WHAT IS CLAIMED IS:

1. A fused human IL10 (hIL10) polypeptide comprising a polypeptide of the formula:

$$(\text{hIL10A})\text{-}L_n\text{-}(\text{hIL10B}),$$

wherein:

(a) hIL10A and hIL10B are each human IL10 (hIL10) sequences independently selected from the group consisting of a wild-type hIL10 (SEQ ID NO:4) and hIL10 muteins, wherein the hIL10 muteins each independently comprises one or more amino acid substitutions at positions corresponding to residues T100, H14, N18, N21, M22, R24, D25, D28, R32, E74, H90, N92, S93, E96, and R104 of SEQ ID NO: 4, optionally the hIL10A has an amino-terminal deletion of 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid residues relative to SEQ ID NO:4, and/or the hIL10B has an amino-terminal deletion of 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid residues relative to SEQ ID NO:4;

(b) L is an amino acid linker of from 1 to 30 amino acids in length; and

(c) n= 0 (absent) or 1 (present).

2. The fused hIL10 polypeptide of claim 1, wherein:

(a) the amino acid substitution at position T100 is selected from the group consisting of T100L, T100D, T100V, T100E, T100A, T100R, T100N, T100Q, T100E, T100I, T100K, T100M, and T100S;

(b) the amino acid substitution at position H14 is selected from the group consisting of H14C, H14F, H14P, H14W, H14G, H14A, H14D, H14E, H14I, H14K, H14L, H14M, H14N, H14Q, H14R, H14S, H14T, H14Y, and H14V;

(c) the amino acid substitution at position N18 is selected from the group consisting of N18Y, N18F, N18A, N18D, N18E, N18L, N18V, N18S, N18T, N18I, N18V, N18M, N18R, N18K, and N18H;

(d) the amino acid substitution at position N21 is selected from the group consisting of N21A, N21R, N21Q, N21H, N21K, N21S, N21V, N21I, N21L, N21M, N21T N21C, N21D, and N21E;

(e) the amino acid substitution at position M22 is selected from the group consisting of M22A, M22V, M22I, M22L, M22N, M22D, M22S, M22T, M22W, and M22Q;

(f) the amino acid substitution at position R24 is selected from the group consisting of R24E, R24D, R24N, R24Q, R24A, R24S, and R24T;

(g) the amino acid substitution at position D25 is selected from the group consisting of D25A, D25N, D25H, D25I, D25K, D25L, D25P, D25Q, and D25V;

(h) the amino acid substitution at position D28 is selected from the group consisting of D28A, D28E, D28L, D28V, D28S, D28T, D28I, D28V, D28M, D28H, D28K, and D28R;

(i) the amino acid substitution at position R32 is selected from the group consisting of R32A, R32D, R32E, R32L, R32V, R32S, R32T, R32I, R32V, R32M, R32N, R32Q, R32G, R32C, R32P, R32F, R32Y, and R32H;

(j) the amino acid substitution at position E74 is selected from the group consisting of E74A, E74D, E74L, E74V, E74S, E74T, E74I, E74V, E74M, E74H, E74K, and E74R;

(k) the amino acid substitution at position H90 is selected from the group consisting of H90A, H90D, H90E, H90I, H90K, H90L, H90M, H90N, H90Q, H90R, H90S, H90T, H90Y, and H90V;

(l) the amino acid substitution at position N92 is selected from the group consisting of N92D, N92Q, N92E, N92H, N92K, N92S, N92V, N92I, N92L, N92M, N92T, and N92A;

(m) the amino acid substitution at position S93 is selected from the group consisting of S93E, S93A, S93R, S93N, S93D, S93Q, S93E, S93I, S93L, S93K, S93M, S93G, and S93V;

(n) the amino acid substitution at position E96 is selected from the group consisting of E96C, E96F, E96Y, E96W, E96A, E96N, E96D, E96Q, E96H, E96K, and E96S; and

(o) the amino acid substitution at position R104 is selected from the group consisting of R104A, R104W, R104Y, R104F, R104H, R104D, R104E, R104N, R104Q, R104S, R104T, R104I, R104L, R104V, and R104M.

3. The fused hIL10 polypeptide of claim 1 or 2, wherein at least one of the hIL10A and the hIL10B is an hIL10 mutein.

4. The fused hIL10 polypeptide of any one of claims 1-3, wherein hIL10A and the hIL10B are both hIL10 muteins.

5. The fused hIL10 polypeptide of any one of claims 1-4, wherein hIL10A and the hIL10B are the same.

6. The fused hIL10 polypeptide of any one of claims 1-4, wherein hIL10A and the hIL10B are different.

7. The fused hIL10 polypeptide of any one of claims 1-6, wherein n= 0 (absent).

8. The fused hIL10 polypeptide of any one of claims 1-6, wherein n= 1 (present) and L is a polypeptide having 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 amino acids.

