CLAIMS

1. A method of treating macular degeneration in a human subject comprising administering to the diseased eye of the subject a composition comprising a recombinant adeno-associated virus (rAAV) virion comprising a polynucleotide encoding a soluble protein comprising at least one domain of VEGFR-1 (Flt-1) capable of modulating VEGF activity, wherein from about 1 x 10^7 to about 1 x 10^{13} rAAV virions are delivered to the eye.

2. The method of claim 1, wherein the method comprises reducing intraocular pressure, retinal thickness, subretinal fluids, or intraretinal fluids.

3. A method of treating macular edema in a human subject comprising administering to the diseased eye of the subject a composition comprising a recombinant adeno-associated virus (rAAV) virion comprising a polynucleotide encoding a soluble protein comprising at least one domain of VEGFR-1 (Flt-1) capable of modulating VEGF activity, wherein from about 1 x 10^7 to about 1 x 10^{13} rAAV virions are delivered to the eye.

4. The method of claim 3, wherein the method comprises reducing intraocular pressure, retinal thickness, subretinal fluids, or intraretinal fluids.

5. The method of any one of claims 1-4, wherein from about 1 x 10^7 to about 1 x 10^{12}; 1 x 10^8 to about 1 x 10^{12}; about 1 x 10^8 to about 1 x 10^{11}; about 1 x 10^8 to about 1 x 10^{10}; about 1 x 10^8 to about 1 x 10^9; about 2 x 10^7 to about 2 x 10^{12}; about 2 x 10^8 to about 2 x 10^{12}; about 2 x 10^8 to about 2 x 10^{11}; about 2 x 10^8 to about 2 x 10^{10}; about 2 x 10^8 to about 2 x 10^9; 2 x 10^9 to about 2 x 10^{10}; about 1 x 10^{10} to about 1 x 10^{13}; about 1 x 10^{10} to about 1 x 10^{12}; about 1 x 10^{10} to about 1 x 10^{11}; about 2 x 10^{10} to about 1 x 10^{13}; 2 x 10^{10} to about 1 x 10^{12}; about 2 x 10^{10} to about 2 x 10^{12}; about 2 x 10^{10} to about 1 x 10^{11}; or about 2 x 10^{10} to about 2 x 10^{11} rAAV virions are administered to the eye.

6. The method of any one of claims 1-5, wherein about 1 x 10^7, about 2x10^7, about 6 x 10^7, about 1 x 10^8, about 2x10^8, about 6 x 10^8, about 1 x 10^9, about

$2x10^9$, about 6 x 10^9, about 1 x 10^{10}, about $2x10^{10}$, about 6 x 10^{10}, about 1 x 10^{11}, about $2x10^{11}$, about 6 x 10^{11}, about 1 x 10^{12}, about $2x10^{12}$, about 6 x 10^{12}, or about 1 x 10^{13} rAAV virions are administered to the eye.

7. A method of treating macular degeneration in a human subject comprising administering to the diseased eye of the subject a composition comprising a recombinant adeno-associated virus (rAAV) virion comprising a polynucleotide encoding a soluble protein comprising at least one domain of VEGFR-1 (Flt-1) capable of modulating VEGF activity, wherein less than about 2 x 10^{10} rAAV virions are delivered to the eye.

8. The method of claim 7, wherein the method comprises reducing intraocular pressure, retinal thickness, subretinal fluids, or intraretinal fluids.

9. A method of treating macular edema in a human subject comprising administering to the diseased eye of the subject a composition comprising a recombinant adeno-associated virus (rAAV) virion comprising a polynucleotide encoding a soluble protein comprising at least one domain of VEGFR-1 (Flt-1) capable of modulating VEGF activity, wherein less than about 2 x 10^{10} rAAV virions are delivered to the eye.

10. The method of claim 9, wherein the method comprises reducing intraocular pressure, retinal thickness, subretinal fluids, or intraretinal fluids.

11. The method of any one of claims 7-10, wherein from about 2 x 10^8 to less than 2 x 10^{10} rAAV virions are delivered to the eye.

12. The method of any one of claims 7-10, wherein up to about 2 x 10^8 rAAV virions are delivered to the eye.

13. The method of any one of claims 7-10, wherein up to about 2 x 10^9 rAAV virions are delivered to the eye.

14. The method of any one of claims 1-13, wherein the composition further comprises an opthalmalogically acceptable vehicle.

15. The method of any one of claims 1-14, wherein a single intravitreal injection of rAAV virions is administered to the eye.

