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Binding molecule specific for CD39 and use thereof

Abstract

Provided is a binding molecule specifically for CD39 and the use thereof. Specifically, provided is an antibody that binds to CD39 and inhibits the activity of CD39 or an antigen binding part thereof, the use of the antibody or the antigen binding part thereof in the treatment of diseases, a nucleic acid molecule encoding the antibody or the antigen binding part thereof, an expression vector for expressing the antibody or the antigen binding part thereof, a host cell, and a preparation method.

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Background/Summary

CROSS-REFERENCE TO RELATED APPLICATIONS

(1) This application is a U.S. National Phase application of Int'l Appl. No. PCT/CN2020/126351, filed Nov. 4, 2020, which claims priority to Int'l Appl. No. PCT/CN2019/115505, filed Nov. 5, 2019, each of which are incorporated herein by reference in their entireties.

TECHNICAL FIELD

(2) This invention relates to an antibody or antigen-binding fragment thereof specifically binds to CD39, and to use of the antibody or antigen-binding fragment thereof of this invention in the treatment of a disease, and to a treatment method using the antibody or antigen-binding fragment thereof of this invention.

BACKGROUND ART

(3) CD39 is a membrane protein that hydrolyzes ATP and ADP in a Ca.sup.2+ and Mg.sup.2+ fashion to yield AMP. Human CD39 has 510 amino acids, predicted with seven N-linked glycosylation sites, 11 Cys residues, and two transmembrane regions. CD39 is composed of two transmembrane domains, a small cytoplasmic domain comprising the NH.sub.2— and COOH— terminal segments, and a large extracellular hydrophobic domain consisting of five highly conserved domains, known as apyrase conserved regions (ACR) 1-5, which are pivotal for the catabolic activity of the enzyme. The amino acid sequences of ACR1 and ACR5 contain a phosphate-binding motif (DXG), which is critical for stabilizing the interaction between the enzyme and its nucleotide substrate during phosphate cleavage. In addition, two ACR residues, i.e., Glu 174 of ACR 3 and Ser 218 of ACR 4 are also necessary for enzyme function. CD39 becomes catalytically active when located on the cell surface, and its glycosylation is crucial for correct protein folding, membrane targeting, and enzyme activity (Antonioli L et al (2013), Trends Mol Med, 19(6):355-367).

(4) CD39 is constitutively expressed in spleen, thymus, lung, and placenta, and in these organs, it is associated primarily with endothelial cells and immune cell populations, such as B cells, natural killer (NK) cells, dendritic cells, Langerhans cells, monocytes, macrophages, mesangial cell, neutrophils and regulatory T cells (Tregs). The expression of CD39 is regulated by several pro-inflammatory cytokines, oxidative stress and hypoxia through the transcription factors Sp1, Stat3, and zinc finger protein growth factor independent-1 transcription factor (Antonioli L et al (2013), Trends Mol Med, 19(6):355-367).

(5) Under physiological conditions, purine medium ATP mainly exists in the cytoplasm, with a concentration of about 1˜10 mM; while the extracellular ATP concentration is at a low level, 10˜100 nM; and when the body appears disorder, such as inflammation, ischemia, malignant tumors and the like, ATP in the cytoplasm is released to the outside of the cell in a large amount, triggering an immune response as a sensory signal and an outgoing signal. After ATP is released to the outside of the cell, it is hydrolyzed by extracellular CD39 into ADP and AMP, and an immunosuppressive adenosine is produced from AMP under the synergistic action of CD37. In this process, CD39 is rate-limiting enzyme (Faas M M et al. (2017), Mol Aspects Med, 55:9-19). CD39 and CD73 can regulate the function of several immune cells, including lymphocytes, neutrophils, monocytes/macrophages, and dendritic cells and so on (Antonioli L et al (2013), Trends Mol Med, 19(6):355-367). In the tumor microenvironment, CD39 is highly expressed on the surface of Treg cells, and CD39 is gradually recognized as a specific marker molecule on the surface of Treg cells (Gu J et al (2017), Cell Mol Immunol, 14(6):521-528). Adenosine derived from Treg cells acts on A2A receptors on the surface of lymphocytes (Sundstrom P S H et al (2016), Cancer Immunol Res, 4(3):183-193; Ma S R et al (2017), Mol Cancer, 16(1):99) to inhibit the proliferation, migration and anti-tumor effects of effector T cells; and inhibit the cytotoxicity of NK cells and the production of cytokines, and mediate a series of immunosuppressive effects (Lokshin A et al (2006), Cancer Res, 66(15):7758-7765; Hu G et al (2017), Oncoimmunology, 6(2): e1277305).

(6) CD39 is highly expressed in many malignant tumors (Allard B et al (2017), Immunol Rev, 276(1):121-144; Bastid J et al (2013), Oncogene, 32(14):1743-1751). Compared with normal tissues, the expression level of CD39 in tumor tissues such as kidney, lung, ovary, pancreas, thyroid and so on is significantly increased, suggesting that the abnormally high expression of CD39 is associated with the development of malignant tumors (Bastid J et al. (2015), Cancer Immunol Res, 3(3): 254-265). In addition, changes in the CD39/CD73 system may disrupt potentially complex mechanisms, such as immune tolerance of autoantigens driven by Treg, and thus contribute to the

development of some autoimmune diseases (Karen M. Dwyer et al. (2007), Purinergic Signal, 3(1-2): 171-180).
(7) Currently, there is no drug for an inhibitor against the CD39 target in the market. There is an urgent need for research and development of a CD39 inhibitor and development of a treatment method for a disease related to CD39.

SUMMARY OF INVENTION

(8) The invention provides an antibody or antigen-binding fragment specifically binding to CD39 and use thereof in the treatment of a disease.
(9) In one respect, the invention provides an antibody or antigen-binding fragment thereof comprising a heavy chain variable region that comprises HCDR1, HCDR2, HCDR3; and a light chain variable region that comprises LCDR1, LCDR2, LCDR3, wherein: (a) the HCDR1 comprises an amino acid sequence selected from a group consisting of SEQ ID NOs: 5, 19, 33 and/or 47, and conservative modifications thereof; (b) the HCDR2 comprises an amino acid sequence selected from a group consisting of SEQ ID NOs: 6, 20, 34 and/or 48, and conservative modifications thereof; (c) the HCDR3 comprises an amino acid sequence selected from a group consisting of SEQ ID NOs: 7, 21, 35 and/or 49, and conservative modifications thereof; (d) the LCDR1 comprises an amino acid sequence selected from a group consisting of SEQ ID NOs: 10, 24, 38 and/or 52, and conservative modifications thereof; (e) the LCDR2 comprises an amino acid sequence selected from a group consisting of SEQ ID NOs: 11, 25, 39, 53 and/or 59, and conservative modifications thereof; and (f) the LCDR3 comprises an amino acid sequence selected from a group consisting of SEQ ID NOs: 12, 26, 40 and/or 54, and conservative modifications thereof.
(10) In some embodiments, the antibody or antigen-binding fragment thereof comprises: 1) (a) HCDR1 comprising SEQ ID NO: 5, (b) HCDR2 comprising SEQ ID NO: 6, (c) HCDR3 comprising SEQ ID NO: 7, (d) LCDR1 comprising SEQ ID NO: 10, (e) LCDR2 comprising SEQ ID NO: 11, and (f) LCDR3 comprising SEQ ID NO: 12; 2) (a) HCDR1 comprising SEQ ID NO: 19, (b) HCDR2 comprising SEQ ID NO: 20, (c) HCDR3 comprising SEQ ID NO: 21, (d) LCDR1 comprising SEQ ID NO: 24, (e) LCDR2 comprising SEQ ID NO: 25, and (f) LCDR3 comprising SEQ ID NO: 26; 3) (a) HCDR1 comprising SEQ ID NO: 33, (b) HCDR2 comprising SEQ ID NO: 34, (c) HCDR3 comprising SEQ ID NO: 35, (d) LCDR1 comprising SEQ ID NO: 38, (e) LCDR2 comprising SEQ ID NO:39, and (f) LCDR3 comprising SEQ ID NO: 40; 4) (a) HCDR1 comprising SEQ ID NO: 47, (b) HCDR2 comprising SEQ ID NO: 48, (c) HCDR3 comprising SEQ ID NO: 49, (d) LCDR1 comprising SEQ ID NO: 52, (e) LCDR2 comprising SEQ ID NO: 53, and (f) LCDR3 comprising SEQ ID NO: 54; 5) (a) HCDR1 comprising SEQ ID NO: 5, (b) HCDR2 comprising SEQ ID NO: 6, (c) HCDR3 comprising SEQ ID NO: 7, (d) LCDR1 comprising SEQ ID NO: 52, (e) LCDR2 comprising SEQ ID NO: 59, and (f) LCDR3 comprising SEQ ID NO: 54; and/or 6) (a) HCDR1 comprising SEQ ID NO: 5, (b) HCDR2 comprising SEQ ID NO: 6, (c) HCDR3 comprising SEQ ID NO: 7, (d) LCDR1 comprising SEQ ID NO: 10, (e) LCDR2 comprising SEQ ID NO: 59, and (f) LCDR3 comprising SEQ ID NO: 12.
(11) In some embodiments, the antibody or antigen-binding fragment thereof comprises: (a) HCDR1 comprising SEQ ID NO: 5, (b) HCDR2 comprising SEQ ID NO: 6, (c) HCDR3 comprising SEQ ID NO: 7, (d) LCDR1 comprising SEQ ID NO: 10, (e) LCDR2 comprising SEQ ID NO: 11, and (f) LCDR3 comprising SEQ ID NO: 12.
(12) In some embodiments, the antibody or antigen-binding fragment thereof comprises: (a) HCDR1 comprising SEQ ID NO: 19, (b) HCDR2 comprising SEQ ID NO: 20, (c) HCDR3 comprising SEQ ID NO: 21, (d) LCDR1 comprising SEQ ID NO: 24, (e) LCDR2 comprising SEQ ID NO:25, and (f) LCDR3 comprising SEQ ID NO: 26.
(13) In some embodiments, the antibody or antigen-binding fragment thereof comprises: (a) HCDR1 comprising SEQ ID NO: 33, (b) HCDR2 comprising SEQ ID NO: 34, (c) HCDR3 comprising SEQ ID NO: 35, (d) LCDR1 comprising SEQ ID NO: 38, (e) LCDR2 comprising SEQ

ID NO: 39, and (f) LCDR3 comprising SEQ ID NO: 40.
(14) In some embodiments, the antibody or antigen-binding fragment thereof comprises: (a) HCDR1 comprising SEQ ID NO: 47, (b) HCDR2 comprising SEQ ID NO: 48, (c) HCDR3 comprising SEQ ID NO: 49, (d) LCDR1 comprising SEQ ID NO: 52, (e) LCDR2 comprising SEQ ID NO: 53, and (f) LCDR3 comprising SEQ ID NO: 54.
(15) In some embodiments, the antibody or antigen-binding fragment thereof comprises: (a) HCDR1 comprising SEQ ID NO: 5, (b) HCDR2 comprising SEQ ID NO: 6, (c) HCDR3 comprising SEQ ID NO: 7, (d) LCDR1 comprising SEQ ID NO: 52, (e) LCDR2 comprising SEQ ID NO: 59, and (f) LCDR3 comprising SEQ ID NO: 54.
(16) In some embodiments, the antibody or antigen-binding fragment thereof comprises: (a) HCDR1 comprising SEQ ID NO: 5, (b) HCDR2 comprising SEQ ID NO: 6, (c) HCDR3 comprising SEQ ID NO: 7, (d) LCDR1 comprising SEQ ID NO: 10, (e) LCDR2 comprising SEQ ID NO: 59, and (f) LCDR3 comprising SEQ ID NO:12.
(17) In some embodiments, the antibody or antigen-binding fragment thereof comprises: (i) the heavy chain variable region (VH) comprising an amino acid sequence with at least 85% identity to an amino acid sequence selected from a group consisting of SEQ ID NOs: 3, 17, 31, 45, 60 and/or 72, and conservative modifications thereof; and (ii) the light chain variable region (VL) comprising an amino acid sequence with at least 85% identity to an amino acid sequence selected from a group consisting of SEQ ID NOs: 8, 22, 36, 50, 62, 68 and/or 74, and conservative modifications thereof.
(18) In some embodiments, the heavy chain variable region comprises an amino acid sequence with at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to the heavy chain variable region selected from (i); and the light chain variable region comprises an amino acid sequence with at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to the light chain variable region selected from (ii).
(19) In some embodiments, the antibody or antigen-binding fragment thereof comprises: 1) a heavy chain variable region (VH) that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 3, and a light chain variable region (VL) that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 8; 2) a heavy chain variable region (VH) that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 17, and a light chain variable region (VL) that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 22; 3) a heavy chain variable region (VH) that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 31, and a light chain variable region (VL) that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 36; 4) a heavy chain variable region (VH) that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 45, and a light chain variable region (VL) that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 50; 5) a heavy chain variable region (VH) that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 60, and a light chain variable region (VL) that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 62; 6) a heavy chain variable region (VH) that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 60, and a light chain variable region (VL) that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 68; and/or 7) a heavy chain variable region (VH) that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 72, and a light chain variable region (VL) that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 74.
(20) In some embodiments, the heavy chain variable region and the light chain variable region comprise an amino acid sequence with at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to the heavy chain variable region and the light chain

variable region selected from 1)-7), respectively.
(21) In some embodiments, the heavy chain constant region of the antibody is an IgG.
(22) In some embodiments, the heavy chain constant region of the antibody is selected from IgG1, IgG2 or IgG4.
(23) In some embodiments, the antibody is a monoclonal antibody, a chimeric antibody, a humanized antibody, a human engineered antibody, a human antibody, Fv, a single chain antibody (scFv), Fab, Fab′, Fab′-SH or F(ab′)2.
(24) In some embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain and a light chain, wherein: (I) the heavy chain comprises an amino acid sequence with at least 85% identity to an amino acid sequence selected from a group of SEQ ID NOs: 13, 27, 41, 55, 64 and/or 76, and conservative modifications thereof; and (II) the light chain comprises an amino acid sequence with at least 85% identity to an amino acid sequence selected from a group of SEQ ID NOs: 15, 29, 43, 57, 66, 70 and/or 78, and conservative modifications thereof.
(25) In some embodiments, the heavy chain comprises an amino acid sequence with at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to the heavy chain selected from (I); and the light chain comprises an amino acid sequence with at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to the light chain selected from (II).
(26) In some embodiments, the antibody or antigen-binding fragment thereof comprises: 1) a heavy chain that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 13, and a light chain that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 15; 2) a heavy chain that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO:27, and a light chain that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 29; 3) a heavy chain that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 41, and a light chain that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 43; 4) a heavy chain that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 55, and a light chain that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 57; 5) a heavy chain that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 64, and a light chain that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 66; 6) a heavy chain that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 64, and a light chain that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 70; and/or 7) a heavy chain that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 76, and a light chain that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 78.
(27) In some embodiments, the heavy chain and the light chain comprise an amino acid sequence with at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to the heavy chain and the light chain selected from 1)-7), respectively.
(28) In another respect, the invention provides an antibody or antigen-binding fragment thereof that comprises a heavy chain variable region (VH) consisting of SEQ ID NO: 3 and a light chain variable region (VL) consisting of SEQ ID NO: 8.
(29) In yet another respect, the invention provides an antibody or antigen-binding fragment thereof that comprises a heavy chain variable region (VH) consisting of SEQ ID NO: 17 and a light chain variable region (VL) consisting of SEQ ID NO: 22.
(30) In still yet another respect, the invention provides an antibody or antigen-binding fragment thereof that comprises a heavy chain variable region (VH) consisting of SEQ ID NO: 31 and a light chain variable region (VL) consisting of SEQ ID NO: 36.

(31) In one respect, the invention provides an antibody or antigen-binding fragment thereof that comprises a heavy chain variable region (VH) consisting of SEQ ID NO: 45 and a light chain variable region (VL) consisting of SEQ ID NO: 50.
(32) In another respect, the invention provides an antibody or antigen-binding fragment thereof that comprises a heavy chain variable region (VH) consisting of SEQ ID NO: 60 and a light chain variable region (VL) consisting of SEQ ID NO: 62.
(33) In yet another respect, the invention provides an antibody or antigen-binding fragment thereof that comprises a heavy chain variable region (VH) consisting of SEQ ID NO: 60 and a light chain variable region (VL) consisting of SEQ ID NO: 68.
(34) In still yet another respect, the invention provides an antibody or antigen-binding fragment thereof, which comprises a heavy chain variable region (VH) consisting of SEQ ID NO: 72 and a light chain variable region (VL) consisting of SEQ ID NO: 74.
(35) In some embodiments, the antibody or antigen-binding fragment thereof is an antagonist of CD39.
(36) In some embodiments, the CD39 is human CD39 or machin CD39.
(37) In some embodiments, the antibody or antigen-binding fragment thereof may reduce the ATP enzyme (ATPase) activity of CD39.
(38) In one respect, the invention provides a nucleic acid composition, which comprises: (I) a first nucleic acid comprising a nucleotide sequence selected from a group consisting of SEQ ID NOs: 4, 18, 32, 46, 61 and/or 73; and (II) a second nucleic acid comprising a nucleotide sequence selected from a group consisting of SEQ ID NOs: 9, 23, 37, 51, 63, 69 and/or 75.
(39) In some embodiments, the nucleic acid composition comprises: 1) the first nucleic acid comprising SEQ ID NO: 4 and the second nucleic acid comprising SEQ ID NO: 9; 2) the first nucleic acid comprising SEQ ID NO: 18 and the second nucleic acid comprising SEQ ID NO: 23; 3) the first nucleic acid comprising SEQ ID NO: 32 and the second nucleic acid comprising SEQ ID NO: 37; 4) the first nucleic acid comprising SEQ ID NO: 46 and the second nucleic acid comprising SEQ ID NO: 51; 5) the first nucleic acid comprising SEQ ID NO: 61 and the second nucleic acid comprising SEQ ID NO: 63; 6) the first nucleic acid comprising SEQ ID NO: 61 and the second nucleic acid comprising SEQ ID NO: 69; and/or 7) the first nucleic acid comprising SEQ ID NO: 73 and the second nucleic acid comprising SEQ ID NO: 75.
(40) In another respect, the invention provides an expression vector composition, which comprises: (I) a first expression vector comprising a nucleotide sequence selected from a group consisting of SEQ ID NOs: 4, 18, 32, 46, 61 and/or 73; and (II) a second expression vector comprising a nucleotide sequence selected from a group consisting of SEQ ID NO: 9, 23, 37, 51, 63, 69 and/or 75.
(41) In some embodiments, the expression vector composition comprises: 1) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 4 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 9; 2) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 18 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 23; 3) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 32 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 37; or 4) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 46 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 51; 5) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 61 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 63; 6) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 61 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 69; and/or 7) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 73 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 75.
(42) In yet another respect, the invention provides an expression vector, which comprises: (I) a first nucleic acid sequence comprising a nucleotide sequence selected from a group consisting of SEQ

