

METHODS FOR MODULATING AN IMMUNE RESPONSE

CROSS-REFERENCE

- [0001]** This application claims the benefit of U.S. Provisional Patent Application No. 62/471,832, filed March 15, 2017, and of U.S. Provisional Patent Application No. 62/521,009, filed June 16, 2017, which applications are incorporated herein by reference in their entirety.

INTRODUCTION

- [0002]** An adaptive immune response involves the engagement of the T cell receptor (TCR), present on the surface of a T cell, with a small peptide antigen non-covalently presented on the surface of an antigen presenting cell (APC) by a major histocompatibility complex (MHC; also referred to in humans as a human leukocyte antigen (HLA) complex). This engagement represents the immune system's targeting mechanism and is a requisite molecular interaction for T cell modulation (activation or inhibition) and effector function. Following epitope-specific cell targeting, the targeted T cells are activated through engagement of costimulatory proteins found on the APC with counterpart costimulatory proteins the T cells. Both signals – epitope/TCR binding and engagement of APC costimulatory proteins with T cell costimulatory proteins – are required to drive T cell specificity and activation or inhibition. The TCR is specific for a given epitope; however, the costimulatory protein not epitope specific and instead is generally expressed on all T cells or on large T cell subsets.

SUMMARY

- [0003]** The present disclosure provides methods of modulating an immune response in an individual. The present disclosure provides methods of treatment. The present disclosure provides methods comprising administering a multimeric polypeptide (synTac) and an immune checkpoint inhibitor to an individual. The present disclosure provides methods comprising administering a multimeric polypeptide (synTac) to an individual who is undergoing treatment with immune checkpoint inhibitor.
- [0003a]** In an aspect, there is provided use of an immune checkpoint inhibitor in the manufacture of a medicament for modulating an immune response or treating cancer, wherein the medicament is to be administered in combination with a composition comprising a multimeric polypeptide, wherein:
- the multimeric polypeptide composition comprises a heterodimeric polypeptide, wherein the heterodimeric polypeptide comprises:

a) a first polypeptide comprising

i) a peptide epitope comprising a human papilloma virus E7 epitope; and

ii) a first major histocompatibility complex (MHC) polypeptide, wherein the first MHC polypeptide is a β 2-microglobulin polypeptide;

b) a second polypeptide comprising a second MHC polypeptide, wherein the second MHC polypeptide is an MHC class I heavy chain polypeptide; and

optionally wherein the first and/or the second polypeptide comprises an immunoglobulin (Ig) Fc polypeptide,

wherein the multimeric polypeptide comprises one or more immunomodulatory domains,

wherein at least one of the one or more immunomodulatory domains is a variant IL2 polypeptide that exhibits reduced binding affinity to an IL-2 receptor (IL2R) comprising alpha, beta, and gamma polypeptides having amino acid sequences depicted in FIG. 3A-3C, compared to the binding affinity of the IL-2 amino acid sequence set forth in SEQ ID NO: 1 for the IL2R, and

wherein the immune checkpoint inhibitor and the composition comprising the multimeric polypeptide are to be administered at the same time or at different times.

[0003b] In another aspect, there is provided use of a composition comprising a multimeric polypeptide in the manufacture of a medicament for modulating an immune response or treating cancer, wherein the medicament is to be administered in combination with an immune checkpoint inhibitor, wherein:

the multimeric polypeptide composition comprises a heterodimeric polypeptide, wherein the heterodimeric polypeptide comprises:

a) a first polypeptide comprising

i) a peptide epitope comprising a human papilloma virus E7 epitope; and

ii) a first major histocompatibility complex (MHC) polypeptide, wherein the first MHC polypeptide is a β 2-microglobulin polypeptide;

b) a second polypeptide comprising a second MHC polypeptide, wherein the second MHC polypeptide is an MHC class I heavy chain polypeptide; and

optionally wherein the first and/or the second polypeptide comprises an immunoglobulin (Ig) Fc polypeptide,

wherein the multimeric polypeptide comprises one or more immunomodulatory domains,

wherein at least one of the one or more immunomodulatory domains is a variant IL2 polypeptide that exhibits reduced binding affinity to an IL-2 receptor (IL2R) comprising alpha, beta, and gamma polypeptides having amino acid sequences depicted in FIG. 3A-3C, compared to the binding affinity of the IL-2 amino acid sequence set forth in SEQ ID NO: 1 for the IL2R, and

wherein the immune checkpoint inhibitor and the composition comprising the multimeric polypeptide are to be administered at the same time or at different times.

