

CLAIMS

1. A bispecific antibody, comprising a first binding arm that binds human CD3 and a second binding arm that binds human MUC16, wherein the first binding arm comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 1961 and a light chain comprising the amino acid sequence of SEQ ID NO: 1960, and wherein the second binding arm comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 1959 and a light chain comprising the amino acid sequence of SEQ ID NO: 1960.
2. A bispecific antibody, comprising a first binding arm that binds human CD3 and a second binding arm that binds human MUC16, wherein the first binding arm comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 1962 and a light chain comprising the amino acid sequence of SEQ ID NO: 1960, and wherein the second binding arm comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 1959 and a light chain comprising the amino acid sequence of SEQ ID NO: 1960.
3. An isolated antibody or antigen-binding fragment thereof that binds human MUC16, wherein the antibody or antigen-binding fragment comprises heavy and light chain complementarity determining regions (CDRs) of a heavy chain variable region and light chain variable region (HCVR/LCVR) amino acid sequence pair selected from the group consisting of: SEQ ID NOs: 18/26, 82/858, and 98/170.
4. The isolated antibody or antigen-binding fragment of claim 3, wherein the antibody or antigen-binding fragment comprises HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 domains, respectively, selected from the group consisting of: SEQ ID NOs: 20-22-24-28-30-32, 84-86-88-860-862-864, and 100-102-104-172-174-176.
5. The isolated antibody or antigen-binding fragment of claim 4, wherein the antibody or antigen-binding fragment comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of: SEQ ID NOs: 18/26, 82/858, and 98/170.

6. The isolated antibody or antigen-binding fragment of any one of claims 3-5 that binds human MUC16 within an epitope ranging from residue 428 to residue 481 of SEQ ID NO: 1902.

7. The isolated antibody or antigen-binding fragment of claim 6 that interacts with amino acid residues 428-434, 429-434, 453-467, 459-467, 460-467 and/or 474-481 of SEQ ID NO: 1902.

8. A bispecific antigen-binding molecule comprising a first antigen-binding domain that binds human CD3 and a second antigen-binding domain that binds human MUC16, wherein the second antigen-binding domain is derived from the antibody or antigen-binding fragment of any one of claims 3-7.

9. The bispecific antigen-binding molecule of claim 8, wherein the first antigen-binding domain binds human cells expressing human CD3 and cynomolgus monkey cells expressing cynomolgus CD3.

10. The bispecific antigen-binding molecule of claim 8, wherein the antigen-binding molecule binds both human CD3 and human MUC16 and induces T cell-mediated cell killing of MUC16-expressing cells.

11. The bispecific antigen-binding molecule of claim 8 wherein the antigen-binding molecule inhibits tumor growth in immunocompromised mice bearing human ovarian cancer xenografts.

12. The bispecific antigen-binding molecule of claim 8, wherein the antigen-binding molecule suppresses tumor growth of established tumors in immunocompromised mice bearing human ovarian cancer xenografts.

13. The bispecific antigen-binding molecule of any one of claims 8-12, wherein the antigen-binding molecule induces T cell-mediated tumor cell killing with an EC₅₀ value of less than about 31 pM, as measured in an *in vitro* T cell-mediated tumor cell killing assay.

14. The bispecific antigen-binding molecule of any one of claims 8-13, wherein the second antigen-binding domain specifically binds human MUC16 with an K_D value of less than about 7 nM, as measured in an *in vitro* surface plasmon resonance binding assay.

15. The bispecific antigen-binding molecule of any one of claims 8-14, wherein the second antigen-binding domain specifically binds each of human MUC16 with an K_D value of less than about 5 nM, less than about 2 nM, less than about 1 nM, less than about 800 pM, or less than about 600 pM, as measured in an *in vitro* surface plasmon resonance binding assay.

16. The bispecific antigen-binding molecule of any one of claims 8-15 that is a bispecific antibody or bispecific antigen-binding fragment thereof.

17. The bispecific antigen-binding molecule of claim 8, wherein the second antigen-binding domain that specifically binds human MUC16 comprises the heavy and light chain CDRs of a HCVR/LCVR amino acid sequence pair comprising SEQ ID NOs:18/26.

18. The bispecific antigen-binding molecule of claim 17, wherein the first antigen-binding domain that specifically binds human CD3 comprises the heavy and light chain CDRs of a HCVR/LCVR amino acid sequence pair selected from the group consisting of: SEQ ID NOs: 1730/26, 1762/26, 1778/26, 1786/26, and 1866/26.

