Claims

What is claimed is:

1. A recombinant adeno-associated virus (rAAV) virion comprising:

a) a variant AAV capsid protein, wherein the variant AAV capsid protein comprises a peptide insertion relative to a corresponding parental AAV capsid protein, wherein the insertion site is located between two adjacent amino acids at a position between amino acids 570 and 611 of VP1 of AAV2 or the corresponding position in the capsid protein of another AAV serotype, wherein the peptide insertion is a peptide of Formula I, Formula IIa, Formula IIb, Formula III, or Formula IV, and wherein the AAV variant capsid protein confers 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, wherein:

i) Formula I is $Y_1Y_2X_1X_2X_3X_4X_5X_6X_7Y_3Y_4$, wherein:

each of Y1 –Y4, if present, is independently selected from Ala, Leu, Gly, Ser, and Thr;

X1, if present, is selected from Leu, Asn, and Lys;

X2 is selected from Gly, Glu, Ala, and Asp;

X3 is selected from Glu, Thr, Gly, and Pro;

X4 is selected from Thr, Ile, Gln, and Lys;

X5 is selected from Thr and Ala;

X6 is selected from Arg, Asn, and Thr; and

X7, if present, is selected from Pro and Asn;

ii) Formula IIa is $Y_1Y_2X_1X_2X_3X_4X_5X_6X_7Y_3Y_4$, wherein:

each of Y1 –Y4, if present, is independently selected from Ala, Leu, Gly, Ser, and Thr;

each of X1 – X4 is any amino acid;

X5 is Thr;

X6 is Arg; and

X7 is Pro;

iii) Formula IIb is $Y_1Y_2X_1X_2X_3X_4X_5X_6X_7Y_3Y_4$, wherein:

each of Y1 –Y4, if present, is independently selected from Ala, Leu, Gly, Ser, and Thr;

X1, if present, is selected from Leu and Asn;

X2, if present, is selected from Gly and Glu;

X3 is selected from Glu and Thr;

X4 is selected from Thr and Ile;

X5 is Thr;

X6 is Arg; and

X7 is Pro;

iv) Formula III is $Y_1Y_2X_1X_2X_3X_4X_5X_6X_7Y_3Y_4$, wherein:

each of Y1 –Y4, if present, is independently selected from Ala, Leu, Gly, Ser, and Thr;

X1, if present, is Lys;

X2 is selected from Ala and Asp;

X3 is selected from Gly and Pro;

X4 is selected from Gln and Lys;

X5 is selected from Thr and Ala;

X6 is selected from Asn and Thr; and

X7, if present, is Asn; and

v) Formula IV is $Y_1Y_2X_1X_2X_3X_4X_5X_6X_7Y_3Y_4$, wherein:

each of Y1 –Y4, if present, is independently selected from Ala, Leu, Gly, Ser, and Thr;

X1, if present, is selected from Leu, Asn, Arg, Ala, Ser, and Lys;

X2 is selected from Gly, Glu, Ala, Val, Thr, and Asp;

X3 is selected from Glu, Thr, Gly, Asp, or Pro;

X4 is selected from Thr, Ile, Gly, Lys, Asp, and Gln;

X5 is selected from Thr, Ser, Val, and Ala;

X6 is selected from Arg, Val, Lys, Pro, Thr, and Asn; and

X7 is selected from Pro, Gly, Phe, Asn, and Arg; and

b) a heterologous nucleic acid comprising a nucleotide sequence encoding a gene product.

2. The rAAV virion of claim 1, wherein the insertion comprises an amino acid sequence selected from LGETTRP (SEQ ID NO:13), NETITRP (SEQ ID NO:14), KAGQANN (SEQ ID NO:15), KDPKTTN (SEQ ID NO:16), KDTDTTR (SEQ ID NO:57), RAGGSVG (SEQ ID NO:58), AVDTTKF (SEQ ID NO:59), and STGKVPN (SEQ ID NO:60).

3. The rAAV virion of claim 1, wherein the retinal cell is a photoreceptor, a retinal ganglion cell, a Müller cell, a bipolar cell, an amacrine cell, a horizontal cell, or a retinal pigmented epithelium cell.

4. The rAAV virion of claim 1, wherein the insertion site is between amino acids 587 and 588 of the AAV2 capsid protein or the corresponding position in the capsid protein of another AAV serotype.

