CLAIMS

WHAT IS CLAIMED IS:

1. A polypeptide comprising an amino acid sequence of the formula 1:

[A]-L1x-[B]-L2-[C]-L3-[D]-L4y-[E]-L5-[F] (1)

wherein:

x and y are independently selected from 0 (absent) or 1 (present);

[A] is a polypeptide having 0, 1 or 2 amino acid substitutions relative to the amino acid sequence SKAVEQVKNAFNKL (SEQ ID NO:1);

x = 1 and L1 comprises a polypeptide linker of from 1 to 5 amino acids, or x = 0 (no linker, L1 is absent);

[B] is a polypeptide having 0, 1 or 2 amino acid substitutions relative to the amino acid sequence “EKGIYKAMSEFDIFINYIEAYMTMKIR” (SEQ ID NO:2);

L2 comprises a linker of from 10 to 25 amino acids;

[C] is a polypeptide having 0, 1 or 2 amino acid substitutions relative to the amino acid sequence “NLPNMLRDLRDAFSRVKTFFQMKD” (SEQ ID NO:3);

L3 comprises a linker of from 4 to 11 amino acids;

[D] is a polypeptide having 0, 1 or 2 amino acid substitutions relative to the amino acid sequence “KESLLEDFKG” (SEQ ID NO:4);

y = 1 and L4 comprises a polypeptide linker of from 1 to 5 amino acids, or y = 0 (L4 is absent);

[E] is a polypeptide having 0, 1 or 2 amino acid substitutions relative to the amino acid sequence “LGCQALSEMIQFYLEEVMPQAEN” (SEQ ID NO:5);

L5 comprises a linker of from 1 to 7 amino acids; and

[F] is a polypeptide having 0, 1 or 2 amino acid substitutions relative to the amino acid sequence “IKAHVNSLGENLKTLRLRLRRC” (SEQ ID NO:6),

optionally wherein L1, L2, L3, L4 and/or L5 comprise a GS-linker,

optionally wherein L1 is the amino acid glutamine (Q),

optionally wherein L2 is a polypeptide having the amino acid sequence NSPGQGTQSENSCTHFPG (SEQ ID NO:7) or NTSPGQGTQSENSCTHFPG (SEQ ID NO:23),

optionally wherein L3 is a polypeptide having the amino acid sequence QLDNLLL (SEQ ID NO:8),

optionally wherein L4 is the amino acid glycine (“G”) or comprises the amino acid sequence GY,

optionally wherein L5 is a polypeptide having the amino acid sequence QDPD (SEQ ID NO:9),

wherein optionally the polypeptide comprises an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity hIL10 inverted monomer selected from the group consisting of SEQ ID NO: 10, SEQ ID NO:11, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, and SEQ ID NO:98, or

optionally wherein the polypeptide comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO:10 or SEQ ID NO:11.

2. The polypeptide of claim 1, wherein the polypeptide comprises the amino acid sequence

KSKAVEQVKNAFNKLQEKGIYKAMSEFDIFINYIEAYMTMKIRNSPGQGTQSENSCTHFPGNLPNMLRDLRDAFSRVKTFFQMKDQLDNLLLKESLLEDFKGYLGCQALSEMIQFYLEEVMPQAENQDPDIKAHVNSLGENLKTLRLRLRRCHRFLPCEN (SEQ ID NO:10) or

the amino acid sequence

KSKAVEQVKNAFNKLQEKGIYKAMSEFDIFINYIEAYMTMKIRNTSPGQGTQSENSCTHFPGNLPNMLRDLRDAFSRVKTFFQMKDQLDNLLLKESLLEDFKGYLGCQALSEMIQFYLEEVMPQAENQDPDIKAHVNSLGENLKTLRLRLRRCHRFLPCEN (SEQ ID NO:11).

3. A polypeptide comprising formula (2):

[Monomer 1]-linker$_x$-[Monomer 2] (2)

wherein Monomer 1 and Monomer 2 each, independently, comprise a polypeptide selected from a polypeptide of claim 1, and x = 0 (linker absent) or 1 (linker present),

wherein optionally Monomer 1 and Monomer 2 each, independently, comprise a polypeptide comprising an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO: 90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, and SEQ ID NO:98, optionally wherein x is 1 (linker present) and the linker comprises a GS-linker.

4. The polypeptide of claim 3, wherein Monomer 1 and Monomer 2 each comprise a polypeptide comprising the amino acid sequence of SEQ ID NO:10 or SEQ ID NO:11.