[0003c] In another aspect, there is provided use of an immune checkpoint inhibitor in the manufacture of a medicament for modulating an immune response or treating cancer, wherein the medicament is to be administered in combination with a composition comprising a multimeric polypeptide, wherein the composition comprising a multimeric polypeptide comprises a protein comprising two of the heterodimeric polypeptides disclosed herein, wherein each of the two heterodimeric polypeptides comprises an immunoglobulin (Ig) Fc polypeptide, and wherein the immune checkpoint inhibitor and the composition comprising the multimeric polypeptide are to be administered at the same time or at different times.

[0003d] In yet another aspect, there is provided use of a composition comprising a multimeric polypeptide in the manufacture of a medicament for modulating an immune response or treating cancer, wherein the medicament is to be administered in combination with an immune checkpoint inhibitor, wherein the composition comprising a multimeric polypeptide comprises a protein comprising two of the heterodimeric polypeptides disclosed herein, wherein each of the two heterodimeric polypeptides comprises an immunoglobulin (Ig) Fc polypeptide, and wherein the immune checkpoint inhibitor and the composition comprising the multimeric polypeptide are to be administered at the same time or at different times.

[0003e] In a further aspect, there is provided use of an immune checkpoint inhibitor in the manufacture of a medicament for modulating an immune response or treating cancer, wherein the medicament is to be administered in combination with a composition comprising a multimeric polypeptide, wherein:

the multimeric polypeptide composition comprises a heterodimeric polypeptide, wherein the heterodimeric polypeptide comprises:

a) a first polypeptide comprising:

i) a peptide comprising an epitope present in a cancer-associated antigen; and

ii) a first class I major histocompatibility complex (MHC) polypeptide; and

b) a second polypeptide comprising a second class I MHC polypeptide;

wherein the multimeric polypeptide comprises one or more immunomodulatory polypeptide, optionally wherein the first and/or the second polypeptide comprises an immunoglobulin (Ig) Fc polypeptide, and

wherein the immune checkpoint inhibitor and the composition comprising the multimeric polypeptide are to be administered at the same time or at different times.

[0003f] In yet another aspect, there is provided use of a composition comprising a multimeric polypeptide in the manufacture of a medicament for modulating an immune response or treating

cancer, wherein the medicament is to be administered in combination with an immune checkpoint inhibitor, wherein:

the multimeric polypeptide composition comprises a heterodimeric polypeptide, wherein the heterodimeric polypeptide comprises:

a) a first polypeptide comprising:

- i) a peptide comprising an epitope present in a cancer-associated antigen; and
- ii) a first class I major histocompatibility complex (MHC) polypeptide; and

b) a second polypeptide comprising a second class I MHC polypeptide;

wherein the multimeric polypeptide comprises one or more immunomodulatory polypeptide, optionally wherein the first and/or the second polypeptide comprises an immunoglobulin (Ig) Fc polypeptide, and

wherein the immune checkpoint inhibitor and the composition comprising the multimeric polypeptide are to be administered at the same time or at different times.

[0003g] In another aspect, there is provided use of an immune checkpoint inhibitor in the manufacture of a medicament for modulating an immune response or treating cancer, wherein the medicament is to be administered in combination with a composition comprising a multimeric polypeptide, wherein the composition comprising a multimeric polypeptide comprises a protein comprising two of the heterodimeric polypeptides disclosed herein, wherein each of the two heterodimeric polypeptides comprises an immunoglobulin (Ig) Fc polypeptide, and wherein the immune checkpoint inhibitor and the composition comprising the multimeric polypeptide are to be administered at the same time or at different times.

[0003h] In yet another aspect, there is provided use of a composition comprising a multimeric polypeptide in the manufacture of a medicament for modulating an immune response or treating cancer, wherein the medicament is to be administered in combination with an immune checkpoint inhibitor, wherein the composition comprising a multimeric polypeptide comprises a protein comprising two of the heterodimeric polypeptides disclosed herein, wherein each of the two heterodimeric polypeptides comprises an immunoglobulin (Ig) Fc polypeptide, and wherein the immune checkpoint inhibitor and the composition comprising the multimeric polypeptide are to be administered at the same time or at different times.

[0003i] In a further aspect, there is provided use of a composition comprising a multimeric polypeptide as disclosed herein in the preparation of a medicament for treating cancer in a subject previously treated with an immune checkpoint inhibitor.