5. The rAAV virion of claim 1, wherein the insertion site is between amino acids 587 and 588 of the AAV2 capsid protein or the corresponding position in the capsid protein of another AAV serotype.

6. The rAAV virion of claim 5, wherein the insertion site is between amino acids 587 and 588 of AAV2.

7. The rAAV virion of claim 6, wherein the insertion comprises the amino acid sequence LGETTRP (SEQ ID NO:13).

8. The rAAV virion of claim 1, wherein the rAAV virion exhibits at least 10-fold 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.

9. The rAAV virion of claim 1, wherein the rAAV virion exhibits at least 50-fold 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.

10. The rAAV virion of claim 1, wherein gene product is an interfering RNA or an aptamer.

11. The rAAV virion of claim 1, wherein the gene product is a polypeptide.

12. The rAAV virion of claim 11, wherein the polypeptide is a neuroprotective polypeptide, an anti-angiogenic polypeptide, or a polypeptide that enhances function of a retinal cell.

13. A pharmaceutical composition comprising:

a) a recombinant adeno-associated virus virion of any one of claims 1-12; and

b) a pharmaceutically acceptable excipient.

14. Use of a recombinant adeno-associated virus (rAAV) virion according to any one of claims 1-12 in the manufacture of a medicament for delivering a gene product to a retinal cell in an individual.

15. Use of claim 14, wherein the gene product is a polypeptide.

16. Use of claim 14, wherein the gene product is a short interfering RNA or an aptamer.

17. Use of claim 15, wherein the polypeptide is a neuroprotective factor, an anti-angiogenic polypeptide, an anti-apoptotic factor, or a polypeptide that enhances function of a retinal cell.

18. Use of claim 15, wherein the polypeptide is glial derived neurotrophic factor, fibroblast growth factor 2, neurturin, ciliary neurotrophic factor, nerve growth factor, brain derived neurotrophic factor, epidermal growth factor, rhodopsin, X-linked inhibitor of apoptosis, retinoschisin, RPE65, retinitis pigmentosa GTPase-interacting protein-1, peripherin, peripherin-2, a rhodopsin, or Sonic hedgehog.

19. Use of a recombinant adeno-associated virus (rAAV) virion according to any one of claims 1-12 in the manufacture of a medicament for treating a retinal disease in an individual.

20. Use of claim 19, wherein the medicament is for intraocular injection.

21. Use of claim 19, wherein the medicament is for intravitreal injection.

22. Use of claim 19, wherein the ocular disease is glaucoma, retinitis pigmentosa, macular degeneration, retinoschisis, Leber's Congenital Amaurosis, diabetic retinopathy, achromotopsia, or color blindness.

23. An isolated nucleic acid comprising a nucleotide sequence that encodes a variant adeno-associated virus (AAV) capsid protein, wherein the variant AAV capsid protein comprises a peptide insertion relative to a corresponding parental AAV capsid protein,

wherein the insertion site is located between two adjacent amino acids at a position between amino acids 570 and 611 of VP1 of AAV2 or the corresponding position in the capsid protein of another AAV serotype,

wherein the peptide insertion is a peptide of Formula I, Formula IIa, Formula IIb, Formula III, or Formula IV, wherein:

i) Formula I is $Y_1Y_2X_1X_2X_3X_4X_5X_6X_7Y_3Y_4$, wherein:

each of Y1 –Y4, if present, is independently selected from Ala, Leu, Gly, Ser, and Thr;

X1, if present, is selected from Leu, Asn, and Lys;

X2 is selected from Gly, Glu, Ala, and Asp;

X3 is selected from Glu, Thr, Gly, and Pro;

X4 is selected from Thr, Ile, Gln, and Lys;

X5 is selected from Thr and Ala;

X6 is selected from Arg, Asn, and Thr; and

X7, if present, is selected from Pro and Asn;

ii) Formula IIa is $Y_1Y_2X_1X_2X_3X_4X_5X_6X_7Y_3Y_4$, wherein:

each of Y1 –Y4, if present, is independently selected from Ala, Leu, Gly, Ser, and Thr;

each of X1 – X4 is any amino acid;

X5 is Thr;

X6 is Arg; and

X7 is Pro;

iii) Formula IIb is $Y_1Y_2X_1X_2X_3X_4X_5X_6X_7Y_3Y_4$, wherein:

each of Y1 –Y4, if present, is independently selected from Ala, Leu, Gly, Ser, and Thr;

