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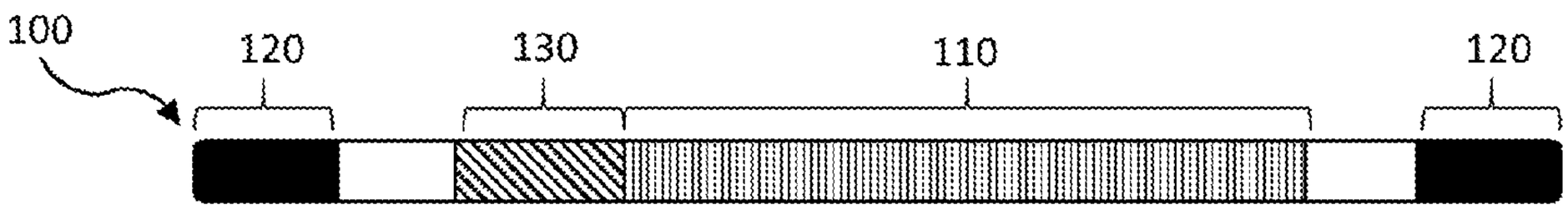
(54) Title: MODULATORY POLYNUCLEOTIDES

FIG. 1



(57) Abrégé/Abstract:
The present invention relates to adeno-associated viral (AAV) particles modulatory polynucleotides encoding at least one siRNA molecules and methods of use thereof.

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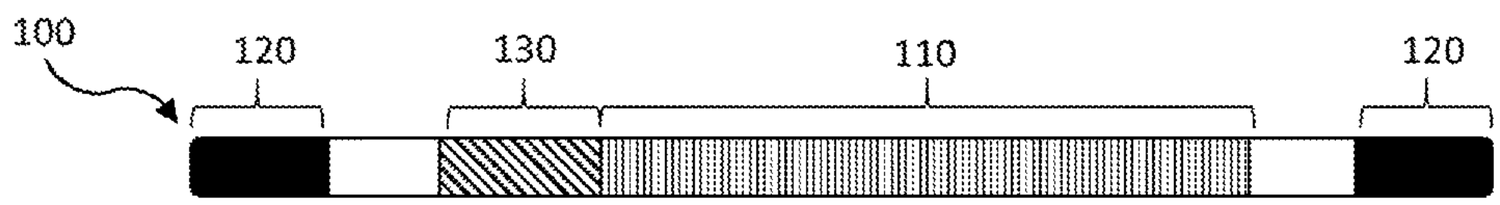
(54) Title: MODULATORY POLYNUCLEOTIDES

FIG. 1



(57) Abstract: The present invention relates to adeno-associated viral (AAV) particles modulatory polynucleotides encoding at least one siRNA molecules and methods of use thereof.

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

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CONTENANT LES PAGES 1 À 283

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JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

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MODULATORY POLYNUCLEOTIDES

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 62/501,787, filed May 5, 2017, U.S. Provisional Patent Application No. 62/507,923, filed May 18, 2017, and U.S. Provisional Patent Application No. 62/520,093, filed June 15, 2017, the contents of each of which is incorporated by reference herein in its entirety.

REFERENCE TO THE SEQUENCE LISTING

[0002] The present application is being filed along with a Sequence Listing in electronic format as an ASCII text file. The Sequence Listing is provided as an ASCII text file entitled 14482_155_228_SEQ_LISTING.txt, created on May 3, 2018, which is 6,853,639 bytes in size. The Sequence Listing is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0003] The present invention relates to compositions, methods and processes for the design, preparation, manufacture, use and/or formulation of AAV particles comprising modulatory polynucleotides, e.g., polynucleotides encoding at least one small interfering RNA (siRNA) molecules which targets at least one gene of interest. Targeting the gene of interest may interfere with the gene expression and the resultant protein production. The AAV particles comprising modulatory polynucleotides encoding at least one siRNA molecules may be inserted into recombinant adeno-associated virus (AAV) vectors. Methods for using the AAV particles to inhibit the expression of the gene of interest in a subject are also disclosed.

BACKGROUND OF THE INVENTION

[0004] MicroRNAs (or miRNAs or miRs) are small, non-coding, single stranded ribonucleic acid molecules (RNAs), which are usually 19-25 nucleotides in length. More than a thousand microRNAs have been identified in mammalian genomes. The mature microRNAs primarily bind to the 3' untranslated region (3'-UTR) of target messenger RNAs (mRNAs) through partially or fully pairing with the complementary sequences of target mRNAs, promoting the degradation of target mRNAs at a post-transcriptional level, and in some cases, inhibiting the initiation of translation. MicroRNAs play a critical role in many key biological processes, such as the regulation of cell cycle and growth, apoptosis, cell proliferation and tissue development.

[0005] miRNA genes are generally transcribed as long primary transcripts of miRNAs (i.e. pri-miRNAs). The pri-miRNA is cleaved into a precursor of a miRNA (i.e. pre-miRNA) which is further processed to generate the mature and functional miRNA.

[0006] While many target expression strategies employ nucleic acid based modalities, there remains a need for improved nucleic acid modalities which have higher specificity and with fewer off target effects.

[0007] The present invention provides such improved modalities in the form of artificial pri-, pre- and mature microRNA constructs and methods of their design. These novel constructs may be synthetic stand-alone molecules or be encoded in a plasmid or expression vector for delivery to cells. Such vectors include, but are not limited to adeno-associated viral vectors such as vector genomes of any of the AAV serotypes or other viral delivery vehicles such as lentivirus, etc.

SUMMARY OF THE INVENTION

[0008] Described herein are methods, processes, compositions, kits and devices for the administration of AAV particles comprising modulatory polynucleotides encoding at least one siRNA molecule for the treatment, prophylaxis, palliation and/or amelioration of a disease and/or disorder.

[0009] The details of various embodiments of the invention are set forth in the description below. Other features, objects, and advantages of the invention will be apparent from the description and the drawings, and from the claims.

[0010] Set forth below are non-limiting embodiments that are representative of the subject matter description herein:

[0011] 1. An adeno-associated viral (AAV) viral genome comprising a nucleic acid sequence positioned between two inverted terminal repeats (ITRs), wherein said nucleic acid when expressed inhibits or suppresses the expression of a target gene in a cell, wherein said nucleic acid sequence comprises, in a 5' to 3' order: a first region encoding a first sense strand sequence, a second region encoding a first antisense strand sequence, a third region encoding a second sense strand, and a fourth region encoding a second antisense strand sequence, wherein the first and second sense strand sequences comprise at least 15 contiguous nucleotides and the first and second antisense strand sequences are complementary to an mRNA produced by the target gene and comprise at least 15 contiguous nucleotides, and wherein said first sense strand sequence and first antisense strand sequence share a region of complementarity of at least four nucleotides in length and said second sense strand sequence and second antisense strand sequence share a region of complementarity of at least four nucleotides in length.

[0012] 2. An adeno-associated viral (AAV) viral genome comprising a nucleic acid sequence positioned between two inverted terminal repeats (ITRs), wherein said nucleic acid when expressed inhibits or suppresses the expression of a first target gene and a second target gene in a

cell, wherein said nucleic acid sequence comprises, in a 5' to 3' order: a first region encoding a first sense strand sequence, a second region encoding a first antisense strand sequence, a third region encoding a second sense strand, and a fourth region encoding a second antisense strand sequence, wherein the first and second sense strand sequences comprise at least 15 contiguous nucleotides and the first antisense strand sequence is complementary to an mRNA produced by the first target gene and the second antisense strand sequence is complementary to an mRNA produced by the second target gene and comprise at least 15 contiguous nucleotides, and wherein said first sense strand sequence and first antisense strand sequence share a region of complementarity of at least four nucleotides in length and said second sense strand sequence and second antisense strand sequence share a region of complementarity of at least four nucleotides in length.

[0013] 3. The AAV viral genome of embodiment 2, further comprising, in a 5' to 3' order, a fifth region encoding a third sense strand sequence and a sixth region encoding a third antisense strand sequence, wherein the third sense strand sequence comprises at least 15 contiguous nucleotides and the third antisense strand sequence is complementary to an mRNA produced by a third target gene and comprises at least 15 contiguous nucleotides, and wherein said third sense strand sequence and third antisense strand sequence share a region of complementarity of at least four nucleotides.

[0014] 4. The AAV viral genome of embodiment 3, further comprising, in a 5' to 3' order, a seventh region encoding a fourth sense strand sequence and a eighth region encoding a fourth antisense strand sequence, wherein the fourth sense strand sequence comprises at least 15 contiguous nucleotides and the fourth antisense strand sequence is complementary to an mRNA produced by a fourth target gene and comprises at least 15 contiguous nucleotides, and wherein said fourth sense strand sequence and fourth antisense strand sequence share a region of complementarity of at least four nucleotides.

[0015] 5. The AAV viral genome of embodiment 2, wherein the first target gene is the same as the second target gene.

[0016] 6. The AAV viral genome of embodiment 3, wherein the third target gene is the same as the first target gene.

[0017] 7. The AAV viral genome of embodiment 3, wherein the third target gene is the same as the second target gene.

[0018] 8. The AAV viral genome of embodiment 3, wherein the first target gene, the second target gene and the third target gene are the same.

[0019] 9. The AAV viral genome of embodiment 4, wherein the fourth target gene is the same as the first target gene.

[0020] 10. The AAV viral genome of embodiment 4, wherein the fourth target gene is the same as the second target gene.

[0021] 11. The AAV viral genome of embodiment 4, wherein the fourth target gene is the same as the third target gene.

[0022] 12. The AAV viral genome of embodiment 4, wherein the fourth target gene is the same as the first target gene and the second target gene.

[0023] 13. The AAV viral genome of embodiment 4, wherein the fourth target gene is the same as the second target gene and the third target gene.

[0024] 14. The AAV viral genome of embodiment 4, wherein the fourth target gene is the same as the first target gene, the second target gene and the third target gene.

[0025] 15. The AAV viral genome of any one of embodiments 1-14 wherein the first target gene, the second target gene, the third target gene and/or the fourth target gene is Huntingtin.

[0026] 16. The AAV viral genome of any one of embodiments 1-14 wherein the first target gene, the second target gene, the third target gene and/or the fourth target gene is SOD1.

[0027] 17. The AAV viral genome of any one of embodiments 1-14 wherein the first target gene, the second target gene, the third target gene and/or the fourth target gene is Huntingtin or SOD1.

[0028] 18. The AAV viral genome of embodiment 1 or 2, wherein the region of complementarity between the first sense strand and the first antisense strand is at least 12 nucleotides in length.

[0029] 19. The AAV viral genome of embodiment 18, wherein the region of complementarity between the first sense strand and the first antisense strand is between 14 and 21 nucleotides in length.

[0030] 20. The AAV viral genome of embodiment 19, wherein the region of complementarity between the first sense strand and the first antisense strand is 19 nucleotides in length.

[0031] 21. The AAV viral genome of embodiment 1 or 2, wherein the region of complementarity between the second sense strand and the second antisense strand is at least 12 nucleotides in length.

[0032] 22. The AAV viral genome of embodiment 21, wherein the region of complementarity between the second sense strand and the second antisense strand is between 14 and 21 nucleotides in length.

[0033] 23. The AAV viral genome of embodiment 22, wherein the region of complementarity between the second sense strand and the second antisense strand is 19 nucleotides in length.

[0034] 24. The AAV viral genome of embodiment 3, wherein the region of complementarity between the third sense strand and the third antisense strand is at least 12 nucleotides in length.

[0035] 25. The AAV viral genome of embodiment 24, wherein the region of complementarity between the third sense strand and the third antisense strand is between 14 and 21 nucleotides in length.

[0036] 26. The AAV viral genome of embodiment 25, wherein the region of complementarity between the third sense strand and the third antisense strand is 19 nucleotides in length.

[0037] 27. The AAV viral genome of embodiment 4, wherein the region of complementarity between the fourth sense strand and the fourth antisense strand is at least 12 nucleotides in length.

[0038] 28. The AAV viral genome of embodiment 27, wherein the region of complementarity between the fourth sense strand and the fourth antisense strand is between 14 and 21 nucleotides in length.

[0039] 29. The AAV viral genome of embodiment 25, wherein the region of complementarity between the fourth sense strand and the fourth antisense strand is 19 nucleotides in length.

[0040] 30. The AAV viral genome of embodiment 1 or 2, wherein the first sense strand sequence, the second sense strand sequence, the first antisense strand sequence, and the second antisense strand sequence are, independently, 30 nucleotides or less.

[0041] 31. The AAV viral genome of embodiment 3, wherein the first sense strand sequence, the second sense strand sequence, the third sense strand sequence, the first antisense strand sequence, the second antisense strand sequence and the third antisense strand sequence, are, independently, 30 nucleotides or less.

[0042] 32. The AAV viral genome of embodiment 4 wherein the first sense strand sequence, the second sense strand sequence, the third sense strand sequence, the fourth sense strand sequence, the first antisense strand sequence, the second antisense strand sequence, the third antisense strand sequence and the fourth antisense strand sequence, are, independently, 30 nucleotides or less.

[0043] 33. The AAV viral genome of embodiment 1 or 2, wherein at least one of the first sense strand sequence and the first antisense strand sequence or the second sense strand sequence and the second antisense strand sequence comprise a 3' overhang of at least 1 nucleotide.

[0044] 34. The AAV viral genome of embodiment 1 or 2, wherein at least one of the first sense strand sequence and the first antisense strand sequence or the second sense strand sequence and the second antisense strand sequence comprise a 3' overhang of at least 2 nucleotides.

[0045] 35. The AAV viral genome of embodiment 3, wherein the third sense strand sequence and the third antisense strand sequence comprise a 3' overhang of at least 1 nucleotide.

[0046] 36. The AAV viral genome of embodiment 3, wherein the third sense strand sequence and the third antisense strand sequence comprise a 3' overhang of at least 2 nucleotides.

[0047] 37. The AAV viral genome of embodiment 4 wherein the fourth sense strand sequence and the fourth antisense strand sequence comprise a 3' overhang of at least 1 nucleotide.

[0048] 38. The AAV viral genome of embodiment 4 wherein the fourth sense strand sequence and the fourth antisense strand sequence comprise a 3' overhang of at least 2 nucleotides.

[0049] 39. The AAV viral genome of any one of embodiments 1-38, wherein the first region comprises, a promoter 5' of the first sense strand sequence followed by the first sense strand sequence, and the second region comprises the first antisense strand sequence followed by a promoter terminator 3' of the first antisense strand sequence; or the third region comprises a promoter 5' of the second sense strand sequence followed by the second sense strand sequence, and the fourth region comprises the second antisense strand sequence followed by a promoter terminator 3' of the second antisense strand sequence.

[0050] 40. The AAV viral genome of any one of embodiments 1-38, wherein the first region comprises, a promoter 5' of the first sense strand sequence followed by the first sense strand sequence, and the second region comprises the first antisense strand sequence followed by a promoter terminator 3' of the first antisense strand sequence; and the third region comprises a promoter 5' of the second sense strand sequence followed by the second sense strand sequence, and the fourth region comprises the second antisense strand sequence followed by a promoter terminator 3' of the second antisense strand sequence.

[0051] 41. The AAV viral genome of any one of embodiments 3-40, wherein the fifth region comprises a promoter 5' of the third sense strand sequence followed by the third sense strand sequence and the sixth region comprises the third antisense strand sequence followed by a promoter terminator 3' of the third antisense strand sequence.

[0052] 42. The AAV viral genome of any one of embodiments 4-41 wherein the seventh region comprises a promoter 5' of the fourth sense strand sequence followed by the fourth sense strand sequence and the eighth region comprises the fourth antisense strand sequence followed by a promoter terminator 3' of the fourth antisense strand sequence.

[0053] 43. The AAV viral genome of embodiment 3, wherein the fifth region is 3' of the fourth region.

[0054] 44. The AAV viral genome of embodiment 4, wherein the seventh region is 3' of the sixth region.

[0055] 45. The AAV viral genome of any one of embodiments 39-44 wherein a promoter is a Pol III promoter and the promoter terminator is a Pol III promoter terminator.

[0056] 46. The AAV viral genome of embodiment 45, wherein the Pol III promoter is a U3, U6, U7, 7SK, H1, or MRP, EBER, seleno-cysteine tRNA, 7SL, adenovirus VA-1, or telomerase gene promoter, and the Pol III promoter terminator is a U3, U6, U7, 7SK, H1, or MRP, EBER, seleno-cysteine tRNA, 7SL, adenovirus VA-1, or telomerase gene promoter terminator, respectively.

[0057] 47. The AAV viral genome of embodiment 46, wherein the Pol III promoter is an H1 promoter and the Pol III promoter terminator is an H1 promoter terminator.

[0058] 48. The AAV viral genome of any one of embodiments 1-47, wherein the AAV viral genome is a monospecific polycistronic AAV viral genome.

[0059] 49 The AAV viral genome of any one of embodiments 1-47, wherein the AAV viral genome is a bispecific polycistronic AAV viral genome.

[0060] 50. The AAV viral genome of embodiment 1 or 2, wherein the first region and the second region encode a first siRNA molecule, and the third region and the fourth region encode a second siRNA molecule, wherein the first and the second siRNA molecules target a different target gene.

[0061] 51. The AAV viral genome of embodiment 3, wherein the fifth region and the sixth region encode a third siRNA molecule, wherein the first siRNA molecule, the second siRNA molecule and the third siRNA molecule each target a different target gene.

[0062] 52. The AAV viral genome of embodiment 4, wherein the seventh region and the eighth region encode a fourth siRNA molecule, wherein the first siRNA molecule, the second siRNA molecule, the third siRNA molecule and the fourth siRNA molecule each target a different target gene.

[0063] 53. An adeno-associated viral (AAV) viral genome comprising a nucleic acid sequence positioned between two inverted terminal repeats (ITRs), wherein said nucleic acid sequence comprises a first molecular scaffold region and a second molecular scaffold region, wherein said first molecular scaffold region comprises a first molecular scaffold nucleic acid sequence encoding:

(a) a first stem and loop to form a first stem-loop structure, the sequence of said first stem-loop structure from 5' to 3' comprising:

i. a first UG motif at or near the base of the first 5' stem of the first stem-loop structure;

ii. a first 5' stem arm comprising a first sense strand and optional first 5' spacer region, wherein said first 5' spacer region, when present, is located between said first UG motif and said first sense strand;

iii. a first loop region comprising a first UGUG motif at the 5' end of said first loop region;

iv. a first 3' stem arm comprising a first antisense strand and optionally a first 3' spacer region, wherein a uridine is present at the 5' end of said first antisense strand and wherein said first 3' spacer region, when present, has a length sufficient to form one helical turn;

(b) a first 5' flanking region located 5' to said first stem-loop structure; and

(c) a first 3' flanking region located 3' to said first stem-loop structure, said first 3' flanking region comprising a CNNC motif, and

a second molecular scaffold region comprising a second molecular scaffold nucleic acid sequence encoding

(d) a second stem and loop to form a second stem-loop structure, the sequence of said second stem-loop structure from 5' to 3' comprising:

v. a second UG motif at or near the base of the second 5' stem of the second stem-loop structure;

vi. a second 5' stem arm comprising a second sense strand and optional second 5' spacer region, wherein said second 5' spacer region, when present, is located between said second UG motif and said second sense strand;

vii. a second loop region comprising a second UGUG motif at the 5' end of said second loop region;

viii. a second 3' stem arm comprising a second antisense strand and optionally a second 3' spacer region, wherein a uridine is present at the 5' end of said second antisense strand and wherein said second 3' spacer region, when present, has a length sufficient to form one helical turn;

ix. a second 5' flanking region located 5' to said second stem-loop structure; and

(e) a second 3' flanking region located 3' to said second stem-loop structure, said second

3’ flanking region comprising a CNNC motif, and

wherein said first antisense strand and said first sense strand form a first siRNA duplex and said second antisense strand and said second sense strand form a second siRNA duplex, where the first siRNA duplex, when expressed, inhibits or suppresses the expression of a first target gene in a cell, and the second siRNA duplex, when expressed, inhibits or suppresses the expression of a second target gene in a cell, wherein the first and second sense strand sequences comprise at least 15 nucleotides, the first antisense strand sequence is complementary to an mRNA produced by the first target gene and second antisense strand sequences is complementary to an mRNA produced by the second target gene, and wherein said first sense strand sequence and first antisense strand sequence share a region of complementarity of at least four nucleotides in length and said second sense strand sequence and second antisense strand sequence share a region of complementarity of at least four nucleotides in length.

[0064] 54. Adeno-associated viral (AAV) viral genome comprising a nucleic acid sequence positioned between two inverted terminal repeats (ITRs), wherein said nucleic acid sequence comprises a first molecular scaffold region and a second molecular scaffold region, wherein said first molecular scaffold region comprises a first molecular scaffold nucleic acid sequence encoding:

(a) a first stem and loop to form a first stem-loop structure, the sequence of said first stem-loop structure from 5’ to 3’ comprising:
   i. a first UG motif at or near the base of the first 5’ stem of the first stem-loop structure;
   ii. a first 5’ stem arm comprising a first antisense strand and optional first 5’ spacer region, wherein said first 5’ spacer region, when present, is located between said first UG motif and said first antisense strand;
   iii. a first loop region comprising a first UGUG motif at the 5’ end of said first loop region;
   iv. a first 3’ stem arm comprising a first sense strand and optionally a first 3’ spacer region, wherein a uridine is present at the 5’ end of said first sense strand and wherein said first 3’ spacer region, when present, has a length sufficient to form one helical turn;
(b) a first 5’ flanking region located 5’ to said first stem-loop structure; and
(c) a first 3’ flanking region located 3’ to said first stem-loop structure, said first 3’

flanking region comprising a CNNC motif, and

a second molecular scaffold region comprising a second molecular scaffold nucleic acid sequence encoding

(d) a second stem and loop to form a second stem-loop structure, the sequence of said second stem-loop structure from 5' to 3' comprising:

v. a second UG motif at or near the base of the second 5' stem of the second stem-loop structure;

vi. a second 5' stem arm comprising a second antisense strand and optional second 5' spacer region, wherein said second 5' spacer region, when present, is located between said second UG motif and said second antisense strand;

vii. a second loop region comprising a second UGUG motif at the 5' end of said second loop region;

viii. a second 3' stem arm comprising a second sense strand and optionally a second 3' spacer region, wherein a uridine is present at the 5' end of said second sense strand and wherein said second 3' spacer region, when present, has a length sufficient to form one helical turn;

(e) a second 5' flanking region located 5' to said second stem-loop structure; and

(f) a second 3' flanking region located 3' to said second stem-loop structure, said second 3' flanking region comprising a CNNC motif, and

wherein said first antisense strand and said first sense strand form a first siRNA duplex and said second antisense strand and said second sense strand form a second siRNA duplex, where the first siRNA duplex, when expressed, inhibits or suppresses the expression of a first target gene in a cell, and the second siRNA duplex, when expressed, inhibits or suppresses the expression of a second target gene in a cell, wherein the first and second sense strand sequences comprise at least 15 nucleotides, the first antisense strand sequence is complementary to an mRNA produced by the first target gene and second antisense strand sequences is complementary to an mRNA produced by the second target gene, and wherein said first sense strand sequence and first antisense strand sequence share a region of complementarity of at least four nucleotides in length and said second sense strand sequence and second antisense strand sequence share a region of complementarity of at least four nucleotides in length.

[0065] 55. The AAV viral genome of embodiment 53 or 54, wherein the first antisense strand sequence or the second antisense strand sequence inhibits or suppresses the expression of Huntingtin.

[0066] 56. The AAV viral genome of embodiment 53 or 54, wherein the first antisense strand sequence and the second antisense sequence strand inhibits or suppresses the expression of Huntingtin.

[0067] 57. The AAV viral genome of embodiment 53 or 54, wherein the first antisense strand sequence or the second antisense strand sequence inhibits or suppresses the expression of SOD1.

[0068] 58. The AAV viral genome of embodiment 53 or 54, wherein the first antisense strand sequence and the second antisense strand sequence inhibits or suppresses the expression of SOD1.

[0069] 59. The AAV viral genome of embodiment 53 or 54, wherein the first 5' flanking region is selected from the sequences listed in Table 10.

[0070] 60. The AAV viral genome of embodiment 53 or 54, wherein the second 5' flanking region is selected from the sequences listed in Table 10.

[0071] 61. The AAV viral genome of embodiment 59, wherein the second 5' flanking region is selected from the sequences listed in Table 10.

[0072] 62. The AAV viral genome of embodiment 53 or 54, wherein the first loop region is selected from the sequences listed in Table 11.

[0073] 63. The AAV viral genome of embodiment 53 or 54, wherein the second loop region is selected from the sequences listed in Table 11.

[0074] 64. The AAV viral genome of embodiment 62, wherein the second loop region is selected from the sequences listed in Table 11.

