C G G C A C G A A G T T A A C C G T C C T A
	HC full sequence (SEQ ID NO:38)	Q V Q L L E S G G G L V Q P G G S L R L S C A A S G F T F N T Y G I H W V R Q A P G K G L E W V S Y I H Y S G S S T Y Y A D S V K G R F T I S R D N S K N T L Y L Q M N S L R A E D T A V Y Y C A R H A Y G Y M D F W G Q G T L V T V S S A S T K G P S V F P L A P S S K S T S G G T A A L G C L V K D Y F P E P V T V S W N S G A L T S G V H T F P A V L Q S S G L Y S L S S V V T V P S S S L G T Q T Y I C N V N H K P S N T K V D K R V E P K S C D K T H T C P P C A P E L L G G P S V F L F P P K P K D T L M I S R T P E V

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	LC full sequence (SEQ ID NO:39)	DIALTPASVSGSPGQSITISCTGTSSDVGAANYVSWYQQHPGK APKLMYGVSKRPSGVSNRFSKSGNTASLTISGLQAEDEADY YCQSYDHLLHVVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQA NKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSN KYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
	HC DNA sequence (SEQ ID NO:40)	CAGGTGCAATTGCTGGAAGCGGCGGTGGCCTGGTGCAGCC GGGTGGCAGCCTGCGTCTGAGCTGCGCGGCGTCCGGATTCA CCTTTAACACTTACGGTATCCATTGGGTGCGCCAGGCCCGG GCAAAGGTCTCGAGTGGGTTTCTACATCCATTACTCTGGTT CTTCTACCTACTATGCGGATAGCGTGAAAGGCCGCTTTACCA TCAGCCGCGATAATTGAAAAACACCCTGTATCTGCAAAATG AACAGCCTGCGTGCGGAAGATACGGCCGTGTATTATTGCGC GCGTCATGCTTACGGTTACATGGATTTCTGGGGCCAAAGCA CCCTGGTGACTGTTAGCTCAGCCTCCACCAAGGGTCCATCG GTCTTCCCCCTGGCACCTCCTCCAAGAGCACCTCTGGGGGC ACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGA ACCGGTGACGGTGTCGTGGAACCTCAGGCGCCCTGACCAGCG GCGTGACACCTTCCCGGCTGTCTACAGTCTCAGGACTCT ACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTG GGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAG CAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTG ACAAAACCTACACATGCCCACCGTGCCCGAGCACCTGAACTC CTGGGGGGACCGTCAGTCTTCTCTTCCCCCAAAACCCAA GGACACCCTCATGATCTCCCGGACCCCTGAGGTCAATGCG TGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTC AACTGGTACGTGGACGGCGTGAGGTGCATAATGCCAAGAC AAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGGGTG GTCAGCGTCTCACCGTCTGCAACAGGACTGGCTGAATGG CAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCAG CCCCATCGAGAAAACCATCTCCAAAGCCAAAGGCGAGCCC CGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGA GATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAG GCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAAT GGGCAGCCGGAGAACAACCTACAAGACCACGCCTCCCGTGCT GGACTCCGACGGCTCCTTCTCTCTACAGCAAGCTCACCGT GGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCT CCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAG AGCCTCTCCCTGTCTCCGGGTAAA
	LC DNA sequence (SEQ ID NO:41)	GATATCGCGCTGACCCAGCCGGCGAGCGTGAGCGGTAGCCC GGGCCAGAGCATTACCATTAGCTGCACCGGCACCAAGCAGCG ATGTGGGCGCTTACAACCTACGTGTCTTGGTAAAGCAGCAGC CCGGGCAAGGCGCCGAAACTGATGATCTACGGTGTCTTCTAA ACGTCCGAGCGGCGTGAGCAACCGTTTTAGCGGATCCAAAA GCGGCAACACCGCGAGCCTGACCATTAGCGGCCTGCAAGCG GAAGACGAAGCGGATTATTACTGCCAGTCTTACGACCATCT GCTGCATGTTGTGTTTGGCGGCGGCACGAAGTTAACCCTCT AGGTCAGCCCCAAGGCTGCCCCCTCGGTCACTCTGTCCCGC CTCCTCTGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGT GTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCC

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NOV0674	LCDR1 (Kabat) (SEQ ID NO:42)	SGSSSNIGYNYVS
	LCDR2 (Kabat) (SEQ ID NO:43)	RDNQRPS
	LCDR3 (SEQ ID NO:44)	AAWTSGSIGWV
	HCDR1 (Kabat) (SEQ ID NO:45)	SYAMT
	HCDR2 (Kabat) (SEQ ID NO:46)	GISGGGSNTYYADSVKG
	HCDR3 (Kabat) (SEQ ID NO:47)	GGGQYFDY
	vH full sequence (SEQ ID NO:48)	QVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMTWVRQAPG KGLEWVSGISGGGSNTYYADSVKGRFTISRDNKNTLYLQMNS LRAEDTAVYYCARGGGQYFDYWGQGLVTVSS
	vL full sequence (SEQ ID NO:49)	DIVLTQPPSVSGAPGQRVTISCSGSSSNIGYNYVSWYQQLPGTA PKLLIYRDNQRPSGVPDRFSGSKSGTSASLAITGLQAEDEADYY CAAWTSGSIGWVFGGGTKLTVL
	vH DNA sequence (SEQ ID NO:50)	CAGGTGCAATTGCTGGAAAGCGGCGGTGGCCTGGTGCAGCC GGGTGGCAGCCTGCGTCTGAGCTGCGCGGCGTCCGGATTCA CCTTTTCTTCTTACGCTATGACTTGGGTGCGCCAGGCCCGG GCAAAGGTCTCGAGTGGGTTTCCGGTATCTCTGGTGGTGGTT CTAACACCTACTATGCGGATAGCGTGAAAGGCCGCTTTACC ATCAGCCGCGATAATTGAAAAACACCCTGTATCTGCAAAAT GAACAGCCTGCGTGCGGAAGATACGGCCGTGTATTATTGCG CGCGTGGTGGTGGTCAGTACTTCGATTACTGGGGCCAAGGC ACCCTGGTGA CTGTTAGCTCA
	vL DNA sequence (SEQ ID NO:51)	GATATCGTGCTGACCCAGCCGCCGAGCGTGAGCGGTGCACC GGGCCAGCGCGTGACCATTAGCTGTAGCGGCAGCAGCAGCA ACATTGGTTACAACCTACGTGTCTTGGTACCAGCAGCTGCCG GGCACGGCGCCGAACTGCTGATCTACCGTGACAACCAGCG CCCAGCGGCGTGCCGGATCGCTTTAGCGGATCCAAAAGCG GCACCAGCGCCAGCCTGGCGATTACCGGCCTGCAAGCAGAA GACGAAGCGGATTATTACTGCGCTGCTTGGACTTCTGTTCT ATCGGTTGGGTGTTTGGCGGCGGCACGAAGTTAACCGTCCT

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		A
	HC full sequence (SEQ ID NO:52)	QVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMTWVRQAPG KGLEWVSGISGGGSNTYYADSVKGRFTISRDN SKNTLYLQMN LRAEDTAVYYCARGGGQYFDYWGQGLTVTVSSASTKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKR VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVHLQDNLNGKEYKCKVSNKALPAPIEKTIKAKGQ PREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSSV MHEALHNHYTQKSLSLSPGK
	LC full sequence (SEQ ID NO:53)	DIVLTQPPSVSGAPGQRVTISCSGSSSNIGYNYVSWYQQLPGTA PKLLIYRDNQRPSPGVPDRFSGSKSGTSASLAITGLQAEDEADYY CAAWTSGSIGWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQA NKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTPSKQSN KYAASSYLSTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
	HC DNA sequence (SEQ ID NO:54)	CAGGTGCAATTGCTGGAAAGCGGCGGTGGCCTGGTGCAGCC GGGTGGCAGCCTGCGTCTGAGCTGCGCGGCGTCCGGATTCA CCTTTTCTTCTACGCTATGACTTGGGTGCGCCAGGCCCGG GCAAAGGTCTCGAGTGGGTTTCCGGTATCTCTGGTGGTGGTT CTAACACCTACTATGCGGATAGCGTGAAAGGCCGCTTTACC ATCAGCCGCGATAATTGAAAAACACCCTGTATCTGCAAT GAACAGCCTGCGTGCGGAAGATACGGCCGTGTATTATTGCG CGCGTGGTGGTGGTCAGTACTTCGATTACTGGGGCCAAGGC ACCCTGGTGA CTGTAGCTCAGCCTCCACCAAGGGTCCATC GGTCTTCCCCCTGGCACCTCCTCCAAGAGCACCTCTGGGGG CACAGCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCG AACCAGGTGACGGTGCTGGAAGTCAAGGCGCCCTGACCAGC GGCGTGACACCTTCCCGGCTGTCTACAGTCCTCAGGACTC TACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTG GGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAG CAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTG ACAAAACCTCACACATGCCACCGTGCCAGCAGCACTGAACTC CTGGGGGGACCGTCAGTCTTCTCTTCCCCCAAAACCCAA GGACACCTCATGATCTCCCGGACCCCTGAGGTACATGCG TGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTC AACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGAC AAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGGGTG GTCAGCGTCCTACCGTCCTGCACCAGGACTGGCTGAATGG CAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCAG CCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCC CGAGAACCAAGGTGTACACCTGCCCCCATCCCGGGAGGA GATGACCAAGAACCAGGTGACCTGACCTGCCTGGTCAAAG GCTTCTATCCAGCGACATCGCCGTGGAGTGGGAGAGCAAT GGGCAGCCGGAGAACTACAAGACCACGCCTCCCGTGCT GGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTACCGT GGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCT CCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAG AGCCTCTCCCTGTCTCCGGGTAAA
	LC DNA sequence (SEQ ID	GATATCGTGCTGACCCAGCCGCGAGCGTGAGCGGTGCACC GGGCCAGCGCTGACCATTAAGCTGTAGCGGCAGCAGCAGCA ACATTGGTTACAACCTACGTGTCTTGGTACCAGCAGCTGCCG

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	NO:55)	GGCACGGCGCCGAAACTGCTGATCTACCGTGACAACCAGCG CCCGAGCGGCGTGCCGGATCGCTTTAGCGGATCCAAAAGCG GCACCAGCGCCAGCCTGGCGATTACCGGCCTGCAAGCAGAA GACGAAGCGGATTATTACTGCGCTGCTTGGACTTCTGGTTCT ATCGGTTGGGTGTTTGGCGGCGGCACGAAGTTAACCGTCCT AGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCC CTCCTCTGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGT GTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCC TGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGA CCACCACACCCTCCAAACAAAGCAACAACAAGTACGCGGCC AGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAAGTCCCA CAGAAGCTACAGCTGCCAGGTACGCATGAAGGGAGCACC GTGGAGAAGACAGTGGCCCCCTACAGAATGTTCA
NOV0682	LCDR1 (Kabat) (SEQ ID NO:56)	RASQTINSYLN
	LCDR2 (Kabat) (SEQ ID NO:57)	RASNLQS
	LCDR3 (SEQ ID NO:58)	QQGDSSWT
	HCDR1 (Kabat) (SEQ ID NO:59)	SYAIS
	HCDR2 (Kabat) (SEQ ID NO:60)	FIKSNADGYTTNYAAPVKG
	HCDR3 (Kabat) (SEQ ID NO:61)	IRYFRNWDY
	vH full sequence (SEQ ID NO:62)	QVQLVESGGGLVKGPGSLRLSCAASGFTFSSYAISWVRQAPGK GLEWVGFNIKSNADGYTTNYAAPVKGRFTISRDDSKNTLYLQM NSLKTEDTAVYYCARIRYFRNWDYWGQGTLVTVSS
	vL full sequence (SEQ ID NO:63)	DIQMTQSPSSLSASVGDRVTITCRASQTINSYLNWYQOKPGKA PKLLIYRASNLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQGDSSWTFGQGTKVEIK
	vH DNA sequence (SEQ ID NO:64)	CAGGTGCAATTGGTGGAAGCGGCGGTGGCCTGGTGAAACC AGGCGGCAGCCTGCGCCTGAGCTGCGCCGCTCCGGATTCA CCTTTTCTTCTTACGCTATCTTGGGTGCGCCAGGCCCCCG GCAAAGGTCTCGAGTGGGTGGGCTTCATCAAATCTAACGCT GACGGTTACACTACTAACTATGCCGCCCCAGTGAAAGGCCG CTTTACCATTAGCCGCGATGATTGAAAAACACCCTGTATCT GCAAATGAACAGCCTGAAAACCGAAGATACGGCCGTGTATT ATTGCGCGCGTATCCGTTACTTCCGTAAGTGGGATTACTGGG GCCAAGGCACCCTGGTGACTGTTAGCTCA

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	vL DNA sequence (SEQ ID NO:65)	GATATCCAGATGACCCAGAGCCCGAGCAGCCTGAGCGCCAG CGTGGGCGATCGCGTGACCATTACCTGCAGAGCCAGCCAGA CTATTAACCTCTTACCTGAACTGGTACCAGCAGAAACCGGGC AAAGCGCCGAAACTATTAATCTACCGTGCTTCTAACCTGCA AAGCGGCGTGCCGAGCCGCTTTAGCGGCAGCGGATCCGGCA CCGATTTTACCCTGACCATTAGCTCTCTGCAACCGGAAGACT TTGCGACCTATTATTGCCAGCAGGGTGACTCTTCTTGACCT TTGGCCAGGGCACGAAAGTTGAAATTAAA
	HC full sequence (SEQ ID NO:66)	QVQLVESGGGLVKPGGSLRLSCAASGFTFSSYAISWVRQAPGK GLEWVGFISNADGYTTNYAAPVKGRFTISRDDSKNTLYLQM NSLKTEDTAVYYCARIRYFRNWDYWQGGLTVTVSSASTKGPS VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSKV HTFPAVLQSSGLYSLSSVVPSSSLGTQTYICNVNHKPSNTKV DKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTSKA KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFC SVMHEALHNYHTQKSLSLSPGK
	LC full sequence (SEQ ID NO:67)	DIQMTQSPSSLSASVGDRTITCRASQTINSYLNWYQQKPGKA PKLLIYRASNLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYC QQGDSWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSL SSTLTLSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC
	HC DNA sequence (SEQ ID NO:68)	CAGGTGCAATTGGTGGAAGCGGCGGTGGCCTGGTGAAACC AGGCGGCAGCCTGCGCCTGAGCTGCGCCGCTCCGGATTCA CCTTTTCTTCTTACGCTATCTCTTGGGTGCGCCAGGCCCCGG GCAAAGGTCTCGAGTGGGTGGGCTTCATCAAATCTAACGCT GACGGTTACACTACTAACTATGCCGCCCCAGTGAAAGGCCG CTTTACCATTAGCCGCGATGATTGAAAAACACCCTGTATCT GCAAATGAACAGCCTGAAACCGAAGATACGGCCGTGTATT ATTGCGCGCGTATCCGTTACTTCCGTAAGTGGGATTACTGGG GCCAAGGCACCCTGGTGACTGTTAGCTCAGCCTCCACCAAG GGTCCATCGGTCTTCCCCCTGGCACCCCTCCTCCAAGACAC TCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTA CTTCCCCGAACCGGTGACGGTGTCGTGGAAGTCAAGGCGCC TGACCAGCGCGTGACACACCTTCCCGGTGTCTTACAGTCT CAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCC AGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCA CAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCC AAATCTTGTGACAAAACCTCACACATGCCACCGTGCCAGC ACCTGAACTCCTGGGGGGACCGTCAGTCTTCTCTTCCCCC AAAACCCAAGGACACCTCATGATCTCCCGGACCCCTGAGG TCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCTGAG GTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAA TGCCAAGACAAAAGCCGCGGGAGGAGCAGTACAACAGCACG TACCGGGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTG GCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAA GCCCTCCCAGCCCCATCGAGAAAACCATCTCCAAGCCAA AGGGCAGCCCCGAGAACCACAGGTGTACACCTGCCCCCAT CCCGGGAGGAGATGACCAAGAACCAGGTACGCTGACCTGC CTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTG GGAGAGCAATGGGCAGCCGAGAACAACTACAAGACCACG

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		CCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTACAGC AAGCTCACCGTGAGACAAGAGCAGGTGGCAGCAGGGGAACG TCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACT ACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA
	LC DNA sequence (SEQ ID NO:69)	GATATCCAGATGACCCAGAGCCGAGCAGCCTGAGCGCCAG CGTGGGCGATCGCGTGACCATTACCTGCAGAGCCAGCCAGA CTATTAACCTCTTACCTGAACTGGTACCAGCAGAAACCGGGC AAAGCGCCGAAACTATTAATCTACCGTGCTTCTAACCTGCA AAGCGGCGTGCCGAGCCGCTTTAGCGGCAGCGGATCCGGCA CCGATTTACCCCTGACCATTAGCTCTCTGCAACCGGAAGACT TTGCGACCTATTATTGCCAGCAGGGTGACTCTTCTTGGACCT TTGGCCAGGGCACGAAAGTTGAAATTAAACGTACGGTGGCC GCTCCAGCGTGTTTCATCTTCCCCCCCCAGCGACGAGCAGCTG AAGAGCGGCACCGCCAGCGTGGTGTGCCTGCTGAACAACCT CTACCCCCGGGAGGCCAAGGTGCAAGTGAAGGTGGACAAC GCCCTGCAGAGCGGCAACAGCCAGGAAAGCGTCACCGAGC AGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCACCTG ACCCTGAGCAAGGCCGACTACGAGAAGCACAAAGGTGTACG CCTGCGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGACC AAGAGCTTCAACCGGGGCGAGTGT
NOV0685	LCDR1 (Kabat) (SEQ ID NO:70)	SGSSSNIGSYYS
	LCDR2 (Kabat) (SEQ ID NO:71)	YNTKRPS
	LCDR3 (Kabat) (SEQ ID NO:72)	QSWDKLGKGYV
	HCDR1 (Kabat) (SEQ ID NO:73)	GNSAAWN
	HCDR2 (Kabat) (SEQ ID NO:74)	IYYRSKWYNDYAVSVKS
	HCDR3 (Kabat) (SEQ ID NO:75)	SSYSGGFDY
	vH full sequence (SEQ ID NO:76)	QVQLQQSGPGLVKPSQTLSTCAISGDSVSGNSAAWNWIRQSP SRGLEWLGIIYYRSKWYNDYAVSVKSRITINPDTSKNQFSLQLN SVTPEDTAVYYCARSSYSGGFDYWGQGLVTVSS
	vL full sequence (SEQ ID NO:77)	DIVLTQPPSVSGAPGQRVTISCSGSSSNIGSYYSWYQQLPGTA PKLLIYYNTRPSGVPDRFSGSKSGTSASLAITGLQAEDEADYY CQSWDKLGKGYVFGGGTKLTVL
	vH DNA sequence	CAGGTGCAATTGCAGCAGAGCGGTCCGGGCCTGGTGAACCC GAGCCAGACCCTGAGCCTGACCTGCGCGATTTCGGAGATA

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	(SEQ ID NO:78)	GCGTGAGCGGTAACCTCTGCTGCTTGGAACCTGGATTTCGTCAG AGCCCCGAGCCGTGGCCTCGAGTGGCTGGGCATCATCTACTA CCGTAGCAAATGGTACAACGACTATGCCGTGAGCGTGAAAA GCCGCATTACCATTAACCCGGATACTTCGAAAAAACAGTTT AGCCTGCAACTGAACAGCGTGACCCCGGAAGATACGGCCGT GTATTATTGCGCGCGTTCTTCTTACTCTGGTGGTTTCGATTAC TGGGGCCAAGGCACCCTGGTGACTGTAGCTCA
	vL DNA sequence (SEQ ID NO:79)	GATATCGTGCTGACCCAGCCGCCGAGCGTGAGCGGTGCACC GGGCCAGCGCGTGACCATTAGCTGTAGCGGCAGCAGCAGCA ACATTGGTTCTTACTACGTGTCTTGGTACCAGCAGTGCCTG GCACGGCGCCGAAACTGCTGATCTACTACAACATAAACGC CCGAGCGCGGTGCCGGATCGCTTTAGCGGATCCAAAAGCGG CACCAGCGCCAGCCTGGCGATTACCGGCCTGCAAGCAGAAG ACGAAGCGGATTATTACTGCCAGTCTTGGGACAAACTGGGT AAAGGTTACGTGTTTGGCGGCGGCACGAAGTTAACCGTCCT A
	HC full sequence (SEQ ID NO:80)	QVQLQQSGPGLVKPSQTLSTCAISGDSVSGNSAAWNWIRQSP SRGLEWLGIIYYRSK WYNDYAVSVKSRITINPDTSKNQFSLQLN SVTPEDTAVYYCARSSYSGGFDYWGQGLTVTVSSASTKGPSVF PLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDK RVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKG QPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN GPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK
	LC full sequence (SEQ ID NO:81)	DIVLTQPPSVSGAPGQRVTISCSGSSSNIGSYVSWYQQLPGTA PKLLIYYNTRPSGVPDRFSGSKSGTSASLAITGLQAEDEADYY CQSWDKLGKGYVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQA NKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSN KYAASSYLSTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
	HC DNA sequence (SEQ ID NO:82)	CAGGTGCAATTGCAGCAGAGCGGTCCGGGCTGGTGAAACC GAGCCAGACCCTGAGCCTGACCTGCGCGATTTCCGGAGATA GCGTGAGCGGTAACCTCTGCTGCTTGGAACCTGGATTTCGTCAG AGCCCCGAGCCGTGGCCTCGAGTGGCTGGGCATCATCTACTA CCGTAGCAAATGGTACAACGACTATGCCGTGAGCGTGAAAA GCCGCATTACCATTAACCCGGATACTTCGAAAAAACAGTTT AGCCTGCAACTGAACAGCGTGACCCCGGAAGATACGGCCGT GTATTATTGCGCGCGTTCTTCTTACTCTGGTGGTTTCGATTAC TGGGGCCAAGGCACCCTGGTGACTGTAGCTCAGCCTCCAC CAAGGGTCCATCGGTCTTCCCCCTGGCACCTCCTCCAAGAG CACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGG ACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAACCTCAGG GCCCTGACCAGCGGCGTGACACACCTTCCCGGCTGTCTACA GTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCC CTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGA ATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGA GCCCAAATCTTGTGACAAAACCTCACACATGCCACCGTGCC CAGCACCTGAACCTCTGGGGGGACCGTCAGTCTTCTTCC CCCCAAAACCAAGGACACCCTCATGATCTCCCGGACCCCT GAGGTCACATGCGTGGTGGTGACGTGAGCCACGAAGACCC

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		TGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGC ATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAG CACGTACCGGGTGGTCAGCGTCCTCACCCTCCTGCACCAGG ACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAAC AAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGC CAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCC CATCCCGGGAGGAGATGACCAAGAACCAGGTACGCCTGACC TGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGA GTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACC ACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTAC AGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGA ACGTCTTCTCATGTCTCCGTGATGCATGAGGCTCTGCACAACC ACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA
	LC DNA sequence (SEQ ID NO:83)	GATATCGTGCTGACCCAGCCGCCGAGCGTGAGCGGTGCACC GGGCCAGCGCGTGACCATTAGCTGTAGCGGCAGCAGCAGCA ACATTGGTTCTTACTACGTGTCTTGGTACCAGCAGCTGCCGG GCACGGCGCCGAAACTGCTGATCTACTACAACACTAAACGC CCGAGCGCGGTGCCGGATCGCTTTAGCGGATCCAAAAGCGG CACCAGCGCCAGCCTGGCGATTACCGGCCTGCAAGCAGAAG ACGAAGCGGATTATTACTGCCAGTCTTGGGACAAACTGGGT AAAGGTTACGTGTTTGGCGGGCGGCACGAAGTTAACCGTCCT AGGTACAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCC CTCCTCTGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGT GTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCC TGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGA CCACCACACCCCTCCAAACAAAGCAACAACAAGTACGCGGCC AGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAAGTCCCA CAGAAGCTACAGCTGCCAGGTACGCATGAAGGGAGCACC GTGGAGAAGACAGTGGCCCCCTACAGAATGTTCA
NOV0689	LCDR1 (Kabat) (SEQ ID NO:84)	SGSSSNIGSNFVS
	LCDR2 (Kabat) (SEQ ID NO:85)	DNSNRPS
	LCDR3 (Kabat) (SEQ ID NO:86)	SSYDSFDHSWV
	HCDR1 (Kabat) (SEQ ID NO:87)	SFAMN
	HCDR2 (Kabat) (SEQ ID NO:88)	VISSSGSNTNYADSVKG
	HCDR3 (Kabat) (SEQ ID NO:89)	PSYFQAMDY
	vH full	QVQLLESGLVQPGGSLRLSCAASGFTFSSFAMNWVRQAPG

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	sequence (SEQ ID NO:90)	KGLEWVSVISSSGSNTNYADSVKGRFTISRDN SKNTLYLQMNS LRAEDTAVYYCARPSYFQAMDYWGQGLVTVSS
	vL full sequence (SEQ ID NO:91)	DIVLTQPPSVSGAPGQRVTISCSGSSSNIGSNFVSWYQQLPGTAP KLLIYDNSNRPSGVPDRFSGSKSGTSASLAITGLQAEDEADYYC SSYDSFDHSWVFGGGTKLTVL
	vH DNA sequence (SEQ ID NO:92)	CAGGTGCAATTGCTGGAAAGCGGCGGTGGCCTGGTGCAGCC GGGTGGCAGCCTGCGTCTGAGCTGCGCGGCGTCCGGATTCA CCTTTTCTTCTTTCGCTATGAACTGGGTGCGCCAGGCCCGG GCAAAGGTCTCGAGTGGGTTTCCGTTATCTCTTCTTCTGGT CTAACACCAACTATGCGGATAGCGTGAAAGGCCGCTTACC ATCAGCCGCGATAATTGAAAAACACCCTGTATCTGCAAAAT GAACAGCCTGCGTGCGGAAGATACGGCCGTGTATTATTGCG CGCGTCCGTCTTACTTCCAGGCTATGGATTACTGGGGCCAAG GCACCCTGGTGACTGTAGCTCA
	vL DNA sequence (SEQ ID NO:93)	GATATCGTGCTGACCCAGCCGCCGAGCGTGAGCGGTGCACC GGGCCAGCGCGTGACCATTAGCTGTAGCGGCAGCAGCAGCA ACATTGGTTCTAACTTCGTGTCTTGGTACCAGCAGCTGCCGG GCACGGCGCCGAAACTGCTGATCTACGACAACTCTAACCGC CCGAGCGGCGTGCCGGATCGCTTTAGCGGATCCAAAAGCGG CACCAGCGCCAGCCTGGCGATTACCGGCCTGCAAGCAGAAG ACGAAGCGGATTATTACTGCTCTTCTTACGACTCTTTCGACC ATTCTTGGGTGTTTGGCGGCGGCACGAAGTTAACCGTCCTA
	HC full sequence (SEQ ID NO:94)	QVQLLESGGGLVQPGGSLRLSCAASGFTFSSFAMNWRQAPG KGLEWVSVISSSGSNTNYADSVKGRFTISRDN SKNTLYLQMNS LRAEDTAVYYCARPSYFQAMDYWGQGLVTVSSASTKGPSVF PLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDK RVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG QPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCNV MHEALHNHYTQKSLSLSPGK
	LC full sequence (SEQ ID NO:95)	DIVLTQPPSVSGAPGQRVTISCSGSSSNIGSNFVSWYQQLPGTAP KLLIYDNSNRPSGVPDRFSGSKSGTSASLAITGLQAEDEADYYC SSYDSFDHSWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQAN KATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNK YAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
	HC DNA sequence (SEQ ID NO:96)	CAGGTGCAATTGCTGGAAAGCGGCGGTGGCCTGGTGCAGCC GGGTGGCAGCCTGCGTCTGAGCTGCGCGGCGTCCGGATTCA CCTTTTCTTCTTTCGCTATGAACTGGGTGCGCCAGGCCCGG GCAAAGGTCTCGAGTGGGTTTCCGTTATCTCTTCTTCTGGT CTAACACCAACTATGCGGATAGCGTGAAAGGCCGCTTACC ATCAGCCGCGATAATTGAAAAACACCCTGTATCTGCAAAAT GAACAGCCTGCGTGCGGAAGATACGGCCGTGTATTATTGCG CGCGTCCGTCTTACTTCCAGGCTATGGATTACTGGGGCCAAG GCACCCTGGTGACTGTAGCTCAGCCTCCACCAAGGGTCCA TCGGTCTTCCCCCTGGCACCCCTCCTCCAAGAGCACCTCTGGG GGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCC CGAACCGGTGACGGTGTCTGTGAACTCAGGCGCCCTGACCA

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		<p>GCGGCGTGACACCTTCCCGGCTGTCCTACAGTCCTCAGGA CTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGC TTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCC CAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTT GTGACAAAACCTACACATGCCCACCGTGCCCAGCACCTGAA CTCCTGGGGGGACCGTCAGTCTTCTCTTCCCCCAAAACCC AAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATG CGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGT TCAACTGGTACGTGGACGGCGTGAGGTGCATAATGCCAAG ACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGGG TGGTCAGCGTCTCACCGTCTGACACGAGTGGCTGAAT GGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCC AGCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGC CCCGAGAACCACAGGTGTACACCCTGCCCCATCCCGGGAG GAGATGACCAAGAACCAGGTGACCTGACCTGCCTGGTCAA AGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCA ATGGGCAGCCGGAGAACTACAAGACCACGCCTCCCGTG CTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACC GTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATG CTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGA AGAGCCTCTCCCTGTCTCCGGGTAAA</p>
	LC DNA sequence (SEQ ID NO:97)	<p>GATATCGTGCTGACCCAGCCGCCGAGCGTGAGCGGTGCACC GGGCCAGCGCGTGACCATTAGCTGTAGCGGCAGCAGCAGCA ACATTGGTTCTAACTTCGTGTCTTGGTACCAGCAGCTGCCGG GCACGGCGCCGAACTGCTGATCTACGACAACCTTAACCGC CCGAGCGGCGTGCCGGATCGCTTAGCGGATCCAAAAGCGG CACCAGCGCCAGCCTGGCGATTACCGGCCTGCAAGCAGAAG ACGAAGCGGATTATTACTGCTCTTCTTACGACTCTTTCGACC ATTCTTGGGTGTTTGGCGCGGCACGAAGTTAACCGTCTTA GGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCC TCCTCTGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTG TCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCCT GGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGAC CACCACACCCTCCAAACAAGCAACAACAAGTACGCGGCCA GCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCAC AGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGT GGAGAAGACAGTGGCCCCCTACAGAATGTTCA</p>
NOV0690	LCDR1 (Kabat) (SEQ ID NO:98)	SGDAIGTKFAH
	LCDR2 (Kabat) (SEQ ID NO:99)	YDHERPS
	LCDR3 (Kabat) (SEQ ID NO:100)	YSRASSNLV
	HCDR1 (Kabat) (SEQ ID NO:101)	DHAID
	HCDR2	VIAGDGSITYYADSVKG

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	(Kabat) (SEQ ID NO:102)	
	HCDR3 (Kabat) (SEQ ID NO:103)	DTGVYREYMDV
	vH full sequence (SEQ ID NO:104)	QVQLLESGGGLVQPGGSLRLSCAASGFTFSFDAIDWVRQAPGK GLEWVSVIAGDGSITYYADSVKGRFTISRDN SKNTLYLQMNSL RAEDTAVYYCARDTGVYREYMDVWGQGLTVTVSS
	vL full sequence (SEQ ID NO:105)	DIELTQPPSVSVSPGQTASITCSGDAIGTKFAHWYQQKPGQAPV LVIIYDHERPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCY SRASSNLVFGGGTKLTVL
	vH DNA sequence (SEQ ID NO:106)	CAGGTGCAATTGCTGGAAAGCGGCGGTGGCCTGGTGACGCC GGGTGGCAGCCTGCGTCTGAGCTGCGCGGCGTCCGGATTCA CCTTTTCTGACCATGCTATCGACTGGGTGCGCCAGGCCCGG GCAAAGGTCTCGAGTGGGTTTCCGTTATCGCTGGTGACGGTT CTATCACCTACTATGCGGATAGCGTGAAAGGCCGCTTTACC ATCAGCCGCGATAATTGAAAAACACCCTGTATCTGCAAAT GAACAGCCTGCGTGCGGAAGATACGGCCGTGATTATTGCG CGCGTGACACTGGTGTTTACCGTGAATACATGGATGTTTGG GGCCAAGGCACCCTGGTGACTGTTAGCTCA
	vL DNA sequence (SEQ ID NO:107)	GATATCGAACTGACCCAGCCGCCGAGCGTGAGCGTGAGCCC GGGCCAGACCGCGAGCATTACCTGTAGCGGCGATGCTATCG GTACTAAATTGCTCATTGGTACCAGCAGAAACCGGGCCAG GCGCCGGTGCTGGTGATCTACTACGACCATGAACGTCCGAG CGGCATCCCGGAACGTTTTAGCGGATCCAACAGCGGCAACA CCGCGACCCTGACCATTAGCGGCACCCAGGCGGAAGACGAA GCGGATTATTACTGCTACTCTCGTGCTTCTTCTAACCTGGTG TTTGGCGGCGGCACGAAGTTAACCGTCCTA
	HC full sequence (SEQ ID NO:108)	QVQLLESGGGLVQPGGSLRLSCAASGFTFSFDAIDWVRQAPGK GLEWVSVIAGDGSITYYADSVKGRFTISRDN SKNTLYLQMNSL RAEDTAVYYCARDTGVYREYMDVWGQGLTVTVSSASTKGPS VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSKV HTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKV DKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFC SVMHEALHNHYTQKSLSLSPGK
	LC full sequence (SEQ ID NO:109)	DIELTQPPSVSVSPGQTASITCSGDAIGTKFAHWYQQKPGQAPV LVIIYDHERPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCY SRASSNLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATL VCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAA SSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
	HC DNA sequence (SEQ ID NO:110)	CAGGTGCAATTGCTGGAAAGCGGCGGTGGCCTGGTGACGCC GGGTGGCAGCCTGCGTCTGAGCTGCGCGGCGTCCGGATTCA CCTTTTCTGACCATGCTATCGACTGGGTGCGCCAGGCCCGG GCAAAGGTCTCGAGTGGGTTTCCGTTATCGCTGGTGACGGTT

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		<p>CTATCACCTACTATGCGGATAGCGTGAAAGGCCGCTTTACC ATCAGCCGCGATAATTGAAAAACACCCTGTATCTGCAAAT GAACAGCCTGCGTGCGGAAGATACGGCCGTGTATTATTGCG CGCGTGACACTGGTGTTTACCGTGAATACATGGATGTTTGG GGCCAAGGCACCCTGGTGACTGTAGCTCAGCCTCCACCAA GGGTCCATCGGTCTTCCCCCTGGCACCTCCTCCAAGAGCAC CTCTGGGGGACACAGCGGCCCTGGGCTGCCTGGTCAAGGACT ACTTCCCCGAACCGGTGACGGTGTCTGTGGAACCTCAGGCGCC CTGACCAGCGGCGTGACACCTTCCCGGTGTCTTACAGTCC TCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCC AGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCA CAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCC AAATCTTGTGACAAAACCTCACACATGCCCCACCGTGCCAGC ACCTGAACTCCTGGGGGGACCGTCAGTCTTCTCTTCCCCC AAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGG TCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAG GTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAA TGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACG TACCGGGTGGTCAGCGTCTCACCCTCCTGCACCAGGACTG GCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAA GCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAA AGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCAT CCCGGGAGGAGATGACCAAGAACCAGGTGACCTGACCTGC CTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTG GGAGAGCAATGGGCAGCCGAGAACAACTACAAGACCACG CCTCCCGTGCTGGACTCCGACGGCTCCTTCTCTCTACAGC AAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACG TCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACT ACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA</p>
	LC DNA sequence (SEQ ID NO:111)	<p>GATATCGAACTGACCCAGCCGCCGAGCGTGAGCGTGAGCCC GGGCCAGACCGCGAGCATTACCTGTAGCGGCGATGCTATCG GTACTAAATTGCTCATTTGGTACCAGCAGAAACCGGGCCAG GCGCCGGTGCTGGTGATCTACTACGACCATGAACGTCCGAG CGGCATCCCGGAACGTTTTAGCGGATCCAACAGCGGCAACA CCGCGACCCCTGACCATTAGCGGCACCCAGGCGGAAGACGAA GCGGATTATTACTGCTACTCTCGTGCTTCTTCTAACCTGGTG TTTGGCGGCGGCACGAAGTTAACCGTCCTAGGTGAGCCCAA GGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGA GCTTCAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTG ACTTCTACCCGGGAGCCGTGACAGTGGCCTGGAAGGCAGAT AGCAGCCCCGTCAAGGCGGGAGTGGAGACCACACACCCTC CAAACAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTG AGCCTGACGCTGAGCAGTGGAAGTCCCACAGAAGCTACAG CTGCCAGGTACGCATGAAGGGAGCACCGTGGAGAAGACA GTGGCCCCCTACAGAATGTTCA</p>
NOV0691	LCDR1 (Kabat) (SEQ ID NO:112)	TGTSSDVGRYNFVS
	LCDR2 (Kabat) (SEQ ID NO:113)	RVSNRPS
	LCDR3	QSWTTYSNVV

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	(Kabat) (SEQ ID NO: 114)	
	HCDR1 (Kabat) (SEQ ID NO:115)	SYALN
	HCDR2 (Kabat) (SEQ ID NO:116)	RIKSKTYGGSTDYAAPVKG
	HCDR3 (Kabat) (SEQ ID NO:117)	DRGGYVGFDS
	vH full sequence (SEQ ID NO:118)	QVQLVESGGGLVKPGGSLRLSCAASGFTFSSYALNWVRQAPG KGLEWVGRIKSKTYGGSTDYAAPVKGRFTISRDDSKNTLYLQ MNSLKTEDTAVYYCARDGGYVGFDSWGQGLTVTVSS
	vL full sequence (SEQ ID NO:119)	DIALTQPASVSGSPGQSITISCTGTSSDVGRYNFVSWYQQHPGK APKLMYRVSNRPSGVSNRFSGSKSGNTASLTISGLQAEDEADY YCQSWTTYSNVVFGGGTKLTVL
	vH DNA sequence (SEQ ID NO:120)	CAGGTGCAATTGGTGGAAGCGGCGGTGGCCTGGTGAAACC AGGCGGCAGCCTGCGCCTGAGCTGCGCCGCTCCGGATTCA CCTTTTCTTCTTACGCTCTGAACTGGGTGCGCCAGGCCCGG GCAAAGGTCTCGAGTGGGTGGGCGGTATCAAATCTAAACT TACGGTGGTTCTACTGACTATGCCGCCCCAGTGAAAGGCCG CTTTACCATTAGCCGCGATGATTGAAAAACACCCTGTATCT GCAAATGAACAGCCTGAAAACCGAAGATACGGCCGTGTATT ATTGCGCGCGTGACCGTGGTGGTTACGTTGGTTTCGATTCTT GGGGCCAAGGCACCCTGGTGACTGTTAGCTCA
	vL DNA sequence (SEQ ID NO:121)	GATATCGCGCTGACCCAGCCGGCGAGCGTGAGCGGTAGCCC GGGCCAGAGCATTACCATAGCTGCACCGGCACAGCAGCG ATGTGGGCCGTTACAACTTCGTGTCTTGGTACCAGCAGCATC CGGGCAAGGCGCCGAACTGATGATCTACCGTGTTTCTAAC CGTCCGAGCGCGTGAGCAACCGTTTTAGCGGATCCAAAAG CGGCAACACCGCGAGCCTGACCATTAGCGGCCTGCAAGCGG AAGACGAAGCGGATTATTACTGCCAGTCTTGGACTACTTAC TCTAACGTTGTGTTTGGCGGCGGCACGAAGTTAACCGTCCTA
	HC full sequence (SEQ ID NO:122)	QVQLVESGGGLVKPGGSLRLSCAASGFTFSSYALNWVRQAPG KGLEWVGRIKSKTYGGSTDYAAPVKGRFTISRDDSKNTLYLQ MNSLKTEDTAVYYCARDGGYVGFDSWGQGLTVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNT KVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
	LC full	DIALTQPASVSGSPGQSITISCTGTSSDVGRYNFVSWYQQHPGK

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	sequence (SEQ ID NO:123)	APKLMYRVSNNRPSGVSNRFGSGKSGNTASLTISGLQAEDEADY YCQSWTTYSNVVFVGGGKLTVLGQPKAAPSVTLFPPSPSEELQA NKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSN KYAASSYLSTPEQWKSQRSYSCQVTHEGSTVEKTVAPTECS
	HC DNA sequence (SEQ ID NO:124)	CAGGTGCAATTGGTGGAAGCGGCGGTGGCCTGGTGAAACC AGGCGGCAGCCTGCGCCTGAGCTGCGCCGCTCCGGATTCA CCTTTTCTTCTTACGCTCTGAACTGGGTGCGCCAGGCCCGG GCAAAGGTCTCGAGTGGGTGGGCCGTATCAAATCTAAACT TACGGTGGTTCTACTGACTATGCCGCCCCAGTGAAAGGCCG CTTTACCATTAGCCGCGATGATTGAAAAACACCCTGTATCT GCAAATGAACAGCCTGAAAACCGAAGATACGGCCGTGTATT ATTGCGCGCGTGACCGTGGTGGTTACGTTGGTTTCGATTCTT GGGGCCAAGGCACCCTGGTGACTGTTAGCTCAGCCTCCACC AAGGGTCCATCGGTCTTCCCCCTGGCACCTCCTCCAAGAGC ACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGA CTACTTCCCCGAACCGGTGACGGTGTCTGTGAACTCAGGCG CCCTGACCAGCGCGTGACACCTTCCCGGCTGCTCTACAGT CCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCT CCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAAT CACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGC CCAAATCTTGTGACAAAACCTCACACATGCCACCCGTGCCCA GCACCTGAACTCCTGGGGGGACCGTCAGTCTTCTCTTCCCC CCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGA GGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTG AGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCAT AATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCA CGTACCGGGTGGTCAGCGTCCTCACCGTCTGCACCAGGAC TGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAA AGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAGGCCA AAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCA TCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTG CCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGT GGGAGAGCAATGGGCAGCCGGAGAACAACCTACAAGACCAC GCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTACAG CAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAAC GTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCAC TACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAA
	LC DNA sequence (SEQ ID NO:125)	GATATCGCGCTGACCCAGCCGGCGAGCGTGAGCGGTAGCCC GGGCCAGAGCATTACCATTAGCTGCACCGGCACCAGCAGCG ATGTGGGCGGTTACAACCTTCGTGTCTTGGTACCAGCAGCATC CGGGCAAGGCGCCGAAACTGATGATCTACCGTGTCTTAAC CGTCCGAGCGGCGTGAGCAACCGTTTTAGCGGATCCAAAAG CGGCAACACCGCGAGCCTGACCATTAGCGGCCTGCAAGCGG AAGACGAAGCGGATTATTACTGCCAGTCTTGGACTACTTAC TCTAACGTTGTGTTTGGCGGCGGCACGAAGTTAACCGTCTTA GGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCC TCCTCTGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTG TCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCCT GGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGAC CACCACACCCTCCAAACAAAGCAACAACAAGTACGCGGCCA GCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAAGTCCCAC AGAAGCTACAGCTGCCAGGTACGCATGAAGGGAGCACCGT GGAGAAGACAGTGGCCCCCTACAGAATGTTCA
NOV0692	LCDR1	SGDSIGSKYAQ

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(Kabat) (SEQ ID NO:126)	
LCDR2 (Kabat) (SEQ ID NO:127)	YNSERPS
LCDR3 (Kabat) (SEQ ID NO:128)	QSWDGQSTIRV
HCDR1 (Kabat) (SEQ ID NO:129)	RYWMD
HCDR2 (Kabat) (SEQ ID NO:130)	RIKSKANGGITDYAAPVKG
HCDR3 (Kabat) (SEQ ID NO:131)	GMTFLGI
vH full sequence (SEQ ID NO:132)	QVQLVESGGGLVKPGGSLRLSCAASGFTFSRYWMDWVRQAP GKGLEWVGRIKSKANGGITDYAAPVKG RFTISRDDSKNTLYLQ MNSLKTEDTAVYYCARGMTFLGIWGQGLTVTVSS
vL full sequence (SEQ ID NO:133)	DIELTQPPSVSVSPGQTASITCSGDSIGSKYAQWYQQKPGQAPV LVIYYNSERPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQS WDGQSTIRVFVGGGTKLTVL
vH DNA sequence (SEQ ID NO:134)	CAGGTGCAATTGGTGGAAAGCGGCGGTGGCCTGGTGA AAC AGGCGGCAGCCTGCGCCTGAGCTGCGCCGCTCCGGATTCA CCTTTTCTCGTTACTGGATGGACTGGGTGCGCCAGGCCCCGG GCAAAGGTCTCGAGTGGGTGGGCGGTATCAAATCTAAAGCT AACGGTGGTATCACTGACTATGCCGCCCCAGTGAAAGGCCG CTTTACCATTAGCCGCGATGATTCGAAAAACACCCTGTATCT GCAAATGAACAGCCTGAAAACCGAAGATACGGCCGTGTATT ATTGCGCGCGTGGTATGACTTTCTGGGTATCTGGGGCCAA GGCACCTGGTGA CTGTTAGCTCA
vL DNA sequence (SEQ ID NO:135)	GATATCGAACTGACCCAGCCGCCGAGCGTGAGCGTGAGCCC GGGCCAGACCGCGAGCATTACCTGTAGCGGCGATTCTATCG GTTCTAAATACGCTCAGTGGTACCAGCAGAAACCGGGCCAG GCGCCGGTGCTGGTGATCTACTACAACTCTGAACGTCCGAG CGGCATCCCGGAACGTTTTAGCGGATCCAACACGCGCAACA CCGCGACCCTGACCATTAGCGGCACCCAGGCGGAAGACGAA GCGGATTATTACTGCCAGTCTTGGGACGGTCAGTCTACTATC CGTGTGTTTGGCGGCGGCACGAAGTTAACCGTCCTA
HC full sequence (SEQ ID NO:136)	QVQLVESGGGLVKPGGSLRLSCAASGFTFSRYWMDWVRQAP GKGLEWVGRIKSKANGGITDYAAPVKG RFTISRDDSKNTLYLQ MNSLKTEDTAVYYCARGMTFLGIWGQGLTVTVSSASTKGPSV

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	NO:136)	FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD KRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRT EVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSS VMHEALHNHYTQKSLSLSPGK
	LC full sequence (SEQ ID NO:137)	DIETQPPSVSVSPGQTASITCSGDSIGSKYAQWYQQKPGQAPV LVIIYNSEKPSGIPERFSGNSNGNTATLTISGTQAEDEADYYCQS WDGQSTIRVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKA TLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNKYYA ASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
	HC DNA sequence (SEQ ID NO:138)	CAGGTGCAATTGGTGGAAAGCGGCGGTGGCCTGGTGAACCC AGGCGGCAGCCTGCGCCTGAGCTGCGCCGCTCCGGATTCA CCTTTTCTCGTTACTGGATGGACTGGGTGCGCCAGGCCCGG GCAAAGGTCTCGAGTGGGTGGGCCGTATCAAATCTAAAGCT AACGGTGGTATCACTGACTATGCGGCCCAAGTGAAGGCCG CTTTACCATTAGCCGCGATGATTGAAAAACACCCTGTATCT GCAAATGAACAGCCTGAAAACCGAAGATACGGCCGTGTATT ATTGCGCGCGTGGTATGACTTTCCTGGGTATCTGGGGCCAA GGCACCCCTGGTGAAGTGTAGCTCAGCCTCCACCAAGGGTCC ATCGGTCTTCCCCCTGGCACCCCTCCTCCAAGAGCACCTTGG GGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCC CCGAACCGGTGACGGTGTCTGTGGAAGTCAAGGCGCCCTGACC AGCGGCGTGCACACCTTCCCGGCTGTCTACAGTCCTCAGG ACTCTACTCCCTCAGCAGCGTGGTGAAGCTGCCCTCCAGCA GCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAAG CCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAAT CTTGTGACAAAACCTCACACATGCCCCACCGTGCCAGCACCT GAACTCCTGGGGGGACCGTCAGTCTTCTCTTCCCCCAAAA CCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTAC ATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCA AGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCC AAGACAAAGCCGCGGAGGAGCAGTACAACACAGTACC GGGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTG AATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCT CCCAGCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGC AGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCCG GAGGAGATGACCAAGAACCAGGTGACCTGACCTGCCTGGT CAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGA GCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCC GTGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTC ACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTC ATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGC AGAAGAGCCTCTCCCTGTCTCCGGGTAAA
	LC DNA sequence (SEQ ID NO:139)	GATATCGAACTGACCCAGCCGCCGAGCGTGAGCGTGAGCCC GGGCCAGACCGCGAGCATTACCTGTAGCGGCGATTCTATCG GTTCTAAATACGCTCAGTGGTACCAGCAGAAACCGGGCCAG GCGCCGGTGCTGGTGTATCTACTAACTCTGAACGTCCGAG CGGCATCCCCGAACGTTTTAGCGGATCCAACAGCGGCAACA CCGCGACCCTGACCATTAGCGGCACCCAGGCGGAAGACGAA GCGGATTATTACTGCCAGTCTTGGGACGGTCAGTCTACTATC CGTGTGTTTGGCGGCGGCACGAAGTTAACCGTCCTAGGTCA

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		GCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTC TGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGTCTCA TAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCCTGGAAG GCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCA CACCTCCAAACAAAGCAACAACAAGTACGCGGCCAGCAG CTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAA GCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAG AAGACAGTGGCCCCTACAGAATGTTC
NOV0693	LCDR1 (Kabat) (SEQ ID NO:140)	RASQSIIFYLA
	LCDR2 (Kabat) (SEQ ID NO:141)	GASTLQS
	LCDR3 (Kabat) (SEQ ID NO:142)	HQYSYWLRT
	HCDR1 (Kabat) (SEQ ID NO:143)	SYALH
	HCDR2 (Kabat) (SEQ ID NO:144)	YIFYDSSSTYYADSVKG
	HCDR3 (Kabat) (SEQ ID NO:145)	FLYSAYGVAN
	vH full sequence (SEQ ID NO:146)	QVQLLESGGGLVQPGGSLRLSCAASGFTFSSYALHWVRQAPG KGLEWVSYIFYDSSSTYYADSVKGRFTISRDNKNTLYLQMNS LRAEDTAVYYCARFLYSAYGVANWGQGTLVTVSS
	vL full sequence (SEQ ID NO:147)	DIQMTQSPSSLSASVGDRTITCRASQSIIFYLAWYQQKPGKAP KLLIYGASTLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCH QYSYWLRTFGQGTKVEIK
	vH DNA sequence (SEQ ID NO:148)	CAGGTGCAATTGCTGGAAAGCGGCGGTGGCCTGGTGCAGCC GGGTGGCAGCCTGCGTCTGAGCTGCGCGGCGTCCGGATTCA CCTTTTCTTCTTACGCTCTGCATTGGGTGCGCCAGGCCCGG GCAAAGGTCTCGAGTGGGTTTCTACATCTTCTACGACTCTT CTTCTACCTACTATGCGGATAGCGTGAAAGGCCGCTTTACCA TCAGCCGCGATAATTGAAAAACACCCTGTATCTGCAAAATG AACAGCCTGCGTGCGGAAGATACGGCCGTGTATTATTGCGC GCGTTTCTGTACTCTGCTTACGGTGTGCTAACTGGGGCCA AGGCACCCTGGTGACTGTTAGCTCA
	vL DNA sequence (SEQ ID NO:149)	GATATCCAGATGACCCAGAGCCGAGCAGCCTGAGCGCCAG CGTGGGCGATCGCGTGACCATTACCTGCAGAGCCAGCCAGT CTATTTCTTTCTACCTGGCTTGGTACCAGCAGAAACCGGGCA AAGCGCCGAAACTATTAATCTACGGTGCTTCTACTCTGCAA

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		AGCGGCGTGCCGAGCCGCTTTAGCGGCAGCGGATCCGGCAC CGATTTACCCCTGACCATTAGCTCTCTGCAACCGGAAGACTT TGCGACCTATTATTGCCATCAGTACTCTTACTGGCTGCGTAC CTTTGGCCAGGGCACGAAAGTTGAAATTAA
	HC full sequence (SEQ ID NO:150)	QVQLLESGGGLVQPGGSLRLSCAASGFTFSSYALHWVRQAPG KGLEWVSYIFYDSSSTYYADSVKGRFTISRDNKNTLYLQMNS LRAEDTAVYYCARFLYSAYGVANWGQGLVTVSSASTKGPSV FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD KRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRT EVTCTVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKISKAK GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCS VMHEALHNHYTQKSLSLSPGK
	LC full sequence (SEQ ID NO:151)	DIQMTQSPSSLSASVGDRVTITCRASQSISFYLAWYQQKPGKAP KLLIYGASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCH QYSYWLRTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV CLLNNFYBREAKVQWKVDNALQSGNSQESVTEQDSKDSYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
	HC DNA sequence (SEQ ID NO:152)	CAGGTGCAATTGCTGGAAAGCGGCGGTGGCCTGGTGCAGCC GGGTGGCAGCCTGCGTCTGAGCTGCGCGGCGTCCGGATTCA CCTTTTCTTCTTACGCTCTGCATTGGGTGCGCCAGGCCCCCG GCAAAGGTCTCGAGTGGGTTTCTACATCTTCTACGACTCTT CTTCTACCTACTATGCGGATAGCGTGAAAGGCCGCTTTACCA TCAGCCGCGATAATTGAAAAACACCCTGTATCTGCAAAATG AACAGCCTGCGTGCGGAAGATACGGCCGTGTATTATTGCGC GCGTTTCCCTGTACTCTGCTTACGGTGTTGTGCTAACTGGGGCCA AGGCACCCTGGTGACTGTTAGCTCAGCCTCCACCAAGGGTC CATCGGTCTTCCCCCTGGCACCCCTCCTCCAAGAGCACCTCTG GGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTC CCCGAACCGGTGACGGTGTCGTGGAACCTCAGGCGCCCTGAC CAGCGGCGTGACACCTTCCCGGCTGTCTACAGCTCCTCAG GACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGC AGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAA GCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCAAA TCTTGTGACAAAACCTCACACATGCCACCGTGCCACGACC TGAACCTCCTGGGGGGACCGTCAGTCTTCTCTTCCCCC ACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCA CATGCGTGGTGGTGACGTGAGCCACGAAGACCTGAGGTC AAGTTCAACTGGTACGTGGACGCGTGGAGGTGCATAATGC CAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTAC CGGGTGGTCAGCGTCTCACCCTCCTGCACCAGGACTGGCT GAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCC CTCCCAGCCCCCATCGAGAAAACCATCTCCAAGCCAAAGG GCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCC GGGAGGAGATGACCAAGAACCAGGTACGCTGACCTGCCTG GTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGA GAGCAATGGGCAGCCGGAGAACAACCTACAAGACCACGCCT CCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAG CTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTT CTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACA CGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

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	LC DNA sequence (SEQ ID NO:153)	GATATCCAGATGACCCAGAGCCCGAGCAGCCTGAGCGCCAGCGTGGGCGATCGCGTGACCATTACCTGCAGAGCCAGCCAGTCTATTTCTTTCTACCTGGCTTGGTACCAGCAGAAACCGGGCA AAGCGCCGAAACTATTAATCTACGGTGCTTCTACTCTGCAAAGCGGCGTGCCGAGCCGCTTTAGCGGCAGCGGATCCGGCACGATTTACACCTGACCATTAGCTCTCTGCAACCGGAAGACTT TGCGACCTATTATTGCCATCAGTACTCTTACTGGCTGCGTACCTTTGGCCAGGGCACGAAAGTTGAAATTAAACGTACGGTGGCCGCTCCCAGCGTGTTTCATCTTCCCCCCCAGCGACGAGCAGC TGAAGAGCGGCACCGCCAGCGTGGTGTGCCTGCTGAACAAC TTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGACAA CGCCCTGCAGAGCGGCAACAGCCAGGAAAGCGTCACCGAG CAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCACCCCT GACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTAC GCCTGCGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGAC CAAGAGCTTCAACCGGGGCGAGTGT
NOV0695	LCDR1 (Kabat) (SEQ ID NO:154)	RASQGIFTYLN
	LCDR2 (Kabat) (SEQ ID NO:155)	AATSLQS
	LCDR3 (Kabat) (SEQ ID NO:156)	QYYSTSLT
	HCDR1 (Kabat) (SEQ ID NO:157)	SNSAAWN
	HCDR2 (Kabat) (SEQ ID NO:158)	RIYYRSKWYNDYAVSVKS
	HCDR3(Kabat) (SEQ ID NO:159)	ERSYRDYFDY
	vH full sequence (SEQ ID NO:160)	QVQLQQSGPGLVKPSQTLSTCAISGDSVSSNSAAWNWIRQSP SRGLEWLGRIYYRSKWYNDYAVSVKSRITINPDTSKNQFSLQL NSVTPEDTAVYYCARERSYRDYFDYWGQGTLVTVSS
	vL full sequence (SEQ ID NO:161)	DIQMTQSPSSLSASVGDRVTITCRASQGIFTYLNWYQQKPGKA PKLLISAATSLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYC QYYSTSLTFGQGTKVEIK
	vH DNA sequence (SEQ ID NO:162)	CAGGTGCAATTGCAGCAGAGCGGTCCGGGCCTGGTGAAACC GAGCCAGACCCTGAGCCTGACCTGCGGATTTCCGGAGATA GCGTGAGCTCTAACTCTGCTGCTTGGAAGTGGATTCGTCAGA GCCCGAGCCGTGGCCTCGAGTGGCTGGGCCGTATCTACTAC CGTAGCAAATGGTACAACGACTATGCCGTGAGCGTGAAAAG CCGCATTACCATTAAACCGGATACTTCGAAAAACCAGTTTA

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		GCCTGCAACTGAACAGCGTGACCCCGGAAGATACGGCCGTG TATTATTGCGCGCGTGAAACGTTCTTACCGTGACTACTTCGAT TACTGGGGCCAAGGCACCCTGGTGACTGTTAGCTCA
	vL DNA sequence (SEQ ID NO:163)	GATATCCAGATGACCCAGAGCCCGAGCAGCCTGAGCGCCAG CGTGGGCGATCGCGTGACCATTACCTGCAGAGCCAGCCAGG GTATTTTCACCTTACCTGAACTGGTACCAGCAGAAACCGGGC AAAGCGCCGAAACTATTAATCTCTGCTGCTTCTACTCTGCAA AGCGGCGTGCCGAGCCGCTTTAGCGGCAGCGGATCCGGCAC CGATTTACCCCTGACCATTAGCTCTCTGCAACCGGAAGACTT TGCGACCTATTATTGCCAGCAGTACTACTCTACTTCTCTGAC CTTTGGCCAGGGCACGAAAGTTGAAATTAA
	HC full sequence (SEQ ID NO:164)	QVQLQQSGPGLVKPSQTLSTCAISGDSVSSNSAAWNWIRQSP SRGLEWLGRYYRSK WYNDYAVSVKSRITINPDTSKNQFSLQL NSVTPEDTAVYYCARERSYRDYFDYWGGQTLVTVSSASTKGP SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS VHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHPKPSNTK VDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
	LC full sequence (SEQ ID NO:165)	DIQMTQSPSSLSASVGDRTITCRASQGIFTYLNWYQQKPGKA PKLLISAASLTQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYC QQYYSTSLTFGQGTKVEIKRTVAAPSFIFFPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTYS LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
	HC DNA sequence (SEQ ID NO:166)	CAGGTGCAATTGCAGCAGAGCGGTCCGGGCTGGTGAAACC GAGCCAGACCCTGAGCCTGACCTGCGCGATTTCCGGAGATA GCGTGAGCTCTAACTCTGCTGCTTGGAACCTGGATTCGTCAGA GCCCCAGCCGTGGCCTCGAGTGCTGGGCGGTATCTACTAC CGTAGCAAAATGGTACAACGACTATGCCGTGAGCGTGAAAAG CCGATTACCATTAACCCGGATACTTCGAAAAACAGTTTA GCCTGCAACTGAACAGCGTGACCCCGGAAGATACGGCCGTG TATTATTGCGCGCGTGAAACGTTCTTACCGTGACTACTTCGAT TACTGGGGCCAAGGCACCCTGGTGACTGTTAGCTCAGCCTC CACCAAGGGTCCATCGGTCTTCCCCCTGGCACCCTCCTCCAA GAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCA AGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAACCTCA GGCGCCCTGACCAGCGCGGTGCACACCTTCCCGGTGTCTCT ACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCG TGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAAC GTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAG TTGAGCCCCAAATCTTGTGACAAAACCTCACACATGCCACCG TGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCTCTC TTCCCCC AAAACCAAGGACACCCTCATGATCTCCCGGAC CCCTGAGGTACATGCGTGGTGGTGGACGTGAGCCACGAAG ACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAG GTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACA ACAGCAGTACCGGTGGTCAGCGTCCTCACCCTCTGAC CAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTC CAACAAAGCCCTCCAGCCCCCATCGAGAAAACCATCTCCA

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		AAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCT GCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCC TGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCC GTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACCTACA AGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCC TCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAG GGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCAC AACCCTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAA A
	LC DNA sequence (SEQ ID NO:167)	GATATCCAGATGACCCAGAGCCCCGAGCAGCCTGAGCGCCAG CGTGGGCGATCGCGTGACCATACCTGCAGAGCCAGCCAGG GTATTTTCACTTACCTGAAGTGGTACCAGCAGAAACCGGGC AAAGCGCCGAAACTATTAATCTCTGCTGCTTCTACTCTGCAA AGCGGGCGTGCCGAGCCGCTTTAGCGGCAGCGGATCCGGCAC CGATTTACCCCTGACCATTAAGCTCTCTGCAACCGGAAGACTT TGCGACCTATTATTGCCAGCAGTACTACTCTACTTCTCTGAC CTTTGGCCAGGGCACGAAAGTTGAAATTAACGTACGGTGG CCGCTCCCAGCGTGTTTCATCTTCCCCCCCCAGCGACGAGCAGC TGAAGAGCGGCACCGCCAGCGTGGTGTGCCTGCTGAACAAC TTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGACAA CGCCCTGCAGAGCGGCAACAGCCAGGAAAGCGTCACCGAG CAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCACCCCT GACCCTGAGCAAGGCCGACTACGAGAAGCACAAAGGTGTAC GCCTGCGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGAC CAAGAGCTTCAACCGGGGCGAGTGT
NOV0699	LCDR1 (Kabat) (SEQ ID NO:168)	SGDNIRKYVVH
	LCDR2 (Kabat) (SEQ ID NO:169)	RDNNRPS
	LCDR3 (Kabat) (SEQ ID NO:170)	QSWDSFLAVV
	HCDR1 (Kabat) (SEQ ID NO:171)	SYAMH
	HCDR2 (Kabat) (SEQ ID NO:172)	FISLGSYTYYADSVKG
	HCDR3 (Kabat) (SEQ ID NO:173)	ETAGYGYAFDP
	vH full sequence (SEQ ID NO:174)	QVQLLES GGGLVQPGGSLRLSCAASGFTFSSYAMHWVRQAPG KGLEWVSFISLGSYTYYADSVKGRFTISRDN SKNTLYLQMNS LRAEDTAVYYCARETAGYGYAFDPWGQGT LTVVSS
	vL full	DIELTQPPSVSVSPGQTASITCSGDNIRKYVVHWYQQKPGQAP

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	sequence (SEQ ID NO:175)	VLVIYRDNNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYC QSWDSFLAVVFGGGTKLTVL
	vH DNA sequence (SEQ ID NO:176)	CAGGTGCAATTGCTGGAAAGCGGCGGTGGCCTGGTGCAGCC GGGTGGCAGCCTGCGTCTGAGCTGCGCGGCGTCCGGATTCA CCTTTTCTTCTTACGCTATGCATTGGGTGCGCCAGGCCCCGG GCAAAGGTCTCGAGTGGGTTTCCTTCATCTCTTCTCTGGGTT CTTACACCTACTATGCGGATAGCGTGAAAGGCCGCTTTACC ATCAGCCGCGATAATTCGAAAAACACCCTGTATCTGCAAAT GAACAGCCTGCGTGCGGAAGATACGGCCGTGATTATTGCG CGCGTGAAACTGCTGGTTACGGTTACGCTTTCGATCCGTGGG GCCAAGGCACCCTGGTGACTGTTAGCTCA
	vL DNA sequence (SEQ ID NO:177)	GATATCGAACTGACCCAGCCGCCGAGCGTGAGCGTGAGCCC GGGCCAGACCGCGAGCATTACCTGTAGCGGCGATAACATCC GTAAATACGTTGTTTCATTGGTACCAGCAGAAACCGGGCCAG GCGCCGGTGCTGGTGATCTACCGTGACAACAACCGTCCGAG CGGCATCCCGGAACGTTTTAGCGGATCCAACAGCGCAACA CCGCGACCCTGACCATTAGCGGCACCCAGGCGGAAGACGAA GCGGATTATTACTGCCAGTCTTGGGACTCTTCTCTGGCTGTT GTGTTTGGCGGCGGCACGAAGTTAACCCTCCTA
	HC full sequence (SEQ ID NO:178)	QVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMHWVRQAPG KGLEWVSFISSLGSYTYADSVKGRFTISRDNKNTLYLQMNS LRAEDTAVYYCARETAGYGYAFDPWGQGLTVTVSSASTKGPS VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSKV HTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTKV DKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFC SVMHEALHNHYTQKSLSPGK
	LC full sequence (SEQ ID NO:179)	DIELTQPPSVSVSPGQTASITCSGDNIRKYVVHWYQQKPGQAP VLVIYRDNNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYC QSWDSFLAVVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANK ATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKY AASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
	HC DNA sequence (SEQ ID NO:180)	CAGGTGCAATTGCTGGAAAGCGGCGGTGGCCTGGTGCAGCC GGGTGGCAGCCTGCGTCTGAGCTGCGCGGCGTCCGGATTCA CCTTTTCTTCTTACGCTATGCATTGGGTGCGCCAGGCCCCGG GCAAAGGTCTCGAGTGGGTTTCCTTCATCTCTTCTCTGGGTT CTTACACCTACTATGCGGATAGCGTGAAAGGCCGCTTTACC ATCAGCCGCGATAATTCGAAAAACACCCTGTATCTGCAAAT GAACAGCCTGCGTGCGGAAGATACGGCCGTGATTATTGCG CGCGTGAAACTGCTGGTTACGGTTACGCTTTCGATCCGTGGG GCCAAGGCACCCTGGTGACTGTTAGCTCAGCCTCCACCAAG GGTCCATCGGTCTTCCCCCTGGCACCCCTCCTCCAAGAGCACC TCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTA CTTCCCCGAACCGGTGACGGTGTCGTGGAAGTCAAGGCGCCC TGACCAGCGCGTGACACCTTCCCGGCTGTCCTACAGTCTT CAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCC AGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCA CAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCC

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		AAATCTTGTGACAAAACCTCACACATGCCCACCGTGCCCAGC ACCTGAACTCCTGGGGGGACCGTCAGTCTTCCCTCTTCCCCC AAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGG TCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCCTGAG GTCAAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAA TGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACG TACCGGGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTG GCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAA GCCCTCCCAGCCCCATCGAGAAAACCATCTCCAAGCCAA AGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCAT CCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGC CTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTG GGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACG CCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTACAGC AAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACG TCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACT ACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA
	LC DNA sequence (SEQ ID NO:181)	GATATCGAACTGACCCAGCCGCCGAGCGTGAGCGTGAGCCC GGGCCAGACCGCGAGCATTACCTGTAGCGGCGATAACATCC GTAAATACGTTGTTTCATTGGTACCAGCAGAAACCGGGCCAG GCGCCGGTGCTGGTGATCTACCGTGACAACAACCGTCCGAG CGGCATCCCGGAACGTTTTAGCGGATCCAACAGCGGCAACA CCGCGACCCTGACCATTAGCGGCACCCAGGCGGAAGACGAA GCGGATTATTACTGCCAGTCTTGGGACTCTTTCTCTGGCTGTT GTGTTTGGCGGCGGCACGAAGTTAACCGTCCTAGGTACGCC CAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGA GGAGCTTCAAGCCAACAAGGCCACACTGGTGTGTCTCATAA GTGACTTCTACCCGGGAGCCGTGACAGTGGCCTGGAAGGCA GATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACAC CCTCCAACAAAGCAACAACAAGTACGCGGCCAGCAGCTAT CTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTA CAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAG ACAGTGGCCCCCTACAGAATGTTCA
NOV0705	LCDR1 (Kabat) (SEQ ID NO:182)	SGSSSNIGLDYVN
	LCDR2 (Kabat) (SEQ ID NO:183)	RNKQRPS
	LCDR3 (Kabat) (SEQ ID NO:184)	QAWAGRTNYVV
	HCDR1 (Kabat) (SEQ ID NO:185)	NYWIG
	HCDR2 (Kabat) (SEQ ID NO:186)	FIDPGVSYTRYSPSFQG
	HCDR3	VLAHSTEYNWPAF

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	(Kabat) (SEQ ID NO:187)	
	vH full sequence (SEQ ID NO:188)	QVQLVQSGAEVKKPGESLKISCKGSGYSFTNYWIGWVRQMPG KGLEWMGFIDPGVSYTRYSPSFQGVQVTISADKSISTAYLQWSSL KASDTAMYICARVLAHSTEYNWPAFWGQGLVTVSS
	vL full sequence (SEQ ID NO:189)	DIVLTQPPSVSGAPGQRVTISCSGSSSNIGLDYVNWYQQLPGTA PKLLIYRNKQRPSGVPDRFSGSKSGTSASLAITGLQAEDEADYY CQAWAGRRTNYVVFVGGGTLTVL
	vH DNA sequence (SEQ ID NO:190)	CAGGTGCAATTGGTGCAGAGCGGTGCGGAAGTGAAAAAAC CGGGCGAAAGCCTGAAAATTAGCTGCAAAGGCTCCGGATAT AGCTTCACTAACTACTGGATCGGTTGGGTGCGCCAGATGCC GGGCAAAGGTCTCGAGTGGATGGGCTTCATCGACCCGGGTG TTAGCTACACCCGTTATAGCCCGAGCTTTCAGGGCCAGGTG ACCATTAGCGCGGATAAAAAGCATCAGCACCGCGTATCTGCA ATGGAGCAGCCTGAAAGCGAGCGATACCGCGATGTATTATT GCGCGCGTGTCTGGCTCATTCTACTGAATACAACCTGGCCGG CTTCTGCGGCAAGGCACCCTGGTGACTGTAGCTCA
	vL DNA sequence (SEQ ID NO:191)	GATATCGTGCTGACCCAGCCGCCGAGCGTGAGCGGTGCACC GGGCCAGCGCGTGACCATTAGCTGTAGCGGCAGCAGCAGCA ACATTGGTCTGGACTACGTGAACCTGGTACCAGCAGCTGCCG GGCACGGCGCCGAAACTGCTGATCTACCGTAACAAACAGCG CCCGAGCGCGGTGCCGGATCGCTTTAGCGGATCCAAAAGCG GCACCAGCGCCAGCCTGGCGATTACCGGCCTGCAAGCAGAA GACGAAGCGGATTATTACTGCCAGGCTTGGGCTGGTTCGTAC TAACTACGTTGTGTTTGGCGGCGGCACGAAGTTAACCGTCCT A
	HC full sequence (SEQ ID NO:192)	QVQLVQSGAEVKKPGESLKISCKGSGYSFTNYWIGWVRQMPG KGLEWMGFIDPGVSYTRYSPSFQGVQVTISADKSISTAYLQWSSL KASDTAMYICARVLAHSTEYNWPAFWGQGLVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHPKNTK VDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
	LC full sequence (SEQ ID NO:193)	DIVLTQPPSVSGAPGQRVTISCSGSSSNIGLDYVNWYQQLPGTA PKLLIYRNKQRPSGVPDRFSGSKSGTSASLAITGLQAEDEADYY CQAWAGRRTNYVVFVGGGTLTVLGQPKAAPSVTLFPPSSEELQ ANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSN NKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
	HC DNA sequence (SEQ ID NO:194)	CAGGTGCAATTGGTGCAGAGCGGTGCGGAAGTGAAAAAAC CGGGCGAAAGCCTGAAAATTAGCTGCAAAGGCTCCGGATAT AGCTTCACTAACTACTGGATCGGTTGGGTGCGCCAGATGCC GGGCAAAGGTCTCGAGTGGATGGGCTTCATCGACCCGGGTG TTAGCTACACCCGTTATAGCCCGAGCTTTCAGGGCCAGGTG ACCATTAGCGCGGATAAAAAGCATCAGCACCGCGTATCTGCA ATGGAGCAGCCTGAAAGCGAGCGATACCGCGATGTATTATT GCGCGCGTGTCTGGCTCATTCTACTGAATACAACCTGGCCGG

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		<p>CTTTCTGGGGCCAAGGCACCCTGGTGACTGTTAGCTCAGCCT CCACCAAGGGTCCATCGGTCTTCCCCCTGGCACCCCTCCTCCA AGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTC AAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAATC AGGCGCCCTGACCAGCGGCGTGACACCTTCCCGGCTGTCC TACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACC GTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAA CGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGA GTTGAGCCCCAAATCTTGTGACAAAACACACATGCCACC GTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCC TCTTCCCCC AAAACCCAAGGACACCCCTCATGATCTCCCGG ACCCCTGAGGTACATGCGTGGTGGTGACGTGAGCCACGA AGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGG AGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTA CAACAGCACGTACCGGGTGGTCAGCGTCTCACCGTCCTGC ACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGT CTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCT CCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACAC CCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCA GCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATC GCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACCT ACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCT TCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAG CAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCT GCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGG GTAAA</p>
	LC DNA sequence (SEQ ID NO:195)	<p>GATATCGTGCTGACCCAGCCGCCGAGCGTGAGCGGTGCACC GGGCCAGCGCGTGACCATTAGCTGTAGCGGCAGCAGCAGCA ACATTGGTCTGGACTACGTGAACTGGTACCAGCAGCTGCCG GGCACGGCGCCGAAACTGCTGATCTACCGTAACAAACAGCG CCCGAGCGGCGTGCCGGATCGCTTTAGCGGATCCAAAAGCG GCACCAGCGCCAGCCTGGCGATTACCGGCCTGCAAGCAGAA GACGAAGCGGATTATTACTGCCAGGCTTGGGCTGGTTCGTAC TAACTACGTTGTGTTTGGCGGCGGCACGAAGTTAACCCTCT AGGTACAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCC CTCCTCTGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGT GTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCC TGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGA CCACCACACCCTCCAAACAAAGCAACAACAAGTACGCGGCC AGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCA CAGAAGCTACAGCTGCCAGGTACGCATGAAGGGAGCACC GTGGAGAAGACAGTGGCCCCCTACAGAATGTTCA</p>
NOV0709	LCDR1 (Kabat) (SEQ ID NO:196)	TGTSSDVGSYNYVS
	LCDR2 (Kabat) (SEQ ID NO:197)	YVSNRPS
	LCDR3 (Kabat) (SEQ ID NO:198)	ASYTHQGSWV

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HCDR1 (Kabat) (SEQ ID NO:199)	TYVMH
HCDR2 (Kabat) (SEQ ID NO:200)	VISSDGSFTFYADSVKG
HCDR3 (Kabat) (SEQ ID NO:201)	HGYGAFDY
vH full sequence (SEQ ID NO:202)	QVQLLES G G G L V Q P G G S L R L S C A A S G F T F S T Y Y M H W V R Q A P G K G L E W V S V I S S D G S F T F Y A D S V K G R F T I S R D N S K N T L Y L Q M N S L R A E D T A V Y Y C A R H G Y G A F D Y W G Q G T L V T V S S
vL full sequence (SEQ ID NO:203)	D I A L T Q P A S V S G S P G S I T I S C T G T S S D V G S Y N Y V S W Y Q Q H P G K A P K L M I Y Y V S N R P S G V S N R F S G S K S G N T A S L T I S G L Q A E D E A D Y Y C A S Y T H Q G S W V F G G G T K L T V L
vH DNA sequence (SEQ ID NO:204)	C A G G T G C A A T T G C T G G A A A G C G G C G G T G G C C T G G T G C A G C C G G G T G G C A G C C T G C G T C T G A G C T G C G C G G C G T C C G G A T T C A C C T T T T C T A C T T A C T A C A T G C A T T G G G T G C G C C A G G C C C C G G G C A A A G G T C T C G A G T G G G T T T C C G T T A T C T C T T C T G A C G G T T C T T T C A C C T T C T A T G C G G A T A G C G T G A A A G G C C G C T T T A C C A T C A G C C G C G A T A A T T C G A A A A A C A C C C T G T A T C T G C A A A T G A A C A G C C T G C G T G C G G A A G A T A C G G C C G T G T A T T A T T G C G C G C G T C A T G G T T A C G G T G C T T T C G A T T A C T G G G G C C A A G G C A C C C T G G T G A C T G T T A G C T C A
vL DNA sequence (SEQ ID NO:205)	G A T A T C G C G C T G A C C C A G C C G G C G A G C G T G A G C G G T A G C C C G G G C C A G A G C A T T A C C A T T A G C T G C A C C G G C A C C A G C A G C G A T G T G G G C T C T T A C A A C T A C G T G T C T T G G T A C C A G C A G C A T C C G G G C A A G G C G C C G A A A C T G A T G A T C T A C T A C G T T T C T A A C C G T C C G A G C G C G T G A G C A A C C G T T T A G C G G A T C C A A A A G C G G C A A C A C C G C G A G C C T G A C C A T T A G C G G C C T G C A A G C G G A A G A C G A A G C G G A T T A T T A C T G C G C T T C T T A C A C T C A T C A G G G T T C T T G G G T G T T T G G C G G C G G C A C G A A G T T A A C C G T C C T A
HC full sequence (SEQ ID NO:206)	Q V Q L L E S G G G L V Q P G G S L R L S C A A S G F T F S T Y Y M H W V R Q A P G K G L E W V S V I S S D G S F T F Y A D S V K G R F T I S R D N S K N T L Y L Q M N S L R A E D T A V Y Y C A R H G Y G A F D Y W G Q G T L V T V S S A S T K G P S V F P L A P S S K S T S G G T A A L G C L V K D Y F P E P V T V S W N S G A L T S G V H T F P A V L Q S S G L Y S L S S V V T V P S S S L G T Q T Y I C N V N H K P S N T K V D K R V E P K S C D K T H T C P P C P A P E L L G G P S V F L F P P K P K D T L M I S R T P E V T C V V V D V S H E D P E V K F N W Y V D G V E V H N A K T K P R E E Q Y N S T Y R V V S V L T V L H Q D W L N G K E Y K C K V S N K A L P A P I E K T I S K A K G Q P R E P Q V Y T L P P S R E E M T K N Q V S L T C L V K G F Y P S D I A V E W E S N G Q P E N N Y K T T P P V L D S D G S F F L Y S K L T V D K S R W Q Q G N V F S C S V M H E A L H N H Y T Q K S L S L S P G K
LC full sequence (SEQ ID)	D I A L T Q P A S V S G S P G S I T I S C T G T S S D V G S Y N Y V S W Y Q Q H P G K A P K L M I Y Y V S N R P S G V S N R F S G S K S G N T A S L T I S G L Q A E D E A D Y Y C A S Y T H Q G S W V F G G G T K L T V L G Q P K A A P S V T L F P P S S E E L Q A

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	NO:207)	NKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSN KYAASSYLSLTPEQWKSHRYSYSCQVTHEGSTVEKTVAPTECS
	HC DNA sequence (SEQ ID NO:208)	CAGGTGCAATTGCTGGAAAGCGCGGTGGCCTGGTGCAGCC GGGTGGCAGCCTGCGTCTGAGCTGCGCGGCGTCCGGATTCA CCTTTTCTACTTACTACATGCATTGGGTGCGCCAGGCCCGG GCAAAGGTCTCGAGTGGGTTTCCGTTATCTCTTCTGACGGTT CTTTCACCTTCTATGCGGATAGCGTGAAAGGCCGCTTTACCA TCAGCCGCGATAATTGAAAAACACCCTGTATCTGCAATG AACAGCCTGCGTGCGGAAGATACGGCCGTGTATTATTGCGC GCGTCATGGTTACGGTGCTTTTCGATTACTGGGGCCAAGGCA CCCTGGTGACTGTTAGCTCAGCCTCCACCAAGGTCCATCG GTCTTCCCCCTGGCACCTCCTCCAAGAGCACCTCTGGGGGG ACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGA ACCGGTGACGGTGTCGTGGAACCTCAGGCGCCCTGACCAGCG GCGTGACACCTTCCCGGCTGTCTACAGTCTCAGGACTCT ACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTG GGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCAG CAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTG ACAAAACCTACACATGCCCACCGTGCCCAGCACCTGAACTC CTGGGGGGACCGTCAGTCTTCTCTTCCCCCAAAACCCAA GGACACCTCATGATCTCCCGGACCCCTGAGGTACATGCG TGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTC AACTGGTACGTGGACGGCGTGAGGTGCATAATGCCAAGAC AAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGGGTG GTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGG CAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCAG CCCCATCGAGAAAACCATCTCCAAGCCAAAGGGCAGCCC CGAGAACCACAGGTGTACACCCTGCCCCATCCCGGGAGGA GATGACCAAGAACCAGGTACGCTGACCTGCCTGGTCAAAAG GCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAAT GGGCAGCCGGAGAACAACCTACAAGACCACGCCTCCCGTGCT GGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGT GGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCT CCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAG AGCCTCTCCCTGTCTCCGGGTAAA
	LC DNA sequence (SEQ ID NO:209)	GATATCGCGCTGACCCAGCCGGCGAGCGTGAGCGGTAGCCC GGGCCAGAGCATTACCATTAGCTGCACCGGCACCAGCAGCG ATGTGGGCTCTTACAACTACGTGTCTTGGTACCAGCAGCATC CGGGCAAGGCGCCGAACTGATGATCTACTACGTTTCTAAC CGTCCGAGCGGCGTGAGCAACCGTTTTAGCGGATGCCAAAG CGGCAACACCGCGAGCCTGACCATTAGCGGCCTGCAAGCGG AAGACGAAGCGGATTATTACTGCGCTTCTTACACTCATCAG GGTTCTTGGGTGTTTGGCGGCGGCACGAAGTTAACCGTCT AGGTACAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCC CTCCTCTGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGT GTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCC TGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGAGGA CCACCACACCCTCCAAACAAAGCAACAACAAGTACGCGGCC AGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCA CAGAAGCTACAGCTGCCAGGTACGCATGAAGGGAGCACC GTGGAGAAGACAGTGGCCCCCTACAGAATGTTCA
NOV0710	LCDR1 (Kabat) (SEQ ID	RASQSISLWLN

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	NO:210)	
	LCDR2 (Kabat) (SEQ ID NO:211)	AASTLQS
	LCDR3 (Kabat) (SEQ ID NO:212)	QQYYTSPYT
	HCDR1 (Kabat) (SEQ ID NO:213)	SYAMS
	HCDR2 (Kabat) (SEQ ID NO:214)	VIRSSGSSTYYADSVKG
	HCDR3 (Kabat) (SEQ ID NO:215)	GGGYFDY
	vH full sequence (SEQ ID NO:216)	QVQLLES GGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPG KGLEWVSVIRSSGSSTYYADSVKGRFTISRDN SKNTLYLQMNS LRAEDTAVYYCARGGGYFDYWGQGT LVTVSS
	vL full sequence (SEQ ID NO:217)	DIQMTQSPSSLSASVGDRTITCRASQSISLWLNWYQQKPGKA PKLLIYAASTLQSGVPSRFS GSGSGTDFTLTISSLQPEDFATYYC QQYYTSPYTFGQGTKVEIK
	vH DNA sequence (SEQ ID NO:218)	CAGGTGCAGCTGCTGGAATCAGGCGGCGGACTGGTGCAACC TGGCGGATCCCTGAGGCTGAGCTGCGCTGCTAGTGGCTTCA CCTTCTCTAGCTACGCTATGAGCTGGGTCCGCCAGGCCCTG GTAAAGGCCTCGAGTGGGTGTCAGTGATTAGATCTAGCGGC TCTAGCACCTACTACGCCGATAGCGTGAAAGGGCCGGTTCAC TATCTCTAGGGATAACTCTAAGAACACCCTGTACCTGCAGA TGAATCCCTGAGGGCCGAGGACACCGCCGTCTACTACTGC GCTAGAGGCGGAGGCTACTTCGACTACTGGGGTCAAGGCAC CCTGGTCACCGTGTCTAGC
	vL DNA sequence (SEQ ID NO:219)	GATATT CAGATGACTCAGTCACCTAGTAGCCTGAGCGCTAG TGTGGGCGATAGAGTGACTATCACCTGTAGAGCCTCTCAGT CTATTAGCCTGTGGCTGAACTGGTATCAGCAGAAGCCCCGT AAAGCCCCTAAGCTGCTGATCTACGCCGCCTCTACCCTGCA GTCAGGCGTGCCCTCTAGGTTTAGCGGTAGCGGTAGTGGCA CCGACTTCACCCTGACTATCTCTAGCCTGCAGCCCGAGGACT TCGCTACCTACTACTGT CAGCAGTACTACACTAGCCCCTACA CCTTCGGTCAGGGCACTAAGGTCGAGATTAAG
	HC full sequence (SEQ ID NO:220)	QVQLLES GGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPG KGLEWVSVIRSSGSSTYYADSVKGRFTISRDN SKNTLYLQMNS LRAEDTAVYYCARGGGYFDYWGQGT LVTVSSASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKR VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV

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		TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQ PREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK
	LC full sequence (SEQ ID NO:221)	DIQMTQSPSSLSASVGDRVTITCRASQSISLWLNWYQQKPGKA PKLLIYAASTLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYC QQYYTSPYTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
	HC DNA sequence (SEQ ID NO:222)	CAGGTGCAGCTGCTGGAATCAGGCGGCGGACTGGTGCAACC TGGCGGATCCCTGAGGCTGAGCTGCGCTGCTAGTGGCTTCA CCTTCTCTAGCTACGCTATGAGCTGGGTCCGCCAGGCCCTG GTAAAGGCCTCGAGTGGGTGTCAGTGATTAGATCTAGCGGC TCTAGCACCTACTACGCCGATAGCGTGAAAGGGCCGGTTCAC TATCTCTAGGGATAACTCTAAGAACACCCTGTACCTGCAGA TGAATCCCTGAGGGCCGAGGACACCGCCGTCTACTACTGC GCTAGAGGCGGAGGCTACTTCGACTACTGGGGTCAAGGCAC CCTGGTCACCGTGTCTAGCGCTAGCACTAAGGGCCCAAGTG TGTTTCCCTGGCCCCCAGCAGCAAGTCTACTTCCGGCGGAA CTGCTGCCCTGGGTGCTGCTGGTGAAGGACTACTTCCCCGAGC CCGTGACAGTGTCTGGAACCTCTGGGGCTCTGACTTCCGGC GTGCACACCTTCCCCGCGGTGCTGCAGAGCAGCGGCTGTA CAGCCTGAGCAGCGTGGTGACAGTGCCCTCCAGCTCTCTGG GAACCCAGACCTATATCTGCAACGTGAACCACAAGCCCAGC AACACCAAGGTGGACAAGAGAGTGGAGCCCAAGAGCTGCG ACAAGACCCACACCTGCCCCCCTGCCCAGCTCCAGAACTG CTGGGAGGGCCTTCCGTGTTCTGTTCCTCCCCCAAGCCCAAG GACACCTGATGATCAGCAGGACCCCCGAGGTGACCTGCGT GGTGGTGGACGTGTCCACGAGGACCCAGAGGTGAAGTTCA ACTGGTACGTGGACGGCGTGGAGGTGCACAACGCCAAGACC AAGCCAGAGAGGAGCAGTACAACAGCACCTACAGGGTGG TGTCCTGTCTGACCGTGTCTGCACCAGGACTGGCTGAACGGC AAAGAATACAAGTGCAAAGTCTCCAACAAGGCCCTGCCAGC CCCAATCGAAAAGACAATCAGCAAGGCCAAGGGCCAGCCA CGGGAGCCCCAGGTGTACACCCTGCCCCCAGCCGGGAGGA GATGACCAAGAACCAGGTGTCCCTGACCTGTCTGGTGAAGG GCTTCTACCCCAAGCAGATATCGCCGTGGAGTGGGAGAGCAAC GGCCAGCCCCGAGAACAACCTACAAGACCACCCCCCAGTGCT GGACAGCGACGGCAGCTTCTTCTGTACAGCAAGCTGACCG TGGACAAAGTCCAGGTGGCAGCAGGGCAACGTGTTCAGCTGC AGCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAA GTCCCTGAGCCTGAGCCCCGGCAAG
	LC DNA sequence (SEQ ID NO:223)	GATATTGAGATGACTCAGTCACCTAGTAGCCTGAGCGCTAG TGTGGGCGATAGAGTGACTATCACCTGTAGAGCCTCTCAGT CTATTAGCCTGTGGCTGAACTGGTATCAGCAGAAAGCCCGT AAAGCCCCCTAAGCTGCTGATCTACCGCGCCTCTACCCTGCA GTCAGGCGTGCCCTCTAGGTTTACCGGTAGCGGTAGTGGCA CCGACTTCACCCTGACTATCTCTAGCCTGCAGCCCGAGGACT TCGCTACCTACTACTGTGACGAGTACTACACTAGCCCCCTACA CCTTCGGTCAGGGCACTAAGGTCGAGATTAAGCGTACGGTG GCCGCTCCCAAGCGTGTTCATCTTCCCCCAGCGACGAGCA GCTGAAGAGCGGCACCGCCAGCGTGGTGTGCTGCTGAACA ACTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGAC

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		AACGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTCACCG AGCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCACC CTGACCCTGAGCAAGGCCGACTACGAGAAGCATAAGGTGTA CGCCTGCGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGA CCAAGAGCTTCAACAGGGGCGAGTGC
NOV0712	LCDR1 (Kabat) (SEQ ID NO:224)	RASQSISSYLN
	LCDR2 (Kabat) (SEQ ID NO:225)	AVSTLQS
	LCDR3 (Kabat) (SEQ ID NO:226)	QQSGTFPPTT
	HCDR1 (Kabat) (SEQ ID NO:227)	SHGMH
	HCDR2 (Kabat) (SEQ ID NO:228)	VISGSGSNTGYADSVKG
	HCDR3 (Kabat) (SEQ ID NO:229)	QWGSYAFDS
	vH full sequence (SEQ ID NO:230)	QVQLLESGLVQPGGSLRLSCAASGFTFSSHGMHWVRQAPG KGLEWVSVISGSGSNTGYADSVKGRFTISRDN SKNTLYLQMNS LRAEDTAVYYCARQWGSYAFDSWGQGLVTVSS
	vL full sequence (SEQ ID NO:231)	DIQMTQSPSSLSASVGDRTITCRASQSISSYLNWYQQKPGKAP KLLIYAVSTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQ QSGTFPPTTFGQGTKVEIK
	vH DNA sequence (SEQ ID NO:232)	CAGGTGCAGCTGCTGGAATCAGGCGGCGGACTGGTGCAGCC TGGCGGATCCCTGAGGCTGAGCTGCGCTGCTAGTGCTTCA CCTTTAGCTCTCACGGAATGCACTGGGTCCGCCAGGCCCCCTG GTAAAGGCCTCGAGTGGGTGTCAGTGATTAGCGGTAGCGGC TCTAACACCGGCTACGCCGATAGCGTGAAGGGCCGGTTCAC TATCTCTAGGGATAACTCTAAGAACACCCTGTACCTGCAGA TGAATCCCTGAGGGCCGAGGACACCGCCGTCTACTACTGC GCTAGACAGTGGGGCTCCTACGCCCTTCGATAGCTGGGGTCA AGGCACCCTGGTCACCGTGTCTAGC
	vL DNA sequence (SEQ ID NO:233)	GATATTGATGACTCAGTCACCTAGTAGCCTGAGCGCTAG TGTGGGCGATAGAGTGACTATCACCTGTAGAGCCTCTCAGT CTATCTCTAGCTACCTGAACTGGTATCAGCAGAAGCCCCGGT AAAGCCCCCTAAGCTGCTGATCTACGCCGTGTCTACCCTGCA GTCAGGCGTGCCCTCTAGGTTTACGCGGTAGCGGTAGTGGCA CCGACTTCACCTGACTATTAGTAGCCTGCAGCCCCGAGGAC TTCGCTACCTACTACTGTGTCAGCAGTCAGGCACCTTCCCCCCT

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		ACTACCTTCGGTCAGGGCACTAAGGTCGAGATTAAG
	HC full sequence (SEQ ID NO:234)	QVQLLESGGGLVQPGGSLRLSCAASGFTFSSHGMHWVRQAPG KGLEWVSVISGSGSNTGYADSVKGRFTISRDN SKNTLYLQMNS LRAEDTAVYYCARQWGSYAFDSWGQGLVTVSSASTKGPSVF PLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDK RVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG QPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN GPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVVFSCSV MHEALHNHYTQKSLSLSPGK
	LC full sequence (SEQ ID NO:235)	DIQMTQSPSSLSASVGRVTITCRASQSISSYLNWYQQKPGKAP KLLIYAVSTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQ QSGTFPPTTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSITYSL SSTLTLSKADYEHKVVYACEVTHQGLSSPVTKSFNRGEC
	HC DNA sequence (SEQ ID NO:236)	CAGGTGCAGCTGCTGGAATCAGGCGGCGGACTGGTGCAGCC TGGCGGATCCCTGAGGCTGAGCTGCGCTGCTAGTGGCTTCA CCTTTAGCTCTCACGGAATGCACTGGGTCCGCCAGGCCCTG GTAAAGGCCTCGAGTGGGTGTCAGTGATTAGCGGTAGCGGC TCTAACACCGGCTACGCCGATAGCGTGAAGGGCCGGTTCAC TATCTCTAGGGATAACTCTAAGAACACCCGTGACCTGCAGA TGAAGTCCCTGAGGGCCGAGGACACCGCCGTCTACTACTGC GCTAGACAGTGGGGCTCCTACGCCTTCGATAGCTGGGGTCA AGGCACCCCTGGTCACCGTGTCTAGCGCTAGCACTAAGGGCC CAAGTGTGTTTTCCCTGGCCCCCAGCAGCAAGTCTACTTCCG GCGGAAGTGTGCCCTGGGTTGCCTGGTGAAGGACTACTC CCCGAGCCCGTGACAGTGTCTGGAAGTCTGGGGCTCTGAC TTCCGGCGTGCACACCTTCCCCGCGGTGCTGCAGAGCAGCG GCCTGTACAGCCTGAGCAGCGTGGTGACAGTGCCCTCCAGC TCTCTGGGAACCCAGACCTATATCTGCAACGTGAACCACAA GCCCAGCAACACCAAGGTGGACAAGAGAGTGGAGGCCAAAG AGCTGCGACAAGACCCACACCTGCCCCCCTGCCCCAGCTCC AGAACTGCTGGGAGGGCCTTCCGTGTTCCCTGTTCCCCCCCCAA GCCCCAAGGACACCCTGATGATCAGCAGGACCCCCGAGGTGA CCTGCGTGGTGGTGGACGTGTCCACGAGGACCCAGAGGTG AAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAACGC CAAGACCAAGCCCAGAGAGGAGCAGTACAACAGCACCTAC AGGGTGGTGTCCGTGCTGACCGTGCTGCACCAAGGACTGGCT GAACGGCAAAGAATACAAGTGCAAAGTCTCCAACAAGGCC CTGCCAGCCCCAATCGAAAAGACAATCAGCAAGGCCAAGG GCCAGCCACGGGAGCCCCAGGTGTACACCCTGCCCCCAGC CGGGAGGAGATGACCAAGAACCAGGTGTCCCTGACCTGTCT GGTGAAGGGCTTCTACCCCAGCGATATCGCCGTGGAGTGGG AGAGCAACGGCCAGCCGAGAACAACTACAAGACCAACCC CCCAGTGCTGGACAGCGACGGCAGCTTCTTCCTGTACAGCA AGCTGACCGTGGACAAGTCCAGGTGGCAGCAGGGCAACGT GTTCAGCTGCAGCGTGATGCACGAGGCCCTGCACAACCACT ACACCCAGAAGTCCCTGAGCCTGAGCCCCGGCAAG
	LC DNA sequence (SEQ ID)	GATATTCAGATGACTCAGTCACCTAGTAGCCTGAGCGCTAG TGTGGGCGATAGAGTACTATACCTGTAGAGCCTCTCAGT CTATCTCTAGCTACCTGAACTGGTATCAGCAGAAGCCCGGT

