

## CLAIMS

- ~~1.— An isolated antibody against human CLDN18.2 or an antigen-binding fragment thereof, capable of binding to an epitope comprising at least one, two, or three of amino acid residues at positions D28, W30, V43, N45, Y46, L49, W50, R51, R55, E56, F60, E62, Y66, L72, L76, V79 and R80 in the amino acid sequence of SEQ ID NO: 30.~~
- ~~2.— The isolated antibody or an antigen-binding fragment thereof of claim 1, wherein the epitope comprises the amino acid residue at position E56.—~~
- ~~3.— The isolated antibody or an antigen-binding fragment thereof of claim 1 or 2, wherein the epitope does not contain at least one of the following residues: A42, or N45.—~~
- ~~4.— The isolated antibody or an antigen-binding fragment thereof of any of preceding claims, wherein the epitope comprises the amino acid residue at position W30, L49, W50, R55, and E56.—~~
- ~~5.— The isolated antibody or an antigen-binding fragment thereof of any of preceding claims, wherein the epitope further comprises one or more amino acid residues: T41, N45, Y46, R51, F60, E62, and R80.—~~
- ~~6.— The isolated antibody or an antigen-binding fragment thereof of any of preceding claims, wherein the epitope further comprises one or more amino acid residues: D28, V43, N45, Y46, Y66, L72, L76, and V79.—~~
- ~~7.— An isolated antibody or an antigen-binding fragment thereof, capable of specifically binding to human CLDN18.2 and having at least one of the following characteristics:~~
  - ~~a) binding to a cell expressing human CLDN18.2 at a K<sub>d</sub> value of no more than 2.5nM (or no more than 2.0, 1.5, 1, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4 nM) as measured by KinExA assay;—~~
  - ~~b) binding to a cell expressing human CLDN18.2 at an EC<sub>50</sub> value of no more than 70 µg/ml (or no more than 65, 60, 55, 50, 45, 40, 35, 30, 25, 20, 15, 12, —~~

- or 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 µg/ml) as measured by flow cytometry;
- e) inducing complement dependent cytotoxicity (CDC) on a cell expressing human CLDN18.2 at an EC50 value of no more than 1 µg/ml (or no more than 0.9, 0.8, 0.7, 0.6, 0.5 µg/ml) as measured by cytotoxicity assay;
- d) inducing antibody dependent cell cytotoxicity (ADCC) on a cell expressing human CLDN18.2 at an EC50 value of no more than 2 µg/ml (or no more than 1.9, 1.8, 1.7, 1.6, 1.5, 1.4, 1.3, 1.2, 1.1, 1.0, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, or 0.1 µg/ml) as measured by an ADCC reporter assay.
8. The isolated antibody or an antigen-binding fragment thereof of claim 7, wherein the cell comprises NUGC4 cell, SNU-620 cell, SNU-601 cell, KATOIII cell, or a comparable cell thereof having a human CLDN18.2 protein expression level comparable to or no more than that of NUGC4 cell, SNU-620 cell, SNU-601 cell, or KATOIII cell.
9. The isolated antibody or an antigen-binding fragment thereof of claim 7, wherein the cell comprises a human CLDN18.2 high-expressing cell, a human CLDN18.2 medium-expressing cell, or a human CLDN18.2 low-expressing cell, wherein the human CLDN18.2 high-expressing cell expresses human CLDN18.2 at an intensity of at least 2+ as measured by IHC and at a level where at least 40% of the cells are stained positive in Immunohistochemistry (IHC); the human CLDN18.2 medium-expressing cell expresses human CLDN18.2 at an intensity of at least 1+ and below 2+ as measured by IHC and at a level where at least 30% but below 40% of the cells are stained positive in IHC; and the human CLDN18.2 low-expressing cell expresses human CLDN18.2 at an intensity of above 0 but below 1+ as measured by IHC and at a level where above 0 but below 30% of the cells are stained positive in IHC.
10. The isolated antibody or an antigen-binding fragment thereof of claim 7, wherein the EC50 value for binding to NUGC4 cells is no more than 70 µg/ml (or no more than 65, 60, 55, 50, 45, 40, 35, 30, 25, 20, 15, 12, or 10 µg/ml).
11. The isolated antibody or an antigen-binding fragment thereof of claim 7, wherein

