

Claims

1. A therapeutic composition comprising a multivalent antibody comprising a first variable domain that binds a first tumor antigen (TA1), a second variable domain that binds a second tumor antigen (TA2) and a third variable domain that binds an immune cell engaging antigen (IEA); and wherein the composition further comprises a second binding molecule that binds TA1 or TA2.
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2. The therapeutic composition of claim 1, wherein the multivalent antibody comprises an Fc region.
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3. The therapeutic composition of claim 1 or 2, wherein the third variable domain that binds an immune cell engaging antigen (IEA) and the second variable domain that binds a second tumor antigen (TA2) are associated with an Fc region, and the first variable domain that binds a first tumor antigen (TA1) is linked to the third variable domain that binds an immune cell engaging antigen (IEA).
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4. The therapeutic composition of claim 1 or 2, wherein the third variable domain that binds an immune cell engaging antigen (IEA) and the first variable domain that binds a first tumor antigen (TA1) are associated with an Fc region, and the second variable domain that binds a second tumor antigen (TA2) is linked to the third variable domain that binds an immune cell engaging antigen (IEA).
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5. The therapeutic composition of any one of claims 1-4, wherein the first, second, and/or third variable domain comprises a common light chain variable region.
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6. The therapeutic composition of any one of claims 1-5, wherein the variable domain that binds an immune cell engaging antigen binds to CD3, TCR- α chain, TCR- β chain, CD2, CD4, CD5, CD7, CD8, CD137, CD28, CD16, CD16A, CD64, OX40, CD27, CD40, ICOS, GITR, NKG2D, NKp46, NKp44, or NKp30; preferably to CD3, TCR- α chain, TCR- β chain, CD2, or CD5; more preferably to CD3.
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7. The therapeutic composition of any one of claims 1-6, wherein the variable domain that binds a first tumor associated antigen (TA1) binds to PD-L1, PD-L2, HVEM, CD47, B7-H3, B7-H4, B7-H7, or Siglec-15; preferably PD-L1 or PD-L2; more preferably PD-L1.
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8. The therapeutic composition of any one of claims 1-7, wherein the variable domain that binds a second tumor associated antigen (TA2) binds to CLEC12A or EGFR, preferably EGFR.
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9. The therapeutic composition of any one of claims 1-8, wherein the first tumor associated antigen (TA1) is expressed on non-tumor cells.
10. The therapeutic composition of any one of claims 1-9, wherein the second
5 binding molecule binds to TA1.
11. The therapeutic composition of any one of claims 1-10, wherein the second binding molecule is a bivalent monospecific antibody.
- 10 12. The therapeutic composition of any one of claims 1-11, wherein the second binding molecule has a binding affinity to TA1 or TA2 that is comparable to, equal to, or lower than the binding affinity to TA1 or TA2 of the first variable domain or second variable domain of the multivalent antibody.
- 15 13. The therapeutic composition of any one of claims 1-12, wherein the second binding molecule has reduced effector function.
14. A kit of parts comprising a multivalent antibody and a second binding
20 molecule as defined in any one of claims 1-13.
15. A kit of parts comprising a therapeutic composition of any one of claims 1-13 and instructions for administering the composition to a subject in need thereof.
- 25 16. The kit of parts of claim 14 or 15, wherein the kit comprises instructions for administering the multivalent antibody and second binding molecule simultaneously or consecutively to a subject in need thereof.
17. The kit of parts of any one of claims 14-16, wherein the kit comprises
30 instructions to administer the second binding molecule prior to administering the multivalent antibody.
18. A pharmaceutical composition comprising a multivalent antibody and a second binding molecule as defined in any one of claims 1-13, and a pharmaceutically acceptable carrier, diluent, or excipient.
- 35 19. A combination of a multivalent antibody and a second binding molecule as defined in any one of claims 1-13, a composition comprising a multivalent antibody and a second binding molecule as defined in any one of claims 1-13, a therapeutic composition of any one of claims 1-13, a kit of parts of any one of claims 14-17, or a
40 pharmaceutical composition of claim 18, for mitigating or reducing binding of the multivalent antibody to non-tumor cells, and/or for mitigating or reducing cell killing of non-tumor cells induced by the multivalent antibody.

