

Summary

In one aspect, the present disclosure refers to a use of first RNA encoding a first peptide or polypeptide in the manufacture of a first medicament and use of second RNA encoding a second peptide or polypeptide in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat a subject having a disease, disorder or condition characterized by cells expressing a target antigen; wherein the subject is to be provided immune effector cells genetically modified to express a chimeric antigen receptor (CAR); wherein the first peptide or polypeptide comprises a binding moiety for the CAR; wherein the second peptide or polypeptide comprises a binding moiety binding to the target antigen and a binding moiety for the CAR; and the use comprises allowing expression of the first peptide or polypeptide by antigen presenting cells in the subject such that the binding moiety for the CAR is available for binding by the immune effector cells said binding resulting in expansion of the immune effector cells; and allowing expression of the second peptide or polypeptide by cells in the subject such that the second peptide or polypeptide becomes associated with cells expressing the target antigen and the binding moiety for the CAR is available for binding by the immune effector cells.

In one example, the disclosure relates to a method for treating a subject having a disease, disorder or condition characterized by cells expressing a target antigen, comprising:

- (i) providing to the subject immune effector cells genetically modified to express a chimeric antigen receptor (CAR);

- (ii) administering to the subject first RNA encoding a first peptide or polypeptide, wherein the first peptide or polypeptide comprises a binding moiety for the CAR;
- (iii) allowing expression of the first peptide or polypeptide by antigen presenting cells in the subject such that the binding moiety for the CAR is available for binding by the immune effector cells said binding resulting in expansion of the immune effector cells;
- (iv) administering to the subject second RNA encoding a second peptide or polypeptide, wherein the second peptide or polypeptide comprises a binding moiety binding to the target antigen and a binding moiety for the CAR; and
- (v) allowing expression of the second peptide or polypeptide by cells in the subject such that the second peptide or polypeptide becomes associated with cells expressing the target antigen and the binding moiety for the CAR is available for binding by the immune effector cells.

In some examples, the antigen presenting cells are transfected with the first RNA.

In some examples, the first RNA is administered as particulate formulation such as formulated as lipoplex particles.

In some examples, the cells expressing the second peptide or polypeptide are transfected with the second RNA.

In some examples, the second RNA is administered as particulate formulation such as formulated as lipid nanoparticles.

In some examples, the antigen presenting cells express the first peptide or polypeptide such that it remains associated with the antigen presenting cells.

In some examples, the first peptide or polypeptide is a membrane peptide or polypeptide.

In some examples, the first peptide or polypeptide is a fusion protein of the binding moiety for the CAR and a membrane peptide or polypeptide.

In some examples, binding of the immune effector cells to the second peptide or polypeptide associated with cells expressing the target antigen results in killing of cells expressing the target antigen.

In some examples, the cells expressing the second peptide or polypeptide secrete the second peptide or polypeptide.

In some examples, the cells expressing the second peptide or polypeptide express the second peptide or polypeptide such that it is released into the bloodstream.

In some examples, the target antigen is a cell surface antigen.

In some examples, the second peptide or polypeptide is a fusion peptide or polypeptide of the binding moiety binding to the target antigen and the binding moiety for the CAR.

In some examples, the binding moiety binding to the target antigen comprises an antibody or an antibody derivative.

In some examples, the binding moiety for the CAR comprises a peptide tag.

In some examples, the CAR comprises an antibody or an antibody derivative.

In some examples, the antibody derivative is an antibody fragment.

In some examples, the method comprises administering the immune effector cells genetically modified to express a CAR to the subject.

In some examples, the method comprises generating the immune effector cells genetically modified to express a CAR in the subject.

In some examples, the disease, disorder or condition is cancer.

In some examples, the cells expressing a target antigen are diseased cells.

In some examples, the cells expressing a target antigen are cancer cells.

In some examples, the target antigen is a tumor antigen.

