

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_001PC02_SL_ST25.txt~~4372_001SG02_Seqlisting_ST25~~; Size: ~~82,704~~ 82,889 bytes; and Date of Creation: ~~June 27, 2019~~ 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).

~~WHAT IS CLAIMED IS:~~

CLAIMS

1. An isolated antibody or antigen-binding fragment thereof that specifically binds to the same-L1 Cell Adhesion Molecule (L1CAM)-epitope as a reference), wherein

~~1. —the~~ antibody comprising or antigen-binding fragment thereof comprises a heavy chain variable region (VH) ~~and a light chain variable region (VL), wherein:~~

~~(a) the VH of the reference antibody comprises SEQ ID NO: 23 and the VL of the reference antibody comprises SEQ ID NO: 24;~~

~~(b) the VH of the reference antibody comprises SEQ ID NO: 25 and the VL of the reference antibody comprises SEQ ID NO: 26;~~

~~(c) the VH of the reference antibody comprises SEQ ID NO: 27 and the VL of the reference antibody comprises SEQ ID NO: 28;~~

~~(d) the VH of the reference antibody comprises SEQ ID NO: 29 and the VL of the reference antibody comprises SEQ ID NO: 30; or~~

~~(e) the VH of the reference antibody comprises SEQ ID NO: 31 and the VL of the reference antibody comprises SEQ ID NO: 32.~~

~~The antibody or antigen binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises VH complementarity determining region 1 (CDR1), VH CDR2, and VH CDR3; and a light chain variable region (VL) CDR1, VL CDR2, and VL CDR3;~~

2. ~~—(i) wherein at least one amino acid in the VH CDR1, VH CDR2, and VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3 of the antibody or antigen-binding fragment thereof is different from the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3 of the mAb417 antibody, and wherein~~

~~the VH CDR1 of the mAb417 antibody comprises RFGMH (SEQ ID NO: 2);~~

~~the VH CDR2 of the mAb417 antibody comprises FISNDGSNKYYADSVKG);~~
FISNEGSNKYYADSVKG (SEQ ID NO: 9);

~~the VH CDR3 of the mAb417 antibody comprises 10), and~~ GRAYGSGSLFDP (SEQ ID NO: ~~10~~;4),
respectively; and

wherein the VL CDR1 of the mAb417 antibody, VL CDR2, and VL CDR3 comprises
RASRTISYVNRASRTISSYVN (SEQ ID NO: 6);

~~the VL CDR2 of the mAb417 antibody comprises 12), AASNLHS (SEQ ID NO: 7);), and~~
~~the VL CDR3 of the mAb417 antibody comprises QQSIGRGVVT QQSIGRGPVT (SEQ ID NO:~~
~~11)-13), respectively;~~

~~3. — An isolated antibody or antigen-binding fragment thereof that cross-competes for binding~~
~~to an L1 Cell Adhesion Molecule (L1CAM) epitope with a reference antibody comprising a heavy~~
~~chain variable region (VH) and a light chain variable region (VL);(ii) wherein:~~

~~(a) the VH of the reference antibody comprises SEQ ID NO: 23 and the VL of the~~
~~reference antibody comprises SEQ ID NO: 24;~~

~~(b) the VH of the reference antibody comprises SEQ ID NO: 25 and the VL of the~~
~~reference antibody comprises SEQ ID NO: 26;~~

~~(c) the VH of the reference antibody comprises SEQ ID NO: 27 and the VL of the~~
~~reference antibody comprises SEQ ID NO: 28;~~

~~(d) the VH of the reference antibody comprises SEQ ID NO: 29 and the VL of the~~
~~reference antibody comprises SEQ ID NO: 30, or~~

~~(e) the VH of the reference antibody comprises SEQ ID NO: 31 and the VL of the~~
~~reference antibody comprises SEQ ID NO: 32;~~