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	NO:237)	AAAGCCCCTAAGCTGCTGATCTACGCCGTGTCTACCCTGCA GTCAGGCGTGCCCTCTAGGTTTACGCGGTAGCGGTAGTGGCA CCGACTTCACCCTGACTATTAGTAGCCTGCAGCCCCGAGGAC TTCGCTACCTACTACTGTCAGCAGTCAGGCACCTTCCCCCT ACTACCTTCGGTCAGGGCACTAAGGTCGAGATTAAGCGTAC GGTGGCCGCTCCCAGCGTGTTTCATCTTCCCCCAGCGACGA GCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCTGCTGA ACAACCTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTG GACAACGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTCA CCGAGCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGC ACCCTGACCCTGAGCAAGGCCGACTACGAGAAGCATAAGGT GTACGCCTGCGAGGTGACCCACCAGGGCCTGTCCAGCCCCG TGACCAAGAGCTTCAACAGGGGCGAGTGC
NOV0713	LCDR1 (Kabat) (SEQ ID NO:238)	SGDNLRSYYVH
	LCDR2 (Kabat) (SEQ ID NO:239)	GNNKRPS
	LCDR3 (Kabat) (SEQ ID NO:240)	GVYTLSSVV
	HCDR1 (Kabat) (SEQ ID NO:241)	SNSAAWN
	HCDR2 (Kabat) (SEQ ID NO:242)	RIYYRSKWYNDYAVSVKS
	HCDR3 (Kabat) (SEQ ID NO:243)	GLVGRYGQPYHFDV
	vH full sequence (SEQ ID NO:244)	QVQLQQSGPGLVKPSQTLSTCAISGDSVSSNSAAWNWIRQSP SRGLEWLGRYYRSKWYNDYAVSVKSRITINPDTSKNQFSLQL NSVTPEDTAVYYCARGLVGRYGQPYHFDVWGQGLVTVSS
	vL full sequence (SEQ ID NO:245)	DIELTQPPSVSVSPGQTASITCSGDNLRSYYVHWYQKPGQAP VLVIYGNNKRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYC GVYTLSSVVFGGGTKLTVL
	vH DNA sequence (SEQ ID NO:246)	CAGGTGCAATTGCAGCAGAGCGGTCCGGGCCTGGTGAAACC GAGCCAGACCCTGAGCCTGACCTGCGCGATTTCCGGAGATA GCGTGAGCTCTAACTCTGCTGCTTGGAAGTGGATTCGTCAGA GCCCCAGCCGTGGCCTCGAGTGGCTGGGCCGTATCTACTAC CGTAGCAAAATGGTACAACGACTATGCCGTGAGCGTGAAAAG CCGATTACCATTAACCCGGATACTTCGAAAAACAGTTTA GCCTGCAACTGAACAGCGTGACCCCGGAAGATACGGCCGTG TATTATTGCGCGCGTGGTCTGGTTGGTTCGTTACGGTCAGCCG TACCATTTCGATGTTTGGGGCCAAGGCACCCTGGTGACTGTT

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		AGCTCA
	vL DNA sequence (SEQ ID NO:247)	GATATCGAACTGACCCAGCCGCCGAGCGTGAGCGTGAGCCC GGGCCAGACCGCGAGCATTACCTGTAGCGGCGATAACCTGC GTTCTTACTACGTTTCATTGGTACCAGCAGAAACCGGGCCAG GCGCCGGTGCTGGTGATCTACGGTAACAACAAACGTCGGAG CGGCATCCCGGAACGTTTTAGCGGATCCAACAGCGGCAACA CCGCGACCCTGACCATTAGCGGCACCCAGGCGGAAGACGAA GCGGATTATTACTGCGGTGTTTACACTCTGTCTTCTGTTGTG TTTGGCGGCGGCACGAAGTTAACCGTCCTA
	HC full sequence (SEQ ID NO:248)	QVQLQQSGPGLVKPSQTLSTCAISGDSVSSNSAAWNWIRQSP SRGLEWLGRYYRSKWYNDYAVSVKSRITINPDTSKNQFSLQL NSVTPEDTAVYYCARGLVGRYGQPYHFDVWGQGLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKP SNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHREALHNHYTQKSLSLSPGK
	LC full sequence (SEQ ID NO:249)	DIELTQPPSVSVSPGQTASITCSGDNLRSYVHVWYQKPGQAP VLVIYGNNKRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYC GVYTLSSVVFVGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKA TLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNKYA ASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
	HC DNA sequence (SEQ ID NO:250)	CAGGTGCAATTGCAGCAGAGCGGTCCGGGCCTGGTGAAACC GAGCCAGACCCTGAGCCTGACCTGCGCGATTTCGGGAGATA GCGTGAGCTCTAACTCTGCTGCTTGGAACCTGGATTCTGTCAGA GCCCCAGCCGTGGCCTCGAGTGCTGGGCCGTATCTACTAC CGTAGCAAATGGTACAACGACTATGCCGTGAGCGTGAAAAG CCGATTACCATTAACCCGGATACTTCGAAAAACCAGTTTA GCCTGCAACTGAACAGCGTGACCCCGGAAGATACGGCCGTG TATTATTGCGCGCGTGGTCTGGTTGGTCTGTTACGGTCAGCCG TACCATTTTCGATGTTTGGGGCCAAGGCACCCTGGTGACTGTT AGCTCAGCCTCCACCAAGGGTCCATCGGTCTTCCCCCTGGCA CCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGG CTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGT CGTGGAACCTCAGGCGCCCTGACCAGCGGCGTGACACACCTTC CCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGC GTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTA CATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGG ACAAGAGAGTTGAGCCCAATCTTGAGCAAAAACCTCACACA TGCCCCACCGTGCCAGCACCTGAACCTCTGGGGGGACCGTC AGTCTTCCTCTTCCCCCAAAACCAAGGACACCCTCATGAT CTCCCGGACCCCTGAGGTACATGCGTGGTGGTGACGTGA GCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGAC GGCGTGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGG AGCAGTACAACAGCACGTACCGGGTGGTCAGCGTCCCTACC GTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTG CAAGGTCTCCAACAAAGCCCTCCAGCCCCGAGAGAAA CCATCTCCAAGCCAAAGGGCAGCCCCGAGAACACAGGTG TACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCA

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		GGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCG ACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAA CAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCT CCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGG TGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGA GGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGT CTCCGGGTAAA
	LC DNA sequence (SEQ ID NO:251)	GATATCGAACTGACCCAGCCGCCGAGCGTGAGCGTGAGCCC GGGCCAGACCGCGAGCATTACCTGTAGCGGCGATAACCTGC GTTCTTACTACGTTTCATTGGTACCAGCAGAAACCGGGCCAG GCGCCGGTGCTGGTGATCTACGGTAACAACAACGTCCGAG CGGCATCCCGGAACGTTTTAGCGGATCCAACAGCGGCAACA CCGCGACCTTGACCATTAGCGGCACCCAGGCGGAAGACGAA GCGGATTATTACTGCGGTGTTTACACTCTGTCTTCTGTTGTG TTTGGCGGCGGCACGAAGTTAACCGTCCTAGGTCAGCCCCA GGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGA GCTTCAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTG ACTTCTACCCGGGAGCCGTGACAGTGGCCTGGAAGGCAGAT AGCAGCCCCGTCAAGGCGGGAGTGGAGACCACACCCCTC CAAACAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTG AGCCTGACGCCTGAGCAGTGGAAAGTCCCACAGAAGCTACAG CTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACA GTGGCCCCCTACAGAATGTTCA
NOV0718	LCDR1 (Kabat) (SEQ ID NO:252)	SGDKIPTYTVH
	LCDR2 (Kabat) (SEQ ID NO:253)	DDNKRPS
	LCDR3 (Kabat) (SEQ ID NO:254)	QSTASGTVV
	HCDR1 (Kabat) (SEQ ID NO:255)	SYALH
	HCDR2 (Kabat) (SEQ ID NO:256)	RIKSKTNGGTTDYAAPVKG
	HCDR3 (Kabat) (SEQ ID NO:257)	VDATYSYSGYYYPMDY
	vH full sequence (SEQ ID NO:258)	QVQLVESGGGLVKPGGSLRLSCAASGFTFNSYALHWVRQAPG KGLEWVGRIKSKTNGGTTDYAAPVKGRFTISRDDSKNTLYLQ MNSLKTEDTAVYYCARVDATYSYSGYYYPMDYWGQGLVT VSS
	vL full sequence	DIETQPPSVSVSPGQTASITCSGDKIPTYTVHWYQQKPGQAPV LVYDDNKRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQ

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	(SEQ ID NO:259)	STASGTVVFGGGTKLTVL
	vH DNA sequence (SEQ ID NO:260)	CAGGTGCAATTGGTGGAAAGCGGCGGTGGCCTGGTGA AAC AGGCGGCAGCCTGCGCCTGAGCTGCGCCGCTCCGGATTCA CCTTTAACTCTTACGCTCTGCATTGGGTGCGCCAGGCCCGG GCAAAGGTCTCGAGTGGGTGGGCCGTATCAAATCTAAAACT AACGGTGGTACTACTGACTATGCCGCCCCAGTGAAAGGCCG CTTTACCATTAGCCGCGATGATTGAAAAACACCCTGTATCT GCAAATGAACAGCCTGAAAACCGAAGATACGGCCGTGTATT ATTGCGCGCGTGTGACGCTACTTACTCTTACTCTGGTTACT ACTACCCGATGGATTACTGGGGCCAAGGCACCCTGGTGACT GTTAGCTCA
	vL DNA sequence (SEQ ID NO:261)	GATATCGAACTGACCCAGCCGCCGAGCGTGAGCGTGAGCCC GGGCCAGACCGCGAGCATTACCTGTAGCGGCGATAAAATCC CGACTTACACTGTTTATTGGTACCAGCAGAAACCGGGCCAG GCGCCGGTGCTGGTGATCTACGACGACAACAAACGTCGAG CGGCATCCCGGAACGTTTTAGCGGATCCAACAGCGGCAACA CCGCGACCCTGACCATTAGCGGCACCCAGGCGGAAGACGAA GCGGATTATTACTGCCAGTCTACTGCTTCTGGTACTGTTGTG TTTGGCGGCGGCACGAAGTTAACCGTCCTA
	HC full sequence (SEQ ID NO:262)	QVQLVESGGGLVKPGGSLRLSCAASGFTFNSYALHWVRQAPG KGLEWVGRIKSKTNGGTTDYAAPVKGRFTISRDDSKNTLYLQ MNSLKTEDTAVYYCARVDATYSYSGYYPMQYWGQGLVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQYICNV NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRW QQGNVVFSCSVMEALHNHYTQKSLSLSPGK
	LC full sequence (SEQ ID NO:263)	DIELTQPPSVSVSPGQTASITCSGDKIPTYT VHWYQQKPGQAPV LVIYDDNKRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQ STASGTVVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKAT LVCLISDFYPGAVTVAWKADSSPVKAGVETTTSPKQSNKYA ASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
	HC DNA sequence (SEQ ID NO:264)	CAGGTGCAATTGGTGGAAAGCGGCGGTGGCCTGGTGA AAC AGGCGGCAGCCTGCGCCTGAGCTGCGCCGCTCCGGATTCA CCTTTAACTCTTACGCTCTGCATTGGGTGCGCCAGGCCCGG GCAAAGGTCTCGAGTGGGTGGGCCGTATCAAATCTAAAACT AACGGTGGTACTACTGACTATGCCGCCCCAGTGAAAGGCCG CTTTACCATTAGCCGCGATGATTGAAAAACACCCTGTATCT GCAAATGAACAGCCTGAAAACCGAAGATACGGCCGTGTATT ATTGCGCGCGTGTGACGCTACTTACTCTTACTCTGGTTACT ACTACCCGATGGATTACTGGGGCCAAGGCACCCTGGTGACT GTTAGCTCAGCCTCCACCAAGGGTCCATCGGTCTTCCCCCTG GCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCT GGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGG TGTCGTGGAACCTCAGGCGCCCTGACCAGCGGCGTGACACCC TTCCCGGCTGTCTACAGTCTCAGGACTCTACTCCCTCAGC AGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGAC CTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGG

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		<p>TGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACCTCAC ACATGCCCACCGTGCCAGCACCTGAACTCCTGGGGGGGACC GTCAGTCTTCTCTTCCCCCAAAACCCAAGGACACCCCTCAT GATCTCCCGGACCCCTGAGGTACATGCGTGGTGGTGGACG TGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTG GACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGG AGGAGCAGTACAACAGCACGTACCGGGTGGTCAGCGTCCTC ACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAA GTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGA AAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACA GGTGTACACCTGCCCCCATCCCGGGAGGAGATGACCAAGA ACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCC AGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGG AGAACAACCTACAAGACCACGCCTCCCGTGCTGGACTCCGAC GGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAGAG CAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGC ATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCC CTGTCTCCGGGTAAA</p>
	LC DNA sequence (SEQ ID NO:265)	<p>GATATCGAACTGACCCAGCCGCCGAGCGTGAGCGTGAGCCC GGGCCAGACCGCGAGCATTACCTGTAGCGGCGATAAAATCC CGACTTACACTGTTTATTGGTACCAGCAGAAACCGGGCCAG GCGCCGGTGCTGGTGATCTACGACGACAACAACGTCCGAG CGGCATCCCGGAACGTTTTAGCGGATCCAACAGCGGCAACA CCGCGACCCCTGACCATTAGCGGCACCCAGGCGGAAGACGAA GCGGATTATTACTGCCAGTCTACTGCTTCTGGTACTGTTGTG TTTGGCGGCGGCACGAAGTTAACCGTCCTAGGTCAGCCCCAA GGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGA GCTTCAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTG ACTTCTACCCGGGAGCCGTGACAGTGGCCTGGAAGGCAGAT AGCAGCCCCGTCAAGGCGGGAGTGGAGACCACACCCCTC CAAACAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTG AGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAG CTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACA GTGGCCCCCTACAGAATGTTCA</p>
NOV0719	LCDR1 (Kabat) (SEQ ID NO:266)	RASQSIVSYLN
	LCDR2 (Kabat) (SEQ ID NO:267)	DASSLQS
	LCDR3 (Kabat) (SEQ ID NO:268)	QQSGSHSIT
	HCDR1 (Kabat) (SEQ ID NO:269)	SHWVH
	HCDR2 (Kabat) (SEQ ID NO:270)	VISYMGSSSTYYADSVKG

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	HCDR3 (Kabat) (SEQ ID NO:271)	GSYDMAFDV
	vH full sequence (SEQ ID NO:272)	QVQLLESGGGLVQPGGSLRLSCAASGFTFSSHWVHWVRQAPG KGLEWVSVISYMGSSYYADSVKGRFTISRDN SKNTLYLQMNS LRAEDTAVYYCARGSYDMAFDVWGQGLVTVSS
	vL full sequence (SEQ ID NO:273)	DIQMTQSPSSLSASVGDRVITTCRASQSIYSYLNWYQQKPGKAP KLLIYDASSLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQ QSGSHSITFGQGTKVEIK
	vH DNA sequence (SEQ ID NO:274)	CAGGTGCAGCTGCTGGAATCAGGCGGCGGACTGGTGCAGCC TGGCGGTAGCCTGAGACTGAGCTGCGCTGCTAGTGGCTTCA CCTTTAGCTCTCACTGGGTGCACTGGGTGAGACAGGCCCTG GTAAAGGCCTGGAGTGGGTGTCAGTGATTAGCTATATGGGC TCTAGCACCTACTACGCCGATAGCGTGAAGGGCCGGTTCAC TATCTCTAGGGATAACTCTAAGAACACCCTGTACCTGCAGA TGAATAGCCTGAGAGCCGAGGACACCGCCGTCTACTACTGC GCTAGAGGCTCCTACGATATGGCCTTCGACGTGTGGGGTCA GGGCACCCTGGTCACCGTGTCTAGC
	vL DNA sequence (SEQ ID NO:275)	GATATTCAGATGACTCAGTCACCTAGTAGCCTGAGCGCTAG TGTGGGCGATAGAGTGACTATCACCTGTAGAGCCTCTCAGT CTATCGTCAGCTACCTGAAGTGGTATCAGCAGAAGCCCGGT AAAGCCCCTAAGCTGCTGATCTACGACGCCTCTAGCCTGCA GTCAGGCGTGCCCTCTAGGTTTAGCGGTAGCGGTAGTGGCA CCGACTTCACCCTGACTATTAGTAGCCTGCAGCCCCGAGGAC TTCGTACCTACTACTGTGTCAGCAGTCAGGCTCTCACTCTATC ACCTTCGGTCAGGGCACTAAGGTTCGAGATTAAG
	HC full sequence (SEQ ID NO:276)	QVQLLESGGGLVQPGGSLRLSCAASGFTFSSHWVHWVRQAPG KGLEWVSVISYMGSSYYADSVKGRFTISRDN SKNTLYLQMNS LRAEDTAVYYCARGSYDMAFDVWGQGLVTVSSASTKGPSVF PLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHPKNTKVDK RVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKG QPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN GPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK
	LC full sequence (SEQ ID NO:277)	DIQMTQSPSSLSASVGDRVITTCRASQSIYSYLNWYQQKPGKAP KLLIYDASSLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQ QSGSHSITFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSL STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
	HC DNA sequence (SEQ ID NO:278)	CAGGTGCAGCTGCTGGAATCAGGCGGCGGACTGGTGCAGCC TGGCGGTAGCCTGAGACTGAGCTGCGCTGCTAGTGGCTTCA CCTTTAGCTCTCACTGGGTGCACTGGGTGAGACAGGCCCTG GTAAAGGCCTGGAGTGGGTGTCAGTGATTAGCTATATGGGC TCTAGCACCTACTACGCCGATAGCGTGAAGGGCCGGTTCAC TATCTCTAGGGATAACTCTAAGAACACCCTGTACCTGCAGA TGAATAGCCTGAGAGCCGAGGACACCGCCGTCTACTACTGC GCTAGAGGCTCCTACGATATGGCCTTCGACGTGTGGGGTCA

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		GGGCACCCTGGTCACCGTGTCTAGCGCTAGCACTAAGGGCC CAAGTGTGTTTCCCCTGGCCCCCAGCAGCAAGTCTACTTCCG GCGGAACTGCTGCCCTGGGTTGCCTGGTGAAGGACTACTTC CCCGAGCCCCGTGACAGTGTCTGGAACCTCTGGGGCTCTGAC TTCCGGCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCG GCCTGTACAGCCTGAGCAGCGTGGTGACAGTGCCCTCCAGC TCTCTGGGAACCCAGACCTATATCTGCAACGTGAACCACAA GCCCAGCAACACCAAGGTGGACAAGAGAGTGGAGCCCAAG AGCTGCGACAAGACCCACACCTGCCCCCCCCTGCCAGCTCC AGAACTGCTGGGAGGGCCTTCCGTGTTCCCTGTTCCCCCCAA GCCCCAAGGACACCCTGATGATCAGCAGGACCCCCGAGGTGA CCTGCGTGGTGGTGGACGTGTCCACGAGGACCCAGAGGTG AAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAACGC CAAGACCAAGCCCAGAGAGGAGCAGTACAACAGCACCTAC AGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGACTGGCT GAACGGCAAAGAATACAAGTGCAAAGTCTCCAACAAGGCC CTGCCAGCCCCAATCGAAAAGACAATCAGCAAGGCCAAGG GCCAGCCACGGGAGCCCCAGGTGTACACCCTGCCCCCAGC CGGGAGGAGATGACCAAGAACCAGGTGTCCCTGACCTGTCT GGTGAAGGGCTTCTACCCAGCGATATCGCCGTGGAGTGGG AGAGCAACGGCCAGCCGAGAACAACTACAAGACCACCCC CCCAGTGCTGGACAGCGACGGCAGCTTCTTCCTGTACAGCA AGCTGACCGTGGACAAGTCCAGGTGGCAGCAGGGCAACGT GTTCACTGCAGCGTGTGACGAGGCCCTGCACAACCACT ACACCCAGAAGTCCCTGAGCCTGAGCCCCGGCAAG
	LC DNA sequence (SEQ ID NO:279)	GATATTGAGATGACTCAGTCACCTAGTAGCCTGAGCGCTAG TGTGGGCGATAGAGTGACTATCACCTGTAGAGCCTCTCAGT CTATCGTCAGCTACCTGAACTGGTATCAGCAGAAGCCCCGT AAAGCCCCCTAAGCTGCTGATCTACGACGCCTCTAGCCTGCA GTCAGGCGTGCCCTCTAGGTTTACGCGTAGCGGTAGTGGCA CCGACTTCACCCTGACTATTAGTAGCCTGCAGCCCCGAGGAC TTCGCTACCTACTACTGTCAGCAGTCAGGCTCTCACTCTATC ACCTTCGGTCAGGGCACTAAGGTGCGAGATTAAGCGTACGGT GGCCGCTCCCAGCGTGTTCATCTTCCCCCAGCGCAGCAGC AGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCTGTGTAAC AACTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGA CAACGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTCACC GAGCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCA CCCTGACCCTGAGCAAGGCCGACTACGAGAAGCATAAGGTG TACGCCTGCGAGGTGACCCACCAGGGCCTGTCCAGCCCCGT GACCAAGAGCTTCAACAGGGGCGAGTGC
NOV0720	LCDR1 (Kabat) (SEQ ID NO:280)	SGDNIGSMTAH
	LCDR2 (Kabat) (SEQ ID NO:281)	DKNERPS
	LCDR3 (Kabat) (SEQ ID NO:282)	QSWDDSYNSVV
	HCDR1	SNSAGWN

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(Kabat) (SEQ ID NO:283)	
HCDR2 (Kabat) (SEQ ID NO:284)	RIYYRSK WYNDY AVSVKS
HCDR3 (Kabat) (SEQ ID NO:285)	EKYTVSFYDFFDY
vH full sequence (SEQ ID NO:286)	QVQLQQSGPGLVKPSQTLSTCAISGDSVSSNSAGWNWIRQSP SRGLEWLGRYYRSK WYNDY AVSVKSRITINPDTSKNQFSLQL NSVTPEDTAVYYCAREKYTVSFYDFFDYWGQGTLLTVSS
vL full sequence (SEQ ID NO:287)	DIELTQPPSVSVSPGQTASITCSGDNIGSMTAHWYQQKPGQAPV LVIYDKNERPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQ SWDDSYNSVVFVGGGKLTVL
vH DNA sequence (SEQ ID NO:288)	CAGGTGCAATTGCAGCAGAGCGGTCCGGGCTGGTGAAACC GAGCCAGACCCTGAGCCTGACCTGCGCGATTTCCGGAGATA GCGTGAGCTCTAACTCTGCTGGTTGGAAGTGGATTCTGTCAG AGCCCCGAGCCGTGGCCTCGAGTGGCTGGGCCGTATCTACTA CCGTAGCAAATGGTACAACGACTATGCCGTGAGCGTGAAAA GCCGCATTACCATTAACCCGATACTTCGAAAAACAGTTT AGCCTGCAACTGAACAGCGTGACCCCGGAAGATACGGCCGT GTATTATTGCGCGCGTGAAAAATACACTGTTTCTTTCTACGA CTTCTTCGATTACTGGGGCCAAGGCACCCTGGTGACTGTTAG CTCA
vL DNA sequence (SEQ ID NO:289)	GATATCGAACTGACCCAGCCGCCGAGCGTGAGCGTGAGCCC GGGCCAGACCGCGAGCATTACCTGTAGCGGCGATAACATCG GTTCTATGACTGCTCATTGGTACCAGCAGAAACCGGGCCAG GCGCCGGTGCTGGTGATCTACGACAAAAACGAACGTCGAG CGGCATCCCGGAACGTTTTAGCGGATCCAACAGCGGCAACA CCGCGACCCCTGACCATTAGCGGCACCCAGGCGGAAGACGAA GCGGATTATTACTGCCAGTCTTGGGACGACTCTTACAACCTCT GTTGTGTTTGGCGGCGGCACGAAGTTAACCGTCCTA
HC full sequence (SEQ ID NO:290)	QVQLQQSGPGLVKPSQTLSTCAISGDSVSSNSAGWNWIRQSP SRGLEWLGRYYRSK WYNDY AVSVKSRITINPDTSKNQFSLQL NSVTPEDTAVYYCAREKYTVSFYDFFDYWGQGTLLTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS NTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMEALHNHYTQKSLSLSPGK
LC full sequence (SEQ ID NO:291)	DIELTQPPSVSVSPGQTASITCSGDNIGSMTAHWYQQKPGQAPV LVIYDKNERPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQ SWDDSYNSVVFVGGGKLTVLGQPKAAPSVTLFPPSSEELQANK ATLVCLISDFYPGAVTVAWKADSSPVKAGVETTPPSKQSNKY

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		AASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
	HC DNA sequence (SEQ ID NO:292)	CAGGTGCAATTGCAGCAGAGCGGTCCGGGCTGGTGAAACC GAGCCAGACCCTGAGCCTGACCTGCGCGATTTCCGGAGATA GCGTGAGCTCTAACTCTGCTGGTTGGAACGGATTCGTCAG AGCCCCGAGCCGTGGCCTCGAGTGGCTGGGCCGTATCTACTA CCGTAGCAAATGGTACAACGACTATGCCGTGAGCGTGAAAA GCCGCATTACCATTAACCCGGATACTTCGAAAAACCAAGTTT AGCCTGCAACTGAACAGCGTGACCCCGGAAGATACGGCCGT GTATTATTGCGCGCGTGAAAAATACACTGTTTCTTTCTACGA CTTCTTCGATTACTGGGGCCAAGGCACCCTGGTGACTGTTAG CTCAGCCTCCACCAAGGGTCCATCGGTCTTCCCCCTGGCACC CTCCTCCAAGAGCACCTCTGGGGGACAGCGGCCCTGGGCT GCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCG TGGAACCTCAGGCGCCCTGACCAGCGGCGTGACACACCTCCC GGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGT GGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACA TCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGAC AAGAGAGTTGAGCCCAAATCTTGACAAAACTCACACATG CCCACCGTGCCAGCACCTGAACTCCTGGGGGGACCGTCAG TCTTCCTCTTCCCCC AAAACCCAAGGACACCCTCATGATCT CCCGGACCCCTGAGGTACATGCGTGGTGGTGGACGTGAGC CACGAAGACCCCTGAGGTCAAGTTCAACTGGTACGTGGACGG CGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAG CAGTACAACAGCACGTACCGGGTGGTCAGCGTCCTCACCGT CCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCA AGGTCTCCAACAAAGCCCTCCCAGCCCCATCGAGAAAACC ATCTCCAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTA CACCCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGG TCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAGCGAC ATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAA ACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCC TTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTG GCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGG CTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTC CGGGTAAA
	LC DNA sequence (SEQ ID NO:293)	GATATCGAACTGACCCAGCCGCCGAGCGTGAGCGTGAGCCC GGGCCAGACCGCGAGCATTACCTGTAGCGGCGATAACATCG GTTCTATGACTGCTCATTGGTACCAGCAGAAACCGGGCCAG GCGCCGGTGCTGGTGATCTACGACAAAAACGAACGTCCGAG CGGCATCCCGGAACGTTTTAGCGGATCCAACAGCGGCAACA CCGCGACCCTGACCATTAGCGGCACCCAGGCGGAAGACGAA GCGGATTATTACTGCCAGTCTTGGGACGACTCTTACAACCTCT GTTGTGTTTGGCGGCGGCACGAAGTTAACCGTCCTAGGTCA GCCCAAGGTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTC TGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGTCTCA TAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCCTGGAAG GCAGATAGCAGCCCCGTCAAGGCGGGAGTGAGAGACCACCA CACCCCTCCAACAAAGCAACAACAAGTACGCGGCCAGCAG CTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAA GCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAG AAGACAGTGGCCCCCTACAGAATGTTCA

NOV1126	LCDR1	SGDAIGTKFAH
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	(Kabat) (SEQ ID NO:294)	
	LCDR2 (Kabat) (SEQ ID NO:295)	YDHERPS
	LCDR3 (Kabat) (SEQ ID NO:296)	YSRASSNLV
	HCDR1 (Kabat) (SEQ ID NO:297)	DHAID
	HCDR2 (Kabat) (SEQ ID NO:298)	VIAGSGSITYYADSVKG
	HCDR3 (Kabat) (SEQ ID NO:299)	DTGVYREYMDV
	vH full sequence (SEQ ID NO:300)	EVQLLES GGGLVQPGGSLRLSCAASGFTFS DHAIDWVRQAPGK GLEWVSVIAGSGSITYYADSVKGRFTISRDN SKNTLYLQMNSL RAEDTAVYYCARDTGVYREYMDVWGQGLTVSS
	vL full sequence (SEQ ID NO:301)	SYELTQPLSVSVALGQTARITCSGDAIGTKFAHWYQQKPGQAP VLVIYYDHERPSGIPERFSGSNSGNTATLTISR AQAQGEADYYC YSRASSNLVFGGGTKLTVL
	vH DNA sequence (SEQ ID NO:302)	GAAGTGCAATTGCTGGAAAGCGGCGGTGGCCTGGTG CAGCC GGGTGGCAGCCTGCGTCTGAGCTGCGCGGCGTCCGGATTCA CCTTTTCTGACCATGCTATCGACTGGGTGCGCCAGGCCCGG GCAAAGGTCTCGAGTGGGTTTCCGTTATCGCTGGTAGCGGTT CTATCACCTACTATGCGGATAGCGTGAAAGGCCGCTTACC ATCAGCCGCGATAATTGAAAAACACCCTGTATCTGCAAAAT GAACAGCCTGCGTGCGGAAGATACGGCCGTGTATTATTGCG CGCGTGACACTGGTGTTTACCGTGAATACATGGATGTTTGG GGCCAAGGCACCCTGGTGACTGTTAGCTCA
	vL DNA sequence (SEQ ID NO:303)	AGCTATGAACTGACCCAGCCGCTGAGCGTGAGCGTG GCGCT GGGCCAGACCGCGCGCATTACCTGTAGCGGCGATGCTATCG GTACTAAATTCGCTCATTGGTACCAGCAGAAACCGGGCCAG GCGCCGGTGCTGGTGATCTACTACGACCATGAACGTCCGAG CGGCATCCCCGAACGTTTTAGCGGATCCAACAGCGGCAACA CCGCGACCCTGACCATTAGCCGCGCGCAGGCGGGCGACGAA GCGGATTATTACTGCTACTCTCGTGCTTCTTCTAACCTGGTG TTTGCGGCGGCGCACGAAGTTAACCGTCCTA
	HC full sequence (SEQ ID NO:304)	EVQLLES GGGLVQPGGSLRLSCAASGFTFS DHAIDWVRQAPGK GLEWVSVIAGSGSITYYADSVKGRFTISRDN SKNTLYLQMNSL RAEDTAVYYCARDTGVYREYMDVWGQGLTVSSASTKGPS VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV

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		HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTTPVLDSGDGSFFLYSKLTVDKSRWQQGNVFC SVMHEALHNHYTQKSLSLSPGK
	LC full sequence (SEQ ID NO:305)	SYELTQPLSVSVALGQTARITCSGDAIGTKFAHWYQQKPGQAP VLVIYYDHERPSGIPERFSGSNSGNTATLTISRAGQAGDEADYYC YSRASSNLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKA TLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKSNKYA ASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
	HC DNA sequence (SEQ ID NO:306)	GAAGTGCAATTGCTGGAAAGCGGCGGTGGCCTGGTGCAGCC GGGTGGCAGCCTGCGTCTGAGCTGCGCGGCGTCCGGATTCA CCTTTTCTGACCATGCTATCGACTGGGTGCGCCAGGCCCGG GCAAAGGTCTCGAGTGGGTTTCCGTTATCGCTGGTAGCGGTT CTATCACCTACTATGCGGATAGCGTGAAAGGCCGCTTTACC ATCAGCCGCGATAATTTCGAAAAACACCCTGTATCTGCAAA GAACAGCCTGCGTGCGGAAGATACGGCCGTGTATTATTGCG CGCGTGACACTGGTGTTTACCGTGAATACATGGATGTTTGG GGCCAAGGCACCCTGGTGACTGTTAGCTCAGCCTCCACCAA GGGTCCATCGGTCTTCCCCCTGGCACCCCTCCTCCAAGAGCAC CTCTGGGGGACAGCGGCCCTGGGCTGCCTGGTCAAGGACT ACTTCCCCGAACCGGTGACGGTGTCGTGGAACCTCAGGCGCC CTGACCAGCGGCGTGACACCTTCCCGGCTGTCCTACAGTCC TCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCC AGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCA CAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCC AAATCTTGTGACAAAACCTCACACATGCCACCGTGCACGAGC ACCTGAACTCCTGGGGGGACCGTCAGTCTTCTCTTCCCCCCC AAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGG TCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAG GTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAA TGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCAGC TACCGGGTGGTCAAGCGTCTCACCCTCCTGCACAGGACTG GCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAA GCCCTCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAA AGGGCAGCCCCGAGAACCACAGGTGTACACCTGCCCCCAT CCCGGGAGGAGATGACCAAGAACCAGGTGAGCCTGACCTGC CTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTG GGAGAGCAATGGGCAGCCGAGAAACAACCTACAAGACCACG CCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTACAGC AAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACG TCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACT ACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA
	LC DNA sequence (SEQ ID NO:307)	AGCTATGAACTGACCCAGCCGCTGAGCGTGAGCGTGGCGCT GGGCCAGACCGCGCGCATTACCTGTAGCGGCGATGCTATCG GTACTAAATTCGCTCATTGGTACCAGCAGAAACCGGGCCAG GCGCCGGTGCTGGTGATCTACTACGACCATGAACGTCCGAG CGGCATCCCGGAACGTTTTAGCGGATCCAACAGCGGCAACA CCGCGACCCTGACCATTAGCCGCGCGCAGGCGGGCGACGAA GCGGATTATTACTGCTACTCTCGTGCTTCTTCTAACCTGGTG TTTGGCGGCGGCACGAAGTTAACCGTCTAGGTGAGCCCAA GGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGA

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		GCTTCAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTG ACTTCTACCCGGGAGCCGTGACAGTGGCCTGGAAGGCAGAT AGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTC CAAACAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTG AGCCTGACGCCTGAGCAGTGGAAAGTCCCACAGAAGCTACAG CTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACA GTGGCCCCTACAGAATGTTCA
NOV1127	LCDR1 (Kabat) (SEQ ID NO:308)	RASQGIFTYLN
	LCDR2 (Kabat) (SEQ ID NO:309)	AASTLQS
	LCDR3 (Kabat) (SEQ ID NO:310)	QQYYSTSLT
	HCDR1 (Kabat) (SEQ ID NO:311)	SQSAAWN
	HCDR2 (Kabat) (SEQ ID NO:312)	RIYYRSKWYNDYAVSVKS
	HCDR3 (Kabat) (SEQ ID NO:313)	ERSYRDYFDY
	vH full sequence (SEQ ID NO:314)	QVQLQQSGPGLVKPSQTLSTCAISGDSVSSQSAAWNWIRQSP SRGLEWLGRYYRSKWYNDYAVSVKSRITINPDTSKNQFSLQL NSVTPEDTAVYYCARERSYRDYFDYWGGQTLVTVSS
	vL full sequence (SEQ ID NO:315)	DIQMTQSPSSLSASVGDRTITCRASQGIFTYLNWYQQKPGKA PKLLIYAASTLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYC QQYYSTSLTFGQGTKVEIK
	vH DNA sequence (SEQ ID NO:316)	CAGGTGCAGCTGCAGCAGTCAGGCCCTGGCCTGGTCAAGCC TAGTCAGACCCTGAGCCTGACCTGCGCTATTAGCGGCGATA GTGTGTCTAGTCAGTCAGCCGCCTGGAAGTGGATTAGACAG TCACCCTCTAGGGGCCCTGGAGTGGCTGGGTAGAATCTACTA TAGGTCTAAGTGGTATAACGACTACGCCGTCAGCGTGAAGT CTAGGATCACTATTAACCCCGACACCTCTAAGAATCAGTTTA GCCTGCAGCTGAATAGCGTGACCCCGAGGACACCGCCGTC TACTACTGCGCTAGAGAGCGGTCTATAGAGACTACTTCGA CTACTGGGGTCAGGGCACCCCTGGTCACCGTGTCTAGC
	vL DNA sequence (SEQ ID NO:317)	GATATTCAGATGACTCAGTCACCTAGTAGCCTGAGCGCTAG TGTGGGCGATAGAGTGACTATCACCTGTAGAGCCTCTCAGG GAATCTTCACCTACCTGAAGTGGTATCAGCAGAAGCCCGGT AAAGCCCCTAAGCTGCTGATCTACGCCGCCTCTACCCTGCA GTCAGGCGTGCCCTCTAGGTTTAGCGGTAGCGGTAGTGCCA

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		CCGACTTCACCCTGACTATCTCTAGCCTGCAGCCCGAGGACT TCGCTACCTACTACTGTCAGCAGTACTACTCTACTAGCCTGA CCTTCGGTCAGGGCACTAAGGTCGAGATTAAG
	HC full sequence (SEQ ID NO:318)	QVQLQQSGPGLVKPSQTLSTCAISGDSVSSQSAAWNWIQSP SRGLEWLGRIYYRSKWYNDYAVSVKSRITINPDTSKNQFSLQL NSVTPEDTAVYYCARERSYRDYFDYWGGQTLVTVSSASTKGP SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK VDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNYHTQKSLSLSPGK
	LC full sequence (SEQ ID NO:319)	DIQMTQSPSSLSASVGDRTITCRASQGIFTYLNWYQQKPGKA PKLLIYAASLTQSGVPSRFSGSGSGTDFLTITSLQPEDFATYYC QQYYSTSLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSTYS LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
	HC DNA sequence (SEQ ID NO:320)	CAGGTGCAGCTGCAGCAGTCAGGCCCTGGCCTGGTCAAGCC TAGTCAGACCCTGAGCCTGACCTGCGCTATTAGCGGCGATA GTGTGTCTAGTCAGTCAGCCGCTGGAAGTGGATTAGACAG TCACCCTCTAGGGGCCTGGAGTGGCTGGGTAGAATCTACTA TAGGTCTAAGTGGTATAACGACTACGCCGTCAGCGTGAAGT CTAGGATCACTATTAACCCCGACACCTCTAAGAATCAGTTTA GCCTGCAGCTGAATAGCGTGACCCCCGAGGACACCGCCGTC TACTACTGCGCTAGAGAGCGGTCTATAGAGACTACTTTCGA CTACTGGGGTCAGGGCACCTGGTCACCGTGTCTAGCGTA GACTAAGGGCCCAAGTGTGTTTCCCCTGGCCCCCAGCAGC AAGTCTACTTCCGGCGGAAGTGTGCTGCCCTGGGTTGCCTGGT AAGGACTACTTCCCCGAGCCCGTGACAGTGTCTGGAAGTC TGGGGCTCTGACTTCCGGCGTGACACCTTCCCCGCCGTGCT GCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACAG TGCCCTCCAGCTCTCTGGGAACCCAGACCTATATCTGCAACG TGAACCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGT GGAGCCCAAGAGCTGCGACAAGACCCACACCTGCCCCCCT GCCAGCTCCAGAACTGCTGGGAGGGCCTTCCGTGTTCTGT TCCCCCACAAGCCAAGGACACCTGATGATCAGCAGGACC CCCGAGGTGACCTGCGTGGTGGTGGACGTGTCCACGAGGA CCCAGAGGTGAAGTTCAACTGGTACGTGGACGGCGTGGAGG TGCACAACGCCAAGACCAAGCCCAGAGAGGAGCAGTACAA CAGCACCTACAGGGTGGTGTCCGTGCTGACCGTGTGACACC AGGACTGGCTGAACGGCAAAGAATACAAAGTGCAAAGTCTCC AACAAGGCCCTGCCAGCCCCAATCGAAAAGACAATCAGCA AGGCCAAGGGCCAGCCACGGGAGCCCCAGGTGTACACCTG CCCCCAGCCGGGAGGAGATGACCAAGAACCAGGTGTCCCT GACCTGTCTGGTGAAGGGCTTCTACCCCAGCGATATCGCCG TGGAGTGGGAGAGCAACGGCCAGCCCGAGAACAACTACAA GACCACCCCCCAGTGCTGGACAGCGACGGCAGCTTCTTCC TGTACAGCAAGCTGACCGTGGACAAGTCCAGGTGGCAGCAG GGCAACGTGTTACAGCTGCAGCGTGATGCACGAGGCCCTGCA CAACCACTACACCCAGAAGTCCCTGAGCCTGAGCCCCGGCA AG

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	LC DNA sequence (SEQ ID NO:321)	GATATTCAGATGACTCAGTCACCTAGTAGCCTGAGCGCTAG TGTGGGCGATAGAGTGACTATCACCTGTAGAGCCTCTCAGG GAATCTTCACCTACCTGAACTGGTATCAGCAGAAGCCCGGT AAAGCCCCTAAGCTGCTGATCTACGCCGCCTCTACCCTGCA GTCAGGCGTGCCCTCTAGGTTTAGCGGTAGCGGTAGTGGCA CCGACTTCACCCTGACTATCTCTAGCCTGCAGCCCCGAGGACT TCGCTACCTACTACTGTCAGCAGTACTACTCTACTAGCCTGA CCTTCGGTCAGGGCACTAAGGTCGAGATTAAGCGTACGGTG GCCGCTCCCAGCGTGTTTCATCTCCCCCCCAGCGACGAGCA GCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCTGCTGAACA ACTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGAC AACGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTCACCG AGCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCACC CTGACCCTGAGCAAGGCCGACTACGAGAAGCATAAGGTGTA CGCCTGCGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGA CCAAGAGCTTCAACAGGGGCGAGTGC
NOV1132	LCDR1 (Kabat) (SEQ ID NO:322)	SGDNIGSMTAH
	LCDR2 (Kabat) (SEQ ID NO:323)	DKNERPS
	LCDR3 (Kabat) (SEQ ID NO:324)	QSWDDSYTSVV
	HCDR1 (Kabat) (SEQ ID NO:325)	SQSAGWN
	HCDR2 (Kabat) (SEQ ID NO:326)	RIYYRSKWYNDYAVSVKS
	HCDR3 (Kabat) (SEQ ID NO:327)	EKYTVSFYDFFDY
	vH full sequence (SEQ ID NO:328)	QVQLQQSGPGLVKPSQTLSTCAISGDSVSSQSAGWNWIRQSP SRGLEWLGRYYRSKWYNDYAVSVKSRITINPDTSKNQFSLQL NSVTPEDTAVYYCAREKYTVSFYDFFDYWGQGLTVVSS
	vL full sequence (SEQ ID NO:329)	SYELTQPLSVSVALGQTARITCSGDNIGSMTAHWYQQKPGQAP VLVYIDKNERPSGIPERFSGSNSGNTATLTISRAQAGDEADYYC QSWDDSYTSVVFGGGTKLTVL
	vH DNA sequence (SEQ ID NO:330)	CAGGTGCAATTGCAGCAGAGCGGTCCGGGCCTGGTGAAACC GAGCCAGACCCTGAGCCTGACCTGCGCGATTTCCGGAGATA GCGTGAGCTCTCAGTCTGCTGGTTGGAAGTGGATTCGTCAG AGCCCCGAGCCGTGGCCTCGAGTGGCTGGGCCGTATCTACTA CCGTAGCAAAATGGTACAACGACTATGCCGTGAGCGTGAAAA GCCGCATTACCATTAACCCGATACCTTCGAAAAACCAGTTT

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		AGCCTGCAACTGAACAGCGTGACCCCGGAAGATACGGCCGT GTATTATTGCGCGCGTGAAAAATACACTGTTTCTTTCTACGA CTTCTTCGATTACTGGGGCCAAGGCACCCTGGTGACTGTTAG CTCA
	vL DNA sequence (SEQ ID NO:331)	AGCTATGAACTGACCCAGCCGCTGAGCGTGAGCGTGCGCGCT GGGCCAGACCGCGCGCATTACCTGTAGCGGCGATAACATCG GTTCTATGACTGCTCATTGGTACCAGCAGAAACCGGGCCAG GCGCCGGTGCTGGTGATCTACGACAAAAACGAACGTCCGAG CGGCATCCCGGAACGTTTTAGCGGATCCAACAGCGGCAACA CCGCGACCCTGACCATTAGCCGCGCGCAGGCGGGCGACGAA GCGGATTATTACTGCCAGTCTTGGGACGACTCTTACACCTCT GTTGTGTTTGGCGGCGGCACGAAGTTAACCCTCCTA
	HC full sequence (SEQ ID NO:332)	QVQLQQSGPGLVKPSQTLSTCAISGDSVSSQSAGWNWIRQSP SRGLEWLGRYYRSKWYNDYAVSVKSRITINPDTSKNQFSLQL NSVTPEDTAVYYCAREKYTVSFYDFFDYWGQGLTVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS NTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMEALHNHYTQKSLSLSPGK
	LC full sequence (SEQ ID NO:333)	SYELTQPLSVSVALGQTARITCSGDNIGSMTAHWYQQKPGQAP VLVIYDKNERPSGIPERFSGSNSGNTATLTISRAGQAGDEADYYC QSWDDSYTSVVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQAN KATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNK YAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
	HC DNA sequence (SEQ ID NO:334)	CAGGTGCAATTGCAGCAGAGCGGTCCGGGCCTGGTGAAACC GAGCCAGACCCTGAGCCTGACCTGCGCGATTTCCGGAGATA GCGTGAGCTCTCAGTCTGCTGGTTGGAACCTGGATTCGTCAG AGCCCCGAGCCGTGGCCTCGAGTGGCTGGGCGCATCTACTA CCGTAGCAAAATGGTACAACGACTATGCCGTGAGCTGAAAA GCCGCATTACCATTAACCCGGATACTTCGAAAAACCAAGTTT AGCCTGCAACTGAACAGCGTGACCCCGGAAGATACGGCCGT GTATTATTGCGCGCGTGAAAAATACACTGTTTCTTTCTACGA CTTCTTCGATTACTGGGGCCAAGGCACCCTGGTGACTGTTAG CTCAGCCTCCACCAAGGGTCCATCGGTCTTCCCCCTGGCACC CTCCTCCAAGAGCACCTCTGGGGGACAGCGGCCCTGGGCT GCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTG TGGAACCTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCC GGCTGTCCTACAGTCCCTCAGGACTCTACTCCCTCAGCAGCGT GGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACA TCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGAC AAGAGAGTTGAGCCCAAATCTTGAGACAAAACCTCACACATG CCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAG TCTTCCTCTTCCCCCAAAACCAAGGACACCCTCATGATCT CCCGGACCCCTGAGGTACATGCGTGGTGGTGGACGTGAGC CACGAAGACCCCTGAGGTCAAGTTCAACTGGTACGTGGACGG CGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAG CAGTACAACAGCACGTACCGGGTGGTCAGCGCTCCTCAGCGT CCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCA

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		AGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACC ATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTA CACCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGG TCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGAC ATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACA ACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCC TTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTG GCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGG CTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTC CGGGTAAA
	LC DNA sequence (SEQ ID NO:335)	AGCTATGAACTGACCCAGCCGCTGAGCGTGAGCGTGCGCT GGGCCAGACCGCGCGCATTACCTGTAGCGGCGATAACATCG GTTCTATGACTGCTCATTGGTACCAGCAGAAACCGGGCCAG GCGCCGGTGCTGGTGATCTACGACAAAACGAACGTCCGAG CGGCATCCCGGAACGTTTTAGCGGATCCAACAGCGGCAACA CCGCGACCCTGACCATTAGCCGCGCGCAGGCGGGCGACGAA GCGGATTATTACTGCCAGTCTTGGGACGACTTTACACCTCT GTTGTGTTTGGCGGCGGCACGAAGTTAACCGTCCTAGGTCA GCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTC TGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGTCTCA TAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCCTGGAAG GCAGATAGCAGCCCCGTCAAGGCGGGAGTGAGACCACCA CACCTCCAAACAAAGCAACAACAAGTACGCGGCCAGCAG CTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAA GCTACAGCTGCCAGGTACGCATGAAGGGAGCACCGTGGAG AAGACAGTGGCCCTACAGAATGTTCA

Example 2: GITR antibody isolation

[00333] Human antibodies GITR.MAB2, GITR.MAB3, GITR.MAB4, GITR.MAB5, GITR.MAB6, GITR.MAB7 and GITR.MAB8 were generated by engineering a murine monoclonal GITR agonist antibody GITR.MAB1 to have greater sequence homology to a human germline antibody. GITR.MAB2, GITR.MAB3, GITR.MAB4, GITR.MAB5, GITR.MAB6, GITR.MAB7 and GITR.MAB8 retain the epitope specificity, affinity, and cynomolgus macaque GITR cross-reactivity of the parental murine antibody, GITR.MAB1. GITR.MAB2, GITR.MAB3, GITR.MAB4, GITR.MAB5, GITR.MAB6, GITR.MAB7 and GITR.MAB8 have much higher homology to the human germline sequence than the original murine antibody and should therefore be better tolerated by the human immune system.

[00334] Mouse monoclonal MAB1 was engineered to bring its protein sequence closer to a human germline sequence and decrease its immunogenicity using the Humaneered® technology platform available through KaloBios (South San Francisco, CA). Humaneered® antibodies are very close to human antibodies with V-region sequences that have high homology to a human germline sequence while still retaining the specificity and affinity of the parent or reference antibody (U.S. Patent Publ. 2005/0255552 and 2006/0134098). The process first identifies the minimum antigen binding specificity determinants (BSDs) in heavy and light chain variable regions of a reference Fab

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(typically sequences within the heavy chain CDR3 and the light chain CDR3). As these heavy and light chain BSDs are maintained in all libraries constructed during the process, each library is epitope-focused, and the resulting Humaneered[®] antibodies retain the epitope specificity of the original mouse antibody.

[00335] Next, full chain libraries (in which an entire light or heavy chain variable region is replaced with a library of human sequences) and/or cassette libraries (in which a portion of the heavy or light chain variable region of the mouse Fab is replaced with a library of human sequences) are generated. A bacterial secretion system is used to express members of the library as antibody Fab fragments, and the library is screened for Fabs that bind antigen using a colony lift binding assay (CLBA). Positive clones are further characterized to identify those with the highest affinity. Identified human cassettes supporting binding in the context of residual murine sequences are the combined in a final library screen to generate completely human V-regions.

[00336] Resulting Humaneered[®] antibody Fabs have V-segment sequences derived from human libraries, retain the short BSD sequences identified within the CDR3 regions, and have human germline Framework 4 regions. These Fabs are converted to full IgGs by cloning variable regions of the heavy and light chains into IgG expression vectors. Humaneered[®] antibodies generated in this process retain the binding specificity of the parent, murine antibody, typically having equivalent or higher affinity for antigen than the parent antibody, and have V-regions with a high degree of sequence identity compared with human germline antibody genes at the protein level.

[00337] Bcl-2 transgenic mice (C57BL/6-Tgn (bcl-2) 22 wehi strain) were immunized with the N-terminal region of human GITR (aa 26-161) using a procedure that calls for Repetitive Immunization at Multiple Sites (RIMMS) (McIntyre GD. Hybridoma 1997) followed by hybridoma generation from high titer mice. A hybridoma secreting MAB1 was identified and selected using a sandwich ELISA against hGITR and an NFκB Reporter Gene Assay to confirm hGITR binding and agonist activity.

Human GITR (SEQ ID NO:336) aa 26-161 is bolded and underlined

MAQHGMGAFRALCGLALLCALS <u>LQRP</u> TGGPGCGPGRLL <u>LGTGTDARCCRVHTTRCC</u> <u>RDYPGEECCSEWDCMCVQPEFHCGDPCCTTCRHHPCPPGQGVOSQGFSGFOCIDCA</u> <u>SGTFSGGHEGHCKPWTDC</u> T <u>QFGFLT</u> VFPG <u>NKTHNAVCVPGSPPAE</u> PLGWLTVVLLAVAA CVLLLTSAQLGLHIWQLRSQCMWPRETQLLLEVPSTEDARSCQFPPEERGERSAEEKGRLGLD LWV

[00338] Variable region DNA from murine monoclonal MAB1 was amplified by RT-PCR from RNA obtained from the hybridoma cell line using standard methods. Heavy chain variable region was amplified from MAB1 cDNA with HV3 (5'-GGGTCTAGACACCATGGCTGTCTTGGGGCTGCTCTTC-3' (SEQ ID NO: 337)) and HCconstant (5'-GCGTCTAGAACTCCACACACAGGRRCCAGTGGATAGAC-3' (SEQ ID NO: 338)). Light chain variable region was amplified from the same cDNA with

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LV3 (5'-GGGTCTAGACACCATGGAGWCACAKWCTCAGGTCTTTTTRTA-3' (SEQ ID NO: 339)) and LCconstant (5'- GCGTCTAGAACTGGATGGTGGGAAGATGG-3' (SEQ ID NO: 340)). Variable heavy and light chain products were inserted into a pcDNA3.1 vector and sequence verified. The heavy and light vectors were used as templates for PCR incorporating restriction enzyme sites for cloning into KaloBios vectors: Vh into KB1292-His (modified version of KB1292 that encodes a C-terminal flexible linker and 6-His tag of amino acid sequence AAGASHHHHHH (SEQ ID NO:341) on CH1) at *NcoI* (5') and *NheI* (3'); Vk into KB1296 at *NcoI* (5') and *BsiWI* (3'). These separate heavy and light chain vectors were then combined into a single dicistronic KaloBios Fab expression vector by restriction digest with *BssHII* and *ClaI* and ligation. Fab fragments were expressed in *E. coli* from this vector. This Fab was tested for hGITR-antigen binding and is referred to as MAB1rFab.

[00339] Fab fragments were expressed by secretion from *E. coli* using KaloBios expression vectors. Cells were grown in 2 x YT medium to an OD500 of ~0.6. Expression was induced by adding IPTG to 100 μ M and shaking for 4 hours at 33°C. Assembled Fab was obtained from periplasmic fractions by osmotic lysis and purification by affinity chromatography using Ni-NTA columns HisTrap HP columns; GE Healthcare catalog #17-5247-01) according to standard methods. Fabs were eluted in buffer containing 500 mM imidazole and thoroughly dialyzed against PBS pH7.4 without calcium and magnesium.

[00340] To limit the complexity to identify complimentary human CDRs that support BSD-FR4 in human GITR binding, a cassette library approach, in which only part of the parent murine V-segment is replaced by a library of human sequences, was taken. The original murine MAB1 Vk is closest to human germline VkIII, so a mixture of two KaloBios libraries that contains VkIII germlines (KB1423 and KB1424) was used in making the Vk cassette libraries. KaloBios libraries that contains VH3 germlines (KB1413, KB1414) were used to construct Vh cassette libraries. Two types of cassettes were constructed by overlap PCR: front-end cassettes (8C1VK3FE-01, and MAB1VH3FE-01) containing human sequences in FR1, CDR1, and FR2, and FR3 cassettes (MAB1VK3FR3-01, and MAB1VH3FR3-01) containing human sequences in the FR3 were amplified using the above mentioned germline restricted KaloBios libraries. Each Vh cassette library was cloned into vector KB1292-His at *NcoI* (5') and *KpnI* (3'); each Vk cassette library was cloned into vector KB1296-B (modified version of KaloBios vector KB1296 which has a silent *HindIII* site added in FR4) at *NcoI* (5') and *HindIII* (3'). Resultant Vh or Vk plasmid libraries were then combined with the complementary chain from the optimized reference Fab (MAB1opVK or MAB1 opVH (e.g., the Vh front-end library was combined with the optimized reference

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Vk vector) by digestion with *Bss*HII and *Cla*I and subsequent ligation to create libraries of dicistronic vectors expressing full Fabs.

Table 6

Sequence information of the IgGs selected for in-depth characterization.

Antibody ID	Category	Value
GITR.MAB1	LCDR1 (Kabat) (SEQ ID NO: 342)	KASENVDTFVS
	LCDR2 (Kabat) (SEQ ID NO: 343)	GASNRYT
	LCDR3 (Kabat) (SEQ ID NO: 344)	GQSYSYPFT
	HCDR1 (Kabat) (SEQ ID NO: 345)	SYGVD
	HCDR2 (Kabat) (SEQ ID NO: 346)	VIWGGGGTNYNSALMA
	HCDR3 (Kabat) (SEQ ID NO: 347)	HAYGHDGGFAMDY
	vH full sequence (SEQ ID NO: 348)	QVQLKESGPGLVAPSQLSITCTVSGFSLRSYGVDWVRQPPGK GLEWLGVIWGGGGTNYNSALMAKLSISKDKSKSQVFLKMNSL QTDDTAMYYCAKHAYGHDGGFAMDYWGQGTSTVSS
	vL full sequence (SEQ ID NO: 349)	NIVMTQSPKSMSMSVGERVTLSCASENVDTFVSWYQQKPDH SPKLLIYGASNRYTGVPDRFTGSGSATDFTLTISSVQAEDLADY HCGQSYSYPFTFGSGTKLEIK
	vH DNA sequence (SEQ ID NO: 350)	CAGGTGCAGCTGAAGGAGTCAGGACCTGGCCTGGTGGCGCC CTCACAGAGCCTGTCCATCACTTGCACTGTCTCTGGGTTTTTC ATTAAGGAGCTATGGTGTAGACTGGGTTCGCCAGCCTCCAG GAAAGGGTCTGGAGTGGCTGGGAGTTATATGGGGTGGTGGA GGCACAAATTATAATTCAGCTCTCATGGCCAACTGAGTAT CAGCAAAGACAAGTCCAAGAGCCAAGTTTTCTTAAAAATGA ACAGTCTGCAAACTGATGACACAGCCATGTACTACTGTGCC AAACATGCCTATGGTCACGACGGCGGTTTTTGCTATGGACTA CTGGGGTCAAGGAACCTCAGTCACCGTCTCCTCA

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	vL DNA sequence (SEQ ID NO: 351)	AACATTGTAATGACCCAATCTCCCAAATCCATGTCCATGTCA GTAGGAGAGAGGGTCACCTTGAGCTGCAAGGCCAGTGAGA ATGTGGATACTTTTGTATCCTGGTATCAACAGAAACCAGAC CACTCTCCTAAACTACTGATATACGGGGCATCCAACCGGTA CACTGGGGTCCCCGATCGCTTCACAGGCAGTGGATCTGCAA CAGATTTCACTCTGACCATCAGCAGTGTGCAGGCTGAAGAC CTTGCAGATTATCACTGTGGACAGAGTTACAGCTATCCATTC ACGTTTCGGCTCGGGGACAAAGTTGAAATAAAA
GITR.MAB2	LCDR1 (Kabat) (SEQ ID NO: 352)	RASESVSSNVA
	LCDR2 (Kabat) (SEQ ID NO: 353)	GASNRAT
	LCDR3 (Kabat) (SEQ ID NO: 354)	GQSYSPFT
	HCDR1 (SEQ ID NO: 355)	SYGVD
	HCDR2 (Kabat) (SEQ ID NO: 356)	VIWGGGGTYTASSVMA
	HCDR3 (Kabat) (SEQ ID NO: 357)	HAYGHDGGFAMDY
	vH full sequence (SEQ ID NO: 358)	QVQLVESGGGLVQPGLSLRLSCAASGFLSSYGVDWVRQAPG KGLEWVGVWGGGGTYTASSVMARFTISRDN SKNTLYLQMNS LRAEDTAVYYCAKHAYGHDGGFAMDYWGQGLTVTVSS
	vL full sequence (SEQ ID NO: 359)	EIVMTQSPATLSVSPGERATLSCRASESVSSNVAWYQQRPGQA PRLLIYGASNRATGIPARFSGSGSGTDFTLTISRLEPEDFAVYYC GQSYSPFTFGQGTKLEIK
	vH DNA sequence (SEQ ID NO: 360)	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCC TGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCTC CCTCAGCAGCTATGGTGTGGACTGGGTTCGCCAGGCTCCAG GAAAGGGTCTGGAGTGGGTGGGAGTTATATGGGGTGGTGGGA GGCACATATTATGCTTCTTCTGTCTATGGCCAGATTACCATC TCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAAATGAA CAGCCTGAGAGCTGAGGACACGGCCGTGTATTACTGCGCCA AACATGCCTATGGCCATGATGGCGGCTTTGTATGGATTATT GGGGCCAGGGTACCCTTGTGACCGTGAGCTCA
	vL DNA sequence (SEQ ID NO: 361)	GAAATAGTGATGACGCAGTCTCCAGCCACCCTGTCTGTTTCT CCAGGAGAAAGAGCCACCCTCTCCTGCAGGGCCAGTGAGAG TGTTAGCAGTAATGTAGCCTGGTACCAGCAGAGACCTGGCC AGGCACCCAGGCTCCTCATCTACGGGGCATCCAACCGGGCC ACTGGCATCCAGCCAGGTTTCAGTGGCAGTGGGTCTGGGAC AGACTTCACTCTCACCATCAGCAGACTGGAGCCTGAAGATT

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		TTGCAGTGTACTACTGCGGCCAGAGCTATAGCTATCCATTTA CCTTTGGCCAGGGCACCAAGCTTGAAATTAAG
	HC full sequence (SEQ ID NO: 362)	QVQLVESGGGLVQPGGSLRLSCAASGFSLSYGVVDWVRQAPG KGLEWVGVWGGGGTYIYASSVMARFTISRDNKNTLYLQMNS LRAEDTAVYYCAKHAYGHDGGFAMDYWGQGLTVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNT KVDKRVPEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
	LC full sequence (SEQ ID NO: 363)	EIVMTQSPATLSVSPGERATLSCRASESVSSNVAWYQQRPGQA PRLLIYGASNRTGIPARFSGSGSGTDFTLTISRLEPEDFAVYYC GQSYSPFTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVV CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
	HC DNA sequence (SEQ ID NO: 364)	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCC TGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCTC CCTCAGCAGCTATGGTGTGGACTGGGTTCGCCAGGCTCCAG GAAAGGGTCTGGAGTGGGTGGGAGTTATATGGGGTGGTGGA GGCACATATTATGCTTCTTCTGTTCATGGCCAGATTACCATC TCCAGAGACAATTCCAAGAACACGCTGTATCTGCAATGAA CAGCCTGAGAGCTGAGGACACGGCCGTGTATTACTGCGCCA AACATGCCTATGGCCATGATGGCGGCTTGTCTATGGATTATT GGGGCCAGGGTACCCTTGTGACCGTGAGCTCAGCTAGCACC AAGGGCCCCAGCGTGTTCCCCCTGGCCCCAGCAGCAAGAG CACCAGCGGCGGCACAGCCGCCCTGGGCTGCCTGGTGAAGG ACTACTTCCCCGAGCCCGTGACCGTGTCTGGAACAGCGGA GCCCTGACCTCCGCGGTGCACACCTTCCCCGCCGTGTGTCAG AGCAGCGGCCTGTACAGCCTGTCCAGCGTGGTGACAGTGCC CAGCAGCAGCCTGGGCACCCAGACCTACATCTGCAACGTGA ACCAACAGCCCAAGACCAAGCCCAAGAGAGGAGCAGTACAACAG GCCCAAGAGCTGCGACAAGACCCACACCTGCCCCCCTGCC CAGCCCCAGAGCTGCTGGGCGGACCCTCCGTGTTCTCTGTTCC CCCCCAAGCCCAAGGACACCCCTGATGATCAGCAGGACCCCC GAGGTGACCTGCGTGGTGGTGGACGTGAGCCACGAGGACCC AGAGGTGAAGTTCAACTGGTACGTGGACGGCGTGAGGTGC ACAACGCCAAGACCAAGCCCAAGAGAGGAGCAGTACAACAG CACCTACAGGGTGGTGTCCGTGCTGACCGTGTGTCACCAGG ACTGGCTGAACGGCAAGGAATACAAGTGCAAGGTCTCCAAC AAGGCCCTGCCAGCCCCCATCGAAAAGACCATCAGCAAGGC CAAGGGCCAGCCACGGGAGCCCCAGGTGTACACCCCTGCCCC CCTCCCGGGAGGAGATGACCAAGAACCAGGTGTCCCTGACC TGTCTGGTGAAGGGCTTCTACCCCAAGCGACATCGCCGTGGA GTGGGAGAGCAACGGCCAGCCCGAGAACAACACTACAAGACC ACCCCCCAGTGCTGGACAGCGACGGCAGCTTCTTCTCTGTA CAGCAAGCTGACCGTGGACAAGTCCAGGTGGCAGCAGGGC AACGTGTTCACTGTCAGCGTGATGCACGAGGCCCTGCACAA CCTACTACCCAGAAGAGCCTGAGCCTGTCCCCCGGCAAG
	LC DNA sequence	GAAATAGTGATGACGCAGTCTCCAGCCACCCTGTCTGTTTCT CCAGGAGAAAGAGCCACCCTCTCCTGCAGGGCCAGTGAGAG

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	(SEQ ID NO: 365)	TGTTAGCAGTAATGTAGCCTGGTACCAGCAGAGACCTGGCC AGGCACCCAGGCTCCTCATCTACGGGGCATCCAACCGGGCC ACTGGCATCCCAGCCAGGTTCACTGGCAGTGGGTCTGGGAC AGACTTCACTCTCACCATCAGCAGACTGGAGCCTGAAGATT TTGCAGTGTACTACTGCGGCCAGAGCTATAGCTATCCATTTA CCTTTGGCCAGGGCACCAAGCTTGAAATTAAGCGTACGGTG GCCGCTCCCAGCGTGTTTCATCTTCCCCCCCAGCGACGAGCA GCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCTGCTGAACA ACTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGAC AACGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTCACCG AGCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGACC CTGACCCTGAGCAAGGCCGACTACGAGAAGCATAAGGTGTA CGCCTGCGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGA CCAAGAGCTTCAACAGGGGCGAGTGC
GITR.MAB3	LCDR1 (Kabat) (SEQ ID NO: 366)	RASQSVSSNLA
	LCDR2 (Kabat) (SEQ ID NO: 367)	GASNRAT
	LCDR3 (SEQ ID NO: 368)	GQSYSYPFT
	HCDR1 (Kabat) (SEQ ID NO: 369)	SYGVD
	HCDR2 (Kabat) (SEQ ID NO: 370)	VIWGGGGTYYTASLMG
	HCDR3 (Kabat) (SEQ ID NO: 371)	HAYGHDGGFAMDY
	vH full sequence (SEQ ID NO: 372)	QVQLVESGGGLVQPGGSLRLSCAASGFSLSYGV DWVRQAPG KGLEWLGVIWGGGGTYYTASLMGRFTISRDN SKNTLYLQMNS LRAEDTAVYYCAKHAYGHDGGFAMDYWGQGLVTVSS
	vL full sequence (SEQ ID NO: 373)	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQA PRLLIYGASNRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC GQSYSYPFTFGQGTKLEIK
	vH DNA sequence (SEQ ID NO: 374)	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCC TGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCTC CCTCAGCAGCTATGGTGTGGACTGGGTTCGCCAGGCTCCAG GAAAGGGTCTGGAGTGGCTGGGAGTTATATGGGGTGGTGGGA GGCACATATTATACTGCTTCTCTCATGGGCAGATTCCACATC TCCAGAGACAAATCCAAGAACACGCTGTATCTGCAAAATGAA CAGCCTGAGAGCTGAGGACACGGCCGTGTATTACTGCGCCA AACATGCCTATGGCCATGATGGCGGCTTGTGATTGGATTATT GGGGCCAGGGTACCCTTGTGACCGTGAGCTCA

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	vL DNA sequence (SEQ ID NO: 375)	GAAATAGTGATGACGCAGTCTCCAGCCACCCTGTCTGTGTCT CCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAG TGTTAGCAGCAACTTAGCCTGGTACCAGCAGAAACCTGGCC AGGCTCCCAGGCTCCTCATCTACGGGGCATCCAACCGGGCC ACTGGCATCCCAGACAGGTTCACTGGCAGTGGGTCTGGGAC AGACTTCACTCTCACCATCAGCAGACTGGAGCCTGAAGATT TTGCAGTTTACTACTGCGGCCAGAGCTATAGCTATCCATTTA CCTTTGGCCAGGGCACCAAGCTTGAAATTTAA
	HC full sequence (SEQ ID NO: 376)	QVQLVESGGGLVQPGGSLRLSCAASGFSLSYGVDFWVRQAPG KGLEWLGVIWGGGGTYTASLMGRFTISRDNKNTLYLQMNS LRAEDTAVYYCAKHAYGHDGGFAMDYWGQGLVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNT KVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
	LC full sequence (SEQ ID NO: 377)	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQA PRLLIYGASNRTGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC GQSYSPFTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVV CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSTSL SSTLTLSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC
	HC DNA sequence (SEQ ID NO: 378)	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCC TGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCTC CCTCAGCAGCTATGGTGTGGACTGGGTTCGCCAGGCTCCAG GAAAGGGTCTGGAGTGGCTGGGAGTTATATGGGTGGTGA GGCACATATTATACTGCTTCTCTCATGGGCAGATTCACCATC TCCAGAGACAATTCCAAGAACACGCTGTATCTGCAATGAA CAGCCTGAGAGCTGAGGACACGGCCGTGTATTACTGCGCCA AACATGCCTATGGCCATGATGGCGGCTTTGCTATGGATTATT GGGGCCAGGGTACCCTTGTGACCGTGAGCTCAGCTAGCACC AAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAG CACCAGCGGCGGCACAGCCGCCCTGGGCTGCCTGGTGAAGG ACTACTTCCCCGAGCCCGTGACCGTGTCTGGAACAGCGGA GCCCTGACCTCCGGCGTGCACACCTTCCCCCGCGTGCTGCAG AGCAGCGGCCTGTACAGCCTGTCCAGCGTGGTGACAGTGCC CAGCAGCAGCCTGGGCACCCAGACCTACATCTGCAACGTGA ACCACAAGCCAGCAACACCAAGGTGGACAAGAGAGTGGGA GCCCAAGAGCTGCGACAAGACCCACACCTGCCCCCCTGCC CAGCCCCAGAGCTGCTGGGCGGACCCTCCGTGTTCTGTTCC CCCCCAAGCCCAAGGACACCCTGATGATCAGCAGGACCCCC GAGGTGACCTGCGTGGTGGTGGACGTGAGCCACGAGGACCC AGAGGTGAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGC ACAACGCCAAGACCAAGCCCAGAGAGGAGCAGTACAACAG CACCTACAGGGTGGTGTCCGTGCTGACCGTGTGACACAGG ACTGGCTGAACGGCAAGGAATACAAGTGCAAGGTCTCCAAC AAGGCCCTGCCAGCCCCCATCGAAAAGACCATCAGCAAGGC CAAGGGCCAGCCACGGGAGCCCCAGGTGTACACCCTGCCCC CCTCCCGGAGGAGATGACCAAGAACCAGGTGTCCCTGACC TGTCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGA GTGGGAGAGCAACGGCCAGCCCGAGAACAACACTACAAGACC

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		ACCCCCCCAGTGCTGGACAGCGACGGCAGCTTCTTCCTGTA CAGCAAGCTGACCGTGGACAAGTCCAGGTGGCAGCAGGGC AACGTGTTTCAGCTGCAGCGTGATGCACGAGGCCCTGCACAA CCACTACACCCAGAAGAGCCTGAGCCTGTCCCCCGGCAAG GAAATAGTGATGACGCAGTCTCCAGCCACCCTGTCTGTGTCT CCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAG TGTTAGCAGCAACTTAGCCTGGTACCAGCAGAAACCTGGCC AGGCTCCCAGGCTCCTCATCTACGGGGCATCCAACCGGGCC ACTGGCATCCCAGACAGGTTCACTGGCAGTGGGTCTGGGAC AGACTTCACTCTCACCATCAGCAGACTGGAGCCTGAAGATT TTGCAGTTTACTACTGCGGCCAGAGCTATAGCTATCCATTTA CCTTTGGCCAGGGCACCAAGCTTGAAATTAAACGTACGGTG GCCGCTCCCAGCGTGTTTCATCTTCCCCCCCAGCGACGAGCA GCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCTGCTGAACA ACTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGAC AACGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTCACCG AGCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCACC CTGACCCTGAGCAAGGCCGACTACGAGAAGCATAAGGTGTA CGCCTGCGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGA CCAAGAGCTTCAACAGGGGCGAGTGC
GITR.MAB4	LC DNA sequence (SEQ ID NO: 379)	
	LCDR1 (Kabat) (SEQ ID NO: 380)	RASESVSSNVA
	LCDR2 (Kabat) (SEQ ID NO: 381)	GASNRAT
	LCDR3 (SEQ ID NO: 382)	GQSYSYPFT
	HCDR1 (Kabat) (SEQ ID NO: 383)	SYGVD
	HCDR2 (Kabat) (SEQ ID NO: 384)	VIWGGGGTYYASSLMG
	HCDR3 (Kabat) (SEQ ID NO: 385)	HAYGHDGGFAMDY
	vH full sequence (SEQ ID NO: 386)	EVQLVESGGGLVQSGGSLRLSCAASGFSLSYGVDFWVRQAPG KGLEWVGVWGGGGTYYASSLMGRFTISRDN SKNTLYLQMNS LRAEDTAVYYCAKHAYGHDGGFAMDYWGQGLVTVSS
	vL full sequence (SEQ ID NO: 387)	EIVMTQSPATLSVSPGERATLSCRASESVSSNVAWYQQRPGQA PRLLIYGASNRATGIPARFSGSGTDFTLTISRLEPEDFAVYYC GQSYSYPFTFGQGTKLEIK
	vH DNA sequence (SEQ ID	GAGGTGCAGCTGGTGGAGTCCGGGGGAGGCTTAGTTCAGTC TGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCTC CCTCAGCAGCTATGGTGTGGACTGGGTTCGCCAGGCTCCAG

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	NO: 388)	GAAAGGGTCTGGAGTGGGTGGGAGTTATATGGGGTGGTGGAGGCACATATTATGCTTCTTCTCTCATGGGCAGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAAATGAACAGCCTGAGAGCTGAGGACACGGCCGTGTATTACTGCGCCAACATGCCTATGGCCATGATGGCGGCTTTGCTATGGATTATTGGGGCCAGGGTACCCTTGTGACCGTGAGCTCA
	vL DNA sequence (SEQ ID NO: 389)	GAAATAGTGATGACGCAGTCTCCAGCCACCCTGTCTGTTTCTCCAGGAGAAAGAGCCACCCTCTCCTGCAGGGCCAGTGAGAGTGTTAGCAGTAATGTAGCCTGGTACCAGCAGAGACCTGGCCAGGCACCCAGGCTCCTCATCTACGGGGCATCCAACCGGGCCACTGGCATCCCAGCCAGGTTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGCAGACTGGAGCCTGAAGATTTGACAGTGTACTACTGCGGCCAGAGCTATAGCTATCCATTATCCTTTGGCCAGGGCACCAAGCTTGAAATTAAG
	HC full sequence (SEQ ID NO: 390)	EVQLVESGGGLVQSGGSLRLSCAASGFSLSYGVDWVRQAPGKGLEWVGVWGGGGTYTASSLMGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKHAYGHDGGFAMDYWGQGLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
	LC full sequence (SEQ ID NO: 391)	EIVMTQSPATLSVSPGERATLSCRASESVSSNVAWYQQRPGQAPRLLIYGASNRTGIPARFSGSGSGTDFTLTISRLEPEDFAVYYC GQSYSPFTFGQGTKLEIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYLS SSSLTSLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
	HC DNA sequence (SEQ ID NO: 392)	GAGGTGCAGCTGGTGGAGTCCGGGGGAGGCTTAGTTTCAGTCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCTCCTCAGCAGCTATGGTGTGGACTGGGTTCGCCAGGCTCCAGGAAAGGGTCTGGAGTGGGTGGGAGTTATATGGGGTGGTGGAGGCACATATTATGCTTCTTCTCTCATGGGCAGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAAATGAACAGCCTGAGAGCTGAGGACACGGCCGTGTATTACTGCGCCAACATGCCTATGGCCATGATGGCGGCTTTGCTATGGATTATTGGGGCCAGGGTACCCTTGTGACCGTGAGCTCAGCTAGCACC AAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCCCGTGACCGTGTCTGGAACAGCGGAGCCCTGACCTCCGGCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGTCCAGCGTGGTGACAGTGCC CAGCAGCAGCCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTGGA GCCCAAGAGCTGCGACAAGACCCACACCTGCCCCCTGCC CAGCCCCAGAGCTGCTGGGCGGACCCTCCGTGTTCTCTGTTCC CCCCCAAGCCCAAGGACACCCTGATGATCAGCAGGACCCCC GAGGTGACCTGCGTGGTGGTGGACGTGAGCCACGAGGACCC AGAGGTGAAGTTCAACTGGTACGTGGACGGCGTGAGGTGC ACAACGCCAAGACCAAGCCCAGAGAGGAGCAGTACAACAG CACCTACAGGGTGGTGTCCGTGCTGACCGTGCTGCACCAAG ACTGGCTGAACGGCAAGGAATACAAGTGCAAGGTCTCCAAC

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		AAGGCCCTGCCAGCCCCCATCGAAAAGACCATCAGCAAGGC CAAGGGCCAGCCACGGGAGCCCCAGGTGTACACCCTGCCCC CCTCCCGGGAGGAGATGACCAAGAACCAGGTGTCCCTGACC TGTCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGA GTGGGAGAGCAACGGCCAGCCCGAGAACAACACTACAAGACC ACCCCCCAGTGCTGGACAGCGACGGCAGCTTCTTCTGTGA CAGCAAGCTGACCGTGGACAAGTCCAGGTGGCAGCAGGGC AACGTGTTTACGCTGCAGCGTGATGCACGAGGCCCTGCACAA CCACTACACCCAGAAGAGCCTGAGCCTGTCCCCCGGCAAG
	LC DNA sequence (SEQ ID NO: 393)	GAAATAGTGATGACGCAGTCTCCAGCCACCCTGTCTGTTTCT CCAGGAGAAAAGAGCCACCCTCTCCTGCAGGGCCAGTGAGAG TGTTAGCAGTAATGTAGCCTGGTACCAGCAGAGACCTGGCC AGGCACCCAGGCTCCTCATCTACGGGGCATCCAACCGGGCC ACTGGCATCCCAGCCAGGTTTCACTGGCAGTGCGGTCTGGGAC AGACTTCACTCTCACCATCAGCAGACTGGAGCCTGAAGATT TTGCAGTGTACTACTGCGGCCAGAGCTATAGCTATCCATTTA CCTTTGGCCAGGGCACCAAGCTTGAAATTAAGCGTACGGTG GCCGCTCCCAGCGTGTTTCATCTTCCCCCCCAGCGACGAGCA GCTGAAGAGCGGCACCGCCAGCGTGCGTGTGCCTGCTGAACA ACTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGAC AACGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTCACCG AGCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCACC CTGACCCTGAGCAAGGCCGACTACGAGAAGCATAAAGGTGTA CGCCTGCGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGA CCAAGAGCTTCAACAGGGGCGAGTGC
<u>GITR.MAB5</u>	LCDR1 (Kabat) (SEQ ID NO: 394)	RASESVSSNVA
	LCDR2 (Kabat) (SEQ ID NO: 395)	GASNRAT
	LCDR3 (Kabat) (SEQ ID NO: 396)	GQSYSYPFT
	HCDR1 (Kabat) (SEQ ID NO: 397)	SYGVD
	HCDR2 (Kabat) (SEQ ID NO: 398)	VIWGGGGTYTSSLMG
	HCDR3 (Kabat) (SEQ ID NO: 399)	HAYGHDGGFAMDY
	vH full sequence (SEQ ID NO: 400)	EVQLVESGGGLVQSGGSLRLSCAASGFSLSYGVDFWVRQAPG KGLEWLGVIWGGGGTYTSSLMGRFTISRDNKNTLYLQMNS LRAEDTAVYYCAKHAYGHDGGFAMDYWGQGLVTVSS
	vL full	EIVMTQSPATLSVSPGERATLSCRASESVSSNVAWYQQRPGQA

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	sequence (SEQ ID NO: 401)	PRLLIYGASN RATGIPARFSGSGSGTDFLTISRLEPEDFAVYYC GQSYSPFTFGQGTKLEIK
	vH DNA sequence (SEQ ID NO: 402)	GAGGTGCAGCTGGTGGAGTCCGGGGGAGGCTTAGTTCAGTC TGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCTC CCTCAGCAGCTATGGTGTGGACTGGGTTCGCCAGGCTCCAG GAAAGGGTCTGGAGTGGCTGGGAGTTATATGGGGTGGTGGGA GGCACATATTATACTTCTTCTCTCATGGGCAGATTACCATC TCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAAATGAA CAGCCTGAGAGCTGAGGACACGGCCGTGTATTACTGCGCCA AACATGCCTATGGCCATGATGGCGGCTTTGCTATGGATTATT GGGGCCAGGGTACCCTTGTGACCGTGAGCTCA
	vL DNA sequence (SEQ ID NO: 403)	GAAATAGTGATGACGCAGTCTCCAGCCACCCTGTCTGTTTCT CCAGGAGAAAGAGCCACCCTCTCCTGCAGGGCCAGTGAGAG TGTTAGCAGTAATGTAGCCTGGTACCAGCAGAGACCTGGCC AGGCACCCAGGCTCCTCATCTACGGGGCATCCAACCGGGCC ACTGGCATCCCAGCCAGGTTTCAGTGGCAGTGGGTCTGGGAC AGACTTCACTCTACCATCAGCAGACTGGAGCCTGAAGATT TTGCAGTGTACTACTGCGGCCAGAGCTATAGCTATCCATTTA CCTTTGGCCAGGGCACCAAGCTTGAAATTAAG
	HC full sequence (SEQ ID NO: 404)	EVQLVESGGGLVQSGGSLRLSCAASGFSLSYGVVDWVRQAPG KGLEWLGVIWGGGTYTSSLMGRFTISRDN SKNTLYLQMNS LRAEDTAVYYCAKHAYGHDGGFAMDYWGQGLVTVVSSASTK GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNT KVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
	LC full sequence (SEQ ID NO: 405)	EIVMTQSPATLSVSPGERATLSCRASESVSSNVAWYQQRPGQA PRLLIYGASN RATGIPARFSGSGSGTDFLTISRLEPEDFAVYYC GQSYSPFTFGQGTKLEIKRTVAAPS VFIFPPSDEQLKSGTASVV CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
	HC DNA sequence (SEQ ID NO: 406)	GAGGTGCAGCTGGTGGAGTCCGGGGGAGGCTTAGTTCAGTC TGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCTC CCTCAGCAGCTATGGTGTGGACTGGGTTCGCCAGGCTCCAG GAAAGGGTCTGGAGTGGCTGGGAGTTATATGGGGTGGTGGGA GGCACATATTATACTTCTTCTCTCATGGGCAGATTACCATC TCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAAATGAA CAGCCTGAGAGCTGAGGACACGGCCGTGTATTACTGCGCCA AACATGCCTATGGCCATGATGGCGGCTTTGCTATGGATTATT GGGGCCAGGGTACCCTTGTGACCGTGAGCTCAGCTAGCACC AAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAG CACCAGCGGCGGCACAGCCGCCCTGGGCTGCCTGGTGAAGG ACTACTTCCCCGAGCCCCGTGACCGTGTCTGGAACAGCGGA GCCCTGACCTCCGCGCTGCACACCTTCCCCGCCGTGCTGCAG AGCAGCGGCCTGTACAGCCTGTCCAGCGTGGTGACAGTGCC CAGCAGCAGCCTGGGCACCCAGACCTACATCTGCAACGTGA ACCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTGGA GCCCAAGAGCTGCGACAAGACCCACACCTGCCCCCTGCC CAGCCCCAGAGCTGCTGGGCGGACCCTCCGTGTTCTCTGTTCC

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		CCCCCAAGCCCAAGGACACCCTGATGATCAGCAGGACCCCC GAGGTGACCTGCGTGGTGGTGGACGTGAGCCACGAGGACCC AGAGGTGAAGTTCAACTGGTACGTGGACGGCGTGAGGTGC ACAACGCCAAGACCAAGCCCAGAGAGGAGCAGTACAACAG CACCTACAGGGTGGTGTCCGTGCTGACCGTGCTGCACCAAG ACTGGCTGAACGGCAAGGAATACAAGTGCAAGGTCTCCAAC AAGGCCCTGCCAGCCCCCATCGAAAAGACCATCAGCAAGGC CAAGGGCCAGCCACGGGAGCCCCAGGTGTACACCCTGCCCC CCTCCCGGGAGGAGATGACCAAGAACCAGGTGTCCCTGACC TGTCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGA GTGGGAGAGCAACGGCCAGCCCCAGAACAACTACAAGACC ACCCCCCCAGTGCTGGACAGCGACGGCAGCTTCTTCTGTGA CAGCAAGCTGACCGTGGACAAGTCCAGGTGGCAGCAGGGC AACGTGTTTCAGCTGCAGCGTGATGCACGAGGCCCTGCACAA CCACTACACCCAGAAGAGCCTGAGCCTGTCCCCCGGCAAG
	LC DNA sequence (SEQ ID NO: 407)	GAAATAGTGATGACGCAGTCTCCAGCCACCCTGTCTGTTTCT CCAGGAGAAAGAGCCACCCTCTCCTGCAGGGCCAGTGAGAG TGTTAGCAGTAATGTAGCCTGGTACCAGCAGAGACCTGGCC AGGCACCCAGGCTCCTCATCTACGGGGCATCCAACCGGGCC ACTGGCATCCCAGCCAGGTTTCAGTGGCAGTGGGTCTGGGAC AGACTTCACTCTCACCATCAGCAGACTGGAGCCTGAAGATT TTGCAGTGTACTACTGCGGCCAGAGCTATAGCTATCCATTTA CCTTTGGCCAGGGCACCAAGCTTGAAATTAAGCGTACGGTG GCCGCTCCCAGCGTGTTTCATCTTCCCCCCCAGCGACGAGCA GCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCTGCTGAACA ACTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGAC AACGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTCACCG AGCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCACC CTGACCCTGAGCAAGGCCGACTACGAGAAGCATAAGGTGTA CGCCTGCGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGA CCAAGAGCTTCAACAGGGGCGAGTGC
<u>GITR.MAB6</u>	LCDR1 (Kabat) (SEQ ID NO: 408)	RASESVSSNVA
	LCDR2 (Kabat) (SEQ ID NO: 409)	GASNRAT
	LCDR3 (Kabat) (SEQ ID NO: 410)	GQSYSYPFT
	HCDR1 (Kabat) (SEQ ID NO: 411)	SYGVD
	HCDR2 (Kabat) (SEQ ID NO: 412)	VIWGGGGTYTSSLMA
	HCDR3 (Kabat) (SEQ ID	HAYGHDGGFAMDY

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	NO: 413)	
	vH full sequence (SEQ ID NO: 414)	EVQLVESGGGLVQSGGSLRLSCAASGFSLSYGVVDWVRQAPG KGLEWLGVIWGGGGTYYTSSLMARFTISRDN SKNTLYLQMN S LRAEDTAVYYCAKHAYGHDGGFAMDYWGQGLVTVSS
	vL full sequence (SEQ ID NO: 415)	EIVMTQSPATLSVSPGERATLSCRASESVSSNVAWYQORPGQA PRLLIYGASNRTGIPARFSGSGSGTDFTLTISRLEPEDFAVYYC GQSYSPFTFGQGTKLEIK
	vH DNA sequence (SEQ ID NO: 416)	GAGGTGCAGCTGGTGGAGTCCGGGGGAGGCTTAGTTCAGTC TGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCTC CCTCAGCAGCTATGGTGTGGACTGGGTTCGCCAGGCTCCAG GAAAGGGTCTGGAGTGGCTGGGAGTTATATGGGGTGGTGGA GGCACATATTATACTTCTTCTCTCATGGCCAGATTACCATC TCCAGAGACAATTCCAAGAACACGCTGTATCTGCAATGAA CAGCCTGAGAGCTGAGGACACGGCCGTGTATTACTGCGCCA AACATGCCTATGGCCATGATGGCGGCTTTGCTATGGATTATT GGGGCCAGGGTACCCTTGTGACCGTGAGCTCA
	vL DNA sequence (SEQ ID NO: 417)	GAAATAGTGATGACGCAGTCTCCAGCCACCCTGTCTGTTTCT CCAGGAGAAAGAGCCACCCTCTCCTGCAGGGCCAGTGAGAG TGTTAGCAGTAATGTAGCCTGGTACCAGCAGAGACCTGGCC AGGCACCCAGGCTCCTCATCTACGGGGCATCCAACCGGGCC ACTGGCATCCCAGCCAGGTTCACTGGCAGTGGGTCTGGGAC AGACTTCACCTCTACCATCAGCAGACTGGAGCCTGAAGATT TTGCAGTGTACTACTGCGGCCAGAGCTATAGCTATCCATTTA CCTTTGGCCAGGGCACCAAGCTTGAAATTAAG
	HC full sequence (SEQ ID NO: 418)	EVQLVESGGGLVQSGGSLRLSCAASGFSLSYGVVDWVRQAPG KGLEWLGVIWGGGGTYYTSSLMARFTISRDN SKNTLYLQMN S LRAEDTAVYYCAKHAYGHDGGFAMDYWGQGLVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNT KVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPETCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTTPVLDSDGSEFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
	LC full sequence (SEQ ID NO: 419)	EIVMTQSPATLSVSPGERATLSCRASESVSSNVAWYQORPGQA PRLLIYGASNRTGIPARFSGSGSGTDFTLTISRLEPEDFAVYYC GQSYSPFTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVV CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSTSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
	HC DNA sequence (SEQ ID NO: 420)	GAGGTGCAGCTGGTGGAGTCCGGGGGAGGCTTAGTTCAGTC TGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCTC CCTCAGCAGCTATGGTGTGGACTGGGTTCGCCAGGCTCCAG GAAAGGGTCTGGAGTGGCTGGGAGTTATATGGGGTGGTGGA GGCACATATTATACTTCTTCTCTCATGGCCAGATTACCATC TCCAGAGACAATTCCAAGAACACGCTGTATCTGCAATGAA CAGCCTGAGAGCTGAGGACACGGCCGTGTATTACTGCGCCA AACATGCCTATGGCCATGATGGCGGCTTTGCTATGGATTATT GGGGCCAGGGTACCCTTGTGACCGTGAGCTCAGCTAGCACC AAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAG CACCAGCGCGGCACAGCCGCCCTGGGCTGCCTGGTGAAGG ACTACTTCCCCAGCCCCGTGACCGTGTCTGGAACAGCGGA

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		GCCCTGACCTCCGGCGTGACACACCTTCCCCGCCGTGCTGCAG AGCAGCGGCCTGTACAGCCTGTCCAGCGTGGTGACAGTGCC CAGCAGCAGCCTGGGCACCCAGACCTACATCTGCAACGTGA ACCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTGGA GCCCAAGAGCTGCGACAAGACCCACACCTGCCCCCCTGCC CAGCCCCAGAGCTGCTGGGCGGACCCTCCGTGTTCTGTTCC CCCCCAAGCCCAAGGACACCCTGATGATCAGCAGGACCCCC GAGGTGACCTGCGTGGTGGTGGACGTGAGCCACGAGGACCC AGAGGTGAAGTTCAACTGGTACGTGGACGGCGTGAGGTGC ACAACGCCAAGACCAAGCCCAGAGAGGAGCAGTACAACAG CACCTACAGGGTGGTGTCCGTGCTGACCGTGTGCACCAGG ACTGGCTGAACGGCAAGGAATACAAGTGCAAGGTCTCCAAC AAGGCCCTGCCAGCCCCATCGAAAAGACCATCAGCAAGGC CAAGGGCCAGCCACGGGAGCCCCAGGTGTACACCCTGCCCC CCTCCCGGGAGGAGATGACCAAGAACCAGGTGTCCCTGACC TGTCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGA GTGGGAGAGCAACGGCCAGCCCCAGAACAACTACAAGACC ACCCCCCCAGTGCTGGACAGCGACGGCAGCTTCTTCTGTGA CAGCAAGCTGACCGTGGACAAGTCCAGGTGGCAGCAGGGC AACGTGTTCACTGTCAGCGTGATGCACGAGGCCCTGCACAA CCACTACACCCAGAAGAGCCTGAGCCTGTCCCCCGGCAAG GAAATAGTGATGACGCAGTCTCCAGCCACCCTGTCTGTTTCT CCAGGAGAAAGAGCCACCCTCTCCTGCAGGGCCAGTGAGAG TGTTAGCAGTAATGTAGCCTGGTACCAGCAGAGACCTGGCC AGGCACCCAGGCTCCTCATCTACGGGGCATCCAACCGGGCC ACTGGCATCCCAGCCAGGTTCACTGGCAGTGGGTCTGGGAC AGACTTCACTCTCACCATCAGCAGACTGGAGCCTGAAGATT TTGCAGTGTACTACTGCGGCCAGAGCTATAGCTATCCATTTA CCTTTGGCCAGGGCACCAAGCTTGAAATTAAGCGTACGGTG GCCGCTCCCAGCGTGTTTCATCTTCCCCCCCAGCGACGAGCA GCTGAAGAGCGGCACCGCCAGCGTGGTGTGCTGCTGAACA ACTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGAC AACGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTCACCG AGCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCACC CTGACCCTGAGCAAGGCCGACTACGAGAAGCATAAGGTGTA CGCCTGCGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGA CCAAGAGCTTCAACAGGGGCGAGTGC
	LC DNA sequence (SEQ ID NO: 421)	GAAATAGTGATGACGCAGTCTCCAGCCACCCTGTCTGTTTCT CCAGGAGAAAGAGCCACCCTCTCCTGCAGGGCCAGTGAGAG TGTTAGCAGTAATGTAGCCTGGTACCAGCAGAGACCTGGCC AGGCACCCAGGCTCCTCATCTACGGGGCATCCAACCGGGCC ACTGGCATCCCAGCCAGGTTCACTGGCAGTGGGTCTGGGAC AGACTTCACTCTCACCATCAGCAGACTGGAGCCTGAAGATT TTGCAGTGTACTACTGCGGCCAGAGCTATAGCTATCCATTTA CCTTTGGCCAGGGCACCAAGCTTGAAATTAAGCGTACGGTG GCCGCTCCCAGCGTGTTTCATCTTCCCCCCCAGCGACGAGCA GCTGAAGAGCGGCACCGCCAGCGTGGTGTGCTGCTGAACA ACTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGAC AACGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTCACCG AGCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCACC CTGACCCTGAGCAAGGCCGACTACGAGAAGCATAAGGTGTA CGCCTGCGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGA CCAAGAGCTTCAACAGGGGCGAGTGC
<u>GITR.MAB7</u>	LCDR1 (Kabat) (SEQ ID NO: 422)	RASESVSSNVA
	LCDR2 (Kabat) (SEQ ID NO: 423)	GASNRAT
	LCDR3 (Kabat) (SEQ ID NO: 424)	GQSYSYPFT
	HCDR1 (Kabat) (SEQ ID NO: 425)	SYGVD
	HCDR2	VIWGGGGTYYASSLMG