[0075] 65. The AAV viral genome of embodiment 53 or 54, wherein the first 3' flanking region is selected from the sequences listed in Table 12.

[0076] 66. The AAV viral genome of embodiment 53 or 54, wherein the second 3' flanking region is selected from the sequences listed in Table 12.

[0077] 67. The AAV viral genome of embodiment 65, wherein the second 3' flanking region is selected from the sequences listed in Table 12.

[0078] 68. The AAV viral genome of embodiment 53 or 54, wherein the nucleic acid sequence comprises a promoter sequence between the first molecular scaffold nucleic acid sequence and the second molecular scaffold nucleic acid sequence.

[0079] 69. The AAV viral genome of embodiment 53 or 54, further comprising, in (b), a promoter 5' of the first 5' flanking region followed by the first 5' flanking region and in (c) the first 3' flanking region followed by a promoter terminator 3' of the first '3 flanking region, and in (d), a promoter 5' of the second 5' flanking region followed by the second 5' flanking region and in (e) the second 3' flanking region followed by a promoter terminator 3' of the second 3' flanking region.

[0080] 70. The AAV viral genome of embodiment 69, wherein the promoter is a Pol III promoter.

[0081] 71. The AAV viral genome of embodiment 70, wherein the Pol III promoter sequence is a U3, U6, U7, 7SK, H1, or MRP, EBER, seleno-cysteine tRNA, 7SL, adenovirus VA-1, or telomerase gene promoter.

[0082] 72. The AAV viral genome of embodiment 71, wherein the Pol III promoter is an H1 promoter.

[0083] 73. The AAV viral genome of embodiment 53, wherein the nucleic acid sequence further comprises a third molecular scaffold region comprising a third molecular scaffold nucleic acid sequence encoding:

(g) a third stem and loop to form a third stem-loop structure, the sequence of said third stem-loop structure from 5' to 3' comprising:

ix. a third UG motif at or near the base of the third 5' stem of the third stem-loop structure;

x. a third 5' stem arm comprising a third sense strand and optional third 5' spacer region, wherein said third 5' spacer region, when present, is located between said third UG motif and said third sense strand;

xi. a third loop region comprising a third UGUG motif at the 5' end of said third loop region;

xii. a third 3' stem arm comprising a third antisense strand and optionally a third 3' spacer region, wherein a uridine is present at the 5' end of said third antisense strand and wherein said third 3' spacer region, when present, has a length sufficient to form one helical turn;

(h) a third 5' flanking region located 5' to said third stem-loop structure; and

(i) a third 3' flanking region located 3' to said third stem-loop structure, said third 3' flanking region comprising a CNNC motif, and

wherein said third antisense strand and said third sense strand form a third siRNA duplex, wherein the third siRNA duplex, when expressed, inhibits or suppresses the expression of a third target gene in a cell, wherein the third sense strand sequence comprises at least 15 nucleotides, the third antisense strand sequence is complementary to an mRNA produced by the third target gene, and wherein said third sense strand sequence and third antisense strand sequence share a region of complementarity of at least four nucleotides in length.

[0084] 74. The AAV viral genome of embodiment 73, further comprising, in (h), a promoter 5' of the third 5' flanking region followed by the third 5' flanking region, and in (i) the third 3' flanking region followed by a promoter terminator 3' of the third '3 flanking region.

[0085] 75. The AAV viral genome of embodiment 74, wherein the promoter is a Pol III promoter.

[0086] 76. The AAV viral genome of embodiment 75, wherein the Pol III promoter sequence is a U3, U6, U7, 7SK, H1, or MRP, EBER, seleno-cysteine tRNA, 7SL, adenovirus VA-1, or telomerase gene promoter.

[0087] 77. The AAV viral genome of embodiment 76, wherein the Pol III promoter is an H1 promoter.

[0088] 78. The AAV viral genome of embodiment 73, wherein the nucleic acid sequence further comprises a fourth molecular scaffold region comprising a fourth molecular scaffold nucleic acid sequence encoding

(j) a fourth stem and loop to form a fourth stem-loop structure, the sequence of said fourth stem-loop structure from 5' to 3' comprising:

xiii. a fourth UG motif at or near the base of the fourth 5' stem of the fourth stem-loop structure;

xiv. a fourth 5' stem arm comprising a fourth sense strand and optional fourth 5' spacer region, wherein said fourth 5' spacer region, when present, is located between said fourth UG motif and said fourth sense strand;

xv. a fourth loop region comprising a fourth UGUG motif at the 5' end of said fourth loop region;

xvi. a fourth 3' stem arm comprising a fourth antisense strand and optionally a fourth 3' spacer region, wherein a uridine is present at the 5' end of said fourth antisense strand and wherein said fourth 3' spacer region, when present, has a length sufficient to form one helical turn;

(k) a fourth 5' flanking region located 5' to said fourth stem-loop structure; and

(l) a fourth 3' flanking region located 3' to said fourth stem-loop structure, said fourth 3' flanking region comprising a CNNC motif, and

wherein said fourth antisense strand and said fourth sense strand form a fourth siRNA duplex, wherein the fourth siRNA duplex, when expressed, inhibits or suppresses the expression of a fourth target gene in a cell, wherein the fourth sense strand sequence comprises at least 15 nucleotides, the fourth antisense strand sequence is complementary to an mRNA produced by the fourth target gene, and wherein said fourth sense strand sequence and fourth antisense strand sequence share a region of complementarity of at least four nucleotides in length.

[0089] 79. The AAV viral genome of embodiment 78, further comprising, in (k), a promoter 5' of the fourth 5' flanking region followed by the fourth 5' flanking region, and in (l) the fourth 3' flanking region followed by a promoter terminator 3' of the fourth '3 flanking region.

[0090] 80. The AAV viral genome of embodiment 79, wherein the promoter is a Pol III promoter.

[0091] 81. The AAV viral genome of embodiment 80, wherein the Pol III promoter sequence is a U3, U6, U7, 7SK, H1, or MRP, EBER, seleno-cysteine tRNA, 7SL, adenovirus VA-1, or telomerase gene promoter.

[0092] 82. The AAV viral genome of embodiment 81, wherein the Pol III promoter is an H1 promoter.

[0093] 83. The AAV viral genome of any one of embodiments 53-82, wherein the first target gene is the same as the second target gene.

[0094] 84. The AAV viral genome of any one of embodiments 53-82, wherein the third target gene is the same as the first target gene.

[0095] 85. The AAV viral genome of any one of embodiments 53-82, wherein the third target gene is the same as the second target gene.

[0096] 86. The AAV viral genome of any one of embodiments 53-82, wherein the first target gene, the second target gene and the third target gene are the same.

[0097] 87. The AAV viral genome of any one of embodiments 53-82, wherein the fourth target gene is the same as the first target gene.

[0098] 88. The AAV viral genome of any one of embodiments 53-82, wherein the fourth target gene is the same as the second target gene.

[0099] 89. The AAV viral genome of any one of embodiments 53-82, wherein the fourth target gene is the same as the third target gene.

[00100] 90. The AAV viral genome of any one of embodiments 53-82, wherein the fourth target gene is the same as the first target gene and the second target gene.

[00101] 91. The AAV viral genome of embodiment 53-82, wherein the fourth target gene is the same as the second target gene and the third target gene.

[00102] 92. The AAV viral genome of embodiment 53-82, wherein the fourth target gene is the same as the first target gene and the third target gene.

[00103] 93. The AAV viral genome of any one of embodiments 53-82, wherein the fourth target gene is the same as the first target gene, the second target gene and the third target gene.

[00104] 94. The AAV viral genome of any one of embodiments 53-93 wherein the first target gene, the second target gene, the third target gene and/or the fourth target gene is Huntingtin.

[00105] 95. The AAV viral genome of any one of embodiments 53-93 wherein the first target gene, the second target gene, the third target gene and/or the fourth target gene is SOD1.

[00106] 96. The AAV viral genome of any one of embodiments 53-93 wherein the first target gene, the second target gene, the third target gene and/or the fourth target gene is Huntingtin or SOD1.

[00107] 97. A method for inhibiting the expression of a gene of a target gene in a cell comprising administering to the cell a composition comprising an AAV viral genome of any one of embodiments 1-96.

[00108] 98. The method of embodiment 97, wherein the cell is a mammalian cell.

[00109] 99. The method of embodiment 98, wherein the mammalian cell is a medium spiny neuron.

[00110] 100. The method of embodiment 98, wherein the mammalian cell is a cortical neuron.

[00111] 101. The method of embodiment 98, wherein the mammalian cell is a motor neuron.

[00112] 102. The method of embodiment 98, wherein the mammalian cell is an astrocyte.

[00113] 103. A method for treating a disease and/or disorder in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a composition comprising an AAV viral genome of any one of embodiments 1-96.

[00114] 104. The method of embodiment 103, wherein the expression of a target gene is inhibited or suppressed.

[00115] 105. The method of embodiment 104, wherein the expression of a target gene of interest is inhibited or suppressed by about 30% to about 70%.

[00116] 106. The method of embodiment 104, wherein the expression of a target gene is inhibited or suppressed by about 50% to about 90%.

[00117] 107. A method for inhibiting the expression of a target gene in a cell wherein the target gene causes a gain of function effect inside the cell, comprising administering to the cell a composition comprising an AAV viral genome of any one of embodiments 1-96.

[00118] 108. The method of embodiment 107, wherein the cell is a mammalian cell.

[00119] 109. The method of embodiment 108, wherein the mammalian cell is a medium spiny neuron.

[00120] 110. The method of embodiment 108, wherein the mammalian cell is a cortical neuron.

[00121] 111. The method of embodiment 108, wherein the mammalian cell is a motor neuron.

[00122] 112. The method of embodiment 108, wherein the mammalian cell is an astrocyte.

BRIEF DESCRIPTION OF THE DRAWINGS

[00123] The foregoing and other objects, features and advantages will be apparent from the following description of particular embodiments of the invention, as illustrated in the accompanying drawings. The drawings are not necessarily to scale, emphasis instead being placed upon illustrating the principles of various embodiments of the invention.

[00124] FIG. 1 is a schematic of a viral genome of the invention.

[00125] FIG. 2 is a schematic of a viral genome of the invention.

[00126] FIG. 3 is a schematic of a viral genome of the invention.

[00127] FIG. 4 is a schematic of a viral genome of the invention.

[00128] FIG. 5 is a schematic of a viral genome of the invention.

[00129] FIG. 6 is a schematic of a viral genome of the invention.

[00130] FIG. 7 is a schematic of a viral genome of the invention.

[00131] FIG. 8 is a schematic of a viral genome of the invention.

[00132] FIG. 9 is a schematic of a viral genome of the invention.

[00133] The details of one or more embodiments of the invention are set forth in the accompanying description below. Although any materials and methods similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred materials and methods are now described. Other features, objects and advantages of the invention will be apparent from the description. In the description, the singular forms also include the plural unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. In the case of conflict, the present description will control.

DETAILED DESCRIPTION OF THE INVENTION

I. COMPOSITIONS OF THE INVENTION

[00134] According to the present invention, compositions for delivering modulatory polynucleotides and/or modulatory polynucleotide-based compositions by adeno-associated viruses (AAVs) are provided. AAV particles of the invention may be provided via any of several routes of administration, to a cell, tissue, organ, or organism, in vivo, ex vivo or in vitro.

[00135] As used herein, an "AAV particle" is a virus which comprises a viral genome with at least one payload region and at least one inverted terminal repeat (ITR) region.

[00136] As used herein, "viral genome" or "vector genome" or "viral vector" refers to the nucleic acid sequence(s) encapsulated in an AAV particle. Viral genomes comprise at least one payload region encoding polypeptides or fragments thereof.

[00137] As used herein, a "payload" or "payload region" is any nucleic acid molecule which encodes one or more polypeptides of the invention. At a minimum, a payload region comprises nucleic acid sequences that encode a sense and antisense sequence, an siRNA-based composition, or a fragment thereof, but may also optionally comprise one or more functional or regulatory elements to facilitate transcriptional expression and/or polypeptide translation.

[00138] The nucleic acid sequences and polypeptides disclosed herein may be engineered to contain modular elements and/or sequence motifs assembled to enable expression of the modulatory polynucleotides and/or modulatory polynucleotide-based compositions of the invention. In some embodiments, the nucleic acid sequence comprising the payload region may comprise one or more of a promoter region, an intron, a Kozak sequence, an enhancer or a polyadenylation sequence. Payload regions of the invention typically encode at least one sense and antisense sequence, an siRNA-based composition, or fragments of the foregoing in combination with each other or in combination with other polypeptide moieties.

[00139] The payload regions of the invention may be delivered to one or more target cells, tissues, organs or organisms within the viral genome of an AAV particle.

Adeno-associated viruses (AAVs) and AAV particles

[00140] Viruses of the Parvoviridae family are small non-enveloped icosahedral capsid viruses characterized by a single stranded DNA genome. Parvoviridae family viruses consist of two subfamilies: Parvovirinae, which infect vertebrates, and Densovirinae, which infect invertebrates. Due to its relatively simple structure, easily manipulated using standard molecular biology techniques, this virus family is useful as a biological tool. The genome of the virus may be modified to contain a minimum of components for the assembly of a functional recombinant

virus, or viral particle, which is loaded with or engineered to express or deliver a desired payload, which may be delivered to a target cell, tissue, organ, or organism.

[00141] The parvoviruses and other members of the Parvoviridae family are generally described in Kenneth I. Berns, "Parvoviridae: The Viruses and Their Replication," Chapter 69 in FIELDS VIROLOGY (3d Ed. 1996), the contents of which are incorporated by reference in their entirety.

[00142] The Parvoviridae family comprises the Dependovirus genus which includes adeno-associated viruses (AAV) capable of replication in vertebrate hosts including, but not limited to, human, primate, bovine, canine, equine, and ovine species.

[00143] The AAV viral genome is a linear, single-stranded DNA (ssDNA) molecule approximately 5,000 nucleotides (nt) in length. The AAV viral genome can comprise a payload region and at least one inverted terminal repeat (ITR) or ITR region. ITRs traditionally flank the coding nucleotide sequences for the non-structural proteins (encoded by Rep genes) and the structural proteins (encoded by capsid genes or Cap genes). While not wishing to be bound by theory, an AAV viral genome typically comprises two ITR sequences. The AAV viral genome comprises a characteristic T-shaped hairpin structure defined by the self-complementary terminal 145 nt of the 5' and 3' ends of the ssDNA which form an energetically stable double stranded region. The double stranded hairpin structures comprise multiple functions including, but not limited to, acting as an origin for DNA replication by functioning as primers for the endogenous DNA polymerase complex of the host viral replication cell.

[00144] In addition to the encoded heterologous payload, AAV vectors may comprise the viral genome, in whole or in part, of any naturally occurring and/or recombinant AAV serotype nucleotide sequence or variant. AAV variants may have sequences of significant homology at the nucleic acid (genome or capsid) and amino acid levels (capsids), to produce constructs which are generally physical and functional equivalents, replicate by similar mechanisms, and assemble by similar mechanisms. Chiorini et al., J. Vir. 71: 6823-33(1997); Srivastava et al., J. Vir. 45:555-64 (1983); Chiorini et al., J. Vir. 73:1309-1319 (1999); Rutledge et al., J. Vir. 72:309-319 (1998); and Wu et al., J. Vir. 74: 8635-47 (2000), the contents of each of which are incorporated herein by reference in their entirety.

[00145] In one embodiment, AAV particles of the present invention are recombinant AAV vectors which are replication defective, lacking sequences encoding functional Rep and Cap proteins within their viral genome. These defective AAV vectors may lack most or all parental coding sequences and essentially carry only one or two AAV ITR sequences and the nucleic acid of interest for delivery to a cell, a tissue, an organ or an organism.

[00146] In one embodiment, the viral genome of the AAV particles of the present invention comprise at least one control element which provides for the replication, transcription and translation of a coding sequence encoded therein. Not all of the control elements need always be present as long as the coding sequence is capable of being replicated, transcribed and/or translated in an appropriate host cell. Non-limiting examples of expression control elements include sequences for transcription initiation and/or termination, promoter and/or enhancer sequences, efficient RNA processing signals such as splicing and polyadenylation signals, sequences that stabilize cytoplasmic mRNA, sequences that enhance translation efficacy (e.g., Kozak consensus sequence), sequences that enhance protein stability, and/or sequences that enhance protein processing and/or secretion.

[00147] According to the present invention, AAV particles for use in therapeutics and/or diagnostics comprise a virus that has been distilled or reduced to the minimum components necessary for transduction of a nucleic acid payload or cargo of interest. In this manner, AAV particles are engineered as vehicles for specific delivery while lacking the deleterious replication and/or integration features found in wild-type viruses.

[00148] AAV vectors of the present invention may be produced recombinantly and may be based on adeno-associated virus (AAV) parent or reference sequences. As used herein, a "vector" is any molecule or moiety which transports, transduces or otherwise acts as a carrier of a heterologous molecule such as the nucleic acids described herein.

[00149] In addition to single stranded AAV viral genomes (e.g., ssAAVs), the present invention also provides for self-complementary AAV (scAAVs) viral genomes. scAAV viral genomes contain DNA strands which anneal together to form double stranded DNA. By skipping second strand synthesis, scAAVs allow for rapid expression in the cell.

[00150] In one embodiment, the AAV particle of the present invention is an scAAV.

[00151] In one embodiment, the AAV particle of the present invention is an ssAAV.

[00152] Methods for producing and/or modifying AAV particles are disclosed in the art such as pseudotyped AAV vectors (PCT Patent Publication Nos. WO200028004; WO200123001; WO2004112727; WO 2005005610 and WO 2005072364, the content of each of which is incorporated herein by reference in its entirety).

[00153] AAV particles may be modified to enhance the efficiency of delivery. Such modified AAV particles can be packaged efficiently and be used to successfully infect the target cells at high frequency and with minimal toxicity. In some embodiments the capsids of the AAV

particles are engineered according to the methods described in US Publication Number US 20130195801, the contents of which are incorporated herein by reference in their entirety.

[00154] In one embodiment, the AAV particles comprising a payload region encoding the polypeptides of the invention may be introduced into mammalian cells.

AAV serotypes

[00155] AAV particles of the present invention may comprise or be derived from any natural or recombinant AAV serotype. According to the present invention, the AAV particles may utilize or be based on a serotype selected from any of the following AAV1, AAV2, AAV2G9, AAV3, AAV3a, AAV3b, AAV3-3, AAV4, AAV4-4, AAV5, AAV6, AAV6.1, AAV6.2, AAV6.1.2, AAV7, AAV7.2, AAV8, AAV9, AAV9.11, AAV9.13, AAV9.16, AAV9.24, AAV9.45, AAV9.47, AAV9.61, AAV9.68, AAV9.84, AAV9.9, AAV10, AAV11, AAV12, AAV16.3, AAV24.1, AAV27.3, AAV42.12, AAV42-1b, AAV42-2, AAV42-3a, AAV42-3b, AAV42-4, AAV42-5a, AAV42-5b, AAV42-6b, AAV42-8, AAV42-10, AAV42-11, AAV42-12, AAV42-13, AAV42-15, AAV42-aa, AAV43-1, AAV43-12, AAV43-20, AAV43-21, AAV43-23, AAV43-25, AAV43-5, AAV44.1, AAV44.2, AAV44.5, AAV223.1, AAV223.2, AAV223.4, AAV223.5, AAV223.6, AAV223.7, AAV1-7/rh.48, AAV1-8/rh.49, AAV2-15/rh.62, AAV2-3/rh.61, AAV2-4/rh.50, AAV2-5/rh.51, AAV3.1/hu.6, AAV3.1/hu.9, AAV3-9/rh.52, AAV3-11/rh.53, AAV4-8/r11.64, AAV4-9/rh.54, AAV4-19/rh.55, AAV5-3/rh.57, AAV5-22/rh.58, AAV7.3/hu.7, AAV16.8/hu.10, AAV16.12/hu.11, AAV29.3/bb.1, AAV29.5/bb.2, AAV106.1/hu.37, AAV114.3/hu.40, AAV127.2/hu.41, AAV127.5/hu.42, AAV128.3/hu.44, AAV130.4/hu.48, AAV145.1/hu.53, AAV145.5/hu.54, AAV145.6/hu.55, AAV161.10/hu.60, AAV161.6/hu.61, AAV33.12/hu.17, AAV33.4/hu.15, AAV33.8/hu.16, AAV52/hu.19, AAV52.1/hu.20, AAV58.2/hu.25, AAVA3.3, AAVA3.4, AAVA3.5, AAVA3.7, AAVC1, AAVC2, AAVC5, AAV-DJ, AAV-DJ8, AAVF3, AAVF5, AAVH2, AAVrh.72, AAVhu.8, AAVrh.68, AAVrh.70, AAVpi.1, AAVpi.3, AAVpi.2, AAVrh.60, AAVrh.44, AAVrh.65, AAVrh.55, AAVrh.47, AAVrh.69, AAVrh.45, AAVrh.59, AAVhu.12, AAVH6, AAVLK03, AAVH-1/hu.1, AAVH-5/hu.3, AAVLG-10/rh.40, AAVLG-4/rh.38, AAVLG-9/hu.39, AAVN721-8/rh.43, AAVCh.5, AAVCh.5R1, AAVcy.2, AAVcy.3, AAVcy.4, AAVcy.5, AAVCy.5R1, AAVCy.5R2, AAVCy.5R3, AAVCy.5R4, AAVcy.6, AAVhu.1, AAVhu.2, AAVhu.3, AAVhu.4, AAVhu.5, AAVhu.6, AAVhu.7, AAVhu.9, AAVhu.10, AAVhu.11, AAVhu.13, AAVhu.15, AAVhu.16, AAVhu.17, AAVhu.18, AAVhu.20, AAVhu.21, AAVhu.22, AAVhu.23.2, AAVhu.24, AAVhu.25, AAVhu.27, AAVhu.28, AAVhu.29, AAVhu.29R, AAVhu.31, AAVhu.32, AAVhu.34, AAVhu.35, AAVhu.37, AAVhu.39,

AAVhu.40, AAVhu.41, AAVhu.42, AAVhu.43, AAVhu.44, AAVhu.44R1, AAVhu.44R2, AAVhu.44R3, AAVhu.45, AAVhu.46, AAVhu.47, AAVhu.48, AAVhu.48R1, AAVhu.48R2, AAVhu.48R3, AAVhu.49, AAVhu.51, AAVhu.52, AAVhu.54, AAVhu.55, AAVhu.56, AAVhu.57, AAVhu.58, AAVhu.60, AAVhu.61, AAVhu.63, AAVhu.64, AAVhu.66, AAVhu.67, AAVhu.14/9, AAVhu.t 19, AAVrh.2, AAVrh.2R, AAVrh.8, AAVrh.8R, AAVrh.10, AAVrh.12, AAVrh.13, AAVrh.13R, AAVrh.14, AAVrh.17, AAVrh.18, AAVrh.19, AAVrh.20, AAVrh.21, AAVrh.22, AAVrh.23, AAVrh.24, AAVrh.25, AAVrh.31, AAVrh.32, AAVrh.33, AAVrh.34, AAVrh.35, AAVrh.36, AAVrh.37, AAVrh.37R2, AAVrh.38, AAVrh.39, AAVrh.40, AAVrh.46, AAVrh.48, AAVrh.48.1, AAVrh.48.1.2, AAVrh.48.2, AAVrh.49, AAVrh.51, AAVrh.52, AAVrh.53, AAVrh.54, AAVrh.56, AAVrh.57, AAVrh.58, AAVrh.61, AAVrh.64, AAVrh.64R1, AAVrh.64R2, AAVrh.67, AAVrh.73, AAVrh.74, AAVrh8R, AAVrh8R A586R mutant, AAVrh8R R533A mutant, AAAV, BAAV, caprine AAV, bovine AAV, ovine AAV, AAVhE1.1, AAVhEr1.5, AAVhER1.14, AAVhEr1.8, AAVhEr1.16, AAVhEr1.18, AAVhEr1.35, AAVhEr1.7, AAVhEr1.36, AAVhEr2.29, AAVhEr2.4, AAVhEr2.16, AAVhEr2.30, AAVhEr2.31, AAVhEr2.36, AAVhER1.23, AAVhEr3.1, AAV2.5T , AAV-PAEC, AAV-LK01, AAV-LK02, AAV-LK03, AAV-LK04, AAV-LK05, AAV-LK06, AAV-LK07, AAV-LK08, AAV-LK09, AAV-LK10, AAV-LK11, AAV-LK12, AAV-LK13, AAV-LK14, AAV-LK15, AAV-LK16, AAV-LK17, AAV-LK18, AAV-LK19, AAV-PAEC2, AAV-PAEC4, AAV-PAEC6, AAV-PAEC7, AAV-PAEC8, AAV-PAEC11, AAV-PAEC12, AAV-2-pre-miRNA-101 , AAV-8h, AAV-8b, AAV-h, AAV-b, AAV SM 10-2 , AAV Shuffle 100-1 , AAV Shuffle 100-3, AAV Shuffle 100-7, AAV Shuffle 10-2, AAV Shuffle 10-6, AAV Shuffle 10-8, AAV Shuffle 100-2, AAV SM 10-1, AAV SM 10-8 , AAV SM 100-3, AAV SM 100-10, BNP61 AAV, BNP62 AAV, BNP63 AAV, AAVrh.50, AAVrh.43, AAVrh.62, AAVrh.48, AAVhu.19, AAVhu.11, AAVhu.53, AAV4-8/rh.64, AAVLG-9/hu.39, AAV54.5/hu.23, AAV54.2/hu.22, AAV54.7/hu.24, AAV54.1/hu.21, AAV54.4R/hu.27, AAV46.2/hu.28, AAV46.6/hu.29, AAV128.1/hu.43, true type AAV (ttAAV), UPENN AAV 10, Japanese AAV 10 serotypes, AAV CBr-7.1, AAV CBr-7.10, AAV CBr-7.2, AAV CBr-7.3, AAV CBr-7.4, AAV CBr-7.5, AAV CBr-7.7, AAV CBr-7.8, AAV CBr-B7.3, AAV CBr-B7.4, AAV CBr-E1, AAV CBr-E2, AAV CBr-E3, AAV CBr-E4, AAV CBr-E5, AAV CBr-e5, AAV CBr-E6, AAV CBr-E7, AAV CBr-E8, AAV CHt-1, AAV CHt-2, AAV CHt-3, AAV CHt-6.1, AAV CHt-6.10, AAV CHt-6.5, AAV CHt-6.6, AAV CHt-6.7, AAV CHt-6.8, AAV CHt-P1, AAV CHt-P2, AAV CHt-P5, AAV CHt-P6, AAV CHt-P8, AAV CHt-P9, AAV CKd-1, AAV CKd-10, AAV CKd-2, AAV CKd-3, AAV CKd-4, AAV CKd-6, AAV CKd-7, AAV CKd-8, AAV CKd-B1, AAV