~~wherein the antibody or antigen-binding fragment thereof comprises VH~~
~~complementarity determining region 1(CDR1),₂ VH CDR2, and VH CDR3, and VL CDR1, VL~~
~~CDR2, and VL CDR3, wherein at least one amino acid in the VH CDR1, VH CDR2, VH CDR3,~~
~~VL CDR1, VL CDR2, and/or VL CDR3 of the antibody or antigen-binding fragment thereof is~~
~~different from the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3 of~~
~~the mAb 417 antibody, and wherein~~

~~the VH CDR1 of the mAb417 antibody comprises~~ RFGMH (SEQ ID NO: 2);

~~the VH CDR2 of the mAb417 antibody comprises FISNDGSNKYYADSVKG),~~
FISNEGSNKYYADSVKG (SEQ ID NO: 9);

~~the VH CDR3 of the mAb417 antibody comprises 10), and~~ GRAYGSGSLFDP (SEQ ID
NO: 10);

~~the VL CDR1 of the mAb417 antibody comprises RASRTISIIYVN (SEQ ID NO: 6);
the VL CDR2 of the mAb417 antibody comprises AASNLIHS (SEQ ID NO: 7); and
the VH CDR3 of the mAb417 antibody comprises QQSIIGRGVVT (SEQ ID NO: 11).~~

~~4. — The antibody or antigen-binding fragment thereof of claim 2 or 3, wherein the at least one amino acid difference is in the VH CDR2 of the antibody or antigen-binding fragment thereof, and wherein the VH CDR2 of the antibody or antigen-binding fragment thereof comprises glutamine at residue 5.~~

~~5. — The antibody or antigen-binding fragment thereof of any one of claims 2 to 4, wherein the at least one amino acid difference is in the VL CDR1 of the antibody or antigen-binding fragment thereof, and wherein the VL CDR1 of the antibody or antigen-binding fragment thereof comprises serine at residue 8.~~

~~6. — The antibody or antigen-binding fragment thereof of any one of claims 2 to 5, wherein the at least one amino acid difference is in the VL CDR3 of the antibody or antigen-binding fragment thereof, and wherein the VL CDR3 of the antibody or antigen-binding fragment thereof comprises proline at residue 8.~~

~~7. — The antibody or antigen-binding fragment thereof of any one of claims 2 to 6, wherein the at least one amino acid difference is in the VL CDR3 of the antibody or antigen-binding fragment thereof, and wherein the VL CDR3 of the antibody or antigen-binding fragment thereof comprises alanine, glycine, phenylalanine, tyrosine, threonine, proline, and tryptophan at residues 3 to 9, respectively.~~

~~8. — The antibody or antigen-binding fragment thereof of any one of claims 2 to 7, wherein the at least one amino acid difference is in the VL CDR3 of the antibody or antigen-binding fragment thereof, and wherein the VL CDR3 of the antibody or antigen-binding fragment thereof comprises alanine, glycine, phenylalanine, tyrosine, serine, proline, and tryptophan at residues 3 to 9, respectively.~~

~~The antibody or antigen-binding fragment thereof of any one of claims 2 to 8, wherein the at least one amino acid difference is in the VL CDR3 of the antibody or antigen-binding fragment thereof, and wherein the VL CDR3 of the antibody or antigen-binding fragment thereof comprises leucine, histidine, phenylalanine, tyrosin, proline and tryptophan at residues 4 to 9,4), respectively; and~~

~~9. — The antibody or antigen-binding fragment thereof of any one of claims 2 to 9, wherein the at least one amino acid difference is in the VL CDR3 of the antibody or antigen-binding fragment thereof, and wherein the VL CDR3 of the antibody or antigen-binding fragment thereof comprises leucine, valine, tryptophan, tyrosine, proline, and tryptophan at residues 4 to 9, respectively.~~

~~10. — The antibody or antigen-binding fragment thereof of any one of claims 2 to 10, wherein the VL CDR3 of the antibody or antigen-binding fragment thereof comprises SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 19, or SEQ ID NO: 21.~~

~~11. — The antibody or antigen-binding fragment thereof of any one of claims 2 to 11, wherein the VH CDR1 of the antibody or antigen-binding fragment thereof comprises RFGMH (SEQ ID NO: 2).~~