16. The method of any one of claims 1-15, wherein the soluble protein comprises:

(a) the at least one domain of Flt-1;

(b) a multimerization domain derived from an immunoglobulin heavy chain; and

(c) a linker 5-25 amino acid residues in length linking (a) to (b),

wherein when the soluble protein is expressed, a multimer of the soluble protein is produced.

17. The method of any one of claims 1-16, wherein the at least one domain comprises domain 2 of Flt-1.

18. The method of claim 16 or 17, wherein the multimer is a homodimer.

19. The method of any one of claims 16-18, wherein the multimerization domain comprises the Fc region of an IgG, or an active fragment thereof.

20. The method of any one of claims 16-19, wherein the multimerization domain comprises the CH3 domain of an IgG, or an active fragment thereof.

21. The method of any one of claims 16-20, wherein the multimerization domain is from an IgG1, an IgG2, an IgG3 or an IgG4.

22. The method of claim 21, wherein the multimerization domain is from the constant region of an IgG1 heavy chain.

23. The method of any one of claims 16-22 wherein the linker is selected from the group consisting of:

gly_9 (SEQ ID NO:1);
glu_9 (SEQ ID NO:2);
ser_9 (SEQ ID NO:3);
$gly_5cyspro_2cys$ (SEQ ID NO:4);
$(gly_4ser)_3$ (SEQ ID NO:5);
SerCysValProLeuMetArgCysGlyGlyCysCysAsn (SEQ ID NO:6);
ProSerCysValProLeuMetArgCysGlyGlyCysCysAsn (SEQ ID NO:7);
GlyAspLeuIleTyrArgAsnGlnLys (SEQ ID NO:8); and
Gly_9ProSerCysValProLeuMetArgCysGlyGlyCysCysAsn (SEQ ID NO:9).

24. The method of any one of claims 16-23, wherein the soluble protein has the formula X-Y-Z, wherein X comprises the IgG-like domain 2 of Flt-1, wherein Y is Gly_9, and wherein Z is an IgG Fc region or an IgG CH3 region.

25. The method of any one of claims 16-24, wherein the multimerization domain is humanized.

26. The method of any one of claims 16-25, wherein the soluble protein comprises an amino acid sequence selected from the group consisting of (a) the amino acid sequence depicted in Figures 2A-2B (SEQ ID NO:11); (b) the amino acid sequence depicted in Figure 6 (SEQ ID NO:15); (c) the amino acid sequence depicted in Figure 8 (SEQ ID NO:17); (d) the amino acid sequence depicted in Figure 12 (SEQ ID NO:21); and (e) an active variant of (a), (b), (c) or (d) having at least 90% sequence identity thereto.

27. The method of any one of claims 1, 2, 5-8, and 11-26, wherein the macular degeneration is age-related macular degeneration (AMD).

28. The method of claim 27, wherein the macular degeneration is wet AMD.

29. The method of any one of the preceding claims, wherein the rAAV virion is derived from an AAV serotype selected from AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAVrh8, AAVrh8R, AAV10, AAVrh10, AAV11 or AAV12.

30. The method of claim 29, wherein the rAAV virion is derived from AAV2.

31. Use of a recombinant adeno-associated virus (rAAV) virion comprising a polynucleotide encoding a soluble protein comprising at least one domain of VEGFR-1 (Flt-1) capable of modulating VEGF activity, in the manufacture of a composition for treating macular degeneration in a human subject by delivering about 1 x 10^7 to about 1 x 10^{13} rAAV virions to the eye.

32. The use of claim 31, wherein intraocular pressure, retinal thickness, subretinal fluids, or intraretinal fluids are reduced.

33. Use of a recombinant adeno-associated virus (rAAV) virion comprising a polynucleotide encoding a soluble protein comprising at least one domain of VEGFR-1 (Flt-1) capable of modulating VEGF activity in the manufacture of a composition for treating macular edema in a human subject by delivering about 1 x 10^7 to about 1 x 10^{13} rAAV virions to the eye.

34. The use of claim 33, wherein intraocular pressure, retinal thickness, subretinal fluids, or intraretinal fluids are reduced.