ID NO: 4, 18, 32, 46, 61 and/or 73; and (II) a second nucleic acid sequence comprising a nucleotide sequence selected from a group consisting of SEQ ID NO: 9, 23, 37, 51, 63, 69 and/or 75.
(43) In some embodiments, the expression vector comprises: 1) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 4 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 9; 2) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 18 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 23; 3) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 32 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 37; 4) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 46 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 51; 5) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 61 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 63; 6) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 61 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 69; and/or 7) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 73 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 75.
(44) In still yet another respect, the invention provides a nucleic acid composition, which comprises: (I) a first nucleic acid comprising a nucleotide sequence selected from a group consisting of SEQ ID NOs: 14, 28, 42, 56, 65 and/or 77; and (II) a second nucleic acid comprising a nucleotide sequence selected from a group consisting of SEQ ID NOs: 16, 30, 44, 58, 67, 71 and/or 79.
(45) In some embodiments, the nucleic acid composition comprises: 1) the first nucleic acid comprising a nucleotide sequence of SEQ ID NO: 14 and the second nucleic acid comprising a nucleotide sequence of SEQ ID NO: 16; 2) the first nucleic acid comprising a nucleotide sequence of SEQ ID NO: 28 and the second nucleic acid comprising a nucleotide sequence of SEQ ID NO: 30; 3) the first nucleic acid comprising a nucleotide sequence of SEQ ID NO: 42 and the second nucleic acid comprising a nucleotide sequence of SEQ ID NO: 44; 4) the first nucleic acid comprising a nucleotide sequence of SEQ ID NO: 56 and the second nucleic acid comprising a nucleotide sequence of SEQ ID NO: 58; 5) the first nucleic acid comprising a nucleotide sequence of SEQ ID NO: 65 and the second nucleic acid comprising a nucleotide sequence of SEQ ID NO: 67; 6) the first nucleic acid comprising a nucleotide sequence of SEQ ID NO: 65 and the second nucleic acid comprising a nucleotide sequence of SEQ ID NO: 71; and/or 7) the first nucleic acid comprising a nucleotide sequence of SEQ ID NO: 77 and the second nucleic acid comprising a nucleotide sequence of SEQ ID NO: 79.
(46) In one respect, the invention provides an expression vector composition, which comprises: (I) a first expression vector comprising a nucleotide sequence selected from a group consisting of SEQ ID NOs: 14, 28, 42, 56, 65 and/or 77; and (II) a second expression vector comprising a nucleotide sequence selected from a group consisting of SEQ ID NOs: 16, 30, 44, 58, 67, 71 and/or 79.
(47) In some embodiments, the expression vector composition comprises: 1) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 14 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 16; 2) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 28 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 30; 3) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 42 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 44; or 4) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 56 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 58; 5) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 65 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 67; 6) a first expression vector comprising a nucleotide sequence of SEQ ID NO: 65 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 71; and/or 7) a first expression vector comprising a nucleotide sequence of SEQ ID

NO: 77 and a second expression vector comprising a nucleotide sequence of SEQ ID NO: 79.
(48) In another respect, the invention provides an expression vector, which comprises: (I) a first nucleic acid sequence comprising a nucleotide sequence selected from a group consisting of SEQ ID NOs: 14, 28, 42, 56, 65 and/or 77; and (II) a second nucleic acid sequence comprising a nucleotide sequence selected from a group consisting of SEQ ID NOs: 16, 30, 44, 58, 67, 71 and/or 79.
(49) In some embodiment, the expression vector comprises: 1) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 14 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 16; 2) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 28 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 30; 3) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 42 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 44; 4) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 56 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 58; 5) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 65 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 67; 6) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 65 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 71; and/or 7) a first nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO: 77 and a second nucleic acid sequence comprising a nucleotide sequence of SEQ ID NO:79.
(50) In yet another respect, the invention provides a nucleic acid composition, which comprises: (I) a first nucleic acid comprising a nucleotide sequence encoding a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NOs: 3, 17, 31, 45, 60 and/or 72; and (II) a second nucleic acid comprising a nucleotide sequence encoding a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NOs: 8, 22, 36, 50, 62, 68 and/or 74.
(51) In some embodiments, the nucleic acid composition comprises: 1) the first nucleic acid encoding a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 3 and the second nucleic acid encoding a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 8; 2) the first nucleic acid encoding a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 17 and the second nucleic acid encoding a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 22; 3) the first nucleic acid encoding a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 31 and the second nucleic acid encoding a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 36; 4) the first nucleic acid encoding a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 45 and the second nucleic acid encoding a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 50; 5) the first nucleic acid encoding a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 60 and the second nucleic acid encoding a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 62; 6) the first nucleic acid encoding a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 60 and the second nucleic acid encoding a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 68; and/or 7) the first nucleic acid encoding a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 72 and the second nucleic acid encoding a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 74.
(52) In some embodiments, the nucleic acid composition comprises: 1) the first nucleic acid as represented by SEQ ID NO: 4 which encodes a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 3 and the second nucleic acid as represented by SEQ ID NO: 9 which encodes a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 8; 2) the first nucleic acid as represented by SEQ ID NO: 18 which encodes a

heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 17 and the second nucleic acid as represented by SEQ ID NO: 23 which encodes a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 22; 3) the first nucleic acid as represented by SEQ ID NO: 32 which encodes a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 31 and the second nucleic acid as represented by SEQ ID NO: 37 which encodes a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 36; 4) the first nucleic acid as represented by SEQ ID NO: 46 which encodes a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 45 and the second nucleic acid as represented by SEQ ID NO: 51 which encodes a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 50; 5) the first nucleic acid as represented by SEQ ID NO: 61 which encodes a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 60 and the second nucleic acid as represented by SEQ ID NO: 63 which encodes a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 62; 6) the first nucleic acid as represented by SEQ ID NO: 61 which encodes a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 60 and the second nucleic acid as represented by SEQ ID NO: 69 which encodes a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 68; and/or 7) the first nucleic acid as represented by SEQ ID NO: 73 which encodes a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 72 and the second nucleic acid as represented by SEQ ID NO: 75 which encodes a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 74.

(53) In still yet another respect, the invention provides an expression vector composition, which comprises: (I) a first expression vector comprising a nucleotide sequence encoding a heavy chain variable region (VH) as represented by an amino acid sequence selected from SEQ ID NOs: 3, 17, 31, 45, 60 and/or 72; and (II) a second expression vector comprising a nucleotide sequence encoding a light chain variable region (VL) as represented by an amino acid sequence selected from SEQ ID NOs: 8, 22, 36, 50, 62, 68 and/or 74.

(54) In some embodiments, the expression vector composition comprises: 1) the first expression vector comprising a nucleotide sequence which encodes a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 3 and the second expression vector comprising a nucleotide sequence which encodes a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 8; 2) the first expression vector comprising a nucleotide sequence which encodes a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 17 and the second expression vector comprising a nucleotide sequence which encodes a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 22; 3) the first expression vector comprising a nucleotide sequence which encodes a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 31 and the second expression vector comprising a nucleotide sequence which encodes a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 36; 4) the first expression vector comprising a nucleotide sequence which encodes a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 45 and the second expression vector comprising a nucleotide sequence which encodes a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 50; 5) the first expression vector comprising a nucleotide sequence which encodes a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 60 and the second expression vector comprising a nucleotide sequence which encodes a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 62; 6) the first expression vector comprising a nucleotide sequence which encodes a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 60 and the second expression vector comprising a nucleotide sequence which encodes a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 68; and/or 7)

the first expression vector comprising a nucleotide sequence which encodes a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 72 and the second expression vector comprising a nucleotide sequence which encodes a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 74.

(55) In some embodiment, the expression vector composition comprises: 1) the first expression vector comprising a nucleotide sequence as represented by SEQ ID NO: 4 which encodes a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 3 and the second expression vector comprising a nucleotide sequence as represented by SEQ ID NO: 9 which encodes a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 8; 2) the first expression vector comprising a nucleotide sequence as represented by SEQ ID NO: 18 which encodes a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 17 and the second expression vector comprising a nucleotide sequence as represented by SEQ ID NO: 23 which encodes a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 22; 3) the first expression vector comprising a nucleotide sequence as represented by SEQ ID NO: 32 which encodes a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 31 and the second expression vector comprising a nucleotide sequence as represented by SEQ ID NO: 37 which encodes a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 36; 4) the first expression vector comprising a nucleotide sequence as represented by SEQ ID NO: 46 which encodes a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 45 and the second expression vector comprising a nucleotide sequence as represented by SEQ ID NO: 51 which encodes a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 50; 5) the first expression vector comprising a nucleotide sequence as represented by SEQ ID NO: 61 which encodes a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 60 and the second expression vector comprising a nucleotide sequence as represented by SEQ ID NO: 63 which encodes a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 62; 6) the first expression vector comprising a nucleotide sequence as represented by SEQ ID NO: 61 which encodes a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 60 and the second expression vector comprising a nucleotide sequence as represented by SEQ ID NO: 69 which encodes a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 68; and/or 7) the first expression vector comprising a nucleotide sequence as represented by SEQ ID NO: 73 which encodes a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 72 and the second expression vector comprising a nucleotide sequence as represented by SEQ ID NO: 75 which encodes a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 74.

(56) In one respect, the invention provides an expression vector, which comprises: (I) a first nucleic acid sequence comprising a nucleotide sequence encoding a heavy chain variable region (VH) as represented by an amino acid sequence selected from SEQ ID NOs: 3, 17, 31, 45, 60 and/or 72; and (II) a second nucleic acid sequence comprising a nucleotide sequence encoding a light chain variable region (VL) as represented by an amino acid sequence selected from SEQ ID NOs: 8, 22, 36, 50, 62, 68 and/or 74.

(57) In some embodiment, the expression vector comprises: 1) the first nucleic acid sequence comprising a nucleotide sequence encoding a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 3 and the second nucleic acid sequence comprising a nucleotide sequence encoding a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 8; 2) the first nucleic acid sequence comprising a nucleotide sequence encoding a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 17 and the second nucleic acid sequence comprising a nucleotide sequence encoding a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 22; 3) the

first nucleic acid sequence comprising a nucleotide sequence encoding a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 31 and the second nucleic acid sequence comprising a nucleotide sequence encoding a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 36; 4) the first nucleic acid sequence comprising a nucleotide sequence encoding a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 45 and the second nucleic acid sequence comprising a nucleotide sequence encoding a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 50; 5) the first nucleic acid sequence comprising a nucleotide sequence encoding a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 60 and the second nucleic acid sequence comprising a nucleotide sequence encoding a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 62; 6) the first nucleic acid sequence comprising a nucleotide sequence encoding a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 60 and the second nucleic acid sequence comprising a nucleotide sequence encoding a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 68; and/or 7) the first nucleic acid sequence comprising a nucleotide sequence encoding a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 72 and the second nucleic acid sequence comprising a nucleotide sequence encoding a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 74.

(58) In some embodiments, the expression vector comprises: 1) the first nucleic acid sequence comprising a nucleotide sequence as represented by SEQ ID NO: 4 which encodes a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 3 and the second nucleic acid sequence comprising a nucleotide sequence as represented by SEQ ID NO: 9 which encodes a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 8; 2) the first nucleic acid sequence comprising a nucleotide sequence as represented by SEQ ID NO: 18 which encodes a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 17 and the second nucleic acid sequence comprising a nucleotide sequence as represented by SEQ ID NO: 23 which encodes a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 22; 3) the first nucleic acid sequence comprising a nucleotide sequence as represented by SEQ ID NO: 32 which encodes a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 31 and the second nucleic acid sequence comprising a nucleotide sequence as represented by SEQ ID NO: 37 which encodes a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 36; 4) the first nucleic acid sequence comprising a nucleotide sequence as represented by SEQ ID NO: 46 which encodes a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 45 and the second nucleic acid sequence comprising a nucleotide sequence as represented by SEQ ID NO: 51 which encodes a light chain variable region (VL) as represented by an amino acid sequence of NO: 50; 5) the first nucleic acid sequence comprising a nucleotide sequence as represented by SEQ ID NO: 61 which encodes a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 60 and the second nucleic acid sequence comprising a nucleotide sequence as represented by SEQ ID NO: 63 which encodes a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 62; 6) the first nucleic acid sequence comprising a nucleotide sequence as represented by SEQ ID NO: 61 which encodes a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 60 and the second nucleic acid sequence comprising a nucleotide sequence as represented by SEQ ID NO: 69 which encodes a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 68; and/or 7) the first nucleic acid sequence comprising a nucleotide sequence as represented by SEQ ID NO: 73 which encodes a heavy chain variable region (VH) as represented by an amino acid sequence of SEQ ID NO: 72 and the second nucleic acid sequence comprising a nucleotide sequence as represented by SEQ ID NO: 75 which encodes

a light chain variable region (VL) as represented by an amino acid sequence of SEQ ID NO: 74.
(59) In another respect, the invention provides a nucleic acid composition that comprises: (I) a first nucleic acid comprising a nucleotide sequence encoding a heavy chain as represented by an amino acid sequence of SEQ ID NOs: 13, 27, 41, 55, 64 and/or 76; and (II) a second nucleic acid comprising a nucleotide sequence encoding a light chain as represented by an amino acid sequence of SEQ ID NOs: 15, 29, 43, 57, 66, 70 and/or 78.
(60) In some embodiment, the nucleic acid composition comprises: 1) the first nucleic acid encoding a heavy chain as represented by an amino acid sequence of SEQ ID NO: 13 and the second nucleic acid encoding a light chain as represented by an amino acid sequence of SEQ ID NO: 15; 2) the first nucleic acid encoding a heavy chain as represented by an amino acid sequence of SEQ ID NO: 27 and the second nucleic acid encoding a light chain as represented by an amino acid sequence of SEQ ID NO: 29; 3) the first nucleic acid encoding a heavy chain as represented by an amino acid sequence of SEQ ID NO: 41 and the second nucleic acid encoding a light chain as represented by an amino acid sequence of SEQ ID NO: 43; 4) the first nucleic acid encoding a heavy chain as represented by an amino acid sequence of SEQ ID NO: 55 and the second nucleic acid encoding a light chain as represented by an amino acid sequence of SEQ ID NO: 57; 5) the first nucleic acid encoding a heavy chain as represented by an amino acid sequence of SEQ ID NO: 64 and the second nucleic acid encoding a light chain as represented by an amino acid sequence of SEQ ID NO: 66; 6) the first nucleic acid encoding a heavy chain as represented by an amino acid sequence of SEQ ID NO: 64 and the second nucleic acid encoding a light chain as represented by an amino acid sequence of SEQ ID NO: 70; and/or 7) the first nucleic acid encoding a heavy chain as represented by an amino acid sequence of SEQ ID NO: 76 and the second nucleic acid encoding a light chain as represented by an amino acid sequence of SEQ ID NO: 78.
(61) In some embodiments, the nucleic acid composition comprises: 1) the first nucleic acid as represented by SEQ ID NO: 14 which encodes a heavy chain as represented by an amino acid sequence of SEQ ID NO: 13 and the second nucleic acid as represented by SEQ ID NO: 16 which encodes a light chain as represented by an amino acid sequence of SEQ ID NO: 15; 2) the first nucleic acid as represented by SEQ ID NO: 28 which encodes a heavy chain as represented by an amino acid sequence of SEQ ID NO: 27 and the second nucleic acid as represented by SEQ ID NO: 30 which encodes a light chain as represented by an amino acid sequence of SEQ ID NO: 29; 3) the first nucleic acid as represented by SEQ ID NO: 42 which encodes a heavy chain as represented by an amino acid sequence of SEQ ID NO: 41 and the second nucleic acid as represented by SEQ ID NO: 44 which encodes a light chain as represented by an amino acid sequence of SEQ ID NO: 43; 4) the first nucleic acid as represented by SEQ ID NO: 56 which encodes a heavy chain as represented by an amino acid sequence of SEQ ID NO: 55 and the second nucleic acid as represented by SEQ ID NO: 58 which encodes a light chain as represented by an amino acid sequence of SEQ ID NO: 57; 5) the first nucleic acid as represented by SEQ ID NO: 65 which encodes a heavy chain as represented by an amino acid sequence of SEQ ID NO: 64 and the second nucleic acid as represented by SEQ ID NO: 67 which encodes a light chain as represented by an amino acid sequence of SEQ ID NO: 66; 6) the first nucleic acid as represented by SEQ ID NO: 65 which encodes a heavy chain as represented by an amino acid sequence of SEQ ID NO: 64 and the second nucleic acid as represented by SEQ ID NO: 71 which encodes a light chain as represented by an amino acid sequence of SEQ ID NO: 70; and/or 7) the first nucleic acid as represented by SEQ ID NO: 77 which encodes a heavy chain as represented by an amino acid sequence of SEQ ID NO: 76 and the second nucleic acid as represented by SEQ ID NO: 79 which encodes a light chain as represented by an amino acid sequence of SEQ ID NO: 78.
(62) In yet another respect, the invention provides an expression vector composition, which comprises: (I) a first expression vector comprising a nucleotide sequence encoding a heavy chain as represented by an amino acid sequence selected from SEQ ID NOs: 13, 27, 41, 55, 64 and/or 76; and (II) a second expression vector comprising a nucleotide sequence encoding a light chain as

represented by an amino acid sequence selected from SEQ ID NOs: 15, 29, 43, 57, 66, 70 and/or 78.

(63) In some embodiments, the expression vector composition comprises: 1) the first expression vector comprising a nucleotide sequence which encodes a heavy chain as represented by an amino acid sequence of SEQ ID NO: 13 and the second expression vector comprising a nucleotide sequence which encodes a light chain as represented by an amino acid sequence of SEQ ID NO: 15; 2) the first expression vector comprising a nucleotide sequence which encodes a heavy chain as represented by an amino acid sequence of SEQ ID NO: 27 and the second expression vector comprising a nucleotide sequence which encodes a light chain as represented by an amino acid sequence of SEQ ID NO: 29; 3) the first expression vector comprising a nucleotide sequence which encodes a heavy chain as represented by an amino acid sequence of SEQ ID NO: 41 and the second expression vector comprising a nucleotide sequence which encodes a light chain as represented by an amino acid sequence of SEQ ID NO: 43; 4) the first expression vector comprising a nucleotide sequence which encodes a heavy chain as represented by an amino acid sequence of SEQ ID NO: 55 and the second expression vector comprising a nucleotide sequence which encodes a light chain as represented by an amino acid sequence of SEQ ID NO: 57; 5) the first expression vector comprising a nucleotide sequence which encodes a heavy chain as represented by an amino acid sequence of SEQ ID NO: 64 and the second expression vector comprising a nucleotide sequence which encodes a light chain as represented by an amino acid sequence of SEQ ID NO: 66; 6) the first expression vector comprising a nucleotide sequence which encodes a heavy chain as represented by an amino acid sequence of SEQ ID NO: 64 and the second expression vector comprising a nucleotide sequence which encodes a light chain as represented by an amino acid sequence of SEQ ID NO: 70; and/or 7) the first expression vector comprising a nucleotide sequence which encodes a heavy chain as represented by an amino acid sequence of SEQ ID NO: 76 and the second expression vector comprising a nucleotide sequence which encodes a light chain as represented by an amino acid sequence of SEQ ID NO: 78.

(64) In some embodiments, the expression vector composition comprises: 1) the first expression vector comprising a nucleotide sequence as represented by SEQ ID NO: 14 which encodes a heavy chain as represented by an amino acid sequence of SEQ ID NO: 13 and the second expression vector comprising a nucleotide sequence as represented by SEQ ID NO: 16 which encodes a light chain as represented by an amino acid sequence of SEQ ID NO: 15; 2) the first expression vector comprising a nucleotide sequence as represented by SEQ ID NO: 28 which encodes a heavy chain as represented by an amino acid sequence of SEQ ID NO: 27 and the second expression vector comprising a nucleotide sequence as represented by SEQ ID NO: 30 which encodes a light chain as represented by an amino acid sequence of SEQ ID NO: 29; 3) the first expression vector comprising a nucleotide sequence as represented by SEQ ID NO: 42 which encodes a heavy chain as represented by an amino acid sequence of SEQ ID NO: 41 and the second expression vector comprising a nucleotide sequence as represented by SEQ ID NO: 44 which encodes a light chain as represented by an amino acid sequence of SEQ ID NO: 43; 4) the first expression vector comprising a nucleotide sequence as represented by SEQ ID NO: 56 which encodes a heavy chain as represented by an amino acid sequence of SEQ ID NO: 55 and the second expression vector comprising a nucleotide sequence as represented by SEQ ID NO: 58 which encodes a light chain as represented by an amino acid sequence of SEQ ID NO: 57; 5) the first expression vector comprising a nucleotide sequence as represented by SEQ ID NO: 65 which encodes a heavy chain as represented by an amino acid sequence of SEQ ID NO: 64 and the second expression vector comprising a nucleotide sequence as represented by SEQ ID NO: 67 which encodes a light chain as represented by an amino acid sequence of SEQ ID NO: 66; 6) the first expression vector comprising a nucleotide sequence as represented by SEQ ID NO: 65 which encodes a heavy chain as represented by an amino acid sequence of SEQ ID NO: 64 and the second expression vector comprising a nucleotide sequence as represented by SEQ ID NO: 71 which encodes a light chain as

represented by an amino acid sequence of SEQ ID NO: 70; and/or 7) the first expression vector comprising a nucleotide sequence as represented by SEQ ID NO: 77 which encodes a heavy chain as represented by an amino acid sequence of SEQ ID NO: 76 and the second expression vector comprising a nucleotide sequence as represented by SEQ ID NO: 79 which encodes a light chain as represented by an amino acid sequence of SEQ ID NO: 78.