19. The bispecific antigen-binding molecule of claim 18, wherein the first antigen-binding domain that binds human CD3 comprises a heavy chain variable region (HCVR) comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 1730, 1762, 1778, 1786, and 1866, and a light chain variable region (LCVR) comprising an amino acid sequence of SEQ ID NO: 26.

20. The bispecific antigen-binding molecule of claim 19, wherein the first antigen-binding domain comprises a HCVR comprising the amino acid sequence of SEQ ID NO: 1730 and a LCVR comprising the amino acid sequence of SEQ ID NO: 26, and wherein the bispecific antigen-binding molecule is a bispecific antibody.

21. The bispecific antigen-binding molecule of claim 19, wherein the first antigen-binding domain comprises a HCVR comprising the amino acid sequence of SEQ ID NO:

1762 and a LCVR comprising the amino acid sequence of SEQ ID NO: 26, and wherein the bispecific antigen-binding molecule is a bispecific antibody.

22. The bispecific antigen-binding molecule of claim 19, wherein the first antigen-binding domain comprises a HCVR comprising the amino acid sequence of SEQ ID NO: 1778 and a LCVR comprising the amino acid sequence of SEQ ID NO: 26, and wherein the bispecific antigen-binding molecule is a bispecific antibody.

23. The bispecific antigen-binding molecule of claim 19, wherein the first antigen-binding domain comprises a HCVR comprising the amino acid sequence of SEQ ID NO: 1786 and a LCVR comprising the amino acid sequence of SEQ ID NO: 26, and wherein the bispecific antigen-binding molecule is a bispecific antibody.

24. The bispecific antigen-binding molecule of claim 19, wherein the first antigen-binding domain comprises a HCVR comprising the amino acid sequence of SEQ ID NO: 1866 and a LCVR comprising the amino acid sequence of SEQ ID NO: 26, and wherein the bispecific antigen-binding molecule is a bispecific antibody.

25. A bispecific antibody comprising a first antigen-binding domain that specifically binds human CD3 and a second antigen-binding domain that specifically binds human MUC16, wherein the first antigen-binding domain comprises three heavy chain complementarity determining regions (A1-HCDR1, A1-HCDR2 and A1-HCDR3) and three light chain complementarity determining regions (A1-LCDR1, A1-LCDR2 and A1-LCDR3), and the second antigen-binding domain comprises three heavy chain complementarity determining regions (A2-HCDR1, A2-HCDR2 and A2-HCDR3) and three light chain complementarity determining regions (A2-LCDR1, A2-LCDR2 and A2-LCDR3);

wherein A1-HCDR1, A1-HCDR2 and A1-HCDR3 comprise the amino acid sequences, respectively, of SEQ ID NOs: 1732-1734-1736, and A1-LCDR1, A1-LCDR2 and A1-LCDR3 comprise the amino acid sequences, respectively, of SEQ ID NOs: 28-30-32; and

wherein A2-HCDR1, A2-HCDR2 and A2-HCDR3 comprise the amino acid sequences, respectively, of SEQ ID NO: 20-22-24, and A2-LCDR1, A2-LCDR2 and A2-LCDR3 comprise the amino acid sequences, respectively, of SEQ ID NO: 28-30-32.

26. A bispecific antibody comprising a first antigen-binding domain that specifically binds human CD3 and a second antigen-binding domain that specifically binds human MUC16, wherein the first antigen-binding domain comprises three heavy chain complementarity determining regions (A1-HCDR1, A1-HCDR2 and A1-HCDR3) and three light chain complementarity determining regions (A1-LCDR1, A1-LCDR2 and A1-LCDR3), and the second antigen-binding domain comprises three heavy chain complementarity determining regions (A2-HCDR1, A2-HCDR2 and A2-HCDR3) and three light chain complementarity determining regions (A2-LCDR1, A2-LCDR2 and A2-LCDR3);

wherein A1-HCDR1, A1-HCDR2 and A1-HCDR3 comprise the amino acid sequences, respectively, of SEQ ID NOs: 1868-1870-1872, and A1-LCDR1, A1-LCDR2 and A1-LCDR3 comprise the amino acid sequences, respectively, of SEQ ID NOs: 28-30-32; and

wherein A2-HCDR1, A2-HCDR2 and A2-HCDR3 comprise the amino acid sequences, respectively, of SEQ ID NO: 20-22-24, and A2-LCDR1, A2-LCDR2 and A2-LCDR3 comprise the amino acid sequences, respectively, of SEQ ID NO: 28-30-32.

27. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof of any one of claims 3-7 a pharmaceutically acceptable carrier or diluent.

28. A pharmaceutical composition comprising the bispecific antigen-binding molecule of any one of claims 1, 2, and 8-26 and a pharmaceutically acceptable carrier or diluent.

29. Use of the pharmaceutical composition of claim 27 or 28 in the manufacture of a medicament for treating a MUC16-expressing cancer in a subject.

30. The use of claim 29, wherein the cancer is selected from the group consisting of ovarian cancer, breast cancer, pancreatic cancer, non-small-cell lung cancer, intrahepatic cholangiocarcinoma-mass forming type, adenocarcinoma of the uterine cervix, and adenocarcinoma of the gastric tract.

31. The use of claim 30, wherein the cancer is ovarian cancer.

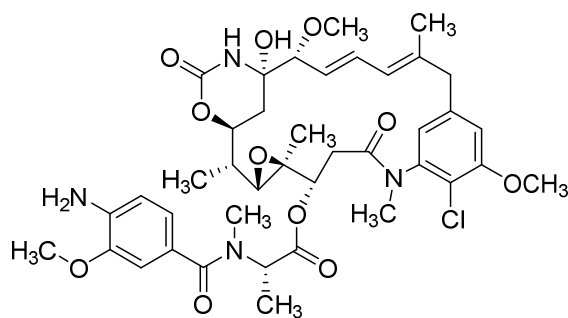
32. An antibody-drug conjugate (ADC) comprising an anti-MUC16 antibody or antigen-binding fragment thereof of any one of claims 3-7, and a cytotoxic agent, wherein the

33. The ADC of claim 32, wherein the cytotoxic agent is selected from an auristatin, a maytansinoid, a tubulysin, a tomaymycin derivative, or a dolastatin derivative.

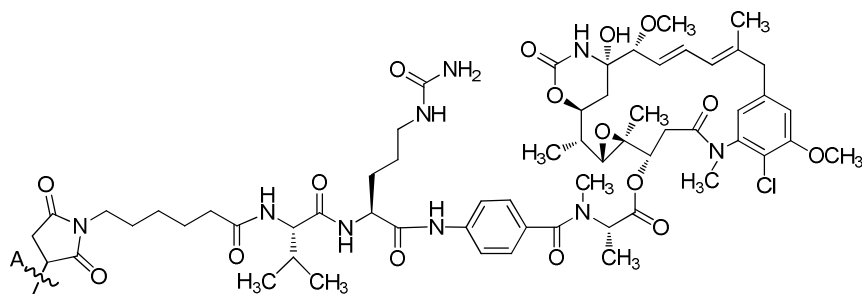
35. The ADC of claim 32 or 33, wherein the cytotoxic agent is a maytansinoid having the structure of Formula (I) or Formula (II).

The chemical structure of the major metabolite is a complex polycyclic molecule. It features a central bicyclic core with a bridgehead oxygen atom. Attached to this core are several side chains: a 4-methoxyphenyl group, a 4-chlorophenyl group, a 3-methoxyphenyl group, and a 4-methoxyphenyl group. The molecule also contains an amide group, an ester group, and a methoxy group. Stereochemistry is indicated with wedges and dashes.

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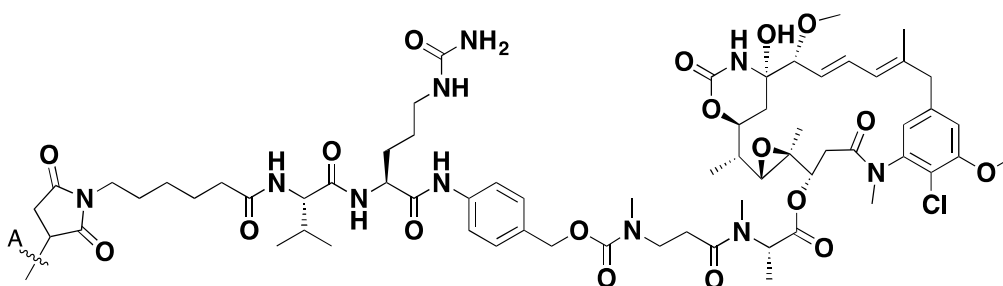