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	(Kabat) (SEQ ID NO: 426)	
	HCDR3 (Kabat) (SEQ ID NO: 427)	HAYGHDGGFAMDY
	vH full sequence (SEQ ID NO: 428)	EVQLVESGGGLVQSGGSLRLSCAASGFSLSYGV DWVRQAPG KGLEWVGVWGGGGTY YASSLMGRFTISRDN SKNTLYLQMNS LRAEDTAVYYCARHAYGHDGGFAMDYWGQGLTVTVSS
	vL full sequence (SEQ ID NO: 429)	EIVMTQSPATLSVSPGERATLSCRASESVSSNVAWYQORPGQA PRLLIYGASN RATGIPARFSGSGSGTDFTLTISRLEPEDFAVYYC GQSYSPFTFGQGTKLEIK
	vH DNA sequence (SEQ ID NO: 430)	GAGGTGCAGCTGGTGAATCTGGCGGCGGACTGGTGCAGTC CGGCGGCTCTCTGAGACTGTCTTGCCTGCCTCCGGCTTCTC CCTGTCCTCTTACGGCGTGGACTGGGTGCGACAGGCCCTG GCAAGGGCCTGGAATGGGTGGGAGTGATCTGGGGCGGAGG CGGCACCTACTACGCCTCTTCCCTGATGGGCCGTTACCAT CTCCCGGGACA ACTCCAAGAACACCCTGTACCTGCAGATGA ACTCCCTGCGGGCCGAGGACACCGCCGTGTACTACTGCGCC AGACACGCCTACGGCCACGACGGCGGCTTCGCCATGGATTA TTGGGGCCAGGGCACCTGGTGACAGTGTCCTCC
	vL DNA sequence (SEQ ID NO: 431)	GAGATCGTGATGACCCAGTCCCCCGCCACCCTGTCTGTGTCT CCCGGCGAGAGAGCCACCCTGAGCTGCAGAGCCTCCGAGTC CGTGTCTCTCAACGTGGCCTGGTATCAGCAGAGACCTGGTC AGGCCCCCTCGGCTGCTGATCTACGGCGCCTCTAACCGGGCC ACCGGCATCCCTGCCAGATTCTCCGGCTCCGGCAGCGGCAC CGACTTCACCTTGACCATCTCCCGGCTGGAACCCGAGGACT TCGCCGTGTACTACTGCGGCCAGTCTACTCATACCCCTTCA CCTTCGGCCAGGGCACCAAGCTGGAAATCAAG
	HC full sequence (SEQ ID NO: 432)	EVQLVESGGGLVQSGGSLRLSCAASGFSLSYGV DWVRQAPG KGLEWVGVWGGGGTY YASSLMGRFTISRDN SKNTLYLQMNS LRAEDTAVYYCARHAYGHDGGFAMDYWGQGLTVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTS GVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNT KVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
	LC full sequence (SEQ ID NO: 433)	EIVMTQSPATLSVSPGERATLSCRASESVSSNVAWYQORPGQA PRLLIYGASN RATGIPARFSGSGSGTDFTLTISRLEPEDFAVYYC GQSYSPFTFGQGTKLEIKRTVAAPS VFIFPPSDEQLKSGTASVV CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
	HC DNA sequence (SEQ ID NO: 434)	GAGGTGCAGCTGGTGAATCTGGCGGCGGACTGGTGCAGTC CGGCGGCTCTCTGAGACTGTCTTGCCTGCCTCCGGCTTCTC CCTGTCCTCTTACGGCGTGGACTGGGTGCGACAGGCCCTG GCAAGGGCCTGGAATGGGTGGGAGTGATCTGGGGCGGAGG CGGCACCTACTACGCCTCTTCCCTGATGGGCCGTTACCAT CTCCCGGGACA ACTCCAAGAACACCCTGTACCTGCAGATGA

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		<p>ACTCCCTGCGGGCCGAGGACACCGCCGTGTACTACTGCGCC AGACACGCCTACGGCCACGACGGCGGCTTCGCCATGGATTA TTGGGGCCAGGGCACCTGGTGACAGTGTCTCCGCTAGCA CCAAGGGCCCAAGTGTGTTTCCCCTGGCCCCCAGCAGCAAG TCTACTTCCGGCGGAACTGCTGCCCTGGGTTGCCTGGTGAAG GACTACTTCCCCGAGCCCGTGACAGTGTCTGGAACCTCTGG GGCTCTGACTTCCGGCGTGACACCTTCCCCGCCGTGCTGCA GAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACAGTGC CCTCCAGCTCTCTGGGAACCCAGACCTATATCTGCAACGTG AACCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTGG AGCCCAAGAGCTGCGACAAGACCCACACCTGCCCCCCTGC CCAGCTCCAGAACTGCTGGGAGGGCCTTCCGTGTTCTGTTC CCCCCAAGCCCAAGGACACCTGATGATCAGCAGGACCCC CGAGGTGACCTGCGTGGTGGTGGACGTGTCCACGAGGACC CAGAGGTGAAGTTCAACTGGTACGTGGACGGCGTGGAGGTG CACAACGCCAAGACCAAGCCCAGAGAGGAGCAGTACAACA GCACCTACAGGTGGTGTCCGTGCTGACCGTGTGCACCAAG GACTGGCTGAACGGCAAAGAATACAAGTGCAAAGTCTCCAA CAAGGCCCTGCCAGCCCCAATCGAAAAGACAATCAGCAAG GCCAAGGGCCAGCCACGGGAGCCCCAGGTGTACACCCTGCC CCCCAGCCGGGAGGAGATGACCAAGAACCAGGTGTCCCTGA CCTGTCTGGTGAAGGGCTTCTACCCAGCGATATCGCCGTG GAGTGGGAGAGCAACGGCCAGCCCGAGAACAATAACAAGA CCACCCCCCAGTGCTGGACAGCGACGGCAGCTTCTTCTGT ACAGCAAGCTGACCGTGGACAAGTCCAGGTGGCAGCAGGG CAACGTGTTCACTGTCAGCGTGATGCACGAGGCCCTGCACA ACCACTACACCCAGAAGTCCCTGAGCCTGAGCCCCGGCAAG GAGATCGTGATGACCCAGTCCCCCGCCACCCTGTCTGTGTCT CCCGGCGAGAGAGCCACCCTGAGCTGCAGAGCCTCCGAGTC CGTGTCTCTCCAACGTGGCCTGGTATCAGCAGAGACCTGGTC AGGCCCCCTCGGCTGCTGATCTACGGCGCCTCTAACCAGGGCC ACCGGCATCCCTGCCAGATTCTCCGGCTCCGCGCAGCGGCAC CGACTTACCCCTGACCATCTCCCGGCTGGAACCCGAGGACT TCGCCGTGTACTACTGCGGCCAGTCTACTCATACCCCTTCA CCTTCGGCCAGGGCACCAAGCTGGAAATCAAGCGTACGGTG GCCGCTCCCAGCGTGTTTCATCTTCCCCCCCAGCGACGAGCA GCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCTGCTGAACA ACTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGAC AACGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTCACCG AGCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCACC CTGACCCTGAGCAAGGCCGACTACGAGAAGCATAAGGTGTA CGCCTGCGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGA CCAAGAGCTTCAACAGGGGCGAGTGC</p>
	LC DNA sequence (SEQ ID NO: 435)	<p>GAGATCGTGATGACCCAGTCCCCCGCCACCCTGTCTGTGTCT CCCGGCGAGAGAGCCACCCTGAGCTGCAGAGCCTCCGAGTC CGTGTCTCTCCAACGTGGCCTGGTATCAGCAGAGACCTGGTC AGGCCCCCTCGGCTGCTGATCTACGGCGCCTCTAACCAGGGCC ACCGGCATCCCTGCCAGATTCTCCGGCTCCGCGCAGCGGCAC CGACTTACCCCTGACCATCTCCCGGCTGGAACCCGAGGACT TCGCCGTGTACTACTGCGGCCAGTCTACTCATACCCCTTCA CCTTCGGCCAGGGCACCAAGCTGGAAATCAAGCGTACGGTG GCCGCTCCCAGCGTGTTTCATCTTCCCCCCCAGCGACGAGCA GCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCTGCTGAACA ACTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGAC AACGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTCACCG AGCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCACC CTGACCCTGAGCAAGGCCGACTACGAGAAGCATAAGGTGTA CGCCTGCGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGA CCAAGAGCTTCAACAGGGGCGAGTGC</p>
GITR.MAB8	LCDR1 (Kabat) (SEQ ID NO: 436)	RASESVSSNVA
	LCDR2 (Kabat) (SEQ ID NO: 437)	GASNRAT
	LCDR3 (Kabat) (SEQ ID	GQSYSYPFT

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	NO: 438)	
	HCDR1 (Kabat) (SEQ ID NO: 439)	SYGVD
	HCDR2 (Kabat) (SEQ ID NO: 440)	VIWGGGGTTYASSLMG
	HCDR3 (Kabat) (SEQ ID NO: 441)	NAYGHDGGFAMDY
	vH full sequence (SEQ ID NO: 442)	EVQLVESGGGLVQSGGSLRLSCAASGFSLSYGV DWVRQAPG KGLEWVGVIWGGGGTTYASSLMGRFTISRDN SKNTLYLQMNS LRAEDTAVYYCARNAYGHDGGFAMDYWGQGLTVTVSS
	vL full sequence (SEQ ID NO: 443)	EIVMTQSPATLSVSPGERATLSCRASESVSSNVAWYQORPGQA PRLLIYGASNRTGIPARFSGSGSGTDFTLTISRLEPEDFAVYYC GQSYSPFTFGQGTKLEIK
	vH DNA sequence (SEQ ID NO: 444)	GAGGTGCAGCTGGTGAATCAGGCGGCGGACTGGTGCAGTC AGGCGGTAGCCTGAGACTGAGCTGCGCCGCTCCGGCTTTA GCCTGTCTAGCTACGGCGTGGACTGGGTCCGACAGGCCCT GGCAAAGGCCTGGAGTGGGTCGGAGTGATCTGGGGCGGAG GCGGAACCTACTACGCCTCTAGCCTGATGGGCGCGTTCACT ATCTCTAGGGACA ACTCTAAGAACACCCTGTACCTGCAGAT GA ACTCACTGAGAGCCGAGGACACCGCCGTCTACTACTGCG CTAGAAACGCCTACGGTCACGACGCGCGCTTCGCTATGGAC TACTGGGGTCAGGGCACCTGGTCACCGTGAGTTCA
	vL DNA sequence (SEQ ID NO: 445)	GAGATCGTGATGACCCAGTCCCCCGCCACCCTGTCTGTGTCT CCCGGCGAGAGAGCCACCCTGAGCTGCAGAGCCTCCGAGTC CGTGTCCTCCAACGTGGCCTGGTATCAGCAGAGACCTGGTC AGGCCCCCTCGGCTGCTGATCTACGGCGCCTCTAACCGGGCC ACCGGCATCCCTGCCAGATTCTCCGGCTCCGGCAGCGGCAC CGACTTCACCCTGACCATCTCCCGCTGGAACCCGAGGACT TCGCCGTGTACTACTGCGGCCAGTCCTACTCATACCCCTTCA CCTTCGGCCAGGGCACCAAGCTGGAAATCAAG
	HC full sequence (SEQ ID NO: 446)	EVQLVESGGGLVQSGGSLRLSCAASGFSLSYGV DWVRQAPG KGLEWVGVIWGGGGTTYASSLMGRFTISRDN SKNTLYLQMNS LRAEDTAVYYCARNAYGHDGGFAMDYWGQGLTVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNT KVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPETCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
	LC full sequence (SEQ ID NO: 447)	EIVMTQSPATLSVSPGERATLSCRASESVSSNVAWYQORPGQA PRLLIYGASNRTGIPARFSGSGSGTDFTLTISRLEPEDFAVYYC GQSYSPFTFGQGTKLEIKRTVAAPS VFIFPPSDEQLKSGTASVV CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

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	<p>HC DNA sequence (SEQ ID NO: 448)</p>	<p>GAGGTGCAGCTGGTGAATCAGGCGGCGGACTGGTGCAGTC AGGCGGTAGCCTGAGACTGAGCTGCGCCGCTCCGGCTTTA GCCTGTCTAGCTACGGCGTGGACTGGGTCCGACAGGCCCT GGCAAAGGCCTGGAGTGGGTCCGAGTGATCTGGGGCGGAG GCGGAACCTACTACGCCTCTAGCCTGATGGGCCGGTTCAT ATCTCTAGGGACAACCTCTAAGAACACCCTGTACCTGCAGAT GAACTCACTGAGAGCCGAGGACACCGCCGTCTACTACTGCG CTAGAAACGCCTACGGTCACGACGGCGGCTTCGCTATGGAC TACTGGGGTCAGGGCACCTGGTCACCGTGAGTTTCAGCTAG CACTAAGGGCCCAAGTGTGTTTCCCCTGGCCCCCAGCAGCA AGTCTACTTCCGGCGGAAGTGTGCTGCCCTGGGTGGCTGGA AGGACTACTTCCCCGAGCCCGTGACAGTGTCTGGAAGTCT GGGGCTCTGACTTCCGGCGTGACACCTTCCCCGCCGTGCTG CAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACAGT GCCCTCCAGCTCTCTGGGAACCCAGACCTATATCTGCAACGT GAACCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTG GAGCCCAAGAGCTGCGACAAGACCCACACCTGCCCCCTG CCCAGCTCCAGAACTGCTGGGAGGGCCTTCCGTGTTCTGTT CCCCCCAAGCCAAGGACACCCTGATGATCAGCAGGACCC CCGAGGTGACCTGCGTGGTGGTGACGTGTCCACGAGGAC CCAGAGGTGAAGTTCAACTGGTACGTGGACGGCGTGGAGGT GCACAACGCCAAGACCAAGCCCAGAGAGGAGCAGTACAAC AGCACCTACAGGGTGGTGCCGTGCTGACCGTGCTGCACCA GGACTGGCTGAACGGCAAAGAATACAAGTGCAAAGTCTCCA ACAAGGCCCTGCCAGCCCCAATCGAAAAGACAATCAGCAA GGCCAAGGGCCAGCCACGGGAGCCCCAGGTGTACACCCTGC CCCCCAGCCGGGAGGAGATGACCAAGAACCAGGTGTCCCTG ACCTGTCTGGTGAAGGGCTTCTACCCAGCGATATCGCCGT GGAGTGGGAGAGCAACGGCCAGCCCGAGAACAACCTACAAG ACCACCCCCCAGTGCTGGACAGCGACGGCAGCTTCTTCCT GTACAGCAAGCTGACCGTGGACAAGTCCAGGTGGCAGCAG GGCAACGTGTTTCAGCTGCAGCGTGATGCACGAGGCCCTGCA CAACCACTACACCCAGAAGTCCCTGAGCCTGAGCCCCGGCA AG</p>
	<p>LC DNA sequence (SEQ ID NO: 449)</p>	<p>GAGATCGTGATGACCCAGTCCCCCGCCACCCTGTCTGTGTCT CCCGGCGAGAGAGCCACCCTGAGCTGCAGAGCCTCCGAGTC CGTGTCTCCAACGTGGCCTGGTATCAGCAGAGACCTGGTC AGGCCCCCTCGGCTGCTGATCTACGGCGCCTCTAACCGGGCC ACCGGCATCCCTGCCAGATTCTCCGGCTCCGGCAGCGGCAC CGACTTCACCCTGACCATCTCCCGGCTGGAACCCGAGGACT TCGCCGTGTACTACTGCGGCCAGTCTACTCATACCCCTTCA CCTTCGGCCAGGGCACCAAGCTGGAAATCAAGCGTACGGTG GCCGCTCCCAGCGTGTTTCATCTCCCCCCCAGCGACGAGCA GCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCTGCTGAACA ACTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGAC AACGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTCACCG AGCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCACC CTGACCCTGAGCAAGGCCGACTACGAGAAGCATAAGGTGTA CGCCTGCGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGA CCAAGAGCTTCAACAGGGGCGAGTGC</p>

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Example 3: In vivo efficacy of anti-CDH6 ADCs as a single agent in a xenograft mouse model of ovarian cancer

[00341] The anti-tumor activity of a selection of anti-CDH6 ADCs were evaluated in the OVCAR-3 ovarian xenograft model. Female NOD-scid-gamma mice were implanted subcutaneously on the right flank with 10×10^6 OVCAR-3 cells containing 50% Matrigel™ (BD Biosciences, San Jose, CA) in PBS. The total injection volume containing cells in suspension was 200 μ l. Mice were enrolled in the study 21 days post implantation with average tumor volume of 174 mm³. After being randomly assigned to one of nine groups (n = 5/group), mice were administered a single i.v. dose of PBS, (10 ml/kg), a non-target isotype control hIgG1-SPDB-DM4 (5 mg/kg), a non-target isotype control hIgG1-SMCC-DM1 (5 mg/kg), NOV0712-SMCC-DM1 (5 mg/kg), or one of seven anti-CDH6-SPDB-DM4 (5 mg/kg). Tumor volumes and body weights were measured 1-2 times weekly. None of the mice showed a decrease in body weight, indicating that the ADC was well tolerated at this dosage (data not shown). Of all the anti-CDH6-SPDB-DM4 agents, NOV0712-SPDB-DM4 elicited the greatest anti-tumor effect with regression 70 days post dose. NOV0710-SPDB-DM4 was the second most active anti-CDH6-SPDB-DM4 in this study (Figure 1).

Example 4: GITR antibodies have anti-tumor activity as a single agent

[00342] hGITR knock-in mice were generated by replacing the entire coding sequence (exons and introns) of mouse GITR with the human GITR cDNA sequence. Untranslated sequences upstream of the start codon and downstream of the stop codon are from mouse genome. Gene targeting was done by standard techniques in BALB/c ES cells with targeting vectors bearing BALB/c derived homology arms. Several ES cell clones were identified by PCR and confirmed by Southern blotting to contain the exact human cDNA knock in. Following standard mouse embryology techniques, positive ES cell clones were injected into blastocysts, which were transferred into pseudopregnant recipient foster mothers to derive chimeric offspring. Male chimeric mice were crossed with BALB/c females expressing Cre recombinase in their germline to excise the loxP flanked neomycin resistance cassette. One clone resulted in white offspring indicating germline transmission of the targeted ES cells. Excision of the loxP-flanked cassette was confirmed by PCR genotyping. A subsequent breeding step with BALB/c wt mice removed the Cre recombinase.

[00343] hGITRL knock-in mice were generated by replacing mouse the coding portion of exon 1 with the human GITRL cDNA sequence followed by a bovine growth hormone poly-A signal. All ES cell work and mouse embryology were done similar to the procedures described above. hGITR-hGITRL double knock-in mice were generated by intercrossing the two founder lines for 2 generations to produce homozygous double knock-in mice.

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[00344] The Colon26 murine colon carcinoma cell line was obtained from the Division of Cancer Treatment and Diagnosis at the National Cancer Institute (vial: 0507238). Murine Colon26 carcinoma cells were cultured in RPMI 1640 medium (HyClone SH30027.02) supplemented with 10% FBS (Gibco 10099-141), 10mM HEPES (Gibco 15630-080) and 1mM sodium pyruvate (Gibco 11360-070). 8-10 week old female hGTR-hGITRL knock-in mice were injected subcutaneously with 0.5×10^6 Colon26 cells in 100uL of RPMI in the flank. Tumors were measured using digital calipers and tumor volume calculated using the equation $(L \times W^2)/2$. When tumors reached an average size of 180mm^3 , mice were randomized and dosed with a single intraperitoneal injection of vehicle (PBS) or therapeutic antibody (15mg/kg) in 200uL PBS. Mice were sacrificed and tumors collected for analysis by flow cytometry 7 days after dosing with therapeutic antibodies. All animal experiments were performed in an AAALAC accredited facility using IACUC approved protocols. Statistical analysis was performed in Prism software using student's t-test with two-tailed 95% confidence interval or One-way ANOVA with Tukey correction.

[00345] hGTR-hGITRL double knock-in mice with established Colon26 tumors were treated with a single dose of vehicle (n=8/timepoint) or GTR.MAB7 (n=10/timepoint) antibody. Figure 2 depicts results of tumor measurements twice per week and tumor volume calculated using the equation $(L \times W^2)/2$. Data shown is from the fifteen (15)-day time point group. This demonstrates the anti-GTR antibodies have anti-tumor activity as a single agent.

Example 5: Generating the RENCAmCDH6 Cell line

[00346] Murine RENCA kidney adenocarcinoma cells (CRL-2947) were purchased from ATCC and transduced with a lentiviral construct delivering murine CDH6 (obtained from Transomics and cloned into pLenti6.3). Cells expressing CDH6 were selected by two rounds of fluorescence activated cell sorting using a PE-conjugated CDH6 antibody (R&D Systems #FAB2715) and isolated into distinct cell lines. The FACs plots and an indication of tumor growth in mice are shown in Figure 3. After treatment with the CDH6 ADC for ten days, the number of Tregs associated with the tumor increase, and this is shown in Figure 4.

Example 6: RENCAmCDH6 Clone5F5 Efficacy study

[00347] The anti-tumor activity of the combination of CDH6-sulfo-SPDB-DM4 and the mouse surrogate agonistic anti-GTR IgG2a antibody mDTA-1 (Bulliard et al., J.Exp.Med. 2013; 210(9):1685-1693) was evaluated in the RENCAmCDH6 Clone 5F5 xenograft model. This cell line model had been engineered from the syngeneic RENCA cell line to express murine CDH6, and had been validated as tumorigenic and sensitive to CDH6-sulfo-SPDB-DM4 treatment in a previous

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experiment. Female BALB/cJ mice were implanted subcutaneously on the right flank with 5×10^5 RENCAmCDH6 clone5F5 cells Hanks Balanced salt solution (HBSS). The total injection volume containing cells in suspension was 100 μ l. At 15 days post implantation mice were randomized into to one of eight groups of equal mean tumor volume of 176 mm³ (n = 10/group), mice were administered a single i.v. dose of either CDH6-sulfo-SPDB-DM4 5 mg/kg or a non-target isotype control hIgG1-sulfo-SPDB-DM4 5 mg/kg, in combination with either mDTA-1 5mg/kg or a non-target isotype control mIgG2a. The administration regimen was 5 mg/kg for the initial timepoint, then 3 days later or 6 days later. Tumor volumes and body weights were measured at least once weekly. In addition to tumor growth kinetics up to day 39, a time to endpoint (TTE) data are plotted in Figure 5. The endpoint employed was 1000mm³, once tumors surpassed this volume they were removed from study. Across the CDH6-sulfo-SPDB-DM4 and mDTA-1 treated groups, 5 mice were tumor free up to 112 days post tumor implant (Figure 6). This data indicated a significant survival benefit of the combination of CDH6-sulfo-SPDB-DM4 and GITR agonist antibody when compared to the combination of CDH6-sulfo-SPDB-DM4 with the mIgG2a control, (p = 0.0061 Mantel-Cox test).

Example 7: RENCAmCDH6Clone5F5 re-challenge study

[00348] On day 112 a second implant of 5×10^5 RENCAmCDH6 clone5F5 cells was administered as a re-challenge alongside a cohort of ten naïve BALB/cJ control mice. In this experiment tumors and bodyweights were measured at least once weekly. There was no further administration of anti-CDH6 or anti-GITR agents to either the re-challenged or the control mice. All ten control mice grew tumors whereas none of the re-challenged mice grew palpable tumors up to day 51 post re-challenge. This data is shown with the mouse cohort, plotted as mean tumor volume over time in Figure 7, with individual tumor growth plotted in Figure 8. Five of these mice were euthanized alongside a new cohort of non-tumor-bearing BALB/cJ mice to provide control tissue. The same 1000mm³ endpoint was employed, TTE data are plotted illustrating the significant difference between the groups (p = 0.0005, Mantel-Cox test), and this data is shown in Figure 9.

Example 8: ELISPOT assay to confirm functional T cell response to tumor antigen

[00349] Spleens were harvested from re-challenged and control mice in preparation for the ELISPOT assay. The spleens were smashed in a 70 μ m filter placed on top of a 50ml tube using a 3ml syringe barrel. The filter was then rinsed with 2ml RPMI. The splenocytes collected in the tube were washed at 1200rpm for 5 minutes and the pellet was resuspended in 1mL ACK lysis buffer to lyse the

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RBCs for 5 minutes and then resuspended in 9ml of RPMI to quench the reaction. The cells were washed once and resuspended in 5ml X-Vivo 15 media. The cells were then counted and kept on ice. The frozen vials of irradiated Renca 5F5 cells were thawed, suspended in the X-Vivo 15 media and counted.

[00350] These splenocytes (control mice and re-challenged mice) and irradiated tumor cells were used in the co-culture Mouse IFN- γ Single-Color ELISPOT assay (Cellular Technology Limited, Cat no: mIFNg-1M/2). An Effector: Tumor (E: T) ratio of 10:1 was used in the assay and absolute cell numbers were as follows:

Table 7:

Number of Splenocytes	Number of Tumor cells
500000	50000
200000	20000
50000	5000
500000	0

[00351] The positive control used in this assay was 500K splenocytes (pooled) + Dynabeads® Mouse T-Activator CD3/CD28 (ThermoFisher Cat no: 11456D) in 1:1 ratio. The cells were then seeded in the IFN-gamma capture antibody coated plates as described in Table 7. This plate was placed in the incubator (37°C, 5% CO₂) and left undisturbed for 24 hrs. The processing of the plate was carried out as per the protocol provided with the ELISPOT kit and the developed plate was read using the ImmunoSpot® S6 CORE (Cellular Technology Limited). Results showed a significant IFN-gamma signal in the presence of splenocytes from re-challenged mice incubated with target cells compared to control splenocytes ($p < 0.0001$, 2 way ANOVA). Incubation in the absence of tumor antigen also elicited an IFN-gamma signal but to a significantly lower extent ($p < 0.001$, Mann-Whitney Rank Sum Test). The difference between these two responses depicts the magnitude of the tumor specific T cell mediated response and this is shown graphically in Figure 10.

Example 9: Generating Colon26mCDH6 Cell line

[00352] Murine Colon epithelial carcinoma cells (Colon26) were purchased from ATCC (CRL-2638) and transduced with a lentiviral construct delivering murine CDH6 (obtained from Transomics and cloned into pLenti6.3). A population expressing CDH6 was selected by two rounds of fluorescence activated cell sorting using a PE-conjugated CDH6 antibody (R&D Systems #FAB2715).

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Example 10: GITR expression increases on Tregs following CDH6-sulfo-SPDB-DM4 treatment in Colon26mCDH6 model

[00353] The anti-tumor activity of CDH6-sulfo-SPDB-DM4 was evaluated in the Colon26mCDH6 model. Female BALB/cJ mice were implanted subcutaneously on the right flank with 5×10^5 Colon26mCDH6 cells in Hanks Balanced salt solution (HBSS). The total injection volume containing cells in suspension was 100 μ l. At 14 days post implantation mice were randomized into two groups (n=5) of equal mean tumor volume of 160 mm³, one group was dosed with CDH6-sulfo-SPDB-DM4 and the other acted as untreated control. Figure 11 demonstrates that CDH6-sulfo-SPDB-DM4 was efficacious, with a tumoricidal response out to day 24. Tumors were harvested 10 days post dose (day 24) and were dissociated using a mixture of DNase 1 (Roche), Collagenase P (Roche) and Dispase (Gibco, Life Tech) in RPMI (Gibco, Life Tech). The tumor went through five total cycles of digestion, each lasting 20min and was agitated every five minutes. Collected cells were then pelleted (1500 rpm, 5 min) and strained through a 70 μ m filter. The resulting single cell suspension was then stained for flow cytometric analysis of the following markers: α -CD45-BV510, (Clone 30F-11, Biolegend), α -CD4-BUV395 (Clone GK1.5, BD Biosciences), α -CD8-BV650 (Clone 53-6.7, Biolegend), α -FoxP3-AF488 (Clone FJK-16s, eBioscience), α -GITR-BV421 (Clone DTA-1, eBiosciences), α -CD11b-BUV737 (Clone M1/70, BD Biosciences) α -CD19-BUV737 (Clone 1D3, BD Biosciences). A fixable live/dead (eFluor-780, eBioscience) was used to exclude dead cells. A fixation/permeabilization buffer kit (eBioscience) was used for FoxP3 staining. As shown in Figure 12, analysis of T cell subsets demonstrated that treatment with CDH6-sulfo-SPDB-DM4 resulted in a significant increase in GITR expression on Foxp3⁺CD4⁺ T cells in comparison to untreated controls (p<0.001, unpaired t-test). Based on the level of GITR expression, Tregs could be sub gated into GITR⁺ and GITR^{hi} cells. The significant increase in GITR expression observed on the Tregs correlated with a significant increase in the frequency of GITR^{hi} cells within the Treg subset (p<0.001, unpaired t-test).

[00354] It is understood that the examples and aspects described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims.

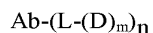
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CLAIMS**What is claimed is:**

1. A combination comprising:

a) an anti-CDH6 antibody drug conjugate of the formula



or a pharmaceutically acceptable salt thereof; wherein

Ab is an antibody or antigen binding fragment thereof that specifically binds to an epitope of human CDH6;

L is a linker;

D is a drug moiety, wherein the drug moiety is N(2')-deacetyl-N2-(4-mercapto-4-methyl-1-oxopentyl)-maytansine (DM4) or N(2')-deacetyl-N(2')-(3-mercapto-1-oxopropyl)-maytansine (DM1);

m is an integer from 1 to 8; and

n is an integer from 1 to 10; and

b) an anti-GITR agonist antibody or antigen binding fragment thereof.

2. The combination of claim 1, wherein in the antibody drug conjugate said n is 3 or 4.

3. The combination of claim 1 or 2, wherein in said antibody drug conjugate said antibody or antigen binding fragment thereof comprises:

(i) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:224, (b) a LCDR2 of SEQ ID NO:225, (c) a LCDR3 of SEQ ID NO:226; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO: 227, (e) a HCDR2 of SEQ ID NO: 228, and (f) a HCDR3 of SEQ ID NO:229;

(ii) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:210, (b) a LCDR2 of SEQ ID NO:211, (c) a LCDR3 of SEQ ID NO:212; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:213, (e) a HCDR2 of SEQ ID NO: 214, and (f) a HCDR3 of SEQ ID NO:215;

(iii) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:266, (b) a LCDR2 of SEQ ID NO:267, (c) a LCDR3 of SEQ ID NO:268; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO: 269, (e) a HCDR2 of SEQ ID NO:270, and (f) a HCDR3 of SEQ ID NO: 271;

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(iv) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:308, (b) a LCDR2 of SEQ ID NO:309, (c) a LCDR3 of SEQ ID NO:310; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:311, (e) a HCDR2 of SEQ ID NO:312, and (f) a HCDR3 of SEQ ID NO:313;

(v) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:14, (b) a LCDR2 of SEQ ID NO:15, (c) a LCDR3 of SEQ ID NO:16; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:17, (e) a HCDR2 of SEQ ID NO:18, and (f) a HCDR3 of SEQ ID NO:19;

(vi) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:28, (b) a LCDR2 of SEQ ID NO:29, (c) a LCDR3 of SEQ ID NO:30; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:31, (e) a HCDR2 of SEQ ID NO:32, and (f) a HCDR3 of SEQ ID NO:33;

(vii) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:42, (b) a LCDR2 of SEQ ID NO:43, (c) a LCDR3 of SEQ ID NO:44; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:45, (e) a HCDR2 of SEQ ID NO:46, and (f) a HCDR3 of SEQ ID NO:47;

(viii) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:56, (b) a LCDR2 of SEQ ID NO:57, (c) a LCDR3 of SEQ ID NO:58; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:59, (e) a HCDR2 of SEQ ID NO:60, and (f) a HCDR3 of SEQ ID NO:61;

(ix) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:70, (b) a LCDR2 of SEQ ID NO:71, (c) a LCDR3 of SEQ ID NO:72; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:73, (e) a HCDR2 of SEQ ID NO:74, and (f) a HCDR3 of SEQ ID NO:75;

(x) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:84, (b) a LCDR2 of SEQ ID NO:85, (c) a LCDR3 of SEQ ID NO:86; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:87, (e) a HCDR2 of SEQ ID NO: 88, and (f) a HCDR3 of SEQ ID NO: 89;

(xi) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:98, (b) a LCDR2 of SEQ ID NO:99, (c) a LCDR3 of SEQ ID NO:100; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:101, (e) a HCDR2 of SEQ ID NO:102, and (f) a HCDR3 of SEQ ID NO:103;

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(xii) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:112, (b) a LCDR2 of SEQ ID NO:113, (c) a LCDR3 of SEQ ID NO:114; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:115, (e) a HCDR2 of SEQ ID NO:116, and (f) a HCDR3 of SEQ ID NO:117;

(xiii) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:126, (b) a LCDR2 of SEQ ID NO:127, (c) a LCDR3 of SEQ ID NO:128; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:129, (e) a HCDR2 of SEQ ID NO:130, and (f) a HCDR3 of SEQ ID NO:131;

(xiv) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:140, (b) a LCDR2 of SEQ ID NO:141, (c) a LCDR3 of SEQ ID NO:142; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:143, (e) a HCDR2 of SEQ ID NO:144, and (f) a HCDR3 of SEQ ID NO:145;

(xv) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:154, (b) a LCDR2 of SEQ ID NO:155, (c) a LCDR3 of SEQ ID NO:156; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:157, (e) a HCDR2 of SEQ ID NO:158, and (f) a HCDR3 of SEQ ID NO:159;

(xvi) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:168, (b) a LCDR2 of SEQ ID NO:169, (c) a LCDR3 of SEQ ID NO:170; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:171, (e) a HCDR2 of SEQ ID NO:172, and (f) a HCDR3 of SEQ ID NO:173;

(xvii) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:182, (b) a LCDR2 of SEQ ID NO:183, (c) a LCDR3 of SEQ ID NO:184; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:185, (e) a HCDR2 of SEQ ID NO:186, and (f) a HCDR3 of SEQ ID NO:187;

(xviii) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:196, (b) a LCDR2 of SEQ ID NO:197, (c) a LCDR3 of SEQ ID NO:198; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:199, (e) a HCDR2 of SEQ ID NO:200, and (f) a HCDR3 of SEQ ID NO:201;

(xix) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:238, (b) a LCDR2 of SEQ ID NO:239, (c) a LCDR3 of SEQ ID NO:240; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:241, (e) a HCDR2 of SEQ ID NO:242, and (f) a HCDR3 of SEQ ID NO:243;

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(xx) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:252, (b) a LCDR2 of SEQ ID NO:253, (c) a LCDR3 of SEQ ID NO:254; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:255, (e) a HCDR2 of SEQ ID NO:256, and (f) a HCDR3 of SEQ ID NO:257;

(xxi) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:280, (b) a LCDR2 of SEQ ID NO:281, (c) a LCDR3 of SEQ ID NO:282; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:283, (e) a HCDR2 of SEQ ID NO:284, and (f) a HCDR3 of SEQ ID NO:285;

(xxii) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:294, (b) a LCDR2 of SEQ ID NO:295, (c) a LCDR3 of SEQ ID NO:296; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:297, (e) a HCDR2 of SEQ ID NO:298, and (f) a HCDR3 of SEQ ID NO:299; or

(xxiii) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:322, (b) a LCDR2 of SEQ ID NO:323, (c) a LCDR3 of SEQ ID NO:324; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO:325, (e) a HCDR2 of SEQ ID NO:326, and (f) a HCDR3 of SEQ ID NO:327.

4. The combination of any one of claims 1 to 3, wherein in said antibody drug conjugate said antibody or antigen binding fragment thereof comprises:

(i) a heavy chain variable region (vH) that comprises SEQ ID NO: 230, and a light chain variable region (vL) that comprises SEQ ID NO:231;

(ii) a heavy chain variable region (vH) that comprises SEQ ID NO: 216, and a light chain variable region (vL) that comprises SEQ ID NO:217;

(iii) a heavy chain variable region (vH) that comprises SEQ ID NO: 272, and a light chain variable region (vL) that comprises SEQ ID NO:273;

(iv) a heavy chain variable region (vH) that comprises SEQ ID NO:314, and a light chain variable region (vL) that comprises SEQ ID NO:315;

(v) a heavy chain variable region (vH) that comprises SEQ ID NO:20, and a light chain variable region (vL) that comprises SEQ ID NO:21;

(vi) a heavy chain variable region (vH) that comprises SEQ ID NO: 34, and a light chain variable region (vL) that comprises SEQ ID NO:35;

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- (vii) a heavy chain variable region (vH) that comprises SEQ ID NO:48, and a light chain variable region (vL) that comprises SEQ ID NO:49;
- (viii) a heavy chain variable region (vH) that comprises SEQ ID NO:62, and a light chain variable region (vL) that comprises SEQ ID NO:63;
- (ix) a heavy chain variable region (vH) that comprises SEQ ID NO:76, and a light chain variable region (vL) that comprises SEQ ID NO:77;
- (x) a heavy chain variable region (vH) that comprises SEQ ID NO:90, and a light chain variable region (vL) that comprises SEQ ID NO:91;
- (xi) a heavy chain variable region (vH) that comprises SEQ ID NO:104, and a light chain variable region (vL) that comprises SEQ ID NO:105;
- (xii) a heavy chain variable region (vH) that comprises SEQ ID NO: 118, and a light chain variable region (vL) that comprises SEQ ID NO:119;
- (xiii) a heavy chain variable region (vH) that comprises SEQ ID NO: 132, and a light chain variable region (vL) that comprises SEQ ID NO:133;
- (xiv) a heavy chain variable region (vH) that comprises SEQ ID NO: 146, and a light chain variable region (vL) that comprises SEQ ID NO:147;
- (xv) a heavy chain variable region (vH) that comprises SEQ ID NO:160, and a light chain variable region (vL) that comprises SEQ ID NO:161;
- (xvi) a heavy chain variable region (vH) that comprises SEQ ID NO: 174, and a light chain variable region (vL) that comprises SEQ ID NO:175;
- (xvii) a heavy chain variable region (vH) that comprises SEQ ID NO: 188, and a light chain variable region (vL) that comprises SEQ ID NO:189;
- (xviii) a heavy chain variable region (vH) that comprises SEQ ID NO: 202, and a light chain variable region (vL) that comprises SEQ ID NO:203;
- (xix) a heavy chain variable region (vH) that comprises SEQ ID NO: 244, and a light chain variable region (vL) that comprises SEQ ID NO:245;
- (xx) a heavy chain variable region (vH) that comprises SEQ ID NO:258, and a light chain variable region (vL) that comprises SEQ ID NO:259;

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(xxi) a heavy chain variable region (vH) that comprises SEQ ID NO:286, and a light chain variable region (vL) that comprises SEQ ID NO:287;

(xxii) a heavy chain variable region (vH) that comprises SEQ ID NO:300, and a light chain variable region (vL) that comprises SEQ ID NO:301; or

(xxiii) a heavy chain variable region (vH) that comprises SEQ ID NO:328, and a light chain variable region (vL) that comprises SEQ ID NO:329.

5. The combination of any one of claims 1 to 4, wherein in said antibody drug conjugate the linker (L) is selected from the group consisting of a cleavable linker, a non-cleavable linker, a hydrophilic linker, a procharged linker and a dicarboxylic acid based linker.

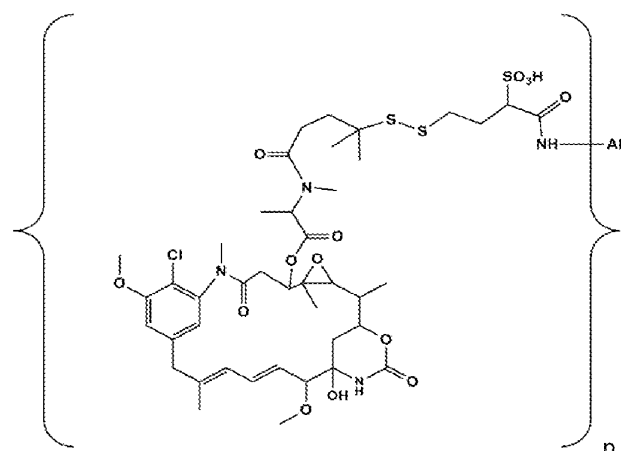
6. The combination of any one of claims 1 to 5, wherein in said antibody drug conjugate the linker is derived from a cross-linking reagent selected from the group consisting of: N-succinimidyl-4-(2-pyridyldithio)2-sulfo-butanoate (sulfo-SPDB), N-succinimidyl-3-(2-pyridyldithio)propionate (SPDP), N-succinimidyl 4-(2-pyridyldithio)pentanoate (SPP), N-succinimidyl 4-(2-pyridyldithio)butanoate (SPDB), N-succinimidyl iodoacetate (SIA), N-succinimidyl(4-iodoacetyl)aminobenzoate (SIAB), maleimide PEG NHS, N-succinimidyl 4-(maleimidomethyl) cyclohexanecarboxylate (SMCC), N-sulfosuccinimidyl 4-(maleimidomethyl) cyclohexanecarboxylate (sulfo-SMCC) or 2,5-dioxopyrrolidin-1-yl 17-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-5,8,11,14-tetraoxo-4,7,10,13-tetraazaheptadecan-1-oate (CX1-1).

7. The combination of any one of claims 1 to 6, wherein in said antibody drug conjugate the linker is derived from N-succinimidyl-4-(2-pyridyldithio)2-sulfo-butanoate (sulfo-SPDB).

8. The combination of any one of claims 1 to 7, wherein in said antibody drug conjugate D and L consist of:

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Ab-sulfo-SPDB-DM4

or a pharmaceutically acceptable salt thereof.

9. The combination of any one of claims 1 to 8, wherein the anti-GITR agonist antibody or antigen binding fragment thereof, specifically binds to SEQ ID NO:336.

10. The combination of any one of claims 1 to 9, wherein the anti-GITR agonist antibody or antigen binding fragment thereof comprises:

(i) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:422, (b) a LCDR2 of SEQ ID NO:423, (c) a LCDR3 of SEQ ID NO:424; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO: 425, (e) a HCDR2 of SEQ ID NO: 426, and (f) a HCDR3 of SEQ ID NO: 427;

(ii) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:352, (b) a LCDR2 of SEQ ID NO:353, (c) a LCDR3 of SEQ ID NO:354; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO: 355, (e) a HCDR2 of SEQ ID NO: 356, and (f) a HCDR3 of SEQ ID NO: 357;

(iii) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:366, (b) a LCDR2 of SEQ ID NO:367, (c) a LCDR3 of SEQ ID NO:368; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO: 369, (e) a HCDR2 of SEQ ID NO:370, and (f) a HCDR3 of SEQ ID NO:371;

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(iv) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:380, (b) a LCDR2 of SEQ ID NO:381, (c) a LCDR3 of SEQ ID NO:382; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO: 383, (e) a HCDR2 of SEQ ID NO: 384, and (f) a HCDR3 of SEQ ID NO: 385;

(vi) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:394, (b) a LCDR2 of SEQ ID NO:395, (c) a LCDR3 of SEQ ID NO:396; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO: 397, (e) a HCDR2 of SEQ ID NO: 398, and (f) a HCDR3 of SEQ ID NO: 399;

(vii) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:408, (b) a LCDR2 of SEQ ID NO:409, (c) a LCDR3 of SEQ ID NO:410; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO: 411, (e) a HCDR2 of SEQ ID NO: 412, and (f) a HCDR3 of SEQ ID NO: 413; or

(viii) a light chain variable region that comprises (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:436, (b) a LCDR2 of SEQ ID NO:437, (c) a LCDR3 of SEQ ID NO:438; and a heavy chain variable region that comprises: (d) a HCDR1 of SEQ ID NO: 439, (e) a HCDR2 of SEQ ID NO: 440, and (f) a HCDR3 of SEQ ID NO: 441.

11. The combination of any one of claims 1 to 10, wherein the anti-GITR agonist antibody or antigen binding fragment thereof comprises:

(i) a heavy chain variable region (vH) that comprises SEQ ID NO: 428, and a light chain variable region (vL) that comprises SEQ ID NO:429;

(ii) a heavy chain variable region (vH) that comprises SEQ ID NO: 358, and a light chain variable region (vL) that comprises SEQ ID NO:359;

(iii) a heavy chain variable region (vH) that comprises SEQ ID NO: 372, and a light chain variable region (vL) that comprises SEQ ID NO:373;

(iv) a heavy chain variable region (vH) that comprises SEQ ID NO: 386, and a light chain variable region (vL) that comprises SEQ ID NO:387;

(v) a heavy chain variable region (vH) that comprises SEQ ID NO: 400, and a light chain variable region (vL) that comprises SEQ ID NO:401;

(vi) a heavy chain variable region (vH) that comprises SEQ ID NO: 414, and a light chain variable region (vL) that comprises SEQ ID NO:415; or

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(vii) a heavy chain variable region (vH) that comprises SEQ ID NO: 442, and a light chain variable region (vL) that comprises SEQ ID NO:443.

12. The combination of any one of claims 1 to 11, wherein the anti-GITR agonist antibody or antigen binding fragment thereof comprises:

(i) a heavy chain that comprises SEQ ID NO: 432, and a light chain that comprises SEQ ID NO:433;

(ii) a heavy chain that comprises SEQ ID NO: 362, and a light chain that comprises SEQ ID NO:363;

(iii) a heavy chain that comprises SEQ ID NO: 376, and a light chain that comprises SEQ ID NO:377;

(iv) a heavy chain that comprises SEQ ID NO: 390, and a light chain that comprises SEQ ID NO:391;

(v) a heavy chain that comprises SEQ ID NO: 404, and a light chain that comprises SEQ ID NO:405;

(vi) a heavy chain that comprises SEQ ID NO: 418, and a light chain that comprises SEQ ID NO:419;

or

(vii) a heavy chain that comprises SEQ ID NO: 446, and a light chain that comprises SEQ ID NO:447.

13. The combination of any one of claims 1 to 12, wherein the anti-GITR agonist antibody or antigen binding fragment thereof consists of: (i) a light chain variable region that consists of (a) a LCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:422, (b) a LCDR2 of SEQ ID NO:423, (c) a LCDR3 of SEQ ID NO:424; and a heavy chain variable region that consists of: (d) a HCDR1 of SEQ ID NO: 425, (e) a HCDR2 of SEQ ID NO: 426, and (f) a HCDR3 of SEQ ID NO: 427.

14. The combination of any one of claims 1 to 13, wherein the anti-GITR agonist antibody or antigen binding fragment thereof is selected from the group consisting of: BMS-986156, INCAGN01876, AMG 228, TRX518, MEDI1873, MK-4166, MK-1248 and FPA-154.

15. The combination of any one of claims 1 to 14, wherein the antibody drug conjugate and anti-GITR antibody or antigen binding fragment thereof are in separate forms.

16. The combination of any one of claims 1 to 15, wherein the antibody drug conjugate and the anti-GITR antibody or antigen binding fragment thereof are in a fixed combination.

17. A method of treating a CDH6 positive cancer in a patient in need thereof, comprising administering to said patient the combination of any one of claims 1 to 16.

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18. The method of claim 17, wherein said cancer is selected from the group consisting of: ovarian cancer, renal cancer, hepatic cancer, soft tissue cancer, CNS cancers, thyroid cancer and cholangiocarcinoma.
19. The method of claim 17 or 18, wherein the antibody drug conjugate and the anti-GITR antibody or antigen binding fragment thereof are administered simultaneously or separately.
20. The method of claim 17 or 18, wherein the antibody drug conjugate is administered prior to the administration of the anti-GITR antibody or antigen binding fragment thereof.
21. A method of decreasing Treg cells in a tumor, the method comprising:
- c) administration of an antibody drug conjugate, wherein the administration of the antibody drug conjugate induces GITR expression on Treg cells;
 - d) administration of an anti-GITR agonist antibody or antigen binding fragment thereof, which decreases the number of Treg cells associated with the tumor.
22. The method of claim 21, which decreases reoccurrence of the tumor in a patient.
23. The method of claim 21 or 22, which increases progression-free survival in a patient.
24. Combination for use in treating cancer, wherein the combination is as in any one of claims 1 to 16.
25. Combination for use in treating cancer according to claim 24, wherein said cancer is selected from the group consisting of: ovarian cancer, renal cancer, hepatic cancer, soft tissue cancer, CNS cancers, thyroid cancer and cholangiocarcinoma.
26. Use of the combination according to any one of claims 1 to 16 in the manufacture of a medicament for the treatment of cancer.
27. Use according to claim 26, wherein said cancer is selected from the group consisting of: ovarian cancer, renal cancer, hepatic cancer, soft tissue cancer, CNS cancers, thyroid cancer and cholangiocarcinoma.

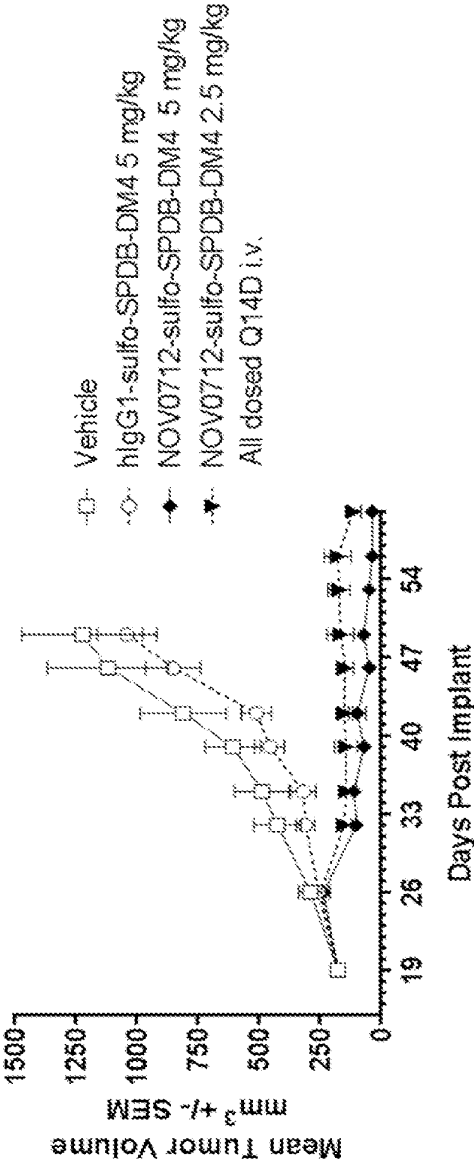
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FIGURE 1

In vivo efficacy of anti-CDH6 antibodies as sulfo-SPDB-DM4 conjugates in a xenograft mouse model of ovarian cancer



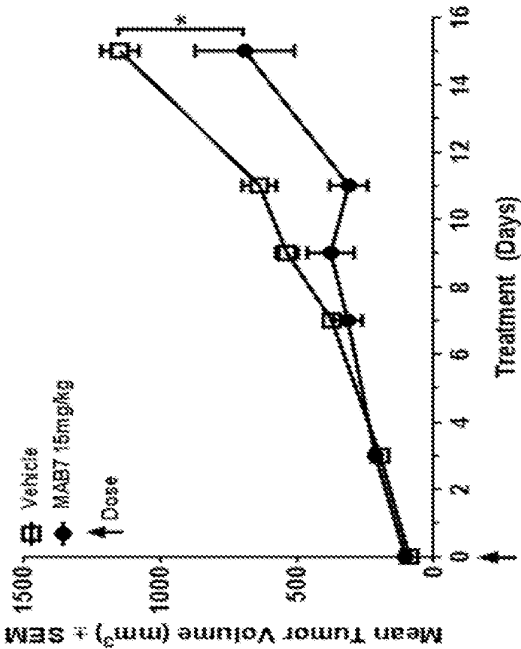
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FIGURE 2

hGITR-hGITRL double knock-in mice with established Colon26 tumors were treated with a single dose of vehicle (n=8/timepoint) or GITR.MAB7 (n=10/timepoint) antibody.



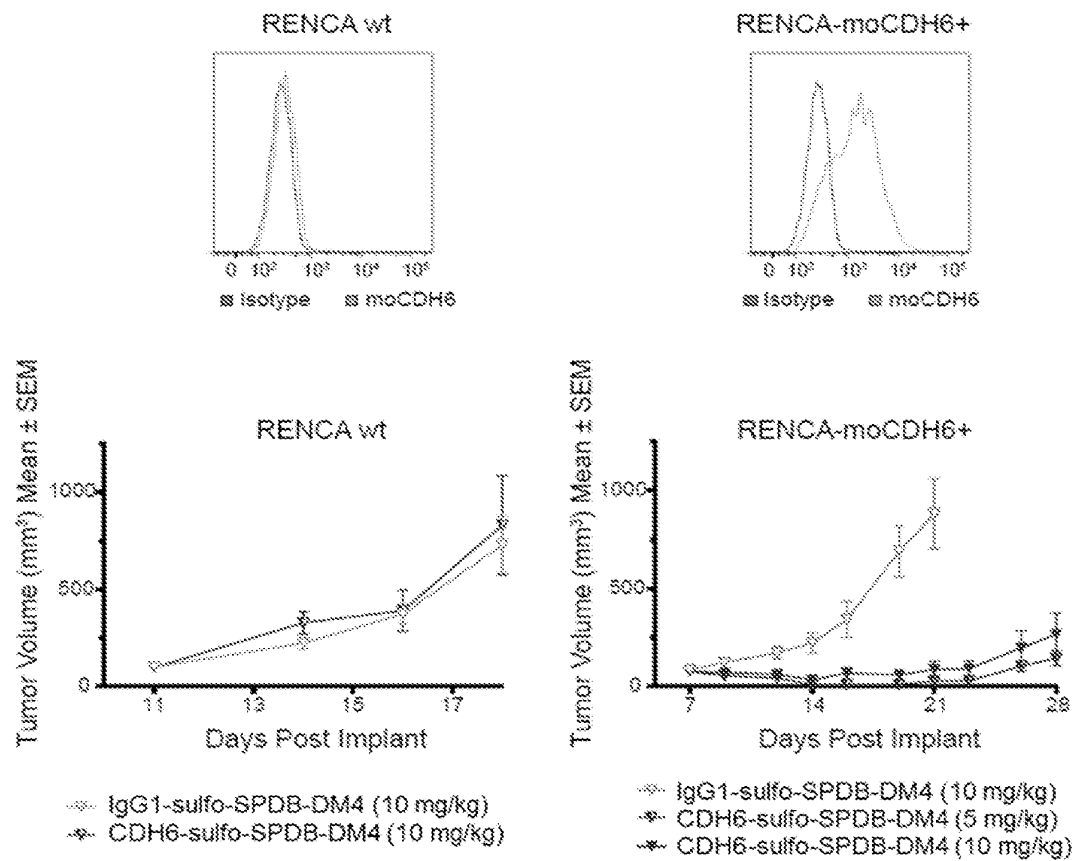
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FIGURE 3

Generation and validation of RENCAmCDH6 model



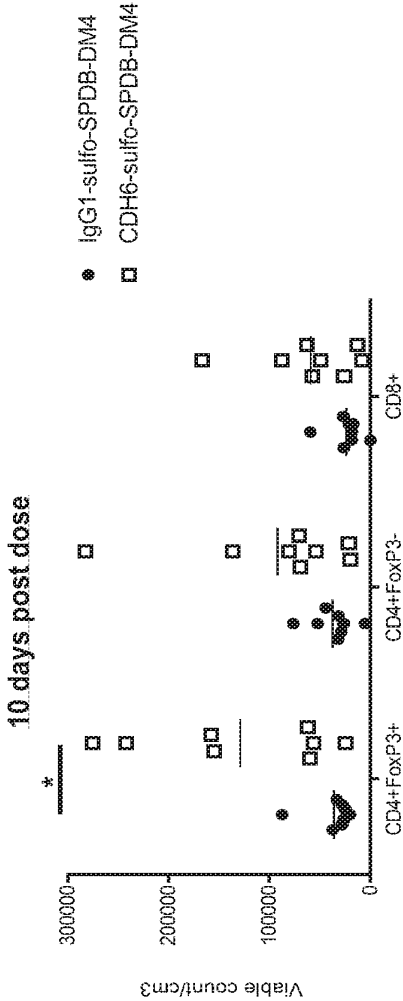
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FIGURE 4

T_{Regs} increase following CDH6 ADC treatment in the renal tumor mouse model



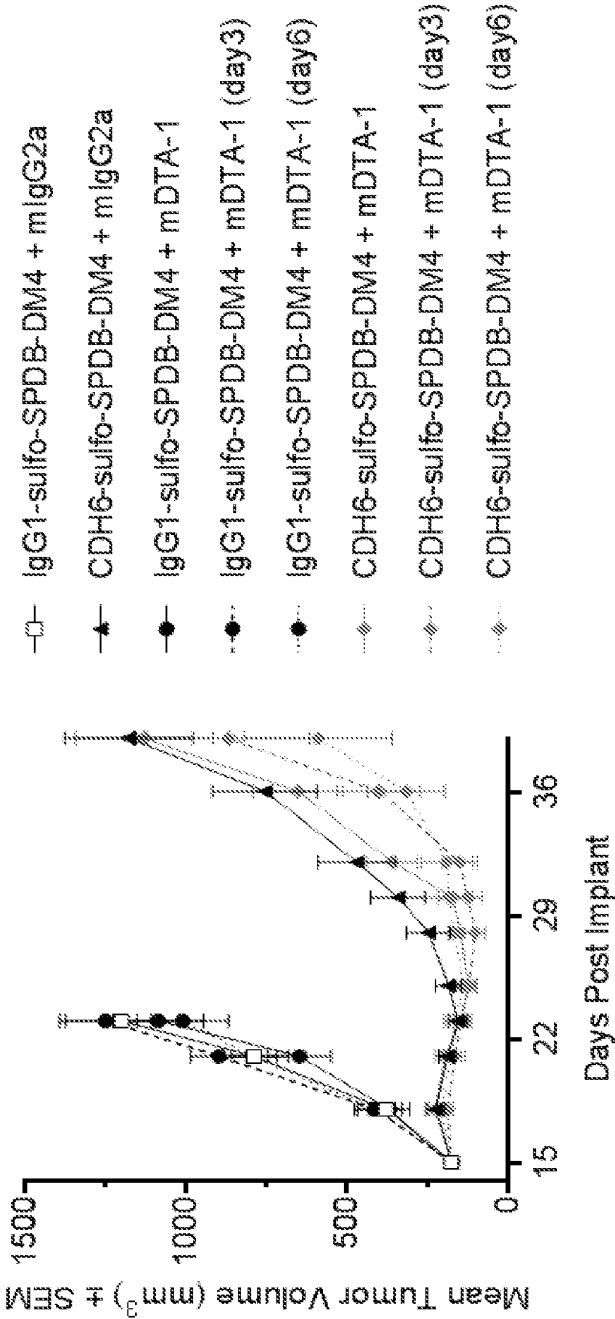
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FIGURE 5

Tumor volume of RENCAmCDH6 mouse model when treated with the CDH6 ADC/GITR combination



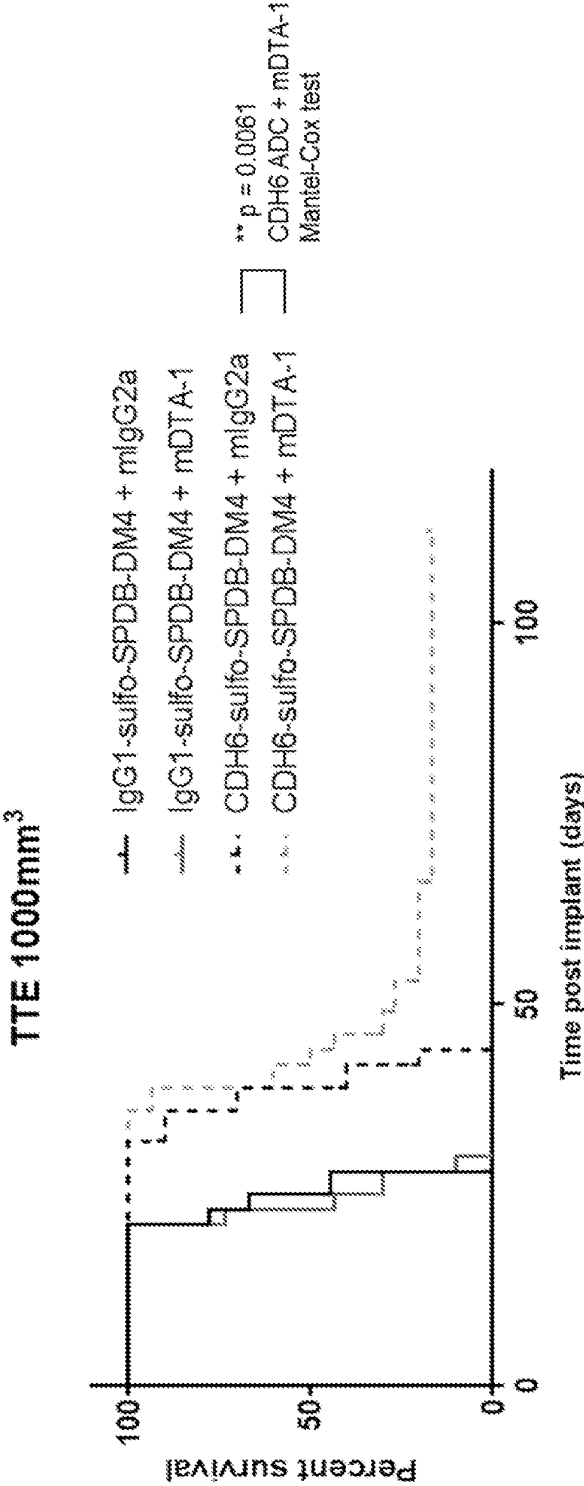
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FIGURE 6

CDH6 ADC/GITR combination increases survival in a RENCAmCDH6 mouse model



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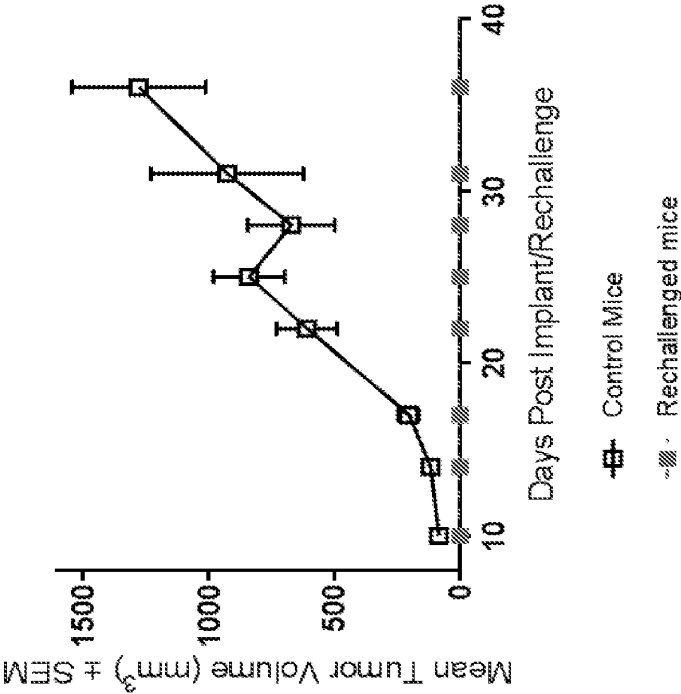
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FIGURE 7

The RENCAmCDH6 mouse model was re-challenged with RENCAmCDH6 tumor cells

7860RENCAmCDH6C1one5F5 Rechallenge Xef



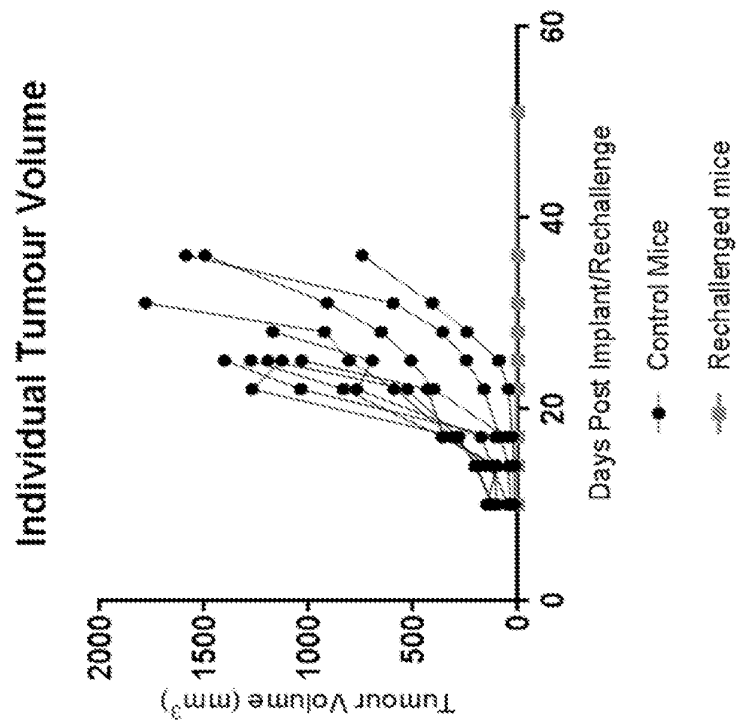
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FIGURE 8

The RENCAmCDH6 mouse model was re-challenged with RENCAmCDH6 tumor cells



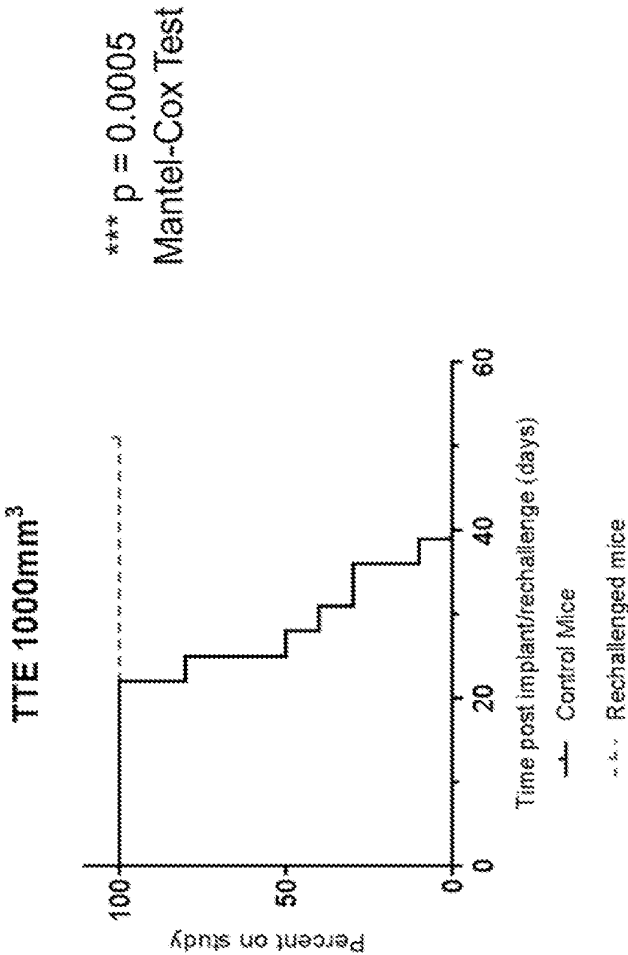
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PCT/IB2018/052151

FIGURE 9

The RENCAmCDH6 mouse model was re-challenged with RENCAmCDH6 tumor cells



Mice were tumor free on day 51 post rechallenge.
Spleen and axial lymph nodes sampled for ELISPOT assay.
Control tissues sampled from naive mice.

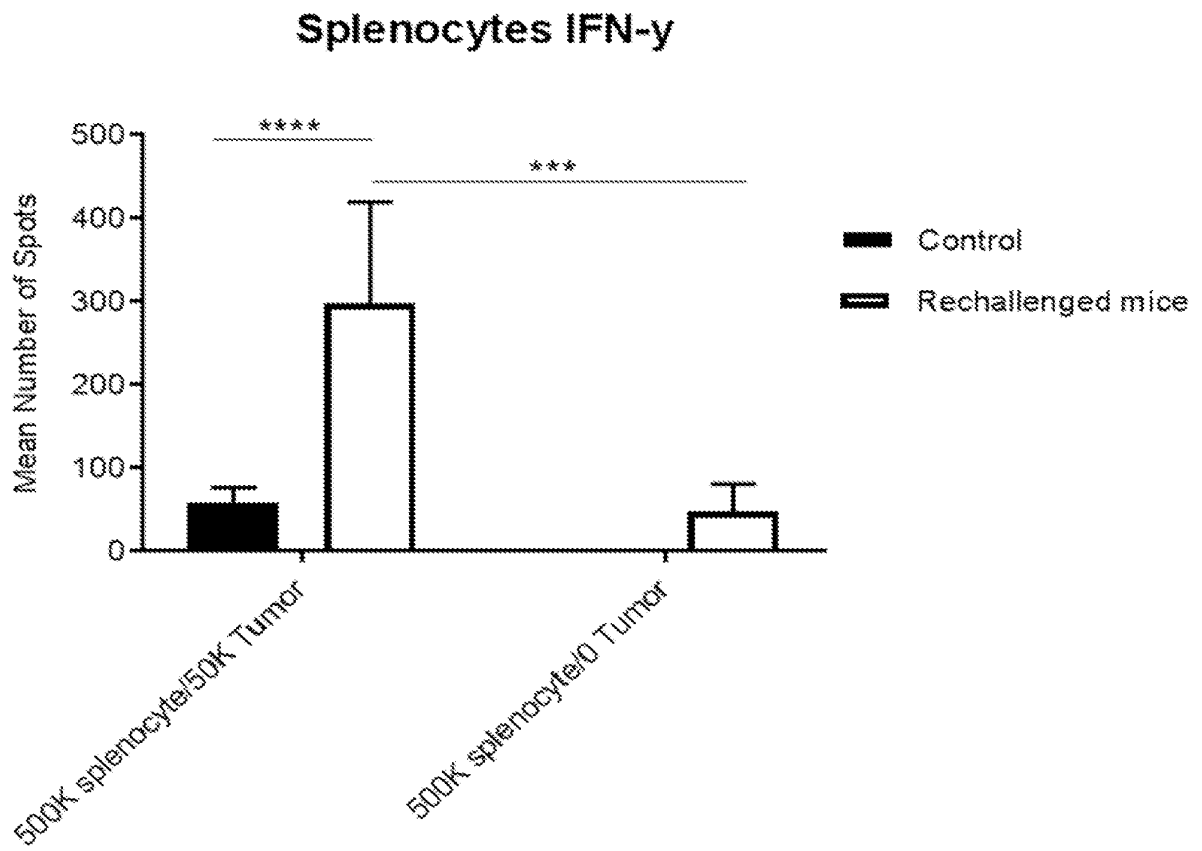
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FIGURE 10

IFN-gamma signal in the presence of splenocytes from re-challenged mice incubated with target cells



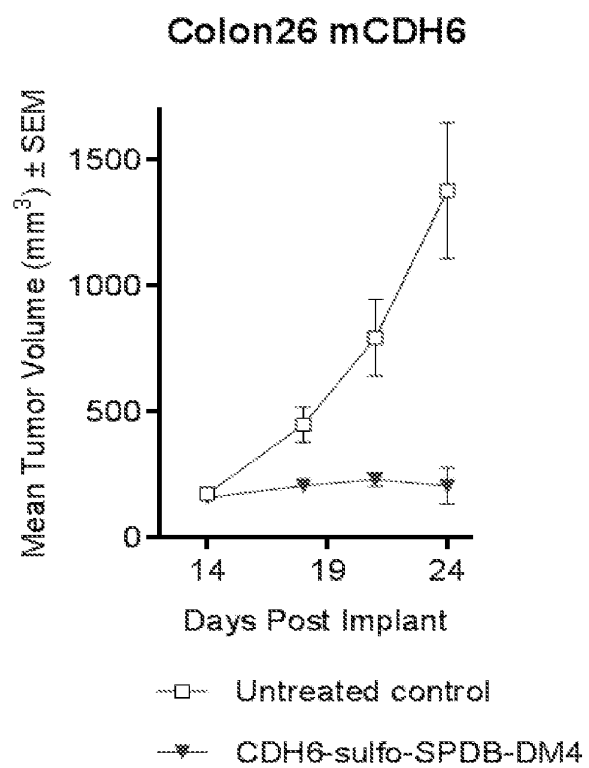
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FIGURE 11

A colon tumor mouse xenograft model was treated with CDH6 ADC



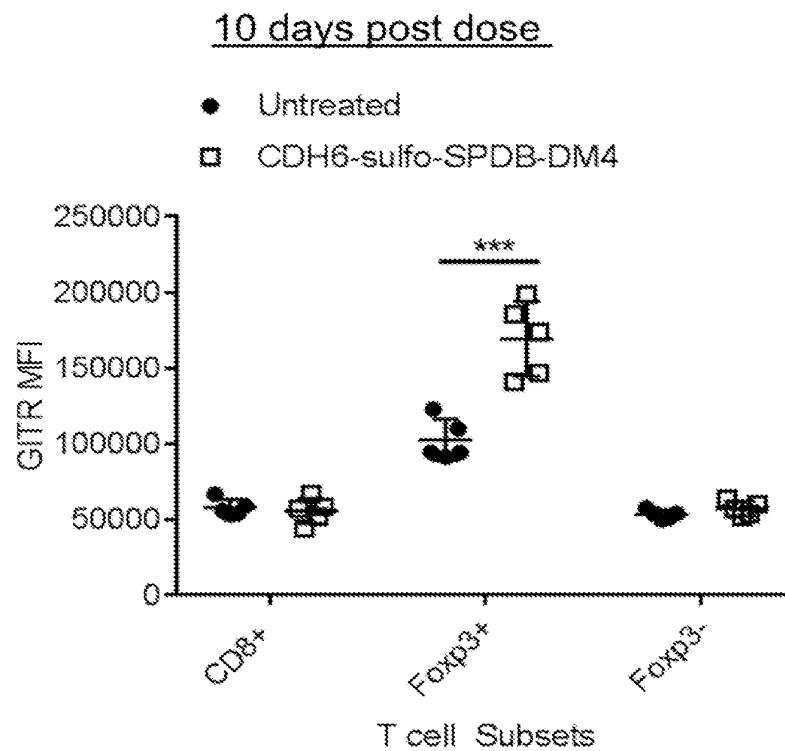
WO 2018/185618

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FIGURE 12

GITR expression increases on T_{regs} following CDH6 ADC treatment in the colon tumor mouse model



INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2018/052151

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K47/68 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2016/024195 A1 (NOVARTIS AG [CH]; BIALUCHA CARL ULI [US]; COLLINS SCOTT [US]; DÜRR CLE) 18 February 2016 (2016-02-18) paragraphs [0419], [0452]; claims 1-10, 49	1-27
A	----- KNEE DEBORAH A ET AL: "Rationale for anti-GITR cancer immunotherapy", EUROPEAN JOURNAL OF CANCER, ELSEVIER, AMSTERDAM, NL, vol. 67, 31 August 2016 (2016-08-31), pages 1-10, XP029758970, ISSN: 0959-8049, DOI: 10.1016/J.EJCA.2016.06.028 abstract page 5, column 1, last paragraph - page 6, column 1, paragraph 1 ----- -/-	1-27



Further documents are listed in the continuation of Box C.



See patent family annex.

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search

18 June 2018

Date of mailing of the international search report

09/07/2018

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INTERNATIONAL SEARCH REPORT

International application No PCT/IB2018/052151

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2016/057846 A1 (NOVARTIS AG [CH]; BROGDON JENNIFER [US]; CIPOLLETTA DANIELA [US]; DRAN) 14 April 2016 (2016-04-14) -----	1-27

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2018/052151

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2016024195 A1	18-02-2016	AR 104664 A1	09-08-2017
		AU 2015302959 A1	02-02-2017
		CA 2954599 A1	18-02-2016
		CL 2017000170 A1	14-07-2017
		CN 106659790 A	10-05-2017
		CU 20170014 A7	05-04-2017
		DO P2017000045 A	15-05-2017
		EA 201790334 A1	30-06-2017
		EP 3180360 A1	21-06-2017
		JP 2017524364 A	31-08-2017
		KR 20170040249 A	12-04-2017
		PE 09032017 A1	12-07-2017
		PH 12017500002 A1	15-05-2017
		SG 11201700254Q A	27-02-2017
		TW 201613643 A	16-04-2016
		US 2016046711 A1	18-02-2016
		US 2017224836 A1	10-08-2017
		UY 36266 A	01-04-2016
		WO 2016024195 A1	18-02-2016
-----	-----	-----	-----
WO 2016057846 A1	14-04-2016	AU 2015330771 A1	20-04-2017
		BR 112017007093 A2	06-03-2018
		CA 2964146 A1	14-04-2016
		CL 2017000836 A1	15-09-2017
		CN 107001476 A	01-08-2017
		CR 20170138 A	21-08-2017
		CU 20170045 A7	06-09-2017
		EP 3204419 A1	16-08-2017
		EP 3204421 A1	16-08-2017
		JP 2017535257 A	30-11-2017
		KR 20170065029 A	12-06-2017
		PE 16542017 A1	13-11-2017
		PH 12017500634 A1	25-09-2017
		SG 11201702596Y A	27-04-2017
		US 2017306037 A1	26-10-2017
		US 2017306038 A1	26-10-2017
		WO 2016057841 A1	14-04-2016
		WO 2016057846 A1	14-04-2016
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English Translation
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JAPAN PATENT OFFICE

This is to certify that the annexed is a true copy of the following application
as filed with this Office.

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Application Number : Patent Application No. 2017-096749

The country code and number : JP2017-096749
of your priority application,
to be used for filing abroad
under the Paris Convention, is

Applicant : DAIICHI SANKYO COMPANY, LIMITED

Date : May 24, 2018

Commissioner, Naoko Munakata
Japan Patent Office

Official Seal

[Name of Document]	Patent Application
[Docket Number]	DS2017002
[Address To]	Commissioner, Japan Patent Office
[International Patent Classification]	C07K 16/28
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[Name or Designation] Reiko Kinpara

[Indication of Official Fee]

[Prepayment Register Number] 353135
[Amount to be paid] 14,000 yen

[List of Materials to be submitted]

[Name of Material]	Description	1
[Name of Material]	Claims	1
[Name of Material]	Abstract	1
[Name of Material]	Drawings	1
[Number of General Power of Attorney]		0704434
[Number of General Power of Attorney]		0906688
[Number of General Power of Attorney]		0909034
[Number of General Power of Attorney]		0906690

Applicant's History

307010166

20070308

Newly registered

3-5-1, Nihonbashi Honcho, Chuo-ku, Tokyo, Japan

DAIICHI SANKYO COMPANY, LIMITED

- 1 -

[Document Name] Description

[Title of Invention:] ANTI-CDH6 ANTIBODY AND ANTI-CDH6 ANTIBODY-
DRUG CONJUGATE

[Technical Field]

[0001]

The present invention relates to an anti-CDH6 antibody binding to CDH6 and having an internalization effect, a method for producing the anti-CDH6 antibody, an antibody-drug conjugate comprising the antibody, an antitumor agent comprising the antibody-drug conjugate, and the like.

[Background Art]

[0002]

Cadherins are glycoproteins present on the surface of cell membranes and function as cell-cell adhesion molecules through the calcium ion-dependent binding of their N-terminal extracellular domains, or as signal molecules responsible for cell-cell interaction. Classic cadherins are in the cadherin superfamily and are single-pass transmembrane proteins composed of five extracellular domains (EC domains), one transmembrane region, and an intracellular domain. The classic cadherins are classified into the type I family typified by E-cadherin and N-cadherin, and the type II family according to the homologies of their amino acid sequences.

[0003]

Cadherin-6 (CDH6) is a single-pass transmembrane protein composed of 790 amino acids, which is classified into the type II cadherin family, and this protein has N-terminal extracellular and C-terminal intracellular domains. The human CDH6 gene was cloned for the first time in 1995 (Non Patent Literature 1), and its sequence can be referred to under, for example, accession Nos. NM_004932 and NP_004923 (NCBI).

[0004]

- 2 -

CDH6 is specifically expressed in the brain or the kidney at the stage of development and has been reported to play an important role in the circuit formation of the central nervous system (Non Patent Literature 2 and 3) and nephron development in the kidney (Non Patent Literature 4 and 5). The expression of CDH6 in the normal tissues of adult humans is localized to the tubules of the kidney, bile duct epithelial cells, and the like.

[0005]

Meanwhile, it is known that CDH6 is specifically overexpressed at tumor sites in some types of human adult cancers. The correlation of CDH6 expression with poor prognosis and its applicability as a tumor marker has been reported with respect to human renal cell carcinoma, particularly, renal clear cell carcinoma (Non Patent Literature 6 and 7). The high expression of CDH6 has also been reported with respect to human ovarian cancer (Non Patent Literature 8). It has also been reported that CDH6 is involved in the epithelial-mesenchymal transition of human thyroid cancer (Non Patent Literature 9).

[0006]

Cancers rank high in causes of death. Although the number of cancer patients is expected to increase with aging of the population, treatment needs have not yet been sufficiently satisfied. The problems of conventional chemotherapeutics are that: due to their low selectivity, these chemotherapeutics are toxic not only to tumor cells but also to normal cells and thereby have adverse reactions; and the chemotherapeutics cannot be administered in sufficient amounts and thus cannot produce their effects sufficiently. Hence, in recent years, more highly selective molecular target drugs or antibody drugs have been developed, which target molecules that exhibit mutations or a high expression characteristic in cancer cells, or specific molecules involved in malignant transformation of cells.

[0007]

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Antibodies are highly stable in blood, and specifically bind to their target antigens. For these reasons, a reduction in adverse reaction is expected, and a large number of antibody drugs have been developed for molecules highly expressed on the surface of cancer cells. One of the techniques relying on the antigen-specific binding ability of antibodies is to use an antibody-drug conjugate (ADC). ADC is a conjugate in which an antibody that binds to an antigen expressed on the surface of cancer cells and can internalize the antigen into the cell through the binding is conjugated to a drug having cytotoxic activity. ADC can efficiently deliver the drug to cancer cells, and can thereby be expected to kill the cancer cells by accumulating the drug in the cancer cells (Non Patent Literature 10). With regard to ADC, for example, Adcetris(TM) (brentuximab vedotin) comprising an anti-CD30 monoclonal antibody conjugated to monomethyl auristatin E has been approved as a therapeutic drug for Hodgkin's lymphoma and anaplastic large cell lymphoma. Also, Kadcyla(TM) (trastuzumab emtansine) comprising an anti-HER2 monoclonal antibody conjugated to emtansine is used in the treatment of HER2-positive progressive or recurrent breast cancer.

[0008]

The features of a target antigen suitable for ADC as an antitumor drug are that: the antigen is specifically highly expressed on the surface of cancer cells but has low expression or is not expressed in normal cells; the antigen can be internalized into cells; the antigen is not secreted from the cell surface; etc. The internalization ability of the antibody depends on the properties of both the target antigen and the antibody. It is difficult to predict an antigen-binding site suitable for internalization from the molecular structure of a target or to predict an antibody having high internalization ability from binding strength, physical properties, and the like of the antibody. Hence, an important challenge in developing ADC having high efficacy

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is obtaining an antibody having high internalization ability against the target antigen (Non Patent Literature 11).

[0009]

ADC comprising DM4 conjugated to an anti-CDH6 antibody specifically binding to EC domain 5 (EC5) of CDH6 are known as ADC targeting CDH6 (Patent Literature 1).

[Citation List]

[Patent Literature]

[0010]

[Patent Literature 1] WO2016/024195

[Non Patent Literature]

[0011]

[Non Patent Literature 1] Shimoyama Y, et al., Cancer Research, 2206-2211, 55, May 15, 1995

[Non Patent Literature 2] Inoue T, et al., Developmental Biology, 183-194, 1997

[Non Patent Literature 3] Osterhout J A, et al., Neuron, 632-639, 71, Aug 25, 2011

[Non Patent Literature 4] Cho E A, et al., Development, 803-812, 125, 1998

[Non Patent Literature 5] Mah S P, et al., Development Biology, 38-53, 223, 2000

[Non Patent Literature 6] Paul R, et al., Cancer Research, 2741-2748, July 1, 57, 1997

[Non Patent Literature 7] Shimazui T, et al., Cancer, 963-968, 101(5), Sep.1, 2004

[Non Patent Literature 8] Koebel M, et al., PLoS Medicine, 1749-1760, 5(12), e232, Dec.2008

[Non Patent Literature 9] Gugnoni M, et al., Oncogene, 667-677, 36, 2017

[Non Patent Literature 10] Polakis P., Pharmacological Reviews, 3-19, 68, 2016

[Non Patent Literature 11] Peters C, et al., Bioscience Reports, 1-20, 35, 2015

[Summary of Invention]

- 5 -

[Technical Problem]

[0012]

It is an object of the present invention to provide an antibody specifically binding to CDH6 and having high internalization activity, an antibody-drug conjugate comprising the antibody and having high antitumor activity, a pharmaceutical product comprising the antibody-drug conjugate and having therapeutic effects on a tumor, a method for treating a tumor using the antibody, the antibody-drug conjugate or the pharmaceutical product, and the like.

[Solution to Problem]

[0013]

The present inventors have conducted intensive studies directed towards achieving the above-described object, and found that, surprisingly, an antibody specifically binding to extracellular domain 3 (in the present description, also referred to as EC3) of CDH6 has exceedingly high internalization activity against cells expressing CDH6 and is useful as an antibody for ADC. The inventors have further found that an anti-CDH6 antibody-drug conjugate comprising the aforementioned anti-CDH6 antibody conjugated to a drug exerting toxicity in cells via a linker having a specific structure exhibits stronger antitumor activity than that of conventional CDH6-drug conjugates.