5. The polypeptide of claim 3, wherein the polypeptide of formula (2) comprises in the following amino to carboxyl order:

(a) Monomer 1 comprising:

(i) a first polypeptide comprising an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to a polypeptide selected from the group consisting amino acid residues 117-158 of human IL-10 (SEQ ID NO:12); amino acid residues 117-159 of human IL-10 (SEQ ID NO:13); and amino acid residues 117-160 of human IL-10 (SEQ ID NO:14), numbered in accordance with mature wild-type human IL-10 (SEQ ID NO:20);

(ii) a first $linker_x$, wherein x = 0 (linker absent) or 1 (linker present); and

(iii) a second polypeptide comprising an amino acid having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to a polypeptide sequence selected from the group consisting of amino acid residues 11-160 of human IL-10 (SEQ ID NO:45), amino acid residues 1-160 of human IL-10 (SEQ ID NO:20); amino acid residues 2-160 of human IL-10 (SEQ ID NO:36); amino acid residues 3-160 of human IL-10 (SEQ ID NO:37); amino acid residues 4-160 of human IL-10 (SEQ ID NO:38); amino acid residues 5-160 of human IL-10 (SEQ ID NO:39); amino acid residues 6-160 of human IL-10 (SEQ

ID NO:40); amino acid residues 7-160 of human IL-10 (SEQ ID NO:41); amino acid residues 8-160 of human IL-10 (SEQ ID NO:42); amino acid residues 9-160 of human IL-10 (SEQ ID NO:43); and amino acid residues 10-160 of human IL-10 (SEQ ID NO:44); numbered in accordance with mature wild-type hIL10 (SEQ ID NO:20);

(b) a second $linker_y$, wherein y = 0 (linker absent) or 1 (linker present); and

(c) Monomer 2 comprising a polypeptide having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to a polypeptide sequence selected from the group consisting of amino acid residues 11-116 of human IL-10 (SEQ ID NO:34); amino acid residues 1-116 of human IL-10 (SEQ ID NO:15); amino acid residues 2-116 of human IL-10 (SEQ ID NO:16); amino acid residues 3-116 of human IL-10 (SEQ ID NO:17), amino acid residues 4-116 of human IL-10 (SEQ ID NO:18), amino acid residues 5-116 of human IL-10 (SEQ ID NO:19), amino acid residues 6-116 of human IL-10 (SEQ ID NO:29), amino acid residues 7-116 of human IL-10 (SEQ ID NO:30), amino acid residues 8-116 of human IL-10 (SEQ ID NO:31), amino acid residues 9-116 of human IL-10 (SEQ ID NO:32), and amino acid residues 10-116 of human IL-10 (SEQ ID NO:33) numbered in accordance with mature human IL-10 (SEQ ID NO:20), or monomer 2 comprising

(i) a first polypeptide comprising an amino acid sequence selected from the group consisting amino acid residues 117-158 of human IL-10 (SEQ ID NO:12); amino acid residues 117-159 of human IL-10 (SEQ ID NO:13); and amino acid residues 117-160 of human IL-10 (SEQ ID NO:14), numbered in accordance with mature human IL-10 (SEQ ID NO:20),

(ii) a third $linker_z$, wherein z = 0 (linker absent) or 1 (linker present); and

(iii) a second polypeptide comprising an amino acid sequence selected from the group consisting of amino acid residues 1-116 of human IL-10 (SEQ ID NO:15).

6. The polypeptide of claim 3, wherein the polypeptide comprises an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity hIL10 inverted monomer selected from the group consisting of SEQ ID NOS: 46-51.

7. The polypeptide of any one of claims 1 to 6, wherein the polypeptide is PEGylated,

optionally wherein the PEG molecule is linear or branched and has a molecular weight of from about 10kD to about 80kD,

optionally wherein the PEG molecule is a 40kD branched PEG molecule comprising two 20kD arms,

optionally wherein the PEG molecule is covalently attached to the N-terminus of the polypeptide.

8. The polypeptide of any one of claims 1 to 7, wherein the polypeptide exhibits cell type biased activity relative to the wild type IL10 species from which the inverted IL10 monomer was derived, wherein optionally,

the polypeptide: (a) exhibits a significant level of at least one anti-inflammatory property of wild type IL10 and (b) exhibits a significantly reduced level of at least one pro-inflammatory property of wild type IL10,

optionally wherein the at least one anti-inflammatory property is selected from the group consisting of suppression of expression or secretion of IL1b, TNFa or IL6 in a myeloid cell,

optionally wherein the at least one pro-inflammatory property is selected from the group consisting of suppression of expression or secretion of IFNγ, granzyme A or granzyme B in a T cell,

optionally wherein the at least one anti-inflammatory property is selected from the group consisting of suppression of expression or secretion of IL1b, TNFa or IL6 in a myeloid cell and the at least one pro-inflammatory property is selected from the group consisting of suppression of expression or secretion of IFNγ, granzyme A or granzyme B in a T cell, or

optionally wherein the cell type biased activity is the production of phospho-STAT3.

