

CLAIMS

WHAT IS CLAIMED IS:

1. ~~An modified adeno-associated virus (AAV) capsid that comprises an exogenous polypeptide sequence in a VP domain of the AAV capsid as compared to an otherwise comparable unmodified AAV capsid, the exogenous polypeptide sequence comprising a sequence of formula 1 comprising a polypeptide sequence of:~~

~~(a) L-A-L-G-X3-X1-X1-X4 (SEQ ID NO: 94);~~

~~(b) L-K-L-G-X3-X1-X1-X4 (SEQ ID NO: 95); or~~

~~(c) V-K-L-G-X3-X1-X1-X4 (SEQ ID NO: 96), wherein:
X0-X1-X2-X1-X3-X1-X1-X4-X5 (SEQ ID NO: 93)~~

~~wherein X0 is Valine (V), Isoleucine (I), Leucine (L), Phenylalanine (F), Tryptophan (W), Tyrosine (Y) or Methionine (M);~~

~~wherein X1 is Alanine (A), Asparagine (N), Glutamine (Q), Serine (S), Threonine (T), Glutamic Acid (E), Aspartic Acid (D), Lysine (K), Arginine (R), or Histidine (H);~~

~~wherein X2 is V, I, L, or M;~~

~~wherein X3 is E, S, or Q;~~ and

~~wherein X4 is K, R, E, or A, and~~

~~optionally wherein the polypeptide sequence is in a VP domain of the AAV capsid formula 1 further comprises X5 being Proline (P) or R.~~

~~2. The modified AAV capsid of claim 1, wherein formula 1 comprises the X₅, and wherein the X₅ is the Proline (P) or R.~~

~~3. The modified AAV capsid of any one of claims 1-2, wherein the capsid is of serotype AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12, AAV13, and any combination thereof.~~

~~4. The modified AAV capsid of claim 3, wherein the capsid comprises AAV2.~~

~~5. The modified AAV capsid of claim 3, wherein the capsid comprises at least two serotypes.~~

~~6. The modified capsid of claim 5, wherein the at least two serotypes are selected from AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV8, AAV9, AAV11, AAV12, and AAV13.~~

~~7. The modified AAV capsid of any one of claims 1-6, wherein formula 1 comprises: L-A-L-G-X3-X1-X1-X4 (SEQ ID NO: 94), L-K-L-G-X3-X1-X1-X4 (SEQ ID NO: 95), or V-K-L-G-X3-X1-X1-X4 (SEQ ID NO: 96).~~

8. ~~The modified AAV capsid of claim 6, wherein formula 1 comprises the V-K-L-G-X3-X1-X1-X4 (SEQ ID NO: 96), and wherein the V-K-L-G-X3-X1-X1-X4 (SEQ ID NO: 96) comprises: V-K-L-G-X3-X1-T-X4 (SEQ ID NO: 97) or V-K-L-G-X3-X1-X1-K (SEQ ID NO: 98).~~

9.2. The modified AAV capsid of claim 61, wherein the polypeptide sequence is (a), and wherein (a) is: formula 1 comprises the L-A-L-G-X3-X1-X1-X4 (SEQ ID NO: 94), and wherein the L-A-L-G-X3-X1-X1-X4 (SEQ ID NO: 94) comprises:

(i) L-A-L-G- X3-X1-T-X4 (SEQ ID NO: 99); or

(ii) L-A-L-G-X3-X1-S-X4 (SEQ ID NO: 100).

10.3. The modified AAV capsid of claim 29, wherein the polypeptide sequence is (i), and wherein (i) is: the L-A-L-G-X3-X1-T-X4 (SEQ ID NO: 99) comprises:

(aA) L-A-L-G- X3-X1-T-R (SEQ ID NO: 101);

(bB) L-A-L-G- X3-X1-T-K (SEQ ID NO: 102);

(cC) L-A-L-G- X3-X1-T-E (SEQ ID NO: 103); or

(dD) L-A-L-G- X3-X1-T-A (SEQ ID NO: 104).

