

Claims

1. A fully human antibody that specifically binds to mesothelin, wherein the fully human antibody is selected from a group consisting of:

(a) an antibody comprising a heavy chain variable region having CDR1 comprising the amino acid sequence of SEQ ID NO: 54, CDR2 comprising the amino acid sequence of SEQ ID NO: 55, CDR3 comprising the amino acid sequence of SEQ ID NO: 56; and

a light chain variable region having CDR1 comprising the amino acid sequence of SEQ ID NO: 51, CDR2 comprising the amino acid sequence of SEQ ID NO: 52, CDR3 comprising the amino acid sequence of SEQ ID NO: 53; or

(d) an antibody comprising a heavy chain variable region having CDR1 comprising the amino acid sequence of SEQ ID NO: 60, CDR2 comprising the amino acid sequence of SEQ ID NO: 61, CDR3 of the amino acid sequence of ID NO: 62; and

a light chain variable region having CDR1 comprising the amino acid sequence of SEQ ID NO: 57, CDR2 comprising the amino acid sequence of SEQ ID NO: 58, CDR3 of the amino acid of ID NO: 59.

2. The fully human antibody of claim 1, wherein the fully human antibody comprises a heavy chain variable region and a light chain variable region, the amino acid sequence of the heavy chain variable region is shown in positions 1 to 123 of SEQ ID NO: 6; and the amino acid sequence of the light chain variable region is shown in positions 139-254 of SEQ ID NO: 6; or

the fully human antibody comprises a heavy chain variable region and a light chain variable region, the amino acid sequence of the heavy chain variable region is shown in positions 1 to 124 of SEQ ID NO: 8; and the amino acid sequence of the light chain variable region is shown in positions 140-247 of SEQ ID NO: 8.

3. A nucleic acid encoding the antibody of claim 1 or 2.

4. An expression vector comprising the nucleic acid of claim 3.

5. A host cell, comprising the expression vector of claim 4 or having the nucleic acid of claim 3 integrated into the genome.

6. Use of the antibody of claim 1 or 2 for the preparation of a targeted drug, antibody-drug conjugate, or a polyfunctional antibody that specifically targets tumor cells expressing mesothelin; or

for the preparation of a reagent for diagnosing a tumor expressing mesothelin; or

for the preparation of chimeric antigen receptor-modified immune cells.

7. A chimeric antigen receptor, wherein said chimeric antigen receptor comprises

sequentially linked: the antibody of claim 1 or 2, a transmembrane region and intracellular signal region.

8. The chimeric antigen receptor of claim 7, wherein the intracellular signal region is selected from a group consisting of intracellular signal region sequences of CD3 ζ , Fc ϵ RI γ , CD27, CD28, CD137, CD134, MyD88, CD40 or a combination thereof.

9. The chimeric antigen receptor of claim 7, wherein the transmembrane region comprises a transmembrane region of CD8 or CD28.

10. The chimeric antigen receptor of claim 7, comprising the following sequentially linked antibody, transmembrane region and intracellular signal region:

The antibody of claim 1 or 2, CD8 and CD3 ζ ;

The antibody of claim 1 or 2, CD8, CD137 and CD3 ζ ;

The antibody of claim 1 or 2, the transmembrane region of CD28 molecule, the intracellular signal region of CD28 molecule and CD3 ζ ; or

The antibody of claim 1 or 2, the transmembrane region of CD28 molecule, the intracellular signal region of CD28 molecule, CD137 and CD3 ζ .

11. The chimeric antigen receptor of claim 7, wherein the antibody is a single chain antibody or domain antibody.

12. The chimeric antigen receptor of claim 7, wherein the chimeric antigen receptor has:

SEQ ID NO: 41 or the amino acid sequence shown in positions 22-353 thereof;

SEQ ID NO: 42 or the amino acid sequence shown in positions 22-454 thereof;

SEQ ID NO: 43 or the amino acid sequence shown in positions 22-498 thereof;

SEQ ID NO: 44 or the amino acid sequence shown in positions 22-501 thereof;

SEQ ID NO: 45 or the amino acid sequence shown in positions 22-543 thereof;

SEQ ID NO: 46 or the amino acid sequence shown in positions 22-346 thereof;

SEQ ID NO: 47 or the amino acid sequence shown in positions 22-447 thereof;

SEQ ID NO: 48 or the amino acid sequence shown in positions 22-491 thereof;

SEQ ID NO: 49 or the amino acid sequence shown in positions 22-494 thereof; or

SEQ ID NO: 50 or the amino acid sequence shown in positions 22-536 thereof.