(65) In still yet another respect, the invention provides an expression vector, which comprises: (I) a first nucleic acid sequence comprising a nucleotide sequence encoding a heavy chain as represented by an amino acid sequence selected from SEQ ID NOs: 13, 27, 41, 55, 64 and/or 76; and (II) a second nucleic acid sequence comprising a nucleotide sequence encoding a light chain as represented by an amino acid sequence selected from SEQ ID NOs: 15, 29, 43, 57, 66, 70 and/or 78.

(66) In some embodiment, the expression vector comprises: 1) the first nucleic acid sequence comprising a nucleotide sequence encoding a heavy chain as represented by an amino acid sequence of SEQ ID NO: 13 and the second nucleic acid sequence comprising a nucleotide sequence encoding a light chain as represented by an amino acid sequence of SEQ ID NO: 15; 2) the first nucleic acid sequence comprising a nucleotide sequence encoding a heavy chain as represented by an amino acid sequence of SEQ ID NO: 27 and the second nucleic acid sequence comprising a nucleotide sequence encoding a light chain as represented by an amino acid sequence of SEQ ID NO: 29; 3) the first nucleic acid sequence comprising a nucleotide sequence encoding a heavy chain as represented by an amino acid sequence of SEQ ID NO: 41 and the second nucleic acid sequence comprising a nucleotide sequence encoding a light chain as represented by an amino acid sequence of SEQ ID NO: 43; 4) the first nucleic acid sequence comprising a nucleotide sequence encoding a heavy chain as represented by an amino acid sequence of SEQ ID NO: 55 and the second nucleic acid sequence comprising a nucleotide sequence encoding a light chain as represented by an amino acid sequence of SEQ ID NO: 57; 5) the first nucleic acid sequence comprising a nucleotide sequence encoding a heavy chain as represented by an amino acid sequence of SEQ ID NO: 64 and the second nucleic acid sequence comprising a nucleotide sequence encoding a light chain as represented by an amino acid sequence of SEQ ID NO: 66; 6) the first nucleic acid sequence comprising a nucleotide sequence encoding a heavy chain as represented by an amino acid sequence of SEQ ID NO: 64 and the second nucleic acid sequence comprising a nucleotide sequence encoding a light chain as represented by an amino acid sequence of SEQ ID NO: 70; and/or 7) the first nucleic acid sequence comprising a nucleotide sequence encoding a heavy chain as represented by an amino acid sequence of SEQ ID NO: 76 and the second nucleic acid sequence comprising a nucleotide sequence encoding a light chain as represented by an amino acid sequence of SEQ ID NO: 78.

(67) In some embodiments, the expression vector comprises: 1) the first nucleic acid sequence comprising a nucleotide sequence as represented by SEQ ID NO: 14 which encodes a heavy chain as represented by an amino acid sequence of SEQ ID NO: 13 and the second nucleic acid sequence comprising a nucleotide sequence as represented by SEQ ID NO: 16 which encodes a light chain as represented by an amino acid sequence of SEQ ID NO: 15; 2) the first nucleic acid sequence comprising a nucleotide sequence as represented by SEQ ID NO: 28 which encodes a heavy chain as represented by an amino acid sequence of SEQ ID NO: 27 and the second nucleic acid sequence comprising a nucleotide sequence as represented by SEQ ID NO: 30 which encodes a light chain as represented by an amino acid sequence of SEQ ID NO: 29; 3) the first nucleic acid sequence comprising a nucleotide sequence as represented by SEQ ID NO: 42 which encodes a heavy chain as represented by an amino acid sequence of SEQ ID NO: 41 and the second nucleic acid sequence comprising a nucleotide sequence as represented by SEQ ID NO: 44 which encodes a light chain as represented by an amino acid sequence of SEQ ID NO: 43; 4) the first nucleic acid sequence comprising a nucleotide sequence as represented by SEQ ID NO: 56 which encodes a heavy chain as represented by an amino acid sequence of SEQ ID NO: 55 and the second nucleic acid sequence

comprising a nucleotide sequence as represented by SEQ ID NO: 58 which encodes a light chain as represented by an amino acid sequence of SEQ ID NO: 57; 5) the first nucleic acid sequence comprising a nucleotide sequence as represented by SEQ ID NO: 65 which encodes a heavy chain as represented by an amino acid sequence of SEQ ID NO: 64 and the second nucleic acid sequence comprising a nucleotide sequence as represented by SEQ ID NO: 67 which encodes a light chain as represented by an amino acid sequence of SEQ ID NO: 66; 6) the first nucleic acid sequence comprising a nucleotide sequence as represented by SEQ ID NO: 65 which encodes a heavy chain as represented by an amino acid sequence of SEQ ID NO: 64 and the second nucleic acid sequence comprising a nucleotide sequence as represented by SEQ ID NO: 71 which encodes a light chain as represented by an amino acid sequence of SEQ ID NO: 70; and/or 7) the first nucleic acid sequence comprising a nucleotide sequence as represented by SEQ ID NO: 77 which encodes a heavy chain as represented by an amino acid sequence of SEQ ID NO: 76 and the second nucleic acid sequence comprising a nucleotide sequence as represented by SEQ ID NO: 79 which encodes a light chain as represented by an amino acid sequence of SEQ ID NO: 78.

(68) In one respect, the invention provides a cell comprising the expression vector composition or the expression vector.

(69) In another respect, the invention provides a method of preparing the antibody or antigen-binding fragment thereof, comprising expressing the antibody or antigen-binding fragment thereof in the cell and separating the antibody or antigen-binding fragment thereof from the cell.

(70) In yet another respect, the invention provides a pharmaceutical composition comprising the antibody or antigen-binding fragment thereof, and a pharmaceutically acceptable carrier.

(71) In still yet another respect, the invention provides a kit comprising the antibody or antigen-binding fragment thereof. In one respect, the invention provides a bispecific antibody or a multispecific antibody comprising the light chain variable region and the heavy chain variable region.

(72) In another respect, the invention provides a single chain antibody comprising the light chain variable region and the heavy chain variable region.

(73) In yet another respect, the invention provides an antibody-drug conjugate comprising the light chain variable region and the heavy chain variable region.

(74) In still yet another respect, the invention provides a method of treating a disease comprising administering to a subject in need a therapeutically effective amount of the antibody or antigen-binding fragment thereof, the pharmaceutical composition, the bispecific antibody or multispecific antibody, the single chain antibody, and/or the antibody-drug conjugate.

(75) In some embodiment, the disease is cancer.

(76) In some embodiment, the cancer is solid tumor or hematological cancer.

(77) In some embodiment, the solid tumor is selected from multiple myeloma, melanoma, stomach cancer, pancreatic cancer, breast cancer, colon cancer, lung cancer, head and neck cancer, liver cancer, ovarian cancer, bladder cancer, renal cancer, salivary gland carcinoma, esophageal cancer, glioma, glioblastoma, thyroid cancer, thymic cancer, epithelial cancer, lymphoma, T and/or B cell lymphoma, gastrointestinal stromal tumor, soft tissue neoplasm, testicular cancer, endometrial carcinoma, prostate cancer, and/or brain cancer.

(78) In some embodiment, the hematological cancer is leukemia.

(79) In another respect, the invention provides use of the antibody or antigen-binding fragment thereof, the pharmaceutical composition, the bispecific antibody or multispecific antibody, the single chain antibody, and/or the antibody-drug conjugate for the manufacture of a medicament.

(80) In some embodiment, the medicament is used for the treatment of cancer.

(81) In some embodiment, the cancer is solid tumor or hematological cancer.

(82) In some embodiment, the solid tumor is selected from multiple myeloma, melanoma, stomach cancer, pancreatic cancer, breast cancer, colon cancer, lung cancer, head and neck cancer, liver cancer, ovarian cancer, bladder cancer, renal cancer, salivary gland carcinoma, esophageal cancer,

glioma, glioblastoma, thyroid cancer, thymic cancer, epithelial cancer, lymphoma, T and/or B cell lymphoma, gastrointestinal stromal tumor, soft tissue neoplasm, testicular cancer, endometrial carcinoma, prostate cancer, and/or brain cancer.
(83) In some embodiment, the hematological cancer is leukemia.
(84) In still another respect, the invention provides the antibody or antigen-binding fragment thereof, the pharmaceutical composition, the bispecific antibody or multispecific antibody, the single chain antibody, and/or the antibody-drug conjugate for use in the treatment of a disease.
(85) In some embodiments, the disease is a cancer.
(86) In some embodiments, the cancer is solid tumor or hematological cancer.
(87) In some embodiments, the solid tumor is selected from multiple myeloma, melanoma, stomach cancer, pancreatic cancer, breast cancer, colon cancer, lung cancer, head and neck cancer, liver cancer, ovarian cancer, bladder cancer, renal cancer, salivary gland carcinoma, esophageal cancer, glioma, glioblastoma, thyroid cancer, thymic cancer, epithelial cancer, lymphoma, T and/or B cell lymphoma, gastrointestinal stromal tumor, soft tissue neoplasm, testicular cancer, endometrial carcinoma, prostate cancer, and/or brain cancer.
(88) In some embodiment, the hematological cancer is leukemia.
(89) In yet another respect, the invention provides a method of treating a disease comprising administering to a subject in need a therapeutically effective amount of the antibody or antigen-binding fragment thereof, the pharmaceutical composition, the bispecific antibody or multispecific antibody, the single chain antibody, and/or the antibody-drug conjugate.
(90) In some embodiments, the disease is a disease related to CD39.
(91) In one respect, the invention provides use of the antibody or antigen-binding fragment thereof, the pharmaceutical composition, the bispecific antibody or multispecific antibody, the single chain antibody, and/or the antibody-drug conjugate for the manufacture of a medicament.
(92) In some embodiment, the medicament is used for the treatment of a disease related to CD39.
(93) In another respect, the invention provides the antibody or antigen-binding fragment thereof, the pharmaceutical composition, the bispecific antibody or multispecific antibody, the single chain antibody, and/or the antibody-drug conjugate for use in the treatment of a disease.
(94) In some embodiments, the disease is a disease related to CD39.
(95) In still another respect, the invention provides a method of increasing T-cell activity in a cancer patient comprising administering to the cancer patient in need a therapeutically effective amount of the antibody or antigen-binding fragment thereof, the pharmaceutical composition, the bispecific antibody or multispecific antibody, the single chain antibody, and/or the antibody-drug conjugate.
(96) In yet another respect, the invention provides a method of attenuating adenosine-mediated suppression of T-cell activity in a cancer patient comprising administering to the cancer patient in need a therapeutically effective amount of the antibody or antigen-binding fragment thereof, the pharmaceutical composition, the bispecific antibody or multispecific antibody, the single chain antibody, and/or the antibody-drug conjugate.
(97) In one respect, the invention provides a method of increasing T cell activity in the tumor microenvironment of a patient comprising administering the cancer patient a therapeutically effective amount of the antibody or antigen-binding fragment thereof, the pharmaceutical composition, the bispecific antibody or multispecific antibody, the single chain antibody, and/or the antibody-drug conjugate.
(98) In another respect, the invention provides a method of treating or preventing a tumor, which comprises: (1) detecting CD39 polypeptide in a cell in the tumor microenvironment, optionally in a tumor tissue and/or the adjacent tissue, optionally in a tumor cell, and (2) based on the measurement of cell expression of CD39 polypeptide in the tumor microenvironment, optionally, if the cell expression of CD39 polypeptide in the tumor microenvironment increased compared to the reference level of CD39 polypeptide, administering to a subject in need a therapeutically effective

amount of the antibody or antigen-binding fragment thereof, the pharmaceutical composition, the bispecific antibody or multispecific antibody, the single chain antibody, and/or the antibody-drug conjugate.

(99) In some embodiment, detecting CD39 polypeptide in the cell in the tumor microenvironment in step (1) comprises obtaining a biological sample from an individual, contacting the cell with an antibody binding to the CD39 polypeptide, and measuring the expression of CD39 in the cell, wherein the biological sample comprises a tumor tissue and/or the adjacent tissue.

(100) TABLE-US-00001 TABLE 1 Description of the sequence listing of the invention Sequence SEQ ID NO: Description Sequence 1. huCD39 TQNKALPENVKYGIVLDAGSSHTSLYIYKWPAEKEND amino acid TGVVHQVEECRVKGPGISKFVQKVNEIGIYLTDCMER sequence AREVIPRSQHQETPVYLGATAGMRLLRMESEELADRV LDVVERSLSNYPFDFQGARIITGQEEGAYGWITINYL LGKFSQKTRWFSIVPYETNNQETFGALDLGGASTQVT FVPQNQTIESPDNALQFRLYGKDYNVYTHSFLCYGKD QALWQKLAKDIQVASNEILRDPCFHPGYKKVVNVSDL YKTPCTKRFEMTLPFQQFEIQGIGNYQQCHQSILELF NTSYCPYSQCAFNGIFLPPLQGDFGAFSAFYFVMKFL NLTSEKVSQEKVTEMMKKFCAQPWEEIKTSYAGVKEK YLSEYCFSGTYILSLLLQGYHFTADSWEHIHFIGKIQ GSDAGWTLGYMLNLTNMIPAEQPLSTPLSHSTYVAHH HHHHHHHH 2. cynoCD39 MLFDSILSTVGLSKLVSVVSSPAAALSKSNVKTFCSK amino acid NILAILGFSSIIAVIALLAVGLTQNKALPENIKYGIV sequence LDAGSSHTSLYIYKWPAEKENDTGVVHQVEECRVKGP GISKYVQKVNEIGIYLTDCMERAREVIPRSQHQETPV YLGATAGMRLLRMESEELADRVLDVVERSLSNYPFDF QGARIITGQEEGAYGWITINYLLGKFSQKTRWFSIVP YETNNQETFGALDLGGASTQITFVPQNQTTESPDNAL QFRLYGKDYNVYTHSFLCYGKDQALWQKLAKDIQVAS NEILRDPCFHPGYKKVVNVSDLYKTPCTKRFEMTLPF QQFEIQGIGNYQQCHQSVLELFNTSYCPYSQCAFNGI FLPPLQGDFGAFSAFYFVMNFLNLTSEKVSQEKVTEM MKKFCSQPWEEIKTSYAGVKEKYLSEYCFSGTYILSL LLQGYHFTADSWEHIHFIGKIQGSDAGWTLGYMLNLT NMIPAEQPLSTPLSHSTYVFLMVLFSLVLVIVAIIGL LIFHKPSYFWKDMV 3. 201 hIgG2 EVQLVESGGGLVKPGGSLKLSCAASGFTFSDYGMHWV VH amino RQAPEKGLEWVAYISSGSSIMYYADTVKGRFTISRDN acid sequence AKNTLFLQMASLRSEDTAMYYCARDLYYDHVLDYWGQ GTTLTVSS 4. 201 hIgG2 GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTAGTGA VH AGCCTGGAGGGTCCCTGAAACTCTCCTGTGCAGCCTC nucleotide TGGATTCACTTTCAGTGACTATGGAATGCACTGGGTT sequence CGTCAGGCTCCAGAGAAGGGGCTGGAGTGGGTTGCAT ACATTAGTAGTGGCAGTAGTATCATGTACTATGCAGA CACAGTGAAGGGCCGATTCACCATCTCCAGAGACAAT GCCAAGAACACCCTGTTCCTGCAAATGGCCAGTCTGA GGTCTGAGGACACGGCCATGTATTATTGTGCAAGGGA CCTCTACTATGATCACGTCCTTGACTACTGGGGCCAA GGCACCACTCTCACAGTCTCCTCA 5. 201 hIgG2, DYGMH h201H3.1 + h219L1.1 G2C, h201H3.1 + h201L1.1dmut G2C or M201 HuH1L1(D-E) G2C VH HCDR1 amino acid sequence 6. 201 hIgG2, YISSGSSIMYYADTVKG h201H3.1 + h219L1.1 G2C, h201H3.1

+ h201L1.1dmut G2C or M201 HuH1L1(D-E) G2C VH HCDR2 amino acid sequence 7. 201 hIgG2, DLYYDHVLDY h201H3.1 + h219L1.1 G2C, h201H3.1 + h201L1.1dmut G2C or M201 HuH1L1(D-E) G2C VH HCDR3 amino acid sequence 8. 201 hIgG2 DIQMTQSPSSLSASLGERVSLTCRASQEIRGYLIWLQ VL amino QKPGGTIKRLIYAASTLDSGVPKRFSGSRSGSDYSLT acid sequence ISSLESEDFADYYCLQYTSYPRTFGGGTKLEIK 9. 201 hIgG2 GACATCCAGATGACCCAGTCTCCATCCTCCTTATCTG VL CCTCTCTGGGAGAAAGAGTCAGTCTCACTTGTCGGGC nucleotide AAGTCAGGAAATTCGTGGTTACTTAATTTGGCTTCAG sequence CAGAAACCAGGTGGAACTATTAAACGCCTGATCTACG CCGCATCCACTTTAGATTCTGGTGTCCCAAAGAGGTT CAGTGGCAGTAGGTCTGGGTCAGATTATTCTCTCACC ATCAGCAGCCTTGAGTCTGAAGATTTTGCAGACTATT ACTGTCTACAATATACTAGTTATCCTCGGACGTTCGG TGGAGGCACCAAGCTGGAAATCAAA 10. 201 hIgG2, RASQEIRGYLI h201H3.1 + h201L1.1dmut G2C orM201 HuH1L1(D-E) G2C VL LCDR1 amino acid sequence 11. 201 hIgG2 AASTLDS VL LCDR2 amino acid sequence 12. 201 hIgG2, LQYTSYPRT h201H3.1 + h201L1.1dmut G2C or M201 HuH1L1(D-E) G2C VL LCDR3 amino acid sequence 13. 201 hIgG2 EVQLVESGGGLVKPGGSLKLSCAASGFTFSDYGMHWV full length RQAPEKGLEWVAYISSGSSIMYYADTVKGRFTISRDN amino acid AKNTLFLQMASLRSEDTAMYYCARDLYYDHVLDYWGQ sequence of GTTLTVSSASTKGPSVFPLAPCSRSTSESTAALGCLV heavy chain KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCC VECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNS TFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKT ISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG K 14. 201 hIgG2 GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTAGTGA full length AGCCTGGAGGGTCCCTGAAACTCTCCTGTGCAGCCTC nucleotide TGGATTCACTTTCAGTGACTATGGAATGCACTGGGTT sequence of CGTCAGGCTCCAGAGAAGGGGCTGGAGTGGGTTGCAT heavy chain ACATTAGTAGTGGCAGTAGTATCATGTACTATGCAGA CACAGTGAAGGGCCGATTCACCATCTCCAGAGACAAT GCCAAGAACACCCTGTTCCTGCAAATGGCCAGTCTGA GGTCTGAGGACACGGCCATGTATTATTGTGCAAGGGA CCTCTACTATGATCACGTCCTTGACTACTGGGGCCAA GGCACCACTCTCACAGTCTCCTCAGCTAGCACCAAGG GACCCTCCGTGTTTCCTCTGGCTCCTTGCTCCAGATC TACCTCCGAGTCTACCGCCGCTCTGGGTTGTCTGGTG AAGGACTACTTCCCCGAGCCAGTGACCGTGTCTTGGA ACAGCGGAGCTCTGACATCCGGAGTGCACACCTTTCC AGCCGTGCTGCAGTCTTCCGGCCTGTATTCTCTGTCC TCCGTGGTGACCGTGCCTTCTTCCAACTTCGGCACCC AGACCTACACTTGCAACGTGGACCACAAGCCCTCCAA CACCAAGGTGGACAAGACCGTGGAGCGCAAGTGTTGC GTCGAGTGCCCTCCTTGCCCAGCTCCTCCAGTGGCCG GACCTTCTGTGTTTCTGTTCCCCCCTAAGCCTAAGGA

