pursue follow-on biologics (biosimilars, generic biologics) exemplified by the recent introduction of an abbreviated FDA approval pathway.

[0009] The present invention addresses the need for precision therapeutics for immuno-oncology and autoimmunity - tailored therapeutics that clonally target only the disease-related T cells for upregulation (e.g., in the case of cancer) or suppression (e.g., in the case of autoimmunity) as opposed to the global and "pseudo-targeted" modulators currently on the market or in development.

SUMMARY

[0009a] In one aspect of the present disclosure, there is provided a multimeric polypeptide comprising:

a heterodimeric polypeptide comprising

a) a first polypeptide comprising, in order from N-terminus to C-terminus:

i) a peptide epitope; and

ii) a first major histocompatibility complex (MHC) polypeptide;

b) a second polypeptide comprising a second MHC polypeptide, and

c) at least one immunomodulatory polypeptide,

wherein the first and/or the second polypeptide comprises the at least one immunomodulatory polypeptide, wherein the at least one immunomodulatory polypeptide is a T-cell modulatory polypeptide,

wherein the first MHC polypeptide is a β2-microglobulin polypeptide; and wherein the second MHC polypeptide is an MHC class I heavy chain polypeptide,

wherein the peptide epitope is a cancer-associated epitope, and

optionally, wherein the multimeric polypeptide comprises an immunoglobulin (Ig) Fc polypeptide or a non-Ig scaffold.

[0009b] In another aspect of the present disclosure, there is provided a protein comprising two of the multimeric polypeptides disclosed herein, wherein each of the two multimeric polypeptides comprises an immunoglobulin (Ig) Fc polypeptide, and wherein the two multimeric polypeptides are joined by one or more disulfide bonds between the respective Ig Fc polypeptides.

[0009c] In a further aspect of the present disclosure, there is provided a nucleic acid comprising a nucleotide sequence encoding a first and/or second polypeptide disclosed herein, wherein the first or the second polypeptide comprises at least one immunomodulatory polypeptide.

[0009d] In another aspect of the present disclosure, there is provided an expression vector comprising the nucleic acid disclosed herein.

[0009e] In a further aspect of the present disclosure, there is provided a host cell genetically modified with the expression vector disclosed herein.

[0009f] In another aspect of the present disclosure, there is provided a method of selectively modulating the activity of a T cell that binds to a cancer-associated epitope, the method comprising contacting the T cell *in vitro* with the multimeric polypeptide disclosed herein, or the protein disclosed herein, wherein said contacting selectively modulates the activity of T cell.

[0009g] In a further aspect of the present disclosure, there is provided the multimeric polypeptide, or the protein, or the nucleic acid, or the expression vector disclosed herein, or the protein disclosed herein, for use in a method of selectively modulating the activity of a T cell that binds to a cancer-associated epitope in an individual, wherein said multimeric polypeptide or the protein or the nucleic acid or the expression vector is administered to selectively modulate the activity of the T cell in the individual.

[0009h] In another aspect of the present disclosure, there is provided the multimeric polypeptide, or the protein, or the nucleic acid disclosed herein, or recombinant expression vector disclosed herein, or one or more mRNAs comprising nucleotide sequences encoding the multimeric polypeptide disclosed herein, or the protein disclosed herein, for use in a method of treating a cancer in an individual.

[0009i] In a further aspect of the present disclosure, there is provided a composition comprising:

a) the multimeric polypeptide disclosed herein or the protein disclosed herein; and

b) a pharmaceutically acceptable excipient.

[0009j] In another aspect of the present disclosure, there is provided a multimeric, or the protein, or the nucleic acid, or the expression vector disclosed herein, for the use disclosed herein, wherein the T cell is a CD8+ T cell, a CD4+ T cell, or a T-regulatory cell.