11.4. The modified AAV capsid of claim 29, wherein the polypeptide sequence is (ii), and wherein (ii) is: L-A-L-G-X3-X1-S-X4 (SEQ ID NO: 100) comprises L-A-L-G- X3-X1-S-K (SEQ ID NO: 105).

12.5. The modified AAV capsid of claim 16, wherein the polypeptide sequence is (b), and wherein (b) is formula 1 comprises the L-K-L-G-X3-X1-X1-X4 (SEQ ID NO: 95), and wherein the L-K-L-G-X3-X1-X1-X4 (SEQ ID NO: 95) comprises

(i) L-K-L-G- X3-X1-T-X4 (SEQ ID NO: 106).

13.6. The modified AAV capsid of claim 512, wherein (i) is the L-K-L-G-X3-X1-T-X4 (SEQ ID NO: 106) comprises L-K-L-G- X3-X1-T-K (SEQ ID NO: 107).

7. The AAV capsid of claim 1, wherein the polypeptide sequence is (c), and wherein (c) is:

(i) V-K-L-G-X3-X1-T-X4 (SEQ ID NO: 97); or

(ii) V-K-L-G-X3-X1-X1-K (SEQ ID NO: 98).

8. The AAV capsid of any one of claims 1-7, wherein the serotype of the AAV capsid is selected from the group consisting of: AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12, and AAV13.

9. The AAV capsid of any one of claims 1-7, wherein the AAV capsid is a chimeric AAV capsid comprising an amino acid sequence from two or more serotypes selected from the group consisting of: AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12, and AAV13.

10. The AAV capsid of any one of claims 1-9, wherein the AAV capsid is of serotype AAV2 or is a chimeric AAV capsid comprising an amino acid sequence from serotype AAV2.

- ~~14. The modified AAV capsid of any one of claims 1-13, wherein formula 1 comprises a polypeptide sequence having at least 60%, 70%, 80%, 90%, 95%, 98%, or 99% identity with a sequence of Table 2.~~
- ~~15. The modified AAV capsid of claim 14, wherein formula 1 comprises a polypeptide sequence of Table 2.~~
- ~~16. The modified AAV capsid of any one of claims 1-15, wherein the VP domain of the AAV capsid is VP1.~~
- ~~17. The modified AAV capsid of any one of claims 1-15, wherein the VP domain of the AAV capsid is VP2.~~
- ~~18. The modified AAV capsid of any one of claims 1-15, wherein the VP domain of the AAV capsid is VP3.~~
- ~~19. The modified AAV capsid of any one of claims 1-18, wherein the AAV capsid further comprises a mutation.~~
- ~~20. The modified AAV capsid of claim 19, wherein the mutation is in a VP1 or VP2 region.~~
- ~~21. The modified AAV capsid of claim 19, wherein the mutation is in a VP1 or VP3 region.~~
- ~~22. The modified AAV capsid of claim 19, wherein the mutation is in a VP2 or VP3 region.~~
- ~~23. The modified AAV capsid of claim 19, wherein the mutation is in VP1, VP2, and VP3 regions.~~
- ~~24. The modified AAV capsid of any one of claims 19-23, wherein the mutation is a point mutation, missense mutation, nonsense mutation, deletion, duplication, frameshift, or repeat expansion.~~
- ~~25. The modified AAV capsid of claim 24, wherein the mutation is a point mutation.~~
- ~~26. The modified AAC capsid of claim 24, wherein the point mutation comprises a conservative mutation.~~
- ~~27. The modified AAV capsid of claim 26, wherein the conservative mutation is selected from the group consisting of: a nonpolar aliphatic amino acid to a nonpolar aliphatic amino acid, a polar amino acid to a polar amino acid, a positively charged amino acid to a positively charged amino acid, a negatively charged amino acid to a negatively charged amino acid, and an aromatic amino acid to an aromatic amino acid.~~
- ~~28. The modified AAV capsid of claim 27, wherein the point mutation comprises a change from a charged amino acid residue to a polar or non-polar amino acid residue.~~
- ~~29. The modified AAV capsid of claim 28, wherein the charged amino acid is positively charged.~~
- ~~30. The modified AAV capsid of claim 28, wherein the charged amino acid is negatively charged.~~

