SUMMARY ~~OF THE INVENTION~~

The present ~~invention~~ disclosure provides an antibody or antigen-binding fragment thereof (*e.g.*, an antibody, an antigen-binding fragment, monoclonal antibodies, polyclonal antibodies, a multispecific antibody, a humanized antibody, an isolated antibody or antigen-binding fragment thereof, a humanized antagonist antibody, a fully human antibody, a chimeric antibody and a camelized single domain antibody) that specifically binds LAG3 (*e.g.*, human and/or *Macaqa fascicularis*, *e.g.*, SEQ ID NOs: 443 or 445) comprising: a heavy chain immunoglobulin variable region having at least 78.99% amino acid sequence identity to amino acids 1-119 of SEQ ID NO: 106; and/or a light chain immunoglobulin variable region having at least 78.38% amino acid sequence identity to amino acids 1-111 of SEQ ID NO: 224.

In an embodiment of the ~~invention~~disclosure, an anti-LAG3 antibody or antigen-binding fragment thereof of the present disclosure ~~invention~~ comprises the light and heavy chain immunoglobulin (*e.g.*, heavy and light chain variable domains or heavy and light chain CDRs) of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8 or Ab9 as set forth herein.

The present disclosure ~~invention~~ provides an antibody or antigen-binding fragment thereof that specifically binds LAG3 (*e.g.*, human or cynomolgous monkey LAG3) comprising (a) the CDR1, CDR2, and CDR3 of a V_L domain of an immunoglobulin chain that comprises the amino acid sequence set forth in SEQ ID NO: 7, 17, 27, 37, 57, 59, 61, 63, 65, 101, 126, 130, 132, 136, 138, 208, 210, 224, 226, 228, 230, 232, 241, 257, 259, 261, 263, 351, 369, 371, 373, 375, 401, 403, 405, 426, 427, 450-453 or 459-461; and/or (b) the CDR1, CDR2, and CDR3 of a V_H domain of an immunoglobulin chain that comprises the amino acid sequence set forth in SEQ ID NO: 2, 12, 22, 32, 45, 47, 49, 51, 53, 55, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 103, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 128, 134, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204, 206, 212, 214, 216, 218, 220, 222, 234, 235, 237, 239, 243, 245, 247, 249, 251, 253, 255, 265, 267, 269, 271, 273, 275, 277, 279, 281, 283, 285, 287, 289, 291, 293, 295, 297, 299, 301, 303, 305, 307, 309, 311, 313, 315, 317, 319, 321, 323, 325, 327, 329, 331, 333, 335, 337, 339, 341, 343, 345, 347, 349, 353, 355, 357, 359, 361, 363, 365, 367, 377, 379, 381, 383, 385, 387, 389, 391, 393, 395, 397, 399, 406-419, 434-442, 448, 449, 462, 463 or 464.

In one aspect, the disclosure provides an antibody or antigen-binding fragment thereof that specifically binds human LAG3 comprising:

(a) the CDR1, CDR2, and CDR3 of a V_L domain of an immunoglobulin chain that comprises the amino acid sequence set forth in SEQ ID NO: 7, 17, 27, 37, 57, 59, 61, 63, 65, 101, 126, 130, 132, 136, 138, 208, 210, 224, 226, 228, 230, 232, 241, 257, 259, 261, 263, 351, 369, 371, 373, 375, 401, 403, 405, 426, 427, 450-453 or 459-461 ; and/or

(b) the CDR1, CDR2, and CDR3 of a V_H domain of an immunoglobulin chain that comprises the amino acid sequence set forth in SEQ ID NO: 2, 12, 22, 32, 45, 47, 49, 51, 53, 55, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 103, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 128, 134, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204, 206, 212, 214, 216, 218, 220, 222, 234, 235, 237, 239, 243, 245, 247, 249, 251, 253, 255, 265, 267, 269, 271, 273, 275, 277, 279, 281, 283, 285, 287, 289, 291, 293, 295, 297, 299, 301, 303, 305, 307, 309, 311, 313, 315, 317, 319, 321, 323, 325, 327, 329, 331, 333, 335, 337, 339, 341, 343, 345, 347, 349, 353, 355, 357, 359, 361, 363, 365, 367, 377, 379, 381, 383, 385, 387, 389, 391, 393, 395, 397, 399, 406-419, 434-442, 448, 449, 462, 463 or 464.

The present disclosure ~~invention~~ also provides an antibody or antigen-binding fragment thereof that specifically binds LAG3 (*e.g.*, human or cynomolgous monkey) comprising (1) a light chain variable domain comprising CDR-L1 that comprises the amino acid sequence:

In an embodiment of the disclosure~~invention~~, the antibody or antigen-binding fragment thereof that specifically binds LAG3 (*e.g.*, human or cynomolgous monkey LAG3) comprises the CDRs of various light and/or heavy chain variable regions and having at least 90% overall amino acid sequence identity to the variable region, *i.e.*, variability in the chain occurs outside the CDRs, *e.g.*, (1) a light chain immunoglobulin comprising CDR-L1, CDR-L2 and CDR-L3 of the immunoglobulin comprising the amino acid sequence of SEQ ID NO: 126 or amino acids 21-131 thereof, and having at least 90% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO: 126 or amino acids 21-131 thereof, and/or a heavy chain immunoglobulin comprising CDR-H1, CDR-H2 and CDR-H3 of the immunoglobulin comprising the amino acid sequence of SEQ ID NO: 106 or amino acids 1-119 thereof, and having at least 90% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO: 106 or amino acids 1-119 thereof; (2) a light chain immunoglobulin comprising CDR-L1, CDR-L2 and CDR-L3 of the immunoglobulin comprising the amino acid sequence of SEQ ID NO: 126 or amino acids 21-131 thereof, and having at least 90% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO: 126 or amino acids 21-131 thereof, and/or a heavy chain immunoglobulin comprising CDR-H1, CDR-H2 and CDR-H3 of the immunoglobulin comprising the amino acid sequence of SEQ ID NO: 108 or amino acids 1-119 thereof, and having at least 90% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO: 108 or amino acids 1-119 thereof; (3) a light chain immunoglobulin comprising CDR-L1, CDR-L2 and CDR-L3 of the immunoglobulin comprising the amino acid sequence of SEQ ID NO: 126 or amino acids 21-131 thereof, and having at least 90% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO: 126 or amino acids 21-131 thereof, and/or a heavy chain immunoglobulin comprising CDR-H1, CDR-H2 and CDR-H3 of the immunoglobulin comprising the amino acid sequence of SEQ ID NO: 110 or amino acids 1-119 thereof, and having at least 90% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO: 110 or amino acids 1-119 thereof; (4) a light chain immunoglobulin comprising CDR-L1, CDR-L2 and CDR-L3 of the immunoglobulin comprising the amino acid sequence of SEQ ID NO: 126 or amino acids 21-131 thereof, and having at least 90% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO: 126 or amino acids 21-131 thereof, and/or a heavy chain immunoglobulin comprising CDR-H1, CDR-H2 and CDR-H3 of the immunoglobulin comprising the amino acid sequence of SEQ ID NO: 112 or amino acids 1-119 thereof, and having at least 90% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO: 112 or amino acids 1-119 thereof; (5) a light chain immunoglobulin comprising CDR-L1, CDR-L2 and CDR-L3 of the immunoglobulin comprising the amino acid sequence of SEQ ID NO: 126 or amino acids 21-131

thereof, and having at least 90% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO: 126 or amino acids 21-131 thereof, and/or a heavy chain immunoglobulin comprising CDR-H1, CDR-H2 and CDR-H3 of the immunoglobulin comprising the amino acid sequence of SEQ ID NO: 114 or amino acids 1-119 thereof, and having at least 90% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO: 114 or amino acids 1-119 thereof; (6) a light chain immunoglobulin comprising CDR-L1, CDR-L2 and CDR-L3 of the immunoglobulin comprising the amino acid sequence of SEQ ID NO: 126 or amino acids 21-131 thereof, and having at least 90% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO: 126 or amino acids 21-131 thereof, and/or a heavy chain immunoglobulin comprising CDR-H1, CDR-H2 and CDR-H3 of the immunoglobulin comprising the amino acid sequence of SEQ ID NO: 116 or amino acids 1-119 thereof, and having at least 90% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO: 116 or amino acids 1-119 thereof; (7) a light chain immunoglobulin comprising CDR-L1, CDR-L2 and CDR-L3 of the immunoglobulin comprising the amino acid sequence of SEQ ID NO: 126 or amino acids 21-131 thereof, and having at least 90% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO: 126 or amino acids 21-131 thereof, and/or a heavy chain immunoglobulin comprising CDR-H1, CDR-H2 and CDR-H3 of the immunoglobulin comprising the amino acid sequence of SEQ ID NO: 118 or amino acids 1-119 thereof, and having at least 90% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO: 118 or amino acids 1-119 thereof; (8) a light chain immunoglobulin comprising CDR-L1, CDR-L2 and CDR-L3 of the immunoglobulin comprising the amino acid sequence of SEQ ID NO: 126 or amino acids 21-131 thereof, and having at least 90% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO: 126 or amino acids 21-131 thereof, and/or a heavy chain immunoglobulin comprising CDR-H1, CDR-H2 and CDR-H3 of the immunoglobulin comprising the amino acid sequence of SEQ ID NO: 120 or amino acids 1-119 thereof, and having at least 90% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO: 120 or amino acids 1-119 thereof; and/or (9) a light chain immunoglobulin comprising CDR-L1, CDR-L2 and CDR-L3 of the immunoglobulin comprising the amino acid sequence of SEQ ID NO: 126 or amino acids 21-131 thereof, and having at least 90% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO: 126 or amino acids 21-131 thereof, and/or a heavy chain immunoglobulin comprising CDR-H1, CDR-H2 and CDR-H3 of the immunoglobulin comprising the amino acid sequence of SEQ ID NO: 122 or amino acids 1-119 thereof, and having at least 90% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO: 122 or amino acids 1-119 thereof. In an embodiment of the disclosure~~invention~~, the antibody or antigen-binding fragment comprises

the various mature light and/or mature heavy chain immunoglobulin variable regions and having at least 90% overall amino acid sequence identity to the unprocessed immunoglobulin variable region (including the signal sequence), *i.e.*, variability occurs outside the mature immunoglobulin chain sequences.