CKd-B2, AAV CKd-B3, AAV CKd-B4, AAV CKd-B5, AAV CKd-B6, AAV CKd-B7, AAV CKd-B8, AAV CKd-H1, AAV CKd-H2, AAV CKd-H3, AAV CKd-H4, AAV CKd-H5, AAV CKd-H6, AAV CKd-N3, AAV CKd-N4, AAV CKd-N9, AAV CLg-F1, AAV CLg-F2, AAV CLg-F3, AAV CLg-F4, AAV CLg-F5, AAV CLg-F6, AAV CLg-F7, AAV CLg-F8, AAV CLv-1, AAV CLv1-1, AAV Clv1-10, AAV CLv1-2, AAV CLv-12, AAV CLv1-3, AAV CLv-13, AAV CLv1-4, AAV Clv1-7, AAV Clv1-8, AAV Clv1-9, AAV CLv-2, AAV CLv-3, AAV CLv-4, AAV CLv-6, AAV CLv-8, AAV CLv-D1, AAV CLv-D2, AAV CLv-D3, AAV CLv-D4, AAV CLv-D5, AAV CLv-D6, AAV CLv-D7, AAV CLv-D8, AAV CLv-E1, AAV CLv-K1, AAV CLv-K3, AAV CLv-K6, AAV CLv-L4, AAV CLv-L5, AAV CLv-L6, AAV CLv-M1, AAV CLv-M11, AAV CLv-M2, AAV CLv-M5, AAV CLv-M6, AAV CLv-M7, AAV CLv-M8, AAV CLv-M9, AAV CLv-R1, AAV CLv-R2, AAV CLv-R3, AAV CLv-R4, AAV CLv-R5, AAV CLv-R6, AAV CLv-R7, AAV CLv-R8, AAV CLv-R9, AAV CSp-1, AAV CSp-10, AAV CSp-11, AAV CSp-2, AAV CSp-3, AAV CSp-4, AAV CSp-6, AAV CSp-7, AAV CSp-8, AAV CSp-8.10, AAV CSp-8.2, AAV CSp-8.4, AAV CSp-8.5, AAV CSp-8.6, AAV CSp-8.7, AAV CSp-8.8, AAV CSp-8.9, AAV CSp-9, AAV.hu.48R3, AAV.VR-355, AAV3B, AAV4, AAV5, AAVF1/HSC1, AAVF11/HSC11, AAVF12/HSC12, AAVF13/HSC13, AAVF14/HSC14, AAVF15/HSC15, AAVF16/HSC16, AAVF17/HSC17, AAVF2/HSC2, AAVF3/HSC3, AAVF4/HSC4, AAVF5/HSC5, AAVF6/HSC6, AAVF7/HSC7, AAVF8/HSC8, AAVF9/HSC9, AAV-PHP.B (PHP.B), AAV-PHP.A (PHP.A), G2B-26, G2B-13, TH1.1-32, TH1.1-35, AAVPHP.B2, AAVPHP.B3, AAVPHP.N/PHP.B-DGT, AAVPHP.B-EST, AAVPHP.B-GGT, AAVPHP.B-ATP, AAVPHP.B-ATT-T, AAVPHP.B-DGT-T, AAVPHP.B-GGT-T, AAVPHP.B-SGS, AAVPHP.B-AQP, AAVPHP.B-QQP, AAVPHP.B-SNP(3), AAVPHP.B-SNP, AAVPHP.B-QGT, AAVPHP.B-NQT, AAVPHP.B-EGS, AAVPHP.B-SGN, AAVPHP.B-EGT, AAVPHP.B-DST, AAVPHP.B-DST, AAVPHP.B-STP, AAVPHP.B-PQP, AAVPHP.B-SQP, AAVPHP.B-QLP, AAVPHP.B-TMP, AAVPHP.B-TTP, AAVPHP.S/G2A12, AAVG2A15/G2A3, AAVG2B4, AAVG2B5 and variants thereof.

[00156] In some embodiments, the AAV serotype may be, or have, a sequence as described in United States Publication No. US20030138772, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV1 (SEQ ID NO: 6 and 64 of US20030138772), AAV2 (SEQ ID NO: 7 and 70 of US20030138772), AAV3 (SEQ ID NO: 8 and 71 of US20030138772), AAV4 (SEQ ID NO: 63 of US20030138772), AAV5 (SEQ ID NO: 114 of US20030138772), AAV6 (SEQ ID NO: 65 of US20030138772), AAV7 (SEQ ID NO: 1-3 of US20030138772), AAV8 (SEQ ID NO: 4 and 95 of US20030138772), AAV9 (SEQ ID NO:

5 and 100 of US20030138772), AAV10 (SEQ ID NO: 117 of US20030138772), AAV11 (SEQ ID NO: 118 of US20030138772), AAV12 (SEQ ID NO: 119 of US20030138772), AAVrh10 (amino acids 1 to 738 of SEQ ID NO: 81 of US20030138772), AAV16.3 (US20030138772 SEQ ID NO: 10), AAV29.3/bb.1 (US20030138772 SEQ ID NO: 11), AAV29.4 (US20030138772 SEQ ID NO: 12), AAV29.5/bb.2 (US20030138772 SEQ ID NO: 13), AAV1.3 (US20030138772 SEQ ID NO: 14), AAV13.3 (US20030138772 SEQ ID NO: 15), AAV24.1 (US20030138772 SEQ ID NO: 16), AAV27.3 (US20030138772 SEQ ID NO: 17), AAV7.2 (US20030138772 SEQ ID NO: 18), AAVC1 (US20030138772 SEQ ID NO: 19), AAVC3 (US20030138772 SEQ ID NO: 20), AAVC5 (US20030138772 SEQ ID NO: 21), AAVF1 (US20030138772 SEQ ID NO: 22), AAVF3 (US20030138772 SEQ ID NO: 23), AAVF5 (US20030138772 SEQ ID NO: 24), AAVH6 (US20030138772 SEQ ID NO: 25), AAVH2 (US20030138772 SEQ ID NO: 26), AAV42-8 (US20030138772 SEQ ID NO: 27), AAV42-15 (US20030138772 SEQ ID NO: 28), AAV42-5b (US20030138772 SEQ ID NO: 29), AAV42-1b (US20030138772 SEQ ID NO: 30), AAV42-13 (US20030138772 SEQ ID NO: 31), AAV42-3a (US20030138772 SEQ ID NO: 32), AAV42-4 (US20030138772 SEQ ID NO: 33), AAV42-5a (US20030138772 SEQ ID NO: 34), AAV42-10 (US20030138772 SEQ ID NO: 35), AAV42-3b (US20030138772 SEQ ID NO: 36), AAV42-11 (US20030138772 SEQ ID NO: 37), AAV42-6b (US20030138772 SEQ ID NO: 38), AAV43-1 (US20030138772 SEQ ID NO: 39), AAV43-5 (US20030138772 SEQ ID NO: 40), AAV43-12 (US20030138772 SEQ ID NO: 41), AAV43-20 (US20030138772 SEQ ID NO: 42), AAV43-21 (US20030138772 SEQ ID NO: 43), AAV43-23 (US20030138772 SEQ ID NO: 44), AAV43-25 (US20030138772 SEQ ID NO: 45), AAV44.1 (US20030138772 SEQ ID NO: 46), AAV44.5 (US20030138772 SEQ ID NO: 47), AAV223.1 (US20030138772 SEQ ID NO: 48), AAV223.2 (US20030138772 SEQ ID NO: 49), AAV223.4 (US20030138772 SEQ ID NO: 50), AAV223.5 (US20030138772 SEQ ID NO: 51), AAV223.6 (US20030138772 SEQ ID NO: 52), AAV223.7 (US20030138772 SEQ ID NO: 53), AAVA3.4 (US20030138772 SEQ ID NO: 54), AAVA3.5 (US20030138772 SEQ ID NO: 55), AAVA3.7 (US20030138772 SEQ ID NO: 56), AAVA3.3 (US20030138772 SEQ ID NO: 57), AAV42.12 (US20030138772 SEQ ID NO: 58), AAV44.2 (US20030138772 SEQ ID NO: 59), AAV42-2 (US20030138772 SEQ ID NO: 9), or variants thereof.

[00157] In some embodiments, the AAV serotype may be, or have, a sequence as described in United States Publication No. US20150159173, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV2 (SEQ ID NO: 7 and 23 of US20150159173), rh20 (SEQ ID NO: 1 of US20150159173), rh32/33 (SEQ ID NO: 2 of

US20150159173), rh39 (SEQ ID NO: 3, 20 and 36 of US20150159173), rh46 (SEQ ID NO: 4 and 22 of US20150159173), rh73 (SEQ ID NO: 5 of US20150159173), rh74 (SEQ ID NO: 6 of US20150159173), AAV6.1 (SEQ ID NO: 29 of US20150159173), rh.8 (SEQ ID NO: 41 of US20150159173), rh.48.1 (SEQ ID NO: 44 of US20150159173), hu.44 (SEQ ID NO: 45 of US20150159173), hu.29 (SEQ ID NO: 42 of US20150159173), hu.48 (SEQ ID NO: 38 of US20150159173), rh54 (SEQ ID NO: 49 of US20150159173), AAV2 (SEQ ID NO: 7 of US20150159173), cy.5 (SEQ ID NO: 8 and 24 of US20150159173), rh.10 (SEQ ID NO: 9 and 25 of US20150159173), rh.13 (SEQ ID NO: 10 and 26 of US20150159173), AAV1 (SEQ ID NO: 11 and 27 of US20150159173), AAV3 (SEQ ID NO: 12 and 28 of US20150159173), AAV6 (SEQ ID NO: 13 and 29 of US20150159173), AAV7 (SEQ ID NO: 14 and 30 of US20150159173), AAV8 (SEQ ID NO: 15 and 31 of US20150159173), hu.13 (SEQ ID NO: 16 and 32 of US20150159173), hu.26 (SEQ ID NO: 17 and 33 of US20150159173), hu.37 (SEQ ID NO: 18 and 34 of US20150159173), hu.53 (SEQ ID NO: 19 and 35 of US20150159173), rh.43 (SEQ ID NO: 21 and 37 of US20150159173), rh2 (SEQ ID NO: 39 of US20150159173), rh.37 (SEQ ID NO: 40 of US20150159173), rh.64 (SEQ ID NO: 43 of US20150159173), rh.48 (SEQ ID NO: 44 of US20150159173), ch.5 (SEQ ID NO 46 of US20150159173), rh.67 (SEQ ID NO: 47 of US20150159173), rh.58 (SEQ ID NO: 48 of US20150159173), or variants thereof including, but not limited to Cy5R1, Cy5R2, Cy5R3, Cy5R4, rh.13R, rh.37R2, rh.2R, rh.8R, rh.48.1, rh.48.2, rh.48.1.2, hu.44R1, hu.44R2, hu.44R3, hu.29R, ch.5R1, rh64R1, rh64R2, AAV6.2, AAV6.1, AAV6.12, hu.48R1, hu.48R2, and hu.48R3.

[00158] In some embodiments, the AAV serotype may be, or have, a sequence as described in United States Patent No. US 7198951, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV9 (SEQ ID NO: 1-3 of US 7198951), AAV2 (SEQ ID NO: 4 of US 7198951), AAV1 (SEQ ID NO: 5 of US 7198951), AAV3 (SEQ ID NO: 6 of US 7198951), and AAV8 (SEQ ID NO: 7 of US7198951).

[00159] In some embodiments, the AAV serotype may be, or have, a mutation in the AAV9 sequence as described by N Pulicherla et al. (Molecular Therapy 19(6):1070-1078 (2011), herein incorporated by reference in its entirety), such as but not limited to, AAV9.9, AAV9.11, AAV9.13, AAV9.16, AAV9.24, AAV9.45, AAV9.47, AAV9.61, AAV9.68, AAV9.84.

[00160] In some embodiments, the AAV serotype may be, or have, a sequence as described in United States Patent No. US 6156303, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV3B (SEQ ID NO: 1 and 10 of US 6156303),

AAV6 (SEQ ID NO: 2, 7 and 11 of US 6156303), AAV2 (SEQ ID NO: 3 and 8 of US 6156303), AAV3A (SEQ ID NO: 4 and 9, of US 6156303), or derivatives thereof.

[00161] In some embodiments, the AAV serotype may be, or have, a sequence as described in United States Publication No. US20140359799, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV8 (SEQ ID NO: 1 of US20140359799), AAVDJ (SEQ ID NO: 2 and 3 of US20140359799), or variants thereof.

[00162] In some embodiments, the serotype may be AAVDJ (AAV-DJ) or a variant thereof, such as AAVDJ8 (or AAV-DJ8), as described by Grimm et al. (Journal of Virology 82(12): 5887-5911 (2008), herein incorporated by reference in its entirety). The amino acid sequence of AAVDJ8 may comprise two or more mutations in order to remove the heparin binding domain (HBD). As a non-limiting example, the AAV-DJ sequence described as SEQ ID NO: 1 in US Patent No. 7,588,772, the contents of which are herein incorporated by reference in their entirety, may comprise two mutations: (1) R587Q where arginine (R; Arg) at amino acid 587 is changed to glutamine (Q; Gln) and (2) R590T where arginine (R; Arg) at amino acid 590 is changed to threonine (T; Thr). As another non-limiting example, may comprise three mutations: (1) K406R where lysine (K; Lys) at amino acid 406 is changed to arginine (R; Arg), (2) R587Q where arginine (R; Arg) at amino acid 587 is changed to glutamine (Q; Gln) and (3) R590T where arginine (R; Arg) at amino acid 590 is changed to threonine (T; Thr).

[00163] In some embodiments, the AAV serotype may be, or have, a sequence of AAV4 as described in International Publication No. WO1998011244, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to AAV4 (SEQ ID NO: 1-20 of WO1998011244).

[00164] In some embodiments, the AAV serotype may be, or have, a mutation in the AAV2 sequence to generate AAV2G9 as described in International Publication No. WO2014144229 and herein incorporated by reference in its entirety.

[00165] In some embodiments, the AAV serotype may be, or have, a sequence as described in International Publication No. WO2005033321, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to AAV3-3 (SEQ ID NO: 217 of WO2005033321), AAV1 (SEQ ID NO: 219 and 202 of WO2005033321), AAV106.1/hu.37 (SEQ ID No: 10 of WO2005033321), AAV114.3/hu.40 (SEQ ID No: 11 of WO2005033321), AAV127.2/hu.41 (SEQ ID NO:6 and 8 of WO2005033321), AAV128.3/hu.44 (SEQ ID No: 81 of WO2005033321), AAV130.4/hu.48 (SEQ ID NO: 78 of WO2005033321), AAV145.1/hu.53 (SEQ ID No: 176 and 177 of WO2005033321), AAV145.6/hu.56 (SEQ ID NO: 168 and 192 of

WO2005033321), AAV16.12/hu.11 (SEQ ID NO:: 153 and 57 of WO2005033321), AAV16.8/hu.10 (SEQ ID NO:: 156 and 56 of WO2005033321), AAV161.10/hu.60 (SEQ ID No: 170 of WO2005033321), AAV161.6/hu.61 (SEQ ID No: 174 of WO2005033321), AAV1-7/rh.48 (SEQ ID NO: 32 of WO2005033321), AAV1-8/rh.49 (SEQ ID NOs: 103 and 25 of WO2005033321), AAV2 (SEQ ID NO: 211 and 221 of WO2005033321), AAV2-15/rh.62 (SEQ ID No: 33 and 114 of WO2005033321), AAV2-3/rh.61 (SEQ ID NO: 21 of WO2005033321), AAV2-4/rh.50 (SEQ ID No: 23 and 108 of WO2005033321), AAV2-5/rh.51 (SEQ ID NO: 104 and 22 of WO2005033321), AAV3.1/hu.6 (SEQ ID NO: 5 and 84 of WO2005033321), AAV3.1/hu.9 (SEQ ID NO: 155 and 58 of WO2005033321), AAV3-11/rh.53 (SEQ ID NO: 186 and 176 of WO2005033321), AAV3-3 (SEQ ID NO: 200 of WO2005033321), AAV33.12/hu.17 (SEQ ID NO:4 of WO2005033321), AAV33.4/hu.15 (SEQ ID No: 50 of WO2005033321), AAV33.8/hu.16 (SEQ ID No: 51 of WO2005033321), AAV3-9/rh.52 (SEQ ID NO: 96 and 18 of WO2005033321), AAV4-19/rh.55 (SEQ ID NO: 117 of WO2005033321), AAV4-4 (SEQ ID NO: 201 and 218 of WO2005033321), AAV4-9/rh.54 (SEQ ID NO: 116 of WO2005033321), AAV5 (SEQ ID NO: 199 and 216 of WO2005033321), AAV52.1/hu.20 (SEQ ID NO: 63 of WO2005033321), AAV52/hu.19 (SEQ ID NO: 133 of WO2005033321), AAV5-22/rh.58 (SEQ ID No: 27 of WO2005033321), AAV5-3/rh.57 (SEQ ID NO: 105 of WO2005033321), AAV5-3/rh.57 (SEQ ID No: 26 of WO2005033321), AAV58.2/hu.25 (SEQ ID No: 49 of WO2005033321), AAV6 (SEQ ID NO: 203 and 220 of WO2005033321), AAV7 (SEQ ID NO: 222 and 213 of WO2005033321), AAV7.3/hu.7 (SEQ ID No: 55 of WO2005033321), AAV8 (SEQ ID NO: 223 and 214 of WO2005033321), AAVH-1/hu.1 (SEQ ID No: 46 of WO2005033321), AAVH-5/hu.3 (SEQ ID No: 44 of WO2005033321), AAVhu.1 (SEQ ID NO: 144 of WO2005033321), AAVhu.10 (SEQ ID NO: 156 of WO2005033321), AAVhu.11 (SEQ ID NO: 153 of WO2005033321), AAVhu.12 (WO2005033321 SEQ ID NO: 59), AAVhu.13 (SEQ ID NO: 129 of WO2005033321), AAVhu.14/AAV9 (SEQ ID NO: 123 and 3 of WO2005033321), AAVhu.15 (SEQ ID NO: 147 of WO2005033321), AAVhu.16 (SEQ ID NO: 148 of WO2005033321), AAVhu.17 (SEQ ID NO: 83 of WO2005033321), AAVhu.18 (SEQ ID NO: 149 of WO2005033321), AAVhu.19 (SEQ ID NO: 133 of WO2005033321), AAVhu.2 (SEQ ID NO: 143 of WO2005033321), AAVhu.20 (SEQ ID NO: 134 of WO2005033321), AAVhu.21 (SEQ ID NO: 135 of WO2005033321), AAVhu.22 (SEQ ID NO: 138 of WO2005033321), AAVhu.23.2 (SEQ ID NO: 137 of WO2005033321), AAVhu.24 (SEQ ID NO: 136 of WO2005033321), AAVhu.25 (SEQ ID NO: 146 of WO2005033321), AAVhu.27 (SEQ ID NO: 140 of WO2005033321), AAVhu.29 (SEQ ID NO: 132 of WO2005033321),

AAVhu.3 (SEQ ID NO: 145 of WO2005033321), AAVhu.31 (SEQ ID NO: 121 of WO2005033321), AAVhu.32 (SEQ ID NO: 122 of WO2005033321), AAVhu.34 (SEQ ID NO: 125 of WO2005033321), AAVhu.35 (SEQ ID NO: 164 of WO2005033321), AAVhu.37 (SEQ ID NO: 88 of WO2005033321), AAVhu.39 (SEQ ID NO: 102 of WO2005033321), AAVhu.4 (SEQ ID NO: 141 of WO2005033321), AAVhu.40 (SEQ ID NO: 87 of WO2005033321), AAVhu.41 (SEQ ID NO: 91 of WO2005033321), AAVhu.42 (SEQ ID NO: 85 of WO2005033321), AAVhu.43 (SEQ ID NO: 160 of WO2005033321), AAVhu.44 (SEQ ID NO: 144 of WO2005033321), AAVhu.45 (SEQ ID NO: 127 of WO2005033321), AAVhu.46 (SEQ ID NO: 159 of WO2005033321), AAVhu.47 (SEQ ID NO: 128 of WO2005033321), AAVhu.48 (SEQ ID NO: 157 of WO2005033321), AAVhu.49 (SEQ ID NO: 189 of WO2005033321), AAVhu.51 (SEQ ID NO: 190 of WO2005033321), AAVhu.52 (SEQ ID NO: 191 of WO2005033321), AAVhu.53 (SEQ ID NO: 186 of WO2005033321), AAVhu.54 (SEQ ID NO: 188 of WO2005033321), AAVhu.55 (SEQ ID NO: 187 of WO2005033321), AAVhu.56 (SEQ ID NO: 192 of WO2005033321), AAVhu.57 (SEQ ID NO: 193 of WO2005033321), AAVhu.58 (SEQ ID NO: 194 of WO2005033321), AAVhu.6 (SEQ ID NO: 84 of WO2005033321), AAVhu.60 (SEQ ID NO: 184 of WO2005033321), AAVhu.61 (SEQ ID NO: 185 of WO2005033321), AAVhu.63 (SEQ ID NO: 195 of WO2005033321), AAVhu.64 (SEQ ID NO: 196 of WO2005033321), AAVhu.66 (SEQ ID NO: 197 of WO2005033321), AAVhu.67 (SEQ ID NO: 198 of WO2005033321), AAVhu.7 (SEQ ID NO: 150 of WO2005033321), AAVhu.8 (WO2005033321 SEQ ID NO: 12), AAVhu.9 (SEQ ID NO: 155 of WO2005033321), AAVLG-10/rh.40 (SEQ ID No: 14 of WO2005033321), AAVLG-4/rh.38 (SEQ ID NO: 86 of WO2005033321), AAVLG-4/rh.38 (SEQ ID No: 7 of WO2005033321), AAVN721-8/rh.43 (SEQ ID NO: 163 of WO2005033321), AAVN721-8/rh.43 (SEQ ID No: 43 of WO2005033321), AAVpi.1 (WO2005033321 SEQ ID NO: 28), AAVpi.2 (WO2005033321 SEQ ID NO: 30), AAVpi.3 (WO2005033321 SEQ ID NO: 29), AAVrh.38 (SEQ ID NO: 86 of WO2005033321), AAVrh.40 (SEQ ID NO: 92 of WO2005033321), AAVrh.43 (SEQ ID NO: 163 of WO2005033321), AAVrh.44 (WO2005033321 SEQ ID NO: 34), AAVrh.45 (WO2005033321 SEQ ID NO: 41), AAVrh.47 (WO2005033321 SEQ ID NO: 38), AAVrh.48 (SEQ ID NO: 115 of WO2005033321), AAVrh.49 (SEQ ID NO: 103 of WO2005033321), AAVrh.50 (SEQ ID NO: 108 of WO2005033321), AAVrh.51 (SEQ ID NO: 104 of WO2005033321), AAVrh.52 (SEQ ID NO: 96 of WO2005033321), AAVrh.53 (SEQ ID NO: 97 of WO2005033321), AAVrh.55 (WO2005033321 SEQ ID NO: 37), AAVrh.56 (SEQ ID NO: 152 of WO2005033321), AAVrh.57 (SEQ ID NO: 105 of WO2005033321), AAVrh.58 (SEQ ID

NO: 106 of WO2005033321), AAVrh.59 (WO2005033321 SEQ ID NO: 42), AAVrh.60 (WO2005033321 SEQ ID NO: 31), AAVrh.61 (SEQ ID NO: 107 of WO2005033321), AAVrh.62 (SEQ ID NO: 114 of WO2005033321), AAVrh.64 (SEQ ID NO: 99 of WO2005033321), AAVrh.65 (WO2005033321 SEQ ID NO: 35), AAVrh.68 (WO2005033321 SEQ ID NO: 16), AAVrh.69 (WO2005033321 SEQ ID NO: 39), AAVrh.70 (WO2005033321 SEQ ID NO: 20), AAVrh.72 (WO2005033321 SEQ ID NO: 9), or variants thereof including, but not limited to, AAVcy.2, AAVcy.3, AAVcy.4, AAVcy.5, AAVcy.6, AAVrh.12, AAVrh.17, AAVrh.18, AAVrh.19, AAVrh.21, AAVrh.22, AAVrh.23, AAVrh.24, AAVrh.25, AAVrh.25/42 15, AAVrh.31, AAVrh.32, AAVrh.33, AAVrh.34, AAVrh.35, AAVrh.36, AAVrh.37, AAVrh14. Non limiting examples of variants include SEQ ID NO: 13, 15, 17, 19, 24, 36, 40, 45, 47, 48, 51-54, 60-62, 64-77, 79, 80, 82, 89, 90, 93-95, 98, 100, 101, , 109-113, 118-120, 124, 126, 131, 139, 142, 151,154, 158, 161, 162, 165-183, 202, 204-212, 215, 219, 224-236, of WO2005033321, the contents of which are herein incorporated by reference in their entirety.