X1, if present, is selected from Leu and Asn;

X2, if present, is selected from Gly and Glu;

X3 is selected from Glu and Thr;

X4 is selected from Thr and Ile;

X5 is Thr;

X6 is Arg; and

X7 is Pro;

iv) Formula III is $Y_1Y_2X_1X_2X_3X_4X_5X_6X_7Y_3Y_4$, wherein:

each of Y1 –Y4, if present, is independently selected from Ala, Leu, Gly, Ser, and Thr;

X1, if present, is Lys;

X2 is selected from Ala and Asp;

X3 is selected from Gly and Pro;

X4 is selected from Gln and Lys;

X5 is selected from Thr and Ala;

X6 is selected from Asn and Thr; and

X7, if present, is Asn; and

v) Formula IV is $Y_1Y_2X_1X_2X_3X_4X_5X_6X_7Y_3Y_4$, wherein:

each of Y1 –Y4, if present, is independently selected from Ala, Leu, Gly, Ser, and Thr;

X1, if present, is selected from Leu, Asn, Arg, Ala, Ser, and Lys;

X2 is selected from Gly, Glu, Ala, Val, Thr, and Asp;

X3 is selected from Glu, Thr, Gly, Asp, or Pro;

X4 is selected from Thr, Ile, Gly, Lys, Asp, and Gln;

X5 is selected from Thr, Ser, Val, and Ala;

X6 is selected from Arg, Val, Lys, Pro, Thr, and Asn; and

X7 is selected from Pro, Gly, Phe, Asn, and Arg,

and wherein the AAV variant capsid protein, when present in an AAV virion, provides for increased infectivity of the AAV virion of a retinal cell.

24. The isolated nucleic acid of claim 23, wherein the insertion site is between amino acids 587 and 588 of the AAV2 capsid protein or the corresponding position in the capsid protein of another AAV serotype.

25. The isolated nucleic acid of claim 24, wherein the insertion comprises an amino acid sequence selected from LGETTRP (SEQ ID NO:13), NETITRP (SEQ ID NO:14), KAGQANN (SEQ ID NO:15), KDPKTTN (SEQ ID NO:16), KDTDTTR (SEQ ID NO:57), RAGGSVG (SEQ ID NO:58), AVDTTKF (SEQ ID NO:59), and STGKVPN (SEQ ID NO:60).

26. An isolated, genetically modified host cell comprising the nucleic acid of any one of claims 23-25.

27. A variant adeno-associated virus (AAV) capsid protein, wherein the variant AAV capsid protein comprises a peptide insertion relative to a corresponding parental AAV capsid protein, wherein the insertion site is located between two adjacent amino acids at a position between amino acids 570 and 611 of VP1 of AAV2 or the corresponding position in the capsid protein of another AAV serotype, wherein the insertion is a peptide of Formula I, Formula IIa, Formula IIb, Formula III, or Formula IV, and wherein:

i) Formula I is $Y_1Y_2X_1X_2X_3X_4X_5X_6X_7Y_3Y_4$, wherein:

each of Y1 –Y4, if present, is independently selected from Ala, Leu, Gly, Ser, and Thr;

X1, if present, is selected from Leu, Asn, and Lys;

X2 is selected from Gly, Glu, Ala, and Asp;

X3 is selected from Glu, Thr, Gly, and Pro;

X4 is selected from Thr, Ile, Gln, and Lys;

X5 is selected from Thr and Ala;

X6 is selected from Arg, Asn, and Thr; and

X7, if present, is selected from Pro and Asn;

ii) Formula IIa is $Y_1Y_2X_1X_2X_3X_4X_5X_6X_7Y_3Y_4$, wherein:

each of Y1 –Y4, if present, is independently selected from Ala, Leu, Gly, Ser, and Thr;

each of X1 – X4 is any amino acid;

X5 is Thr;

X6 is Arg; and

X7 is Pro;

iii) Formula IIb is $Y_1Y_2X_1X_2X_3X_4X_5X_6X_7Y_3Y_4$, wherein:

each of Y1 –Y4, if present, is independently selected from Ala, Leu, Gly, Ser, and Thr;

X1, if present, is selected from Leu and Asn;

X2, if present, is selected from Gly and Glu;

X3 is selected from Glu and Thr;

X4 is selected from Thr and Ile;

X5 is Thr;