~~12. — The antibody or antigen-binding fragment thereof of any one of claims 2 to 12, wherein the VH CDR2 of the antibody or antigen-binding fragment thereof comprises FISNEGSNKYYADSVKG (SEQ ID NO: 10).~~

~~13. — The antibody or antigen-binding fragment thereof of any one of claims 2 to 13, wherein the VH CDR3 of the antibody or antigen-binding fragment thereof comprises GRAYGSGSLFDP (SEQ ID NO: 4).~~

~~14. — The antibody or antigen-binding fragment thereof of any one of claims 2 to 14, wherein the VL CDR1 wherein the VL CDR1, VL CDR2, and VL CDR3 comprises RASRTISSYVN (SEQ ID NO: 12).~~

~~15. The antibody or antigen-binding fragment thereof of any one of claims 2 to 15, wherein the VL CDR2 comprises~~ AASNLHS (SEQ ID NO: 7).

~~16. The antibody or antigen-binding fragment thereof of any one of claims 2 to 16, wherein the VL CDR3 comprises~~ QQSIGRGPVT (SEQ ID NO: 13).

~~17. The antibody or antigen-binding fragment thereof of any one of claims 1 to 17, comprising a heavy chain CDR1, CDR2, and CDR3 and a light chain CDR1, CDR2, and CDR3, wherein the light chain CDR3 comprises~~ QQSIGRGPVT (SEQ ID NO: 13).

~~18. The antibody or antigen-binding fragment thereof of any one of claims 1 to 17, comprising a heavy chain CDR1, CDR2, and CDR3 and a light chain CDR1, CDR2, and CDR3, wherein the light chain CDR3 comprises~~ QQAGFYTPWT (SEQ ID NO: 15).

~~The antibody or antigen-binding fragment thereof of any one of claims 1 to 17, comprising a heavy chain CDR1, CDR2, and CDR3 and a light chain CDR1, CDR2, and CDR3, wherein the light chain CDR3 comprises~~ 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), AASNLHS (SEQ ID NO: 7), and QQSLVWYPWT (SEQ ID NO: 21), respectively.

~~19.~~ 2. The antibody or antigen-binding fragment thereof of ~~any one of claims~~ claim 1 to 17, comprising a heavy chain CDR1, CDR2, and CDR3 and a light chain CDR1, CDR2, and CDR3, wherein the light chain ~~CDR3~~ CDR1 comprises ~~QQSLHFYPWT~~ RASRTISSYVN (SEQ ID NO: ~~19~~).

~~The antibody or antigen-binding fragment thereof of any one of claims 1 to 17, comprising a heavy chain CDR1, CDR2, and CDR3 and a 12), the light chain CDR1, CDR2, and CDR3, wherein comprises AASNLHS (SEQ ID NO: 7), the light chain CDR3 comprises QQSLVWYPWT (SEQ ID NO: 21) 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 ~~any one of claims~~ claim 1 to 22 or 2, wherein the antibody or antigen-binding fragment thereof has one or more characteristics ~~selected from the group consisting 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.

~~20. The antibody or antigen-binding fragment thereof of any one of claims 1 to 23, wherein the antibody or antigen-binding fragment thereof exhibits improved productivity compared to the mAb417 antibody.~~

4. The antibody or antigen-binding fragment thereof of claim ~~24~~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, ~~when expressed according to example 3;~~

~~21. The antibody or antigen-binding fragment thereof of any one of claims 1 to 25, wherein the antibody or antigen-binding fragment thereof exhibits improved K_D compared to the mAb417 antibody.~~

~~The antibody or antigen-binding fragment thereof of claim 26,~~

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;

~~22. The antibody or antigen-binding fragment thereof of any one of claims 1 to 27, wherein the antibody or antigen-binding fragment thereof exhibits improved affinity (K) compared to the mAb417 antibody.~~

~~The antibody or antigen-binding fragment thereof of claim 28, wherein the improved affinity (K)~~

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

~~23. The antibody or antigen binding fragment thereof of any one of claims 1 to 29, wherein the antibody or antigen binding fragment thereof exhibits improved PI value compared to the mAb417 antibody.~~

~~The antibody or antigen binding fragment thereof of claim 30,~~

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.

