

CLAIMS

1. An antibody-drug conjugate (ADC) comprising an antibody or antigen-binding portion thereof conjugated to a drug moiety, wherein the antibody or antigen-binding portion thereof binds P-cadherin and comprises:
 - a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1;
 - a HCDR2 comprising the amino acid sequence of SEQ ID NO: 2;
 - a HCDR3 comprising the amino acid sequence of SEQ ID NO: 3;
 - a LCDR1 comprising the amino acid sequence of SEQ ID NO: 4;
 - a LCDR2 comprising the amino acid sequence of SEQ ID NO: 5; and
 - a LCDR3 comprising the amino acid sequence of SEQ ID NO: 6.
2. The ADC of claim 1, wherein the antibody or antigen-binding portion thereof comprises:
 - (A) a HCDR1 as set forth in SEQ ID NO: 1; a HCDR2 as set forth in SEQ ID NO: 2; and a HCDR3 as set forth in SEQ ID NO: 3; and
 - (B) a LCDR1 as set forth in SEQ ID NO: 4; a LCDR2 as set forth in SEQ ID NO: 5; and a LCDR3 as set forth in SEQ ID NO: 6.
3. The ADC of claim 1 or 2, wherein the drug moiety comprises a cytotoxic agent or cytostatic agent selected from a toxin, a chemotherapeutic agent, an antibiotic, a radioactive isotope, or a nucleolytic enzyme.
4. The ADC of claim 3, wherein the cytotoxic agent is selected from maytansinoids (such as DM1, DM3, DM4), dolastatins, dolostatin peptidic analogs and derivatives thereof, such as auristatins, calicheamicin, trichothecene, and CC1065, optionally the cytotoxic agent is MMAE, DM1 or MMAF.
5. The ADC of any of the preceding claims, wherein the ADC has the formula Ab-(L-D)_p, wherein Ab is the antibody or antigen-binding portion thereof, L is a linker, D is the drug moiety, and p is a integer from 1 to 20.
6. The ADC of claim 5, wherein the linker is cleavable by a protease.
7. The ADC of any of claims 5-6, wherein the linker is attached to the antibody through a thiol group on the antibody.
8. The ADC of any of claims 5-7, wherein the linker is selected from 6-maleimidocaproyl (MC), maleimidopropanoyl (MP), valine-citrulline (val-cit), alanine-phenylalanine (ala-phe), p-aminobenzyloxycarbonyl (PAB), N-Succinimidyl 4-(2-pyridylthio) pentanoate (SPP), N-succinimidyl 4-(N-maleimidomethyl) cyclohexane-1 carboxylate (SMCC), N-Succinimidyl (4-

iodo-acetyl) aminobenzoate (SIAB), and 6-maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl (MC-vc-PAB).

9. The ADC of any of claims 5-8, wherein the ADC has the formula Ab-(L-MMAE)_p, and p ranges from 1 to 8.

10. The ADC of claim 9, wherein the linker is MC-vc-PAB.

11. The ADC of any of the preceding claims, wherein the antibody or antigen-binding portion thereof comprises:

(A) a heavy chain variable region (VH):

(i) comprising the amino acid sequence as set forth in SEQ ID NO: 7; or

(ii) comprising an amino acid sequence at least 85%, 90%, or 95% identical to the amino acid sequence as set forth in SEQ ID NO: 7 yet retaining the specific binding affinity to P-cadherin; ~~or~~

~~(iii) comprising an amino acid sequence with addition, deletion and/or substitution of one or more (e.g. 1, 2 or 3) amino acids compared with the amino acid sequence as set forth in SEQ ID NO: 7; and/or~~

(B) a light chain variable region (VL):

(i) comprising the amino acid sequence as set forth in SEQ ID NO: 8; or

(ii) comprising an amino acid sequence at least 85%, at least 90%, or at least 95% identical to the amino acid sequence as set forth in SEQ ID NO: 8 yet retaining the specific binding affinity to P-cadherin; ~~or~~

~~(iii) comprising an amino acid sequence with addition, deletion and/or substitution of one or more (e.g. 1, 2 or 3) amino acids compared with the amino acid sequence as set forth in SEQ ID NO: 8.~~

~~12. The ADC of any of the preceding claims, wherein the antibody or antigen-binding portion thereof comprises one or more substitutions of amino acids in the framework sequences, e.g. FRW1, FRW2, FRW3, and/or FRW4 of the VH or VL region.~~

~~13. The ADC of any of the preceding claims, wherein the antibody or antigen-binding portion thereof comprises a heavy chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 7; and a light chain variable region comprising the amino acid sequence as set forth in SEQ ID NO: 8.~~

124. The ADC of any of the preceding claims, wherein the antibody or antigen-binding portion thereof further comprises a human IgG constant domain, such as a human IgG1, IgG2, IgG3 or IgG4 constant domain, preferably a human IgG1 constant domain or a variant thereof.

