Claims

1. A bispecific binding molecule comprising:

   a. a first antigen-binding domain that specifically binds to the extracellular domain of human MUC16; and

   b. a second antigen-binding domain that specifically binds human DR5.

2. The bispecific binding molecule of claim 1, wherein the first antigen-binding domain binds to an epitope present in more than one tandem repeat/SEA segment within the extracellular domain of MUC16,
the first antigen-binding domain is competed for MUC16 binding by one or more of the following antibodies: OC125, H185, M11, OV197, 5E11, AR9.6, H1H8794, VK-8, B43.13, or 3A5, or
the first antigen-binding domain binds to a polypeptide or peptide consisting essentially of the amino acid sequence of at least one of SEQ ID NOs:176-181, or to an extracellular fragment of MUC16 isolated from the cell culture media of OVCAR-3 cells.

3. The bispecific binding molecule of claim 1 or 2, wherein the first antigen-binding domain comprises:

   a. a heavy chain variable region comprising three heavy chain complementarity determining regions (CDR-H1, CDR-H2, and CDR-H3), wherein:

      CDR-H1 comprises the amino acid sequence of SEQ ID NO:1;

      CRD-H2 comprises the amino acid sequence of any one of SEQ ID NOs:2-5; and

      CDR2-H3 comprises the amino acid sequence of any one of SEQ ID NOs:6-61 (CDR3-H3); and

   b. a light chain variable region comprising three light chain complementarity determining regions (CDR-L1, CDR-L2, and CDR-L3), wherein:

      CDR-L1 comprises the amino acid sequence of SEQ ID NO:62;

      CDR-L2 comprises the amino acid sequence of SEQ ID NO:63; and

      CDR-L3 comprises the amino acid sequence of SEQ ID NO65, optionally

wherein:

CDR-H1 comprises the amino acid sequence of SEQ ID NO:1;

CDR-H2 comprises the amino acid sequence of SEQ ID NO:2;

CDR-H3 comprises the amino acid sequence of SEQ ID NO:6;

CDR-L1 comprises the amino acid sequence of SEQ ID NO:62;

CDR-L2 comprises the amino acid sequence of SEQ ID NO:63; and

CDR-L3 comprises the amino acid sequence of SEQ ID NO:65, further optionally wherein the first antigen-binding domain comprises a heavy chain variable region that comprises the amino acid sequence of SEQ ID NO:97, or an amino acid sequence having the same three heavy chain CDRs as, and at least 90% sequence identity to SEQ ID NO:97, preferably wherein the first antigen-binding domain comprises a heavy chain variable region that comprises the amino acid sequence of SEQ ID NO:97, more preferably
wherein the first antigen-binding domain comprises a light chain variable region that comprises the amino acid sequence of SEQ ID NOs.:104 or 105, or an amino acid sequence having the same three light chain CDRs as, and at least 90% sequence identity to either SEQ ID NO:104 or SEQ ID NO:105, optionally
wherein the first antigen-binding domain comprises a light chain variable region that comprises the amino acid sequence of SEQ ID NO:104 or SEQ ID NO:105, further optionally
wherein the first antigen-binding domain comprises:

i. a. a heavy chain variable region that comprises the amino acid sequence of SEQ ID NO:97, or an amino acid sequence having the same three light chain CDRs as, and at least 90% sequence identity to SEQ ID NO:97; and

b. a light chain variable region that comprises the amino acid sequences of either SEQ ID NO:104 or 105, or an amino acid sequence having the same three heavy chain CDRs as, and at least 90% sequence identity to either SEQ ID NO:104 or 105, or

ii. a. a heavy chain variable region that comprises the amino acid sequence of SEQ ID NO:97; and

b. a light chain variable region that comprises the amino acid sequences of either SEQ ID NO:104 or 105, more preferably

wherein the first antigen-binding domain comprises a heavy chain comprising the amino acid sequence of any one of SEQ ID NOs.:115-118, or a heavy chain comprising the same three heavy chain CDRs as, and an amino acid sequence having at least 90% sequence identity to, any one of SEQ ID NOs.:115-118, optionally

wherein the first antigen-binding domain comprises a heavy chain comprising the amino acid sequence of any one of SEQ ID NOs.:115-118, further optionally

wherein the first antigen-binding domain comprises a light chain comprising the amino acid sequence of SEQ ID NO:119, the amino acid sequence of SEQ ID NO:120; or an amino acid sequence having the same three light chain CDRs as, and at least 90% sequence identity to, SEQ ID NO:119 or SEQ ID NO:120, preferably

