increased Fcgamma receptor affinity enhances B-cell clearing in nonhuman primates. Zalevsky J, Leung IW, Karki S, Chu SY, Zhukovsky EA, Desjarlais JR, Carmichael DF, Lawrence CE. Blood. 2009 Apr 16; 113(16): 3735-43.

[Non Patent Literature 4] Advances in bispecific biotherapeutics for the treatment of cancer Biochem Pharmacol. 2012 Nov 1; 84(9): 1105-12

[Non Patent Literature 5] Chimeric Antigen Receptor Therapy N Engl J Med 2018; 379: 64-73

[Non Patent Literature 6] Single-domain antibodies for biomedical applications. Immunopharmacol Immunotoxicol. 2016; 38(1): 21-8

[Non Patent Literature 7] Shedding light onto live molecular targets Nat Med. 2003 Jan; 9(1): 123-8

[Non Patent Literature 8] Structure and specificity of an antibody targeting a proteolytically cleaved IgG hinge Malia TJ1, Teplyakov A, Brezski RJ, Luo J, Kinder M, Sweet RW, Almagro JC, Jordan RE, Gilliland GL. Proteins. 2014 Aug; 82(8): 1656-67

[Non Patent Literature 9] Development of a novel immunoassay for the measurement of type II collagen neoepitope generated by collagenase cleavage Clin Chim Acta. 2012 Oct 9; 413(19-20): 1591-9.

[Non Patent Literature 10] Grupp et al. 2013 N Engl J Med 368(16): 1509-18.

[Non Patent Literature 11] Kontermann, mAbs 2012; 4: 182-197.

[Non Patent Literature 12] Mezzanzanica et al., International journal of cancer 1988; 41: 609-615.

[Non Patent Literature 13] Staerz and Bevan, Proceedings of the National Academy of Sciences of the United States of America 1986; 83: 1453-1457.

[Non Patent Literature 14] Staerz et al., Nature 1985; 314: 628-631.

[Non Patent Literature 15] Desnoyers LR et al., Sci Transl Med. 2013 Oct 16; 5(207): 207ra144.

SUMMARY ~~OF INVENTION~~

TECHNICAL PROBLEM

[0014] Probody(R) exerts cytotoxic activity even in normal tissues due to the long circulation time in blood of activated Probody(R) and antigen binding activity possessed in a nonactivated state without protease cleavage. Although high cytotoxic activity is obtained in T cell-redirecting antibody therapy or CAR-T therapy, it is known that the activity takes place even in normal cells, causing severe adverse reactions. Thus, improvement related to the safety of such therapy has been desired.

A single tumor antigen is not universally expressed in all cancers. Therefore, an antigen recognition site in the therapy needs to be constructed on a targeted tumor antigen basis, and economical cost and labor associated with the operation are major problems. Furthermore, targeted tumor antigens may cause immune escape, causing reduction or disappearance of therapeutic effect, in such a way that treatment decreases their expression levels or mutates the tumor antigens.

Although research has been made on CAR-T cells and T cell-redirecting antibodies recognizing tumor antigens that can be changed according to the phase of treatment, and treatment methods using them, there has been a demand for more safe and inexpensive treatment by the development of treatment methods having sufficient therapeutic effects upon administration to patients and having high safety and techniques that can be used for general purposes.

SOLUTION TO PROBLEM

[0015] To solve these problems, the inventors have conducted studies and completed the present ~~invention~~disclosure by finding that an antibody having ADCC activity, a T cell-redirecting antibody or a CAR-T cell binding to an antigen binding domain newly produced through cleavage by protease acts selectively on a therapeutic target cell and is thus useful for treatment. One ~~aspect~~example of the present disclosure discloses a group of versatile therapeutic molecules which are molecules comprising an antigen binding domain that is produced by protease and having a short half-life in blood, and do not exert a pharmacological effect without cleavage by the protease.

[0015a] In one aspect, the present disclosure provides a use of a pharmaceutical composition

comprising a cell expressing a chimeric receptor in the manufacture of a medicament for use in combination therapy, wherein said medicament is to be administered in combination with an antigen binding molecule, wherein

the antigen binding molecule comprises a linker that is cleavable by protease, and has the ability to bind to a target antigen after the cleavage of the linker, and

the chimeric receptor comprises an extracellular binding domain, a transmembrane domain and an intracellular signal transduction domain, and the extracellular binding domain has the ability to bind to the antigen binding molecule after cleavage of the linker, and is capable of binding to a cell expressing the target antigen via binding to the antigen binding molecule after the cleavage of the linker.