9. The fused hIL10 polypeptide of claim 8, wherein L is a GS linker.

10. The fused hIL10 polypeptide of claim 9, wherein the GS linker comprises a sequence of GGGSGSGSGSG (SEQ ID NO:19).

11. The fused hIL10 polypeptide of any one of claims 1 to 10, wherein the hIL10A and the hIL10B are each independently selected from a wild-type hIL10 (SEQ ID NO:4) or an IL10 mutein comprising an amino acid substitution selected from the group consisting of N21D, N21E, N21K, M22A, M22S, M22T, M22D, M22W, R24E, D25K, E96K, E96Q, T100E, T100C and T100L.

12. The fused hIL10 polypeptide of any one of claims 1 to 11, wherein the hIL10A and/or the hIL10B comprises the amino acid substitution T100L.

13. The fused hIL10 polypeptide of any one of claims 1 to 11, wherein the hIL10A and/or hIL10B comprises the amino acid substitution M22A or M22S.

14. The fused hIL10 polypeptide of any one of claims 1 to 11, wherein the hIL10A and/or hIL10B comprises the amino acid substitution E96Q.

15. The fused hIL10 polypeptide of any one of claims 1 to 11, wherein the hIL10A and/or hIL10B comprises the amino acid substitution R24E.

16. The fused hIL10 polypeptide of any one of claims 1 to 11, wherein the hIL10A and/or hIL10B comprises the amino acid substitution D25K.

17. The fused hIL10 polypeptide of any one of claims 1 to 11, wherein the hIL10A and/or hIL10B comprises the amino acid substitution N21K.

18. The fused hIL10 polypeptide of any one of claims 1 to 11, wherein hIL10A and/or hIL10B is each a polypeptide having at least 90% sequence identity to a polypeptide selected from the group consisting of SEQ ID NOS: 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 148, 149, 150, 151, 152, 153, 154, 155, 156, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, and 205, optionally wherein one or both of hIL10A and hIL10B has an N-terminal deletion of 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid residues relative to the sequence of SEQ ID NO:4.

19. The fused hIL10 polypeptide of claim 18, wherein the hIL10A and hIL10B are the same.

20. The fused hIL10 polypeptide claim 18, wherein the hIL10A and hIL10B are different.

21. The fused hIL10 polypeptide of claim 19 or 20, wherein the hIL10A and the hIL10B each comprises an amino acid substitution selected from the group consisting of N21D, N21E, N21K, M22A, M22S, M22T, M22D, M22W, R24E, D25K, E96K, E96Q, T100E, T100C and T100L.

22. The fused hIL10 polypeptide of claim 19 or 20, wherein hIL10A is a polypeptide is selected from the group consisting of SEQ ID NOS:191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, and 205 and hIL10B is a polypeptide is selected from the group consisting of SEQ ID NOS: 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 148, 149, 150, 151, 152, 153, 154, 155, and 156.

23. The fused hIL10 polypeptide of claim 21, wherein the hIL10A and the hIL10B are both hIL10 muteins comprising the amino acid substitution T100L.

24. The fused hIL10 polypeptide of claim 23, wherein the hIL10A and the hIL10B are both hIL10 muteins comprising the amino acid substitution T100L, hIL10A is a polypeptide having 100% sequence identity to SEQ ID NO: 204 and hIL10 B is a polypeptide having 100% sequence identity to SEQ ID NO: 15.

25. The fused hIL10 polypeptide of claim 21, wherein the fused hIL10 polypeptide is a polypeptide comprising an amino acid sequence having having at least 95%, alternatively at least 96%, alternatively at least 97%, alternatively at least 98%, alternatively

at least 99% , alternatively 100% sequence identity to a polypeptide selected from the group consisting of SEQ ID NOS:24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 119, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170 , 171, 172, 173, 174 , 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185 and 186.

26. The fused hIL10 polypeptide of claim 21, wherein the fused hIL10 polypeptide comprises an amino acid sequence having 100% sequence identity to a polypeptide selected from the group consisting of SEQ ID NOS: 44, 123, 124, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170 , 171, 172, 173, 174 , 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185 and 186.

27. The fused hIL10 polypeptide of claim 23, wherein the fused hIL10 polypeptide comprises an amino acid sequence having at least 90% sequence identity to a polypeptide selected from the group consisting of SEQ ID NO: 44, SEQ ID NO: 123, SEQ ID NO: 124, SEQ ID NO: 170 and SEQ ID NO: 185.