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AGTTCAATTGGTACGTGGACGGCGTGGAGGTGCACAA
CGCTAAGACCAAGCCCAGGGAGGAGCAGTTCAACTCC
ACCTTCCGGGTGGTGTCAGTGCTGACAGTGGTGCACC
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TGTACACACTGCCTCCTTCCCGGGAGGAGATGACCAA
GAACCAGGTGTCCCTGACTTGCCTCGTGAAGGGATTC
TACCCCTCCGACATCGCAGTCGAGTGGGAATCCAACG
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CTGACCGTGGACAAGTCCCGTTGGCAGCAGGGCAACG
TGTTCTCTTGCAGCGTGATGCACGAGGCCCTGCACAA
CCACTACACCCAGAAGAGCCTGTCCCTGTCTCCCGGC AAG 15. 201 hIgG2
DIQMTQSPSSLSASLGERVSLTCRASQEIRGYLIWLQ full length
QKPGGTIKRLIYAASTLDSGVPKRFSGSRSGSDYSLT amino acid
ISSLESEDFADYYCLQYTSYPRTFGGGTKLEIKRTVA sequence of
APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW light chain
KVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKAD
YEKHKVYACEVTHQGLSSPVTKSFNRGEC 16. 201 hIgG2
GACATCCAGATGACCCAGTCTCCATCCTCCTTATCTG full length
CCTCTCTGGGAGAAAGAGTCAGTCTCACTTGTCGGGC nucleotide
AAGTCAGGAAATTCGTGGTTACTTAATTTGGCTTCAG sequence of
CAGAAACCAGGTGGAACTATTAAACGCCTGATCTACG light chain
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CAGTGGCAGTAGGTCTGGGTCAGATTATTCTCTCACC
ATCAGCAGCCTTGAGTCTGAAGATTTTGCAGACTATT
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ACCAGGGACTGTCCTCTCCAGTGACCAAGTCCTTCAA CCGCGGCGAGTGT 17. 216
hIgG2 EVQLVESGGGLVKPGGSLKLPCAASGFTFSDYGMHWV VH amino
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GGCACCACTCTCACAGTCGCCTCA 19. 216 hIgG2 DYGMH VH HCDR1 amino acid
sequence 20. 216 hIgG2 YISSGSSIIYYADTVKG VH HCDR2 amino acid sequence 21.
216 hIgG2 DLYYDHVLDY VH HCDR3 amino acid sequence 22. 216 hIgG2
DIQMTQSPSSLSASLGERVSLTCRASQEISGYLIWLQ VL amino
QKPDGTIKRLIYAASTLDSGVPKRFSGNRSGSDYSLT acid sequence
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hIgG2 LQYASYPRT VL LCDR3 amino acid sequence 27. 216 hIgG2
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YEKHKVYACEVTHQGLSSPVTKSFNRGEC 30. 216 hIgG2
GACATCCAGATGACCCAGTCTCCATCCTCCTTATCTG full length
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hIgG2 EVQLVESGGGLVKPGGSLKLSCAASGFTFSDYGMHWV VH amino
RQAPEKGLEWVAYISSGSSVIYYVDTVKGRFTISRDN acid sequence
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ACTGTCTACAATATGCTAGTTATCCTCGGACGTTCGG
TGGAGGCACCAAGCTGGAAATCAAA 38. 217 hIgG2 RASQEIGGYLS VL LCDR1 amino acid sequence 39. 217 hIgG2 AASTLDS VL LCDR2 amino acid sequence 40. 217 VL LQYASYPRT HCDR3 amino acid sequence 41. 217 hIgG2
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RQAPEKGLEWVAYISSGSSVIYYVDTVKGRFTISRDN amino acid
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TCCGTGGTGACCGTGCCTTCTTCCAACTTCGGCACCC
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DIQMTQSPSSLSASLGERVSLTCRASQEIGGYLSWLQ full length
QKPDGTIKRLIYAASTLDSGVPKRFSGSRSGSDYSLT amino acid
ISSLESEDFADYYCLQYASYPRTFGGGTKLEIKRTVA sequence of
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KVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKAD
YEKHKVYACEVTHQGLSSPVTKSFNRGEC 44. 217 hIgG2
GACATCCAGATGACCCAGTCTCCATCCTCCTTATCTG full length
CCTCTCTGGGAGAAAGAGTCAGTCTCACTTGTCGGGC nucleotide
AAGTCAGGAAATTGGTGGTTACTTAAGCTGGCTTCAG sequence of
CAGAAACCAGATGGAACTATTAAACGCCTGATCTACG light chain
CCGCATCCACTTTAGATTCTGGTGTCCCAAAAAGGTT
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CTCCCTGTCTTCCACCCTGACCCTGTCTAAGGCCGAC
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ACCAGGGACTGTCCTCTCCAGTGACCAAGTCCTTCAA CCGCGGCGAGTGT 45. 219
hIgG2 EVQLVESGGGLVKPGGSLKLSCAASGFTFSDYGMHWV VH amino
RQAPEKGLEWVAYISSGSSIRYYADTVKGRFTISRDN acid sequence
AKNTLFLQMTSLRSEDTAIYYCARDLYYDHVLDYWGQ GTTLTVSS 46. 219 hIgG2
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTAGTGA VH
AGCCTGGAGGGTCCCTGAAACTCTCCTGTGCAGCCTC nucleotide
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GGTCTGAGGACACGGCCATATATTACTGTGCAAGGGA

CCTCTACTATGATCACGTCCTTGACTACTGGGGCCAA
GGCACCACTCTCACAGTCTCCTCA 47. 219 hIgG2 DYGMH VH HCDR1 amino acid sequence 48. 219 hIgG2 YISSGSSIRYYADTVKG VH HCDR2 amino acid sequence 49. 219 hIgG2 DLYYDHVLDY VH HCDR3 amino acid sequence 50. 219 hIgG2
DIQMTQSPSSLSASLGERVSLTCRASQEVSGYLNWLQ VL amino
QKPDGTIKRLIYAASTLDSGVPKRFSGSRSGSDYSLT acid sequence
ISSLESEDFADYYCLQYASYPRTFGGGTKVEIK 51. 219 hIgG2
GACATCCAGATGACCCAGTCTCCATCCTCCTTATCTG VL
CCTCTCTGGGAGAAAGAGTCAGTCTCACTTGTCGGGC nucleotide
AAGTCAGGAAGTTAGTGGTTACTTAAACTGGCTTCAG sequence
CAGAAGCCAGATGGAACTATTAAACGCCTGATCTACG
CCGCATCCACTTTAGATTCTGGTGTCCCAAAGAGGTT
CAGTGGCAGTAGGTCTGGGTCAGATTATTCTCTCACC
ATCAGCAGCCTTGAGTCTGAAGATTTTGCAGACTATT
ACTGTCTACAATATGCTAGTTATCCTCGGACGTTCGG
TGGAGGTACCAAGGTGGAAATCAAG 52. 219 hIgG2 or RASQEVSGYLN h201H3.1 + h219L1.1 G2C VL LCDR1 amino acid sequence 53. 219 hIgG2 AASTLDS VL LCDR2 amino acid sequence 54. 219 hIgG2 or LQYASYPRT h201H3.1 + h219L1.1 G2C VL LCDR3 amino acid sequence 55. 219 hIgG2
EVQLVESGGGLVKPGGSLKLSCAASGFTFSDYGMHWV full length
RQAPEKGLEWVAYISSGSSIRYYADTVKGRFTISRDN amino acid
AKNTLFLQMTSLRSEDTAIYYCARDLYYDHVLDYWGQ sequence of
GTTLTVSSASTKGPSVFPLAPCSRSTSESTAALGCLV heavy chain
KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS
SVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCC
VECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTC
VVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNS
TFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKT
ISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF
YPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSK
LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG K 56. 219 hIgG2
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTAGTGA full length
AGCCTGGAGGGTCCCTGAAACTCTCCTGTGCAGCCTC nucleotide
TGGATTCACTTTCAGTGACTATGGAATGCATTGGGTT sequence of
CGTCAGGCTCCAGAGAAGGGGCTGGAGTGGGTTGCAT heavy chain
ACATTAGTAGTGGCAGTAGTATCCGCTACTATGCAGA
CACAGTGAAGGGCCGATTCACCATCTCCAGAGACAAT
GCCAAGAACACCCTGTTCCTGCAAATGACCAGTCTGC
GGTCTGAGGACACGGCCATATATTACTGTGCAAGGGA
CCTCTACTATGATCACGTCCTTGACTACTGGGGCCAA
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GACCCTCCGTGTTTCCTCTGGCTCCTTGCTCCAGATC
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CACCCTGATGATCTCCCGGACCCCAGAAGTGACTTGC
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GTCCAACAAGGGCCTGCCAGCTCCTATCGAGAAGACC
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TGTACACACTGCCTCCTTCCCGGGAGGAGATGACCAA
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TACCCCTCCGACATCGCAGTCGAGTGGGAATCCAACG
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GCTGGACTCCGACGGCTCCTTCTTCCTGTACTCCAAG
CTGACCGTGGACAAGTCCCGTTGGCAGCAGGGCAACG
TGTTCTCTTGCAGCGTGATGCACGAGGCCCTGCACAA
CCACTACACCCAGAAGAGCCTGTCCCTGTCTCCCGGC AAG 57. 219 hIgG2
DIQMTQSPSSLSASLGERVSLTCRASQEVSGYLNWLQ full length
QKPDGTIKRLIYAASTLDSGVPKRFSGSRSGSDYSLT amino acid
ISSLESEDFADYYCLQYASYPRTFGGGTKVEIKRTVA sequence of
APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW light chain
KVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKAD
YEKHKVYACEVTHQGLSSPVTKSFNRGEC 58. 219 hIgG2
GACATCCAGATGACCCAGTCTCCATCCTCCTTATCTG full length
CCTCTCTGGGAGAAAGAGTCAGTCTCACTTGTCGGGC nucleotide
AAGTCAGGAAGTTAGTGGTTACTTAAACTGGCTTCAG sequence of
CAGAAGCCAGATGGAACTATTAAACGCCTGATCTACG light chain
CCGCATCCACTTTAGATTCTGGTGTCCCAAAGAGGTT
CAGTGGCAGTAGGTCTGGGTCAGATTATTCTCTCACC
ATCAGCAGCCTTGAGTCTGAAGATTTTGCAGACTATT
ACTGTCTACAATATGCTAGTTATCCTCGGACGTTCGG
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TACGAGAAGCACAAGGTGTACGCTTGCGAGGTGACAC
ACCAGGGACTGTCCTCTCCAGTGACCAAGTCCTTCAA CCGCGGCGAGTGT 59.
h201H3.1 + AASTLES h219L1.1 G2C h201H3.1 + h201L1.1dmut G2C or M201
HuH1L1(D-E) G2C VL LCDR2 amino acid sequence 60. h201H3.1 +
QVQLVESGGGVVQPGRSLRLSCAASGFTFSDYGMHWV h219L1.1 G2C
RQAPGKGLEWVAYISSGSSIMYYADTVKGRFTISRDN or
SKNTLYLQMNSLRAEDTAVYYCARDLYYDHVLDYWGQ h201H3.1 + GTTVTVSS
h201L1.1dmut G2C VH amino acid sequence 61. h201H3.1 +
CAAGTGCAGCTCGTCGAAAGCGGAGGAGGCGTGGTGC h219L1.1 G2C
AGCCCGGAAGGTCTCTGAGACTGAGCTGTGCTGCCAG VH or
CGGCTTCACTTTCAGCGACTACGGCATGCACTGGGTC h201H3.1 +
AGACAAGCCCCCGGCAAGGGACTGGAATGGGTCGCTt h201L1.1dmut

acATCAGCTCCGGCAGCAGCATCATGTACTACGCCGA G2C VH
CacaGTGAAGGGAAGGTTCACAATCTCTAGGGACAAC nucleotide
AGCAAGAACACACTCTATCTGCAGATGAACTCCCTCA sequence
GAGCCGAGGATACAGCTGTGTACTACTGCGCTAGGGA
TCTGTACTACGACCACGTGCTCGATTACTGGGGCCAA
GGCACAACAGTGACAGTGAGCAGC 62. h201H3.1 +
DIQMTQSPSSLSASVGDRVTITCRASQEVSGYLNWLQ h219L1.1 G2C
QKPGKAIKRLIYAASTLESGVPSRFSGSRSGSDYTLT VL amino
ISSLQPEDFATYYCLQYASYPRTFGQGTKVEIK acid sequence 63. h201H3.1 +
GACATCCAGATGACTCAGAGCCCAAGCTCTCTGAGCG h219L1.1 G2C
CCAGCGTGGGAGATAGGGTCACAATCACTTGTAGGGC VL
CAGCCAAGAGGTGAGCGGCTATCTGAATTGGCTCCAG nucleotide
CAGAAACCCGGCAAGGCCATCAAGAGACTGATCTATG sequence
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CAGCGGCAGCAGAAGCGGCAGCGACTACACTCTCACA
ATCAGCTCCCTCCAGCCAGAAGACTTCGCCACTTACT
ACTGTCTGCAGTATGCCAGCTACCCAAGGACTTTCGG
ACAGGGTACCAAGGTGGAGATCAAA 64. h201H3.1 +
QVQLVESGGGVVQPGRSLRLSCAASGFTFSDYGMHWV h219L1.1 G2C
RQAPGKGLEWVAYISSGSSIMYYADTVKGRFTISRDN or
SKNTLYLQMNSLRAEDTAVYYCARDLYYDHVLDYWGQ h201H3.1 +
GTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLV h201L1.1dmut
KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS G2C full
SVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCC length amino
VECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTC acid sequence
VVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNS of heavy
TFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKT chain
ISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF
YPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSK
LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG K 65. h201H3.1 +
CAAGTGCAGCTCGTCGAAAGCGGAGGAGGCGTGGTGC h219L1.1 G2C
AGCCCGGAAGGTCTCTGAGACTGAGCTGTGCTGCCAG or
CGGCTTCACTTTCAGCGACTACGGCATGCACTGGGTC h201H3.1 +
AGACAAGCCCCCGGCAAGGGACTGGAATGGGTCGCTT h201L1.1dmut
ACATCAGCTCCGGCAGCAGCATCATGTACTACGCCGA G2C full
CACAGTGAAGGGAAGGTTCACAATCTCTAGGGACAAC length
AGCAAGAACACACTCTATCTGCAGATGAACTCCCTCA nucleotide
GAGCCGAGGATACAGCTGTGTACTACTGCGCTAGGGA sequence of
TCTGTACTACGACCACGTGCTCGATTACTGGGGCCAA heavy chain
GGCACAACAGTGACAGTGAGCAGCGCTAGCACCAAGG
GACCCTCCGTGTTTCCTCTGGCTCCTTGCTCCAGATC
TACCTCCGAGTCTACCGCCGCTCTGGGTTGTCTGGTG
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CACCCTGATGATCTCCCGGACCCCAGAAGTGACTTGC
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GAACCAGGTGTCCCTGACTTGCCTCGTGAAGGGATTC
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CTGACCGTGGACAAGTCCCGTTGGCAGCAGGGCAACG
TGTTCTCTTGCAGCGTGATGCACGAGGCCCTGCACAA
CCACTACACCCAGAAGAGCCTGTCCCTGTCTCCCGGC AAG 66. h201H3.1 +
DIQMTQSPSSLSASVGDRVTITCRASQEVSGYLNWLQ 1h29L1.1 G2C
QKPGKAIKRLIYAASTLESGVPSRFSGSRSGSDYTLT full length
ISSLQPEDFATYYCLQYASYPRTFGQGTKVEIKRTVA amino acid
APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW sequence of
KVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKAD light chain
YEKHKVYACEVTHQGLSSPVTKSFNRGEC 67. h201H3.1 +
GACATCCAGATGACTCAGAGCCCAAGCTCTCTGAGCG h219L1.1 G2C
CCAGCGTGGGAGATAGGGTCACAATCACTTGTAGGGC full length
CAGCCAAGAGGTGAGCGGCTATCTGAATTGGCTCCAG nucleotide
CAGAAACCCGGCAAGGCCATCAAGAGACTGATCTATG sequence of
CCGCCAGCACTCTGGAGTCCGGAGTGCCATCTAGGTT light chain
CAGCGGCAGCAGAAGCGGCAGCGACTACACTCTCACA
ATCAGCTCCCTCCAGCCAGAAGACTTCGCCACTTACT
ACTGTCTGCAGTATGCCAGCTACCCAAGGACTTTCGG
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TACGAGAAGCACAAGGTGTACGCTTGCGAGGTGACAC
ACCAGGGACTGTCCTCTCCAGTGACCAAGTCCTTCAA CCGCGGCGAGTGT 68.
h201H3.1 + DIQMTQSPSSLSASVGDRVTITCRASQEIRGYLIWLQ h201L1.1dmut
QKPGKAIKRLIYAASTLESGVPSRFSGSRSGSDYTLT G2CVL
ISSLQPEDFATYYCLQYTSYPRTFGQGTKVEIK amino acid sequence 69. h201H3.1 +
GACATCCAGATGACACAGTCCCCTAGCTCTCTGTCCG h201L1.1dmut
CCAGCGTGGGAGATAGGGTGACAATCACTTGTAGGGC G2CVL
CAGCCAAGAGATTAGGGGCTATCTGATCTGGCTGCAG nucleotide
CAGAAACCCGGCAAGGCCATCAAGAGGCTGATCTACG sequence
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ACTGTCTGCAGTACACAAGCTACCCAAGGACATTCGG

CCAAGGCACTAAGGTGGAGATCAAA 70. h201H3.1 +
DIQMTQSPSSLSASVGDRVTITCRASQEIRGYLIWLQ h201L1.1dmut
QKPGKAIKRLIYAASTLESGVPSRFSGSRSGSDYTLT G2C full
ISSLQPEDFATYYCLQYTSYPRTFGQGTKVEIKRTVA length amino
APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW acid sequence
KVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKAD of light
YEKHKVYACEVTHQGLSSPVTKSFNRGEC chain 71. h201H3.1 +
GACATCCAGATGACACAGTCCCCTAGCTCTCTGTCCG h201L1.1dmut
CCAGCGTGGGAGATAGGGTGACAATCACTTGTAGGGC G2C full
CAGCCAAGAGATTAGGGGCTATCTGATCTGGCTGCAG length
CAGAAACCCGGCAAGGCCATCAAGAGGCTGATCTACG nucleotide
CCGCCAGCACTCTGGAGAGCGGAGTCCCAAGCAGATT sequence of
TTCCGGCAGCCGCTCCGGCAGCGATTACACTCTCACA light chain
ATCAGCTCTCTGCAGCCAGAGGACTTCGCCACTTACT
ACTGTCTGCAGTACACAAGCTACCCAAGGACATTCGG
CCAAGGCACTAAGGTGGAGATCAAAAGAACCGTGGCC
GCTCCTTCCGTGTTCATCTTCCCTCCCTCCGACGAGC
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GAACAACTTCTACCCCCGGGAGGCCAAGGTCCAGTGG
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CTCCCTGTCTTCCACCCTGACCCTGTCTAAGGCCGAC
TACGAGAAGCACAAGGTGTACGCTTGCGAGGTGACAC
ACCAGGGACTGTCCTCTCCAGTGACCAAGTCCTTCAA CCGCGGCGAGTGT 72. M201
EVQLVESGGGLVQPGGSLRLSCAASGFTFSDYGMHWV HuH1L1(D-E)
RQAPGKGLEWVSYISSGSSIMYYADTVKGRFTISRDN G2C VH
AKNSLYLQMNSLRAEDTAVYYCARDLYYDHVLDYWGQ amino acid GTLLTVSS sequence
73. M201 GAGGTGCAGCTGGTGGAGAGCGGCGGCGGCCTGGTGC HuH1L1(D-E)
AGCCCGGCGGCAGCCTGAGACTGAGCTGCGCCGCCAG G2C VH
CGGCTTCACCTTCAGCGACTACGGCATGCACTGGGTG nucleotide
AGACAGGCCCCCGGCAAGGGCCTGGAGTGGGTGAGCT sequence
ACATCAGCAGCGGCAGCAGCATCATGTACTACGCCGA
CACCGTGAAGGGCAGATTCACCATCAGCAGAGACAAC
GCCAAGAACAGCCTGTACCTGCAGATGAACAGCCTGA
GAGCCGAGGACACCGCCGTGTACTACTGCGCCAGAGA
CCTGTACTACGACCACGTGCTGGACTACTGGGGCCAG
GGCACCCTGCTGACCGTGAGCAGC 74. M201
DIQMTQSPSSLSASVGDRVTITCRASQEIRGYLIWLQ HuH1L1(D-E)
QKPGGAIKRLIYAASTLESGVPSRFSGSRSGTDFTLT G2C VL
ISSLQPEDFATYYCLQYTSYPRTFGGGTKVEIK amino acid sequence 75. M201
GACATCCAGATGACCCAGAGCCCCAGCAGCCTGAGCG HuH1L1(D-E)
CCAGCGTGGGCGACAGAGTGACCATCACCTGCAGAGC G2C VL
CAGCCAGGAGATCAGAGGCTACCTGATCTGGCTGCAG nucleotide
CAGAAGCCCGGCGGCGCCATCAAGAGACTGATCTACG sequence
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CAGCGGCAGCAGAAGCGGCACCGACTTCACCCTGACC
ATCAGCAGCCTGCAGCCCGAGGACTTCGCCACCTACT
ACTGCCTGCAGTACACCAGCTACCCCAGAACCTTCGG
CGGCGGtACCAAGGTGGAGATCAAG 76. M201
EVQLVESGGGLVQPGGSLRLSCAASGFTFSDYGMHWV HuH1L1(D-E)