wherein the light chain comprises the amino acid sequence of SEQ ID NO:119 or the amino acid sequence of SEQ ID NO:120, more preferably

wherein the first antigen-binding domain comprises:

i. a. a heavy chain comprising the amino acid sequence of any one of SEQ ID NOs.:115-118, or a heavy chain comprising the same three heavy chain CDRs as, and an amino acid sequence having at least 90% sequence identity to, any one of SEQ ID NOs.:115-118; and

b. a light chain comprising the amino acid sequence of SEQ ID NO:119, the amino acid sequence of SEQ ID NO:120; or an amino acid sequence having the same three light chain CDRs as, and at least 90% sequence identity to, SEQ ID NO:119 or SEQ ID NO:120, or

ii. a. a heavy chain comprising the amino acid sequence of any one of SEQ ID NOs.:115-118; and

b. a light chain comprising the amino acid sequence of SEQ ID NO:119 or SEQ ID NO:120.

4. The bispecific binding molecule of any one of claims 1-4, wherein the first antigen-binding domain comprises two heavy chains and two light chains, optionally

wherein each of the two heavy chains has an identical amino acid sequence and each of the two light chains has an identical amino acids sequence, further optionally

wherein the second antigen-binding domain is competed for DR5 binding by one or more of the

following antibodies: Conatumumab, Drozitumab, Lexatumumab, LBY135, Tigatuzumab, and DS-8273a, preferably
wherein the second antigen-binding domain is competed for DR5 binding by TRAIL or a fragment of TRAIL that binds to DR5.

5. The bispecific binding molecule of any one of claims 1-4, wherein the second antigen-binding domain comprises a second heavy chain variable region comprising second heavy chain complementarity determining regions (CDRs) comprising the amino acid sequences SEQ ID NO:121 (second CDR-H1); SEQ ID NO:122 (second CDR2-H2); and SEQ ID NO:123 (second CDR3-H3); and a second light chain variable region comprising second light chain complementarity determining regions comprising amino acid sequences SEQ ID NO:124 (second CDR-L1); SEQ ID NO:125 (second CDR-L2); and SEQ ID NO:126 (second CDR-L3), optionally
wherein the second heavy chain variable region comprises the amino acid sequence of any one of SEQ ID NO:158, SEQ ID NOs:218-220, or an amino acid sequence having the same three heavy chain CDRs as, and at least 90% sequence identity to any one of SEQ ID NO:158 or SEQ ID NOs:218-220, further optionally
wherein the second heavy chain variable region comprises the amino acid sequence of SEQ ID NO:158, preferably
wherein the second heavy chain variable region comprises the amino acid sequence of any one of SEQ ID NOs:218-220, more preferably
wherein the second light chain variable region comprises the amino acid sequence of any one of SEQ ID NO:165, SEQ ID NOs: 215-217, or an amino acid sequence having the same three heavy chain CDRs as, and at least 90% sequence identity to any one of SEQ ID NO:165 or SEQ ID NOs: 215-217, optionally
wherein the second light chain variable region comprises the amino acid sequence of SEQ ID NO:165, further optionally
wherein the second light chain variable region comprises the amino acid sequence of any one of SEQ ID NOs: 215-217, preferably
wherein:

i. a. the second heavy chain variable region comprises the amino acid sequence of SEQ ID NO:158, or an amino acid sequence having the same three heavy chain CDRs as, and at least 90% sequence identity to SEQ ID NO:158; and

b. the second light chain variable region comprises the amino acid sequence of SEQ ID NO:165, or an amino acid sequence having the same three heavy chain CDRs as, and at least 90% sequence identity to SEQ ID NO:165,

ii. a. the second heavy chain variable region comprises the amino acid sequence of SEQ ID NO:158; and

b. the second light chain variable region comprises the amino acid sequence of SEQ ID NO:165,

iii. a. the second heavy chain variable region comprises the amino acid sequence of SEQ ID NO:218; and

b. the second light chain variable region comprises the amino acid sequence of SEQ ID NO:215,

iv. a. the second heavy chain variable region comprises the amino acid sequence of SEQ ID NO:219; and

b. the second light chain variable region comprises the amino acid sequence of SEQ ID NO:215,

v. a. the second heavy chain variable region comprises the amino acid sequence of SEQ ID NO:219; and

b. the second light chain variable region comprises the amino acid sequence of SEQ ID NO:216, or

vi. a. the second heavy chain variable region comprises the amino acid sequence of SEQ ID NO:220; and

b. the second light chain variable region comprises the amino acid sequence of SEQ ID NO:217.