[00166] In some embodiments, the AAV serotype may be, or have, a sequence as described in International Publication No. WO2015168666, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAVrh8R (SEQ ID NO: 9 of WO2015168666), AAVrh8R A586R mutant (SEQ ID NO: 10 of WO2015168666), AAVrh8R R533A mutant (SEQ ID NO: 11 of WO2015168666), or variants thereof.

[00167] In some embodiments, the AAV serotype may be, or have, a sequence as described in United States Patent No. US9233131, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAVhE1.1 (SEQ ID NO:44 of US9233131), AAVhEr1.5 (SEQ ID NO:45 of US9233131), AAVhER1.14 (SEQ ID NO:46 of US9233131), AAVhEr1.8 (SEQ ID NO:47 of US9233131), AAVhEr1.16 (SEQ ID NO:48 of US9233131), AAVhEr1.18 (SEQ ID NO:49 of US9233131), AAVhEr1.35 (SEQ ID NO:50 of US9233131), AAVhEr1.7 (SEQ ID NO:51 of US9233131), AAVhEr1.36 (SEQ ID NO:52 of US9233131), AAVhEr2.29 (SEQ ID NO:53 of US9233131), AAVhEr2.4 (SEQ ID NO:54 of US9233131), AAVhEr2.16 (SEQ ID NO:55 of US9233131), AAVhEr2.30 (SEQ ID NO:56 of US9233131), AAVhEr2.31 (SEQ ID NO:58 of US9233131), AAVhEr2.36 (SEQ ID NO:57 of US9233131), AAVhER1.23 (SEQ ID NO:53 of US9233131), AAVhEr3.1 (SEQ ID NO:59 of US9233131), AAV2.5T (SEQ ID NO:42 of US9233131), or variants thereof.

[00168] In some embodiments, the AAV serotype may be, or have, a sequence as described in United States Patent Publication No. US20150376607, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV-PAEC (SEQ ID

NO:1 of US20150376607), AAV-LK01 (SEQ ID NO:2 of US20150376607), AAV-LK02 (SEQ ID NO:3 of US20150376607), AAV-LK03 (SEQ ID NO:4 of US20150376607), AAV-LK04 (SEQ ID NO:5 of US20150376607), AAV-LK05 (SEQ ID NO:6 of US20150376607), AAV-LK06 (SEQ ID NO:7 of US20150376607), AAV-LK07 (SEQ ID NO:8 of US20150376607), AAV-LK08 (SEQ ID NO:9 of US20150376607), AAV-LK09 (SEQ ID NO:10 of US20150376607), AAV-LK10 (SEQ ID NO:11 of US20150376607), AAV-LK11 (SEQ ID NO:12 of US20150376607), AAV-LK12 (SEQ ID NO:13 of US20150376607), AAV-LK13 (SEQ ID NO:14 of US20150376607), AAV-LK14 (SEQ ID NO:15 of US20150376607), AAV-LK15 (SEQ ID NO:16 of US20150376607), AAV-LK16 (SEQ ID NO:17 of US20150376607), AAV-LK17 (SEQ ID NO:18 of US20150376607), AAV-LK18 (SEQ ID NO:19 of US20150376607), AAV-LK19 (SEQ ID NO:20 of US20150376607), AAV-PAEC2 (SEQ ID NO:21 of US20150376607), AAV-PAEC4 (SEQ ID NO:22 of US20150376607), AAV-PAEC6 (SEQ ID NO:23 of US20150376607), AAV-PAEC7 (SEQ ID NO:24 of US20150376607), AAV-PAEC8 (SEQ ID NO:25 of US20150376607), AAV-PAEC11 (SEQ ID NO:26 of US20150376607), AAV-PAEC12 (SEQ ID NO:27, of US20150376607), or variants thereof.

[00169] In some embodiments, the AAV serotype may be, or have, a sequence as described in United States Patent No. US9163261, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV-2-pre-miRNA-101 (SEQ ID NO: 1 US9163261), or variants thereof.

[00170] In some embodiments, the AAV serotype may be, or have, a sequence as described in United States Patent Publication No. US20150376240, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV-8h (SEQ ID NO: 6 of US20150376240), AAV-8b (SEQ ID NO: 5 of US20150376240), AAV-h (SEQ ID NO: 2 of US20150376240), AAV-b (SEQ ID NO: 1 of US20150376240), or variants thereof.

[00171] In some embodiments, the AAV serotype may be, or have, a sequence as described in United States Patent Publication No. US20160017295, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV SM 10-2 (SEQ ID NO: 22 of US20160017295), AAV Shuffle 100-1 (SEQ ID NO: 23 of US20160017295), AAV Shuffle 100-3 (SEQ ID NO: 24 of US20160017295), AAV Shuffle 100-7 (SEQ ID NO: 25 of US20160017295), AAV Shuffle 10-2 (SEQ ID NO: 34 of US20160017295), AAV Shuffle 10-6 (SEQ ID NO: 35 of US20160017295), AAV Shuffle 10-8 (SEQ ID NO: 36 of US20160017295), AAV Shuffle 100-2 (SEQ ID NO: 37 of US20160017295), AAV SM 10-1 (SEQ ID NO: 38 of US20160017295), AAV SM 10-8 (SEQ ID NO: 39 of US20160017295), AAV SM 100-3 (SEQ

ID NO: 40 of US20160017295), AAV SM 100-10 (SEQ ID NO: 41 of US20160017295), or variants thereof.

[00172] In some embodiments, the AAV serotype may be, or have, a sequence as described in United States Patent Publication No. US20150238550, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, BNP61 AAV (SEQ ID NO: 1 of US20150238550), BNP62 AAV (SEQ ID NO: 3 of US20150238550), BNP63 AAV (SEQ ID NO: 4 of US20150238550), or variants thereof.

[00173] In some embodiments, the AAV serotype may be or may have a sequence as described in United States Patent Publication No. US20150315612, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAVrh.50 (SEQ ID NO: 108 of US20150315612), AAVrh.43 (SEQ ID NO: 163 of US20150315612), AAVrh.62 (SEQ ID NO: 114 of US20150315612), AAVrh.48 (SEQ ID NO: 115 of US20150315612), AAVhu.19 (SEQ ID NO: 133 of US20150315612), AAVhu.11 (SEQ ID NO: 153 of US20150315612), AAVhu.53 (SEQ ID NO: 186 of US20150315612), AAV4-8/rh.64 (SEQ ID No: 15 of US20150315612), AAVLG-9/hu.39 (SEQ ID No: 24 of US20150315612), AAV54.5/hu.23 (SEQ ID No: 60 of US20150315612), AAV54.2/hu.22 (SEQ ID No: 67 of US20150315612), AAV54.7/hu.24 (SEQ ID No: 66 of US20150315612), AAV54.1/hu.21 (SEQ ID No: 65 of US20150315612), AAV54.4R/hu.27 (SEQ ID No: 64 of US20150315612), AAV46.2/hu.28 (SEQ ID No: 68 of US20150315612), AAV46.6/hu.29 (SEQ ID No: 69 of US20150315612), AAV128.1/hu.43 (SEQ ID No: 80 of US20150315612), or variants thereof.

[00174] In some embodiments, the AAV serotype may be, or have, a sequence as described in International Publication No. WO2015121501, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, true type AAV (ttAAV) (SEQ ID NO: 2 of WO2015121501), "UPenn AAV10" (SEQ ID NO: 8 of WO2015121501), "Japanese AAV10" (SEQ ID NO: 9 of WO2015121501), or variants thereof.

[00175] According to the present invention, AAV capsid serotype selection or use may be from a variety of species. In one embodiment, the AAV may be an avian AAV (AAAV). The AAAV serotype may be, or have, a sequence as described in United States Patent No. US 9238800, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAAV (SEQ ID NO: 1, 2, 4, 6, 8, 10, 12, and 14 of US 9,238,800), or variants thereof.

[00176] In one embodiment, the AAV may be a bovine AAV (BAAV). The BAAV serotype may be, or have, a sequence as described in United States Patent No. US 9,193,769, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, BAAV

(SEQ ID NO: 1 and 6 of US 9193769), or variants thereof. The BAAV serotype may be or have a sequence as described in United States Patent No. US7427396, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, BAAV (SEQ ID NO: 5 and 6 of US7427396), or variants thereof.

[00177] In one embodiment, the AAV may be a caprine AAV. The caprine AAV serotype may be, or have, a sequence as described in United States Patent No. US7427396, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, caprine AAV (SEQ ID NO: 3 of US7427396), or variants thereof.

[00178] In other embodiments the AAV may be engineered as a hybrid AAV from two or more parental serotypes. In one embodiment, the AAV may be AAV2G9 which comprises sequences from AAV2 and AAV9. The AAV2G9 AAV serotype may be, or have, a sequence as described in United States Patent Publication No. US20160017005, the contents of which are herein incorporated by reference in its entirety.

[00179] In one embodiment, the AAV may be a serotype generated by the AAV9 capsid library with mutations in amino acids 390-627 (VP1 numbering) as described by Pulicherla et al. (Molecular Therapy 19(6):1070-1078 (2011), the contents of which are herein incorporated by reference in their entirety. The serotype and corresponding nucleotide and amino acid substitutions may be, but is not limited to, AAV9.1 (G1594C; D532H), AAV6.2 (T1418A and T1436X; V473D and I479K), AAV9.3 (T1238A; F413Y), AAV9.4 (T1250C and A1617T; F417S), AAV9.5 (A1235G, A1314T, A1642G, C1760T; Q412R, T548A, A587V), AAV9.6 (T1231A; F411I), AAV9.9 (G1203A, G1785T; W595C), AAV9.10 (A1500G, T1676C; M559T), AAV9.11 (A1425T, A1702C, A1769T; T568P, Q590L), AAV9.13 (A1369C, A1720T; N457H, T574S), AAV9.14 (T1340A, T1362C, T1560C, G1713A; L447H), AAV9.16 (A1775T; Q592L), AAV9.24 (T1507C, T1521G; W503R), AAV9.26 (A1337G, A1769C; Y446C, Q590P), AAV9.33 (A1667C; D556A), AAV9.34 (A1534G, C1794T; N512D), AAV9.35 (A1289T, T1450A, C1494T, A1515T, C1794A, G1816A; Q430L, Y484N, N98K, V606I), AAV9.40 (A1694T, E565V), AAV9.41 (A1348T, T1362C; T450S), AAV9.44 (A1684C, A1701T, A1737G; N562H, K567N), AAV9.45 (A1492T, C1804T; N498Y, L602F), AAV9.46 (G1441C, T1525C, T1549G; G481R, W509R, L517V), 9.47 (G1241A, G1358A, A1669G, C1745T; S414N, G453D, K557E, T582I), AAV9.48 (C1445T, A1736T; P482L, Q579L), AAV9.50 (A1638T, C1683T, T1805A; Q546H, L602H), AAV9.53 (G1301A, A1405C, C1664T, G1811T; R134Q, S469R, A555V, G604V), AAV9.54 (C1531A, T1609A; L511I, L537M), AAV9.55 (T1605A; F535L), AAV9.58 (C1475T, C1579A; T492I, H527N), AAV.59 (T1336C; Y446H),

AAV9.61 (A1493T; N498I), AAV9.64 (C1531A, A1617T; L511I), AAV9.65 (C1335T, T1530C, C1568A; A523D), AAV9.68 (C1510A; P504T), AAV9.80 (G1441A,;G481R), AAV9.83 (C1402A, A1500T; P468T, E500D), AAV9.87 (T1464C, T1468C; S490P), AAV9.90 (A1196T; Y399F), AAV9.91 (T1316G, A1583T, C1782G, T1806C; L439R, K528I), AAV9.93 (A1273G, A1421G, A1638C, C1712T, G1732A, A1744T, A1832T; S425G, Q474R, Q546H, P571L, G578R, T582S, D611V), AAV9.94 (A1675T; M559L) and AAV9.95 (T1605A; F535L).

[00180] In some embodiments, the AAV serotype may be, or have, a sequence as described in International Publication No. WO2016049230, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to AAVF1/HSC1 (SEQ ID NO: 2 and 20 of WO2016049230), AAVF2/HSC2 (SEQ ID NO: 3 and 21 of WO2016049230), AAVF3/HSC3 (SEQ ID NO: 5 and 22 of WO2016049230), AAVF4/HSC4 (SEQ ID NO: 6 and 23 of WO2016049230), AAVF5/HSC5 (SEQ ID NO: 11 and 25 of WO2016049230), AAVF6/HSC6 (SEQ ID NO: 7 and 24 of WO2016049230), AAVF7/HSC7 (SEQ ID NO: 8 and 27 of WO2016049230), AAVF8/HSC8 (SEQ ID NO: 9 and 28 of WO2016049230), AAVF9/HSC9 (SEQ ID NO: 10 and 29 of WO2016049230), AAVF11/HSC11 (SEQ ID NO: 4 and 26 of WO2016049230), AAVF12/HSC12 (SEQ ID NO: 12 and 30 of WO2016049230), AAVF13/HSC13 (SEQ ID NO: 14 and 31 of WO2016049230), AAVF14/HSC14 (SEQ ID NO: 15 and 32 of WO2016049230), AAVF15/HSC15 (SEQ ID NO: 16 and 33 of WO2016049230), AAVF16/HSC16 (SEQ ID NO: 17 and 34 of WO2016049230), AAVF17/HSC17 (SEQ ID NO: 13 and 35 of WO2016049230), or variants or derivatives thereof.

[00181] In some embodiments, the AAV serotype may be, or have, a sequence as described in United States Patent No. US 8734809, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV CBr-E1 (SEQ ID NO: 13 and 87 of US8734809), AAV CBr-E2 (SEQ ID NO: 14 and 88 of US8734809), AAV CBr-E3 (SEQ ID NO: 15 and 89 of US8734809), AAV CBr-E4 (SEQ ID NO: 16 and 90 of US8734809), AAV CBr-E5 (SEQ ID NO: 17 and 91 of US8734809), AAV CBr-e5 (SEQ ID NO: 18 and 92 of US8734809), AAV CBr-E6 (SEQ ID NO: 19 and 93 of US8734809), AAV CBr-E7 (SEQ ID NO: 20 and 94 of US8734809), AAV CBr-E8 (SEQ ID NO: 21 and 95 of US8734809), AAV CLv-D1 (SEQ ID NO: 22 and 96 of US8734809), AAV CLv-D2 (SEQ ID NO: 23 and 97 of US8734809), AAV CLv-D3 (SEQ ID NO: 24 and 98 of US8734809), AAV CLv-D4 (SEQ ID NO: 25 and 99 of US8734809), AAV CLv-D5 (SEQ ID NO: 26 and 100 of US8734809), AAV CLv-D6 (SEQ ID NO: 27 and 101 of US8734809), AAV CLv-D7 (SEQ ID NO: 28 and 102 of US8734809), AAV CLv-D8 (SEQ ID NO: 29 and 103 of US8734809), AAV CLv-E1 (SEQ ID

NO: 13 and 87 of US8734809), AAV CLv-R1 (SEQ ID NO: 30 and 104 of US8734809), AAV CLv-R2 (SEQ ID NO: 31 and 105 of US8734809), AAV CLv-R3 (SEQ ID NO: 32 and 106 of US8734809), AAV CLv-R4 (SEQ ID NO: 33 and 107 of US8734809), AAV CLv-R5 (SEQ ID NO: 34 and 108 of US8734809), AAV CLv-R6 (SEQ ID NO: 35 and 109 of US8734809), AAV CLv-R7 (SEQ ID NO: 36 and 110 of US8734809), AAV CLv-R8 (SEQ ID NO: 37 and 111 of US8734809), AAV CLv-R9 (SEQ ID NO: 38 and 112 of US8734809), AAV CLg-F1 (SEQ ID NO: 39 and 113 of US8734809), AAV CLg-F2 (SEQ ID NO: 40 and 114 of US8734809), AAV CLg-F3 (SEQ ID NO: 41 and 115 of US8734809), AAV CLg-F4 (SEQ ID NO: 42 and 116 of US8734809), AAV CLg-F5 (SEQ ID NO: 43 and 117 of US8734809), AAV CLg-F6 (SEQ ID NO: 43 and 117 of US8734809), AAV CLg-F7 (SEQ ID NO: 44 and 118 of US8734809), AAV CLg-F8 (SEQ ID NO: 43 and 117 of US8734809), AAV CSp-1 (SEQ ID NO: 45 and 119 of US8734809), AAV CSp-10 (SEQ ID NO: 46 and 120 of US8734809), AAV CSp-11 (SEQ ID NO: 47 and 121 of US8734809), AAV CSp-2 (SEQ ID NO: 48 and 122 of US8734809), AAV CSp-3 (SEQ ID NO: 49 and 123 of US8734809), AAV CSp-4 (SEQ ID NO: 50 and 124 of US8734809), AAV CSp-6 (SEQ ID NO: 51 and 125 of US8734809), AAV CSp-7 (SEQ ID NO: 52 and 126 of US8734809), AAV CSp-8 (SEQ ID NO: 53 and 127 of US8734809), AAV CSp-9 (SEQ ID NO: 54 and 128 of US8734809), AAV CHt-2 (SEQ ID NO: 55 and 129 of US8734809), AAV CHt-3 (SEQ ID NO: 56 and 130 of US8734809), AAV CKd-1 (SEQ ID NO: 57 and 131 of US8734809), AAV CKd-10 (SEQ ID NO: 58 and 132 of US8734809), AAV CKd-2 (SEQ ID NO: 59 and 133 of US8734809), AAV CKd-3 (SEQ ID NO: 60 and 134 of US8734809), AAV CKd-4 (SEQ ID NO: 61 and 135 of US8734809), AAV CKd-6 (SEQ ID NO: 62 and 136 of US8734809), AAV CKd-7 (SEQ ID NO: 63 and 137 of US8734809), AAV CKd-8 (SEQ ID NO: 64 and 138 of US8734809), AAV CLv-1 (SEQ ID NO: 35 and 139 of US8734809), AAV CLv-12 (SEQ ID NO: 66 and 140 of US8734809), AAV CLv-13 (SEQ ID NO: 67 and 141 of US8734809), AAV CLv-2 (SEQ ID NO: 68 and 142 of US8734809), AAV CLv-3 (SEQ ID NO: 69 and 143 of US8734809), AAV CLv-4 (SEQ ID NO: 70 and 144 of US8734809), AAV CLv-6 (SEQ ID NO: 71 and 145 of US8734809), AAV CLv-8 (SEQ ID NO: 72 and 146 of US8734809), AAV CKd-B1 (SEQ ID NO: 73 and 147 of US8734809), AAV CKd-B2 (SEQ ID NO: 74 and 148 of US8734809), AAV CKd-B3 (SEQ ID NO: 75 and 149 of US8734809), AAV CKd-B4 (SEQ ID NO: 76 and 150 of US8734809), AAV CKd-B5 (SEQ ID NO: 77 and 151 of US8734809), AAV CKd-B6 (SEQ ID NO: 78 and 152 of US8734809), AAV CKd-B7 (SEQ ID NO: 79 and 153 of US8734809), AAV CKd-B8 (SEQ ID NO: 80 and 154 of US8734809), AAV CKd-H1 (SEQ ID NO: 81 and 155 of US8734809), AAV CKd-H2 (SEQ ID

NO: 82 and 156 of US8734809), AAV CKd-H3 (SEQ ID NO: 83 and 157 of US8734809), AAV CKd-H4 (SEQ ID NO: 84 and 158 of US8734809), AAV CKd-H5 (SEQ ID NO: 85 and 159 of US8734809), AAV CKd-H6 (SEQ ID NO: 77 and 151 of US8734809), AAV CHt-1 (SEQ ID NO: 86 and 160 of US8734809), AAV CLv1-1 (SEQ ID NO: 171 of US8734809), AAV CLv1-2 (SEQ ID NO: 172 of US8734809), AAV CLv1-3 (SEQ ID NO: 173 of US8734809), AAV CLv1-4 (SEQ ID NO: 174 of US8734809), AAV Clv1-7 (SEQ ID NO: 175 of US8734809), AAV Clv1-8 (SEQ ID NO: 176 of US8734809), AAV Clv1-9 (SEQ ID NO: 177 of US8734809), AAV Clv1-10 (SEQ ID NO: 178 of US8734809), AAV.VR-355 (SEQ ID NO: 181 of US8734809), AAV.hu.48R3 (SEQ ID NO: 183 of US8734809), or variants or derivatives thereof.

[00182] In some embodiments, the AAV serotype may be, or have, a sequence as described in International Publication No. WO2016065001, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to AAV CHt-P2 (SEQ ID NO: 1 and 51 of WO2016065001), AAV CHt-P5 (SEQ ID NO: 2 and 52 of WO2016065001), AAV CHt-P9 (SEQ ID NO: 3 and 53 of WO2016065001), AAV CBr-7.1 (SEQ ID NO: 4 and 54 of WO2016065001), AAV CBr-7.2 (SEQ ID NO: 5 and 55 of WO2016065001), AAV CBr-7.3 (SEQ ID NO: 6 and 56 of WO2016065001), AAV CBr-7.4 (SEQ ID NO: 7 and 57 of WO2016065001), AAV CBr-7.5 (SEQ ID NO: 8 and 58 of WO2016065001), AAV CBr-7.7 (SEQ ID NO: 9 and 59 of WO2016065001), AAV CBr-7.8 (SEQ ID NO: 10 and 60 of WO2016065001), AAV CBr-7.10 (SEQ ID NO: 11 and 61 of WO2016065001), AAV CKd-N3 (SEQ ID NO: 12 and 62 of WO2016065001), AAV CKd-N4 (SEQ ID NO: 13 and 63 of WO2016065001), AAV CKd-N9 (SEQ ID NO: 14 and 64 of WO2016065001), AAV CLv-L4 (SEQ ID NO: 15 and 65 of WO2016065001), AAV CLv-L5 (SEQ ID NO: 16 and 66 of WO2016065001), AAV CLv-L6 (SEQ ID NO: 17 and 67 of WO2016065001), AAV CLv-K1 (SEQ ID NO: 18 and 68 of WO2016065001), AAV CLv-K3 (SEQ ID NO: 19 and 69 of WO2016065001), AAV CLv-K6 (SEQ ID NO: 20 and 70 of WO2016065001), AAV CLv-M1 (SEQ ID NO: 21 and 71 of WO2016065001), AAV CLv-M11 (SEQ ID NO: 22 and 72 of WO2016065001), AAV CLv-M2 (SEQ ID NO: 23 and 73 of WO2016065001), AAV CLv-M5 (SEQ ID NO: 24 and 74 of WO2016065001), AAV CLv-M6 (SEQ ID NO: 25 and 75 of WO2016065001), AAV CLv-M7 (SEQ ID NO: 26 and 76 of WO2016065001), AAV CLv-M8 (SEQ ID NO: 27 and 77 of WO2016065001), AAV CLv-M9 (SEQ ID NO: 28 and 78 of WO2016065001), AAV CHt-P1 (SEQ ID NO: 29 and 79 of WO2016065001), AAV CHt-P6 (SEQ ID NO: 30 and 80 of WO2016065001), AAV CHt-P8 (SEQ ID NO: 31 and 81 of

WO2016065001), AAV CHt-6.1 (SEQ ID NO: 32 and 82 of WO2016065001), AAV CHt-6.10 (SEQ ID NO: 33 and 83 of WO2016065001), AAV CHt-6.5 (SEQ ID NO: 34 and 84 of WO2016065001), AAV CHt-6.6 (SEQ ID NO: 35 and 85 of WO2016065001), AAV CHt-6.7 (SEQ ID NO: 36 and 86 of WO2016065001), AAV CHt-6.8 (SEQ ID NO: 37 and 87 of WO2016065001), AAV CSp-8.10 (SEQ ID NO: 38 and 88 of WO2016065001), AAV CSp-8.2 (SEQ ID NO: 39 and 89 of WO2016065001), AAV CSp-8.4 (SEQ ID NO: 40 and 90 of WO2016065001), AAV CSp-8.5 (SEQ ID NO: 41 and 91 of WO2016065001), AAV CSp-8.6 (SEQ ID NO: 42 and 92 of WO2016065001), AAV CSp-8.7 (SEQ ID NO: 43 and 93 of WO2016065001), AAV CSp-8.8 (SEQ ID NO: 44 and 94 of WO2016065001), AAV CSp-8.9 (SEQ ID NO: 45 and 95 of WO2016065001), AAV CBr-B7.3 (SEQ ID NO: 46 and 96 of WO2016065001), AAV CBr-B7.4 (SEQ ID NO: 47 and 97 of WO2016065001), AAV3B (SEQ ID NO: 48 and 98 of WO2016065001), AAV4 (SEQ ID NO: 49 and 99 of WO2016065001), AAV5 (SEQ ID NO: 50 and 100 of WO2016065001), or variants or derivatives thereof.