~~the ADCC on NUGC4 cells at an EC50 value of no more than 2 µg/ml (or no more than 1.9, 1.8, 1.7, 1.6, 1.5, 1.4, 1.3, 1.2, 1.1, 1.0, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, or 0.1 µg/ml) as measured by an ADCC reporter assay.~~

~~12. An isolated antibody or an antigen-binding fragment thereof, capable of specifically binding to human CLDN18.2 and having at least one of the following characteristics:—~~

~~a) binding to human CLDN18.2 at an Kd value no more than 80%, 70%, 60%, 50%, 40%, 30%, 20%, 15% of that of IMAB362, as measured by KinExA assay;—~~

~~b) binding to a cell expressing human or mouse CLDN18.2 at an EC50 value no more than 80%, 70%, 60%, 50%, 40%, 30%, 20%, 15% or 10% of that of IMAB362, as measured by flow cytometry assay;—~~

~~e) inducing complement dependent cytotoxicity (CDC) on a cell expressing human CLDN18.2 at an EC50 value no more than 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, or 5% of than that of IMAB362, as measured by cytotoxicity assay; and~~

~~d) inducing antibody-dependent cell cytotoxicity (ADCC) on a cell expressing human CLDN18.2 at an EC50 value no more than 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 5%, or 1% of that of IMAB362, as measured by an ADCC reporter assay,~~

~~wherein IMAB362 is an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 72, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 73.~~

~~13. The isolated antibody or an antigen-binding fragment thereof of claim 12, wherein the cell comprises a NUGC4 cell, SNU-620 cell, SNU-601 cell, KATOIII cell, or a cell line having a human CLDN18.2 protein expression level comparable to or no more than that of NUGC4 cell, SNU-620 cell, SNU-601 cell, KATOIII cell.~~

~~14. The isolated antibody or an antigen-binding fragment thereof of claim 12, wherein the cell comprises a human CLDN18.2 high-expressing cell, a human~~

~~CLDN18.2 medium-expressing cell, or a human CLDN18.2 low-expressing cell, wherein the human CLDN18.2 high-expressing cell expresses human CLDN18.2 at an intensity of at least 2+ as measured by IHC and at a level where at least 40% of the cells are stained positive in IHC; the human CLDN18.2 medium-expressing cell expresses human CLDN18.2 at an intensity of at least 1+ and below 2+ as measured by IHC and at a level where at least 30% but below 40% of the cells are stained positive in IHC; and the human CLDN18.2 low-expressing cell expresses human CLDN18.2 at an intensity of above 0 but below 1+ as measured by IHC and at a level where above 0 but below 30% of the cells are stained positive in IHC.~~

~~15. The isolated antibody or an antigen-binding fragment thereof of any of claims 7-14, wherein the antibody binds to an epitope comprising at least one, two, or three of amino acid residues at positions D28, W30, V43, N45, Y46, L49, W50, R51, R55, E56, F60, E62, Y66, L72, L76, V79 and R80 in the amino acid sequence of SEQ ID NO: 30, optionally, the epitope comprises the amino acid residue at position E56; optionally, the epitope does not contain at least one of the following residues: A42, or N45; optionally, the epitope comprises the amino acid residue at position W30, L49, W50, R55, and E56; optionally, the epitope further comprises one or more amino acid residues: T41, N45, Y46, R51, F60, E62, and R80; and optionally, the epitope further comprises one or more amino acid residues: D28, V43, N45, Y46, Y66, L72, L76, and V79.~~

16. An anti-CLDN18.2 antibody or an antigen-binding fragment thereof, comprising heavy chain HCDR1, HCDR2 and HCDR3 and ~~for~~ light chain LCDR1, LCDR2 and LCDR3 sequences, wherein:

the HCDR1 sequence comprises GYNMN (SEQ ID NO: 1), or **TYFIGVG** (SEQ ID NO: 13), or a homologue sequence of at least 80% sequence identity thereof;

the HCDR2 sequence comprises **X<sub>1</sub>IDPYYX<sub>2</sub>X<sub>3</sub>TX<sub>4</sub>YNQKFX<sub>5</sub>G** (SEQ ID NO: 32), or HIWWNDNKYYNTALKS (SEQ ID NO: 15), or a homologue sequence of at least 80% sequence identity thereof;

the HCDR3 sequence comprises **X<sub>6</sub>X<sub>7</sub>X<sub>8</sub>GNAFDY** (SEQ ID NO: 33), or