[0014]

The present invention includes the following aspects of the invention:

[1]

an antibody specifically binding to the amino acid sequence shown in SEQ ID NO: 4 and having internalization ability that permits cellular uptake, or a functional fragment of the antibody;

[2]

- 6 -

the antibody or the functional fragment of the antibody according to [1], which has competitive inhibitory activity, for binding to the amino acid sequence shown in SEQ ID NO: 4, against at least any one antibody selected from the group consisting of the following antibodies (1) to (5):

- (1) an antibody having a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 53 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 56,
- (2) an antibody having a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 69,
- (3) an antibody having a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 73,
- (4) an antibody having a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 65 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 73, and
- (5) an antibody having a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 77;

[3]

the antibody or the functional fragment of the antibody according to [1] or [2], which comprises CDRL1, CDRL2 and CDRL3 in any one combination selected from the group consisting of the following combinations (1) to (4):

- (1) CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 12, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 13, and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 14,

- 7 -

(2) CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 22, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 23, and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 24,

(3) CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 32, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 33, and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 34, and

(4) CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 42, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 43, and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 44, and CDRH1, CDRH2 and CDRH3 in any one combination selected from the group consisting of the following combinations (5) to (9):

(5) CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 17, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 18, and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 19,

(6) CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 27, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 28, and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 29,

(7) CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 37, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 38, and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 39,

(8) CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 47, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 48, and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 49, and

(9) CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 17, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 60, and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 19;

[4]

- 8 -

the antibody or the functional fragment of the antibody according to any one of [1] to [3], which comprises CDRL1, CDRL2 and CDRL3, and CDRH1, CDRH2 and CDRH3 in any combination selected from the group consisting of the following combinations (1) to (5):

- (1) CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 12, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 13, and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 14, and CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 17, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 18, and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 19,
- (2) CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 22, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 23, and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 24, and CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 27, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 28, and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 29,
- (3) CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 32, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 33, and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 34, and CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 37, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 38, and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 39,
- (4) CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 42, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 43, and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 44, and CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 47, CDRH2 consisting

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of the amino acid sequence shown in SEQ ID NO: 48, and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 49, and

(5) CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 12, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 13, and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 14, and CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 17, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 60, and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 19;

[5]

the antibody or the functional fragment of the antibody according to any one of [1] to [4], which is humanized;

[6]

the antibody or the functional fragment of the antibody according to any one of [1] to [5], which has any one light chain variable region selected from the group consisting of the following variable regions (1) to (4):

(1) a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 63,

(2) a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 67,

(3) an amino acid sequence having a sequence identity of at least 95% or more to the sequence of a framework region other than at each CDR sequence in the amino acid sequences of (1) and (2), and

(4) an amino acid sequence comprising a deletion, substitution or addition of one or several amino acids in the sequence of a framework region other than at each CDR sequence in the amino acid sequences of (1) to (3), and

any one heavy chain variable region selected from the group consisting of the following variable regions (5) to (9):

- 10 -

- (5) a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 71,
 - (6) a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 75,
 - (7) a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 79,
 - (8) an amino acid sequence having a sequence homology of at least 95% or more to the sequence of a framework region other than at each CDR sequence in the amino acid sequences of (5) to (7), and
 - (9) an amino acid sequence comprising a deletion, substitution or addition of one or several amino acids in the sequence of a framework region other than at each CDR sequence in the amino acid sequences of (5) to (8);
- [7]

the antibody or the functional fragment of the antibody according to any one of [1] to [6], which comprises a light chain variable region and a heavy chain variable region in any of the following combinations (1) to (4):

- (1) a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 63 and a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 71,
- (2) a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 63 and a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 75,
- (3) a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 67 and a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 75, and

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(4) a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 63 and a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 79;

[8]

the antibody or the functional fragment of the antibody according to any one of [1] to [7], which has any of the following combinations (1) to (4):

(1) a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 69,

(2) a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 73,

(3) a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 65 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 73, and

(4) a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 77;

[9]

the antibody or the functional fragment of the antibody according to [8], which has a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 69;

[10]

the antibody or the functional fragment of the antibody according to [8], which has a light chain consisting of the amino acid sequence at positions 21 to 233

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in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 73;

[0015]

[11]

the antibody or the functional fragment of the antibody according to [8], which has a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 65 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 73;

[12]

the antibody or the functional fragment of the antibody according to [8], which has a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 77;

[13]

the functional fragment of the antibody according to any one of [1] to [12], wherein the functional fragment is selected from the group consisting of Fab, F(ab')₂, Fab' and Fv;

[14]

a polynucleotide encoding the antibody or the functional fragment of the antibody according to any one of [1] to [13];

[15]

the polynucleotide according to [14], which comprises polynucleotides in any one combination selected from the group consisting of the following combinations

(1) to (5):

(1) a polynucleotide encoding a light chain variable region comprising CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 12, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 13 and CDRL3 consisting of the

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amino acid sequence shown in SEQ ID NO: 14, and a polynucleotide encoding a heavy chain variable region comprising CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 17, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 18 and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 19,

(2) a polynucleotide encoding a light chain variable region comprising CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 22, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 23 and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 24, and a polynucleotide encoding a heavy chain variable region comprising CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 27, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 28 and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 29,

(3) a polynucleotide encoding a light chain variable region comprising CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 32, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 33 and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 34, and a polynucleotide encoding a heavy chain variable region comprising CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 37, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 38 and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 39,

(4) a polynucleotide encoding a light chain variable region comprising CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 42, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 43 and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 44, and a polynucleotide encoding a heavy chain variable region comprising CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 47, CDRH2 consisting of the amino acid sequence

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shown in SEQ ID NO: 48 and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 49, and

(5) a polynucleotide encoding a light chain variable region comprising CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 12, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 13 and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 14, and a polynucleotide encoding a heavy chain variable region comprising CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 17, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 60 and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 19;

[16]

the polynucleotide according to [14] or [15], which comprises a polynucleotide encoding a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a polynucleotide encoding a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 69;

[17]

the polynucleotide according to [14] or [15], which comprises a polynucleotide encoding a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a polynucleotide encoding a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 73;

[18]

the polynucleotide according to [14] or [15], which comprises a polynucleotide encoding a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 65 and a polynucleotide encoding a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 73;

[19]

- 15 -

the polynucleotide according to [14] or [15], which comprises a polynucleotide encoding a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a polynucleotide encoding a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 77;
[20]

an expression vector comprising the polynucleotide according to any one of [14] to [19];
[21]

host cells transformed with the expression vector according to [20];
[22]

the host cells according to [21], wherein the host cells are eukaryotic cells;
[23]

a method for producing an antibody of interest or a functional fragment of the antibody, which comprises the step of culturing the host cells according to [21] or [22], and the step of collecting an antibody of interest or a functional fragment of the antibody from the culture obtained by the aforementioned step;
[24]

the antibody or the functional fragment of the antibody according to any one of [1] to [13], wherein the heavy chain or the light chain has undergone one or two or more modifications selected from the group consisting of N-linked glycosylation, O-linked glycosylation, N-terminal processing, C-terminal processing, deamidation, isomerization of aspartic acid, oxidation of methionine, addition of a methionine residue to the N-terminus, amidation of a proline residue, conversion of N-terminal glutamine or N-terminal glutamic acid to pyroglutamic acid, and a deletion of one or two amino acids from the carboxyl terminus;
[25]

- 16 -

the antibody according to [24], wherein one or two amino acids are deleted from the carboxyl terminus of a heavy chain thereof;

[26]

the antibody according to [25], wherein one amino acid is deleted from each of the carboxyl termini of both of the heavy chains thereof;

[27]

the antibody according to any one of [24] to [26], wherein a proline residue at the carboxyl terminus of a heavy chain thereof is further amidated;

[28]

the antibody or the functional fragment of the antibody according to any one of [1] to [13] and [24] to [27], wherein sugar chain modification is regulated in order to enhance antibody-dependent cellular cytotoxic activity;

[29]

an antibody-drug conjugate comprising the antibody or the functional fragment of the antibody according to any one of [1] to [13] and [24] to [28] conjugated to a drug;

[30]

the antibody-drug conjugate according to [29], wherein the drug is an antitumor compound;

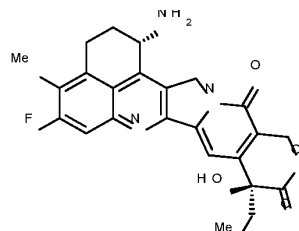
[31]

the antibody-drug conjugate according to [30], wherein the antitumor compound is an antitumor compound represented by the following formula:

[0016]

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[Formula 1]



[0017]

[32]

the antibody-drug conjugate according to any one of [29] to [31], wherein the antibody is conjugated to the drug via a linker having any structure selected from the group consisting of the following formulas (a) to (f):

- (a) $-(\text{Succinimid-3-yl-N})-\text{CH}_2\text{CH}_2-\text{C}(=\text{O})-\text{GGFG}-\text{NH}-\text{CH}_2\text{CH}_2\text{CH}_2-\text{C}(=\text{O})-$,
- (b) $-(\text{Succinimid-3-yl-N})-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{C}(=\text{O})-\text{GGFG}-\text{NH}-\text{CH}_2\text{CH}_2\text{CH}_2-\text{C}(=\text{O})-$,
- (c) $-(\text{Succinimid-3-yl-N})-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{C}(=\text{O})-\text{GGFG}-\text{NH}-\text{CH}_2-\text{O}-\text{CH}_2-\text{C}(=\text{O})-$,
- (d) $-(\text{Succinimid-3-yl-N})-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{C}(=\text{O})-\text{GGFG}-\text{NH}-\text{CH}_2\text{CH}_2-\text{O}-\text{CH}_2-\text{C}(=\text{O})-$,
- (e) $-(\text{Succinimid-3-yl-N})-\text{CH}_2\text{CH}_2-\text{C}(=\text{O})-\text{NH}-\text{CH}_2\text{CH}_2\text{O}-\text{CH}_2\text{CH}_2\text{O}-\text{CH}_2\text{CH}_2-\text{C}(=\text{O})-\text{GGFG}-\text{NH}-\text{CH}_2\text{CH}_2\text{CH}_2-\text{C}(=\text{O})-$, and
- (f) $-(\text{Succinimid-3-yl-N})-\text{CH}_2\text{CH}_2-\text{C}(=\text{O})-\text{NH}-\text{CH}_2\text{CH}_2\text{O}-\text{CH}_2\text{CH}_2\text{O}-\text{CH}_2\text{CH}_2\text{O}-\text{CH}_2\text{CH}_2-\text{C}(=\text{O})-\text{GGFG}-\text{NH}-\text{CH}_2\text{CH}_2\text{CH}_2-\text{C}(=\text{O})-$,

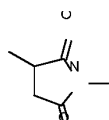
wherein the antibody is connected to the terminus of $-(\text{Succinimid-3-yl-N})$, the antitumor compound is connected to the carbonyl group of the $-(\text{CH}_2)_n-\text{C}(=\text{O})-$ moiety with the nitrogen atom of the amino group at position 1 as a connecting position, GGFG represents an amino acid sequence consisting of glycine-glycine-phenylalanine-glycine linked through peptide bonds, and

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-(Succinimid-3-yl-N)- has a structure represented by the following formula:

[0018]

[Formula 2]



[0019]

which is connected to the antibody at position 3 thereof and is connected to a methylene group in the linker structure containing this structure on the nitrogen atom at position 1;

[33]

the antibody-drug conjugate according to any one of [29] to [32], wherein the linker is represented by any formula selected from the group consisting of the following formulas (c), (d) and (e):

(c) -(Succinimid-3-yl-N)-CH₂CH₂CH₂CH₂CH₂-C(=O)-GGFG-NH-CH₂-O-CH₂-C(=O)-,

(d) -(Succinimid-3-yl-N)-CH₂CH₂CH₂CH₂CH₂-C(=O)-GGFG-NH-CH₂CH₂-O-CH₂-C(=O)-, and

(e) -(Succinimid-3-yl-N)-CH₂CH₂-C(=O)-NH-CH₂CH₂O-CH₂CH₂O-CH₂CH₂-C(=O)-GGFG-NH-CH₂CH₂CH₂-C(=O)-;

[34]

the antibody-drug conjugate according to any one of [29] to [33], wherein the linker is represented by the following formula (c) or (e):

(c) -(Succinimid-3-yl-N)-CH₂CH₂CH₂CH₂CH₂-C(=O)-GGFG-NH-CH₂-O-CH₂-C(=O)-, and

(e) -(Succinimid-3-yl-N)-CH₂CH₂-C(=O)-NH-CH₂CH₂O-CH₂CH₂O-CH₂CH₂-C(=O)-GGFG-NH-CH₂CH₂CH₂-C(=O)-;

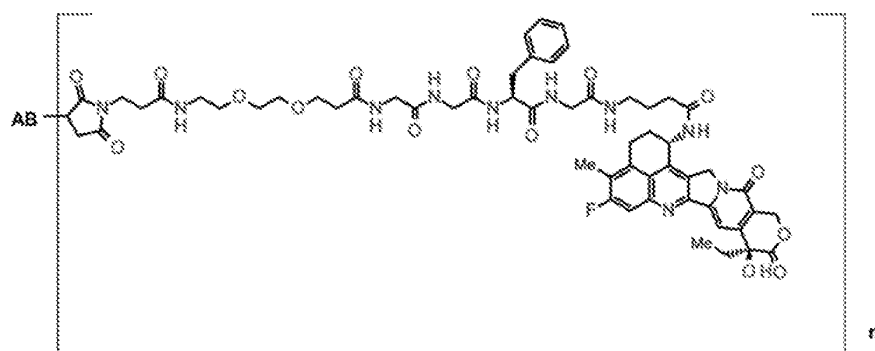
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[35]

the antibody-drug conjugate according to any one of [29] to [34], which has a structure represented by the following formula:

[0020]

[Formula 3]



[0021]

wherein AB represents the antibody or the functional fragment of the antibody, n represents the average number of units of the drug-linker structure conjugated to the antibody per antibody, and the antibody is connected to the linker via a sulfhydryl group derived from the antibody;

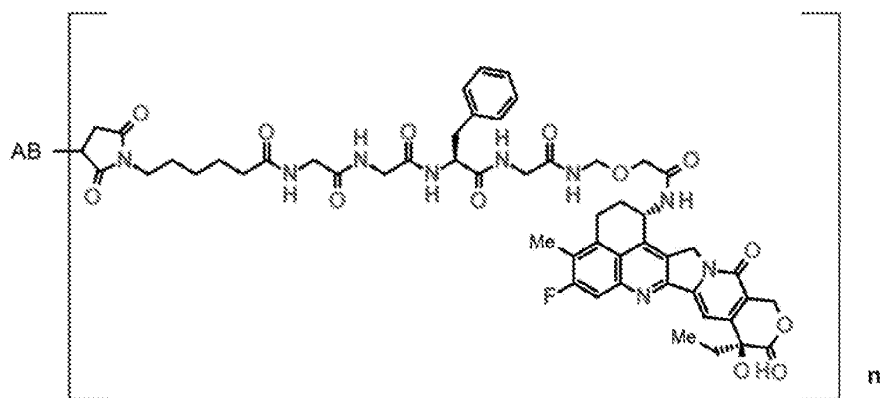
[36]

the antibody-drug conjugate according to any one of [29] to [34], which has a structure represented by the following formula:

[0022]

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[Formula 4]



[0023]

wherein AB represents the antibody or the functional fragment of the antibody, n represents the average number of units of the drug-linker structure conjugated to the antibody per antibody, and the antibody is connected to the linker via a sulfhydryl group derived from the antibody;

[37]

the antibody-drug conjugate according to any one of [29] to [36], wherein the antibody is an antibody comprising a light chain and a heavy chain in any one combination selected from the group consisting of the following combinations (1) to (4), or a functional fragment of the antibody:

- (1) a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 69,
- (2) a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 73,

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(3) a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 65 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 73, and

(4) a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 77;

[38]

the antibody-drug conjugate according to [37], wherein the antibody is an antibody comprising a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 69, or a functional fragment of the antibody;

[39]

the antibody-drug conjugate according to [37], wherein the antibody is an antibody comprising a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 77, or a functional fragment of the antibody;

[40]

the antibody-drug conjugate according to any one of [29] to [39], wherein the heavy chain or the light chain has undergone one or two or more modifications selected from the group consisting of N-linked glycosylation, O-linked glycosylation, N-terminal processing, C-terminal processing, deamidation, isomerization of aspartic acid, oxidation of methionine, addition of a methionine residue to the N-terminus, amidation of a proline residue, conversion of N-terminal glutamine or N-terminal glutamic acid to pyroglutamic acid, and a deletion of one or two amino acids from the carboxyl terminus;

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[41]

the antibody-drug conjugate according to any one of [29] to [40], wherein the average number of units of the selected drug-linker structure conjugated per antibody is in the range of from 1 to 10;

[42]

the antibody-drug conjugate according to [41], wherein the average number of units of the selected drug-linker structure conjugated per antibody is in the range of from 2 to 8;

[43]

the antibody-drug conjugate according to [42], wherein the average number of units of the selected drug-linker structure conjugated per antibody is in the range of from 5 to 8;

[44]

the antibody-drug conjugate according to [43], wherein the average number of units of the selected drug-linker structure conjugated per antibody is in the range of from 7 to 8;

[45]

a pharmaceutical composition comprising the antibody-drug conjugate according to any one of [29] to [44], a salt thereof, or a hydrate of the conjugate or the salt;

[46]

the pharmaceutical composition according to [45], which is an antitumor drug;

[47]

the antitumor drug according to [46], wherein the tumor is a tumor expressing CDH6;

[48]

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the antitumor drug according to [46] or [47], wherein the tumor is renal cell carcinoma, renal clear cell carcinoma, papillary renal cell carcinoma, ovarian cancer, ovarian serous adenocarcinoma or thyroid cancer;

[49]

a method for treating a tumor, which comprises administering any component selected from the antibody-drug conjugate according to any one of [29] to [44], a salt thereof, and a hydrate of the conjugate or the salt to an individual;

[50]

the treatment method according to [49], wherein the tumor is a tumor expressing CDH6;

[51]

the treatment method according to [49] or [50], wherein the tumor is renal cell carcinoma, renal clear cell carcinoma, papillary renal cell carcinoma, ovarian cancer, ovarian serous adenocarcinoma or thyroid cancer;

[52]

a method for treating a tumor, which comprises administering a pharmaceutical composition comprising at least one component selected from the antibody-drug conjugate according to any one of [29] to [44], a salt thereof, and a hydrate of the conjugate or the salt, and at least one antitumor drug to an individual, simultaneously, separately, or continuously;

[53]

a method for producing an antibody-drug conjugate, which comprises the step of culturing the host cells according to [21] or [22], the step of collecting an antibody of interest or a functional fragment of the antibody from the culture obtained by the aforementioned step, and the step of reacting the antibody or the functional fragment of the antibody obtained by the aforementioned step with a drug-linker intermediate compound.

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[Advantageous Effects of Invention]

[0024]

Features of the anti-CDH6 antibody of the present invention are to specifically recognize EC domain 3 (EC3) of CDH6 and to have high internalization activity. An anti-CDH6 antibody-drug conjugate comprising the anti-CDH6 antibody of the present invention conjugated to a drug exerting toxicity in cells via a linker having a specific structure can be expected to achieve an excellent antitumor effect and safety by administration to patients having cancer cells expressing CDH6. Specifically, the anti-CDH6 antibody-drug conjugate of the present invention is useful as an antitumor agent.

[Brief Description of Drawings]

[0025]

[Figure 1] Figure 1 shows flow cytometry results of examining the binding of four rat anti-CDH6 monoclonal antibodies (clone Nos. rG019, rG055, rG056 and rG061) or rat IgG control to control cells or hCDH6-transfected 293T cells. The abscissa depicts FITC fluorescence intensity indicating the amount of the antibody bound, and the ordinate depicts cell count.

[Figure 2-1] Figure 2-1 shows the binding activity of four rat anti-CDH6 monoclonal antibodies (rG019, rG055, rG056 and rG061) or negative control antibody Rat IgG2b against control cells or full-length hCDH6-transfected 293 cells. The abscissa depicts FITC fluorescence intensity indicating the amount of the antibody bound, and the ordinate depicts cell count.

[Figure 2-2] Figure 2-2 shows the binding activity of four rat anti-CDH6 monoclonal antibodies (rG019, rG055, rG056 and rG061) or rat IgG control against control cells or EC1-deleted hCDH6-transfected 293 cells. The abscissa depicts FITC fluorescence intensity indicating the amount of the antibody bound, and the ordinate depicts cell count.

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[Figure 2-3] Figure 2-3 shows the binding activity of four rat anti-CDH6 monoclonal antibodies (rG019, rG055, rG056 and rG061) or rat IgG control against control cells or EC2-deleted hCDH6-transfected 293 cells. The abscissa depicts FITC fluorescence intensity indicating the amount of the antibody bound, and the ordinate depicts cell count.

[Figure 2-4] Figure 2-4 shows the binding activity of four rat anti-CDH6 monoclonal antibodies (rG019, rG055, rG056 and rG061) or rat IgG control against control cells or EC3-deleted hCDH6-transfected 293 cells. The abscissa depicts FITC fluorescence intensity indicating the amount of the antibody bound, and the ordinate depicts cell count.

[Figure 2-5] Figure 2-5 shows the binding activity of four rat anti-CDH6 monoclonal antibodies (rG019, rG055, rG056 and rG061) or rat IgG control against control cells or EC4-deleted hCDH6-transfected 293 cells. The abscissa depicts FITC fluorescence intensity indicating the amount of the antibody bound, and the ordinate depicts cell count.

[Figure 2-6] Figure 2-6 shows the binding activity of four rat anti-CDH6 monoclonal antibodies (rG019, rG055, rG056 and rG061) or rat IgG control against control cells or EC5-deleted hCDH6-transfected 293 cells. The abscissa depicts FITC fluorescence intensity indicating the amount of the antibody bound, and the ordinate depicts cell count.

[Figure 3] Figure 3 shows flow cytometry results of evaluating the expression of CDH6 on the cell membrane surface of 4 types of human tumor cell lines (human ovarian tumor cell lines NIH:OVCAR-3, PA-1, and ES-2 and human renal cell tumor cell line 786-O). The abscissa depicts FITC fluorescence intensity indicating the amount of the antibody bound, and the ordinate depicts cell count.

[Figure 4] Figure 4 shows a graph on which the internalization activity of 4 types of rat anti-CDH6 antibodies (rG019, rG055, rG056 and rG061) or rat IgG control was

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evaluated in NIH:OVCAR-3 cells and 786-O cells using anti-rat IgG reagent Rat-ZAP conjugated with a toxin (saporin) inhibiting protein synthesis, or Goat Anti-Rat IgG, Fc (gamma) Fragment Specific unconjugated with the toxin as a negative control. The ordinate of the graph depicts ATP activity (RLU). A cell survival rate (%), calculated as a relative survival rate when the number of live cells in a well supplemented with the negative control instead of Rat-ZAP was defined as 100%, is shown below each graph.

[Figure 5] Figure 5 shows the binding of human chimeric anti-CDH6 antibody chG019 to human CDH6 and monkey CDH6. The abscissa depicts antibody concentration, and the ordinate depicts the amount of antibody bound based on mean fluorescence intensity.

[Figure 6-1] Figures 6-1 and 6-2 each show the binding activity of four humanized hG019 antibodies (H01L02, H02L02, H02L03 and H04L02) or a negative control antibody human IgG1 against human CDH6, monkey CDH6, mouse CDH6, and rat CDH6. The abscissa depicts antibody concentration, and the ordinate depicts the amount of the antibody bound based on mean fluorescence intensity.

[Figure 6-2] Figures 6-1 and 6-2 each show the binding activity of four humanized hG019 antibodies (H01L02, H02L02, H02L03 and H04L02) or negative control antibody human IgG1 against human CDH6, monkey CDH6, mouse CDH6, and rat CDH6. The abscissa depicts antibody concentration, and the ordinate depicts the amount of the antibody bound based on mean fluorescence intensity.

[Figure 7-1] Figure 7-1 shows the binding activity of four humanized hG019 antibodies (H01L02, H02L02, H02L03 and H04L02), anti-CDH6 antibody NOV0712 or negative control antibody hIgG1 against control cells or full-length hCDH6-transfected 293 α cells. The abscissa depicts APC fluorescence intensity indicating the amount of the antibody bound. The ordinate depicts cell count.

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[Figure 7-2] Figure 7-2 shows the binding activity of four humanized hG019 antibodies (H01L02, H02L02, H02L03 and H04L02), anti-CDH6 antibody NOV0712 or negative control antibody hIgG1 against control cells or EC1-deleted hCDH6-transfected 293 α cells. The abscissa depicts APC fluorescence intensity indicating the amount of the antibody bound. The ordinate depicts cell count.

[Figure 7-3] Figure 7-3 shows the binding activity of four humanized hG019 antibodies (H01L02, H02L02, H02L03 and H04L02), anti-CDH6 antibody NOV0712 or negative control antibody hIgG1 against control cells or EC2-deleted hCDH6-transfected 293 α cells. The abscissa depicts APC fluorescence intensity indicating the amount of the antibody bound. The ordinate depicts cell count.

[Figure 7-4] Figure 7-4 shows the binding activity of four humanized hG019 antibodies (H01L02, H02L02, H02L03 and H04L02), anti-CDH6 antibody NOV0712 or negative control antibody hIgG1 against control cells or EC3-deleted hCDH6-transfected 293 α cells. The abscissa depicts APC fluorescence intensity indicating the amount of the antibody bound. The ordinate depicts cell count.

[Figure 7-5] Figure 7-5 shows the binding activity of four humanized hG019 antibodies (H01L02, H02L02, H02L03 and H04L02), anti-CDH6 antibody NOV0712 or negative control hIgG1 against control cells or EC4-deleted hCDH6-transfected 293 α cells. The abscissa depicts APC fluorescence intensity indicating the amount of the antibody bound. The ordinate depicts cell count.

[Figure 7-6] Figure 7-6 shows the binding activity of four humanized hG019 antibodies (H01L02, H02L02, H02L03 and H04L02), anti-CDH6 antibody NOV0712 or negative control hIgG1 against control cells or EC5-deleted hCDH6-transfected 293 α cells. The abscissa depicts APC fluorescence intensity indicating the amount of the antibody bound. The ordinate depicts cell count.

[Figure 8] Figure 8 shows flow cytometry results of examining the expression of human CDH6 in 786-O/hCDH6 stably expressing cell line and its parent cell line

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786-O. The abscissa depicts Alexa Fluor 647 fluorescence intensity indicating the amount of the antibody bound, and the ordinate depicts a cell count.

[Figure 9] Figure 9 shows the binding competition assay of four unlabeled humanized hG019 antibodies (H01L02, H02L02, H02L03 and H04L02), anti-CDH6 antibody NOV0712 or negative control hIgG1 using (a) labeled NOV0712 or (b) labeled H01L02. The abscissa depicts the final concentration of the added unlabeled antibody, and the ordinate depicts the amount of the antibody bound based on mean fluorescence intensity.

[Figure 10-1] Figure 10-1 shows a graph on which the internalization activity of four humanized hG019 antibodies (H01L02, H02L02, H02L03 and H04L02), anti-CDH6 antibody NOV0712 and a negative control antibody was evaluated in NIH:OVCAR-3 cells using anti-human IgG reagent Hum-ZAP conjugated with a toxin (saporin) inhibiting protein synthesis, or F(ab')₂ Fragment Goat Anti-human IgG, Fc (gamma) Fragment Specific unconjugated with the toxin as a negative control. The ordinate of the graph depicts ATP activity (RLU). A cell survival rate (%), calculated as a relative survival rate when the number of live cells in a well supplemented with the negative control instead of Hum-ZAP was defined as 100%, is shown below each graph.

[Figure 10-2] Figure 10-2 shows a graph on which the internalization activity of four humanized hG019 antibodies (H01L02, H02L02, H02L03 and H04L02), anti-CDH6 antibody NOV0712 and a negative control antibody was evaluated in 786-O cells using anti-human IgG reagent Hum-ZAP conjugated with a toxin (saporin) inhibiting protein synthesis, or F(ab')₂ Fragment Goat Anti-human IgG, Fc (gamma) Fragment Specific unconjugated with the toxin as a negative control. The ordinate of the graph depicts ATP activity (RLU). A cell survival rate (%), calculated as a relative survival rate when the number of live cells in a well supplemented with the negative control instead of Hum-ZAP was defined as 100%, is shown below each graph.

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[Figure 10-3] Figure 10-3 shows a graph on which the internalization activity of four humanized hG019 antibodies (H01L02, H02L02, H02L03 and H04L02), anti-CDH6 antibody NOV0712 and a negative control antibody was evaluated in PA-1 cells using anti-human IgG reagent Hum-ZAP conjugated with a toxin (saporin) inhibiting protein synthesis, or F(ab')₂ Fragment Goat Anti-human IgG, Fc (gamma) Fragment Specific unconjugated with the toxin as a negative control. The ordinate of the graph depicts ATP activity (RLU). A cell survival rate (%), calculated as a relative survival rate when the number of live cells in a well supplemented with the negative control instead of Hum-ZAP was defined as 100%, is shown below each graph.

[Figure 11] Figure 11 shows results of evaluating the *in vitro* cell growth inhibition activity of four humanized hG019-drug conjugates (H01L02-DXd, H02L02-DXd, H02L03-DXd and H04L02-DXd) or NOV0712-DM4 against PA-1 cells. The abscissa depicts an antibody-drug conjugate concentration, and the ordinate depicts cell survival rate (%).

[Figure 12] Figure 12 shows the *in vivo* antitumor effects of four humanized hG019-drug conjugates (H01L02-DXd, H02L02-DXd, H02L03-DXd and H04L02-DXd) or NOV0712-DM4. The evaluation was conducted using animal models in which CDH6-positive human renal cell tumor cell line 786-O was inoculated into immunodeficient mice. The abscissa depicts the number of days, and the ordinate depicts tumor volume. The error range depicts a standard error (SE) value.

[Figure 13] Figure 13 shows the *in vivo* antitumor effects of the humanized hG019-drug conjugate H01L02-DXd or NOV0712-DM4 or NOV0712-DXd. The evaluation was conducted using animal models in which CDH6-positive human ovarian tumor cell line PA-1 was inoculated into immunodeficient mice. The abscissa depicts the number of days, and the ordinate depicts tumor volume. The error range depicts a SE value.

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[Figure 14] Figure 14 shows the *in vivo* antitumor effects of the humanized hG019-drug conjugate H01L02-DXd or NOV0712-DM4. The evaluation was conducted using animal models in which CDH6-positive human ovarian tumor cell line NIH:OVCAR-3 was inoculated into immunodeficient mice. The abscissa depicts the number of days, and the ordinate depicts tumor volume. The error range depicts a SE value.

[Figure 15] Figure 15 shows the *in vivo* antitumor effects of the humanized hG019-drug conjugate H01L02-DXd or NOV0712-DM4. The evaluation was conducted using animal models in which CDH6-positive human renal cell tumor cell line 786-O was inoculated into immunodeficient mice. The abscissa depicts the number of days, and the ordinate depicts tumor volume. The error range depicts a SE value.

[Figure 16] Figure 16 shows the *in vivo* antitumor effects of the humanized hG019-drug conjugate H01L02-DXd or NOV0712-DM4. The evaluation was conducted using animal models in which CDH6-negative human ovarian tumor cell line ES-2 was inoculated into immunodeficient mice. The abscissa depicts the number of days, and the ordinate depicts tumor volume. The error range depicts a SE value.

[Description of Embodiments]

[0026]

Hereinafter, the preferred embodiments for carrying out the present invention will be described with reference to the drawings. It is to be noted that the embodiments described below merely illustrate the representative embodiments of the present invention, and the scope of the present invention shall not be narrowly interpreted due to these examples.

[0027]

In the present description, the term "cancer" is used to have the same meaning as that of the term "tumor".

[0028]

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In the present description, the term "gene" is used to include not only DNA but also its mRNA and cDNA, and cRNA thereof.

[0029]

In the present description, the term "polynucleotide" or "nucleotide" is used to have the same meaning as that of a nucleic acid, and also includes DNA, RNA, a probe, an oligonucleotide, and a primer. In the present description, the terms "polynucleotide" and "nucleotide" can be used interchangeably with each other unless otherwise specified.

[0030]

In the present description, the terms "polypeptide" and "protein" can be used interchangeably with each other.

In the present description, the term "cell" includes cells in an individual animal, and cultured cells.

[0031]

In the present description, the term "CDH6" can be used to have the same meaning as that of the CDH6 protein. In the present description, human CDH6 is also referred to as "hCDH6".

[0032]

In the present description, the term "cytotoxic activity" is used to mean that a pathologic change is caused to cells in any given way. The term not only means a direct trauma, but also means all types of structural or functional damage caused to cells, such as DNA cleavage, formation of a base dimer, chromosomal cleavage, damage to cell mitotic apparatus, and a reduction in the activities of various types of enzymes.

[0033]

In the present description, the phrase "exerting toxicity in cells" is used to mean that toxicity is exhibited in cells in any given way. The term not only means

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a direct trauma, but also means all types of structural, functional, or metabolic influences caused to cells, such as DNA cleavage, formation of a base dimer, chromosomal cleavage, damage to cell mitotic apparatus, a reduction in the activities of various types of enzymes, and suppression of effects of cell growth factors.

[0034]

In the present description, the term "functional fragment of an antibody", also called "antigen-binding fragment of an antibody", is used to mean a partial fragment of the antibody having binding activity against an antigen, and includes Fab, F(ab')₂, scFv, a diabody, a linear antibody and a multispecific antibody formed from antibody fragments, and the like. Fab', which is a monovalent fragment of antibody variable regions obtained by treating F(ab')₂ under reducing conditions, is also included in the antigen-binding fragment of an antibody. However, the antigen-binding fragment of an antibody is not limited to these molecules, as long as the antigen-binding fragment has antigen-binding ability. These antigen-binding fragments include not only those obtained by treating a full-length molecule of an antibody protein with an appropriate enzyme, but proteins produced in appropriate host cells using a genetically engineered antibody gene.

[0035]

In the present description, the term "epitope" is used to mean the partial peptide or partial three-dimensional structure of CDH6, to which a specific anti-CDH6 antibody binds. Such an epitope, which is the above-described partial peptide of CDH6, can be determined by a method well known to a person skilled in the art, such as an immunoassay. First, various partial structures of an antigen are produced. As regards production of such partial structures, a known oligopeptide synthesis technique can be applied. For example, a series of polypeptides, in which CDH6 has been successively truncated at an appropriate length from the C-terminus or N-terminus thereof, are produced by a genetic recombination technique well

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known to a person skilled in the art. Thereafter, the reactivity of an antibody to such polypeptides is studied, and recognition sites are roughly determined. Thereafter, further shorter peptides are synthesized, and the reactivity thereof to these peptides can then be studied, so as to determine an epitope. When an antibody binding to a membrane protein having a plurality of extracellular domains is directed to a three-dimensional structure composed of a plurality of domains as an epitope, the domain to which the antibody binds can be determined by modifying the amino acid sequence of a specific extracellular domain, and thereby modifying the three-dimensional structure. The epitope, which is a partial three-dimensional structure of an antigen that binds to a specific antibody, can also be determined by specifying the amino acid residues of an antigen adjacent to the antibody by X-ray structural analysis.

[0036]

In the present description, the phrase "antibodies binding to the same epitope" is used to mean antibodies that bind to a common epitope. If a second antibody binds to a partial peptide or a partial three-dimensional structure to which a first antibody binds, it can be determined that the first antibody and the second antibody bind to the same epitope. Alternatively, by confirming that a second antibody competes with a first antibody for the binding of the first antibody to an antigen (i.e., a second antibody interferes with the binding of a first antibody to an antigen), it can be determined that the first antibody and the second antibody bind to the same epitope, even if the specific sequence or structure of the epitope has not been determined. In the present description, the phrase "binding to the same epitope" refers to the case where it is determined that the first antibody and the second antibody bind to a common epitope by any one or both of these determination methods. When a first antibody and a second antibody bind to the same epitope and further, the first antibody has special effects such as antitumor activity or

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internalization activity, the second antibody can be expected to have the same activity as that of the first antibody.

[0037]

In the present description, the term "CDR" is used to mean a complementarity determining region. It is known that the heavy chain and light chain of an antibody molecule each have three CDRs. Such a CDR is also referred to as a hypervariable region, and is located in the variable regions of the heavy chain and light chain of an antibody. These regions have a particularly highly variable primary structure and are separated into three sites on the primary structure of the polypeptide chain in each of the heavy chain and light chain. In the present description, with regard to the CDR of an antibody, the CDRs of a heavy chain are referred to as CDRH1, CDRH2 and CDRH3, respectively, from the amino-terminal side of the amino acid sequence of the heavy chain, whereas the CDRs of a light chain are referred to as CDRL1, CDRL2 and CDRL3, respectively, from the amino-terminal side of the amino acid sequence of the light chain. These sites are located close to one another on the three-dimensional structure, and determine the specificity of the antibody to an antigen to which the antibody binds.

[0038]

In the present invention, the phrase "hybridizing under stringent conditions" is used to mean that hybridization is carried out in the commercially available hybridization solution ExpressHyb Hybridization Solution (manufactured by Clontech Laboratories, Inc.) at 68°C, or that hybridization is carried out under conditions in which hybridization is carried out using a DNA-immobilized filter in the presence of 0.7 to 1.0 M NaCl at 68°C, and the resultant is then washed at 68°C with a 0.1- to 2-fold concentration of SSC solution (wherein 1-fold concentration of SSC consists of 150 mM NaCl and 15 mM sodium citrate) for identification, or conditions equivalent thereto.

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[0039]

In the present description, the term "one to several" is used to mean 1 to 10, 1 to 9, 1 to 8, 1 to 7, 1 to 6, 1 to 5, 1 to 4, 1 to 3, or 1 or 2.

[0040]

1. CDH6

Cadherins are glycoproteins present on the surface of cell membranes and function as cell-cell adhesion molecules through the calcium ion-dependent binding of their N-terminal extracellular domains, or as signal molecules responsible for cell-cell interaction. Classic cadherins are in the cadherin superfamily and are single-pass transmembrane proteins composed of five extracellular domains (EC domains), one transmembrane region, and an intracellular domain.

[0041]

CDH6 (cadherin-6) is a single-pass transmembrane protein composed of 790 amino acids, which is classified into the type II cadherin family, and this protein has N-terminal extracellular and C-terminal intracellular domains. The human CDH6 gene was cloned for the first time in 1995 (Non Patent Literature 1), and its sequence can be referred to under, for example, accession Nos. NM_004932 and NP_004923 (NCBI).

[0042]

The CDH6 protein used in the present invention can be directly purified from the CDH6-expressing cells of a human or a non-human mammal (e.g., a rat, a mouse or a monkey) and can then be used, or a cell membrane fraction of the aforementioned cells can be prepared and can be used as the CDH6 protein. Alternatively, CDH6 can also be obtained by synthesizing it *in vitro*, or by allowing host cells to produce CDH6 by genetic manipulation. According to such genetic manipulation, the CDH6 protein can be obtained, specifically, by incorporating CDH6 cDNA into a vector capable of expressing the CDH6 cDNA, and then

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synthesizing CDH6 in a solution containing enzymes, substrate and energetic materials necessary for transcription and translation, or by transforming the host cells of other prokaryotes or eukaryotes, so as to allow them to express CDH6. Also, CDH6-expressing cells based on the above-described genetic manipulation, or a cell line expressing CDH6 may be used to present the CDH6 protein. Alternatively, the expression vector into which CDH6 cDNA has been incorporated can be directly administered to an animal to be immunized, and CDH6 can be expressed in the body of the animal thus immunized.

[0043]

Moreover, a protein which consists of an amino acid sequence comprising a substitution, deletion and/or addition of one or several amino acids in the above-described amino acid sequence of CDH6, and has a biological activity equivalent to that of the CDH6 protein, is also included within the term "CDH6".

[0044]

The human CDH6 protein has the amino acid sequence shown in SEQ ID NO:

1. The extracellular region of the human CDH6 protein is composed of extracellular domain 1 (in the present description, also referred to as EC1) having the amino acid sequence at positions 54 to 159 in the amino acid sequence shown in SEQ ID NO: 1, extracellular domain 2 (in the present description, also referred to as EC2) having the amino acid sequence at positions 160 to 268 in the amino acid sequence shown in SEQ ID NO: 1, extracellular domain 3 (in the present description, also referred to as EC3) having the amino acid sequence at positions 269 to 383 in the amino acid sequence shown in SEQ ID NO: 1, extracellular domain 4 (in the present description, also referred to as EC4) having the amino acid sequence at positions 384 to 486 in the amino acid sequence shown in SEQ ID NO: 1, and extracellular domain 5 (in the present description, also referred to as EC5) having the amino acid sequence at positions 487 to 608 in the amino acid sequence shown in

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SEQ ID NO: 1. The amino acid sequences of EC1 to EC5 are shown in SEQ ID NOs: 2 to 6, respectively (Table 1-1 to Table 1-15).

[0045]

2. Production of anti-CDH6 antibody

One example of the anti-CDH6 antibody of the present invention can include an anti-CDH6 antibody which recognizes an amino acid sequence comprising the amino acid sequence shown in SEQ ID NO: 4, and has internalization activity. One example of the anti-CDH6 antibody of the present invention can include an anti-CDH6 antibody which specifically recognizes an amino acid sequence comprising the amino acid sequence shown in SEQ ID NO: 4, and has internalization activity. One example of the anti-CDH6 antibody of the present invention can include an anti-CDH6 antibody which recognizes an amino acid sequence consisting of the amino acid sequence shown in SEQ ID NO: 4, and has internalization activity. One example of the anti-CDH6 antibody of the present invention can include an anti-CDH6 antibody which specifically recognizes an amino acid sequence consisting of the amino acid sequence shown in SEQ ID NO: 4, and has internalization activity.

[0046]

The anti-CDH6 antibody of the present invention may be derived from any species. Preferred examples of the species can include humans, monkeys, rats, mice and rabbits. When the anti-CDH6 antibody of the present invention is derived from a species other than humans, it is preferred to chimerize or humanize the anti-CDH6 antibody by a well-known technique. The antibody of the present invention may be a polyclonal antibody or may be a monoclonal antibody, and a monoclonal antibody is preferred.

[0047]

The anti-CDH6 antibody of the present invention is an antibody that can target tumor cells. Specifically, the anti-CDH6 antibody of the present invention

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possesses the property of being able to recognize tumor cells, the property of being able to bind to tumor cells, and/or the property of being internalized into tumor cells by cellular uptake, and the like. Accordingly, the anti-CDH6 antibody of the present invention can be conjugated to a compound having antitumor activity via a linker to prepare an antibody-drug conjugate.

[0048]

The binding activity of an antibody against tumor cells can be confirmed by flow cytometry. The uptake of an antibody into tumor cells can be confirmed by (1) an assay of visualizing a cellularly taken-up antibody under a fluorescent microscope using a secondary antibody (fluorescently labeled) binding to the antibody (Cell Death and Differentiation, 2008, 15, 751-761), (2) an assay of measuring the amount of cellularly taken-up fluorescence using a secondary antibody (fluorescently labeled) binding to the antibody (Molecular Biology of the Cell Vol. 15, 5268-5282, December 2004) or (3) a Mab-ZAP assay using an immunotoxin binding to the antibody, wherein the toxin is released upon cellular uptake, so as to suppress cell growth (Bio Techniques 28: 162-165, January 2000). A recombinant conjugated protein of a catalytic region of diphtheria toxin and protein G may be used as the immunotoxin.

[0049]

In the present description, the term "high internalization ability" is used to mean that the survival rate (which is indicated by a ratio relative to a cell survival rate without antibody addition defined as 100%) of CDH6-expressing cells to which the aforementioned antibody and a saporin-labeled anti-rat IgG antibody have been administered is preferably 70% or less, and more preferably 60% or less.

[0050]

The antitumor antibody-drug conjugate of the present invention comprises a conjugated compound exerting an antitumor effect. Therefore, it is preferred, but

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not essential, that the antibody itself should have an antitumor effect. For the purpose of specifically and/or selectively exerting the cytotoxicity of the antitumor compound in tumor cells, it is important and preferred that the antibody should have a property of being internalized and transferred into tumor cells.

[0051]

The anti-CDH6 antibody can be obtained by immunizing an animal with a polypeptide serving as an antigen by a method usually performed in this field, and then collecting and purifying an antibody produced in a living body thereof. It is preferred to use CDH6 retaining a three-dimensional structure as an antigen. Examples of such a method can include a DNA immunization method.

[0052]

The origin of the antigen is not limited to a human, and thus, an animal can also be immunized with an antigen derived from a non-human animal such as a mouse or a rat. In this case, an antibody applicable to the disease of a human can be selected by examining the cross-reactivity of the obtained antibody binding to the heterologous antigen with the human antigen.

[0053]

Furthermore, antibody-producing cells that produce an antibody against the antigen can be fused with myeloma cells according to a known method (e.g., Kohler and Milstein, *Nature* (1975) 256, 495-497; and Kennet, R. ed., *Monoclonal Antibodies*, 365-367, Plenum Press, N. Y. (1980)) to establish hybridomas, so as to obtain a monoclonal antibody.

[0054]

Hereinafter, the method for obtaining an antibody against CDH6 will be specifically described.

[0055]

(1) Preparation of antigen

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The antigen can be obtained by allowing host cells to produce a gene encoding the antigen protein according to genetic manipulation. Specifically, a vector capable of expressing the antigen gene is produced, and the vector is then introduced into host cells, so that the gene is expressed therein, and thereafter, the expressed antigen may be purified. The antibody can also be obtained by a method of immunizing an animal with the antigen-expressing cells based on the above-described genetic manipulation, or a cell line expressing the antigen.

[0056]

Alternatively, the antibody can also be obtained, without the use of the antigen protein, by incorporating cDNA of the antigen protein into an expression vector, then administering the expression vector to an animal to be immunized, and expressing the antigen protein in the body of the animal thus immunized, so that an antibody against the antigen protein is produced therein.

[0057]

(2) Production of anti-CDH6 monoclonal antibody

The anti-CDH6 antibody used in the present invention is not particularly limited. For example, an antibody specified by an amino acid sequence shown in the sequence listing of the present application can be suitably used. The anti-CDH6 antibody used in the present invention is desirably an antibody having the following properties:

(1) an antibody having the following properties:

(a) specifically binding to CDH6, and

(b) having the activity of being internalized into CDH6-expressing cells by binding to CDH6;

(2) the antibody according to the above (1) or the aforementioned antibody, wherein the CDH6 is human CDH6; or

(3) specifically recognizing EC3 of human CDH6, and having internalization activity.

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The method for obtaining the antibody against CDH6 of the present invention is not particularly limited as long as an anti-CDH6 antibody can be obtained. It is preferred to use CDH6 retaining its conformation as an antigen.

[0058]

One preferred example of the method for obtaining the antibody can include a DNA immunization method. The DNA immunization method is an approach which involves transfecting an animal (e.g., mouse or rat) individual with an antigen expression plasmid, and then expressing the antigen in the individual to induce immunity against the antigen. The transfection approach includes a method of directly injecting the plasmid to the muscle, a method of injecting a transfection reagent such as a liposome or polyethylenimine to the vein, an approach using a viral vector, an approach of injecting gold particles attached with the plasmid using a gene gun, a hydrodynamic method of rapidly injecting a plasmid solution in a large amount to the vein, and the like. With regard to the transfection method of injecting the expression plasmid to the muscle, a technique called *in vivo* electroporation, which involves applying electroporation to the intramuscular injection site of the plasmid, is known as an approach for improving expression levels (Aihara H, Miyazaki J. Nat Biotechnol. 1998 Sep; 16 (9): 867-70 or Mir LM, Bureau MF, Gehl J, Rangara R, Rouy D, Caillaud JM, Delaere P, Branellec D, Schwartz B, Scherman D. Proc Natl Acad Sci U S A. 1999 Apr 13; 96 (8): 4262-7). This approach further improves the expression level by treating the muscle with hyaluronidase before the intramuscular injection of the plasmid (McMahon JM1, Signori E, Wells KE, Fazio VM, Wells DJ., Gene Ther. 2001 Aug; 8 (16): 1264-70). Furthermore, the hybridoma production can be performed by a known method, and can also be performed using, for example, a Hybrimmune Hybridoma Production System (Cytoscreen, Inc.).

[0059]

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Specific examples of obtaining a monoclonal antibody can include the following procedures:

- (a) immune response can be induced by incorporating CDH6 cDNA into an expression vector (e.g., pcDNA3.1; Thermo Fisher Scientific Inc.), and directly administering the vector to an animal (e.g., a rat or a mouse) to be immunized by a method such as electroporation or a gene gun, so as to express CDH6 in the body of the animal. The administration of the vector by electroporation or the like may be performed one or more times, preferably a plurality of times, if necessary for enhancing antibody titer;
- (b) collection of tissue (e.g., a lymph node) containing antibody-producing cells from the aforementioned animal in which the immune response has been induced;
- (c) preparation of myeloma cells (hereinafter, referred to as "myelomas") (e.g., mouse myeloma SP2/0-ag14 cells);
- (d) cell fusion between the antibody-producing cells and the myelomas;
- (e) selection of a hybridoma group producing an antibody of interest;
- (f) division into single cell clones (cloning);
- (g) optionally, the culture of hybridomas for the mass production of monoclonal antibodies, or the breeding of animals into which the hybridomas are inoculated; and/or
- (h) study of the physiological activity (internalization activity) and binding specificity of the monoclonal antibody thus produced, or examination of the properties of the antibody as a labeling reagent.

[0060]

Examples of the method for measuring the antibody titer used herein can include, but are not limited to, flow cytometry and Cell-ELISA.

[0061]

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Examples of the hybridoma strain thus established can include anti-CDH6 antibody-producing hybridomas rG019, rG055, rG056 and rG061. It is to be noted that, in the present description, an antibody produced by the anti-CDH6 antibody-producing hybridoma rG019 is referred to as a "rG019 antibody" or simply "rG019", an antibody produced by the hybridoma rG055 is referred to as a "rG055 antibody" or simply "rG055", an antibody produced by the hybridoma rG056 is referred to as a "rG056 antibody" or simply "rG056", and an antibody produced by the hybridoma rG061 is referred to as a "rG061 antibody" or simply "rG061".

[0062]

The light chain variable region of the rG019 antibody consists of the amino acid sequence shown in SEQ ID NO: 10. The amino acid sequence of the light chain variable region of the rG019 antibody is encoded by the nucleotide sequence shown in SEQ ID NO: 11. The light chain variable region of the rG019 antibody has CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 12, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 13, and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 14. The heavy chain variable region of the rG019 antibody consists of the amino acid sequence shown in SEQ ID NO: 15. The amino acid sequence of the heavy chain variable region of the rG019 antibody is encoded by the nucleotide sequence shown in SEQ ID NO: 16. The heavy chain variable region of the rG019 antibody has CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 17, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 18, and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 19. The sequence of the rG019 antibody is shown in Table 1-1 to Table 1-15.

[0063]

The light chain variable region of the rG055 antibody consists of the amino acid sequence shown in SEQ ID NO: 20. The amino acid sequence of the light

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chain variable region of the rG055 antibody is encoded by the nucleotide sequence shown in SEQ ID NO: 21. The light chain variable region of the rG055 antibody has CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 22, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 23, and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 24. The heavy chain variable region of the rG055 antibody consists of the amino acid sequence shown in SEQ ID NO: 25. The amino acid sequence of the heavy chain variable region of the rG055 antibody is encoded by the nucleotide sequence shown in SEQ ID NO: 26. The heavy chain variable region of the rG055 antibody has CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 27, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 28, and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 29. The sequence of the rG055 antibody is shown in Table 1-1 to Table 1-15.

[0064]

The light chain variable region of the rG056 antibody consists of the amino acid sequence shown in SEQ ID NO: 30. The amino acid sequence of the light chain variable region of the rG056 antibody is encoded by the nucleotide sequence shown in SEQ ID NO: 31. The light chain variable region of the rG056 antibody has CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 32, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 33, and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 34. The heavy chain variable region of the rG056 antibody consists of the amino acid sequence shown in SEQ ID NO: 35. The amino acid sequence of the heavy chain variable region of the rG056 antibody is encoded by the nucleotide sequence shown in SEQ ID NO: 36. The heavy chain variable region of the rG056 antibody has CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 37, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 38, and CDRH3

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consisting of the amino acid sequence shown in SEQ ID NO: 39. The sequence of the rG056 antibody is shown in Table 1-1 to Table 1-15.

[0065]

The light chain variable region of the rG061 antibody consists of the amino acid sequence shown in SEQ ID NO: 40. The amino acid sequence of the light chain variable region of the rG061 antibody is encoded by the nucleotide sequence shown in SEQ ID NO: 41. The light chain variable region of the rG061 antibody has CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 42, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 43, and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 44. The heavy chain variable region of the rG061 antibody consists of the amino acid sequence shown in SEQ ID NO: 45. The amino acid sequence of the heavy chain variable region of the rG061 antibody is encoded by the nucleotide sequence shown in SEQ ID NO: 46. The heavy chain variable region of the rG061 antibody has CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 47, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 48, and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 49. The sequence of the rG061 antibody is shown.

[0066]

Furthermore, in the case where the steps (a) to (h) in the above "2. Production of anti-CDH6 antibody" are carried out again to obtain independently a monoclonal antibody separately and also in the case where a monoclonal antibody is obtained separately by other methods, an antibody having internalization activity equivalent to that of the rG019 antibody, the rG055 antibody, the rG056 antibody or the rG061 antibody can be obtained. One example of such an antibody can include an antibody binding to the same epitope to which the rG019 antibody, the rG055 antibody, the rG056 antibody or the rG061 antibody binds. If a newly prepared

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monoclonal antibody binds to a partial peptide or a partial three-dimensional structure to which the rG019 antibody, the rG055 antibody, the rG056 antibody or the rG061 antibody binds, it can be determined that the monoclonal antibody binds to the same epitope to which the rG019 antibody, the rG055 antibody, the rG056 antibody or the rG061 antibody binds. Moreover, by confirming that the monoclonal antibody competes with the rG019 antibody, the rG055 antibody, the rG056 antibody or the rG061 antibody in the binding of the antibody to CDH6 (i.e., the monoclonal antibody interferes with the binding of the rG019 antibody, the rG055 antibody, the rG056 antibody or the rG061 antibody to CDH6), it can be determined that the monoclonal antibody binds to the same epitope to which the anti-CDH6 antibody binds, even if the specific sequence or structure of the epitope has not been determined. When it is confirmed that the monoclonal antibody binds to the same epitope to which the rG019 antibody, the rG055 antibody, the rG056 antibody or the rG061 antibody binds, then it is strongly expected that the monoclonal antibody should have antigen-binding ability, biological activity and/or internalization activity equivalent to that of the rG019 antibody, the rG055 antibody, the rG056 antibody or the rG061 antibody.

[0067]

(3) Other antibodies

The antibody of the present invention also includes genetically recombinant antibodies that have been artificially modified for the purpose of reducing heterogenetic antigenicity to humans, such as a chimeric antibody, a humanized antibody and a human antibody, as well as the above-described monoclonal antibody against CDH6. These antibodies can be produced by known methods.

[0068]

Example of the chimeric antibody can include antibodies in which a variable region and a constant region are heterologous to each other, such as a chimeric

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antibody formed by conjugating the variable region of a mouse- or rat-derived antibody to a human-derived constant region (see Proc. Natl. Acad. Sci. U.S.A., 81, 6851-6855, (1984)).

[0069]

Examples of the chimeric antibody derived from the rat anti-human CDH6 antibody include an antibody consisting of a light chain comprising the light chain variable region of each rat anti-human CDH6 antibody described in the present description (e.g., the rG019 antibody, the rG055 antibody, the rG056 antibody or the rG061 antibody) and a human-derived constant region, and a heavy chain comprising the heavy chain variable region thereof and a human-derived constant region.

[0070]

Other examples of the chimeric antibody derived from the rat anti-human CDH6 antibody include an antibody consisting of a light chain comprising a light chain variable region having a substitution of one to several residues, 1 to 3 residues, 1 or 2 residues, preferably 1 residue, of amino acids in the light chain variable region of each rat anti-human CDH6 antibody described in the present description (e.g., the rG019 antibody, the rG055 antibody, the rG056 antibody or the rG061 antibody) with other amino acid residues, and a heavy chain comprising a heavy chain variable region having a substitution of one to several residues, 1 to 3 residues, 1 or 2 residues, preferably 1 residue, of amino acids in the heavy chain variable region thereof with other amino acid residues. This antibody may have any given human-derived constant region.

[0071]

Other examples of the chimeric antibody derived from the rat anti-human CDH6 antibody include an antibody consisting of a light chain comprising a light chain variable region having a substitution of 1 or 2 residues, preferably 1 residue, of amino acids in any 1 to 3 CDRs in the light chain variable region of each rat anti-

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human CDH6 antibody described in the present description (e.g., the rG019 antibody, the rG055 antibody, the rG056 antibody or the rG061 antibody) with other amino acid residues, and a heavy chain comprising a heavy chain variable region having a substitution of 1 or 2 residues, preferably 1 residue, of amino acids in any 1 to 3 CDRs in the heavy chain variable region thereof with other amino acid residues. This antibody may have any given human-derived constant region.

[0072]

Examples of the chimeric antibody derived from the rG019 antibody include an antibody consisting of a light chain comprising a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 10, and a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 15. This antibody may have any given human-derived constant region.

[0073]

Other examples of the chimeric antibody derived from the rG019 antibody include an antibody consisting of a light chain comprising a light chain variable region having a substitution of one to several residues, 1 to 3 residues, 1 or 2 residues, preferably 1 residue, of amino acids in the light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 10 with other amino acid residues, and a heavy chain comprising a heavy chain variable region having a substitution of one to several residues, 1 to 3 residues, 1 or 2 residues, preferably 1 residue, of amino acids in the heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 15 with other amino acid residues. This antibody may have any given human-derived constant region.

[0074]

Other examples of the chimeric antibody derived from the rG019 antibody include an antibody consisting of a light chain comprising a light chain variable

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region having a substitution of 1 or 2 residues (preferably 1 residue) of amino acids in any 1 to 3 CDRs in the light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 10 with other amino acid residues, and a heavy chain comprising a heavy chain variable region having a substitution of 1 or 2 residues (preferably 1 residue) of amino acids in any 1 to 3 CDRs in the heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 15 with other amino acid residues. This antibody may have any given human-derived constant region.

[0075]

Other examples of the chimeric antibody derived from the rG019 antibody include an antibody consisting of a light chain comprising a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 10, and a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 58. This antibody may have any given human-derived constant region. The amino acid sequence shown in SEQ ID NO: 58 is a sequence with a cysteine residue substituted with a proline residue in CDRH2 in the amino acid sequence shown in SEQ ID NO: 15.

[0076]

Specific examples of the chimeric antibody derived from the rG019 antibody include an antibody consisting of a light chain consisting of the light chain full-length amino acid sequence shown in SEQ ID NO: 53, and a heavy chain consisting of the heavy chain full-length amino acid sequence shown in SEQ ID NO: 56. In the present description, this chimeric anti-human CDH6 antibody is referred to as a "chimeric G019 antibody", a "chG019 antibody" or "chG019". The light chain full-length amino acid sequence of the chG019 antibody is encoded by the nucleotide sequence shown in SEQ ID NO: 54, and the heavy chain full-length amino acid

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sequence of the chG019 antibody is encoded by the nucleotide sequence shown in SEQ ID NO: 57.

[0077]

The amino acid sequence of the light chain variable region of the chG019 antibody is identical to the amino acid sequence of the light chain variable region of the rG019 antibody, and consists of the amino acid sequence shown in SEQ ID NO: 10. The light chain of the chG019 antibody has CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 12, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 13, and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 14, which are identical to the light chain CDRL1, CDRL2 and CDRL3, respectively, of rG019. The amino acid of the light chain variable region of the chG019 antibody is encoded by the nucleotide sequence shown in SEQ ID NO: 55.

[0078]

The amino acid sequence of the heavy chain variable region of the chG019 antibody consists of the amino acid sequence shown in SEQ ID NO: 58. The heavy chain of the chG019 antibody has CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 17, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 60, and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 19. The amino acid sequence shown in SEQ ID NO: 58 is a sequence with a cysteine residue substituted with a proline residue in CDRH2 in the amino acid sequence shown in SEQ ID NO: 15. The CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 60 is a sequence with a cysteine residue substituted with a proline residue in the rG019 CDRH2 shown in SEQ ID NO: 18. The amino acid sequence of the heavy chain variable region of the chG019 antibody is encoded by the nucleotide sequence shown in SEQ ID NO: 59.

[0079]

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The sequence of the chG019 antibody is shown in Table 1-1 to Table 1-15.

[0080]

Examples of the chimeric antibody derived from the rat anti-human CDH6 antibody rG055 antibody include a chimeric antibody consisting of a light chain comprising a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 20, and a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 25. This antibody may have any given human-derived constant region.

[0081]

Examples of the chimeric antibody derived from the rat anti-human CDH6 antibody rG056 antibody include a chimeric antibody consisting of a light chain comprising a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 30, and a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 35. This antibody may have any given human-derived constant region.

[0082]

Examples of the chimeric antibody derived from the rat anti-human CDH6 antibody rG061 antibody include a chimeric antibody consisting of a light chain comprising a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 40, and a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 45. This antibody may have any given human-derived constant region.

[0083]

Examples of the humanized antibody can include an antibody formed by incorporating only complementarity determining regions (CDRs) into a human-derived antibody (see Nature (1986) 321, p. 522-525), an antibody formed by incorporating the amino acid residues from some frameworks, as well as CDR

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sequences, into a human antibody according to a CDR grafting method (International Publication No. WO90/07861), and an antibody formed by modifying the amino acid sequences of some CDRs while maintaining antigen-binding ability.

[0084]

In the present description, the humanized antibody derived from the rG019 antibody, the rG055 antibody, the rG056 antibody, the rG061 antibody or the chG019 antibody is not limited to a specific humanized antibody as long as the humanized antibody retains all 6 CDR sequences unique to the rG019 antibody, the rG055 antibody, the rG056 antibody, the rG061 antibody or the chG019 antibody and has internalization activity. The amino acid sequences of some CDRs of this humanized antibody may be further modified as long as it has internalization activity.

[0085]

Concrete examples of the humanized antibody of the chG019 antibody can include any given combination of: a light chain comprising a light chain variable region consisting of any one amino acid sequence selected from the group consisting of (1) the amino acid sequence shown in SEQ ID NO: 63 or 67, (2) an amino acid sequence having an identity of at least 95% or more (preferably an amino acid sequence having a sequence identity of at least 95% or more to the sequence of a framework region other than at each CDR sequence) to the above-described amino acid sequence (1), and (3) an amino acid sequence comprising a deletion, substitution or addition of one or several amino acids in the above-described amino acid sequence (1); and a heavy chain comprising a heavy chain variable region consisting of any one amino acid sequence selected from the group consisting of (4) the amino acid sequence shown in SEQ ID NO: 71, 75 or 79, (5) an amino acid sequence having an identity of at least 95% or more (preferably an amino acid sequence having a sequence identity of at least 95% or more to the sequence of a framework region other than at each CDR sequence) to the above-described amino acid sequence (4),

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and (6) an amino acid sequence comprising a deletion, substitution or addition of one or several amino acids in the above-described amino acid sequence (4).

[0086]

Alternatively, an antibody having a humanized heavy chain or light chain and the other chain derived from a rat antibody or a chimeric antibody can also be used. Examples of such an antibody can include any given combination of: a light chain comprising a light chain variable region consisting of any one amino acid sequence selected from the group consisting of (1) the amino acid sequence shown in SEQ ID NO: 63 or 67, (2) an amino acid sequence having an identity of at least 95% or more (preferably an amino acid sequence having a sequence identity of at least 95% or more to the sequence of a framework region other than at each CDR sequence) to the above-described amino acid sequence (1), and (3) an amino acid sequence comprising a deletion, substitution or addition of one or several amino acids in the above-described amino acid sequence (1); and a heavy chain comprising a heavy chain variable region consisting of any one amino acid sequence selected from the group consisting of (4) the amino acid sequence shown in SEQ ID NO: 15, 25, 35, 45 or 58, (5) an amino acid sequence having an identity of at least 95% or more (preferably an amino acid sequence having a sequence identity of at least 95% or more to the sequence of a framework region other than at each CDR sequence) to the above-described amino acid sequence (4), and (6) an amino acid sequence comprising a deletion, substitution or addition of one or several amino acids in the above-described amino acid sequence (4). Other examples of such an antibody can include any given combination of: a light chain comprising a light chain variable region consisting of any one amino acid sequence selected from the group consisting of (1) the amino acid sequence shown in SEQ ID NO: 10, 20, 30 or 40, (2) an amino acid sequence having an identity of at least 95% or more (preferably an amino acid sequence having a sequence identity of at least 95% or more to the sequence of a

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framework region other than at each CDR sequence) to the above-described amino acid sequence (1), and (3) an amino acid sequence comprising a deletion, substitution or addition of one or several amino acids in the above-described amino acid sequence (1); and a heavy chain comprising a heavy chain variable region consisting of any one amino acid sequence selected from the group consisting of (4) the amino acid sequence shown in SEQ ID NO: 71, 75 or 79, (5) an amino acid sequence having an identity of at least 95% or more (preferably an amino acid sequence having a sequence identity of at least 95% or more to the sequence of a framework region other than at each CDR sequence) to the above-described amino acid sequence (4), and (6) an amino acid sequence comprising a deletion, substitution or addition of one or several amino acids in the above-described amino acid sequence (4).

[0087]

The amino acid substitution in the present description is preferably a conservative amino acid substitution. The conservative amino acid substitution is a substitution occurring within an amino acid group associated with certain amino acid side chains. Preferred amino acid groups are the following: acidic group = aspartic acid and glutamic acid; basic group = lysine, arginine, and histidine; non-polar group = alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, and tryptophan; and uncharged polar family = glycine, asparagine, glutamine, cysteine, serine, threonine, and tyrosine. Other preferred amino acid groups are the following: aliphatic hydroxy group = serine and threonine; amide-containing group = asparagine and glutamine; aliphatic group = alanine, valine, leucine and isoleucine; and aromatic group = phenylalanine, tryptophan and tyrosine. Such amino acid substitution is preferably carried out without impairing the properties of a substance having the original amino acid sequence.

[0088]

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Examples of the antibody having a preferred combination of the above-described light chains and heavy chains include an antibody consisting of a light chain having the light chain variable region amino acid sequence shown in SEQ ID NO: 63 (in the present description, also referred to as a hL02 light chain variable region amino acid sequence) or a light chain having the light chain variable region amino acid sequence shown in SEQ ID NO: 67 (in the present description, also referred to as a hL03 light chain variable region amino acid sequence), and a heavy chain having the heavy chain variable region amino acid sequence shown in SEQ ID NO: 71 (in the present description, also referred to as a hH01 heavy chain variable region amino acid sequence), a heavy chain having the heavy chain variable region amino acid sequence shown in SEQ ID NO: 75 (in the present description, also referred to as a hH02 heavy chain variable region amino acid sequence) or a heavy chain having the heavy chain variable region amino acid sequence shown in SEQ ID NO: 79 (in the present description, also referred to as a hH04 heavy chain variable region amino acid sequence). Preferred examples thereof include: an antibody consisting of a light chain having the light chain variable region amino acid sequence shown in SEQ ID NO: 63 and a heavy chain having the heavy chain variable region amino acid sequence shown in SEQ ID NO: 71; an antibody consisting of a light chain having the light chain variable region amino acid sequence shown in SEQ ID NO: 63 and a heavy chain having the heavy chain variable region amino acid sequence shown in SEQ ID NO: 75; an antibody consisting of a light chain having the light chain variable region amino acid sequence shown in SEQ ID NO: 63 and a heavy chain having the heavy chain variable region amino acid sequence shown in SEQ ID NO: 79; an antibody consisting of a light chain having the light chain variable region amino acid sequence shown in SEQ ID NO: 67 and a heavy chain having the heavy chain variable region amino acid sequence shown in SEQ ID NO: 71; an antibody consisting of a light chain having the light chain variable region

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amino acid sequence shown in SEQ ID NO: 67 and a heavy chain having the heavy chain variable region amino acid sequence shown in SEQ ID NO: 75; and an antibody consisting of a light chain having the light chain variable region amino acid sequence shown in SEQ ID NO: 67 and a heavy chain having the heavy chain variable region amino acid sequence shown in SEQ ID NO: 79. More preferred examples thereof include: an antibody consisting of a light chain having the light chain variable region amino acid sequence shown in SEQ ID NO: 63 and a heavy chain having the heavy chain variable region amino acid sequence shown in SEQ ID NO: 71; an antibody consisting of a light chain having the light chain variable region amino acid sequence shown in SEQ ID NO: 63 and a heavy chain having the heavy chain variable region amino acid sequence shown in SEQ ID NO: 75; an antibody consisting of a light chain having the light chain variable region amino acid sequence shown in SEQ ID NO: 63 and a heavy chain having the heavy chain variable region amino acid sequence shown in SEQ ID NO: 79; and an antibody consisting of a light chain having the light chain variable region amino acid sequence shown in SEQ ID NO: 67 and a heavy chain having the heavy chain variable region amino acid sequence shown in SEQ ID NO: 75.

[0089]

Other examples of the antibody having a preferred combination of the above-described light chains and heavy chains include an antibody consisting of a light chain consisting of the amino acid sequence at positions 21 to 233 in the light chain full-length amino acid sequence shown in SEQ ID NO: 61 (in the present description, also referred to as the hL02 light chain full-length amino acid sequence) or a light chain consisting of the amino acid sequence at positions 21 to 233 in the light chain full-length amino acid sequence shown in SEQ ID NO: 65 (in the present description, also referred to as the hL03 light chain full-length amino acid sequence), and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in the heavy chain

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full-length amino acid sequence shown in SEQ ID NO: 69 (in the present description, also referred to as the hH01 heavy chain full-length amino acid sequence), a heavy chain consisting of the amino acid sequence at positions 20 to 471 in the heavy chain full-length amino acid sequence shown in SEQ ID NO: 73 (in the present description, also referred to as the hH02 heavy chain full-length amino acid sequence) or a heavy chain consisting of the amino acid sequence at positions 20 to 471 in the heavy chain full-length amino acid sequence shown in SEQ ID NO: 77 (in the present description, also referred to as the hH04 heavy chain full-length amino acid sequence).

Preferred examples thereof include: an antibody consisting of a light chain consisting of the amino acid sequence at positions 21 to 233 in the light chain full-length amino acid sequence shown in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in the heavy chain full-length amino acid sequence shown in SEQ ID NO: 69; an antibody consisting of a light chain consisting of the amino acid sequence at positions 21 to 233 in the light chain full-length amino acid sequence shown in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in the heavy chain full-length amino acid sequence shown in SEQ ID NO: 73; an antibody consisting of a light chain consisting of the amino acid sequence at positions 21 to 233 in the light chain full-length amino acid sequence shown in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in the heavy chain full-length amino acid sequence shown in SEQ ID NO: 77; an antibody consisting of a light chain consisting of the amino acid sequence at positions 21 to 233 in the light chain full-length amino acid sequence shown in SEQ ID NO: 65 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in the heavy chain full-length amino acid sequence shown in SEQ ID NO: 69; an antibody consisting of a light chain consisting of the amino acid sequence at positions 21 to 233 in the light chain full-length amino acid sequence shown in SEQ ID NO: 65 and a heavy chain

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consisting of the amino acid sequence at positions 20 to 471 in the heavy chain full-length amino acid sequence shown in SEQ ID NO: 73; and an antibody consisting of a light chain consisting of the amino acid sequence at positions 21 to 233 in the light chain full-length amino acid sequence shown in SEQ ID NO: 65 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in the heavy chain full-length amino acid sequence shown in SEQ ID NO: 77. More preferred examples thereof include: an antibody consisting of a light chain consisting of the amino acid sequence at positions 21 to 233 in the light chain full-length amino acid sequence shown in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in the heavy chain full-length amino acid sequence shown in SEQ ID NO: 69 (in the present description, also referred to as the "H01L02 antibody" or "H01L02"); an antibody consisting of a light chain consisting of the amino acid sequence at positions 21 to 233 in the light chain full-length amino acid sequence shown in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in the heavy chain full-length amino acid sequence shown in SEQ ID NO: 73 (in the present description, also referred to as the "H02L02 antibody" or "H02L02"); an antibody consisting of a light chain consisting of the amino acid sequence at positions 21 to 233 in the light chain full-length amino acid sequence shown in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in the heavy chain full-length amino acid sequence shown in SEQ ID NO: 77 (in the present description, also referred to as the "H04L02 antibody" or "H04L02"); and an antibody consisting of a light chain consisting of the amino acid sequence at positions 21 to 233 in the light chain full-length amino acid sequence shown in SEQ ID NO: 65 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in the heavy chain full-length amino acid sequence shown in SEQ ID NO: 73 (in the present description, also referred to as the "H02L03 antibody" or "H02L03"). The sequences of the H01L02 antibody, the H02L02

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antibody, the H02L03 antibody or the H04L02 antibody are shown in Table 1-1 to Table 1-15.

[0090]

By combining together sequences showing a high identity to the above-described heavy chain amino acid sequences and light chain amino acid sequences, it is possible to select an antibody having a biological activity equivalent to that of each of the above-described antibodies. Such an identity is an identity of generally 80% or more, preferably 90% or more, more preferably 95% or more, and most preferably 99% or more. Moreover, also by combining amino acid sequences of a heavy chain and a light chain comprising a substitution, deletion or addition of one or several amino acid residues thereof with respect to the amino acid sequence of a heavy chain or a light chain, it is possible to select an antibody having a biological activity equivalent to that of each of the above-described antibodies.

[0091]

The identity between two types of amino acid sequences can be determined by aligning the sequences using the default parameters of Clustal W version 2 (Larkin MA, Blackshields G, Brown NP, Chenna R, McGettigan PA, McWilliam H, Valentin F, Wallace IM, Wilm A, Lopez R, Thompson JD, Gibson TJ and Higgins DG (2007), "Clustal W and Clustal X version 2.0", *Bioinformatics*. 23 (21): 2947-2948).

[0092]

It is to be noted that, in the hL02 light chain full-length amino acid sequence shown in SEQ ID NO: 61, the amino acid sequence consisting of the amino acid residues at positions 1 to 20 is the signal sequence, the amino acid sequence consisting of the amino acid residues at positions 21 to 128 is the variable region, and the amino acid sequence consisting of the amino acid residues at positions 129 to 233 is the constant region. In the hL02 light chain full-length nucleotide sequence

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shown in SEQ ID NO: 62, the nucleotide sequence consisting of the nucleotides at positions 1 to 60 encodes the signal sequence, the nucleotide sequence consisting of the nucleotides at positions 61 to 384 encodes the variable region, and the nucleotide sequence consisting of the nucleotides at positions 385 to 699 encodes the constant region.

[0093]

In the hL03 light chain full-length amino acid sequence shown in SEQ ID NO: 65, the amino acid sequence consisting of the amino acid residues at positions 1 to 20 is the signal sequence, the amino acid sequence consisting of the amino acid residues at positions 21 to 128 is the variable region, and the amino acid sequence consisting of the amino acid residues at positions 129 to 233 is the constant region.

In the hL03 light chain full-length nucleotide sequence shown in SEQ ID NO: 66, the nucleotide sequence consisting of the nucleotides at positions 1 to 60 encodes the signal sequence, the nucleotide sequence consisting of the nucleotides at positions 61 to 384 encodes the variable region, and the nucleotide sequence consisting of the nucleotides at positions 385 to 699 encodes the constant region.

[0094]

In the hH01 heavy chain full-length amino acid sequence shown in SEQ ID NO: 69, the amino acid sequence consisting of the amino acid residues at positions 1 to 19 is the signal sequence, the amino acid sequence consisting of the amino acid residues at positions 20 to 141 is the variable region, and the amino acid sequence consisting of the amino acid residues at positions 142 to 471 is the constant region.

In the hH01 heavy chain full-length nucleotide sequence shown in SEQ ID NO: 70, the nucleotide sequence consisting of the nucleotides at positions 1 to 57 encodes the signal sequence, the nucleotide sequence consisting of the nucleotides at positions 58 to 423 encodes the variable region, and the nucleotide sequence consisting of the nucleotides at positions 424 to 1413 encodes the constant region.

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[0095]

In the hH02 heavy chain full-length amino acid sequence shown in SEQ ID NO: 73, the amino acid sequence consisting of the amino acid residues at positions 1 to 19 is the signal sequence, the amino acid sequence consisting of the amino acid residues at positions 20 to 141 is the variable region, and the amino acid sequence consisting of the amino acid residues at positions 142 to 471 is the constant region. In the hH02 heavy chain full-length nucleotide sequence shown in SEQ ID NO: 74, the nucleotide sequence consisting of the nucleotides at positions 1 to 57 encodes the signal sequence, the nucleotide sequence consisting of the nucleotides at positions 58 to 423 encodes the variable region, and the nucleotide sequence consisting of the nucleotides at positions 424 to 1413 encodes the constant region.

[0096]

In the hH04 heavy chain full-length amino acid sequence shown in SEQ ID NO: 77, the amino acid sequence consisting of the amino acid residues at positions 1 to 19 is the signal sequence, the amino acid sequence consisting of the amino acid residues at positions 20 to 141 is the variable region, and the amino acid sequence consisting of the amino acid residues at positions 142 to 471 is the constant region. In the hH04 heavy chain full-length nucleotide sequence shown in SEQ ID NO: 78, the nucleotide sequence consisting of the nucleotides at positions 1 to 57 encodes the signal sequence, the nucleotide sequence consisting of the nucleotides at positions 58 to 423 encodes the variable region, and the nucleotide sequence consisting of the nucleotides at positions 424 to 1413 encodes the constant region.

[0097]

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[Table 1-1]

SEQ ID NO		Sequence
1	Amino acid sequence of human CDH6 ORF	MRTYRYFLLLFVVGQPYPTLSTPLSKRTSGFPAKKRALELSGNSKNEINRSKRSMWV NQFFLLEEYTGSDYQYVGKLHSDQDRGDGSLKYILSGDGAGDLFIINENTGDIQATK RLDREEKPVYILRAQAINRRTRGRPVEPESEFI IKIHDINDNEPIFTKEVYTATVPEM SDVGTFFVQVTATDADDPYTGNSAKVVYSILQGQPYFSVESETGIK TALLNMDREN REQYQVV IQAKDMGGMGGLSGTTT VNI TLTVNDNPPRFQSTYQFKTPESSPPGT PIGR IKASDADVG ENAEI EYSI TDGEG LDMFDV I TDQETQEG I ITVKLLDFEKKKV YTLKVEASNPYVEPRFLYLGPFKDSATVRIVVEDVDEPPVFSKLAYILQIREDAQIN TTIGSVTAQDPDAARNPVKYSVDRHTDMDRIFNIDSGNGSIFTSKLLDRETL LWHNI TVIATEINNPKQSSRPVLYIKVLDVNDNAPEFAEFYETFVCEKAKADQLIQTLHAVD KDDPYSGHQFSFSLAPEAASGSNFTIQDNKONTAGILTRKNGYNRHEMSTYLLPVVI SDNDYPVQSSGTGTVTRVCACDHGNGMSCHAEALIHPTGLSTGALVAILLCIVILL VTVVLFAALRRQRKKEPLIISKEDIRDNI VSYNDEGGGEEDTQAFDIGTLRNPEATE DNKLRDIVPEALFLPRRTPTARDNTDVRDFINQRLKENDTDPAPPYDSLATYAYE GTGSVADSLSSLESVTTDAGQDYDYLSDWGPFRFKKLADMYGGVDSKDS
2	Human CDH6 EC1	SWMNNQFFLLEEYTGSDYQYVGKLHSDQDRGDGSLKYILSGDGAGDLFIINENTGDI QATKRLDREEKPVYILRAQAINRRTRGRPVEPESEFI IKIHDINDNEPIF
3	Human CDH6 EC2	TKEVYTATVPEMSDVGTFFVQVTATDADDPYTGNSAKVVYSILQGQPYFSVESETGI IK TALLNMDRENREQYQVV IQAKDMGGMGGLSGTTT VNI TLTVNDNPPRF
4	Human CDH6 EC3	QSTYQFKTPESSPPGTPIGR IKASDADVG ENAEI EYSI TDGEG LDMFDV I TDQETQ EG I ITVKLLDFEKKKVYTLKVEASNPYVEPRFLYLGPFKDSATVRIVVEDVDEPPV F
5	Human CDH6 EC4	SKLAYILQIREDAQINTTIGSVTAQDPDAARNPVKYSVDRHTDMDRIFNIDSGNGSIF FTSKLLDRETL LWHNI TVIATEINNPKQSSRPVLYIKVLDVNDNAP
6	Human CDH6 EC5	EFAEFYETFVCEKAKADQLIQTLHAVDKDDPYSGHQFSFSLAPEAASGSNFTIQDNK DNTAGILTRKNGYNRHEMSTYLLPVVI SDNDYPVQSSGTGTVTRVCACDHGNGMSCH AEALIHPT
7	Amino acid sequence of mouse CDH6 ORF	MRTYRYFLLLFVVGQPYPTFSNPLSKRTSGFPAKKRALELSANSRNELSRSKRSMWV NQFFLLEEYTGSDYQYVGKLHSDQDRGDGSLKYILSGDGAGDLFIINENTGDIQATK RLDREEKPVYILRAQAVNRRTRGRPVEPESEFI IKIHDINDNEPIFTKQVYTATVPEM ADVGTFFVQVTATDADDPYTGNSAKVVYSILQGQPYFSVESETGIK TALLNMDREN REQYQVV IQAKDMGGMGGLSGTTT VNI TLTVNDNPPRFQSTYQFKTPESSPPGT PIGR IKASDADVG ENAEI EYSI TDGEG HEMFDV I TDQETQEG I ITVKLLDFEKKKV YTLKVEASNPYVEPRFLYLGPFKDSATVRIVVDVDEPPVFSKLAYILQIREDA RIN TTIGSVAAGDPDAARNPVKYSVDRHTDMDRIFNIDSGNGSIFTSKLLDRETL LWHNI TVIATEINNPKQSSRPVLYIKVLDVNDNAPEFAEFYETFVCEKAKADQLIQTLRAVD KDDPYSGHQFSFSLAPEAASSNFTIQDNKONTAGILTRKNGYNRHEMSTYLLPVVI SDNDYPVQSSGTGTVTRVCACDHGNGMSCHAEALIHPTGLSTGALVAILLCIVILL VTVVLFAALRRQRKKEPLIISKEDIRDNI VSYNDEGGGEEDTQAFDIGTLRNPEAME DSKSRDIVPEALFLPRRTPTARDNTDVRDFINQRLKENDTDPAPPYDSLATYAYE GTGSVADSLSSLESVTTDAGQDYDYLSDWGPFRFKKLADMYGGVDSKDS

[0098]

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[Table 1-2]

8	Amino acid sequence of rat CDH6 ORF	MRTYRYFLLLFVVGQPYPTFSNPLSKRTSGFPAKRRLELSANSRNELSRKRSWNW NQFFLLEEYTGSDYQYVVKLHSDQDRGDGSLKYILSGDGAGDLFIINENTGDIQATK RLDREEKPYVILRAGAINRRRTGRPVEPESEFIKIHNDINNEPIFTKDYVYATVP ADVGTFFVQVATDADDPTYGNSAKVVYSILQGQPYFSVESETGIKTALLNMDREN REQYQVVIQAKDMGGQMGGLSGTTTNNITLTDVNDNPPRFQSTYQFKTPESSPPGT PIGRIKASDADVGENAEIYSITDGEHDMFDVITDQETOEGIIIVKLLDFEKKRV YTLKVEASNPHIEPRFLYLGPFKDSATVRIVVDVDEPPVFSKPAYILQIREDAQIN TTIGSVAADPDAAARNPVKYSVDRHTMDRIFNIDSGNGSIFTSKLLDRETLWHNI TVIATEINNPKQSSRVPLYIKVLDVNDNAPEFAEFYETFVCEKAKADQLIQTLHAVD KDDPYSGHQFSFLAPEAASGSNFTIQDNKDNAGILTRKNGYNRHEMSTYLLPVVI SDNDYPVQSSTGTVTVRVCACDHGNNMQSCHAEALIHPTGLSTGALVAIILLCIVILL VTVVLFAALRRQRKKEPLISKEDIRDNIVSYNDEGGGEEDTQAFDIGTLRNPKPWR QQRSDMVPEALFLPRRTPTARDNTDVRDFISQRLKMNIDPTAPPYDSLATYAYEG TGSVADSLSSLESVTTDGGQDYGLSDWGPRFKKLADMYGGMDSKDS
9	Amino acid sequence of cynomolgus monkey CDH6 ORF	MRTYRYFLLLFVVGQPYPTLSTPLSKRTSGFPAKRRLELSGNSKNELNRSKRSWNW NQFFLLEEYTGSDYQYVVKLHSDQDRGDGSLKYILSGDGAGDLFIINENTGDIQATK RLDREEKPYVILRAGAINRRRTGRPVEPESEFIKIHNDINNEPIFTKEYVYATVP SDVGTFFVQVATDADDPTYGNSAKVVYSILQGQPYFSVESETGIKTALLNMDREN REQYQVVIQAKDMGGQMGGLSGTTTNNITLTDVNDNPPRFQSTYQFKTPESSPPGT PIGRIKASDADVGENAEIYSITDGEGLDMFDVITDQETOEGIIIVKLLDFEKKRV YTLKVEASNPHVEPRFLYLGPFKDSATVRIVVEDVDEPPVFSKLAYILQIREDAQIN TTIGSVTAQDPDAARNPVKYSVDRHTMDRIFNIDSGNGSIFTSKLLDRETLWHNI TVIATEINNPKQSSRVPLYIKVLDVNDNAPEFAEFYETFVCEKAKADQLIQTLRAVD KDDPYSGHQFSFLAPEAASGSNFTIQDNKDNAGILTRKNGYNRHEMSTYLLPVVI SDNDYPVQSSTGTVTVRVCACDHGNNMQSCHAEALIHPTGLSTGALVAIILLCIVILL VTVVLFAALRRQRKKEPLISKEDIRDNIVSYNDEGGGEEDTQAFDIGTLRNPEATE DNKLRRDIVPEALFLPRRTPTARDNTDVRDFINQRLKENDTPTAPPYDSLATYAYE GTGSVADSLSSLESVTTDGGQDYGLSDWGPRFKKLADMYGGVDSKDS
10	rG019 light chain variable region amino acid sequence	DTQMTQSPSLLSASVGRVTLNCKASONIYKNLAWYQOKLGEQPKLLTYDANTLQTG IPSRFSGSGSGSDFTLTISLQPEDVATYFCQQYYSQWAFGGVTNLELKRA
11	rG019 light chain variable region nucleotide sequence	GACATCCAGATGACCCAGTCTCCTTCACTCCTGTCTGCATCTGTGGGAGACAGAGTC ACTCTCAACTGCAAAGCAAGTCAGAATATTATAAGAACTTAGCCTGGTATCAGCAA AAGCTTGGAGAAGGTCCCAAACCTCGATTATGATGCAAAACACTTTGCAAACGGGC ATCCCATCAAGGTTCAAGTGGCAGTGGATCTGGTTGAGATTTCACACTCACCATCAGC AGCCTGCAGCCTGAAGATGTTGCCACATATTTCTGCCAGCAGTACTATACGGGGTGG GCGTTCCGTTGGAGTCACCAACCTGGAATTGAAACGGGCT
12	rG019 CDRL1	KASONIYKNLA
13	rG019 CDRL2	DANTLQ*
14	rG019 CDRL3	QQYYSQWA

[0099]

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[Table 1-3]

15	rG019 heavy chain variable region amino acid sequence	QVQLQSGAELVKPGSSVKISCKASGYTFRNFMHWIKQDPGNLEWIGWIYCGDGE TEYNQKFNGKATLTADRSSSTAYMELSRITSEDSAVYFCARGVYGGFAGGYDFWGO GVMVTVSS
16	rG019 heavy chain variable region nucleotide sequence	CAGGTACAGCTGCAGCAATCTGGGGCTGAACCTGGTGAAGCCTGGGTCTCAGTGAAA ATTTCTGCAAGGCTTCTGGCTACAGCTTCACCAGGAACCTTATGCACTGGATAAAA CAGCAGCCTGGAAATGGCCTTGAGTGGATTGGGTGGATTATTGTGGAGATGGTGAG ACAGAGTACAATCAAAAGTCAATGGGAAGGCAACACTCACTGCCGACAGATCCTCC AGCACAGCCTATATGGAGCTCAGCAGACTGACATCTGAGGACTCTGCAGTCTATTTG TGTGCAAGAGGGGTTACGGAGGGTTGCCGGGGCTACTTTGATTCTGGGGCCAA GGAGTCATGGTCACAGTCTCCTCA
17	rG019 CDRH1	GYTFRNFMH
18	rG019 CDRH2	WIYCGDGETE
19	rG019 CDRH3	GVYGGFAGGYDF
20	rG055 light chain variable region amino acid sequence	DVQMTHTSPSYLAASPGESVSTISCKTSKNISNYLVWYQKPGEAYKLLIYSGSTLQSG TPSRFSGSGSDFTLTIRSLPEDFGLYFCQQYYEKPFIFGSGTKLEIKRA
21	rG055 light chain variable region nucleotide sequence	GATGTCCAGATGACCCACTCTCCGCTTATCTTGCTCGCTCTCCTGGAGAAAGTGT TCCATCAGTTGCAAGACAAGTAAGAACATTAGTAATTATTAGTCTGGTATCAACAG AAACCTGGGAAGCATATAAGCTTCTTATCTATTCTGGTCAACTTTGCAATCTGGA ACTCCATCAAGGTTCACTGGCAGTGGATCTGGTACAGATTTCACTCTCACTATCAGA AGCCTGGAGCCTGAAGATTTGGACTCTATTTCTGTCAACAGTATTATGAAAACCA TTCAGGTTCCGCTCAGGGACGAAGTTGGAATAAAACGGGCT
22	rG055 CDRL1	RTSKNISNYLV
23	rG055 CDRL2	SGSTLQS
24	rG055 CDRL3	QQYYEKPFT
25	rG055 heavy chain variable region amino acid sequence	EVQLQESGPGLVRPSSLSLSCSVTDYSITSNYWGWIIRFPGNKMEWMGYITYSGYT SYNPSLQSRISITRDTSKNQFFLQLNSVTAEDTATYYCARSLNHGGYSYVVDWGPQ ASVTVSS
26	rG055 heavy chain variable region nucleotide sequence	GAGGTGCAACTTCAGGAGTCAGGACCTGGCCTTGTGAGACCTCACAGTCACTCTCC CTCTCCTGTTCTGTCACTGATTACTCCATCACTAGTAATTACTGGGGCTGGATCCGG AGGTTCCAGGAAATAAAATGGAGTGGATGGGATACA~AACCTATAGTGGTTACACT AGCTACAACCCATCTCTCAAAGTCGAATCTCCATTACTAGAGACACATCGAAGAAT CAGTTCTTCTGCGAGTTGAAGTCTGTAAGTCTGAGGACACAGGCACATATTACTGT GCAAGATCGATTAACACGGAGGATATAGTTATGTTG~GGATGCCTGGGTCGGGA GCTTCAGTCACTGTCTCCTCA
27	rG055 CDRH1	DYSITSNYWG
28	rG055 CDRH2	YITYSGYTS
29	rG055 CDRH3	SINHHGYSYVDA

[0100]

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[Table 1-4]

30	rG056 light chain variable region amino acid sequence	DVQMTQSPSSLAAPGESVSI SCRATKSI GIYLAWYQQKPGKTFKLLIYSGSTLQSG TPSRFSGSGSGTDFTLTIRSLPEPDFGLYFCQQFYENPFTFGSGTKLEIRRA
31	rG056 light chain variable region nucleotide sequence	GATGTCCAGATGACCCAGTCTCCGTCTTCTCTTGCTGCGTCTCCTGGAGAAAGTGT TCCATCAGTTGCAGGGCAACTAAGAGCATTGGTATTTATTAGCCTGGTATCAACAG AAACCTGGGAAACATTTAAGCTTCTTATCTACTCTGGTCAACTTTGCAATCTGGA ACTCCATCAAGGTTCAAGTGGCAGTGGGTCTGGTACAGATTTCAGTCTCAGCATCAGA AGCCTGGAGCCTGAAGATTTTGGACTCTATTTCTGTCAACAGTTTATGAAAACCA TTCAGGTTCCGCTCAGGGACGAAGTTGGAATAAGACGGGCT
32	rG056 CDR1	RATKSI GIYLA
33	rG056 CDR2	SGSTLQS
34	rG056 CDR3	QQFYENPFT
35	rG056 heavy chain variable region amino acid sequence	EVQLDQESGPGLVKPSQSLSLTCSVTDSYITTYFWGWIRKFPGNKMEWMGYMSYRGGT SYNPSLKSRI S I TRDTSKNQFFLQLNSVTTEDTATYYCARCPNYGGHSLVFDYWGGG VMVTVSS
36	rG056 heavy chain variable region nucleotide sequence	GAGGTGCAGCTTCAGGAGTCAGGACCTGGCCTTGTAACCCCTCAGAGTCAGTCTCC CTCAGCTGTTCTGTCACTGATTACTCCATCACTACTTATTCTGGGGCTGGATCCGG AAGTTCCAGGAAATAAAATGGAGTGGATGGATACATGAGCTACCGTGGTGGCACT TCCTACAACCCATCTCTCAAGAGTCGAATCTCCATTACTAGAGACACATCGAAGAAT CAGTTCTTCTGCACTTGAAGTCTGTAAGTACTGAGGACACAGCCACATATTACTGT GCAAGATGCCCTAAGTACGGAGGGCATTCCCTTGTTTTGATTACTGGGGCCAAGGA GTGATGGTCAGAGTCTCTCA
37	rG056 CDRH1	DYSITTYFWG
38	rG056 CDRH2	YMSYRGGTS
39	rG056 CDRH3	CPNYGGHSLVFDY
40	rG061 light chain variable region amino acid sequence	DVQMTQSPSYLAAPGESVSI SCKATKSI SNYLAWYQQKPGEAYKVL IYSGSTLQSG TPSRFSGSGSGTDFTLTIRSLPEPDFGLYSQQYYEKPLTFGSGTKLEIKRA
41	rG061 light chain variable region nucleotide sequence	GATGTCCAGATGACCCAGTCTCCGTCTTATCTTGCTGCGTCTCCTGGAGAAAGTGT TCCATCAGTTGCAAGGCAACTAAGAGCATTAGTAATTATTAGCCTGGTATCAACAG AAACCTGGGGAAGCATATAAGGTTCTTATCTATTCTGGTCAACTTTGCAATCTGGA ACTCCATCAAGGTTCAAGTGGCAGTGGATCTGGTACAGATTTCAGTCTCAGCATCAGA AGCCTGGAGCCTGAAGATTTTGGACTCTATTCTGTCAACAGTATTATGAAAACCG CTCAGGTTCCGTTCTGGACCAAGCTGGAGATCAAACGGGCT
42	rG061 CDR1	KATKSI SNYLA
43	rG061 CDR2	SGSTLQS
44	rG061 CDR3	QQYYEKPLT

[0101]

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[Table 1-5]

45	rG061 heavy chain variable region amino acid sequence	EVQLQESGPGLVKPSQSLSLTCSVTGYSITITYYWGWI RKFPGNKMEHWGYISYSGRT SYNPSLKSRRMSITRDASKNQFFLQLNSVTTDDTATYYCARSPINHGYYWYDFWGP TMVTYSS
46	rG061 heavy chain variable region nucleotide sequence	GAGGTGCAGCTTCAGGAGTCAGGACCTGGCCTTGTAACCCCTCACAGTCACCTCC CTCACCTGTTCTGTCACTGGTACTCCATCACTACTTATTACTGGGCTGGATCCGG AAGTTCCAGGAAATAAAATGGAGTGGATGGGTACATAAGCTACAGTGGTCGCACT AGTTATAACCCATCTCTCAAAGTCGAATGTCCATTACTAGAGACGCATCGAAGAAT CAGTTCTTCTACAGTTGAACCTGTGAACTACTGACGACACAGCCACATATTACTGT GCAAGATCCCAATTAACACGGAGGGTACTGGTACTTTGACTTCTGGGGCCAGGA ACCATGGTCACCGTGTCTCA
47	rG061 CDRH1	GYSITITYWG
48	rG061 CDRH2	YISYSGRTS
49	rG061 CDRH3	SPINHGYYWYDF
50	DNA fragment comprising DNA sequence encoding human light chain signal sequence and human κ chain constant region	gcctccggactctagagccaccATGGTGCTGCAGACCCAGGTGTTATCTCCCTGCT GCTGTGGATCTCCGGCGGTACGGCGATATCGTGATGATTAAAGTACGGTGGCCGC CCCCCTCCGTGTTATCTTCCCCCCTCCGACGAGCAGCTGAAGTCCGGCACCGCCTC CGTGGTGTGCTGCTGAATAACTTCTACCCAGAGAGGCCAAGGTGCAGTGGAGGT GGACAACGCCCTGCAGTCCGGGAACCTCCAGGAGAGGCTGACCGAGCAGGACAGCAA GGACAGCACCTACAGCCTGAGCAGCACCTGACCCCTGAGCAAAGCCGACTACGAGAA GCACAAGGTGTACGCCTGCGAGGTGACCCACAGGGCCTGAGCTCCCCCGTACCCAA GAGCTTCAACAGGGGGAGTGTtaggggcccgtttaacggggaggcta

[0102]

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[Table 1-6]

51	DNA fragment comprising DNA sequence encoding human heavy chain signal sequence and human IgG1 constant region	<p>gcctccggactctagagccaccATGAACACCTGTGGTTCTTCCTCCTGCTGGTGGC AGCTCCAGATGGGTGCTGAGCCAGGTGCAATTGTGCAGGCGGTTAGCTCAGCCTCC ACCAAGGGCCCAAGCGTCTTCCCTTGGCAGCCTCCTCCAAGAGCACCTCTGGCGGC ACAGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCGAAGCCGTGACCGTGAGC TGGAACTCAGGCGCCTGACCAGCGGGGTGCACACCTTCCCGCTGTCTGCAGTCC TCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACC CAGACCTACATCTGCAACGTGAATCACAAGCCAGCAACCAAGGTGGACAAGAGA GTTGAGCCCAATCTTGTGACAAACTCACACATGCCACCCCTGCCAGCACCTGAA CTCCTGGGGGACCCCTCAGTCTTCTCTTCCCGCAAAACCAAGGACCCCTCATG ATCTCCCGGACCCCTGAGGTACATGCGTGGTGGTGGACGTGAGCCACGAAGACCT GAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAG CCCGGGAGGAGCAGTACAACAGCAGGTACCGGGTGGTCAGCGTCTCACCCTCCTG CACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAGCCCTC CCAGCCCCATCGAGAAACCATCTCCAAGCCAAAGGCCAGCCCCGGGAACACAG GTGTACACCCTGCCCCATCCCGGAGGAGATGACCAAGAACAGGTACCGCTGACC TGCTGGTCAAGGCTTCTATCCAGCGACATCGCGTGGAGTGGGAGAGCAATGGC CAGCCCGAGAACACTACAAGACACCCCTCCCGTGTGACTCCGACGGCTCCTTC TTCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGCAACGCTTC TCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACCCAGAAGAGCCTCTCC CTGTCTCCCGCAATgagatatcgggcccggttaaacggggaggcta</p>
52	DNA fragment comprising DNA sequence encoding chG019 light chain	<p>ccagcctccggactctagagccaccATGGTGTGCAGACCCAGGTGTTTCATCAGCCT GCTGCTGTGGATCAGCGGCGCCTACGGCGACATCCAGATGACCCAGAGCCCTAGCCT GCTGAGCGCCAGCGTGGGCGATAGAGTGACCTGAACTGCAAGGCCAGCCAGAACAT CTACAAGAACCTGGCCTGGTATCAGCAGAACCTGGGCGAGGGCCCCAAGCTGCTGAT CTACGACGCCAACCCCTGCAGACCGGCATCCCGAGCAGATTTTCTGGCAGCGGAG CGGCTCCGACTTCACCCTGACAATCAGCAGCCTGCAGCCCGAGGAGGTGCCACCTA CTTTTCCAGCAGTACTACAGCGGCTGGGCTTGGGCGGCGTGACCAACCTGGAAC GAAGAGAGCGGTGGCGCTCCCTCCGTGTTTCATCTTCCACCTAGCGACGAGGAGCT GAAGTCCGGCAGCAGCCTCTGTGTGTGCTGCTGAACAACTTCTACCCCGCGAGGC CAAGGTGCAGTGGAAAGGTGGACAATGCCCTGCAGTCTGGCAACAGCCAGGAAGCGT GACCGAGCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCACCCTGACCTGAG CAAGGCCGACTACGAGAAGCACAAGGTGTACGCTGCGAAGTGACCCACCAGGGCT GTCTAGCCCCGTGACCAAGAGCTTCAACCGGGCGAGTGTgagtttaaacggggaggga ggctaact</p>
53	chG019 light chain full-length amino acid sequence	<p>MVLQTQVFI SLLLWISGAYGDIQMTQSPSLLSASVGDRTVLNCKASQNIYKNLAWYQ QKLGEQPKLLIYDANTLQTGIPSRFSGSGSSDFTLTISLQPEDVATYFCQYYSG WAFGGVTNLELKRAVAAPSVFIFPPSDEQLKSGTASVCLLNFPYPREAKVQWKVDN ALQSGNSQESVTEGDSKSTYSLSSTLTLSKADYEKHKVYACEVTHOGLSSPVTKSF NRGEC</p>

[0103]

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[Table 1-7]