X6 is Arg; and

X7 is Pro;

iv) Formula III is $Y_1Y_2X_1X_2X_3X_4X_5X_6X_7Y_3Y_4$, wherein:

each of Y1 –Y4, if present, is independently selected from Ala, Leu, Gly, Ser, and Thr;

X1, if present, is Lys;

X2 is selected from Ala and Asp;

X3 is selected from Gly and Pro;

X4 is selected from Gln and Lys;

X5 is selected from Thr and Ala;

X6 is selected from Asn and Thr; and

X7, if present, is Asn; and

v) Formula IV is $Y_1Y_2X_1X_2X_3X_4X_5X_6X_7Y_3Y_4$, wherein:

each of Y1 –Y4, if present, is independently selected from Ala, Leu, Gly, Ser, and Thr;

X1, if present, is selected from Leu, Asn, Arg, Ala, Ser, and Lys;

X2 is selected from Gly, Glu, Ala, Val, Thr, and Asp;

X3 is selected from Glu, Thr, Gly, Asp, or Pro;

X4 is selected from Thr, Ile, Gly, Lys, Asp, and Gln;

X5 is selected from Thr, Ser, Val, and Ala;

X6 is selected from Arg, Val, Lys, Pro, Thr, and Asn; and

X7 is selected from Pro, Gly, Phe, Asn, and Arg.

28. The variant AAV capsid protein of claim 27, wherein the insertion comprises an amino acid sequence selected from LGETTRP (SEQ ID NO:13), NETITRP (SEQ ID NO:14), KAGQANN (SEQ ID NO:15), KDPKTTN (SEQ ID NO:16), KDTDTTR (SEQ ID NO:57), RAGGSVG (SEQ ID NO:58), AVDTTKF (SEQ ID NO:59), and STGKVPN (SEQ ID NO:60).

29. The variant AAV capsid protein of claim 27, wherein the insertion site is between amino acids 587 and 588 of the AAV2 capsid protein or the corresponding position in the capsid protein of another AAV serotype.

30. A nucleic acid comprising a nucleotide sequence encoding the variant AAV capsid protein according to any one of claims 27-29.

Claims

What is claimed is:

1. A recombinant adeno-associated virus (rAAV) virion comprising:

a) a variant AAV capsid protein, wherein the variant AAV capsid protein comprises a peptide insertion relative to a corresponding parental AAV capsid protein, wherein the insertion site is located between two adjacent amino acids at a position between amino acids 570 and 611 of VP1 of AAV2 or the corresponding position in the capsid protein of another AAV serotype, wherein the peptide insertion is a peptide of Formula I, Formula IIa, Formula IIb, Formula III, or Formula IV, and wherein the AAV variant capsid protein confers 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; and

b) a heterologous nucleic acid comprising a nucleotide sequence encoding a gene product.

2. The rAAV virion of claim 1, wherein:

i) Formula I is $Y_1Y_2X_1X_2X_3X_4X_5X_6X_7Y_3Y_4$, wherein:

each of Y1 –Y4, if present, is independently selected from Ala, Leu, Gly, Ser, and Thr;

X1, if present, is selected from Leu, Asn, and Lys;

X2 is selected from Gly, Glu, Ala, and Asp;

X3 is selected from Glu, Thr, Gly, and Pro;

X4 is selected from Thr, Ile, Gln, and Lys;

X5 is selected from Thr and Ala;

X6 is selected from Arg, Asn, and Thr; and

X7, if present, is selected from Pro and Asn;

ii) Formula IIa is $Y_1Y_2X_1X_2X_3X_4X_5X_6X_7Y_3Y_4$, wherein:

each of Y1 –Y4, if present, is independently selected from Ala, Leu, Gly, Ser, and Thr;

each of X1 – X4 is any amino acid;

X5 is Thr;

X6 is Arg; and

X7 is Pro;

iii) Formula IIb is $Y_1Y_2X_1X_2X_3X_4X_5X_6X_7Y_3Y_4$, wherein:

each of Y1 –Y4, if present, is independently selected from Ala, Leu, Gly, Ser, and Thr;

X1, if present, is selected from Leu and Asn;

X2, if present, is selected from Gly and Glu;

X3 is selected from Glu and Thr;

X4 is selected from Thr and Ile;

X5 is Thr;