- ~~31. The modified AAV capsid of any one of claims 16-27, wherein the mutation is in a residue of SEQ ID NO: 1.~~
- ~~32. The modified AAV capsid of claim 31, wherein the mutation is in a residue selected from the group consisting of: 452, 453, 466, 467, 468, 471, 585, 586, 587, and 588 of SEQ ID NO: 1.~~
- ~~33. The modified AAV capsid of any one of claims 25-32, wherein the point mutation is R to A at position 585 or 588 of SEQ ID NO: 1.~~
- ~~34. The modified AAV capsid of any one of claim 1-33, wherein the AAV capsid further comprises at least a second exogenous polypeptide sequence in the VP1 domain of the AAV capsid.~~
- ~~35. The modified AAV capsid of claim 34, wherein the exogenous polypeptide sequence and the second exogenous polypeptide sequence are each independently in a loop of the AAV capsid.~~
- ~~36. The modified AAV capsid of claim 35, wherein the exogenous polypeptide sequence and the second exogenous polypeptide sequence are each independently in loop 3 and/or loop 4 of the VP1 domain of the AAV capsid.~~
- ~~37. An adeno-associated virus (AAV) vector that comprises: (a) a modified capsid that comprises an exogenous sequence in at least two loops of a VP domain as compared to an otherwise comparable AAV capsid sequence that lacks the exogenous sequence; and (b) a transgene, wherein said vector, upon contacting with a plurality of cells, has at least 3 fold increased expression of the transgene post the contacting in said plurality of cells as compared to contacting the plurality of cells with an otherwise comparable AAV vector that lacks (a).~~
- ~~38. The vector of claim 37, wherein the exogenous sequence encodes for a polypeptide that comprises formula 1: X0-X1-X2-X1-X3-X1-X1-X4 (SEQ ID NO: 108), wherein X0 is Valine (V), Isoleucine (I), Leucine (L), Phenylalanine (F), Tryptophan (W), Tyrosine (Y) or Methionine (M), wherein X1 is Alanine (A), Asparagine (N), Glutamine (Q), Serine (S), Threonine (T), Glutamic Acid (E), Aspartic Acid (D), Lysine (K), Arginine (R), or Histidine (H), wherein X2 is V, I, L, or M, wherein X3 is E, S, or Q, and wherein X4 is K, R, E, or A, optionally wherein formula 1 further comprises X5 being Proline (P) or R.~~
- ~~39. The vector of claim 38, wherein formula 1 comprises the X₅, and wherein the X₅ is Proline (P) or R.~~
- ~~40. The vector of any one of claims 37-39, wherein the capsid is of serotype AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12, AAV13, and any combination thereof.~~
- ~~41. The vector of claim 40, wherein the capsid comprises AAV2.~~
- ~~42. The vector of claim 40, wherein the capsid comprises at least two serotypes.~~