54	chG019 light chain full-length nucleotide sequence	ATGGTGCTGCAGACCCAGGTGTTTCATCAGCCTGCTGCTGTGGATCAGCGGCGCTAC GGCGACATCCAGATGACCCAGAGCCCTAGCCTGCTGAGCGCCAGCGTGGGCGATAGA GTGACCCCTGAAGTGAAGGCCAGCCAGAATCTACAAGAACCCTGGCCTGGTATCAG CAGAAGCTGGGCGAGGGCCCAAGCTGCTGATCTACGACGCCAACCCCTGCAGACC GGCATGCCGAGCAGATTTTCTGGCAGCGGCAGCGGCTCCGACTTCACCCCTGACAATC AGCAGCCTGCAGCCGAGGACGTGGCCACCTACTTTTGGCAGCAGTACTACAGCGGC TGGGCCTTCGGGGGGGTGACCAACCTGGAACCTGAAGAGAGCCGTGGCGGCTCCCTCC GTGTTTCATCTTCCACCTAGCGACGAGCAGCTGAAGTCCGGCAGGCTCTGTCTGTG TGCCTGCTGAACAACCTTCTACCCCGCGAGGCCAAGGTGCAGTGGAGGTGGACAAT GCCCTGCAGTCTGGCAACAGCCAGGAAAGCGTGACCGAGCAGGACAGCAAGGACTCC ACCTACAGCCTGAGCAGCAGCCCTGACCTGAGCAAGGCCGACTACGAGAAGCACAAG GTGTACGCCTGCGAAGTGACCCACGAGGCGCTGTCTAGCCCGTGACCAAGAGCTTC AACCGGGGCGAGTGT
10	chG019 light chain variable region amino acid sequence	DIQMTQSPSLLSASVGDRTVLNCKASQNIYKNLAWYQQKLGEGPKLLIYDANTLQTG IPSRFSGSGSGSDFTLTISSLQPEDVATYFCQQYYSQWAFGGVTNLELKRA
55	chG019 light chain variable region nucleotide sequence	GACATCCAGATGACCCAGAGCCCTAGCCTGCTGAGCGCCAGCGTGGGCGATAGAGTG ACCCCTGAAGTGAAGGCCAGCCAGAATCTACAAGAACCCTGGCCTGGTATCAGCAG AAGCTGGGCGAGGGCCCAAGCTGCTGATCTACGACGCCAACCCCTGCAGACCGGC ATCCCGCAGCAGATTTTCTGGCAGCGGCAGCGGCTCCGACTTCACCCCTGACAATCAGC AGCCTGCAGCCGAGGACGTGGCCACCTACTTTTGGCAGCAGTACTACAGCGGCTGG GCCTTCGGCGGCGTGACCAACCTGGAACCTGAAGAGAGCG
12	chG019 CDRL1	KASQNIYKNLA
13	chG019 CDRL2	DANTLQT
14	chG019 CDRL3	QQYYSQWA
56	chG019 heavy chain full-length amino acid sequence	MKHLWFFLLVAAPRWVLSQVQLQSGAELVKPGSSVKISCKASGYTFTNFMHWIK QQPGNGLEWIGWIYPGGGETEYNQKFNGKATLTADRSSSTAYMELSRLTSEDSAVYF CARGVYGGFAGGYDFWGGQVMVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNH KPSNTKVDKRVPEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC VYVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCQSVMHEAL NNHYTQKSLSLSPGK

[0104]

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[Table 1-8]

57	chG019 heavy chain full-length nucleotide sequence	ATGAAACACCTGTGGTTCTTCTCTCTGCTGGTGGCAGCTCCAGATGGGTGCTGAGC CAGGTGCAGCTGCAGCAGTCTGGCGCCGAGCTCGTGAAGCCTGGCAGCAGCGTGAAG ATCAGCTGCAAGGCCAGCGGCTACACCTTCACCCGGAACCTTCATGCACTGGATCAAG CAGCAGCCCGGCAACGGCTGGAATGGATCGGCTGGATCTATCCCGCCGACGGCGAG ACAGAGTACAACCAAGATTCAACGGCAAGGCCACCTGACCGCCGACAGAAAGCAGC TCCACCGCTACATGGAAGTGAAGCGGCTGACCAGCGAGGACAGCGCGGTGTAATTT TGGCCAGAGGGGTGTACGGCGGCTTCGCTGGCGGCTACTTCGATTTTGGGGCCAG GGCGTGATGGTCACCGTCAGCTCAGGCTCCACCAAGGGCCCAAGCGTCTTCCCGCTG GCACCTCTCTCAAGAGCACTCTGGCGGCACAGCCGCCCTGGGCTGCCGTGGTCAAG GACTACTTCCCGAAGCGTGACCGTGAGCTGGAAGTCAAGGGCCCTGACCAGCGGC GTGCACACCTTCCCGCTGTCTGTGAGTCTCAGGACTCTACTCCCTGAGCAGCGTG GTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAAGGTGAATCAC AAGCCAGCAACACCAAGGTGGACAAGAGATTGAGCCCAAATCTTGTGACAAAATC CACAGATGCCACCTGCCAGCAGCTGAAGTCTGGGGGACCCCTCAGTCTTCTC TTCCCGCCAAACCAAGGACACCTCATGATCTCCCGGACCCCTGAGGTGAGATGC GTGGTGGTGGAGTGAAGCAAGACCCCTGAGGTCAAGTTCAAGTGGTACGTGGAC GCGTGGAGGTGCATAATGCCAAGACAAAGCCCGGGAGGAGCAGTACACAGCAAGC TACCGGGTGGTCAAGCTCTCAGCGTCTGACCCAGGACTGGCTGAATGGCAAGGAG TACAAGTGAAGGTCTCCAACAAAGCCCTCCGAGCCGCTATCGAGAAACCATCTCC AAAGCCAAAGGCCAGCCCGGGAACACAGGTGTACACCTGCCCCCATCCCGGGAG GAGATGACCAAGAACCGGTGAGCTGACCTGCTGGTCAAAGGCTTCTATCCGAGC GACATCGCGTGGAGTGGGAGAGCAATGGCCAGCCGAGAACAACTACAAGACCAAC CCTCCCGTGTGAGTCCGACGGCTCTTCTTCTCTACAGCAAGCTCACCGTGGAC AAGAGCAGGTGGCAGCAGGGCAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTG CACAACCACTACCCAGAAAGAGCTCTCCCTGTCTCCCGCAAA
58	chG019 heavy chain variable region amino acid sequence	QVQLQSGAELVKPSSVKISCKASGYTFRNFMHWIQQPGNGLEWIGWIYPGDGE TEYNQKFNGKATLTADRSSSTAYMELSRLTSEDSAVYFCARGVYGGFAGGYFDWQG GVMVTVSS
59	chG019 heavy chain variable region nucleotide sequence	CAGGTGCAGCTGCAGCAGTCTGGCGCCGAGCTCGTGAAGCCTGGCAGCAGCGTGAAG ATCAGCTGCAAGGCCAGCGGCTACACCTTCACCCGGAACCTTCATGCACTGGATCAAG CAGCAGCCCGGCAACGGCTGGAATGGATCGGCTGGA"CTATCCCGCCGACGGCGAG ACAGAGTACAACCAAGATTCAACGGCAAGGCCACCT"GAACCGCCGACAGAAAGCAGC TCCACCGCTACATGGAAGTGAAGCGGCTGACCAGCGAGGACAGCGCGGTGTAATTT TGGCCAGAGGGGTGTACGGCGGCTTCGCTGGCGGCTACTTCGATTTTGGGGCCAG GGCGTGATGGTCACCGTCAGCTCA
17	chG019 CDRH1	GYTFRNFMH
60	chG019 CDRH2	WIYPGDGETE
19	chG019 CDRH3	GVYGGFAGGYFDF

[0105]

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[Table 1-9]

61	hL02 light chain full-length amino acid sequence	MVLQTQVFISLLWISGAYGDIQMTQSPSSLSASVGDRTITCKASONIYKNLAWYQ QKPGKAPKLLIYDANTLQTGVPSRFSGSGSGSDFTLTISLQPEDFATYFCQQYYSG WAFGGGKVEIKRTVAAPSVFIFPPSDEQLKSGTASVYCLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKOSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF NRGEC
62	hL02 light chain full-length nucleotide sequence	ATGGTGCTGCAGACCCAGGTGTTTCATCTCCCTGGTGGTGTGGATCTCGGCGGTAC GGCGACATCCAGATGACCCAGAGCCCTAGCAGCCTGAGCGCCAGCGTGGGCGACAGA GTGACCATCACATGCAAGGCCAGCCAGAACATCTACAAGAACCTGGCCTGGTATCAG CAGAAAGCCCGCAAGGCCCCCAAGCTGCTGATCTACGAGCCCAACACCTGCAGACC GGCGTGCCGAGCAGATTTTCTGGCAGCGGCAGCGGCTCGGACTTCACCCGTGACAACTC AGCAGCCTGCAGCCGAGGACTTCGCCACCTACTTTTGGCAGCAGTACTACAGCGGC TGGGCTTCGGCCAGGGCAGCAAGGTGGAATCAAGCGTACGGTGGCCGCCCTCC GTGTTTCATCTTCCCCCTCCGACGAGCAGTGAAGTCCGGCAGCGCTCCGTGGTG TGCTGCTGAATAACTTCTACCCAGAGAGGCCAAGGTGCAGTGGAGGTGGACAAC GCCCTGCAGTCCGGGAAGTCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACAGC ACCTACAGCCTGAGCAGCAGCCTGACCTGAGCAAGCGGACTACGAGAGCACAAG GTGTACGCTGCGAGGTGACCCACAGGCGCTGAGCTCCCGCTCACCAGAGCTTC AACAGGGGGAGTGT
63	hL02 light chain variable region amino acid sequence	DIQMTQSPSSLSASVGDRTITCKASONIYKNLAWYQKPGKAPKLLIYDANTLQTG VPSRFSGSGSGSDFTLTISLQPEDFATYFCQQYYSGWAFGGGKVEIKRT
64	hL02 light chain variable region nucleotide sequence	GACATCCAGATGACCCAGAGCCCTAGCAGCCTGAGCGCCAGCGTGGGCGACAGAGTG ACCATCACATGCAAGGCCAGCCAGAACATCTACAAGAACCTGGCCTGGTATCAGCAG AAGCCCGCAAGGCCCCCAAGCTGCTGATCTACGAGCCCAACACCTGCAGACCGGC GTGCCAGCAGATTTTCTGGCAGCGGCAGCGGCTCGGACTTCACCCGTGACAACTCAGC AGCCTGCAGCCGAGGACTTCGCCACCTACTTTTGGCAGGAGTACTACAGCGGCTGG GCCTTCGGCCAGGGCAGCAAGGTGGAATCAAGCGTACG
65	hL03 light chain full-length amino acid sequence	MVLQTQVFISLLWISGAYGDIQMTQSPSSLSASVGDRTITCKASONIYKNLAWYQ QKLGEQPKLLIYDANTLQTGVPSRFSGSGSGSDFTLTISLQPEDFATYFCQQYYSG WAFGGGKVEIKRTVAAPSVFIFPPSDEQLKSGTASVYCLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKOSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF NRGEC

[0106]

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[Table 1-10]

66	hL03 light chain full-length nucleotide sequence	ATGGTGCTGCAGACCCAGGTGTTTCATCTCCCTGGTGTGGATCTCCGGCGGTAC GGCGACATCCAGATGACCCAGAGCCCTAGCAGCCTGAGCGCCAGCGTGGGCGACAGA GTGACCATCACATGCAAGGCCAGCCAGAAGATGTACAAGAACCCTGGCTGGTATCAG CAGAAAGCTGGGCGAGGGCCCCAAGCTGCTGATCTACGAGGCCAACACCCCTGCAGACC GGCGTGCCGAGCAGATTTTCTGGCAGCGGCTCCGGCACCGACTTCACCCCTGACAATC AGCAGCCTGCAGCCGAGGACTTCGCCACCTACTACTGCCAGCAGTACTACAGCGGC TGGGCGTTTGGCCAGGGCACCAGGTGGAATCAAGCGTACGGTGGCGGCCCTCC GTGTTTCATCTTCCCCCTCCGACGAGCAGCTGAAGTCCGGCACCGCTCCGTGGTG TGCTTGCTGAATAACTTCTACCCAGAGAGGCCAAGGTGCAGTGGAGGTGGACAAC GCCCTGCAGTCCGGGAACCTCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACAGC ACCTACAGCCTGAGCAGCAGCCTGACCTGAGCAAGCCGACTACGAGAGCACAAG GTGTACGCTGCGAGGTGAGCCACCAGGCGCTGAGCTCCCCGTACCAAGAGCTTC AACAGGGGGAGTGT
67	hL03 light chain variable region amino acid sequence	DIQMTQSPSSLSASVGRVTITCKASQNIYKNLAWYQQKLGEGPKLLIYDANTLQTG VPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYYSQWAFGGTKVEIKRT
68	hL03 light chain variable region nucleotide sequence	GACATCCAGATGACCCAGAGCCCTAGCAGCCTGAGCGCCAGCGTGGGCGACAGAGTG AGCATCACATGCAAGGCCAGCCAGAAGATGTACAAGAACCCTGGCTGGTATCAGCAG AAGCTGGGCGAGGGCCCCAAGCTGCTGATCTACGAGGCCAACACCCCTGCAGACCGGC GTGCCAGCAGATTTTCTGGCAGCGGCTCCGGCACCGACTTCACCCCTGACAATCAGC AGCCTGCAGCCGAGGACTTCGCCACCTACTACTGCCAGCAGTACTACAGCGGCTGG GCCCTTGGCCAGGGCACCAGGTGGAATCAAGCGTACG
69	hH01 heavy chain full-length amino acid sequence	MKHLWFFLLLVAAPRWVLSEVLVQSGAEVKKPGASVKVSCKASGYTFTRNFMHWVR GAPGGGLEWMMGIYPGDGETEYAGKFGGRVTITADTSYSTAYMELSSLRSEDATVYY CARGVYGGFAGGYFDWGGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYIQNVNH KPSNTKVDKRVKPKSCDKHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSYTRVVSIVLTVLHDDWLNKKE YKCKVSNKALPAPIEKTIISKAKGQPREPQVYTLPPSREENTKNQVSLTCLVKGFPYS DIAVEWESNGOPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVVFSCSVNHEAL HNHYTQKSLSLSPGK

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[Table 1-11]

70	hH01 heavy chain full-length nucleotide sequence	ATGAAACACCTGTGGTTCTTCCTCCTGCTGGTGGCAGCTCCAGATGGGTGCTGAGC GAAGTGCAGCTGGTGCAGTCTGGCGCCGAAGTGAAGAAACCAGGCCAGCGTGAAG GTGTCTGCAAGGCCAGCGGCTACACCTTTACCGGAAGTTTCATGCACTGGGTGCGC CAGGCTCCAGGCCAGGGAAGTGAATGGATGGGTGGATCTATCCCGGCGACGGCGAG ACAGAGTACGCCAGAAATTCCAGGGCAGAGTGACCATACCGCCGACACCGACACC TCCACCGCTACATGGAAGTGAAGCAGCTGCGGAGCGAGGACACCGCGGTGTACTAT TGTGCCAGAGGGGTGTACGGCGGCTTCGCTGGCGGCTACTTCGATTTTGGGGCCAG GGCACCCTCGTGACCGTCAGCTCAGCCTCCACCAAGGGCCAAAGCGTCTTCCCGCTG GCACCTCCTCCAAGAGCACCTCTGGCGGCACAGCGCGCTGGGCTGCCGTGGTCAAG GACTACTTCCCGAACCCTGACCGTGAGCTGGAAGTCAAGCGCCCTGACACGGCGC GTGCACACCTTCCCGCTGTCTGCAGTCTCAGGACTCTACTCCCTCAGCAGCGTG GTGACCGTGCCCTCCAGCAGCTTGGGCACCGAGCTACATCGCAACGTGAATCAC AAGCCGACCAACCAAGGTGGACAAGAGAGTTGAGCCCAATCTTGTGACAAAAT CACACATGCCACCTGCCAGCACCTGAAGTCTGGGGGACCTCAGTCTTCTCTC TTCCCGCAAAAGCCCAAGGACACCTCATGATCTCCCGGACCGCTGAGGTACATGC GTGGTGGTGGACGTGAGCCAGAACCTGAGGTCAAGTTCAACTGGTACGTGGAC GGCGTGGAGGTGCATAATGCCAAGACAAAGCCCGGGAGGAGCAGTACACAGCAGC TACCGGGTGGTACGCTCCTCAGCTCCTGCACCGAGTGGTGAATGGCAAGGAG TACAAGTGCAAGGTCTCCAACAAGGCTCCAGCGCCCATCGAGAAAACCATCTCC AAAGCCAAAGGCCAGCCCGGGAACACAGGTGTACACCTGCCCATCCCGGGAG GAGATGACCAAGAACCAGGTACGCTGACCTGGCTGGTCAAAGGCTTCTATCCAGC GACATCGCGTGGAGTGGAGAGCAATGCCAGCCGAGAACAACTACAAGACCACC CCTCCGCTGCTGGACTCCGACGGCTCCTTCTTCTCTCAGCAAGGTACCGTGGAG AAGAGCAGGTGGCAGCAGGCAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTG CACAACCACTACACCGAGAAGAGCTCTCCTGTCTCCCGGCAAA
71	hH01 heavy chain variable region amino acid sequence	EVQLVDSGAIEVKKPGASVKVSCKASGYTFTRNFMHWVRQAPGGGLEWMGWITPGDGE TEYAQKFGQRTVITADTSTSTAYMELSSLRSEDTAVYFCARGVYGGFAGGYFDWFGQ GTLVTVSS
72	hH01 heavy chain variable region nucleotide sequence	GAAGTGCAGCTGGTGCAGTCTGGCGCCGAAGTGAAGAAACCAGGCCAGCGTGAAG GTGTCTGCAAGGCCAGCGGCTACACCTTTACCGGAAGTTTCATGCACTGGGTGCGC CAGGCTCCAGGCCAGGGAAGTGAATGGATGGGTGGATCTATCCCGGCGACGGCGAG ACAGAGTACGCCAGAAATTCCAGGGCAGAGTGACCATACCGCCGACACCGACACC TCCACCGCTACATGGAAGTGAAGCAGCTGCGGAGCGAGGACACCGCGGTGTACTAT TGTGCCAGAGGGGTGTACGGCGGCTTCGCTGGCGGCTACTTCGATTTTGGGGCCAG GGCACCCTCGTGACCGTCAGCTCA

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[Table 1-12]

73	hH02 heavy chain full-length amino acid sequence	MKHLWFFLLVAAPRWVLSEVLVQSGAEVKKPGASVKVSKASGYTFRNFMHWVR QAPGGGLEWMGWIYPGDGETEYNQKFQGRVTITADRSTSTAYMELSSLRSEDVAVYF CARGVYGGFAGGYDFWGGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNH KPSNTKVDKRVEPKSCDKHTHTCPCPAPELLGGPSVFLFPPPKDITLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHODNLNGKE YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQSYMHEAL HNHYTQKSLSLSPGK
74	hH02 heavy chain full-length nucleotide sequence	ATGAAACACCTGTGGTTCTTCTCTCTGCTGGTGGCAGCTCCAGATGGGTGCTGAGC GAAGTGACAGCTGGTGCAGTCTGGCGCCGAAGTGAAGAAACAGGCGCCAGCGTGAAG GTGTCTCTGCAAGGCCAGCGGCTACACCTTTACCGGGAACCTCATGCACTGGGTGCGC CAGGCTCCAGGCCAGGGACTGGAATGGATGGGCTGGATCTATCCCGGCGACGCGCAG ACAGAGTACAACCCAGAAATTCCAGGGCAGAGTGACCATCACCGCCGACAGAAGCACC AGCACCGCCTACATGGAAGTGAAGCAGCCTGCGGAGCGAGGATACCGCGGTGACTTTC TGTGCCAGAGGCGTGTACGGCGGCTTGGCTGGCGGGTAAGTTCGATTTTGGGGCCAG GGCACCTCTGTGACCGTCAGCTCAGCCTCCACCAAGGGCCCAAGCGTCTTCCCGCTG GCACCTCTCTCCCAAGAGCAGCTGTGGCGGCACAGCCGCGCTGGGCTGGCTGGTCAAG GACTACTTCCCGAACCCTGACCGTGAGCTGGAAGTCAAGGCGCGTGAACAGCGGC GTGCACAGCTTCCCGGCTGTCTGAGTCTCAGGACTCTACTCCCTCAGCAGCGTG GTGACCGTGGCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCAC AAGCCACGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAAT CACACATGCCACCTGCCCAGCACCTGAACCTCTGGGGGACCGCTCAGTCTTCTCTC TTCCCCCAAAACCCCAAGGACAGCCTCATGATCTCCCGGACCGCTGAGGTACATGG GTGGTGGTGGACGTGAGCCACGAAGACCTGAGGTCAAGTTCAACTGGTACGTGGAC GGCGTGGAGGTGCATAATGCCAAGACAAGCCCGGGAGGAGCAGTACAACAGCACG TACCGGGTGGTCAGCGTCTCACCGTCTGCACACAGGACTGGCTGAATGGCAAGGAG TACAAGTGCAAGGTCTCCAACAAGCCCTCCAGCCCGCATCGAGAAAACCATCTCC AAAGCCAAAGGCCAGCCCGGGGAACACAGGTGTACACCTGCCCCATCCCGGGAG GAGATGACCAAGAACCAGGTGAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAGC GACATCGCCGTGGAGTGGGAGAGCAATGCCAGCCCGAACAACACTACAAGACCACC CCTCCCGTGTGGACTCCGACGGCTCTTCTTCTCTCTACAGCAAGCTCAGCGTGGAC AAGAGCAGGTGGCAGCAGGGCAAGCTTCTCATGCTCGGTGATGCATGAGGCTCTG CACAACCACTACACCCAGAAGAGCCTCTCCTGTCTCCCGGCAAA
75	hH02 heavy chain variable region amino acid sequence	EVQLVQSGAEVKKPGASVKVSKASGYTFRNFMHWVRQAPGGGLEWMGWIYPGDGE TEYNQKFQGRVTITADRSTSTAYMELSSLRSEDVAVYFCARGVYGGFAGGYDFWGG GTLVTVSS

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[Table 1-13]

76	hH02 heavy chain variable region nucleotide sequence	GAAGTGCAGCTGGTGCAGTCTGGCGCCGAAGTGAAGAAACAGGCGCCAGCGTGAAG GTGTCTCTGCAAGGCCAGCGGCTACACCTTTACCGGAACCTCATGCAGTGGGTGCCG CAGGCTCCAGGCCAGGGACTGGAATGGATGGGTGGATCTATCCCGGCAGCGCGAG ACAGAGTACAACCAGAAATTCCAGGGCAGAGTGACCATCACCGCCGACAGAAACACC AGCAGCGCTACATGGAAGTGAACAGCTGCGGAGCGAGGATACCGCGGTGTAATTC TGTGCCAGAGGCGTGTACGGCGGCTTCGCTGGCGGCTACTTCGATTTTGGGGCCAG GGCACCCTCGTGACCGTCAGCTCA
77	hH04 heavy chain full-length amino acid sequence	MKHLWFFLLVAAPRWVLSQVLVQSGAEVKKPGASVKVSCKASGYTFTRNFMHWIR QAPGGGLEWNGWIYPGDGETEYAKFGQGRVLTADRSTSTAYMELSSLRSEDAVYY CARGVYGGFAGGYDFWGGGLVTVSSASTKGPSVFLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSQVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYIENVNH KPSNTKVDKRVKPEKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALPAPIEKTIISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEAL HNHYTQKSLSLSPGK
78	hH04 heavy chain full-length nucleotide sequence	ATGAAACACCTGTGGTTCTTCTCTCTGCTGGTGGCAGCTCCAGATGGGTGCTGAGC CAGGTGCAGCTGGTGCAGTCTGGCGCCGAAGTGAAGAAACAGGCGCCAGCGTGAAG GTGTCTCTGCAAGGCCAGCGGCTACACCTTTACCGGAACCTCATGCAGTGGATCCGG CAGGCGCTGGACAGGGCTGGAATGGATGGGTGGATCTATCCCGGCAGCGCGAG ACAGAGTACGCCAGAAATTCCAGGGCAGAGTGACCTGACCGGCCGACAGAAACACC AGCAGCGCTACATGGAAGTGAACAGCTGCGGAGCGAGGACACCGCGGTGTAATTC TGTGCCAGAGGCGTGTACGGCGGCTTCGCTGGCGGCTACTTCGATTTTGGGGCCAG GGCACCCTCGTGACCGTCAGCTCAGGCTCCACCAAGGGCCCAAGCGTCTTCCCGCTG GCACCTCTCTCCAGAGCACCTCTGGCGGCACAGCGGCTGGCTGGCTGGTCAAG GACTACTTCCCGGAACCGGTGACCGTGAGCTGGAATCAGGCGCCCTGACCAAGCGG GTGCACACCTTCCCGCTGTCTGCACTCTCAGGACTGACTCCCTCAGCAGCGTG GTGACCGTGCCCTCCAGCAGCTTGGGCACCAAGACCTACATCTGCAACGTGAATCAC AAGCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAATCTTGTGACAAAACCT CACACATGCCACCTGCCAGCACCTGAACCTCTGGGGGAGCCTCAGTCTTCTCT TTCCCCCAAAACCAAGGACACCTCATGATCTCCCGGACCCCTGAGGTACATAGC GTGGTGGTGGAGTGAGCCACGAAGACCTGAGGTCAAGTTCAACTGGTACGTGGAC GGCGTGGAGGTGCATAATGCCAAGACAAAGCCCGGGAGGAGCAGTACAACAGCAG TACCGGGTGGTCAGCGTCTCACCGTCTGCACCAAGAGTGGCTGAATGGCAAGGAG TACAAGTGCAAGGTCTCCAACAAGCCCTCCAGCCCGCATCGAGAAAACCATCTCC AAAGCCAAAGGCCAGCCCCGGGAACACAGGTGTACAGCTGCCCCCATCCCGGGAG GAGATGACCAAGAACAGGTGAGCTGACCTGCTGGTCAAAGGCTTCTATCCAGC GACATCGCGTGGAGTGGGAGAGCAATGGCCAGCCCGAGAACAACTACAAGACACC CCTCCCGTGGTGGACTCGGACGGCTCTTCTCTCTGAGCAAGCTCAGCGTGGAC AAGAGCAGGTGGCAGAGGGCAAGCTTCTCATGCTCGGTGATGATGAGGTCTG CACAACCACTACACCAAGAGGCTCTCCCTGTCTCCCGGCAAA

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[Table 1-14]

79	hH04 heavy chain variable region amino acid sequence	QVQLVQSGAEVKKPGASVKVSCKASGYTFRNFMHWIRQAPGQGLEWMGWITPGDGE TEYAQKFQGRVTLTADRSTSTAYNELSSLRSEDVAVYYCARGVYGGFAGGYFDWGG GTLVTVSS
80	hH04 heavy chain variable region nucleotide sequence	CAGGTGCAGCTGGTGCAGTCTGGCGCCGAAGTGAAGAAACAGGCCGACGGTGAAG GTGTCCTGCAAGGCCAGCGGTACACCTTTACCGGAACCTTCATGCACTGGATCCGG CAGGCCCTGGACAGGCCCTGGAATGGATGGGCTGGATCTATCCGGGACAGGCGAG ACAGAGTACGCCAGAAATTCAGGGCAGAGTGACCTGACCGCCGACAGAAGCACC AGCACCGCTACATGGAAGTGAAGAGCTGCGGAGCGAGGACACCGCCGTGTACTAT TGTGCCAGAGCGGTGACGCGGCTTCGCTGCGGCTACTTCGATTTTGGGCCAG GGCACCTCGTGACCGTCACTCA
81	NOV0712 light chain full-length amino acid sequence	MVLQTQVFISLLWISGAYGDIQMTQSPSSLSASVGRVTITCRASQSISSYLNWYQ QKPGKAPKLLIYAVSTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQSGTF PPTTFGGGTQVEIKRTVAAPSVFIFPPSDEQLKSGTASVCLLNNFYPREAKVQWVK DNALQSGNSQESVTEQDSKSTYSLSSLTSLSKADYEKHKVYACEVTHGGLSSPVTK SFNRGEC
82	NOV0712 light chain full-length nucleotide sequence	ATGGTGCTGCAGACCCAGGTGTTTCATCTCCCTGCTGCTGTGGATCTCCGGCGGTAC GGCGACATCCAGATGACCCAGAGCCCTAGCAGCTGAGCGCCAGCGTGGCGACAGA GTGACCATCACCTGTAGAGCCAGCCAGACATCAGCAGCTACCTGAACCTGGTATCAG CAGAAGCCCGGCAAGGCCCCAAACTGCTGATCTACGCGGTGCCACACTGCAGAGC GGCGTGCCGAGCAGATTTCTGGCAGCGGCTCCGGCACCGACTTCACCGTGACAATC AGCAGCTGCAGCCGAGGACTTCGCCAGCTACTACTGTGAGCAGTCCGGCACCTTC CCCCCACCACATTTGGCCAGGACCAAGTGGAAATCAAGCGTACGGTGGCCGCC CCCTCCGTGTTTCATCTTCCCCCCTCCGACGAGCAGCTGAAGTCCGGCACCGCTCC GTGGTGTGCTGCTGAATAACTTCTACCCAGAGAGGCCAAGGTGCAGTGGAAAGGTG GACAACGCCCTGCAGTCCGGGAACCTCCAGSAGAGCGTGACCGAGCAGGACAGCAAG GACAGCACCTACAGCTGAGCAGCACCTGACCTGAGCAAAGCCGACTACGAGAAG CACAAGGTGTACGCTGCGAGGTGACCCACAGGGGCTGAGCTCCCCCGTACCAAG AGCTTCAACAGGGGGAGTGT
83	NOV0712 heavy chain full-length amino acid sequence	MKHLWFFLLVAAPRWVLSQVQLLESQGGLVQPGGSLRLSCAASGFTFSHGMHWVR QAPGKGLEWVSVISGSGSNTGYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYY CARQWGSYAFDSWGGTLVTSSASTKGPSVFPLAPSSKSTSGGTAAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSN TKVDKRVPEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCK VSNKALPAPIEKTSKAKGQPREPQVYTLPPSREEMTKNOVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCGSMHEALHNHY TOKLSLSLSPGK

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[Table 1-15]

84	NOV0712 heavy chain full-length nucleotide sequence	ATGAAACACCTGTGGTTCTTCTCCTGCTGGTGGCAGCTCCAGATGGGTGGTGAAG CAGGTGCAGCTGTGGAATCTGGCGGAGGACTGGTGCAGCCTGGCGGCTCTGTGAGA CTGTCTTGTGCGGCCAGCGGCTTCACTTCAGCAGCCACGGAATGCACTGGGTGCAG CAGGCCCTGGAAAGGGACTGGAATGGGTGTCCGTGATCAGCGGCAGCGGCTCCAAT ACCGGCTACGCGGATAGCGTGAAGGGCGGTTCAACATCAGCGGAGACAACAGCAAG AACACCTGTACCTGCAGATGAACAGCCTGCGGGCCGAGGACACCGCGGTACTAT TGTGCCAGACAGTGGGGCAGCTACGGCTTCGATTCTTGGGGCCAGGGCACCGCTCGTG ACCGTCAGCTCAGCCTCCACCAAGGGCCCAAGCGTCTTCCCGCTGGCAGCCTCCTCC AAGAGCACCTCTGGCGGCACAGCGCCCTGGGCTGGCTGGTCAAGGACTACTTCCCG GAACCGGTGACCGTGAGCTGGAAGTCAAGGCGCCTGACCAGCGGCGTGACACCTTC CCCGCTGTCTGAGTCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGGCC TCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGGCCAGCAAC ACCAAGGTGGACAAGAGAGTTGAGCCCAATCTTGTGACAAACTCACACATGCCCA CCCTGCCAGCACCTGAAGTCTGGGGGACCTCAGTCTTCTCTTCCCGCAAAA CCCAAGGACACCTCATGATCTCCGGACCCCTGAGGTACATCGGTGGTGGTGAC GTGAGCCACGAGACCTGAGGTCAAGTTCAAGTGGTACGTGGACGGCGTGGAGGTG CATAATGCCAAGACAAAGCCCGGGAGGAGCAGTACAACAGCACGTACCGGTGGTC AGCGTCTCAGCGTCTGCAACAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAG GTCTCCAAACAAAGCCTCCAGCCCGCATCGAGAAAACCATCTCCAAAGCCAAAGGC CAGCCCGGGGAACACAGGTGTACACCTGCCCCCATCCCGGAGGAGATGACCAAG AACCAGGTACGCTGACCTGCTGGTCAAAGGCTTCTATCCAGCGACATCGCGGTG GAGTGGGAGAGCAATGGCCAGCCGAGAACTACAAGACCCCTCCCGTGGTG GACTCCGAGGGCTCCTTCTCTCTACAGCAAGCTACCGTGGACAAGAGCAGGTGG CAGCAGGGCAACGTCTTCTCATGCTCGGTGATGAGGCTCTGACAAACCACTAC ACCCAGAAGAGCCTCTCCTGTCTCCCGCAAA
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[0107]

Further examples of the antibody of the present invention can include a human antibody binding to CDH6. The anti-CDH6 human antibody means a human antibody having only the gene sequence of an antibody derived from human chromosomes. The anti-CDH6 human antibody can be obtained by a method using a human antibody-producing mouse having a human chromosomal fragment comprising the heavy chain and light chain genes of a human antibody (see Tomizuka, K. et al., Nature Genetics (1997) 16, p. 133-143; Kuroiwa, Y. et al., Nucl. Acids Res. (1998) 26, p. 3447-3448; Yoshida, H. et al., Animal Cell Technology: Basic and Applied Aspects vol. 10, p. 69-73 (Kitagawa, Y., Matsuda, T. and Iijima, S. eds.), Kluwer Academic Publishers, 1999; Tomizuka, K. et al., Proc. Natl. Acad. Sci. USA (2000) 97, p. 722-727; etc.).

[0108]

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Such a human antibody-producing mouse can be specifically produced by using a genetically modified animal, the gene loci of endogenous immunoglobulin heavy chain and light chain of which have been disrupted and instead the gene loci of human immunoglobulin heavy chain and light chain have been then introduced using a yeast artificial chromosome (YAC) vector or the like, then producing a knock-out animal and a transgenic animal from such a genetically modified animal, and then breeding such animals with one another.

[0109]

Otherwise, the anti-CDH6 human antibody can also be obtained by transforming eukaryotic cells with cDNA encoding each of the heavy chain and light chain of such a human antibody, or preferably with a vector comprising the cDNA, according to genetic recombination techniques, and then culturing the transformed cells producing a genetically modified human monoclonal antibody, so that the antibody can be obtained from the culture supernatant.

[0110]

In this context, eukaryotic cells, and preferably, mammalian cells such as CHO cells, lymphocytes or myelomas can, for example, be used as a host.

[0111]

Furthermore, a method of obtaining a phage display-derived human antibody that has been selected from a human antibody library (see Wormstone, I. M. et al., *Investigative Ophthalmology & Visual Science*. (2002) 43 (7), p. 2301-2308; Carmen, S. et al., *Briefings in Functional Genomics and Proteomics* (2002), 1 (2), p. 189-203; Siriwardena, D. et al., *Ophthalmology* (2002) 109 (3), p. 427-431; etc.) is also known.

[0112]

For example, a phage display method, which comprises allowing the variable regions of a human antibody to express as a single chain antibody (scFv) on the

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surface of phages, and then selecting a phage binding to an antigen, can be applied (Nature Biotechnology (2005), 23, (9), p. 1105-1116).

[0113]

By analyzing the phage gene that has been selected because of its binding ability to the antigen, DNA sequences encoding the variable regions of a human antibody binding to the antigen can be determined.

[0114]

Once the DNA sequence of scFv binding to the antigen is determined, an expression vector having the aforementioned sequence is produced, and the produced expression vector is then introduced into an appropriate host and can be allowed to express therein, thereby obtaining a human antibody (International Publication Nos. WO92/01047, WO92/20791, WO93/06213, WO93/11236, WO93/19172, WO95/01438, and WO95/15388, Annu. Rev. Immunol (1994) 12, p. 433-455, Nature Biotechnology (2005) 23 (9), p. 1105-1116).

[0115]

If a newly produced human antibody binds to a partial peptide or a partial three-dimensional structure to which any one rat anti-human CDH6 antibody, chimeric anti-human CDH6 antibody or humanized anti-human CDH6 antibody described in the present description (e.g., the rG019 antibody, the rG055 antibody, the rG056 antibody, the rG061 antibody, the chG019 antibody, the H01L02 antibody, the H02L02 antibody, the H02L03 antibody or the H04L02 antibody) binds, it can be determined that the human antibody binds to the same epitope to which the rat anti-human CDH6 antibody, the chimeric anti-human CDH6 antibody or the humanized anti-human CDH6 antibody binds. Alternatively, by confirming that the human antibody competes with the rat anti-human CDH6 antibody, the chimeric anti-human CDH6 antibody or the humanized anti-human CDH6 antibody described in the present description (e.g., the rG019 antibody, the rG055 antibody, the rG056

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antibody, the rG061 antibody, the chG019 antibody, the H01L02 antibody, the H02L02 antibody, the H02L03 antibody or the H04L02 antibody) in the binding of the antibody to CDH6 (e.g., the human antibody interferes with the binding of the rG019 antibody, the rG055 antibody, the rG056 antibody, the rG061 antibody, the chG019 antibody, the H01L02 antibody, the H02L02 antibody, the H02L03 antibody or the H04L02 antibody to CDH6, preferably EC3 of CDH6), it can be determined that the human antibody binds to the same epitope to which the rat anti-human CDH6 antibody, the chimeric anti-human CDH6 antibody or the humanized anti-human CDH6 antibody described in the present description binds, even if the specific sequence or structure of the epitope has not been determined. In the present description, when it is determined by at least one of these determination methods that the human antibody "binds to the same epitope", it is concluded that the newly prepared human antibody "binds to the same epitope" as that for the rat anti-human CDH6 antibody, the chimeric anti-human CDH6 antibody or the humanized anti-human CDH6 antibody described in the present description. When it is confirmed that the human antibody binds to the same epitope, then it is expected that the human antibody should have a biological activity equivalent to that of the rat anti-human CDH6 antibody, the chimeric anti-human CDH6 antibody or the humanized anti-human CDH6 antibody (e.g., the rG019 antibody, the rG055 antibody, the rG056 antibody, the rG061 antibody, the chG019 antibody, the H01L02 antibody, the H02L02 antibody, the H02L03 antibody or the H04L02 antibody).

[0116]

The chimeric antibodies, the humanized antibodies, or the human antibodies obtained by the above-described methods are evaluated for their binding activity against the antigen according to a known method, etc., so that a preferred antibody can be selected.

[0117]

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One example of another indicator for comparison of the properties of antibodies can include the stability of an antibody. A differential scanning calorimeter (DSC) is an apparatus capable of promptly and exactly measuring a thermal denaturation midpoint (T_m) serving as a good indicator for the relative structural stability of a protein. By using DSC to measure T_m values and making a comparison regarding the obtained values, differences in thermal stability can be compared. It is known that the preservation stability of an antibody has a certain correlation with the thermal stability of the antibody (Lori Burton, et al., *Pharmaceutical Development and Technology* (2007) 12, p. 265-273), and thus, a preferred antibody can be selected using thermal stability as an indicator. Other examples of the indicator for selection of an antibody can include high yield in suitable host cells and low agglutination in an aqueous solution. For example, since an antibody with the highest yield does not always exhibit the highest thermal stability, it is necessary to select an antibody most suitable for administration to a human by comprehensively determining it based on the aforementioned indicators. [0118]

The antibody of the present invention also includes a modification of an antibody. The modification is used to mean the antibody of the present invention, which is chemically or biologically modified. Examples of such a chemical modification include the binding of a chemical moiety to an amino acid skeleton, and the chemical modification of an N-linked or O-linked carbohydrate chain. Examples of such a biological modification include antibodies which have undergone a posttranslational modification (e.g., N-linked or O-linked glycosylation, N-terminal or C-terminal processing, deamidation, isomerization of aspartic acid, oxidation of methionine, and conversion of N-terminal glutamine or N-terminal glutamic acid to pyroglutamic acid), and antibodies, to the N-terminus of which a methionine residue is added as a result of having been allowed to be expressed using

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prokaryote host cells. In addition, such a modification is also meant to include labeled antibodies for enabling detection or isolation of the antibody of the present invention or an antigen, for example, an enzymatically labeled antibody, a fluorescently labeled antibody, and an affinity-labeled antibody. Such a modification of the antibody of the present invention is useful for the improvement of the stability and retention in blood of an antibody; a reduction in antigenicity; detection or isolation of an antibody or an antigen; etc.

[0119]

Moreover, by regulating a sugar chain modification (glycosylation, defucosylation, etc.) that binds to the antibody of the present invention, antibody-dependent cellular cytotoxic activity can be enhanced. As techniques of regulating the sugar chain modification of an antibody, those described in International Publication Nos. WO1999/54342, WO2000/61739, and WO2002/31140, etc. are known, though the techniques are not limited thereto. The antibody of the present invention also includes antibodies in respect of which the aforementioned sugar chain modification has been regulated.

[0120]

Once an antibody gene is isolated, the gene can be introduced into an appropriate host to produce an antibody, using an appropriate combination of a host and an expression vector. A specific example of the antibody gene can be a combination of a gene encoding the heavy chain sequence of the antibody described in the present description and a gene encoding the light chain sequence of the antibody described therein. Upon transformation of host cells, such a heavy chain sequence gene and a light chain sequence gene may be inserted into a single expression vector, or these genes may instead each be inserted into different expression vectors.

[0121]

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When eukaryotic cells are used as hosts, animal cells, plant cells or eukaryotic microorganisms can be used. In particular, examples of the animal cells can include mammalian cells such as COS cells which are monkey cells (Gluzman, Y., Cell (1981) 23, p. 175-182, ATCC CRL-1650), mouse fibroblasts NIH3T3 (ATCC No. CRL-1658), a dihydrofolate reductase-deficient cell line of Chinese hamster ovary cells (CHO cells, ATCC CCL-61) (Urlaub, G. and Chasin, L. A. Proc. Natl. Acad. Sci. U.S.A. (1980) 77, p. 4126-4220), and FreeStyle 293F cells (Invitrogen Corp.).

[0122]

When prokaryotic cells are used as hosts, *Escherichia coli* or *Bacillus subtilis* can be used, for example.

[0123]

An antibody gene of interest is introduced into these cells for transformation, and the transformed cells are then cultured *in vitro* to obtain an antibody. In the aforementioned culture, there are cases where yield is different depending on the sequence of the antibody, and thus, it is possible to select an antibody, which is easily produced as a medicament, from antibodies having equivalent binding activity, using the yield as an indicator. Accordingly, the antibody of the present invention also includes an antibody obtained by the above-described method for producing an antibody, which comprises a step of culturing the transformed host cells and a step of collecting an antibody of interest or a functional fragment of the antibody from the culture obtained in the aforementioned step.

[0124]

It is known that the lysine residue at the carboxyl terminus of the heavy chain of an antibody produced in cultured mammalian cells is deleted (Journal of Chromatography A, 705: 129-134 (1995)), and also, it is known that the two amino acid residues at the heavy chain carboxyl terminus, glycine and lysine, are deleted, and that the proline residue newly positioned at the carboxyl terminus is amidated

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(Analytical Biochemistry, 360: 75-83 (2007)). However, such deletion and modification of these heavy chain sequences does not have an influence on the antigen-binding activity and effector function (activation of complement, antibody-dependent cellular cytotoxicity, etc.) of an antibody. Accordingly, the antibody according to the present invention also includes an antibody that has undergone the aforementioned modification, and a functional fragment of the antibody, and specific examples of such an antibody include a deletion mutant comprising a deletion of 1 or 2 amino acids at the heavy chain carboxyl terminus, and a deletion mutant formed by amidating the aforementioned deletion mutant (e.g., a heavy chain in which the proline residue at the carboxyl-terminal site is amidated). However, deletion mutants involving a deletion at the carboxyl terminus of the heavy chain of the antibody according to the present invention are not limited to the above-described deletion mutants, as long as they retain antigen-binding activity and effector function. Two heavy chains constituting the antibody according to the present invention may be any one type of heavy chain selected from the group consisting of a full-length antibody and the above-described deletion mutants, or may be a combination of any two types selected from the aforementioned group. The ratio of individual deletion mutants can be influenced by the types of cultured mammalian cells that produce the antibody according to the present invention, and the culture conditions. Examples of the main ingredient of the antibody according to the present invention can include antibodies where one amino acid residue is deleted at each of the carboxyl termini of the two heavy chains.

[0125]

Examples of the isotype of the antibody of the present invention can include IgG (IgG1, IgG2, IgG3, and IgG4). Among others, IgG1 and IgG4 are preferable.

[0126]

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Examples of the biological activity of an antibody can generally include antigen-binding activity, activity of being internalized into cells expressing an antigen by binding to the antigen, activity of neutralizing the activity of an antigen, activity of enhancing the activity of an antigen, antibody-dependent cellular cytotoxic (ADCC) activity, complement-dependent cytotoxic (CDC) activity, and antibody-dependent cellular phagocytosis (ADCP). The function of the antibody according to the present invention is binding activity against CDH6 and is preferably the activity of being internalized into CDH6-expressing cells by binding to CDH6. Moreover, the antibody of the present invention may have ADCC activity, CDC activity and/or ADCP activity, as well as cellular internalization activity.

[0127]

The obtained antibody can be purified to a homogenous state. For separation and purification of the antibody, separation and purification methods used for ordinary proteins may be used. For example, column chromatography, filtration, ultrafiltration, salting-out, dialysis, preparative polyacrylamide gel electrophoresis, and isoelectric focusing are appropriately selected and combined with one another, so that the antibody can be separated and purified (Strategies for Protein Purification and Characterization: A Laboratory Course Manual, Daniel R. Marshak et al. eds., Cold Spring Harbor Laboratory Press (1996); and Antibodies: A Laboratory Manual. Ed Harlow and David Lane, Cold Spring Harbor Laboratory (1988)), though examples of the separation and purification methods are not limited thereto.

[0128]

Examples of the chromatography can include affinity chromatography, ion exchange chromatography, hydrophobic chromatography, gel filtration chromatography, reverse phase chromatography, and absorption chromatography.

[0129]

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These chromatographic techniques can be carried out using liquid chromatography such as HPLC or FPLC.

[0130]

Examples of the column used in the affinity chromatography can include a Protein A column and a Protein G column. Examples of the column involving the use of Protein A can include Hyper D, POROS, and Sepharose F. F. (Pharmacia).

[0131]

Also, using an antigen-immobilized carrier, the antibody can be purified by utilizing the binding activity of the antibody to the antigen.

[0132]

3. Anti-CDH6 antibody-drug conjugate

(1) Drug

The anti-CDH6 antibody obtained in the above "2. Production of anti-CDH6 antibody" can be conjugated to a drug via a linker structure moiety to prepare an anti-CDH6 antibody-drug conjugate. The drug is not particularly limited as long as it has a substituent or a partial structure that can be connected to a linker structure. The anti-CDH6 antibody-drug conjugate can be used for various purposes according to the conjugated drug. Examples of such a drug can include substances having antitumor activity, substances effective for blood diseases, substances effective for autoimmune diseases, anti-inflammatory substances, antimicrobial substances, antifungal substances, antiparasitic substances, antiviral substances, and anti-anesthetic substances.

[0133]

(1)-1 Antitumor compound

An example using an antitumor compound as a compound to be conjugated in the anti-CDH6 antibody-drug conjugate of the present invention will be described below. The antitumor compound is not particularly limited as long as the

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compound has an antitumor effect and has a substituent or a partial structure that can be connected to a linker structure. Upon cleavage of a part or the whole of the linker in tumor cells, the antitumor compound moiety is released so that the antitumor compound exhibits an antitumor effect. As the linker is cleaved at a connecting position with the drug, the antitumor compound is released in its original structure to exert its original antitumor effect.

[0134]

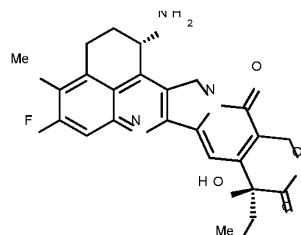
The anti-CDH6 antibody obtained in the above "2. Production of anti-CDH6 antibody" can be conjugated to the antitumor compound via a linker structure moiety to prepare an anti-CDH6 antibody-drug conjugate.

[0135]

As one example of the antitumor compound used in the present invention, exatecan, a camptothecin derivative ((1S,9S)-1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-10,13(9H,15H)-dione represented by the following formula) can preferably be used.

[0136]

[Formula 5]



[0137]

The compound can be easily obtained by, for example, a method described in U.S. Patent Publication No. US2016/0297890 or other known methods, and the amino group at position 1 can be preferably used as a connecting position to the linker structure. Further, exatecan may be released in tumor cells while a part of the

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linker is still attached thereto. However, the compound exerts an excellent antitumor effect even in such a state.

[0138]

Since exatecan has a camptothecin structure, it is known that the equilibrium shifts to a structure with a formed lactone ring (closed ring) in an acidic aqueous medium (e.g., of the order of pH 3) whereas the equilibrium shifts to a structure with an opened lactone ring (open ring) in a basic aqueous medium (e.g., of the order of pH 10). A drug conjugate into which exatecan residues corresponding to such a closed ring structure and an open ring structure have been introduced is also expected to have an equivalent antitumor effect, and it is needless to say that any of such drug conjugate is included within the scope of the present invention.

[0139]

Other examples of the antitumor compound can include antitumor compounds described in the literature (Pharmacological Reviews, 68, p. 3-19, 2016). Specific examples thereof can include doxorubicin, calicheamicin, dolastatin 10, auristatins such as monomethyl auristatin E (MMAE) and monomethyl auristatin F (MMAF), maytansinoids such as DM1 and DM4, a pyrrolobenzodiazepine dimer SG2000 (SJG-136), a camptothecin derivative SN-38, duocarmycins such as CC-1065, amanitin, daunorubicin, mitomycin C, bleomycin, cyclocytidine, vincristine, vinblastine, methotrexate, platinum-based antitumor agents (cisplatin and derivatives thereof), and Taxol and derivatives thereof.

[0140]

In the antibody-drug conjugate, the number of conjugated drug molecules per antibody molecule is a key factor having an influence on the efficacy and safety thereof. The production of the antibody-drug conjugate is carried out by specifying reaction conditions such as the amounts of starting materials and reagents used for reaction, so as to attain a constant number of conjugated drug molecules. Unlike

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the chemical reaction of a low-molecular-weight compound, a mixture containing different numbers of conjugated drug molecules is usually obtained. The number of conjugated drug molecules per antibody molecule is defined and indicated as an average value, i.e., the average number of conjugated drug molecules. Unless otherwise specified, i.e., except in the case of representing an antibody-drug conjugate having a specific number of conjugated drug molecules that is included in an antibody-drug conjugate mixture having different numbers of conjugated drug molecules, the number of conjugated drug molecules according to the present invention also means an average value as a rule. The number of exatecan molecules conjugated to an antibody molecule is controllable, and as an average number of conjugated drug molecules per antibody, approximately 1 to 10 exatecan molecules can be conjugated. The number of exatecan molecules is preferably 2 to 8, 3 to 8, 4 to 8, 5 to 8, 6 to 8, or 7 to 8, more preferably 5 to 8, further preferably 7 to 8, still further preferably 8. It is to be noted that a person skilled in the art can design a reaction for conjugating a required number of drug molecules to an antibody molecule based on the description of Examples of the present application, and can obtain an antibody-drug conjugate with a controlled number of conjugated exatecan molecules.

[0141]

(2) Linker structure

The linker structure which conjugates the drug to the anti-CDH6 antibody in the anti-CDH6 antibody-drug conjugate of the present invention will be described.

[0142]

In the antibody-drug conjugate of the present application, the linker structure which conjugates the anti-CDH6 antibody to the drug is not particularly limited as long as the resulting antibody-drug conjugate can be used. The linker structure may be appropriately selected and used according to the purpose of use. One example of

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the linker structure can include a linker described in known literature (Pharmacol Rev 68: 3-19, January 2016, Protein Cell DOI 10.1007/s13238-016-0323-0, etc.). Further specific examples thereof can include VC (valine-citrulline), MC (maleimidocaproyl), SMCC (succinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate), SPP (N-succinimidyl 4-(2-pyridyldithio)pentanoate, SS (disulfide), SPDB (N-succinimidyl 4-(2-pyridyldithio)butyrate, SS/hydrazone, hydrazone and carbonate.

[0143]

Another example can include a linker structure described in U.S. Patent Publication No. US2016/0297890 (as one example, those described in paragraphs [0260] to [0289] thereof). Any linker structure given below can preferably be used. It is to be noted that the left terminus of the structure is a connecting position to the antibody, and the right terminus thereof is a connecting position to the drug. Furthermore, GGFG in the linker structures given below represents an amino acid sequence consisting of glycine-glycine-phenylalanine-glycine (GGFG) linked through peptide bonds.

-(Succinimid-3-yl-N)-CH₂CH₂-C(=O)-GGFG-NH-CH₂CH₂CH₂-C(=O)-,
 -(Succinimid-3-yl-N)-CH₂CH₂CH₂CH₂CH₂-C(=O)-GGFG-NH-CH₂CH₂CH₂-C(=O)-,
 -(Succinimid-3-yl-N)-CH₂CH₂CH₂CH₂CH₂-C(=O)-GGFG-NH-CH₂-O-CH₂-C(=O)-,
 -(Succinimid-3-yl-N)-CH₂CH₂CH₂CH₂CH₂-C(=O)-GGFG-NH-CH₂CH₂-O-CH₂-C(=O)-,
 -(Succinimid-3-yl-N)-CH₂CH₂-C(=O)-NH-CH₂CH₂O-CH₂CH₂O-CH₂CH₂-C(=O)-GGFG-NH-CH₂CH₂CH₂-C(=O)-, and
 -(Succinimid-3-yl-N)-CH₂CH₂-C(=O)-NH-CH₂CH₂O-CH₂CH₂O-CH₂CH₂O-CH₂CH₂O-CH₂CH₂-C(=O)-GGFG-NH-CH₂CH₂CH₂-C(=O)-.

[0144]

More preferred are the following:

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-(Succinimid-3-yl-N)-CH₂CH₂CH₂CH₂CH₂-C(=O)-GGFG-NH-CH₂-O-CH₂-C(=O)-,
 -(Succinimid-3-yl-N)-CH₂CH₂CH₂CH₂CH₂-C(=O)-GGFG-NH-CH₂CH₂-O-CH₂-
 C(=O)-, and
 -(Succinimid-3-yl-N)-CH₂CH₂-C(=O)-NH-CH₂CH₂O-CH₂CH₂O-CH₂CH₂-C(=O)-
 GGFG-NH-CH₂CH₂CH₂-C(=O)-.

Still more preferred are the following:

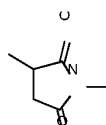
-(Succinimid-3-yl-N)-CH₂CH₂CH₂CH₂CH₂-C(=O)-GGFG-NH-CH₂-O-CH₂-C(=O)-,
 and
 -(Succinimid-3-yl-N)-CH₂CH₂-C(=O)-NH-CH₂CH₂O-CH₂CH₂O-CH₂CH₂-C(=O)-
 GGFG-NH-CH₂CH₂CH₂-C(=O)-.

[0145]

The antibody is connected to the terminus of -(Succinimid-3-yl-N) (e.g., a terminus opposite (left terminus) to the terminus to which -CH₂CH₂CH₂CH₂CH₂- is connected in -(Succinimid-3-yl-N)-CH₂CH₂CH₂CH₂CH₂-C(=O)-GGFG-NH-CH₂-O-CH₂-C(=O)-), and the antitumor compound is connected to a terminus (the carbonyl group of CH₂-O-CH₂-C(=O)- at the right terminus in the above-described example) opposite to the terminus to which the antibody is connected to - (Succinimid-3-yl-N). -(Succinimid-3-yl-N)-" has a structure represented by the following formula:

[0146]

[Formula 6]



[0147]

Position 3 of this partial structure is the connecting position to the anti-CDH6 antibody. This connection to the antibody at position 3 is characterized by forming

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a thioether bond. The nitrogen atom at position 1 of this structure moiety is connected to the carbon atom of methylene which is present within the linker including the structure.

[0148]

In the antibody-drug conjugate of the present invention having exatecan as the drug, a drug-linker structure moiety having any structure given below is preferred for conjugation to the antibody. For these drug-linker structure moieties, the average number conjugated per antibody may be 1 to 10 and is preferably 2 to 8, more preferably 5 to 8, further preferably 7 to 8, and still further preferably 8.

-(Succinimid-3-yl-N)-CH₂CH₂-C(=O)-GGFG-NH-CH₂CH₂CH₂-C(=O)-(NH-DX),
 -(Succinimid-3-yl-N)-CH₂CH₂CH₂CH₂CH₂-C(=O)-GGFG-NH-CH₂CH₂CH₂-C(=O)-(NH-DX),
 -(Succinimid-3-yl-N)-CH₂CH₂CH₂CH₂CH₂-C(=O)-GGFG-NH-CH₂-O-CH₂-C(=O)-(NH-DX),
 -(Succinimid-3-yl-N)-CH₂CH₂CH₂CH₂CH₂-C(=O)-GGFG-NH-CH₂CH₂-O-CH₂-C(=O)-(NH-DX),
 -(Succinimid-3-yl-N)-CH₂CH₂-C(=O)-NH-CH₂CH₂O-CH₂CH₂O-CH₂CH₂-C(=O)-GGFG-NH-CH₂CH₂CH₂-C(=O)-(NH-DX), and
 -(Succinimid-3-yl-N)-CH₂CH₂-C(=O)-NH-CH₂CH₂O-CH₂CH₂O-CH₂CH₂O-CH₂CH₂O-CH₂CH₂-C(=O)-GGFG-NH-CH₂CH₂CH₂-C(=O)-(NH-DX).

[0149]

More preferred are the following:

-(Succinimid-3-yl-N)-CH₂CH₂CH₂CH₂CH₂-C(=O)-GGFG-NH-CH₂-O-CH₂-C(=O)-(NH-DX),
 -(Succinimid-3-yl-N)-CH₂CH₂CH₂CH₂CH₂-C(=O)-GGFG-NH-CH₂CH₂-O-CH₂-C(=O)-(NH-DX), and

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-(Succinimid-3-yl-N)-CH₂CH₂-C(=O)-NH-CH₂CH₂O-CH₂CH₂O-CH₂CH₂-C(=O)-GGFG-NH-CH₂CH₂CH₂-C(=O)-(NH-DX).

[0150]

Still more preferred are the following:

-(Succinimid-3-yl-N)-CH₂CH₂CH₂CH₂CH₂-C(=O)-GGFG-NH-CH₂-O-CH₂-C(=O)-(NH-DX), and

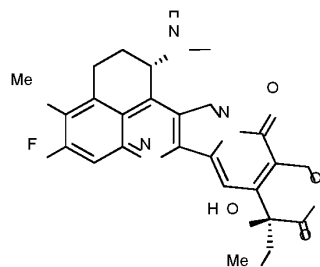
-(Succinimid-3-yl-N)-CH₂CH₂-C(=O)-NH-CH₂CH₂O-CH₂CH₂O-CH₂CH₂-C(=O)-GGFG-NH-CH₂CH₂CH₂-C(=O)-(NH-DX).

[0151]

-(NH-DX) has a structure represented by the following formula:

[0152]

[Formula 7]



[0153]

and it represents a group that is derived by removing one hydrogen atom from the amino group at position 1 of exatecan.

[0154]

(3) Method for producing antibody-drug conjugate

The antibody that can be used in the antibody-drug conjugate of the present invention is not particularly limited as long as it is an anti-CDH6 antibody having internalization activity or a functional fragment of the antibody, as described in the above section "2. Production of anti-CDH6 antibody" and the Examples.

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[0155]

Next, a typical method for producing the antibody-drug conjugate of the present invention will be described. It is to be noted that, in the description below, "compound No." shown in each reaction scheme is used to represent a compound. Specifically, each compound is referred to as a "compound of formula (1)", "compound (1)", or the like. The same holds true for the other compound Nos.

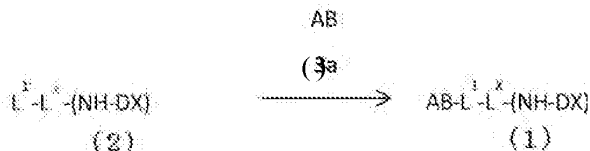
[0156]

(3)-1 Production method 1

The antibody-drug conjugate represented by formula (1) given below in which the anti-CDH6 antibody is connected to the linker structure via a thioether can be produced by reacting an antibody having a sulfhydryl group converted from a disulfide bond by the reduction of the anti-CDH6 antibody, with the compound (2), the compound (2) being obtainable by a known method (e.g., obtainable by a method described in the patent publication literature US2016/297890 (e.g., a method described in the paragraphs [0336] to [0374])). This antibody-drug conjugate can be produced by the following method, for example.

[0157]

[Expression 1]



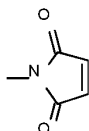
[0158]

wherein AB represents an antibody with a sulfhydryl group, wherein L^1 has a structure represented by -(Succinimid-3-yl-N)-, and L^x represents a maleimidyl group represented by the following formula.

[0159]

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[Formula 8]



[0160]

$-L^1-L^X$ has a structure represented by any of the following formulas:

$-(\text{Succinimid-3-yl-N})-\text{CH}_2\text{CH}_2-\text{C}(=\text{O})-\text{GGFG}-\text{NH}-\text{CH}_2\text{CH}_2\text{CH}_2-\text{C}(=\text{O})-$,
 $-(\text{Succinimid-3-yl-N})-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{C}(=\text{O})-\text{GGFG}-\text{NH}-\text{CH}_2\text{CH}_2\text{CH}_2-\text{C}(=\text{O})-$,
 $-(\text{Succinimid-3-yl-N})-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{C}(=\text{O})-\text{GGFG}-\text{NH}-\text{CH}_2-\text{O}-\text{CH}_2-\text{C}(=\text{O})-$,
 $-(\text{Succinimid-3-yl-N})-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{C}(=\text{O})-\text{GGFG}-\text{NH}-\text{CH}_2\text{CH}_2-\text{O}-\text{CH}_2-\text{C}(=\text{O})-$,
 $-(\text{Succinimid-3-yl-N})-\text{CH}_2\text{CH}_2-\text{C}(=\text{O})-\text{NH}-\text{CH}_2\text{CH}_2\text{O}-\text{CH}_2\text{CH}_2\text{O}-\text{CH}_2\text{CH}_2-\text{C}(=\text{O})-\text{GGFG}-\text{NH}-\text{CH}_2\text{CH}_2\text{CH}_2-\text{C}(=\text{O})-$, and
 $-(\text{Succinimid-3-yl-N})-\text{CH}_2\text{CH}_2-\text{C}(=\text{O})-\text{NH}-\text{CH}_2\text{CH}_2\text{O}-\text{CH}_2\text{CH}_2\text{O}-\text{CH}_2\text{CH}_2\text{O}-\text{CH}_2\text{CH}_2-\text{C}(=\text{O})-\text{GGFG}-\text{NH}-\text{CH}_2\text{CH}_2\text{CH}_2-\text{C}(=\text{O})-$.

[0161]

Among them, more preferred are the following:

$-(\text{Succinimid-3-yl-N})-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{C}(=\text{O})-\text{GGFG}-\text{NH}-\text{CH}_2-\text{O}-\text{CH}_2-\text{C}(=\text{O})-$,
 $-(\text{Succinimid-3-yl-N})-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{C}(=\text{O})-\text{GGFG}-\text{NH}-\text{CH}_2\text{CH}_2-\text{O}-\text{CH}_2-\text{C}(=\text{O})-$, and
 $-(\text{Succinimid-3-yl-N})-\text{CH}_2\text{CH}_2-\text{C}(=\text{O})-\text{NH}-\text{CH}_2\text{CH}_2\text{O}-\text{CH}_2\text{CH}_2\text{O}-\text{CH}_2\text{CH}_2-\text{C}(=\text{O})-\text{GGFG}-\text{NH}-\text{CH}_2\text{CH}_2\text{CH}_2-\text{C}(=\text{O})-$.

[0162]

Further preferred are the following:

$-(\text{Succinimid-3-yl-N})-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{C}(=\text{O})-\text{GGFG}-\text{NH}-\text{CH}_2-\text{O}-\text{CH}_2-\text{C}(=\text{O})-$,
 and

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-(Succinimid-3-yl-N)-CH₂CH₂-C(=O)-NH-CH₂CH₂O-CH₂CH₂O-CH₂CH₂-C(=O)-GGFG-NH-CH₂CH₂CH₂-C(=O)-.

[0163]

In the above-described reaction scheme, the antibody-drug conjugate (1) can be understood as having a structure in which one structure moiety from the drug to the linker terminus is connected to one antibody. However, this description is given for the sake of convenience, and there are actually many cases in which a plurality of the aforementioned structure moieties is connected to one antibody molecule. The same holds true for the explanation of the production method described below.

[0164]

Specifically, the antibody-drug conjugate (1) can be produced by reacting the compound (2) obtainable by a known method (e.g., obtainable by a method described in the patent publication literature US2016/297890 (e.g., obtainable by a method described in the paragraphs [0336] to [0374])), with the antibody (3a) having a sulfhydryl group.

[0165]

The antibody (3a) having a sulfhydryl group can be obtained by a method well known to a person skilled in the art (Hermanson, G.T, Bioconjugate Techniques, pp. 56-136, pp. 456-493, Academic Press (1996)). Examples of the method can include, but are not limited to: Traut's reagent being reacted with the amino group of the antibody; N-succinimidyl S-acetylthioalkanoates being reacted with the amino group of the antibody followed by reaction with hydroxylamine; N-succinimidyl 3-(pyridyldithio)propionate being reacted with the antibody, followed by reaction with a reducing agent; the antibody being reacted with a reducing agent such as dithiothreitol, 2-mercaptoethanol, or tris(2-carboxyethyl)phosphine hydrochloride (TCEP) to reduce the interchain disulfide bond in the antibody, so as to form a sulfhydryl group.

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[0166]

Specifically, an antibody with interchain disulfide bonds partially or completely reduced can be obtained by using 0.3 to 3 molar equivalents of TCEP as a reducing agent per interchain disulfide bond in the antibody, and reacting the reducing agent with the antibody in a buffer solution containing a chelating agent. Examples of the chelating agent can include ethylenediaminetetraacetic acid (EDTA) and diethylenetriaminepentaacetic acid (DTPA). The chelating agent can be used at a concentration of 1 mM to 20 mM. A solution of sodium phosphate, sodium borate, sodium acetate, or the like can be used as the buffer solution. As a specific example, the antibody (3a) having partially or completely reduced sulfhydryl groups can be obtained by reacting the antibody with TCEP at 4°C to 37°C for 1 to 4 hours.

[0167]

It is to be noted that by carrying out an addition reaction of a sulfhydryl group to a drug-linker moiety, the drug-linker moiety can be conjugated by a thioether bond.

[0168]

Then, using 2 to 20 molar equivalents of the compound (2) per antibody (3a) having a sulfhydryl group, the antibody-drug conjugate (1) in which 2 to 8 drug molecules are conjugated per antibody can be produced. Specifically, a solution containing the compound (2) dissolved therein may be added to a buffer solution containing the antibody (3a) having a sulfhydryl group for the reaction. In this context, a sodium acetate solution, sodium phosphate, sodium borate, or the like can be used as the buffer solution. pH for the reaction is 5 to 9, and more preferably, the reaction may be performed near pH 7. An organic solvent such as dimethyl sulfoxide (DMSO), dimethylformamide (DMF), dimethylacetamide (DMA), or N-methyl-2-pyrrolidone (NMP) can be used as a solvent for dissolving the compound (2). The reaction may be performed by adding the solution containing the compound (2) dissolved in the organic solvent at 1 to 20% v/v to a buffer solution

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containing the antibody (3a) having a sulfhydryl group. The reaction temperature is 0 to 37°C, more preferably 10 to 25°C, and the reaction time is 0.5 to 2 hours. The reaction can be terminated by deactivating the reactivity of unreacted compound (2) with a thiol-containing reagent. The thiol-containing reagent is, for example, cysteine or N-acetyl-L-cysteine (NAC). More specifically, the reaction can be terminated by adding 1 to 2 molar equivalents of NAC to the compound (2) used, and incubating the obtained mixture at room temperature for 10 to 30 minutes.

[0169]

(4) Identification of antibody-drug conjugate

The produced antibody-drug conjugate (1) can be subjected to concentration, buffer exchange, purification, and measurement of antibody concentration and the average number of conjugated drug molecules per antibody molecule according to common procedures described below, to identify the antibody-drug conjugate (1).

[0170]

(4)-1 Common procedure A: Concentration of aqueous solution of antibody or antibody-drug conjugate

To an Amicon Ultra (50,000 MWCO, Millipore Corporation) container, a solution of an antibody or an antibody-drug conjugate was added, and the solution of the antibody or the antibody-drug conjugate was concentrated by centrifugation (centrifugation at 2000 G to 3800 G for 5 to 20 minutes) using a centrifuge (Allegra X-15R, Beckman Coulter, Inc.)

[0171]

(4)-2 Common procedure B: Measurement of antibody concentration

Using a UV detector (Nanodrop 1000, Thermo Fisher Scientific Inc.), measurement of the antibody concentration was carried out according to the method defined by the manufacturer. In this respect, 280 nm absorption coefficient differing among antibodies ($1.3 \text{ mLmg}^{-1}\text{cm}^{-1}$ to $1.8 \text{ mLmg}^{-1}\text{cm}^{-1}$) was used.

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[0172]

(4)-3 Common procedure C: Buffer exchange for antibody

A NAP-25 column (Cat. No. 17-0852-02, GE Healthcare Japan Corporation) using Sephadex G-25 carrier was equilibrated with a phosphate buffer (50 mM, pH 6.0) (referred to as PBS6.0/EDTA in the present description) containing sodium chloride (50 mM) and EDTA (2 mM) according to the method defined by the manufacturer. An aqueous solution of the antibody was applied in an amount of 2.5 mL per NAP-25 column, and thereafter, a fraction (3.5 mL) eluted with 3.5 mL of PBS6.0/EDTA was collected. This fraction was concentrated by common procedure A. After measurement of the concentration of the antibody using common procedure B, the antibody concentration was adjusted to 20 mg/mL using PBS6.0/EDTA.

[0173]

(4)-4 Common procedure D: Purification of antibody-drug conjugate

A NAP-25 column was equilibrated with any commercially available buffer solution such as an acetate buffer containing sorbitol (5%) (10 mM, pH 5.5; referred to as ABS in the present description). An aqueous reaction solution of the antibody-drug conjugate (approximately 2.5 mL) was applied to the NAP-25 column, and thereafter, elution was carried out with the buffer solution in an amount defined by the manufacturer, so as to collect an antibody fraction. A gel filtration purification process, in which the collected fraction was applied again to the NAP-25 column, and elution was carried out with the buffer solution, was repeated a total of 2 or 3 times to obtain the antibody-drug conjugate excluding non-conjugated drug linker and low-molecular-weight compounds (tris(2-carboxyethyl)phosphine hydrochloride (TCEP), N-acetyl-L-cysteine (NAC), and dimethyl sulfoxide).

[0174]

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(4)-5 Common procedure E: Measurement of antibody concentration in antibody-drug conjugate and average number of conjugated drug molecules per antibody molecule

The conjugated drug concentration in the antibody-drug conjugate can be calculated by measuring UV absorbance of an aqueous solution of the antibody-drug conjugate at two wavelengths of 280 nm and 370 nm, and thereafter performing the calculation shown below.

[0175]

The total absorbance at any given wavelength is equal to the sum of the absorbance of all light-absorbing chemical species that are present in a system [additivity of absorbance]. Therefore, based on the hypothesis that the molar absorption coefficients of the antibody and the drug do not vary between before and after conjugation between the antibody and the drug, the antibody concentration and the drug concentration in the antibody-drug conjugate are represented by the following equations.

$$A_{280} = A_{D,280} + A_{A,280} = \epsilon_{D,280}C_D + \epsilon_{A,280}C_A \text{ Equation (1)}$$

$$A_{370} = A_{D,370} + A_{A,370} = \epsilon_{D,370}C_D + \epsilon_{A,370}C_A \text{ Equation (2)}$$

[0176]

In this context, A_{280} represents the absorbance of an aqueous solution of the antibody-drug conjugate at 280 nm, A_{370} represents the absorbance of an aqueous solution of the antibody-drug conjugate at 370 nm, $A_{A,280}$ represents the absorbance of the antibody at 280 nm, $A_{A,370}$ represents the absorbance of the antibody at 370 nm, $A_{D,280}$ represents the absorbance of a conjugate precursor at 280 nm, $A_{D,370}$ represents the absorbance of a conjugate precursor at 370 nm, $\epsilon_{A,280}$ represents the molar absorption coefficient of the antibody at 280 nm, $\epsilon_{A,370}$ represents the molar absorption coefficient of the antibody at 370 nm, $\epsilon_{D,280}$ represents the molar absorption coefficient of a conjugate precursor at 280 nm, $\epsilon_{D,370}$ represents the molar

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absorption coefficient of a conjugate precursor at 370 nm, C_A represents the antibody concentration in the antibody-drug conjugate, and C_D represent the drug concentration in the antibody-drug conjugate.

[0177]

In this context, with regard to $\epsilon_{A,280}$, $\epsilon_{A,370}$, $\epsilon_{D,280}$, and $\epsilon_{D,370}$, preliminarily prepared values (estimated values based on calculation or measurement values obtained by UV measurement of the compound) are used. For example, $\epsilon_{A,280}$ can be estimated from the amino acid sequence of the antibody by a known calculation method (Protein Science, 1995, vol. 4, 2411-2423). $\epsilon_{A,370}$ is generally zero. $\epsilon_{D,280}$ and $\epsilon_{D,370}$ can be obtained according to Lambert-Beer's law (Absorbance = Molar concentration $\times$ Molar absorption coefficient $\times$ Cell path length) by measuring the absorbance of a solution in which the conjugate precursor used is dissolved at a certain molar concentration. C_A and C_D can be determined by measuring A_{280} and A_{370} of an aqueous solution of the antibody-drug conjugate, and then solving the simultaneous equations (1) and (2) by substitution of these values. Further, by dividing C_D by C_A , the average number of conjugated drug molecules per antibody can be determined.

[0178]

(4)-6 Common procedure F: Measurement of average number of conjugated drug molecules per antibody molecule in antibody-drug conjugate - (2)

The average number of conjugated drug molecules per antibody molecule in the antibody-drug conjugate can also be determined by high-performance liquid chromatography (HPLC) analysis using the following method, in addition to the aforementioned "(4)-5 Common procedure E". Hereinafter, the method for measuring the average number of conjugated drug molecules by HPLC when the antibody is conjugated to the drug linker by a disulfide bond will be described. A person skilled in the art is capable of appropriately measuring the average number of

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conjugated drug molecules by HPLC, depending on the connecting manner between the antibody and the drug linker, with reference to this method.

[0179]

F-1. Preparation of sample for HPLC analysis (Reduction of antibody-drug conjugate)

An antibody-drug conjugate solution (approximately 1 mg/mL, 60 μ L) is mixed with an aqueous solution of dithiothreitol (DTT) (100 mM, 15 μ L). By incubating the mixture at 37°C for 30 minutes, the disulfide bond between the light chain and heavy chain of the antibody-drug conjugate is cleaved. The resulting sample is used in HPLC analysis.

[0180]

F-2. HPLC analysis

The HPLC analysis is carried out under the following measurement conditions.

HPLC system: Agilent 1290 HPLC system (Agilent Technologies, Inc.)

Detector: Ultraviolet absorption spectrometer (measurement wavelength: 280 nm)

Column: ACQUITY UPLC BEH Phenyl (2.1 $\times$ 50 mm, 1.7 μ m, 130 angstroms; Waters Corp., P/N 186002884)

Column temperature: 80°C

Mobile phase A: Aqueous solution containing 0.10% trifluoroacetic acid (TFA) and 15% 2-propanol

Mobile phase B: Acetonitrile solution containing 0.075% TFA and 15% 2-propanol

Gradient program: 14%-36% (0 min-15 min), 36%-80% (15 min-17 min), 80%-14% (17 min-17.01 min.), and 14% (17.01 min-25 min)

Sample injection: 10 μ L

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[0181]

F-3. Data analysis

F-3-1. Compared with non-conjugated antibody light (L0) and heavy (H0) chains, a light chain bound to drug molecule(s) (light chain bound to i drug molecule(s): L_i) and a heavy chain bound to drug molecule(s) (heavy chain bound to i drug molecule(s): H_i) exhibit higher hydrophobicity in proportion to the number of conjugated drug molecules and thus have a larger retention time. These chains are therefore eluted in the order of, for example, L0 and L1 or H0, H1, H2, and H3. Detection peaks can be assigned to any of L0, L1, H0, H1, H2, and H3 by the comparison of retention times with L0 and H0. The number of conjugated drug molecules can be defined by a person skilled in the art, but is preferably L0, L1, H0, H1, H2, and H3.

[0182]

F-3-2. Since the drug linker has UV absorption, peak area values are corrected in response to the number of conjugated drug linker molecules according to the following expression using the molar absorption coefficients of the light chain or heavy chain and the drug linker.

[0183]

[Expression 2]

Corrected value of peak area of light chain bound to i drug molecule(s) (A_{Li}) = Peak area

$$\frac{\text{Molar absorption coefficient of light chain}}{\text{Molar absorption coefficient of light chain} + \text{The number of conjugated drug molecules (i)} \times \text{Molar absorption coefficient of drug linker}}$$

[0184]

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[Expression 3]

Corrected value of peak area of heavy chain bound to i drug molecule(s) (A_{HI}) = Peak area

Molar absorption coefficient of heavy chain

Molar absorption coefficient of heavy chain + The number of conjugated drug molecules
(i) × Molar absorption coefficient of drug linker

[0185]

In this context, a value estimated from the amino acid sequence of the light chain or heavy chain of each antibody by a known calculation method (Protein Science, 1995, vol. 4, 2411-2423) can be used as the molar absorption coefficient (280 nm) of the light chain or heavy chain of the antibody. In the case of H01L02, a molar absorption coefficient of 31710 and a molar absorption coefficient of 79990 were used as estimated values for the light chain and heavy chain, respectively, according to the amino acid sequence of the antibody. The actually measured molar absorption coefficient (280 nm) of a compound in which the maleimide group has been converted to succinimide thioether by the reaction of each drug linker with mercaptoethanol or N-acetylcysteine was used as the molar absorption coefficient (280 nm) of the drug linker. The wavelength for absorbance measurement can be appropriately set by a person skilled in the art, but is preferably a wavelength at which the peak of the antibody can be measured, and more preferably 280 nm.

[0186]

F-3-3. The peak area ratio (%) of each chain is calculated for the total of the corrected values of peak areas according to the following expression.

[0187]

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[Expression 4]

$$\text{Peak area ratio of light chain bound to } i \text{ drug molecule(s)} = \frac{A_{Li}}{A_{L0} + A_{L1}} \times 100$$

$$\text{Peak area ratio of heavy chain bound to } i \text{ drug molecule(s)} = \frac{A_{Hi}}{A_{H0} + A_{H1} + A_{H2} + A_{H3}} \times 100$$

A_{Li} and A_{Hi} : Corrected values of peak areas of L_i and H_i , respectively

[0188]

F-3-4. The average number of conjugated drug molecules per antibody molecule in the antibody-drug conjugate is calculated according to the following expression.

[0189]

Average number of conjugated drug molecules = $(L_0 \text{ peak area ratio} \times 0 + L_1 \text{ peak area ratio} \times 1 + H_0 \text{ peak area ratio} \times 0 + H_1 \text{ peak area ratio} \times 1 + H_2 \text{ peak area ratio} \times 2 + H_3 \text{ peak area ratio} \times 3) / 100 \times 2$

[0190]

It is to be noted that, in order to secure the amount of the antibody-drug conjugate, a plurality of antibody-drug conjugates having almost the same average number of conjugated drug molecules (e.g., on the order of ± 1), which have been produced under similar conditions, can be mixed to prepare a new lot. In this case, the average number of drug molecules of the new lot falls between the average numbers of drug molecules before the mixing.

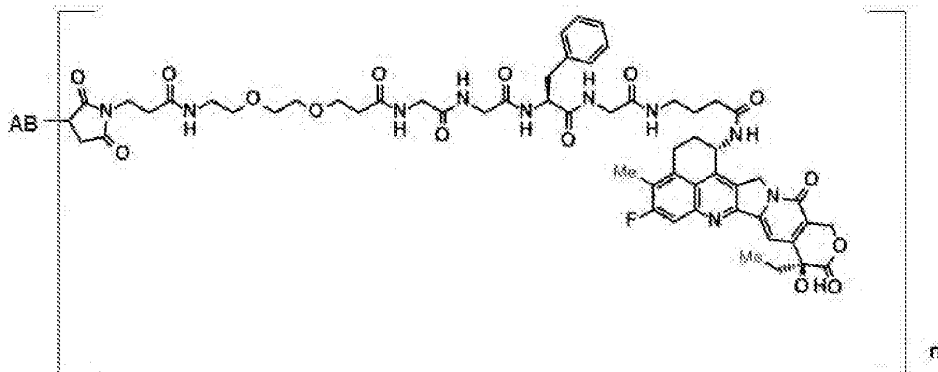
[0191]

One specific example of the antibody-drug conjugate of the present invention can include an antibody-drug conjugate having a structure represented by the following formula:

[0192]

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[Formula 9]

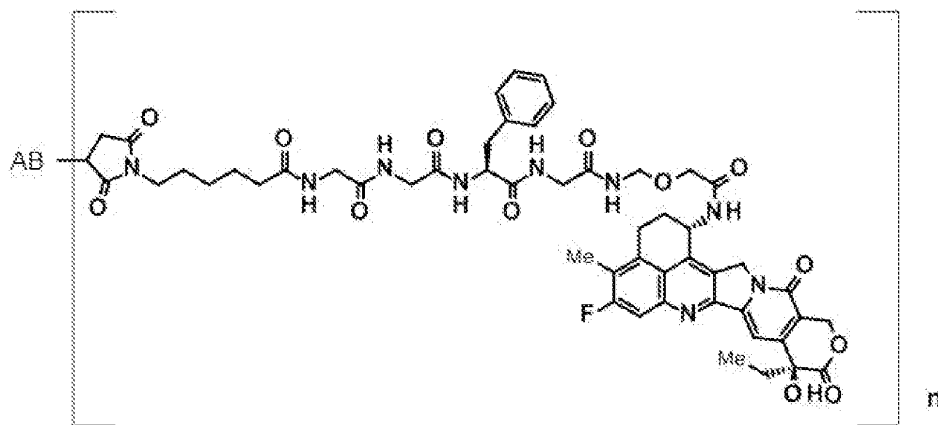


[0193]

or the following formula:

[0194]

[Formula 10]



[0195]

[0196]

In this context, AB represents the anti-CDH6 antibody disclosed in the present description, and the antibody is conjugated to the drug linker via a sulfhydryl group stemming from the antibody. In this context, n has the same meaning as that of the so-called DAR (drug-to-antibody Ratio), and represents a drug-to-antibody ratio per antibody. Specifically, n represents the number of conjugated drug

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molecules per antibody molecule, which is a numeric value defined and indicated as an average value, i.e., the average number of conjugated drug molecules. In the case of the antibody-drug conjugate represented by [Formula 9] or [Formula 10] of the present invention, n can be 2 to 8 and is preferably 5 to 8, more preferably 7 to 8, and still more preferably 8, in measurement by common procedure F.

[0197]

One example of the antibody-drug conjugate of the present invention can include an antibody-drug conjugate having a structure represented by the above-described formula [Formula 9] or [Formula 10] wherein the antibody represented by AB comprises any one antibody selected from the group consisting of the following antibodies (a) to (g), or a functional fragment of the antibody, or a pharmacologically acceptable salt of the antibody-drug conjugate:

- (a) an antibody consisting of a light chain consisting of the amino acid sequence at positions 21 to 233 in the light chain full-length amino acid sequence shown in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in the heavy chain full-length amino acid sequence shown in SEQ ID NO: 69;
- (b) an antibody consisting of a light chain consisting of the amino acid sequence at positions 21 to 233 in the light chain full-length amino acid sequence shown in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in the heavy chain full-length amino acid sequence shown in SEQ ID NO: 73;
- (c) an antibody consisting of a light chain consisting of the amino acid sequence at positions 21 to 233 in the light chain full-length amino acid sequence shown in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in the heavy chain full-length amino acid sequence shown in SEQ ID NO: 77;
- (d) an antibody consisting of a light chain consisting of the amino acid sequence at positions 21 to 233 in the light chain full-length amino acid sequence shown in SEQ

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ID NO: 65 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in the heavy chain full-length amino acid sequence shown in SEQ ID NO: 69;

(e) an antibody consisting of a light chain consisting of the amino acid sequence at positions 21 to 233 in the light chain full-length amino acid sequence shown in SEQ ID NO: 65 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in the heavy chain full-length amino acid sequence shown in SEQ ID NO: 73;

(f) an antibody consisting of a light chain consisting of the amino acid sequence at positions 21 to 233 in the light chain full-length amino acid sequence shown in SEQ ID NO: 65 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in the heavy chain full-length amino acid sequence shown in SEQ ID NO: 77;

and

(g) any one antibody selected from the group consisting of the antibodies (a) to (f), wherein the heavy chain or the light chain comprises one or two or more modifications selected from the group consisting of posttranslational modifications typified by N-linked glycosylation, O-linked glycosylation, N-terminal processing, C-terminal processing, deamidation, isomerization of aspartic acid, oxidation of methionine, addition of a methionine residue to the N-terminus, amidation of a proline residue, and conversion of N-terminal glutamine or N-terminal glutamic acid to pyroglutamic acid, and a deletion of one or two amino acids at the carboxyl terminus

[0198]

4. Medicament

Since the anti-CDH6 antibody of the present invention and the functional fragment of the antibody described in the above section "2. Production of anti-CDH6 antibody" and the Examples bind to CDH6 on the surface of tumor cells and have internalization activity, it can be used as a medicament, and in particular, as a

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therapeutic agent for cancer such as renal cell tumor or ovarian tumor, either alone or in combination with an additional drug.

[0199]

Furthermore, the anti-CDH6 antibody of the present invention or the functional fragment of the antibody can be used in the detection of cells expressing CDH6.

[0200]

Moreover, since the anti-CDH6 antibody of the present invention or the functional fragment of the antibody has internalization activity, it can be applied as the antibody in an antibody-drug conjugate.

[0201]

When a drug having antitumor activity such as cytotoxic activity is used as the drug, the anti-CDH6 antibody-drug conjugate of the present invention described in the above section "3. Anti-CDH6 antibody-drug conjugate" and the Examples is a conjugate of the anti-CDH6 antibody and/or the functional fragment of the antibody having internalization activity, and the drug having antitumor activity such as cytotoxic activity. Since this anti-CDH6 antibody-drug conjugate exhibits antitumor activity against cancer cells expressing CDH6, it can be used as a medicament, and in particular, as a therapeutic agent and/or a prophylactic agent for cancer.

[0202]

The anti-CDH6 antibody-drug conjugate of the present invention may absorb moisture or have adsorption water, for example, to turn into a hydrate when it is left in air or subjected to recrystallization or purification procedures. Such a compound or a pharmacologically acceptable salt containing water is also included in the present invention.

[0203]

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When the anti-CDH6 antibody-drug conjugate of the present invention has a basic group such as an amino group, it can form a pharmacologically acceptable acid-addition salt, if desired. Examples of such an acid-addition salt can include: hydrohalides such as hydrofluoride, hydrochloride, hydrobromide, and hydroiodide; inorganic acid salts such as nitrate, perchlorate, sulfate, and phosphate; lower alkanesulfonates such as methanesulfonate, trifluoromethanesulfonate, and ethanesulfonate; arylsulfonates such as benzenesulfonate and p-toluenesulfonate; organic acid salts such as formate, acetate, trifluoroacetate, malate, fumarate, succinate, citrate, tartrate, oxalate, and maleate; and amino acid salts such as ornithine salt, glutamate, and aspartate.

[0204]

When the anti-CDH6 antibody-drug conjugate of the present invention has an acidic group such as a carboxy group, it can form a pharmacologically acceptable base-addition salt, if desired. Examples of such a base-addition salt can include: alkali metal salts such as a sodium salt, a potassium salt, and lithium salt; alkaline earth metal salts such as a calcium salt and a magnesium salt; inorganic salts such as an ammonium salt; and organic amine salts such as a dibenzylamine salt, a morpholine salt, a phenylglycine alkyl ester salt, an ethylenediamine salt, an N-methylglucamine salt, a diethylamine salt, a triethylamine salt, a cyclohexylamine salt, a dicyclohexylamine salt, an N,N'-dibenzylethylenediamine salt, a diethanolamine salt, an N-benzyl-N-(2-phenylethoxy)amine salt, a piperazine salt, tetramethylammonium salt, and a tris(hydroxymethyl)aminomethane salt.

[0205]

The present invention can also include an anti-CDH6 antibody-drug conjugate in which one or more atoms constituting the antibody-drug conjugate are replaced with isotopes of the atoms. There exist two types of isotopes: radioisotopes and stable isotopes. Examples of the isotope can include isotopes of hydrogen (^2H and

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3H), isotopes of carbon (^{11}C , ^{13}C and ^{14}C), isotopes of nitrogen (^{13}N and ^{15}N), isotopes of oxygen (^{15}O , ^{17}O and ^{18}O), and isotopes of fluorine (^{18}F). A composition comprising the antibody-drug conjugate labeled with such an isotope is useful as, for example, a therapeutic agent, a prophylactic agent, a research reagent, an assay reagent, a diagnostic agent, and an *in vivo* diagnostic imaging agent. Each and every antibody-drug conjugate labeled with an isotope, and mixtures of antibody-drug conjugates labeled with an isotope at any given ratio are included in the present invention. The antibody-drug conjugate labeled with an isotope can be produced, for example, by using a starting material labeled with an isotope, instead of a starting material for the production method of the present invention mentioned later, according to a method known in the art.

[0206]

In vitro cytotoxicity can be measured based on the activity of suppressing the proliferative responses of cells, for example. For example, a cancer cell line overexpressing CDH6 is cultured, and the anti-CDH6 antibody-drug conjugate is added at different concentrations to the culture system. Thereafter, its suppressive activity against focus formation, colony formation and spheroid growth can be measured. In this context, by using a renal cell tumor- or ovarian tumor-derived cancer cell line, cell growth inhibition activity against renal cell tumor or ovarian tumor can be examined.

[0207]

In vivo therapeutic effects on cancer in an experimental animal can be measured, for example, by administering the anti-CDH6 antibody-drug conjugate to a nude mouse into which a tumor cell line highly expressing CDH6 has been inoculated, and then measuring a change in the cancer cells. In this context, by using an animal model derived from an immunodeficient mouse by the inoculation of renal cell carcinoma-, renal clear cell carcinoma-, papillary renal cell carcinoma-,

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ovarian cancer-, ovarian serous adenocarcinoma- or thyroid cancer-derived cells, therapeutic effects on renal cell carcinoma, renal clear cell carcinoma, papillary renal cell carcinoma, ovarian cancer, ovarian serous adenocarcinoma or thyroid cancer can be measured.

[0208]

The type of cancer to which the anti-CDH6 antibody-drug conjugate of the present invention is applied is not particularly limited as long as the cancer expresses CDH6 in cancer cells to be treated. Examples thereof can include renal cell carcinoma, renal clear cell carcinoma, papillary renal cell carcinoma, ovarian cancer, ovarian serous adenocarcinoma and thyroid cancer, though the cancer is not limited thereto as long as the cancer expresses CDH6. More preferred examples of the cancer can include renal cell carcinoma and ovarian cancer.

[0209]

The anti-CDH6 antibody-drug conjugate of the present invention can preferably be administered to a mammal, and more preferably to a human.

[0210]

A substance used in a pharmaceutical composition comprising the anti-CDH6 antibody-drug conjugate of the present invention can be appropriately selected from pharmaceutical additives and others usually used in this field, in terms of the applied dose or the applied concentration, and then used.

[0211]

The anti-CDH6 antibody-drug conjugate of the present invention can be administered as a pharmaceutical composition comprising one or more pharmaceutically compatible components. For example, the pharmaceutical composition typically comprises one or more pharmaceutical carriers (e.g., sterilized liquids (e.g., water and oil (including petroleum oil and oil of animal origin, plant origin, or synthetic origin (e.g., peanut oil, soybean oil, mineral oil, and sesame oil))).

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Water is a more typical carrier when the pharmaceutical composition is intravenously administered. An aqueous saline solution, an aqueous dextrose solution, and an aqueous glycerol solution can also be used as a liquid carrier, in particular, for an injection solution. Suitable pharmaceutical vehicles are known in the art. If desired, the composition may also comprise a trace amount of a moisturizing agent, an emulsifying agent, or a pH buffering agent. Examples of suitable pharmaceutical carriers are disclosed in "Remington's Pharmaceutical Sciences" by E. W. Martin. The prescription corresponds to an administration mode.

[0212]

Various delivery systems are known, and they can be used for administering the anti-CDH6 antibody-drug conjugate of the present invention. Examples of the administration route can include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, and subcutaneous routes. The administration can be made by injection or bolus injection, for example. According to a specific preferred embodiment, the administration of the above-described antibody-drug conjugate is performed by injection. Parenteral administration is a preferred administration route.

[0213]

According to a representative embodiment, the pharmaceutical composition is prescribed, as a pharmaceutical composition suitable for intravenous administration to a human, according to conventional procedures. The composition for intravenous administration is typically a solution in a sterile and isotonic aqueous buffer solution. If necessary, the medicament may also contain a solubilizing agent and a local anesthetic to alleviate pain at an injection area (e.g., lignocaine). In general, the above-described ingredients are provided, either separately or together in a mixture in unit dosage form, as a freeze-dried powder or an anhydrous concentrate contained in a container which is obtained by sealing in, for example, an ampoule or

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a sachet indicating the amount of the active agent. When the medicament is to be administered by injection, it may be administered using, for example, an injection bottle containing water or saline of sterile pharmaceutical grade. When the medicament is to be administered by injection, an ampoule of sterile water or saline for injection may be provided such that the above-described ingredients are admixed with one another before administration.

[0214]

The pharmaceutical composition of the present invention may be a pharmaceutical composition comprising only the anti-CDH6 antibody-drug conjugate of the present application, or may be a pharmaceutical composition comprising the anti-CDH6 antibody-drug conjugate and at least one other therapeutic agent for cancer. The anti-CDH6 antibody-drug conjugate of the present invention can also be administered together with an additional therapeutic agent for cancer, and can thereby enhance an anticancer effect. The additional anticancer agent used for such a purpose may be administered to an individual, simultaneously, separately, or continuously, together with the antibody-drug conjugate. Otherwise, the additional anticancer agent and the anti-CDH6 antibody-drug conjugate may each be administered to the subject at different administration intervals. Examples of such a therapeutic agent for cancer can include tyrosine kinase inhibitors including imatinib, sunitinib, and regorafenib, CDK4/6 inhibitors including palbociclib, HSP90 inhibitors including TAS-116, MEK inhibitors including MEK162, and immune checkpoint inhibitors including nivolumab, pembrolizumab, and ipilimumab, though the therapeutic agent for cancer is not limited thereto as long as the drug has antitumor activity.

