CLAIMS

The invention claimed is:

1. A polypeptide selected from the group consisting of hfB3-292S (amino acids 1-764 or 26-764 of SEQ ID NO:2), hfB3-292SN480 (amino acids 1-480 or 26-480 of SEQ ID NO:2), and hfB3-292S/Fc (1-990 or 26-990 of SEQ ID NO:22).

2. A nucleic acid comprising a nucleotide sequence encoding the polypeptide of claim 1.

3. A viral vector comprising the nucleic acid of claim 2.

4. The viral vector of claim 3, wherein said viral vector is selected from the group consisting of a retroviral vector, a lentiviral vector, an adenoviral vector, a Herpes viral vector, a Hepatitis viral vector, an SV40 viral vector, an AAV vector, an EBV vector and an NDV vector.

5. The viral vector of claim 4, wherein said lentiviral vector is a BIV, HIV, EIAV, SIV or FIV vector.

6. The viral vector of claim 5, wherein the viral vector comprises a decay accelerating factor.

7. A pharmaceutical preparation comprising the polypeptide of claim 1, the nucleic acid of claim 2, the viral vector of any one of claims 3-6 or any combination thereof.

8. The pharmaceutical preparation of claim 7, comprising at least one ingredient selected from the group consisting of histidine, $MgCl_2$, trehalose, a polysorbate, polysorbate 20, sucrose, arginine and proline.

9. Use of the polypeptide of claim 1, the nucleic acid of claim 2, the viral vector of any one of claims 3-6, the pharmaceutical composition of any one of claims 7-8, or any

combination thereof in the manufacture of a medicament for inhibiting complement activity, wherein the use comprises introduction or administration to a site of the complement activity the polypeptide of claim 1, the nucleic acid of claim 2, the viral vector of any one of claims 3-6, the pharmaceutical composition of any one of claims 7-8, or any combination thereof in an amount sufficient to inhibit the complement activity, wherein the polypeptide inhibits the complement activity.

10. Use of the polypeptide, the nucleic acid, the viral vector, the pharmaceutical composition or any combination thereof, as defined in claim 9, in the manufacture of a medicament for treating a complement mediated disease in a patient.

11. The use of claim 10, wherein the complement-mediated disease is a disease of the eye.

12. The use of claim 11, wherein the pharmaceutical composition is to be administered to the eye.

13. The use of claim 12, wherein the pharmaceutical composition is to be administered by intravitreal injection, subretinal injection, injection to the intraanterior chamber of the eye, injection or application locally to the cornea, subconjunctival injection, subtenon injection, or by eye drops.

14. The use of any one of claims 10-13, wherein the complement-mediated disease is macular degeneration, age-related macular degeneration (AMD), geographic atrophy, wet AMD, myocardial infarction, dry AMD, drusen formation, arthritis, stroke, ischemic reperfusion injury, diabetic retinopathy, vitreoretinopathy, traumatic organ injury, corneal inflammation, corneal neovascularization, uveitis, ocular hypertension or glaucoma.

15. The use of any one of claims 10-13, wherein the complement-mediated disease is selected from the group consisting of atherosclerosis, airway hyperresponsiveness, immune related diseases, autoimmune related diseases, lupus nephritis, systemic lupus erythematosus (SLE), arthritis, rheumatologic diseases, anti-phospholipid antibody syndrome, intestinal and renal I/R injury, asthma, atypical hemolytic-uremic syndrome, Type II membranoproliferative glomerulonephritis, non-proliferative glomerulonephritis, fetal loss,

brain injury, post-traumatic organ damage, post infarction organ damage, vasculitis, hereditary angioedema, paroxysmal nocturnal hemoglobinuria, cerebrovascular accident, Alzheimer's disease, transplant rejection, infections, sepsis, septic shock, Sjögren's syndrome, myasthenia gravis, antibody-mediated skin diseases, Type I and Type II diabetes mellitus, insulin resistance syndrome, gestational diabetes, thyroiditis, idiopathic thrombocytopenic purpura and hemolytic anemia, neuropathies, multiple sclerosis, cardiopulmonary bypass injury, polyarteritis nodosa, Henoch Schonlein purpura, serum sickness, Goodpasture's disease, systemic necrotizing vasculitis, post streptococcal glomerulonephritis, idiopathic pulmonary fibrosis, membranous glomerulonephritis, acute shock lung syndrome, adult respiratory distress syndrome, and reperfusion.

16. A cell comprising the nucleic acid of claim 2, wherein the cell expresses the polypeptide.

17. The cell of claim 16, wherein the cell is a mammalian cell.

18. The cell of claim 16, wherein the cell is selected from the group consisting of a 293 cell, a CHO cell, a PerC6 cell or a Vero cell.