43. The vector of claim 42, wherein the at least two serotypes are AAV2 and AAV5, AAV2 and AAV6, AAV2 and AAV8, AAV2 and AAV9, AAV2 and AAV1, and AAV2 and AAV12.
44. The vector of any one of claims 38-43, wherein formula 1 comprises: ~~L-A-L-G-X3-X1-X1-X4 (SEQ ID NO: 94), L-K-L-G-X3-X1-X1-X4 (SEQ ID NO: 95), or V-K-L-G-X3-X1-X1-X4 (SEQ ID NO: 96).~~
45. The vector of claim 44, wherein formula 1 comprises the ~~V-K-L-G-X3-X1-X1-X4 (SEQ ID NO: 96), and wherein the V-K-L-G-X3-X1-X1-X4 (SEQ ID NO: 96) comprises: V-K-L-G-X3-X1-T-X4 (SEQ ID NO: 97) or V-K-L-G-X3-X1-X1-K (SEQ ID NO: 98).~~
46. The vector of claim 44, wherein formula 1 comprises the ~~L-A-L-G-X3-X1-X1-X4 (SEQ ID NO: 94), and wherein the L-A-L-G-X3-X1-X1-X4 (SEQ ID NO: 94) comprises: L-A-L-G-X3-X1-T-X4 (SEQ ID NO: 99) or L-A-L-G-X3-X1-S-X4 (SEQ ID NO: 100).~~
47. The vector of claim 46, wherein the ~~L-A-L-G-X3-X1-T-X4 (SEQ ID NO: 99) comprises:~~
- a) ~~L-A-L-G-X3-X1-T-R (SEQ ID NO: 101);~~
 - b) ~~L-A-L-G-X3-X1-T-K (SEQ ID NO: 102);~~
 - c) ~~L-A-L-G-X3-X1-T-E (SEQ ID NO: 103); or~~
 - d) ~~L-A-L-G-X3-X1-T-A (SEQ ID NO: 104).~~
48. The vector of claim 46, wherein the ~~L-A-L-G-X3-X1-S-X4 (SEQ ID NO: 100) comprises L-A-L-G-X3-X1-S-K (SEQ ID NO: 105).~~
49. The vector of claim 44, wherein formula 1 comprises the ~~L-K-L-G-X3-X1-X1-X4 (SEQ ID NO: 95), and wherein the L-K-L-G-X3-X1-X1-X4 (SEQ ID NO: 95) comprises L-K-L-G-X3-X1-T-X4 (SEQ ID NO: 106).~~
50. The vector of claim 49, wherein the ~~L-K-L-G-X3-X1-T-X4 (SEQ ID NO: 106) comprises L-K-L-G-X3-X1-T-K (SEQ ID NO: 107).~~
51. The vector of any one of claims 38-50, wherein formula 1 comprises a polypeptide sequence having at least 60%, 70%, 80%, 90%, 95%, 98%, or 99% identity with a sequence of Table 2.
52. The vector of claim 51, wherein formula 1 comprises a polypeptide sequence of Table 2.
53. The vector of any one of claims 37-52, wherein the VP is VP1.
54. The vector of any one of claims 37-52, wherein the VP is VP2.
55. The vector of any one of claims 37-52, wherein the VP is VP3.
56. The vector of any one of claims 37-53, wherein the at least two loops are loop 3 and loop 4 of the VP1 domain.
57. The vector of any one of claims 37-56, wherein the transgene encodes for an ocular therapeutic.
58. The vector of claim 57, wherein the ocular therapeutic is effective to: reduce at least a symptom of a retinal disease, treat a retinal disease, or eliminate a retinal disease.

~~59. The vector of claim 58, wherein the ocular therapeutic is selected from the group consisting of: an antibody or biologically active fragment thereof and a biologic.~~

~~60. The vector of claim 59, wherein the therapeutic is the biologic, and wherein the biologic comprises a polypeptide selected from: Lipoprotein Lipase, Retinoid Isomerohydrolase RPE65, or complement H.~~

~~61. The vector of claim 59, wherein the therapeutic is the antibody or biologically active fragment thereof, and wherein the antibody or biologically active fragment thereof is selected from: anti-VEGF, anti-VEGFL, anti-thrombospondin 1, anti-CD47, anti-TNF-alpha, anti-CD20, anti-CD52, and anti-CD11a, anti-complement 5, and anti-complement 3.~~

~~62. The vector of any one of claims 58-61, wherein the retinal disease is selected from the group consisting of: Achromatopsia, Age-related macular degeneration (AMD), wet Age-related macular degeneration (wAMD), Geographic atrophy (GA), Diabetic retinopathy (DR), Diabetic macular edema (DME), Glaucoma, Bardet-Biedl Syndrome, Best Disease, Choroideremia, Leber Congenital Amaurosis, Leber Hereditary Optic Neuropathy (LHON), Macular degeneration, Polypoidal choroidal vasculopathy (PCV), Retinitis pigmentosa, Refsum disease, Stargardt disease, Usher syndrome, X-linked retinoschisis (XLRS), Inherited Retinal Disease (IRD), Rod-cone dystrophy, Cone-rod dystrophy, Oguchi disease, Malattia Leventinese (Familial Dominant Drusen), Blue-cone monochromacy, retina vein occlusion (RVO), and Uveitic Macular Oedema (UMO).~~