[0215]

Such a pharmaceutical composition can be prepared as a formulation having a selected composition and a necessary purity in the form of a freeze-dried formulation

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or a liquid formulation. The pharmaceutical composition prepared as a freeze-dried formulation may be a formulation containing an appropriate pharmaceutical additive used in this field. Likewise, the liquid formulation can be prepared such that the liquid formulation contains various pharmaceutical additives used in this field.

[0216]

The composition and concentration of the pharmaceutical composition also vary depending on the administration method. With regard to the affinity of the anti-CDH6 antibody-drug conjugate comprised in the pharmaceutical composition of the present invention for the antigen, i.e., the dissociation constant (K_d value) of the anti-CDH6 antibody-drug conjugate to the antigen, as the affinity increases (i.e., the K_d value is low), the pharmaceutical composition can exert medicinal effects, even if the applied dose thereof is decreased. Accordingly, the applied dose of the antibody-drug conjugate can also be determined by setting the applied dose based on the status of the affinity of the antibody-drug conjugate for the antigen. When the antibody-drug conjugate of the present invention is administered to a human, it may be administered at a dose of, for example, from approximately 0.001 to 100 mg/kg once or a plurality of times at intervals of 1 to 180 days. It can be administered preferably at a dose of from 0.1 to 50 mg/kg and more preferably 1 to 15 mg/kg a plurality of times at intervals of 2 to 3 weeks.

[Examples]

[0217]

Hereinafter, the present invention will be specifically described in the following examples. However, these examples are not intended to limit the scope of the present invention. Furthermore, these examples should not be construed in a limited manner by any means. It is to be noted that, in the following examples, unless otherwise specified, individual operations regarding genetic manipulation have been carried out according to the method described in "Molecular Cloning"

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(Sambrook, J., Fritsch, E. F. and Maniatis, T., published by Cold Spring Harbor Laboratory Press in 1989) or other methods described in experimental manuals used by persons skilled in the art, or when commercially available reagents or kits have been used, the examples have been carried out in accordance with the instructions included in the commercially available products. In the present description, reagents, solvents and starting materials are readily available from commercially available sources, unless otherwise specified.

[0218]

[Example 1: Obtaining rat anti-human CDH6 antibody having internalization activity]

1)-1 Construction of human, mouse, rat and cynomolgus monkey CDH6 expression vectors

Using a human CDH6 protein (NP_004923)-encoding cDNA expression vector (OriGene Technologies Inc., RC217889), the cDNA was incorporated into a vector for mammalian expression according to a method known to a person skilled in the art to produce human CDH6 expression vector pcDNA3.1-hCDH6. The amino acid sequence of the human CDH6 ORF (open reading frame) is shown in SEQ ID NO: 1.

Using a mouse CDH6 protein (NP_031692)-encoding cDNA expression vector (OriGene Technologies Inc., MC221619), the cDNA was incorporated into a vector for mammalian expression according to a method known to a person skilled in the art to produce mouse CDH6 expression vectors pcDNA3.1-mCDH6 and p3xFLAG-CMV-9-mCDH6. The amino acid sequence of the mouse CDH6 ORF is shown in SEQ ID NO: 7.

Using each cDNA moiety of the rat CDH6 protein (NP_037059)-encoding cDNA expression vector (OriGene Technologies Inc., RN211850), the cDNA was incorporated into a vector for mammalian expression according to a method known

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to a person skilled in the art to produce human CDH6 expression vectors pcDNA3.1-rCDH6 and p3xFLAG-CMV-9-rCDH6. The amino acid sequence of the rat CDH6 ORF is shown in SEQ ID NO: 8.

cDNA encoding cynomolgus monkey CDH6 protein was cloned with cDNA synthesized from total RNA of the cynomolgus monkey kidney as a template using primer 1 (5'-CACCATGAGAACTTACCGCTACTTCTTGCTGCTC-3') (SEQ ID NO: 85) and primer 2 (5'-TTAGGAGTCTTTGTCACTGTCCACTCCTCC-3') (SEQ ID NO: 86). It was confirmed that the obtained sequence corresponded to the extracellular region of cynomolgus monkey CDH6 (NCBI, XP_005556691.1). It was also confirmed that the sequence corresponded to the full-length sequence of cynomolgus monkey CDH6 (EHH54180.1) registered in EMBL. The cDNA was incorporated into a vector for mammalian expression according to a method known to a person skilled in the art to produce cynomolgus monkey CDH6 expression vector pcDNA3.1-cynoCDH6. The amino acid sequence of the cynomolgus monkey CDH6 ORF is shown in SEQ ID NO: 9.

EndoFree Plasmid Giga Kit (Qiagen N.V.) was used for mass production of the produced plasmid DNA.

[0219]

1)-2 Immunization

For immunization, WKY/Izm female rats (Japan SLC, Inc.) were used. First, the lower limbs of each rat were pre-treated with Hyaluronidase (Sigma-Aldrich Co. LLC), and thereafter, the human CDH6 expression vector pcDNA3.1-hCDH6 produced in Example 1)- 1 was intramuscularly injected into the same sites. Subsequently, employing ECM830 (BTX), *in vivo* electroporation was carried out on the same sites using a two-needle electrode. Approximately once every two weeks, the same *in vivo* electroporation was repeated, and thereafter, lymph nodes or the spleen were collected from the rat, and then used in production of hybridomas.

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[0220]

1)-3 Production of hybridomas

The lymph node cells or the spleen cells were fused with mouse myeloma SP2/0-ag14 cells (ATCC, No. CRL-1 581) according to electrical cell fusion, using a LF301 Cell Fusion Unit (BEX Co., Ltd.), and the cells were then suspended and diluted with ClonaCell-HY Selection Medium D (StemCell Technologies Inc.), and then cultured under conditions of 37°C and 5% CO₂. Individual hybridoma colonies that appeared in the culture medium were collected as monoclonal hybridomas, then suspended in ClonaCell-HY Selection Medium E (StemCell Technologies Inc.), and then cultured under conditions of 37°C and 5% CO₂. After moderate proliferation of cells, frozen stocks of individual hybridoma cells were produced, while the obtained hybridoma culture supernatant was used to screen for anti-human CDH6 antibody-producing hybridomas.

[0221]

1)-4 Antibody-producing hybridoma screening according to Cell-ELISA method

1)-4-1 Preparation of antigen gene-expressing cells for use in Cell-ELISA

293 α cells (a stable expression cell line derived from HEK293 cells expressing integrin α_v and integrin β_3) were prepared at 5×10^5 cells/mL in DMEM medium supplemented with 10% FBS. In accordance with transduction procedures for using Lipofectamine 2000 (Thermo Fisher Scientific Inc.), DNA of pcDNA3.1-hCDH6 or pcDNA3.1-cynoCDH6, or pcDNA3.1 as a negative control was introduced into the 293 α cells, and the cells were dispensed in an amount of 100 μ L/well onto a 96-well plate (Corning Inc.). Thereafter, the cells were cultured under conditions of 37°C and 5% CO₂ in DMEM medium supplemented with 10% FBS for 24 to 27 hours. The obtained transfected cells were used for Cell-ELISA in an adhesive state.

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[0222]

1)-4-2 Cell-ELISA

The culture supernatant of the 293 α cells transfected with the expression vector prepared in Example 1)-4-1 was removed, and the culture supernatant from each hybridoma was then added to the 293 α cells transfected with pcDNA3.1-hCDH6 or pcDNA3.1-cynoCDH6, or pcDNA3.1. The cells were left standing at 4°C for 1 hour. The cells in the wells were washed once with PBS (+) supplemented with 5% FBS, and thereafter, Anti-Rat IgG-Peroxidase antibody produced in rabbit (Sigma-Aldrich Co. LLC) that had been 500-fold diluted with PBS (+) supplemented with 5% FBS was added to the wells. The cells were left standing at 4°C for 1 hour. The cells in the wells were washed three times with PBS (+) supplemented with 5% FBS, and thereafter, OPD coloring solution (which had been prepared by dissolving o-phenylenediamine dihydrochloride (Wako Pure Chemical Industries, Ltd.) and H₂O₂ in an OPD solution (0.05 M trisodium citrate, 0.1 M disodium hydrogen phosphate 12-water; pH 4.5), so that the substances became 0.4 mg/ml and 0.6% (v/v), respectively, was added in an amount of 100 μ L/well to the wells. A coloring reaction was carried out with occasional stirring. Thereafter, 1 M HCl was added to the plate (100 μ L/well) to terminate the coloring reaction, followed by measurement of the absorbance at 490 nm using a plate reader (ENVISION; PerkinElmer, Inc.). Hybridomas that produced a culture supernatant exhibiting higher absorbance in the 293 α cells transfected with the pcDNA3.1-hCDH6 or pcDNA3.1-cynoCDH6 expression vector than that in the 293 α cells transfected with the control pcDNA3.1 were selected as hybridomas producing antibodies binding to human CDH6 and cynomolgus monkey CDH6.

[0223]

1)-5 Selective screening for antibody binding to cynomolgus monkey CDH6 according to flow cytometry

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1)-5-1 Preparation of antigen gene-expressing cells for use in flow cytometry analysis

293T cells were seeded in a 225-cm² flask (Sumitomo Bakelite Co., Ltd.) at 5×10^4 cells/cm², and the cells were then cultured overnight under conditions of 37°C and 5% CO₂ in DMEM medium supplemented with 10% FBS. pcDNA3.1-cynoCDH6 or pcDNA3.1 as a negative control was introduced into the 293T cells using Lipofectamine 2000, and the cells were further cultured overnight under conditions of 37°C and 5% CO₂. The 293T cells transfected with each vector were treated with TrypLE Express (Thermo Fisher Scientific Corp.), and the cells were washed with DMEM supplemented with 10% FBS, and then suspended in PBS supplemented with 5% FBS. The obtained cell suspension was used in flow cytometry analysis.

[0224]

1)-5-2 Flow cytometry analysis

The binding specificity to cynomolgus monkey CDH6 of an antibody produced from the human CDH6- and cynomolgus monkey CDH6-binding antibody-producing hybridomas that had been selected by Cell-ELISA in Example 1)-4 was further confirmed by flow cytometry. The suspension of the transiently expressing 293T cells prepared in Example 1)-5-1 was centrifuged, and the supernatant was then removed. Thereafter, the cells were suspended by the addition of the culture supernatant from each hybridoma. The cells were left standing at 4°C for 1 hour. The cells were washed twice with PBS supplemented with 5% FBS, and thereafter, the cells were suspended by the addition of Anti-Rat IgG FITC conjugate (Sigma-Aldrich Co. LLC) that had been 500-fold diluted with PBS supplemented with 5% FBS. The cells were left standing at 4°C for 1 hour. The cells were washed twice with PBS supplemented with 5% FBS, and then re-suspended in PBS supplemented with 5% FBS and 2 µg/ml 7-aminoactinomycin D (Molecular Probes, Inc.), followed

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by detection using a flow cytometer (FC500; Beckman Coulter, Inc.). The data was analyzed using FlowJo (Tree Star, Inc.). After dead cells were removed from analysis by gating out 7-aminoactinomycin D-positive cells, a histogram of the FITC fluorescence intensity of live cells was generated. Hybridomas producing antibodies specifically binding to cynomolgus monkey CDH6 expressed on the cell membrane surface were selected based on results where the histogram for the antibody shifted to the strong fluorescence intensity side in the 293T cells transfected with pcDNA3.1-cynoCDH6 compared with the 293T cells transfected with the control pcDNA3.1.

[0225]

1)-6 Determination of isotype of rat monoclonal antibody

Clones rG019, rG055, rG056, and rG061 suggested to bind specifically and strongly to human CDH6 and monkey CDH6 were selected from among the rat anti-CDH6 antibody-producing hybridomas selected in Example 1)-5, and the isotype of each antibody was identified. The heavy chain subclass and the light chain type of the antibody were determined using a RAT MONOCLONAL ANTIBODY ISOTYPING TEST KIT (DS Pharma Biomedical Co., Ltd.). As a result, it was confirmed that all of these 4 clones rG019, rG055, rG056, and rG061 had a heavy chain of IgG2b subclass and a light chain of κ chain type.

[0226]

1)-7 Preparation of rat anti-human CDH6 antibody

1)-7-1 Production of culture supernatant

The rat anti-human CDH6 monoclonal antibodies were purified from the hybridoma culture supernatants. First, the volume of each rat anti-CDH6 monoclonal antibody-producing hybridoma was sufficiently increased with ClonaCell-HY Selection Medium E (StemCell Technologies Inc.), and thereafter, the medium was exchanged with Hybridoma SFM (Thermo Fisher Scientific Corp.) to

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which 20% of Ultra Low IgG FBS (Thermo Fisher Scientific Corp.) had been added. Thereafter, the hybridoma was cultured for 4 to 5 days. The resulting culture supernatant was harvested, and insoluble matter was removed therefrom by passing through a 0.8- μ m filter, and through a 0.2- μ m filter.

[0227]

1)-7-2 Purification of rat anti-CDH6 antibody

An antibody (rat anti-CDH6 antibody (rG019, rG055, rG056 or rG061)) was purified from the culture supernatant of hybridomas prepared in Example 1)-7-1 according to Protein G affinity chromatography. The antibody was adsorbed on a Protein G column (GE Healthcare Biosciences Corp.), the column was then washed with PBS, and the antibody was then eluted with a 0.1 M glycine/HCl aqueous solution (pH 2.7). 1 M Tris-HCl (pH 9.0) was added to the eluate, so that the pH was adjusted to pH 7.0 to 7.5. Thereafter, using Centrifugal UF Filter Device VIVASPIN20 (molecular weight cutoff: UF30K, Sartorius Inc.), the buffer was replaced with HBSor (25 mM histidine/5% sorbitol, pH 6.0), while the antibody was concentrated, so that the concentration of the antibody was adjusted to 1 mg/mL. Finally, the antibody was filtrated through a Minisart-Plus filter (Sartorius Inc.) to obtain a purified sample.

[0228]

[Example 2: *In vitro* evaluation of rat anti-CDH6 antibody]

2)-1 Evaluation of binding ability of rat anti-CDH6 antibody by flow cytometry

The human CDH6-binding activity of the rat anti-CDH6 antibody produced in Example 1)-7 was evaluated by flow cytometry. Using Lipofectamine 2000 (Thermo Fisher Scientific Inc.), pcDNA3.1-hCDH6 produced in Example 1)-1 was transiently introduced into 293T cells (ATCC). The cells were cultured overnight under conditions of 37°C and 5% CO₂, and thereafter, a cell suspension was prepared.

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The suspension of the transfected 293T cells was centrifuged, and the supernatant was then removed. Thereafter, the cells were suspended by the addition of each of the 4 rat anti-CDH6 monoclonal antibodies (clone Nos: rG019, rG055, rG056 and rG061), which had been prepared in Example 1)-7, or rat IgG control (R&D Systems, Inc.) (final concentration: 10 ng/mL). The cells were left standing at 4°C for 1 hour. The cells were washed twice with PBS supplemented with 5% FBS, and then suspended by the addition of Anti-Rat IgG (whole molecule)-FITC antibody produced in rabbit (Sigma-Aldrich Co. LLC) that had been 50-fold diluted with PBS supplemented with 5% FBS. The cells were left standing at 4°C for 1 hour. The cells were washed twice with PBS supplemented with 5% FBS, followed by detection using a flow cytometer (FC500; Beckman Coulter, Inc.). The data was analyzed using FlowJo (Tree Star, Inc.). The results are shown in Figure 1. In the histogram of Figure 1, the abscissa depicts FITC fluorescence intensity indicating the amount of the antibody bound, and the ordinate depicts a cell count. The shaded histogram shows that negative control 293T cells untransfected with hCDH6 were used, and the open solid line histogram shows that hCDH6-transfected 293T cells were used. As seen, fluorescence intensity was enhanced by the binding of the antibody to hCDH6 on the cell surface. The rat IgG control binds to neither of the cells. As a result, it was confirmed that the 4 produced rat anti-CDH6 monoclonal antibodies bind to 293T cells transfected with pcDNA3.1-hCDH6.

[0229]

2)-2 Analysis of CDH6-binding site of rat anti-CDH6 antibody by flow cytometry

2)-2-1 Construction of expression vector for each domain deletion mutant of human CDH6

The full-length extracellular region of human CDH6 has five extracellular domains, EC1 (SEQ ID NO: 2), EC2 (SEQ ID NO: 3), EC3 (SEQ ID NO: 4), EC4

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(SEQ ID NO: 5), and EC5 (SEQ ID NO: 6). A gene to be expressed such that each one of the five EC domains could be deleted from full-length human CDH6 was synthesized by GeneArt, and incorporated into p3xFLAG-CMV-9 vectors for mammalian expression (Sigma-Aldrich Co. LLC) according to a method known to a person skilled in the art in order to produce an expression vector for each domain deletion mutant lacking any one of EC1 to EC5.

[0230]

2)-2-2 Epitope analysis of rat anti-CDH6 antibody by flow cytometry using domain deletion mutant

The epitopes to which the rat anti-human CDH6 antibodies bound were identified by flow cytometry analysis using a 293 α cell line transfected with each EC domain deletion vector. Using Lipofectamine 2000 (Thermo Fisher Scientific Inc.), each domain deletion mutant expression vector produced in Example 2)-2-1, or pcDNA3.1-hCDH6 for the expression of full-length human CDH6 was transiently introduced into a 293 α cell line, which was a cell line derived from HEK293 cells by stable transfection with integrin α v and integrin β 3 expression vectors. The cells were cultured overnight under conditions of 37°C and 5% CO₂, and thereafter, a cell suspension was prepared. The suspension of the transfected 293 α cells was centrifuged, and a supernatant was then removed. Thereafter, the cells were suspended by the addition of each of the 4 rat anti-CDH6 monoclonal antibodies (clone Nos: rG019, rG055, rG056 and rG061), which had been prepared in Example 1)-7, or rat IgG control (R&D Systems, Inc.) (final concentration: 20 nM). The cells were left standing at 4°C for 1 hour. The cells were washed twice with PBS supplemented with 5% FBS, and then suspended by the addition of Anti-Rat IgG (whole molecule)-FITC antibody produced in rabbit (Sigma-Aldrich Co. LLC) that had been 50-fold diluted with PBS supplemented with 5% FBS. The cells were left standing at 4°C for 1 hour. The cells were washed twice with PBS supplemented

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with 5% FBS, followed by detection using a flow cytometer (Canto II; BD Biosciences). The data was analyzed using FlowJo (Tree Star, Inc.). The results are shown in Figures 2-1 to 2-6. In the histograms of Figures 2-1 to 2-6, the abscissa depicts FITC fluorescence intensity indicating the amount of the antibody bound, and the ordinate depicts cell count. The shaded histogram shows that negative control untransfected 293 α cells were used, and the open solid line histogram shows that 293 cells expressing full-length hCDH6 or each EC domain deletion mutant were used. Fluorescence intensity is enhanced when the antibody binds to full-length hCDH6 or each EC domain deletion mutant on the surface of cells. The rat IgG control binds to none of the transfected cells. The 4 produced rat anti-CDH6 monoclonal antibodies bind to the full-length hCDH6, the EC1 deletion mutant, the EC2 deletion mutant, the EC4 deletion mutant, and the EC5 deletion mutant, but do not bind to the EC3 deletion mutant. From this result, it was demonstrated that the 4 rat anti-CDH6 monoclonal antibodies specifically bind to hCDH6 with EC3 as an epitope.

[0231]

2)-3 Internalization activity of rat anti-CDH6 antibody

2)-3-1 Confirmation of CDH6 expression in human tumor cell line

In order to select a CDH6-positive human tumor cell line for use in the evaluation of the obtained antibodies, CDH6 expression information was retrieved from a known database, and the expression of CDH6 on the cell membrane surface was evaluated by flow cytometry. Human ovarian tumor cell lines NIH:OVCAR-3, PA-1 and ES-2 and human renal cell tumor cell line 786-O (all obtained from ATCC) were each cultured under conditions of 37°C and 5% CO₂, and thereafter, a cell suspension was prepared. The cells were centrifuged, and the supernatant was then removed. Thereafter, the cells were suspended by the addition of a commercially available anti-human CDH6 antibody (MABU2715, R&D Systems,

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Inc.) or mouse IgG1 (BD Pharmingen) as a negative control (final concentration: 50 $\mu\text{g/mL}$). The cells were left standing at 4°C for 1 hour. The cells were washed twice with PBS supplemented with 5% FBS, and then suspended by the addition of F(ab')₂ Fragment of FITC-conjugated Goat Anti-mouse immunoglobulins (Dako) that had been 50-fold diluted with PBS supplemented with 5% FBS. The cells were left standing at 4°C for 1 hour. The cells were washed twice with PBS supplemented with 5% FBS, followed by detection using a flow cytometer (Canto II; BD Biosciences). The data was analyzed using FlowJo (Tree Star, Inc.). The results are shown in Figure 3. In the histogram of Figure 3, the abscissa depicts FITC fluorescence intensity indicating the amount of the antibody bound, and the ordinate depicts cell count. The shaded histogram shows that the negative control mIgG1 was used in staining, and the open solid line histogram shows that the anti-human CDH6 antibody was used in staining. As seen, fluorescence intensity was enhanced by the binding of the antibody to hCDH6 on the surface of cells. The mIgG1 control binds to none of the cells. As a result, it was confirmed that the NIH:OVCAR-3, PA-1 and 786-O cell lines endogenously express CDH6 on the cell surface. On the other hand, it was demonstrated that the ES-2 cell line expresses no CDH6.

[0232]

2)-3-2 Evaluation of internalization activity of rat anti-CDH6 antibody

The internalization activity of the rat anti-CDH6 antibodies was evaluated using an anti-rat IgG reagent Rat-ZAP (Advanced Targeting Systems) conjugated with a toxin (saporin) inhibiting protein synthesis. Specifically, human CDH6-positive ovarian tumor cell line NIH:OVCAR-3 (ATCC) was seeded at 4×10^3 cells/well on a 96-well plate, and then cultured overnight under conditions of 37°C and 5% CO₂. Human CDH6-positive renal cell tumor cell line 786-O (ATCC) was seeded at 1×10^3 cells/well on a 96-well plate, and then cultured overnight. On the

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next day, each rat anti-CDH6 antibody (final concentration: 1 nM) or rat IgG2b antibody (R&D Systems, Inc.) as a negative control antibody was added to the plate. Rat-ZAP (final concentration: 0.5 nM) or Goat Anti-Rat IgG, Fc (gamma) Fragment Specific (Jackson ImmunoResearch Laboratories, Inc.) unconjugated with the toxin (final concentration: 0.5 nM) as a negative control was further added to the plate, and the cells were cultured under conditions of 37°C and 5% CO₂ for 3 days. The number of live cells was measured by the quantification of ATP activity (RLU) using a CellTiter-Glo(TM) Luminescent Cell Viability Assay (Promega Corp.). In this evaluation, Rat-ZAP is taken up into cells in a manner dependent on the internalization activity of the rat anti-CDH6 antibody, so that saporin inhibiting protein synthesis is released into the cells, so as to suppress cell growth. A cell growth inhibition effect brought about by the addition of the anti-CDH6 antibody was indicated by a relative survival rate when the number of live cells in a well supplemented with the negative control instead of Rat-ZAP was defined as 100%. Figure 4 shows a graph and a table of the cell survival rate. As a result, it was demonstrated that the rat anti-CDH6 antibodies bind to CDH6 and cause internalization.

[0233]

[Example 3: Determination of nucleotide sequence of cDNA encoding variable region of rat anti-CDH6 antibody]

3)-1 Amplification and sequencing of rG019 heavy chain variable region and light chain variable region gene fragments

3)-1-1 Preparation of total RNA from G019

In order to amplify cDNA encoding each variable region of rG019, total RNA was prepared from G019 using TRIzol Reagent (Ambion, Inc.).

[0234]

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3)-1-2 Amplification of cDNA encoding rG019 heavy chain variable region by 5'-RACE PCR and determination of nucleotide sequence

cDNA encoding the heavy chain variable region was amplified using approximately 1 µg of the total RNA prepared in Example 3)-1-1 and a SMARTer RACE cDNA Amplification Kit (Clontech Laboratories, Inc.). As primers used to amplify the cDNA of the variable region of the rG019 heavy chain gene according to PCR, UPM (Universal Primer A Mix: included with SMARTer RACE cDNA Amplification Kit) and primers designed from the sequences of the constant regions of known rat heavy chains were used.

The heavy chain variable region-encoding cDNA amplified by 5'-RACE PCR was cloned into a plasmid, and thereafter, the nucleotide sequence of the cDNA of the heavy chain variable region was subjected to sequence analysis.

The determined nucleotide sequence of the cDNA encoding the heavy chain variable region of rG019 is shown in SEQ ID NO: 16, and the amino acid sequence thereof is shown in SEQ ID NO: 15.

[0235]

3)-1-3 Amplification of cDNA encoding rG019 light chain variable region by 5'-RACE PCR and determination of nucleotide sequence

Amplification and sequencing were carried out by the same method as that applied in Example 3)-1-2. However, as primers used to amplify the cDNA of the variable region of the rG019 light chain gene according to PCR, UPM (Universal Primer A Mix: included with SMARTer RACE cDNA Amplification Kit) and primers designed from the sequences of the constant regions of known rat light chains were used.

The determined nucleotide sequence of the cDNA encoding the light chain variable region of rG019 is shown in SEQ ID NO: 11, and the amino acid sequence thereof is shown in SEQ ID NO: 10.

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[0236]

3)-2 Amplification and sequencing of rG055 heavy chain variable region and light chain variable region gene fragments

The sequences were determined by the same method as that applied in Example 3)-1.

The determined nucleotide sequence of the cDNA encoding the heavy chain variable region of rG055 is shown in SEQ ID NO: 26, and the amino acid sequence thereof is shown in SEQ ID NO: 25. The nucleotide sequence of the cDNA encoding the light chain variable region of rG055 is shown in SEQ ID NO: 21, and the amino acid sequence thereof is shown in SEQ ID NO: 20.

[0237]

3)-3 Amplification and sequencing of rG056 heavy chain variable region and light chain variable region gene fragments

The sequences were determined by the same method as that applied in Example 3)-1.

The determined nucleotide sequence of the cDNA encoding the heavy chain variable region of rG056 is shown in SEQ ID NO: 36, and the amino acid sequence thereof is shown in SEQ ID NO: 35. The nucleotide sequence of the cDNA encoding the light chain variable region of rG056 is shown in SEQ ID NO: 31, and the amino acid sequence thereof is shown in SEQ ID NO: 30.

[0238]

3)-4 Amplification and sequencing of rG061 heavy chain variable region and light chain variable region gene fragments

The sequences were determined by the same method as that applied in Example 3)-1.

The determined nucleotide sequence of the cDNA encoding the heavy chain variable region of rG061 is shown in SEQ ID NO: 46, and the amino acid sequence

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thereof is shown in SEQ ID NO: 45. The nucleotide sequence of the cDNA encoding the light chain variable region of rG061 is shown in SEQ ID NO: 41, and the amino acid sequence thereof is shown in SEQ ID NO: 40.

[0239]

[Example 4: Production of human chimeric anti-CDH6 antibody chG019]

4)-1 Construction of human chimeric anti-CDH6 antibody chG019 expression vector

4)-1-1 Construction of chimeric and humanized light chain expression vector pCMA-LK

An approx. 5.4-kb fragment, which had been obtained by digesting plasmid pcDNA3.3-TOPO/LacZ (Invitrogen Corp.) with the restriction enzymes XbaI and PmeI, was bound to a DNA fragment comprising a DNA sequence (SEQ ID NO: 50) encoding a human light chain signal sequence and a human κ chain constant region, using an In-Fusion Advantage PCR cloning kit (Clontech Laboratories, Inc.), to produce pcDNA3.3/LK.

A neomycin expression unit was removed from pcDNA3.3/LK to construct pCMA-LK.

[0240]

4)-1-2 Construction of chimeric and humanized IgG1 type heavy chain expression vector pCMA-G1

A DNA fragment, which had been obtained by digesting pCMA-LK with XbaI and PmeI to remove the DNA sequence encoding the light chain signal sequence and the human κ chain constant region therefrom, was bound to a DNA fragment comprising a DNA sequence (SEQ ID NO: 51) encoding a human heavy chain signal sequence and a human IgG1 constant region, using an In-Fusion Advantage PCR cloning kit (Clontech Laboratories, Inc.), to construct pCMA-G1.

[0241]

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4)-1-3 Construction of chG019 heavy chain expression vector

A DNA fragment from nucleotide positions 36 to 440 in the nucleotide sequence of the chG019 heavy chain shown in SEQ ID NO: 57 was synthesized (GENEART). Using an In-Fusion HD PCR cloning kit (Clontech Laboratories, Inc.), the synthesized DNA fragment was inserted into a site of pCMA-G1 that had been cleaved with the restriction enzyme BspI, so as to construct a chG019 heavy chain expression vector. It is to be noted that, for the chG019 heavy chain, a CDR sequence with cysteine substituted with proline was used in order to prevent unpredictable disulfide bonds.

[0242]

4)-1-4 Construction of chG019 light chain expression vector

A DNA fragment comprising a DNA sequence (SEQ ID NO: 52) encoding the chG019 light chain was synthesized (GENEART). Using an In-Fusion HD PCR cloning kit (Clontech Laboratories, Inc.), the synthesized DNA fragment was bound to a DNA fragment, which had been obtained by digesting pCMA-LK with XbaI and PmeI to remove the DNA sequence encoding the light chain signal sequence and the human κ chain constant region therefrom, so as to construct a chG019 light chain expression vector.

[0243]

4)-2 Production and purification of human chimeric anti-CDH6 antibody chG019

4)-2-1 Production of chG019

In accordance with the manual, FreeStyle 293F cells (Invitrogen Corp.) were cultured and passaged. 1.2×10^9 FreeStyle 293F cells (Invitrogen Corp.) in the logarithmic growth phase were seeded on a 3-L Fernbach Erlenmeyer Flask (Corning Inc.), then diluted with FreeStyle 293 expression medium (Invitrogen Corp.) at 2.0×10^6 cells/mL. To 40 ml of Opti-Pro SFM medium (Invitrogen Corp.), 0.24 mg of

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the heavy chain expression vector, 0.36 mg of the light chain expression vector and 1.8 mg of Polyethyleneimine (Polyscience #24765) were added, and the obtained mixture was gently stirred. After incubation for 5 minutes, the mixture was added to the FreeStyle 293F cells. The cells were shake-cultured at 90 rpm in an 8% CO₂ incubator at 37°C for 4 hours, and thereafter, 600 mL of EX-CELL VPRO medium (SAFC Biosciences Inc.), 18 mL of GlutaMAX I (GIBCO), and 30 mL of Yeastolate Ultrafiltrate (GIBCO) were added to the culture. The cells were further shake-cultured at 90 rpm in an 8% CO₂ incubator at 37°C for 7 days. The obtained culture supernatant was filtrated through a Disposable Capsule Filter (Advantec #CCS-045-E1H).

[0244]

4)-2-2 Purification of chG019

An antibody was purified from the culture supernatant obtained in Example 4)-2-1 by a one-step process according to rProtein A affinity chromatography. The culture supernatant was applied to a column that had been packed with MabSelectSuRe (GE Healthcare Biosciences Corp.) equilibrated with PBS, and thereafter, the column was washed with PBS in an amount of two or more times the volume of the column. Subsequently, the antibody was eluted with a 2 M arginine hydrochloride solution (pH 4.0), so that a fraction containing an antibody was collected. The fraction was dialyzed (Thermo Fisher Scientific Inc., Slide-A-Lyzer Dialysis Cassette), so that the buffer was replaced with HBSor (25 mM histidine/5% sorbitol, pH 6.0). Using a Centrifugal UF Filter Device VIVASPIN20 (molecular weight cutoff: UF10K, Sartorius Inc.), the antibody was concentrated, so that the concentration of IgG was adjusted to 5 mg/ml or more. Finally, the antibody was filtrated through a Minisart-Plus filter (Sartorius Inc.) to obtain a purified sample.

[0245]

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4)-3 Evaluation of binding activity of human chimeric anti-CDH6 antibody chG019

The CDH6-binding activity of the human chimeric anti-CDH6 antibody chG019 purified in 4)-2 was confirmed by flow cytometry. Using Lipofectamine 2000, pcDNA3.1-hCDH6 or pcDNA3.1-cynoCDH6 produced in Example 1)-1, or pcDNA3.1 was transiently introduced into 293 α cells. The cells were cultured overnight under conditions of 37°C and 5% CO₂, and thereafter, a cell suspension was prepared. chG019 was added to the suspension of each of these cells. The cells were left standing at 4°C for 1 hour. Thereafter, the cells were washed twice with PBS supplemented with 5% FBS, and then suspended by the addition of PE-labeled F(ab')₂ Fragment anti-human IgG, Fc γ antibody (Jackson ImmunoResearch Laboratories, Inc.) that had been 500-fold diluted with PBS supplemented with 5% FBS. The cells were left standing at 4°C for 1 hour. The cells were washed twice with PBS supplemented with 5% FBS, and then re-suspended in PBS supplemented with 5% FBS, followed by detection using a flow cytometer (Canto II; BD Biosciences). The data was analyzed using FlowJo (Tree Star, Inc.). As shown in Figure 5, chG019 did not bind to the 293T cells transfected with pcDNA3.1 as a negative control, but did bind to the 293T cells transfected with pcDNA3.1-hCDH6 or pcDNA3.1-cynoCDH6 in an antibody concentration-dependent manner. In Figure 5, the abscissa depicts antibody concentration, and the ordinate depicts the amount of the antibody bound, based on mean fluorescence intensity. It is evident from this result that chG019 specifically binds to human CDH6 and cynomolgus monkey CDH6 with almost equivalent binding activity.

[0246]

[Example 5: Production of humanized anti-CDH6 antibody]

5)-1 Design of humanized form of anti-CDH6 antibody

5)-1-1 Molecular modeling of chG019 variable region

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The molecular modeling of the variable regions of chG019 exploited a method known as homology modeling (Methods in Enzymology, 203, 121-153, (1991)). The commercially available protein three-dimensional structure analysis program BioLuminate (manufactured by Schrodinger, LLC) was employed using, as a template, a structure (PDB ID: 2I9L) registered in Protein Data Bank (Nuc. Acid Res. 35, D301-D303 (2007)) with a high sequence identity to the heavy chain and light chain variable regions of chG019.

[0247]

5)-1-2 Design of amino acid sequence of humanized hG019

chG019 was humanized by CDR grafting (Proc. Natl. Acad. Sci. USA 86, 10029-10033 (1989)). The consensus sequences of human gamma chain subgroup 1 and kappa chain subgroup 1 determined by KABAT et al. (Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service National Institutes of Health, Bethesda, MD. (1991)) had high identity to the framework regions of chG019, and based on this, they were selected as acceptors for the heavy chain and the light chain, respectively. Donor residues to be grafted onto the acceptors were selected by analyzing three-dimensional models with reference to, for example, the criteria given by Queen et al. (Proc. Natl. Acad. Sci. USA 86, 10029-10033 (1989)).

[0248]

5)-2 Humanization of chG019 heavy chain

Three heavy chains thus designed were named hH01, hH02 and hH04. The full-length amino acid sequence of the hH01 heavy chain is shown in SEQ ID NO: 69. The nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 69 is shown in SEQ ID NO: 70. The full-length amino acid sequence of the heavy chain hH02 is shown in SEQ ID NO: 73. The nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 73 is shown in SEQ ID NO: 74. The full-length amino acid sequence of the heavy chain hH04 is shown in SEQ ID NO: 77.

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The nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 77 is shown in SEQ ID NO: 78.

[0249]

5)-3 Humanization of chG019 light chain

Two light chains thus designed were named hL02 and hL03. The full-length amino acid sequence of the hL02 light chain is shown in SEQ ID NO: 61. The nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 61 is shown in SEQ ID NO: 62. The full-length amino acid sequence of the light chain hL03 is shown in SEQ ID NO: 65. The nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 65 is shown in SEQ ID NO: 66.

[0250]

5)-4 Design of humanized hG019 by combination of heavy chain and light chain

An antibody consisting of hH01 and hL02 was named "H01L02 antibody" or "H01L02". An antibody consisting of hH02 and hL02 was named "H02L02 antibody" or "H02L02". An antibody consisting of hH02 and hL03 was named "H02L03 antibody" or "H02L03". An antibody consisting of hH04 and hL02 was named "H04L02 antibody" or "H04L02".

[0251]

5)-5 Expression of humanized anti-CDH6 antibody

5)-5-1 Construction of humanized hG019 heavy chain expression vector

5)-5-1-1 Construction of humanized hG019-H01 type heavy chain expression vector

A DNA fragment from nucleotide positions 36 to 440 in the nucleotide sequence of the humanized hG019-H01 type heavy chain shown in SEQ ID NO: 70 was synthesized (GENEART). A humanized hG019-H01 type heavy chain

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expression vector was constructed by the same method as that applied in Example 4)-1-3.

[0252]

5)-5-1-2 Construction of humanized hG019-H02 type heavy chain expression vector

A DNA fragment from nucleotide positions 36 to 440 in the nucleotide sequence of the humanized hG019-H02 type heavy chain shown in SEQ ID NO: 74 was synthesized (GENEART). A humanized hG019-H02 type heavy chain expression vector was constructed by the same method as that applied in Example 4)-1-3.

[0253]

5)-5-1-3 Construction of humanized hG019-H04 type heavy chain expression vector

A DNA fragment from nucleotide positions 36 to 440 in the nucleotide sequence of the humanized hG019-H04 type heavy chain shown in SEQ ID NO: 78 was synthesized (GENEART). A humanized hG019-H04 type heavy chain expression vector was constructed by the same method as that applied in Example 4)-1-3.

[0254]

5)-5-2 Construction of humanized hG019 light chain expression vector

5)-5-2-1 Construction of humanized hG019-L02 type light chain expression vector

A DNA fragment comprising a humanized hG019-L02 type light chain variable region-encoding DNA sequence from nucleotide positions 37 to 399 in the nucleotide sequence of the humanized hG019-L02 type light chain shown in SEQ ID NO: 62 was synthesized (GENEART). Using an In-Fusion HD PCR cloning kit (Clontech Laboratories, Inc.), the synthesized DNA fragment was inserted into a site

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of pCMA-LK that had been cleaved with the restriction enzyme BsiWI, so as to construct a humanized hG019-L02 type light chain expression vector.

[0255]

5)-5-2-2 Construction of humanized hG019-L03 type light chain expression vector

A DNA fragment comprising a humanized hG019-L03 type light chain variable region-encoding DNA sequence from nucleotide positions 37 to 399 in the nucleotide sequence of the humanized hG019-L03 type light chain shown in SEQ ID NO: 66 was synthesized (GENEART). A humanized hG019-L03 type light chain expression vector was constructed by the same method as that applied in Example 5)-5-2-1.

[0256]

5)-5-3 Preparation of humanized hG019

5)-5-3-1 Production of H01L02, H02L02, H02L03 and H04L02

The antibodies were produced by the same method as that applied in Example 4)-2-1. H01L02, H02L02, H02L03 and H04L02 were produced by the combination of the heavy chain and the light chain shown in Example 5)-4.

[0257]

5)-5-3-2 Two-step purification of H01L02, H02L02, H02L03 and H04L02

The antibody was purified from the culture supernatant obtained in Example 5)-5-3-1, by a two-step process, namely, by rProtein A affinity chromatography and ceramic hydroxyapatite. The culture supernatant was applied to a column that had been packed with MabSelectSuRe (manufactured by GE Healthcare Biosciences Corp.) equilibrated with PBS, and thereafter, the column was washed with PBS in an amount of two or more times the volume of the column. Subsequently, the antibody was eluted using a 2 M arginine hydrochloride solution (pH 4.0). A fraction containing the antibody was dialyzed (Thermo Fisher Scientific Inc., Slide-

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A-Lyzer Dialysis Cassette), so that the buffer was replaced with PBS. The antibody solution was 5-fold diluted with a buffer of 5 mM sodium phosphate/50 mM MES/pH 7.0, and then applied to a ceramic hydroxyapatite column (Bio-Rad Laboratories, Inc., Bio-Scale CHT Type-1 Hydroxyapatite Column) that had been equilibrated with a buffer of 5 mM NaPi/50 mM MES/30 mM NaCl/pH 7.0. Elution was carried out on a linear concentration gradient of sodium chloride, so that a fraction containing an antibody was collected. This fraction was dialyzed (Thermo Fisher Scientific Inc., Slide-A-Lyzer Dialysis Cassette), so that the buffer was replaced with HBSor (25 mM histidine/5% sorbitol, pH 6.0). The antibody was concentrated with Centrifugal UF Filter Device VIVASPIN20 (molecular weight cutoff: UF10K, Sartorius Inc.), thereby adjusting the IgG concentration to 20 mg/ml. Finally, the antibody was filtrated through a Minisart-Plus filter (Sartorius Inc.) to obtain a purified sample.

[0258]

[Reference Example 1: Production of anti-CDH6 antibody NOV0712]

The anti-CDH6 antibody NOV0712 used in the Examples was produced with reference to the light chain full-length and heavy chain full-length amino acid sequences (SEQ ID NO: 235 and SEQ ID NO: 234, respectively, in International Publication No. WO 2016/024195) of NOV0712 described in International Publication No. WO 2016/024195.

[0259]

Reference Example 1)-1 Anti-CDH6 antibody NOV0712

Reference Example 1)-1-1 Construction of anti-CDH6 antibody NOV0712 heavy chain expression vector

A NOV0712 heavy chain variable region-encoding DNA fragment from nucleotide positions 36 to 428 in the nucleotide sequence of the NOV0712 heavy chain shown in SEQ ID NO: 84 was synthesized (GENEART). A NOV0712 heavy

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chain expression vector was constructed by the same method as that applied in Example 4)-1-3. The amino acid sequence of the NOV0712 heavy chain expressed by the NOV0712 heavy chain expression vector is shown in SEQ ID NO: 83. In the amino acid sequence shown in SEQ ID NO: 83, the amino acid sequence consisting of the amino acid residues at positions 1 to 19 is a signal sequence.

[0260]

Reference Example 1)-1-2 Construction of anti-CDH6 antibody NOV0712 light chain expression vector

A DNA fragment comprising a NOV0712 light chain variable region-encoding DNA sequence from nucleotide positions 37 to 405 in the nucleotide sequence of the NOV0712 light chain shown in SEQ ID NO: 82 was synthesized (GENEART). A NOV0712 light chain expression vector was constructed by the same method as that applied in Example 5)-5-2-1. The amino acid sequence of the NOV0712 light chain expressed by the NOV0712 light chain expression vector is shown in SEQ ID NO: 81. In the amino acid sequence shown in SEQ ID NO: 81, the amino acid sequence consisting of the amino acid residues at positions 1 to 20 is a signal sequence.

[0261]

Reference Example 1)-2 Preparation of anti-CDH6 antibody NOV0712

Reference Example 1)-2-1 Production of anti-CDH6 antibody NOV0712

NOV0712 was produced by the same method as that applied in Example 4)-2-1.

[0262]

Reference Example 1)-2-2 One-step purification of anti-CDH6 antibody NOV0712

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The anti-CDH6 antibody NOV0712 was purified from the culture supernatant obtained in Reference Example 1)-2-1 by the same method as that applied in Example 4)-2-2 (antibody concentration: 5 mg/l HBSor).

[0263]

[Example 6: *In vitro* evaluation of humanized hG019 and NOV0712]

6)-1 Evaluation of binding activity of humanized hG019

6)-1-1 Human CDH6 antigen-binding ability of humanized hG019

The dissociation constant between the antibody and the antigen (Recombinant Human CDH6 Fc His chimera, R&D Systems, Inc.) was measured by using Biacore T200 (GE Healthcare Biosciences Corp.), according to a capture method, which comprises capturing the antigen as a ligand with the immobilized anti-His antibody and then measuring the dissociation constant using an antibody as an analyte. Approximately 1000 RU of the anti-histidine antibody (His capture kit, GE Healthcare Biosciences Corp.) was covalently bound to sensor chip CM5 (GE Healthcare Biosciences Corp.) by the amine coupling method. The antibody was also immobilized onto reference cells in the same manner as above. HBS-P+ (10 mM HEPES pH 7.4, 0.15 M NaCl, 0.05% Surfactant P20) supplemented with 1 mM CaCl₂ was used as a running buffer. The antigen was added onto the anti-histidine antibody-immobilized chip for 60 seconds, and a dilution series solution (0.391 to 100 nM) of the antibody was then added at a flow rate of 30 µl/min for 300 seconds. Subsequently, the dissociation phase was monitored for 600 seconds. As a regeneration solution, a glycine solution (pH 1.5) supplemented with 5 M MgCl₂ was added twice at a flow rate of 10 µl/min for 30 seconds. A Steady State Affinity model in analysis software (BIAevaluation software, version 4.1) was used in data analysis, and the dissociation constant (KD) was calculated. The results are shown in Table 2.

[0264]

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[Table 2]

	Antibody	KD(M)
1	H02L02	1.5E-09
2	H02L02	1.1E-09
3	H02L03	1.4E-09
4	H04L02	1.1E-09

[0265]

6)-1-2 Binding activity against human, monkey, mouse or rat CDH6

Using Lipofectamine 2000 (Thermo Fisher Scientific Inc.), pcDNA3.1-hCDH6, pcDNA3.1-cynoCDH6, p3xFLAG-CMV-9-mCDH6, or p3xFLAG-CMV-9-rCDH6 produced in Example 1)-1 was transiently introduced into 293 α cells. The cells were cultured overnight under conditions of 37°C and 5% CO₂, and thereafter, a cell suspension was prepared. Untransfected 293 α cells were used as a negative control. The suspension of the 293 α cells produced as described above was centrifuged, and the supernatant was then removed. Thereafter, the cells were suspended by the addition of each of the 4 humanized hG019 antibodies (clone Nos: H01L02, H02L02, H02L03 and H04L02), which had been prepared in Example 5)-5-3, or human IgG1 control (Calbiochem). The cells were left standing at 4°C for 1 hour. The cells were washed twice with PBS supplemented with 5% FBS, and then suspended by the addition of anti-human IgG, Fc(gamma) PE goat F(ab') (Jackson ImmunoResearch Laboratories, Inc.) that had been 500-fold diluted with PBS supplemented with 5% FBS. The cells were left standing at 4°C for 1 hour. The cells were washed twice with PBS supplemented with 5% FBS, followed by detection using a flow cytometer (Canto II; BD Biosciences). The data was analyzed using FlowJo (Tree Star, Inc.). In Figures 6-1 and 6-2, the abscissa depicts antibody concentration, and the ordinate depicts the amount of the antibody bound based on mean fluorescence intensity. As shown in Figures 6-1 and 6-2, the

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human IgG1 control as a negative control binds to none of the CDH6-transfected cells. The 4 humanized hG019 antibodies (clone Nos: H01L02, H02L02, H02L03 and H04L02) bind to human CDH6 and cynomolgus monkey CDH6, but bind to neither mouse nor rat CDH6. None of the antibodies bind to the cells transfected with the empty vector pcDNA3.1 as a negative control. On the other hand, International Publication No. WO 2016/024195 discloses that the NOV0712 antibody exhibits binding activity against all of human CDH6, cynomolgus monkey CDH6, mouse CDH6, and rat CDH6. As a result, it was demonstrated that the 4 humanized hG019 antibodies obtained in the present description are anti-CDH6 antibodies that exhibit binding properties different from those of the NOV0712 antibody.

[0266]

6)-2 Analysis of CDH6-binding sites of humanized hG019 and NOV0712

6)-2-1 Epitope analysis using domain deletion mutant

Using Lipofectamine 2000 (Thermo Fisher Scientific Inc.), each domain deletion mutant expression vector produced in Example 2)-2-1, or pcDNA3.1-hCDH6 for the expression of full-length human CDH6 was transiently introduced into cells. The cells were cultured overnight under conditions of 37°C and 5% CO₂, and thereafter, a cell suspension was prepared. The suspension of the transfected 293α cells was centrifuged, and the supernatant was then removed. Thereafter, the cells were suspended by the addition of each of the 4 humanized hG019 antibodies (clone Nos: H01L02, H02L02, H02L03 and H04L02), which had been prepared in Example 5)-5-3, or the anti-CDH6 antibody NOV0712, which had been prepared in Reference Example 1, or human IgG1 (Calbiochem) as a negative control. The cells were left standing at 4°C for 1 hour. The cells were washed twice with PBS supplemented with 5% FBS, and then suspended by the addition of APC-anti-human IgG goat F(ab')₂ (Jackson ImmunoResearch Laboratories, Inc.) that had been 500-

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fold diluted with PBS supplemented with 5% FBS. The cells were left standing at 4°C for 1 hour. The cells were washed twice with PBS supplemented with 5% FBS, followed by detection using a flow cytometer (Canto II; BD Biosciences). The data was analyzed using FlowJo (Tree Star, Inc.). The results are shown in Figures 7-1 to 7-6. In the histograms of Figures 7-1 to 7-6, the abscissa depicts APC fluorescence intensity indicating the amount of the antibody bound, and the ordinate depicts cell count. The shaded histogram shows that negative control untransfected 293 α cells were used, and the open solid line histogram shows that 293 α cells expressing full-length hCDH6 or each EC domain deletion mutant were used. Fluorescence intensity is enhanced when the antibody binds to full-length hCDH6 or each EC domain deletion mutant on cell surface. The human IgG1 control binds to none of the transfected cells. The 4 humanized hG019 antibodies (clone Nos: H01L02, H02L02, H02L03 and H04L02) bind to the full-length hCDH6, the EC1 deletion mutant, the EC2 deletion mutant, the EC4 deletion mutant, and the EC5 deletion mutant, but do not bind to the EC3 deletion mutant. Specifically, it was demonstrated that the 4 humanized hG019 antibodies specifically bind to hCDH6 with EC3 as an epitope. On the other hand, the anti-CDH6 antibody NOV0712 binds to the full-length hCDH6, the EC1 deletion mutant, the EC2 deletion mutant, the EC3 deletion mutant, and the EC4 deletion mutant, but does not bind to the EC5 deletion mutant. Specifically, it was demonstrated that the anti-CDH6 antibody NOV0712 specifically binds to hCDH6 with EC5 as an epitope. This is consistent with epitope information on NOV0712 described in International Publication No. WO 2016/024195. From this result, it was demonstrated that the 4 humanized hG019 antibodies obtained in the present description are anti-CDH6 antibodies that exhibit properties different from those of NOV0712.

[0267]

6)-2-2 Binding competition assay of antibodies

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6)-2-2-1 Production of 786-O/hCDH6 stably expressing cell line

The 786-O/hCDH6 stably expressing cell line was produced by infecting 786-O cells (ATCC) with a recombinant retrovirus for full-length human CDH6 expression. A human CDH6 expression retrovirus vector (pQCXIN-hCDH6) was produced by using a human CDH6 protein (NP_004923)-encoding cDNA expression vector (OriGene Technologies Inc., RC217889), and incorporating the cDNA into retrovirus vector pQCXIN (Clontech Laboratories, Inc.) according to a method known to a person skilled in the art. Using FuGene HD (Promega Corp.), pQCXIN-hCDH6 was transiently introduced into retrovirus packaging cells RetroPack PT67 (Clontech Laboratories, Inc.). After 48 hours, a culture supernatant containing recombinant retrovirus was recovered, and then added to the 786-O cell culture system, so that the cells were infected. From 3 days after the infection, the infected cells were cultured under conditions of 37°C and 5% CO₂ in a medium supplemented with G418 (Gibco) (final concentration: 50 mg/mL) and screened with the drug, so as to establish cell line 786-O/hCDH6 stably expressing human CDH6. The high expression of human CDH6 in the stably expressing line was confirmed by flow cytometry in the same manner as that applied in Example 2)-3-1 (Figure 8). Goat anti-Mouse IgG1 Secondary Antibody Alexa Fluor 647 (Thermo Fisher Scientific Inc.) that had been 500-fold diluted with PBS supplemented with 5% FBS was used as an antibody for detection. The results are shown in Figure 8. In the histogram of Figure 8, the abscissa depicts Alexa Fluor 647 fluorescence intensity indicating the amount of the antibody bound, and the ordinate depicts cell count. The shaded histogram shows that the negative control mIgG1 was used in staining, and the open solid line histogram shows that the anti-human CDH6 antibody was used in staining. As seen, fluorescence intensity was enhanced by the binding of the antibody to hCDH6 on cell surface. The mIgG1 control binds to none of the cells. As a result, it was demonstrated that the 786-

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O/hCDH6 stably expressing cell line more highly expresses human CDH6 than the parent line 786-O cells.

[0268]

6)-2-2-2 Binding competition assay using labeled H01L02 and labeled NOV0712

Labeled H01L02 and labeled NOV0712 were produced using an Alexa Fluor 488 Monoclonal Antibody Labeling Kit (Thermo Fisher Scientific Inc.). The cell suspension of the 786-O/hCDH6 stably expressing cell line produced in 7)-2-2-1 was centrifuged, and the supernatant was then removed. Thereafter, the cells were suspended by the addition of labeled NOV0712 or labeled H01L02 (final concentration: 5 nM) and, further, the addition of each of the 4 humanized hG019 antibodies (clone Nos: H01L02, H02L02, H02L03 and H04L02), which had been prepared in Example 5)-5-3, or the anti-CDH6 antibody NOV0712, which had been prepared in Reference Example 1, or human IgG1 (Calbiochem) as a negative control (final concentration: as shown in the abscissa of Figure 9). The cells were left standing at 4°C for 1 hour. Thereafter, the cells were washed twice with PBS supplemented with 5% FBS, followed by detection using a flow cytometer (Canto II; BD Biosciences). The data was analyzed using FlowJo (Tree Star, Inc.). The results are shown in Figure 9. The abscissa depicts the final concentration of the added unlabeled antibody, and the ordinate depicts the amount of the antibody bound based on mean fluorescence intensity. When unlabeled NOV0712 is added to cells supplemented with labeled NOV0712, the amount of the labeled antibody bound is decreased by replacement with the unlabeled antibody in an addition concentration-dependent manner because they compete with each other for binding to the same epitope. On the other hand, even if each of the 4 humanized hG019 antibodies or human IgG1 as a negative control is added to cells supplemented with labeled NOV0712, there is no change in the amount of the labeled antibody bound,

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indicating that these antibodies differ in epitope and thus do not compete with each other for binding. Likewise, when each of the 4 unlabeled humanized hG019 antibodies is added to cells supplemented with labeled H01L02, the amount of the labeled antibody bound is decreased by replacement with the unlabeled antibody in an addition concentration-dependent manner because they compete with each other for binding to the same epitope. On the other hand, even if NOV0712 or human IgG1 as a negative control is added to cells supplemented with labeled H01L02, there is no change in the amount of the labeled antibody bound, indicating that these antibodies differ in epitope and thus do not compete with each other for binding.

[0269]

6)-3 Evaluation of internalization activity of humanized hG019 and NOV0712

The internalization activity of humanized hG019 and NOV0712 was evaluated using an anti-human IgG reagent Hum-ZAP (Advanced Targeting Systems) conjugated with a toxin (saporin) inhibiting protein synthesis. Specifically, human CDH6-positive ovarian tumor cell line NIH:OVCAR-3 (ATCC) was seeded at 4×10^3 cells/well on a 96-well plate, and then cultured overnight under conditions of 37°C and 5% CO₂. Human CDH6-positive renal cell tumor cell line 786-O (ATCC) was seeded at 1×10^3 cells/well on a 96-well plate, and then cultured overnight. Human CDH6-positive ovarian tumor cell line PA-1 (ATCC) was seeded at 1×10^3 cells/well on a 96-well plate, and then cultured overnight under conditions of 37°C and 5% CO₂. On the next day, each anti-CDH6 antibody (final concentration: 1 nM) or human IgG1 antibody (Calbiochem) as a negative control antibody was added to the plate. Hum-ZAP (final concentration: 0.5 nM) or F(ab')₂ Fragment Goat Anti-human IgG, Fc (gamma) Fragment Specific (Jackson ImmunoResearch Laboratories, Inc.) unconjugated with the toxin (final concentration: 0.5 nM) as a negative control was further added to the plate, and the cells were cultured under conditions of 37°C and 5% CO₂ for 3 days. The number

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of live cells was measured by the quantification of ATP activity (RLU) using CellTiter-Glo(TM) Luminescent Cell Viability Assay. In this evaluation, Hum-ZAP is taken up into cells in a manner dependent on the internalization activity of the humanized anti-CDH6 antibody, so that saporin, which inhibits protein synthesis, is released into the cells, so as to suppress cell growth. A cell growth inhibition effect brought about by the addition of the anti-CDH6 antibody was indicated by a relative survival rate when the number of live cells in a well supplemented with the negative control instead of Hum-ZAP was defined as 100%. Figures 10-1 to 10-3 each show a graph and a table of the cell survival rate. In this experiment, an antibody having strong internalization activity is considered to offer a low cell survival rate. As a result, the 4 humanized hG019 antibodies have an internalization rate of approximately 50 to 75% predicted from the cell survival rates for all of the 3 cell lines. Thus, the 4 humanized hG019 antibodies exhibit very high internalization activity and exhibit much higher internalization activity than that of NOV0712. From the mechanism of the medicinal effects of ADC, an antibody having higher internalization activity is considered to be more suitable as an ADC antibody.

[0270]

[Example 7: Production of humanized hG019-drug conjugate]

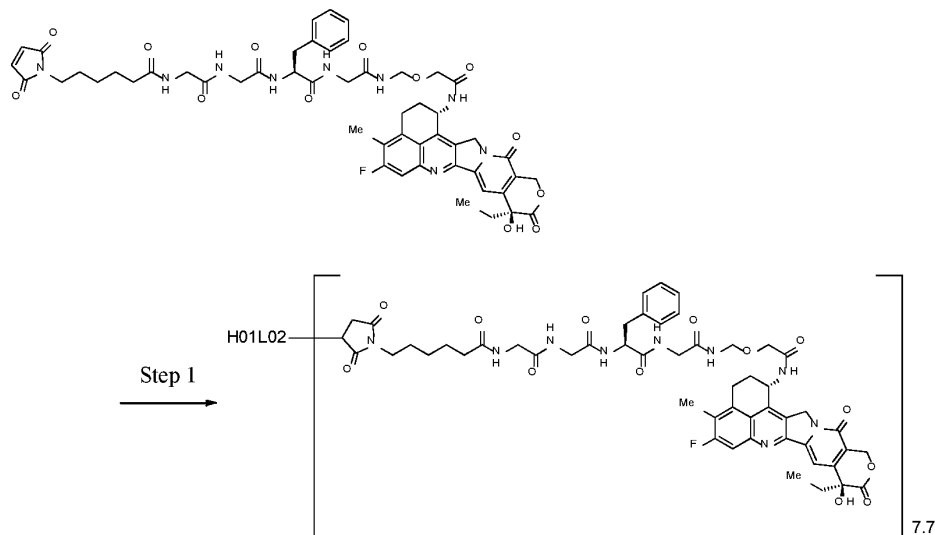
7)-1 Production of antibody-drug conjugate H01L02-DXd

Step 1: Antibody-drug conjugate (1)

[0271]

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[Formula 11]



[0272]

Reduction of antibody: H01L02 produced in Example 5 was adjusted to 9.85 mg/mL with PBS6.0/EDTA by using common procedures B (using 1.53 mLmg⁻¹cm⁻¹ as 280 nm absorption coefficient) and C described in production method 1. To this solution (5.7 mL), an aqueous solution of 10 mM TCEP (Tokyo Chemical Industry Co., Ltd.) (0.231 mL; 6.0 equivalents per antibody molecule) and a 1 M aqueous dipotassium hydrogen phosphate solution (Nacalai Tesque, Inc.; 0.0855 mL) were added. After confirming that the solution had a pH within 7.0 ± 0.1, the interchain disulfide bond in the antibody was reduced by incubating the solution at 37°C for 2 hours.

[0273]

Conjugation between antibody and drug linker: The above-described solution was incubated at 15°C for 10 minutes. Subsequently, a 10 mM solution of N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]glycylglycyl-L-phenylalanyl-N-(2-[(1S,9S)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-

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yl]amino}-2-oxoethoxy)methyl]glycinamide in dimethyl sulfoxide (0.386 mL; 10 equivalents per antibody molecule) was added thereto, and the obtained mixture was incubated at 15°C for 1 hour to conjugate the drug linker to the antibody. Subsequently, an aqueous solution of 100 mM NAC (Sigma-Aldrich Co. LLC) (0.0347 mL; 9 equivalents per antibody molecule) was added thereto, and the obtained mixture was further stirred at room temperature for 20 minutes to terminate the reaction of the drug linker.

[0274]

Purification: The above-described solution was purified by common procedure D described in production method 1 to obtain 19 mL of a solution containing the title antibody-drug conjugate "H01L02-ADC".

[0275]

Characterization: Using common procedure E (using $\epsilon_{D,280} = 5440$ and $\epsilon_{D,370} = 21240$) described in production method 1, the following characteristic values were obtained.

Antibody concentration: 2.26 mg/mL, antibody yield: 42.9 mg (76%), average number of conjugated drug molecules (n) per antibody molecule measured by common procedure E: 5.9, and average number of conjugated drug molecules (n) per antibody molecule measured by common procedure F: 7.7.

[0276]

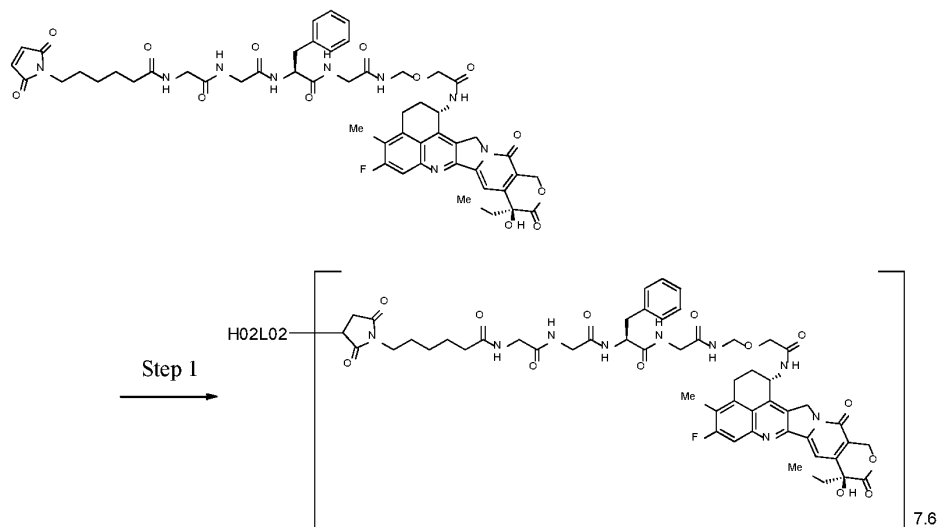
7)-2 Production of antibody-drug conjugate H02L02-DXd

Step 1: Antibody-drug conjugate (2)

[0277]

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[Formula 12]



[0278]

Reduction of antibody: H02L02 produced in Example 5 was adjusted to 9.95 mg/mL with PBS6.0/EDTA by using common procedures B (using 1.51 mLmg⁻¹cm⁻¹ as 280 nm absorption coefficient) and C described in production method 1. To this solution (5.7 mL), an aqueous solution of 10 mM TCEP (Tokyo Chemical Industry Co., Ltd.) (0.234 mL; 6.0 equivalents per antibody molecule) and a 1 M aqueous dipotassium hydrogen phosphate solution (Nacalai Tesque, Inc.; 0.0855 mL) were added. After confirming that the solution had a pH within 7.0 ± 0.1, the interchain disulfide bond in the antibody was reduced by incubating the solution at 37°C for 2 hours.

[0279]

Conjugation between antibody and drug linker: The above-described solution was incubated at 15°C for 10 minutes. Subsequently, a 10mM solution of N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]glycylglycyl-L-phenylalanyl-N-[(2-[(1S,9S)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-

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yl]amino}-2-oxoethoxy)methyl]glycinamide in dimethyl sulfoxide (0.389 mL; 10 equivalents per antibody molecule) was added thereto, and the obtained mixture was incubated at 15°C for 1 hour to conjugate the drug linker to the antibody. Subsequently, an aqueous solution of 100 mM NAC (Sigma-Aldrich Co. LLC) (0.0350 mL; 9 equivalents per antibody molecule) was added thereto, and the obtained mixture was further stirred at room temperature for 20 minutes to terminate the reaction of the drug linker.

[0280]

Purification: The above-described solution was purified by common procedure D described in production method 1 to obtain 19 mL of a solution containing the title antibody-drug conjugate "H02L02-ADC".

[0281]

Characterization: Using common procedure E (using $\epsilon_{D,280} = 5440$ and $\epsilon_{D,370} = 21240$) described in production method 1, the following characteristic values were obtained.

Antibody concentration: 2.61 mg/mL, antibody yield: 49.6 mg (87%), average number of conjugated drug molecules (n) per antibody molecule measured by common procedure E: 5.9, and average number of conjugated drug molecules (n) per antibody molecule measured by common procedure F: 7.6.

[0282]

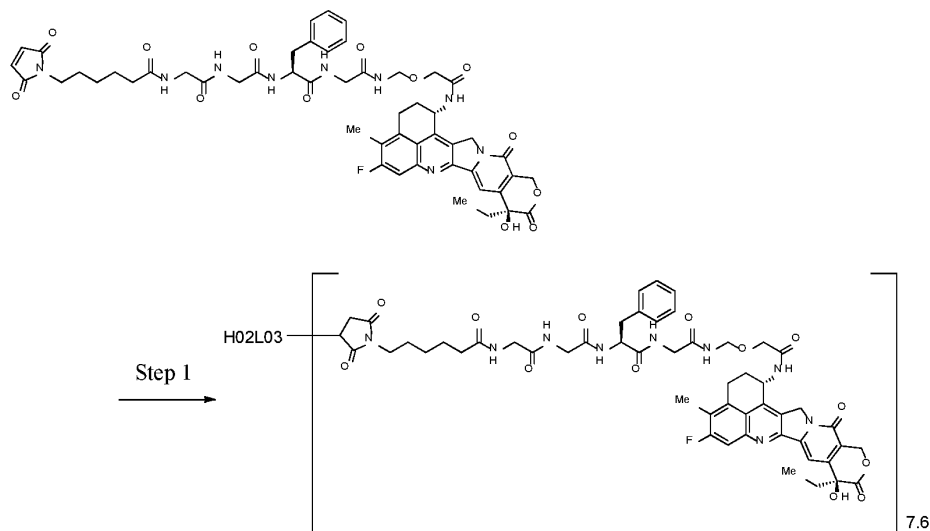
7)-3 Production of antibody-drug conjugate H02L03-DXd

Step 1: Antibody-drug conjugate (3)

[0283]

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[Formula 13]



[0284]

Reduction of antibody: H02L03 produced in Example 5 was adjusted to 9.86 mg/mL with PBS6.0/EDTA by using common procedures B (using 1.53 mLmg⁻¹cm⁻¹ as 280 nm absorption coefficient) and C described in production method 1. To this solution (5.7 mL), an aqueous solution of 10 mM TCEP (Tokyo Chemical Industry Co., Ltd.) (0.270 mL; 7.0 equivalents per antibody molecule) and a 1 M aqueous dipotassium hydrogen phosphate solution (Nacalai Tesque, Inc.; 0.0855 mL) were added. After confirming that the solution had a pH within 7.0 ± 0.1, the interchain disulfide bond in the antibody was reduced by incubating the solution at 37°C for 2 hours.

[0285]

Conjugation between antibody and drug linker: The above-described solution was incubated at 15°C for 10 minutes. Subsequently, a 10 mM solution of N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]glycylglycyl-L-phenylalanyl-N-[(2-[(1S,9S)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-

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yl]amino}-2-oxoethoxy)methyl]glycinamide in dimethyl sulfoxide (0.386 mL; 10 equivalents per antibody molecule) was added thereto, and the obtained mixture was incubated at 15°C for 1 hour to conjugate the drug linker to the antibody. Subsequently, an aqueous solution of 100 mM NAC (Sigma-Aldrich Co. LLC) (0.0347 mL; 9 equivalents per antibody molecule) was added thereto, and the obtained mixture was further stirred at room temperature for 20 minutes to terminate the reaction of the drug linker.

[0286]

Purification: The above-described solution was purified by common procedure D described in production method 1 to obtain 19 mL of a solution containing the title antibody-drug conjugate "H01L02-ADC".

[0287]

Characterization: Using common procedure E ((using $\epsilon_{D,280} = 5440$ and $\epsilon_{D,370} = 21240$) described in production method 1, the following characteristic values were obtained.

Antibody concentration: 2.71 mg/mL, antibody yield: 51.4 mg (91%), average number of conjugated drug molecules (n) per antibody molecule measured by common procedure E: 5.7, and average number of conjugated drug molecules (n) per antibody molecule measured by common procedure F: 7.6.

[0288]

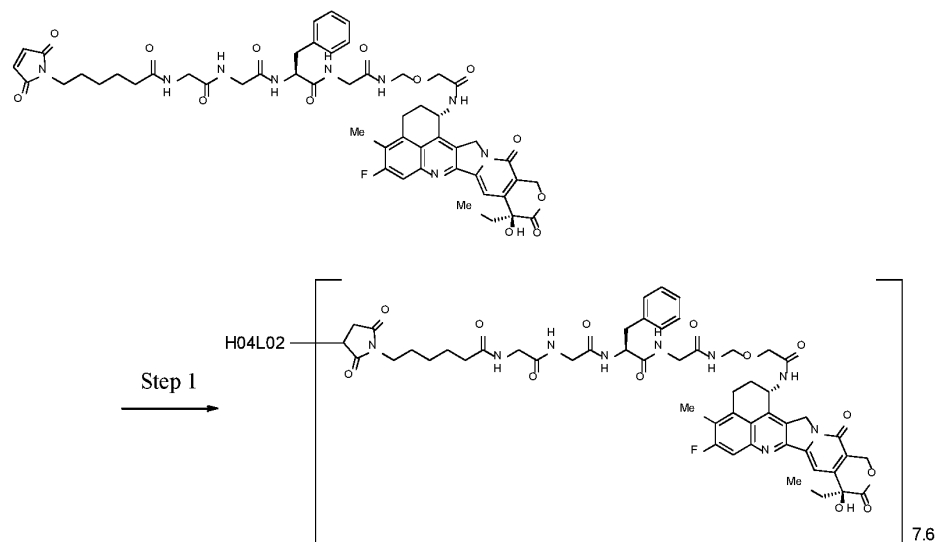
7)-4 Production of antibody-drug conjugate H04L02-DXd

Step 1: Antibody-drug conjugate (4)

[0289]

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[Formula 14]



[0290]

Reduction of antibody: H04L02 produced in Example 5 was adjusted to 9.86 mg/mL with PBS6.0/EDTA by using common procedures B (using $1.53 \text{ mLmg}^{-1}\text{cm}^{-1}$ as 280 nm absorption coefficient) and C described in production method 1. To this solution (5.7 mL), an aqueous solution of 10 mM TCEP (Tokyo Chemical Industry Co., Ltd.) (0.232 mL; 6.0 equivalents per antibody molecule) and a 1 M aqueous dipotassium hydrogen phosphate solution (Nacalai Tesque, Inc.; 0.0855 mL) were added. After confirming that the solution had a pH within 7.0 ± 0.1 , the interchain disulfide bond in the antibody was reduced by incubating the solution at 37°C for 2 hours.

[0291]

Conjugation between antibody and drug linker: The above-described solution was incubated at 15°C for 10 minutes. Subsequently, a 10 mM solution of N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]glycylglycyl-L-phenylalanyl-N-[(2-((1S,9S)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-

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hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-yl]amino}-2-oxoethoxy)methyl]glycinamide in dimethyl sulfoxide (0.386 mL; 10 equivalents per antibody molecule) was added thereto, and the obtained mixture was incubated at 15°C for 1 hour to conjugate the drug linker to the antibody. Subsequently, an aqueous solution of 100 mM NAC (Sigma-Aldrich Co. LLC) (0.0347 mL; 9 equivalents per antibody molecule) was added thereto, and the obtained mixture was further stirred at room temperature for 20 minutes to terminate the reaction of the drug linker.

[0292]

Purification: The above-described solution was purified by common procedure D described in production method 1 to obtain 19 mL of a solution containing the title antibody-drug conjugate "H04L02-ADC".

[0293]

Characterization: Using common procedure E (using $\epsilon_{D,280} = 5440$ and $\epsilon_{D,370} = 21240$) described in production method 1, the following characteristic values were obtained.

Antibody concentration: 2.56 mg/mL, antibody yield: 48.7 mg (87%), average number of conjugated drug molecules (n) per antibody molecule measured by common procedure E: 5.8, and average number of conjugated drug molecules (n) per antibody molecule measured by common procedure F: 7.6.

[0294]

[Reference Example 2: Production of NOV0712-drug conjugate]

Reference Example 2)-1 Production of antibody-drug conjugate NOV0712-DM4

Antibody-drug conjugate(5)

Conjugation between antibody and drug linker: NOV0712 produced in Reference Example 1 was adjusted to 9.7 mg/mL with 20 mM HEPES8.1 (HEPES, 1

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M Buffer Solution (20 mL) manufactured by Life Technologies Corp. was pH-adjusted to 8.1 with 1 M sodium hydroxide, and then brought to 1 L with distilled water) by using common procedures B (using $1.51 \text{ mLmg}^{-1}\text{cm}^{-1}$ as 280 nm absorption coefficient) and C described in production method 1. The solution was incubated at 20°C for 10 minutes. Subsequently, a 10 mM solution of 1-(2,5-dioxopyrrolidin-1-yloxy)-1-oxo-4-(pyridin-2-yl)disulfanylbutane-2-sulfonic acid described in WO2016/024195 in DMA (0.366 mL; 5.2 equivalents per antibody molecule), a 10 mM solution of N2-deacetyl-deacetyl-N2-(4-methyl-4-mercapto-1-oxopentyl)-maytansine (DM4) in DMA (0.366 mL; 6.8 equivalents per antibody molecule), and 0.243 mL of DMA were added thereto, and the obtained mixture was incubated at 20°C for 16 hours to conjugate the drug linker to the antibody. Subsequently, an aqueous solution of 1 M acetic acid was added thereto to adjust the pH to 5.0, and the obtained mixture was further stirred at room temperature for 20 minutes to terminate the reaction of the drug linker.

Purification: The above-described solution was purified by common procedure D described in production method 1 to obtain 28 mL of a solution containing the title antibody-drug conjugate "NOV0712-DM4".

Characterization: Using common procedure E (using $\epsilon_{A,280} = 200500$, $\epsilon_{A,252} = 76295$, $\epsilon_{D,280} = 43170$, and $\epsilon_{D,252} = 23224$) described in production method 1, the following characteristic values were obtained.

Antibody concentration: 2.58 mg/mL, antibody yield: 72.2 mg (93%), and average number of conjugated drug molecules (n) per antibody molecule measured by common procedure E: 3.0.

[0295]

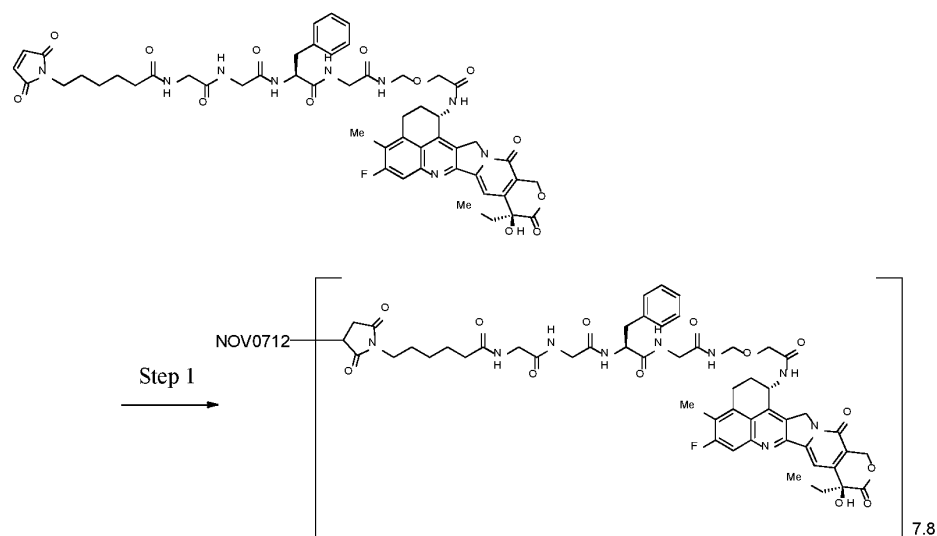
Reference Example 2)-2 Production of antibody-drug conjugate NOV0712-DXd

Step 1: Antibody-drug conjugate (6)

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[0296]

[Formula 15]



[0297]

Reduction of antibody: NOV0712 produced in Reference Example 1 was adjusted to 9.26 mg/mL with PBS6.0/EDTA by using common procedures B (using $1.5 \text{ mLmg}^{-1}\text{cm}^{-1}$ as 280 nm absorption coefficient) and C described in production method 1. To this solution (6.6 mL), an aqueous solution of 10 mM TCEP (Tokyo Chemical Industry Co., Ltd.) (0.254 mL; 6.0 equivalents per antibody molecule) and a 1 M aqueous dipotassium hydrogen phosphate solution (Nacalai Tesque, Inc.; 0.0990 mL) were added. After confirming that the solution had a pH within 7.0 ± 0.1 , the interchain disulfide bond in the antibody was reduced by incubating the solution at 37°C for 2 hours.

Conjugation between antibody and drug linker: The above-described solution was incubated at 15°C for 10 minutes. Subsequently, a 10 mM solution of N-[6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoyl]glycylglycyl-L-phenylalanyl-N-[(2-((1S,9S)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-1-

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yl]amino}-2-oxoethoxy)methyl]glycinamide in dimethyl sulfoxide (0.381 mL; 9 equivalents per antibody molecule) was added thereto, and the obtained mixture was incubated at 15°C for 1 hour to conjugate the drug linker to the antibody. Subsequently, an aqueous solution of 100 mM NAC (Sigma-Aldrich Co. LLC) (0.0381 mL; 9 equivalents per antibody molecule) was added thereto, and the obtained mixture was further stirred at room temperature for 20 minutes to terminate the reaction of the drug linker.

Purification: The above-described solution was purified by common procedure D described in production method 1 to obtain 23.5 mL of a solution containing the title antibody-drug conjugate "NOV0712-ADC".

Characterization: Using common procedure E (using $\epsilon_{D,280} = 5440$ and $\epsilon_{D,370} = 21240$) described in production method 1, the following characteristic values were obtained.

Antibody concentration: 2.26 mg/mL, antibody yield: 56.4 mg (92%), average number of conjugated drug molecules (n) per antibody molecule measured by common procedure E: 6.4, and average number of conjugated drug molecules (n) per antibody molecule measured by common procedure F: 7.8.

[0298]

[Example 8: Evaluation of *in vitro* activity of antibody-drug conjugate]

8)-1 Evaluation of *in vitro* cell growth inhibition activity of antibody-drug conjugate against CDH6-positive human tumor cell line

CDH6-positive human ovarian tumor cell line PA-1 was seeded over a 96-well plate at 2×10^3 cells/100 μ L/well in MEM medium supplemented with 10% FBS, and the cells were then cultured overnight under conditions of 37°C and 5% CO₂. On the next day, each of the 4 humanized hG019-drug conjugates (clone names: H01L02-DXd, H02L02-DXd, H02L03-DXd and H04L02-DXd) produced in Example 7, or the NOV0712-drug conjugate (NOV0712-DM4) produced in

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Reference Example 2 was added to the cells such that the final concentrations were from 0.0001 (nM) to 100 (nM). After culture for 4 days, the number of live cells was measured by the quantification of ATP using CellTiter-Glo(TM) Luminescent Cell Viability Assay (Promega Corp.). Figure 11 shows concentration-dependent cell growth inhibition activity when each antibody-drug conjugate was added to the cells. From this result, it was demonstrated that the 4 humanized hG019-drug conjugates exhibit growth inhibition activity against tumor cells from a lower addition concentration than that of the NOV0712-drug conjugate, and have high antitumor activity.

[0299]

[Example 9: *In vivo* antitumor effect of antibody-drug conjugate]

The antitumor effects of the antibody-drug conjugates were evaluated using animal models derived from immunodeficient mice by the inoculation of CDH6-positive human tumor cell line cells. Four- to 5-week-old BALB/c nude mice (CAnN.Cg-Foxnl[nu]/CrJCrJ[Foxnlnu/Foxnlnu], Charles River Laboratories Japan Inc.) and SCID mice (CB17/Icr-Prkdc[scid]/CrJCrJ, Charles River Laboratories Japan Inc.) were acclimatized for 3 days or longer under SPF conditions before use in the experiment. The mice were fed with a sterilized solid diet (FR-2, Funabashi Farms Co., Ltd) and given sterilized tap water (which had been prepared by adding a 5 to 15 ppm sodium hypochlorite solution to tap water). The long diameter and short diameter of the inoculated tumor were measured twice a week using electronic digital calipers (CD-15CX, Mitutoyo Corp.), and the volume of the tumor was then calculated according to the following expression.

$$\text{Tumor volume (mm}^3\text{)} = 1/2 \times \text{Long diameter (mm)} \times [\text{Short diameter (mm)}]^2$$

Each antibody-drug conjugate was diluted with ABS buffer (10 mM acetate buffer, 5% sorbitol, pH 5.5) (Nacalai Tesque, Inc.), and the dilution was intravenously administered at a dose shown in each Example to the tail of each

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mouse. ABS buffer was administered in the same manner as above to a control group (vehicle group). Six mice per group were used in the experiment.

[0300]

9)-1 Antitumor effect - (1)

The CDH6-positive human renal cell tumor cell line 786-O (ATCC), the CDH6 expression of which had been confirmed in Example 2)-3-1, was suspended in Matrigel (Corning Inc.), and the cell suspension was subcutaneously inoculated at a dose of 5×10^6 cells to the right flank region of each male SCID mouse (Day 0). On Day 18, the mice were randomly grouped. On the day of grouping, each of the 4 antibody-drug conjugates (clone names: H01L02-DXd, H02L02-DXd, H02L03-DXd and H04L02-DXd) produced in Example 7, or NOV0712-DM4 produced in Reference Example 2 was intravenously administered at a dose of 3 mg/kg to the tail of each mouse. The results are shown in Figure 12. The abscissa depicts the number of days, and the ordinate depicts tumor volume. The error range depicts a SE value.

NOV0712-DM4 exhibited no significant antitumor effect in this tumor model. All the 4 antibody-drug conjugates produced in Example 7 decreased tumor volume after administration, exerted significant tumor regression, and sustained the tumor regression effect for 24 days after administration (Figure 12).

[0301]

9)-2 Antitumor effect - (2)

The CDH6-positive human ovarian tumor cell line PA-1(ATCC), the CDH6 expression of which had been confirmed in Example 2)-3-1, was suspended in Matrigel (Corning Inc.), and the cell suspension was subcutaneously inoculated at a dose of 8.5×10^6 cells to the right flank region of each female nude mouse (Day 0). On Day 11, the mice were randomly grouped. On the day of grouping, the antibody-drug conjugate H01L02-DXd produced in Example 7, or NOV0712-DM4

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or NOV0712-DXd produced in Reference Example 2 was intravenously administered at doses of 1 or 3 mg/kg to the tail of each mouse. The results are shown in Figure 13. The abscissa depicts the number of days, and the ordinate depicts tumor volume. The error range depicts a SE value.

NOV0712-DM4 exhibited no antitumor effect at any of the doses of 1 and 3 mg/kg in this tumor model. On the other hand, H01L02-DXd significantly decreased tumor volume after administration at both the doses of 1 and 3 mg/kg and exerted a tumor regression effect (Figure 13). The H01L02 antibody obtained in the present description and the NOV0712 antibody were conjugated to the same drug DXd, and the medicinal effects of the resulting samples were compared. As a result, H01L02-DXd exerted a stronger antitumor effect than that of NOV0712-DXd at both the doses of 1 and 3 mg/kg. Specifically, it was demonstrated that the H01L02 antibody of the present invention is a superior antibody for antibody-drug conjugates as antitumor agents to the NOV0712 antibody (Figure 13).

[0302]

9)-3 Antitumor effect - (3)

The CDH6-positive human ovarian tumor cell line NIH:OVCAR-3 (ATCC), the CDH6 expression of which had been confirmed in Example 2)-3-1, was suspended in Matrigel (Corning Inc.), and the cell suspension was subcutaneously inoculated at a dose of 1×10^7 cells to the right flank region of each female nude mouse (Day 0). On Day 22, the mice were randomly grouped. On the day of grouping, the antibody-drug conjugate H01L02-DXd produced in Example 7, or NOV0712-DM4 produced in Reference Example 2 was intravenously administered at doses of 1 or 3 mg/kg to the tail of each mouse. The results are shown in Figure 14. The abscissa depicts the number of days, and the ordinate depicts tumor volume. The error range depicts a SE value.

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NOV0712-DM4 exhibited no antitumor effect at the dose of 1 mg/kg, and exhibited an antitumor effect at the dose of 3 mg/kg, though tumor regrowth was observed from 2 weeks after administration. On the other hand, H01L02-DXd significantly suppressed increase in tumor volume after administration at both the doses of 1 and 3 mg/kg, and sustained, particularly, at the dose of 3 mg/kg, the tumor growth inhibition effect over a long period of 31 days after administration (Figure 14).

[0303]

9)-4 Antitumor effect - (4)

The CDH6-positive human renal cell tumor cell line 786-O (ATCC), the CDH6 expression of which had been confirmed in Example 2)-3-1, was suspended in Matrigel (Corning Inc.), and the cell suspension was subcutaneously inoculated at a dose of 5×10^6 cells to the right flank region of each male SCID mouse (Day 0). On Day 20, the mice were randomly grouped. On the day of grouping, the antibody-drug conjugate H01L02-DXd produced in Example 7, or NOV0712-DM4 produced in Reference Example 2 was intravenously administered at doses of 1 or 3 mg/kg to the tail of each mouse. The results are shown in Figure 15. The abscissa depicts the number of days, and the ordinate depicts tumor volume. The error range depicts a SE value.

NOV0712-DM4 exhibited no significant antitumor effect at any of the doses of 1 and 3 mg/kg in this tumor model. On the other hand, H01L02-DXd decreased tumor volume after administration at both the doses of 1 and 3 mg/kg, and exerted, particularly, at the dose of 3 mg/kg, significant tumor regression, and sustained the tumor regression effect for 20 days after administration (Figure 15).

[0304]

9)-5 Antitumor effect - (5)

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The CDH6-negative human ovarian tumor cell line ES-2 (ATCC), the absence of the CDH6 expression of which had been confirmed in Example 2)-3-1, was suspended in physiological saline, and the cell suspension was subcutaneously inoculated at a dose of 1×10^6 cells to the right flank region of each female nude mouse (Day 0). On Day 7, the mice were randomly grouped. On the day of grouping, the antibody-drug conjugate H01L02-DXd produced in Example 7, or NOV0712-DM4 produced in Reference Example 2 was intravenously administered at doses of 1 or 3 mg/kg to the tail of each mouse. The results are shown in Figure 16. The abscissa depicts the number of days, and the ordinate depicts tumor volume. The error range depicts a SE value.

In this tumor model expressing no CDH6, H01L02-DXd and NOV0712-DM4 exhibited no antitumor effect at any of the doses. From this result, the antitumor effect of the antibody-drug conjugate in the CDH6-positive tumor model demonstrated in Examples 9)-1, 9)-2, 9)-3, and 9)-4 is an effect dependent on CDH6 expression in the tumor cells. Thus, the antibody-drug conjugate of the present invention is considered as a selective and safe antitumor drug that specifically exhibits an antitumor effect on CDH6-positive tumor without causing cytotoxicity to CDH6-negative normal tissues (Figure 16).

[Industrial Applicability]

[0305]

The present invention provides an anti-CDH6 antibody having internalization activity and an antibody-drug conjugate comprising the antibody. The antibody-drug conjugate can be used as a therapeutic drug for cancer, and the like.

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[Document Name] Claims

[Claim 1]

An antibody specifically binding to the amino acid sequence shown in SEQ ID NO: 4 and having internalization ability that permits cellular uptake, or a functional fragment of the antibody.

[Claim 2]

The antibody or the functional fragment of the antibody according to claim 1, which has competitive inhibitory activity, for binding to the amino acid sequence shown in SEQ ID NO: 4, against at least any one antibody selected from the group consisting of the following antibodies (1) to (5):

- (1) an antibody having a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 53 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 56,
- (2) an antibody having a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 69,
- (3) an antibody having a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 73,
- (4) an antibody having a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 65 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 73, and
- (5) an antibody having a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 77.

[Claim 3]

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The antibody or the functional fragment of the antibody according to claim 1 or 2, which comprises CDRL1, CDRL2 and CDRL3 in any one combination selected from the group consisting of the following combinations (1) to (4):

(1) CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 12, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 13, and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 14,

(2) CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 22, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 23, and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 24,

(3) CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 32, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 33, and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 34, and

(4) CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 42, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 43, and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 44, and

CDRH1, CDRH2 and CDRH3 in any one combination selected from the group consisting of the following combinations (5) to (9):

(5) CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 17, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 18, and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 19,

(6) CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 27, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 28, and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 29,

(7) CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 37, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 38, and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 39,

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(8) CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 47, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 48, and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 49, and
(9) CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 17, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 60, and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 19.

[Claim 4]

The antibody or the functional fragment of the antibody according to any one of claims 1 to 3, which comprises CDRL1, CDRL2 and CDRL3, and CDRH1, CDRH2 and CDRH3 in any combination selected from the group consisting of the following combinations (1) to (5):

- (1) CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 12, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 13, and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 14, and CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 17, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 18, and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 19,
- (2) CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 22, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 23, and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 24, and CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 27, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 28, and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 29,
- (3) CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 32, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 33, and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 34, and CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 37, CDRH2 consisting

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of the amino acid sequence shown in SEQ ID NO: 38, and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 39,

(4) CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 42, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 43, and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 44, and CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 47, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 48, and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 49, and

(5) CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 12, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 13, and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 14, and CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 17, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 60, and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 19.

[Claim 5]

The antibody or the functional fragment of the antibody according to any one of claims 1 to 4, which is humanized.

[Claim 6]

The antibody or the functional fragment of the antibody according to any one of claims 1 to 5, which has any one light chain variable region selected from the group consisting of the following variable regions (1) to (4):

(1) a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 63,

(2) a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 67,

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(3) an amino acid sequence having a sequence identity of at least 95% or more to the sequence of a framework region other than at each CDR sequence in the amino acid sequences of (1) and (2), and

(4) an amino acid sequence comprising a deletion, substitution or addition of one or several amino acids in the sequence of a framework region other than at each CDR sequence in the amino acid sequences of (1) to (3), and

any one heavy chain variable region selected from the group consisting of the following variable regions (5) to (9):

(5) a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 71,

(6) a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 75,

(7) a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 79,

(8) an amino acid sequence having a sequence homology of at least 95% or more to the sequence of a framework region other than at each CDR sequence in the amino acid sequences of (5) to (7), and

(9) an amino acid sequence comprising a deletion, substitution or addition of one or several amino acids in the sequence of a framework region other than at each CDR sequence in the amino acid sequences of (5) to (8).

[Claim 7]

The antibody or the functional fragment of the antibody according to any one of claims 1 to 6, which comprises a light chain variable region and a heavy chain variable region in any of the following combinations (1) to (4):

(1) a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 63 and a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 71,

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(2) a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 63 and a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 75,

(3) a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 67 and a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 75, and

(4) a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 63 and a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 79.

[Claim 8]

The antibody or the functional fragment of the antibody according to any one of claims 1 to 7, which has any of the following combinations (1) to (4):

(1) a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 69,

(2) a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 73,

(3) a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 65 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 73, and

(4) a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 77.

[Claim 9]

The antibody or the functional fragment of the antibody according to claim 8, which has a light chain consisting of the amino acid sequence at positions 21 to 233

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in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 69.

[Claim 10]

The antibody or the functional fragment of the antibody according to claim 8, which has a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 73.

[Claim 11]

The antibody or the functional fragment of the antibody according to claim 8, which has a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 65 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 73.

[Claim 12]

The antibody or the functional fragment of the antibody according to claim 8, which has a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 77.

[Claim 13]

The functional fragment of the antibody according to any one of claims 1 to 12, wherein the functional fragment is selected from the group consisting of Fab, F(ab')₂, Fab' and Fv.

[Claim 14]

A polynucleotide encoding the antibody or the functional fragment of the antibody according to any one of claims 1 to 13.

[Claim 15]

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The polynucleotide according to claim 14, which comprises polynucleotides in any one combination selected from the group consisting of the following combinations (1) to (5):

(1) a polynucleotide encoding a light chain variable region comprising CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 12, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 13 and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 14, and a polynucleotide encoding a heavy chain variable region comprising CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 17, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 18 and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 19,

(2) a polynucleotide encoding a light chain variable region comprising CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 22, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 23 and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 24, and a polynucleotide encoding a heavy chain variable region comprising CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 27, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 28 and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 29,

(3) a polynucleotide encoding a light chain variable region comprising CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 32, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 33 and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 34, and a polynucleotide encoding a heavy chain variable region comprising CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 37, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 38 and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 39,

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(4) a polynucleotide encoding a light chain variable region comprising CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 42, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 43 and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 44, and a polynucleotide encoding a heavy chain variable region comprising CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 47, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 48 and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 49, and

(5) a polynucleotide encoding a light chain variable region comprising CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 12, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 13 and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 14, and a polynucleotide encoding a heavy chain variable region comprising CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 17, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 60 and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 19.

[Claim 16]

The polynucleotide according to claim 14 or 15, which comprises a polynucleotide encoding a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a polynucleotide encoding a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 69.

[Claim 17]

The polynucleotide according to claim 14 or 15, which comprises a polynucleotide encoding a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a polynucleotide encoding a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 73.

[Claim 18]

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The polynucleotide according to claim 14 or 15, which comprises a polynucleotide encoding a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 65 and a polynucleotide encoding a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 73.

[Claim 19]

The polynucleotide according to claim 14 or 15, which comprises a polynucleotide encoding a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a polynucleotide encoding a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 77.

[Claim 20]

An expression vector comprising the polynucleotide according to any one of claims 14 to 19.

[Claim 21]

Host cells transformed with the expression vector according to claim 20.

[Claim 22]

The host cells according to claim 21, wherein the host cells are eukaryotic cells.

[Claim 23]

A method for producing an antibody of interest or a functional fragment of the antibody, which comprises the step of culturing the host cells according to claim 21 or 22, and the step of collecting an antibody of interest or a functional fragment of the antibody from the culture obtained by the aforementioned step.

[Claim 24]

The antibody or the functional fragment of the antibody according to any one of claims 1 to 13, wherein the heavy chain or the light chain has undergone one or two or more modifications selected from the group consisting of N-linked glycosylation, O-linked glycosylation, N-terminal processing, C-terminal processing,

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deamidation, isomerization of aspartic acid, oxidation of methionine, addition of a methionine residue to the N-terminus, amidation of a proline residue, conversion of N-terminal glutamine or N-terminal glutamic acid to pyroglutamic acid, and a deletion of one or two amino acids from the carboxyl terminus.