In another aspect, the disclosure provides an antibody or antigen-binding fragment thereof that specifically binds human LAG3 comprising a light chain immunogoblin, a heavy chain immunogoblin, or both a light and heavy chain immunoglobulin, selected from the group consisting of:

(1)

a light chain immunoglobulin comprising an amino acid sequence having at least 90% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO: 126 or amino acids 21-131 thereof, and/or

a heavy chain immunoglobulin comprising an amino acid sequence having at least 90% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO: 106 or amino acids 1-119 thereof;

(2)

a light chain immunoglobulin comprising an amino acid sequence having at least 90% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO: 126 or amino acids 21-131 thereof, and/or

a heavy chain immunoglobulin comprising an amino acid sequence having at least 90% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO: 108 or amino acids 1-119 thereof;

(3)

a light chain immunoglobulin comprising an amino acid sequence having at least 90% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO: 126 or amino acids 21-131 thereof, and/or

a heavy chain immunoglobulin comprising an amino acid sequence having at least 90% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO: 110 or amino acids 1-119 thereof;

(4)

a light chain immunoglobulin comprising an amino acid sequence having at least 90% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO: 126 or amino acids 21-131 thereof, and/or

a heavy chain immunoglobulin comprising an amino acid sequence having at least 90% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO: 112 or amino acids 1-119 thereof;

(5)

a light chain immunoglobulin comprising an amino acid sequence having at least 90% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO: 126 or amino acids 21-131 thereof, and/or

a heavy chain immunoglobulin comprising an amino acid sequence having at least 90% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO: 114 or amino acids 1-119 thereof;

(6)

a light chain immunoglobulin comprising an amino acid sequence having at least 90% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO: 126 or amino acids 21-131 thereof, and/or

a heavy chain immunoglobulin comprising an amino acid sequence having at least 90% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO: 116 or amino acids 1-119 thereof;

(7)

a light chain immunoglobulin comprising an amino acid sequence having at least 90% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO: 126 or amino acids 21-131 thereof, and/or

a heavy chain immunoglobulin comprising an amino acid sequence having at least 90% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO: 118 or amino acids 1-119 thereof;

(8)

a light chain immunoglobulin comprising an amino acid sequence having at least 90% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO: 126 or amino acids 21-131 thereof, and/or

a heavy chain immunoglobulin comprising an amino acid sequence having at least 90% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO: 120 or amino acids 1-119 thereof; and

(9)

a light chain immunoglobulin comprising an amino acid sequence having at least 90% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO: 126 or amino acids 21-131 thereof, and/or

a heavy chain immunoglobulin comprising an amino acid sequence having at least 90% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO: 122 or amino acids 1-119 thereof.

The present disclosure ~~invention~~ provides an antibody or antigen-binding fragment thereof that specifically binds LAG3 (*e.g.*, human or cynomolgous monkey LAG3) that comprises a mature or unprocessed V_L domain or light chain immunoglobulin of SEQ ID NO: 7, 17, 27, 37, 57, 59, 61, 63, 65, 101, 126, 130, 132, 136, 138, 208, 210, 224, 226, 228, 230, 232, 241, 257, 259, 261, 263, 351, 369, 371, 373, 375, 401, 403, 405, 426, 427, 451-453 or 459-461; and/or a mature or unprocessed V_H domain or heavy chain immunoglobulin of SEQ ID NO: 2, 12, 22, 32, 45, 47, 49, 51, 53, 55, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 103, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 128, 134, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204, 206, 212, 214, 216, 218, 220, 222, 234, 235, 237, 239, 243, 245, 247, 249, 251, 253, 255, 265, 267, 269, 271, 273, 275, 277, 279, 281, 283, 285, 287, 289, 291, 293, 295, 297, 299, 301, 303, 305, 307, 309, 311, 313, 315, 317, 319, 321, 323, 325, 327, 329, 331, 333, 335, 337, 339, 341, 343, 345, 347, 349, 353, 355, 357, 359, 361, 363, 365, 367, 377, 379, 381, 383, 385, 387, 389, 391, 393, 395, 397, 399, 406-419, 434-442, 448, 449, 462, 463 or 464. In an embodiment of the disclosure~~invention~~, the antibody or antigen-binding fragment thereof comprises: (1) a light chain variable domain comprising: CDR-L1 that comprises the amino acid sequence: KASQSLDYEGDSDMN (SEQ ID NO: 38); CDR-L2 that comprises the amino acid sequence: GASNLES (SEQ ID NO: 39); and CDR-L3 that comprises the amino acid sequence: QQSTEDPRT (SEQ ID NO: 40); and/or a heavy chain variable domain comprising: CDR-H1 that comprises the amino acid sequence: DYNVD (SEQ ID NO: 33); CDR-H2 that comprises the amino acid sequence: DINPNNGGTIYAQKFQE (SEQ ID NO: 458); and CDR-H3 that comprises the amino acid sequence: NYRWFGAMDH (SEQ ID NO: 35); or (2) a light chain variable domain comprising: CDR-L1 that comprises the amino acid sequence: KASQSLDYEGDSDMN (SEQ ID NO: 38); CDR-L2 that comprises the amino acid sequence: GASNLES (SEQ ID NO: 39); and CDR-L3 that comprises the amino acid sequence: QQSTEDPRT (SEQ ID NO: 40); and/or a heavy chain variable domain comprising: CDR-H1 that comprises the amino acid sequence: DYNVD (SEQ ID NO: 33); CDR-H2 that comprises the amino acid sequence: DINPNSGGTIYAQKFQE (SEQ ID NO: 456); and CDR-H3

that comprises the amino acid sequence: NYRWFGAMDH (SEQ ID NO: 35); or (3) a light chain variable domain comprising: CDR-L1 that comprises the amino acid sequence:

KASQSLDYEGDSDMN (SEQ ID NO: 38); CDR-L2 that comprises the amino acid sequence: GASNLES (SEQ ID NO: 39); and CDR-L3 that comprises the amino acid sequence: QQSTEDPRT (SEQ ID NO: 40); and/or a heavy chain variable domain comprising: CDR-H1 that comprises the amino acid sequence: DYNVD (SEQ ID NO: 33); CDR-H2 that comprises the amino acid sequence: DINPNDGGTIYAQKFQE (SEQ ID NO: 457); and CDR-H3 that comprises the amino acid sequence: NYRWFGAMDH (SEQ ID NO: 35); or (4) a light chain variable domain comprising: CDR-L1 that comprises the amino acid sequence: KASQSLDYEGDSDMN (SEQ ID NO: 38); CDR-L2 that comprises the amino acid sequence: GASNLES (SEQ ID NO: 39); and CDR-L3 that comprises the amino acid sequence: QQSTEDPRT (SEQ ID NO: 40); and/or a heavy chain variable domain comprising: CDR-H1 that comprises the amino acid sequence: DYNVD (SEQ ID NO: 33); CDR-H2 that comprises the amino acid sequence: DINPNQGGTIYAQKFQE (SEQ ID NO: 455); and CDR-H3 that comprises the amino acid sequence: NYRWFGAMDH (SEQ ID NO: 35); or (5) a light chain variable domain comprising: CDR-L1 that comprises the amino acid sequence: KASQSLDYEGDSDMN (SEQ ID NO: 38); CDR-L2 that comprises the amino acid sequence: GASNLES (SEQ ID NO: 39); and CDR-L3 that comprises the amino acid sequence: QQSTEDPRT (SEQ ID NO: 40); and/or a heavy chain variable domain comprising: CDR-H1 that comprises the amino acid sequence: DYNVD (SEQ ID NO: 33); CDR-H2 that comprises the amino acid sequence: DINPNGGGTIYAQKFQE (SEQ ID NO: 454); and CDR-H3 that comprises the amino acid sequence: NYRWFGAMDH (SEQ ID NO: 35). In an embodiment of the disclosure~~invention~~, the antibody or fragment is glycosylated with engineered yeast N-linked glycans or CHO N-linked glycans. Optionally, any of the anti-LAG3 antibodies or antigen-binding fragments thereof of the disclosure ~~invention~~ are characterized by one or more of the following properties: Inhibits LAG3 binding to MHC class II molecules; Competes with MHC class II molecules for LAG3 binding; Binds the extraloop of LAG3; Binds LAG3 with a K_D of about 10^{-9}M to about 2 X 10^{-12}M; Binds to native LAG3 on the surface of activated CD4+ and/or CD8+ T-cells; Binds to human and/or cynomolgous monkey LAG3; Inhibits LAG3 homodimerization; Stimulates antigen-specific T-cell production of IL-2; labels tonsil tissue; does not label brain, heart, kidney, liver, lung, pancreas, and/or pituitary tissue; binds to human LAG3 by contacting residues QEGAPAQL (amino acids 35-42 of SEQ ID NO: 443) and RPARRADAGEYRAAVH (amino acids 137-152 of SEQ ID NO: 443) and, optionally, residues DERGRQRGDFSLW (amino acids 123-135 of SEQ ID NO: 443) of LAG3; or residues SPTIPLQDL (amino acids 45-53 of SEQ ID NO: 443) and, optionally DERGRQRGDFSL (amino acids 123-134 of SEQ ID NO: 443) of LAG3; or residues HPLAPGPHPAAPSSWGPRPRRYTVL (amino acids 78-102 of SEQ ID NO: 443) of LAG3;

and/or by protecting hydrogens on the amide backbone of such residues from exchange with a deuterium. The present disclosure ~~invention~~ also provides any such antibody or fragment in a pharmaceutically acceptable carrier or diluent. In an embodiment of the disclosure~~invention~~, the anti-LAG3 antibody or fragment is immobilized to a solid substrate. In an embodiment of the disclosure ~~invention~~ the anti-LAG3 antibody or antigen-binding fragment thereof is Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8 or Ab9 (as set forth herein).

In another aspect, the disclosure provides an antibody or antigen-binding fragment thereof that specifically binds human LAG3 that:

(i) binds to human LAG3 by contacting residues QEGAPAQL (amino acids 35-42 of SEQ ID NO: 443) and RPARRADAGEYRAAVH (amino acids 137-152 of SEQ ID NO: 443) and, optionally, residues DERGRQRGDFSLW (amino acids 123-135 of SEQ ID NO: 443) of LAG3; or residues SPTIPLQDL (amino acids 45-53 of SEQ ID NO: 443) and, optionally DERGRQRGDFSL (amino acids 123-134 of SEQ ID NO: 443); or residues HPLAPGPHPAAPSSWGPRPRRYTVL (amino acids 78-102 of SEQ ID NO: 443); and/or

(ii) specifically binds to human LAG3 and comprises a heavy chain immunoglobulin variable region having at least 78.99% amino acid sequence identity to amino acids 1-119 of SEQ ID NO: 106; and/or a light chain immunoglobulin variable region having at least 78.38% amino acid sequence identity to amino acids 1-111 of SEQ ID NO: 224;

wherein the antibody or fragment optionally cross-blocks or is cross-blocked by an antibody or fragment as defined herein.

