

CLAIMS

1. An isolated antibody that specifically binds to human LAG-3, the antibody comprising a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2 and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2 and CDRL3, wherein CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 comprise the amino acid sequences set forth in SEQ ID NOs: 78, 83, 94, 100, 104, and 105; 78, 85, 95, 100, 104, and 105; 78, 86, 96, 100, 104, and 105; 78, 86, 96, 100, 104, and 109; 78, 86, 96, 100, 104, and 110; 78, 86, 96, 101, 104, and 108; 78, 86, 96, 103, 104, and 111; 78, 86, 97, 102, 104, and 112; 78, 91, 94, 100, 104, and 107; 78, 92, 96, 100, 104, and 105; 78, 92, 96, 100, 104, and 109; 79, 84, 95, 100, 104, and 105; 79, 84, 95, 100, 104, and 106; 79, 84, 95, 102, 104, and 105; 79, 88, 95, 100, 104, and 105; 79, 89, 95, 100, 104, and 105; 79, 90, 95, 100, 104, and 105; 79, 90, 98, 100, 104, and 105; 79, 90, 99, 100, 104, and 105; 80, 85, 96, 100, 104, and 105; 81, 87, 96, 100, 104, and 105; 81, 87, 96, 100, 104, and 107; or, 82, 93, 95, 100, 104, and 105, respectively.
2. An isolated antibody that specifically binds to human LAG-3, the antibody comprising a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2 and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2 and CDRL3, wherein CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 comprise the amino acid sequences set forth in SEQ ID NOs: 79, 90, 98, 100, 104, and 105, respectively.
3. The isolated antibody of claim 1 or claim 2, wherein the heavy chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 61, 63-72, and 220; and/or the light chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 73-77, 152, 221, or 224.
4. The isolated antibody of any one of claims 1-3, wherein the heavy chain variable region and the light chain variable region, respectively, comprise the amino acid sequences set forth in SEQ ID NOs: 61 and 73; 61 and 74; 61 and 75; 61 and 76; 61 and 77; 61 and 221; 63 and 73; 63 and 74; 63 and 75; 63 and 76; 63 and 77; 63 and 221; 64 and 73; 64 and 74; 64 and 75; 64 and 76; 64 and 77; 64 and 221; 65 and 73;

65 and 74; 65 and 75; 65 and 76; 65 and 77; 65 and 221; 66 and 73; 66 and 74; 66 and 75; 66 and 76; 66 and 77; 66 and 221; 67 and 73; 67 and 74; 67 and 75; 67 and 76; 67 and 77; 67 and 221; 68 and 73; 68 and 74; 68 and 75; 68 and 76; 68 and 77; 68 and 221; 69 and 73; 69 and 74; 69 and 75; 69 and 76; 69 and 77; 69 and 221; 70 and 73; 70 and 74; 70 and 75; 70 and 76; 70 and 77; 70 and 221; 71 and 73; 71 and 74; 71 and 75; 71 and 76; 71 and 77; 71 and 221; 72 and 73; 72 and 74; 72 and 75; 72 and 76; 72 and 77; 72 and 221; 220 and 73; 220 and 74; 220 and 75; 220 and 76; 220 and 77; or 220 and 221.

5. The isolated antibody of claim 4, wherein the heavy chain variable region and the light chain variable region, respectively, comprise SEQ ID NO: 65 and 73.
6. The isolated antibody of any one of claims 1-5, wherein the antibody comprises a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 168, 169, 170, 176, 178-186, and 225-227.
7. The isolated antibody of any one of claims 1-6, wherein the antibody comprises a light chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 187-191 and 228.
8. The isolated antibody of any one of claims 1-7, wherein the antibody comprises a heavy chain constant region, wherein the heavy chain constant region:
 - (a) is selected from the group consisting of human IgG₁, IgG₂, IgG₃, IgG₄, IgA₁, and IgA₂;
 - (b) is an IgG₁ heavy chain constant region;
 - (c) is an IgG₁ heavy chain constant region comprising a N297A mutation, numbered according to the EU numbering system;
 - (d) comprises the amino acid sequence of SEQ ID NO: 194;
 - (e) is an IgG₁ heavy chain constant region comprising a N297Q mutation, numbered according to the EU numbering system;
 - (f) is a non-fucosylated IgG₁;
 - (g) is an IgG₄ heavy chain constant region;
 - (h) is an IgG₄ heavy chain constant region comprising a S228P mutation, numbered according to the EU numbering system; or
 - (i) comprises the amino acid sequence of SEQ ID NO: 196.