In another aspect, the present disclosure refers to a use of first RNA encoding a first peptide or polypeptide in the manufacture of a first medicament and use of second RNA encoding a second peptide or polypeptide such that the second peptide or polypeptide is expressed in and secreted by cells of the subject in the manufacture of a second medicament, wherein the first and second medicaments are to be administered in

combination to a subject having a disease, disorder or condition characterized by cells expressing a target antigen;

wherein the subject is to be provided immune effector cells genetically modified to express a chimeric antigen receptor (CAR) binding to a peptide tag;

such that the first peptide or polypeptide is expressed in antigen presenting cells of the subject, wherein the first peptide or polypeptide is a membrane protein which comprises in an extracellular domain a peptide tag to which the CAR binds; and

wherein the second peptide or polypeptide comprises a binding moiety binding to the target antigen and a peptide tag to which the CAR binds.

In a further example, the disclosure relates to a method for treating a subject having a disease, disorder or condition characterized by cells expressing a target antigen, comprising:

- (i) providing to the subject immune effector cells genetically modified to express a chimeric antigen receptor (CAR) binding to a peptide tag;

- (ii) administering to the subject first RNA encoding a first peptide or polypeptide such that the first peptide or polypeptide is expressed in antigen presenting cells of the subject, wherein the first peptide or polypeptide is a membrane protein which comprises in an extracellular domain a peptide tag to which the CAR binds; and
- (iii) administering to the subject second RNA encoding a second peptide or polypeptide such that the second peptide or polypeptide is expressed in and secreted by cells of the subject, wherein the second peptide or polypeptide comprises a binding moiety binding to the target antigen and a peptide tag to which the CAR binds.

In some examples, binding of the immune effector cells to the first peptide or polypeptide results in expansion of the immune effector cells.

In some examples, binding of the immune effector cells to the second peptide or polypeptide bound to target antigen results in killing of cells expressing the target antigen.

In some examples, the antigen presenting cells are transfected with the first RNA.

In some examples, the first RNA is administered as particulate formulation such as formulated as lipoplex particles.

In some examples, the cells expressing the second peptide or polypeptide are transfected with the second RNA.

In some examples, the second RNA is administered as particulate formulation such as formulated as lipid nanoparticles.

In some examples, the antigen presenting cells express the first peptide or polypeptide such that it remains associated with the antigen presenting cells.

In some examples, the first peptide or polypeptide is a fusion protein of a peptide tag to which the CAR binds and a membrane peptide or polypeptide.

In some examples, the second peptide or polypeptide is secreted into the bloodstream.

In some examples, the target antigen is a cell surface antigen.

In some examples, the second peptide or polypeptide is a fusion peptide or polypeptide of the binding moiety binding to the target antigen and a peptide tag to which the CAR binds.

In some examples, the binding moiety binding to the target antigen comprises an antibody or an antibody derivative.

In some examples, the CAR comprises an antibody or an antibody derivative.

In some examples, the antibody derivative is an antibody fragment.

In some examples, the method comprises administering the immune effector cells genetically modified to express a CAR to the subject.

In some examples, the method comprises generating the immune effector cells genetically modified to express a CAR in the subject.

In some examples, the disease, disorder or condition is cancer.

In some examples, the cells expressing a target antigen are diseased cells.

In some examples, the cells expressing a target antigen are cancer cells.

In some examples, the target antigen is a tumor antigen.

In a further aspect, the disclosure relates to a kit, comprising:

- (i) nucleic acid for genetically modifying immune effector cells to express a chimeric antigen receptor (CAR) binding to a peptide tag, or immune effector cells genetically modified to express a chimeric antigen receptor (CAR) binding to a peptide tag;
- (ii) first RNA encoding a first peptide or polypeptide which is a membrane protein which comprises in an extracellular domain a peptide tag to which the CAR binds, or nucleic acid for obtaining said first RNA; and optionally
- (iii) second RNA encoding a second peptide or polypeptide which comprises a binding moiety binding to a target antigen and a peptide tag to which the CAR binds, or nucleic acid for obtaining said second RNA.