19. The cell of claim 16, wherein the cell is a prokaryotic cell.

20. The cell of claim 16, wherein the cell is an E. coli cell.

21. An *in vitro* method of producing a polypeptide comprising a complement factor B protein analog, the method comprising:

a. expressing in a cell the polypeptide of claim 1; and

b. purifying said polypeptide.

CLAIMS

The invention claimed is:

1. A polypeptide comprising a complement factor B protein analog, wherein the complement factor B analog comprises a mutation of a free cysteine amino acid.

2. The polypeptide of claim 1, wherein the mutation comprises a substitution of the free cysteine.

3. The polypeptide of claim 2, wherein the free cysteine is substituted with more than one amino acid.

4. The polypeptide of claim 1, wherein the complement factor B protein analog is an analog of SEQ ID NO:4 and the complement factor B protein analog has cysteine amino acids that form disulfide bonds and a free cysteine amino acid has been substituted by another amino acid.

5. The polypeptide of any one of the above claims, wherein the free cysteine is substituted with an amino acid selected from the group consisting of alanine, histidine, isoleucine, leucine, methionine, phenylalanine, serine, threonine, tyrosine and valine.

6. The polypeptide of any one of the above claims, wherein the human complement factor B analog competes with binding of a native complement factor B.

7. The polypeptide of claim 1, wherein the mutation comprises a deletion of the free cysteine.

8. The polypeptide of any one of the above claims, wherein the complement factor B protein analog is a human complement factor B protein analog.

9. The polypeptide of any one of the above claims, wherein the free cysteine corresponds to amino acid 292 of SEQ ID NO:1.

10. The polypeptide of any one of the above claims, wherein the complement factor B protein analog comprises at least one mutation corresponding to a mutation of SEQ ID NO:1 selected from the group consisting of K258A, R259A, K260A, D279G, N285D and D740N.

11. The polypeptide of any one of the above claims, wherein the complement factor B protein analog comprises mutations corresponding to K258A, R259A, K260A, D279G and N285D of SEQ ID NO:1.

12. The polypeptide of any one of the above claims, wherein the complement factor B protein analog comprises a mutation corresponding to D740N of SEQ ID NO:1

13. The polypeptide of claim 1, wherein the complement factor B protein analog comprises amino acids 26-480 of SEQ ID NO:2.

14. The polypeptide of claim 1, wherein the complement factor B protein analog does not comprise amino acids 481-764 of SEQ ID NO:2.

15. The polypeptide of any of claims 1-9, wherein said complement factor B protein analog has increased C3b binding affinity as compared to a corresponding native complement factor B protein and said complement factor B protein analog comprises

(i) diminished protease activity as compared to the corresponding native complement factor B protein;

(ii) diminished ability to be cleaved by factor D protein as compared to the corresponding native complement factor B protein; or

(iii) diminished protease activity as compared to the corresponding native complement factor B protein and diminished ability to be cleaved by a factor D protein as compared to the corresponding native complement factor B protein.

16. The polypeptide of any one of the above claims, wherein the complement factor B protein analog comprises a mutation in the C3b binding domain and the complement factor B protein analog exhibits increased binding affinity to C3b as compared to the binding affinity of a corresponding native complement factor B protein to C3b.

17. The polypeptide of claim 16, wherein the mutation in the C3b binding domain comprises:

(i) a substitution or deletion of an aspartic acid corresponding to amino acid 279 of SEQ ID NO:1, a substitution or deletion of an asparagine corresponding to amino acid 285 of SEQ ID NO:1 or both; or

(ii) an insertion of at least one amino acid next to said aspartic acid or said asparagine.

18. The polypeptide of claim 17, wherein said aspartic acid, said asparagine or both are substituted with one or more amino acids.

19. The polypeptide of claim 17 or 18, wherein said aspartic acid is substituted with glycine, alanine or asparagine.

20. The polypeptide of claim 17, 18 or 19, wherein said asparagine is substituted

with glycine, alanine, or aspartic acid.

21. The polypeptide of claim 17, wherein said substitution comprises replacing said aspartic acid with glycine and said asparagine with aspartic acid.

22. The polypeptide of claim 15, wherein said complement factor B protein analog comprises an alteration in the complement factor D cleavage site wherein the alteration decreases or ablates cleavage of the complement factor B protein analog by factor D protein.

