CLAIMS

~~It is claimed:~~

1. An isolated monoclonal antibody or antigen-binding fragment thereof comprising a heavy chain complementarity determining region 1 (HCDR1), HCDR2, HCDR3, a light chain complementarity determining region 1 (LCDR1), LCDR2, and LCDR3, having the polypeptide sequences of:

~~a. SEQ ID NOs: 33, 34, 35, 63, 64 and 65, respectively;~~

(a) SEQ ID NOs: 21, 22, 23, 51, 52, and 53, respectively; or

~~b. SEQ ID NOs: 24, 25, 26, 54, 55 and 56, respectively;~~

~~c. SEQ ID NOs: 27, 28, 29, 57, 58 and 59, respectively;~~

~~d. SEQ ID NOs: 30, 31, 32, 60, 61 and 62, respectively;~~

~~e.~~ (b) SEQ ID NOs: 36, 37, 38, 66, 67, and 68, respectively;

~~f. SEQ ID NOs: 39, 40, 41, 69, 70 and 71, respectively;~~

~~g. SEQ ID NOs: 42, 43, 44, 72, 73 and 74, respectively;~~

~~h. SEQ ID NOs: 45, 46, 47, 75, 76 and 77, respectively; or~~

~~i. SEQ ID NOs: 48, 49, 50, 78, 79 and 80, respectively;~~

wherein the antibody or antigen-binding fragment thereof specifically binds claudin 18.2 (CLDN18.2~~), preferably human CLDN18.~~).

2.

~~2. An isolated monoclonal antibody or antigen-binding fragment thereof comprising a heavy chain complementarity determining region 1 (HCDR1), HCDR2, HCDR3, a light chain complementarity determining region 1 (LCDR1), LCDR2, and LCDR3, having the polypeptide sequences of:~~

~~a. SEQ ID NOs: 93, 94, 95, 123, 124 and 125, respectively;~~

~~b. SEQ ID NOs: 81, 82, 83, 111, 112 and 113, respectively;~~

~~c. SEQ ID NOs: 84, 85, 86, 114, 115 and 116, respectively;~~

~~d. SEQ ID NOs: 87, 88, 89, 117, 118 and 119, respectively;~~

~~e. SEQ ID NOs: 90, 91, 92, 120, 121 and 122, respectively;~~

~~f. SEQ ID NOs: 96, 97, 98, 126, 127 and 128, respectively;~~

~~g. SEQ ID NOs: 99, 100, 101, 129, 130 and 131, respectively;~~

~~h. SEQ ID NOs: 102, 103, 104, 132, 133 and 134, respectively;~~

~~i. SEQ ID NOs: 105, 106, 107, 135, 136 and 137, respectively; or~~

~~j. SEQ ID NOs: 108, 109, 110, 138, 139 and 140, respectively;~~

~~wherein the antibody or antigen-binding fragment thereof specifically binds claudin 18.2 (CLDN18.2), preferably human CLDN18.2.~~

~~3.~~ The isolated monoclonal antibody or antigen-binding fragment thereof of claim 1~~ or 2~~, comprising a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO: ~~9,~~ 1~~, 3, 5, 7, 11, 13, 15, 17~~ or ~~19~~11, or a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO: ~~10,~~ 2~~, 4, 6, 8, 12, 14, 16, 18~~ or ~~20~~12.

~~4~~

3. The isolated monoclonal antibody or antigen-binding fragment thereof of claim 1~~ or 2~~, comprising~~:~~

a. (a heavy chain variable region having the polypeptide sequence of SEQ ID NO:9, and a light chain variable region having the polypeptide sequence of SEQ ID NO:10;

) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:1, and a light chain variable region having the polypeptide sequence of SEQ ID NO:2; or

b. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:3, and a light chain variable region having the polypeptide sequence of SEQ ID NO:4;

c. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:5, and a light chain variable region having the polypeptide sequence of SEQ ID NO:6;

d. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:7, and a light chain variable region having the polypeptide sequence of SEQ ID NO:8;

(b) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:11, and a light chain variable region having the polypeptide sequence of SEQ ID NO:12;.

e. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:13, and a light chain variable region having the polypeptide sequence of SEQ ID NO:14;

f. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:15, and a light chain variable region having the polypeptide sequence of SEQ ID NO:16;

g. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:17, and a light chain variable region having the polypeptide sequence of SEQ ID NO:18;

h. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:19, and a light chain variable region having the polypeptide sequence of SEQ ID NO:20.

5. The isolated monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-4, wherein the monoclonal antibody or antigen-binding fragment thereof is capable of inducing effector-mediated tumor cell lysis.

6. The isolated monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-5, wherein the antibody or antigen-binding fragment thereof is chimeric.

7. The isolated monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-6, wherein the antibody or antigen-binding fragment thereof is human or humanized.

8. The isolated monoclonal antibody or antigen-binding fragment thereof of claim 71, wherein the antibody or antigen-binding fragment thereof is chimeric or human or humanized.