13. A nucleic acid encoding the chimeric antigen receptor of any one of claims 7-12.

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

15. A virus, wherein the virus comprises the vector of claim 14.

16. Use of the chimeric antigen receptor of any one of claims 7-12, or the nucleic acid of claim 13, or the expression vector of claim 14, or the virus of claim 15 for the preparation of genetically modified immune cells targeting tumor cells expressing mesothelin.

17. The chimeric antigen receptor of claim 16, wherein the mesothelin-expressing tumor includes: pancreatic cancer, ovarian cancer and thymus mesothelioma.

18. A genetically modified immune cell, wherein it is transduced with the nucleic acid of claim 13, or the expression vector of claim 14 or the virus of claim 15; or

expresses the chimeric antigen receptor of any one of claims 7-12 on its cell surface.

19. The immune cell of claim 18, wherein it further carries an encoding sequence of an exogenous cytokine; and preferably, the cytokine includes: IL-12, IL-15 or IL-21.

20. The immune cell of claim 18, wherein the immune cell also expresses another chimeric antigen receptor which does not contain CD3 ζ but contains the intracellular signaling domain of CD28, the intracellular signaling domain of CD137, or a combination of both.

21. The immune cell of claim 18, wherein the immune cell further expresses a chemokine receptor; and preferably, the chemokine receptor includes: CCR2.

22. The immune cell of claim 18, wherein the immune cell further expresses siRNA which can reduce expression of PD-1 or a protein which blocks PD-L1.

23. The immune cell of claim 18, wherein the immune cell further expresses a safety switch; and preferably, the safety switch includes: iCaspase-9, Truncated EGFR or RQR8.

24. The immune cell of claim 18, wherein the immune cell includes: T lymphocyte, NK cell or NKT cell.

25. Use of the genetically modified immune cell of any one of claims 18-24 for the preparation of a tumor-inhibiting drug, and the tumor is a tumor expressing mesothelin.

26. A multi-functional immunoconjugate, wherein the multi-functional immunoconjugate comprises:

The antibody of claim 1 or 2; and

a functional molecule linked thereto; and the functional molecule is selected from a molecule that targets a tumor surface marker, a tumor-suppressing molecule, a molecule that targets a surface marker of an immune cell, or a detectable label.

27. The multi-functional immunoconjugate of claim 26, wherein the molecule that targets the tumor surface marker is an antibody or ligand that binds to a tumor surface marker; or

the tumor-suppressing molecule is an anti-tumor cytokine or an anti-tumor toxin; and preferably, the cytokine includes: IL-12, IL-15, IFN-beta, TNF-alpha.

28. The multi-functional immunoconjugate of claim 26, wherein the detectable label includes a fluorescent label or a chromogenic label.

29. The multi-functional immunoconjugate of claim 27, wherein the antibody that binds

to a tumor surface marker refers to an antibody that recognizes an antigen other than mesothelin, and the other antigen includes EGFR EGFRvIII, mesothelin, HER2, EphA2, Her3, EpCAM, MUC1, MUC16, CEA, Claudin 18.2, folate receptor, Claudin 6, CD3, WT1, NY-ESO- 1, MAGE 3, ASGPR1 or CDH16.

30. The multi-functional immunoconjugate of claim 26, wherein the molecule that targets the surface marker of the immune cell is an antibody that binds to T cell surface marker and forms a T-cell-engaging bifunctional antibody with the antibody of claim 1 or 2.

31. The multi-functional immunoconjugate of claim 30, wherein the antibody that binds to T cell surface marker is an anti-CD3 antibody.

32. The multi-functional immunoconjugate of claim 31, wherein it is a fusion polypeptide, and further comprises a linker peptide between the antibody of claim 1 or 2 and the functional molecule linked thereto.

33. A nucleic acid encoding the multi-functional immunoconjugate of any one of claims 26-32.

34. Use of the multi-functional immunoconjugate of any one of claims 26-32 for the preparation of an antineoplastic agent or an agent for diagnosis of tumors that express mesothelin; or

for the preparation of chimeric antigen receptor modified immune cells; and preferably, the immune cells include T lymphocyte, NK cell or NKT lymphocyte.

35. A pharmaceutical composition, comprising:

the antibody of claim 1 or 2 or a nucleic acid encoding the antibody; or

the immunoconjugate of any one of claims 26-32 or a nucleic acid encoding the conjugate; or

the chimeric antigen receptor of any one of claims 7-12 or a nucleic acid encoding the chimeric antigen receptor; or

the genetically modified immune cell of any one of claims 18-24.