[0015b] In another aspect, the present disclosure provides a use of a pharmaceutical composition comprising an antigen binding molecule in the manufacture of a medicament for use in combination therapy, wherein said medicament is to be administered in combination with a cell expressing a chimeric receptor, wherein

the antigen binding molecule comprises a linker that is cleavable by protease, and has the ability to bind to a target antigen after the cleavage of the linker,

the chimeric receptor comprises an extracellular binding domain, a transmembrane domain and an intracellular signal transduction domain, and the extracellular binding domain has the ability to bind to the antigen binding molecule after the cleavage of the linker, and is capable of binding to a cell expressing the target antigen via binding to the antigen binding molecule after the cleavage of the linker.

[0015c] In a further aspect, the present disclosure provides a use a pharmaceutical composition comprising a bispecific antibody in the manufacture of a medicament for use in combination therapy, wherein said medicament is to be administered in combination with an antigen binding molecule, wherein

the antigen binding molecule comprises a linker that is cleavable by protease, and has the ability to bind to a target antigen after cleavage of the linker,

the bispecific antibody comprises antibody variable regions having binding activity

against the antigen binding molecule after the cleavage of the linker by the protease, and antibody variable regions having binding activity against a molecule expressed on T cell surface, and

the bispecific antibody is capable of binding to a cell expressing the target antigen via binding to the antigen binding molecule after the cleavage of the linker.

[0015d] In a further aspect, the present disclosure provides a use of a pharmaceutical composition comprising an antigen binding molecule in the manufacture of a medicament for use in combination therapy, wherein said medicament is to be administered in combination with a bispecific antibody, wherein

the antigen binding molecule comprises a linker that is cleavable by protease, and has the ability to bind to a target antigen after the cleavage of the linker,

the bispecific antibody comprises antibody variable regions having binding activity against the antigen binding molecule after the cleavage of the linker by the protease, and antibody variable regions having binding activity against a molecule expressed on T cell surface, and

the bispecific antibody is capable of binding to a cell expressing the target antigen via binding to the antigen binding molecule after the cleavage of the linker.

[0015e] In yet another aspect, the present disclosure provides a use of a pharmaceutical composition comprising an IgG antibody having enhanced antibody-dependent cellular cytotoxicity in the manufacture of a medicament for use in combination therapy, wherein said medicament is to be administered in combination with an antigen binding molecule, wherein

the antigen binding molecule comprises a linker that is cleavable by protease, and has binding activity against an antigen expressed on target cell surface after cleavage of the linker by the protease,

the IgG antibody comprises antibody variable regions having binding activity against the antigen binding molecule after cleavage of the linker by the protease, and

the IgG antibody is capable of binding to the target cell via binding to the antigen binding molecule after cleavage of the linker.

[0015f] In yet another aspect, the present disclosure provides a use of a pharmaceutical composition comprising an antigen binding molecule in the manufacture of a medicament for use in combination therapy, wherein said medicament is to be administered in combination with an IgG antibody having enhanced antibody-dependent cellular cytotoxicity, wherein

the antigen binding molecule comprises a linker that is cleavable by protease, and has binding activity against an antigen expressed on target cell surface after cleavage of the linker by the protease, and

the IgG comprises antibody variable regions having binding activity against the antigen binding molecule after the cleavage of the linker by the protease, and

the IgG antibody is capable of binding to the target cell via binding to the antigen binding molecule after cleavage of the linker.

[0016] The present disclosure provides, for example, a pharmaceutical composition

CLAIMS

1. ~~A~~ Use of a pharmaceutical composition comprising a cell expressing a chimeric receptor~~,~~ in the manufacture of a medicament for use in combination therapy, wherein said medicament is to be administered in combination with ~~the administration of~~ an antigen binding molecule, wherein

the antigen binding molecule comprises a linker that is cleavable by protease, and has the ability to bind to a target antigen after the cleavage of the linker, and

the chimeric receptor comprises an extracellular binding domain, a transmembrane domain and an intracellular signal transduction domain, and the extracellular binding domain has the ability to bind to the antigen binding molecule after cleavage of the linker, and is capable of binding to a cell expressing the target antigen via binding to the antigen binding molecule after the cleavage of the linker.

2. ~~A~~ Use of a pharmaceutical composition comprising an antigen binding molecule~~,~~ in the manufacture of a medicament for use in combination therapy, wherein said medicament is to be administered in combination with ~~the administration of~~ a cell expressing a chimeric receptor, wherein

the antigen binding molecule comprises a linker that is cleavable by protease, and has the ability to bind to a target antigen after the cleavage of the linker,

the chimeric receptor comprises an extracellular binding domain, a transmembrane domain and an intracellular signal transduction domain, and the extracellular binding domain has the ability to bind to the antigen binding molecule after the cleavage of the linker, and is capable of binding to a cell expressing the target antigen via binding to the antigen binding molecule after the cleavage of the linker.