20. A combination of a multivalent antibody and a second binding molecule as defined in any one of claims 1-13, a composition comprising a multivalent antibody and a second binding molecule as defined in any one of claims 1-13, a therapeutic composition of any one of claims 1-13, a kit of parts of any one of claims 14-17, or a pharmaceutical composition of claim 18, for use as a medicament.

21. A combination of a multivalent antibody and a second binding molecule as defined in any one of claims 1-13, a composition comprising a multivalent antibody and a second binding molecule as defined in any one of claims 1-13, a therapeutic composition of any one of claims 1-13, a kit of parts of any one of claims 14-17, or a pharmaceutical composition of claim 18, for use in the treatment of a subject in need thereof, in particular a subject that has cancer.

22. Use of a combination of a multivalent antibody and a second binding molecule as defined in any one of claims 1-13, a composition comprising a multivalent antibody and a second binding molecule as defined in any one of claims 1-13, a therapeutic composition of any one of claims 1-13, a kit of parts of any one of claims 14-17, or a pharmaceutical composition of claim 18, in the manufacture of a medicament for the treatment of cancer.

23. A method for mitigating or reducing binding of a multivalent antibody as defined in any one of claims 1-13 to non-tumor cells expressing TA1 or TA2, wherein the method comprises using a second binding molecule as defined in any one of claims 1-13 that binds to TA1 or TA2 in conjunction with the multivalent antibody.

24. The method of claim 23, wherein the non-tumor cells express TA1 and the second binding molecule binds to TA1.

25. The method of claim 23 or 24, wherein binding of the multivalent antibody to non-tumor cells expressing TA1 or TA2 is reduced as compared to binding of the multivalent antibody to non-tumor cells expressing TA1 or TA2 in a method not using the second binding molecule.

26. A method of treatment of cancer, wherein the method comprises:
- administering to a subject in need thereof a multivalent antibody as defined in any one of claims 1-13 and additionally administering to the subject a second binding molecule as defined in any one of claims 1-13;
- administering to a subject in need thereof a composition comprising a multivalent antibody and second binding molecule as defined in any one of claims 1-13; or
- administering to a subject in need thereof a therapeutic composition of any one of claims 1-13; or

- administering to a subject in need thereof a pharmaceutical composition of claim 18.

27. The combination, composition, therapeutic composition, or kit of parts for use of any one of claims 19-21, or the method of any one of claims 23-26, wherein the multivalent antibody and second binding molecule are administered simultaneously as a single composition or as two separate compositions.

28. The combination, composition, therapeutic composition, or kit of parts for use of any one of claims 19-21 or the method of any one of claims 23-26, wherein the multivalent antibody is administered prior to the second binding molecule.

29. The combination, composition, therapeutic composition, or kit of parts for use of any one of claims 19-21, or the method of any one of claims 23-26, wherein the second binding molecule is administered prior to the multivalent antibody.

30. A vector comprising a nucleic acid encoding the heavy chain variable region of the first, second, and third variable domain of a multivalent antibody as defined in any one of claims 1-13, wherein the vector further comprises a different nucleic acid encoding the heavy chain variable region of a second binding molecule as defined in any one of claims 1-13.

31. A host cell comprising a nucleic acid encoding the heavy chain variable region of the first, second, and third variable domain of a multivalent antibody as defined in any one of claims 1-13, wherein the host cell further comprises a different nucleic acid encoding the heavy chain variable region of a second binding molecule as defined in any one of claims 1-13.

32. The host cell of claim 31, wherein the host cell further comprises a nucleic acid encoding the light chain variable region of the first, second, and third variable domain of a multivalent antibody, and the light chain variable region of a second binding molecule, as defined in any one of claims 1-13.