23. The polypeptide of claim 22, wherein said alteration in the factor D cleavage site comprises:

(i) a substitution or deletion of an arginine corresponding to amino acid 259 of SEQ ID NO:1, a substitution or deletion of one or both lysines corresponding to amino acid 258 or 260 of SEQ ID NO:1 or a substitution or deletion of the arginine and both lysines; or

(ii) an insertion next to the arginine, next to the one or both lysines, or next to the arginine and one or both of the lysines.

24. The polypeptide of claim 23, wherein said amino acids corresponding to amino acids 258-260 of SEQ ID NO:1 are each replaced with alanine.

25. The polypeptide of any one of the above claims, wherein the complement factor B protein analog comprises a mutation in the active site of the serine protease domain, wherein the mutation decreases or ablates the complement factor B protein analog's ability to cleave complement factor C3 as compared to a corresponding native complement factor B protein.

26. The polypeptide of claim 25, wherein said mutation comprises a deletion or a substitution of an aspartic acid corresponding to amino acid 740 of SEQ ID NO:1.

27. The polypeptide of claim 26, wherein said aspartic acid corresponding to amino acid 740 of SEQ ID NO:1 is substituted with a serine, tyrosine, glycine, alanine or glutamic acid.

28. The polypeptide of claim 26, wherein said substitution comprises substituting said aspartic acid with asparagine.

29. The polypeptide of any one of the above claims, wherein the human complement factor B protein analog is at least 90%, at least 95%, at least 98% or at least 99% identical to SEQ ID NO:1, 2, 3, 22, 23 or 26.

30. The polypeptide of any one of claims 1-28, wherein the human complement

factor B protein analog is at least 90%, at least 95%, at least 98% or at least 99% identical to amino acids 26-764 of SEQ ID NOs:1, 2 or 3; to amino acids 26-990 of SEQ ID NOs:22 or 23; to amino acids 26-480 of SEQ ID NO:2; or to amino acids 26-1003 of SEQ ID NO:26.

31. The polypeptide of claim 1, wherein the complement factor B protein analog comprises SEQ ID NO:2, 3, 22, 23, 26, or amino acids 1-480 of SEQ ID NO:2.

32. The polypeptide of claim 1, wherein the complement factor B protein analog comprises amino acids 26-764 of SEQ ID NO:2, amino acids 26-764 of SEQ ID NO:3, amino acids 26-480 of SEQ ID NO:2, amino acids 26-990 of SEQ ID NO:22, amino acids 26-990 of SEQ ID NO:23, or amino acids 26-1009 of SEQ ID NO:26.

33. The polypeptide of claim 1, wherein the complement factor B protein analog consists essentially of amino acids 26-764 of SEQ ID NO:2, amino acids 26-764 of SEQ ID NO:3, amino acids 26-480 of SEQ ID NO:2, amino acids 26-990 of SEQ ID NO:22, amino acids 26-990 of SEQ ID NO:23 or amino acids 26-1009 of SEQ ID NO:26.

34. The polypeptide of claim 1, wherein the polypeptide comprises an immunoglobulin Fc domain.

35. The polypeptide of claim 34, wherein the Fc domain is C-terminal to the complement factor B analog.

36. The polypeptide of claim 34 or 35, wherein the Fc domain has one or mutations of a cysteine(s) in the Fc domain sequence, wherein the one or more mutations inhibit dimer formation.

37. The polypeptide of any one of claims 34-36, wherein an Fc domain comprises a mutation of one or more cysteines corresponding to amino acids 17 or 20 of SEQ ID NO:27.

38. The polypeptide of any one of claims 36-37, wherein the one or more cysteines are substituted with an amino acid selected from the group consisting of histidine, isoleucine, leucine, methionine, phenylalanine, serine, threonine, tyrosine, and valine.

39. The polypeptide of claim 34 or 35, wherein the Fc domain comprises an amino acid sequence selected from amino acids 766-990 of SEQ ID NO:21, 766-1003 of SEQ ID NO:26, 786-1003 of SEQ ID NO:26, 1-238 of SEQ ID NO:27.

40. The polypeptide of anyone of claims 1-3 or 34-39, wherein the amino acid sequence of the complement factor B analog corresponds to a fragment of a complement factor B.

41. The polypeptide of claim 40, wherein the complement factor B analog comprises a truncation corresponding to an N-terminal truncation of factor B.

42. The polypeptide of claim 40 or 41, wherein the complement factor B analog comprises a truncation corresponding to a C-terminal truncation of factor B.

43. The polypeptide of claim 42, wherein the complement factor B analog comprises a C-terminal truncation corresponding to a truncation C-terminal to an amino acid corresponding to amino acid 407, 427, 457, 477, 480, 484, 487, 507 or 527 of SEQ ID NOs:1, 2 or 4.