~~24. An isolated antibody or antigen binding fragment thereof specifically binding to L1CAM, wherein the antibody or antigen binding fragment thereof comprises a VH CDR1, CDR2, and CDR3 and a VL CDR1, CDR2, and CDR3;~~

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

~~wherein the VL CDR1, CDR2, and CDR3 comprises RASRTISSYVN (SEQ ID NO: 12), AASNLHS (SEQ ID NO: 7), and QQSI GRGPVT (SEQ ID NO: 13), respectively.~~

~~25. An isolated antibody or antigen binding fragment thereof specifically binding to L1CAM, wherein the antibody or antigen binding fragment thereof comprises a VH CDR1, CDR2, CDR3 and a VL CDR1, CDR2, CDR3;~~

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

wherein the VL CDR1, CDR2, and CDR3 comprises ~~RASRTISSYVN (SEQ ID NO: 12), AASNLS (SEQ ID NO: 7), and QQAGFYSPWT (SEQ ID NO: 17), respectively.~~

~~26. — An isolated antibody or antigen-binding fragment thereof specifically binding to L1CAM, wherein the antibody or antigen-binding fragment thereof comprises a VH CDR1, CDR2, CDR3 and a VL CDR1, CDR2, CDR3;~~

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

~~wherein the VL CDR1, CDR2, and CDR3 comprises RASRTISSYVN (SEQ ID NO: 12), AASNLS (SEQ ID NO: 7), and QQAGFYTPWT (SEQ ID NO: 17), respectively.~~

~~27. — An isolated antibody or antigen-binding fragment thereof specifically binding to L1CAM, wherein the antibody or antigen-binding fragment thereof comprises a VH CDR1, CDR2, CDR3 and a VL CDR1, CDR2, CDR3;~~

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

~~wherein the VL CDR1, CDR2, and CDR3 comprises RASRTISSYVN (SEQ ID NO: 12), AASNLS (SEQ ID NO: 7), and QQSLHFYTPWT (SEQ ID NO: 19), respectively.~~

~~28. — An isolated antibody or antigen-binding fragment thereof specifically binding to L1CAM, wherein the antibody or antigen-binding fragment thereof comprises a VH CDR1, CDR2, CDR3 and a VL CDR1, CDR2, CDR3;~~

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

~~wherein the VL CDR1, CDR2, and CDR3 comprises RASRTISSYVN (SEQ ID NO: 12), AASNLS (SEQ ID NO: 7), and QQSLVWYTPWT (SEQ ID NO: 19), respectively.~~

~~29. — 5. —~~ The antibody or antigen-binding fragment thereof of any one of claims 1 ~~to 36~~ 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 ~~EVQLVESGGG WQPGGSLRLSCAASGFTFSRFGMHWVRQAPGKGLEWVAFISNEGSNKYYADSVKGRFTISRDN S~~ ~~ANTLYLQMNSLRAEDTAVYYCARGRAYGSGSLFDPWCQGTTLVTVSS (SEQ ID NO: 23).~~

~~The antibody or antigen-binding fragment thereof of any one of claims 1 to~~

~~37, EVQLVESGGGVVQPGGSLRLSCAASGFTFSRFGMHWVRQAPGKGLEWVAFISNEGSNKYYAD SVKGRFTISRDN S~~ ~~ANTLYLQMNSLRAEDTAVYYCARGRAYGSGSLFDPWCQGTTLVTVSS (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 ~~DIQLTQSPSS~~

~~LSASVGDRVTITCRASRTISSYVNWYRQRP GKAPESLIYAASN LHSGVPSRFS GSGSGTDFTLT ISSLPEDFATYYCQQSIGRGPVTFGQGTKLEIK (SEQ ID NO: 24).~~

~~DIQLTQSPSSLSASVGDRVTITCRASRTISSYVNWYRQRP GKAPESLIYAASN LHSGVPSRFS GSGSGTDFTLT ISSLPEDFATYYCQQSIGRGPVTFGQGTKLEIK (SEQ ID NO: 24);~~

~~The antibody or antigen-binding fragment thereof of any one of claims 1 to 38,~~