BRIEF DESCRIPTION OF THE DRAWINGS

[0004] FIG. 1A-1D schematically depict various embodiments of a T-cell modulatory multimeric polypeptide. In these embodiments, disulfide bonds are formed between MHC (e.g., HLA) polypeptides present in separate polypeptides.

CLAIMS

What is claimed is:

1. Use of an immune checkpoint inhibitor in the manufacture of a medicament for modulating an immune response or treating cancer, wherein the medicament is to be administered in combination with a composition comprising a multimeric polypeptide, wherein:

the multimeric polypeptide composition comprises a heterodimeric polypeptide, wherein the heterodimeric polypeptide comprises:

a) a first polypeptide comprising

i) a peptide epitope comprising a human papilloma virus E7 epitope; and

ii) a first major histocompatibility complex (MHC) polypeptide, wherein the first MHC polypeptide is a β 2-microglobulin polypeptide;

b) a second polypeptide comprising a second MHC polypeptide, wherein the second MHC polypeptide is an MHC class I heavy chain polypeptide; and

optionally wherein the first and/or the second polypeptide comprises an immunoglobulin (Ig) Fc polypeptide,

wherein the multimeric polypeptide comprises one or more immunomodulatory domains,

wherein at least one of the one or more immunomodulatory domains is a variant IL2 polypeptide that exhibits reduced binding affinity to an IL-2 receptor (IL2R) comprising alpha, beta, and gamma polypeptides having amino acid sequences depicted in FIG. 3A-3C, compared to the binding affinity of the IL-2 amino acid sequence set forth in SEQ ID NO: 1 for the IL2R, and

wherein the immune checkpoint inhibitor and the composition comprising the multimeric polypeptide are to be administered at the same time or at different times.

2. Use of a composition comprising a multimeric polypeptide in the manufacture of a medicament for modulating an immune response or treating cancer, wherein the medicament is to be administered in combination with an immune checkpoint inhibitor, wherein:

the multimeric polypeptide composition comprises a heterodimeric polypeptide, wherein the heterodimeric polypeptide comprises:

a) a first polypeptide comprising

i) a peptide epitope comprising a human papilloma virus E7 epitope; and

ii) a first major histocompatibility complex (MHC) polypeptide, wherein the first MHC polypeptide is a β 2-microglobulin polypeptide;

b) a second polypeptide comprising a second MHC polypeptide, wherein the second MHC polypeptide is an MHC class I heavy chain polypeptide; and

optionally wherein the first and/or the second polypeptide comprises an immunoglobulin (Ig) Fc polypeptide,

wherein the multimeric polypeptide comprises one or more immunomodulatory domains,

wherein at least one of the one or more immunomodulatory domains is a variant IL2 polypeptide that exhibits reduced binding affinity to an IL-2 receptor (IL2R) comprising alpha, beta, and gamma polypeptides having amino acid sequences depicted in FIG. 3A-3C, compared to the binding affinity of the IL-2 amino acid sequence set forth in SEQ ID NO: 1 for the IL2R, and

wherein the immune checkpoint inhibitor and the composition comprising the multimeric polypeptide are to be administered at the same time or at different times.

3. A use according to claim 1 or claim 2, wherein the second polypeptide comprises one or two immunomodulatory polypeptides, and wherein each immunomodulatory polypeptide is selected from the group consisting of

a variant IL-2 polypeptide comprising an H16A substitution relative to set forth in SEQ ID NO:1; and

a variant IL-2 polypeptide comprising an H16A substitution and an F42A substitution relative to set forth in SEQ ID NO:1.

4. A use according to any one of claims 1-3, wherein the peptide epitope comprises the amino acid sequence selected from the group consisting of HPV16E7/82-90 (LLMGTLGIV; SEQ ID NO:75), HPV16E7/86-93 (TLGIVCPI; SEQ ID NO:76), HPV16E7/11-20 (YMLDLQPETT; SEQ ID NO:77), and HPV16E7/11-19 (YMLDLQPET; SEQ ID NO:78).

5. A use according to any of claims 1-4, wherein the multimeric polypeptide comprises an Ig Fc polypeptide, and wherein the Ig Fc polypeptide comprises L234A and L235A substitutions.

6. A use according to any one of claims 1-5, wherein the β 2-microglobulin polypeptide comprises amino acids 21-119 of any one of the amino acid sequences set forth in FIG.6, optionally wherein the amino acid sequence comprises an R12C substitution.

