

CLAIMS

1. An antibody or fragment thereof binding to CLDN18.2, wherein the antibody or
fragment thereof exhibits increased binding to tumor tissue expressing CLDN18.2
over healthy tissue expressing CLDN18.2.
2. An antibody or fragment thereof binding to CLDN18.2 comprising the HCDR1,
HCDR2 and HCDR3 sequences of SEQ ID NO: 21, SEQ ID NO: 22, and SEQ ID
NO: 23, respectively, and the LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NO:
24, SEQ ID NO: 25, and SEQ ID NO: 26, respectively.
3. The antibody or fragment thereof of claim 1 or 2, comprising:
 - a. the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NO: 1, SEQ ID
NO: 15 and SEQ ID NO: 3, respectively, and the LCDR1, LCDR2 and
LCDR3 sequences of SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6,
respectively;
 - b. the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NO: 1, SEQ ID
NO: 16 and SEQ ID NO: 3, respectively, and the LCDR1, LCDR2 and
LCDR3 sequences of SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6,
respectively;
 - c. the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NO: 1, SEQ ID
NO: 16 and SEQ ID NO: 3, respectively, and the LCDR1, LCDR2 and
LCDR3 sequences of SEQ ID NO: 17, SEQ ID NO: 14 and SEQ ID NO:
11, respectively;
 - d. the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NO: 1, SEQ ID
NO: 16 and SEQ ID NO: 3, respectively, and the LCDR1, LCDR2 and
LCDR3 sequences of SEQ ID NO: 18, SEQ ID NO: 19 and SEQ ID NO:
11, respectively;
 - e. the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NO: 12, SEQ ID
NO: 15 and SEQ ID NO: 3, respectively, and the LCDR1, LCDR2 and
LCDR3 sequences of SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6,
respectively;
 - f. the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NO: 1, SEQ ID
NO: 20 and SEQ ID NO: 3, respectively, and the LCDR1, LCDR2 and
LCDR3 sequences of SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6,
respectively;
 - g. the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NO: 1, SEQ ID
NO: 20 and SEQ ID NO: 3, respectively, and the LCDR1, LCDR2 and
LCDR3 sequences of SEQ ID NO: 18, SEQ ID NO: 19 and SEQ ID NO:
11, respectively;
 - h. the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NO: 12, SEQ ID
NO: 20 and SEQ ID NO: 8, respectively, and the LCDR1, LCDR2 and

LCDR3 sequences of SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6, respectively; or

- i. the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NO: 12, SEQ ID NO: 20 and SEQ ID NO: 8, respectively, and the LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NO: 17, SEQ ID NO: 14 and SEQ ID NO: 11, respectively.

4. The antibody or fragment thereof of claim 1 or 2, comprising:

- a. the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NO: 1, SEQ ID NO: 2 and SEQ ID NO: 3, respectively, and the LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6, respectively;
- b. the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NO: 1, SEQ ID NO: 7 and SEQ ID NO: 8, respectively, and the LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NO: 9, SEQ ID NO: 10 and SEQ ID NO: 11, respectively; or
- c. the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NO: 12, SEQ ID NO: 2 and SEQ ID NO: 3, respectively, and the LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NO: 13, SEQ ID NO: 14 and SEQ ID NO: 11, respectively,

preferably comprising:

- d. a VH sequence of SEQ ID NO: 27 and a VL sequence of SEQ ID NO: 28;
- e. a VH sequence of SEQ ID NO: 29 and a VL sequence of SEQ ID NO: 30; or
- f. a VH sequence of SEQ ID NO: 31 and a VL sequence of SEQ ID NO: 32.