MGSGAWFTY (SEQ ID NO: 17), or a homologue sequence of at least 80% sequence identity thereof;

the LCDR1 sequence comprises **KSSQX<sub>9</sub>LX<sub>10</sub>NX<sub>11</sub>GNX<sub>12</sub>KNYLT** (SEQ ID NO: 34) or a homologue sequence of at least 80% sequence identity thereof;

the LCDR2 sequence comprises **WASTRX<sub>13</sub>S** (SEQ ID NO: 35) or a homologue sequence of at least 80% sequence identity thereof;

the LCDR3 sequence comprises **QNDYX<sub>14</sub>X<sub>15</sub>PX<sub>16</sub>T** (SEQ ID NO: 36) or a homologue sequence of at least 80% sequence identity thereof;

wherein X<sub>1</sub> is N or Y or H, X<sub>2</sub> is G or V, X<sub>3</sub> is A or G or T, X<sub>4</sub> is R or T or S, X<sub>5</sub> is K or R, X<sub>6</sub> is S or M, X<sub>7</sub> is Y or F, X<sub>8</sub> is Y or H, X<sub>9</sub> is S or N, X<sub>10</sub> is L or F, X<sub>11</sub> is S or N, X<sub>12</sub> is Q or L, X<sub>13</sub> is E or K, X<sub>14</sub> is S or Y, X<sub>15</sub> is F or Y and X<sub>16</sub> is F or L.

~~172. An~~The anti-CLDN18.2 antibody or an antigen-binding fragment thereof of claim 1, wherein the heavy chain variable region comprises:

- a) a HCDR1 comprises a sequence selected from SEQ ID NO: 1, and SEQ ID NO: 13,
- b) a HCDR2 comprises a sequence selected from SEQ ID NO: 3, SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 15, SEQ ID NO: 19, and SEQ ID NO: 22, and
- c) a HCDR3 comprises a sequence selected from SEQ ID NO: 5, SEQ ID NO: 11, SEQ ID NO: 17, and SEQ ID NO: 21,

and~~or~~

a light chain variable region comprising:

- d) a LCDR1 comprises a sequence of SEQ ID NO: 2, SEQ ID NO: 10, SEQ ID NO: 14, and SEQ ID NO: 20,
- e) a LCDR2 comprises a sequence of SEQ ID NO: 4, and SEQ ID NO: 16, and
- f) a LCDR3 comprises a sequence selected from SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 12, and SEQ ID NO: 18.

~~18. The antibody or an antigen-binding fragment thereof of any of the preceding~~

~~claims, wherein the heavy chain variable region is selected from the group consisting of:~~

~~a heavy chain variable region comprising 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;~~

~~a heavy chain variable region comprising 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;~~

~~a heavy chain variable region comprising 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;~~

~~a heavy chain variable region comprising 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;~~

~~a heavy chain variable region comprising 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~~

~~a heavy chain variable region comprising 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.~~

~~19. The antibody or an antigen-binding fragment thereof of any of the preceding claims, wherein the light chain variable region is selected from the group consisting of:~~

~~a light chain variable region comprising 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;~~

~~a light chain variable region comprising 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;~~

~~a light chain variable region comprising 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;~~

~~a light chain variable region comprising 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;~~

~~a light chain variable region comprising 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; and~~

~~a light chain variable region comprising 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.~~

**203.** The antibody or an antigen-binding fragment thereof of ~~any of the preceding~~ claims 1, wherein:

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;

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;

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;

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;

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

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.

~~214~~. The antibody or an antigen-binding fragment thereof of ~~any one of the preceding~~ claims 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 **QVQLVQSGAEVKKPGASVKVSCKASGYX<sub>17</sub>FT** (SEQ ID NO: 54) or a homologous sequence of at least 80% sequence identity thereof,

the HFR2 comprises **WVX<sub>18</sub>QAPGQGLEWX<sub>19</sub>G** (SEQ ID NO: 55) or a homologous sequence of at least 80% sequence identity thereof,

the HFR3 sequence comprises **RVTX<sub>20</sub>TIDKSTSTVYMELSSLRSEDTAVYYCAR** (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 **DIVMTQSPDSLAVSLGERATX<sub>21</sub>NC** (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 **GVPDRFX<sub>22</sub>GSGSGTDFTLTISLQAEDVAVYYC** (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 X<sub>17</sub> is T or S, X<sub>18</sub> is R or K, X<sub>19</sub> is M or I, X<sub>20</sub> is M or L, X<sub>21</sub> is I or M, and X<sub>22</sub> is S or T.

