

CLAIMS

1. An isolated antibody comprising:
 - i) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 1; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 2; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 3; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 11; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 12; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 13; or
 - ii) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 4; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 5; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 6; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 14; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 15; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 16; or
 - iii) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 53; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 54; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 55; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 63; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 64; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 65; or
 - iv) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 56; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 57; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 58; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 66; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 67; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 68; or
 - v) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 79; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 80; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 81; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 89; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 90; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 91; or

- vi) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 82; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 83; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 84; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 92; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 93; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 94; or
- vii)(a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 105; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 106; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 107; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 115; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 116; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 117; or
- viii) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 108; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 109; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 110; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 118; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 119; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 120.

2. The antibody of claim 1, which comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein:

- i) the VH is at least 90% identical to the amino acid sequence of SEQ ID NO: 7 and the VL is at least 90% identical to the amino acid sequence of SEQ ID NO: 17; or
- ii) the VH is at least 90% identical to the amino acid sequence of SEQ ID NO: 59 and the VL is at least 90% identical to the amino acid sequence of SEQ ID NO: 69; or
- iii) the VH is at least 90% identical to the amino acid sequence of SEQ ID NO: 85 and the VL is at least 90% identical to the amino acid sequence of SEQ ID NO: 95; or
- iv) the VH is at least 90% identical to the amino acid sequence of SEQ ID NO: 111 and the VL is at least 90% identical to the amino acid sequence of SEQ ID NO: 121.

3. An isolated antibody comprising a heavy chain variable region (VH) and a light chain variable region (VL), wherein:
- i) the VH is at least 90% identical to the amino acid sequence of SEQ ID NO: 7 and the VL is at least 90% identical to the amino acid sequence of SEQ ID NO: 17; or
 - ii) the VH is at least 90% identical to the amino acid sequence of SEQ ID NO: 59 and the VL is at least 90% identical to the amino acid sequence of SEQ ID NO: 69; or
 - iii) the VH is at least 90% identical to the amino acid sequence of SEQ ID NO: 85 and the VL is at least 90% identical to the amino acid sequence of SEQ ID NO: 95; or
 - iv) the VH is at least 90% identical to the amino acid sequence of SEQ ID NO: 111 and the VL is at least 90% identical to the amino acid sequence of SEQ ID NO: 121.
4. The antibody of claim 2 or 3, which comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein:
- i) the VH comprises the amino acid sequence of SEQ ID NO: 7 and the VL comprises the amino acid sequence of SEQ ID NO: 17; or
 - ii) the VH comprises the amino acid sequence of SEQ ID NO: 59 and the VL comprises the amino acid sequence of SEQ ID NO: 69; or
 - iii) the VH comprises the amino acid sequence of SEQ ID NO: 85 and the VL comprises the amino acid sequence of SEQ ID NO: 95; or
 - iv) the VH comprises the amino acid sequence of SEQ ID NO: 111 and the VL comprises the amino acid sequence of SEQ ID NO: 121.
5. An isolated antibody comprising a heavy chain and a light chain, wherein:
- i) the heavy chain is at least 90% identical to the amino acid sequence of SEQ ID NO: 9, 21, 23, or 25 and the light chain is at least 90% identical to the amino acid sequence of SEQ ID NO: 19; or
 - ii) the heavy chain is at least 90% identical to the amino acid sequence of SEQ ID NO: 61, 73, 75, or 77 and the light chain is at least 90% identical to the amino acid sequence of SEQ ID NO: 71; or