The present ~~invention~~ disclosure also provides a complex comprising an anti-LAG3 antibody or fragment discussed herein (*e.g.*, 4A10, 19E8, 11C9 and/or 22D2; *e.g.*, Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8 and/or Ab9) complexed with LAG3 (*e.g.*, human or cynomolgous monkey) or a fragment thereof or with a secondary antibody (*e.g.*, detectably labeled secondary antibody) that binds specifically to the anti-LAG3 antibody or fragment. In an embodiment of the disclosure~~invention~~, the antibody or fragment is *in vitro* (*e.g.*, is immobilized to a solid substrate) or is in the body of a subject. In an embodiment of the disclosure~~invention~~, the LAG3 is *in vitro* (*e.g.*, is immobilized to a solid substrate) or is on the surface of a cell or is in the body of a subject.

The present disclosure ~~invention~~ further provides a composition comprising a plurality of anti-LAG3 antibodies or antigen-binding fragments of the present disclosure ~~invention~~ which are isolated, monoclonal antibodies or antigen-binding fragments thereof, *e.g.*, which are humanized, *e.g.*, humanized antagonistic antibodies and antigen-binding fragments thereof.

In another aspect, the disclosure provides a composition or kit comprising the antibody or fragment as discussed herein in association with a further therapeutic agent. The present disclosure ~~invention~~ also provides a composition comprising anti-LAG3 antibodies or antigen-binding fragments thereof as discussed herein in association with a further therapeutic agent (*e.g.*, a monoclonal antibody or antigen-binding fragment thereof or an organic small molecule) such as an inhibitor of an immunomodulatory receptor, an anti-emetic, an MTOR (mammalian target of rapamycin) inhibitor, a cytotoxic agent, a platinum agent, an EGFR (epidermal growth factor receptor) inhibitor, a VEGF (vascular epidermal growth factor) inhibitor, a microtubule stabilizer, a taxane, a CD20 inhibitor, a CD52 inhibitor, a CD30 inhibitor, a RANK (Receptor activator of nuclear factor kappa-B) inhibitor, a RANKL (Receptor activator of nuclear factor kappa-B ligand) inhibitor, an ERK inhibitor, a MAP Kinase inhibitor, an AKT inhibitor, a MEK inhibitor, a PI3K inhibitor, a HER1 inhibitor, a HER2 inhibitor, a HER3 inhibitor, a HER4 inhibitor, a Bcl2 inhibitor, a CD22 inhibitor, a CD79b inhibitor, an ErbB2 inhibitor, and/or a farnesyl protein transferase inhibitor. In an embodiment of the disclosure~~invention~~, the further therapeutic agent is an anti-PD1 antibody or an antigen-binding fragment thereof, pembrolizumab, nivolumab, CT-011, anti-CTLA4 antibody or an antigen-binding fragment thereof, anti-TIM3 antibody or an antigen-binding fragment thereof, anti-CS1 antibody or an antigen-binding fragment thereof, elotuzumab, anti-KIR2DL1/2/3 antibody or an antigen-

binding fragment thereof, lirilumab, anti-CD137 antibody or an antigen-binding fragment thereof, urelumab, anti-GITR antibody or an antigen-binding fragment thereof, TRX518, anti-PD-L1 antibody or an antigen-binding fragment thereof, BMS-936559, MSB0010718C, MPDL3280A, anti-PD-L2 antibody or an antigen-binding fragment thereof, anti-ILT1 antibody or an antigen-binding fragment thereof, anti-ILT2 antibody or an antigen-binding fragment thereof, anti-ILT3 antibody or an antigen-binding fragment thereof, anti-ILT4 antibody or an antigen-binding fragment thereof, anti-ILT5 antibody or an antigen-binding fragment thereof, anti-ILT6 antibody or an antigen-binding fragment thereof, anti-ILT7 antibody or an antigen-binding fragment thereof, anti-ILT8 antibody or an antigen-binding fragment thereof, anti-CD40 antibody or an antigen-binding fragment thereof, anti-OX40 antibody or an antigen-binding fragment thereof, anti-CD137 antibody or an antigen-binding fragment thereof, anti-KIR2DL1 antibody or an antigen-binding fragment thereof, anti-KIR2DL2/3 antibody or an antigen-binding fragment thereof, anti-KIR2DL4 antibody or an antigen-binding fragment thereof, anti-KIR2DL5A antibody or an antigen-binding fragment thereof, anti-KIR2DL5B antibody or an antigen-binding fragment thereof, anti-KIR3DL1 antibody or an antigen-binding fragment thereof, anti-KIR3DL2 antibody or an antigen-binding fragment thereof, anti-KIR3DL3 antibody or an antigen-binding fragment thereof, anti-NKG2A antibody or an antigen-binding fragment thereof, anti-NKG2C antibody or an antigen-binding fragment thereof, and/or an anti-NKG2E antibody or an antigen-binding fragment thereof, or any small organic molecule inhibitor of such targets; IL-10, anti-IL10, anti-TSLP and/or PEGylated IL-10. In an embodiment of the disclosure~~invention~~, the further therapeutic agent is 13-cis-retinoic acid, 3-[5-(methylsulfonylpiperadinemethyl)-indolyl]-quinolone, 4-hydroxytamoxifen, 5-deooxyuridine, 5'-deoxy-5-fluorouridine, 5-fluorouracil, 6-mecaptopurine, 7-hydroxystaurosporine, A-443654, abirateroneacetate, abraxane, ABT-578, acolbifene, ADS-100380, aflibercept, ALT-110, altretamine, amifostine, aminoglutethimide, amrubicin, amsacrine, anagrelide, anastrozole, angiostatin, AP-23573, ARQ-197, arzoxifene, AS-252424, AS-605240, asparaginase, AT-9263, ATI3387, atrasentan, axitinib, AZD1152, *Bacillus Calmette-Guerin* (BCG) vaccine, batabulin, BC-210, BGJ398, besodutox, bevacizumab, bicalutamide, Bio111, BIO140, BKM120, bleomycin, BMS-214662, BMS-247550, BMS-275291, BMS-310705, bortezimib, buserelin, busulfan, calcitriol, camptothecin, canertinib, capecitabine, carboplatin, carmustine, CC8490, cediranib, CG-1521, CG-781, chlamydocin, chlorambucil, chlorotoxin, cilengitide, cimitidine, cisplatin, cladribine, clodronate, cobimetnib, COL-3, CP-724714, cyclophosphamide, cyproterone, cyproteroneacetate, cytarabine, cytosinearabinoside, dabrafenib, dacarbazine, dacinostat, dactinomycin, dalotuzumab, danusertib, dasatanib, daunorubicin, decatanib, deguelin,