7. A use according to any one of claims 1-6, wherein the MHC class I heavy chain polypeptide is an HLA-A heavy chain.

8. A use according to any one of claims 1-7, wherein the MHC class I heavy chain polypeptide comprises amino acids 25 to 365 of the amino acid sequence set forth in FIG. 5A (SEQ ID NO:29), optionally wherein the amino acid sequence comprises a Y84A substitution, an A236C substitution, or both a Y84A substitution and an A236C substitution.

9. A use according to any one of claims 1-8, wherein the first polypeptide and the second polypeptide are covalently linked to one another via a disulfide bond, wherein the disulfide bond joins a Cys residue in the β 2M polypeptide and a Cys residue in the MHC heavy chain polypeptide.

10. A use according to claim 9, wherein a Cys at amino acid residue 12 of the β 2M polypeptide is disulfide bonded to a Cys at amino acid residue 236 of the MHC heavy chain polypeptide.

11. A use according to claim 9, wherein the first polypeptide chain comprises a linker between the peptide epitope and the β 2M polypeptide, and wherein the disulfide bond links a Cys present in the linker with a Cys of the MHC heavy chain polypeptide.

12. A use according to claim 1 or claim 2, wherein the heterodimeric polypeptide comprises:

- a) a first polypeptide comprising, in order from N-terminus to C-terminus:
 - i) a peptide epitope, wherein the peptide epitope comprises the amino acid sequence YMLDLQPETT (SEQ ID NO:77) and has a length of 10 amino acids; and
 - ii) a first major histocompatibility complex (MHC) polypeptide, wherein the first MHC polypeptide is a β 2-microglobulin polypeptide;
- b) a second polypeptide comprising in order from N-terminus to C-terminus:
 - i) a first immunomodulatory polypeptide, wherein the first immunomodulatory polypeptide is a variant IL-2 polypeptide comprising an H16A substitution and an F42A substitution relative to set forth in SEQ ID NO:1;
 - ii) a second immunomodulatory polypeptide, wherein the second immunomodulatory polypeptide is a variant IL-2 polypeptide comprising an H16A substitution and an F42A substitution relative to set forth in SEQ ID NO:1;
 - iii) a second MHC polypeptide, wherein the second MHC polypeptide is an MHC class I heavy chain polypeptide; and
 - iv) an immunoglobulin (Ig) Fc polypeptide,

and wherein:

the β 2-microglobulin polypeptide comprises amino acids 21-119 of any one of the amino acid sequences set forth in FIG.6, optionally wherein the amino acid sequence comprises an R12C substitution,

the MHC class I heavy chain polypeptide comprises amino acids 25 to 365 of the amino acid sequence set forth in FIG. 5A (SEQ ID NO:29), optionally wherein the amino acid sequence comprises a Y84A substitution, an A236C substitution, or both a Y84A substitution and an A236C substitution, and

the first polypeptide and the second polypeptide are covalently linked to one another via a disulfide bond, and wherein the disulfide bond joins Cys at amino acid residue 12 of the β 2M polypeptide to a Cys at amino acid residue 236 of the MHC heavy chain polypeptide.

13. A use according to claim 12, wherein
- i) the β 2-microglobulin polypeptide comprises the amino acid sequence depicted in FIG. 34A;
 - ii) the first and second variant IL-2 polypeptide comprise the amino acid sequence depicted in FIG. 34B;
 - iii) the MHC Class I heavy chain polypeptide comprises the amino acid sequence depicted in FIG. 34C; and
 - iv) the Ig Fc polypeptide comprises the amino acid sequence depicted in FIG. 33A, 33B, 33C, or 33D.

14. A use according to claim 13, wherein the first polypeptide comprises a linker between the epitope and the β 2-microglobulin polypeptide, and the second polypeptide comprises a peptide linker between one or more of:

- a) a first copy of the variant IL-2 polypeptide and a second copy of the variant IL-2 polypeptide;
- b) the variant IL-2 polypeptide and the MHC heavy chain polypeptide; and
- c) the MHC heavy chain polypeptide and the IgG1 Fc polypeptide.