**225.** The antibody or antigen-binding fragment thereof of claim **214**, 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.

~~236.~~ The antibody or an antigen-binding fragment thereof of ~~any of the preceding~~ claims 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 a homologous sequence thereof having at least 80% sequence identity yet retaining specific binding affinity to CLDN18.2-; and

~~24. The antibody or an antigen-binding fragment thereof of any of the preceding~~ ~~claims~~, 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, SEQ ID NO: 48, and a homologous sequence thereof having at least 80% sequence identity yet retaining specific binding affinity to CLDN18.2.

~~257.~~ The antibody or an antigen-binding fragment thereof of ~~any of the preceding~~ claims 1, wherein:

a heavy chain variable region comprising the sequence of SEQ ID NO: 23 and a light chain variable region comprising the sequence of SEQ ID NO: 24;

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.

~~26. The antibody or antigen-binding fragment thereof of any of the preceding claims, further comprising one or more amino acid residue substitutions or modifications yet retains specific binding affinity to human CLDN18.2.~~

~~27. The antibody or antigen-binding fragment thereof of claim 26, wherein at least one of the substitutions or modifications is in one or more of the CDR sequences, and/or in one or more of the non-CDR regions of the VH or VL sequences.~~

~~28. The antibody or an antigen-binding fragment thereof of any of claims 16-27, wherein the antibody binds to an epitope comprising at least one, two, or three of amino acid residues at positions D28, W30, V43, N45, Y46, L49, W50, R51, R55, E56, F60, E62, Y66, L72, L76, V79 and R80 of human CLDN18.2 having the amino acid sequence of SEQ ID NO: 30.~~

~~29.~~ The antibody or antigen-binding fragment thereof of ~~any of the preceding claims~~ 1, further comprising an immunoglobulin constant region, ~~optionally further comprising~~ comprising a constant region of human Ig, or ~~optionally further comprising~~ comprising a constant region of human IgG.

~~30. The antibody or antigen-binding fragment thereof of claim 29, wherein the constant region comprises a constant region of human IgG1, IgG2, IgG3, or IgG4.~~

~~31. The antibody or antigen-binding fragment thereof of claim 30, wherein the constant region of human IgG1 comprises SEQ ID NO: 49, or a homologous sequence having at least 80% sequence identity thereof.~~

~~32. The antibody or antigen-binding fragment thereof of any of claims 29-31,~~

~~wherein the constant region comprises one or more amino acid residue substitutions or modifications conferring increased CDC or ADCC relative to wild-type constant region.~~

~~339.~~ The antibody or antigen-binding fragment thereof of claim ~~328~~, 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.

~~3410.~~ The antibody or antigen-binding fragment thereof of claim ~~339~~, wherein the constant region comprises the sequence of SEQ ID NO: 51.

~~3511.~~ The antibody or an antigen-binding fragment thereof of ~~any of the preceding claims 1~~, which is humanized or afucosylated.

~~36. The antibody or antigen-binding fragment thereof of any of the preceding claims, which is afucosylated.~~

~~3712.~~ The antibody or antigen-binding fragment thereof of ~~any of the preceding claims 1~~, which is a diabody, a Fab, a Fab', a F(ab')<sub>2</sub>, a Fd, an Fv fragment, a disulfide stabilized Fv fragment (dsFv), a (dsFv)<sub>2</sub>, a bispecific dsFv (dsFv-dsFv'), a disulfide stabilized diabody (ds diabody), a single-chain antibody molecule (scFv), an scFv dimer (bivalent diabody), a multispecific antibody, a camelized single domain antibody, a nanobody, a domain antibody, and a bivalent domain antibody.

~~3813.~~ The antibody or antigen-binding fragment thereof of ~~any of the preceding claims 1~~, which is bispecific, capable of specifically binding to a first antigen of CLDN18.2 and a second antigen

~~39. The antibody or antigen-binding fragment thereof of claim 38, capable of specifically binding to a first and a second epitope of CLDN18.2, or capable of specifically binding to CLDN18.2 and a second antigen.~~

~~4014.~~ The antibody or antigen-binding fragment thereof of claim ~~3913~~, wherein the second antigen is an immune related target, optionally 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  $\beta$ , VISTA, BTLA, TIGIT, LAIR1, OX40, CD2, CD27, ICAM-1, NKG2C, SLAMF7, NKp80, CD160, B7-H3, LFA-1, ICOS, 4-1BB, GITR, CD30, CD40, BAFFR, HVEM, CD7, LIGHT, IL-2, IL-15, CD3, CD16 and CD83.