5. The antibody or fragment thereof of any one of claims 1-3, comprising:

- a. a VH sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of SEQ ID NO: 33;
- b. a VH sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of SEQ ID NO: 34;
- c. a VH sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of SEQ ID NO: 35;
- d. a VH sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of SEQ ID NO: 36; or

- e. a VH sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of SEQ ID NO: 37;

and

- f. a VL sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of SEQ ID NO: 38;

- g. a VL sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of SEQ ID NO: 39;

- h. a VL sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of SEQ ID NO: 40; or

- i. a VL sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of SEQ ID NO: 41,

preferably comprising:

- a. a VH sequence of: SEQ ID NO: 33;
- b. a VH sequence of SEQ ID NO: 34;
- c. a VH sequence of SEQ ID NO: 35;
- d. a VH sequence of SEQ ID NO: 36; or
- e. a VH sequence of SEQ ID NO: 37;

and

- f. a VL sequence of SEQ ID NO: 38;
- g. a VL sequence of SEQ ID NO: 39;
- h. a VL sequence of SEQ ID NO: 40; or
- i. a VL sequence of SEQ ID NO: 41.

6. The antibody or fragment thereof of claim 1 or 2, comprising:

- a. a VH sequence of SEQ ID NO: 33 and a VL sequence of SEQ ID NO: 38;
- b. a VH sequence of SEQ ID NO: 34 and a VL sequence of SEQ ID NO: 38;
- c. a VH sequence of SEQ ID NO: 34 and a VL sequence of SEQ ID NO: 39;
- d. a VH sequence of SEQ ID NO: 34 and a VL sequence of SEQ ID NO: 40;
- e. a VH sequence of SEQ ID NO: 35 and a VL sequence of SEQ ID NO: 38;
- f. a VH sequence of SEQ ID NO: 36 and a VL sequence of SEQ ID NO: 41;

- g. a VH sequence of SEQ ID NO: 36 and a VL sequence of SEQ ID NO: 40;
 - h. a VH sequence of SEQ ID NO: 37 and a VL sequence of SEQ ID NO: 41;
 - i. a VH sequence of SEQ ID NO: 37 and a VL sequence of SEQ ID NO: 38;
or
 - 5 j. a VH sequence of SEQ ID NO: 37 and a VL sequence of SEQ ID NO: 39.
7. The antibody of any one of claims 1-3, comprising:
- 10 a. a heavy chain sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of the heavy chain sequence of SEQ ID NO: 46 and a light chain sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of the light chain sequence of SEQ ID NO: 51;
 - 15 b. a heavy chain sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of the heavy chain sequence of SEQ ID NO: 47 and a light chain sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of the light chain sequence of SEQ ID NO: 51;
 - 20 c. a heavy chain sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of the heavy chain sequence of SEQ ID NO: 47 and a light chain sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of the light chain sequence of SEQ ID NO: 52;
 - 25 d. a heavy chain sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of the heavy chain sequence of SEQ ID NO: 47 and a light chain sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of the light chain sequence of SEQ ID NO: 53;
 - 30 e. a heavy chain sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of the heavy chain sequence of SEQ ID NO: 48 and a light chain sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of the light chain sequence of SEQ ID NO: 51;
 - 35 f. a heavy chain sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of the heavy chain sequence of SEQ ID NO: 47 and a light chain sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98%
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sequence identity with the amino acid sequence of the light chain sequence of SEQ ID NO: 54;

- 5 g. a heavy chain sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of the heavy chain sequence of SEQ ID NO: 49 and a light chain sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of the light chain sequence of SEQ ID NO: 53;
- 10 h. a heavy chain sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of the heavy chain sequence of SEQ ID NO: 50 and a light chain sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of the light chain sequence of SEQ ID NO: 54;
- 15 i. a heavy chain sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of the heavy chain sequence of SEQ ID NO: 50 and a light chain sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of the light chain sequence of SEQ ID NO: 51;
- 20 j. a heavy chain sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of the heavy chain sequence of SEQ ID NO: 50 and a light chain sequence having at least 80%, at least 85%, at least 90%, at least 95% or at least 98% sequence identity with the amino acid sequence of the light chain sequence of SEQ ID NO: 52

preferably comprising:

- k. the heavy chain sequence of SEQ ID NO: 46 and light chain sequence of SEQ ID NO: 51;
- 30 l. the heavy chain sequence of SEQ ID NO: 47 and light chain sequence of SEQ ID NO: 51;
- m. the heavy chain sequence of SEQ ID NO: 47 and light chain sequence of SEQ ID NO: 52;
- 35 n. the heavy chain sequence of SEQ ID NO: 47 and light chain sequence of SEQ ID NO: 53;
- o. the heavy chain sequence of SEQ ID NO: 48 and light chain sequence of SEQ ID NO: 51;
- p. the heavy chain sequence of SEQ ID NO: 47 and light chain sequence of SEQ ID NO: 54;