[00183] In some embodiments, the AAV serotype may be, or have, a modification as described in United States Publication No. US 20160361439, the contents of which are herein incorporated by reference in their entirety, such as but not limited to, Y252F, Y272F, Y444F, Y500F, Y700F, Y704F, Y730F, Y275F, Y281F, Y508F, Y576F, Y612G, Y673F, and Y720F of the wild-type AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12, and hybrids thereof.

[00184] In some embodiments, the AAV serotype may be, or have, a mutation as described in United States Patent No. US 9546112, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, at least two, but not all the F129L, D418E, K531E, L584F, V598A and H642N mutations in the sequence of AAV6 (SEQ ID NO:4 of US 9546112), AAV1 (SEQ ID NO:6 of US 9546112), AAV2, AAV3, AAV4, AAV5, AAV7, AAV9, AAV10 or AAV11 or derivatives thereof. In yet another embodiment, the AAV serotype may be, or have, an AAV6 sequence comprising the K531E mutation (SEQ ID NO:5 of US 9546112).

[00185] In some embodiments, the AAV serotype may be, or have, a mutation in the AAV1 sequence, as described in in United States Publication No. US 20130224836, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, at least one of the surface-exposed tyrosine residues, preferably, at positions 252, 273, 445, 701, 705 and 731 of AAV1 (SEQ ID NO: 2 of US 20130224836) substituted with another amino acid, preferably with a phenylalanine residue. In one embodiment, the AAV serotype may be, or have, a mutation in the AAV9 sequence, such as, but not limited to, at least one of the surface-exposed

tyrosine residues, preferably, at positions 252, 272, 444, 500, 700, 704 and 730 of AAV2 (SEQ ID NO: 4 of US 20130224836) substituted with another amino acid, preferably with a phenylalanine residue. In one embodiment, the tyrosine residue at position 446 of AAV9 (SEQ ID NO: 6 US 20130224836) is substituted with a phenylalanine residue.

[00186] In some embodiments, the serotype may be AAV2 or a variant thereof, as described in International Publication No. WO2016130589, herein incorporated by reference in its entirety. The amino acid sequence of AAV2 may comprise N587A, E548A, or N708A mutations. In one embodiment, the amino acid sequence of any AAV may comprise a V708K mutation.

[00187] In one embodiment, the AAV may be a serotype selected from any of those found in Table 1.

[00188] In one embodiment, the AAV may comprise a sequence, fragment or variant thereof, of the sequences in Table 1.

[00189] In one embodiment, the AAV may be encoded by a sequence, fragment or variant as described in Table 1.

Table 1. AAV Serotypes

Serotype	SEQ ID NO	Reference Information
AAV1	1	US20150159173 SEQ ID NO: 11, US20150315612 SEQ ID NO: 202
AAV1	2	US20160017295 SEQ ID NO: 1US20030138772 SEQ ID NO: 64, US20150159173 SEQ ID NO: 27, US20150315612 SEQ ID NO: 219, US7198951 SEQ ID NO: 5
AAV1	3	US20030138772 SEQ ID NO: 6
AAV1.3	4	US20030138772 SEQ ID NO: 14
AAV10	5	US20030138772 SEQ ID NO: 117
AAV10	6	WO2015121501 SEQ ID NO: 9
AAV10	7	WO2015121501 SEQ ID NO: 8
AAV11	8	US20030138772 SEQ ID NO: 118
AAV12	9	US20030138772 SEQ ID NO: 119
AAV2	10	US20150159173 SEQ ID NO: 7, US20150315612 SEQ ID NO: 211
AAV2	11	US20030138772 SEQ ID NO: 70, US20150159173 SEQ ID NO: 23, US20150315612 SEQ ID NO: 221, US20160017295 SEQ ID NO: 2, US6156303 SEQ ID NO: 4, US7198951 SEQ ID NO: 4, WO2015121501 SEQ ID NO: 1
AAV2	12	US6156303 SEQ ID NO: 8
AAV2	13	US20030138772 SEQ ID NO: 7
AAV2	14	US6156303 SEQ ID NO: 3
AAV2.5T	15	US9233131 SEQ ID NO: 42
AAV223.10	16	US20030138772 SEQ ID NO: 75
AAV223.2	17	US20030138772 SEQ ID NO: 49
AAV223.2	18	US20030138772 SEQ ID NO: 76
AAV223.4	19	US20030138772 SEQ ID NO: 50
AAV223.4	20	US20030138772 SEQ ID NO: 73

AAV223.5	21	US20030138772 SEQ ID NO: 51
AAV223.5	22	US20030138772 SEQ ID NO: 74
AAV223.6	23	US20030138772 SEQ ID NO: 52
AAV223.6	24	US20030138772 SEQ ID NO: 78
AAV223.7	25	US20030138772 SEQ ID NO: 53
AAV223.7	26	US20030138772 SEQ ID NO: 77
AAV29.3	27	US20030138772 SEQ ID NO: 82
AAV29.4	28	US20030138772 SEQ ID NO: 12
AAV29.5	29	US20030138772 SEQ ID NO: 83
AAV29.5 (AAVbb.2)	30	US20030138772 SEQ ID NO: 13
AAV3	31	US20150159173 SEQ ID NO: 12
AAV3	32	US20030138772 SEQ ID NO: 71, US20150159173 SEQ ID NO: 28, US20160017295 SEQ ID NO: 3, US7198951 SEQ ID NO: 6
AAV3	33	US20030138772 SEQ ID NO: 8
AAV3.3b	34	US20030138772 SEQ ID NO: 72
AAV3-3	35	US20150315612 SEQ ID NO: 200
AAV3-3	36	US20150315612 SEQ ID NO: 217
AAV3a	37	US6156303 SEQ ID NO: 5
AAV3a	38	US6156303 SEQ ID NO: 9
AAV3b	39	US6156303 SEQ ID NO: 6
AAV3b	40	US6156303 SEQ ID NO: 10
AAV3b	41	US6156303 SEQ ID NO: 1
AAV4	42	US20140348794 SEQ ID NO: 17
AAV4	43	US20140348794 SEQ ID NO: 5
AAV4	44	US20140348794 SEQ ID NO: 3
AAV4	45	US20140348794 SEQ ID NO: 14
AAV4	46	US20140348794 SEQ ID NO: 15
AAV4	47	US20140348794 SEQ ID NO: 19
AAV4	48	US20140348794 SEQ ID NO: 12
AAV4	49	US20140348794 SEQ ID NO: 13
AAV4	50	US20140348794 SEQ ID NO: 7
AAV4	51	US20140348794 SEQ ID NO: 8
AAV4	52	US20140348794 SEQ ID NO: 9
AAV4	53	US20140348794 SEQ ID NO: 2
AAV4	54	US20140348794 SEQ ID NO: 10
AAV4	55	US20140348794 SEQ ID NO: 11
AAV4	56	US20140348794 SEQ ID NO: 18
AAV4	57	US20030138772 SEQ ID NO: 63, US20160017295 SEQ ID NO: 4, US20140348794 SEQ ID NO: 4
AAV4	58	US20140348794 SEQ ID NO: 16
AAV4	59	US20140348794 SEQ ID NO: 20
AAV4	60	US20140348794 SEQ ID NO: 6
AAV4	61	US20140348794 SEQ ID NO: 1
AAV42.2	62	US20030138772 SEQ ID NO: 9

AAV42.2	63	US20030138772 SEQ ID NO: 102
AAV42.3b	64	US20030138772 SEQ ID NO: 36
AAV42.3B	65	US20030138772 SEQ ID NO: 107
AAV42.4	66	US20030138772 SEQ ID NO: 33
AAV42.4	67	US20030138772 SEQ ID NO: 88
AAV42.8	68	US20030138772 SEQ ID NO: 27
AAV42.8	69	US20030138772 SEQ ID NO: 85
AAV43.1	70	US20030138772 SEQ ID NO: 39
AAV43.1	71	US20030138772 SEQ ID NO: 92
AAV43.12	72	US20030138772 SEQ ID NO: 41
AAV43.12	73	US20030138772 SEQ ID NO: 93
AAV43.20	74	US20030138772 SEQ ID NO: 42
AAV43.20	75	US20030138772 SEQ ID NO: 99
AAV43.21	76	US20030138772 SEQ ID NO: 43
AAV43.21	77	US20030138772 SEQ ID NO: 96
AAV43.23	78	US20030138772 SEQ ID NO: 44
AAV43.23	79	US20030138772 SEQ ID NO: 98
AAV43.25	80	US20030138772 SEQ ID NO: 45
AAV43.25	81	US20030138772 SEQ ID NO: 97
AAV43.5	82	US20030138772 SEQ ID NO: 40
AAV43.5	83	US20030138772 SEQ ID NO: 94
AAV4-4	84	US20150315612 SEQ ID NO: 201
AAV4-4	85	US20150315612 SEQ ID NO: 218
AAV44.1	86	US20030138772 SEQ ID NO: 46
AAV44.1	87	US20030138772 SEQ ID NO: 79
AAV44.5	88	US20030138772 SEQ ID NO: 47
AAV44.5	89	US20030138772 SEQ ID NO: 80
AAV4407	90	US20150315612 SEQ ID NO: 90
AAV5	91	US7427396 SEQ ID NO: 1
AAV5	92	US20030138772 SEQ ID NO: 114
AAV5	93	US20160017295 SEQ ID NO: 5, US7427396 SEQ ID NO: 2, US20150315612 SEQ ID NO: 216
AAV5	94	US20150315612 SEQ ID NO: 199
AAV6	95	US20150159173 SEQ ID NO: 13
AAV6	96	US20030138772 SEQ ID NO: 65, US20150159173 SEQ ID NO: 29, US20160017295 SEQ ID NO: 6, US6156303 SEQ ID NO: 7
AAV6	97	US6156303 SEQ ID NO: 11
AAV6	98	US6156303 SEQ ID NO: 2
AAV6	99	US20150315612 SEQ ID NO: 203
AAV6	100	US20150315612 SEQ ID NO: 220
AAV6.1	101	US20150159173
AAV6.12	102	US20150159173
AAV6.2	103	US20150159173
AAV7	104	US20150159173 SEQ ID NO: 14
AAV7	105	US20150315612 SEQ ID NO: 183

AAV7	106	US20030138772 SEQ ID NO: 2, US20150159173 SEQ ID NO: 30, US20150315612 SEQ ID NO: 181, US20160017295 SEQ ID NO: 7
AAV7	107	US20030138772 SEQ ID NO: 3
AAV7	108	US20030138772 SEQ ID NO: 1, US20150315612 SEQ ID NO: 180
AAV7	109	US20150315612 SEQ ID NO: 213
AAV7	110	US20150315612 SEQ ID NO: 222
AAV8	111	US20150159173 SEQ ID NO: 15
AAV8	112	US20150376240 SEQ ID NO: 7
AAV8	113	US20030138772 SEQ ID NO: 4, US20150315612 SEQ ID NO: 182
AAV8	114	US20030138772 SEQ ID NO: 95, US20140359799 SEQ ID NO: 1, US20150159173 SEQ ID NO: 31, US20160017295 SEQ ID NO: 8, US7198951 SEQ ID NO: 7, US20150315612 SEQ ID NO: 223
AAV8	115	US20150376240 SEQ ID NO: 8
AAV8	116	US20150315612 SEQ ID NO: 214
AAV-8b	117	US20150376240 SEQ ID NO: 5
AAV-8b	118	US20150376240 SEQ ID NO: 3
AAV-8h	119	US20150376240 SEQ ID NO: 6
AAV-8h	120	US20150376240 SEQ ID NO: 4
AAV9	121	US20030138772 SEQ ID NO: 5
AAV9	122	US7198951 SEQ ID NO: 1
AAV9	123	US20160017295 SEQ ID NO: 9
AAV9	124	US20030138772 SEQ ID NO: 100, US7198951 SEQ ID NO: 2
AAV9	125	US7198951 SEQ ID NO: 3
AAV9 (AAVhu.14)	126	US7906111 SEQ ID NO: 3; WO2015038958 SEQ ID NO: 11
AAV9 (AAVhu.14)	127	US7906111 SEQ ID NO: 123; WO2015038958 SEQ ID NO: 2
AAVA3.1	128	US20030138772 SEQ ID NO: 120
AAVA3.3	129	US20030138772 SEQ ID NO: 57
AAVA3.3	130	US20030138772 SEQ ID NO: 66
AAVA3.4	131	US20030138772 SEQ ID NO: 54
AAVA3.4	132	US20030138772 SEQ ID NO: 68
AAVA3.5	133	US20030138772 SEQ ID NO: 55
AAVA3.5	134	US20030138772 SEQ ID NO: 69
AAVA3.7	135	US20030138772 SEQ ID NO: 56
AAVA3.7	136	US20030138772 SEQ ID NO: 67
AAV29.3 (AAVbb.1)	137	US20030138772 SEQ ID NO: 11
AAVC2	138	US20030138772 SEQ ID NO: 61
AAVCh.5	139	US20150159173 SEQ ID NO: 46, US20150315612 SEQ ID NO: 234
AAVcy.2 (AAV13.3)	140	US20030138772 SEQ ID NO: 15
AAV24.1	141	US20030138772 SEQ ID NO: 101
AAVcy.3 (AAV24.1)	142	US20030138772 SEQ ID NO: 16
AAV27.3	143	US20030138772 SEQ ID NO: 104
AAVcy.4 (AAV27.3)	144	US20030138772 SEQ ID NO: 17

AAVcy.5	145	US20150315612 SEQ ID NO: 227
AAV7.2	146	US20030138772 SEQ ID NO: 103
AAVcy.5 (AAV7.2)	147	US20030138772 SEQ ID NO: 18
AAV16.3	148	US20030138772 SEQ ID NO: 105
AAVcy.6 (AAV16.3)	149	US20030138772 SEQ ID NO: 10
AAVcy.5	150	US20150159173 SEQ ID NO: 8
AAVcy.5	151	US20150159173 SEQ ID NO: 24
AAVCy.5R1	152	US20150159173
AAVCy.5R2	153	US20150159173
AAVCy.5R3	154	US20150159173
AAVCy.5R4	155	US20150159173
AAVDJ	156	US20140359799 SEQ ID NO: 3, US7588772 SEQ ID NO: 2
AAVDJ	157	US20140359799 SEQ ID NO: 2, US7588772 SEQ ID NO: 1
AAVDJ-8	158	US7588772; Grimm et al 2008
AAVDJ-8	159	US7588772; Grimm et al 2008
AAVF5	160	US20030138772 SEQ ID NO: 110
AAVH2	161	US20030138772 SEQ ID NO: 26
AAVH6	162	US20030138772 SEQ ID NO: 25
AAVhE1.1	163	US9233131 SEQ ID NO: 44
AAVhEr1.14	164	US9233131 SEQ ID NO: 46
AAVhEr1.16	165	US9233131 SEQ ID NO: 48
AAVhEr1.18	166	US9233131 SEQ ID NO: 49
AAVhEr1.23 (AAVhEr2.29)	167	US9233131 SEQ ID NO: 53
AAVhEr1.35	168	US9233131 SEQ ID NO: 50
AAVhEr1.36	169	US9233131 SEQ ID NO: 52
AAVhEr1.5	170	US9233131 SEQ ID NO: 45
AAVhEr1.7	171	US9233131 SEQ ID NO: 51
AAVhEr1.8	172	US9233131 SEQ ID NO: 47
AAVhEr2.16	173	US9233131 SEQ ID NO: 55
AAVhEr2.30	174	US9233131 SEQ ID NO: 56
AAVhEr2.31	175	US9233131 SEQ ID NO: 58
AAVhEr2.36	176	US9233131 SEQ ID NO: 57
AAVhEr2.4	177	US9233131 SEQ ID NO: 54
AAVhEr3.1	178	US9233131 SEQ ID NO: 59
AAVhu.1	179	US20150315612 SEQ ID NO: 46
AAVhu.1	180	US20150315612 SEQ ID NO: 144
AAVhu.10 (AAV16.8)	181	US20150315612 SEQ ID NO: 56
AAVhu.10 (AAV16.8)	182	US20150315612 SEQ ID NO: 156
AAVhu.11 (AAV16.12)	183	US20150315612 SEQ ID NO: 57
AAVhu.11 (AAV16.12)	184	US20150315612 SEQ ID NO: 153

AAVhu.12	185	US20150315612 SEQ ID NO: 59
AAVhu.12	186	US20150315612 SEQ ID NO: 154
AAVhu.13	187	US20150159173 SEQ ID NO: 16, US20150315612 SEQ ID NO: 71
AAVhu.13	188	US20150159173 SEQ ID NO: 32, US20150315612 SEQ ID NO: 129
AAVhu.136.1	189	US20150315612 SEQ ID NO: 165
AAVhu.140.1	190	US20150315612 SEQ ID NO: 166
AAVhu.140.2	191	US20150315612 SEQ ID NO: 167
AAVhu.145.6	192	US20150315612 SEQ ID No: 178
AAVhu.15	193	US20150315612 SEQ ID NO: 147
AAVhu.15 (AAV33.4)	194	US20150315612 SEQ ID NO: 50
AAVhu.156.1	195	US20150315612 SEQ ID No: 179
AAVhu.16	196	US20150315612 SEQ ID NO: 148
AAVhu.16 (AAV33.8)	197	US20150315612 SEQ ID NO: 51
AAVhu.17	198	US20150315612 SEQ ID NO: 83
AAVhu.17 (AAV33.12)	199	US20150315612 SEQ ID NO: 4
AAVhu.172.1	200	US20150315612 SEQ ID NO: 171
AAVhu.172.2	201	US20150315612 SEQ ID NO: 172
AAVhu.173.4	202	US20150315612 SEQ ID NO: 173
AAVhu.173.8	203	US20150315612 SEQ ID NO: 175
AAVhu.18	204	US20150315612 SEQ ID NO: 52
AAVhu.18	205	US20150315612 SEQ ID NO: 149
AAVhu.19	206	US20150315612 SEQ ID NO: 62
AAVhu.19	207	US20150315612 SEQ ID NO: 133
AAVhu.2	208	US20150315612 SEQ ID NO: 48
AAVhu.2	209	US20150315612 SEQ ID NO: 143
AAVhu.20	210	US20150315612 SEQ ID NO: 63
AAVhu.20	211	US20150315612 SEQ ID NO: 134
AAVhu.21	212	US20150315612 SEQ ID NO: 65
AAVhu.21	213	US20150315612 SEQ ID NO: 135
AAVhu.22	214	US20150315612 SEQ ID NO: 67
AAVhu.22	215	US20150315612 SEQ ID NO: 138
AAVhu.23	216	US20150315612 SEQ ID NO: 60
AAVhu.23.2	217	US20150315612 SEQ ID NO: 137
AAVhu.24	218	US20150315612 SEQ ID NO: 66
AAVhu.24	219	US20150315612 SEQ ID NO: 136
AAVhu.25	220	US20150315612 SEQ ID NO: 49
AAVhu.25	221	US20150315612 SEQ ID NO: 146
AAVhu.26	222	US20150159173 SEQ ID NO: 17, US20150315612 SEQ ID NO: 61

AAVhu.26	223	US20150159173 SEQ ID NO: 33, US20150315612 SEQ ID NO: 139
AAVhu.27	224	US20150315612 SEQ ID NO: 64
AAVhu.27	225	US20150315612 SEQ ID NO: 140
AAVhu.28	226	US20150315612 SEQ ID NO: 68
AAVhu.28	227	US20150315612 SEQ ID NO: 130
AAVhu.29	228	US20150315612 SEQ ID NO: 69
AAVhu.29	229	US20150159173 SEQ ID NO: 42, US20150315612 SEQ ID NO: 132
AAVhu.29	230	US20150315612 SEQ ID NO: 225
AAVhu.29R	231	US20150159173
AAVhu.3	232	US20150315612 SEQ ID NO: 44
AAVhu.3	233	US20150315612 SEQ ID NO: 145
AAVhu.30	234	US20150315612 SEQ ID NO: 70
AAVhu.30	235	US20150315612 SEQ ID NO: 131
AAVhu.31	236	US20150315612 SEQ ID NO: 1
AAVhu.31	237	US20150315612 SEQ ID NO: 121
AAVhu.32	238	US20150315612 SEQ ID NO: 2
AAVhu.32	239	US20150315612 SEQ ID NO: 122
AAVhu.33	240	US20150315612 SEQ ID NO: 75
AAVhu.33	241	US20150315612 SEQ ID NO: 124
AAVhu.34	242	US20150315612 SEQ ID NO: 72
AAVhu.34	243	US20150315612 SEQ ID NO: 125
AAVhu.35	244	US20150315612 SEQ ID NO: 73
AAVhu.35	245	US20150315612 SEQ ID NO: 164
AAVhu.36	246	US20150315612 SEQ ID NO: 74
AAVhu.36	247	US20150315612 SEQ ID NO: 126
AAVhu.37	248	US20150159173 SEQ ID NO: 34, US20150315612 SEQ ID NO: 88
AAVhu.37 (AAV106.1)	249	US20150315612 SEQ ID NO: 10, US20150159173 SEQ ID NO: 18
AAVhu.38	250	US20150315612 SEQ ID NO: 161
AAVhu.39	251	US20150315612 SEQ ID NO: 102
AAVhu.39 (AAVLG-9)	252	US20150315612 SEQ ID NO: 24
AAVhu.4	253	US20150315612 SEQ ID NO: 47
AAVhu.4	254	US20150315612 SEQ ID NO: 141
AAVhu.40	255	US20150315612 SEQ ID NO: 87
AAVhu.40 (AAV114.3)	256	US20150315612 SEQ ID No: 11
AAVhu.41	257	US20150315612 SEQ ID NO: 91
AAVhu.41 (AAV127.2)	258	US20150315612 SEQ ID NO: 6
AAVhu.42	259	US20150315612 SEQ ID NO: 85
AAVhu.42 (AAV127.5)	260	US20150315612 SEQ ID NO: 8
AAVhu.43	261	US20150315612 SEQ ID NO: 160
AAVhu.43	262	US20150315612 SEQ ID NO: 236
AAVhu.43 (AAV128.1)	263	US20150315612 SEQ ID NO: 80

