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:

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 immunomodulatory polypeptide,

optionally, wherein the first or the second 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.

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

[0009d] In another aspect of the present disclosure, there is provided a recombinant 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 recombinant expression vector disclosed herein.

[0009f] In another aspect of the present disclosure, there is provided a method of selectively modulating the activity of an epitope-specific T cell, 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 the epitope-specific T cell.

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

[0009h] In another aspect of the present disclosure, there is provided the multimeric polypeptide 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 an infection in an individual,

wherein the epitope is a pathogen-associated epitope, wherein the immunomodulatory polypeptide is an activating polypeptide, and wherein said polypeptide, vector, mRNAs, or protein are administered to selectively modulate the activity of a pathogen-associated epitope-specific T cell in the individual.

[0009i] In a further aspect of the present disclosure, there is provided the multimeric polypeptide 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 an autoimmune disorder in an individual.

[0009j] In another aspect of the present disclosure, there is provided the multimeric polypeptide 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.

[0009k] 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.

[0010] This present disclosure provides a recombinant polypeptide comprising a sequence of amino acids identical to a first B2M leader sequence contiguous with a candidate epitope peptide contiguous with a first amino acid linker sequence contiguous with a sequence of amino acids identical to a human native B2M peptide sequence contiguous with a second amino acid linker sequence contiguous with a T cell modulatory domain peptide sequence contiguous with a third amino acid linker contiguous with a second B2M leader sequence contiguous with a sequence of amino acids identical to a MHC heavy chain contiguous with a sequence of amino acids identical to an immunoglobulin Fc domain.

[0011] This present disclosure also provides recombinant polypeptide comprising a sequence of amino acids identical to a first B2M leader sequence contiguous with a candidate epitope peptide contiguous with a first amino acid linker sequence contiguous with a sequence of amino acids identical to a human native B2M peptide sequence contiguous with a second amino acid linker sequence contiguous with a second B2M leader sequence contiguous with a T cell modulatory domain peptide sequence contiguous with a third amino acid linker contiguous with a sequence of amino acids identical to a MHC heavy chain contiguous with a sequence of amino acids identical to an immunoglobulin Fc domain.

[0012] Also provided is a method of inhibiting a T cell clone which recognizes an epitope peptide comprising contacting a T cell of the clone with a recombinant peptide as described herein, wherein the recombinant peptide comprises the epitope peptide and comprises a T cell modulatory domain which is an inhibitory domain, in an amount effective to inhibit a T cell clone.

CLAIMS

What is claimed is:

1. A multimeric polypeptide comprising:

a heterodimeric polypeptide comprising

a) a first polypeptide comprising:

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 immunomodulatory polypeptide,

optionally, wherein the first or the second 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) an 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 domain;

iii) a second MHC polypeptide; and

ii) an immunoglobulin (Ig) Fc polypeptide; or

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

i) an epitope;

ii) a first MHC polypeptide; and

iii) at least one immunomodulatory domain; 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) an 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 domain; or

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

i) an 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 domain; or

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

i) an 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 domain; and

ii) a second MHC polypeptide; or

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

i) an epitope;

ii) a first MHC polypeptide; and

iii) at least one immunomodulatory domain; 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 first MHC polypeptide is a β2-microglobulin polypeptide; and wherein the second MHC polypeptide is an MHC class I heavy chain polypeptide.

5. The multimeric polypeptide of any one of claims 1-3, wherein the first MHC polypeptide is an MHC Class II alpha chain polypeptide; and wherein the second MHC polypeptide is an MHC class II beta chain polypeptide.

6. The multimeric polypeptide of any one of claims 1-5, wherein the epitope is a T-cell epitope.

7. The multimeric polypeptide of any one of claims 1-6, 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.

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

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

10. A protein comprising two of the multimeric polypeptides of any one of claims 1 to 9.

11. A nucleic acid comprising a nucleotide sequence encoding a first or second polypeptide according to any one of claims 1-9, wherein the first or the second polypeptide comprises at least one immunomodulatory domain.

12. A recombinant expression vector comprising the nucleic acid of claim 11.

13. A host cell genetically modified with the recombinant expression vector of claim 12.

14. A method of selectively modulating the activity of an epitope-specific T cell, the method comprising contacting the T cell *in vitro* with the multimeric polypeptide of any one of claims 1-9, or the protein of claim 10, wherein said contacting selectively modulates the activity of the epitope-specific T cell.

15. The multimeric polypeptide of any one of claims 1-9, or the protein of claim 10, for use in a method of selectively modulating the activity of an epitope-specific T cell in an individual, wherein said multimeric polypeptide or the protein is administered to selectively modulate the activity of an epitope-specific T cell in the individual.

16. The multimeric polypeptide for use according to claim 15, wherein the immunomodulatory polypeptide is an activating polypeptide, and wherein the multimeric polypeptide or the protein activates the epitope-specific T cell, and optionally wherein the epitope is a cancer-associated epitope.

17. The multimeric polypeptide for use according to claim 15, wherein the immunomodulatory polypeptide is an inhibitory domain, and wherein the multimeric polypeptide or the protein suppresses the epitope-specific T cell, and optionally wherein the epitope is an autoimmune-associated epitope.

18. The multimeric polypeptide of any one of claims 1-9, or recombinant expression vector according to claim 12, or one or more mRNAs comprising nucleotide sequences encoding the multimeric polypeptide of any one of claims 1-9, or the protein of claim 10, for use in a method of treating an infection in an individual,

wherein the epitope is a pathogen-associated epitope, wherein the immunomodulatory polypeptide is an activating polypeptide, and wherein said polypeptide, vector, mRNAs, or

protein are administered to selectively modulate the activity of a pathogen-associated epitope-specific T cell in the individual.

19. The multimeric polypeptide of any one of claims 1-9, or recombinant expression vector according to claim 12, or one or more mRNAs comprising nucleotide sequences encoding the multimeric polypeptide of any one of claims 1-9, or the protein of claim 10, for use in a method of treating an autoimmune disorder in an individual.

20. The multimeric polypeptide of any one of claims 1-9, or recombinant expression vector according to claim 12, or one or more mRNAs comprising nucleotide sequences encoding the multimeric polypeptide of any one of claims 1-9, or the protein of claim 10, for use in a method of treating a cancer in an individual.

21. A composition comprising:

a) the multimeric polypeptide of any one of claims 1-9 or the protein of claim 10; and

b) a pharmaceutically acceptable excipient.