- q. the heavy chain sequence of SEQ ID NO: 49 and light chain sequence of SEQ ID NO: 53;
- r. the heavy chain sequence of SEQ ID NO: 50 and light chain sequence of SEQ ID NO: 54;
- 5 s. the heavy chain sequence of SEQ ID NO: 50 and light chain sequence of SEQ ID NO: 51;
- t. the heavy chain sequence of SEQ ID NO: 50 and light chain sequence of SEQ ID NO: 52,
- or versions thereof with an engineered Fc domain.
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8. An antibody or fragment thereof binding to CLDN18.2, wherein the antibody or fragment thereof
- i. binds to the same epitope as an antibody comprising a heavy chain sequence of SEQ ID NO: 46 and a light chain sequence of SEQ ID NO: 51;
- 15 ii. competes for binding with an antibody comprising a heavy chain sequence of SEQ ID NO: 46 and a light chain sequence of SEQ ID NO: 51; and/or
- iii. competitively inhibits binding of an antibody comprising a heavy chain sequence of SEQ ID NO: 46 and a light chain sequence of SEQ ID NO: 51 to CLDN18.2.
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9. The antibody or fragment thereof of any one of claims 1 to 8, wherein the antibody or fragment thereof
- a. is IgA1, IgA2, IgD, IgE, IgG1, IgG2, IgG3, IgG4, synthetic IgG, IgM, F(ab)₂, Fv, scFv, IgGACH2, F(ab')₂, scFvCH3, Fab, VL, VH, scFv4, scFv3, scFv2, dsFv, Fv, scFv-Fc, (scFv)₂, a non-depleting IgG, a diabody, a bivalent antibody or Fc-engineered versions thereof;
- 25 b. is humanized;
- c. does not bind to CLDN18.1;
- 30 d. is isolated; and/or
- e. is less susceptible to posttranslational deamidation than IMAB362.
10. The antibody or fragment thereof of any one of claims 1 to 9, wherein the increased binding to tumor tissue expressing CLDN18.2 over healthy tissue expressing CLDN18.2 is measured by flow cytometry or by immunohistochemistry.
- 35 11. The antibody or fragment thereof of any one of claims 1 to 9 wherein the antibody or fragment thereof binds to CLDN18.2 expressed in HEK293T cells or PA-TU-8988-High cells with an EC₅₀ value that is at least 1.1 times higher, at least 1.2 times

higher, at least 1.5 times higher, at least 2 times higher or at least 2.5 times higher but not more than 3 times higher than the EC50 value of IMAB362 binding to CLDN18.2 expressed in HEK293T cells or PA-TU-8988-High cells, optionally wherein binding is measured by flow cytometry (FC) titration.

- 5 12. A nucleic acid encoding the antibody or fragment thereof of any of claims 1 to 11.
13. A vector comprising the nucleic acid of claim 12.
14. A host cell comprising the nucleic acid of claim 12 or the vector of claim 13.
- 10 15. The antibody or fragment thereof of any one of claims 1 to 11, the nucleic acid of claim 12, the vector of claim 13 or the host cell of claim 14 for use in the treatment of a subject
- a. suffering from,
- b. at risk of developing, and/or
- c. being diagnosed for
- 15 a neoplastic disease; optionally wherein the neoplastic disease is selected from the group consisting of pancreatic, gastric, esophageal, ovarian and lung cancer.
16. Use of the antibody or fragment thereof of any one of claims 1 to 11, the nucleic acid of claim 12, the vector of claim 13 or the host cell of claim 14 in the manufacture of a medicament for the treatment of a subject
- 20 a. suffering from,
- b. at risk of developing, and/or
- c. being diagnosed for
- a neoplastic disease; optionally wherein the neoplastic disease is selected from the group consisting of pancreatic, gastric, esophageal, ovarian and lung cancer.

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