35. The use of any one of claims 31-34, wherein from about 1 x 10^7 to about 1 x 10^{12}; 1 x 10^8 to about 1 x 10^{12}; about 1 x 10^8 to about 1 x 10^{11}; about 1 x 10^8 to about 1 x 10^{10}; about 1 x 10^8 to about 1 x 10^9; about 2 x 10^7 to about 2 x 10^{12}; about 2 x 10^8 to about 2 x 10^{12}; about 2 x 10^8 to about 2 x 10^{11}; about 2 x 10^8 to about 2 x 10^{10}; about 2 x 10^8 to about 2 x 10^9; 2 x 10^9 to about 2 x 10^{10}; about 1 x 10^{10} to about 1 x 10^{13}; about 1 x 10^{10} to about 1 x 10^{12}; about 1 x 10^{10} to about 1 x 10^{11}; about 2 x 10^{10} to about 1 x 10^{13}; 2 x 10^{10} to about 1 x 10^{12}; about 2 x 10^{10} to about 2 x 10^{12}; about 2 x 10^{10} to about 1 x 10^{11}; or about 2 x 10^{10} to about 2 x 10^{11} rAAV virions are delivered to the eye.

36. The use of any one of claims 31-35, wherein about 1 x 10^7, about 2x10^7, about 6 x 10^7, about 1 x 10^8, about 2x10^8, about 6 x 10^8, about 1 x 10^9, about 2x10^9, about 6 x 10^9, about 1 x 10^{10}, about 2x10^{10}, about 6 x 10^{10}, about 1 x 10^{11}, about

$2x10^{11}$, about 6 x 10^{11}, about 1 x 10^{12}, about $2x10^{12}$, about 6 x 10^{12}, or about 1 x 10^{13} rAAV virions are delivered to the eye.

37. Use of a recombinant adeno-associated virus (rAAV) virion comprising a polynucleotide encoding a soluble protein comprising at least one domain of VEGFR-1 (Flt-1) capable of modulating VEGF activity in the manufacture of a composition for treating macular degeneration in a human subject by delivering less than about 2 x 10^{10} rAAV virions to the eye.

38. The use of claim 37, wherein intraocular pressure, retinal thickness, subretinal fluids, or intraretinal fluids are reduced.

39. Use of a recombinant adeno-associated virus (rAAV) virion comprising a polynucleotide encoding a soluble protein comprising at least one domain of VEGFR-1 (Flt-1) capable of modulating VEGF activity in the manufacture of a composition for treating macular edema in a human subject by delivering less than about 2 x 10^{10} rAAV virions to the eye.

40. The use of claim 39, wherein intraocular pressure, retinal thickness, subretinal fluids, or intraretinal fluids are reduced.

41. The use of any one of claims 37-40, wherein from about 2 x 10^{8} to less than 2 x 10^{10} rAAV virions are delivered to the eye.

42. The use of any one of claims 37-40, wherein up to about 2 x 10^{8} rAAV virions are delivered to the eye.

43. The use of any one of claims 37-40, wherein up to about 2 x 10^{9} rAAV virions are delivered to the eye.

44. The use of any one of claims 31-43, wherein the composition further comprises an opthalmalogically acceptable vehicle.

45. The use of any one of claims 31-44, wherein a single intravitreal injection of rAAV virions is delivered to the eye.

46. The use of any one of claims 31-45, wherein the soluble protein comprises:

(a) the at least one domain of Flt-1;

(b) a multimerization domain derived from an immunoglobulin heavy chain; and

(c) a linker 5-25 amino acid residues in length linking (a) to (b),

wherein when the soluble protein is expressed, a multimer of the soluble protein is produced.

47. The use of any one of claims 31-46, wherein the at least one domain comprises domain 2 of Flt-1.

48. The use of claim 46 or 47, wherein the multimer is a homodimer.

49. The use of any one of claims 46-48, wherein the multimerization domain comprises the Fc region of an IgG, or an active fragment thereof.

50. The use of any one of claims 46-49, wherein the multimerization domain comprises the CH3 domain of an IgG, or an active fragment thereof.

51. The use of any one of claims 46-50, wherein the multimerization domain is from an IgG1, an IgG2, an IgG3 or an IgG4.

52. The use of claim 51, wherein the multimerization domain is from the constant region of an IgG1 heavy chain.

53. The use of any one of claims 46-52 wherein the linker is selected from the group consisting of:

gly_9 (SEQ ID NO:1);

glu_9 (SEQ ID NO:2);

ser_9 (SEQ ID NO:3);

$gly_5cyspro_2cys$ (SEQ ID NO:4);

$(gly_4ser)_3$ (SEQ ID NO:5);

SerCysValProLeuMetArgCysGlyGlyCysCysAsn (SEQ ID NO:6);

ProSerCysValProLeuMetArgCysGlyGlyCysCysAsn (SEQ ID NO:7);

GlyAspLeuIleTyrArgAsnGlnLys (SEQ ID NO:8); and

Gly_9ProSerCysValProLeuMetArgCysGlyGlyCysCysAsn (SEQ ID NO:9).

