

ANTI-L1CAM ANTIBODIES AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is the Singaporean National Phase of International Application No. PCT/IB2019/055472, filed on June 27, 2019, which claims priority to U.S. Provisional Application No. 62/865,871, filed June 24, 2019 and Korean Application No. 10-2018-0075955, filed June 29, 2018, each of which is herein incorporated by reference in its entirety.

REFERENCE TO SEQUENCE LISTING SUBMITTED ELECTRONICALLY

[0002] The content of the electronically submitted sequence listing in ASCII text file (Name: 4372_001SG02_Seqlisting_ST25; Size: 82,889 bytes; and Date of Creation: June 21, 2022) filed with the application is incorporated herein by reference in its entirety.

FIELD OF THE DISCLOSURE

[0003] The present disclosure provides antibodies that specifically bind to L1 Cell Adhesion Molecule (L1CAM), compositions comprising such antibodies, and method of using such antibodies for preventing or treating diseases or conditions which comprise a tumor (*e.g.*, a bile duct cancer, a melanoma, pancreatic cancer, glioma, breast cancer, lymphoma, lung cancer, kidney cancer, prostate cancer, fibrosarcoma, colon adenocarcinoma, liver cancer, and/or ovarian cancer) in a subject.

BACKGROUND OF THE DISCLOSURE

[0004] L1 Cell Adhesion Molecule (L1CAM) is one of the immunoglobulin superfamily cell adhesion molecules (CAMs) that mediates cell-to-cell adhesion on the cell surface. It has a molecular weight of 200 to 220 kDa. L1CAM was first known as a protein that mediates neuron-neuron adhesion and is involved in neurite outgrowth and neuronal migration. Lee V. *et al.*, *Proc. Natl. Acad. Sci.* 74:5021-5025 (1997); McGuire JC. *et al.*, *Cell*. 15(2):357-365 (1978).

[0005] L1CAM is predominantly expressed in the normal human brain. In addition, L1CAM expression is found in some hematopoietic and renal cells, peripheral nerves, intestinal crypt cells, and ganglions, but it is not found in other normal cells. Huszar M. *et al.*, *Human Pathology* 37:1000-1008 (2006).

CLAIMS

1. An isolated antibody or antigen-binding fragment thereof that specifically binds to L1 Cell Adhesion Molecule (L1CAM), wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (VH) complementarity determining region 1 (CDR1), CDR2, and CDR3 and a light chain variable region (VL) CDR1, CDR2, and CDR3;
- (i) wherein the VH CDR1, VH CDR2, and VH CDR3 comprises RFGMH (SEQ ID NO: 2), FISNEGSNKYYADSVKG (SEQ ID NO: 10), and GRAYGSGSLFDP (SEQ ID NO: 4), respectively; and wherein the VL CDR1, VL CDR2, and VL CDR3 comprises RASRTISSYVN (SEQ ID NO: 12), AASNLHS (SEQ ID NO: 7), and QQSIGRGPVT (SEQ ID NO: 13), respectively;
- (ii) wherein the VH CDR1, VH CDR2, and VH CDR3 comprises RFGMH (SEQ ID NO: 2), FISNEGSNKYYADSVKG (SEQ ID NO: 10), and GRAYGSGSLFDP (SEQ ID NO: 4), respectively; and wherein the VL CDR1, VL CDR2, and VL CDR3 comprises RASRTISSYVN (SEQ ID NO: 12), AASNLHS (SEQ ID NO: 7), and QQAGFYSPWT (SEQ ID NO: 17), respectively;
- (iii) wherein the VH CDR1, VH CDR2, and VH CDR3 comprises RFGMH (SEQ ID NO: 2), FISNEGSNKYYADSVKG (SEQ ID NO: 10), and GRAYGSGSLFDP (SEQ ID NO: 4), respectively; and wherein the VL CDR1, VL CDR2, and VL CDR3 comprises RASRTISSYVN (SEQ ID NO: 12), AASNLHS (SEQ ID NO: 7), and QQAGFYTPWT (SEQ ID NO: 15), respectively;
- (iv) wherein the VH CDR1, VH CDR2, and VH CDR3 comprises RFGMH (SEQ ID NO: 2), FISNEGSNKYYADSVKG (SEQ ID NO: 10), and GRAYGSGSLFDP (SEQ ID NO: 4), respectively; and wherein the VL CDR1, VL CDR2, and VL CDR3 comprises RASRTISSYVN (SEQ ID NO: 12), AASNLHS (SEQ ID NO: 7), and QQSLHFYPWT (SEQ ID NO: 19), respectively; or

