

[Non Patent Literature 9] Mardiana S et al, Cancer Res. (2017) 77, 1296

SUMMARY ~~OF INVENTION~~

TECHNICAL PROBLEM

[0008] A problem of treatment of cancer by adoptive cell immunotherapy using CAR is a poor effect on solid tumors. This may be caused by an immunosuppressive mechanism in tumor microenvironments in addition to the fact that CAR-expressing cells which recognize only a single target antigen cannot recognize all tumor cells because tumor antigens expressed on individual cancer cells in cancer tissues are not uniform. As a strategy for solving this problem, not only CAR-expressing cells but also endogenous immunocytes may be activated to develop an antitumor effect in coordination with endogenous immunocytes, and one of approaches thereof may be therapy in which a CD137 agonist antibody activating immunocytes is used in combination. However, there is a problem that clinically and non-clinically, a C137 agonist antibody induces activation of immunocytes in nontumor tissues such as those in the liver to develop toxicity.

As another problem of treatment of cancer by adoptive cell immunotherapy using CAR, the following is pointed out. First, an antigen recognition site of CAR needs to be constructed for each targeted tumor antigen because the tumor antigen expressed on the surface of a tumor cell varies depending on a cancer cell. Secondly, tumor antigens targeted by CAR may cause tumor antigen escape because treatment decreases their expression levels or mutates the tumor antigens. Most of existing CAR-expressing cells recognize only a single target antigen. Therefore, the tumor antigen escape deteriorates therapeutic effects. Thirdly, economical cost and labor burden for identifying antigen-binding molecules for various tumor antigens and establishing CAR-expressing cells fused with these molecules are problems. Therefore, there is need for preparation of a versatile CAR-expressing cell capable of universally recognizing various target antigens and changing the recognized tumor antigen depending on the properties of target antigen cells and the treatment stage in a patient, and development of a treatment method using the CAR-expressing cell.

SOLUTION TO PROBLEM

[0009] 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 for treating or preventing a cancer, wherein said medicament is to be administered in combination with an antigen-binding molecule, wherein the chimeric receptor comprises an extracellular domain, and the extracellular domain comprises an extracellular domain of an immunoreceptor, an extracellular domain variant of an immunoreceptor, or a fraction thereof, and the antigen-binding molecule is a multispecific antigen-binding molecule having a target antigen recognition site and an immunoreceptor recognition site which recognizes the immunoreceptor. 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 for treating or preventing a cancer, wherein said medicament is to be administered in combination with a cell expressing a chimeric receptor, wherein the chimeric receptor comprises an extracellular domain, and the extracellular domain comprises an extracellular domain of an immunoreceptor, an extracellular domain variant of an immunoreceptor, or a portion thereof, and the antigen-binding molecule is a multispecific antigen-binding molecule having a target antigen recognition site and an immunoreceptor recognition site which recognizes the immunoreceptor.

[009a] In yet another aspect, the present disclosure provides a chimeric receptor comprising an extracellular domain comprising an extracellular domain of an immunoreceptor, an extracellular domain variant of an immunoreceptor, or a portion thereof. In yet another aspect, the present disclosure provides a cell expressing the chimeric receptor as described herein. In yet another aspect, the present disclosure provides a composition comprising the cell as described herein. In a further aspect, the present disclosure provides a nucleic acid encoding the chimeric receptor as described herein. In a further aspect, the present disclosure provides a vector harboring the nucleic acid as described herein. In a

further aspect, the present disclosure provides a method for producing the cell as described herein, comprising transfecting or transducing a cell with the nucleic acid as described herein or the vector as described herein.

[009b] The present disclosure provides a treatment method using a multispecific antigen-binding molecule having a site exhibiting agonist activity on an immunoreceptor and a site recognizing a target antigen in combination with immunocytes transduced with a chimeric receptor having an immunoreceptor recognized by the antigen-binding molecule in an extracellular domain. In one ~~aspect~~example, the antigen-binding molecule in the present disclosure accumulates in lesion sites expressing a target antigen, and therefore the agonist activity of the molecules is selectively expressed in the lesion sites, so that it is possible to avoid development of toxicity. The chimeric receptor in the present disclosure has no target antigen-binding activity unlike conventional CAR, and therefore does not inhibit binding of the antigen-binding molecule in the present disclosure to the target antigen. Further, the chimeric receptor in the present disclosure has binding activity against the antigen-binding molecule in the present disclosure, so that activation of endogenous immunocytes and activation of immunocytes expressing a chimeric receptor can be simultaneously induced by an antigen-binding molecule single agent.

That is, the present invention discloses the following.

[0010] More specifically, one aspect of the present disclosure provides the following invention.

[0011] [1] A pharmaceutical composition comprising a cell expressing a chimeric receptor, for use in combination with the administration of an antigen-binding molecule, wherein the chimeric receptor comprises an extracellular domain, and the extracellular domain comprises an extracellular domain of an immunoreceptor, an extracellular domain variant of an immunoreceptor, or a portion thereof, and

the antigen-binding molecule is a multispecific antigen-binding molecule having a target antigen recognition site and an immunoreceptor recognition site recognizing the

immunoreceptor.