RQAPGKGLEWVSYISSGSSIMYYADTVKGRFTISRDN G2C full
AKNSLYLQMNSLRAEDTAVYYCARDLYYDHVLDYWGQ length amino
GTLLTVSSASTKGPSVFPLAPCSRSTSESTAALGCLV acid sequence
KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS of heavy
SVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCC chain
VECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTC
VVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNS
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ISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF
YPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSK
LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG K 77. M201
GAGGTGCAGCTGGTGGAGAGCGGCGGCGGCCTGGTGC HuH1L1(D-E)
AGCCCGGCGGCAGCCTGAGACTGAGCTGCGCCGCCAG G2C full
CGGCTTCACCTTCAGCGACTACGGCATGCACTGGGTG length
AGACAGGCCCCCGGCAAGGGCCTGGAGTGGGTGAGCT nucleotide
ACATCAGCAGCGGCAGCAGCATCATGTACTACGCCGA sequence of
CACCGTGAAGGGCAGATTCACCATCAGCAGAGACAAC heavy chain
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CTGACCGTGGACAAGTCCCGTTGGCAGCAGGGCAACG
TGTTCTCTTGCAGCGTGATGCACGAGGCCCTGCACAA
CCACTACACCCAGAAGAGCCTGTCCCTGTCTCCCGGC AAG 78. M201
DIQMTQSPSSLSASVGDRVTITCRASQEIRGYLIWLQ HuH1L1(D-E)
QKPGGAIKRLIYAASTLESGVPSRFSGSRSGTDFTLT G2C full
ISSLQPEDFATYYCLQYTSYPRTFGGGTKVEIKRTVA length amino

APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW acid sequence
KVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKAD of light
YEKHKVYACEVTHQGLSSPVTKSFNRGEC chain 79. M201
GACATCCAGATGACCCAGAGCCCCAGCAGCCTGAGCG HuH1L1(D-E)
CCAGCGTGGGCGACAGAGTGACCATCACCTGCAGAGC G2C full
CAGCCAGGAGATCAGAGGCTACCTGATCTGGCTGCAG length
CAGAAGCCCGGCGGCGCCATCAAGAGACTGATCTACG nucleotide
CCGCCAGCACCCTGGAGAGCGGCGTGCCCAGCAGATT sequence of
CAGCGGCAGCAGAAGCGGCACCGACTTCACCCTGACC light chain
ATCAGCAGCCTGCAGCCCGAGGACTTCGCCACCTACT
ACTGCCTGCAGTACACCAGCTACCCCAGAACCTTCGG
CGGCGGtACCAAGGTGGAGATCAAGAGAACCGTGGCC
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AGAGCGTGACAGAGCAGGACTCCAAGGACTCCACCTA
CTCCCTGTCTTCCACCCTGACCCTGTCTAAGGCCGAC
TACGAGAAGCACAAGGTGTACGCTTGCGAGGTGACAC
ACCAGGGACTGTCCTCTCCAGTGACCAAGTCCTTCAA CCGCGGCGAGTGT

Description

BRIEF DESCRIPTION OF THE DRAWING

(1) FIG. **1** shows the binding ability assay of chimeric CD39 antibody and soluble huCD39 protein;
(2) FIG. **2** shows the binding ability assay of chimeric CD39 antibody and natural CD39 protein;
(3) FIG. **3** shows the blocking ability of chimeric CD39 antibody against ATPase activity on cell surface;
(4) FIG. **4** shows the binding ability assay of humanized CD39 antibody and soluble huCD39 protein;
(5) FIG. **5** shows the binding ability assay of humanized CD39 antibody and huCD39 protein on the cell surface;
(6) FIG. **6** shows the blocking ability of humanized CD39 antibody against ATPase activity on cell surface;
(7) FIG. **7** shows the reversal effect of humanized CD39 antibody against ATP-mediated proliferation inhibition of human CD4+ T cell;
(8) FIG. **8** shows the reversal effect of humanized CD39 antibody against ATP-mediated proliferation inhibition of human CD8+ T cell;
(9) FIG. **9** shows the ability of humanized CD39 antibody to reverse the release of IFN-γ from CD4+ T cell;
(10) FIG. **10** shows the endocytosis of CD39 mediated by humanized CD39 antibody;
(11) FIG. **11** shows the activation effect of humanized CD39 antibody against DC cell;
(12) FIG. **12** shows the pharmacodynamics evaluation of humanized CD39 antibody on MOLP-8 xenograft model;
(13) FIG. **13** shows the tumor growth inhibition effect of humanized CD39 antibody against MOLP-8 in MOLP-8 xenograft model;
(14) FIG. **14** shows the tumor growth inhibition effect of humanized CD39 antibody against IM-9 in IM-9 xenograft tumor model.

DETAILED DESCRIPTION

Definitions

(15) In order that the present description may be more readily understood, certain terms are firstly defined. Additional definitions are set forth throughout the detailed description.

(16) Human CD39, also known as NTPdasel, ENTPD1, ATPDase and vascular ATP diphosphohydrolase, International Enzymology Commission number of EC 3.6.1.5, exhibits ATPase activity. CD39 hydrolyzes extracellular ATP and ADP to AMP, and AMP is further converted to adenosine by 5-prime nucleotidase. The amino acid sequence of the human CD39 mature polypeptide chain is shown in Genbank under accession number of P49961.

(17) The term “antibody” as used herein may include whole antibodies and any antigen binding fragments (i.e., “antigen-binding portions”) or single chains thereof. An “antibody” refers, in one embodiment, to a glycoprotein or an antigen binding portion thereof 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. In some naturally occurring IgG, IgD and IgA antibodies, the heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. In some naturally occurring antibodies, 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), and regions that are more conserved, termed framework regions (FR), both of which are intermingled arrangement. Herein, the CDRs of the VH region are abbreviated as HCDRs, that is, the three CDRs of the VH region can be abbreviated as HCDR1, HCDR2, and HCDR3; the CDRs of the VL region are abbreviated as LCDR, that is, the three CDRs of the VL region can be abbreviated as LCDR1, LCDR2. LCDR3. 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, 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 of the classical complement system (C1q).

(18) The heavy chain of an antibody may or may not contain a terminal lysine (K), or a terminal glycine and lysine (GK). Thus, any of the heavy chain sequences and heavy chain constant region sequences provided herein can end in either GK or K, or lack K or GK, regardless of what the last amino acid of the sequence provides. This is because the terminal lysine and sometimes glycine and lysine are cleaved during expression of the antibody.

(19) Antibodies typically bind specifically to their cognate antigen with high affinity, reflected by a dissociation constant (K.sub.D) of 10.sup.−7 to 10.sup.−11 M or less. Any K.sub.D greater than about 10.sup.−6 M is generally considered to indicate binding nonspecifically. As used herein, an antibody that “binds specifically” to an antigen refers to an antibody that binds to the antigen and substantially identical antigens with high affinity, which means having a K.sub.D of 10.sup.−7M or less, preferably 10.sup.−8M or less, even more preferably 5×10.sup.−9 M or less, and most preferably between 10.sup.−8 M and 10.sup.−10M or less, but does not bind with high affinity to unrelated antigens. An antigen is “substantially identical” to a given antigen if it exhibits a high degree of sequence identity to the given antigen, for example, if it exhibits at least 80%, at least 90%, at least 95%, at least 97%, or at least 99% or greater sequence identity to the sequence of the given antigen. An immunoglobulin may be from any of the commonly known isotypes, including but not limited to IgA, secretory IgA, IgG and IgM. The IgG isotype is divided in subclasses in some species: IgG1, IgG2, IgG3 and IgG4 in humans, and IgG1, IgG2a, IgG2b and IgG3 in mice. In certain embodiments, the anti-CD39 antibodies described herein are of the human IgG1 or IgG2 subtype. Immunoglobulins, e.g., human IgG1, exist in several allotypes, which differ from each other in at most a few amino acids. “Antibody” may include, by way of example, both naturally

occurring and non-naturally occurring antibodies; monoclonal and polyclonal antibodies; chimeric and humanized antibodies; human and nonhuman antibodies; wholly synthetic antibodies; and single chain antibodies.

(20) The term “antigen-binding portion” of an antibody, as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to an antigen (e.g., human CD39). It has been shown that the antigen-binding function of an antibody can be performed by fragments of a full-length antibody. Examples of binding fragments encompassed within the term “antigen-binding portion” of an antibody, e.g., an anti-CD39 antibody described herein, include (i) a Fab fragment, which is a monovalent fragment consisting of the VL, VH, CL and CH1 domains; (ii) a F(ab′).sub.2 fragment, which is a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the VH and CH1 domains; (iv) a Fv fragment consisting of the VL and VH domains of a single arm of an antibody, (v) a dAb fragment (Ward et al., (1989) *Nature* 341:544-546), which consists of a VH domain; and (vi) an isolated complementarity determining region (CDR) or (vii) a combination of two or more isolated CDRs which may optionally be linked by a synthetic linker. Furthermore, although the two domains of the Fv fragment, VL and VH, are encoded by different genes, they can be linked, 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. (1988) Science 242:423-426; and Huston et al. (1988) *Proc. Natl. Acad. Sci. USA* 85:5879-5883). Such single chain antibodies are also intended to be encompassed within the term “antigen-binding portion” of an antibody. These and other potential constructs are described at Chan & Carter (2010) *Nat. Rev. Immunol.* 10:301. These antibody fragments are obtained using conventional techniques known to those with skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies. Antigen-binding portions can be produced by recombinant DNA techniques, or by enzymatic or chemical cleavage of intact immunoglobulins.

(21) The term “amino acid sequence of conservative modifications form” refers to the amino acid modifications that do not significantly affect or alter the binding characteristics of the antibody containing the amino acid sequence, and the modifications include amino acid substitutions, additions and deletions. Modifications can be introduced into an antibody of the invention by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis. Conservative amino acid substitutions are ones in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine, tryptophan), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Thus, one or more amino acid residues within the CDR regions of an antibody of the invention can be replaced with other amino acid residues from the same side chain family and the altered antibody can be tested for retained function using the functional assays described herein. Preferably, the conservative modifications are no more than one or two in number.

(22) A “bispecific” or “bifunctional antibody” is an artificial hybrid antibody having two different heavy/light chain pairs, giving rise to two antigen binding sites with specificity for different antigens. Bispecific antibodies can be produced by a variety of methods including fusion of hybridomas or linking of Fab′ fragments. See, e.g., Songsivilai & Lachmann, Clin. Exp. Immunol. 79:315-321 (1990); Kostelny et al., J. Immunol. 148, 1547-1553 (1992).

(23) The term “monoclonal antibody,” as used herein, refers to an antibody that displays a single binding specificity and affinity for a specific epitope or a composition of antibodies in which all

antibodies display a single binding specificity and affinity for a specific epitope. Typically such monoclonal antibodies will be derived from a single antibody encoding cell or nucleic acid, and will be propagated without intentionally introducing any sequence alterations. Accordingly, the term “human monoclonal antibody” refers to a monoclonal antibody that has variable and optional constant regions derived from human germ line immunoglobulin sequences. In one embodiment, human monoclonal antibodies are produced by a hybridoma, for example, obtained by fusing a B cell derived from a transgenic or transchromosomal non-human animal (e.g., a transgenic mouse having a genome comprising a human heavy chain transgene and a light chain transgene), with an immortalized cell.

(24) The term “recombinant human antibody,” as used herein, includes all human antibodies that are prepared, expressed, produced or isolated by recombinant means, such as (a) antibodies isolated from an animal (e.g., a mouse) that is transgenic or transchromosomal for human immunoglobulin genes or a hybridoma prepared therefrom, (b) antibodies isolated from a host cell transformed to express the antibody, e.g., from a transfectoma, (c) antibodies isolated from a recombinant, combinatorial human antibody library, and (d) antibodies prepared, expressed, produced or isolated by any other means that involve splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies comprise variable and constant regions that utilize specific human germline immunoglobulin sequences and are encoded by the germline genes, but include subsequent rearrangements and mutations that occur, for example, during antibody maturation. As known in the art (see, e.g., Lonberg (2005) Nature Biotech. 23(9): 1117-1125), the variable region contains the antigen binding domain, which is encoded by various genes that rearrange to form an antibody specific for an exogenous antigen. In addition to rearrangement, the variable region can be further modified by multiple single amino acid changes (referred to as somatic mutation or hypermutation) to increase the affinity of the antibody to the exogenous antigen. The constant region will change in further response to an antigen (i.e., isotype switch). Therefore, the rearranged and somatically mutated nucleic acid sequences that encode the light chain and heavy chain immunoglobulin polypeptides in response to an antigen may not be identical to the original germline sequences, but instead will be substantially identical or similar (i.e., have at least 80% identity).

(25) A “human” antibody (HuMAb) refers to an antibody having variable regions in which both the framework and CDR regions are derived from human germ line immunoglobulin sequences. Furthermore, if the antibody contains a constant region, the constant region is also derived from human germ line immunoglobulin sequences. The antibodies described herein may include amino acid residues not encoded by human germ line immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis in vitro or by somatic mutation in vivo). However, the term “human antibody”, as used herein, is not intended to include antibodies in which CDR sequences derived from the germ line of another mammalian species, such as a mouse, have been grafted onto human framework sequences. The terms “human” antibodies and “fully human” antibodies are used synonymously.

(26) A “humanized” antibody refers to an antibody in which some, most or all of the amino acids outside the CDR domains of a non-human antibody are replaced with corresponding amino acids derived from human immunoglobulins. In one embodiment of an antibody in humanized form, some, most or all of the amino acids outside the CDR domains have been replaced with amino acids from human immunoglobulins, whereas some, most or all amino acids within one or more CDR regions are unchanged. Small additions, deletions, insertions, substitutions or modifications of amino acids are permissible as long as they do not abrogate the ability of the antibody to bind to a specific antigen. A “humanized” antibody retains an antigenic specificity similar to that of the original antibody.

(27) A “chimeric antibody” refers to an antibody in which the variable regions are derived from one species and the constant regions are derived from another species, such as an antibody in which the

variable regions are derived from a mouse antibody and the constant regions are derived from a human antibody.
(28) A “modified heavy chain constant region” refers to a heavy chain constant region comprising the constant domains CH1, hinge, CH2, and CH3, wherein one or more of the constant domains are from a different isotype (e.g. IgG1, IgG2, IgG3, IgG4). In some embodiments, the modified constant region includes a human IgG2 CH1 domain and a human IgG2 hinge fused to a human IgG1 CH2 domain and a human IgG1 CH3 domain. In certain embodiments, such modified constant regions also include amino acid modifications within one or more of the domains relative to the wild type amino acid sequence.
(29) As used herein, “isotype” refers to the antibody class (e.g., IgG1, IgG2, IgG3, IgG4, IgM, IgA1, IgA2, IgD, and IgE antibody) that is encoded by the heavy chain constant region genes.
(30) “Allotype” refers to naturally occurring variants in a specific isotype group, which variants differ in a few amino acids (see, e.g., Jefferis et al. (2009) mAbs 1: 1). Antibodies described herein may be of any allotype.
(31) Unless specified otherwise herein, all amino acid numbers are according to the EU index of the Kabat system (Kabat, E. A., et al. (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242).
(32) The terms “an antibody recognizing an antigen” and “an antibody specific for an antigen” are used interchangeably herein with the term “an antibody which binds specifically to an antigen.”
(33) An “effector function” refers to the interaction of an antibody Fc region with an Fc receptor or ligand, or a biochemical event that results therefrom. Exemplary “effector functions” include C1q binding, complement dependent cytotoxicity (CDC), Fc receptor binding, FcγR-mediated effector functions such as ADCC and antibody dependent cell-mediated hagocytosis (ADCP), and downregulation of a cell surface receptor (e.g., the B cell receptor; BCR). Such effector functions generally require the Fc region to be combined with a binding domain (e.g., an antibody variable domain).
(34) An “Fc receptor” or “FcR” is a receptor that binds to the Fc region of an immunoglobulin. FcRs that bind to an IgG antibody comprise receptors of the FcγR family, including allelic variants and alternatively spliced forms of these receptors. The FcγR family consists of three activating receptors (FcγRI, FcγRIII, and FcγRIV in mice; FcγRIA, FcγRIIA, and FcγRIIIA in humans) and one inhibitory receptor (FcγRIIB) Various properties of human FcγRs are summarized in Table A. The majority of innate effector cell types coexpress one or more activating FcγR and the inhibitory FcγRIIB, whereas natural killer (NK) cells selectively express one activating Fc receptor (FcγRIII in mice and FcγRIIIA in humans) but does not express the inhibitory FcγRIIB in mice and humans. Human IgG1 binds to most human Fc receptors and is considered that the types of activating Fc receptors which it binds to are equivalent to murine IgG2a.
(35) TABLE-US-00002 TABLE A Characteristics of human FcγRs Affinity for Fcγ Allelic variants human IgG Isotype preference Cellular distribution FcγRI None described High (K.sub.D IgG1 = 3 > 4 >> 2 Monocytes, macrophages, ~10 nM) activated neutrophils, dentritic cells FcγRIIA H131 Low to medium IgG1 > 3 > 2 > 4 Neutrophils, monocytes, R131 Low IgG1 > 3 > 4 > 2 macrophages, eosinophils, dentritic cells, platelets FcγRIIIA V158 Medium IgG1 = 3 >> 4 > 2 NK cell, monocytes, F158 Low IgG1 = 3 >> 4 > 2 macrophages, mast cells, eosinophils, dentritic cell FcγRIIB I232 Low IgG1 = 3 = 4 > 2 B cells, monocytes, T232 Low IgG1 = 3 = 4 > 2 macrophages, dentritic cells, mast cells
(36) A “hinge”, “hinge domain” or “hinge region” or “antibody hinge region” refers to the domain of a heavy chain constant region that links the CH1 domain to the CH2 domain and includes the upper, middle, and lower portions of the hinge (Roux et al. J. Immunol. 1998 161:4083). The hinge provides varying levels of flexibility between the binding and effector regions of an antibody and also provides sites for intermolecular disulfide bonding between the two heavy chain constant regions. The term “hinge” includes wildtype hinges, as well as variants thereof (e.g., non-naturally-

occurring hinges or modified hinges). For example, the term “IgG2 hinge” includes wildtype IgG2 hinge, and variants having 1, 2, 3, 4, 5, 1-3, 1-5, 3-5 and/or at most 5, 4, 3, 2, or 1 mutations, e.g., substitutions, deletions or additions.

(37) The term “CH1 domain” refers to the heavy chain constant region linking the variable domain to the hinge in a heavy chain constant domain. The term “CH1 domain” includes wildtype CH1 domains, as well as variants thereof (e.g., non-naturally-occurring CH1 domains or modified CH1 domains). For example, the term “CH1 domain” includes wildtype CH1 domains and variants thereof having 1, 2, 3, 4, 5, 1-3, 1-5, 3-5 and/or at most 5, 4, 3, 2, or 1 mutations, e.g., substitutions, deletions or additions.