~~63. The vector of claim 62, wherein the retinal disease is AMD.~~

~~64. The vector of claim 63, wherein the AMD is wet AMD.~~

~~65. The vector of claim 63, wherein the AMD is dry AMD.~~

~~66. The vector of any one of claims 37-65, wherein the vector further comprises a sequence encoding Rep.~~

~~67. The vector of claim 66, wherein the Rep is modified, and wherein the modification is in at least one of Rep-78, Rep-68, Rep-52 or Rep-40.~~

~~68. The vector of any one of claims 66-67, wherein the Rep is of a different AAV serotype than the capsid.~~

~~69. The vector of any one of claims 37-68, wherein the VP is VP1.~~

~~70. The vector of any one of claims 37-68, wherein the VP is VP2.~~

~~71. The vector of any one of claims 37-68, wherein the VP is VP3.~~

~~72. The vector of any one of claims 37-71, wherein the increased expression comprises at least a 5-fold, 10-fold, 20-fold, 50-fold, 100-fold, 200-fold, or 500-fold increase as compared to the contacting the plurality of cells with the otherwise comparable AAV vector that lacks (a).~~

- ~~73.11. The AAV capsid of any one of claims 1-10~~~~vector of any one of claims 37-72~~, wherein the ~~AAV~~~~modified~~ capsid comprises an amino acid sequence having at least about 60%, ~~70%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%~~ sequence identity to the amino acid sequence ~~that comprises of any one of~~ SEQ ID NOS: 28-~~SEQ ID NO: 47~~.
- ~~74. The vector of claim 73, wherein the vector comprises the modified capsid of SEQ ID NO: 34.~~
- ~~75. An engineered adeno-associated virus (AAV) virion that comprises the modified adeno-associated virus (AAV) capsid of any one of claims 1-36.~~
- ~~76. A composition that comprises a plurality of the AAV virion of claim 75.~~
- ~~77. An engineered cell generated by transfecting a cell with the vector of any one of claims 37-74, or the engineered virion of claims 75-76.~~
- ~~78. A plurality of adeno-associated viral (AAV) particles isolated from the engineered cell of claim 77.~~
- ~~79. A composition that comprises the adeno-associated viral particles of claim 78 in unit dosage form.~~
- ~~80. The composition of claim 79, wherein said composition is cryopreserved.~~
- ~~81. A container that comprises: a) the modified adeno-associated virus (AAV) capsid of any one of claims 1-36; b) the vector of any one of any one of claims 37-74; or c) the engineered virion of any one of claims 75-76.~~
- ~~82. The container of claim 81, wherein the container is a vial, syringe, or needle.~~
- ~~83. The container of any one of claims 81-82, wherein the container is configured for ocular delivery.~~
- ~~84. A pharmaceutical composition that comprises a) the modified adeno-associated virus (AAV) capsid of any one of claims 1-36; b) the vector of any one of any one of claims 37-74; or c) the engineered virion of any one of claims 75-76.~~
- ~~85. The pharmaceutical composition of claim 84, wherein the pharmaceutical composition is in unit dose form.~~
- ~~86. A method of making engineered cells comprising contacting a plurality of cells with the vector of any one of any one of claims 37-74 or the engineered virion of any one of claims 75-76.~~
- ~~87. A modified adeno-associated virus (AAV) capsid that comprises an exogenous sequence from Table 2.~~
- ~~88. The modified AAV capsid of claim 87, wherein the capsid is of a serotype selected from the group consisting of: AAV1, AAV2, AAV5, AAV8, AAV9, and combinations thereof.~~
- ~~89. A method of making a modified adeno-associated virus (AAV) capsid, the method comprising introducing a polynucleic acid that encodes a sequence of Table 2 into a sequence encoding an AAV capsid, thereby generating a modified AAV capsid.~~