6. The bispecific binding molecule of any one of claims 1-4, wherein the second antigen-binding domain is a scFv fragment of an antibody, optionally
wherein the scFv fragment comprises, in N- to C-terminal order, a light chain variable region, a peptide linker, and a heavy chain variable region, further optionally

wherein the scFv fragment comprises the amino acid sequence of SEQ ID NO:172; or an amino acid sequence having the same three heavy chain CDRs and the same three light chain CDRs as, and at least 90% sequence identity to, SEQ ID NO:172, preferably
wherein the scFv fragment comprises the amino acid sequence of SEQ ID NO:172,
the amino acid sequence of SEQ ID NO:210,
the amino acid sequence of SEQ ID NO:211,
the amino acid sequence of SEQ ID NO:212,
the amino acid sequence of SEQ ID NO:213, or
the amino acid sequence of SEQ ID NO:214.

7. The bispecific binding molecule of claim 6, wherein the N-terminus of the second antigen-binding domain is fused directly or through a peptide linker having a length of 4 to 20 amino acids to the C-terminus of one of the heavy chains of the first antigen-binding domain, optionally
wherein the peptide linker has the amino acid sequence of SEQ ID NO:173.

8. The bispecific binding molecule of claim 6, comprising two scFv fragments that specifically bind DR5, wherein each of the two scFv fragments is bound to a different heavy chain of the first antigen-binding domain, optionally
wherein each of the two scFv fragments have the identical amino acid sequence.

9. A bispecific binding molecule comprising:

a. two antibody light chains, wherein each light chain has an amino acid sequence independently selected from SEQ ID NO:119 and SEQ ID NO:120; and

b. two antibody heavy chain fusions, wherein each heavy chain fusion has an amino acid sequence independently selected from the formula: X-L-Y, wherein:

X is the amino acid sequence of any one of SEQ ID NOs.:115-118;

L is the amino acid sequence of SEQ ID NO:173; and

Y is the amino acid sequence of any one of SEQ ID NO:172 or SEQ ID NOs:210-214.

10. The bispecific binding molecule of claim 9, wherein each light chain has the identical amino acid sequence, and each heavy chain fusion has the identical amino acid sequence, optionally

wherein each light chain comprises the amino acid sequence of SEQ ID NO:119, and each heavy chain fusion comprises the amino acid sequence of SEQ ID NO:174,

each light chain comprises the amino acid sequence of SEQ ID NO:119, and each heavy chain fusion comprises the amino acid sequence of SEQ ID NO:175,

each light chain comprises the amino acid sequence of SEQ ID NO:119, and each heavy chain fusion comprises the amino acid sequence of SEQ ID NO:186,

each light chain comprises the amino acid sequence of SEQ ID NO:119, and each heavy chain fusion comprises the amino acid sequence of SEQ ID NO:187,

each light chain comprises the amino acid sequence of SEQ ID NO:119, and each heavy chain fusion comprises the amino acid sequence of SEQ ID NO:210,

each light chain comprises the amino acid sequence of SEQ ID NO:119, and each heavy chain fusion comprises the amino acid sequence of SEQ ID NO:211,

each light chain comprises the amino acid sequence of SEQ ID NO:119, and each heavy chain fusion comprises the amino acid sequence of SEQ ID NO:212,

each light chain comprises the amino acid sequence of SEQ ID NO:119, and each heavy chain fusion comprises the amino acid sequence of SEQ ID NO:213,

each light chain comprises the amino acid sequence of SEQ ID NO:119, and each heavy chain fusion comprises the amino acid sequence of SEQ ID NO:214,

each light chain comprises the amino acid sequence of SEQ ID NO:120, and each heavy chain fusion comprises the amino acid sequence of SEQ ID NO:174,

each light chain comprises the amino acid sequence of SEQ ID NO:120, and each heavy chain fusion comprises the amino acid sequence of SEQ ID NO:175,

each light chain comprises the amino acid sequence of SEQ ID NO:120, and each heavy chain fusion comprises the amino acid sequence of SEQ ID NO:186,

each light chain comprises the amino acid sequence of SEQ ID NO:120, and each heavy chain fusion comprises the amino acid sequence of SEQ ID NO:187,

each light chain comprises the amino acid sequence of SEQ ID NO:120, and each heavy chain fusion comprises the amino acid sequence of SEQ ID NO:210,

each light chain comprises the amino acid sequence of SEQ ID NO:120, and each heavy chain fusion comprises the amino acid sequence of SEQ ID NO:211,
each light chain comprises the amino acid sequence of SEQ ID NO:120, and each heavy chain fusion comprises the amino acid sequence of SEQ ID NO:212,
each light chain comprises the amino acid sequence of SEQ ID NO:120, and each heavy chain fusion comprises the amino acid sequence of SEQ ID NO:213, or
each light chain comprises the amino acid sequence of SEQ ID NO:120, and each heavy chain fusion comprises the amino acid sequence of SEQ ID NO:214.