(38) Exemplary CH1 domains include CH1 domains with mutations that change a biological activity of an antibody, such as ADCC, CDC or half-life period. Modifications to the CH1 domain that affect a biological activity of an antibody are provided herein.

(39) The term “CH2 domain” refers to the heavy chain constant region linking the hinge in a heavy chain constant domain to the CH3 domain. The term “CH2 domain” includes wildtype CH2 domains, as well as variants thereof (e.g., non-naturally-occurring CH2 domains or modified CH2 domains). For example, the term “CH2 domain” includes wildtype CH2 domains and variants thereof having 1, 2, 3, 4, 5, 1-3, 1-5, 3-5 and/or at most 5, 4, 3, 2, or 1 mutations, e.g., substitutions, deletions or additions. Exemplary CH2 domains include CH2 domains with mutations that change a biological activity of an antibody, such as ADCC, CDC or half-life.

(40) The term “CH3 domain” refers to the heavy chain constant region that is C-terminal to the CH2 domain in a heavy chain constant domain. The term “CH3 domain” includes wildtype CH3 domains, as well as variants thereof (e.g., non-naturally-occurring CH3 domains or modified CH3 domains). For example, the term “CH3 domain” includes wildtype CH3 domains and variants thereof having 1, 2, 3, 4, 5, 1-3, 1-5, 3-5 and/or at most 5, 4, 3, 2, or 1 mutations, e.g., substitutions, deletions or additions. Exemplary CH3 domains include CH3 domains with mutations that change a biological activity of an antibody, such as ADCC, CDC or half-life period. Modifications to the CH3 domain that affect a biological activity of an antibody are provided herein.

(41) A “CL domain” refers to the constant domain of a light chain. The term “CL domain” includes wildtype CL domains and variants thereof.

(42) A “native sequence Fc region” or “native sequence Fc” comprises an amino acid sequence that is identical to the amino acid sequence of an Fc region found in nature. Native sequence human Fc regions include a native sequence human IgG1 Fc region; native sequence human IgG2 Fc region; native sequence human IgG3 Fc region; and native sequence human IgG4 Fc region as well as naturally occurring variants thereof.

(43) Native sequence Fc includes the various allotypes of Fcs (see, e.g., Jefferis et al. (2009) mAbs 1: 1).

(44) The term “epitope” or “antigenic determinant” refers to a site on an antigen (e.g., CD39) to which an immunoglobulin or antibody specifically binds. Epitopes within protein antigens can be formed both from contiguous amino acids (usually a linear epitope) or noncontiguous amino acids juxtaposed by tertiary folding of the protein (usually a conformational epitope). Epitopes formed from contiguous amino acids are typically, but not always, retained when exposing to denaturing solvents, whereas epitopes formed by tertiary folding are typically lost when treating 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 for determining what epitopes are bound by a given antibody (i.e., epitope mapping) are well known in the art and include, for example, immunoblotting and immunoprecipitation analysis, wherein overlapping or contiguous peptides (e.g., from CD39) are tested for reactivity with a given antibody (e.g., anti-CD39 antibody). Methods of determining spatial conformation of epitopes include techniques in the art and those described herein, for example, x-ray crystallography, 2-dimensional nuclear magnetic resonance and HDX-MS (see, e.g., Epitope Mapping Protocols in Methods in Molecular Biology, Vol. 66, G.

E. Morris, Ed. (1996)).
(45) The term “epitope mapping” refers to the process of identification of the molecular determinants on the antigen involved in antibody-antigen recognition.
(46) The term “binds to the same epitope” with reference to two or more antibodies means that the antibodies bind to the same segment of amino acid residues, as determined by a given method. Techniques for determining whether antibodies bind to the “same epitope on CD39” of the antibodies described herein include, for example, epitope mapping methods, such as, x-ray analyses of crystals of antigen: antibody complexes, which provide atomic resolution of the epitope, and hydrogen/deuterium exchange mass spectrometry (HDX-MS). Other methods that monitor the binding of the antibody to antigen fragments (e.g. proteolytic fragments) or to mutated variations of the antigen where loss of binding due to a modification of an amino acid residue in the antigen sequence is often considered an indication of an epitope component (e.g. alanine scanning mutagenesis—Cunningham & Wells (1985) Science 244: 1081). In addition, computational combinatorial methods for epitope mapping can also be used. These methods rely on the ability of the antibody of interest from combinatorial phage display peptide libraries to affinity isolate specific short peptides.
(47) Antibodies that “compete with another antibody for binding to a target” refer to antibodies that inhibit (partially or completely inhibit) the binding of another antibody to the target. Whether the two antibodies compete with each other for binding to a target, i.e., whether and to what extent one antibody inhibits the binding of another antibody to a target, may be determined using known competition experiments, such as those described in the Examples. In certain embodiments, an antibody competes with another antibody, and inhibit at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 100% of the binding. The extent of inhibition or competition may be different depending on which antibody is the “blocking antibody” (i.e., the cold antibody that is incubated first with the target). Competition assays can be conducted as described, for example, in Ed Harlow and David Lane, Cold Spring Harb Pro toe; 2006; doi: 10.1101/pdb.prot4277 or in Chapter 11 of “Using Antibodies” by Ed Harlow and David Lane, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, USA 1999. Competing antibodies bind to the same epitope, the overlapping epitope or the adjacent epitopes (e.g., as evidenced by steric hindrance).
(48) Other competitive binding assays include: solid phase direct or indirect radioimmunoassay (MA), solid phase direct or indirect enzyme immunoassay (EIA), sandwich competition assay (see Stahli et al., Methods in Enzymology 9:242 (1983)); solid phase direct biotin-avidin EIA (see Kirkland et al., J. Immunol. 137:3614 (1986)); solid phase direct labeled assay, solid phase direct labeled sandwich analysis (see Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Press (1988)); solid phase direct label MA using 1-125 label (see Morel et al., Mol. Immunol. 25(1):7 (1988)); solid phase direct biotin-avidin EIA (Cheung et al., Virology 176:546 (1990)); and direct labeled RIA. (Moldenhauer et al., Scand. J. Immunol. 32:77 (1990)).
(49) As used herein, the terms “specific binding,” “selective binding,” “selectively binds,” and “specifically binds,” refer to antibody binding to an epitope on a predetermined antigen but not to other antigens. Typically, the antibody (i) binds with an equilibrium dissociation constant (K.sub.D) of approximately less than 10.sup.−7M, such as approximately less than 10.sup.−8M, 10.sup.−9M or 10.sup.−10 M or even lower when determined by, e.g., surface plasmon resonance (SPR) technology in a BIACORE® 2000 surface plasmon resonance instrument using the predetermined antigen, e.g., recombinant human CD39, as the analyte and the antibody as the ligand, or Scatchard analysis of binding of the antibody to antigen positive cells, and (ii) binds to the predetermined antigen with an affinity that is at least two-times greater than its affinity for binding to a non-specific antigen (e.g., BSA, casein) other than the predetermined antigen or a closely-related antigen. Accordingly, unless otherwise indicated, an antibody that “specifically binds to human CD39” refers to an antibody that binds to soluble or cell bound human CD39 with a K.sub.D of 10.sup.−7M or less, such as approximately less than 10.sup.−8M, 10.sup.−9M or 10.sup.−10 M or

even lower. An antibody that “cross-reacts with cynomolgus CD39” refers to an antibody that binds to cynomolgus CD39 with a K.sub.D of 10.sup.−7M or less, such as less than 10.sup.−8M, 10.sup.−9M or 10.sup.−10 M or even lower. In certain embodiments, antibodies that do not cross-react with CD39 from a non-human species exhibit essentially undetectable binding against these proteins in standard binding assays.

(50) The term “Kassoc” or “Ka”, as used herein, is intended to refer to the association rate constant of a specific antibody-antigen interaction, whereas the term “Kdis” or “Kd” as used herein, is intended to refer to the dissociation rate constant of a specific antibody-antigen interaction. The term “K.sub.D”, as used herein, is intended to refer to the equilibrium dissociation constant, which is obtained from the ratio of Kd to Ka (i.e., Kd/Ka) and is expressed as a molar concentration (M). K.sub.D values of antibodies can be determined using methods well established in the art. A preferred method for determining the K.sub.D of an antibody is to analyze by using surface plasmon resonance, preferably using a biosensor system such as a Biacore® surface plasmon resonance system or flow cytometry and Scatchard.

(51) The term “EC50” in the context of an in vitro or in vivo assay using an antibody or antigen binding fragment thereof, refers to the concentration of an antibody or an antigen-binding portion thereof that induces a response that is 50% of the maximal response, i.e., halfway between the maximal response and the baseline.

(52) The term “naturally-occurring” as used herein as applied to an object refers to the fact that an object can be found in nature. For example, a polypeptide or polynucleotide sequence that is present in an organism (including viruses) that can be isolated from a source in nature and which has not been intentionally modified by man in the laboratory is naturally-occurring.

(53) A “polypeptide” refers to a chain comprising at least two consecutively linked amino acid residues, with no upper limit on the length of the chain. One or more amino acid residues in the protein may contain a modification such as, but not limited to, glycosylation, phosphorylation or a disulfide bond. A “protein” may comprise one or more polypeptides.

(54) The term “nucleic acid molecule,” as used herein, is intended to include DNA molecules and RNA molecules. A nucleic acid molecule may be a single chain or a double chain, and may be cDNA. Also provided are “conservative sequence modifications” of the sequences set forth in SEQ ID NOs described herein, i.e., nucleotide and amino acid sequence modifications which do not abrogate the binding of the antibody encoded by the nucleotide sequence or containing the amino acid sequence, to the antigen. Such conservative sequence modifications include conservative nucleotide and amino acid substitutions, as well as, nucleotide and amino acid additions and deletions. For example, modifications can be introduced into SEQ ID NOs described herein by standard techniques known in the art, such as site-directed mutagenesis and PCR-mediated mutagenesis. Conservative sequence modifications include conservative amino acid substitutions, in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine, tryptophan), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Thus, a predicted nonessential amino acid residue in an anti-CD39 antibody is preferably replaced with another amino acid residue from the same side chain family. Methods of identifying nucleotide and amino acid conservative substitutions that do not eliminate antigen binding are well-known in the art (see, e.g., Brummell et al., Biochem. 32: 1180-1187 (1993); Kobayashi et al. Protein Eng. 12(10):879-884 (1999); and Burks et al. Proc. Natl. Acad. Sci. USA 94:412-417 (1997)). Alternatively, in another embodiment, mutations can be introduced randomly along all or part of an anti-CD39 antibody encoding sequence, such as by saturation mutagenesis, and the

resulting modified anti-CD39 antibodies can be screened through improved binding activity.
(55) For nucleic acids, the term “substantial identity” indicates that two nucleic acids, or designated sequences thereof, when optimally aligned and compared, are identical, with appropriate nucleotide insertions or deletions, in at least about 80% of the nucleotides, usually at least about 90% to 95%, and more preferably at least about 98% to 99.5% of the nucleotides. Alternatively, substantial identity exists when the segments will hybridize under selective hybridization conditions, to the complement of the chain.
(56) For polypeptides, the term “substantial identity” indicates that two polypeptides, or designated sequences thereof, when optimally aligned and compared, are identical, with appropriate amino acid insertions or deletions, in at least about 80% of the amino acids, usually at least about 90% to 95%, and more preferably at least about 98% to 99.5% of the amino acids.
(57) The identity % between two sequences is a function of the number of identical positions shared by the sequences when the sequences are optimally aligned (i.e., identity %=number of identical positions/total number of positions×100), with optimal alignment determined taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm, as described in the non-limiting examples below.
(58) The percent identity between two nucleotide sequences can be determined using the GAP program in the GCG software package (available at http://www.gcg.com), using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. The percent identity between two nucleotide or amino acid sequences can also be determined using the algorithm of E. Meyers and W. Miller (CABIOS, 4: 11-17 (1989)) 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 algorithm of Needleman and Wunsch (J. Mol. Biol. (48):444-453 (1970)) which has been incorporated into the GAP program in the GCG software package (available at http://www.gcg.com), 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.
(59) The nucleic acid and protein sequences described herein can further be used as a “query sequence” to perform searches against public databases to, for example, identify related sequences. Such searches can be performed with the NBLAST and XBLAST programs (version 2.0) of Altschul, et al. (1990) J. Mol. Biol. 215:403-10. BLAST nucleotide searches can be performed with the NBLAST program, score=100, wordlength=12 to obtain nucleotide sequences identical to the nucleic acid molecules described herein. BLAST protein searches can be performed with the XBLAST program, score=50, wordlength=3 to obtain amino acid sequences identical to the protein molecules described herein. To obtain gapped alignments for comparison purposes, Gapped BLAST can be used as described in Altschul et al., (1997) Nucleic Acids Res. 25(17):3389-3402. When using BLAST and Gapped BLAST programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) can be used. See www.ncbi.nlm.nih.gov.
(60) These nucleic acids may be present in whole cells, in a cell lysate, or in a partially purified or substantially pure form. The nucleic acid is “isolated” or “rendered substantially pure” when purified away from other cellular components or other contaminants, e.g., other cellular nucleic acids (e.g., the other parts of the chromosome) or proteins, by standard techniques, including alkaline/SDS treatment, CsCl banding, column chromatography, agarose gel electrophoresis and others well known in the art. See, F. Ausubel, et al., ed. Current Protocols in Molecular Biology, Greene Publishing and Wiley Interscience, New York (1987).
(61) Nucleic acids, e.g., cDNA, may be mutated, in accordance with standard techniques to provide gene sequences. For encoding sequences, these mutations may affect amino acid sequence as

desired. Specifically, DNA sequences substantially identical to or derived from native V, D, J, constant, switches and other such sequences described herein are contemplated.

(62) The term “vector,” as used herein, is intended to refer to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is “plasmid,” which refers to a circular double chains DNA loop into which other DNA segments may be linked. Another type of vector is a viral vector, wherein other DNA segments may be linked into the viral genome. Some vectors are capable of autonomous replication in a host cell into which they are introduced (e.g., bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (e.g., non-episomal mammalian vectors) can be integrated into the genome of a host cell when introduced into the host cell, and thereby are replicated along with the host genome. Moreover, some vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as “recombinant expression vectors” (or simply, “expression vectors”). In general, expression vectors used in recombinant DNA techniques are often in the form of plasmids. In the present description, “plasmid” and “vector” may be used interchangeably as the plasmid is the most commonly used form of vector. However, also included are other forms of expression vectors, such as viral vectors (e.g., replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

(63) The term “recombinant host cell” (or simply “host cell”), as used herein, is intended to refer to a cell that comprises a nucleic acid that is not naturally present in the cell, and maybe a cell into which a recombinant expression vector has been introduced. It should be understood that such terms are intended to refer not only to the specific subject cell but to the progeny of such a cell. Since certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term “host cell” as used herein.

(64) As used herein, the term “antigen” refers to any natural or synthetic immunogenic substance, such as a protein, peptide, or hapten. An antigen may be CD39 or a fragment thereof.

(65) An “immune response” refers to a biological response in a vertebrate for exogenous agents, such response protects the organism against these agents and diseases caused by them. An immune response is mediated by the action of a cell of the immune system (for example, a T lymphocyte, B lymphocyte, natural killer (NK) cell, macrophage, eosinophil, mast cell, dendritic cell or neutrophil) and soluble macromolecules produced by any of these cells or the liver (including antibodies, cytokines, and complement), the action results in selective targeting, binding to, damage to, destruction of, and/or elimination from the vertebrate's body of invading pathogens, cells or tissues infected with pathogens, cancerous or other abnormal cells, or, in cases of autoimmunity or pathological inflammation, normal human cells or tissues. An immune response or reaction includes, e.g., activation or inhibition of a T cell, e.g., an effector T cell or a Th cell, such as a CD4+ or CD8+ T cell, or inhibition of a Treg cell.

(66) An “immunomodulator” or “immunoregulator” refers to an agent, e.g., a component of a signaling pathway, which may be involved in modulating, regulating, or modifying an immune response. “Modulating,” “regulating,” or “modifying” an immune response refers to any changes in a cell of the immune system or in the activity of such cell (e.g., an effector T cell). Such modulation includes stimulation or suppression of the immune system which may be manifested by an increase or decrease in the number of various cell types, an increase or decrease in the activity of these cells, or any other changes which can occur within the immune system. Both inhibitory and stimulatory immunomodulators have been identified, some of which may have enhanced function in a tumor microenvironment. The immunomodulator may be located on the surface of a T cell. An “immunomodulatory target” or “immunoregulatory target” is an immunomodulator that is targeted for binding by, and whose activity is altered by the binding of, a substance, agent, moiety, compound or molecule. Immunomodulatory targets include, for example, receptors on the surface of a cell (“immunomodulatory receptors”) and receptor ligands (“immunomodulatory ligands”).

(67) An increased ability of stimulating an immune response, or the immune system, can result from an enhanced agonist activity of T cell co-stimulatory receptors and/or an enhanced antagonist activity of inhibitory receptors. An increased ability of stimulating an immune response or the immune system may be reflected by a time increase of the EC50 or maximal level of activity in an assay that measures an immune response, e.g., an assay that measures changes in cytokine or chemokine release, cytolytic activity (determined directly on target cells or indirectly via detecting CD 107a or granzymes) and proliferation. The ability of stimulating an immune response or the immune system activity may be enhanced by at least 10%, 30%, 50%, 75%, 2 times, 3 times, 5 times or more.
(68) “Immunotherapy” refers to the treatment of a subject afflicted with, or at risk of contracting or suffering a recurrence of, a disease by a method comprising inducing, enhancing, suppressing or otherwise modifying an immune response.
(69) “Immuno stimulating therapy” or “immuno stimulatory therapy” refers to a therapy that results in increasing (inducing or enhancing) an immune response in a subject for, e.g., treating cancer.
(70) “Potentiating an endogenous immune response” means increasing the effectiveness or potency of an existing immune response in a subject. This increase in effectiveness and potency may be achieved, for example, by overcoming mechanisms that suppress the endogenous host immune response or by stimulating mechanisms that enhance the endogenous host immune response.
(71) “T effector” (“Teff”) cells refers to T cells (e.g., CD4+ and CD8+ T cells) as well as T helper (Th) cells with cytolytic activities, which secrete cytokines and activate and direct other immune cells, but does not include regulatory T cells (Treg cells).
(72) As used herein, the term “linkage” refers to the association of two or more molecules. The linkage can be covalent or non-covalent. The linkage also can be genetic (i.e., recombinantly fused). Such linkages can be achieved using a wide variety of art recognized techniques, such as chemical coupling and recombinant protein production.
(73) As used herein, “administering” refers to the physical introduction of a composition comprising a therapeutic agent to a subject, using any of the various methods and delivery systems known to those skilled in the art. Preferred routes of administration for antibodies described herein include intravenous, intraperitoneal, intramuscular, subcutaneous, spinal or other parenteral routes of administration, for example by injection or infusion. The phrase “parenteral administration” as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, but not limited, intravenous, intraperitoneal, intramuscular, intraarterial, intrathecal, intralymphatic, intralesional, intracapsular, intraorbital, intracardiac, intradermal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection and infusion, as well as in vivo electroporation. Alternatively, an antibody described herein 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. Administering can also be performed, for example, once, a plurality of times, and/or over one or more extended periods.
(74) As used herein, the term “T cell-mediated response” refers to a response mediated by T cells, including effector T cells (e.g., CD8+ cells) and helper T cells (e.g., CD4+ cells). T cell mediated responses include, for example, T cell cytotoxicity and proliferation.
(75) As used herein, the term “cytotoxic T lymphocyte (CTL) response” refers to an immune response induced by cytotoxic T cells. CTL responses are mediated primarily by CD8+ T cells.
(76) In the context herein, when referring to the CD39 polypeptide, “inhibit”, “neutralize” or “neutralizing” (e.g., “neutralize CD39”, “neutralize the activity of CD39” or “neutralize the enzymatic activity of CD39”, etc.) refers to a process in which the ATP hydrolysis activity (ATPase) of CD39 is inhibited. This particularly comprises the inhibition of CD39-mediated generation of AMP and/or ADP, i.e., the inhibition of CD39-mediated catabolism of ATP to AMP and/or ADP. This can be measured for example in a cellular assay that measures the capacity of a