54. The use of any one of claims 46-53, wherein the soluble protein has the formula X-Y-Z, wherein X comprises the IgG-like domain 2 of Flt-1, wherein Y is Gly_9, and wherein Z is an IgG Fc region or an IgG CH3 region.

55. The use of any one of claims 46-54, wherein the multimerization domain is humanized.

56. The use of any one of claims 46-55, wherein the soluble protein comprises an amino acid sequence selected from the group consisting of (a) the amino acid sequence depicted in Figures 2A-2B (SEQ ID NO:11); (b) the amino acid sequence depicted in Figure 6 (SEQ ID NO:15); (c) the amino acid sequence depicted in Figure 8 (SEQ ID NO:17); (d) the amino acid sequence depicted in Figure 12 (SEQ ID NO:21); and (e) an active variant of (a), (b), (c) or (d) having at least 90% sequence identity thereto.

57. The use of any one of claims 31, 32, 35-38, and 41-56, wherein the macular degeneration is age-related macular degeneration (AMD).

58. The use of claim 57, wherein the macular degeneration is wet AMD.

59. The use of any one of claims 31-58, wherein the rAAV virion is derived from an AAV serotype selected from AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAVrh8, AAVrh8R, AAV10, AAVrh10, AAV11 or AAV12.

60. The use of claim 59, wherein the rAAV virion is derived from AAV2.

CLAIMS

1. Use of a recombinant adeno-associated virus (rAAV) virion comprising a polynucleotide encoding a soluble protein comprising at least one domain of VEGFR-1 (Flt-1) capable of modulating VEGF activity, in the manufacture of a composition for treating macular degeneration in a human subject by delivering about 1 x 10^7 to about 1 x 10^{13} rAAV virions to the eye.

2. The use of claim 1, wherein intraocular pressure, retinal thickness, subretinal fluids, or intraretinal fluids are reduced.

3. Use of a recombinant adeno-associated virus (rAAV) virion comprising a polynucleotide encoding a soluble protein comprising at least one domain of VEGFR-1 (Flt-1) capable of modulating VEGF activity in the manufacture of a composition for treating macular edema in a human subject by delivering about 1 x 10^7 to about 1 x 10^{13} rAAV virions to the eye.

4. The use of claim 3, wherein intraocular pressure, retinal thickness, subretinal fluids, or intraretinal fluids are reduced.

5. The use of any one of claims 1-4, wherein from about 1 x 10^7 to about 1 x 10^{12}; 1 x 10^8 to about 1 x 10^{12}; about 1 x 10^8 to about 1 x 10^{11} ; about 1 x 10^8 to about 1 x 10^{10}; about 1 x 10^8 to about 1 x 10^9; about 2 x 10^7 to about 2 x 10^{12}; about 2 x 10^8 to about 2 x 10^{12}; about 2 x 10^8 to about 2 x 10^{11} ; about 2 x 10^8 to about 2 x 10^{10}; about 2 x 10^8 to about 2 x 10^9; 2 x 10^9 to about 2 x 10^{10}; about 1 x 10^{10} to about 1 x 10^{13}; about 1 x 10^{10} to about 1 x 10^{12}; about 1 x 10^{10} to about 1 x 10^{11} ; about 2 x 10^{10} to about 1 x 10^{13}; 2 x 10^{10} to about 1 x 10^{12}; about 2 x 10^{10} to about 2 x 10^{12}; about 2 x 10^{10} to about 1 x 10^{11} ; or about 2 x 10^{10} to about 2 x 10^{11} rAAV virions are delivered to the eye.

6. The use of any one of claims 1 -5, wherein about 1 x 10^7, about 2x10^7, about 6 x 10^7, about 1 x 10^8, about 2x10^8, about 6 x 10^8, about 1 x 10^9, about 2x10^9, about 6 x 10^9, about 1 x 10^{10}, about 2xl0^{10}, about 6 x 10^{10}, about 1 x 10^{11}, about 2x10^{11}, about 6 x 10^{11}, about 1 x 10^{12}, about 2x10^{12}, about 6 x 10^{12}, or about 1 x 10^{13} rAAV virions are delivered to the eye.

7. Use of a recombinant adeno-associated virus (rAAV) virion comprising a polynucleotide encoding a soluble protein comprising at least one domain of VEGFR-1 (Fit- 1) capable of modulating VEGF activity in the manufacture of a composition for treating macular degeneration in a human subject by delivering less than about 2 x 10^{10} rAAV virions to the eye.