Examples of the nucleic acid for genetically modifying immune effector cells to express a chimeric antigen receptor (CAR) binding to a peptide tag, the immune effector cells genetically modified to express a chimeric antigen receptor (CAR) binding to a peptide tag, the first RNA, the first peptide or polypeptide, the second RNA and/or the second peptide or polypeptide are described herein, e.g., in the context of the method of the disclosure.

In one example, the disclosure relates to an agent or composition described herein (e.g., nucleic acid for genetically modifying immune effector cells, immune effector cells genetically

modified to express a chimeric antigen receptor (CAR), first RNA, second RNA and/or kit) for use in a method described herein.

Claims

1. Use of first RNA encoding a first peptide or polypeptide in the manufacture of a first medicament
and use of second RNA encoding a second peptide or polypeptide in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat a subject having a disease, disorder or condition characterized by cells expressing a target antigen;
wherein the subject is to be provided immune effector cells genetically modified to express a chimeric antigen receptor (CAR);
wherein the first peptide or polypeptide comprises a binding moiety for the CAR;
wherein the second peptide or polypeptide comprises a binding moiety binding to the target antigen and a binding moiety for the CAR; and
the use comprises allowing expression of the first peptide or polypeptide by antigen presenting cells in the subject such that the binding moiety for the CAR is available for binding by the immune effector cells said binding resulting in expansion of the immune effector cells; and
allowing expression of the second peptide or polypeptide by cells in the subject such that the second peptide or polypeptide becomes associated with cells expressing the target antigen and the binding moiety for the CAR is available for binding by the immune effector cells.
2. The use of claim 1, wherein the antigen presenting cells are transfected with the first RNA.
3. The use of claim 1 or 2, wherein the first RNA is to be administered as particulate formulation such as formulated as lipoplex particles.
4. The use of any one of claims 1 to 3, wherein the cells expressing the second peptide or polypeptide are transfected with the second RNA.

5. The use of any one of claims 1 to 4, wherein the second RNA is to be administered as particulate formulation such as formulated as lipid nanoparticles.
6. The use of any one of claims 1 to 5, wherein the antigen presenting cells express the first peptide or polypeptide such that it remains associated with the antigen presenting cells.
7. The use of any one of claims 1 to 6, wherein the first peptide or polypeptide is a membrane peptide or polypeptide.
8. The use of any one of claims 1 to 7, wherein the first peptide or polypeptide is a fusion protein of the binding moiety for the CAR and a membrane peptide or polypeptide.
9. The use of any one of claims 1 to 8, wherein binding of the immune effector cells to the second peptide or polypeptide associated with cells expressing the target antigen results in killing of cells expressing the target antigen.
10. The use of any one of claims 1 to 9, wherein the cells expressing the second peptide or polypeptide secrete the second peptide or polypeptide.
11. The use of any one of claims 1 to 10, wherein the cells expressing the second peptide or polypeptide express the second peptide or polypeptide such that it is released into the bloodstream.
12. The use of any one of claims 1 to 11, wherein the target antigen is a cell surface antigen.
13. The use of any one of claims 1 to 12, wherein the second peptide or polypeptide is a fusion peptide or polypeptide of the binding moiety binding to the target antigen and the binding moiety for the CAR.
14. The use of any one of claims 1 to 13, wherein the binding moiety binding to the target antigen comprises an antibody or an antibody derivative.

15. The use of any one of claims 1 to 14, wherein the binding moiety for the CAR comprises a peptide tag.
16. The use of any one of claims 1 to 16, wherein the CAR comprises an antibody or an antibody derivative.
17. The use of any one of claims 14 to 16, wherein the antibody derivative is an antibody fragment.
18. The use of any one of claims 1 to 17, wherein the use comprises that the immune effector cells genetically modified to express a CAR are to be administered to the subject.
19. The use of any one of claims 1 to 17, wherein the use comprises generating the immune effector cells genetically modified to express a CAR in the subject.
20. The use of any one of claims 1 to 19, wherein the disease, disorder or condition is cancer.
21. The use of any one of claims 1 to 20, wherein the cells expressing a target antigen are diseased cells.
22. The use of any one of claims 1 to 21, wherein the cells expressing a target antigen are cancer cells.
23. The use of any one of claims 1 to 22, wherein the target antigen is a tumor antigen.
24. Use of first RNA encoding a first peptide or polypeptide in the manufacture of a first medicament and
use of second RNA encoding a second peptide or polypeptide such that the second peptide or polypeptide is expressed in and secreted by cells of the subject in the manufacture of a second medicament, wherein the first and second medicaments are to be administered in