(v) wherein the VH CDR1, VH CDR2, and VH CDR3 comprises RFGMH (SEQ ID NO: 2), FISNEGSNKYYADSVKG (SEQ ID NO: 10), and GRAYGSGSLFDP (SEQ ID NO: 4), respectively; and

wherein the VL CDR1, VL CDR2, and VL CDR3 comprises RASRTISSYVN (SEQ ID NO: 12), AASNLS (SEQ ID NO: 7), and QQSLVWYPWT (SEQ ID NO: 21), respectively.

2. The antibody or antigen-binding fragment thereof of claim 1, comprising a heavy chain CDR1, CDR2, and CDR3 and a light chain CDR1, CDR2, and CDR3, wherein the light chain CDR1 comprises RASRTISSYVN (SEQ ID NO: 12), the light chain CDR2 comprises AASNLS (SEQ ID NO: 7), the light chain CDR3 comprises QQSIGRGPVT (SEQ ID NO: 13), the heavy chain CDR1 comprises RFGMH (SEQ ID NO: 2), the heavy chain CDR2 comprises FISNEGSNKYYADSVKG (SEQ ID NO: 10), and the heavy chain CDR3 comprises GRAYGSGSLFDP (SEQ ID NO: 4).

3. The antibody or antigen-binding fragment thereof of claim 1 or 2, wherein the antibody or antigen-binding fragment thereof has one or more characteristics of:

- (a) the antibody or antigen-binding fragment thereof exhibits improved productivity;
- (b) the antibody or antigen-binding fragment thereof exhibits improved affinity as measured by the equilibrium dissociation constant (K_D);
- (c) the antibody or antigen-binding fragment thereof exhibits improved isoelectric point (PI) value,
- (d) the antibody or antigen-binding fragment thereof exhibits improved affinity as measured by the association constant (K_A); or
- (e) any combination thereof.

4. The antibody or antigen-binding fragment thereof of claim 3, wherein the improved productivity is at least 55 mg/L, at least 56 mg/L, at least 57 mg/L, at least 58 mg/L, at least 59 mg/L, at least about 60 mg/L, at least about 61 mg/L, at least about 62 mg/L, at least about 63 mg/L, at least about 64 mg/L, at least about 65 mg/L, at least about 66 mg/L, at least about 67 mg/L, at least about 68 mg/L, at least about 69 mg/L, at least about 70 mg/L, at least about 71 mg/L, at least about 72 mg/L, at least about 73 mg/L, at least about 74 mg/L, at least about 75

mg/L, at least about 76 mg/L, at least about 77 mg/L, at least about 78 mg/L, at least about 79 mg/L, at least about 80 mg/L, at least about 81 mg/L, at least about 82 mg/L, at least about 83 mg/L, at least about 84 mg/L, or at least about 85 mg/L;

wherein the improved K_D is less than 2.6×10^{-10} M, less than 2.5×10^{-10} M, less than 2.0×10^{-10} M, less than 1.5×10^{-10} M, less than 1.0×10^{-10} M, less than 9×10^{-11} M, less than 8×10^{-11} M, less than 7×10^{-11} M, less than 6×10^{-11} M, less than 5×10^{-11} M, less than 4×10^{-11} M, less than 3×10^{-11} M, less than 2×10^{-11} M, less than 1×10^{-11} M, less than 9×10^{-12} M, less than 8×10^{-12} M, less than 7×10^{-12} M, less than 6×10^{-12} M, less than 5×10^{-12} M, less than 4×10^{-12} M, less than 3×10^{-12} M, less than 2×10^{-12} M, less than 1×10^{-12} M, less than 9×10^{-13} M, or less than 8×10^{-13} M;