90. The method of claim 89, wherein the AAV capsid is of a serotype selected from the group consisting of: AAV1, AAV2, AAV5, AAV8, AAV9, and combinations thereof.
91. A method for treating a disease or condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a pharmaceutical composition that comprises an adeno-associated virus (AAV) vector that comprises a modified capsid that comprises an exogenous polypeptide sequence in at least two loops of a VP domain as compared to an otherwise comparable AAV capsid sequence that lacks the exogenous polypeptide sequence, wherein the exogenous polypeptide sequence comprises a sequence of Table 2.
92. The method of claim 80, wherein the AAV vector further comprises a sequence that comprises a transgene.
93. A method for treating a disease or condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a pharmaceutical composition that comprises an adeno-associated virus (AAV) vector that comprises: (a) a modified capsid that comprises an exogenous sequence in at least two loops of a VP domain as compared to an otherwise comparable AAV capsid sequence that lacks the exogenous sequence; and (b) a transgene, wherein the vector, upon contacting with a plurality of cells, has at least 3 fold increased expression of the transgene post transfection in the plurality of cells as compared to contacting the plurality of cells with an otherwise comparable AAV vector that lacks (a).
94. The method of claim 82, wherein the increased expression comprises at least a 5-fold, 10-fold, 20-fold, 50-fold, 100-fold, 200-fold, or 500-fold increase as compared to the contacting the plurality of cells with the otherwise comparable AAV vector that lacks (a).
95. A method for treating a disease or condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a pharmaceutical composition that comprises an adeno-associated virus (AAV) vector that comprises a modified capsid that comprises an exogenous polypeptide sequence in a VP domain of the AAV capsid as compared to an otherwise comparable unmodified AAV capsid, the exogenous polypeptide sequence comprising a sequence of formula 1:
- X0-X1-X2-X1-X3-X1-X1-X4 (SEQ ID NO: 108),
- wherein X0 is Valine (V), Isoleucine (I), Leucine (L), Phenylalanine (F), Tryptophan (W), Tyrosine (Y) or Methionine (M),
- wherein X1 is Alanine (A), Asparagine (N), Glutamine (Q), Serine (S), Threonine (T), Glutamic Acid (E), Aspartic Acid (D), Lysine (K), Arginine (R), or Histidine (H),
- wherein X2 is V, I, L, or M,
- wherein X3 is E, S, or Q, and

wherein X4 is K, R, E, or A, optionally wherein formula 1 further comprises X5 being Proline (P) or R.

96. The method of claim 95, wherein formula 1 comprises the X₅, and wherein the X₅ is Proline (P) or R.

97. The method of any one of claims 95-96, wherein the capsid is of serotype AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12, AAV13, and any combination thereof.

98. The method of claim 97, wherein the capsid comprises AAV2.

99. The method of claim 97, wherein the capsid comprises at least two serotypes.

100. The modified capsid of claim 99, wherein the at least two serotypes are selected from AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV8, AAV9, AAV11, AAV12, and AAV13.

101. The method of any one of claims 95-100, wherein formula 1 comprises: L-A-L-G-X₃-X₁-X₁-X₄ (SEQ ID NO: 94), L-K-L-G-X₃-X₁-X₁-X₄ (SEQ ID NO: 95), or V-K-L-G-X₃-X₁-X₁-X₄ (SEQ ID NO: 96).

102. The method of claim 101, wherein formula 1 comprises the V-K-L-G-X₃-X₁-X₁-X₄ (SEQ ID NO: 96), and wherein the V-K-L-G-X₃-X₁-X₁-X₄ (SEQ ID NO: 96) comprises: V-K-L-G-X₃-X₁-T-X₄ (SEQ ID NO: 97) or V-K-L-G-X₃-X₁-X₁-K (SEQ ID NO: 98).

