[Patent Literature 4] WO2017/161333

[Patent Literature 5] WO2018/177966

[Patent Literature 6] WO2018/189611

[Patent Literature 7] WO2012/073985

[Patent Literature 8] WO2013/180200

NON PATENT LITERATURE

[0008] [Non Patent Literature 1] Grupp et al. 2013 N Engl J Med 368(16): 1509- 18

[Non Patent Literature 2] Maude et al. 2014 2014 N Engl J Med 371(16): 1507-17

[Non Patent Literature 3] Kim et al. J Am Chem Soc 2015; 137: 2832-2835

[Non Patent Literature 4] Tamada et al. Clin Cancer Res 2012; 18(23): 6436-6445

[Non Patent Literature 5] Kontermann, mAbs 2012; 4: 182-197.

[Non Patent Literature 6] Mezzanzanica et al., International journal of cancer 1988; 41: 609-615.

[Non Patent Literature 7] Staerz and Bevan, Proceedings of the National Academy of Sciences of the United States of America 1986; 83: 1453-1457.

[Non Patent Literature 8] Staerz et al., Nature 1985; 314: 628-631.

SUMMARY

[0008a] In one aspect, the present disclosure relates to a pharmaceutical composition for use in combination with a mutated antibody having a mutation, including substitution, deletion, addition or modification, of at least one amino acid in a CH1 region, a CH2 region, a CH3 region, a CL region, or a framework region, wherein the pharmaceutical composition comprises a cell expressing a chimeric receptor, the chimeric receptor comprises an extracellular binding domain, a transmembrane domain and an intracellular signaling domain, the mutated antibody is capable of binding to the extracellular binding domain of the chimeric receptor via a moiety having the mutation, and the extracellular binding domain does not specifically bind to an antibody free of the mutation.

[0008b] In another aspect, the present disclosure relates to a pharmaceutical composition for use in combination with a cell expressing a chimeric receptor, wherein the pharmaceutical

composition comprises a mutated antibody having a mutation, including substitution, deletion, addition or modification, of at least one amino acid in a CH1 region, a CH2 region, a CH3 region, a CL region, or a framework region, the chimeric receptor comprises an extracellular binding domain, a transmembrane domain and an intracellular signaling domain, the mutated antibody is capable of binding to the extracellular binding domain of the chimeric receptor via a moiety having the mutation, and the extracellular binding domain does not specifically bind to an antibody free of the mutation.

[0008c] In another aspect, the present disclosure relates to a pharmaceutical composition for use in combination with a mutated antibody having a mutation, including substitution, deletion, addition or modification, of at least one amino acid in a CH1 region, a CH2 region, a CH3 region, a CL region, or a framework region, wherein the pharmaceutical composition comprises a bispecific antibody, and the bispecific antibody comprises (1) a domain comprising antibody variable regions that specifically bind to the mutated antibody via a moiety having the mutation, and (2) a domain comprising antibody variable regions having binding activity against a molecule expressed on T cell surface, and does not specifically bind to an antibody free of the mutation.

[0008d] In another aspect, the present disclosure relates to a pharmaceutical composition for use in combination with a bispecific antibody, wherein the pharmaceutical composition comprises a mutated antibody having a mutation, including substitution, deletion, addition or modification, of at least one amino acid in a CH1 region, a CH2 region, a CH3 region, a CL region, or a framework region, and the bispecific antibody comprises (1) a domain comprising antibody variable regions that specifically bind to the mutated antibody via a moiety having the mutation, and (2) a domain comprising antibody variable regions having binding activity against a molecule expressed on T cell surface, and does not specifically bind to an antibody free of the mutation.

[0008e] In yet another aspect, the present disclosure relates to an isolated nucleic acid encoding a chimeric receptor or a bispecific antibody contained in a pharmaceutical composition as described herein. In yet another aspect, the present disclosure relates to a

vector comprising an isolated nucleic acid as described herein. In yet another aspect, the present disclosure relates to a cell transformed or transduced with an isolated nucleic acid as described herein or a vector as described herein.