wherein the improved affinity is less than 5×10^{-10} M, less than 4×10^{-10} M, less than 3×10^{-10} M, less than 2×10^{-10} M, less than 1.0×10^{-10} M, less than 9×10^{-11} M, less than 8×10^{-11} M, less than 7×10^{-11} M, less than 6×10^{-11} M, less than 5×10^{-11} M, less than 4×10^{-11} M, less than 3×10^{-11} M, less than 2×10^{-11} M, less than 1×10^{-11} M, less than 9×10^{-12} M, less than 8×10^{-12} M, less than 7×10^{-12} M, less than 6×10^{-12} M, less than 5×10^{-12} M, less than 4×10^{-12} M, less than 3×10^{-12} M, less than 2×10^{-12} M, less than 1×10^{-12} M, less than 9×10^{-13} M, or less than 8×10^{-13} M; and/or

wherein the improved PI Value is less than 9.6, less than 9.5, less than 9.4, less than 9.3, less than 9.2, less than 9.1, less than 9.0, less than 8.9, less than 8.8, less than 8.7, less than 8.6, less than 8.5, less than 8.4, less than 8.3, less than 8.2, less than 8.1, less than 8.0, less than 7.9, less than 7.8, less than 7.7, or less than 7.6.

5. The antibody or antigen-binding fragment thereof of any one of claims 1-4, wherein the VH comprises an amino acid sequence which is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to the amino acid sequence set forth as

EVQLVESGGGVVQPGGSLRLSCAASGFTFSRFGMHWVRQAPGKGLEWVAFISNEGSNKYYADSVKGRFTISRDNSTLYLQMNSLRAEDTAVYYCARGRAYGSGSLFDPWGQGTLVTVSS(SEQ ID NO: 23) and wherein the VL

comprises an amino acid sequence which is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to the amino acid sequence set forth as

DIQLTQSPSSLSASVGDRVTTITCRASRTISSYVNWYRQRP GKAPESLIYAASN LHSGVPSRFSGSGSGTDFTLTISS
LQPEDFATYYCQQSIGRGPVTFGQGTKLEIK (SEQ ID NO: 24);

wherein the VH comprises an amino acid sequence which is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to the amino acid sequence set forth as
EVQLVESGGGVVQPGGSLRLSCAASGFTFSRFGMHWVRQAPGKGLEWVAFISNEGSNKYYADSVKGRFTISRDN SAN
TLYLQMNSLRAEDTAVYYCARGRAYGSGSLFD PWGQGT LVT VSS (SEQ ID NO: 27) and wherein the VL
comprises an amino acid sequence which is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to the amino acid sequence set forth as

DIQLTQSPSSLSASVGDRVTTITCRASRTISSYVNWYRQRP GKAPESLIYAASN LHSGVPSRFSGSGSGTDFTLTISS
LQPEDFATYYCQQAGFYSPWTFGQGTKLEIK (SEQ ID NO: 28);

wherein the VH comprises an amino acid sequence which is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to the amino acid sequence set forth as
EVQLVESGGGVVQPGGSLRLSCAASGFTFSRFGMHWVRQAPGKGLEWVAFISNEGSNKYYADSVKGRFTISRDN SAN
TLYLQMNSLRAEDTAVYYCARGRAYGSGSLFD PWGQGT LVT VSS (SEQ ID NO: 25) and wherein the VL
comprises an amino acid sequence which is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to the amino acid sequence set forth as

DIQLTQSPSSLSASVGDRVTTITCRASRTISSYVNWYRQRP GKAPESLIYAASN LHSGVPSRFSGSGSGTDFTLTISS
LQPEDFATYYCQQAGFYTPWTFGQGTKLEIK (SEQ ID NO: 26);

wherein the VH comprises an amino acid sequence which is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to the amino acid sequence set forth as