135. The ADC of any of the preceding claims, wherein:

- (a) the heavy chain of the antibody comprises a heavy chain variable region as set forth in SEQ ID NO: 7, and a heavy chain constant region as set forth in SEQ ID NO: 9; and
- (b) the light chain of the antibody comprises a light chain variable region as set forth in SEQ ID NO: 8, and a light chain constant region as set forth in SEQ ID NO: 10.

146. The ADC of any of the preceding claims, wherein the antibody is a chimeric antibody, a humanized antibody or a fully human antibody, preferably is a fully human monoclonal antibody.

157. A pharmaceutical composition comprising the ADC as defined in any of claims 146-14 and a pharmaceutically acceptable carrier.

168. A method for producing the ADC as defined in any of claims 146-14 comprising the steps of:

- cultivating a host cell comprising a vector encoding the antibody or antigen-binding portion thereof under suitable conditions for the expression of the vector;
- isolating the antibody or antigen-binding portion thereof from the host cell; and
- reacting a nucleophilic group of a drug moiety with a linker reagent to form drug-linker intermediate D-L, and then reacting D-L with the antibody or antigen-binding portion thereof, alternatively, reacting the antibody with a linker reagent to form antibody-linker intermediate Ab-L, and then reacting Ab-L with an activated drug moiety D, whereby the antibody-drug conjugate is formed.

179. The method of claim 168, wherein the average DAR of ADCs is in a range of about 1 to about 8, preferably is about 4.

~~20. A method of modulating a P-cadherin related immune response in a subject, comprising administering to the subject the ADC as defined in any of claims 1-16 or the pharmaceutical composition of claim 17 such that the P-cadherin related immune response is modulated in the subject.~~

~~21. A method for treating or preventing P-cadherin positive cancer in a subject, comprising administering an effective amount of the ADC as defined in any of claims 1-16 or the pharmaceutical composition of claim 17 to the subject.~~

~~22. The method of claim 21, wherein the cancer is selected from breast cancer, colorectal cancer, lung cancer, ovarian cancer, melanoma, bladder cancer, renal cell carcinoma, liver cancer, prostate cancer, stomach cancer, pancreatic cancer, cervical cancer, esophageal carcinoma, endometrial cancer, skin cancer, head and neck cancer, testis cancer, thyroid cancer, urothelial cancer, non-~~

~~Hodgkin's lymphoma, chronic lymphocytic leukemia, diffuse large B-cell lymphoma, and multiple myeloma.~~

~~23. The method of claim 22, wherein the cancer is breast cancer (such as breast ductal carcinoma), lung cancer (such as NSCLC) or colorectal cancer.~~

~~1824. Use of the ADC as defined in any of claims 1-146 in the manufacture of a medicament for diagnosing, preventing or treating p-Cadherin positive cancer.~~

~~1925. ADC as defined in any of claims 1-146 for use in treating or preventing P-cadherin positive cancer.~~

~~20. The use of claim 18 or the ADC of claim 19, wherein the cancer is selected from breast cancer, colorectal cancer, lung cancer, ovarian cancer, melanoma, bladder cancer, renal cell carcinoma, liver cancer, prostate cancer, stomach cancer, pancreatic cancer, cervical cancer, esophageal carcinoma, endometrial cancer, skin cancer, head and neck cancer, testis cancer, thyroid cancer, urothelial cancer, non-Hodgkin's lymphoma, chronic lymphocytic leukemia, diffuse large B-cell lymphoma, and multiple myeloma.~~

~~21. The use or ADC of claim 20, wherein the cancer is breast cancer, lung cancer or colorectal cancer.~~

~~226. A kit for treating or diagnosing cancer, comprising a container comprising the ADC as defined in any of claims 1-146.~~