~~30.~~—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 ~~EVQLVESGGG~~

~~WQPGGSLRLSCAASGFTFSRFGMHWVRQAPGKGLEWVAFISNEGSNKYYADSVKGRFTISRDN S~~ ~~ANTLYLQMNSLRAEDTAVYYCARGRAYGSGSLFDPWCQGTTLVTVSS (SEQ ID NO: 27).~~

~~The antibody or antigen-binding fragment thereof of any one of claims 1 to~~

~~39, EVQLVESGGGVVQPGGSLRLSCAASGFTFSRFGMHWVRQAPGKGLEWVAFISNEGSNKYYAD SVKGRFTISRDN S~~ ~~ANTLYLQMNSLRAEDTAVYYCARGRAYGSGSLFDPWCQGTTLVTVSS (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 ~~DIQLTQSPSS~~

~~LSASVGDRVITITCRASRTISSYVNWYRQRPCKAPESLIYAASNLSHSGVPSRFSGSGSGCTDFTLT
ISSLQPEDFATYYCQQAGFYSPWTFGQGTKLEIK (SEQ ID NO: 28).~~

~~DIQLTQSPSSLSASVGDRVITITCRASRTISSYVNWYRQRPCKAPESLIYAASNLSHSGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYCQQAGFYSPWTFGQGTKLEIK (SEQ ID NO: 28);~~

~~The antibody or antigen-binding fragment thereof of any one of claims 1 to 40,~~

31.—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
EVQLVESGGG

~~WQPGGSLRLSCAASGFTFSRFGMHWRQAPCKGLEWVAFISNEGSNKYYADSVKGRFTISRDN
ANTLYLQMNSLRAEDTAVYYCARGRAYGSGSLFDPWGQGTTLTVSS (SEQ ID NO: 25).~~

~~The antibody or antigen-binding fragment thereof of any one of claims 1 to~~

~~41, EVQLVESGGGVVQPGGSLRLSCAASGFTFSRFGMHWRQAPCKGLEWVAFISNEGSNKYYAD
SVKGRFTISRDN~~

~~ANTLYLQMNSLRAEDTAVYYCARGRAYGSGSLFDPWGQGTTLTVSS (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 ~~DIQLTQSPSS~~

~~LSASVGDRVITITCRASRTISSYVNWYRQRPCKAPESLIYAASNLSHSGVPSRFSGSGSGCTDFTLT
ISSLQPEDFATYYCQQAGFYTPWTFGQGTKLEIK (SEQ ID NO: 26).~~

~~DIQLTQSPSSLSASVGDRVITITCRASRTISSYVNWYRQRPCKAPESLIYAASNLSHSGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYCQQAGFYTPWTFGQGTKLEIK (SEQ ID NO: 26);~~

~~The antibody or antigen-binding fragment thereof of any one of claims 1 to 42,~~

32.—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
EVQLVESGGG

~~WQPGGSLRLSCAASGFTFSRFGMHWRQAPCKGLEWVAFISNEGSNKYYADSVKGRFTISRDN
ANTLYLQMNSLRAEDTAVYYCARGRAYGSGSLFDPWGQGTTLTVSS (SEQ ID NO: 29).~~

~~The antibody or antigen-binding fragment thereof of any one of claims 1 to~~

~~43, EVQLVESGGGVVQPGGSLRLSCAASGFTFSRFGMHWVRQAPGKGLEWVAFISNEGSNKYYADSVKGRFTISRDN~~

~~SANTLYLQMNSLRAEDTAVYYCARGRAYGSGSLFDPWGQGTLVTVSS (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 LHSGVPSRFSGSGSGTDFTLT

~~33. The antibody or antigen-binding fragment thereof of any one of claims 1 to 44, 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~~

~~The antibody or antigen-binding fragment thereof of any one of claims 1 to~~

~~45, EVQLVESGGGVVQPGGSLRLSCAASGFTFSRFGMHWVRQAPGKGLEWVAFISNEGSNKYYADSVKGRFTISRDN~~

~~SANTLYLQMNSLRAEDTAVYYCARGRAYGSGSLFDPWGQGTLVTVSS (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 ~~DIQLTQSPSS~~

~~LSASVGDRVTITCRASRTISSYVNWYRQRP GKAPESLIYAASN LHSGVPSRFSGSGSGTDFTLT~~
~~ISSLQPEDFATYYC~~DIQLTQSPSSLSASVGDRVTITCRASRTISSYVNWYRQRP GKAPESLIYA
ASN LHSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQSLVWYPWTFGQGTKLEIK (SEQ ID NO: 32).

