CLAIMS

1. A recombinant adeno-associated virus (rAAV) virion comprising (a) a variant adeno-associated virus (AAV) capsid protein comprising a peptide insertion in the GH-loop of the capsid protein relative to a corresponding parental AAV capsid protein, wherein the peptide insertion comprises the amino acid sequence ISDQTKH (SEQ ID NO:14), and (b) a heterologous nucleic acid comprising a nucleotide sequence encoding a polypeptide that inhibits the activity of a vascular endothelial growth factor (VEGF), operably linked to an expression control sequence, wherein the nucleotide sequence is selected from the group consisting of:

(i) the nucleotide sequence set forth as SEQ ID NO:65 (aflibercept);

(ii) the nucleotide sequence set forth as SEQ ID NO: 69 (sc ranibizumab LH1);

(iii) nucleotides 79-1377 of SEQ ID NO:65;

(iv) nucleotides 61-1578 of SEQ ID NO:69;

and

(v) a nucleotide sequence at least 90% identical to any one of (i)-(iv).

2. The rAAV according to claim 1, wherein the peptide insertion is 7 to 10 amino acids in length and comprises the amino acid sequence Y_1Y_2ISDQTKHY_3, wherein each of Y_1-Y_3 is independently selected from Ala, Leu, Gly, Ser, Thr, and Pro.

3. The rAAV according to claim 2, wherein the peptide insertion comprises the amino acid sequence LAISDQTKHA (SEQ ID NO:28).

4. The rAAV according to any one of claims 1-3, wherein the insertion site is between amino acids corresponding to amino acids 587 and 588 of VP1 of AAV2 (SEQ ID NO:2) or the corresponding position in the capsid protein of another AAV serotype.

5. The rAAV according to any one of claims 1-4, wherein the capsid protein comprises one or more amino acid substitutions relative to VP1 capsid of AAV2 (SEQ ID NO:2) or one or more corresponding substitutions in another AAV serotype.

6. The rAAV according to any one of claims 1-5, wherein the capsid protein comprises a P34A amino acid substitution relative to VP1 capsid of AAV2 (SEQ ID NO:2) or the corresponding substitution in another AAV serotype.

7. The rAAV according to any one of claims 1-6, wherein the capsid protein comprises (i) the amino acid sequence ISDQTKH (SEQ ID NO:14) and (ii) a P34A amino acid substitution, and is at least 90% identical to the sequence set forth as SEQ ID NO:42.

8. The rAAV according to claim 7, wherein the capsid protein comprises the amino acid sequence set forth as SEQ ID NO:42.

9. The rAAV according to claim 8, wherein the nucleotide sequence is at least 90% identical to the entire length of the sequence set forth as SEQ ID NO:69 (sc-Ranibizumab LH) or to nucleotides 61-1578 of SEQ ID NO:69 and encodes the amino acid sequence set forth as SEQ ID NO:71 or encodes the amino acid sequence of amino acids 21-525 of SEQ ID NO:71.

10. The rAAV according to claim 9, wherein the nucleotide sequence comprises nucleotides 61-1578 of SEQ ID NO:69.

11. The rAAV according to claim 8, wherein the nucleotide sequence is at least 90% identical to the entire length of the sequence set forth as SEQ ID NO:65 (aflibercept) or to nucleotides 79-1377 of SEQ ID NO:65 and encodes the amino acid sequence set forth as SEQ ID NO:66 or encodes the amino acid sequence of amino acids 27-458 of SEQ ID NO:66.

12. The rAAV according to claim 11, wherein the nucleotide sequence comprises nucleotides 79-1377 of SEQ ID NO:65.

13. The rAAV according to claim 8, wherein the heterologous nucleic acid comprises the nucleotide sequence set forth as SEQ ID NO: 65 or a sequence at least 90% identical thereto and encodes the amino acid sequence set forth as SEQ ID NO:66.

14. The rAAV according to claim 13, wherein the heterologous nucleic acid comprises the nucleotide sequence set forth as SEQ ID NO:65 or a sequence at least 98% identical thereto and encodes the amino acid sequence set forth as SEQ ID NO:66.

15. The rAAV according to any one of claims 1-14, wherein the heterologous nucleic acid further comprises nucleotide sequence encoding a polypeptide or interfering RNA that inhibits angiogenesis.

16. The rAAV according to claim 15, wherein the polypeptide is selected from endostatin; tumstatin; angiostatin; and pigment epithelium-derived factor (PEDF) and/or wherein the interfering RNA decreases expression of a pro-angiogenic gene product selected from VEGFa, VEGFb, VEGFc, VEGFd, VEGFR1, VEGFR2, VEGFR3, PGF, PDGF and an angiopoietin.

17. The rAAV of any one of claims 1-16, wherein the expression control sequence comprises a ubiquitous promoter.

18. The rAAV according to claim 17, wherein the expression control sequence is selected from a CMV, CAG and CBA promoter.

19. The rAAV of any one of claims 1-18, wherein the variant capsid protein confers increased infectivity of a retinal cell compared to the infectivity of the corresponding parental AAV capsid protein for the retinal cell.

20. A pharmaceutical composition comprising an rAAV according to any one of claims 1-19 and a pharmaceutically acceptable carrier.

21. An in vitro method for delivering a VEGF inhibitor to a retinal cell, choroidal cell, lenticular cell, ciliary cell, iris cell, optic nerve cell and/or corneal cell comprising contacting the retinal cell, choroidal cell, lenticular cell, ciliary cell, iris cell, optic nerve cell and/or corneal cell with an rAAV virion according to any one of claims 1-19 or a pharmaceutical composition according to claim 20.

22. The use of an rAAV according to any one of claims 1-19 in the manufacture of a medicament for the treatment of a VEGFa-associated ocular disease selected from wet (neovascular, exudative) age-related macular degeneration; macular edema following retinal vein occlusion; retinal neovascularization resulting from retinal vein occlusion; diabetic macular edema, diabetic retinopathy (including all stages of non-proliferative diabetic retinopathy and proliferative diabetic retinopathy); myopic macular degeneration; branch retinal vein occlusion, hemi-retinal vein occlusion, and central retinal vein occlusion; retinopathy of prematurity; idiopathic choroidal neovascularization; myopia macular degeneration and secondary retinal and choridal neovascularization; retinal telangiectasia; neovascular glaucoma; vitreous

hemorrhage; retinal and choroidal neovascularization secondary to retinal diseases, including but not limited to uvetis, trauma, retinal degenerative disorders, genetic retinal and/or choroidal disease, tumors of the eye, corneal and iris neovascularization.

23. The use of an rAAV viron according to claim 22, wherein the VEGFa-associated ocular disease is selected from wet (neovascular, exudative) age-related macular degeneration; diabetic macular edema; macular edema following retinal vein occlusion; diabetic retinopathy; and myopic choroidal neovascularization.

24. The use of an rAAV viron according to claim 22 or 23, wherein the rAAV is for administration by intravitreal administration.

25. The rAAV virion according to claim 1, wherein the heterologous nucleic acid further comprises a nucleotide sequence encoding an interfering RNA that inhibits angiogenesis, wherein the interfering RNA decreases expression of VEGFc.

26. A pharmaceutical composition comprising the rAAV virion according to claim 25 and a pharmaceutically acceptable excipient.

27. The use of an rAAV according to claim 25 or a pharmaceutical composition according to claim 26 in the manufacture of a medicament for the treatment of a VEGFa-associated ocular disease selected from wet (neovascular, exudative) age-related macular degeneration; diabetic macular edema; macular edema following retinal vein occlusion; diabetic retinopathy; and myopic choroidal neovascularization.