~~41~~15. The antibody or antigen-binding fragment thereof of claim ~~39~~13, 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 $\beta$ 1, IGF-1 receptor, EGF $\alpha$ , c-Kit receptor, transferrin receptor, IL-2R or CO17-1A.

~~42. The antibody or antigen-binding fragment thereof of claim 41, wherein the tumor antigen is present in a CLDN18.2-expressing cell.~~

~~43. The antibody or antigen-binding fragment thereof of claim 42, 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 $\beta$ 1, IGF-1 receptor, EGF $\alpha$ , c-Kit receptor, transferrin receptor, IL-2R or CO17-1A.~~

~~44. The antibody or an antigen-binding fragment thereof of any of the preceding claims, capable of specifically binding to mouse CLDN18.2.~~

~~45. The antibody or an antigen-binding fragment thereof of any of the preceding claims, which does not bind to human CLDN18.1.~~

~~46~~16. The antibody or antigen-binding fragment thereof of ~~any of the preceding claims~~ 1 linked to one or more conjugate moieties-<sub>1</sub>

~~47. The antibody or antigen-binding fragment thereof of claim 46, wherein the~~

conjugate moiety comprises a clearance-modifying agent, 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.

~~48. An antibody or an antigen-binding fragment thereof, which competes for binding to CLDN18.2 with the antibody or antigen-binding fragment thereof of any of claims 1-6, and 16-47.~~

~~49. A composition comprising the anti-CLDN18.2 antibody or antigen-binding fragment thereof of any of claims 1-48, wherein the antibodies or antigen-binding fragments thereof is afucosylated.~~

~~50. The composition of claim 49, wherein the anti-CLDN18.2 antibody in the composition has an amount of fucose of 60% or less (e.g. less than 55%, 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15% or 10%) of the total amount of oligosaccharides at Asn297 according to the EU numbering system.~~

~~51~~17. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof of ~~any of the preceding~~ claims 1, and one or more pharmaceutically acceptable carriers.

~~52~~18. An isolated polynucleotide encoding the antibody or an antigen-binding fragment thereof of ~~the preceding~~ claims 1.

~~53~~19. A vector comprising the isolated polynucleotide of claim ~~52~~18.

~~54~~20. A host cell comprising the vector of claim ~~53~~19.

~~55~~21. A method of expressing the antibody or antigen-binding fragment thereof of ~~any of~~ claims ~~1-48~~, comprising culturing ~~thea~~ host cell ~~of claim 54~~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 ~~of claim 53~~ is expressed.

~~56~~22. ~~A method of~~ Use of the antibody or antigen-binding fragment thereof of

claim 1 and/or the pharmaceutical composition of claim 17 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 administering to the subject a therapeutically effective amount of the ~~antibody or antigen-binding fragment thereof of any of claims 1-48 and/or the pharmaceutical composition of claim 51~~medicament.

~~57. The method of claim 56, wherein the disease or condition is a CLDN18.2 related disease or condition.~~

~~58~~23. The ~~method~~duse of claim ~~57~~22, wherein the disease or condition is cancer, optionally the cancer is a CLDN18.2-expressing cancer.

~~59. The method of any of claims 56-58, wherein the subject is identified as having a CLDN18.2-expressing cancer cell.~~

~~60. The method of claims 59, wherein the subject is identified as having a CLDN18.2 high-expressing cancer cell, a CLDN18.2 medium-expressing cancer cell, or a CLDN18.2 low-expressing cancer cell.~~

~~61. The method of claim 60, wherein the CLDN18.2 high-expressing cancer cell expresses CLDN18.2 at an intensity of at least 2+ as measured by IHC and at a level where at least 40% of the cells are stained positive in IHC; the CLDN18.2 medium-expressing cancer cell expresses CLDN18.2 at an intensity of at least 1+ and below 2+ as measured by IHC and at a level where at least 30% but below 40% of the cells are stained positive in IHC, and the CLDN18.2 low-expressing cancer cell expresses CLDN18.2 at an intensity of above 0 but below 1+ as measured by IHC and at a level where above 0 but below 30% of the cells are stained positive in IHC.~~

~~62~~24. The ~~method~~duse of ~~any of~~ claims ~~56-61~~23, 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.

