WHAT IS CLAIMED IS:

1. An anti-HER3/MUC1 antibody or antigen-binding fragment thereof, comprising: a first antigen-binding domain that specifically binds to HER3; and a second antigen-binding domain that specifically binds to MUC1.

2. The anti-HER3/MUC1 antibody or antigen-binding fragment thereof of claim 1, wherein the first antigen-binding domain comprises a first heavy chain variable region (VH1) and a first light chain variable region (VL1); and the second antigen-binding domain comprises a second heavy chain variable region (VH2) and a second light chain variable region (VL2); and wherein:

(i) the first heavy chain variable region (VH1) comprises complementarity determining regions (CDRs) 1, 2, and 3, wherein the VH1 CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected VH1 CDR1 amino acid sequence, the VH1 CDR2 region comprises an amino acid sequence that is at least 80% identical to a selected VH1 CDR2 amino acid sequence, and the VH1 CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected VH1 CDR3 amino acid sequence; and

the first light chain variable region (VL1) comprises CDRs 1, 2, and 3, wherein the VL1 CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected VL1 CDR1 amino acid sequence, the VL1 CDR2 region comprises an amino acid sequence that is at least 80% identical to a selected VL1 CDR2 amino acid sequence, and the VL1 CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected VL1 CDR3 amino acid sequence,

wherein the selected VH1 CDRs 1, 2, and 3 amino acid sequences, the selected VL1 CDRs 1, 2, and 3 amino acid sequences are one of the following:

(1) the selected VH1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 7-9, respectively, and the selected VL1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 1-3, respectively;

(2) the selected VH1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 19-21, respectively, and the selected VL1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 13-15, respectively;

(3) the selected VH1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 4-6, respectively, and the selected VL1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 1-3, respectively; and

(4) the selected VH1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 16-18, respectively, and the selected VL1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 13-15, respectively;

and/or,

(ii) the second heavy chain variable region (VH2) comprises CDRs 1, 2, and 3, wherein the VH2 CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected VH2 CDR1 amino acid sequence, the VH2 CDR2 region comprises an amino acid sequence that is at least 80% identical to a selected VH2 CDR2 amino acid sequence, and the VH2 CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected VH2 CDR3 amino acid sequence; and

the second light chain variable region (VL2) comprises CDRs 1, 2, and 3, wherein the VL2 CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected VL2 CDR1 amino acid sequence, the VL2 CDR2 region comprises an amino acid sequence that is at least 80%

identical to a selected VL2 CDR2 amino acid sequence, and the VL2 CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected VL2 CDR3 amino acid sequence,

wherein the selected VH2 CDRs 1, 2, and 3 amino acid sequences, and the selected VL2 CDRs 1, 2, and 3 amino acid sequences are one of the following:

(1) the selected VH2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 10-12, respectively, and the selected VL2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 1-3, respectively; and

(2) the selected VH2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 22-24, respectively, and the selected VL2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 13-15, respectively.

3. The anti-HER3/MUC1 antibody or antigen-binding fragment thereof of claim 2, wherein

(1) the selected VH1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 7-9, respectively, and the selected VL1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 1-3, respectively, and the selected VH2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 10-12, respectively, and the selected VL2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 1-3, respectively;

(2) the selected VH1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 19-21, respectively, and the selected VL1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 13-15, respectively, and the selected VH2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 22-24, respectively, and the selected VL2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 13-15, respectively;

(3) the selected VH1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 4-6, respectively, and the selected VL1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 1-3, respectively, and the selected VH2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 10-12, respectively, and the selected VL2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 1-3, respectively; or

(4) the selected VH1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 16-18, respectively, and the selected VL1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 13-15, respectively, and the selected VH2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 22-24, respectively, and the selected VL2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 13-15, respectively.

4. The anti-HER3/MUC1 antibody or antigen-binding fragment thereof of any one of claims 2-3, wherein:

(i) the VH1 comprises a sequence that is at least 80%, 85%, 90%, 95%, 99%, or 100% identical to SEQ ID NO: 27, the VL1 comprises a sequence that is at least 80%, 85%, 90%, 95%, 99%, or 100% identical to SEQ ID NO: 25, the VH2 comprises a sequence that is at least 80%, 85%, 90%, 95%, 99%, or 100% identical to SEQ ID NO: 28, and the VL2 comprises a sequence that is at least 80%, 85%, 90%, 95%, 99%, or 100% identical to SEQ ID NO: 25; or,

(ii) the VH1 comprises a sequence that is at least 80%, 85%, 90%, 95%, 99%, or 100% identical to SEQ ID NO: 26, the VL1 comprises a sequence that is at least 80%, 85%, 90%, 95%, 99%, or 100% identical to SEQ ID NO: 25, the VH2 comprises a sequence that is at least 80%, 85%, 90%, 95%, 99%, or 100% identical to SEQ ID NO: 28, and the VL2 comprises a sequence that is at least 80%, 85%, 90%, 95%, 99%, or 100% identical to SEQ ID NO: 25;

optionally wherein:

(i) (a) the VH1 comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 27, and the VL1 comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 25; or (b) the VH1 comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 26, and the VL1 comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 25; and/or,

(ii) the VH2 comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 28, and the VL2 comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 25;

optionally wherein:

(i) (a) the VH1 comprises the sequence of SEQ ID NO: 27 and the VL1 comprises the sequence of SEQ ID NO: 25; or (b) the VH1 comprises the sequence of SEQ ID NO: 26 and the VL1 comprises the sequence of SEQ ID NO: 25; and/or,

(ii) the VH2 comprises the sequence of SEQ ID NO: 28 and the VL2 comprises the sequence of SEQ ID NO: 25.

5. The anti-HER3/MUC1 antibody or antigen-binding fragment thereof of any one of claims 2-4, wherein:

(i) the VH1 comprises VH1 CDR1, VH1 CDR2, and VH1 CDR3 that are identical to VH CDR1, VH CDR2, and VH CDR3 of a selected VH sequence; and the VL1 comprising VL1 CDR1, VL1 CDR2, and VL1 CDR3 that are identical to VL CDR1, VL CDR2, and VL CDR3 of a selected VL sequence, wherein the selected VH sequence and the selected VL sequence are one of the following:

(1) the selected VH sequence is SEQ ID NO: 26, and the selected VL sequence is SEQ ID NO: 25; and

(2) the selected VH sequence is SEQ ID NO: 27, and the selected VL sequence is SEQ ID NO: 25;

and/or,

(ii) the VH2 comprises VH2 CDR1, VH2 CDR2, and VH2 CDR3 that are identical to VH CDR1, VH CDR2, and VH CDR3 of a selected VH sequence; and the VL2 comprising VL2 CDR1, VL2 CDR2, and VL2 CDR3 that are identical to VL CDR1, VL CDR2, and VL CDR3 of a selected VL sequence, wherein the selected VH sequence is SEQ ID NO: 28, and the selected VL sequence is SEQ ID NO: 25.

6. The anti-HER3/MUC1 antibody or antigen-binding fragment thereof of one of claims 1-5, wherein the anti-HER3/MUC1 antibody or antigen-binding fragment thereof is characterized by one or more of the following:

(i) the first antigen-binding domain specifically binds to human or monkey HER3; and/or the second antigen-binding domain specifically binds to human or monkey MUC1;

(ii) the first antigen-binding domain is human or humanized; and/or the second antigen-binding domain is human or humanized;

(iii) the antibody is a multispecific antibody (e.g., a bispecific antibody);

(iv) the first antigen-binding domain is a single-chain variable fragment (scFv); and/or the second antigen-binding domain is a scFv;

(v) the first light chain variable region and the second light chain variable region are identical.

7. A nucleic acid comprising a polynucleotide encoding the anti-HER3/MUC1 antibody or antigen-binding fragment thereof of any one of claims 1-6.

8. A vector comprising the nucleic acid of claim 7.

9. A cell comprising the nucleic acid of claim 7 or a vector comprising the nucleic acid.

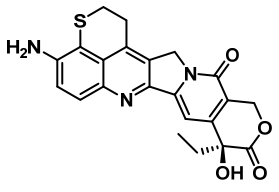
10. A method of producing an anti-HER3/MUC1 antibody or an antigen-binding fragment thereof, the method comprising

(a) culturing the cell of claim 9 under conditions sufficient for the cell to produce the anti-HER3/MUC1 antibody or the antigen-binding fragment thereof; and

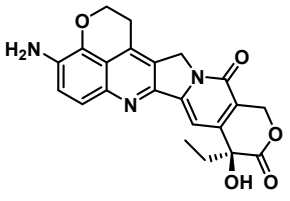
(b) collecting the anti-HER3/MUC1 antibody or the antigen-binding fragment thereof produced by the cell.

11. An anti-HER3/MUC1 antibody-drug conjugate (ADC) comprising a therapeutic agent covalently bound to the anti-HER3/MUC1 antibody or antigen-binding fragment thereof of any one of claims 1-6.

