

CLAIMS

1. An anti-CLDN18.2 antibody or an antigen-binding fragment thereof, comprising a heavy chain variable region and a light chain variable region, the heavy chain variable region comprises heavy chain HCDR1, HCDR2 and HCDR3 sequences, and the light chain variable region comprises light chain LCDR1, LCDR2 and LCDR3 sequences, wherein:

the HCDR1 sequence comprises GYNMN (SEQ ID NO: 1), or **TYFIGVG** (SEQ ID NO: 13);

the HCDR2 sequence comprises **X₁IDPYYX₂X₃TX₄YNQKFX₅G** (SEQ ID NO: 32), or HIWWNDNKYYNTALKS (SEQ ID NO: 15);

the HCDR3 sequence comprises **X₆X₇X₈GNAFDY** (SEQ ID NO: 33), or MGSGAWFTY (SEQ ID NO: 17);

the LCDR1 sequence comprises **KSSQX₉LX₁₀NX₁₁GNX₁₂KNYLT** (SEQ ID NO: 34);

the LCDR2 sequence comprises **WASTRX₁₃S** (SEQ ID NO: 35);

the LCDR3 sequence comprises **QNDYX₁₄X₁₅PX₁₆T** (SEQ ID NO: 36);

wherein X₁ is N or Y or H, X₂ is G or V, X₃ is A or G or T, X₄ is R or T or S, X₅ is K or R, X₆ is S or M, X₇ is Y or F, X₈ is Y or H, X₉ is S or N, X₁₀ is L or F, X₁₁ is S or N, X₁₂ is Q or L, X₁₃ is E or K, X₁₄ is S or Y, X₁₅ is F or Y and X₁₆ is F or L, and wherein:

(a) the heavy chain variable region comprises a HCDR1 comprising the sequence of SEQ ID NO: 1, a HCDR2 comprising the sequence of SEQ ID NO: 3, and a HCDR3 comprising the sequence of SEQ ID NO: 5; and the light chain variable region comprises a LCDR1 comprising the sequence of SEQ ID NO: 2, a LCDR2 comprising the sequence of SEQ ID NO: 4, and a LCDR3 comprising the sequence of SEQ ID NO: 6;

(b) the heavy chain variable region comprises a HCDR1 comprising the sequence of SEQ ID NO: 1, a HCDR2 comprising the sequence of SEQ ID NO: 7, and a HCDR3 comprising the sequence of SEQ ID NO: 5; and the light chain variable region comprises a LCDR1 comprising the sequence of SEQ ID NO: 2, a LCDR2

comprising the sequence of SEQ ID NO: 4, and a LCDR3 comprising the sequence of SEQ ID NO: 8;

(c) the heavy chain variable region comprises a HCDR1 comprising the sequence of SEQ ID NO: 1, a HCDR2 comprising the sequence of SEQ ID NO: 9, and a HCDR3 comprising the sequence of SEQ ID NO: 11; and the light chain variable region comprises a LCDR1 comprising the sequence of SEQ ID NO: 10, a LCDR2 comprising the sequence of SEQ ID NO: 4, and a LCDR3 comprising the sequence of SEQ ID NO: 6;

(d) the heavy chain variable region comprises a HCDR1 comprising the sequence of SEQ ID NO: 13, a HCDR2 comprising the sequence of SEQ ID NO: 15, and a HCDR3 comprising the sequence of SEQ ID NO: 17; and the light chain variable region comprises a LCDR1 comprising the sequence of SEQ ID NO: 2, a LCDR2 comprising the sequence of SEQ ID NO: 4, and a LCDR3 comprising the sequence of SEQ ID NO: 12;

(e) the heavy chain variable region comprises a HCDR1 comprising the sequence of SEQ ID NO: 1, a HCDR2 comprising the sequence of SEQ ID NO: 19, and a HCDR3 comprising the sequence of SEQ ID NO: 21; and the light chain variable region comprises a LCDR1 comprising the sequence of SEQ ID NO: 14, a LCDR2 comprising the sequence of SEQ ID NO: 16, and a LCDR3 comprising the sequence of SEQ ID NO: 18; or

(f) the heavy chain variable region comprises a HCDR1 comprising the sequence of SEQ ID NO: 1, a HCDR2 comprising the sequence of SEQ ID NO: 22, and a HCDR3 comprising the sequence of SEQ ID NO: 5; and the light chain variable region comprises a LCDR1 comprising the sequence of SEQ ID NO: 20, a LCDR2 comprising the sequence of SEQ ID NO: 4, and a LCDR3 comprising the sequence of SEQ ID NO: 6.