[Claim 25]

The antibody according to claim 24, wherein one or two amino acids are deleted from the carboxyl terminus of a heavy chain thereof.

[Claim 26]

The antibody according to claim 25, wherein one amino acid is deleted from each of the carboxyl termini of both of the heavy chains thereof.

[Claim 27]

The antibody according to any one of claims 24 to 26, wherein a proline residue at the carboxyl terminus of a heavy chain thereof is further amidated.

[Claim 28]

The antibody or the functional fragment of the antibody according to any one of claims 1 to 13 and 24 to 27, wherein sugar chain modification is regulated in order to enhance antibody-dependent cellular cytotoxic activity.

[Claim 29]

An antibody-drug conjugate comprising the antibody or the functional fragment of the antibody according to any one of claims 1 to 13 and 24 to 28 conjugated to a drug.

[Claim 30]

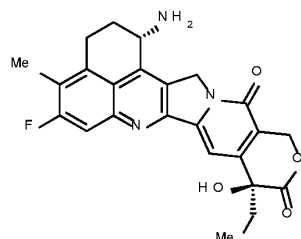
The antibody-drug conjugate according to claim 29, wherein the drug is an antitumor compound.

[Claim 31]

The antibody-drug conjugate according to claim 30, wherein the antitumor compound is an antitumor compound represented by the following formula:

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[Formula 1]



[Claim 32]

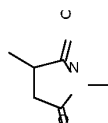
The antibody-drug conjugate according to any one of claims 29 to 31, wherein the antibody is conjugated to the drug via a linker having any structure selected from the group consisting of the following formulas (a) to (f):

- (a) -(Succinimid-3-yl-N)-CH₂CH₂-C(=O)-GGFG-NH-CH₂CH₂CH₂-C(=O)-,
- (b) -(Succinimid-3-yl-N)-CH₂CH₂CH₂CH₂CH₂-C(=O)-GGFG-NH-CH₂CH₂CH₂-C(=O)-,
- (c) -(Succinimid-3-yl-N)-CH₂CH₂CH₂CH₂CH₂-C(=O)-GGFG-NH-CH₂-O-CH₂-C(=O)-,
- (d) -(Succinimid-3-yl-N)-CH₂CH₂CH₂CH₂CH₂-C(=O)-GGFG-NH-CH₂CH₂-O-CH₂-C(=O)-,
- (e) -(Succinimid-3-yl-N)-CH₂CH₂-C(=O)-NH-CH₂CH₂O-CH₂CH₂O-CH₂CH₂-C(=O)-GGFG-NH-CH₂CH₂CH₂-C(=O)-, and
- (f) -(Succinimid-3-yl-N)-CH₂CH₂-C(=O)-NH-CH₂CH₂O-CH₂CH₂O-CH₂CH₂O-CH₂CH₂O-CH₂CH₂-C(=O)-GGFG-NH-CH₂CH₂CH₂-C(=O)-,

wherein the antibody is connected to the terminus of -(Succinimid-3-yl-N), the antitumor compound is connected to the carbonyl group of the -(CH₂)_n²-C(=O)- moiety with the nitrogen atom of the amino group at position 1 as a connecting position, GGFG represents an amino acid sequence consisting of glycine-glycine-phenylalanine-glycine linked through peptide bonds, and -(Succinimid-3-yl-N)- has a structure represented by the following formula:

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[Formula 2]



which is connected to the antibody at position 3 thereof and is connected to a methylene group in the linker structure containing this structure on the nitrogen atom at position 1.

[Claim 33]

The antibody-drug conjugate according to any one of claims 29 to 32, wherein the linker is represented by any formula selected from the group consisting of the following formulas (c), (d) and (e):

(c) -(Succinimid-3-yl-N)-CH₂CH₂CH₂CH₂CH₂-C(=O)-GGFG-NH-CH₂-O-CH₂-C(=O)-,

(d) -(Succinimid-3-yl-N)-CH₂CH₂CH₂CH₂CH₂-C(=O)-GGFG-NH-CH₂CH₂-O-CH₂-C(=O)-, and

(e) -(Succinimid-3-yl-N)-CH₂CH₂-C(=O)-NH-CH₂CH₂O-CH₂CH₂O-CH₂CH₂-C(=O)-GGFG-NH-CH₂CH₂CH₂-C(=O)-.

[Claim 34]

The antibody-drug conjugate according to any one of claims 29 to 33, wherein the linker is represented by the following formula (c) or (e):

(c) -(Succinimid-3-yl-N)-CH₂CH₂CH₂CH₂CH₂-C(=O)-GGFG-NH-CH₂-O-CH₂-C(=O)-, and

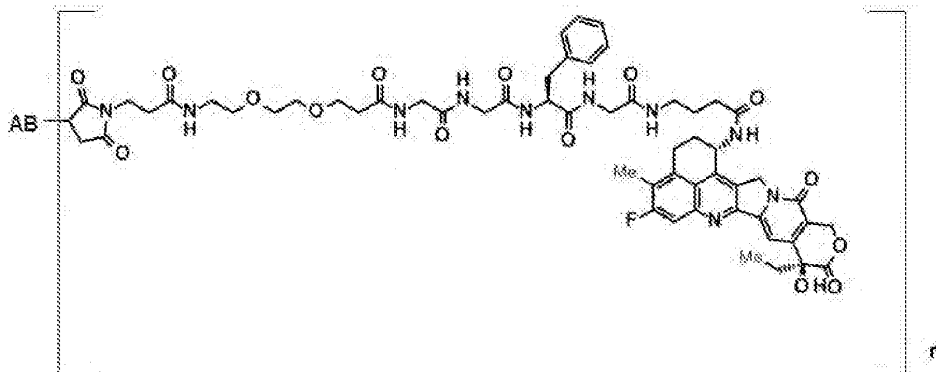
(e) -(Succinimid-3-yl-N)-CH₂CH₂-C(=O)-NH-CH₂CH₂O-CH₂CH₂O-CH₂CH₂-C(=O)-GGFG-NH-CH₂CH₂CH₂-C(=O)-.

[Claim 35]

The antibody-drug conjugate according to any one of claims 29 to 34, which has a structure represented by the following formula:

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[Formula 3]

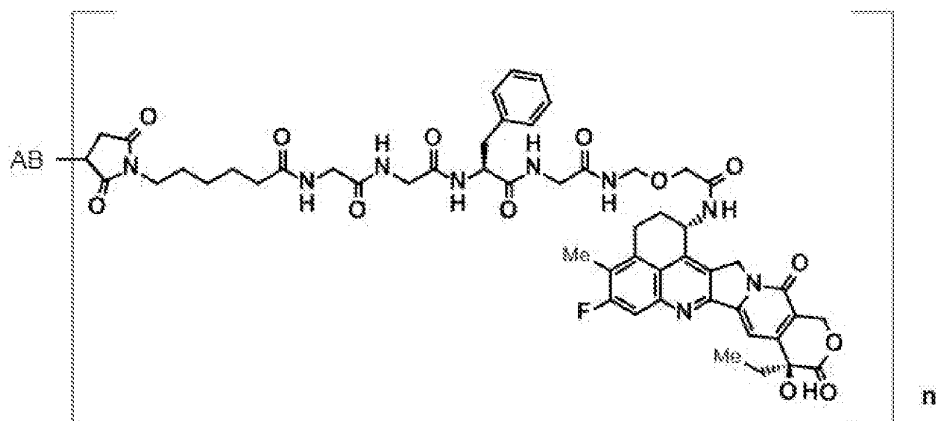


wherein AB represents the antibody or the functional fragment of the antibody, n represents the average number of units of the drug-linker structure conjugated to the antibody per antibody, and the antibody is connected to the linker via a sulfhydryl group derived from the antibody.

[Claim 36]

The antibody-drug conjugate according to any one of claims 29 to 34, which has a structure represented by the following formula:

[Formula 4]



wherein AB represents the antibody or the functional fragment of the antibody, n represents the average number of units of the drug-linker structure conjugated to the

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antibody per antibody, and the antibody is connected to the linker via a sulfhydryl group derived from the antibody.

[Claim 37]

The antibody-drug conjugate according to any one of claims 29 to 36, wherein the antibody is an antibody comprising a light chain and a heavy chain in any one combination selected from the group consisting of the following combinations (1) to (4), or a functional fragment of the antibody:

- (1) a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 69,
- (2) a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 73,
- (3) a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 65 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 73, and
- (4) a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 77.

[Claim 38]

The antibody-drug conjugate according to claim 37, wherein the antibody is an antibody comprising a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 69, or a functional fragment of the antibody.

[Claim 39]

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The antibody-drug conjugate according to claim 37, wherein the antibody is an antibody comprising a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 77, or a functional fragment of the antibody.

[Claim 40]

The antibody-drug conjugate according to any one of claims 29 to 39, wherein the heavy chain or the light chain has undergone one or two or more modifications selected from the group consisting of N-linked glycosylation, O-linked glycosylation, N-terminal processing, C-terminal processing, deamidation, isomerization of aspartic acid, oxidation of methionine, addition of a methionine residue to the N-terminus, amidation of a proline residue, conversion of N-terminal glutamine or N-terminal glutamic acid to pyroglutamic acid, and a deletion of one or two amino acids from the carboxyl terminus.

[Claim 41]

The antibody-drug conjugate according to any one of claims 29 to 40, wherein the average number of units of the selected drug-linker structure conjugated per antibody is in the range of from 1 to 10.

[Claim 42]

The antibody-drug conjugate according to claim 41, wherein the average number of units of the selected drug-linker structure conjugated per antibody is in the range of from 2 to 8.

[Claim 43]

The antibody-drug conjugate according to claim 42, wherein the average number of units of the selected drug-linker structure conjugated per antibody is in the range of from 5 to 8.

[Claim 44]

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The antibody-drug conjugate according to claim 43, wherein the average number of units of the selected drug-linker structure conjugated per antibody is in the range of from 7 to 8.

[Claim 45]

A pharmaceutical composition comprising the antibody-drug conjugate according to any one of claims 29 to 44, a salt thereof, or a hydrate of the conjugate or the salt.

[Claim 46]

The pharmaceutical composition according to claim 45, which is an antitumor drug.

[Claim 47]

The antitumor drug according to claim 46, wherein the tumor is a tumor expressing CDH6.

[Claim 48]

The antitumor drug according to claim 46 or 47, wherein the tumor is renal cell carcinoma, renal clear cell carcinoma, papillary renal cell carcinoma, ovarian cancer, ovarian serous adenocarcinoma or thyroid cancer.

[Claim 49]

A method for treating a tumor, which comprises administering any component selected from the antibody-drug conjugate according to any one of claims 29 to 44, a salt thereof, and a hydrate of the conjugate or the salt to an individual.

[Claim 50]

The treatment method according to claim 49, wherein the tumor is a tumor expressing CDH6.

[Claim 51]

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The treatment method according to claim 49 or 50, wherein the tumor is renal cell carcinoma, renal clear cell carcinoma, papillary renal cell carcinoma, ovarian cancer, ovarian serous adenocarcinoma or thyroid cancer.

[Claim 52]

A method for treating a tumor, which comprises administering a pharmaceutical composition comprising at least one component selected from the antibody-drug conjugate according to any one of claims 29 to 44, a salt thereof, and a hydrate of the conjugate or the salt, and at least one antitumor drug to an individual, simultaneously, separately, or continuously.

[Claim 53]

A method for producing an antibody-drug conjugate, which comprises the step of culturing the host cells according to claim 21 or 22, the step of collecting an antibody of interest or a functional fragment of the antibody from the culture obtained by the aforementioned step, and the step of reacting the antibody or the functional fragment of the antibody obtained by the aforementioned step with a drug-linker intermediate compound.

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[Document Name] Abstract

[Abstract]

[Problem to be solved]

It is an object of the present invention to provide an antibody binding to CDH6 and having internalization activity, an antibody-drug conjugate of the antibody and a drug having antitumor activity, a pharmaceutical product comprising the antibody-drug conjugate and having therapeutic effects on a tumor, a method for treating a tumor using the antibody, the antibody-drug conjugate or the pharmaceutical product, and the like.

[Solution]

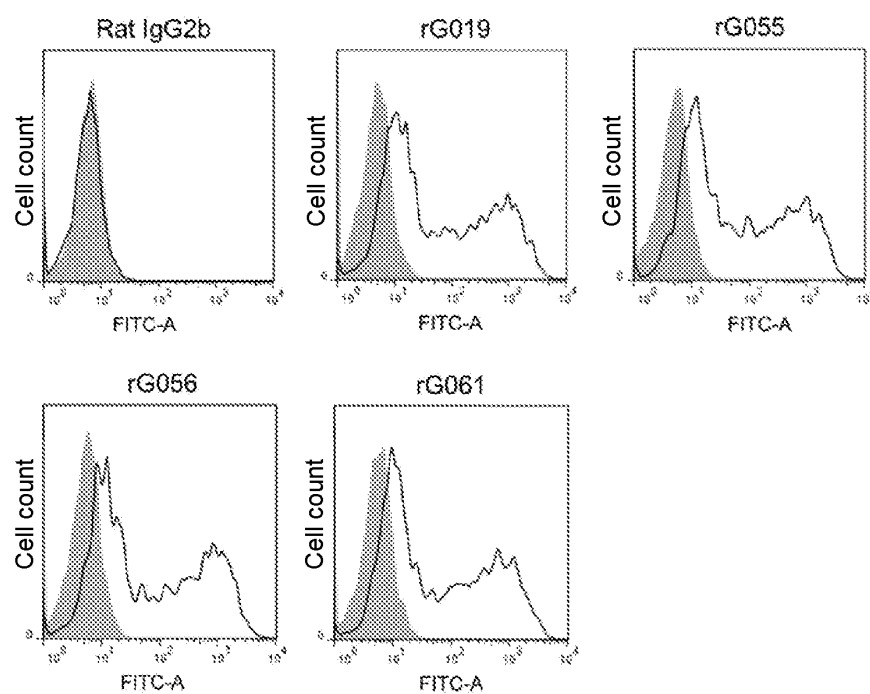
The above problem can be solved by an anti-CDH6 antibody having internalization activity, and an antibody-drug conjugate of the antibody and a drug having antitumor activity.

[Selected Drawing] None

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[Document Name] Figures

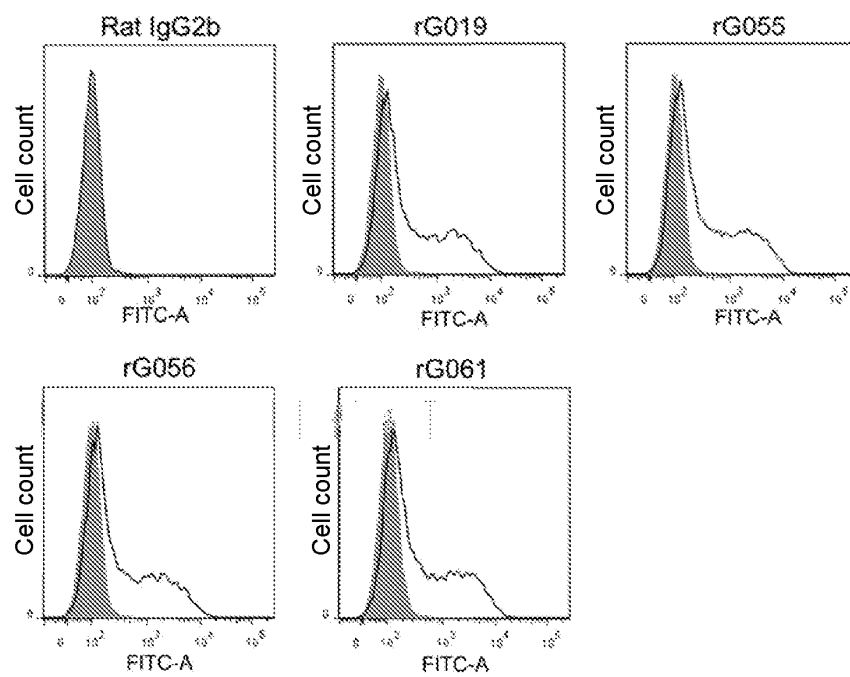
[Figure 1]



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[Figure 2-1]

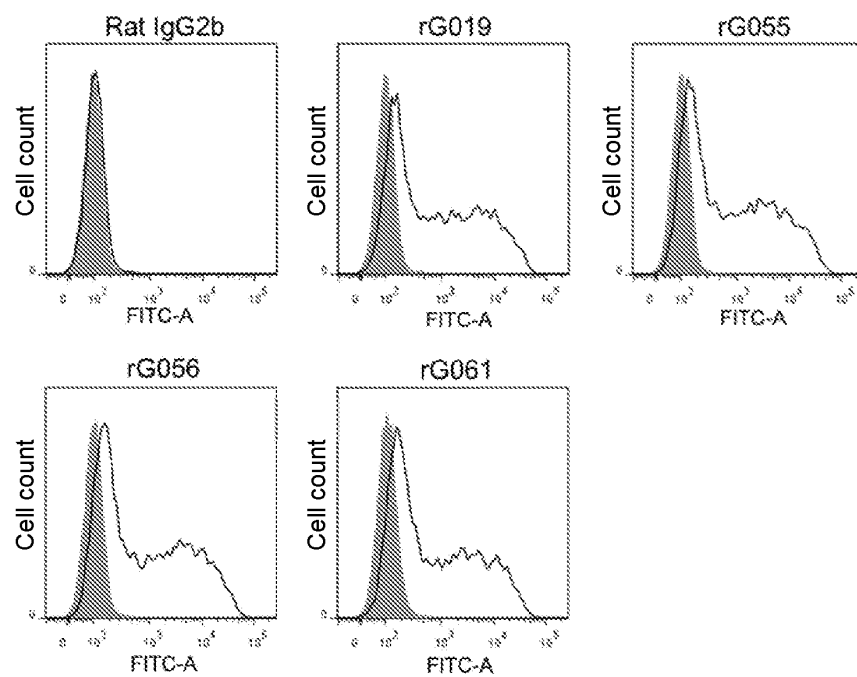
(1) Control cell or full-length hCDH6-transfected cell



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[Figure 2-2]

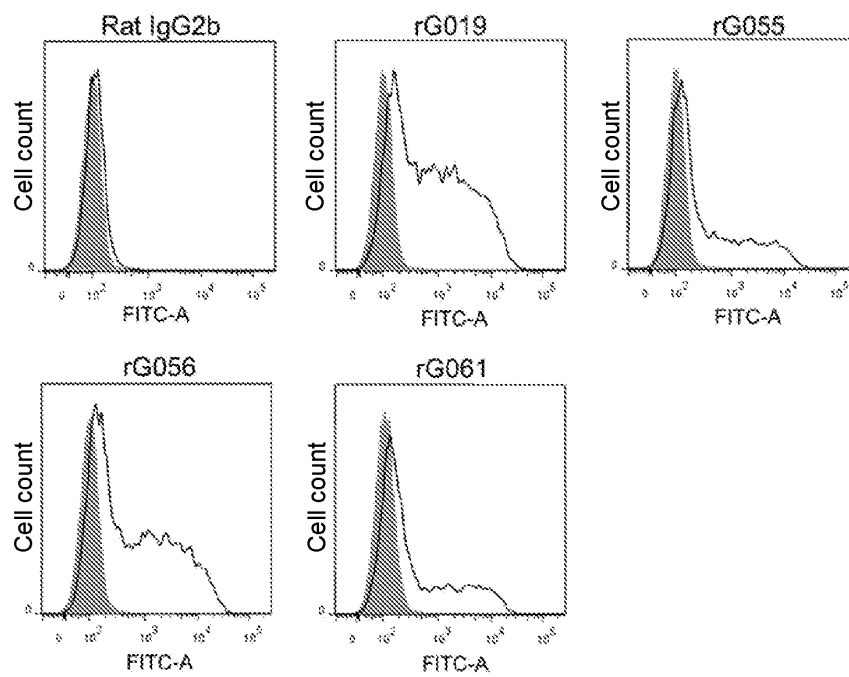
(2) Control cell or EC1-deleted hCDH6-transfected cell



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[Figure 2-3]

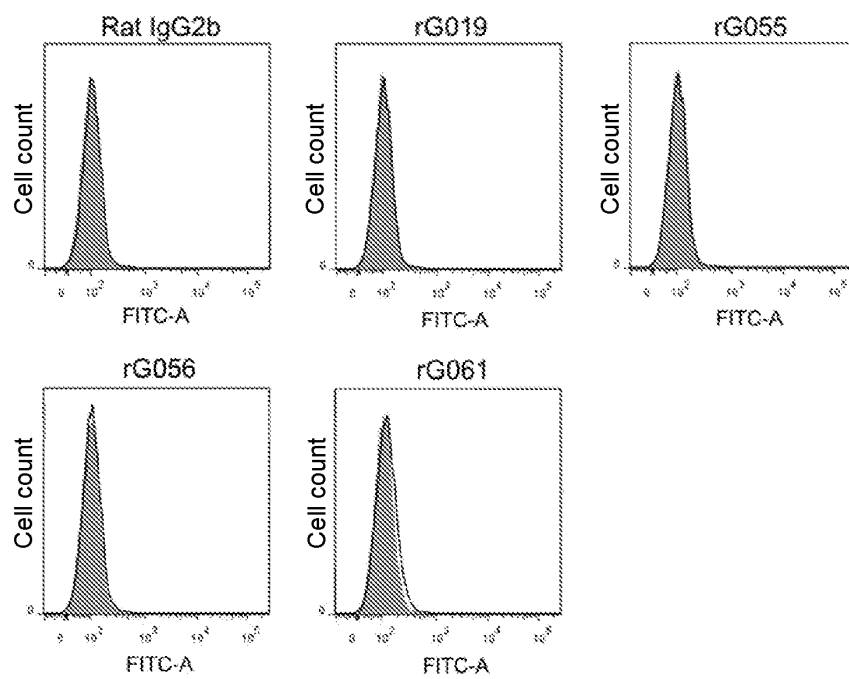
(3) Control cell or EC2-deleted hCDH6-transfected cell



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[Figure 2-4]

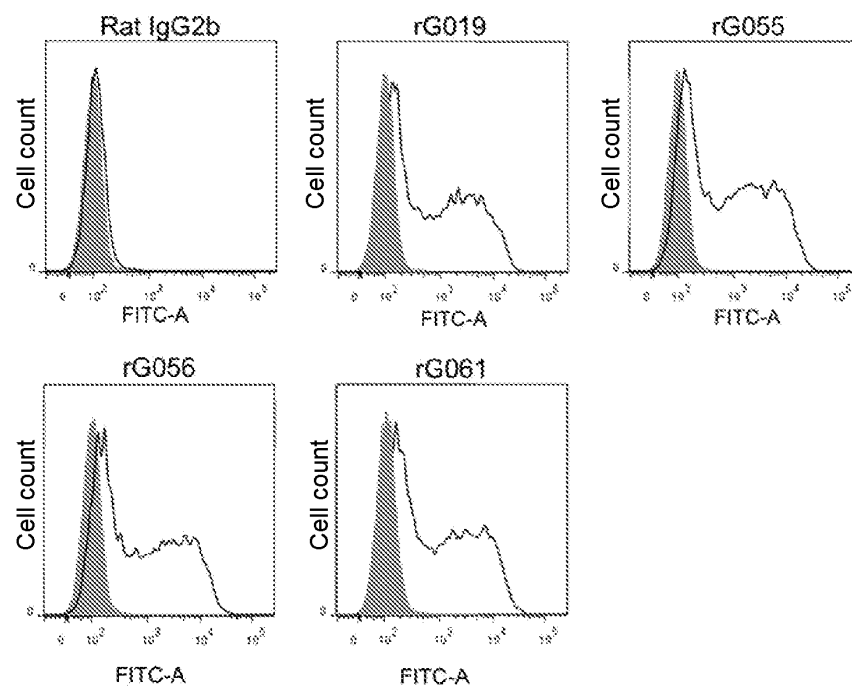
(4) Control cell or EC3-deleted hCDH6-transfected cell



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[Figure 2-5]

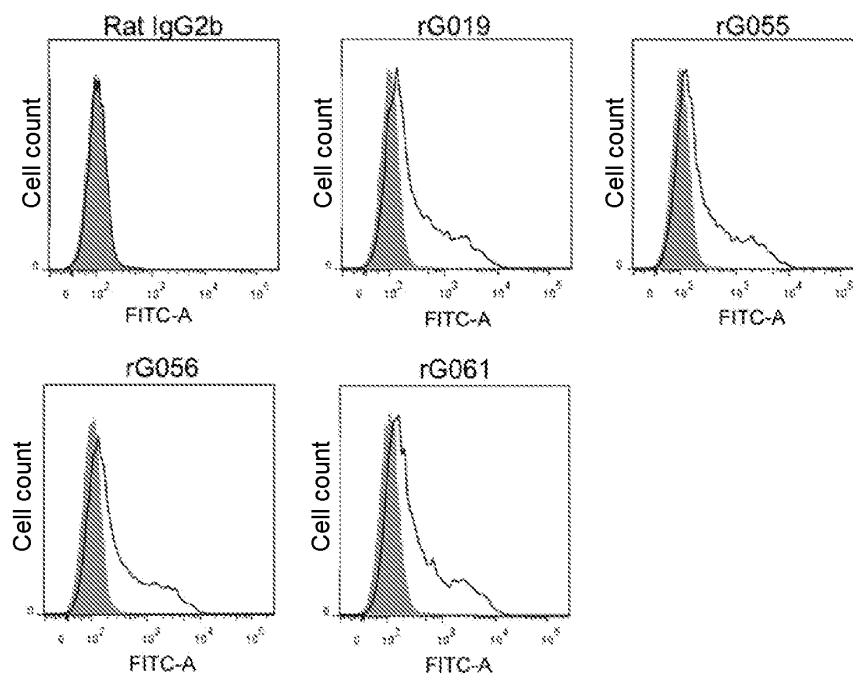
(5) Control cell or EC4-deleted hCDH6-transfected cell



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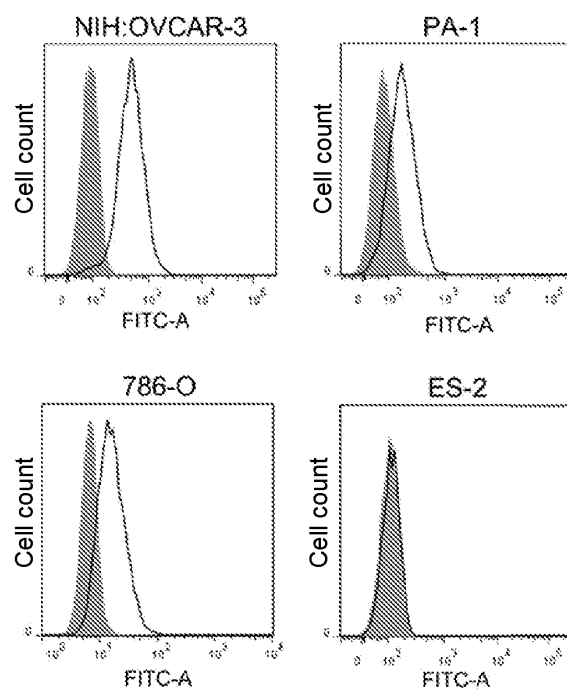
[Figure 2-6]

(6) Control cell or EC5-deleted hCDH6-transfected cell



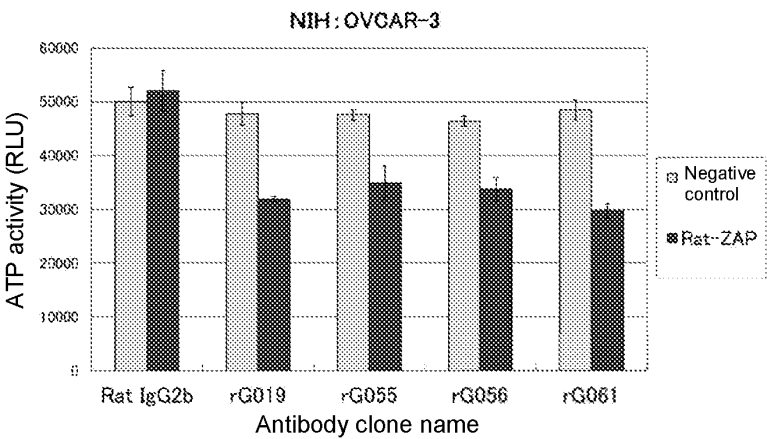
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[Figure 3]



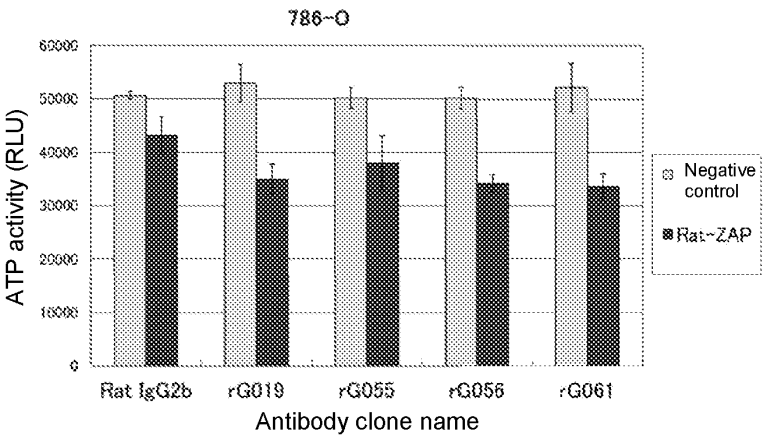
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[Figure 4]



NIH:OVCAR-3 cell survival rate using Rat-ZAP (%)

Rat IgG2b	rG019	rG055	rG056	rG061
104.1	66.8	73.3	72.8	61.2

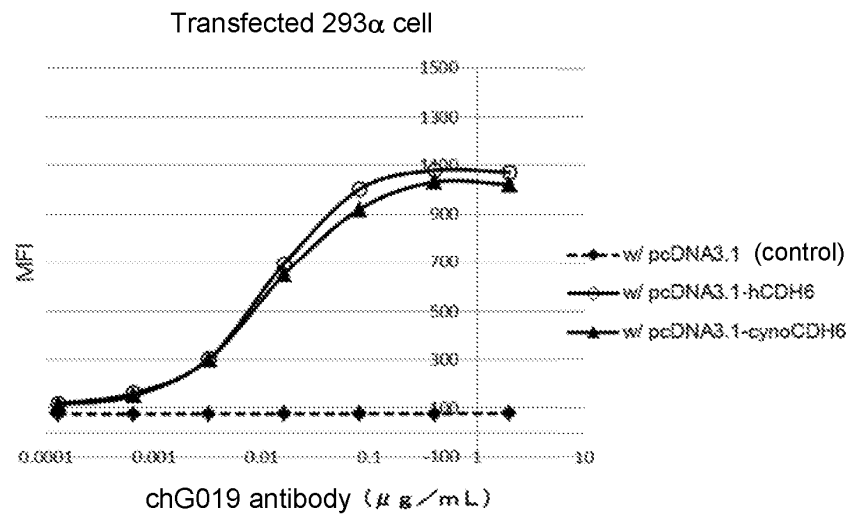


786-O cell survival rate using Rat-ZAP (%)

Rat IgG2b	rG019	rG055	rG056	rG061
85.2	66.1	75.7	68.1	64.2

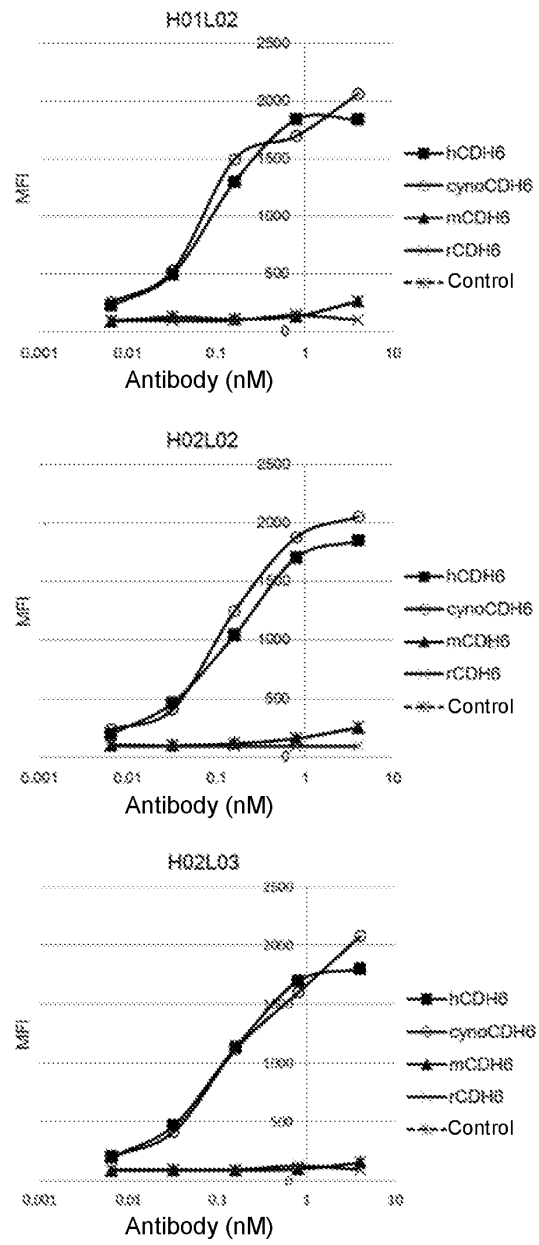
10/29

[Figure 5]



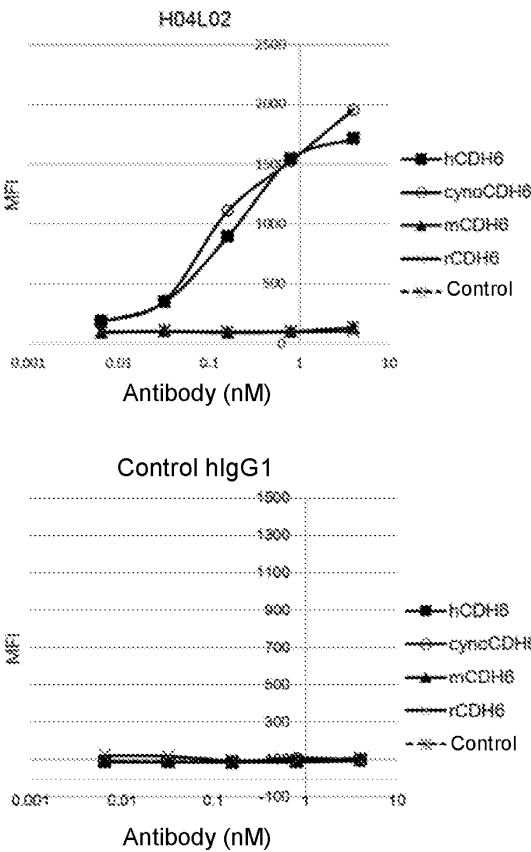
11/29

[Figure 6-1]



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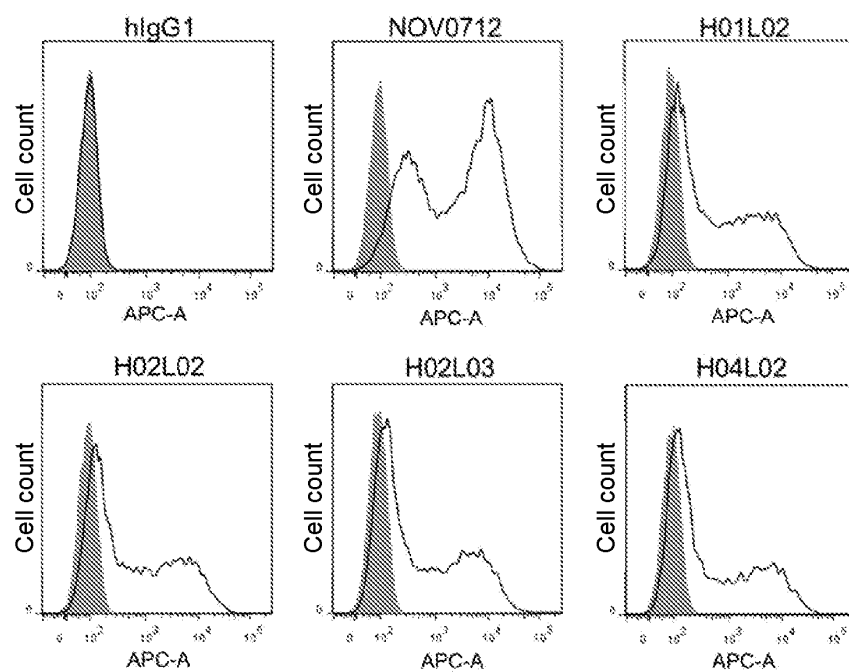
[Figure 6-2]



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[Figure 7-1]

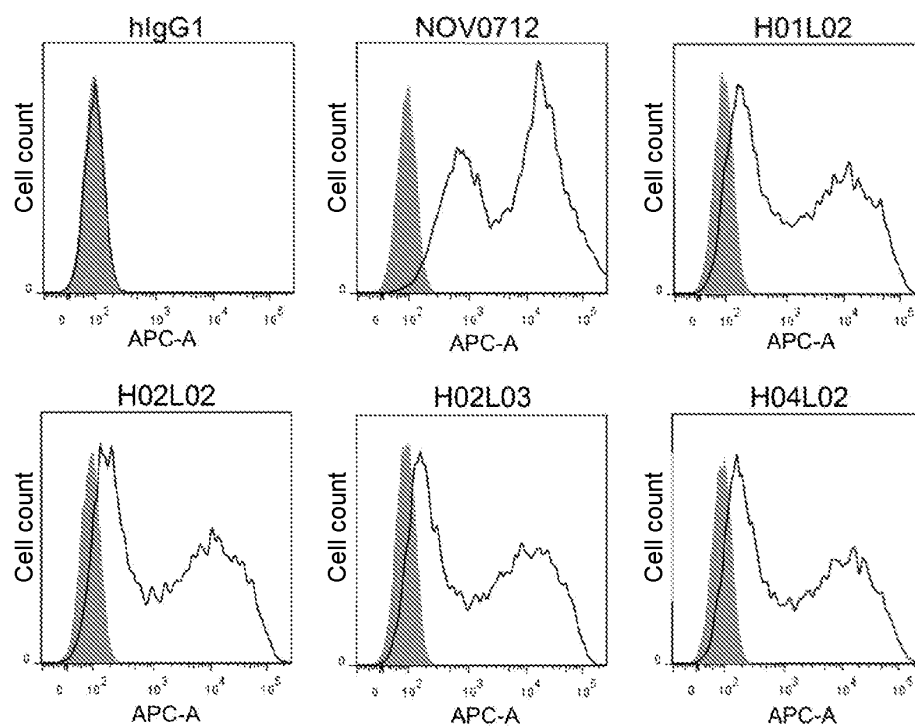
(1) Control cell or full-length hCDH6-transfected cell



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[Figure 7-2]

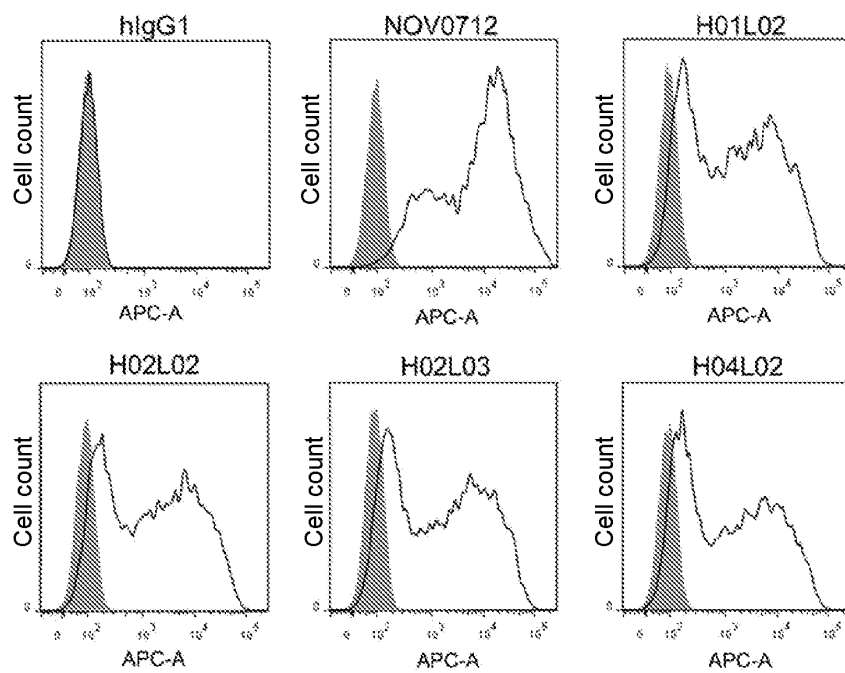
(2) Control cell or EC1-deleted hCDH6-transfected cell



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[Figure 7-3]

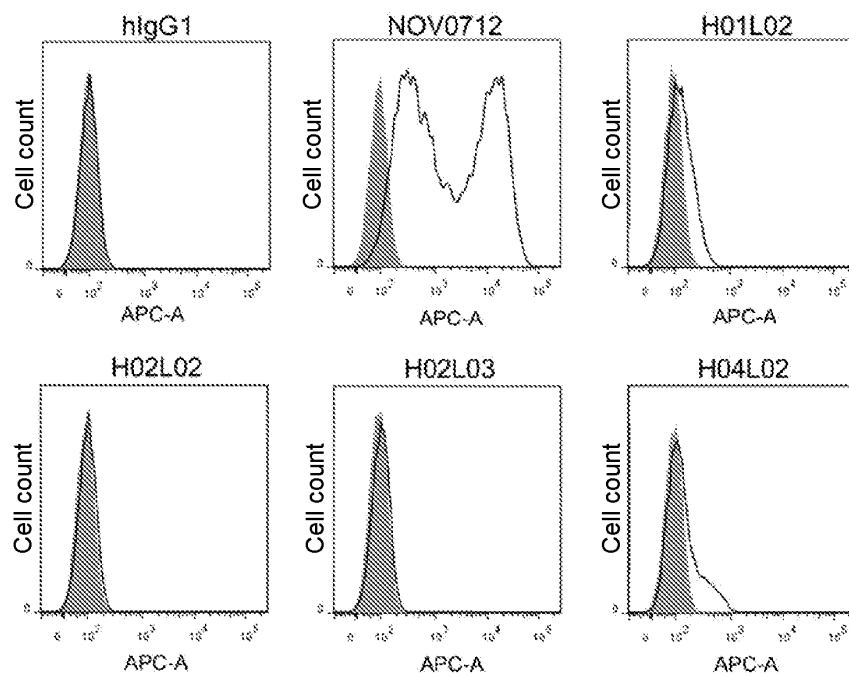
(3) Control cell or EC2-deleted hCDH6-transfected cell



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[Figure 7-4]

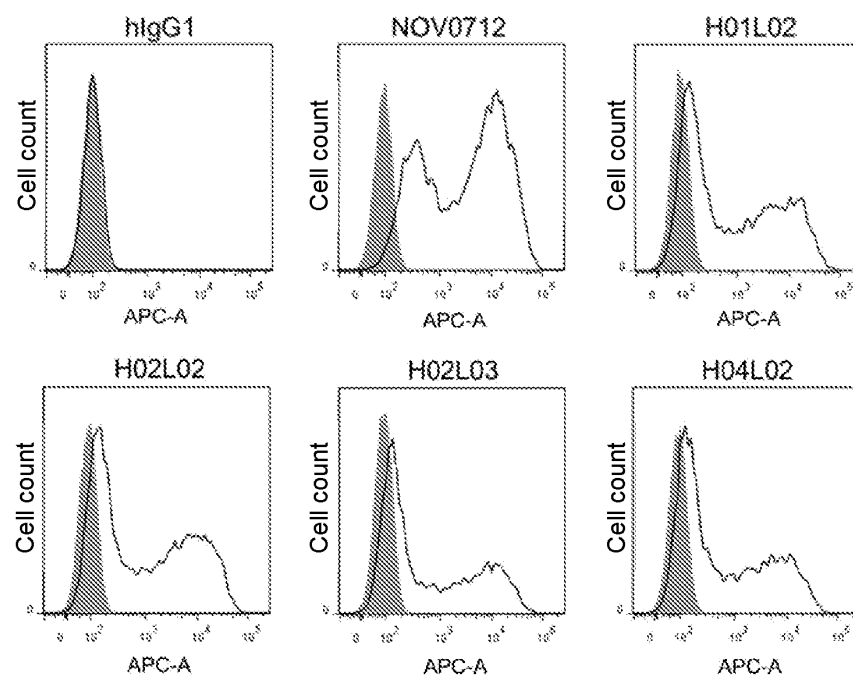
(4) Control cell or EC3-deleted hCDH6-transfected cell



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[Figure 7-5]

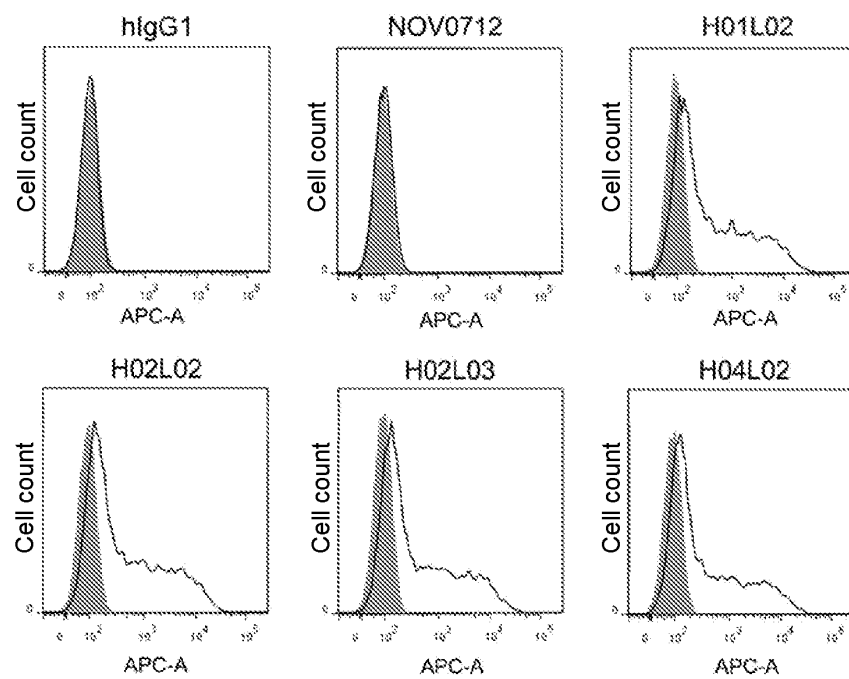
(5) Control cell or EC4-deleted hCDH6-transfected cell



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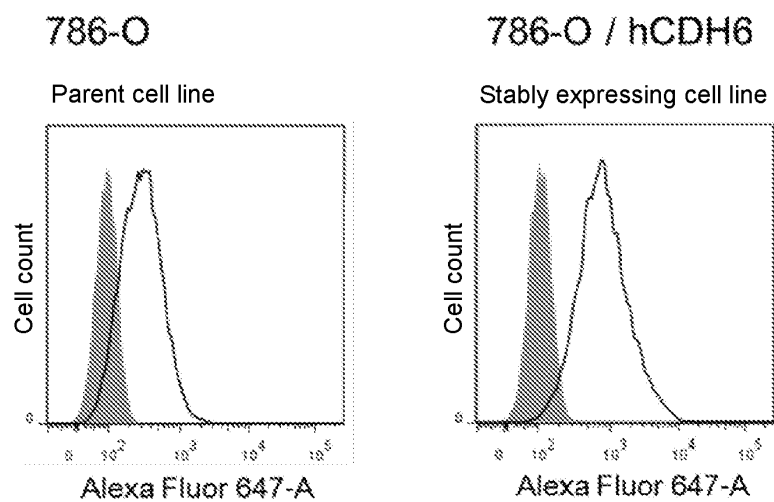
[Figure 7-6]

(6) Control cell or EC5-deleted hCDH6-transfected cell

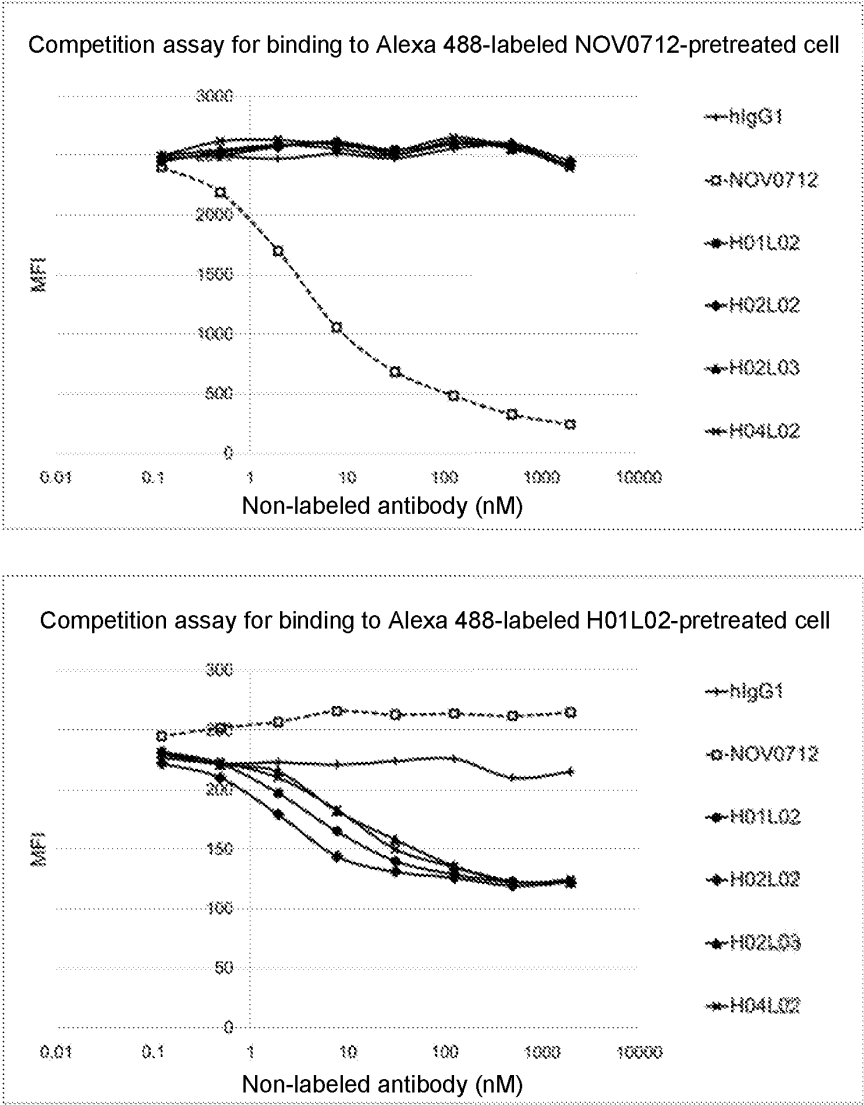


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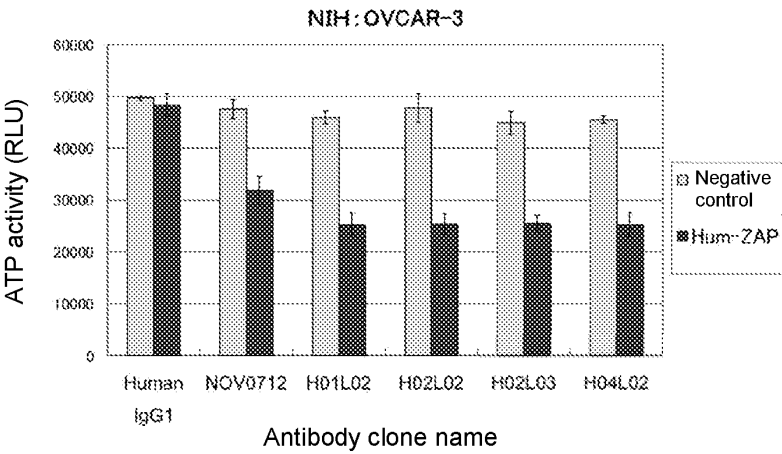
[Figure 8]



[Figure 9]



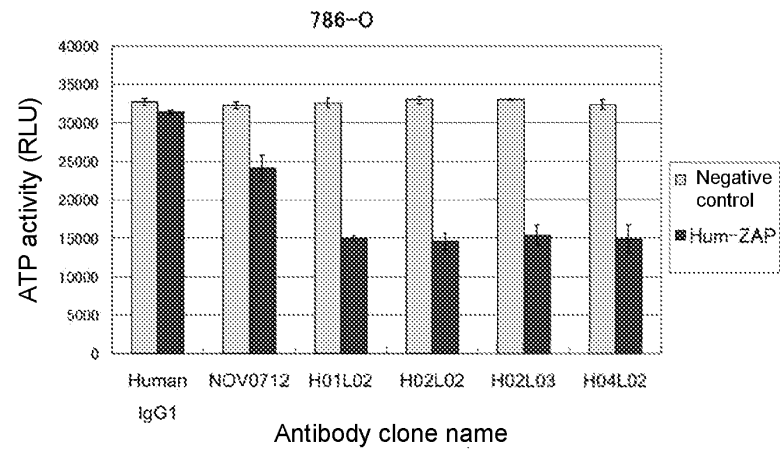
[Figure 10-1]



NIH:OVCAR-3 cell survival rate using Hum-ZAP (%)

Human IgG1	NOV0712	H01L02	H02L02	H02L03	H04L02
97.3	67.0	55.1	53.1	56.7	55.6

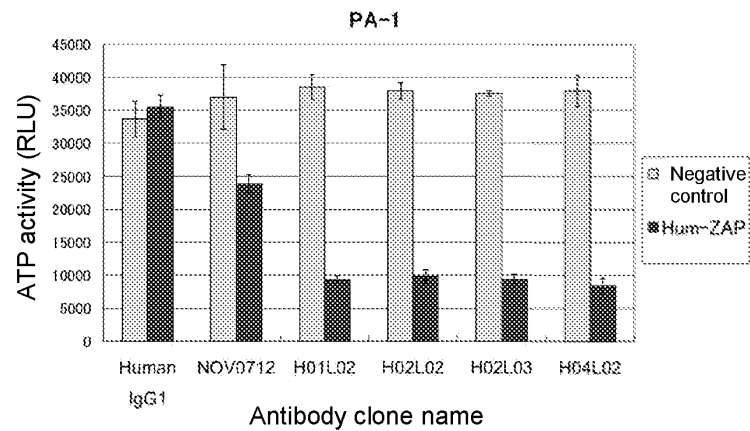
[Figure 10-2]



786-O cell survival rate using Hum-ZAP (%)

Human IgG1	NOV0712	H01L02	H02L02	H02L03	H04L02
95.9	74.8	46.0	44.1	46.5	45.9

[Figure 10-3]

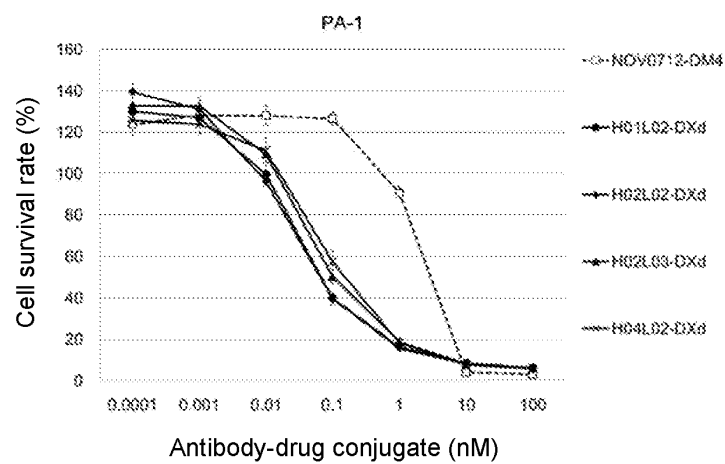


PA-1 cell survival rate using Hum-ZAP (%)

Human IgG1	NOV0712	H01L02	H02L02	H02L03	H04L02
105.6	64.5	24.3	25.8	25.1	22.2

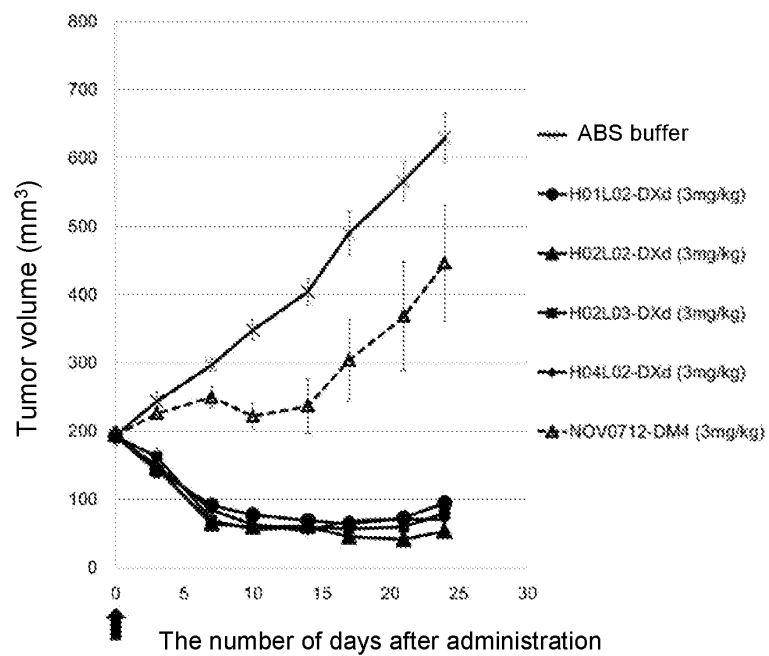
24/29

[Figure 11]



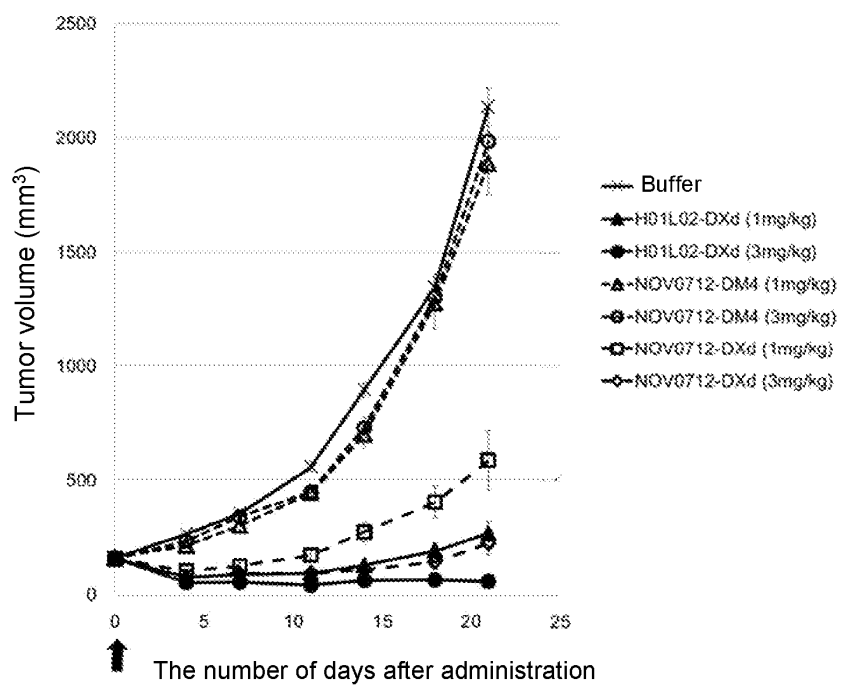
25/29

[Figure 12]



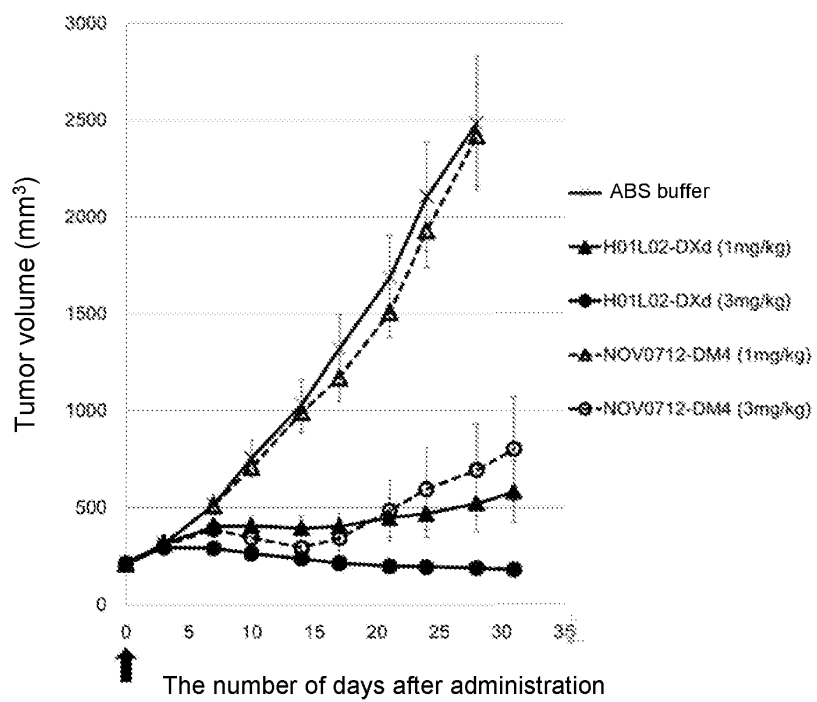
26/29

[Figure 13]



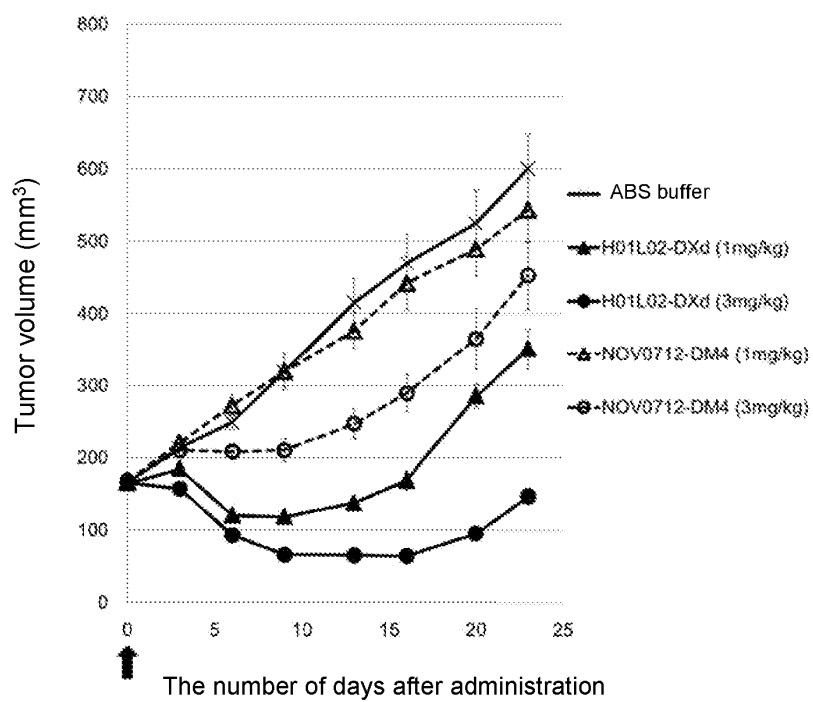
27/29

[Figure 14]



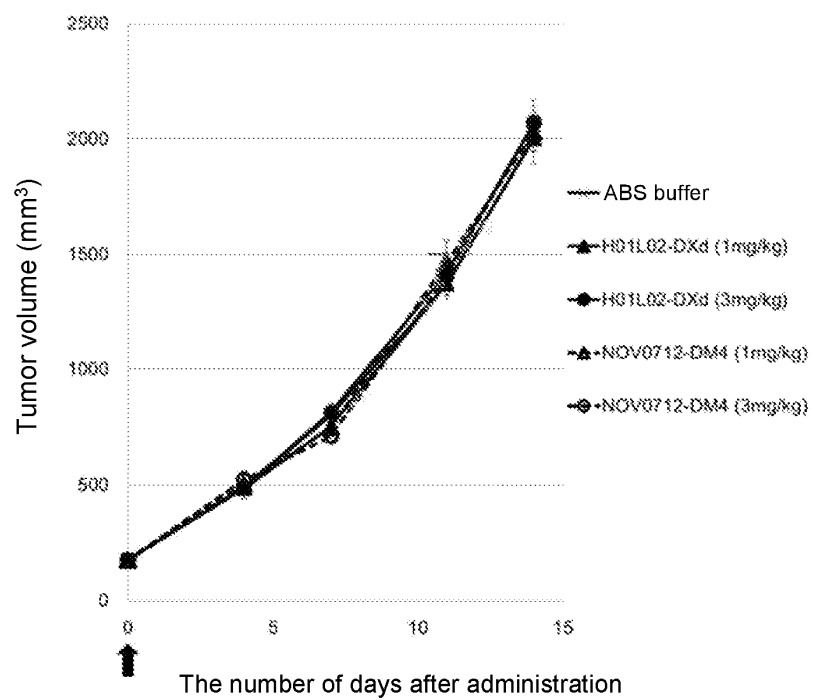
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[Figure 15]



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[Figure 16]



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Ala Lys Lys Arg Ala Leu Glu Leu Ser Gly Asn Ser Lys Asn Glu Leu
 35 40 45

Asn Arg Ser Lys Arg Ser Trp Met Trp Asn Gln Phe Phe Leu Leu Glu
 50 55 60

Glu Tyr Thr Gly Ser Asp Tyr Gln Tyr Val Gly Lys Leu His Ser Asp
 65 70 75 80

Gln Asp Arg Gly Asp Gly Ser Leu Lys Tyr Ile Leu Ser Gly Asp Gly
 85 90 95

Ala Gly Asp Leu Phe Ile Ile Asn Glu Asn Thr Gly Asp Ile Gln Ala
 100 105 110

Thr Lys Arg Leu Asp Arg Glu Glu Lys Pro Val Tyr Ile Leu Arg Ala
 115 120 125

Gln Ala Ile Asn Arg Arg Thr Gly Arg Pro Val Glu Pro Glu Ser Glu
 130 135 140

Phe Ile Ile Lys Ile His Asp Ile Asn Asp Asn Glu Pro Ile Phe Thr
145 150 155 160

Lys Glu Val Tyr Thr Ala Thr Val Pro Glu Met Ser Asp Val Gly Thr
165 170 175

Phe Val Val Gln Val Thr Ala Thr Asp Ala Asp Asp Pro Thr Tyr Gly
180 185 190

Asn Ser Ala Lys Val Val Tyr Ser Ile Leu Gln Gly Gln Pro Tyr Phe
195 200 205

Ser Val Glu Ser Glu Thr Gly Ile Ile Lys Thr Ala Leu Leu Asn Met
210 215 220

Asp Arg Glu Asn Arg Glu Gln Tyr Gln Val Val Ile Gln Ala Lys Asp
225 230 235 240

Met Gly Gly Gln Met Gly Gly Leu Ser Gly Thr Thr Thr Val Asn Ile
245 250 255

Thr Leu Thr Asp Val Asn Asp Asn Pro Pro Arg Phe Pro Gln Ser Thr
260 265 270

Tyr Gln Phe Lys Thr Pro Glu Ser Ser Pro Pro Gly Thr Pro Ile Gly
275 280 285

Arg Ile Lys Ala Ser Asp Ala Asp Val Gly Glu Asn Ala Glu Ile Glu
290 295 300

Tyr Ser Ile Thr Asp Gly Glu Gly Leu Asp Met Phe Asp Val Ile Thr
305 310 315 320

Asp Gln Glu Thr Gln Glu Gly Ile Ile Thr Val Lys Lys Leu Leu Asp
325 330 335

Phe Glu Lys Lys Lys Val Tyr Thr Leu Lys Val Glu Ala Ser Asn Pro
340 345 350

Tyr Val Glu Pro Arg Phe Leu Tyr Leu Gly Pro Phe Lys Asp Ser Ala
355 360 365

Thr Val Arg Ile Val Val Glu Asp Val Asp Glu Pro Pro Val Phe Ser
370 375 380

Lys Leu Ala Tyr Ile Leu Gln Ile Arg Glu Asp Ala Gln Ile Asn Thr
385 390 395 400

Thr Ile Gly Ser Val Thr Ala Gln Asp Pro Asp Ala Ala Arg Asn Pro
405 410 415

Val Lys Tyr Ser Val Asp Arg His Thr Asp Met Asp Arg Ile Phe Asn
420 425 430

Ile Asp Ser Gly Asn Gly Ser Ile Phe Thr Ser Lys Leu Leu Asp Arg
435 440 445

Glu Thr Leu Leu Trp His Asn Ile Thr Val Ile Ala Thr Glu Ile Asn
450 455 460

Asn Pro Lys Gln Ser Ser Arg Val Pro Leu Tyr Ile Lys Val Leu Asp
465 470 475 480

Val Asn Asp Asn Ala Pro Glu Phe Ala Glu Phe Tyr Glu Thr Phe Val
485 490 495

Cys Glu Lys Ala Lys Ala Asp Gln Leu Ile Gln Thr Leu His Ala Val
500 505 510

Asp Lys Asp Asp Pro Tyr Ser Gly His Gln Phe Ser Phe Ser Leu Ala
515 520 525

Pro Glu Ala Ala Ser Gly Ser Asn Phe Thr Ile Gln Asp Asn Lys Asp
530 535 540

Asn Thr Ala Gly Ile Leu Thr Arg Lys Asn Gly Tyr Asn Arg His Glu
545 550 555 560

Met Ser Thr Tyr Leu Leu Pro Val Val Ile Ser Asp Asn Asp Tyr Pro
565 570 575

Val Gln Ser Ser Thr Gly Thr Val Thr Val Arg Val Cys Ala Cys Asp
580 585 590

His His Gly Asn Met Gln Ser Cys His Ala Glu Ala Leu Ile His Pro
595 600 605

Thr Gly Leu Ser Thr Gly Ala Leu Val Ala Ile Leu Leu Cys Ile Val
610 615 620

Ile Leu Leu Val Thr Val Val Leu Phe Ala Ala Leu Arg Arg Gln Arg
625 630 635 640

Lys Lys Glu Pro Leu Ile Ile Ser Lys Glu Asp Ile Arg Asp Asn Ile
645 650 655

Val Ser Tyr Asn Asp Glu Gly Gly Gly Glu Glu Asp Thr Gln Ala Phe
660 665 670

Asp Ile Gly Thr Leu Arg Asn Pro Glu Ala Ile Glu Asp Asn Lys Leu
675 680 685

Arg Arg Asp Ile Val Pro Glu Ala Leu Phe Leu Pro Arg Arg Thr Pro
690 695 700

Thr Ala Arg Asp Asn Thr Asp Val Arg Asp Phe Ile Asn Gln Arg Leu
705 710 715 720

Lys Glu Asn Asp Thr Asp Pro Thr Ala Pro Pro Tyr Asp Ser Leu Ala
725 730 735

Thr Tyr Ala Tyr Glu Gly Thr Gly Ser Val Ala Asp Ser Leu Ser Ser
740 745 750

Leu Glu Ser Val Thr Thr Asp Ala Asp Gln Asp Tyr Asp Tyr Leu Ser
755 760 765

Asp Trp Gly Pro Arg Phe Lys Lys Leu Ala Asp Met Tyr Gly Gly Val
770 775 780

Asp Ser Asp Lys Asp Ser
785 790

<210> 2
<211> 106
<212> PRT
<213> Homo sapiens

<400> 2

Ser Trp Met Trp Asn Gln Phe Phe Leu Leu Glu Glu Tyr Thr Gly Ser
1 5 10 15

Asp Tyr Gln Tyr Val Gly Lys Leu His Ser Asp Gln Asp Arg Gly Asp
20 25 30

Gly Ser Leu Lys Tyr Ile Leu Ser Gly Asp Gly Ala Gly Asp Leu Phe
35 40 45

Ile Ile Asn Glu Asn Thr Gly Asp Ile Gln Ala Thr Lys Arg Leu Asp
50 55 60

Arg Glu Glu Lys Pro Val Tyr Ile Leu Arg Ala Gln Ala Ile Asn Arg
65 70 75 80

Arg Thr Gly Arg Pro Val Glu Pro Glu Ser Glu Phe Ile Ile Lys Ile
85 90 95

His Asp Ile Asn Asp Asn Glu Pro Ile Phe
100 105

<210> 3
<211> 109
<212> PRT
<213> Homo sapiens

<400> 3

Thr Lys Glu Val Tyr Thr Ala Thr Val Pro Glu Met Ser Asp Val Gly
1 5 10 15

Thr Phe Val Val Gln Val Thr Ala Thr Asp Ala Asp Asp Pro Thr Tyr
20 25 30

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

Phe Ser Val Glu Ser Glu Thr Gly Ile Ile Lys Thr Ala Leu Leu Asn
50 55 60

Met Asp Arg Glu Asn Arg Glu Gln Tyr Gln Val Val Ile Gln Ala Lys
65 70 75 80

Asp Met Gly Gly Gln Met Gly Gly Leu Ser Gly Thr Thr Thr Val Asn
85 90 95

Ile Thr Leu Thr Asp Val Asn Asp Asn Pro Pro Arg Phe
100 105

<210> 4
<211> 115
<212> PRT
<213> Homo sapiens

<400> 4

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

Thr Pro Ile Gly Arg Ile Lys Ala Ser Asp Ala Asp Val Gly Glu Asn
20 25 30

Ala Glu Ile Glu Tyr Ser Ile Thr Asp Gly Glu Gly Leu Asp Met Phe
35 40 45

Asp Val Ile Thr Asp Gln Glu Thr Gln Glu Gly Ile Ile Thr Val Lys
50 55 60

Lys Leu Leu Asp Phe Glu Lys Lys Lys Val Tyr Thr Leu Lys Val Glu
65 70 75 80

Ala Ser Asn Pro Tyr Val Glu Pro Arg Phe Leu Tyr Leu Gly Pro Phe
85 90 95

Lys Asp Ser Ala Thr Val Arg Ile Val Val Glu Asp Val Asp Glu Pro
100 105 110

Pro Val Phe
115

<210> 5
<211> 103
<212> PRT
<213> Homo sapiens

<400> 5

Ser Lys Leu Ala Tyr Ile Leu Gln Ile Arg Glu Asp Ala Gln Ile Asn
1 5 10 15

Thr Thr Ile Gly Ser Val Thr Ala Gln Asp Pro Asp Ala Ala Arg Asn
20 25 30

Pro Val Lys Tyr Ser Val Asp Arg His Thr Asp Met Asp Arg Ile Phe
35 40 45

Asn Ile Asp Ser Gly Asn Gly Ser Ile Phe Thr Ser Lys Leu Leu Asp
50 55 60

Arg Glu Thr Leu Leu Trp His Asn Ile Thr Val Ile Ala Thr Glu Ile
65 70 75 80

Asn Asn Pro Lys Gln Ser Ser Arg Val Pro Leu Tyr Ile Lys Val Leu
85 90 95

Asp Val Asn Asp Asn Ala Pro
100

<210> 6
<211> 122
<212> PRT
<213> Homo sapiens

<400> 6

Glu Phe Ala Glu Phe Tyr Glu Thr Phe Val Cys Glu Lys Ala Lys Ala
1 5 10 15

Asp Gln Leu Ile Gln Thr Leu His Ala Val Asp Lys Asp Asp Pro Tyr
20 25 30

Ser Gly His Gln Phe Ser Phe Ser Leu Ala Pro Glu Ala Ala Ser Gly
35 40 45

Ser Asn Phe Thr Ile Gln Asp Asn Lys Asp Asn Thr Ala Gly Ile Leu
50 55 60

Thr Arg Lys Asn Gly Tyr Asn Arg His Glu Met Ser Thr Tyr Leu Leu
65 70 75 80

Pro Val Val Ile Ser Asp Asn Asp Tyr Pro Val Gln Ser Ser Thr Gly
85 90 95

Thr Val Thr Val Arg Val Cys Ala Cys Asp His His Gly Asn Met Gln
100 105 110

Ser Cys His Ala Glu Ala Leu Ile His Pro
115 120

<210> 7
<211> 790
<212> PRT
<213> Mus musculus

<400> 7

Met Arg Thr Tyr Arg Tyr Phe Leu Leu Leu Phe Trp Val Gly Gln Pro
1 5 10 15

Tyr Pro Thr Phe Ser Asn Pro Leu Ser Lys Arg Thr Ser Gly Phe Pro
20 25 30

Ala Lys Arg Lys Ala Leu Glu Leu Ser Ala Asn Ser Arg Asn Glu Leu
35 40 45

Ser Arg Ser Lys Arg Ser Trp Met Trp Asn Gln Phe Phe Leu Leu Glu
50 55 60

Glu Tyr Thr Gly Ser Asp Tyr Gln Tyr Val Gly Lys Leu His Ser Asp
65 70 75 80

Gln Asp Arg Gly Asp Gly Ser Leu Lys Tyr Ile Leu Ser Gly Asp Gly
85 90 95

Ala Gly Asp Leu Phe Ile Ile Asn Glu Asn Thr Gly Asp Ile Gln Ala
100 105 110

Thr Lys Arg Leu Asp Arg Glu Glu Lys Pro Val Tyr Ile Leu Arg Ala
115 120 125

Gln Ala Val Asn Arg Arg Thr Gly Arg Pro Val Glu Pro Glu Ser Glu
130 135 140

Phe Ile Ile Lys Ile His Asp Ile Asn Asp Asn Glu Pro Ile Phe Thr
145 150 155 160

Lys Asp Val Tyr Thr Ala Thr Val Pro Glu Met Ala Asp Val Gly Thr
165 170 175

Phe Val Val Gln Val Thr Ala Thr Asp Ala Asp Asp Pro Thr Tyr Gly
180 185 190

Asn Ser Ala Lys Val Val Tyr Ser Ile Leu Gln Gly Gln Pro Tyr Phe
195 200 205

Ser Val Glu Ser Glu Thr Gly Ile Ile Lys Thr Ala Leu Leu Asn Met
210 215 220

Asp Arg Glu Asn Arg Glu Gln Tyr Gln Val Val Ile Gln Ala Lys Asp
225 230 235 240

Met Gly Gly Gln Met Gly Gly Leu Ser Gly Thr Thr Thr Val Asn Ile
245 250 255

Thr Leu Thr Asp Val Asn Asp Asn Pro Pro Arg Phe Pro Gln Ser Thr
260 265 270

Tyr Gln Phe Lys Thr Pro Glu Ser Ser Pro Pro Gly Thr Pro Ile Gly
275 280 285

Arg Ile Lys Ala Ser Asp Ala Asp Val Gly Glu Asn Ala Glu Ile Glu
290 295 300

Tyr Ser Ile Thr Asp Gly Glu Gly His Glu Met Phe Asp Val Ile Thr
305 310 315 320

Asp Gln Glu Thr Gln Glu Gly Ile Ile Thr Val Lys Lys Leu Leu Asp
325 330 335

Phe Glu Lys Lys Lys Val Tyr Thr Leu Lys Val Glu Ala Ser Asn Pro
340 345 350

His Val Glu Pro Arg Phe Leu Tyr Leu Gly Pro Phe Lys Asp Ser Ala
355 360 365

Thr Val Arg Ile Val Val Asp Asp Val Asp Glu Pro Pro Val Phe Ser
370 375 380

Lys Leu Ala Tyr Ile Leu Gln Ile Arg Glu Asp Ala Arg Ile Asn Thr
385 390 395 400

Thr Ile Gly Ser Val Ala Ala Gln Asp Pro Asp Ala Ala Arg Asn Pro
405 410 415

Val Lys Tyr Ser Val Asp Arg His Thr Asp Met Asp Arg Ile Phe Asn
420 425 430

Ile Asp Ser Gly Asn Gly Ser Ile Phe Thr Ser Lys Leu Leu Asp Arg
435 440 445

Glu Thr Leu Leu Trp His Asn Ile Thr Val Ile Ala Thr Glu Ile Asn
450 455 460

Asn Pro Lys Gln Ser Ser Arg Val Pro Leu Tyr Ile Lys Val Leu Asp
465 470 475 480

Val Asn Asp Asn Ala Pro Glu Phe Ala Glu Phe Tyr Glu Thr Phe Val
485 490 495

Cys Glu Lys Ala Lys Ala Asp Gln Leu Ile Gln Thr Leu Arg Ala Val
500 505 510

Asp Lys Asp Asp Pro Tyr Ser Gly His Gln Phe Ser Phe Ser Leu Ala
515 520 525

Pro Glu Ala Ala Ser Ser Ser Asn Phe Thr Ile Gln Asp Asn Lys Asp
530 535 540

Asn Thr Ala Gly Ile Leu Thr Arg Lys Asn Gly Tyr Asn Arg His Glu
545 550 555 560

Met Ser Thr Tyr Leu Leu Pro Val Val Ile Ser Asp Asn Asp Tyr Pro
565 570 575

Val Gln Ser Ser Thr Gly Thr Val Thr Val Arg Val Cys Ala Cys Asp
580 585 590

His His Gly Asn Met Gln Ser Cys His Ala Glu Ala Leu Ile His Pro
595 600 605

Thr Gly Leu Ser Thr Gly Ala Leu Val Ala Ile Leu Leu Cys Ile Val
610 615 620

Ile Leu Leu Val Thr Val Val Leu Phe Ala Ala Leu Arg Arg Gln Arg
625 630 635 640

Lys Lys Glu Pro Leu Ile Ile Ser Lys Glu Asp Ile Arg Asp Asn Ile
645 650 655

Val Ser Tyr Asn Asp Glu Gly Gly Gly Glu Glu Asp Thr Gln Ala Phe
660 665 670

Asp Ile Gly Thr Leu Arg Asn Pro Glu Ala Met Glu Asp Ser Lys Ser
675 680 685

Arg Arg Asp Ile Val Pro Glu Ala Leu Phe Leu Pro Arg Arg Thr Pro
690 695 700

Thr Ala Arg Asp Asn Thr Asp Val Arg Asp Phe Ile Asn Gln Arg Leu
705 710 715 720

Lys Glu Asn Asp Thr Asp Pro Thr Ala Pro Pro Tyr Asp Ser Leu Ala
725 730 735

Thr Tyr Ala Tyr Glu Gly Thr Gly Ser Val Ala Asp Ser Leu Ser Ser
740 745 750

Leu Glu Ser Val Thr Thr Asp Gly Asp Gln Asp Tyr Asp Tyr Leu Ser
755 760 765

Asp Trp Gly Pro Arg Phe Lys Lys Leu Ala Asp Met Tyr Gly Gly Met
770 775 780

Asp Ser Asp Lys Asp Ser
785 790

<210> 8

<211> 789

<212> PRT

<213> Rattus norvegicus

<400> 8

Met Arg Thr Tyr Arg Tyr Phe Leu Leu Leu Phe Trp Val Gly Gln Pro
1 5 10 15

Tyr Pro Thr Phe Ser Asn Pro Leu Ser Lys Arg Thr Ser Gly Phe Pro
20 25 30

Ala Lys Arg Arg Ala Leu Glu Leu Ser Ala Asn Ser Arg Asn Glu Leu
35 40 45

Ser Arg Ser Lys Arg Ser Trp Met Trp Asn Gln Phe Phe Leu Leu Glu
50 55 60

Glu Tyr Thr Gly Ser Asp Tyr Gln Tyr Val Gly Lys Leu His Ser Asp
65 70 75 80

Gln Asp Arg Gly Asp Gly Ser Leu Lys Tyr Ile Leu Ser Gly Asp Gly
85 90 95

Ala Gly Asp Leu Phe Ile Ile Asn Glu Asn Thr Gly Asp Ile Gln Ala
100 105 110

Thr Lys Arg Leu Asp Arg Glu Glu Lys Pro Val Tyr Ile Leu Arg Ala
115 120 125

Gln Ala Ile Asn Arg Arg Thr Gly Arg Pro Val Glu Pro Glu Ser Glu
130 135 140

Phe Ile Ile Lys Ile His Asp Ile Asn Asp Asn Glu Pro Ile Phe Thr
145 150 155 160

Lys Asp Val Tyr Thr Ala Thr Val Pro Glu Met Ala Asp Val Gly Thr
165 170 175

Phe Val Val Gln Val Thr Ala Thr Asp Ala Asp Asp Pro Thr Tyr Gly
180 185 190

Asn Ser Ala Lys Val Val Tyr Ser Ile Leu Gln Gly Gln Pro Tyr Phe
195 200 205

Ser Val Glu Ser Glu Thr Gly Ile Ile Lys Thr Ala Leu Leu Asn Met
210 215 220

Asp Arg Glu Asn Arg Glu Gln Tyr Gln Val Val Ile Gln Ala Lys Asp
225 230 235 240

Met Gly Gly Gln Met Gly Gly Leu Ser Gly Thr Thr Thr Val Asn Ile
245 250 255

Thr Leu Thr Asp Val Asn Asp Asn Pro Pro Arg Phe Pro Gln Ser Thr
260 265 270

Tyr Gln Phe Lys Thr Pro Glu Ser Ser Pro Pro Gly Thr Pro Ile Gly
275 280 285

Arg Ile Lys Ala Ser Asp Ala Asp Val Gly Glu Asn Ala Glu Ile Glu
290 295 300

Tyr Ser Ile Thr Asp Gly Glu Gly His Asp Met Phe Asp Val Ile Thr
305 310 315 320

Asp Gln Glu Thr Gln Glu Gly Ile Ile Thr Val Lys Lys Leu Leu Asp
325 330 335

Phe Glu Lys Lys Arg Val Tyr Thr Leu Lys Val Glu Ala Ser Asn Pro

340 345 350

His Ile Glu Pro Arg Phe Leu Tyr Leu Gly Pro Phe Lys Asp Ser Ala
355 360 365

Thr Val Arg Ile Val Val Asp Asp Val Asp Glu Pro Pro Val Phe Ser
370 375 380

Lys Pro Ala Tyr Ile Leu Gln Ile Arg Glu Asp Ala Gln Ile Asn Thr
385 390 395 400

Thr Ile Gly Ser Val Ala Ala Gln Asp Pro Asp Ala Ala Arg Asn Pro
405 410 415

Val Lys Tyr Ser Val Asp Arg His Thr Asp Met Asp Arg Ile Phe Asn
420 425 430

Ile Asp Ser Gly Asn Gly Ser Ile Phe Thr Ser Lys Leu Leu Asp Arg
435 440 445

Glu Thr Leu Leu Trp His Asn Ile Thr Val Ile Ala Thr Glu Ile Asn
450 455 460

Asn Pro Lys Gln Ser Ser Arg Val Pro Leu Tyr Ile Lys Val Leu Asp
465 470 475 480

Val Asn Asp Asn Ala Pro Glu Phe Ala Glu Phe Tyr Glu Thr Phe Val
485 490 495

Cys Glu Lys Ala Lys Ala Asp Gln Leu Ile Gln Thr Leu His Ala Val
500 505 510

Asp Lys Asp Asp Pro Tyr Ser Gly His Gln Phe Ser Phe Ser Leu Ala
515 520 525

Pro Glu Ala Ala Ser Gly Ser Asn Phe Thr Ile Gln Asp Asn Lys Asp
530 535 540

Asn Thr Ala Gly Ile Leu Thr Arg Lys Asn Gly Tyr Asn Arg His Glu
545 550 555 560

Met Ser Thr Tyr Leu Leu Pro Val Val Ile Ser Asp Asn Asp Tyr Pro
565 570 575

Val Gln Ser Ser Thr Gly Thr Val Thr Val Arg Val Cys Ala Cys Asp
580 585 590

His His Gly Asn Met Gln Ser Cys His Ala Glu Ala Leu Ile His Pro
595 600 605

Thr Gly Leu Ser Thr Gly Ala Leu Val Ala Ile Leu Leu Cys Ile Val
610 615 620

Ile Leu Leu Val Thr Val Val Leu Phe Ala Ala Leu Arg Arg Gln Arg
625 630 635 640

Lys Lys Glu Pro Leu Ile Ile Ser Lys Glu Asp Ile Arg Asp Asn Ile
645 650 655

Val Ser Tyr Asn Asp Glu Gly Gly Gly Glu Glu Asp Thr Gln Ala Phe
660 665 670

Asp Ile Gly Thr Leu Arg Asn Pro Lys Pro Trp Arg Gln Gln Ser Arg
675 680 685

Arg Asp Met Val Pro Glu Ala Leu Phe Leu Pro Arg Arg Thr Pro Thr
690 695 700

Ala Arg Asp Asn Thr Asp Val Arg Asp Phe Ile Ser Gln Arg Leu Arg
705 710 715 720

Lys Met Asn Thr Asp Pro Thr Ala Pro Pro Tyr Asp Ser Leu Ala Thr
725 730 735

Tyr Ala Tyr Glu Gly Thr Gly Ser Val Ala Asp Ser Leu Ser Ser Leu
740 745 750

Glu Ser Val Thr Thr Asp Gly Asp Gln Asp Tyr Gly Tyr Leu Ser Asp
755 760 765

Trp Gly Pro Arg Phe Lys Lys Leu Ala Asp Met Tyr Gly Gly Met Asp

770 775 780

Ser Asp Lys Asp Ser
785

<210> 9

<211> 790

<212> PRT

<213> Macaca fascicularis

<400> 9

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

Lys Glu Val Tyr Thr Ala Thr Val Pro Glu Met Ser Asp Val Gly Thr
165 170 175

Phe Val Val Gln Val Thr Ala Thr Asp Ala Asp Asp Pro Thr Tyr Gly
180 185 190

Asn Ser Ala Lys Val Val Tyr Ser Ile Leu Gln Gly Gln Pro Tyr Phe
195 200 205

Ser Val Glu Ser Glu Thr Gly Ile Ile Lys Thr Ala Leu Leu Asn Met
210 215 220

Asp Arg Glu Asn Arg Glu Gln Tyr Gln Val Val Ile Gln Ala Lys Asp
225 230 235 240

Met Gly Gly Gln Met Gly Gly Leu Ser Gly Thr Thr Thr Val Asn Ile
245 250 255

Thr Leu Thr Asp Val Asn Asp Asn Pro Pro Arg Phe Pro Gln Ser Thr
260 265 270

Tyr Gln Phe Lys Thr Pro Glu Ser Ser Pro Pro Gly Thr Pro Ile Gly
275 280 285

Arg Ile Lys Ala Ser Asp Ala Asp Val Gly Glu Asn Ala Glu Ile Glu
290 295 300

Tyr Ser Ile Thr Asp Gly Glu Gly Leu Asp Met Phe Asp Val Ile Thr
305 310 315 320

Asp Gln Glu Thr Gln Glu Gly Ile Ile Thr Val Lys Lys Leu Leu Asp
325 330 335

Phe Glu Lys Lys Lys Val Tyr Thr Leu Lys Val Glu Ala Ser Asn Pro
340 345 350

His Val Glu Pro Arg Phe Leu Tyr Leu Gly Pro Phe Lys Asp Ser Ala
355 360 365

Thr Val Arg Ile Val Val Glu Asp Val Asp Glu Pro Pro Val Phe Ser
370 375 380

Lys Leu Ala Tyr Ile Leu Gln Ile Arg Glu Asp Ala Gln Ile Asn Thr
385 390 395 400

Thr Ile Gly Ser Val Thr Ala Gln Asp Pro Asp Ala Ala Arg Asn Pro
405 410 415

Val Lys Tyr Ser Val Asp Arg His Thr Asp Met Asp Arg Ile Phe Asn
420 425 430

Ile Asp Ser Gly Asn Gly Ser Ile Phe Thr Ser Lys Leu Leu Asp Arg
435 440 445

Glu Thr Leu Leu Trp His Asn Ile Thr Val Ile Ala Thr Glu Ile Asn
450 455 460

Asn Pro Lys Gln Ser Ser Arg Val Pro Leu Tyr Ile Lys Val Leu Asp
465 470 475 480

Val Asn Asp Asn Ala Pro Glu Phe Ala Glu Phe Tyr Glu Thr Phe Val
485 490 495

Cys Glu Lys Ala Lys Ala Asp Gln Leu Ile Gln Thr Leu Arg Ala Val
500 505 510

Asp Lys Asp Asp Pro Tyr Ser Gly His Gln Phe Ser Phe Ser Leu Ala
515 520 525

Pro Glu Ala Ala Ser Gly Ser Asn Phe Thr Ile Gln Asp Asn Lys Asp
530 535 540

Asn Thr Ala Gly Ile Leu Thr Arg Lys Asn Gly Tyr Asn Arg His Glu
545 550 555 560

Met Ser Thr Tyr Leu Leu Pro Val Val Ile Ser Asp Asn Asp Tyr Pro
565 570 575

Val Gln Ser Ser Thr Gly Thr Val Thr Val Arg Val Cys Ala Cys Asp
580 585 590

His His Gly Asn Met Gln Ser Cys His Ala Glu Ala Leu Ile His Pro
595 600 605

Thr Gly Leu Ser Thr Gly Ala Leu Val Ala Ile Leu Leu Cys Ile Val
610 615 620

Ile Leu Leu Val Thr Val Val Leu Phe Ala Ala Leu Arg Arg Gln Arg
625 630 635 640

Lys Lys Glu Pro Leu Ile Ile Ser Lys Glu Asp Ile Arg Asp Asn Ile
645 650 655

Val Ser Tyr Asn Asp Glu Gly Gly Gly Glu Glu Asp Thr Gln Ala Phe
660 665 670

Asp Ile Gly Thr Leu Arg Asn Pro Glu Ala Ile Glu Asp Asn Lys Leu
675 680 685

Arg Arg Asp Ile Val Pro Glu Ala Leu Phe Leu Pro Arg Arg Thr Pro
690 695 700

Thr Ala Arg Asp Asn Thr Asp Val Arg Asp Phe Ile Asn Gln Arg Leu
705 710 715 720

Lys Glu Asn Asp Thr Asp Pro Thr Ala Pro Pro Tyr Asp Ser Leu Ala
725 730 735

Thr Tyr Ala Tyr Glu Gly Thr Gly Ser Val Ala Asp Ser Leu Ser Ser
740 745 750

Leu Glu Ser Val Thr Thr Asp Gly Asp Gln Asp Tyr Asp Tyr Leu Ser
755 760 765

Asp Trp Gly Pro Arg Phe Lys Lys Leu Ala Asp Met Tyr Gly Gly Val
770 775 780

Asp Ser Asp Lys Asp Ser
785 790

<210> 10

<211> 108

12768 of 14295

<212> PRT

<213> Rattus norvegicus

<400> 10

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

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

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

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

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

Glu Asp Val Ala Thr Tyr Phe Cys Gln Gln Tyr Tyr Ser Gly Trp Ala
85 90 95

Phe Gly Gly Val Thr Asn Leu Glu Leu Lys Arg Ala
100 105

<210> 11

<211> 324

<212> DNA

<213> Rattus norvegicus

<400> 11

gacatccaga tgaccagtc tccttcactc ctgtctgcat ctgtgggaga cagagtcact 60

ctcaactgca aagcaagtca gaatattat aagaacttag cctggtatca gcaaaagctt 120

ggagaaggtc ccaaactcct gatttatgat gcaaactt tgcaaacggg catcccatca 180

aggttcagtg gcagtggatc tggttcagat ttacactca ccatcagcag cctgcagcct 240

gaagatgttg ccacatattt ctgccagcag tactatagcg ggtgggcgtt cggtggagtc 300

accaacctgg aattgaaacg ggct 324

<210> 12

<211> 11

<212> PRT

<213> Rattus norvegicus

<400> 12

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

<210> 13

<211> 7

<212> PRT

<213> Rattus norvegicus

<400> 13

Asp Ala Asn Thr Leu Gln Thr
1 5

<210> 14

<211> 8

<212> PRT

<213> Rattus norvegicus

<400> 14

Gln Gln Tyr Tyr Ser Gly Trp Ala
1 5

<210> 15

<211> 122

<212> PRT

<213> Rattus norvegicus

<400> 15

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

<400> 18

Trp Ile Tyr Cys Gly Asp Gly Glu Thr Glu
1 5 10

<210> 19
<211> 13
<212> PRT
<213> Rattus norvegicus

<400> 19

Gly Val Tyr Gly Gly Phe Ala Gly Gly Tyr Phe Asp Phe
1 5 10

<210> 20
<211> 109
<212> PRT
<213> Rattus norvegicus

<400> 20

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

Glu Ser Val Ser Ile Ser Cys Lys Thr Ser Lys Asn Ile Ser Asn Tyr
20 25 30

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

Tyr Ser Gly Ser Thr Leu Gln Ser Gly Thr Pro Ser Arg Phe Ser Gly
50 55 60

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

Glu Asp Phe Gly Leu Tyr Phe Cys Gln Gln Tyr Tyr Glu Lys Pro Phe
85 90 95

Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Arg Ala
100 105

<210> 21
<211> 327
<212> DNA

<213> Rattus norvegicus

<400> 21

gatgtccaga tgaccactc tccgtcttat cttgctgcgt ctctggaga aagtgttcc 60

atcagttgca agacaagtaa gaacattagt aattatttag tctggtatca acagaaacct 120

ggggaagcat ataagcttct tatctattct gggtaactt tgcaatctgg aactccatca 180

aggttcagtgc gcagtggatc tggtagatc ttactctca ctatcagaag cctggagcct 240

gaagattttg gactctattt ctgtcaacag tattatgaaa aaccattcac gttcggctca 300

gggacgaagt tggaaataaa acgggct 327

<210> 22

<211> 11

<212> PRT

<213> Rattus norvegicus

<400> 22

Lys Thr Ser Lys Asn Ile Ser Asn Tyr Leu Val

1 5 10

<210> 23

<211> 7

<212> PRT

<213> Rattus norvegicus

<400> 23

Ser Gly Ser Thr Leu Gln Ser

1 5

<210> 24

<211> 9

<212> PRT

<213> Rattus norvegicus

<400> 24

Gln Gln Tyr Tyr Glu Lys Pro Phe Thr

1 5

<210> 25

<211> 121

<212> PRT

<213> Rattus norvegicus

<400> 25

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

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

Tyr Trp Gly Trp Ile Arg Arg Phe Pro Gly Asn Lys Met Glu Trp Met
35 40 45

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

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

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

Arg Ser Ile Asn His Gly Gly Tyr Ser Tyr Val Val Asp Ala Trp Gly
100 105 110

Pro Gly Ala Ser Val Thr Val Ser Ser
115 120

<210> 26

<211> 363

<212> DNA

<213> Rattus norvegicus

<400> 26

gaggtgcaac ttcaggagtc aggacctggc ctgtgagac cctcacagtc actctccctc 60

tcctgttctg tcactgatta ctccatcact agtaattact ggggctggat ccggagggtc 120

ccaggaaata aaatggagtg gatgggatac ataacctata gtgggttacac tagctacaac 180

ccatctctcc aaagtgaat ctccattact agagacacat cgaagaatca gtctctctg 240

cagtggaact ctgtaactgc tgaggacaca gccacatatt actgtgcaag atcgattaac 300

cacggaggat atagttaigt tgtggatgcc tggggtccgg gagcttcagt cactgtctcc 360

tca 363

<210> 27
<211> 10
<212> PRT
<213> Rattus norvegicus

<400> 27

Asp Tyr Ser Ile Thr Ser Asn Tyr Trp Gly
1 5 10

<210> 28
<211> 9
<212> PRT
<213> Rattus norvegicus

<400> 28

Tyr Ile Thr Tyr Ser Gly Tyr Thr Ser
1 5

<210> 29
<211> 13
<212> PRT
<213> Rattus norvegicus

<400> 29

Ser Ile Asn His Gly Gly Tyr Ser Tyr Val Val Asp Ala
1 5 10

<210> 30
<211> 109
<212> PRT
<213> Rattus norvegicus

<400> 30

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

Glu Ser Val Ser Ile Ser Cys Arg Ala Thr Lys Ser Ile Gly Ile Tyr
20 25 30

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

Tyr Ser Gly Ser Thr Leu Gln Ser Gly Thr Pro Ser Arg Phe Ser Gly

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50 55 60

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

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

Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Arg Arg Ala
100 105

<210> 31
<211> 327
<212> DNA
<213> Rattus norvegicus

<400> 31
gatgtccaga tgaccagtc tccgtcttct ctgctgcgt ctctggaga aagtgttcc 60
atcagttgca gggcaactaa gagcattggt atttatttag cctggatca acagaaacct 120
gggaaaacat ttaagcttct tatctactct gggtaactt tgcaatctgg aactccatca 180
aggttcagtg gcagtgggtc tggtagatg ttactctca ccatcagaag cctggagcct 240
gaagattttg gactctattt ctgtcaacag tttatgaaa accattcac gttcggctca 300
gggacgaagt tggaaataag acgggct 327