AAVhu.44	264	US20150159173 SEQ ID NO: 45, US20150315612 SEQ ID NO: 158
AAVhu.44 (AAV128.3)	265	US20150315612 SEQ ID NO: 81
AAVhu.44R1	266	US20150159173
AAVhu.44R2	267	US20150159173
AAVhu.44R3	268	US20150159173
AAVhu.45	269	US20150315612 SEQ ID NO: 76
AAVhu.45	270	US20150315612 SEQ ID NO: 127
AAVhu.46	271	US20150315612 SEQ ID NO: 82
AAVhu.46	272	US20150315612 SEQ ID NO: 159
AAVhu.46	273	US20150315612 SEQ ID NO: 224
AAVhu.47	274	US20150315612 SEQ ID NO: 77
AAVhu.47	275	US20150315612 SEQ ID NO: 128
AAVhu.48	276	US20150159173 SEQ ID NO: 38
AAVhu.48	277	US20150315612 SEQ ID NO: 157
AAVhu.48 (AAV130.4)	278	US20150315612 SEQ ID NO: 78
AAVhu.48R1	279	US20150159173
AAVhu.48R2	280	US20150159173
AAVhu.48R3	281	US20150159173
AAVhu.49	282	US20150315612 SEQ ID NO: 209
AAVhu.49	283	US20150315612 SEQ ID NO: 189
AAVhu.5	284	US20150315612 SEQ ID NO: 45
AAVhu.5	285	US20150315612 SEQ ID NO: 142
AAVhu.51	286	US20150315612 SEQ ID NO: 208
AAVhu.51	287	US20150315612 SEQ ID NO: 190
AAVhu.52	288	US20150315612 SEQ ID NO: 210
AAVhu.52	289	US20150315612 SEQ ID NO: 191
AAVhu.53	290	US20150159173 SEQ ID NO: 19
AAVhu.53	291	US20150159173 SEQ ID NO: 35
AAVhu.53 (AAV145.1)	292	US20150315612 SEQ ID NO: 176
AAVhu.54	293	US20150315612 SEQ ID NO: 188
AAVhu.54 (AAV145.5)	294	US20150315612 SEQ ID No: 177
AAVhu.55	295	US20150315612 SEQ ID NO: 187
AAVhu.56	296	US20150315612 SEQ ID NO: 205
AAVhu.56 (AAV145.6)	297	US20150315612 SEQ ID NO: 168
AAVhu.56 (AAV145.6)	298	US20150315612 SEQ ID NO: 192
AAVhu.57	299	US20150315612 SEQ ID NO: 206
AAVhu.57	300	US20150315612 SEQ ID NO: 169
AAVhu.57	301	US20150315612 SEQ ID NO: 193
AAVhu.58	302	US20150315612 SEQ ID NO: 207
AAVhu.58	303	US20150315612 SEQ ID NO: 194

AAVhu.6 (AAV3.1)	304	US20150315612 SEQ ID NO: 5
AAVhu.6 (AAV3.1)	305	US20150315612 SEQ ID NO: 84
AAVhu.60	306	US20150315612 SEQ ID NO: 184
AAVhu.60 (AAV161.10)	307	US20150315612 SEQ ID NO: 170
AAVhu.61	308	US20150315612 SEQ ID NO: 185
AAVhu.61 (AAV161.6)	309	US20150315612 SEQ ID NO: 174
AAVhu.63	310	US20150315612 SEQ ID NO: 204
AAVhu.63	311	US20150315612 SEQ ID NO: 195
AAVhu.64	312	US20150315612 SEQ ID NO: 212
AAVhu.64	313	US20150315612 SEQ ID NO: 196
AAVhu.66	314	US20150315612 SEQ ID NO: 197
AAVhu.67	315	US20150315612 SEQ ID NO: 215
AAVhu.67	316	US20150315612 SEQ ID NO: 198
AAVhu.7	317	US20150315612 SEQ ID NO: 226
AAVhu.7	318	US20150315612 SEQ ID NO: 150
AAVhu.7 (AAV7.3)	319	US20150315612 SEQ ID NO: 55
AAVhu.71	320	US20150315612 SEQ ID NO: 79
AAVhu.8	321	US20150315612 SEQ ID NO: 53
AAVhu.8	322	US20150315612 SEQ ID NO: 12
AAVhu.8	323	US20150315612 SEQ ID NO: 151
AAVhu.9 (AAV3.1)	324	US20150315612 SEQ ID NO: 58
AAVhu.9 (AAV3.1)	325	US20150315612 SEQ ID NO: 155
AAV-LK01	326	US20150376607 SEQ ID NO: 2
AAV-LK01	327	US20150376607 SEQ ID NO: 29
AAV-LK02	328	US20150376607 SEQ ID NO: 3
AAV-LK02	329	US20150376607 SEQ ID NO: 30
AAV-LK03	330	US20150376607 SEQ ID NO: 4
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AAV-LK05	334	US20150376607 SEQ ID NO: 6
AAV-LK05	335	US20150376607 SEQ ID NO: 33
AAV-LK06	336	US20150376607 SEQ ID NO: 7
AAV-LK06	337	US20150376607 SEQ ID NO: 34
AAV-LK07	338	US20150376607 SEQ ID NO: 8
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AAV-LK09	342	US20150376607 SEQ ID NO: 10
AAV-LK09	343	US20150376607 SEQ ID NO: 37

AAV-LK10	344	US20150376607 SEQ ID NO: 11
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AAV-LK13	350	US20150376607 SEQ ID NO: 14
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AAV-LK16	356	US20150376607 SEQ ID NO: 17
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AAV-PAEC12	368	US20150376607 SEQ ID NO: 27
AAV-PAEC12	369	US20150376607 SEQ ID NO: 51
AAV-PAEC13	370	US20150376607 SEQ ID NO: 28
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AAV-PAEC4	375	US20150376607 SEQ ID NO: 55
AAV-PAEC6	376	US20150376607 SEQ ID NO: 23
AAV-PAEC6	377	US20150376607 SEQ ID NO: 52
AAV-PAEC7	378	US20150376607 SEQ ID NO: 24
AAV-PAEC7	379	US20150376607 SEQ ID NO: 53
AAV-PAEC8	380	US20150376607 SEQ ID NO: 25
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AAVpi.1	382	US20150315612 SEQ ID NO: 28
AAVpi.1	383	US20150315612 SEQ ID NO: 93
AAVpi.2	384	US20150315612 SEQ ID NO: 30

AAVpi.2	385	US20150315612 SEQ ID NO: 95
AAVpi.3	386	US20150315612 SEQ ID NO: 29
AAVpi.3	387	US20150315612 SEQ ID NO: 94
AAVrh.10	388	US20150159173 SEQ ID NO: 9
AAVrh.10	389	US20150159173 SEQ ID NO: 25
AAV44.2	390	US20030138772 SEQ ID NO: 59
AAVrh.10 (AAV44.2)	391	US20030138772 SEQ ID NO: 81
AAV42.1B	392	US20030138772 SEQ ID NO: 90
AAVrh.12 (AAV42.1b)	393	US20030138772 SEQ ID NO: 30
AAVrh.13	394	US20150159173 SEQ ID NO: 10
AAVrh.13	395	US20150159173 SEQ ID NO: 26
AAVrh.13	396	US20150315612 SEQ ID NO: 228
AAVrh.13R	397	US20150159173
AAV42.3A	398	US20030138772 SEQ ID NO: 87
AAVrh.14 (AAV42.3a)	399	US20030138772 SEQ ID NO: 32
AAV42.5A	400	US20030138772 SEQ ID NO: 89
AAVrh.17 (AAV42.5a)	401	US20030138772 SEQ ID NO: 34
AAV42.5B	402	US20030138772 SEQ ID NO: 91
AAVrh.18 (AAV42.5b)	403	US20030138772 SEQ ID NO: 29
AAV42.6B	404	US20030138772 SEQ ID NO: 112
AAVrh.19 (AAV42.6b)	405	US20030138772 SEQ ID NO: 38
AAVrh.2	406	US20150159173 SEQ ID NO: 39
AAVrh.2	407	US20150315612 SEQ ID NO: 231
AAVrh.20	408	US20150159173 SEQ ID NO: 1
AAV42.10	409	US20030138772 SEQ ID NO: 106
AAVrh.21 (AAV42.10)	410	US20030138772 SEQ ID NO: 35
AAV42.11	411	US20030138772 SEQ ID NO: 108
AAVrh.22 (AAV42.11)	412	US20030138772 SEQ ID NO: 37
AAV42.12	413	US20030138772 SEQ ID NO: 113
AAVrh.23 (AAV42.12)	414	US20030138772 SEQ ID NO: 58
AAV42.13	415	US20030138772 SEQ ID NO: 86
AAVrh.24 (AAV42.13)	416	US20030138772 SEQ ID NO: 31
AAV42.15	417	US20030138772 SEQ ID NO: 84
AAVrh.25 (AAV42.15)	418	US20030138772 SEQ ID NO: 28
AAVrh.2R	419	US20150159173
AAVrh.31 (AAV223.1)	420	US20030138772 SEQ ID NO: 48
AAVC1	421	US20030138772 SEQ ID NO: 60

AAVrh.32 (AAVC1)	422	US20030138772 SEQ ID NO: 19
AAVrh.32/33	423	US20150159173 SEQ ID NO: 2
AAVrh.33 (AAVC3)	424	US20030138772 SEQ ID NO: 20
AAVC5	425	US20030138772 SEQ ID NO: 62
AAVrh.34 (AAVC5)	426	US20030138772 SEQ ID NO: 21
AAVF1	427	US20030138772 SEQ ID NO: 109
AAVrh.35 (AAVF1)	428	US20030138772 SEQ ID NO: 22
AAVF3	429	US20030138772 SEQ ID NO: 111
AAVrh.36 (AAVF3)	430	US20030138772 SEQ ID NO: 23
AAVrh.37	431	US20030138772 SEQ ID NO: 24
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AAVrh.37	433	US20150315612 SEQ ID NO: 229
AAVrh.37R2	434	US20150159173
AAVrh.38 (AAVLG-4)	435	US20150315612 SEQ ID NO: 7
AAVrh.38 (AAVLG-4)	436	US20150315612 SEQ ID NO: 86
AAVrh.39	437	US20150159173 SEQ ID NO: 20, US20150315612 SEQ ID NO: 13
AAVrh.39	438	US20150159173 SEQ ID NO: 3, US20150159173 SEQ ID NO: 36, US20150315612 SEQ ID NO: 89
AAVrh.40	439	US20150315612 SEQ ID NO: 92
AAVrh.40 (AAVLG-10)	440	US20150315612 SEQ ID No: 14
AAVrh.43 (AAVN721-8)	441	US20150315612 SEQ ID NO: 43, US20150159173 SEQ ID NO: 21
AAVrh.43 (AAVN721-8)	442	US20150315612 SEQ ID NO: 163, US20150159173 SEQ ID NO: 37
AAVrh.44	443	US20150315612 SEQ ID NO: 34
AAVrh.44	444	US20150315612 SEQ ID NO: 111
AAVrh.45	445	US20150315612 SEQ ID NO: 41
AAVrh.45	446	US20150315612 SEQ ID NO: 109
AAVrh.46	447	US20150159173 SEQ ID NO: 22, US20150315612 SEQ ID NO: 19
AAVrh.46	448	US20150159173 SEQ ID NO: 4, US20150315612 SEQ ID NO: 101
AAVrh.47	449	US20150315612 SEQ ID NO: 38
AAVrh.47	450	US20150315612 SEQ ID NO: 118
AAVrh.48	451	US20150159173 SEQ ID NO: 44, US20150315612 SEQ ID NO: 115
AAVrh.48.1	452	US20150159173
AAVrh.48.1.2	453	US20150159173
AAVrh.48.2	454	US20150159173
AAVrh.48 (AAV1-7)	455	US20150315612 SEQ ID NO: 32
AAVrh.49 (AAV1-8)	456	US20150315612 SEQ ID NO: 25

AAVrh.49 (AAV1-8)	457	US20150315612 SEQ ID NO: 103
AAVrh.50 (AAV2-4)	458	US20150315612 SEQ ID NO: 23
AAVrh.50 (AAV2-4)	459	US20150315612 SEQ ID NO: 108
AAVrh.51 (AAV2-5)	460	US20150315612 SEQ ID No: 22
AAVrh.51 (AAV2-5)	461	US20150315612 SEQ ID NO: 104
AAVrh.52 (AAV3-9)	462	US20150315612 SEQ ID NO: 18
AAVrh.52 (AAV3-9)	463	US20150315612 SEQ ID NO: 96
AAVrh.53	464	US20150315612 SEQ ID NO: 97
AAVrh.53 (AAV3-11)	465	US20150315612 SEQ ID NO: 17
AAVrh.53 (AAV3-11)	466	US20150315612 SEQ ID NO: 186
AAVrh.54	467	US20150315612 SEQ ID NO: 40
AAVrh.54	468	US20150159173 SEQ ID NO: 49, US20150315612 SEQ ID NO: 116
AAVrh.55	469	US20150315612 SEQ ID NO: 37
AAVrh.55 (AAV4-19)	470	US20150315612 SEQ ID NO: 117
AAVrh.56	471	US20150315612 SEQ ID NO: 54
AAVrh.56	472	US20150315612 SEQ ID NO: 152
AAVrh.57	473	US20150315612 SEQ ID NO: 26
AAVrh.57	474	US20150315612 SEQ ID NO: 105
AAVrh.58	475	US20150315612 SEQ ID NO: 27
AAVrh.58	476	US20150159173 SEQ ID NO: 48, US20150315612 SEQ ID NO: 106
AAVrh.58	477	US20150315612 SEQ ID NO: 232
AAVrh.59	478	US20150315612 SEQ ID NO: 42
AAVrh.59	479	US20150315612 SEQ ID NO: 110
AAVrh.60	480	US20150315612 SEQ ID NO: 31
AAVrh.60	481	US20150315612 SEQ ID NO: 120
AAVrh.61	482	US20150315612 SEQ ID NO: 107
AAVrh.61 (AAV2-3)	483	US20150315612 SEQ ID NO: 21
AAVrh.62 (AAV2-15)	484	US20150315612 SEQ ID No: 33
AAVrh.62 (AAV2-15)	485	US20150315612 SEQ ID NO: 114
AAVrh.64	486	US20150315612 SEQ ID No: 15
AAVrh.64	487	US20150159173 SEQ ID NO: 43, US20150315612 SEQ ID NO: 99
AAVrh.64	488	US20150315612 SEQ ID NO: 233
AAVRh.64R1	489	US20150159173
AAVRh.64R2	490	US20150159173
AAVrh.65	491	US20150315612 SEQ ID NO: 35
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AAVrh.67	495	US20150159173 SEQ ID NO: 47, US20150315612 SEQ ID NO: 113
AAVrh.68	496	US20150315612 SEQ ID NO: 16
AAVrh.68	497	US20150315612 SEQ ID NO: 100
AAVrh.69	498	US20150315612 SEQ ID NO: 39
AAVrh.69	499	US20150315612 SEQ ID NO: 119
AAVrh.70	500	US20150315612 SEQ ID NO: 20
AAVrh.70	501	US20150315612 SEQ ID NO: 98
AAVrh.71	502	US20150315612 SEQ ID NO: 162
AAVrh.72	503	US20150315612 SEQ ID NO: 9
AAVrh.73	504	US20150159173 SEQ ID NO: 5
AAVrh.74	505	US20150159173 SEQ ID NO: 6
AAVrh.8	506	US20150159173 SEQ ID NO: 41
AAVrh.8	507	US20150315612 SEQ ID NO: 235
AAVrh.8R	508	US20150159173, WO2015168666 SEQ ID NO: 9
AAVrh.8R A586R mutant	509	WO2015168666 SEQ ID NO: 10
AAVrh.8R R533A mutant	510	WO2015168666 SEQ ID NO: 11
BAAV (bovine AAV)	511	US9193769 SEQ ID NO: 8
BAAV (bovine AAV)	512	US9193769 SEQ ID NO: 10
BAAV (bovine AAV)	513	US9193769 SEQ ID NO: 4
BAAV (bovine AAV)	514	US9193769 SEQ ID NO: 2
BAAV (bovine AAV)	515	US9193769 SEQ ID NO: 6
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BAAV (bovine AAV)	517	US9193769 SEQ ID NO: 5
BAAV (bovine AAV)	518	US9193769 SEQ ID NO: 3
BAAV (bovine AAV)	519	US9193769 SEQ ID NO: 11
BAAV (bovine AAV)	520	US7427396 SEQ ID NO: 5

BAAV (bovine AAV)	521	US7427396 SEQ ID NO: 6
BAAV (bovine AAV)	522	US9193769 SEQ ID NO: 7
BAAV (bovine AAV)	523	US9193769 SEQ ID NO: 9
BNP61 AAV	524	US20150238550 SEQ ID NO: 1
BNP61 AAV	525	US20150238550 SEQ ID NO: 2
BNP62 AAV	526	US20150238550 SEQ ID NO: 3
BNP63 AAV	527	US20150238550 SEQ ID NO: 4
caprine AAV	528	US7427396 SEQ ID NO: 3
caprine AAV	529	US7427396 SEQ ID NO: 4
true type AAV (ttAAV)	530	WO2015121501 SEQ ID NO: 2
AAAV (Avian AAV)	531	US9238800 SEQ ID NO: 12
AAAV (Avian AAV)	532	US9238800 SEQ ID NO: 2
AAAV (Avian AAV)	533	US9238800 SEQ ID NO: 6
AAAV (Avian AAV)	534	US9238800 SEQ ID NO: 4
AAAV (Avian AAV)	535	US9238800 SEQ ID NO: 8
AAAV (Avian AAV)	536	US9238800 SEQ ID NO: 14
AAAV (Avian AAV)	537	US9238800 SEQ ID NO: 10
AAAV (Avian AAV)	538	US9238800 SEQ ID NO: 15
AAAV (Avian AAV)	539	US9238800 SEQ ID NO: 5
AAAV (Avian AAV)	540	US9238800 SEQ ID NO: 9
AAAV (Avian AAV)	541	US9238800 SEQ ID NO: 3
AAAV (Avian AAV)	542	US9238800 SEQ ID NO: 7
AAAV (Avian AAV)	543	US9238800 SEQ ID NO: 11
AAAV (Avian AAV)	544	US9238800 SEQ ID NO: 13
AAAV (Avian AAV)	545	US9238800 SEQ ID NO: 1
AAV Shuffle 100-1	546	US20160017295 SEQ ID NO: 23
AAV Shuffle 100-1	547	US20160017295 SEQ ID NO: 11
AAV Shuffle 100-2	548	US20160017295 SEQ ID NO: 37
AAV Shuffle 100-2	549	US20160017295 SEQ ID NO: 29

AAV Shuffle 100-3	550	US20160017295 SEQ ID NO: 24
AAV Shuffle 100-3	551	US20160017295 SEQ ID NO: 12
AAV Shuffle 100-7	552	US20160017295 SEQ ID NO: 25
AAV Shuffle 100-7	553	US20160017295 SEQ ID NO: 13
AAV Shuffle 10-2	554	US20160017295 SEQ ID NO: 34
AAV Shuffle 10-2	555	US20160017295 SEQ ID NO: 26
AAV Shuffle 10-6	556	US20160017295 SEQ ID NO: 35
AAV Shuffle 10-6	557	US20160017295 SEQ ID NO: 27
AAV Shuffle 10-8	558	US20160017295 SEQ ID NO: 36
AAV Shuffle 10-8	559	US20160017295 SEQ ID NO: 28
AAV SM 100-10	560	US20160017295 SEQ ID NO: 41
AAV SM 100-10	561	US20160017295 SEQ ID NO: 33
AAV SM 100-3	562	US20160017295 SEQ ID NO: 40
AAV SM 100-3	563	US20160017295 SEQ ID NO: 32
AAV SM 10-1	564	US20160017295 SEQ ID NO: 38
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AAV SM 10-2	566	US20160017295 SEQ ID NO: 10
AAV SM 10-2	567	US20160017295 SEQ ID NO: 22
AAV SM 10-8	568	US20160017295 SEQ ID NO: 39
AAV SM 10-8	569	US20160017295 SEQ ID NO: 31
AAV SM 100-10	560	US20160017295 SEQ ID NO: 41
AAV SM 100-10	561	US20160017295 SEQ ID NO: 33
AAV SM 100-3	562	US20160017295 SEQ ID NO: 40
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AAV SM 10-1	565	US20160017295 SEQ ID NO: 30
AAV SM 10-2	566	US20160017295 SEQ ID NO: 10
AAV SM 10-2	567	US20160017295 SEQ ID NO: 22
AAV SM 10-8	568	US20160017295 SEQ ID NO: 39

AAV SM 10-8	569	US20160017295 SEQ ID NO: 31
AAVF1/HSC1	570	WO2016049230 SEQ ID NO: 20
AAVF2/HSC2	571	WO2016049230 SEQ ID NO: 21
AAVF3/HSC3	572	WO2016049230 SEQ ID NO: 22
AAVF4/HSC4	573	WO2016049230 SEQ ID NO: 23
AAVF5/HSC5	574	WO2016049230 SEQ ID NO: 25
AAVF6/HSC6	575	WO2016049230 SEQ ID NO: 24
AAVF7/HSC7	576	WO2016049230 SEQ ID NO: 27
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AAVF9/HSC9	578	WO2016049230 SEQ ID NO: 29
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AAVF14/HSC14	582	WO2016049230 SEQ ID NO: 32
AAVF15/HSC15	583	WO2016049230 SEQ ID NO: 33
AAVF16/HSC16	584	WO2016049230 SEQ ID NO: 34
AAVF17/HSC17	585	WO2016049230 SEQ ID NO: 35
AAVF1/HSC1	586	WO2016049230 SEQ ID NO: 2
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AAVF11/HSC11	595	WO2016049230 SEQ ID NO: 4
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AAV CBr-E6	608	US8734809 SEQ ID NO: 19
AAV CBr-E7	609	US8734809 SEQ ID NO: 20
AAV CBr-E8	610	US8734809 SEQ ID NO: 21
AAV CLv-D1	611	US8734809 SEQ ID NO: 22
AAV CLv-D2	612	US8734809 SEQ ID NO: 23
AAV CLv-D3	613	US8734809 SEQ ID NO: 24
AAV CLv-D4	614	US8734809 SEQ ID NO: 25
AAV CLv-D5	615	US8734809 SEQ ID NO: 26
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AAV CLv-R4	623	US8734809 SEQ ID NO: 33
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AAV CLv-R9	628	US8734809 SEQ ID NO: 38
AAV CLg-F1	629	US8734809 SEQ ID NO: 39
AAV CLg-F2	630	US8734809 SEQ ID NO: 40

AAV CLg-F3	631	US8734809 SEQ ID NO: 41
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AAV CLg-F5	633	US8734809 SEQ ID NO: 43
AAV CLg-F6	634	US8734809 SEQ ID NO: 43
AAV CLg-F7	635	US8734809 SEQ ID NO: 44
AAV CLg-F8	636	US8734809 SEQ ID NO: 43
AAV CSp-1	637	US8734809 SEQ ID NO: 45
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AAV CSp-7	644	US8734809 SEQ ID NO: 52
AAV CSp-8	645	US8734809 SEQ ID NO: 53
AAV CSp-9	646	US8734809 SEQ ID NO: 54
AAV CHt-2	647	US8734809 SEQ ID NO: 55
AAV CHt-3	648	US8734809 SEQ ID NO: 56
AAV CKd-1	649	US8734809 SEQ ID NO: 57
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AAV CLv-6	663	US8734809 SEQ ID NO: 71
AAV CLv-8	664	US8734809 SEQ ID NO: 72
AAV CKd-B1	665	US8734809 SEQ ID NO: 73
AAV CKd-B2	666	US8734809 SEQ ID NO: 74
AAV CKd-B3	667	US8734809 SEQ ID NO: 75
AAV CKd-B4	668	US8734809 SEQ ID NO: 76
AAV CKd-B5	669	US8734809 SEQ ID NO: 77
AAV CKd-B6	670	US8734809 SEQ ID NO: 78

AAV CKd-B7	671	US8734809 SEQ ID NO: 79
AAV CKd-B8	672	US8734809 SEQ ID NO: 80
AAV CKd-H1	673	US8734809 SEQ ID NO: 81
AAV CKd-H2	674	US8734809 SEQ ID NO: 82
AAV CKd-H3	675	US8734809 SEQ ID NO: 83
AAV CKd-H4	676	US8734809 SEQ ID NO: 84
AAV CKd-H5	677	US8734809 SEQ ID NO: 85
AAV CKd-H6	678	US8734809 SEQ ID NO: 77
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AAV CLv1-2	681	US8734809 SEQ ID NO: 172
AAV CLv1-3	682	US8734809 SEQ ID NO: 173
AAV CLv1-4	683	US8734809 SEQ ID NO: 174
AAV Clv1-7	684	US8734809 SEQ ID NO: 175
AAV Clv1-8	685	US8734809 SEQ ID NO: 176
AAV Clv1-9	686	US8734809 SEQ ID NO: 177
AAV Clv1-10	687	US8734809 SEQ ID NO: 178
AAV.VR-355	688	US8734809 SEQ ID NO: 181
AAV.hu.48R3	689	US8734809 SEQ ID NO: 183
AAV CBr-E1	690	US8734809 SEQ ID NO: 87
AAV CBr-E2	691	US8734809 SEQ ID NO: 88
AAV CBr-E3	692	US8734809 SEQ ID NO: 89
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AAV CBr-E5	694	US8734809 SEQ ID NO: 91
AAV CBr-e5	695	US8734809 SEQ ID NO: 92
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AAV CBr-E7	697	US8734809 SEQ ID NO: 94
AAV CBr-E8	698	US8734809 SEQ ID NO: 95
AAV CLv-D1	699	US8734809 SEQ ID NO: 96
AAV CLv-D2	700	US8734809 SEQ ID NO: 97
AAV CLv-D3	701	US8734809 SEQ ID NO: 98
AAV CLv-D4	702	US8734809 SEQ ID NO: 99
AAV CLv-D5	703	US8734809 SEQ ID NO: 100
AAV CLv-D6	704	US8734809 SEQ ID NO: 101
AAV CLv-D7	705	US8734809 SEQ ID NO: 102