9. The isolated antibody of any one of claims 1-8, wherein the antibody comprises a human kappa or human lambda light chain constant region.
10. The isolated antibody of claim 9, wherein the light chain constant region is a human kappa light chain constant region.
11. The isolated antibody of claim 10, wherein the antibody comprises a light chain constant region comprising the amino acid sequence of SEQ ID NO: 198 or 219.
12. The isolated antibody of any one of claims 1-11, comprising a heavy chain and a light chain, wherein the heavy chain and the light chain, respectively, comprise the amino acid sequences set forth in SEQ ID NOs: 168 and 187; 168 and 188; 168 and 189; 168 and 190; 168 and 191; 168 and 228; 169 and 187; 169 and 188; 169 and 189; 169 and 190; 169 and 191; 169 and 228; 170 and 187; 170 and 188; 170 and 189; 170 and 190; 170 and 191; 170 and 228; 176 and 187; 176 and 188; 176 and 189; 176 and 190; 176 and 191; 176 and 228; 178 and 187; 178 and 188; 178 and 189; 178 and 190; 178 and 191; 178 and 228; 179 and 187; 179 and 188; 179 and 189; 179 and 190; 179 and 191; 179 and 228; 180 and 187; 180 and 188; 180 and 189; 180 and 190; 180 and 191; 180 and 228; 181 and 187; 181 and 188; 181 and 189; 181 and 190; 181 and 191; 181 and 228; 182 and 187; 182 and 188; 182 and 189; 182 and 190; 182 and 191; 182 and 228; 183 and 187; 183 and 188; 183 and 189; 183 and 190; 183 and 191; 183 and 228; 184 and 187; 184 and 188; 184 and 189; 184 and 190; 184 and 191; 184 and 228; 185 and 187; 185 and 188; 185 and 189; 185 and 190; 185 and 191; 185 and 228; 186 and 187; 186 and 188; 186 and 189; 186 and 190; 186 and 191; 186 and 228; 225 and 187; 225 and 188; 225 and 189; 225 and 190; 225 and 191; 225 and 228; 226 and 187; 226 and 188; 226 and 189; 226 and 190; 226 and 191; 226 and 228; 227 and 187; 227 and 188; 227 and 189; 227 and 190; 227 and 191; or 227 and 228.
13. The isolated antibody of claim 12, wherein the heavy chain and the light chain, respectively comprise the amino acid sequences set forth in SEQ ID NOs: 169 and 187.
14. The isolated antibody of claim 13, wherein the amino acid sequences of the heavy chain and the light chain, respectively, consist of the amino acid sequences set forth

in SEQ ID NOs: 169 and 187.

15. The isolated antibody of any one of claims 1-14, wherein the antibody:
 - (a) is a human antibody,
 - (b) is a humanized antibody,
 - (c) is antagonistic to human LAG-3,
 - (d) deactivates, reduces, or inhibits an activity of human LAG-3,
 - (e) inhibits binding of human LAG-3 to MHC class II,
 - (f) induces IL-2 production by peripheral blood mononuclear cells (PBMCs) stimulated with staphylococcal enterotoxin A (SEA), and/or
 - (g) induces TNF α production by tumor infiltrating lymphocytes (TILs) stimulated with anti-CD3 and anti-CD28 antibodies.
16. The isolated antibody of any one of claims 1-15, conjugated to a cytotoxic agent, cytostatic agent, toxin, radionuclide, or detectable label.
17. A pharmaceutical composition comprising the antibody of any one of claims 1-16 and a pharmaceutically acceptable carrier or excipient.
18. Use of the antibody or pharmaceutical composition of any one of claims 1-17 in the manufacture of a medicament for:
 - (a) the treatment of cancer in a subject in need thereof;
 - (b) increasing T cell activation in response to an antigen in a subject;
 - (c) the treatment of an infectious disease in a subject in need thereof.
19. The antibody or pharmaceutical composition of any one of claims 1-17 for use in the treatment of cancer in a subject in need thereof.
20. An isolated polynucleotide encoding
 - a) a heavy chain variable region and/or a light chain variable region of the antibody of any one of claims 1-16; or
 - b) a heavy chain and/or a light chain of the antibody of any one of claims 1-16; or
 - c) the amino acid sequence of any one of SEQ ID NOs: 61, 63-77, 152, 168-170, 176, 178-191, 220, 221, or 224-228.

21. A vector comprising the polynucleotide of claim 20.
22. A recombinant host cell comprising:
 - a) the polynucleotide of claim 20;
 - b) an isolated polynucleotide encoding a heavy chain variable region of the antibody of any one of claims 1-16, and an isolated polynucleotide encoding a light chain variable region of the antibody of any one of claims 1-16; or
 - c) an isolated polynucleotide encoding a heavy chain of the antibody of any one of claims 1-16, and an isolated polynucleotide encoding a light chain of the antibody of any one of claims 1-16.
23. A method of producing an antibody that binds to human LAG-3, the method comprising culturing the host cell of claim 22 so that the polynucleotide is expressed and the antibody is produced.