EVQLVESGGGVVQPGGSLRLSCAASGFTFSRFGMHWVRQAPGKGLEWVAFISNEGSNKYYADSVKGRFTISRDN
SAN TLYLQMNSLR AEDTAVYYCARGRAYGSGSLFDPWGQGTLVTVSS (SEQ ID NO: 29) and wherein the VL
comprises an amino acid sequence which is at least about 80%, at least about 85%, at least about
90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least
about 99%, or about 100% identical to the amino acid sequence set forth as
DIQLTQSPSSLSASVGDRVTITCRASRTISSYVNWYRQRP GKAPESLIYAASN LHSGVPSRFSGSGSGTDFTLTISS
LPEDFATYYCQQSLHFYPWTFGQGTKLEIK (SEQ ID NO: 30); or

wherein the VH comprises an amino acid sequence which is at least about 80%, at least about
85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least
about 98%, at least about 99%, or about 100% identical to the amino acid sequence set forth as
EVQLVESGGGVVQPGGSLRLSCAASGFTFSRFGMHWVRQAPGKGLEWVAFISNEGSNKYYADSVKGRFTISRDN
SAN TLYLQMNSLR AEDTAVYYCARGRAYGSGSLFDPWGQGTLVTVSS (SEQ ID NO: 31) and wherein the VL
comprises an amino acid sequence which is at least about 80%, at least about 85%, at least about
90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least
about 99%, or about 100% identical to the amino acid sequence set forth as
DIQLTQSPSSLSASVGDRVTITCRASRTISSYVNWYRQRP GKAPESLIYAASN LHSGVPSRFSGSGSGTDFTLTISS
LPEDFATYYC QQSLVWYPWTFGQGTKLEIK (SEQ ID NO: 32).

6. A nucleic acid encoding the antibody or antigen-binding fragment thereof of any one of claims 1-5.
7. A vector comprising the nucleic acid of claim 6.
8. A host cell comprising the vector of claim 7.
9. An immunoconjugate comprising the antibody or antigen-binding fragment thereof of any one of claims 1-5, linked to an agent.

10. A bispecific or multispecific antibody comprising the antibody or antigen-binding fragment thereof of any one of claims 1-5, and an antibody or antigen-binding fragment thereof that binds to an antigen.
11. A composition comprising the antibody or antigen-binding fragment thereof of any one of claims 1-5, and a carrier.
12. A kit comprising the antibody or antigen-binding fragment thereof of any one of claims 1-5.
13. An immune cell comprising the nucleic acid of claim 6.
14. The immune cell of claim 13, which is a T cell or an NK cell.
15. An immune cell which comprises a chimeric antigen receptor comprising the antibody or antigen-binding fragment thereof of any one of claims 1-5.
16. A method of producing an antibody or an antigen-binding fragment thereof which specifically binds to a human L1CAM protein, comprising culturing the cell of claim 8 under suitable conditions and isolating the antibody.
17. Use of the antibody or antigen-binding fragment thereof of any one of claims 1-5 in the manufacture of a medicament for the treatment of a disease or condition comprising a tumor.
18. The use of claim 17, further comprising an additional therapeutic agent.
19. The antibody or antigen-binding fragment thereof of any one of claims 1-5 for use in the treatment of a disease or condition comprising a tumor.

20. An antibody or antigen-binding fragment thereof specifically binding to L1CAM, wherein the antibody or antigen-binding fragment thereof comprises a VH and a VL, wherein the VH of the antibody or antigen-binding fragment thereof comprises SEQ ID NO: 23 and the VL of the antibody or antigen-binding fragment thereof comprises SEQ ID NO: 24.

21. The antibody or antigen-binding fragment thereof of claim 5, wherein the antibody or antigen-binding fragment thereof further comprises a heavy chain (HC) constant region and a light chain (LC) constant region, wherein the HC constant region comprises amino acids 122 to 451 of SEQ ID NO: 38 and the LC constant region comprises amino acids 109 to 215 of SEQ ID NO: 39.