Claims

1. 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).

2. The variant AAV capsid protein of claim 1, wherein the peptide insertion 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 variant AAV capsid protein of claim 2, wherein the peptide insertion comprises or consists of the amino acid sequence LAISDQTKHA (SEQ ID NO:28).

4. The variant AAV capsid protein of any one of claims 1-3, wherein the insertion site is located 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 variant AAV capsid protein of any one of claims 1-4, wherein the capsid protein comprises one or more amino acid substitutions relative to VP1 of AAV2 (SEQ ID NO:2) or one or more corresponding substitutions in the capsid protein of another AAV serotype.

6. The variant AAV capsid protein of any one of claims 1-5, wherein the capsid protein comprises one or more of the following amino acid substitutions relative to VP1 of AAV2 (SEQ ID NO:2) or the corresponding substitution(s) in the capsid protein of another AAV serotype: M1L, L15P, P34A, N57D, N66K, R81Q, Q101R, S109T, R144K, R144M, Q164K, T176P, L188I, S196Y, G226E, G236V, I240T, P250S, N312K, P363L, D368H, N449D, T456K, S463Y, D472N, R484C, A524T, P535S, N551S, A593E, I698V, V708I, V719M, S721L, and L735Q.

7. The variant AAV capsid protein of claim 6, wherein the capsid protein comprises a P34A amino acid substitution relative to VP1 of AAV2 (SEQ ID NO:2) or the corresponding substitution in the capsid protein of another AAV serotype.

8. The variant AAV capsid protein of claim 7, wherein the capsid protein comprises an amino acid sequence at least 90% identical, at least 95% identical, at least 99% identical or 100% identical to the entire length of the amino acid sequence set forth as SEQ ID NO:42.

9. The variant AAV capsid protein of claim 8, wherein the capsid protein consists essentially of the amino acid sequence set forth as SEQ ID NO:42.

10. The variant AAV capsid according to any one of claims 1-9, wherein the capsid protein confers to an infectious recombinant AAV (rAAV) virion an increased infectivity of a retinal cell compared to the infectivity of the retinal cell by an AAV virion comprising the corresponding parental AAV capsid protein.

11. An isolated nucleic acid comprising a nucleotide sequence that encodes a variant AAV capsid protein according to any one of claims 1-10.

12. An infectious rAAV virion comprising a variant AAV capsid protein according to any one of claims 1-10.

13. The rAAV virion according to claim 12, further comprising a heterologous nucleic acid encoding a gene product.

14. The rAAV virion according to claim 13, wherein the gene product is a protein or short interfering RNA.

15. The rAAV virion according to claim 14, wherein the variant AAV capsid protein comprises an amino acid sequence having at least 90%, at least 95%, or at least 99% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO:42 and wherein the heterologous nucleic acid comprises a nucleotide sequence encoding a Rab escort protein-1 protein.

16. The rAAV virion according to claim 15, wherein the variant AAV capsid consists of the amino acid sequence set forth as SEQ ID NO:42 and wherein the nucleotide sequence encoding the Rab escort protein-1 protein is operably linked to a CAG promoter.

17. The rAAV virion according to claim 14, wherein the variant AAV capsid protein comprises an amino acid sequence having at least 90%, at least 95%, or at least 99% amino acid

sequence identity to the amino acid sequence set forth in SEQ ID NO:42 and wherein the heterologous nucleic acid comprises a nucleotide sequence encoding a retinitis pigmentosa GTPase regulator protein.

18. The rAAV virion according to claim 17, wherein the variant AAV capsid protein comprises or consists of the amino acid sequence set forth as SEQ ID NO:42.

19. The rAAV virion according to claim 18, wherein the nucleotide sequence encoding the retinitis pigmentosa GTPase regulator protein is operably linked to a rhodopsin kinase promoter.

20. The rAAV virion according to claim 14, wherein the variant AAV capsid protein comprises an amino acid sequence having at least 90%, at least 95%, or at least 99% amino acid identity to the amino acid sequence set forth in SEQ ID NO:42 and wherein the heterologous nucleic acid comprises a nucleotide sequence encoding a polypeptide that inhibits the activity of vascular endothelial growth factor (VEGF).

21. The rAAV virion according to claim 20, wherein the variant AAV capsid protein comprises or consists of the amino acid sequence set forth as SEQ ID NO:42.

22. The rAAV virion according to claim 21, wherein the polypeptide is a fusion protein or antibody.

23. A pharmaceutical composition comprising an rAAV virion according to any one of claims 14 to 22 and a pharmaceutically acceptable excipient.

24. An in vitro method for delivering a heterologous nucleic acid to a retinal cell comprising contacting the retinal cell with an rAAV virion according to any one of claims 14 to 22 or a pharmaceutical composition according to claim 23.

25. The method according to claim 24, wherein the retinal cell is selected from the group consisting of retinal ganglion cells, amacrine cells, horizontal cells, bipolar cells, photoreceptor cells, Müller glial cells, microglial cells and retinal pigment epithelium.

26. The use of an rAAV virion according to claim 15 or 16 or a pharmaceutical composition comprising an rAAV virion according to claim 15 or 16, for the manufacture of a medicament for the treatment of choroideremia.

27. The use of an rAAV virion according to any one of claims 17 to 19 or a pharmaceutical composition comprising an rAAV virion according to any one of claims 17 to 19 for the manufacture of a medicament for the treatment of X-linked retinitis pigmentosa.

28. The use of an rAAV virion according to any one of claims 20 to 22 or a pharmaceutical composition comprising an rAAV virion according to any one of claims 20 to 22, for the manufacture of a medicament for the treatment of wet age-related macular degeneration, diabetic retinopathy, diabetic macular edema, or choroidal neovascularization.

29. The use of an rAAV virion or pharmaceutical composition according to any one of claims 26, 27, and 28, wherein the rAAV virion or pharmaceutical composition is for administration by intravitreal injection.