test compound to inhibit the conversion of ATP to AMP and/or ADP, either directly or indirectly. For example, disappearance of ATP and/or generation of AMP can be assessed, as described herein.
(77) The term “internalization”, used interchangeably with “intracellular internalization”, refers to the molecular, biochemical and cellular events associated with the process of translocating a molecule from the extracellular surface of a cell to the intracellular surface of a cell. The processes responsible for intracellular internalization of molecules are well-known and can particularly involve, inter alia, the internalization of extracellular molecules (such as hormones, antibodies, and small organic molecules); membrane-associated molecules (such as cell-surface receptors); and complexes of membrane-associated molecules bound to extracellular molecules (for example, a ligand bound to a transmembrane receptor or an antibody bound to a membrane-associated molecule). Thus, “inducing and/or increasing internalization” comprises events wherein intracellular internalization is initiated and/or the rate and/or extent of intracellular internalization is increased.
(78) As used herein, “cancer” refers a broad group of diseases characterized by the uncontrolled growth of abnormal cells in the body. Since unregulated cell division may result in the formation of malignant tumors or cells, they would invade neighboring tissues and may metastasize to distant parts of the body through the lymphatic system or bloodstream.
(79) The terms “treat,” “treating,” and “treatment,” as used herein, refer to any type of intervention or process performed on, or administering an active agent to, the subject with the objective of reversing, alleviating, ameliorating, inhibiting, or slowing down or preventing the progression, development, severity or recurrence of a symptom, complication, condition or biochemical indicia associated with a disease. Prophylaxis refers to administration to a subject who does not have a disease, to prevent the disease from occurring or minimize its effects if it does.
(80) A “hematological malignancy” includes lymphoma, leukemia, myeloma or lymphoid malignancy, as well as cancers of the spleen and lymph nodes. Exemplary lymphomas include both B cell lymphomas and T cell lymphomas. B-cell lymphomas include both Hodgkin's lymphomas and most non-Hodgkin's lymphomas. Non-limiting examples of B cell lymphomas include diffuse large B-cell lymphoma, follicular lymphoma, mucosa-associated lymphatic tissue lymphoma, small cell lymphocytic lymphoma (overlaps with chronic lymphocytic leukemia), mantle cell lymphoma (MCL), Burkitt's lymphoma, mediastinal large B cell lymphoma, Waldenstrom macroglobulinemia, nodal marginal zone B cell lymphoma, splenic marginal zone lymphoma, intravascular large B-cell lymphoma, primary effusion lymphoma, lymphomatoid granulomatosis. Non-limiting examples of T cell lymphomas include extranodal T cell lymphoma, cutaneous T cell lymphomas, anaplastic large cell lymphoma, and angioimmunoblastic T cell lymphoma. Hematological malignancies also include leukemia, such as, but not limited to, secondary leukemia, chronic lymphocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, and acute lymphoblastic leukemia. Hematological malignancies further include myelomas, such as, but not limited to, multiple myeloma and smoldering multiple myeloma. Other hematological and/or B cell- or T-cell-related cancers are encompassed by the term hematological malignancy.
(81) The term “effective dose” or “effective dosage” is defined as an amount sufficient to achieve or at least partially achieve a desired effect. A “therapeutically effective dose” or “therapeutically effective dosage” of a drug or therapeutic agent is any amount of the drug that, when used alone or in combination with another therapeutic agent, promotes disease regression evidenced by a decrease in severity of disease symptoms, an increase in frequency and duration of disease symptom-free periods, or a prevention of impairment or disability due to the disease affliction. A “prophylactically effective dose” or a “prophylactically effective dosage” of a drug is an amount of the drug that, when administered alone or in combination with another therapeutic agent to a subject at risk of developing a disease or of suffering a recurrence of disease, inhibits the development or recurrence of the disease. The ability of a therapeutic or prophylactic agent to promote disease regression or inhibit the development or recurrence of the disease can be evaluated

using a variety of methods known to those skilled in the art, such as in human subjects during clinical trials, in animal model systems predictive of efficacy in humans, or by assaying the activity of the agent in in-vitro assays.

(82) By way of example, an anti-cancer agent is a drug that slows cancer progression or promotes cancer regression in a subject. In preferred embodiments, a therapeutically effective amount of the drug promotes cancer regression to the point of eliminating the cancer. “Promoting cancer regression” means that administering an effective amount of the drug, alone or in combination with an anti-neoplastic agent, results in a reduction in tumor growth or size, necrosis of the tumor, a decrease in severity of at least one disease symptom, an increase in frequency and duration of disease symptom-free periods, a prevention of impairment or disability due to the disease affliction, or otherwise amelioration of disease symptoms. Pharmacological effectiveness refers to the ability of the drug to promote cancer regression in the patient. Physiological safety refers to an acceptably low level of toxicity, or other adverse physiological effects at the cellular, organ and/or organism level (adverse effects) resulting from administration of the drug.

(83) By way of example for the treatment of tumors, a therapeutically effective dose or dosage of the drug preferably inhibits cell growth or tumor growth by at least about 20%, more preferably by at least about 40%, even more preferably by at least about 60%, and still more preferably by at least about 80% relative to untreated subjects. In the most preferred embodiments, a therapeutically effective dose or dosage of the drug completely inhibits cell growth or tumor growth, i.e., preferably inhibits cell growth or tumor growth by 100%. The ability of a compound to inhibit tumor growth can be evaluated using the assays described infra. Alternatively, this characteristic of a composition can be evaluated by examining the ability of the compound to inhibit cell growth, such inhibition can be measured in vitro by assays known to the skilled practitioner. In other preferred embodiments described herein, tumor regression may be observed and may continue for a period of at least about 20 days, more preferably at least about 40 days, or even more preferably at least about 60 days.

(84) The terms “patient” and “subject” refer to any human or non-human animal that receives either prophylactic or therapeutic treatment. For example, the methods and compositions described herein can be used to treat a subject having cancer. The term “non-human animal” includes all vertebrates, e.g., mammals and non-mammals, such as non-human primates, sheep, dog, cow, chickens, amphibians, reptiles, etc.

EXAMPLES

Example 1: Screening and Identifying of CD39 Antibody

(85) C57/BL6 mice were immunized with human CD39 extracellular domain recombinant protein (huCD39). The first immunization (intraperitoneal injection) was performed with an emulsion of 50 μg of huCD39 protein and complete Freund's adjuvant, the second immunization (subcutaneous injection) was performed with an emulsion of 25 μg of huCD39 protein and incomplete Freund's adjuvant, the third immunization (intraperitoneal injection) was performed with an emulsion of 25 μg of huCD39 protein and incomplete Freund's adjuvant, and the fourth immunization (subcutaneous injection) was performed with an emulsion of 25 μg of huCD39 protein and incomplete Freund's adjuvant. Finally, a final booster immunization (intraperitoneal injection) was performed with 50 μg of huCD39 protein. A fraction of immunized spleen cells was fused with SP2/0 cells to prepare hybridoma cells by electrofusion after four days of this booster. Primary screening was performed by ELISA and flow cytometry, furthermore, enzyme viability blocking activity was screened with a 293T/17 cell line expressing huCD39 (293T/17-huCD39), and screened by the reversal of CD4+ T cell proliferation inhibition. At last, four murine-derived antibodies with CD39 enzyme activity blocking ability were obtained.

Example 2: The Binding of Chimeric Antibodies to huCD39 Detected by Indirect ELISA

(86) The Fv region of the four mouse-derived antibodies obtained in Example 1 was fused with the human IgG2 Fc region and constructed into the pcDNA3.1 vector. Then transfected 293F cells to

express the antibody proteins, and the antibodies were purified by ProteinA affinity chromatography. Four chimeric antibodies 201 hIgG2, 216 hIgG2, 217 hIgG2 and 219 hIgG2 were obtained, and the sequence descriptions of four chimeric antibodies are detailed in Table I-1. The affinity of the chimeric antibodies was detected by indirect ELISA: 1 μg/mL of huCD39 recombinant protein (Yiqiao Shenzhou, Sino Biological) was coated on ELISA plates (Coning, Inc.) and incubated overnight at 4° C. The next day, the plates were washed 5 times with PBS buffer and blocked with 200 μL/well of 2% skimmed milk powder for 1 h. A certain dose range of chimeric CD39 antibody was incubated for 1 h at room temperature; then washed 5 times with PBST washing buffer (PBS, 0.05% Tween 20). 100 μL of HRP-labeled secondary antibody was added to each well and the plates were incubated for 30 min at room temperature. The plates were washed 5 times again and TMB (Life Technologies) was added for color development for 5 to 10 min. At last, 1N HCl was added to terminate the reaction, and the OD value was measured at 450 nm. GraphPad Prism software was used to generate data plots and the affinity data was counted (FIG. **1**). As shown in Table 1, the EC.sub.50 values of the binding activities of the four chimeric antibodies 201 hIgG2, 216 hIgG2, 217 hIgG2 and 219 hIgG2 were all at the level of 10.sup.−9M.

(87) TABLE-US-00003 TABLE I-1 Variable Variable region region amino nucleotide Amino acid Nucleotide No. acid sequence sequence sequence sequence 201 hIgG2 Heavy SEQ ID SEQ ID SEQ ID SEQ ID chain NO: 3 NO: 4 NO: 13 NO: 14 Light SEQ ID SEQ ID SEQ ID SEQ ID chain NO: 8 NO: 9 NO: 15 NO: 16 216 hIgG2 Heavy SEQ ID SEQ ID SEQ ID SEQ ID chain NO: 17 NO: 18 NO: 27 NO: 28 Light SEQ ID SEQ ID SEQ ID SEQ ID chain NO: 22 NO: 23 NO: 29 NO: 30 217 hIgG2 Heavy SEQ ID SEQ ID SEQ ID SEQ ID chain NO: 31 NO: 32 NO: 41 NO: 42 Light SEQ ID SEQ ID SEQ ID SEQ ID chain NO: 36 NO: 37 NO: 43 NO: 44 219 hIgG2 Heavy SEQ ID SEQ ID SEQ ID SEQ ID chain NO: 45 NO: 46 NO: 55 NO: 56 Light SEQ ID SEQ ID SEQ ID SEQ ID chain NO: 50 NO: 51 NO: 57 NO: 58

(88) TABLE-US-00004 TABLE 1 Affinity of chimeric antibodies Antibody Bottom Top EC.sub.50(nM) 201 hIgG2 0.046 1.636 1.395 216 hIgG2 0.060 1.427 2.426 217 hIgG2 0.070 1.391 4.801 219 hIgG2 0.052 1.330 1.690

Example 3: The Binding of Chimeric Antibodies to Natural CD39 on the Cell Surface Detected by Flow Cytometry

(89) Flow cytometry assay: recombinant host cell line 293T/17-huCD39 cells expressing huCD39 and recombinant host cell line 293T/17-cyno CD39 cells expressing cyno CD39 were used to evaluate the binding ability of the chimeric antibody to the natural CD39 protein on the cell surface. The recombinant cells were resuspended in PBS buffer, and 2×10.sup.6 cells were added to a 96-well U-plate. The chimeric antibody in a certain gradient dilution range incubated for 1 h at 4° C. in a refrigerator or on ice, centrifuged at 1500 rpm for 3 min at 4° C., washed three times with PBS buffer, and then incubated for 30 min at 4° C. in the refrigerator or on ice with diluted Alexa Fluor 488-labeled goat anti-human polyclonal antibody (pAb): Goat anti-Human IgG (H+L) Cross-Adsorbed Secondary Antibody, Alexa Fluor 488 (thermo). Finally the cells were washed three times with PBS as described above and analyzed in MACSQuant flow cytometry. GraphPad Prism software was used to generate data plots and count affinity data (FIG. **2**). The results are shown in Table 2, and the EC.sub.50 values of each chimeric antibody of 293T/17-huCD39 and 293T/17-cyno CD39 was at the level of 10.sup.−9M.

(90) TABLE-US-00005 TABLE 2 Affinity of chimeric antibodies to huCD39 antigen on the cell surface 293T/17-huCD39 293T/17-cyno CD39 Antibody Bottom Top EC.sub.50(nM) Bottom Top EC.sub.50(nM) 201 −6.241 189.0 6.560 3.232 209.1 8.685 hIgG2 216 2.171 151.3 5.915 1.813 191.4 11.030 hIgG2 217 5.802 116.0 3.799 2.998 159.6 9.490 hIgG2 219 3.810 155.5 4.511 3.332 214.5 8.159 hIgG2

Example 4: Blocking of ATPase Activity on Cell Surface by Chimeric CD39 Antibodies

(91) The method is based on 293T/17-huCD39 and 293T/17-cyno CD39 cell lines (pLVX-EF1α-IRES-Puro vector linked with the huCD39 or cyno CD39 gene was transfected with 293T/17 cells,

and cell clones stably expressing huCD39 or cyno CD39 were obtained by puromycin screening) to detect the blocking ability of enzyme activity on cell surface by CD39 antibody, and the biochemical activity of the chimeric antibody was confirmed. 293T/17-huCD39 and 293T/17-cyno CD39 cells were digested with trypsin and the cell density was adjusted to 1.6×10.sup.5 cells/mL, and 50 μL/well was added to the 96-well plate. 50 μL/well of a certain gradient range of antibody was added to the cell wells respectively, and incubated at 37° C. for 1 h. 100 μL of ATP at a concentration of 50 μM was added to each well and incubated at 37° C. for 0.5 h. The mixture was centrifuged at 1500 rpm for 3 min, and a certain volume of culture supernatant was transferred to a transparent 96-well flat-bottom plate (Costar, 3912). Finally, the corresponding volume of CellTiter Glo reagent was added at a ratio of 1:1 according to the Promega instructions, and after equilibration for 5 min at room temperature, luminescence values were read on a Perkin-Elmer Envision microplate reader to determine cellular CD39 enzyme activity by measuring ATP levels. Data plots were generated and enzyme kinetic data were tallied using GraphPad Prism software (FIG. **3**). The results are shown in Table 3. All antibodies could inhibit the ATPase activity of CD39 on cell surface, and EC.sub.50 values of the blocking activity of all four chimeric antibodies were at the level of 10.sup.−11 (Table 3).

(92) TABLE-US-00006 TABLE 3 Blocking ability of chimeric CD39 antibodies against ATPase activity on cell surface 293T/17-huCD39 293T/17-cyno CD39 Antibody Bottom Top EC.sub.50(nM) Bottom Top EC.sub.50(nM) 201 119247 870919 0.004 42339 232384 0.014 hIgG2 216 1280183 1028832 0.011 55613 274761 0.024 hIgG2 217 146730 1193309 0.008 42237 282537 0.029 hIgG2 219 172101 799649 0.010 44475 302601 0.024 hIgG2

Example 5: Humanization of Antibodies

(93) The CDR transplantation method was applied to humanize the two mouse-derived antibodies obtained in Example 1. On the basis of analysis of the sequence identity and structural similarity between the two mouse-derived antibodies and the human-derived antibodies, the CDRs of the mouse-derived antibodies were modified and transplanted to a series of human-derived antibody framework regions respectively. Three humanized antibodies were obtained through screening, and three humanized antibodies were named as h201H3.1+h219L1.1 G2C, h201H3.1+h201L1.1dmut G2C, M201 HuH1L1(D-E) G2C. The sequence descriptions of the three humanized antibodies are detailed in Table 1-2. The humanized antibodies were constructed into pcDNA3.1 vector, and transfected with 293F cells to express the antibody proteins, and the antibodies were purified by ProteinA affinity chromatography.

(94) TABLE-US-00007 TABLE I-2 Variable region Variable amino region Amino acid nucleotide acid Nucleotide No. sequence sequence sequence sequence h201H3.1 + Heavy SEQ ID SEQ ID SEQ ID SEQ ID h219 chain NO: 60 NO: 61 NO: 64 NO: 65 L1.1 G2C Light SEQ ID SEQ ID SEQ ID SEQ ID chain NO: 62 NO: 63 NO: 66 NO: 67 h201H3.1 + Heavy SEQ ID SEQ ID SEQ ID SEQ ID h201 chain NO: 60 NO: 61 NO: 64 NO: 65 L1.1d mut Light SEQ ID SEQ ID SEQ ID SEQ ID G2C chain NO: 68 NO: 69 NO: 70 NO: 71 M201 Heavy SEQ ID SEQ ID SEQ ID SEQ ID HuH1L1 chain NO: 72 NO: 73 NO: 76 NO: 77 (D-E) Light SEQ ID SEQ ID SEQ ID SEQ ID G2C chain NO: 74 NO: 75 NO: 78 NO: 79

Example 6: The Binding of Humanized Antibodies to CD39 Detected by Indirect ELISA

(95) The affinity of humanized antibodies detected by indirect ELISA: 1 μg/mL huCD39 recombinant protein was coated on ELISA plates (Coning) and incubated overnight at 4° C. The next day, washed 5 times with PBS buffer and blocked with 200 μL/well of 2% skim milk powder for 1 h. A certain dose range of CD39 humanized antibody was added, and incubated for 1 h at room temperature. Then, washed 5 times with PBST washing buffer (PBS, 0.05% Tween 20), 100 μL HRP-labeled secondary antibody was added to each well, and incubated for 30 min at room temperature. The plates were washed 5 times again, and TMB (Life Technologies) was added for color development for 5 to 10 min. Finally, 1N HCl was added to terminate the reaction, and the OD value was measured at 450 nm. GraphPad Prism software was used to generate data plots and

count the affinity data (FIG. **4**). The results are shown in Table 4. The EC.sub.50 values of the binding activity of the three humanized antibodies were all at the level of 10.sup.−10 M.

(96) TABLE-US-00008 TABLE 4 Affinity of humanized antibodies Antibody Bottom Top EC.sub.50(nM) h201H3.1 + h219L1.1 G2C 0.085 0.991 0.709 h201H3.1 + h201L1.1d mut G2C 0.109 1.030 0.433 M201 HuH1L1(D-E) G2C 0.068 1.180 0.514

Example 7: The Binding of Humanized Antibodies to Natural CD39 on the Cell Surface Detected by Flow Cytometry

(97) Flow cytometry assay: recombinant host cell line 293T/17-huCD39 cells expressing huCD39 were used to evaluate the binding ability of the humanized antibody to the natural CD39 protein on the cell surface. The recombinant cells were resuspended in PBS buffer, 2×10.sup.6 cells were added to a 96-well U-plate, and a certain gradient dilution range of the humanized antibody was incubated for 1 h at 4° C. in a refrigerator or on ice. The mixture was centrifuged at 1500 rpm for 3 min at 4° C., and washed three times with PBS buffer. Then, incubated for 30 min at 4° C. in the refrigerator or on ice with diluted Alexa Fluor 488-labeled goat anti-human polyclonal antibody (pAb): Goat anti-Human IgG (H+L) Cross-Adsorbed Secondary Antibody, Alexa Fluor 488 (thermo), and finally the cells were washed three times with PBS as described above and analyzed in MACSQuant flow cytometry. Data plots were generated and affinity data were counted using GraphPad Prism software (FIG. **5**). The results are shown in Table 5, and the EC.sub.50 values of 293T/17-huCD39 humanized antibody were all at the level of 10.sup.−9M.

(98) TABLE-US-00009 TABLE 5 Affinity of humanized antibodies to huCD39 antigen on the cell surface 293T/17-huCD39 Antibody Bottom Top EC.sub.50(nM) h201H3.1 + h219L1.1 G2C 8.182 266.0 3.097 h201H3.1 + h201L1.1d mut G2C −1.331 280.2 3.311 M201 HuH1L1(D-E) G2C −2.155 328.7 2.939

Example 8: Blocking of ATPase Activity on Cell Surface by Humanized CD39 Antibody

(99) The method was based on the 293T/17-huCD39 cell line to detect the ability of CD39 antibody to block cell surface enzyme activity and to confirm the biochemical activity of the humanized antibody. 293T/17-huCD39 cells were digested with trypsin and the cell density was adjusted to 1.6×10.sup.5 cells/ml, and 50 μL/well was added to a 96-well plate. 50 μl of antibody in a gradient range of was added to the cell wells, and incubated for 1 h at 37° C. 100 μL of ATP at a concentration of 50 μM was added to each well and incubated for 0.5 h at 37° C., centrifuged at 1500 rpm for 3 min and a volume of culture supernatant was transferred to an opaque 96-well flat-bottom plate (Costar, 3912). Finally, the corresponding volume of CellTiter Glo reagent was added at a ratio of 1:1 according to Promega instructions. After equilibration for 5 min at room temperature, luminescence values were read on a Perkin-Elmer Envision microplate reader and cellular CD39 enzyme activity was determined by measuring ATP levels. Data plots were generated and enzyme kinetic data were tallied using GraphPad Prism software (FIG. **6**). The results are shown in Table 6, all antibodies could inhibit the ATPase activity of cell surface CD39, and the EC.sub.50 values of blocking activity of all three humanized antibodies were in the level of 10.sup.−11 (Table 6).