39. The ADC of claim 32 or 33, comprising an anti-MUC16 antibody or fragment thereof, and



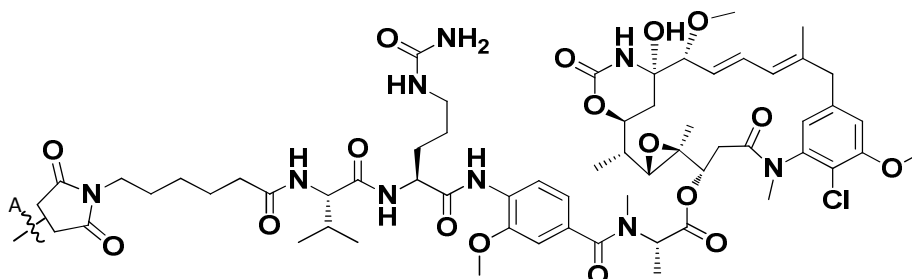
wherein $\text{---}\overset{\text{A}}{\text{---}}$ is a bond to the anti-MUC16 antibody or fragment thereof.

40. The ADC of claim 32 or 33, comprising an anti-MUC16 antibody or fragment thereof, and



wherein $\text{---}\overset{\text{A}}{\text{---}}$ is a bond to the anti-MUC16 antibody or fragment thereof.

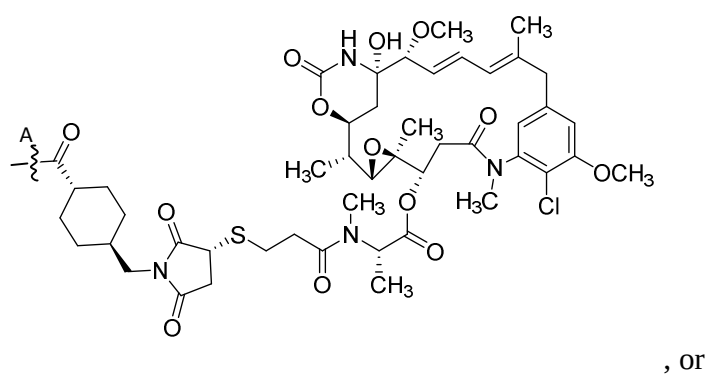
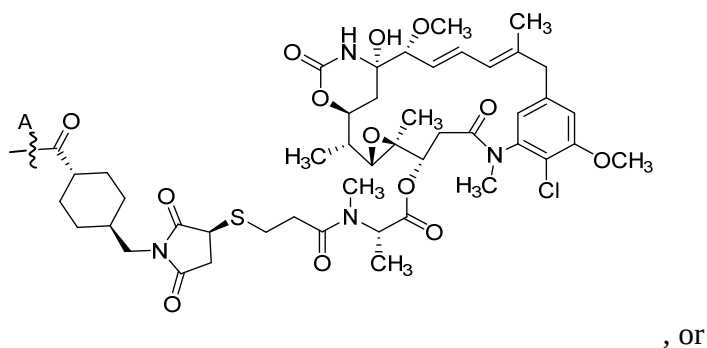
41. The ADC of claim 32 or 33, comprising an anti-MUC16 antibody or fragment thereof, and



wherein $\text{---}\overset{\text{A}}{\text{---}}$ is a bond to the anti-MUC16 antibody or fragment thereof.

42. The ADC of any one of claims 39-41, wherein bond contacts the antibody or fragment thereof via a sulfur constituent of a cysteine residue.

43. The ADC of claim 32 or 33, comprising an anti-MUC16 antibody or fragment thereof, and



a mixture thereof,

wherein $\overset{\text{A}}{\text{---}}$ is a bond to the anti-MUC16 antibody or fragment thereof.

44. The ADC of claim 43, wherein the bond contacts the antibody or fragment thereof via a nitrogen constituent of a lysine residue.

45. The ADC of any one of claims 32-44, wherein the ADC comprises 1 to 4 cytotoxic agents per anti-MUC16 antibody or fragment thereof.

46. A pharmaceutical composition comprising the antibody-drug conjugate of any one of claims 32-45, and a pharmaceutically acceptable carrier or diluent.

47. Use of the antibody or antigen-binding fragment of any one of claims 3-7 or the bispecific antigen-binding molecule of any one of claims 1, 2 or 8-26, or the ADC of any one of claims 32-45 for the manufacture of a medicament for use in the treatment of a MUC16-expressing cancer, optionally wherein the cancer is ovarian cancer.