[2] A pharmaceutical composition comprising an antigen-binding molecule, for use in combination with the administration of a cell expressing a chimeric receptor, wherein the chimeric receptor comprises an extracellular domain, and the extracellular

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 for treating or preventing a cancer, wherein said medicament is to be administered in combination with ~~the administration of~~ an antigen-binding molecule, wherein

the chimeric receptor comprises an extracellular domain, and the extracellular domain comprises an extracellular domain of an immunoreceptor, an extracellular domain variant of an immunoreceptor, or a fraction thereof, and

the antigen-binding molecule is a multispecific antigen-binding molecule having a target antigen recognition site and an immunoreceptor recognition site which recognizes the immunoreceptor.

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

the chimeric receptor comprises an extracellular domain, and the extracellular domain comprises an extracellular domain of an immunoreceptor, an extracellular domain variant of an immunoreceptor, or a portion thereof, and

the antigen-binding molecule is a multispecific antigen-binding molecule having a target antigen recognition site and an immunoreceptor recognition site which recognizes the immunoreceptor.

3. The ~~use pharmaceutical composition~~ according to claim 1 or 2, wherein the immunoreceptor recognition site recognizes the extracellular domain of the chimeric receptor and an endogenous immunoreceptor.

4. The ~~use pharmaceutical composition~~ according to any one of claims 1 to 3, wherein the extracellular domain of the chimeric receptor comprises an extracellular domain variant of an immunoreceptor, or a portion thereof, having attenuated binding to a ligand for the endogenous immunoreceptor.

5. The ~~use pharmaceutical composition~~ according to any one of claims 1 to 4, wherein the immunoreceptor is a costimulatory molecule.
6. The ~~use pharmaceutical composition~~ according to any one of claims 1 to 5, wherein the immunoreceptor is human CD137.
7. The ~~use pharmaceutical composition~~ according to any one of claims 1 to 6, wherein the extracellular domain of the chimeric receptor comprises a human CD137 extracellular domain variant, or a portion thereof, in which at least a part or all of a cysteine-rich domain 3 and a cysteine-rich domain 4 of a human CD137 extracellular domain are deleted.
8. The ~~use pharmaceutical composition~~ according to any one of claims 1 to 7, wherein an intracellular signaling domain of the chimeric receptor comprises an intracellular signaling domain of CD3 zeta.
9. The ~~use pharmaceutical composition~~ according to any one of claims 1 to 8, wherein the target antigen is a receptor, a tumor antigen, an MHC antigen, or a differentiation antigen.
10. The ~~use pharmaceutical composition~~ according to any one of claims 1 to 8, wherein the target antibody is a tumor antigen.
11. The ~~use pharmaceutical composition~~ according to any one of claims 1 to 10, wherein the antigen-binding molecule is a bispecific antibody.
- ~~12. —The pharmaceutical composition according to any one of claims 1 to 11 for use in the treatment or prevention of a cancer.~~
- ~~13~~12. A chimeric receptor comprising an extracellular domain comprising an extracellular domain of an immunoreceptor, an extracellular domain variant of an immunoreceptor, or a portion thereof.
- ~~14~~13. The chimeric receptor according to claim ~~13~~12, wherein the extracellular domain of the chimeric receptor comprises an extracellular domain variant of an immunoreceptor, or a portion thereof, having attenuated binding to a ligand for an endogenous immunoreceptor.
- ~~15~~14. The chimeric receptor according to claim ~~13~~12 or ~~14~~13, wherein the immunoreceptor is a costimulatory molecule.
- ~~16~~15. The chimeric receptor according to any one of claims ~~13~~12 to ~~15~~14, wherein the

immunoreceptor is human CD137.

~~17~~16. The chimeric receptor according to any one of claims ~~13~~12 to ~~16~~15, wherein the extracellular domain of the chimeric receptor is a human CD137 extracellular domain variant, or a portion thereof, in which at least a part or all of a cysteine-rich domain 3 and a cysteine-rich domain 4 of a human CD137 extracellular domain are deleted.

~~18~~17. The chimeric receptor according to any one of claims ~~13~~12 to ~~17~~16, wherein an intracellular signaling domain of the chimeric receptor comprises an intracellular signaling domain of CD3 zeta.

~~19~~18. A cell expressing the chimeric receptor according to any one of claims ~~13~~12 to ~~18~~17.

~~20~~19. A composition comprising the cell according to claim ~~19~~18.

~~21~~20. A nucleic acid encoding the chimeric receptor according to any one of claims ~~13~~12 to ~~18~~17.

~~22~~21. A vector harboring the nucleic acid according to claim ~~21~~20.

~~23~~22. A method for producing the cell according to claim ~~19~~18, comprising transfecting or transducing a cell with the nucleic acid according to claim ~~21~~20 or the vector according to claim ~~22~~21.