X6 is Arg; and

X7 is Pro;

iv) Formula III is $Y_1Y_2X_1X_2X_3X_4X_5X_6X_7Y_3Y_4$, wherein:

each of Y1 –Y4, if present, is independently selected from Ala, Leu, Gly, Ser, and Thr;

X1, if present, is Lys;

X2 is selected from Ala and Asp;

X3 is selected from Gly and Pro;

X4 is selected from Gln and Lys;

X5 is selected from Thr and Ala;

X6 is selected from Asn and Thr; and

X7, if present, is Asn; and

v) Formula IV is $Y_1Y_2X_1X_2X_3X_4X_5X_6X_7Y_3Y_4$, wherein:

each of Y1 –Y4, if present, is independently selected from Ala, Leu, Gly, Ser, and Thr;

X1, if present, is selected from Leu, Asn, Arg, Ala, Ser, and Lys;

X2 is selected from Gly, Glu, Ala, Val, Thr, and Asp;

X3 is selected from Glu, Thr, Gly, Asp, or Pro;

X4 is selected from Thr, Ile, Gly, Lys, Asp, and Gln;

X5 is selected from Thr, Ser, Val, and Ala;

X6 is selected from Arg, Val, Lys, Pro, Thr, and Asn; and

X7 is selected from Pro, Gly, Phe, Asn, and Arg.

3. The rAAV virion of claim 2, wherein the insertion comprises an amino acid sequence selected from LGETTRP (SEQ ID NO:13), NETITRP (SEQ ID NO:14), KAGQANN (SEQ ID NO:15), KDPKTTN (SEQ ID NO:16), KDTDTTR (SEQ ID NO:57), RAGGSVG (SEQ ID NO:58), AVDTTKF (SEQ ID NO:59), and STGKVPN (SEQ ID NO:60).

4. The rAAV virion of claim 1, wherein the retinal cell is a photoreceptor, a retinal ganglion cell, a Müller cell, a bipolar cell, an amacrine cell, a horizontal cell, or a retinal pigmented epithelium cell.

5. The rAAV virion of claim 1, wherein the insertion site is between amino acids 587 and 588 of the AAV2 capsid protein or the corresponding position in the capsid protein of another AAV serotype.

6. The rAAV virion of claim 2, wherein the insertion site is between amino acids 587 and 588 of the AAV2 capsid protein or the corresponding position in the capsid protein of another AAV serotype.

7. The rAAV virion of claim 6, wherein the insertion site is between amino acids 587 and 588 of AAV2.

8. The rAAV virion of claim 7, wherein the insertion comprises the amino acid sequence LGETTRP (SEQ ID NO:13).

9. The rAAV virion of claim 1, wherein the rAAV virion exhibits at least 10-fold 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.

10. The rAAV virion of claim 1, wherein the rAAV virion exhibits at least 50-fold 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. The rAAV virion of claim 1, wherein gene product is an interfering RNA or an aptamer.

12. The rAAV virion of claim 1, wherein the gene product is a polypeptide.

13. The rAAV virion of claim 12, wherein the polypeptide is a neuroprotective polypeptide, an anti-angiogenic polypeptide, or a polypeptide that enhances function of a retinal cell.

14. A pharmaceutical composition comprising:

a) a recombinant adeno-associated virus virion of any one of claims 1-13; and

b) a pharmaceutically acceptable excipient.

15. Use of a recombinant adeno-associated virus (rAAV) virion according to any one of claims 1-13 in the manufacture of a medicament for delivering a gene product to a retinal cell in an individual.

16. The use of claim 15, wherein the gene product is a polypeptide.

17. The use of claim 15, wherein the gene product is a short interfering RNA or an aptamer.

18. The use of claim 16, wherein the polypeptide is a neuroprotective factor, an anti-angiogenic polypeptide, an anti-apoptotic factor, or a polypeptide that enhances function of a retinal cell.

19. The use of claim 16, wherein the polypeptide is glial derived neurotrophic factor, fibroblast growth factor 2, neurturin, ciliary neurotrophic factor, nerve growth factor, brain derived neurotrophic factor, epidermal growth factor, rhodopsin, X-linked inhibitor of apoptosis, retinoschisin, RPE65, retinitis pigmentosa GTPase-interacting protein-1, peripherin, peripherin-2, a rhodopsin, or Sonic hedgehog.

20. Use of a recombinant adeno-associated virus (rAAV) virion according to any one of claims 1-13 in the manufacture of a medicament for treating an occular disease in an individual.