9. The polypeptide of claim 8 wherein the pSTAT3 E_{max} of the polypeptide is greater than 20%, greater than 30%, greater than 40%, greater than 50%, greater than 60%, or greater than 70% of the pSTAT3 E_{max} of wild-type hIL10 in myeloid cells,

optionally wherein the pSTAT3 E_{max} in a lymphocyte less than 70%, less than 60%, less than 50%, less than 40%, or less than 30%, of the pSTAT3 E_{max} of a wild-type hIL10 in the lymphocyte, or

optionally wherein (a) the pSTAT3 E_{max} of the polypeptide is greater than 20%, greater than 30%, greater than 40%, greater than 50%, greater than 60%, or greater than 70% of the pSTAT3 E_{max} of wild-type hIL10 in myeloid cells and (b) the pSTAT3 E_{max} in a lymphocyte less than 70%, less than 60%, less than 50%, less than 40%, or less than 30%, of the pSTAT3 E_{max} of a wild-type hIL10 in the lymphocyte.

10. A nucleic acid molecule having a sequence encoding a polypeptide of any one of claims 1-9.

11. A recombinant vector comprising the nucleic acid molecule of claim 10 operably linked to one or more expression control sequences.

12. A recombinant cell transformed with the recombinant vector of claim 11.

13. A method of making a polypeptide of any one of claims 1 to 9, the method comprising the steps of (a) culturing the host cell of claim 36 under conditions suitable for the expression of the polypeptide and (b) recovering the polypeptide from the host cell culture, optionally wherein the host cell is a mammalian host cell, or optionally wherein the host cell is a bacterial cell.

14. A composition comprising a polypeptide of any one of claims 1 to 9, a nucleic acid molecule of claim 10, or a recombinant vector of claim 11 and one or more pharmaceutically acceptable salts, excipients, and/or diluents.

15. Use of the polypeptide of any one of claims 1 to 9 or the composition of claim 14 in the manufacture of a medicament for treating a mammalian subject suffering from a disease, disorder or condition, wherein a therapeutically effective amount of the polypeptide or the composition is to be administered to said subject, optionally wherein the

disease, disorder or condition is an autoimmune disease, disorder or condition, or optionally wherein the autoimmune disease, disorder or condition is selected from the group consisting of ulcerative colitis, organ rejection, graft versus host disease, autoimmune thyroid disease, multiple sclerosis, allergy, asthma, neurodegenerative diseases including Alzheimer's disease, systemic lupus erythramatosis (SLE), autoinflammatory diseases, inflammatory bowel disease (IBD), Crohn's disease, diabetes including Type 1 or type 2 diabetes, inflammation, autoimmune disease, atopic diseases, paraneoplastic autoimmune diseases, cartilage inflammation, arthritis, rheumatoid arthritis, juvenile arthritis, juvenile rheumatoid arthritis, juvenile rheumatoid arthritis, polyarticular juvenile rheumatoid arthritis, systemic onset juvenile rheumatoid arthritis, juvenile ankylosing spondylitis, juvenile enteropathic arthritis, juvenile reactive arthritis, juvenile Reiter's Syndrome, SEA Syndrome (Seronegativity Enthesopathy Arthropathy Syndrome), juvenile dermatomyositis, juvenile psoriatic arthritis, juvenile scleroderma, juvenile systemic lupus erythematosus, juvenile vasculitis, pauciarticular rheumatoidarthritis, polyarticular rheumatoidarthritis, systemic onset rheumatoidarthritis, ankylosing spondylitis, enteropathic arthritis, reactive arthritis, Reiter's syndrome, and SEA Syndrome (Seronegativity, Enthesopathy, Arthropathy Syndrome),

optionally wherein disease disorder or condition is a cancer associated with chronic inflammation,

optionally wherein the treating prevents the progression of the disease, disorder or condition, or

optionally wherein the treating ameliorates one or more symptoms of the disease, disorder or condition.

16. Use of the composition of claim 14 in the manufacture of a medicament for preventing a disease, disorder or condition in a mammalian subject at risk for developing the disease, disorder or condition, wherein a prophylactically effective amount of the composition is to be administered to said subject prior to the onset of symptoms of the disease, disorder or condition,

optionally wherein the disease disorder or condition is a cancer associated with chronic inflammation.

17. The polypeptide of any one of claims 1 to 9 or the composition of claim 14, for use in therapy.