~~The 6. A nucleic acid encoding the antibody or antigen-binding fragment thereof of any one of claims 1 to 46, 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. 5.~~

~~34. — The antibody or antigen-binding fragment thereof of any one of claims 1 to 46, wherein the VH of the antibody or antigen-binding fragment thereof comprises SEQ ID NO: 25 and the VL of the antibody or antigen-binding fragment thereof comprises SEQ ID NO: 26.~~

~~35. — The antibody or antigen-binding fragment thereof of any one of claims 1 to 46, wherein the VH of the antibody or antigen-binding fragment thereof comprises SEQ ID NO: 27 and the VL of the antibody or antigen-binding fragment thereof comprises SEQ ID NO: 28.~~

~~36. — The antibody or antigen-binding fragment thereof of any one of claims 1 to 46, wherein the VH of the antibody or antigen-binding fragment thereof comprises SEQ ID NO: 29 and the VL of the antibody or antigen-binding fragment thereof comprises SEQ ID NO: 30.~~

~~37. — The antibody or antigen-binding fragment thereof of any one of claims 1 to 46, wherein the VH of the antibody or antigen-binding fragment thereof comprises SEQ ID NO: 31 and the VL of the antibody or antigen-binding fragment thereof comprises SEQ ID NO: 32.~~

~~38. — An antibody or antigen-binding fragment thereof specifically binding to L1CAM, which comprises a heavy chain (HC) and a light chain (LC), wherein the HC of the antibody or antigen-binding fragment thereof comprises SEQ ID NO: 38 and the LC of the antibody or antigen-binding fragment thereof comprises SEQ ID NO: 39.~~

~~39. — An antibody or antigen-binding fragment thereof specifically binding to L1CAM, which comprises a heavy chain (HC) and a light chain (LC), wherein the HC of the antibody or antigen-binding fragment thereof comprises SEQ ID NO: 40 and the LC of the antibody or antigen-binding fragment thereof comprises SEQ ID NO: 41.~~

~~40. — An antibody or antigen binding fragment thereof specifically binding to L1CAM, which comprises a heavy chain (HC) and a light chain (LC), wherein the HC of the antibody or antigen binding fragment thereof comprises SEQ ID NO: 42 and the LC of the antibody or antigen binding fragment thereof comprises SEQ ID NO: 43.~~

~~41. — An antibody or antigen binding fragment thereof specifically binding to L1CAM, which comprises a heavy chain (HC) and a light chain (LC), wherein the HC of the antibody or antigen binding fragment thereof comprises SEQ ID NO: 44 and the LC of the antibody or antigen binding fragment thereof comprises SEQ ID NO: 45.~~

~~42. — An antibody or antigen binding fragment thereof specifically binding to L1CAM, which comprises a heavy chain (HC) and a light chain (LC), wherein the HC of the antibody or antigen binding fragment thereof comprises SEQ ID NO: 46 and the LC of the antibody or antigen binding fragment thereof comprises SEQ ID NO: 20.~~

~~43. — The antibody of any one of claims 1 to 56, wherein the antibody is selected from the group consisting of an IgG1, IgG2, IgG3, IgG4, a variant thereof, and any combination thereof.~~

~~44. — The antibody of any one of claims 1 to 57, which is a chimeric antibody, a human antibody, or a humanized antibody.~~

~~45. — The antibody of any one of claims 1 to 56, comprises a Fab, a Fab', a F(ab')₂, a Fv, or a single chain Fv (scFv).~~

