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

i) an epitope;

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

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

i) a second MHC polypeptide; and

ii) optionally an immunoglobulin (Ig) Fc polypeptide or a non-Ig scaffold,

wherein the multimeric polypeptide comprises one or more immunomodulatory domains, wherein the one or more immunomodulatory domain is:

A) at the C-terminus of the first polypeptide;

B) at the N-terminus of the second polypeptide;

C) at the C-terminus of the second polypeptide; or

D) at the C-terminus of the first polypeptide and at the N-terminus of the second polypeptide.

[0009b] In another aspect of the present disclosure, there is provided a nucleic acid comprising a nucleotide sequence encoding a recombinant polypeptide,

i) wherein the recombinant polypeptide comprises, in order from N-terminus to C-terminus:

a) an epitope;

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

c) an immunomodulatory polypeptide;

d) a proteolytically cleavable linker or a ribosome skipping signal;

e) a second MHC polypeptide; and

f) an immunoglobulin (Ig) Fc polypeptide; or

ii) wherein the recombinant polypeptide comprises, in order from N-terminus to C-terminus:

a) an epitope;

b) a first MHC polypeptide;

c) a proteolytically cleavable linker or a ribosome skipping signal;

d) an immunomodulatory polypeptide

e) a second MHC polypeptide; and

f) an Ig Fc polypeptide.

[0009c] In a further aspect of the present disclosure, there is provided a recombinant expression vector comprising a nucleic acid disclosed herein.

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

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

a) a first nucleic acid comprising a nucleotide sequence encoding a first polypeptide comprising, in order from N-terminus to C-terminus:

i) an epitope;

ii) a first MHC polypeptide; and

iii) an immunomodulatory domain; and

b) a first nucleic acid comprising a nucleotide sequence encoding a second polypeptide comprising, in order from N-terminus to C-terminus:

i) a second MHC polypeptide; and

ii) an Ig Fc polypeptide.

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

a) a first nucleic acid comprising a nucleotide sequence encoding a first polypeptide comprising, in order from N-terminus to C-terminus:

i) an epitope; and

ii) a first MHC polypeptide; and

b) a first nucleic acid comprising a nucleotide sequence encoding a second polypeptide comprising, in order from N-terminus to C-terminus:

i) an immunomodulatory domain

ii) a second MHC polypeptide; and

iii) an Ig Fc polypeptide.

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

[0009h] In another aspect of the present disclosure, there is provided a method of producing a multimeric polypeptide disclosed herein, the method comprising:

a) culturing a host cell disclosed herein *in vitro* in a culture medium under conditions such that the host cell synthesizes the multimeric polypeptide; and

b) isolating the multimeric polypeptide from the host cell and/or from the culture medium.

[0009i] In a further 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 with the multimeric polypeptide of claim 1, wherein said contacting selectively modulates the activity of the epitope-specific T cell, and wherein said contacting is *in vitro*.

[0009j] In another aspect of the present disclosure, there is provided a use of a multimeric polypeptide disclosed herein in the manufacture of a medicament for selectively modulating the activity of an epitope-specific T cell in an individual.

[0009k] In a further aspect of the present disclosure, there is provided a use of

a) a multimeric polypeptide disclosed herein; or

b) one or more recombinant expression vectors comprising nucleotide sequences encoding a multimeric polypeptide disclosed herein; or

c) one or more mRNAs comprising nucleotide sequences encoding a multimeric polypeptide disclosed herein,

in the manufacture of a medicament for 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 medicament is to be administered effective to selectively modulate the activity of a pathogen-associated epitope-specific T cell in an individual.

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

a) a multimeric polypeptide disclosed herein; and

b) a pharmaceutically acceptable excipient.

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

a) a nucleic acid disclosed herein or a recombinant expression vector 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.

[0018] Also provided is a protein comprising two of the recombinant polypeptide constructs described herein joined by one or more disulfide bonds between the respective immunoglobulin Fc domains thereof.

[0019] Also provided is a protein comprising two of the recombinant polypeptide constructs described herein joined by one or more disulfide bonds between the respective immunoglobulin Fc domains thereof.

[0020] This present disclosure provides an isolated suspension-adapted cell transduced by or transfected with a heterologous nucleic acid comprising, in 5' to 3' order a sequence encoding a recombinant polypeptide as described herein.