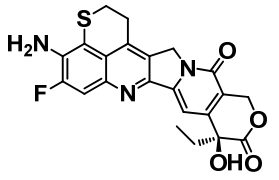
12. The anti-HER3/MUC1 antibody drug conjugate of claim 11, wherein the therapeutic agent is a cytotoxic or cytostatic agent; optionally the therapeutic agent is selected from MMAE, MMAF or one of the following:



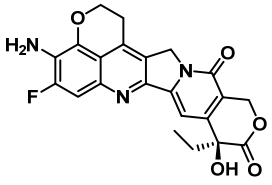
(CPT-1),



(CPT-2),

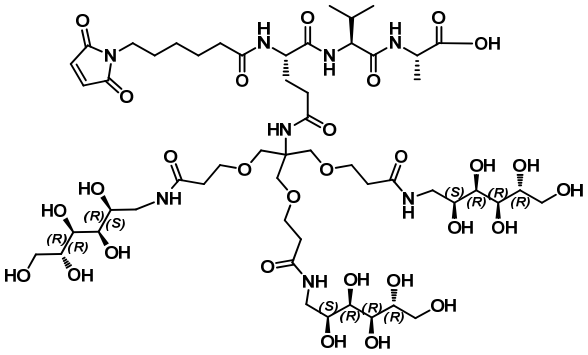


(CPT-3), or

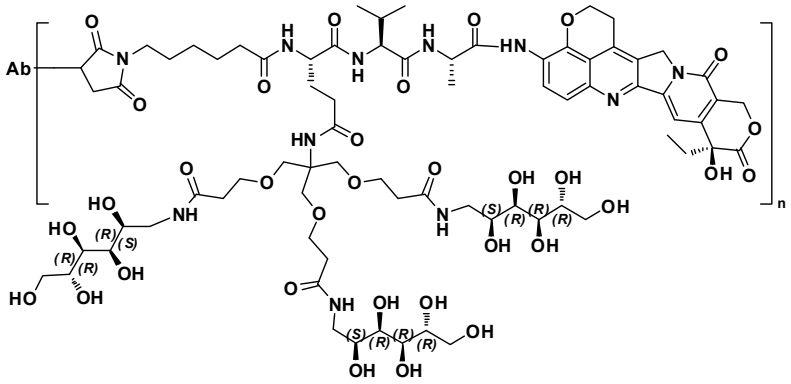


(CPT-4).

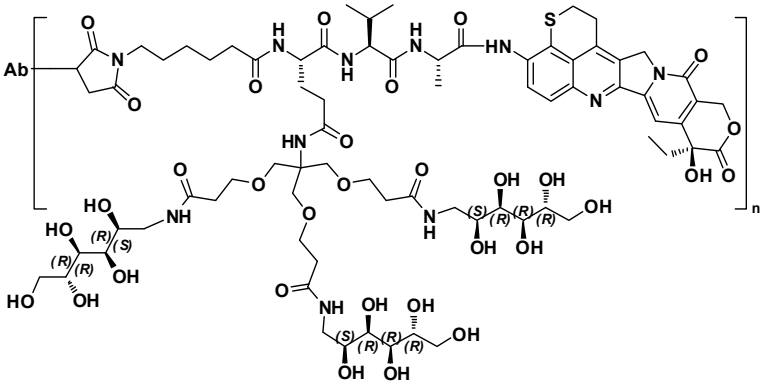
13. The antibody-drug conjugate of claim 11 or 12, wherein the therapeutic agent is linked to the antibody or antigen-binding fragment thereof, or the antigen-binding protein construct via a linker, and the linker has a structure of:



14. The antibody-drug conjugate of any one of claims 11-13, wherein the antibody-drug conjugate has a structure of:



, or



wherein n = 1-8; wherein "Ab" represents the antibody or antigen-binding fragment thereof, or the antigen-binding protein construct.

15. Use of the anti-HER3/MUC1 antibody or antigen-binding fragment thereof of any one of claims 1-6, or the anti-HER3/MUC1 antibody-drug conjugate of any one of claims 11-14, in the manufacture of a medicament for the treatment of a cancer in a subject.

16. The use of claim 15, wherein the cancer is a cancer expressing HER3 and/or MUC1 (e.g., both HER3 and MUC1), or selected from oesophageal cancer, colorectal cancer, gastric cancer, breast cancer, endometrial carcinoma, lung cancer, melanoma, ovarian cancer, bladder cancer, stomach

cancer, Non-Hodgkin Lymphoma, head and neck cancer, pancreatic cancer, lung adenocarcinoma, and cervical cancer.

17. A method of decreasing the rate of tumor growth or killing a tumor cell, the method comprising contacting a tumor cell with an effective amount of a composition comprising the anti-HER3/MUC1 antibody or antigen-binding fragment thereof of any one of claims 1-6, or an anti-HER3/MUC1 antibody-drug conjugate of any one of claims 11-14.

18. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and (a) the anti-HER3/MUC1 antibody or antigen-binding fragment thereof of any one of claims 1-6, and/or (b) the anti-HER3/MUC1 antibody-drug conjugate of any one of claims 11-14.

19. An anti-HER3/MUC1 antibody-drug conjugate (ADC) comprising a therapeutic agent covalently bound to a bispecific antibody or antigen-binding fragment thereof comprising: a first antigen-binding domain that specifically binds to HER3; and a second antigen-binding domain that specifically binds to MUC1.

20. The anti-HER3/MUC1 ADC of any one of claims 11-14 and 19, wherein the drug-to-antibody ratio (DAR) is about 4 or 8.