AAV CLv-D8	706	US8734809 SEQ ID NO: 103
AAV CLv-E1	707	US8734809 SEQ ID NO: 87
AAV CLv-R1	708	US8734809 SEQ ID NO: 104
AAV CLv-R2	709	US8734809 SEQ ID NO: 105
AAV CLv-R3	710	US8734809 SEQ ID NO: 106
AAV CLv-R4	711	US8734809 SEQ ID NO: 107
AAV CLv-R5	712	US8734809 SEQ ID NO: 108
AAV CLv-R6	713	US8734809 SEQ ID NO: 109
AAV CLv-R7	714	US8734809 SEQ ID NO: 110
AAV CLv-R8	715	US8734809 SEQ ID NO: 111
AAV CLv-R9	716	US8734809 SEQ ID NO: 112
AAV CLg-F1	717	US8734809 SEQ ID NO: 113
AAV CLg-F2	718	US8734809 SEQ ID NO: 114
AAV CLg-F3	719	US8734809 SEQ ID NO: 115
AAV CLg-F4	720	US8734809 SEQ ID NO: 116
AAV CLg-F5	721	US8734809 SEQ ID NO: 117
AAV CLg-F6	722	US8734809 SEQ ID NO: 117
AAV CLg-F7	723	US8734809 SEQ ID NO: 118
AAV CLg-F8	724	US8734809 SEQ ID NO: 117
AAV CSp-1	725	US8734809 SEQ ID NO: 119
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AAV CSp-11	727	US8734809 SEQ ID NO: 121
AAV CSp-2	728	US8734809 SEQ ID NO: 122
AAV CSp-3	729	US8734809 SEQ ID NO: 123
AAV CSp-4	730	US8734809 SEQ ID NO: 124
AAV CSp-6	731	US8734809 SEQ ID NO: 125
AAV CSp-7	732	US8734809 SEQ ID NO: 126
AAV CSp-8	733	US8734809 SEQ ID NO: 127
AAV CSp-9	734	US8734809 SEQ ID NO: 128
AAV CHt-2	735	US8734809 SEQ ID NO: 129
AAV CHt-3	736	US8734809 SEQ ID NO: 130
AAV CKd-1	737	US8734809 SEQ ID NO: 131
AAV CKd-10	738	US8734809 SEQ ID NO: 132
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AAV CKd-3	740	US8734809 SEQ ID NO: 134
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AAV CKd-6	742	US8734809 SEQ ID NO: 136
AAV CKd-7	743	US8734809 SEQ ID NO: 137
AAV CKd-8	744	US8734809 SEQ ID NO: 138

AAV CLv-1	745	US8734809 SEQ ID NO: 139
AAV CLv-12	746	US8734809 SEQ ID NO: 140
AAV CLv-13	747	US8734809 SEQ ID NO: 141
AAV CLv-2	748	US8734809 SEQ ID NO: 142
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AAV CLv-4	750	US8734809 SEQ ID NO: 144
AAV CLv-6	751	US8734809 SEQ ID NO: 145
AAV CLv-8	752	US8734809 SEQ ID NO: 146
AAV CKd-B1	753	US8734809 SEQ ID NO: 147
AAV CKd-B2	754	US8734809 SEQ ID NO: 148
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AAV CKd-B8	760	US8734809 SEQ ID NO: 154
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AAV CKd-H5	765	US8734809 SEQ ID NO: 159
AAV CKd-H6	766	US8734809 SEQ ID NO: 151
AAV CHt-1	767	US8734809 SEQ ID NO: 160
AAV CHt-P2	768	WO2016065001 SEQ ID NO: 1
AAV CHt-P5	769	WO2016065001 SEQ ID NO: 2
AAV CHt-P9	770	WO2016065001 SEQ ID NO: 3
AAV CBr-7.1	771	WO2016065001 SEQ ID NO: 4
AAV CBr-7.2	772	WO2016065001 SEQ ID NO: 5
AAV CBr-7.3	773	WO2016065001 SEQ ID NO: 6
AAV CBr-7.4	774	WO2016065001 SEQ ID NO: 7
AAV CBr-7.5	775	WO2016065001 SEQ ID NO: 8
AAV CBr-7.7	776	WO2016065001 SEQ ID NO: 9
AAV CBr-7.8	777	WO2016065001 SEQ ID NO: 10

AAV CBr-7.10	778	WO2016065001 SEQ ID NO: 11
AAV CKd-N3	779	WO2016065001 SEQ ID NO: 12
AAV CKd-N4	780	WO2016065001 SEQ ID NO: 13
AAV CKd-N9	781	WO2016065001 SEQ ID NO: 14
AAV CLv-L4	782	WO2016065001 SEQ ID NO: 15
AAV CLv-L5	783	WO2016065001 SEQ ID NO: 16
AAV CLv-L6	784	WO2016065001 SEQ ID NO: 17
AAV CLv-K1	785	WO2016065001 SEQ ID NO: 18
AAV CLv-K3	786	WO2016065001 SEQ ID NO: 19
AAV CLv-K6	787	WO2016065001 SEQ ID NO: 20
AAV CLv-M1	788	WO2016065001 SEQ ID NO: 21
AAV CLv-M11	789	WO2016065001 SEQ ID NO: 22
AAV CLv-M2	790	WO2016065001 SEQ ID NO: 23
AAV CLv-M5	791	WO2016065001 SEQ ID NO: 24
AAV CLv-M6	792	WO2016065001 SEQ ID NO: 25
AAV CLv-M7	793	WO2016065001 SEQ ID NO: 26
AAV CLv-M8	794	WO2016065001 SEQ ID NO: 27
AAV CLv-M9	795	WO2016065001 SEQ ID NO: 28
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AAV CHt-P6	797	WO2016065001 SEQ ID NO: 30
AAV CHt-P8	798	WO2016065001 SEQ ID NO: 31
AAV CHt-6.1	799	WO2016065001 SEQ ID NO: 32
AAV CHt-6.10	800	WO2016065001 SEQ ID NO: 33
AAV CHt-6.5	801	WO2016065001 SEQ ID NO: 34
AAV CHt-6.6	802	WO2016065001 SEQ ID NO: 35
AAV CHt-6.7	803	WO2016065001 SEQ ID NO: 36
AAV CHt-6.8	804	WO2016065001 SEQ ID NO: 37
AAV CSp-8.10	805	WO2016065001 SEQ ID NO: 38
AAV CSp-8.2	806	WO2016065001 SEQ ID NO: 39
AAV CSp-8.4	807	WO2016065001 SEQ ID NO: 40
AAV CSp-8.5	808	WO2016065001 SEQ ID NO: 41

AAV CSp-8.6	809	WO2016065001 SEQ ID NO: 42
AAV CSp-8.7	810	WO2016065001 SEQ ID NO: 43
AAV CSp-8.8	811	WO2016065001 SEQ ID NO: 44
AAV CSp-8.9	812	WO2016065001 SEQ ID NO: 45
AAV CBr-B7.3	813	WO2016065001 SEQ ID NO: 46
AAV CBr-B7.4	814	WO2016065001 SEQ ID NO: 47
AAV3B	815	WO2016065001 SEQ ID NO: 48
AAV4	816	WO2016065001 SEQ ID NO: 49
AAV5	817	WO2016065001 SEQ ID NO: 50
AAV CHt-P2	818	WO2016065001 SEQ ID NO: 51
AAV CHt-P5	819	WO2016065001 SEQ ID NO: 52
AAV CHt-P9	820	WO2016065001 SEQ ID NO: 53
AAV CBr-7.1	821	WO2016065001 SEQ ID NO: 54
AAV CBr-7.2	822	WO2016065001 SEQ ID NO: 55
AAV CBr-7.3	823	WO2016065001 SEQ ID NO: 56
AAV CBr-7.4	824	WO2016065001 SEQ ID NO: 57
AAV CBr-7.5	825	WO2016065001 SEQ ID NO: 58
AAV CBr-7.7	826	WO2016065001 SEQ ID NO: 59
AAV CBr-7.8	827	WO2016065001 SEQ ID NO: 60
AAV CBr-7.10	828	WO2016065001 SEQ ID NO: 61
AAV CKd-N3	829	WO2016065001 SEQ ID NO: 62
AAV CKd-N4	830	WO2016065001 SEQ ID NO: 63
AAV CKd-N9	831	WO2016065001 SEQ ID NO: 64
AAV CLv-L4	832	WO2016065001 SEQ ID NO: 65
AAV CLv-L5	833	WO2016065001 SEQ ID NO: 66
AAV CLv-L6	834	WO2016065001 SEQ ID NO: 67
AAV CLv-K1	835	WO2016065001 SEQ ID NO: 68
AAV CLv-K3	836	WO2016065001 SEQ ID NO: 69
AAV CLv-K6	837	WO2016065001 SEQ ID NO: 70
AAV CLv-M1	838	WO2016065001 SEQ ID NO: 71
AAV CLv-M11	839	WO2016065001 SEQ ID NO: 72
AAV CLv-M2	840	WO2016065001 SEQ ID NO: 73

AAV CLv-M5	841	WO2016065001 SEQ ID NO: 74
AAV CLv-M6	842	WO2016065001 SEQ ID NO: 75
AAV CLv-M7	843	WO2016065001 SEQ ID NO: 76
AAV CLv-M8	844	WO2016065001 SEQ ID NO: 77
AAV CLv-M9	845	WO2016065001 SEQ ID NO: 78
AAV CHt-P1	846	WO2016065001 SEQ ID NO: 79
AAV CHt-P6	847	WO2016065001 SEQ ID NO: 80
AAV CHt-P8	848	WO2016065001 SEQ ID NO: 81
AAV CHt-6.1	849	WO2016065001 SEQ ID NO: 82
AAV CHt-6.10	850	WO2016065001 SEQ ID NO: 83
AAV CHt-6.5	851	WO2016065001 SEQ ID NO: 84
AAV CHt-6.6	852	WO2016065001 SEQ ID NO: 85
AAV CHt-6.7	853	WO2016065001 SEQ ID NO: 86
AAV CHt-6.8	854	WO2016065001 SEQ ID NO: 87
AAV CSp-8.10	855	WO2016065001 SEQ ID NO: 88
AAV CSp-8.2	856	WO2016065001 SEQ ID NO: 89
AAV CSp-8.4	857	WO2016065001 SEQ ID NO: 90
AAV CSp-8.5	858	WO2016065001 SEQ ID NO: 91
AAV CSp-8.6	859	WO2016065001 SEQ ID NO: 92
AAV CSp-8.7	860	WO2016065001 SEQ ID NO: 93
AAV CSp-8.8	861	WO2016065001 SEQ ID NO: 94
AAV CSp-8.9	862	WO2016065001 SEQ ID NO: 95
AAV CBr-B7.3	863	WO2016065001 SEQ ID NO: 96
AAV CBr-B7.4	864	WO2016065001 SEQ ID NO: 97
AAV3B	865	WO2016065001 SEQ ID NO: 98
AAV4	866	WO2016065001 SEQ ID NO: 99
AAV5	867	WO2016065001 SEQ ID NO: 100
AAVPHP.B or G2B-26	868	WO2015038958 SEQ ID NO: 8 and 13; GenBankALU85156.1
AAVPHP.B	869	WO2015038958 SEQ ID NO: 9
AAVG2B-13	870	WO2015038958 SEQ ID NO: 12
AAVTH1.1-32	871	WO2015038958 SEQ ID NO: 14
AAVTH1.1-35	872	WO2015038958 SEQ ID NO: 15

PHP.N/PHP.B-DGT	1859	WO2017100671 SEQ ID NO: 46
PHP.S/G2A12	1860	WO2017100671 SEQ ID NO: 47
AAV9/hu.14 K449R	1861	WO2017100671 SEQ ID NO: 45
GPV	1862	US9624274B2 SEQ ID NO: 192
B19	1863	US9624274B2 SEQ ID NO: 193
MVM	1864	US9624274B2 SEQ ID NO: 194
FPV	1865	US9624274B2 SEQ ID NO: 195
CPV	1866	US9624274B2 SEQ ID NO: 196
AAV6	1867	US9546112B2 SEQ ID NO: 5
AAV6	1868	US9457103B2 SEQ ID NO: 1
AAV2	1869	US9457103B2 SEQ ID NO: 2
ShH10	1870	US9457103B2 SEQ ID NO: 3
ShH13	1871	US9457103B2 SEQ ID NO: 4
ShH10	1872	US9457103B2 SEQ ID NO: 5
ShH10	1873	US9457103B2 SEQ ID NO: 6
ShH10	1874	US9457103B2 SEQ ID NO: 7
ShH10	1875	US9457103B2 SEQ ID NO: 8
ShH10	1876	US9457103B2 SEQ ID NO: 9
rh74	1877	US9434928B2 SEQ ID NO: 1, US2015023924A1 SEQ ID NO: 2
rh74	1878	US9434928B2 SEQ ID NO: 2, US2015023924A1 SEQ ID NO: 1
AAV8	1879	US9434928B2 SEQ ID NO: 4
rh74	1880	US9434928B2 SEQ ID NO: 5
rh74 (RHM4-1)	1881	US2015023924A1 SEQ ID NO: 5, US20160375110A1 SEQ ID NO: 4
rh74 (RHM15-1)	1882	US2015023924A1 SEQ ID NO: 6, US20160375110A1 SEQ ID NO: 5
rh74 (RHM15-2)	1883	US2015023924A1 SEQ ID NO: 7, US20160375110A1 SEQ ID NO: 6
rh74 (RHM15-3/RHM15-5)	1884	US2015023924A1 SEQ ID NO: 8, US20160375110A1 SEQ ID NO: 7
rh74 (RHM15-4)	1885	US2015023924A1 SEQ ID NO: 9, US20160375110A1 SEQ ID NO: 8
rh74 (RHM15-6)	1886	US2015023924A1 SEQ ID NO: 10, US20160375110A1 SEQ ID NO: 9
rh74 (RHM4-1)	1887	US2015023924A1 SEQ ID NO: 11
rh74 (RHM15-1)	1888	US2015023924A1 SEQ ID NO: 12
rh74 (RHM15-2)	1889	US2015023924A1 SEQ ID NO: 13
rh74 (RHM15-3/RHM15-5)	1890	US2015023924A1 SEQ ID NO: 14
rh74 (RHM15-4)	1891	US2015023924A1 SEQ ID NO: 15
rh74 (RHM15-6)	1892	US2015023924A1 SEQ ID NO: 16

AAV2 (comprising lung specific polypeptide)	1893	US20160175389A1 SEQ ID NO: 9
AAV2 (comprising lung specific polypeptide)	1894	US20160175389A1 SEQ ID NO: 10
Anc80	1895	US20170051257A1 SEQ ID NO: 1
Anc80	1896	US20170051257A1 SEQ ID NO: 2
Anc81	1897	US20170051257A1 SEQ ID NO: 3
Anc80	1898	US20170051257A1 SEQ ID NO: 4
Anc82	1899	US20170051257A1 SEQ ID NO: 5
Anc82	1900	US20170051257A1 SEQ ID NO: 6
Anc83	1901	US20170051257A1 SEQ ID NO: 7
Anc83	1902	US20170051257A1 SEQ ID NO: 8
Anc84	1903	US20170051257A1 SEQ ID NO: 9
Anc84	1904	US20170051257A1 SEQ ID NO: 10
Anc94	1905	US20170051257A1 SEQ ID NO: 11
Anc94	1906	US20170051257A1 SEQ ID NO: 12
Anc113	1907	US20170051257A1 SEQ ID NO: 13
Anc113	1908	US20170051257A1 SEQ ID NO: 14
Anc126	1909	US20170051257A1 SEQ ID NO: 15
Anc126	1910	US20170051257A1 SEQ ID NO: 16
Anc127	1911	US20170051257A1 SEQ ID NO: 17
Anc127	1912	US20170051257A1 SEQ ID NO: 18
Anc80L27	1913	US20170051257A1 SEQ ID NO: 19
Anc80L59	1914	US20170051257A1 SEQ ID NO: 20
Anc80L60	1915	US20170051257A1 SEQ ID NO: 21
Anc80L62	1916	US20170051257A1 SEQ ID NO: 22
Anc80L65	1917	US20170051257A1 SEQ ID NO: 23
Anc80L33	1918	US20170051257A1 SEQ ID NO: 24
Anc80L36	1919	US20170051257A1 SEQ ID NO: 25
Anc80L44	1920	US20170051257A1 SEQ ID NO: 26
Anc80L1	1921	US20170051257A1 SEQ ID NO: 35
Anc80L1	1922	US20170051257A1 SEQ ID NO: 36
AAV-X1	1923	US8283151B2 SEQ ID NO: 11
AAV-X1b	1924	US8283151B2 SEQ ID NO: 12
AAV-X5	1925	US8283151B2 SEQ ID NO: 13
AAV-X19	1926	US8283151B2 SEQ ID NO: 14
AAV-X21	1927	US8283151B2 SEQ ID NO: 15
AAV-X22	1928	US8283151B2 SEQ ID NO: 16
AAV-X23	1929	US8283151B2 SEQ ID NO: 17
AAV-X24	1930	US8283151B2 SEQ ID NO: 18
AAV-X25	1931	US8283151B2 SEQ ID NO: 19
AAV-X26	1932	US8283151B2 SEQ ID NO: 20

AAV-X1	1933	US8283151B2 SEQ ID NO: 21
AAV-X1b	1934	US8283151B2 SEQ ID NO: 22
AAV-X5	1935	US8283151B2 SEQ ID NO: 23
AAV-X19	1936	US8283151B2 SEQ ID NO: 24
AAV-X21	1937	US8283151B2 SEQ ID NO: 25
AAV-X22	1938	US8283151B2 SEQ ID NO: 26
AAV-X23	1939	US8283151B2 SEQ ID NO: 27
AAV-X24	1940	US8283151B2 SEQ ID NO: 28
AAV-X25	1941	US8283151B2 SEQ ID NO: 29
AAV-X26	1942	US8283151B2 SEQ ID NO: 30
AAVrh8	1943	WO2016054554A1 SEQ ID NO: 8
AAVrh8VP2 FC5	1944	WO2016054554A1 SEQ ID NO: 9
AAVrh8VP2 FC44	1945	WO2016054554A1 SEQ ID NO: 10
AAVrh8VP2 ApoB100	1946	WO2016054554A1 SEQ ID NO: 11
AAVrh8VP2 RVG	1947	WO2016054554A1 SEQ ID NO: 12
AAVrh8VP2 Angiopep-2 VP2	1948	WO2016054554A1 SEQ ID NO: 13
AAV9.47VP 1.3	1949	WO2016054554A1 SEQ ID NO: 14
AAV9.47VP 2ICAMg3	1950	WO2016054554A1 SEQ ID NO: 15
AAV9.47VP 2RVG	1951	WO2016054554A1 SEQ ID NO: 16
AAV9.47VP 2Angiopep-2	1952	WO2016054554A1 SEQ ID NO: 17
AAV9.47VP 2A-string	1953	WO2016054554A1 SEQ ID NO: 18
AAVrh8VP2 FC5 VP2	1954	WO2016054554A1 SEQ ID NO: 19
AAVrh8VP2 FC44 VP2	1955	WO2016054554A1 SEQ ID NO: 20
AAVrh8VP2 ApoB100 VP2	1956	WO2016054554A1 SEQ ID NO: 21
AAVrh8VP2 RVG VP2	1957	WO2016054554A1 SEQ ID NO: 22
AAVrh8VP2 Angiopep-2 VP2	1958	WO2016054554A1 SEQ ID NO: 23
AAV9.47VP 2ICAMg3 VP2	1959	WO2016054554A1 SEQ ID NO: 24
AAV9.47VP 2RVG VP2	1960	WO2016054554A1 SEQ ID NO: 25
AAV9.47VP 2Angiopep-2 VP2	1961	WO2016054554A1 SEQ ID NO: 26
AAV9.47VP 2A-string VP2	1962	WO2016054554A1 SEQ ID NO: 27

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rAAV-B3	1965	WO2016054557A1 SEQ ID NO: 3
rAAV-B4	1966	WO2016054557A1 SEQ ID NO: 4
rAAV-B1	1967	WO2016054557A1 SEQ ID NO: 5
rAAV-B2	1968	WO2016054557A1 SEQ ID NO: 6
rAAV-B3	1969	WO2016054557A1 SEQ ID NO: 7
rAAV-B4	1970	WO2016054557A1 SEQ ID NO: 8
rAAV-L1	1971	WO2016054557A1 SEQ ID NO: 9
rAAV-L2	1972	WO2016054557A1 SEQ ID NO: 10
rAAV-L3	1973	WO2016054557A1 SEQ ID NO: 11
rAAV-L4	1974	WO2016054557A1 SEQ ID NO: 12
rAAV-L1	1975	WO2016054557A1 SEQ ID NO: 13
rAAV-L2	1976	WO2016054557A1 SEQ ID NO: 14
rAAV-L3	1977	WO2016054557A1 SEQ ID NO: 15
rAAV-L4	1978	WO2016054557A1 SEQ ID NO: 16
AAV9	1979	WO2016073739A1 SEQ ID NO: 3
rAAV	1980	WO2016081811A1 SEQ ID NO: 1
rAAV	1981	WO2016081811A1 SEQ ID NO: 2
rAAV	1982	WO2016081811A1 SEQ ID NO: 3
rAAV	1983	WO2016081811A1 SEQ ID NO: 4
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rAAV	2003	WO2016081811A1 SEQ ID NO: 24
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rAAV	2006	WO2016081811A1 SEQ ID NO: 27