21. The use of claim 20, wherein said rAAV virion is to be administered by intraocular injection.

22. The use of claim 20, wherein said rAAV virion is to be administered by intravitreal injection.

23. The use of claim 20, wherein the ocular disease is glaucoma, retinitis pigmentosa, macular degeneration, retinoschisis, Leber's Congenital Amaurosis, diabetic retinopathy, achromotopsia, or color blindness.

24. An isolated nucleic acid comprising a nucleotide sequence that encodes a variant adeno-associated virus (AAV) capsid protein, wherein the variant AAV capsid protein comprises a peptide insertion relative to a corresponding parental AAV capsid protein, wherein the insertion site is located between two adjacent amino acids at a position between amino acids 570 and 611 of VP1 of AAV2 or the corresponding position in the capsid protein of another AAV serotype, wherein the peptide insertion is a peptide of Formula I, Formula IIa, Formula IIb, Formula III, or Formula IV, and wherein the AAV variant capsid protein, when present in an AAV virion, provides for increased infectivity of the AAV virion of a retinal cell.

25. The isolated nucleic acid of claim 24, wherein:

i) Formula I is $Y_1Y_2X_1X_2X_3X_4X_5X_6X_7Y_3Y_4$, wherein:

each of Y1 –Y4, if present, is independently selected from Ala, Leu, Gly, Ser, and Thr;

X1, if present, is selected from Leu, Asn, and Lys;

X2 is selected from Gly, Glu, Ala, and Asp;

X3 is selected from Glu, Thr, Gly, and Pro;

X4 is selected from Thr, Ile, Gln, and Lys;

X5 is selected from Thr and Ala;

X6 is selected from Arg, Asn, and Thr; and

X7, if present, is selected from Pro and Asn;

ii) Formula IIa is $Y_1Y_2X_1X_2X_3X_4X_5X_6X_7Y_3Y_4$, wherein:

each of Y1 –Y4, if present, is independently selected from Ala, Leu, Gly, Ser, and Thr;

each of X1 – X4 is any amino acid;

X5 is Thr;

X6 is Arg; and

X7 is Pro;

iii) Formula IIb is $Y_1Y_2X_1X_2X_3X_4X_5X_6X_7Y_3Y_4$, wherein:

each of Y1 –Y4, if present, is independently selected from Ala, Leu, Gly, Ser, and Thr;

X1, if present, is selected from Leu and Asn;

X2, if present, is selected from Gly and Glu;

X3 is selected from Glu and Thr;

X4 is selected from Thr and Ile;

X5 is Thr;

X6 is Arg; and

X7 is Pro;

iv) Formula III is $Y_1Y_2X_1X_2X_3X_4X_5X_6X_7Y_3Y_4$, wherein:

each of Y1 –Y4, if present, is independently selected from Ala, Leu, Gly, Ser, and Thr;

X1, if present, is Lys;

X2 is selected from Ala and Asp;

X3 is selected from Gly and Pro;

X4 is selected from Gln and Lys;

X5 is selected from Thr and Ala;

X6 is selected from Asn and Thr; and

X7, if present, is Asn; and

v) Formula IV is $Y_1Y_2X_1X_2X_3X_4X_5X_6X_7Y_3Y_4$, wherein:

each of Y1 –Y4, if present, is independently selected from Ala, Leu, Gly, Ser, and Thr;

X1, if present, is selected from Leu, Asn, Arg, Ala, Ser, and Lys;

X2 is selected from Gly, Glu, Ala, Val, Thr, and Asp;

X3 is selected from Glu, Thr, Gly, Asp, or Pro;

X4 is selected from Thr, Ile, Gly, Lys, Asp, and Gln;

X5 is selected from Thr, Ser, Val, and Ala;

X6 is selected from Arg, Val, Lys, Pro, Thr, and Asn; and

X7 is selected from Pro, Gly, Phe, Asn, and Arg.

26. The isolated nucleic acid of claim 25, wherein the insertion site is between amino acids 587 and 588 of the AAV2 capsid protein or the corresponding position in the capsid protein of another AAV serotype.

27. The isolated nucleic acid of claim 26, wherein the insertion comprises an amino acid sequence selected from LGETTRP (SEQ ID NO:13), NETITRP (SEQ ID NO:14), KAGQANN (SEQ ID NO:15), KDPKTTN (SEQ ID NO:16), KDTDTTR (SEQ ID NO:57), RAGGSVG (SEQ ID NO:58), AVDTTKF (SEQ ID NO:59), and STGKVPN (SEQ ID NO:60).