5. The isolated monoclonal antibody or antigen-binding fragment thereof of claim 4, wherein the isolated humanized antibody or antigen-binding fragment thereof comprises:

(a) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:142, and a light chain variable region having the polypeptide sequence of SEQ ID NO:144;

(b) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:142, and a light chain variable region having the polypeptide sequence of SEQ ID NO:145;

(c) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:143, and a light chain variable region having the polypeptide sequence of SEQ ID NO:144;

(d) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:143, and a light chain variable region having the polypeptide sequence of SEQ ID NO:145;

~~(a) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:146, and a light chain variable region having the polypeptide sequence of SEQ ID NO:148;~~

~~(b) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:146, and a light chain variable region having the polypeptide sequence of SEQ ID NO:149;~~

~~(c) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:146, and a light chain variable region having the polypeptide sequence of SEQ ID NO:150;~~

~~(d) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:147, and a light chain variable region having the polypeptide sequence of SEQ ID NO:148;~~

~~(e) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:147, and a light chain variable region having the polypeptide sequence of SEQ ID NO:149;~~

~~(f) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:147, and a light chain variable region having the polypeptide sequence of SEQ ID NO:150;~~

(e) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:151, and a light chain variable region having the polypeptide sequence of SEQ ID NO:153; or

(f) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:152, and a light chain variable region having the polypeptide sequence of SEQ ID NO:153~~;~~.

~~(g) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:154, and a light chain variable region having the polypeptide sequence of SEQ ID NO:157;~~

~~(h) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:155, and a light chain variable region having the polypeptide sequence of SEQ ID NO:157;~~

~~(i) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:156, and a light chain variable region having the polypeptide sequence of SEQ ID NO:158;~~

(j) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:159, and a light chain variable region having the polypeptide sequence of SEQ ID NO:163;

(k) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:159, and a light chain variable region having the polypeptide sequence of SEQ ID NO:164;

(l) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:160, and a light chain variable region having the polypeptide sequence of SEQ ID NO:163;

(m)a heavy chain variable region having the polypeptide sequence of SEQ ID NO:160, and a light chain variable region having the polypeptide sequence of SEQ ID NO:164;

(n) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:161, and a light chain variable region having the polypeptide sequence of SEQ ID NO:165; or

(o) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:162, and a light chain variable region having the polypeptide sequence of SEQ ID NO:165.

9. The isolated monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-8, wherein the antibody or antigen-binding fragment thereof is capable of inducing effector-mediated tumor cell lysis through antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent phagocytosis (ADPC), and/or complement-dependent cytotoxicity (CDC), and/or mediating the recruitment of conjugated drugs, and/or forming a bispecific antibody with another mAb or antigen-binding fragment thereof with cancer-killing effect.

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6. An isolated nucleic acid encoding the monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-9claim 1.

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7. A vector comprising the isolated nucleic acid of claim 106.

12

8. A host cell comprising the vector of claim 117.

13

9. A pharmaceutical composition, comprising the isolated monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-9claim 1 and a pharmaceutically acceptable carrier.

14. A method of targeting CLDN18.2 on a cancer cell surface in a subject in need thereof, comprising administering to the subject the

10. The pharmaceutical composition of claim 139 for use in therapy.

15. A method of treating cancer in a subject in need thereof, comprising administering to the subject

11. Use of the pharmaceutical composition of claim ~~13~~9 in the manufacture of a medicament for the treatment of a claudin 18.2 (CLDN18.2) positive cancer in a subject in need thereof, wherein the pharmaceutical composition is to be administered to the subject.

~~16~~

12. The ~~method~~use of claim ~~15~~11, wherein the cancer is selected from the group consisting of a ~~lung cancer, a~~ gastric cancer, an esophageal cancer, a ~~bile duct cancer, a cholangiocarcinoma, a~~ colon cancer, a ~~hepatocellular carcinoma, a renal cell carcinoma, a bladder urothelial carcinoma, a metastatic melanoma, a breast cancer, an ovarian cancer, a cervical cancer, a head and neck cancer, a~~ pancreatic cancer, a ~~glioma, a glioblastoma, and other solid tumors, and a hon-Hodgkin's lymphoma (NHL), an acute lymphocytic leukemia (ALL), a chronic lymphocytic leukemia (CLL), a chronic myelogenous leukemia (CML), a multiple myeloma (MM), an acute myeloid leukemia (AML), and other liquid tumors~~bile duct cancer, and a cholangiocarcinoma.

~~17. A method of treating an inflammatory disease in a subject in need thereof, comprising administering to the subject the pharmaceutical composition of claim 13.~~

~~18.~~

13. A method of producing the monoclonal antibody or antigen-binding fragment thereof of ~~any one of claims~~ claim 1~~-9~~, comprising culturing a cell comprising a nucleic acid encoding the monoclonal antibody or antigen-binding fragment thereof under conditions to produce the monoclonal antibody or antigen-binding fragment thereof and recovering the antibody or antigen-binding fragment thereof from the cell or culture.

~~19~~

14. A method of producing a pharmaceutical composition comprising the monoclonal antibody or antigen-binding fragment of ~~any one of claims 1-9~~claim 1, comprising combining the monoclonal antibody or antigen-binding fragment thereof with a pharmaceutically acceptable carrier to obtain the pharmaceutical composition.

~~20~~

15. A method of determining a level of CLDN18.2 in a subject, the method comprising:

a. obtaining a sample from the subject;

b. contacting the sample with an isolated monoclonal antibody or antigen-binding fragment thereof of ~~any one of claims~~ claim 1~~-9~~; and

c. determining a level of CLDN18.2 in the subject.

~~21~~

16. The method of claim ~~20~~15, wherein the sample is a tissue sample or a blood sample.

~~22~~

17. The method of claim ~~21~~16, wherein the tissue sample is a cancer tissue sample.

~~23. The method of claim 20, wherein the sample is a blood sample.~~