- iii) the heavy chain is at least 90% identical to the amino acid sequence of SEQ ID NO: 87, 99, 101, or 103 and the light chain is at least 90% identical to the amino acid sequence of SEQ ID NO: 97; or
 - iv) the heavy chain is at least 90% identical to the amino acid sequence of SEQ ID NO: 113, 125, 127, or 129 and the light chain is at least 90% identical to the amino acid sequence of SEQ ID NO: 123.
- 6. The isolated antibody of claim 5, wherein the antibody comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein:
 - i) the heavy chain comprises the amino acid sequence of SEQ ID NO: 9, 21, 23, or 25 and the light chain comprises the amino acid sequence of SEQ ID NO: 19; or
 - ii) the heavy chain comprises the amino acid sequence of SEQ ID NO: 61, 73, 75, or 77 and the light chain comprises the amino acid sequence of SEQ ID NO: 71; or
 - iii) the heavy chain comprises the amino acid sequence of SEQ ID NO: 87, 99, 101, or 103 and the light chain comprises the amino acid sequence of SEQ ID NO: 97; or
 - iv) the heavy chain comprises the amino acid sequence of SEQ ID NO: 113, 125, 127, or 129 and the light chain comprises the amino acid sequence of SEQ ID NO: 123.
- 7. The antibody of any one of claims 1-6, wherein the antibody increases proliferation of a lymphocyte.
- 8. The antibody of claim 7, wherein the lymphocyte is a tumor-infiltrating lymphocyte, or CD4⁺ T cell.
- 9. The antibody of any one of claims 1-8, wherein the antibody enhances expression of one or more dendritic cell activation markers.
- 10. The antibody of claim 9, wherein the dendritic cell activation marker is CD86, HLA-DR, or both CD86 and HLA-DR.
- 11. The antibody of any one of claims 1-10, wherein the antibody enhances secretion of one or more cytokines from dendritic cells.
- 12. The antibody of claim 11, wherein the cytokine is IL-16, IL-12/IL-23p40, VEGFA, or any combination thereof.
- 13. The antibody of any one of claims 1-12, wherein the antibody antagonizes human CD39 in a tumor microenvironment.

14. The antibody of claim 13 wherein the antagonism is non-competitive and/or allosteric.
15. The antibody of any one of claims 1-14, wherein the antibody cross-reacts with cynomolgus CD39.
16. The antibody of any one of claims 1-15, wherein the antibody is an IgG1, an IgG2, an IgG3, an IgG4, an IgM, an IgA1, an IgA2, an IgD, or an IgE antibody.
17. The antibody of claim 16, wherein the antibody is a wild type or mutant IgG1 or IgG4 antibody.
18. The antibody of any one of claims 1-17, comprising a mutant IgG4 heavy chain constant region, wherein the mutation i) reduces the ability of the IgG4 to form half-molecules; and/or ii) minimizes binding to Fc receptors.
19. The antibody of any one of claims 1-18, comprising a mutant IgG4 heavy chain constant region comprising an S228P mutation.
20. The antibody of claim 19, comprising a mutant IgG4 heavy chain constant region comprising S228P and L235E mutations.
21. The antibody of any one of claims 1-20, wherein the antibody or antigen binding portion thereof comprises the heavy chain CDR3 sequence set forth in SEQ ID NO: 3.
22. The antibody of any one of claims 1-21, wherein the antibody binds to substantially the same epitope as a reference antibody comprising the heavy chain CDR3 sequence set forth in SEQ ID NO: 3.
23. The antibody of any one of claims 1-22, wherein the antibody is a monoclonal antibody.
24. The antibody of any one of claims 1-23, wherein the antibody is an antibody fragment selected from a Fab, Fab', Fv, scFv or F(ab')₂ fragment.
25. The antibody of any one of claims 1-24, wherein the antibody is a full-length antibody.
26. An isolated nucleic acid encoding an anti-CD39 antibody comprising:
 - i) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 27; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 28; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 29; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 37; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 38; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 39; or