28 The fused hIL10 polypeptide of claim 27, wherein the fused hIL10 polypeptide comprises a polypeptide having 100% identity to the amino acid sequence of SEQ ID NO: 44.

29. The fused hIL10 polypeptide of claim 27, wherein the fused hIL10 polypeptide comprises a polypeptide having 100% identity to the amino acid sequence of SEQ ID NO: 185.

30. The fused hIL10 polypeptide of any one of claims 1 to 29, wherein the fused hIL10 polypeptide modified to extend half-life *in vivo*.

31. The fused hIL10 polypeptide of claim 30, wherein the modification to extend half-life *in vivo* is selected from the group consisting of PEGylation, acylation, albumination or conjugation to an Fc polypeptide.

32. The fused hIL10 polypeptide of claim 31, wherein the modification to extend half-life *in vivo* is acylation.

33. The fused hIL10 polypeptide of claim 31, wherein the modification to extend half-life *in vivo* is conjugation to an Fc polypeptide.

34. The fused hIL10 polypeptide of claim 33, wherein the Fc polypeptide is an Fc domain from hIgG1, hIgG2, hIgG3, or hIgG4, or a variant thereof.

35. The fused hIL10 polypeptide of claim 33 or 34, wherein the Fc polypeptide comprises a sequence that is modified from a wild-type Fc polypeptide sequence to reduce effector function.

36. The fused hIL10 polypeptide of any one of claims 33-35, wherein the Fc polypeptide comprises one or more amino acid substitutions or deletions to promote heterodimerization.

37. The fused hIL10 polypeptide of claim 33, wherein the fused hIL10 polypeptide is a heterodimeric Fc molecule comprising a first polypeptide of the formula #1:

$$\text{IL10FP}-\text{L1}_a-\text{UH1}—\text{Fc1} \quad [1]$$

and a second polypeptide of the formula #2:

$$\text{UH2}—\text{Fc2} \quad [2]$$

wherein:

hIL10FP is a fused hIL10 polypeptide of the present disclosure (*e.g.*, a fused hIL10 polypeptide of formula (hIL10A)-L_n-(hIL10B));

L1 is a linker and a is independently selected from 0 (absent) or 1 (present);

UH1 and UH2 are each an upper hinge domain of human immunoglobulin independently selected from the group consisting of the IgG1, IgG2, IgG3 and IgG4 upper hinge domains, optionally comprising the amino acid substitution C220S (EU numbering);

Fc1 is a polypeptide comprising the lower hinge, CH2 and CH3 domains of a human immunoglobulin selected from the group consisting of IgG1, IgG2, IgG3 and IgG4, comprising one or more amino acid substitutions promote heterodimerization with Fc2, and

Fc2 is a polypeptide comprising the lower hinge, CH2 and CH3 domains of a human immunoglobulin selected from the group consisting of IgG1, IgG2, IgG3 and IgG4, comprising one or more amino acid substitutions promote heterodimerization with Fc1,

and optionally wherein the polypeptide of formula [1] and the polypeptide of formula [2] are linked by at least one interchain disulfide bond.

38. The fused hIL10 polypeptide of claim 31, wherein the modification to extend half-life in vivo is PEGylation.

39. The fused hIL10 polypeptide of claim 38, wherein the PEG is a linear or branched polyethylene glycol molecule having a molecular weight of from about 2,000 to about 80,000 daltons, alternatively about 2,000 to about 70,000 daltons, alternatively about 5,000 to about 50,000 daltons, alternatively about 10,000 to about 50,000 daltons, alternatively about 20,000 to about 50,000 daltons, alternatively about 30,000 to about 50,000 daltons.

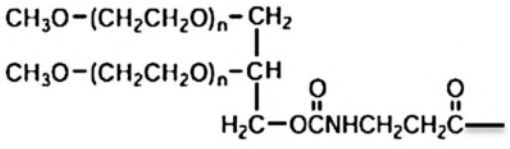
40. The fused hIL10 polypeptide of claim 39, wherein the PEG is linear.

41. The fused hIL10 polypeptide of claim 39, wherein the PEG is branched.

42. The fused hIL10 polypeptide of claim 39, wherein the PEG is a 40kD branched PEG molecule comprising two 20kD arms.

43. The fused hIL10 polypeptide of claim 39, wherein the PEG is covalently attached to the N-terminus of the polypeptide, optionally via a linker.

44. The fused hIL10 polypeptide of claim 39, wherein the PEG is a 40kD branched PEG molecule comprising two 20kD arms of the formula:



covalently bonded to the N-terminus of hIL10A, optionally via a linker.

45. The fused hIL10 polypeptide of claim 44, wherein the PEG covalently bonded to the N-terminus of hIL10A via an aldehyde linker.