103. The method of claim 101, wherein formula 1 comprises the L-A-L-G-X₃-X₁-X₁-X₄ (SEQ ID NO: 94), and wherein the L-A-L-G-X₃-X₁-X₁-X₄ (SEQ ID NO: 94) comprises: L-A-L-G-X₃-X₁-T-X₄ (SEQ ID NO: 99) or L-A-L-G-X₃-X₁-S-X₄ (SEQ ID NO: 100).

104. The method of claim 103, wherein the L-A-L-G-X₃-X₁-T-X₄ (SEQ ID NO: 99) comprises:

- a) L-A-L-G-X₃-X₁-T-R (SEQ ID NO: 101);
- b) L-A-L-G-X₃-X₁-T-K (SEQ ID NO: 102);
- c) L-A-L-G-X₃-X₁-T-E (SEQ ID NO: 103); or
- d) L-A-L-G-X₃-X₁-T-A (SEQ ID NO: 104).

105. The method of claim 103, wherein the L-A-L-G-X₃-X₁-S-X₄ (SEQ ID NO: 100) comprises L-A-L-G-X₃-X₁-S-K (SEQ ID NO: 105).

106. The method of claim 101, wherein formula 1 comprises the L-K-L-G-X₃-X₁-X₁-X₄ (SEQ ID NO: 95), and wherein the L-K-L-G-X₃-X₁-X₁-X₄ (SEQ ID NO: 95) comprises L-K-L-G-X₃-X₁-T-X₄ (SEQ ID NO: 106).

107. The method of claim 106, wherein the L-K-L-G-X₃-X₁-T-X₄ (SEQ ID NO: 106) comprises L-K-L-G-X₃-X₁-T-K (SEQ ID NO: 107).

108. The method of any one of claims 95-107, wherein formula 1 comprises a polypeptide sequence having at least 60%, 70%, 80%, 90%, 95%, 98%, or 99% identity with a sequence of Table 2.

109. The method of claim 108, wherein formula 1 comprises a polypeptide sequence of Table 2.

- ~~110. The method of any one of claims 91-109, wherein the administering is via intravitreal injection, subretinal injection, microinjection, or super-ocular injection.~~
- ~~111. The method of claim 110, wherein the administering is via intravitreal injection.~~
- ~~112. The method of any one of claims 91-111, wherein the disease or condition is ocular.~~
- ~~113. The method of any one of claims 91-111, wherein the disease or condition is non-ocular.~~
- ~~114. The method of any one of claims 91-112, wherein the ocular disease or condition is of the retina.~~
- ~~115. The method of claim 112 or 114, wherein the ocular disease or condition is selected from the group consisting of: Achromatopsia, neovascularization-related retinal disorder such as Age-related macular degeneration (AMD), wet Age-related macular degeneration (wAMD), Geographic atrophy (GA), Diabetic retinopathy (DR), Diabetic macular edema (DME), Glaucoma, Bardet-Biedl Syndrome, Best Disease, Choroideremia, Leber Congenital Amaurosis, Leber Hereditary Optic Neuropathy (LHON), Macular degeneration, Polypoidal choroidal vasculopathy (PCV), Retinitis pigmentosa, Refsum disease, Stargardt disease, Usher syndrome, X-linked retinoschisis (XLRs), Inherited Retinal Disease (IRD), Rod-cone dystrophy, Cone-rod dystrophy, Oguchi disease, Malattia Leventinese (Familial Dominant Drusen), Blue-cone monochromacy, retina vein occlusion (RVO), and Uveitic Macular Oedema (UMO).~~
- ~~116. The method of claim 115, wherein the ocular disease or condition is AMD.~~
- ~~117. The method of claim 116, wherein the AMD is wet AMD.~~
- ~~118. The method of claim 116, wherein the AMD is dry AMD.~~
- ~~119. The method of any one of claims 91-118, wherein the administering is sufficient to reduce at least a symptom of the disease or condition, treat the disease or condition, and/or eliminate the disease or condition.~~
- ~~120. The method of any one of claims 95-119, wherein the vector further comprises a transgene that codes for a therapeutic polypeptide.~~
- ~~121. The method of claim 120, wherein the therapeutic is selected from the group consisting of: an antibody or biologically active fragment thereof or a biologic.~~
- ~~122. The method of claim 121, wherein the therapeutic is the biologic, and wherein the biologic comprises a polypeptide selected from: Lipoprotein Lipase, Retinoid Isomerohydrolase RPE65, complement H.~~
- ~~123. The method of claim 121, wherein the therapeutic is the antibody or biologically active fragment thereof, and wherein the antibody or biologically active fragment thereof is selected from: anti-VEGF, anti-VEGFL, anti-thrombospondin-1, anti-CD47, anti-TNF-alpha, anti-CD20, anti-CD52, and anti-CD11a.~~