44. The polypeptide of claim 42, wherein the complement factor B analog comprises a truncation corresponding to a C-terminal truncation at an amino acid between amino acids corresponding to amino acids 407-487, 470-495 or 477-487 of SEQ ID NOs:1, 2 or 4.

45. The polypeptide of any one of claims 40-42, wherein the complement factor B analog does not comprise amino acids corresponding to amino acids 408-764, 428-764, 458-764, 478-764, 481-764, 485-764, 488-764, 508-764, 528-764 of SEQ ID NOs:1, 2 or 4.

46. The polypeptide of any one of the above claims, wherein the complement factor B analog comprises mutations of amino acids corresponding to those in complement factor B that interact decay acceleration factor.

47. The polypeptide of any one of the above claims, wherein the complement factor B analog comprises one or more mutations of amino acids corresponding to amino acids 290, 291, 323, 363, 364, or 407 of SEQ ID NO:1.

48. The polypeptide of claim 47, wherein the one or more mutations are a substitution or deletion.

49. The polypeptide of claim 48, wherein the one or more mutations correspond to one or more of K290A, K291A, K323E,Y363A, S364A or D407N of SEQ ID NO:1.

50. The polypeptide of claim 49, wherein the complement factor B analog comprises one of the following combinations of mutations corresponding to K290A/K291A, Y363A/S364A or K290A/K291A/Y363A/S364A of SEQ ID NO:1.

51. The polypeptide of any one of the above claims, wherein the complement factor B protein analog is at least 90%, at least 93%, at least 95%, at least 98%, at least 99.5% or at least 99.9% pure in relation to total protein.

52. The polypeptide of any one of the above claims, wherein the polypeptide inhibits or reduces complement activity.

53. The polypeptide of claim 52, wherein the polypeptide inhibits the alternative complement pathway.

54. A nucleic acid comprising a nucleotide sequence encoding the polypeptide of any one of the previous claims.

55. A viral vector comprising the nucleic acid of claim 54.

56. The viral vector of claim 55, wherein said viral vector is selected from the group consisting of a retroviral vector, a lentiviral vector, an adenoviral vector, a Herpes viral vector, a Hepatitis viral vector, an SV40 viral vector, an AAV vector, an EBV vector and an NDV vector.

57. The viral vector of claim 56, wherein said lentiviral vector is a BIV, HIV, EIAV, SIV or FIV vector.

58. The viral vector of claim 57, wherein the viral vector comprises a decay accelerating factor.

59. A pharmaceutical preparation comprising the polypeptide of any one of claims 1-53, the nucleic acid of claim 54, the viral vector of any one of claims 55-58 or any combination thereof.

60. The pharmaceutical preparation of claim 59, comprising at least one ingredient selected from the group consisting of histidine, $MgCl_2$, trehalose, a polysorbate, polysorbate 20, sucrose, arginine and proline.

61. Use of the polypeptide of any one of claims 1-53, the nucleic acid of claim 54, the viral vector of any one of claims 55-58, the pharmaceutical composition of any one of claims 59-60, or any combination thereof in the manufacture of a medicament for inhibiting complement activity, wherein the use comprises introduction or administration to a site of the complement activity the polypeptide of any one of claims 1-53, the nucleic acid of claim 54, the viral vector of any one of claims 55-58, the pharmaceutical composition of any one of claims 59-60, or any combination thereof in an amount sufficient to inhibit the complement activity, wherein the polypeptide inhibits the complement activity.

62. The use of claim 61, comprising the polypeptide, the nucleic acid, the viral vector, the pharmaceutical composition or any combination thereof to be administered to a patient.

63. The use of claim 61 or 62, wherein the polypeptide competes with binding of a native complement factor B.

64. Use of the polypeptide, the nucleic acid, the viral vector, the pharmaceutical composition or any combination thereof, as defined in claim 62, or the polypeptide competing with binding of a native complement factor B, as defined in claim 63, in the manufacture of a medicament for treating a complement mediated disease in a patient.

65. The use of claim 64, wherein the complement-mediated disease is a disease of the eye.

66. The use of claim 65, wherein the pharmaceutical composition is to be administered to the eye.

67. The use of claim 66, wherein the pharmaceutical composition is to be administered by intravitreal injection, subretinal injection, injection to the intraanterior chamber of the eye, injection or application locally to the cornea, subconjunctival injection, subtenon injection, or by eye drops.

68. The use of any one of claims 64-67, wherein the complement-mediated disease is macular degeneration, age-related macular degeneration (AMD), geographic atrophy, wet AMD, myocardial infarction, dry AMD, drusen formation, arthritis, stroke, ischemic reperfusion injury, diabetic retinopathy, vitreoretinopathy, traumatic organ injury, corneal inflammation, corneal neovascularization, uveitis, ocular hypertension or glaucoma.