- ii) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 30; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 31; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 32; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 40; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 41; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 42; or
 - iii) a VH that is at least 90% identical to the amino acid sequence of SEQ ID NO: 33 and a VL that is at least 90% identical to the amino acid sequence of SEQ ID NO: 43; or
 - iv) a heavy chain that is at least 90% identical to the amino acid sequence of SEQ ID NO: 35, 47, 49, or 51 and a light chain is at least 90% identical to the amino acid sequence of SEQ ID NO: 45.
- 27. The isolated nucleic acid of claim 26 encoding an anti-CD39 antibody comprising:
 - i) a VH comprising an amino acid sequence of SEQ ID NO: 33 and a VL comprising the amino acid sequence of SEQ ID NO: 43; or
 - ii) a heavy chain comprising the amino acid sequence of SEQ ID NO: 35, 47, 49, or 51 and a light chain comprising the amino acid sequence of SEQ ID NO: 45.
- 28. An isolated nucleic acid encoding an anti-CD39 antibody comprising a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises the nucleic acid sequence of SEQ ID NO: 34 and the VL comprises the nucleic acid sequence of SEQ ID NO: 44.
- 29. An isolated nucleic acid encoding the antibody of any one of claims 1-25.
- 30. The nucleic acid of any one of claims 26-29, wherein the antibody comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein:
 - i) the VH comprises the nucleic acid sequence of SEQ ID NO: 34 and the VL comprises the nucleic acid sequence of SEQ ID NO: 44; or
 - ii) the VH comprises the nucleic acid sequence of SEQ ID NO: 8 and the VL comprises the nucleic acid sequence of SEQ ID NO: 18; or
 - iii) the VH comprises the nucleic acid sequence of SEQ ID NO: 60 and the VL comprises the nucleic acid sequence of SEQ ID NO: 70; or
 - iv) the VH comprises the nucleic acid sequence of SEQ ID NO: 86 and the VL comprises the nucleic acid sequence of SEQ ID NO: 96; or

- v) the VH comprises the nucleic acid sequence of SEQ ID NO: 112 and the VL comprises the nucleic acid sequence of SEQ ID NO: 122.
31. The nucleic acid of claim 30, wherein the antibody comprises a heavy chain and a light chain, wherein:
- i) the heavy chain comprises the nucleic acid sequence of SEQ ID NO: 36, 48, 50, or 52 and the light chain comprises the nucleic acid sequence of SEQ ID NO: 46; or
 - ii) the heavy chain comprises the nucleic acid sequence of SEQ ID NO: 10, 22, 24, or 26 and the light chain comprises the nucleic acid sequence of SEQ ID NO: 20; or
 - iii) the heavy chain comprises the nucleic acid sequence of SEQ ID NO: 62, 74, 76, or 78 and the light chain comprises the nucleic acid sequence of SEQ ID NO: 72; or
 - iv) the heavy chain comprises the nucleic acid sequence of SEQ ID NO: 88, 100, 102, or 104 and the light chain comprises the nucleic acid sequence of SEQ ID NO: 98; or
 - v) the heavy chain comprises the nucleic acid sequence of SEQ ID NO: 114, 126, 128, or 130 and the light chain comprises the nucleic acid sequence of SEQ ID NO: 124.
32. The nucleic acid of claim 31, wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises the nucleic acid sequence of SEQ ID NO: 36 and the light chain comprises the nucleic acid sequence of SEQ ID NO: 46.
33. A vector comprising the nucleic acid of any one of claims 26-32.
34. A host cell comprising the vector of claim 33.
35. A host cell that produces the antibody encoded by the nucleic acid of any one of claims 26-32.
36. A method for making an anti-CD39 antibody, comprising culturing the host cell of claim 35 under conditions suitable for expression of the antibody, and recovering the antibody produced by the host cell.
37. Use of an isolated anti-CD39 antibody in the manufacture of a medicament for the treatment of a cancer associated with CD39 expression in the tumor microenvironment, wherein the anti-CD39 antibody comprises:

- i) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 27; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 28; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 29; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 37; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 38; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 39; or
 - ii) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 30; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 31; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 32; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 40; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 41; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 42; or
 - iii) a VH that is at least 90% identical to the amino acid sequence of SEQ ID NO: 33 and a VL that is at least 90% identical to the amino acid sequence of SEQ ID NO: 43; or
 - iv) a heavy chain that is at least 90% identical to the amino acid sequence of SEQ ID NO: 35, 47, 49, or 51 and a light chain is at least 90% identical to the amino acid sequence of SEQ ID NO: 45.
- 38. The use of claim 37 wherein the anti-CD39 antibody comprises:
 - i) a VH comprising an amino acid sequence of SEQ ID NO: 33 and a VL comprising the amino acid sequence of SEQ ID NO: 43; or
 - ii) a heavy chain comprising the amino acid sequence of SEQ ID NO: 35, 47, 49, or 51 and a light chain comprising the amino acid sequence of SEQ ID NO: 45.
- 39. Use of an isolated anti-CD39 antibody in the manufacture of a medicament for the treatment of a cancer associated with CD39 expression in the tumor microenvironment, wherein the anti-CD39 antibody comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises the nucleic acid sequence of SEQ ID NO: 34 and the VL comprises the nucleic acid sequence of SEQ ID NO: 44.
- 40. Use of an isolated anti-CD39 antibody in the manufacture of a medicament for the treatment of a cancer associated with CD39 expression in the tumor microenvironment, wherein the anti-CD39 antibody comprises the antibody of any one of claims 1-25.

41. The use according to any one of claims 37-40, wherein the cancer is a solid tumor.
42. The use according to any one of claims 37-41, wherein the cancer is selected from lung cancer, non-small cell lung cancer, ovarian cancer, kidney cancer, testicular cancer, pancreas cancer, breast cancer, triple-negative breast cancer, melanoma, head and neck cancer, squamous head and neck cancer, colorectal cancer, bladder cancer, endometrial cancer, prostate cancer, thyroid cancer, hepatocellular carcinoma, gastric cancer, brain cancer, lymphoma, and renal cancer.
43. The use according to claim 42, wherein the cancer is pancreatic cancer.
44. The use according to any one of claim 42, wherein the cancer is gastric cancer.
45. The use according to any one of claim 42, wherein the cancer is prostate cancer.
46. The use according to any one of claim 42, wherein the cancer is endometrial cancer.
47. The use according to any one of claim 42, wherein the cancer is non-small cell lung cancer.
48. The use according to any one of claim 42, wherein the cancer is colorectal cancer.
49. The use according to any one of claim 42, wherein the cancer is ovarian cancer.
50. The use according to any one of claims 37-49, wherein the anti-CD39 antibody is for use in combination with one or more additional therapeutic agents or procedure, wherein the additional therapeutic agent or procedure is selected from a chemotherapeutic agent, a targeted anti-cancer therapy, an oncolytic drug, a cytotoxic agent, an immune-based therapy, a cytokine, surgical procedure, a radiation procedure, an activator of a costimulatory molecule, an inhibitor of an inhibitory molecule, a vaccine, and a cellular immunotherapy, or a combination thereof.
51. The use according to claim 50, wherein the one or more additional therapeutic agents is a PD-1 antagonist, an adenosine A2AR antagonist, a CD73 inhibitor, a CTLA-4 inhibitor, a TIM-3 inhibitor, a LAG-3 inhibitor, a chimeric antigen receptor (CAR) cell therapy, an anthracycline, a chemotherapeutic agent, or a combination thereof.
52. The use according to claim 51, wherein the one or more additional therapeutic agents is a PD-1 antagonist.
53. The use according to claim 51, wherein the one or more additional therapeutic agents is a CD73 inhibitor.
54. The use according to claim 51, wherein the one or more additional therapeutic agents is an A2AR antagonist.

- 55. The use according to claim 51, wherein the one or more additional therapeutic agents is a chemotherapeutic agent.
- 56. The use according to claim 51, wherein the one or more additional therapeutic agents is a CD73 inhibitor and an A2AR antagonist.
- 57. The use according to claim 51, wherein the one or more additional therapeutic agents is a PD-1 antagonist and an A2AR antagonist.
- 58. A pharmaceutical composition comprising the antibody of any one of claims 1-25 or the antibody produced by the method of claim 36, and a pharmaceutically acceptable carrier.
- 59. A kit comprising the antibody of any one of claims 1-25 or the anti-CD39 antibody produced by the method of claim 36.
- 60. A method of detecting human CD39 in vivo or ex vivo in a biological sample comprising (i) contacting the sample with any one of the antibodies of claims 1-25 or the antibody produced by the method of claim 36, under conditions that allow interaction of the antibody and human CD39 to occur, and (ii) detecting formation of a complex between the antibody and the sample.