2. The antibody or an antigen-binding fragment thereof of claim 1, further comprising one or more of heavy chain HFR1, HFR2, HFR3 and HFR4, and/or one or more of light chain LFR1, LFR2, LFR3 and LFR4, wherein:

the HFR1 comprises **QVQLVQSGAEVKKPGASVKVSCKASGYX₁₇FT** (SEQ ID NO: 54) or a homologous sequence of at least 80% sequence identity thereof,

the HFR2 comprises **WVX₁₈QAPGQGLEWX₁₉G** (SEQ ID NO: 55) or a homologous sequence of at least 80% sequence identity thereof,

the HFR3 sequence comprises **RVTX₂₀TIDKSTSTVYMELSSLRSEDTAVYYCAR** (SEQ ID NO: 56) or a homologous sequence of at least 80% sequence identity thereof,

the HFR4 comprises **WGQGTTVTVSS** (SEQ ID NO: 57) or a homologous sequence of at least 80% sequence identity thereof,

the LFR1 comprises **DIVMTQSPDSLAVSLGERATX₂₁NC** (SEQ ID NO: 58) or a homologous sequence of at least 80% sequence identity thereof,

the LFR2 comprises **WYQQKPGQPPKLLIY** (SEQ ID NO: 59) or a homologous sequence of at least 80% sequence identity thereof,

the LFR3 comprises **GVPDRFX₂₂GSGSGTDFTLTISSLQAEDVAVYYC** (SEQ ID NO: 60) or a homologous sequence of at least 80% sequence identity thereof, and

the LFR4 comprises **FGGGTKVEIK** (SEQ ID NO: 61) or a homologous sequence of at least 80% sequence identity thereof,

wherein X₁₇ is T or S, X₁₈ is R or K, X₁₉ is M or I, X₂₀ is M or L, X₂₁ is I or M, and X₂₂ is S or T.

3. The antibody or antigen-binding fragment thereof of claim 2, wherein:

the HFR1 comprises a sequence selected from the group consisting of SEQ ID NOs: 62 and 63,

the HFR2 comprises a sequence selected from the group consisting of SEQ ID NOs: 64 and 65,

the HFR3 comprises the sequence selected from the group consisting of SEQ ID NOs: 66 and 67,

the HFR4 comprises a sequence of SEQ ID NOs: 57,

the LFR1 comprises the sequence from the group consisting of SEQ ID NOs: 68 and 69,

the LFR2 comprises a sequence of SEQ ID NO: 59,

the LFR3 comprises a sequence selected from the group consisting of SEQ ID NOs: 70 and 71, and
the LFR4 comprises a sequence of SEQ ID NO: 61.

4. The antibody or an antigen-binding fragment thereof of claim 1, wherein the heavy chain variable region comprises a sequence selected from the group consisting of SEQ ID NO: 25, SEQ ID NO: 27, SEQ ID NO: 29, SEQ ID NO: 37, SEQ ID NO: 39, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, and SEQ ID NO: 47; and wherein the light chain variable region comprises a sequence selected from the group consisting of SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, and SEQ ID NO: 48.

5. The antibody or an antigen-binding fragment thereof of claim 1, wherein:
the heavy chain variable region comprises a sequence of SEQ ID NO: 25 and the light chain variable region comprises a sequence of SEQ ID NO: 26;
the heavy chain variable region comprises a sequence of SEQ ID NO: 27 and the light chain variable region comprises a sequence of SEQ ID NO: 28;
the heavy chain variable region comprises a sequence of SEQ ID NO: 29 and the light chain variable region comprises a sequence of SEQ ID NO: 26, or 28;
the heavy chain variable region comprises a sequence of SEQ ID NO: 37 and the light chain variable region comprises a sequence of SEQ ID NO: 38;
the heavy chain variable region comprises a sequence of SEQ ID NO: 39 and the light chain variable region comprises a sequence of SEQ ID NO: 40;
the heavy chain variable region comprises a sequence of SEQ ID NO: 41 and the light chain variable region comprises a sequence of SEQ ID NO: 42;
the heavy chain variable region comprises a sequence of SEQ ID NO: 43 and the light chain variable region comprises a sequence of SEQ ID NO: 44;
the heavy chain variable region comprises a sequence of SEQ ID NO: 45 and the light chain variable region comprises a sequence of SEQ ID NO: 46; or
the heavy chain variable region comprises a sequence of SEQ ID NO: 47 and the light

chain variable region comprises a sequence of SEQ ID NO: 48.

6. The antibody or antigen-binding fragment thereof of claim 1, further comprising an immunoglobulin constant region, further comprising a constant region of human Ig, or further comprising a constant region of human IgG.

7. The antibody or antigen-binding fragment thereof of claim 6, wherein the constant region comprises one or more amino acid residue substitutions relative to SEQ ID NO: 49, selected from the group consisting of: L235V, F243L, R292P, Y300L, P396L, or any combination thereof.

8. The antibody or antigen-binding fragment thereof of claim 7, wherein the constant region comprises the sequence of SEQ ID NO: 51.