darbepoetin alfa. In an embodiment of the disclosure~~invention~~, the anti-LAG3 antibody or antigen-binding fragment thereof is in association with pembrolizumab. In an embodiment of the disclosure~~invention~~, the anti-LAG3 antibody or antigen-binding fragment thereof is in association with novolumab. In an embodiment of the disclosure~~invention~~, the anti-LAG3 antibody or antigen-binding fragment thereof is in association with CT-011. In an embodiment of the disclosure~~invention~~, the anti-LAG3 antibody or antigen-binding fragment thereof is in association with BMS-936559.

In another aspect, the ~~The~~ present disclosure ~~invention also~~ provides a polypeptide comprising an amino acid sequence selected from the group consisting of 2, 3, 4, 5, 7, 8, 9, 10, 12, 13, 14, 15, 17, 18, 19, 20, 22, 23, 24, 25, 27, 28, 29, 30, 32, 33, 34, 35, 37, 38, 39, 40, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, 226, 228, 230, 232, 234, 235, 237, 239, 241, 243, 245, 247, 249, 251, 253, 255, 257, 259, 261, 263, 265, 267, 269, 271, 273, 275, 277, 279, 281, 283, 285, 287, 289, 291, 293, 295, 297, 299, 301, 303, 305, 307, 309, 311, 313, 315, 317, 319, 321, 323, 325, 327, 329, 331, 333, 335, 337, 339, 341, 343, 345, 347, 349, 351, 353, 355, 357, 359, 361, 363, 365, 367, 369, 371, 373, 375, 377, 379, 381, 383, 385, 387, 389, 391, 393, 395, 397, 399, 401, 403, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 426, 427, 434, 435, 436, 437, 438, 439, 440, 441, 442, 446, 448, 449, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463 and 464 for example, SEQ ID NOs: 2, 7, 12, 17, 22, 27, 32 and 37; or a mature fragment and/or variable immunoglobulin domain thereof. In another aspect, the disclosure provides a polynucleotide encoding the polypeptide as discussed herein. The present disclosure ~~invention~~ also provides a polynucleotide encoding any of such polypeptides, *e.g.*, comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1, 6, 11, 16, 21, 26, 31, 36, 46, 48, 50, 52, 54, 56, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 163, 165, 167, 169, 171, 173, 175, 177, 179, 181, 183, 185, 187, 189, 191, 193, 195, 197, 199, 201, 203, 205, 207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 256, 258, 260, 262, 264, 266, 268, 270, 272, 274, 276, 278, 280, 282, 284, 286, 288, 290, 292, 294, 296, 298, 300, 302, 304, 306, 308, 310, 312, 314, 316, 318, 320, 322, 324, 326, 328, 330, 332, 334, 336, 338, 340, 342, 344, 346, 348, 350, 352, 354,

356, 358, 360, 362, 364, 366, 368, 370, 372, 374, 376, 378, 380, 382, 384, 386, 388, 390, 392, 394, 396, 398, 400, 402 and 404; or a mature fragment thereof. In another aspect, the disclosure provides a vector comprising the polynucleotide as discussed herein. Also included in the present disclosure ~~invention~~ is a vector (*e.g.*, a plasmid) comprising the polynucleotide. In another aspect, the disclosure provides a host cell comprising the antibody, fragment, polypeptide, polynucleotide or vector as discussed herein. A host cell (*e.g.*,

mammalian, bacterial, Chinese hamster ovary (CHO), lower eukaryotic, fungal, yeast, *Pichia*, *Pichia pastoris*) is also part of the present disclosure ~~invention~~ wherein the host cell comprises an antibody, fragment, polypeptide, polynucleotide and/or vector set forth herein.

In another aspect, the disclosure provides a composition comprising the antibody, antigen-binding fragment, polypeptide, polynucleotide or vector as discussed herein and a pharmaceutically acceptable carrier or diluent; optionally in association with a further therapeutic agent.

In another aspect, the disclosure provides a vaccine comprising an antigen and a pharmaceutically acceptable carrier in association with an antibody or fragment or composition as discussed herein. The present disclosure ~~invention~~ also provides vaccines comprising an antibody or fragment set forth herein, an antigen (*e.g.*, viral peptide antigen, virus-like particle, tumor peptide antigen) and a pharmaceutically acceptable carrier.