69. The use of any one of claims 64-67, wherein the complement-mediated disease is selected from the group consisting of atherosclerosis, airway hyperresponsiveness, immune related diseases, autoimmune related diseases, lupus nephritis, systemic lupus erythematosus (SLE), arthritis, rheumatologic diseases, anti-phospholipid antibody syndrome, intestinal and renal I/R injury, asthma, atypical hemolytic-uremic syndrome, Type II membranoproliferative glomerulonephritis, non-proliferative glomerulonephritis, fetal loss, brain injury, post-traumatic organ damage, post infarction organ damage, vasculitis, hereditary angioedema, paroxysmal nocturnal hemoglobinuria, cerebrovascular accident, Alzheimer's disease, transplant rejection, infections, sepsis, septic shock, Sjögren's syndrome, myasthenia gravis, antibody-mediated skin diseases, Type I and Type II diabetes mellitus, insulin resistance syndrome, gestational diabetes, thyroiditis, idiopathic thrombocytopenic purpura and hemolytic anemia, neuropathies, multiple sclerosis, cardiopulmonary bypass injury, polyarteritis nodosa, Henoch Schonlein purpura, serum sickness, Goodpasture's disease, systemic necrotizing vasculitis, post streptococcal glomerulonephritis, idiopathic pulmonary fibrosis, membranous glomerulonephritis, acute shock lung syndrome, adult respiratory distress syndrome, and reperfusion.

70. The use of any one of claims 64-69, further comprising

a complement inhibiting factor or an anti-angiogenic factor to be administered to the patient, prior to, concurrently with, or after the administration of the pharmaceutical composition.

71. The use of claim 70, wherein said complement inhibiting factor is selected from the group consisting of a Factor H, a Factor H-like 1, an MCP, a DAF, or a soluble form of an MCP.

72. The use of claim 70 or 71, wherein said anti-angiogenic factor is selected from the group consisting of endostatin, a VEGF binding molecule, PEDF, T2-TrpRS, sFLT, aflibercept and kininostatin.

73. The use of any one of claims 64-72, wherein an anti-inflammatory is to be administered prior to, concurrently with, or after the administration of the pharmaceutical composition.

74. The use of claim 73, wherein the anti-inflammatory is
(i) to be administered concurrently with the pharmaceutical composition or
(ii) the pharmaceutical composition comprises the anti-inflammatory.

75. The use of claim 73 or 74, wherein the anti-inflammatory is to be administered to the eye.

76. The use of claim 73, 74 or 75, wherein the anti-inflammatory is selected from the group consisting of dexamethasone, dexamethasone sodium metasulfobenzoate, dexamethasone sodium phosphate, fluorometholone, bromfenac, pranoprofen, a cyclosporine ophthalmic emulsion, naproxen, glucocorticoids, ketorolac, ibuprofen, tolmetin, non-steroidal anti-inflammatory drugs, steroidal anti-inflammatory drugs, diclofenac, flurbiprofen, indomethacin, and suprofen.

77. The use of any one of claims 62-64, wherein the pharmaceutical preparation comprising the viral vector is to be administered about once every week, month, 2 months, 3 months, 6 months, 9 months, year, 18 months, 2 years, 30 months, 3 years, 5 years, or 10 years.

78. The use of any one of claims 64-77, wherein a compound that inhibits, complement activity, T-cell activation, B-cells, tumor necrosis factor (TNF), estrogen, interleukin-1 or interferon-gamma is to be administered prior to, concurrently with, or after the administration of the pharmaceutical composition.

79. The use of claim 78, wherein the compound is selected from the group

consisting of infliximab, adalimumab, golimumab, etanercept, abatacept and rituximab.

80. The use of any one of claims 62-64, wherein the pharmaceutical preparation comprising the viral vector is to be administered only once to the patient.

81. A cell comprising the nucleic acid of claim 54, wherein the cell expresses the polypeptide.

82. The cell of any one of claims 81, wherein the cell is a mammalian cell.

83. The cell of claim 81, wherein the cell is selected from the group consisting of a 293 cell, a CHO cell, a PerC6 cell or a Vero cell.

84. The cell of claim 81, wherein the cell is a prokaryotic cell.

85. The cell of claim 81, wherein the cell is an E. coli cell.

86. An *in vitro* method of producing a polypeptide comprising a complement factor B protein analog, the method comprising:

a. expressing in a cell the polypeptide of any one of claims 1-53; and

b. purifying said polypeptide.