CLAIMS

What is claimed is:

1. A multimeric polypeptide comprising:

a heterodimeric polypeptide comprising

a) a first polypeptide comprising, in order from N-terminus to C-terminus:

i) a peptide epitope; and

ii) a first major histocompatibility complex (MHC) polypeptide;

b) a second polypeptide comprising a second MHC polypeptide, and

c) at least one immunomodulatory polypeptide,

wherein the first and/or the second polypeptide comprises the at least one immunomodulatory polypeptide, wherein the at least one immunomodulatory polypeptide is a T-cell modulatory polypeptide,

wherein the first MHC polypeptide is a β2-microglobulin polypeptide; and wherein the second MHC polypeptide is an MHC class I heavy chain polypeptide,

wherein the peptide epitope is a cancer-associated epitope, and

optionally, wherein the multimeric polypeptide comprises an immunoglobulin (Ig) Fc polypeptide or a non-Ig scaffold.

2. The multimeric polypeptide of claim 1, wherein the multimeric polypeptide comprises:

a1) a first polypeptide comprising, in order from N-terminus to C-terminus:

i) a peptide epitope; and

ii) a first MHC polypeptide; and

b1) a second polypeptide comprising, in order from N-terminus to C-terminus:

i) at least one immunomodulatory polypeptide;

ii) a second MHC polypeptide; and

iii) an immunoglobulin (Ig) Fc polypeptide; or

a2) a first polypeptide comprising, in order from N-terminus to C-terminus:

i) a peptide epitope;

ii) a first MHC polypeptide; and

iii) at least one immunomodulatory polypeptide; and

b2) a second polypeptide comprising, in order from N-terminus to C-terminus:

i) a second MHC polypeptide; and

ii) an Ig Fc polypeptide; or

a3) a first polypeptide comprising, in order from N-terminus to C-terminus:

i) a peptide epitope; and

ii) a first MHC polypeptide; and

b3) a second polypeptide comprising, in order from N-terminus to C-terminus:

i) a second MHC polypeptide; and

ii) an Ig Fc polypeptide; and

iii) at least one immunomodulatory polypeptide; or

a4) a first polypeptide comprising, in order from N-terminus to C-terminus:

i) a peptide epitope; and

ii) a first MHC polypeptide; and

b4) a second polypeptide comprising, in order from N-terminus to C-terminus:

i) a second MHC polypeptide; and

ii) at least one immunomodulatory polypeptide; or

a5) a first polypeptide comprising, in order from N-terminus to C-terminus:

i) a peptide epitope; and

ii) a first MHC polypeptide; and

b5) a second polypeptide comprising, in order from N-terminus to C-terminus:

i) at least one immunomodulatory polypeptide; and

ii) a second MHC polypeptide; or

a6) a first polypeptide comprising, in order from N-terminus to C-terminus:

i) a peptide epitope;

ii) a first MHC polypeptide; and

iii) at least one immunomodulatory polypeptide; and

b6) a second polypeptide comprising, in order from N-terminus to C-terminus:

i) a second MHC polypeptide.

3. The multimeric polypeptide of claim 1, wherein the non-Ig scaffold is an XTEN polypeptide, a transferrin polypeptide, an Fc receptor polypeptide, an elastin-like polypeptide, a silk-like polypeptide, or a silk-elastin-like polypeptide.

4. The multimeric polypeptide of any one of claims 1-3, wherein the at least one immunomodulatory polypeptide is selected from a 4-1BBL polypeptide, a B7-1 polypeptide; a B7-2 polypeptide, an ICOS-L polypeptide, an OX-40L polypeptide, a CD80 polypeptide, a CD86 polypeptide, a PD-L1 polypeptide, a FasL polypeptide, a cytokine and a PD-L2 polypeptide.

5. The multimeric polypeptide of claim 4, wherein the at least one immunomodulatory polypeptide is a cytokine.

6. The multimeric polypeptide of claim 4, wherein the at least one immunomodulatory polypeptide is selected from a 4-1BBL polypeptide and a CD80 polypeptide.

7. The multimeric polypeptide of any one of claims 1-6, comprising 2 or more immunomodulatory polypeptides.

8. The multimeric polypeptide of claim 7, wherein the 2 or more immunomodulatory polypeptides are in tandem.

9. The multimeric polypeptide of any of claims 1-8, wherein the multimeric polypeptide comprises:

a1) a first polypeptide comprising, in order from N-terminus to C-terminus:

i) a peptide epitope; and

ii) a first MHC polypeptide; and

b1) a second polypeptide comprising, in order from N-terminus to C-terminus:

i) at least one immunomodulatory polypeptide;

ii) a second MHC polypeptide; and

iii) an immunoglobulin (Ig) Fc polypeptide.