15. A use according to claim 14, wherein the peptide linker is selected from (GGGGS)₃, (GGGGS)₄, and AAAGG.

16. A use according to any one of claims 12-15, wherein the heterodimeric polypeptide comprises:

- a) a first polypeptide comprising the amino acid sequence depicted in FIG. 31, and
- b) a second polypeptide comprising the amino acid sequence depicted in FIG. 22,

or

- a) a first polypeptide comprising the amino acid sequence depicted in FIG. 31, and
 - b) a second polypeptide comprising the amino acid sequence depicted in FIG. 25,
- or
- a) a first polypeptide comprising the amino acid sequence depicted in FIG. 31, and
 - b) a second polypeptide comprising the amino acid sequence depicted in FIG. 28.

17. Use of an immune checkpoint inhibitor in the manufacture of a medicament for modulating an immune response or treating cancer, wherein the medicament is to be administered in combination with a composition comprising a multimeric polypeptide, wherein the composition comprising a multimeric polypeptide comprises a protein comprising two of the heterodimeric polypeptides of any one of claims 1 to 16, wherein each of the two heterodimeric polypeptides comprises an immunoglobulin (Ig) Fc polypeptide, and wherein the immune checkpoint inhibitor and the composition comprising the multimeric polypeptide are to be administered at the same time or at different times.

18. Use of a composition comprising a multimeric polypeptide in the manufacture of a medicament for modulating an immune response or treating cancer, wherein the medicament is to be administered in combination with an immune checkpoint inhibitor, wherein the composition comprising a multimeric polypeptide comprises a protein comprising two of the heterodimeric polypeptides of any one of claims 1 to 16, wherein each of the two heterodimeric polypeptides comprises an immunoglobulin (Ig) Fc polypeptide, and wherein the immune checkpoint inhibitor and the composition comprising the multimeric polypeptide are to be administered at the same time or at different times

19. A use according to claim 16 or claim 17, wherein the two heterodimeric polypeptides are disulfide linked to one another via the Fc polypeptides present in the heterodimers.

20. A use according to any one of claims 1-19, wherein the checkpoint inhibitor is an antibody that binds to a polypeptide selected from the group consisting of CD27, CD28, CD40, CD122, CD96, CD73, CD47, OX40, GITR, CSF1R, JAK, PI3K delta, PI3K gamma, TAM, arginase, CD137, ICOS, A2AR, B7-H3, B7-H4, BTLA, CTLA-4, LAG3, TIM3, VISTA, CD96, TIGIT, CD122, PD-1, PD-L1 and PD-L2.

21. A use according to any one of claims 1-19, wherein the checkpoint inhibitor is an antibody specific for PD-L1 or CTLA4.

22. A use according to any one of claims 1-19, wherein the checkpoint inhibitor is an antibody specific for PD-1.

23. Use of an immune checkpoint inhibitor in the manufacture of a medicament for modulating an immune response or treating cancer, wherein the medicament is to be administered in combination with a composition comprising a multimeric polypeptide, wherein:

the multimeric polypeptide composition comprises a heterodimeric polypeptide, wherein the heterodimeric polypeptide comprises:

a) a first polypeptide comprising:

- i) a peptide comprising an epitope present in a cancer-associated antigen; and
- ii) a first class I major histocompatibility complex (MHC) polypeptide; and

b) a second polypeptide comprising a second class I MHC polypeptide;

wherein the multimeric polypeptide comprises one or more immunomodulatory polypeptide, optionally wherein the first and/or the second polypeptide comprises an immunoglobulin (Ig) Fc polypeptide, and

wherein the immune checkpoint inhibitor and the composition comprising the multimeric polypeptide are to be administered at the same time or at different times.

24. Use of a composition comprising a multimeric polypeptide in the manufacture of a medicament for modulating an immune response or treating cancer, wherein the medicament is to be administered in combination with an immune checkpoint inhibitor, wherein:

the multimeric polypeptide composition comprises a heterodimeric polypeptide, wherein the heterodimeric polypeptide comprises:

a) a first polypeptide comprising:

- i) a peptide comprising an epitope present in a cancer-associated antigen; and
- ii) a first class I major histocompatibility complex (MHC) polypeptide; and

b) a second polypeptide comprising a second class I MHC polypeptide;

wherein the multimeric polypeptide comprises one or more immunomodulatory polypeptide, optionally wherein the first and/or the second polypeptide comprises an immunoglobulin (Ig) Fc polypeptide, and

wherein the immune checkpoint inhibitor and the composition comprising the multimeric polypeptide are to be administered at the same time or at different times.