TECHNICAL PROBLEM

[0009] In spite of therapy using CAR-T cells regarded as promising treatment of cancer patients, there are some limitations on the expansion of the clinical application of the CAR-T cells. First of all, a single tumor antigen is not universally expressed in every cancer. Therefore, the antigen recognition site of CAR needs to be constructed for each targeted tumor antigen. Secondly, economical cost and labor associated with operations for identifying antigen recognition sites for various tumor antigens and newly establishing CAR-T cells harboring these sites are major problems. Thirdly, tumor antigens targeted by CAR may cause tumor immune escape in such a way that treatment decreases their expression levels or mutates the tumor antigens. Particularly, existing CAR-T cells recognize only one target antigen. Therefore, the tumor immune escape causes reduction or disappearance of

CLAIMS

1. A pharmaceutical composition for use in combination with a mutated antibody having a mutation, including substitution, deletion, addition or modification, of at least one amino acid in a CH1 region, a CH2 region, a CH3 region, a CL region, or a framework region, wherein

the pharmaceutical composition comprises a cell expressing a chimeric receptor,

the chimeric receptor comprises an extracellular binding domain, a transmembrane domain and an intracellular signaling domain,

the mutated antibody is capable of binding to the extracellular binding domain of the chimeric receptor via a moiety having the mutation, and

the extracellular binding domain does not specifically bind to an antibody free of the mutation.

2. A pharmaceutical composition for use in combination with a cell expressing a chimeric receptor, wherein

the pharmaceutical composition comprises a mutated antibody having a mutation, including substitution, deletion, addition or modification, of at least one amino acid in a CH1 region, a CH2 region, a CH3 region, a CL region, or a framework region,

the chimeric receptor comprises an extracellular binding domain, a transmembrane domain and an intracellular signaling domain,

the mutated antibody is capable of binding to the extracellular binding domain of the chimeric receptor via a moiety having the mutation, and

the extracellular binding domain does not specifically bind to an antibody free of the mutation.

3. A pharmaceutical composition for use in combination with a mutated antibody having a mutation, including substitution, deletion, addition or modification, of at least one amino acid in a CH1 region, a CH2 region, a CH3 region, a CL region, or a framework region, wherein

the pharmaceutical composition comprises a bispecific antibody, and

the bispecific antibody comprises (1) a domain comprising antibody variable regions that specifically bind to the mutated antibody via a moiety having the mutation, and (2) a domain comprising antibody variable regions having binding activity against a molecule expressed on T cell surface, and does not specifically bind to an antibody free of the mutation.

4. A pharmaceutical composition for use in combination with a bispecific antibody, wherein

the pharmaceutical composition comprises a mutated antibody having a mutation, including substitution, deletion, addition or modification, of at least one amino acid in a CH1 region, a CH2 region, a CH3 region, a CL region, or a framework region, and

the bispecific antibody comprises (1) a domain comprising antibody variable regions that specifically bind to the mutated antibody via a moiety having the mutation, and (2) a domain comprising antibody variable regions having binding activity against a molecule expressed on T cell surface, and does not specifically bind to an antibody free of the mutation.

5. The pharmaceutical composition according to any one of claims 1 to 4, wherein the mutated antibody has the mutation in a CH2 region, and the mutated antibody has reduced binding activity against Fc gamma receptor and C1q compared with a corresponding non-mutated antibody.

6. The pharmaceutical composition according to any one of claims 1 to 5, wherein the mutated antibody has a CH2 region mutation at any of positions 234, 235, 236, 237, 238, 265, 266, 267, 268, 269, 270, 271, 295, 296, 298, 300, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, and 337 according to the EU numbering, and the mutated antibody binds to the extracellular binding domain via a moiety having the mutation.

7. The pharmaceutical composition according to any one of claims 1 to 6, wherein

the CH2 region of the mutated antibody has a mutation selected from the group of a mutation of an amino acid at position 235 to arginine,

a mutation of an amino acid at position 236 to arginine,

a mutation of an amino acid at position 239 to lysine,

a mutation of an amino acid at position 250 to valine,

a mutation of an amino acid at position 252 to tyrosine,

a mutation of an amino acid at position 297 to alanine,

a mutation of an amino acid at position 307 to glutamine,

a mutation of an amino acid at position 308 to proline,

a mutation of an amino acid at position 311 to alanine,

a mutation of an amino acid at position 434 to tyrosine, and

a mutation of an amino acid at position 436 to valine,

according to the EU numbering, and

the mutated antibody binds to the extracellular binding domain via a moiety having the mutation.

8. An isolated nucleic acid encoding a chimeric receptor or a bispecific antibody contained in a pharmaceutical composition according to any one of claims 1 to 7.

9. A vector comprising an isolated nucleic acid according to claim 8.

10. The vector according to claim 9, wherein the vector is operably linkable to at least one regulatory element for the expression of the chimeric receptor or the bispecific antibody.

11. A cell transformed or transduced with an isolated nucleic acid according to claim 8 or a vector according to claim 9 or 10.