In another aspect, the disclosure provides a vessel or injection device comprising the antibody, antigen-binding fragment, composition, polypeptide, polynucleotide or vector as discussed herein; optionally, wherein the vessel or device includes a pharmaceutically acceptable carrier or diluent. The prevent disclosure ~~invention~~ also provides a vessel (*e.g.*, plastic or glass vial) or an injection device (*e.g.*, a syringe such as a pre-filled syringe or an autoinjector) comprising any antibody, fragment, polypeptide, polynucleotide, vector, composition or vaccine discussed herein.

The present disclosure ~~invention~~ also provides a method of treating a cancer (*e.g.*, osteosarcoma, rhabdomyosarcoma, neuroblastoma, kidney cancer, leukemia, renal transitional cell cancer, bladder cancer, Wilm's cancer, ovarian cancer, pancreatic cancer, breast cancer, prostate cancer, bone cancer, lung cancer, gastric cancer, colorectal cancer, cervical cancer, synovial sarcoma, head and neck cancer, squamous cell carcinoma, multiple myeloma, renal cell cancer, retinoblastoma, hepatoblastoma, hepatocellular carcinoma, melanoma, rhabdoid tumor of the kidney, Ewing's sarcoma, chondrosarcoma, brain cancer, glioblastoma, meningioma, pituitary adenoma, vestibular schwannoma, a primitive neuroectodermal tumor, *medulloblastoma, astrocytoma, anaplastic astrocytoma, oligodendroglioma, ependymoma*, choroid plexus papilloma, polycythemia vera, thrombocythemia, idiopathic myelfibrosis, soft tissue sarcoma, thyroid cancer, endometrial cancer, carcinoid cancer or liver cancer, breast cancer or gastric cancer) in a subject, comprising administering to the subject a effective amount of an anti-LAG3 antibody or antigen-binding fragment or vaccine discussed herein optionally, in association with a further therapeutic agent or a therapeutic procedure (*e.g.*, surgical tumorectomy or anti-cancer radiation therapy).

The present disclosure ~~invention~~ also provides a method of administering an anti-LAG3 antibody, fragment, composition, polypeptide, vaccine or polynucleotide discussed herein, or a pharmaceutical composition thereof, to a subject comprising injecting the antibody, fragment, polypeptide, vaccine or polynucleotide into the body of the subject using an injection device; and, optionally, also administering a further therapeutic agent to the subject.

The present disclosure ~~invention~~ also provides a method of producing an anti-LAG3 antibody or antigen-binding fragment thereof or polypeptide discussed herein comprising: a. culturing a host cell comprising a polynucleotide encoding the polypeptide or an immunoglobulin chain of the antibody or fragment in culture medium under conditions favorable to expression of the polynucleotide; and b. optionally, recovering the antibody, fragment or polypeptide from the host

cell and/or culture medium. In an embodiment of the disclosure~~invention~~, the method comprises the step of introducing the polynucleotide into the host cell, *e.g.*, by transformation or transfection.

In another aspect, the ~~The~~ present disclosure ~~invention also~~ provides a method for detecting the presence of a LAG3 peptide or a fragment thereof in a sample comprising contacting the sample with an anti-LAG3 antibody or fragment discussed herein and detecting the presence of a complex between the antibody or fragment and the peptide; wherein detection of the complex indicates the presence of the LAG3 peptide.

In another aspect, the disclosure provides the antibody or fragment as discussed herein for use in antagonizing LAG3 in a human patient.

In another aspect, the disclosure provides use of the antibody or antigen-binding fragment or composition or vaccine as discussed herein in the manufacture of a medicament for the treatment of cancer.

In another aspect, the disclosure provides an antibody or antigen-binding fragment thereof that specifically binds human LAG3 or polypeptide which is the product of the method as discussed herein.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1. Binding of anti-human LAG3 clones to human and cynomolgus monkey LAG3 expressing CHO-K1 cells.

Figure 2. Binding of LAG3 clones to cynomolgous monkey and human primary T-cells.

Figure 3. Three-dimensional structure of human LAG3. The location of the antibody 22D2, 11C9 and 4A10 epitopes are indicated.

Figure 4 (a-c). Heat map indicating regions in human LAG3 which are strongly or weakly protected from deuteration by antibody binding. (a) human LAG3 / 22D2 Difference heatmap; (b) human LAG3 / 11C9 Difference heatmap; (c) human LAG3 / 4A10 Difference heatmap.

Figure 5 (a-b). Combined heatmaps indicating (a) regions on human LAG3 which are protected from deuteration by 22D2, 11C9 and 4A10 binding and (b) the location in human LAG3 mediating MHC2 binding.

Figure 6. Predominant N-linked glycans for monoclonal antibodies produced in Chinese hamster ovary cells (CHO N-linked glycans) and in engineered yeast cells (engineered yeast N-linked glycans): squares: N-acetylglucosamine (GlcNac); circles: mannose (Man); diamonds: galactose (Gal); triangles: fucose (Fuc).

Figure 7. Effect of anti-human LAG-3 antibody treatment +/- anti-PD-1 treatment on IL-2 production in SEB stimulated human PBMCs. PBMC were activated by SEB for 3 days and IL-2 concentration in culture supernatants was determined by MSD. Donor 090 : SEB 60 ng/mL, Donor 089 : SEB 30 ng/mL. Anti-PD1 was used at 10 μg/mL.