[0021] The 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. In some cases, the candidate epitope comprises 7-20 amino acids. In some cases, the third amino acid linker is self-cleaving. In some cases, the second amino acid linker is self-cleaving. In some cases, the self-cleaving peptide is a viral 2A peptide or has the sequence thereof. In some cases, the first and/or second B2M leader sequence has the sequence of human B2M leader sequence. In some cases, the MHC heavy chain is a human MHC heavy chain. In some cases, the MHC heavy chain is an MHC I molecule. In some cases, the MHC heavy chain is an HLA-A02:01. In some cases, the MHC heavy chain is an MHC II molecule. In some cases, the immunoglobulin Fc domain is an IgG Fc domain. In some cases, the immunoglobulin Fc domain is an IgA Fc domain. In some cases, the immunoglobulin Fc domain is an IgM Fc domain. In some cases, the immunoglobulin Fc domain is a human immunoglobulin Fc domain. In some cases, the immunoglobulin Fc domain is an IgG1 Fc domain. In some cases, the recombinant polypeptide comprises a His-8 tag contiguous with the C-terminal thereof. In some cases, the T cell modulatory domain is an inhibitory domain. In some cases, the T cell modulatory domain is a stimulating domain. In some cases, the T cell modulatory domain is

55. A method of producing the multimeric polypeptide of claim 1, the method comprising:

a) culturing the host cell of 47 or 54 *in vitro* in a culture medium under conditions such that the host cell synthesizes the multimeric polypeptide; and

b) isolating the multimeric polypeptide from the host cell and/or from the culture medium.

56. The method of claim 55, wherein the second polypeptide comprises an affinity tag, and wherein said isolating comprises contacting the multimeric polypeptide produced by the cell with a binding partner for the affinity tag, wherein the binding partner is immobilized, thereby immobilizing the multimeric polypeptide.

57. The method of claim 55, comprising eluting the immobilized multimeric polypeptide.

58. A method of selectively modulating the activity of an epitope-specific T cell, the method comprising contacting the T cell with the multimeric polypeptide of claim 1, wherein said contacting selectively modulates the activity of the epitope-specific T cell, and wherein said contacting is *in vitro*.

59. The method of claim 58, wherein the immunomodulatory polypeptide is an activating polypeptide, and wherein the multimeric polypeptide activates the epitope-specific T cell.

60. The method of claim 58, wherein the immunomodulatory polypeptide is an inhibiting polypeptide, and wherein the multimeric polypeptide inhibits the epitope-specific T cell.

61. Use of a multimeric polypeptide of claim 1 in the manufacture of a medicament for selectively modulating the activity of an epitope-specific T cell in an individual.

62. The use of claim 61, wherein the immunomodulatory polypeptide is an activating polypeptide, and wherein the multimeric polypeptide activates the epitope-specific T cell.

63. The use of claim 62, wherein the epitope is a cancer-associated epitope, and wherein the medicament is to be administered to selectively increase the activity of a T cell specific for the cancer-associate epitope.

64. The use of claim 61, wherein the immunomodulatory polypeptide is an inhibitory polypeptide, and wherein the multimeric polypeptide inhibits activity of the epitope-specific T cell.

65. The use of claim 64, wherein the epitope is a self-epitope, and wherein the medicament is to be administered to selectively inhibit the activity of a T cell specific for the self-epitope.

66. Use of

a) the multimeric polypeptide of claim 1; or

b) one or more recombinant expression vectors comprising nucleotide sequences encoding the multimeric polypeptide of claim 1; or

c) one or more mRNAs comprising nucleotide sequences encoding the multimeric polypeptide of claim 1,

in the manufacture of a medicament for 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 medicament is to be administered effective to selectively modulate the activity of a pathogen-associated epitope-specific T cell in an individual.

67. The use of claim 66, wherein the pathogen is a virus, a bacterium, or a protozoan.

68. The use of any one of claims 61-66, wherein the medicament is to be administered subcutaneously.

69. The use of any one of claims 61-66, wherein the medicament is to be administered intravenously.

70. The use of any one of claims 61-66, wherein the medicament is to be administered intramuscularly.

71. The use of any one of claims 61-66, wherein the medicament is to be administered systemically.

72. The use of any one of claims 61-66, wherein the medicament is to be administered distally to a treatment site.

73. The use of any one of claims 61-66, wherein the medicament is to be administered locally.

74. The use of any one of claims 61-66, wherein the medicament is to be administered near a treatment site.

75. A composition comprising:

a) the multimeric polypeptide of any one of claims 1-27; and

b) a pharmaceutically acceptable excipient.

76. A composition comprising:

a) the nucleic acid of any one of claims 28-34 or the recombinant expression vector of claim 45 or 46; and

b) a pharmaceutically acceptable excipient.