~~46. — A nucleic acid encoding the antibody of any one of claims 1 to 59.~~

7. A vector comprising the nucleic acid of claim ~~60~~6.

8. A host cell comprising the vector of claim ~~61~~7.

~~47. The host cell of claim 63, which is selected from the group consisting of *E. coli*, *Pseudomonas*, *Bacillus*, *Streptomyces*, yeast, CHO, YB/20, NS0, PER-C6, HEK-293T, NIH-3T3, HeLa, BHK, Hep-G2, SP2/0, R1.1, B-W, L-M, COS-1, COS-7, BSC1, BSC40, BMT10 cell, plant cell, insect cell, and human cell in tissue culture.~~

9. An immunoconjugate comprising the antibody or antigen-binding fragment thereof of any one of claims 1 ~~to 59~~ 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 ~~to 59~~ 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 ~~to 59~~, ~~the nucleic acid of claim 60, the vector of claim 61, the cell of claim 62 or 63, the immunoconjugate of claim 64, or the bispecific or multispecific antibody of claim 65~~ 5, and a carrier.

12. A kit comprising the antibody or antigen-binding fragment thereof of any one of claims 1 ~~to 59~~, ~~the nucleic acid of claim 60, the vector of claim 61, the cell of claim 62 or 63, the immunoconjugate of claim 64, or the bispecific or multispecific antibody of claim 65~~, and an instruction for use 5.

13. An immune cell comprising the nucleic acid of claim ~~60 or the vector of claim 61~~ 6.

14. The immune cell of claim ~~68~~ 13, which is a T cell or an NK cell.

~~The~~ 15. An immune cell ~~of claim 68 or 69~~, which comprises a chimeric antigen receptor comprising the antibody or antigen-binding fragment thereof of any one of claims 1 ~~to 59~~ 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 ~~62 or 63~~ under suitable conditions and isolating the antibody.

~~A method~~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 ~~in a subject in need thereof,~~ comprising ~~administering to the subject the antibody of any one of claims 1 to 59, the nucleic acid~~ tumor.

18. The use of claim ~~60, the vector of claim 61, the cell of claim 62 or 63, the immunoeconjugate of claim 64, the bispecific or multispecific~~ 17, further comprising an additional therapeutic agent.

~~48.—~~19. The antibody of claim 65, the composition of claim 66, or the immune cell or antigen-binding fragment thereof of any one of claims ~~68 to 70.~~

~~The method of claim 72, wherein~~ 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 ~~tumor.~~ 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.

~~49.—~~21. The ~~method~~ antibody or antigen-binding fragment thereof of claim ~~72 or 73~~ 5, wherein the ~~tumor~~ antibody or antigen-binding fragment thereof further comprises a ~~bile duct cancer,~~ heavy chain (HC) constant region and a ~~melanoma, pancreatic cancer, glioma, breast cancer, lymphoma, lung cancer, kidney cancer, prostate cancer, fibrosarcoma, colon adenocarcinoma, liver cancer, or ovarian cancer.~~

50. ~~The method of claim 74~~light chain (LC) constant region, wherein the ~~tumor is a bile duct cancer.~~

51. ~~The method of any one of claims 72~~HC constant region comprises amino acids 122 to 75,
~~wherein~~451 of SEQ ID NO: 38 and ~~the antibody, the nucleic acid, the vector, the cell, the~~
~~immunoconjugate, the bispecific or multispecific antibody, the composition, or the immune cell~~
~~suppresses growth of the tumor.~~

52. ~~The method of any one of claims 72~~LC constant region comprises amino acids 109 to 76,
~~wherein the antibody, the nucleic acid, the vector, the cell, the immunoconjugate, the composition,~~
~~or the immune cell enhances infiltration of immune cells into the tumor.~~

53. ~~The method of any one of claims 72 to 77, comprising administering an additional~~
~~therapeutic agent.~~

54. ~~The method of claim 78, wherein the additional therapeutic agent comprises a~~
~~chemotherapy, immunotherapy, radiotherapy, or combinations thereof.~~

~~The method of claim 79, wherein the additional therapeutic agent is an immune checkpoint~~
~~inhibitor~~215 of SEQ ID NO: 39.