28. An isolated, genetically modified host cell comprising the nucleic acid of any one of claims 24-27.

29. A variant adeno-associated virus (AAV) capsid protein, wherein the variant AAV capsid protein comprises a peptide insertion relative to a corresponding parental AAV capsid protein, wherein the insertion site is located between two adjacent amino acids at a position between amino acids 570 and 611 of VP1 of AAV2 or the corresponding position in the capsid protein of another AAV serotype, wherein the insertion is a peptide of Formula I, Formula IIa, Formula IIb, Formula III, or Formula IV.

30. The variant AAV capsid protein of claim 29, wherein:

i) Formula I is $Y_1Y_2X_1X_2X_3X_4X_5X_6X_7Y_3Y_4$, wherein:

each of Y1 –Y4, if present, is independently selected from Ala, Leu, Gly, Ser, and Thr;

X1, if present, is selected from Leu, Asn, and Lys;

X2 is selected from Gly, Glu, Ala, and Asp;

X3 is selected from Glu, Thr, Gly, and Pro;

X4 is selected from Thr, Ile, Gln, and Lys;

X5 is selected from Thr and Ala;

X6 is selected from Arg, Asn, and Thr; and

X7, if present, is selected from Pro and Asn;

ii) Formula IIa is $Y_1Y_2X_1X_2X_3X_4X_5X_6X_7Y_3Y_4$, wherein:

each of Y1 –Y4, if present, is independently selected from Ala, Leu, Gly, Ser, and Thr;

each of X1 – X4 is any amino acid;

X5 is Thr;

X6 is Arg; and

X7 is Pro;

iii) Formula IIb is $Y_1Y_2X_1X_2X_3X_4X_5X_6X_7Y_3Y_4$, wherein:

each of Y1 –Y4, if present, is independently selected from Ala, Leu, Gly, Ser, and Thr;

X1, if present, is selected from Leu and Asn;

X2, if present, is selected from Gly and Glu;

X3 is selected from Glu and Thr;

X4 is selected from Thr and Ile;

X5 is Thr;

X6 is Arg; and

X7 is Pro;

iv) Formula III is $Y_1Y_2X_1X_2X_3X_4X_5X_6X_7Y_3Y_4$, wherein:

each of Y1 –Y4, if present, is independently selected from Ala, Leu, Gly, Ser, and Thr;

X1, if present, is Lys;

X2 is selected from Ala and Asp;

X3 is selected from Gly and Pro;

X4 is selected from Gln and Lys;

X5 is selected from Thr and Ala;

X6 is selected from Asn and Thr; and

X7, if present, is Asn; and

v) Formula IV is $Y_1Y_2X_1X_2X_3X_4X_5X_6X_7Y_3Y_4$, wherein:

each of Y1 –Y4, if present, is independently selected from Ala, Leu, Gly, Ser, and Thr;

X1, if present, is selected from Leu, Asn, Arg, Ala, Ser, and Lys;

X2 is selected from Gly, Glu, Ala, Val, Thr, and Asp;

X3 is selected from Glu, Thr, Gly, Asp, or Pro;

X4 is selected from Thr, Ile, Gly, Lys, Asp, and Gln;

X5 is selected from Thr, Ser, Val, and Ala;

X6 is selected from Arg, Val, Lys, Pro, Thr, and Asn; and

X7 is selected from Pro, Gly, Phe, Asn, and Arg.

31. The variant AAV capsid protein of claim 30, wherein the insertion comprises an amino acid sequence selected from LGETTRP (SEQ ID NO:13), NETITRP (SEQ ID NO:14), KAGQANN (SEQ ID NO:15), KDPKTTN (SEQ ID NO:16), KDTDTTR (SEQ ID NO:57), RAGGSVG (SEQ ID NO:58), AVDTTKF (SEQ ID NO:59), and STGKVPN (SEQ ID NO:60).

32. The variant AAV capsid protein of claim 29, wherein the insertion site is between amino acids 587 and 588 of the AAV2 capsid protein or the corresponding position in the capsid protein of another AAV serotype.

33. A nucleic acid comprising a nucleotide sequence encoding the variant AAV capsid protein according to any one of claims 29-32.