3. Use of a~~A~~ pharmaceutical composition comprising a bispecific antibody~~,~~ in the manufacture of a medicament for use in combination therapy, wherein said medicament is to be administered in combination with ~~the administration of~~ an antigen binding molecule, wherein

the antigen binding molecule comprises a linker that is cleavable by protease, and has the ability to bind to a target antigen after cleavage of the linker,

the bispecific antibody comprises antibody variable regions having binding activity against the antigen binding molecule after the cleavage of the linker by the protease, and antibody variable regions having binding activity against a molecule expressed on T cell surface, and

the bispecific antibody is capable of binding to a cell expressing the target antigen via binding to the antigen binding molecule after the cleavage of the linker.

4. ~~A~~ Use of a pharmaceutical composition comprising an antigen binding molecule~~,~~ in the manufacture of a medicament for use in combination therapy, wherein said medicament is to be administered in combination with ~~the administration of~~ a bispecific antibody, wherein

the antigen binding molecule comprises a linker that is cleavable by protease, and has the ability to bind to a target antigen after the cleavage of the linker,

the bispecific antibody comprises antibody variable regions having binding activity against the antigen binding molecule after the cleavage of the linker by the protease, and antibody variable regions having binding activity against a molecule expressed on T cell surface, and

the bispecific antibody is capable of binding to a cell expressing the target antigen via binding to the antigen binding molecule after the cleavage of the linker.

5. Use of a~~A~~ pharmaceutical composition comprising an IgG antibody having enhanced antibody-dependent cellular cytotoxicity in the manufacture of a medicament~~,~~ for use in combination therapy, wherein said medicament is to be administered in combination with ~~the administration of~~ an antigen binding molecule, wherein

the antigen binding molecule comprises a linker that is cleavable by protease, and has binding activity against an antigen expressed on target cell surface after cleavage of the linker by the protease,

the IgG antibody comprises antibody variable regions having binding activity against the antigen binding molecule after cleavage of the linker by the protease, and

the IgG antibody is capable of binding to the target cell via binding to the antigen binding molecule after cleavage of the linker.

6. ~~A~~ Use of a pharmaceutical composition comprising an antigen binding molecule~~,~~ in the manufacture of a medicament for use in combination therapy, wherein said medicament is to be administered in combination with ~~the administration of~~ an IgG antibody having enhanced antibody-dependent cellular cytotoxicity, wherein

the antigen binding molecule comprises a linker that is cleavable by protease, and has binding activity against an antigen expressed on target cell surface after cleavage of the linker by the protease, and

the IgG comprises antibody variable regions having binding activity against the antigen binding molecule after the cleavage of the linker by the protease, and

the IgG antibody is capable of binding to the target cell via binding to the antigen binding molecule after cleavage of the linker.

7. The ~~pharmaceutical composition~~use according to any one of claims 1 to 6, wherein a ratio of a K_D value of the antigen binding molecule after cleavage of the linker for the antigen to a K_D value of the antigen binding molecule before cleavage of the linker for the antigen (K_D (after cleavage)/K_D (before cleavage)) is 0.1 or less or 0.01 or less.

8. The ~~pharmaceutical composition~~use according to any one of claims 1 to 7, wherein the antigen binding molecule is an IgG antibody, an IgG antibody-like molecule, a heavy chain antibody or a single domain antibody.

9. The ~~pharmaceutical composition~~use according to any one of claims 1 to 8, wherein the antigen binding molecule comprises variable and constant regions of an antibody, and a linker that is cleaved by protease, wherein the antibody is selected from an IgG antibody, an IgG antibody-like molecule and a heavy chain antibody, and the antigen binding molecule obtained through the cleavage of the linker by the protease comprises an antigen binding domain and a portion of the cleaved linker.

10. The ~~pharmaceutical composition~~use according to any one of claims 1 to 9, wherein in the antigen binding molecule, the linker that is cleaved by protease is located near the

boundary between the variable region and the constant region or near the boundary between CH1 and CH2 in the constant region.

11. The ~~pharmaceutical composition~~use according to any one of claims 1 to 10, wherein the antigen binding molecule is an antibody or an IgG antibody-like molecule comprising a linker that is cleaved by protease, and the antigen binding molecule after cleavage of the linker is VL, VH, or VHH of the antibody or an antigen binding fragment thereof.

12. The ~~pharmaceutical composition~~use according to any one of claims 1 to 11, wherein the antigen binding molecule is a single domain antibody comprising a linker that is cleaved by protease, and the antigen binding molecule after cleavage of the linker is an antigen binding domain of the single domain antibody and a portion of the linker.

13. The use~~pharmaceutical composition~~ according to any one of claims 1 to 12, wherein the linker that is cleaved by protease comprises a protease cleavage sequence.

14. The use~~pharmaceutical composition~~ according to any one of claims 1 to 12, wherein the linker that is cleaved by protease comprises a peptide having any of the protease cleavage sequences of SEQ ID NOs: 1 to 725.

15. The use~~pharmaceutical composition~~ according to any one of claims 1 to 14 for ~~use in~~ the treatment or prevention of a cancer.