<210> 32
<211> 11
<212> PRT
<213> Rattus norvegicus

<400> 32

Arg Ala Thr Lys Ser Ile Gly Ile Tyr Leu Ala
1 5 10

<210> 33
<211> 7
<212> PRT
<213> Rattus norvegicus

<400> 33

Ser Gly Ser Thr Leu Gln Ser
1 5

<210> 34
<211> 9
<212> PRT
<213> Rattus norvegicus

<400> 34

Gln Gln Phe Tyr Glu Asn Pro Phe Thr
1 5

<210> 35
<211> 121
<212> PRT
<213> Rattus norvegicus

<400> 35

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

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

Phe Trp Gly Trp Ile Arg Lys Phe Pro Gly Asn Lys Met Glu Trp Met
35 40 45

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

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

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

Arg Cys Pro Asn Tyr Gly Gly His Ser Leu Val Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Val Met Val Thr Val Ser Ser
115 120

<210> 36
<211> 363

<212> DNA

<213> Rattus norvegicus

<400> 36

gaggtgcagc ttcaggagtc aggacctggc ctgtgaaac cctcacagtc actctccctc 60

acctgttctg tcactgatta ctccatcact acttatttct ggggctggat ccggaagttc 120

ccaggaaata aaatggagtg gatgggatac atgagctacc gtggtggcac ttctacaac 180

ccatctctca agagtccaat ctccattact agagacacat cgaagaatca gttcttctg 240

cagttgaact ctgtaactac tgaggacaca gccacatatt actgtgcaag atgccctaac 300

tacggagggc attcccttgt ttgtgattac tggggccaag gagtcatggt cacagtgtcc 360

tca 363

<210> 37

<211> 10

<212> PRT

<213> Rattus norvegicus

<400> 37

Asp Tyr Ser Ile Thr Thr Tyr Phe Trp Gly

1 5 10

<210> 38

<211> 9

<212> PRT

<213> Rattus norvegicus

<400> 38

Tyr Met Ser Tyr Arg Gly Gly Thr Ser

1 5

<210> 39

<211> 13

<212> PRT

<213> Rattus norvegicus

<400> 39

Cys Pro Asn Tyr Gly Gly His Ser Leu Val Phe Asp Tyr

1 5 10

<210> 40

<211> 109

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<212> PRT

<213> Rattus norvegicus

<400> 40

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

Glu Ser Val Ser Ile Ser Cys Lys Ala Thr Lys Ser Ile Ser Asn Tyr
20 25 30

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

Tyr Ser Gly Ser Thr Leu Gln Ser Gly Thr Pro Ser Arg Phe Ser Gly
50 55 60

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

Glu Asp Phe Gly Leu Tyr Ser Cys Gln Gln Tyr Tyr Glu Lys Pro Leu
85 90 95

Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Arg Ala
100 105

<210> 41

<211> 327

<212> DNA

<213> Rattus norvegicus

<400> 41

gatgtccaga tgaccagtc tccgtcttat ctgctgcgt ctctggaga aagtgttcc 60

atcagttgca aggcaactaa gagcattagt aattatttag cctggtatca acagaaacct 120

ggggaagcat ataaggttct tatctattct gggtaactt tgcaatctgg aactccatca 180

aggttcagt gcaagtggatc tggtagatc ttactctca ccatcagaag cctggagcct 240

gaagattttg gactctattc ctgtcaacag tattatgaaa aaccgctcac gttcggttct 300

gggaccaagc tggagatcaa acgggct 327

<210> 42

<211> 11

<212> PRT

<213> Rattus norvegicus

<400> 42

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

<210> 43

<211> 7

<212> PRT

<213> Rattus norvegicus

<400> 43

Ser Gly Ser Thr Leu Gln Ser
 1 5

<210> 44

<211> 9

<212> PRT

<213> Rattus norvegicus

<400> 44

Gln Gln Tyr Tyr Glu Lys Pro Leu Thr
 1 5

<210> 45

<211> 121

<212> PRT

<213> Rattus norvegicus

<400> 45

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

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

Tyr Trp Gly Trp Ile Arg Lys Phe Pro Gly Asn Lys Met Glu Trp Met
 35 40 45

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

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

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

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

Pro Gly Thr Met Val Thr Val Ser Ser
115 120

<210> 46

<211> 363

<212> DNA

<213> Rattus norvegicus

<400> 46

gaggtgcagc ttcaggagtc aggacctggc cttgtgaaac cctcacagtc actctccctc 60

acctgttctg tcactgggta ctccatcact acttattact ggggctggat ccggaagttc 120

ccaggaaata aaatggagtg gatgggggtac ataagctaca gtggtcgac tagttataac 180

ccatctctca aaagtcgaat gtccattact agagacgcat cgaagaatca gttcttccta 240

cagttgaact ctgtaactac tgacgacaca gccacatatt actgtgcaag atccccaatt 300

aaccacggag ggtactggta ctttgacttc tggggcccag gaaccatggt caccgtgtcc 360

tca 363

<210> 47

<211> 10

<212> PRT

<213> Rattus norvegicus

<400> 47

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

<210> 48

<211> 9

<212> PRT

<213> Rattus norvegicus

<400> 48

Tyr Ile Ser Tyr Ser Gly Arg Thr Ser
1 5

<210> 49
<211> 13
<212> PRT
<213> Rattus norvegicus

<400> 49

Ser Pro Ile Asn His Gly Gly Tyr Trp Tyr Phe Asp Phe
1 5 10

<210> 50
<211> 449
<212> DNA
<213> Artificial Sequence

<220>
<223> DNA comprising DNA sequence coding for human light chain signal
sequence and kappa chain constant region

<400> 50
gcctccggac tctagagcca ccatggtgct gcagaccag gtgtcatct ccctgctgct 60
gtggatctcc ggcgcgtacg gcgatatcgt gatgattaaa cgtacggtgg ccgccccctc 120
cgtgttcac tccccccct ccgacgagca gctgaagtcc ggcaccgcct ccgtggtgtg 180
cctgctgaat aacttctacc ccagagaggc caaggtgcag tggaagggtg acaacgcctt 240
gcagtccggg aactcccagg agagcgtgac cgagcaggac agcaaggaca gcacctacag 300
cctgagcagc accctgaccc tgagcaaagc cgactacgag aagcacaagg tgtacgcctg 360
cgaggtgacc caccagggcc tgagctcccc cgtcaccaag agcttcaaca gggggggagtg 420
ttaggggccc gttaaacgg gggaggcta 449

<210> 51
<211> 1132
<212> DNA
<213> Artificial Sequence

<220>
<223> DNA comprising DNA sequence coding for human heavy chain signal
sequence and IgG1 constant region

<400> 51
gcctccggac tctagagcca ccatgaaaca cctgtggttc ttctcctgc tgggtggcagc 60

tcccagatgg gtgctgagcc aggtgcaatt gtgcaggcgg ttagctcagc ctccaccaag 120
 ggcccaagcg tcttccccct ggcaccctcc tccaagagca cctctggcgg cacagccgcc 180
 ctgggctgcc tggtaagga ctacttcccc gaaccctga ccgtgagctg gaactcaggc 240
 gccctgacca gggcgctgca caccttcccc gctgtcctgc agtctcagg actctactcc 300
 ctcagcagcg tggtgaccgt gccctccagc agcttgggca ccagaccta catctgcaac 360
 gtgaatcaca agcccagca caccaagggt gacaagagag ttgagccaa atcttgtac 420
 aaaactcaca catgcccacc ctgccagca cctgaactcc tggggggacc ctcagtcttc 480
 ctcttcccc caaaaccaa ggacaccctc atgatctcc ggaccctga ggtcacatgc 540
 gtgggtgggg acgtgagcca cgaagaccct gaggtcaagt tcaactggta cgtggacggc 600
 gtggagggtgc ataatgcaa gacaaagccc cgggaggagc agtacaacag cacgtaccgg 660
 gtggtcagcg tcttcaccgt cctgcaccag gactggctga atggcaagga gtacaagtgc 720
 aaggtctcca acaaagccct ccagccccc atcgagaaaa ccatctcaa agccaaaggc 780
 cagccccggg aaccacaggt gtacaccctg ccccatccc gggaggagat gaccaagaac 840
 caggtcagcc tgacctgcct ggtcaaaggc ttctatccca gcgacatgc cgtggagtgg 900
 gagagcaatg gccagcccgga gaacaactac aagaccaccc ctccgtgct ggactccgac 960
 ggctccttct tctctacag caagtcacc gtggacaaga gcaggtggca gcagggaac 1020
 gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacca gaagagcctc 1080
 tcctgtctc ccggcaaatg agatatcggg cccgtttaa cgggggaggc ta 1132

<210> 52

<211> 749

<212> DNA

<213> Artificial Sequence

<220>

<223> DNA comprising DNA sequence coding for chG019 light chain

<400> 52

ccagctccg gactctagag ccacatggt gctgcagacc caggtgttca tcagctgct 60
 gctgtggatc agcggcgcct acggcgacat ccagatgacc cagagcccta gcctgctgag 120
 cgccagcgtg ggcgatagag tgacctgaa ctgcaaggcc agccagaaca tctacaagaa 180
 cctggcctgg tatcagcaga agctgggcga gggccccaag ctgctgatct acgacgcaa 240

cacctgcag accggcatcc ccagcagatt ttctggcagc ggcagcggct ccgacttcac 300
 cctgacaatc agcagcctgc agcccagga cgtggccacc tacttttgcc agcagtacta 360
 cagcggctgg gccttcggcg gcgtgaccaa cctggaactg aagagagccg tggccgctcc 420
 ctccgtgttc atcttccac ctagcgacga gcagctgaag tccggcacag cctctgtcgt 480
 gtgcctgctg aacaacttct acccccgcga ggccaagggtg cagtggaagg tggacaatgc 540
 cctgcagtct ggcaacagcc aggaaagcgt gaccgagcag gacagcaagg actccaccta 600
 cagcctgagc agcaccctga ccctgagcaa ggccgactac gagaagcaca aggtgtacgc 660
 ctgcgaagtg acccaccagg gcctgtctag ccccgtagcc aagagcttca accggggcga 720
 gtgttgagtt taaacggggg aggctaact 749

<210> 53

<211> 233

<212> PRT

<213> Artificial Sequence

<220>

<223> amino acid sequeance of chG019 light chain full-length

<400> 53

Met Val Leu Gln Thr Gln Val Phe Ile Ser Leu Leu Leu Trp Ile Ser
 1 5 10 15

Gly Ala Tyr Gly Asp Ile Gln Met Thr Gln Ser Pro Ser Leu Leu Ser
 20 25 30

Ala Ser Val Gly Asp Arg Val Thr Leu Asn Cys Lys Ala Ser Gln Asn
 35 40 45

Ile Tyr Lys Asn Leu Ala Trp Tyr Gln Gln Lys Leu Gly Glu Gly Pro
 50 55 60

Lys Leu Leu Ile Tyr Asp Ala Asn Thr Leu Gln Thr Gly Ile Pro Ser
 65 70 75 80

Arg Phe Ser Gly Ser Gly Ser Gly Ser Asp Phe Thr Leu Thr Ile Ser
 85 90 95

Ser Leu Gln Pro Glu Asp Val Ala Thr Tyr Phe Cys Gln Gln Tyr Tyr
100 105 110

Ser Gly Trp Ala Phe Gly Gly Val Thr Asn Leu Glu Leu Lys Arg Ala
115 120 125

Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu
130 135 140

Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro
145 150 155 160

Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly
165 170 175

Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr
180 185 190

Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His
195 200 205

Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val
210 215 220

Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230

<210> 54

<211> 699

<212> DNA

<213> Artificial Sequence

<220>

<223> nucleotide sequence of chG019 light chain full-length

<400> 54

atggtgctgc agaccaggt gttcatcagc ctgctgctgt ggatcagcgg cgcctacggc	60
gacatccaga tgaccagag ccctagcctg ctgagcgcca gcgtgggcga tagagtgacc	120
ctgaactgca aggccagcca gaacatctac aagaacctgg cctggtatca gcagaagctg	180
ggcgagggcc ccaagctgct gatctacgac gccaacaccc tgcagaccgg catccccagc	240
agattttctg gcagcggcag cggctccgac ttcaccctga caatcagcag cctgcagccc	300

gaggacgtgg ccacctactt ttgccagcag tactacagcg gctgggcctt cggcggcgtg 360
 accaacctgg aactgaagag agccgtggcc gtcacctccg tttcatctt cccacctagc 420
 gacgagcagc tgaagtccgg cacagcctct gtcgtgtgcc tgctgaacaa cttctacccc 480
 cgcgaggcca aggtgcagtg gaagggtggac aatgccctgc agtctggcaa cagccaggaa 540
 agcgtgaccg agcaggacag caaggactcc acctacagcc tgagcagcac cctgacctg 600
 agcaaggccg actacagaaa gcacaagggt tacgcctgcg aagtgacca ccagggcctg 660
 tctagccccg tgaccaagag cttcaaccgg ggcgagtg 699

<210> 55
 <211> 324
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> nucleotide sequence of chG019 light chain variable region

<400> 55
 gacatccaga tgaccagag ccctagcctg ctgagcgcca gcgtgggcga tagagtgacc 60
 ctgaactgca aggccagcca gaacatctac aagaacctgg cctggatca gcagaagctg 120
 ggcgagggcc ccaagctgct gatctacgac gccaacaccc tgcagaccgg catccccagc 180
 agattttctg gcagcggcag cggctccgac ttcacctga caatcagcag cctgcagccc 240
 gaggacgtgg ccacctactt ttgccagcag tactacagcg gctgggcctt cggcggcgtg 300
 accaacctgg aactgaagag agcc 324

<210> 56
 <211> 471
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> amino acid sequence of chG019 heavy chain full-length

<400> 56

Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
 1 5 10 15

Val Leu Ser Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Lys
 20 25 30

Pro Gly Ser Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe
35 40 45

Thr Arg Asn Phe Met His Trp Ile Lys Gln Gln Pro Gly Asn Gly Leu
50 55 60

Glu Trp Ile Gly Trp Ile Tyr Pro Gly Asp Gly Glu Thr Glu Tyr Asn
65 70 75 80

Gln Lys Phe Asn Gly Lys Ala Thr Leu Thr Ala Asp Arg Ser Ser Ser
85 90 95

Thr Ala Tyr Met Glu Leu Ser Arg Leu Thr Ser Glu Asp Ser Ala Val
100 105 110

Tyr Phe Cys Ala Arg Gly Val Tyr Gly Gly Phe Ala Gly Gly Tyr Phe
115 120 125

Asp Phe Trp Gly Gln Gly Val Met Val Thr Val Ser Ser Ala Ser Thr
130 135 140

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
145 150 155 160

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
165 170 175

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
180 185 190

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
195 200 205

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
210 215 220

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu
225 230 235 240

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
245 250 255

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
260 265 270

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
275 280 285

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
290 295 300

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
305 310 315 320

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
325 330 335

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
340 345 350

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
355 360 365

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
370 375 380

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
385 390 395 400

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
405 410 415

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
420 425 430

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
435 440 445

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
450 455 460

Leu Ser Leu Ser Pro Gly Lys
465 470

<210> 57

<211> 1413

<212> DNA

<213> Artificial Sequence

<220>

<223> nucleotide sequence of chG019 heavy chain full-length

<400> 57

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atgaaacacc tgtggttctt cctcctgctg gtggcagctc ccagatgggt gctgagccag    60
gtgcagctgc agcagtctgg cgccgagctc gtgaagcctg gcagcagcgt gaagatcagc    120
tgcaaggcca gcggctacac cttcaccgga aacttcatgc actggatcaa gcagcagccc    180
ggcaacggcc tggaatggat cggctggatc tatccggcg acggcgagac agagtacaac    240
cagaagtica acggcaaggc caccctgacc gccgacagaa gcagctccac cgctcatg    300
gaactgagcc ggctgaccag cgaggacagc gccgtgtact ttgcgccag aggcgtgtac    360
ggcggcttcg ctggcggtta ctctgatttt tggggccagg gcgtgatggt caccgtcagc    420
tcagcctcca ccaagggccc aagcgtcttc ccctggcac cctctccaa gagcacctct    480
ggcggcacag ccgccctggg ctgcctggtc aaggactact tccccgaacc cgtgaccgtg    540
agctggaact caggcgccct gaccagcggc gtgcacacct tccccgtgt cctgcagtcc    600
tcaggactct actccctcag cagcgtgggt accgtgccct ccagcagctt gggcacccag    660
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cccaaatctt gtgacaaaac tcacacatgc ccaccctgcc cagcacctga actcctgggg    780
ggaccctcag tcttcctctt cccccaaaa cccaaggaca ccctcatgat ctccggacc    840
cctgaggta catgcgtggt ggtggacgtg agccacgaag accctgaggt caagttcaac    900
tggtacgtgg acggcgtgga ggtgcataat gccaagacaa agccccggga ggagcagtac    960
aacagcacgt accgggtggt cagcgtcttc accgtcctgc accaggactg gctgaatggc   1020
aaggagtaca agtgaaggt ctccaacaaa gccctcccag ccccatcga gaaaaccatc   1080
tcaaagcca aaggccagcc ccgggaacca caggtgtaca cctgcccc atccgggag   1140
gagatgacca agaaccaggt cagcctgacc tgctgtgtca aaggcttcta tccagcgac   1200

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atcgccgtgg agtgggagag caatggccag cccgagaaca actacaagac caccctccc 1260

gtgctggact cgcacggctc cttcttcctc tacagcaagc tcaccgtgga caagagcagg 1320

tggcagcagg gcaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccactac 1380

accagaaga gcctctccct gtctcccggc aaa 1413

<210> 58

<211> 122

<212> PRT

<213> Artificial Sequence

<220>

<223> amino acid sequesnce of chG019 heavy chain variable region

<400> 58

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

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

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

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

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

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

Ala Arg Gly Val Tyr Gly Gly Phe Ala Gly Gly Tyr Phe Asp Phe Trp
100 105 110

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

<210> 59

<211> 366

<212> DNA

<213> Artificial Sequence

<220>

<223> nucleotide sequence of chG019 heavy chain variable region

<400> 59

caggtgcagc tgcagcagtc tggcgccgag ctctgaagc ctggcagcag cgtgaagatc 60

agctgcaagg ccagcggcta cacctcacc cggaactca tgcactggat caagcagcag 120

cccggcaacg gcctggaatg gatcggctgg atctatccg gcgacggcga gacagagtac 180

aaccagaagt tcaacggcaa ggccaccctg accgccgaca gaagcagctc caccgcctac 240

atggaactga gccggctgac cagcgaggac agcgccgtgt actttgcgc cagaggcgtg 300

tacggcggct tcgtggcggt ctacttcgat tttggggcc agggcgtgat ggtcaccgtc 360

agctca 366

<210> 60

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> amino acid sequence of chG019 CDRH2

<400> 60

Trp Ile Tyr Pro Gly Asp Gly Glu Thr Glu

1 5 10

<210> 61

<211> 233

<212> PRT

<213> Artificial Sequence

<220>

<223> amino acid sequence of hL02 light chain full-length

<400> 61

Met Val Leu Gln Thr Gln Val Phe Ile Ser Leu Leu Trp Ile Ser

1 5 10 15

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

20 25 30

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Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asn
35 40 45

Ile Tyr Lys Asn Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
50 55 60

Lys Leu Leu Ile Tyr Asp Ala Asn Thr Leu Gln Thr Gly Val Pro Ser
65 70 75 80

Arg Phe Ser Gly Ser Gly Ser Gly Ser Asp Phe Thr Leu Thr Ile Ser
85 90 95

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Tyr Tyr
100 105 110

Ser Gly Trp Ala Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
115 120 125

Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu
130 135 140

Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro
145 150 155 160

Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly
165 170 175

Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr
180 185 190

Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His
195 200 205

Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val
210 215 220

Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230

<210> 62
<211> 699

<212> DNA

<213> Artificial Sequence

<220>

<223> nucleotide sequence of hL02 light chain full-length

<400> 62

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atggtgctgc agaccaggt gttcatctcc ctgctgctgt ggatctccgg cgcgtacggc    60
gacatccaga tgaccagag ccctagcagc ctgagcgcca gcgtgggcca cagagtgacc    120
atcacaatga aggccagcca gaacatctac aagaacctgg cctggatatca gcagaagccc    180
ggcaaggccc ccaagctgct gatctacgac gccaacaccc tcagaccgg cggtgccagc    240
agattttctg gcagcggcag cggctccgac ttcacctga caatcagcag cctgcagccc    300
gaggacttcg ccactactt ttgccagcag tactacagcg gctgggcctt cggccagggc    360
accaaggtgg aaatcaagcg tacggtggcc gcccctccg tttcatctt cccccctcc    420
gacgagcagc tgaagtccgg caccgcctcc gtggtgtgcc tgctgaataa cttctacccc    480
agagaggcca aggtgcagtg gaaggtggac aacgccctgc agtccgggaa ctcccaggag    540
agcgtgaccg agcaggacag caaggacagc acctacagcc tgagcagcac cctgaccctg    600
agcaaagccg actacagaaa gcacaaggtg tacgcctgcg aggtgacca ccagggcctg    660
agctcccccg tcaccaagag cttaacagg ggggagtggt                    699

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<210> 63

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> amino acid sequence of hL02 light chain variable region

<400> 63

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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 Lys Ala Ser Gln Asn Ile Tyr Lys Asn
20        25        30

```

```

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

```

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

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

Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Tyr Tyr Ser Gly Trp Ala
85 90 95

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

<210> 64

<211> 324

<212> DNA

<213> Artificial Sequence

<220>

<223> nucleotide sequence of hL02 light chain variable region

<400> 64

gacatccaga tgaccagag ccctagcagc ctgagcgcca gcgtgggcga cagagtgacc 60

atcacatgca aggccagcca gaacatctac aagaacctgg cctggtatca gcagaagccc 120

ggcaaggccc ccaagctgct gatctacgac gccaacaccc tgcagaccgg cgtgcccagc 180

agattttctg gcagcggcag cggctccgac ttcacctga caatcagcag cctgcagccc 240

gaggacttcg ccacctactt ttgccagcag tactacagcg gctgggcctt cggccagggc 300

accaaggtgg aaatcaagcg tacg 324

<210> 65

<211> 233

<212> PRT

<213> Artificial Sequence

<220>

<223> amino acid sequence of hL03 light chain full-length

<400> 65

Met Val Leu Gln Thr Gln Val Phe Ile Ser Leu Leu Trp Ile Ser
1 5 10 15

Gly Ala Tyr Gly Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser
20 25 30

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asn
35 40 45

Ile Tyr Lys Asn Leu Ala Trp Tyr Gln Gln Lys Leu Gly Glu Gly Pro
50 55 60

Lys Leu Leu Ile Tyr Asp Ala Asn Thr Leu Gln Thr Gly Val Pro Ser
65 70 75 80

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
85 90 95

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr
100 105 110

Ser Gly Trp Ala Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
115 120 125

Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu
130 135 140

Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro
145 150 155 160

Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly
165 170 175

Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr
180 185 190

Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His
195 200 205

Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val
210 215 220

Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230

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<210> 66
<211> 699
<212> DNA
<213> Artificial Sequence

<220>
<223> nucleotide sequesnce of hL03 light chain full-length

<400> 66
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gacatccaga tgaccagag ccctagcagc ctgagcgcca gcgtgggcga cagagtgacc 120
atcacatgca aggccagcca gaacatctac aagaacctgg cctggtatca gcagaagctg 180
ggcgagggcc ccaagctgct gatctacgac gccaacaccc tgcagaccgg cgtgcccagc 240
agattttctg gcagcggctc cggcaccgac ttcacctga caatcagcag cctgcagccc 300
gaggacttcg ccacctacta ctgccagcag tactacagcg gctgggcctt tggccagggc 360
accaaggtgg aaatcaagcg tacggtggcc gcccctccg tgttcattt cccccctcc 420
gacgagcagc tgaagtccgg caccgcctcc gtggtgtgcc tgctgaataa cttctacccc 480
agagaggcca aggtgcagtg gaaggtggac aacgccctgc agtccgggaa ctcccaggag 540
agcgtgaccg agcaggacag caaggacagc acctacagcc tgagcagcac cctgaccctg 600
agcaaagccg actacgagaa gcacaaggtg tacgcctgcg aggtgacca ccagggcctg 660
agctcccccg tcaccaagag cttaacagg ggggagtg 699

<210> 67
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> amino acid sequesnce of hL03 light chain variable region

<400> 67

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 Lys Ala Ser Gln Asn Ile Tyr Lys Asn
20 25 30

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

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

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ser Gly Trp Ala
85 90 95

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

<210> 68

<211> 324

<212> DNA

<213> Artificial Sequence

<220>

<223> nucleotide sequesnce of hL03 light chain variable region

<400> 68

gacatccaga tgaccagag ccctagcagc ctgagcgcca gctggggcga cagagtgacc 60

atcacatgca aggccagcca gaacatctac aagaacctgg cctggatatca gcagaagctg 120

ggcgaggggcc ccaagctgct gatctacgac gccaacaccc tgcagaccgg cgtgcccagc 180

agattttctg gcagcggctc cggcaccgac ttaccctga caatcagcag cctgcagccc 240

gaggacttcg ccacctacta ctgccagcag tactacagcg gctgggcctt tggccagggc 300

accaaggtgg aaatcaagcg tacg 324

<210> 69

<211> 471

<212> PRT

<213> Artificial Sequence

<220>

<223> amino acid sequesnce of hH01 heavy chain full-length

<400> 69

Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
1 5 10 15

Val Leu Ser Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
20 25 30

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
35 40 45

Thr Arg Asn Phe Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
50 55 60

Glu Trp Met Gly Trp Ile Tyr Pro Gly Asp Gly Glu Thr Glu Tyr Ala
65 70 75 80

Gln Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Ser
85 90 95

Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Arg Gly Val Tyr Gly Gly Phe Ala Gly Gly Tyr Phe
115 120 125

Asp Phe Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr
130 135 140

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
145 150 155 160

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
165 170 175

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
180 185 190

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
195 200 205

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
210 215 220

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu
225 230 235 240

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
245 250 255

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
260 265 270

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
275 280 285

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
290 295 300

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
305 310 315 320

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
325 330 335

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
340 345 350

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
355 360 365

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
370 375 380

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
385 390 395 400

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
405 410 415

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
420 425 430

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
435 440 445

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
450 455 460

Leu Ser Leu Ser Pro Gly Lys
465 470

<210> 70

<211> 1413

<212> DNA

<213> Artificial Sequence

<220>

<223> nucleotide sequesnce of hH01 heavy chain full-length

<400> 70

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atgaaacacc tgtggttctt cctcctgctg gtggcagctc ccagatgggt gctgagcgaa    60
gtgcagctgg tgcagtctgg cgccgaagtg aagaaaccag gcgccagcgt gaaggtgtcc    120
tgcaaggcca gcggctacac ctttaccggg aacttcatgc actgggtgcg ccaggctcca    180
ggccagggac tggaatggat gggctggatc tatccggcg acggcgagac agagtacgcc    240
cagaaattcc agggcagagt gaccatcacc gccgacacca gcacctccac cgcctacatg    300
gaactgagca gcctgcggag cgaggacacc gccgtgtact attgtgccag aggcgtgtac    360
ggcggcttcg ctggcggcta cttcgatttt tggggccagg gcacctcgt gaccgtcagc    420
tcagcctcca ccaagggccc aagcgtcttc cccctggcac cctcctcaa gagcacctct    480
ggcggcacag ccgccctggg ctgcctggtc aaggactact tccccgaacc cgtgaccgtg    540
agctggaact caggcgcctt gaccagcggc gtgcacacct tccccgtgt cctgcagtcc    600
tcaggactct actcctcag cagcgtgggt accgtgccct ccagcagctt gggcacccag    660
acctacatct gcaacgtgaa tcacaagccc agcaacacca aggtggacaa gagagttgag    720
cccaaattct gtacaaaaac tcacacatgc ccacctgcc cagcacctga actcctgggg    780
ggacctcag tcttctctt cccccaaaa cccaaggaca cctcatgat ctcccgacc    840
cctgaggta catgcgtggt ggtggacgtg agccacgaag accctgaggt caagttcaac    900
tggtacgtgg acggcgtgga ggtgcataat gccaagacaa agccccggga ggagcagtac    960
aacagcacgt accgggtggt cagcgtctc accgtcctgc accaggactg gctgaatggc   1020
aaggagtaca agtgcaaggt ctcaacaaa gccctcccag ccccatcga gaaaaccatc   1080
tcaaagcca aaggccagcc ccgggaacca caggtgtaca ccctgcccc atccggggag   1140

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gagatgacca agaaccaggt cagcctgacc tgcctggta aaggcttcta tcccagcgac 1200
 atcgccgtgg agtgggagag caatggccag cccgagaaca actacaagac caccctccc 1260
 gtgctggact ccgacggctc cttcttctc tacagcaagc tcaccgtgga caagagcagg 1320
 tggcagcagg gcaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccactac 1380
 acccagaaga gcctctccct gtctcccggc aaa 1413

<210> 71

<211> 122

<212> PRT

<213> Artificial Sequence

<220>

<223> amino acid sequesnce of hH01 heavy chain variable region

<400> 71

Glu 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 Arg Asn
 20 25 30

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

Gly Trp Ile Tyr Pro Gly Asp Gly Glu Thr Glu Tyr Ala Gln Lys Phe
 50 55 60

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

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

Ala Arg Gly Val Tyr Gly Gly Phe Ala Gly Gly Tyr Phe Asp Phe Trp
 100 105 110

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

<210> 72
 <211> 366
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> nucleotide sequesnce of hH01 heavy chain variable region

<400> 72
 gaagtgcagc tgggtgcagtc tggcgccgaa gtgaagaaac caggcgccag cgtgaaggtg 60
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 ccaggccagg gactggaatg gatgggctgg atctatcccg gcgacggcga gacagagtac 180
 gcccgaaaat tccagggcag agtgaccatc accgccgaca ccagcacctc caccgcctac 240
 atggaactga gcagcctgcg gagcgaggac accgccgtgt actattgtgc cagaggcgtg 300
 tacggcgggt tcgtggcgg ctacttcgat tttggggcc agggcaccct cgtgaccgtc 360
 agctca 366

<210> 73
 <211> 471
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> amino acid sequesnce of hH02 heavy chain full-length

<400> 73

Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
 1 5 10 15

Val Leu Ser Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
 20 25 30

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
 35 40 45

Thr Arg Asn Phe Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
 50 55 60

Glu Trp Met Gly Trp Ile Tyr Pro Gly Asp Gly Glu Thr Glu Tyr Asn
 65 70 75 80

Gln Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Arg Ser Thr Ser
85 90 95

Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
100 105 110

Tyr Phe Cys Ala Arg Gly Val Tyr Gly Gly Phe Ala Gly Gly Tyr Phe
115 120 125

Asp Phe Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr
130 135 140

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
145 150 155 160

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
165 170 175

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
180 185 190

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
195 200 205

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
210 215 220

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu
225 230 235 240

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
245 250 255

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
260 265 270

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
275 280 285

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
290 295 300

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
305 310 315 320

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
325 330 335

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
340 345 350

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
355 360 365

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
370 375 380

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
385 390 395 400

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
405 410 415

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
420 425 430

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
435 440 445

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
450 455 460

Leu Ser Leu Ser Pro Gly Lys
465 470

<210> 74

<211> 1413

<212> DNA

<213> Artificial Sequence

<220>

<223> nucleotide sequence of hH02 heavy chain full-length

<400> 74

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atgaaacacc tgtggttctt cctcctgctg gtggcagctc ccagatgggt gctgagcgaa    60
gtgcagctgg tgcagtctgg cgccgaagtg aagaaaccag gcgccagcgt gaaggtgtcc    120
tgcaaggcca gcggctacac ctttaccgga aacttcatgc actgggtgcg ccaggctcca    180
ggccaggggac tggaatggat gggctggatc tatcccggcg acggcgagac agagtacaac    240
cagaaattcc agggcagagt gaccatcacc gccgacagaa gcaccagcac cgcctacatg    300
gaactgagca gcctgcggag cgaggatacc gccgtgtact tctgtgccag aggcgtgtac    360
ggcggcttcg ctggcggcta cttcgatttt tggggccagg gcaccctctg gaccgtcagc    420
tcagcctcca ccaagggccc aagcgtcttc cccctggcac cctcctcaa gagcacctct    480
ggcggcacag ccgccctggg ctgcctggtc aaggactact tccccgaacc cgtgaccgtg    540
agctggaact caggcgcctt gaccagcggc gtgcacacct tccccgtgt cctgcagtcc    600
tcaggactct actccctcag cagcgtgggt accgtgccct ccagcagctt gggcaccag    660
acctacatct gcaacgtgaa tcacaagccc agcaacacca aggtggacaa gagagttgag    720
cccaaattct gtgacaaaac tcacacatgc ccaccctgcc cagcacctga actcctgggg    780
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aacagcacgt accgggtggt cagcgtcttc accgtcctgc accaggactg gctgaatggc   1020
aaggagtaca agtgcaaggt ctcaaacaaa gccctcccag ccccatcga gaaaaccatc   1080
tcaaagcca aaggccagcc ccgggaacca caggtgtaca cctgcccc atcccgggag   1140
gagatgacca agaaccaggt cagcctgacc tgcttggtca aaggcttcta tccagcgac   1200
atgccgtgg agtgggagag caatggccag cccgagaaca actacaagac caccctccc   1260
gtgtggact ccgacggctc cttctcttc tacagcaagc tcaccgtgga caagagcagg   1320
tggcagcagg gcaacgtctt ctatgctcc gtgatgcatg aggtctgca caaccactac   1380
accagaaga gcctctccct gtctccggc aaa                                1413

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<210> 75

<211> 122

<212> PRT

<213> Artificial Sequence

<220>

<223> amino acid sequeance of hH02 heavy chain variable region

<400> 75

Glu 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 Arg Asn
20 25 30

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

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

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

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

Ala Arg Gly Val Tyr Gly Gly Phe Ala Gly Gly Tyr Phe Asp Phe Trp
100 105 110

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

<210> 76

<211> 366

<212> DNA

<213> Artificial Sequence

<220>

<223> nucleotide sequeance of hH02 heavy chain variable region

<400> 76

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ccaggccagg gactggaatg gatgggctgg atctatcccg gcgacggcga gacagagtac 180

aaccagaaat tccagggcag agtgaccatc accgccgaca gaagcaccag caccgcctac 240

atggaactga gcagcctgcg gagcgaggat accgccgtgt acttctgtgc cagaggcgtg 300

tacggcggct tcgtggcgg ctacttcgat tttggggcc agggcaccct cgtgaccgtc 360

agctca 366

<210> 77

<211> 471

<212> PRT

<213> Artificial Sequence

<220>

<223> amino acid sequesnce of hH04 heavy chain full-length

<400> 77

Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
1 5 10 15

Val Leu Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
20 25 30

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
35 40 45

Thr Arg Asn Phe Met His Trp Ile Arg Gln Ala Pro Gly Gln Gly Leu
50 55 60

Glu Trp Met Gly Trp Ile Tyr Pro Gly Asp Gly Glu Thr Glu Tyr Ala
65 70 75 80

Gln Lys Phe Gln Gly Arg Val Thr Leu Thr Ala Asp Arg Ser Thr Ser
85 90 95

Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Arg Gly Val Tyr Gly Gly Phe Ala Gly Gly Tyr Phe
115 120 125

Asp Phe Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr
130 135 140

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
145 150 155 160

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
165 170 175

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
180 185 190

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
195 200 205

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
210 215 220

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu
225 230 235 240

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
245 250 255

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
260 265 270

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
275 280 285

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
290 295 300

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
305 310 315 320

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
325 330 335

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
340 345 350

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
355 360 365

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
370 375 380

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
385 390 395 400

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
405 410 415

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
420 425 430

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
435 440 445

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gaactgagca gcctgcggag cgaggacacc gccgtgtact attgtgccag aggcgtgtac 360
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 cccaaatctt gtgacaaaac tcacacatgc ccacctgcc cagcacctga actcctgggg 780
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<212> PRT

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 20 25 30

Phe Met His Trp Ile Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

Gly Trp Ile Tyr Pro Gly Asp Gly Glu Thr Glu Tyr Ala Gln Lys Phe
50 55 60

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

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

Ala Arg Gly Val Tyr Gly Gly Phe Ala Gly Gly Tyr Phe Asp Phe Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
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<210> 80

<211> 366

<212> DNA

<213> Artificial Sequence

<220>

<223> nucleotide sequence of hH04 heavy chain variable region

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cctggacagg gcctggaatg gatgggctgg atctatcccg ggcacggcga gacagagtac 180

gcccagaaat tccagggcag agtgacctg accgcccaga gaagcaccag caccgcctac 240

atggaactga gcagcctgcg gagcgaggac accgccgtgt actattgtgc cagaggcgtg 300

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agctca

366

<210> 81

<211> 235

<212> PRT

<213> Artificial Sequence

<220>

<223> amino acid sequence of NOV0712 light chain full-length

<400> 81

Met Val Leu Gln Thr Gln Val Phe Ile Ser Leu Leu Leu Trp Ile Ser
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20 25 30

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser
35 40 45

Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
50 55 60

Lys Leu Leu Ile Tyr Ala Val Ser Thr Leu Gln Ser Gly Val Pro Ser
65 70 75 80

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
85 90 95

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Gly
100 105 110

Thr Phe Pro Pro Thr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
115 120 125

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
130 135 140

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
145 150 155 160

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
165 170 175

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
180 185 190

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
195 200 205

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
 210 215 220

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
 225 230 235

<210> 82

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<212> DNA

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 number 81

<400> 82

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<211> 467

<212> PRT

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<400> 83

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20 25 30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
35 40 45

Ser Ser His Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ser Val Ile Ser Gly Ser Gly Ser Asn Thr Gly Tyr Ala
65 70 75 80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
85 90 95

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Arg Gln Trp Gly Ser Tyr Ala Phe Asp Ser Trp Gly
115 120 125

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
130 135 140

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
145 150 155 160

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
165 170 175

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
180 185 190

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
195 200 205

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
210 215 220

Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys
225 230 235 240

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
245 250 255

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
260 265 270

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
275 280 285

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
290 295 300

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
305 310 315 320

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
325 330 335

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
340 345 350

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
355 360 365

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
370 375 380

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
385 390 395 400

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
405 410 415

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
420 425 430

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met

12815 of 14295

435 440 445

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Pro Gly Lys
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ggaaagggac tggaatgggt gtccgtgatc agcggcagcg gctccaatac cggtacgcc 240

gatagcgtga agggccggtt caccatcagc cgggacaaca gcaagaacac cctgtacctg 300

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<400> 85
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<210> 86
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(12) 特許協力条約に基づいて公開された国際出願

(19) 世界知的所有権機関
国際事務局

(43) 国際公開日

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(81) 指定国(表示のない限り、全ての種類の国内保護が可能): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) 指定国(表示のない限り、全ての種類の広域保護が可能): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), ユーラシア (AM, AZ, BY, KG, KZ, RU, TJ, TM), ヨーロッパ (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

添付公開書類:

- 一 国際調査報告(条約第21条(3))
- 一 明細書の別個の部分として表した配列リスト(規則5.2(a))

(54) Title: ANTI-CDH6 ANTIBODY AND ANTI-CDH6 ANTIBODY-DRUG CONJUGATE

(54) 発明の名称: 抗CDH6抗体及び抗CDH6抗体-薬物コンジュゲート

(57) Abstract: The present invention addresses the problem of providing: an antibody having an internalization activity of binding to CDH6; an antibody-drug conjugate consisting of the aforesaid antibody and a drug having an antitumor activity; a medicine using the antibody-drug conjugate, said medicine having a therapeutic effect on tumors; a method for treating tumors using the antibody, the antibody-drug conjugate or the medicine; etc. Provided are: an anti-CDH6 antibody having an internalization activity; an antibody-drug conjugate consisting of the aforesaid antibody and a drug having an antitumor activity; and a medicine and a method for treating tumors using the same.

(57) 要約: 本発明の課題は、CDH6に結合する内在化活性を有する抗体、該抗体と抗腫瘍活性を有する薬物との抗体-薬物コンジュゲート、該抗体-薬物コンジュゲートを用いた腫瘍に対する治療効果を有する医薬品、及び、該抗体、該抗体-薬物コンジュゲート又は該医薬品を用いた腫瘍の治療方法等を提供することである。本発明により、内在化活性を有する抗CDH6抗体、該抗体と抗腫瘍活性を有する薬物との抗体-薬物コンジュゲート、これらを用いる医薬品および腫瘍の治療方法が提供される。

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明 細 書

発明の名称：

抗CDH6抗体及び抗CDH6抗体－薬物コンジュゲート

技術分野

[0001] 本発明は、CDH6に結合し、内在化作用を有する抗CDH6抗体、該抗CDH6抗体の製造方法、ならびに該抗体を含む抗体－薬物コンジュゲート、該抗体－薬物コンジュゲートを含む抗腫瘍剤等に関する。

背景技術

[0002] カドヘリン (C a d h e r i n) は、細胞膜表面に存在する糖タンパク質で、カルシウムイオン依存的にN末端側の細胞外ドメイン同士が結合することで、細胞間接着分子として、また細胞間相互作用を担うシグナル分子として機能する。カドヘリンスーパーファミリーの内、クラシックカドヘリンに分類される分子群は、5個の細胞外ドメイン (e x t r a c e l l u l a r d o m a i n、ECドメイン) と1個の膜貫通領域、及び細胞内ドメインから構成される1回膜貫通タンパク質である。クラシックカドヘリンはアミノ酸配列の相同性から、E－カドヘリンやN－カドヘリンに代表されるタイプIファミリーと、タイプIIファミリーに分類される。

[0003] カドヘリン6 (C a d h e r i n - 6、CDH6) は、タイプIIカドヘリンファミリーに分類される、790アミノ酸からなる1回膜貫通タンパク質であり、N末端側を細胞外、C末端側を細胞内に持つ。ヒトCDH6遺伝子は1995年に初めてクローニングされ (非特許文献1)、NM__004932、NP__004923 (NCBI) 等のアクセッション番号により参照可能である。

[0004] CDH6は発生期において脳や腎臓で特異的に発現しており、中枢神経系の回路形成 (非特許文献2、非特許文献3) や腎臓のネフロン発生時 (非特許文献4、非特許文献5) に重要な役割を担うことが報告されている。成人の正常組織では、CDH6の発現は腎尿細管や胆管上皮細胞などに限局され

ている。

[0005] 一方で、成人のいくつかの癌種において、腫瘍部で特異的にCDH6の発現が亢進することが知られており、ヒト腎細胞癌、特に腎淡明細胞癌では、CDH6発現と予後不良との相関や、腫瘍マーカーとしての利用可能性が報告されている（非特許文献6、非特許文献7）。ヒト卵巣癌でもCDH6の高発現が報告されている（非特許文献8）、ヒト甲状腺癌の上皮間葉変換と転移にCDH6が関与するとの報告もある（非特許文献9）。また、CDH6は、ヒト胆管癌およびヒト小細胞肺癌でも発現していることが報告されている（非特許文献12、13）。

[0006] がんは死亡原因の上位を占め、その罹患数は人口の高齢化と共に増加することが予想されているが、未だ治療ニーズは十分に満たされていない。従来の化学療法剤は、その選択性の低さから腫瘍細胞だけでなく正常細胞に対しても傷害性を持つことによる副作用や、十分な薬剤量を投与できないことで薬剤の効果を十分に得ることが出来ないことが問題となっている。このため近年では、がん細胞に特徴的な変異や高発現を示す分子、細胞のがん化に関与する特定の分子を標的としたより選択性の高い分子標的薬や抗体医薬の開発が行われている。

[0007] 抗体は血中安定性が高く、標的抗原に特異的に結合することから副作用の軽減が期待されており、がん細胞表面に高発現している分子に対する抗体医薬が多数開発されている。抗体の抗原特異的な結合能を利用した技術の一つとして、抗体-薬物コンジュゲート（Antibody-Drug Conjugate；ADC）が挙げられる。ADCは、がん細胞表面に発現している抗原に結合し、その結合によって抗原を細胞内に内在化できる抗体に、細胞傷害活性を有する薬物を結合させたものである。ADCは、がん細胞に効率的に薬物を送達できることによって、がん細胞内に薬物を蓄積させ、がん細胞を死滅させることが期待できる（非特許文献10、特許文献1及び2）。ADCとして例えば、抗CD30モノクローナル抗体にモノメチルアウリスチンEを結合させたアドセトリス（商標）（ブレンツキシマブ ベド

チン) がホジキンリンパ腫と未分化大細胞リンパ腫の治療薬として認可されている。また、抗HER2モノクローナル抗体にエムタンシンを結合させたカドサイラ(商標)(トラスツズマブ エムタンシン) がHER2陽性の進行、再発乳癌の治療に用いられている。

[0008] 抗腫瘍薬としてのADCに適した標的抗原の特徴としては、がん細胞表面で特異的に高発現し、正常細胞では低発現又は発現していないこと、細胞内に内在化できること、抗原が細胞表面から分泌されないことなどが挙げられる。また、ADCに適した抗体の重要な特徴としては、標的となる抗原に特異的に結合することに加えて、高い内在化能を有することが挙げられる。抗体の内在化能は標的抗原と抗体の両方の性質に依存するものであり、標的の分子構造から内在化に適した抗原結合部位を推定したり、抗体の結合強度や物性等から容易に内在化能の高い抗体を推測したりすることは困難である。このため、標的抗原に対して高い内在化能を有する抗体を取得することは、有効性の高いADCを開発する上で重要な課題となっている(非特許文献11)。

[0009] CDH6を標的としたADCとしては、CDH6のECドメイン5(EC5)に特異的に結合する抗CDH6抗体にDM4を結合させたADCが知られている(特許文献3)。

先行技術文献

特許文献

[0010] 特許文献1: WO2014/057687

特許文献2: US2016/0297890

特許文献3: WO2016/024195

非特許文献

[0011] 非特許文献1: Shimoyama Y, et al., Cancer Research, 2206-2211, 55, May 15, 1995

非特許文献2: Inoue T, et al., Developmental Biology, 183-194, 1997

非特許文献3: Osterhout J A, et al., Neuron, 632-639, 71, Aug 25, 2011

非特許文献4: Cho E A, et al., Development, 803-812, 125, 1998

非特許文献5: Mah S P, et al., Developmental Biology, 38-53, 223, 2000

非特許文献6: Paul R, et al., Cancer Research, 2741-2748, July 1, 57, 1997

非特許文献7: Shimazui T, et al., Cancer, 963-968, 101 (5), Sep. 1, 2004

非特許文献8: Koebel M, et al., PLoS Medicine, 1749-1760, 5 (12), e232, Dec. 2008

非特許文献9: Gugnoni M, et al., Oncogene, 667-677, 36, 2017

非特許文献10: Polakis P., Pharmacological Reviews, 3-19, 68, 2016

非特許文献11: Peters C, et al., Bioscience Reports, 1-20, 35, 2015

非特許文献12: Goepfert B, et al., Epigenetics, 780-790, 11 (11), 2016

非特許文献13: Yokoi S, et al., American Journal of Pathology, 207-216, 161, 1, 2002

発明の概要

発明が解決しようとする課題

[0012] 本発明の課題は、CDH6に対して特異的に結合する高い内在化活性を有する抗体、該抗体を含む高い抗腫瘍活性を有する抗体-薬物コンジュゲート、該抗体-薬物コンジュゲートを用いた腫瘍に対する治療効果を有する医薬

品、及び、当該抗体、抗体－薬物コンジュゲート又は医薬品を用いた腫瘍の治療方法等を提供することである。

課題を解決するための手段

[0013] 本発明者らは、上記課題を達成するために鋭意検討したところ、驚くべきことにCDH6の細胞外ドメイン3（本明細書中、EC3とも称する）に特異的に結合する抗体が、CDH6を発現する細胞において極めて高い内在化活性を有しADC抗体として有用であることを見出した。更に、当該抗CDH6抗体に、細胞内で毒性を発揮する薬剤を特定の構造のリンカーを介して結合させた抗CDH6抗体－薬物コンジュゲートは、従来のCDH6薬物複合体よりも強い抗腫瘍活性を示すことを見出した。

[0014] 本願発明は以下の発明を包含する；

[1] 配列番号4に記載のアミノ酸配列に特異的に結合し、細胞内に取り込まれる内在化能を有する、抗体又は当該抗体の機能性断片；

[2] 配列番号4に記載のアミノ酸配列への結合に対して、以下の（1）～（5）：

（1）配列番号53の21～233番目に記載のアミノ酸配列からなる軽鎖及び配列番号56の20～471番目に記載のアミノ酸配列からなる重鎖を有する抗体、

（2）配列番号61の21～233番目に記載のアミノ酸配列からなる軽鎖及び配列番号69の20～471番目に記載のアミノ酸配列からなる重鎖を有する抗体、

（3）配列番号61の21～233番目に記載のアミノ酸配列からなる軽鎖及び配列番号73の20～471番目に記載のアミノ酸配列からなる重鎖を有する抗体、

（4）配列番号65の21～233番目に記載のアミノ酸配列からなる軽鎖及び配列番号73の20～471番目に記載のアミノ酸配列からなる重鎖を有する抗体、及び

（5）配列番号61の21～233番目に記載のアミノ酸配列からなる軽鎖

及び配列番号 77 の 20～471 番目に記載のアミノ酸配列からなる重鎖を有する抗体、

からなる群から選択される抗体のうち少なくともいずれか 1 つと競合阻害活性を有する [1] に記載の抗体又は当該抗体の機能性断片；

[3] 以下の (1)～(4)：

(1) 配列番号 12 に記載のアミノ酸配列からなる C D R L 1、配列番号 13 に記載のアミノ酸配列からなる C D R L 2 及び配列番号 14 に記載のアミノ酸配列からなる C D R L 3、

(2) 配列番号 22 に記載のアミノ酸配列からなる C D R L 1、配列番号 23 に記載のアミノ酸配列からなる C D R L 2 及び配列番号 24 に記載のアミノ酸配列からなる C D R L 3、

(3) 配列番号 32 に記載のアミノ酸配列からなる C D R L 1、配列番号 33 に記載のアミノ酸配列からなる C D R L 2 及び配列番号 34 に記載のアミノ酸配列からなる C D R L 3、及び

(4) 配列番号 42 に記載のアミノ酸配列からなる C D R L 1、配列番号 43 に記載のアミノ酸配列からなる C D R L 2 及び配列番号 44 に記載のアミノ酸配列からなる C D R L 3、

からなる群から選択されるいずれか 1 つに記載の C D R L 1、C D R L 2 及び C D R L 3、並びに、

以下の (5)～(9)：

(5) 配列番号 17 に記載のアミノ酸配列からなる C D R H 1、配列番号 18 に記載のアミノ酸配列からなる C D R H 2 及び配列番号 19 に記載のアミノ酸配列からなる C D R H 3、

(6) 配列番号 27 に記載のアミノ酸配列からなる C D R H 1、配列番号 28 に記載のアミノ酸配列からなる C D R H 2 及び配列番号 29 に記載のアミノ酸配列からなる C D R H 3、

(7) 配列番号 37 に記載のアミノ酸配列からなる C D R H 1、配列番号 38 に記載のアミノ酸配列からなる C D R H 2 及び配列番号 39 に記載のアミ

ノ酸配列からなるCDRH3、

(8) 配列番号47に記載のアミノ酸配列からなるCDRH1、配列番号48に記載のアミノ酸配列からなるCDRH2及び配列番号49に記載のアミノ酸配列からなるCDRH3、及び

(9) 配列番号17に記載のアミノ酸配列からなるCDRH1、配列番号60に記載のアミノ酸配列からなるCDRH2及び配列番号19に記載のアミノ酸配列からなるCDRH3、

からなる群から選択されるいずれか1つに記載のCDRH1、CDRH2及びCDRH3を含む、

[1] 又は [2] のいずれか1項に記載の抗体又は当該抗体の機能性断片；

[4] 以下の(1)～(5)：

(1) 配列番号12に記載のアミノ酸配列からなるCDRL1、配列番号13に記載のアミノ酸配列からなるCDRL2及び配列番号14に記載のアミノ酸配列からなるCDRL3、及び、配列番号17に記載のアミノ酸配列からなるCDRH1、配列番号18に記載のアミノ酸配列からなるCDRH2及び配列番号19に記載のアミノ酸配列からなるCDRH3、

(2) 配列番号22に記載のアミノ酸配列からなるCDRL1、配列番号23に記載のアミノ酸配列からなるCDRL2及び配列番号24に記載のアミノ酸配列からなるCDRL3、及び、配列番号27に記載のアミノ酸配列からなるCDRH1、配列番号28に記載のアミノ酸配列からなるCDRH2及び配列番号29に記載のアミノ酸配列からなるCDRH3、

(3) 配列番号32に記載のアミノ酸配列からなるCDRL1、配列番号33に記載のアミノ酸配列からなるCDRL2及び配列番号34に記載のアミノ酸配列からなるCDRL3、及び、配列番号37に記載のアミノ酸配列からなるCDRH1、配列番号38に記載のアミノ酸配列からなるCDRH2及び配列番号39に記載のアミノ酸配列からなるCDRH3、

(4) 配列番号42に記載のアミノ酸配列からなるCDRL1、配列番号43に記載のアミノ酸配列からなるCDRL2及び配列番号44に記載のアミ

ノ酸配列からなるCDRL3、及び、配列番号47に記載のアミノ酸配列からなるCDRH1、配列番号48に記載のアミノ酸配列からなるCDRH2及び配列番号49に記載のアミノ酸配列からなるCDRH3、及び

(5) 配列番号12に記載のアミノ酸配列からなるCDRL1、配列番号13に記載のアミノ酸配列からなるCDRL2及び配列番号14に記載のアミノ酸配列からなるCDRL3、及び、配列番号17に記載のアミノ酸配列からなるCDRH1、配列番号60に記載のアミノ酸配列からなるCDRH2及び配列番号19に記載のアミノ酸配列からなるCDRH3、からなる群から選択されるCDRL1、CDRL2及びCDRL3、並びに、CDRH1、CDRH2及びCDRH3を含む、

[1]～[3]のいずれか1項に記載の抗体又は当該抗体の機能性断片；

[5] ヒト化されている[1]～[4]のいずれか1項に記載の抗体又は当該抗体の機能性断片；

[6] 以下の(1)～(4)：

(1) 配列番号63に記載のアミノ酸配列からなる軽鎖可変領域、

(2) 配列番号67に記載のアミノ酸配列からなる軽鎖可変領域、

(3) (1)～(2)のアミノ酸配列において各CDR配列以外のフレームワーク領域の配列に対して少なくとも95%以上の配列同一性を有するアミノ酸配列、及び

(4) (1)～(3)のアミノ酸配列において各CDR配列以外のフレームワーク領域の配列において1又は数個のアミノ酸が欠失、置換又は付加されたアミノ酸配列

からなる群から選択されるいずれか1つに記載の軽鎖可変領域、並びに、以下の(5)～(9)：

(5) 配列番号71に記載のアミノ酸配列からなる重鎖可変領域、

(6) 配列番号75に記載のアミノ酸配列からなる重鎖可変領域、

(7) 配列番号79に記載のアミノ酸配列からなる重鎖可変領域、

(8) (5)～(7)のアミノ酸配列において各CDR配列以外のフレーム

ワーク領域の配列に対して少なくとも 95 %以上の配列相同性を有するアミノ酸配列、及び

(9) (5) ~ (8) のアミノ酸配列において各 C D R 配列以外のフレームワーク領域の配列において 1 又は数個のアミノ酸が欠失、置換又は付加されたアミノ酸配列

からなる群から選択されるいずれか 1 つに記載の重鎖可変領域、
を有する [1] ~ [5] のいずれか 1 項に記載の抗体又は当該抗体の機能性断片；

[7] 以下の (1) ~ (4)：

(1) 配列番号 63 に記載のアミノ酸配列からなる軽鎖可変領域及び配列番号 71 に記載のアミノ酸配列からなる重鎖可変領域、

(2) 配列番号 63 に記載のアミノ酸配列からなる軽鎖可変領域及び配列番号 75 に記載のアミノ酸配列からなる重鎖可変領域、

(3) 配列番号 67 に記載のアミノ酸配列からなる軽鎖可変領域及び配列番号 75 に記載のアミノ酸配列からなる重鎖可変領域、又は

(4) 配列番号 63 に記載のアミノ酸配列からなる軽鎖可変領域及び配列番号 79 に記載のアミノ酸配列からなる重鎖可変領域、

のいずれかの軽鎖可変領域及び重鎖可変領域、
を含む [1] ~ [6] のいずれか 1 項に記載の抗体又は当該抗体の機能性断片；

[8] 以下の (1) ~ (4)：

(1) 配列番号 61 の 21 ~ 233 番目のアミノ酸配列からなる軽鎖及び配列番号 69 の 20 ~ 471 番目のアミノ酸配列からなる重鎖、

(2) 配列番号 61 の 21 ~ 233 番目のアミノ酸配列からなる軽鎖及び配列番号 73 の 20 ~ 471 番目のアミノ酸配列からなる重鎖、

(3) 配列番号 65 の 21 ~ 233 番目のアミノ酸配列からなる軽鎖及び配列番号 73 の 20 ~ 471 番目のアミノ酸配列からなる重鎖、又は

(4) 配列番号 61 の 21 ~ 233 番目のアミノ酸配列からなる軽鎖及び配

列番号 77 の 20～471 番目のアミノ酸配列からなる重鎖、
のいずれかを有する [1] ～ [7] のいずれか 1 項に記載の抗体又は当該抗体の機能性断片；

[9] 配列番号 61 の 21～233 番目のアミノ酸配列からなる軽鎖及び配列番号 69 の 20～471 番目のアミノ酸配列からなる重鎖を有する [8] に記載の抗体又は当該抗体の機能性断片；

[10] 配列番号 61 の 21～233 番目のアミノ酸配列からなる軽鎖及び配列番号 73 の 20～471 番目のアミノ酸配列からなる重鎖を有する [8] に記載の抗体又は当該抗体の機能性断片；

[11] 配列番号 65 の 21～233 番目のアミノ酸配列からなる軽鎖及び配列番号 73 の 20～471 番目のアミノ酸配列からなる重鎖を有する [8] に記載の抗体又は当該抗体の機能性断片；

[12] 配列番号 61 の 21～233 番目のアミノ酸配列からなる軽鎖及び配列番号 77 の 20～471 番目のアミノ酸配列からなる重鎖を有する [8] に記載の抗体又は当該抗体の機能性断片；

[13] 機能性断片が Fab、F(ab')₂、Fab' 及び Fv からなる群から選択される [1] ～ [12] のいずれか 1 項に記載の抗体の機能性断片；

[14] [1] ～ [13] のいずれか 1 項に記載の抗体又は当該抗体の機能性断片をコードするポリヌクレオチド；

[15] 以下の (1) ～ (5)：

(1) 配列番号 12 に記載のアミノ酸配列からなる CDR L1、配列番号 13 に記載のアミノ酸配列からなる CDR L2 及び配列番号 14 に記載のアミノ酸配列からなる CDR L3 を含む軽鎖可変領域をコードするポリヌクレオチド、及び、配列番号 17 に記載のアミノ酸配列からなる CDR H1、配列番号 18 に記載のアミノ酸配列からなる CDR H2 及び配列番号 19 に記載のアミノ酸配列からなる CDR H3 を含む重鎖可変領域をコードするポリヌクレオチド、

(2) 配列番号 22 に記載のアミノ酸配列からなる C D R L 1、配列番号 23 に記載のアミノ酸配列からなる C D R L 2 及び配列番号 24 に記載のアミノ酸配列からなる C D R L 3 を含む軽鎖可変領域をコードするポリヌクレオチド、及び、配列番号 27 に記載のアミノ酸配列からなる C D R H 1、配列番号 28 に記載のアミノ酸配列からなる C D R H 2 及び配列番号 29 に記載のアミノ酸配列からなる C D R H 3 を含む重鎖可変領域をコードするポリヌクレオチド、

(3) 配列番号 32 に記載のアミノ酸配列からなる C D R L 1、配列番号 33 に記載のアミノ酸配列からなる C D R L 2 及び配列番号 34 に記載のアミノ酸配列からなる C D R L 3 を含む軽鎖可変領域をコードするポリヌクレオチド、及び、配列番号 37 に記載のアミノ酸配列からなる C D R H 1、配列番号 38 に記載のアミノ酸配列からなる C D R H 2 及び配列番号 39 に記載のアミノ酸配列からなる C D R H 3 を含む重鎖可変領域をコードするポリヌクレオチド、

(4) 配列番号 42 に記載のアミノ酸配列からなる C D R L 1、配列番号 43 に記載のアミノ酸配列からなる C D R L 2 及び配列番号 44 に記載のアミノ酸配列からなる C D R L 3 を含む軽鎖可変領域をコードするポリヌクレオチド、及び、配列番号 47 に記載のアミノ酸配列からなる C D R H 1、配列番号 48 に記載のアミノ酸配列からなる C D R H 2 及び配列番号 49 に記載のアミノ酸配列からなる C D R H 3 を含む重鎖可変領域をコードするポリヌクレオチド、並びに

(5) 配列番号 12 に記載のアミノ酸配列からなる C D R L 1、配列番号 13 に記載のアミノ酸配列からなる C D R L 2 及び配列番号 14 に記載のアミノ酸配列からなる C D R L 3 を含む軽鎖可変領域をコードするポリヌクレオチド、及び、配列番号 17 に記載のアミノ酸配列からなる C D R H 1、配列番号 60 に記載のアミノ酸配列からなる C D R H 2 及び配列番号 19 に記載のアミノ酸配列からなる C D R H 3 を含む重鎖可変領域をコードするポリヌクレオチド、

からなる群から選択されるいずれか1つに記載のポリヌクレオチドを含む〔14〕に記載のポリヌクレオチド；

〔16〕配列番号61の21～233番目のアミノ酸配列からなる軽鎖をコードするポリヌクレオチド及び配列番号69の20～471番目のアミノ酸配列からなる重鎖をコードするポリヌクレオチドを含む〔14〕又は〔15〕に記載のポリヌクレオチド；

〔17〕配列番号61の21～233番目のアミノ酸配列からなる軽鎖をコードするポリヌクレオチド及び配列番号73の20～471番目のアミノ酸配列からなる重鎖をコードするポリヌクレオチドを含む〔14〕又は〔15〕に記載のポリヌクレオチド；

〔18〕配列番号65の21～233番目のアミノ酸配列からなる軽鎖をコードするポリヌクレオチド及び配列番号73の20～471番目のアミノ酸配列からなる重鎖をコードするポリヌクレオチドを含む〔14〕又は〔15〕に記載のポリヌクレオチド；

〔19〕配列番号61の21～233番目のアミノ酸配列からなる軽鎖をコードするポリヌクレオチド及び配列番号77の20～471番目のアミノ酸配列からなる重鎖をコードするポリヌクレオチドを含む〔14〕又は〔15〕に記載のポリヌクレオチド；

〔20〕〔14〕～〔19〕のいずれか1項に記載のポリヌクレオチドを含有する発現ベクター；

〔21〕〔20〕に記載の発現ベクターにより形質転換された宿主細胞；

〔22〕宿主細胞が真核細胞である〔21〕に記載の宿主細胞；

〔23〕〔21〕又は〔22〕に記載の宿主細胞を培養する工程、及び当該工程で得られた培養物から目的の抗体又は当該抗体の機能性断片を採取する工程を含むことを特徴とする当該抗体又は当該抗体の機能性断片の製造方法；

〔24〕重鎖又は軽鎖が、N-結合への糖鎖付加、O-結合への糖鎖付加、N末のプロセッシング、C末のプロセッシング、脱アミド化、アスパラギン

酸の異性化、メチオニンの酸化、N末にメチオニン残基の付加、プロリン残基のアミド化、N末グルタミンもしくはN末グルタミン酸のピログルタミン酸化、及びカルボキシル末端における1つ又は2つのアミノ酸欠失からなる群より選択される1又は2以上の修飾をうけた、[1]～[13]のいずれか1項に記載の抗体又は当該抗体の機能性断片；

[25] 重鎖のカルボキシル末端において1つ又は2つのアミノ酸が欠失している[24]に記載の抗体；

[26] 2本の重鎖の双方でカルボキシル末端において1つのアミノ酸が欠失している[25]に記載の抗体；

[27] 重鎖のカルボキシル末端のプロリン残基が更にアミド化されている[24]～[26]のいずれか1項に記載の抗体；

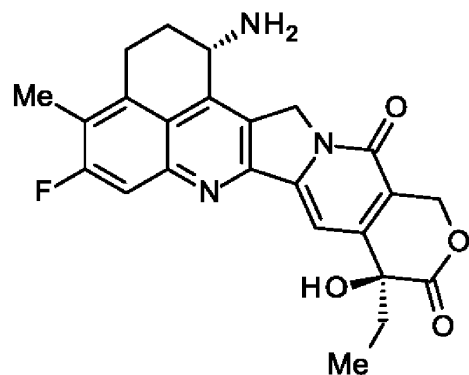
[28] 抗体依存性細胞傷害活性を増強させるために糖鎖修飾が調節されている[1]～[13]及び[24]～[27]からなる群から選択されるいずれか1項に記載の抗体又は当該抗体の機能性断片；

[29] [1]～[13]及び[24]～[28]からなる群から選択されるいずれか1項に記載の抗体又は当該抗体の機能性断片に薬物が結合している抗体－薬物コンジュゲート；

[30] 薬物が抗腫瘍性化合物である、[29]に記載の抗体－薬物コンジュゲート；

[31] 抗腫瘍性化合物が次式：

[0015] [化1]



[0016] で示される抗腫瘍性化合物である [30] に記載の抗体-薬物コンジュゲート；

[32] 抗体と薬物が、次式 (a) ~ (f)：

(a) - (Succinimid-3-yl-N) - CH₂CH₂-C(=O) - GGFG-NH-CH₂CH₂CH₂-C(=O) -、

(b) - (Succinimid-3-yl-N) - CH₂CH₂CH₂CH₂CH₂-C(=O) - GGFG-NH-CH₂CH₂CH₂-C(=O) -、

(c) - (Succinimid-3-yl-N) - CH₂CH₂CH₂CH₂CH₂-C(=O) - GGFG-NH-CH₂-O-CH₂-C(=O) -、

(d) - (Succinimid-3-yl-N) - CH₂CH₂CH₂CH₂CH₂-C(=O) - GGFG-NH-CH₂CH₂-O-CH₂-C(=O) -、

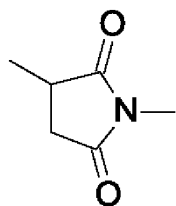
(e) - (Succinimid-3-yl-N) - CH₂CH₂-C(=O) - NH-CH₂CH₂O-CH₂CH₂O-CH₂CH₂-C(=O) - GGFG-NH-CH₂CH₂CH₂-C(=O) -、及び

(f) - (Succinimid-3-yl-N) - CH₂CH₂-C(=O) - NH-CH₂CH₂O-CH₂CH₂O-CH₂CH₂O-CH₂CH₂O-CH₂CH₂-C(=O) - GGFG-NH-CH₂CH₂CH₂-C(=O) -、
からなる群から選択されるいずれかの構造のリンカーを介して結合している、[29] ~ [31] のいずれか1項に記載の抗体-薬物コンジュゲート。

(ここで、抗体は、-(Succinimid-3-yl-N)の末端において結合する。抗腫瘍性化合物は、1位のアミノ基の窒素原子を結合部位として、(a)、(b)、(e)又は(f)の-CH₂CH₂CH₂-C(=O)-部分、(c)のCH₂-O-CH₂-C(=O)-部分又は(d)のCH₂CH₂-O-CH₂-C(=O)-部分のカルボニル基に結合する。上記式中GGFGは、グリシン-グリシン-フェニルアラニン-グリシンからなるペプチド結合でつながっているアミノ酸配列を示す。

-(Succinimid-3-yl-N)-は次式：

[0017] [化2]



[0018] で示される構造であり、このものの3位で抗体と結合し、1位の窒素原子上でこれを含むリンカー構造内のメチレン基と結合する。) ;

[33] リンカーが以下の(c)、(d)及び(e)からなる群から選択されるいずれかの式で示される[29]～[32]のいずれか1項に記載の抗体-薬物コンジュゲート:

(c) - (Succinimid-3-yl-N) - CH₂CH₂CH₂CH₂CH₂-C(=O)-GGFG-NH-CH₂-O-CH₂-C(=O)-、

(d) - (Succinimid-3-yl-N) - CH₂CH₂CH₂CH₂CH₂CH₂-C(=O)-GGFG-NH-CH₂CH₂-O-CH₂-C(=O)-、

(e) - (Succinimid-3-yl-N) - CH₂CH₂-C(=O)-NH-CH₂CH₂O-CH₂CH₂O-CH₂CH₂-C(=O)-GGFG-NH-CH₂CH₂CH₂-C(=O)- ;

[34] リンカーが以下の(c)又は(e)の式で示される[29]～[33]のいずれか1項に記載の抗体-薬物コンジュゲート:

(c) - (Succinimid-3-yl-N) - CH₂CH₂CH₂CH₂CH₂CH₂-C(=O)-GGFG-NH-CH₂-O-CH₂-C(=O)-、

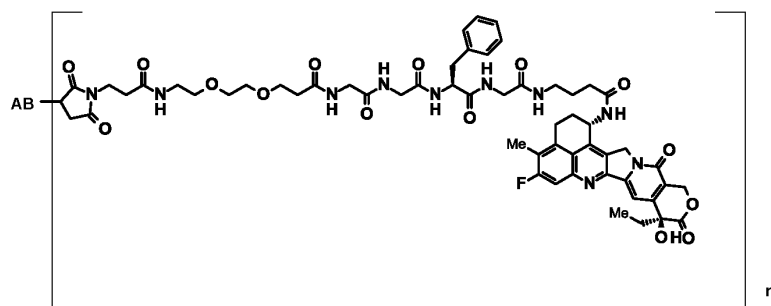
(e) - (Succinimid-3-yl-N) - CH₂CH₂-C(=O)-NH-CH₂CH₂O-CH₂CH₂O-CH₂CH₂-C(=O)-GGFG-NH-CH₂CH₂CH₂-C(=O)- ;

[35]

以下の式:

[0019]

[化3]

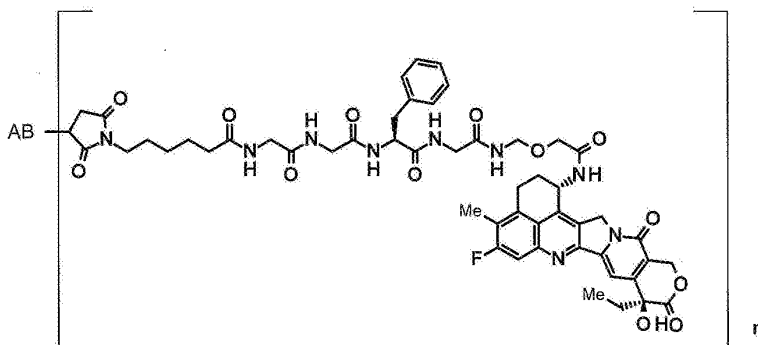


[0020] で示される構造を有する、[29]～[34]のいずれか1項に記載の抗体-薬物コンジュゲート：

ここで、A Bは抗体又は該抗体の機能性断片を示す。nは抗体と結合している薬物-リンカー構造の1抗体あたりの平均結合数を示す。抗体とリンカーは抗体由来のスルフヒドリル基を介して結合している；

[36] 以下の式：

[0021] [化4]



[0022] で示される構造を有する、[29]～[34]のいずれか1項に記載の抗体-薬物コンジュゲート：

ここで、A Bは抗体又は該抗体の機能性断片を示す。nは抗体と結合している薬物-リンカー構造の1抗体あたりの平均結合数を示す。抗体とリンカーは抗体由来のスルフヒドリル基を介して結合している；

[37] 抗体が以下の(1)～(4)：

(1) 配列番号61の21～233番目のアミノ酸配列からなる軽鎖及び配列番号69の20～471番目のアミノ酸配列からなる重鎖、

(2) 配列番号61の21～233番目のアミノ酸配列からなる軽鎖及び配列番号73の20～471番目のアミノ酸配列からなる重鎖、

(3) 配列番号65の21～233番目のアミノ酸配列からなる軽鎖及び配列番号73の20～471番目のアミノ酸配列からなる重鎖、又は

(4) 配列番号61の21～233番目のアミノ酸配列からなる軽鎖及び配列番号77の20～471番目のアミノ酸配列からなる重鎖、

からなる群から選択されるいずれか1つに記載の軽鎖及び重鎖を含む抗体又は当該抗体の機能性断片である、[29]～[36]のいずれか1項に記載の抗体-薬物コンジュゲート；

[38] 抗体が、配列番号61の21～233番目のアミノ酸配列からなる軽鎖及び配列番号69の20～471番目のアミノ酸配列からなる重鎖を含む抗体又は当該抗体の機能性断片である、[37]に記載の抗体-薬物コンジュゲート；

[39] 抗体が、配列番号61の21～233番目のアミノ酸配列からなる軽鎖及び配列番号77の20～471番目のアミノ酸配列からなる重鎖を含む抗体又は当該抗体の機能性断片である、[37]に記載の抗体-薬物コンジュゲート；

[40] 重鎖又は軽鎖が、N-結合への糖鎖付加、O-結合への糖鎖付加、N末のプロセッシング、C末のプロセッシング、脱アミド化、アスパラギン酸の異性化、メチオニンの酸化、N末にメチオニン残基の付加、プロリン残基のアミド化、N末グルタミンもしくはN末グルタミン酸のピログルタミン酸化及びカルボキシル末端における1つ又は2つのアミノ酸欠失からなる群から選択される1又は2以上の修飾をうけた、[29]～[39]のいずれか1項に記載の抗体-薬物コンジュゲート；

[41] 選択された1種の薬物-リンカー構造の1抗体あたりの平均結合数が1～10個の範囲である[29]～[40]のいずれか1項に記載の抗体

ー薬物コンジュゲート；

〔42〕 選択された1種の薬物ーリンカー構造の1抗体あたりの平均結合数が2～8個の範囲である〔41〕に記載の抗体ー薬物コンジュゲート；

〔43〕 選択された1種の薬物ーリンカー構造の1抗体あたりの平均結合数が5～8個の範囲である〔42〕に記載の抗体ー薬物コンジュゲート；

〔44〕 選択された1種の薬物ーリンカー構造の1抗体あたりの平均結合数が7～8個である〔43〕に記載の抗体ー薬物コンジュゲート；

〔45〕 〔29〕～〔44〕のいずれか1項に記載の抗体ー薬物コンジュゲート、その塩、又はそれらの水和物を含むことを特徴とする医薬組成物；

〔46〕 抗腫瘍薬であることを特徴とする、〔45〕に記載の医薬組成物；

〔47〕 腫瘍がCDH6を発現する腫瘍であることを特徴とする、〔46〕に記載の医薬組成物；

〔48〕 腫瘍が、腎細胞癌、腎臓明細胞癌、乳頭状腎細胞癌、卵巣癌、卵巣漿液性腺癌、甲状腺癌、胆管癌、肺癌、小細胞肺癌、神経膠芽腫、中皮腫、子宮癌、膵臓癌、ウィルムス腫瘍又は神経芽腫であることを特徴とする、〔46〕又は〔47〕に記載の医薬組成物；

〔49〕 〔29〕～〔44〕のいずれか1項に記載の抗体ー薬物コンジュゲート、その塩、又はそれらの水和物から選択されるいずれかを個体に投与することを特徴とする腫瘍の治療方法；

〔50〕 腫瘍がCDH6が発現している腫瘍であることを特徴とする、〔49〕に記載の治療方法；

〔51〕 腫瘍が、腎細胞癌、腎臓明細胞癌、乳頭状腎細胞癌、卵巣癌、卵巣漿液性腺癌、甲状腺癌、胆管癌、肺癌、小細胞肺癌、神経膠芽腫、中皮腫、子宮癌、膵臓癌、ウィルムス腫瘍又は神経芽腫であることを特徴とする、〔49〕又は〔50〕に記載の治療方法；

〔52〕 〔29〕～〔44〕のいずれか1項に記載の抗体ー薬物コンジュゲート、その塩、又はそれらの水和物から選択される少なくとも一つを含む医薬組成物及び少なくとも一つの抗腫瘍薬を、同時に、別々に又は連続して個

体に投与することを特徴とする腫瘍の治療方法；

〔５３〕〔１〕～〔１３〕及び〔２４〕～〔２８〕からなる群から選択されるいずれか１項に記載の抗体又は当該抗体の機能性断片或いは〔２３〕に記載の製造方法で得られる抗体又は当該抗体の機能性断片と、薬物－リンカー中間化合物を反応させる工程を含むことを特徴とする、抗体－薬物コンジュゲートの製造方法；又は

〔５４〕〔２１〕又は〔２２〕に記載の宿主細胞を培養する工程、当該工程で得られた培養物から目的の抗体又は当該抗体の機能性断片を採取する工程、及び当該工程で得られた抗体又は当該抗体の機能性断片と薬物－リンカー中間化合物を反応させる工程を含むことを特徴とする、抗体－薬物コンジュゲートの製造方法。

発明の効果

[0023] 本発明の抗ＣＤＨ６抗体は、ＣＤＨ６のＥＣドメイン３（ＥＣ３）を特異的に認識し、高い内在化活性を有することを特徴とする。本発明の抗ＣＤＨ６抗体に、細胞内で毒性を発揮する薬剤を特定の構造のリンカーを介して結合させた抗ＣＤＨ６抗体－薬物コンジュゲートは、ＣＤＨ６を発現するがん細胞を有する患者に投与することによって、優れた抗腫瘍効果及び安全性を達成することが期待できる。即ち、本発明の抗ＣＤＨ６抗体－薬物コンジュゲートは、抗腫瘍剤として有用である。

図面の簡単な説明

[0024] [図１]図１は、ラット抗ＣＤＨ６モノクローナル抗体４種（クローン番号は、ｒＧ０１９、ｒＧ０５５、ｒＧ０５６及びｒＧ０６１）又はラットＩｇＧコントロールの、コントロール細胞又はｈＣＤＨ６導入２９３Ｔ細胞に対する結合を調べたフローサイトメトリーの結果を示す。横軸は抗体結合量を表すＦＩＴＣの蛍光強度、縦軸は細胞数を示す。

[図２-１]図２－１は、ラット抗ＣＤＨ６モノクローナル抗体４種（ｒＧ０１９、ｒＧ０５５、ｒＧ０５６及びｒＧ０６１）又は陰性コントロール抗体ＲａｔｔＩｇＧ２ｂの、コントロール細胞又は全長ｈＣＤＨ６導入２９３細胞に対

する結合性を示す。横軸は抗体結合量を表すF I T Cの蛍光強度、縦軸は細胞数を示す。

[図2-2]図2-2は、ラット抗CDH6モノクローナル抗体4種（r G O 1 9、r G O 5 5、r G O 5 6及びr G O 6 1）又はラットI g Gコントロールの、コントロール細胞又はEC1欠失hCDH6導入293細胞に対する結合性を示す。横軸は抗体結合量を表すF I T Cの蛍光強度、縦軸は細胞数を示す。

[図2-3]図2-3は、ラット抗CDH6モノクローナル抗体4種（r G O 1 9、r G O 5 5、r G O 5 6及びr G O 6 1）又はラットI g Gコントロールの、コントロール細胞又はEC2欠失hCDH6導入293細胞に対する結合性を示す。横軸は抗体結合量を表すF I T Cの蛍光強度、縦軸は細胞数を示す。

[図2-4]図2-4は、ラット抗CDH6モノクローナル抗体4種（r G O 1 9、r G O 5 5、r G O 5 6及びr G O 6 1）又はラットI g Gコントロールの、コントロール細胞又はEC3欠失hCDH6導入293細胞に対する結合性を示す。横軸は抗体結合量を表すF I T Cの蛍光強度、縦軸は細胞数を示す。

[図2-5]図2-5は、ラット抗CDH6モノクローナル抗体4種（r G O 1 9、r G O 5 5、r G O 5 6及びr G O 6 1）又はラットI g Gコントロールの、コントロール細胞又はEC4欠失hCDH6導入293細胞に対する結合性を示す。横軸は抗体結合量を表すF I T Cの蛍光強度、縦軸は細胞数を示す。

[図2-6]図2-6は、ラット抗CDH6モノクローナル抗体4種（r G O 1 9、r G O 5 5、r G O 5 6及びr G O 6 1）又はラットI g Gコントロールの、コントロール細胞又はEC5欠失hCDH6導入293細胞に対する結合性を示す。横軸は抗体結合量を表すF I T Cの蛍光強度、縦軸は細胞数を示す。

[図3]図3は、4種類のヒト腫瘍細胞株（ヒト卵巣腫瘍細胞株N I H : O V C

AR-3, PA-1, ES-2 及びヒト腎細胞腫瘍細胞株 786-O) の細胞膜表面での CDH6 の発現を評価したフローサイトメトリーの結果を示す。横軸は抗体結合量を表す FITC の蛍光強度、縦軸は細胞数を示す。

[図4] 図4は、4種類のラット抗CDH6抗体 (rG019、rG055、rG056 及び rG061) 又はラット IgG コントロールの内在化活性を、タンパク質合成を阻害する毒素 (サポリン) を結合させた抗ラット IgG 試薬 Rat-ZAP 又は陰性コントロールとして毒素を結合していない Goat Anti-Rat IgG, Fc (gamma) Fragment Specific を用いて、NIH: OVCAR-3 細胞及び 786-O 細胞において評価したグラフを示す。グラフの縦軸は、ATP 活性 (RLU) を示す。各グラフの下に、Rat-ZAP の代わりに陰性コントロールを添加したウェルの生存細胞数を 100% とした相対生存率として算出された細胞生存率 (%) を示す。

[図5] 図5は、ヒトキメラ抗CDH6抗体 chG019 のヒトCDH6 及びサルCDH6 に対する結合を示す。横軸は抗体濃度を示し、縦軸は結合量を Mean Fluorescent Intensity (平均蛍光強度) で示す。

[図6-1] 図6-1 及び図6-2 は、ヒト化 hG019 抗体4種 (H01L02、H02L02、H02L03 及び H04L02) 又は陰性コントロール抗体ヒトIgG1 の、ヒトCDH6、サルCDH6、マウスCDH6、ラットCDH6 に対する結合性を示す。横軸は抗体濃度を示し、縦軸は結合量を Mean Fluorescent Intensity (平均蛍光強度) で示す。

[図6-2] 図6-1 及び図6-2 は、ヒト化 hG019 抗体4種 (H01L02、H02L02、H02L03 及び H04L02) 又は陰性コントロール抗体ヒトIgG1 の、ヒトCDH6、サルCDH6、マウスCDH6、ラットCDH6 に対する結合性を示す。横軸は抗体濃度を示し、縦軸は結合量を Mean Fluorescent Intensity (平均蛍光強度) で示す。

す。

[図7-1]図7-1は、ヒト化hG019抗体4種（H01L02、H02L02、H02L03及びH04L02）、抗CDH6抗体NOV0712又は陰性コントロール抗体hIgG1の、コントロール細胞又は全長hCDH6導入293 α 細胞に対する結合性を示す。横軸は抗体結合量を表すAPCの蛍光強度、縦軸は細胞数を示す。

[図7-2]図7-2は、ヒト化hG019抗体4種（H01L02、H02L02、H02L03及びH04L02）、抗CDH6抗体NOV0712又は陰性コントロール抗体hIgG1の、コントロール細胞又はEC1欠失hCDH6導入293 α 細胞に対する結合性を示す。横軸は抗体結合量を表すAPCの蛍光強度、縦軸は細胞数を示す。

[図7-3]図7-3は、ヒト化hG019抗体4種（H01L02、H02L02、H02L03及びH04L02）、抗CDH6抗体NOV0712又は陰性コントロール抗体hIgG1の、コントロール細胞又はEC2欠失hCDH6導入293 α 細胞に対する結合性を示す。横軸は抗体結合量を表すAPCの蛍光強度、縦軸は細胞数を示す。

[図7-4]図7-4は、ヒト化hG019抗体4種（H01L02、H02L02、H02L03及びH04L02）、抗CDH6抗体NOV0712又は陰性コントロール抗体hIgG1の、コントロール細胞又はEC3欠失hCDH6導入293 α 細胞に対する結合性を示す。横軸は抗体結合量を表すAPCの蛍光強度、縦軸は細胞数を示す。

[図7-5]図7-5は、ヒト化hG019抗体4種（H01L02、H02L02、H02L03及びH04L02）、抗CDH6抗体NOV0712又は陰性コントロールのhIgG1の、コントロール細胞又はEC4欠失hCDH6導入293 α 細胞に対する結合性を示す。横軸は抗体結合量を表すAPCの蛍光強度、縦軸は細胞数を示す。

[図7-6]図7-6は、ヒト化hG019抗体4種（H01L02、H02L02、H02L03及びH04L02）、抗CDH6抗体NOV0712又は

陰性コントロールのh I g G 1の、コントロール細胞又はE C 5欠失h C D H 6導入293 α 細胞に対する結合性を示す。横軸は抗体結合量を表すA P Cの蛍光強度、縦軸は細胞数を示す。

[図8]図8は、786-O/hCDH6安定発現細胞株及び親細胞株786-OにおけるヒトCDH6の発現を調べたフローサイトメトリーの結果を示す。横軸は抗体結合量を表すA l e x a F l u o r 647の蛍光強度、縦軸は細胞数を示す。

[図9]図9は、(a)ラベル化NOV0712又は(b)ラベル化H01L02を用いた、ラベル化していないヒト化hG019抗体4種(H01L02、H02L02、H02L03及びH04L02)、抗CDH6抗体NOV0712又は陰性コントロールのh I g G 1との結合競合アッセイを示す。横軸はラベル化していない抗体の添加時の終濃度を示し、縦軸は結合量をM e a n F l u o r e s c e n t I n t e n s i t y (平均蛍光強度)で示す。

[図10-1]図10-1は、ヒト化hG019抗体4種(H01L02、H02L02、H02L03及びH04L02)、抗CDH6抗体NOV0712及び陰性コントロール抗体の内在化活性を、タンパク質合成を阻害する毒素(サポリン)を結合させた抗ヒトI g G試薬H u m - Z A P又は陰性コントロールとして毒素を結合していないF (a b ') 2 F r a g m e n t G o a t A n t i - h u m a n I g G , F c (g a m m a) F r a g m e n t S p e c i f i cを用いて、N I H : O V C A R - 3細胞において評価したグラフを示す。グラフの縦軸は、A T P活性(R L U)を示す。各グラフの下に、H u m - Z A Pの代わりに陰性コントロールを添加したウェルの生存細胞数を100%とした相対生存率として算出された細胞生存率(%)を示す。

[図10-2]図10-2は、ヒト化hG019抗体4種(H01L02、H02L02、H02L03及びH04L02)、抗CDH6抗体NOV0712及び陰性コントロール抗体の内在化活性を、タンパク質合成を阻害する毒素

(サポリン)を結合させた抗ヒトIgG試薬Hum-ZAP又は陰性コントロールとして毒素を結合していないF(ab')₂ Fragment Goat Anti-human IgG, Fc(gamma) Fragment Specificを用いて、786-O細胞において評価したグラフを示す。グラフの縦軸は、ATP活性(RLU)を示す。各グラフの下に、Hum-ZAPの代わりに陰性コントロールを添加したウェルの生存細胞数を100%とした相対生存率として算出された細胞生存率(%)を示す。

[図10-3]図10-3は、ヒト化hG019抗体4種(H01L02、H02L02、H02L03及びH04L02)、抗CDH6抗体NOV0712及び陰性コントロール抗体の内在化活性を、タンパク質合成を阻害する毒素(サポリン)を結合させた抗ヒトIgG試薬Hum-ZAP又は陰性コントロールとして毒素を結合していないF(ab')₂ Fragment Goat Anti-human IgG, Fc(gamma) Fragment Specificを用いて、PA-1細胞において評価したグラフを示す。グラフの縦軸は、ATP活性(RLU)を示す。各グラフの下に、Hum-ZAPの代わりに陰性コントロールを添加したウェルの生存細胞数を100%とした相対生存率として算出された細胞生存率(%)を示す。

[図11]図11は、ヒト化hG019-薬物コンジュゲート4種(H01L02-DXd、H02L02-DXd、H02L03-DXd及びH04L02-DXd)、又はNOV0712-DM4のPA-1細胞に対する*in vitro*細胞増殖抑制活性評価を示す。横軸は抗体-薬物コンジュゲートの濃度を示し、縦軸は細胞生存率(%)を示す。

[図12]図12は、ヒト化hG019-薬物コンジュゲート4種(H01L02-DXd、H02L02-DXd、H02L03-DXd及びH04L02-DXd)、又はNOV0712-DM4の*in vivo*抗腫瘍効果を示す。CDH6陽性ヒト腎細胞腫瘍細胞株786-Oを免疫不全マウスに移植した動物モデルを用いて評価した。横軸は日数、縦軸は腫瘍体積、誤差範囲は標準誤差(SE)値を示す。