9. The antibody or an antigen-binding fragment thereof of claim 1, which is humanized or afucosylated.

10. The antibody or antigen-binding fragment thereof of claim 1, which is a diabody, a Fab, a Fab', a F(ab')₂, a Fd, an Fv fragment, a disulfide stabilized Fv fragment (dsFv), a (dsFv)₂, a bispecific dsFv (dsFv-dsFv'), a disulfide stabilized diabody (ds diabody), a single-chain antibody molecule (scFv), an scFv dimer (bivalent diabody), or a multispecific antibody.

11. The antibody or antigen-binding fragment thereof of claim 1, which is bispecific, capable of specifically binding to a first antigen of CLDN18.2 and a second antigen.

12. The antibody or antigen-binding fragment thereof of claim 11, wherein the second antigen is an immune related target, wherein the immune related target is selected from the group consisting of: PD-L1, PD-L2, PD-1, CLTA-4, TIM-3, LAG3, CD160, 2B4, TGF β , VISTA, BTLA, TIGIT, LAIR1, OX40, CD2, CD27, ICAM-1,

NKG2C, SLAMF7, NKp80, CD160, B7-H3, LFA-1, 1COS, 4-1BB, GITR, CD30, CD40, BAFFR, HVEM, CD7, LIGHT, IL-2, IL-15, CD3, CD16 and CD83.

13. The antibody or antigen-binding fragment thereof of claim 11, wherein the second antigen comprises a tumor antigen, wherein the tumor antigen comprises CA-125, gangliosides G(D2), G(M2) and G(D3), CD20, CD52, CD33, Ep-CAM, CEA, bombesin-like peptides, PSA, HER2/neu, epidermal growth factor receptor (EGFR), erbB2, erbB3/HER3, erbB4, CD44v6, Ki-67, cancer-associated mucin, VEGF, VEGFRs (e.g., VEGFR3), estrogen receptors, Lewis-Y antigen, TGF β 1, IGF-1 receptor, EGF α , c-Kit receptor, transferrin receptor, IL-2R or CO17-1A.

14. The antibody or antigen-binding fragment thereof of claim 1 linked to one or more conjugate moieties, wherein the conjugate moiety comprises a chemotherapeutic agent, a toxin, a radioactive isotope, a lanthanide, a luminescent label, a fluorescent label, an enzyme-substrate label, a DNA-alkylators, a topoisomerase inhibitor, a tubulin-binders (e.g. vcMMAE), or other anticancer drugs.

15. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof of claim 1, and one or more pharmaceutically acceptable carriers.

16. An isolated polynucleotide encoding the antibody or an antigen-binding fragment thereof of claim 1.

17. A vector comprising the isolated polynucleotide of claim 16.

18. A host cell comprising the vector of claim 17.

19. A method of expressing the antibody or antigen-binding fragment thereof of claim 1, comprising culturing a host cell comprising a vector comprising an isolated polynucleotide encoding the antibody or antigen-binding fragment thereof of claim 1

under the condition at which the vector is expressed.

20. Use of the antibody or antigen-binding fragment thereof of claim 1 and/or the pharmaceutical composition of claim 15 in the manufacture of a medicament for treating a disease or condition in a subject that would benefit from modulation of CLDN18.2 activity, comprising is to be administered to the subject a therapeutically effective amount of the medicament, wherein the disease or condition is cancer, or the cancer is a CLDN18.2-expressing cancer.

21. The use of claim 20, wherein the cancer is gastric cancer, lung cancer, bronchial cancer, bone cancer, liver and bile duct cancer, pancreatic cancer, breast cancer, liver cancer, ovarian cancer, testicle cancer, kidney cancer, bladder cancer, head and neck cancer, spine cancer, brain cancer, cervix cancer, uterine cancer, endometrial cancer, colon cancer, colorectal cancer, rectal cancer, anal cancer, esophageal cancer, gastrointestinal cancer, skin cancer, prostate cancer, pituitary cancer, stomach cancer, vagina cancer, thyroid cancer, glioblastoma, astrocytoma, melanoma, myelodysplastic syndrome, sarcoma, teratoma, and adenocarcinoma.

22. The use of claim 20, wherein the subject is human.

23. The use of claim 20, further comprising is to be administered a therapeutically effective amount of a second therapeutic agent.

24. A kit comprising an antibody or an antigen-binding fragment thereof of claim 1, and a second therapeutic agent.

25. A method of detecting CLDN18.2 in a sample of a subject, comprising: a) contacting the sample obtained from the subject with the antibody or antigen binding fragment thereof of claim 1; b) determining presence or amount of CLDN18.2 in the sample; and c) correlating the presence or the amount of CLDN18.2 to existence or

status of the CLDN18.2 related disease or condition in the subject.

26. A kit comprising the antibody or antigen-binding fragment thereof of claim 1, useful in detecting CLDN18.2.

27. A chimeric antigen receptor (CAR) comprising an antigen binding domain, a transmembrane domain, a costimulatory signaling region, and a TCR signaling domain, wherein the antigen binding domain specifically binds to CLDN18.2 and comprises an antigen binding fragment of claim 1.