11. A pharmaceutical composition comprising a bispecific binding molecule of any one of claims 1-10; and a pharmaceutically acceptable carrier.

12. An isolated nucleic acid sequence encoding a heavy chain fusion comprising an amino acid sequence of any one of SEQ ID NOs: 174, 175, 186, 187, or 210-214.

13. The isolated nucleic acid sequence of claim 12 comprising SEQ ID NO:182 or 183.

14. An expression vector comprising the nucleic acid sequence of claim 12 or 13.

15. The expression vector of claim 14, additionally comprising a nucleic acid sequence encoding a light chain comprising the amino acid sequence of any one of SEQ ID NOs: 119 or 120, optionally
wherein the nucleic acid sequence encoding the light chain comprises SEQ ID NO:184 or 185.

16. A host cell harboring a first expression vector of claim 14; and a second expression vector comprising a nucleic acid sequence encoding a light chain comprising the amino acid sequence of any one of SEQ ID NOs: 119 or 120, optionally
wherein nucleic acid sequence encoding the light chain comprises SEQ ID NO:184 or 185.

17. A host cell harboring the expression vector of claim 15.

18. A method of manufacturing a bispecific binding molecule, comprising the steps of:

a. culturing the host cell of claim 16 or 17 under conditions allowing for expression of the nucleic acid sequence encoding the heavy chain fusion and expression of the nucleic acid sequence encoding the light chain, and association of the expressed heavy chain fusion and the expressed light chain into the bispecific binding molecule; and

b. recovering the bispecific binding molecule from the culture.

19. Use of the bispecific binding molecule of any one of claims 1-10, or the pharmaceutical composition of claim 11 in the manufacture of medicament for treating a MUC16-related fibrotic disease disorder, inflammatory disorder, immune disorder, or autoimmune disorder, optionally wherein the MUC16-mediated fibrotic disorder is pulmonary fibrosis, cystic fibrosis, idiopathic pulmonary fibrosis, radiation-induced lung injury, liver fibrosis, cirrhosis, kidney fibrosis, glial scar, myocardial fibrosis, arterial stiffness, arthrofibrosis, chronic kidney disease, Crohn's disease, Dupuytren's contracture, keloid, mediastinal fibrosis, myelofibrosis, Peyronie's disease, nephrogenic systemic fibrosis, progressive massive fibrosis, retroperitoneal fibrosis, scleroderma/systemic sclerosis, or adhesive capsulitis.

20. Use of the bispecific binding molecule of any one of claims 1-10, or the pharmaceutical composition of claim 11 in the manufacture of medicament for treating a cancer or malignancy characterized by over-expression of MUC16, optionally
wherein the cancer or malignancy is a gynecologic cancer (cancer of the female reproductive tract), including the cervix, endometrium, fallopian tubes, ovaries, uterus, and vagina; pancreatic cancer, esophageal cancer, gastric cancer, colorectal cancer, breast cancer, or lung cancer.

21. The bispecific binding molecule of any one of claims 1-10, or the pharmaceutical composition of claim 11 for use in treating a MUC16-related fibrotic disease disorder, inflammatory disorder, immune disorder, or autoimmune disorder, optionally wherein the MUC16-mediated fibrotic disorder is pulmonary fibrosis, cystic fibrosis, idiopathic pulmonary fibrosis, radiation-induced lung injury, liver fibrosis, cirrhosis, kidney fibrosis, glial scar, myocardial fibrosis, arterial stiffness, arthrofibrosis, chronic kidney disease, Crohn's disease,

Dupuytren's contracture, keloid, mediastinal fibrosis, myelofibrosis, Peyronie's disease, nephrogenic systemic fibrosis, progressive massive fibrosis, retroperitoneal fibrosis, scleroderma/systemic sclerosis, or adhesive capsulitis.

22. The bispecific binding molecule of any one of claims 1-10, or the pharmaceutical composition of claim 11 for use in treating a cancer or malignancy characterized by over-expression of MUC16, optionally wherein the cancer or malignancy is a gynecologic cancer (cancer of the female reproductive tract), including the cervix, endometrium, fallopian tubes, ovaries, uterus, and vagina; pancreatic cancer, esophageal cancer, gastric cancer, colorectal cancer, breast cancer, or lung cancer.

23. The bispecific binding molecule of any one of claims 1-10, or the pharmaceutical composition of claim 11 for use as a medicament.