Figure 8. Effect of hu22D2 treatment +/- anti-PD-1 treatment on IFN-γ and TNFα production in MLR stimulated human PBMCs. PBMC were activated with allogeneic monocyte-derived DC for 7 days and IFN-γ and TNF-α concentration in culture supernatants was determined by MSD. Anti-PD-1 was used at 3 μg/mL. Isotype was used at 200nM.

plicamycin, PLX8394, poly-ICLC, porfimer, prednisone, procarbazine, progestins, PSK, PX-866, R-763, raloxifene, raltitrexed, razoxin, ridaforolimus, rituximab, romidepsin, RTA744, rubitecan, scriptaid, Sdx102, seliciclib, selumetinib, semaxanib, SF1126, sirolimus, SN36093, sorafenib, spironolactone, squalamine, SR13668, streptozocin, SU6668, suberoylanalide hydroxamic acid, sunitinib, synthetic estrogen, talampanel, talimogene laherparepvec, tamoxifen, temozolomide, temsirolimus, teniposide, tesmilifene, testosterone, tetrandrine, TGX-221, thalidomide, 6-thioguanine, thiotepa, ticilimumab, tipifarnib, tivozanib, TKI-258, TLK286, TNFα, topotecan, toremifene citrate, trabectedin, trametinib, trastuzumab, tretinoin, trichostatin A, triciribinephosphate monohydrate, triptorelin pamoate, TSE-424, uracil mustard, valproic acid, valrubicin, vandetanib, vatalanib, VEGF trap, vemurafenib, vinblastine, vincristine, vindesine, vinorelbine, vitaxin, vitespan, vorinostat, VX-745, wortmannin, Xr311, zanolimumab, ZK186619, ZK-304709, ZM336372, ZSTK474, Z-100, casopitant, netupitant, palonosetron, aprepitant, diphenhydramine, hydroxyzine, metoclopramide, lorazepam, alprazolam, haloperidol, droperidol, dronabinol, dexamethasone, methylprednisolone, prochlorperazine, granisetron, ondansetron, dolasetron, tropisetron, GCSF, PEG-GCSF, erythropoietin, epoetin alfa, darbepoetin alfa, a Bruton's tyrosine kinase (BTK) inhibitor, a prostate specific antigen vaccine, azacitidine, eribulin mesylate, lenvatinib mesylate, epacadostat, an anti-4-1BB agonist antibody or antigen-binding fragment, crizotinib, a CSF1 receptor kinase inhibitor, entinostat, birinapant, and niraparib.

20. ~~A method for antagonizing LAG3 in a human patient in need thereof comprising administering, to the subject, an effective amount of t~~The antibody or fragment of any one of claims 1-10 for use in antagonizing LAG3 in a human patient.

21. Use of ~~A method of treating a cancer in a subject, comprising administering to the subject an effective amount of~~ the antibody or antigen-binding fragment or composition or vaccine of any one of claims 1-11, 16 and 17 in the manufacture of a medicament for the treatment of cancer~~optionally, in association with a therapeutic procedure~~.

22. The ~~method~~ use of claim 21 wherein the cancer is a member selected from the group consisting of cancer, metastatic cancer, a solid tumor, a hematologic cancer, leukemia, lymphoma, osteosarcoma, rhabdomyosarcoma, neuroblastoma, kidney cancer, leukemia, renal transitional cell cancer, bladder cancer, Wilm's cancer, ovarian cancer, pancreatic cancer, breast cancer, prostate cancer, bone cancer, lung cancer, non-small cell lung cancer, gastric cancer, colorectal cancer, cervical cancer, synovial sarcoma, head and neck cancer, squamous cell carcinoma,

multiple myeloma, renal cell cancer, retinoblastoma, hepatoblastoma, hepatocellular carcinoma, melanoma, rhabdoid tumor of the kidney, Ewing's sarcoma, chondrosarcoma, brain cancer, glioblastoma, meningioma, pituitary adenoma, vestibular schwannoma, a primitive neuroectodermal tumor, medulloblastoma, astrocytoma, anaplastic astrocytoma, oligodendroglioma, ependymoma, choroid plexus papilloma, polycythemia vera, thrombocythemia, idiopathic myelfibrosis, soft tissue sarcoma, thyroid cancer, endometrial cancer, carcinoid cancer or liver cancer, breast cancer and gastric cancer.

~~23. A method of administering the antibody, antigen-binding fragment, composition, polypeptide, vaccine, vector or polynucleotide of any of claims 1-14, 16 and 17, to a subject, comprising injecting the antibody, fragment, polypeptide, vaccine or polynucleotide into the body of the subject using an injection device; and, optionally, also administering a further therapeutic agent or therapeutic procedure to the subject.~~

~~24~~23. A method of producing an antibody or antigen-binding fragment thereof or polypeptide according to any one of claims 1-10 and 12 comprising:

a. culturing a host cell comprising a polynucleotide encoding the polypeptide or an immunoglobulin chain of the antibody or antigen-binding fragment in a culture medium under conditions favorable to expression of the polynucleotide; and

b. optionally, recovering the antibody, antigen-binding fragment or polypeptide from the host cell and/or culture medium.

~~25~~24. The method of claim ~~24~~23 wherein the host cell is a Chinese hamster ovary cell.

~~26~~25. An antibody or antigen-binding fragment thereof that specifically binds human LAG3 or polypeptide which is the product of the method of any one or claims ~~24~~23-~~25~~24.

~~27~~26. A method for detecting the presence of a LAG3 peptide or a fragment thereof in a sample comprising contacting the sample with an antibody or antigen-binding fragment of any one of claims 1-10 and detecting the presence of a complex between the antibody or fragment and the peptide; wherein detection of the complex indicates the presence of the LAG3 peptide.