(100) TABLE-US-00010 TABLE 6 Blocking ability of humanized CD39 antibody against ATPase activity on cell surface 293T/17-huCD39 Antibody Bottom Top EC.sub.50(nM) h201H3.1 + h219L1.1 G2C 38846 250500 0.077 h201H3.1 + h201L1.1d mut G2C 39640 244514 0.038 M201 HuH1L1(D-E) G2C 31278 151674 0.026

Example 9: Reversal Effect of CD39 Humanized Antibody Against ATP-Mediated Proliferation Inhibition of Human CD4+T and CD8+ T Cell

(101) The method is based on the in vitro released ATP-mediated proliferation inhibition of CD4+T and CD8+ T cells by CD39 humanized antibody and IFN-γ levels in cell culture supernatants were detected by ELISA. PBMCs from human peripheral blood were recovered, and after labeled with 5 μM CFSE, adjusted the cell concentration to 1*10.sup.6/mL. Anti-CD28 at a final concentration of 0.5 μg/mL and human IL-2 at a final concentration of 5 ng/mL were added at 100 μL/well to a 96-

well plate previously coated with 2 ug/mL anti-CD3. Gradient diluted CD39 antibody was added and incubated at 37° C. for 1 h; then ATP at a final concentration of 20-100 μM was added. After 6-7 days of incubation at 37° C., CD4+T and CD8+ T cells were collected for proliferation detection by flow cytometry (Miltenyi, Miltenyi). The supernatant was also collected to detect IFN-γ level by ELISA. CD4+T and CD8+ T cell proliferation (FIG. **7** and FIG. **8**) and IFN-γ level data (FIG. **9**) were counted using GraphPad Prism software. The results are shown in Table 7 that the CD39 humanized antibody viability was at the level of 10.sup.−8 to 10.sup.−10 M (Table 7).

(102) TABLE-US-00011 TABLE 7 Reversal effect of CD39 antibody against ATP-mediated proliferation inhibition of human CD4+ T and CD8+ T cell CD4+ T CD8+ T Antibody Bottom Top EC.sub.50(nM) Bottom Top EC.sub.50(nM) h201H3.1 + h219L1.1 0.371 119.7 0.646 −6.060 102.3 1.349 G2C h201H3.1 + h201L1.1d −0.780 116.6 5.081 −1.997 84.1 7.084 mut G2C M201 HuH1L1(D-E) 0.973 101.6 25.480 −2.474 87.2 60.430 G2C

(103) The levels of IFN-γ in cell supernatants were measured using an ELISA assay kit (Dakewe, Dakewe), and the results are shown in Table 8. The EC.sub.50 values of IFN-γ secretion from T cells stimulated by three humanized antibodies were at the level of 10.sup.−8 to 10.sup.−9M.

(104) TABLE-US-00012 TABLE 8 Ability of humanized CD39 antibody to reverse IFN-γ release from CD4 + T cell Antibody Bottom Top ECso(nM) h201H3.1 + h219L1.1 G2C −2793 13557 2.455 h201H3.1 + h201L1.1d mut 140 7087 6.157 G2C M201 HuH1L1(D-E) G2C 146 8031 28.420

Example 10: Humanized CD39 Antibody-Mediated Endocytosis Assay of CD39

(105) Fab-ZAP saporin reagent (Advanced Targeting Systems) was used to detect the endocytosis effect mediated by humanized CD39 antibody on IM-9 cells. The antibody was gradient diluted to a certain dose range with 40 nM Fab-ZAP human reagent (Advanced Targeting Systems) and incubated at room temperature for 30 min to make Fab-ZAP bind to the antibody to be tested to form an antibody premix. 50 μL of this antibody premix was added to IM-9 cell wells of 10,000 cells/well, incubated for 3 days at 37° C. with 5% CO.sub.2, lysed by adding CTG reagent (Promega) for 2 min, and then equilibrated at room temperature for 5 min. The luminescence values were measured with an Enspire enzyme marker (Perkin Elmer). The cell growth curves were calculated by GraphPad Prism software. The results are shown in Table 9 and FIG. **10**. All three humanized antibodies mediated CD39 endocytosis in a dose-dependent manner, and the IC.sub.50 values of each antibody were at the level of 10.sup.−11˜10.sup.−22M.

(106) TABLE-US-00013 TABLE 9 CD39 endocytosis effect mediated by humanized CD39 antibodies Antibody Bottom Top IC.sub.50(pM) h201H3.1 + h219L1.1 G2C −97751 2846167 4.299 h201H3.1 + h201L1.1d mut G2C 96175 2439511 8.901 M201 HuH1L1 (D-E) G2C 40891 2289436 10.300

Example 11: Activation Effect of Humanized CD39 Antibody Against DC Cells

(107) This method was used to determine the activation effect of CD39 humanized antibody against DC cells mainly through detecting the expression levels of cell surface molecules CD86 and HLA-DR in DCs by flow cytometry. Monocytes were recovered and resuspended, and cell density was adjusted to 5*10.sup.5/mL. The cells were cultured in the plates, and stimulated with 1640+10% FBS medium containing M-CSF (50 ng/mL) and IL-4 (long/mL) at 37° C. for 6 days to obtain DC cells. After 6 days, cell supernatant was discarded and 1 μg/mL of humanized CD39 antibody was added, and the cells were incubated at 37° C. for 1 h, and then incubated overnight with or without a certain concentration of ATP. After 24 h, the cells were collected for FACS to detect the expression of CD86 and HLA-DR, and the statistical data was generated by GraphPad Prism software. The results are shown in FIG. **11** that humanized CD39 antibodies enhanced ATP-induced single expression of the cell surface molecule CD86 and co-expression of CD86 and HLA-DR in DCs cells.

Example 12: Pharmacodynamics Evaluation of Humanized CD39 Antibody on MOLP-8 Model

(108) MOLP-8 (human multiple myeloma cells) was diluted with PBS stromal gum at a ratio of

1:1. 6-8 week old female CB-17 SCID mice (purchased from Beijing Viton Lever Laboratory Animal Technology Co., Ltd.) were subcutaneously inoculated with 1×10.sup.7 cells, and each of groups has 26 mice. After subcutaneous inoculation, the mice were grouped when the tumor growth volume reached 300 mm.sup.3 (the largest and smallest animals were excluded from each group) and injected intraperitoneally (I.P.) with PBS, antibody h201H3.1+h201L1.1d mut G2C and M201 HuH1L1(D-E) G2C at a dose of 30 mg/kg once/week (QW), as shown in Table 10.

(109) TABLE-US-00014 TABLE 10 Route of administration, dose and regimen Route of Dosing Dosing Dosing No. Number administration Treatment amount frequency cycle G1 26 I.P. PBS N/A QW 1 week G2 26 I.P. h201H3.1 + h201L1.1d 30 mg/kg QW 1 week mut G2C G3 26 I.P. M201 HuH1L1(D-E) GC 30 mg/kg QW 1 week

(110) On the first, third, and seventh day after drug administration, tumor tissues from 6 mice were taken to prepare into single cell suspensions for enzyme activity assay. The tumor tissues were cut into small pieces and digested with enzymes. After incubation at 37° C. for 40 min, the undigested tissue pieces were removed by filtration with a 70 μm filter and the single cell suspension was collected. 5*10.sup.4 cells were spread in a 96-well plate, and a final concentration of 25 μM ATP solution was added, incubated at 37° C. for 30 min, and a certain volume of culture supernatant was transferred to a tranparent 96-well flat-bottom plate (Costar, 3912). Finally, the appropriate volume of CellTiter Glo reagent at a ratio of 1:1 was added according to the Promega instructions. After equilibration for 5 min at room temperature, the luminescence values were read on a Perkin-Elmer Envision enzyme marker to determine the enzymatic activity of CD39 humanized antibody on MOLP-8 tumor cells by measuring ATP levels. The results were shown in FIG. **12** that both humanized antibodies had enzymatic activity blocking effects on MOLP-8 tumor cells at first, third and seventh day after administration.

Example 13: Growth Inhibition of MOLP-8 Xenograft Tumor Model by Humanized Antibody

(111) MOLP-8 (human multiple myeloma cells) were diluted with PBS stromal gum at a ratio of 1:1 to obtain the cells of 1×10.sup.8. 6-8 week old female CB-17 SCID mice (purchased from Beijing Viton Lever Laboratory Animal Technology Co., Ltd.) were subcutaneously inoculated with 0.1 mL for each. The mice were randomly grouped in each group of 12, i.e. 6 males and 6 females in each group. Each group was administered with 30 mg/kg dose of intraperitoneal (I.P.) PBS, antibodies h201H3.1+h201L1.1d mut G2C and M201 HuH1L1(D-E) G2C, twice/week (BIW) at seventh day after subcutaneous inoculation, and the detailed description was shown in Table 11.

(112) TABLE-US-00015 TABLE 11 Route of administration, dose and regimen Dosage Dosing Dosing amount Route of No. Number Treatment frequency (mg/kg) administration 1 12 PBS BIW N/A IP. (6 female 6 male) 2 12 h201H3.1 + BIW 30 I.P. (6 female h201L1.1d 6 male) mut G2C 3 12 M201 HuH1L1(D-E) BIW 30 I.P. (6 female G2C 6 male)

(113) The body weight and tumor size of the mice were measured twice a week. Tumor size calculation formula: tumor volume (mm.sup.3)=0.5×(tumor long diameter×tumor short diameter.sup.2).

(114) The tumor growth curve was plotted according to the tumor volume. As seen in FIG. **13**, both antibodies h201H3.1+h201L1.1d mut G2C and M201 HuH1L1(D-E) G2C inhibited MOLP-8 tumor growth.

Example 14: Growth Inhibition of IM-9 Xenograft Tumor Model by Humanized Antibodies

(115) IM-9 (human peripheral blood B lymphocytes) were diluted with PBS stromal gum at a ratio of 1:1 to obtain the cells of 1×10.sup.8 cells/ml. 6-8 week old female CB-17 SCID mice (purchased from Beijing Viton Lever Laboratory Animal Technology Co., Ltd.) were subcutaneously inoculated with 0.1 mL for each. The mice were grouped in each group of 12, females. After subcutaneous inoculation, each group were injected intraperitoneally (I.P.) with PBS, antibodies h201H3.1+h201L1.1d mut G2C and M201 HuH1L1(D-E) G2C at a dose of 30 mg/kg, twice/week (BIW), when the tumor growth volume reached 50-70 mm.sup.3 groups (inclusion criteria: mean

tumor volume±3SD range, or tumor volume coefficient of variation CV≤30% (CV=standard deviation/mean)). The detailed description was shown in Table 12.
(116) TABLE-US-00016 TABLE 12 Route of administration, dose and regimen Dosage Dosing Dosing amount Route of No. Number Treatment frequency (mg/kg) administration 1 10 PBS BIW N/A I.P. (female) 2 10 h201H3.1 + h201L1.1d BIW 30 I.P. (female) mut G2C 3 10 M201 HuH1L1(D-E) BIW 30 I.P. (female) G2C
(117) The body weight and tumor size of the mice were measured twice a week. Tumor size calculation formula: tumor volume (mm.sup.3)=0.5×(tumor long diameter×tumor short diameter.sup.2)
(118) The tumor growth curve was plotted according to the tumor volume. As seen in FIG. **14**, both antibodies h201H3.1+h201L1.1d mut G2C and M201 HuH1L1(D-E) G2C were effective in inhibiting IM-9 tumor growth.

Claims

1. An antibody or antigen-binding fragment thereof comprising a heavy chain variable region that comprises sequences of HCDR1, HCDR2, HCDR3; and a light chain variable region that comprises sequences of LCDR1, LCDR2, LCDR3, wherein: (a) the HCDR1 comprises an amino acid sequence of SEQ ID NO: 5; (b) the HCDR2 comprises an amino acid sequence of SEQ ID NO: 6; (c) the HCDR3 comprises an amino acid sequence of SEQ ID NO: 7; (d) the LCDR1 comprises an amino acid sequence of SEQ ID NO: 10; (e) the LCDR2 comprises an amino acid sequence of SEQ ID NO: 59 or 11; and (f) the LCDR3 comprises an amino acid sequence of SEQ ID NO: 12.
2. The antibody or antigen-binding fragment thereof of claim 1, wherein: (i) the heavy chain variable region (VH) comprises an amino acid sequence with at least 85% identity to an amino acid sequence selected from a group consisting of SEQ ID NOs: 3, 60 and 72, and comprises HCDR1 comprising SEQ ID NO: 5, HCDR2 comprising SEQ ID NO: 6, and HCDR3 comprising SEQ ID NO: 7; and (ii) the light chain variable region (VL) comprises an amino acid sequence with at least 85% identity to an amino acid sequence selected from a group consisting of SEQ ID NOs: 8, 68 and 74, and comprises LCDR1 comprising SEQ ID NO: 10, LCDR2 comprising SEQ ID NO: 59 or 11, and LCDR3 comprising SEQ ID NO: 12.
3. The antibody or antigen-binding fragment thereof of claim 1, comprising: 1) a heavy chain variable region (VH) that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 60 and comprises HCDR1 comprising SEQ ID NO: 5, HCDR2 comprising SEQ ID NO: 6, and HCDR3 comprising SEQ ID NO: 7, and a light chain variable region (VL) that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 68 and comprises LCDR1 comprising SEQ ID NO: 10, LCDR2 comprising SEQ ID NO: 59, and LCDR3 comprising SEQ ID NO: 12; or 2) a heavy chain variable region (VH) that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 72 and comprises HCDR1 comprising SEQ ID NO: 5, HCDR2 comprising SEQ ID NO: 6, and HCDR3 comprising SEQ ID NO: 7, and a light chain variable region (VL) that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 74 and comprises LCDR1 comprising SEQ ID NO: 10, LCDR2 comprising SEQ ID NO: 59, and LCDR3 comprising SEQ ID NO: 12; or 3) a heavy chain variable region (VH) that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 3 and comprises HCDR1 comprising SEQ ID NO: 5, HCDR2 comprising SEQ ID NO: 6, and HCDR3 comprising SEQ ID NO: 7, and a light chain variable region (VL) that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 8 and comprises LCDR1 comprising SEQ ID NO: 10, LCDR2 comprising SEQ ID NO: 11, and LCDR3 comprising SEQ ID NO: 12.

4. The antibody or antigen-binding fragment thereof of claim 1, comprising: 1) a heavy chain variable region (VH) comprising an amino acid sequence of SEQ ID NO: 60, and a light chain variable region (VL) comprising an amino acid sequence of SEQ ID NO: 68; or 2) a heavy chain variable region (VH) comprising an amino acid sequence of SEQ ID NO: 72, and a light chain variable region (VL) comprising an amino acid sequence of SEQ ID NO: 74; or 3) a heavy chain variable region (VH) comprising an amino acid sequence of SEQ ID NO: 3, and a light chain variable region (VL) comprising an amino acid sequence of SEQ ID NO: 8.
5. The antibody or antigen-binding fragment thereof of claim 1, further comprising a heavy chain constant region that is an IgG.
6. The antibody or antigen-binding fragment thereof of claim 5, wherein the heavy chain constant region of the antibody is selected from IgG1, IgG2 or IgG4.
7. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody is a monoclonal antibody, a chimeric antibody, a humanized antibody, a human engineered antibody, a human antibody, Fv, a single chain antibody (scFv), Fab, Fab′, Fab′-SH or F(ab′).sub.2.
8. The antibody or antigen-binding fragment thereof of claim 1, comprising a heavy chain and a light chain, wherein: (I) the heavy chain comprises an amino acid sequence with at least 85% identity to an amino acid sequence selected from a group of SEQ ID NOs: 13, 64 and 76, and comprises HCDR1 comprising SEQ ID NO: 5, HCDR2 comprising SEQ ID NO: 6, and HCDR3 comprising SEQ ID NO: 7; and (II) the light chain comprises an amino acid sequence with at least 85% identity to an amino acid sequence selected from a group of SEQ ID NOs: 15, 70 and 78, and comprises LCDR1 comprising SEQ ID NO: 10, LCDR2 comprising SEQ ID NO: 59 or 11, and LCDR3 comprising SEQ ID NO: 12.
9. The antibody or antigen-binding fragment thereof of claim 1, comprising: 1) a heavy chain that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 64 and comprises HCDR1 comprising SEQ ID NO: 5, HCDR2 comprising SEQ ID NO: 6, and HCDR3 comprising SEQ ID NO: 7, and a light chain that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 70 and comprises LCDR1 comprising SEQ ID NO: 10, LCDR2 comprising SEQ ID NO: 59, and LCDR3 comprising SEQ ID NO: 12; or 2) a heavy chain that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 76 and comprises HCDR1 comprising SEQ ID NO: 5, HCDR2 comprising SEQ ID NO: 6, and HCDR3 comprising SEQ ID NO: 7, and a light chain that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 78 and comprises LCDR1 comprising SEQ ID NO: 10, LCDR2 comprising SEQ ID NO: 59, and LCDR3 comprising SEQ ID NO: 12; or 3) a heavy chain that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 13 and comprises HCDR1 comprising SEQ ID NO: 5, HCDR2 comprising SEQ ID NO: 6, and HCDR3 comprising SEQ ID NO: 7, and a light chain that comprises an amino acid sequence with at least 85% identity to an amino acid sequence of SEQ ID NO: 15 and comprises LCDR1 comprising SEQ ID NO: 10, LCDR2 comprising SEQ ID NO: 11, and LCDR3 comprising SEQ ID NO: 12.
10. The antibody or antigen-binding fragment thereof of claim 1, comprising: 1) a heavy chain that comprises an amino acid sequence of SEQ ID NO: 64, and a light chain that comprises an amino acid sequence of SEQ ID NO: 70; or 2) a heavy chain that comprises an amino acid sequence of SEQ ID NO: 76, and a light chain that comprises an amino acid sequence of SEQ ID NO: 78; or 3) a heavy chain that comprises an amino acid sequence of SEQ ID NO: 13, and a light chain that comprises an amino acid sequence of SEQ ID NO: 15.
11. The antibody or antigen-binding fragment thereof of claim 1, which is an antagonist of CD39.
12. The antibody or antigen-binding fragment thereof of claim 11, wherein the CD39 is human CD39 or machin CD39.
13. The antibody or antigen-binding fragment thereof of claim 1, which may reduce the ATP enzyme (ATPase) activity of CD39.

14. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof of claim 1, and a pharmaceutically acceptable carrier.
15. A kit comprising the antibody or antigen-binding fragment thereof of claim 1.
16. A method of treating a disease comprising administering to a subject in need a therapeutically effective amount of the antibody or antigen-binding fragment thereof of claim 1.
17. The method of claim 16, wherein the disease is a disease related to CD39.
18. The method of claim 16, wherein the disease is cancer.
19. The method of claim 18, wherein the cancer is solid tumor or hematological cancer.
20. The method of claim 19, wherein the solid tumor is selected from multiple myeloma, melanoma, stomach cancer, pancreatic cancer, breast cancer, colon cancer, lung cancer, head and neck cancer, liver cancer, ovarian cancer, bladder cancer, renal cancer, salivary gland carcinoma, esophageal cancer, glioma, glioblastoma, thyroid cancer, thymic cancer, epithelial cancer, lymphoma, T and/or B cell lymphoma, gastrointestinal stromal tumor, soft tissue neoplasm, testicular cancer, endometrial carcinoma, prostate cancer, and/or brain cancer.