~~6325.~~ The ~~method~~use of ~~any of~~ claims ~~56-62~~22, wherein the subject is human.

~~64. The method of any of claims 56-63, wherein the administration is via oral, nasal, intravenous, subcutaneous, sublingual, or intramuscular administration.~~

~~6526.~~ The ~~method~~use of ~~any of~~ claims ~~56-64~~22, further comprising administering a therapeutically effective amount of a second therapeutic agent.

~~66. The method of any of claims 65, wherein the second therapeutic agent is selected from a chemotherapeutic agent, an anti-cancer drug, radiation therapy, an immunotherapy agent, anti-angiogenesis agent, a targeted therapy agent, a cellular therapy agent, a gene therapy agent, a hormonal therapy agent, or cytokines.~~

~~6727.~~ A kit comprising an antibody or an antigen-binding fragment thereof of ~~any of~~ claims ~~1-48~~, and a second therapeutic agent.

~~68. A method of modulating CLDN18.2 activity in a CLDN18.2-expressing cell, comprising exposing the CLDN18.2-expressing cell to the antibody or antigen-binding fragment thereof of any of claims 1-48.~~

~~69. A method of detecting presence or amount of CLDN18.2 in a sample, comprising contacting the sample with the antibody or antigen-binding fragment thereof of any of claims 1-48, and determining the presence or the amount of CLDN18.2 in the sample.~~

~~7028.~~ A method of Use of the antibody or antigen-binding fragment thereof of claim 1 in the manufacture of a diagnostic reagent for diagnosing a CLDN18.2 related disease or condition in a subject, comprising: a) contacting a sample obtained from the subject with the ~~antibody or antigen-binding fragment thereof of any of claims 1-48~~reagent; 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.

~~71. Use of the antibody or antigen-binding fragment thereof of any of claims 1-48 in the manufacture of a medicament for treating a CLDN18.2 related disease or condition in a subject.~~

~~72. Use of the antibody or antigen-binding fragment thereof of any of claims 1-48 in the manufacture of a diagnostic reagent for diagnosing a CLDN18.2 related disease or condition.~~

~~73~~29. A kit comprising the antibody or antigen-binding fragment thereof of ~~any of~~ claims ~~1-48~~, useful in detecting CLDN18.2.

~~74~~30. 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 ~~any of~~ claims ~~1-48~~.

~~75. The CAR of claim 74, wherein the antigen binding fragment is a Fab or a scFv.~~

~~76. The CAR of claim 74 or 75, which is bispecific.~~

~~77. The CAR of claim 75, wherein the CAR is capable of further specifically binding to a second antigen other than CLDN18.2, or a second epitope on CLDN18.2.~~

~~78. The CAR of claim 77, wherein the second antigen comprises a tumor antigen.~~

~~79. A nucleic acid sequence encoding the chimeric antigen receptor (CAR) of any one of claims 74-78.~~

~~80. A cell comprising the nucleic acid sequence of claim 79.~~

~~81. A cell genetically modified to express the CAR of any one of claims 74-78.~~

~~82. A vector comprising the nucleic acid sequence of claim 79.~~

~~83. A method for stimulating a T cell-mediated immune response to a CLDN18.2-expressing cell or tissue in a mammal, the method comprising administering to the mammal an effective amount of a cell genetically modified to express the CAR of any one of claims 74-78.~~

~~84. A method of treating a mammal having a CLDN18.2 related disease or condition, comprising administering to the mammal an effective amount of a cell of claim 81, thereby treating the mammal.—~~

~~85. The method of claim 84, wherein the cell is an autologous T cell.—~~

~~86. The method of claim 84, wherein the CLDN18.2 related disease or condition is cancer.—~~

~~87. The method of claim 84, wherein the mammal is a human subject.—~~

~~88. The method claim 84, wherein the mammal is identified as having a CLDN18.2 expressing cancer cell, optionally the mammal is identified as having a CLDN18.2 high-expressing cancer cell, a CLDN18.2 medium-expressing cancer cell, or a CLDN18.2 low-expressing cancer cell.~~