10. The multimeric polypeptide of any of claims 1-8, wherein the multimeric polypeptide comprises:

a3) a first polypeptide comprising, in order from N-terminus to C-terminus:

i) a peptide epitope; and

ii) a first MHC polypeptide; and

b3) a second polypeptide comprising, in order from N-terminus to C-terminus:

i) a second MHC polypeptide; and

ii) an Ig Fc polypeptide; and

iii) at least one immunomodulatory polypeptide.

11. The multimeric polypeptide of any of claims 1-8, wherein the multimeric polypeptide comprises:

a first polypeptide comprising, in order from N-terminus to C-terminus:

i) a peptide epitope; and

ii) a first MHC polypeptide; and

b4) a second polypeptide comprising, in order from N-terminus to C-terminus:

i) a second MHC polypeptide; and

ii) at least one immunomodulatory polypeptide.

12. The multimeric polypeptide of any of claims 1-11, wherein the first polypeptide and the second polypeptide are linked to one another by a disulfide bond.

13. The multimeric polypeptide of claim 12, wherein the β2M polypeptide and the MHC heavy chain polypeptide are joined by a disulfide bond that joins a Cys residue in the β2M polypeptide and a Cys residue in the MHC heavy chain polypeptide.

14. The multimeric polypeptide of claim 13, wherein a Cys at amino acid residue 12 of the β2M polypeptide is disulfide bonded to a Cys at amino acid residue 236 of the MHC heavy chain polypeptide.

15. The multimeric polypeptide of claim 13, wherein the first polypeptide chain comprises a linker between the peptide epitope and the β2M polypeptide, and wherein the disulfide bond links a Cys present in the linker with a Cys of the MHC heavy chain polypeptide.

16. The multimeric polypeptide of claim 15, wherein the first polypeptide chain comprises a linker between the peptide epitope and the β2M polypeptide, and wherein the disulfide bond links a Cys substituted for Gly2 in the linker with a Cys substituted for Tyr84 of the MHC heavy chain polypeptide.

17. A multimeric polypeptide of any one of claims 1-16, wherein the immunomodulatory polypeptide is an activating polypeptide.

18. A protein comprising two of the multimeric polypeptides of any one of claims 1 to 17, wherein each of the two multimeric polypeptides comprises an immunoglobulin (Ig) Fc polypeptide, and wherein the two multimeric polypeptides are joined by one or more disulfide bonds between the respective Ig Fc polypeptides.

19. A nucleic acid comprising a nucleotide sequence encoding a first and/or second polypeptide according to any one of claims 1-17, wherein the first or the second polypeptide comprises at least one immunomodulatory polypeptide.

20. An expression vector comprising the nucleic acid of claim 19.

21. A host cell genetically modified with the expression vector of claim 20.

22. A method of selectively modulating the activity of a T cell that binds to a cancer-associated epitope, the method comprising contacting the T cell *in vitro* with the multimeric polypeptide of any one of claims 1-17, or the protein of claim 18, wherein said contacting selectively modulates the activity of the T cell.

23. The multimeric polypeptide of any one of claims 1-17, or the protein of claim 18, or the nucleic acid of claim 19, or the expression vector of claim 20, for use in a method of selectively modulating the activity of a T cell that binds to a cancer-associated epitope in an individual, wherein said multimeric polypeptide or the protein or the nucleic acid or the expression vector is administered to selectively modulate the activity of the T cell in the individual.

24. The multimeric polypeptide of any one of claims 1-17, or the protein of claim 18, or the nucleic acid of claim 19, or recombinant expression vector according to claim 20, or one or more mRNAs comprising nucleotide sequences encoding the multimeric polypeptide of any one of claims 1-17, or the protein of claim 18, for use in a method of treating a cancer in an individual.

25. A composition comprising:

a) the multimeric polypeptide of any one of claims 1-17, or the protein of claim 18; and

b) a pharmaceutically acceptable excipient.

26. A multimeric polypeptide of any one of claims 1-17, or the protein of claim 18, or the nucleic acid of claim 19, or the expression vector of claim 20, for use according to claim 22 or 23, wherein the T cell is a CD8+ T cell, a CD4+ T cell, or a T-regulatory cell.