

CLAIMS

What is claimed is:

1. An antibody-drug conjugate, comprising a drug moiety covalently attached to an antibody or fragment thereof having binding specificity to a wild-type human claudin 18.2 (CLDN18.2) protein, wherein the antibody or the fragment thereof binds to the β 3- β 4 loop and the β 5 strand of CLDN18.2, wherein the β 3- β 4 loop consists of residues 45-63 of SEQ ID NO:30 (NYQGLWRSCVRESSGFTEC), and the β 5 strand consists of residues 169-172 of SEQ ID NO:30 (YTFG).
2. The antibody-drug conjugate of claim 1, wherein the antibody or fragment thereof is attached to 2 to 10 of the drug moiety.
3. The antibody-drug conjugate of claim 1, wherein the antibody or fragment thereof is attached to 2 to 6 of the drug moiety.
4. The antibody-drug conjugate of any preceding claim, wherein the antibody or the fragment thereof does not bind to β 1 and β 2, or binds to β 1 or β 2 at an affinity that is at least 10 fold lower than to the β 3- β 4 loop or the β 5 strand.
5. The antibody-drug conjugate of any preceding claim, wherein the antibody or the fragment thereof does not bind to the CLDN18.1 protein or binds to the CLDN18.1 protein at an affinity that is at least 10 fold lower to the CLDN18.2 protein.
6. The antibody-drug conjugate of any preceding claim, wherein the antibody or the fragment thereof binds to the CLDN18.2 M149L mutant at an affinity that is at least 1% of the affinity to the wild-type CLDN18.2 protein.

7. The antibody-drug conjugate of any preceding claim, wherein the antibody or the fragment thereof binds to at least an amino acid residue selected from the group consisting of N45, Y46, G48, V54, R55, E56, S58, F60, and E62, and at least an amino acid residue selected from the group consisting of Y169 and G172, of SEQ ID NO:30.

8. The antibody-drug conjugate of any preceding claim, wherein the antibody or the fragment thereof comprises a light chain variable region comprising light chain complementarity determining regions CDRL1, CDRL2, and CDRL3 and a heavy chain variable region comprising heavy chain complementarity determining regions CDRH1, CDRH2, and CDRH3, and wherein:

the CDRL1 comprises an amino acid sequence selected from the group of SEQ ID NO:208-226, 304-305 and 308-309;

the CDRL2 comprises an amino acid sequence selected from the group of SEQ ID NO:227-233;

the CDRL3 comprises an amino acid sequence selected from the group of SEQ ID NO:3, 8, 13, 19, 20 and 42-58;

the CDRH1 comprises an amino acid sequence selected from the group of SEQ ID NO:234-254;

the CDRH2 comprises an amino acid sequence selected from the group of SEQ ID NO:255-280, 306, 310 and 311; and

the CDRH3 comprises an amino acid sequence selected from the group of SEQ ID NO:281-303, 307, and 312-314.

9. The antibody-drug conjugate of claim 8, wherein:

the CDRL1 comprises the amino acid sequence of SEQ ID NO:210, 304 or 305,

the CDRL2 comprises the amino acid sequence of SEQ ID NO:227,

the CDRL3 comprises the amino acid sequence of SEQ ID NO:3, 19 or 20,

the CDRH1 comprises the amino acid sequence of SEQ ID NO:253,

the CDRH2 comprises the amino acid sequence of SEQ ID NO:278 or 306, and
the CDRH3 comprises the amino acid sequence of SEQ ID NO:303 or 307.

10. The antibody-drug conjugate of claim 9, wherein the antibody or the fragment thereof comprises a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NO:141, 192-195 and 206-207, or a peptide having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:141, 192-195 and 206-207.

11. The antibody-drug conjugate of claim 9 or 10, wherein the antibody or the fragment thereof comprises a heavy chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NO:171, 188-191 and 205, or a peptide having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:171, 188-191 and 205.