46. The fused hIL10 polypeptide of any one of claims 1-45, wherein the fused hIL10 polypeptide exhibits a greater fraction of an activity of wild-type hIL10 in activated human monocytes than the fraction of the activity of wild-type hIL10 in activated human CD8 T cells.

47. The fused hIL10 polypeptide of claim 46, wherein the activity of wild-type hIL10 is induction of intracellular STAT3 signaling.

48. The fused hIL10 polypeptide of any one of claims 1-45, wherein the fused hIL10 polypeptide exhibits an Emax of at least 30%, optionally at least 40%, optionally at least 50% of level of activity of wild-type hIL10 in activated human monocytes wherein the activity of wild-type hIL10 in activated human monocytes is selected from the group consisting of inhibition of IL1b secretion and inhibition of TNFa secretion.

49. The fused hIL10 polypeptide of any one of claims 1-45, wherein the fused hIL10 polypeptide exhibits an Emax less than 30%, optionally less than 20%, optionally less than 10% of level of activity of wild-type hIL10 in activated human CD8 T cells wherein the activity of wild-type hIL10 in activated human CD8 T cells is selected from the group consisting of IFNγ secretion, granzyme A secretion and granzyme B secretion.

50. A nucleic acid sequence encoding a fused hIL10 polypeptide of any one of claims 1-45.

51. The nucleic acid sequence of claim 50, wherein the nucleic acid sequence is an mRNA.

52. The nucleic acid sequence of claim 50, wherein the nucleic acid sequence is a DNA.

53. A vector comprising the nucleic acid sequence of any one of claims 50 to 52 operably linked with an expression control sequence.

54. The vector of claim 53, wherein the vector is a viral vector.

55. A cell transformed with the vector of claim 53 or 54.

56. The cell of claim 55, wherein the cell is a mammalian cell.

57. A pharmaceutical formulation comprising as an active ingredient: (a) the fused hIL10 polypeptide of any one of claim 1 to 45; (b) a nucleic acid sequence of any one of claims 50-52; (c) a vector of claim 53 or 54, or (d) a cell of claim 55 or 56, and one or more pharmaceutically acceptable solvents, carriers, stabilizers, preservatives, or diluents.

58. Use of: (a) the fused hIL10 polypeptide of any one of claim 1 to 45; (b) a nucleic acid sequence of any one of claims 50-52; (c) a vector of claim 53 or 54; (d) a cell of claim 55 or 56; or (e) a pharmaceutical formulation of claim 57, in the manufacture of a medicament for preventing or treating a mammalian subject suffering from a disease, disorder, or condition, wherein the fused hIL10 polypeptide, nucleic acid sequence, vector, cell, or pharmaceutical formulation is to be administered to said subject.

59. The use of claim 58, wherein the disease, disorder, or condition is an autoimmune disease, disorder, or condition.

60. The use of claim 59, wherein the autoimmune disease, disorder, or condition is an inflammatory bowel disease (IBD).

61. The use of claim 60, wherein the IBD is Crohn’s disease or ulcerative colitis.

62. The use of claim 58, wherein the disease, disorder, or condition is cancer.

63. The use of claim 62, wherein the cancer is a cancer arising from chronic inflammation.

64. The use of claim 58, wherein the disease, disorder, or condition is macrophage activation syndrome.

65. The use of claim 58, wherein the disease, disorder, or condition is interferon gamma induced anemia.

66. A method of making a fused human IL10 (hIL10) polypeptide of the formula (hIL10A)-Ln-(hIL10B), the method comprising the steps of transfecting a host cell with a vector of claim 53 or 54, culturing said cell in a culture medium under conditions to permit expression of the nucleic acid sequence encoding the fused hIL10 polypeptide, and isolating the fused hIL10 polypeptide from the culture medium, optionally further comprising the step of purification of the fused hIL10 polypeptide.

67. The method of claim 66, wherein the host cell is a procaryotic cell.

68. The method of claim 67, wherein the procaryotic cell is an E. coli cell.

69. The method of any one of claims 66-68, wherein the hIL10A is a polypeptide selected from the group consisting of SEQ ID NOS:191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, and 205, and the hIL10B is a polypeptide selected from the group consisting of SEQ ID NOS: 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 148, 149, 150, 151, 152, 153, 154, 155, and 156.

70. The method ofl claim 69, wherein the hIL10A is a polypeptide selected from the group consisting of SEQ ID NOS: 172, 173, 174 , 175, 176, 177, 178, 179, 180, 181, 182, 183 184, 185, and 186.

71. The fused hIL10 polypeptide of any one of claims 1 to 45, nucleic acid sequence of any one of claims 50-52, vector of claim 53 or 54, cell of claim 55 or 56, or pharmaceutical formulation of claim 57, for use in therapy.