combination to a subject having a disease, disorder or condition characterized by cells expressing a target antigen;
wherein the subject is to be provided immune effector cells genetically modified to express a chimeric antigen receptor (CAR) binding to a peptide tag;
such that the first peptide or polypeptide is expressed in antigen presenting cells of the subject, wherein the first peptide or polypeptide is a membrane protein which comprises in an extracellular domain a peptide tag to which the CAR binds; and
wherein the second peptide or polypeptide comprises a binding moiety binding to the target antigen and a peptide tag to which the CAR binds.

25. The use of claim 24, wherein binding of the immune effector cells to the first peptide or polypeptide results in expansion of the immune effector cells.

26. The use of claim 24 or 25, wherein binding of the immune effector cells to the second peptide or polypeptide bound to target antigen results in killing of cells expressing the target antigen.

27. The use of any one of claims 24 to 26, wherein the antigen presenting cells are transfected with the first RNA.

28. The use of any one of claims 24 to 27, wherein the first RNA is to be administered as particulate formulation such as formulated as lipoplex particles.

29. The use of any one of claims 24 to 28, wherein the cells expressing the second peptide or polypeptide are transfected with the second RNA.

30. The use of any one of claims 24 to 29, wherein the second RNA is to be administered as particulate formulation such as formulated as lipid nanoparticles.

31. The use of any one of claims 24 to 30, wherein the antigen presenting cells express the first peptide or polypeptide such that it remains associated with the antigen presenting cells.

32. The use of any one of claims 24 to 31, wherein the first peptide or polypeptide is a fusion protein of a peptide tag to which the CAR binds and a membrane peptide or polypeptide.
33. The use of any one of claims 24 to 32, wherein the second peptide or polypeptide is secreted into the bloodstream.
34. The use of any one of claims 24 to 33, wherein the target antigen is a cell surface antigen.
35. The use of any one of claims 24 to 34, wherein the second peptide or polypeptide is a fusion peptide or polypeptide of the binding moiety binding to the target antigen and a peptide tag to which the CAR binds.
36. The use of any one of claims 24 to 35, wherein the binding moiety binding to the target antigen comprises an antibody or an antibody derivative.
37. The use of any one of claims 24 to 36, wherein the CAR comprises an antibody or an antibody derivative.
38. The use of claim 36 or 37, wherein the antibody derivative is an antibody fragment.
39. The use of any one of claims 24 to 38, wherein the use comprises that the immune effector cells genetically modified to express a CAR are to be administered to the subject.
40. The use of any one of claims 24 to 38, wherein the use comprises generating the immune effector cells genetically modified to express a CAR in the subject.
41. The use of any one of claims 24 to 40, wherein the disease, disorder or condition is cancer.

42. The use of any one of claims 24 to 41, wherein the cells expressing a target antigen are diseased cells.
43. The use of any one of claims 24 to 42, wherein the cells expressing a target antigen are cancer cells.
44. The use of any one of claims 24 to 43, wherein the target antigen is a tumor antigen.
45. A kit, comprising:
- (i) nucleic acid for genetically modifying immune effector cells to express a chimeric antigen receptor (CAR) binding to a peptide tag, or immune effector cells genetically modified to express a chimeric antigen receptor (CAR) binding to a peptide tag;
 - (ii) first RNA encoding a first peptide or polypeptide which is a membrane protein which comprises in an extracellular domain a peptide tag to which the CAR binds, or nucleic acid for obtaining said first RNA; and optionally
 - (iii) second RNA encoding a second peptide or polypeptide which comprises a binding moiety binding to a target antigen and a peptide tag to which the CAR binds, or nucleic acid for obtaining said second RNA.