12. The antibody-drug conjugate of claim 8, wherein:
the CDRL1 comprises the amino acid sequence of SEQ ID NO:304,
the CDRL2 comprises the amino acid sequence of SEQ ID NO:227,
the CDRL3 comprises the amino acid sequence of SEQ ID NO:19,
the CDRH1 comprises the amino acid sequence of SEQ ID NO:253,
the CDRH2 comprises the amino acid sequence of SEQ ID NO:306, and
the CDRH3 comprises the amino acid sequence of SEQ ID NO:307.

13. The antibody-drug conjugate of claim 12, wherein the antibody or the fragment thereof comprises a light chain variable region comprising an amino acid sequence of SEQ ID NO:206 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:205.

14. The antibody-drug conjugate of 8, wherein:
the CDRL1 comprises the amino acid sequence of SEQ ID NO:216, 308 or 309,
the CDRL2 comprises the amino acid sequence of SEQ ID NO:227,
the CDRL3 comprises the amino acid sequence of SEQ ID NO:13,
the CDRH1 comprises the amino acid sequence of SEQ ID NO:246,
the CDRH2 comprises the amino acid sequence of SEQ ID NO:268, 310 or 311, and
the CDRH3 comprises the amino acid sequence of SEQ ID NO:294, 312, 313 or 314.
15. The antibody-drug conjugate of 14, wherein the antibody or the fragment thereof comprises a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NO:129, 178-180 and 201-202, or a peptide having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:129, 178-180 and 201-202.
16. The antibody-drug conjugate of 14 or 15, wherein the antibody or the fragment thereof comprises a heavy chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NO:159, 175-177 and 196-200, or a peptide having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:159, 175-177 and 196-200.
17. The antibody-drug conjugate of claim 14, wherein:
the CDRL1 comprises the amino acid sequence of SEQ ID NO:309,
the CDRL2 comprises the amino acid sequence of SEQ ID NO:227,
the CDRL3 comprises the amino acid sequence of SEQ ID NO:13,
the CDRH1 comprises the amino acid sequence of SEQ ID NO:246,
the CDRH2 comprises the amino acid sequence of SEQ ID NO:311, and
the CDRH3 comprises the amino acid sequence of SEQ ID NO:294.

18. The antibody-drug conjugate of claim 17, wherein the antibody or the fragment thereof comprises a light chain variable region comprising an amino acid sequence of SEQ ID NO:202 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:197.

19. The antibody-drug conjugate of any preceding claim, wherein the drug moiety is a cytotoxic or cytostatic agent.

20. The antibody-drug conjugate of claim 19, wherein the drug moiety is a maytansinoid or an auristatin.

21. The antibody-drug conjugate of claim 20, wherein the drug moiety comprises DM1 or DM4.

22. The antibody-drug conjugate of claim 20, wherein the drug moiety comprises monomethyl auristatin E (MMAE) or monomethyl auristatin F (MMAF).

23. The antibody-drug conjugate of any preceding claim, wherein the drug moiety is attached to the antibody or fragment thereof through a linker.

24. The antibody-drug conjugate of claim 23, wherein the linker is hydrolyzable under acidic conditions.

~~25. A method of treating cancer in a patient in need thereof, comprising administering to the patient the antibody-drug conjugate of any one of claims 1-24.~~

~~26~~25. Use of the antibody-drug conjugate of any one of claims 1-24 for the manufacture of a medicament for the treatment of cancer.

2726. The ~~method of claim 25 or the~~ use of claim 256, wherein the cancer is selected from the group consisting of bladder cancer, liver cancer, colon cancer, rectal cancer, endometrial cancer, leukemia, lymphoma, pancreatic cancer, small cell lung cancer, non-small cell lung cancer, breast cancer, urethral cancer, head and neck cancer, gastrointestinal cancer, stomach cancer, oesophageal cancer, ovarian cancer, renal cancer, melanoma, prostate cancer and thyroid cancer.

2827. The ~~method of claim 25 or the~~ use of claim 2526, wherein the cancer is gastric cancer.

2928. The ~~method of claim 25 or the~~ use of claim 2526, wherein the patient has a M149L mutant of the CLDN18.2 protein.