25. Use according to claim 23 or claim 24, wherein:

a) the first MHC polypeptide is a β -2 microglobulin (β 2M) polypeptide and the second MHC polypeptide is an MHC class I heavy chain polypeptide; or

b) the first MHC polypeptide is an MHC class I heavy chain polypeptide and the second MHC polypeptide is a β 2M polypeptide.

26. A use according to any one of claims 23-25, wherein at least one of the one or more immunomodulatory polypeptides is a variant immunomodulatory polypeptide that exhibits reduced affinity for a co-immunomodulatory polypeptide, compared to the affinity of a corresponding wild-type immunomodulatory polypeptide for the co-immunomodulatory polypeptide.

27. A use according to any one of claims 23-26, wherein the MHC class I heavy chain polypeptide comprises amino acids 25 to 365 of the amino acid sequence set forth in FIG. 5A (SEQ ID NO:29), optionally wherein the amino acid sequence comprises a Y84A substitution, an A236C substitution, or both a Y84A substitution and an A236C substitution.

28. A use according to any one of claims 23-27, wherein the first polypeptide and the second polypeptide are covalently linked to one another via a disulfide bond, wherein the disulfide bond joins a Cys residue in the β 2M polypeptide and a Cys residue in the MHC heavy chain polypeptide.

29. A use according to claim 28, wherein a Cys at amino acid residue 12 of the β 2M polypeptide is disulfide bonded to a Cys at amino acid residue 236 of the MHC heavy chain polypeptide.

30. A use according to claim 28, wherein the first polypeptide chain comprises a linker between the peptide epitope and the β 2M polypeptide, and wherein the disulfide bond links a Cys present in the linker with a Cys of the MHC heavy chain polypeptide.

31. A use according to any one of claims 23-30, wherein at least one of the one or more immunomodulatory polypeptides is selected from the group consisting of a 4-1BBL polypeptide, a CD80 polypeptide, a CD86 polypeptide, an IL-2 polypeptide, a B7-1 polypeptide; a B7-2 polypeptide, an ICOS-L polypeptide, an OX-40L polypeptide and a CD86 polypeptide, a PD-L1 polypeptide, a FasL polypeptide, and a PD-L2 polypeptide.

32. Use of an immune checkpoint inhibitor in the manufacture of a medicament for modulating an immune response or treating cancer, wherein the medicament is to be administered in combination with a composition comprising a multimeric polypeptide, wherein the composition

comprising a multimeric polypeptide comprises a protein comprising two of the heterodimeric polypeptides of any one of claims 23 to 31, wherein each of the two heterodimeric polypeptides comprises an immunoglobulin (Ig) Fc polypeptide, and wherein the immune checkpoint inhibitor and the composition comprising the multimeric polypeptide are to be administered at the same time or at different times.

33. Use of a composition comprising a multimeric polypeptide in the manufacture of a medicament for modulating an immune response or treating cancer, wherein the medicament is to be administered in combination with an immune checkpoint inhibitor, wherein the composition comprising a multimeric polypeptide comprises a protein comprising two of the heterodimeric polypeptides of any one of claims 23 to 31, wherein each of the two heterodimeric polypeptides comprises an immunoglobulin (Ig) Fc polypeptide, and wherein the immune checkpoint inhibitor and the composition comprising the multimeric polypeptide are to be administered at the same time or at different times.

34. A use according to claim 32 or 33, wherein the two heterodimeric polypeptides are disulfide linked to one another via the Fc polypeptides present in the heterodimers.

35. A use according to any one of claims 23-34, wherein the immune checkpoint inhibitor is an antibody that binds to a polypeptide selected from the group consisting of CD27, CD28, CD40, CD122, CD96, CD73, CD47, OX40, GITR, CSF1R, JAK, PI3K delta, PI3K gamma, TAM, arginase, CD137, ICOS, A2AR, B7-H3, B7-H4, BTLA, CTLA-4, LAG3, TIM3, VISTA, CD96, TIGIT, CD122, PD-1, PD-L1, and PD-L2.

36. A use according to any one of claims 23-34, wherein the immune checkpoint inhibitor is an antibody specific for PD-1.

37. A use according to any one of claims 23-34, wherein the immune checkpoint inhibitor is an antibody specific for PD-L1 or CTLA4.

38. Use of a composition comprising a multimeric polypeptide as set forth in any one of claims 1-19 and 23-34 in the preparation of a medicament for treating cancer in a subject previously treated with an immune checkpoint inhibitor.