- ~~124. The method of any one of claims 91-123, wherein prior to the administering the subject undergoes genetic testing.~~
- ~~125. The method of claim 124, wherein the genetic testing detects a mutation in a gene selected from: RPE65, CRB1, AIPL1, CFH, or RPGRIP.~~
- ~~126. The method of any one of claims 91-125, wherein the administering comprises delivering a dosage of the vector of about 1.0×10^9 -vg, 1.0×10^{10} , 1.0×10^{11} -vg, 3.0×10^{11} -vg, 6×10^{11} -vg, 8.0×10^{11} -vg, 1.0×10^{12} -vg, 1.0×10^{13} -vg, 1.0×10^{14} -vg, or 1.0×10^{15} -vg.~~
- ~~127. The method of any one of claims 91-126, wherein the administering is repeated.~~
- ~~128. The method of claim 118, wherein the administering is performed: twice daily, every other day, twice a week, bimonthly, trimonthly, once a month, every other month, semiannually, annually, or biannually.~~
- ~~129. The method of any one of claims 91-128, wherein the method further comprises administering a secondary therapy.~~
- ~~130. The method of any one of claims 91-129, wherein the VP comprises VP1.~~
- ~~131. The method of any one of claims 91-129, wherein the VP comprises VP2.~~
- ~~132. The method of any one of claims 91-129, wherein the VP comprises VP3.~~

12. The AAV capsid of any one of claims 1-11, wherein the polypeptide sequence is in the GH loop or loop IV of the AAV capsid.

13. The AAV capsid of any one of claims 1-12, wherein the polypeptide sequence is an insertion within:

- (i) amino acid positions 570-611 relative to AAV2 capsid;
- (ii) amino acid positions 571-612 relative to AAV1 capsid;
- (iii) amino acid positions 560-601 relative to AAV5 capsid;
- (iv) amino acid positions 571-612 relative to AAV6 capsid;
- (v) amino acid positions 572 to 613 relative to AAV7 capsid;
- (vi) amino acid positions 573 to 614 relative to AAV8 capsid;
- (vii) amino acid positions 571 to 612 relative to AAV9 capsid; or
- (viii) amino acid positions 573 to 614 relative to AAV10 capsid.

14. The AAV capsid of any one of claims 1-13, wherein the polypeptide sequence is an insertion at position 452, 453, 466, 467, 468, 471, 585, 586, 587, and/or 588 relative to SEQ ID NO: 1.

15. The AAV capsid of any one of claims 1-14, wherein the AAV capsid further comprises at least one amino acid mutation relative to a wild-type AAV capsid.

16. The AAV capsid of claim 15, wherein the at least one amino acid mutation is at amino acid position 452, 453, 466, 467, 468, 471, 585, 586, 587, and/or 588 relative to SEQ ID NO: 1.

17. The AAV capsid of claim 16, wherein the at least one amino acid mutation is R to A at amino

acid position 585 or 588 relative to SEQ ID NO: 1.

18. A vector comprising a polynucleotide sequence encoding the AAV capsid of any one of claims 1-17.

19. The vector of claim 18, wherein the AAV capsid is of serotype AAV2 or is a chimeric AAV capsid comprising an amino acid sequence from serotype AAV2.

20. The vector of claim 18 or 19, wherein the vector comprises a polynucleotide sequence encoding a transgene.