8. The use of claim 7, wherein intraocular pressure, retinal thickness, subretinal fluids, or intraretinal fluids are reduced.

9. Use of a recombinant adeno-associated virus (rAAV) virion comprising a polynucleotide encoding a soluble protein comprising at least one domain of VEGFR-1 (Flt-1) capable of modulating VEGF activity in the manufacture of a composition for treating macular edema in a human subject by delivering less than about 2 x 10^{10} rAAV virions to the eye.

10. The use of claim 9, wherein intraocular pressure, retinal thickness, subretinal fluids, or intraretinal fluids are reduced.

11 . The use of any one of claims 7-10, wherein from about 2 x 10^{8} to less than 2 x 10^{10} rAAV virions are delivered to the eye.

12. The use of any one of claims 7-10, wherein up to about 2 x 10^{8} rAAV virions are delivered to the eye.

13. The use of any one of claims 7-10, wherein up to about 2 x 10^{9} rAAV virions are delivered to the eye.

14. The use of any one of claims 1-13, wherein the composition further comprises an opthalmalogically acceptable vehicle.

15. The use of any one of claims 1-14, wherein a single intravitreal injection of rAAV virions is delivered to the eye.

16. The use of any one of claims 1-15, wherein the soluble protein comprises:

(a) the at least one domain of Flt- 1 ;

(b) a multimerization domain derived from an immunoglobulin heavy chain; and

(c) a linker 5-25 amino acid residues in length linking (a) to (b),

wherein when the soluble protein is expressed, a multimer of the soluble protein is produced.

17. The use of any one of claims 1-16, wherein the at least one domain comprises domain 2 of Flt- 1.

18. The use of claim 16 or 17, wherein the multimer is a homodimer.

19. The use of any one of claims 16-18, wherein the multimerization domain comprises the Fc region of an IgG, or an active fragment thereof.

20. The use of any one of claims 16-19, wherein the multimerization domain comprises the CH3 domain of an IgG, or an active fragment thereof.

21. The use of any one of claims 16-20, wherein the multimerization domain is from an IgG1 , an IgG2, an IgG3 or an IgG4.

22. The use of claim 21, wherein the multimerization domain is from the constant region of an IgG1 heavy chain.

23. The use of any one of claims 16-22 wherein the linker is selected from the group consisting of:

gly_9 (SEQ ID NO: I);

glu_9 (SEQ ID NO:2);

ser_9 (SEQ ID NO:3);

$gly_5cyspro_2cys$ (SEQ ID NO:4);

$(gly_4ser)_3$ (SEQ ID NO:5);

SerCysValProLeuMetArgCysGlyGlyCysCysAsn (SEQ ID NO:6);

ProSerCysValProLeuMetArgCysGlyGlyCysCysAsn (SEQ ID NO:7);

GlyAspLeuIleTyrArgAsnGlnLys (SEQ ID NO : 8) ; and

Gly_9ProSerCysValProLeuMetArgCysGlyGlyCysCysAsn (SEQ ID NO:9).

24. The use of any one of claims 16-23, wherein the soluble protein has the formula X-Y-Z, wherein X comprises the IgG-like domain 2 of Flt- 1 , wherein Y is Gly9, and wherein Z is an IgG Fc region or an IgG CH3 region.

25. The use of any one of claims 16-24, wherein the multimerization domain is humanized.

26. The use of any one of claims 16-25, wherein the soluble protein comprises an amino acid sequence selected from the group consisting of (a) the amino acid sequence depicted in Figures 2A-2B (SEQ ID NO: l 1); (b) the amino acid sequence depicted in Figure 6 (SEQ ID NO: 15); (c) the amino acid sequence depicted in Figure 8 (SEQ ID NO: 17); (d) the amino acid sequence depicted in Figure 12 (SEQ ID NO:21); and (e) an active variant of (a), (b), (c) or (d) having at least 90% sequence identity thereto.

27. The use of any one of claims 1, 2, 5-8, and 11-26, wherein the macular degeneration is age-related macular degeneration (AMD).

28. The use of claim 27, wherein the macular degeneration is wet AMD.

29. The use of any one of claims 1-28, wherein the rAAV virion is derived from an AAV serotype selected from AAVl, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAVrh8, AAVrh8R, AAV10, AAVrhl O, AAVl 1 or AAV12.

30. The use of claim 29, wherein the rAAV virion is derived from AAV2.