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rAAV	2014	WO2016081811A1 SEQ ID NO: 35
rAAV	2015	WO2016081811A1 SEQ ID NO: 36
rAAV	2016	WO2016081811A1 SEQ ID NO: 37
rAAV	2017	WO2016081811A1 SEQ ID NO: 38
rAAV	2018	WO2016081811A1 SEQ ID NO: 39
rAAV	2019	WO2016081811A1 SEQ ID NO: 40
rAAV	2020	WO2016081811A1 SEQ ID NO: 41
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rAAV	2022	WO2016081811A1 SEQ ID NO: 43
rAAV	2023	WO2016081811A1 SEQ ID NO: 44
rAAV	2024	WO2016081811A1 SEQ ID NO: 45
rAAV	2025	WO2016081811A1 SEQ ID NO: 46
rAAV	2026	WO2016081811A1 SEQ ID NO: 47
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rAAV	2047	WO2016081811A1 SEQ ID NO: 68
rAAV	2048	WO2016081811A1 SEQ ID NO: 69
rAAV	2049	WO2016081811A1 SEQ ID NO: 70
rAAV	2050	WO2016081811A1 SEQ ID NO: 71

rAAV	2051	WO2016081811A1 SEQ ID NO: 72
rAAV	2052	WO2016081811A1 SEQ ID NO: 73
rAAV	2053	WO2016081811A1 SEQ ID NO: 74
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rAAV	2091	WO2016081811A1 SEQ ID NO: 112
rAAV	2092	WO2016081811A1 SEQ ID NO: 113
rAAV	2093	WO2016081811A1 SEQ ID NO: 114
rAAV	2094	WO2016081811A1 SEQ ID NO: 115

rAAV	2095	WO2016081811A1 SEQ ID NO: 116
rAAV	2096	WO2016081811A1 SEQ ID NO: 117
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rAAV	2100	WO2016081811A1 SEQ ID NO: 121
rAAV	2101	WO2016081811A1 SEQ ID NO: 122
rAAV	2102	WO2016081811A1 SEQ ID NO: 123
rAAV	2103	WO2016081811A1 SEQ ID NO: 124
rAAV	2104	WO2016081811A1 SEQ ID NO: 125
rAAV	2105	WO2016081811A1 SEQ ID NO: 126
rAAV	2106	WO2016081811A1 SEQ ID NO: 127
rAAV	2107	WO2016081811A1 SEQ ID NO: 128
AAV8 E532K	2108	WO2016081811A1 SEQ ID NO: 133
AAV8 E532K	2109	WO2016081811A1 SEQ ID NO: 134
rAAV4	2110	WO2016115382A1 SEQ ID NO: 2
rAAV4	2111	WO2016115382A1 SEQ ID NO: 3
rAAV4	2112	WO2016115382A1 SEQ ID NO: 4
rAAV4	2113	WO2016115382A1 SEQ ID NO: 5
rAAV4	2114	WO2016115382A1 SEQ ID NO: 6
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rAAV4	2121	WO2016115382A1 SEQ ID NO: 13
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AAV11	2130	WO2016115382A1 SEQ ID NO: 22
AAV12	2131	WO2016115382A1 SEQ ID NO: 23
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rh34	2134	WO2016115382A1 SEQ ID NO: 27
rAAV4	2135	WO2016115382A1 SEQ ID NO: 28
rAAV4	2136	WO2016115382A1 SEQ ID NO: 29
rAAV4	2137	WO2016115382A1 SEQ ID NO: 30

rAAV4	2138	WO2016115382A1 SEQ ID NO: 31
rAAV4	2139	WO2016115382A1 SEQ ID NO: 32
rAAV4	2140	WO2016115382A1 SEQ ID NO: 33
AAV2/8	2141	WO2016131981A1 SEQ ID NO: 47
AAV2/8	2142	WO2016131981A1 SEQ ID NO: 48
ancestral AAV	2143	WO2016154344A1 SEQ ID NO: 7
ancestral AAV variant C4	2144	WO2016154344A1 SEQ ID NO: 13
ancestral AAV variant C7	2145	WO2016154344A1 SEQ ID NO: 14
ancestral AAV variant G4	2146	WO2016154344A1 SEQ ID NO: 15
consensus amino acid sequence of ancestral AAV variants, C4, C7 and G4	2147	WO2016154344A1 SEQ ID NO: 16
consensus amino acid sequence of ancestral AAV variants, C4 and C7	2148	WO2016154344A1 SEQ ID NO: 17
AAV8 (with a AAV2 phospholipase domain)	2149	WO2016150403A1 SEQ ID NO: 13
AAV VR-942n	2150	US20160289275A1 SEQ ID NO: 10
AAV5-A (M569V)	2151	US20160289275A1 SEQ ID NO: 13
AAV5-A (M569V)	2152	US20160289275A1 SEQ ID NO: 14
AAV5-A (Y585V)	2153	US20160289275A1 SEQ ID NO: 16
AAV5-A (Y585V)	2154	US20160289275A1 SEQ ID NO: 17
AAV5-A (L587T)	2155	US20160289275A1 SEQ ID NO: 19
AAV5-A (L587T)	2156	US20160289275A1 SEQ ID NO: 20
AAV5-A (Y585V/L587T)	2157	US20160289275A1 SEQ ID NO: 22
AAV5-A (Y585V/L587T)	2158	US20160289275A1 SEQ ID NO: 23
AAV5-B (D652A)	2159	US20160289275A1 SEQ ID NO: 25

AAV5-B (D652A)	2160	US20160289275A1 SEQ ID NO: 26
AAV5-B (T362M)	2161	US20160289275A1 SEQ ID NO: 28
AAV5-B (T362M)	2162	US20160289275A1 SEQ ID NO: 29
AAV5-B (Q359D)	2163	US20160289275A1 SEQ ID NO: 31
AAV5-B (Q359D)	2164	US20160289275A1 SEQ ID NO: 32
AAV5-B (E350Q)	2165	US20160289275A1 SEQ ID NO: 34
AAV5-B (E350Q)	2166	US20160289275A1 SEQ ID NO: 35
AAV5-B (P533S)	2167	US20160289275A1 SEQ ID NO: 37
AAV5-B (P533S)	2168	US20160289275A1 SEQ ID NO: 38
AAV5-B (P533G)	2169	US20160289275A1 SEQ ID NO: 40
AAV5-B (P533G)	2170	US20160289275A1 SEQ ID NO: 41
AAV5-mutation in loop VII	2171	US20160289275A1 SEQ ID NO: 43
AAV5-mutation in loop VII	2172	US20160289275A1 SEQ ID NO: 44
AAV8	2173	US20160289275A1 SEQ ID NO: 47
Mut A (LK03/AAV8)	2174	WO2016181123A1 SEQ ID NO: 1
Mut B (LK03/AAV5)	2175	WO2016181123A1 SEQ ID NO: 2
Mut C (AAV8/AAV 3B)	2176	WO2016181123A1 SEQ ID NO: 3
Mut D (AAV5/AAV 3B)	2177	WO2016181123A1 SEQ ID NO: 4
Mut E (AAV8/AAV 3B)	2178	WO2016181123A1 SEQ ID NO: 5
Mut F (AAV3B/AA V8)	2179	WO2016181123A1 SEQ ID NO: 6
AAV44.9	2180	WO2016183297A1 SEQ ID NO: 4
AAV44.9	2181	WO2016183297A1 SEQ ID NO: 5
AAVrh8	2182	WO2016183297A1 SEQ ID NO: 6
AAV44.9 (S470N)	2183	WO2016183297A1 SEQ ID NO: 9
rh74 VP1	2184	US20160375110A1 SEQ ID NO: 1
AAV-LK03 (L125I)	2185	WO2017015102A1 SEQ ID NO: 5

AAV3B (S663V+T492V)	2186	WO2017015102A1 SEQ ID NO: 6
Anc80	2187	WO2017019994A2 SEQ ID NO: 1
Anc80	2188	WO2017019994A2 SEQ ID NO: 2
Anc81	2189	WO2017019994A2 SEQ ID NO: 3
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Anc82	2192	WO2017019994A2 SEQ ID NO: 6
Anc83	2193	WO2017019994A2 SEQ ID NO: 7
Anc83	2194	WO2017019994A2 SEQ ID NO: 8
Anc84	2195	WO2017019994A2 SEQ ID NO: 9
Anc84	2196	WO2017019994A2 SEQ ID NO: 10
Anc94	2197	WO2017019994A2 SEQ ID NO: 11
Anc94	2198	WO2017019994A2 SEQ ID NO: 12
Anc113	2199	WO2017019994A2 SEQ ID NO: 13
Anc113	2200	WO2017019994A2 SEQ ID NO: 14
Anc126	2201	WO2017019994A2 SEQ ID NO: 15
Anc126	2202	WO2017019994A2 SEQ ID NO: 16
Anc127	2203	WO2017019994A2 SEQ ID NO: 17
Anc127	2204	WO2017019994A2 SEQ ID NO: 18
Anc80L27	2205	WO2017019994A2 SEQ ID NO: 19
Anc80L59	2206	WO2017019994A2 SEQ ID NO: 20
Anc80L60	2207	WO2017019994A2 SEQ ID NO: 21
Anc80L62	2208	WO2017019994A2 SEQ ID NO: 22
Anc80L65	2209	WO2017019994A2 SEQ ID NO: 23
Anc80L33	2210	WO2017019994A2 SEQ ID NO: 24
Anc80L36	2211	WO2017019994A2 SEQ ID NO: 25
Anc80L44	2212	WO2017019994A2 SEQ ID NO: 26
Anc80L1	2213	WO2017019994A2 SEQ ID NO: 35
Anc80L1	2214	WO2017019994A2 SEQ ID NO: 36
AAVrh10	2215	WO2017019994A2 SEQ ID NO: 41
Anc110	2216	WO2017019994A2 SEQ ID NO: 42
Anc110	2217	WO2017019994A2 SEQ ID NO: 43
AAVrh32.33	2218	WO2017019994A2 SEQ ID NO: 45
AAVrh74	2219	WO2017049031A1 SEQ ID NO: 1
AAV2	2220	WO2017053629A2 SEQ ID NO: 49
AAV2	2221	WO2017053629A2 SEQ ID NO: 50
AAV2	2222	WO2017053629A2 SEQ ID NO: 82
Parvo-like virus	2223	WO2017070476A2 SEQ ID NO: 1
Parvo-like virus	2224	WO2017070476A2 SEQ ID NO: 2
Parvo-like virus	2225	WO2017070476A2 SEQ ID NO: 3
Parvo-like virus	2226	WO2017070476A2 SEQ ID NO: 4

Parvo-like virus	2227	WO2017070476A2 SEQ ID NO: 5
Parvo-like virus	2228	WO2017070476A2 SEQ ID NO: 6
AAVrh.10	2229	WO2017070516A1 SEQ ID NO: 7
AAVrh.10	2230	WO2017070516A1 SEQ ID NO: 14
AAV2tYF	2231	WO2017070491A1 SEQ ID NO: 1
AAV-SPK	2232	WO2017075619A1 SEQ ID NO:28
AAV2.5	2233	US20170128528A1 SEQ ID NO: 13
AAV1.1	2234	US20170128528A1 SEQ ID NO: 15
AAV6.1	2235	US20170128528A1 SEQ ID NO: 17
AAV6.3.1	2236	US20170128528A1 SEQ ID NO: 18
AAV2i8	2237	US20170128528A1 SEQ ID NO: 28
AAV2i8	2238	US20170128528A1 SEQ ID NO: 29
ttAAV	2239	US20170128528A1 SEQ ID NO: 30
ttAAV-S312N	2240	US20170128528A1 SEQ ID NO: 32
ttAAV-S312N	2241	US20170128528A1 SEQ ID NO: 33
AAV6 (Y705, Y731, and T492)	2242	WO2016134337A1 SEQ ID NO: 24
AAV2	2243	WO2016134375A1 SEQ ID NO: 9
AAV2	2244	WO2016134375A1 SEQ ID NO: 10

[00190] Each of the patents, applications and/or publications listed in Table 1 are hereby incorporated by reference in their entirety.

[00191] In one embodiment, the AAV serotype may be, or may have a sequence as described in International Patent Publication WO2015038958, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV9 (SEQ ID NO: 2 and 11 of WO2015038958 or SEQ ID NO: 127 and 126 respectively herein), PHP.B (SEQ ID NO: 8 and 9 of WO2015038958, herein SEQ ID NO: 868 and 869), G2B-13 (SEQ ID NO: 12 of WO2015038958, herein SEQ ID NO: 870), G2B-26 (SEQ ID NO: 13 of WO2015038958, herein SEQ ID NO: 868 and 869), TH1.1-32 (SEQ ID NO: 14 of WO2015038958, herein SEQ ID NO: 871), TH1.1-35 (SEQ ID NO: 15 of WO2015038958, herein SEQ ID NO: 872) or variants thereof. Further, any of the targeting peptides or amino acid inserts described in WO2015038958, may be inserted into any parent AAV serotype, such as, but not limited to, AAV9 (SEQ ID NO: 126 for the DNA sequence and SEQ ID NO: 127 for the amino acid sequence). In one embodiment, the amino acid insert is inserted between amino acids 586-592 of the parent AAV (e.g., AAV9). In another embodiment, the amino acid insert is inserted between amino acids 588-589 of the parent AAV sequence. The amino acid insert may be, but is not limited to, any of the following amino acid sequences, TLAVPFK (SEQ ID NO: 1 of

WO2015038958; herein SEQ ID NO: 873), KFPVALT (SEQ ID NO: 3 of WO2015038958; herein SEQ ID NO: 874), LAVPFK (SEQ ID NO: 31 of WO2015038958; herein SEQ ID NO: 875), AVPFK (SEQ ID NO: 32 of WO2015038958; herein SEQ ID NO: 876), VPFK (SEQ ID NO: 33 of WO2015038958; herein SEQ ID NO: 877), TLAVPF (SEQ ID NO: 34 of WO2015038958; herein SEQ ID NO: 878), TLAVP (SEQ ID NO: 35 of WO2015038958; herein SEQ ID NO: 879), TLAV (SEQ ID NO: 36 of WO2015038958; herein SEQ ID NO: 880), SVSKPFL (SEQ ID NO: 28 of WO2015038958; herein SEQ ID NO: 881), FTLTTPK (SEQ ID NO: 29 of WO2015038958; herein SEQ ID NO: 882), MNATKNV (SEQ ID NO: 30 of WO2015038958; herein SEQ ID NO: 883), QSSQTPR (SEQ ID NO: 54 of WO2015038958; herein SEQ ID NO: 884), ILGTGTS (SEQ ID NO: 55 of WO2015038958; herein SEQ ID NO: 885), TRTNPEA (SEQ ID NO: 56 of WO2015038958; herein SEQ ID NO: 886), NGGTSSS (SEQ ID NO: 58 of WO2015038958; herein SEQ ID NO: 887), or YTLSQGW (SEQ ID NO: 60 of WO2015038958; herein SEQ ID NO: 888). Non-limiting examples of nucleotide sequences that may encode the amino acid inserts include the following, AAGTTTCCTGTGGCGTTGACT (for SEQ ID NO: 3 of WO2015038958; herein SEQ ID NO: 889), ACTTTGGCGGTGCCTTTTAAG (SEQ ID NO: 24 and 49 of WO2015038958; herein SEQ ID NO: 890), AGTGTGAGTAAGCCTTTTTTG (SEQ ID NO: 25 of WO2015038958; herein SEQ ID NO: 891), TTTACGTTGACGACGCCTAAG (SEQ ID NO: 26 of WO2015038958; herein SEQ ID NO: 892), ATGAATGCTACGAAGAATGTG (SEQ ID NO: 27 of WO2015038958; herein SEQ ID NO: 893), CAGTCGTCGCAGACGCCTAGG (SEQ ID NO: 48 of WO2015038958; herein SEQ ID NO: 894), ATTCTGGGGACTGGTACTTCG (SEQ ID NO: 50 and 52 of WO2015038958; herein SEQ ID NO: 895), ACGCGGACTAATCCTGAGGCT (SEQ ID NO: 51 of WO2015038958; herein SEQ ID NO: 896), AATGGGGGGACTAGTAGTTCT (SEQ ID NO: 53 of WO2015038958; herein SEQ ID NO: 897), or TATACTTTGTCGCAGGGTTGG (SEQ ID NO: 59 of WO2015038958; herein SEQ ID NO: 898).

[00192] In one embodiment, the AAV serotype may be engineered to comprise at least one AAV capsid CD8+ T-cell epitope for AAV2 such as, but not limited to, SADNNNSEY (SEQ ID NO: 899), LIDQYLYYL (SEQ ID NO: 900), VPQYGYLTL (SEQ ID NO: 901), TTSTRTWAL (SEQ ID NO: 902), YHLNGRDSL (SEQ ID NO: 903), SQAVGRSSF (SEQ ID NO: 904), VPANPSTTF (SEQ ID NO: 905), FPQSGVLIF (SEQ ID NO: 906), YFDFNRFHCHFSPRD (SEQ ID NO: 907), VGNSSGNWHCDSTWM (SEQ ID NO: 908), QFSQAGASDIRDQSR

(SEQ ID NO: 909), GASDIRQSRNWLP (SEQ ID NO: 910) and GNRQAATADVNTQGV (SEQ ID NO: 911).

[00193] In one embodiment, the AAV serotype may be engineered to comprise at least one AAV capsid CD8+ T-cell epitope for AAV1 such as, but not limited to, LDRLMNPLI (SEQ ID NO: 912), TTSTRTWAL (SEQ ID NO: 902), and QPAKKRLNF (SEQ ID NO: 913)).

[00194] In one embodiment, the AAV serotype may be, or may have a sequence as described in International Patent Publication WO2017100671, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV9 (SEQ ID NO: 45 of WO2017100671, herein SEQ ID NO: 1861), PHP.N (SEQ ID NO: 46 of WO2017100671, herein SEQ ID NO: 1859), PHP.S (SEQ ID NO: 47 of WO2017100671, herein SEQ ID NO: 1860), or variants thereof. Further, any of the targeting peptides or amino acid inserts described in WO2017100671 may be inserted into any parent AAV serotype, such as, but not limited to, AAV9 (SEQ ID NO: 127 or SEQ ID NO: 1861). In one embodiment, the amino acid insert is inserted between amino acids 586-592 of the parent AAV (e.g., AAV9). In another embodiment, the amino acid insert is inserted between amino acids 588-589 of the parent AAV sequence. The amino acid insert may be, but is not limited to, any of the following amino acid sequences, AQTLAVPFKAQ (SEQ ID NO: 1 of WO2017100671; herein SEQ ID NO: 2245), AQSVSKPFLAQ (SEQ ID NO: 2 of WO2017100671; herein SEQ ID NO: 2246), AQFTLTTPKAQ (SEQ ID NO: 3 in the sequence listing of WO2017100671; herein SEQ ID NO: 2247), DGTLAVPFKAQ (SEQ ID NO: 4 in the sequence listing of WO2017100671; herein SEQ ID NO: 2248), ESTLAVPFKAQ (SEQ ID NO: 5 of WO2017100671; herein SEQ ID NO: 2249), GGTLAVPFKAQ (SEQ ID NO: 6 of WO2017100671; herein SEQ ID NO: 2250), AQTLATPFKAQ (SEQ ID NO: 7 and 33 of WO2017100671; herein SEQ ID NO: 2251), ATTLATPFKAQ (SEQ ID NO: 8 of WO2017100671; herein SEQ ID NO: 2252), DGTLATPFKAQ (SEQ ID NO: 9 of WO2017100671; herein SEQ ID NO: 2253), GGTLATPFKAQ (SEQ ID NO: 10 of WO2017100671; herein SEQ ID NO: 2254), SGSLAVPFKAQ (SEQ ID NO: 11 of WO2017100671; herein SEQ ID NO: 2255), AQTLAQPFKAQ (SEQ ID NO: 12 of WO2017100671; herein SEQ ID NO: 2256), AQTLQQPFKAQ (SEQ ID NO: 13 of WO2017100671; herein SEQ ID NO: 2257), AQTLSNPFKAQ (SEQ ID NO: 14 of WO2017100671; herein SEQ ID NO: 2258), AQTLAVPFSNP (SEQ ID NO: 15 of WO2017100671; herein SEQ ID NO: 2259), QGTLAVPFKAQ (SEQ ID NO: 16 of WO2017100671; herein SEQ ID NO: 2260), NQTLAVPFKAQ (SEQ ID NO: 17 of WO2017100671; herein SEQ ID NO: 2261),

EGSLAVPFKAQ (SEQ ID NO: 18 of WO2017100671; herein SEQ ID NO: 2262), SGNLAVPFKAQ (SEQ ID NO: 19 of WO2017100671; herein SEQ ID NO: 2263), EGTLAVPFKAQ (SEQ ID NO: 20 of WO2017100671; herein SEQ ID NO: 2264), DSTLAVPFKAQ (SEQ ID NO: 21 in Table 1 of WO2017100671; herein SEQ ID NO: 2265), AVTLAVPFKAQ (SEQ ID NO: 22 of WO2017100671; herein SEQ ID NO: 2266), AQTLSTPFKAQ (SEQ ID NO: 23 of WO2017100671; herein SEQ ID NO: 2267), AQTLPQPFKAQ (SEQ ID NO: 24 and 32 of WO2017100671; herein SEQ ID NO: 2268), AQTLSQPFKAQ (SEQ ID NO: 25 of WO2017100671; herein SEQ ID NO: 2269), AQTLQLPFKAQ (SEQ ID NO: 26 of WO2017100671; herein SEQ ID NO: 2270), AQTLTMPFKAQ (SEQ ID NO: 27, and 34 of WO2017100671 and SEQ ID NO: 35 in the sequence listing of WO2017100671; herein SEQ ID NO: 2271), AQTLTTPFKAQ (SEQ ID NO: 28 of WO2017100671; herein SEQ ID NO: 2272), AQYTLSQGWAQ (SEQ ID NO: 29 of WO2017100671; herein SEQ ID NO: 2273), AQMNATKNVAQ (SEQ ID NO: 30 of WO2017100671; herein SEQ ID NO: 2274), AQVSGGHHSAQ (SEQ ID NO: 31 of WO2017100671; herein SEQ ID NO: 2275), AQTLTAPFKAQ (SEQ ID NO: 35 in Table 1 of WO2017100671; herein SEQ ID NO: 2276), AQTLSKPFKAQ (SEQ ID NO: 36 of WO2017100671; herein SEQ ID NO: 2277), QAVRTSL (SEQ ID NO: 37 of WO2017100671; herein SEQ ID NO: 2278), YTLSQGW (SEQ ID NO: 38 of WO2017100671; herein SEQ ID NO: 888), LAKERLS (SEQ ID NO: 39 of WO2017100671; herein SEQ ID NO: 2279), TLAVPFK (SEQ ID NO: 40 in the sequence listing of WO2017100671; herein SEQ ID NO: 873), SVSKPFL (SEQ ID NO: 41 of WO2017100671; herein SEQ ID NO: 881), FTLTTPK (SEQ ID NO: 42 of WO2017100671; herein SEQ ID NO: 882), MNSTKNV (SEQ ID NO: 43 of WO2017100671; herein SEQ ID NO: 2280), VSGGHHS (SEQ ID NO: 44 of WO2017100671; herein SEQ ID NO: 2281), SAQTLAVPFKAQAQ (SEQ ID NO: 48 of WO2017100671; herein SEQ ID NO: 2282), SXXXLAVPFKAQAQ (SEQ ID NO: 49 of WO2017100671 wherein X may be any amino acid; herein SEQ ID NO: 2283), SAQXXXVPFKAQAQ (SEQ ID NO: 50 of WO2017100671 wherein X may be any amino acid; herein SEQ ID NO: 2284), SAQTLXXXFKAQAQ (SEQ ID NO: 51 of WO2017100671 wherein X may be any amino acid; herein SEQ ID NO: 2285), SAQTLAVXXXAQAQ (SEQ ID NO: 52 of WO2017100671 wherein X may be any amino acid; herein SEQ ID NO: 2286), SAQTLAVPFXXXAQ (SEQ ID NO: 53 of WO2017100671 wherein X may be any amino acid; herein SEQ ID NO: 2287), TNHQSAQ (SEQ ID NO: 65 of WO2017100671; herein SEQ ID NO: 2288), AQAQTGW (SEQ ID NO: 66 of WO2017100671; herein SEQ ID NO: 2289), DGTLATPFK (SEQ ID NO: 67 of

WO2017100671; herein SEQ ID NO: 2290), DGTLATPFKXX (SEQ ID NO: 68 of WO2017100671 wherein X may be any amino acid; herein SEQ ID NO: 2291), LAVPFKAQ (SEQ ID NO: 80 of WO2017100671; herein SEQ ID NO: 2292), VPFKAQ (SEQ ID NO: 81 of WO2017100671; herein SEQ ID NO: 2293), FKAQ (SEQ ID NO: 82 of WO2017100671; herein SEQ ID NO: 2294), AQTLAV (SEQ ID NO: 83 of WO2017100671; herein SEQ ID NO: 2295), AQTLAVPF (SEQ ID NO: 84 of WO2017100671; herein SEQ ID NO: 2296), QAVR (SEQ ID NO: 85 of WO2017100671; herein SEQ ID NO: 2297), AVRT (SEQ ID NO: 86 of WO2017100671; herein SEQ ID NO: 2298), VRTS (SEQ ID NO: 87 of WO2017100671; herein SEQ ID NO: 2299), RTSL (SEQ ID NO: 88 of WO2017100671; herein SEQ ID NO: 2300), QAVRT (SEQ ID NO: 89 of WO2017100671; herein SEQ ID NO: 2301), AVRTS (SEQ ID NO: 90 of WO2017100671; herein SEQ ID NO: 2302), VRTSL (SEQ ID NO: 91 of WO2017100671; herein SEQ ID NO: 2303), QAVRTS (SEQ ID NO: 92 of WO2017100671; herein SEQ ID NO: 2304), or AVRTSL (SEQ ID NO: 93 of WO2017100671; herein SEQ ID NO: 2305).

[00195] Non-limiting examples of nucleotide sequences that may encode the amino acid inserts include the following, GATGGGACTTTGGCGGTGCCTTTTAAGGCACAG (SEQ ID NO: 54 of WO2017100671; herein SEQ ID NO: 2306), GATGGGACGTTGGCGGTGCCTTTTAAGGCACAG (SEQ ID NO: 55 of WO2017100671; herein SEQ ID NO: 2307), CAGGCGGTTAGGACGTCTTTG (SEQ ID NO: 56 of WO2017100671; herein SEQ ID NO: 2308), CAGGTCTTCACGGACTCAGACTATCAG (SEQ ID NO: 57 and 78 of WO2017100671; herein SEQ ID NO: 2309), CAAGTAAAACCTCTACAAATGTGGTAAAATCG (SEQ ID NO: 58 of WO2017100671; herein SEQ ID NO: 2310), ACTCATCGACCAATACTTGTACTATCTCTCTAGAAC (SEQ ID NO: 59 of WO2017100671; herein SEQ ID NO: 2311), GGAAGTATTCCTTGGTTTTGAACCCA (SEQ ID NO: 60 of WO2017100671; herein SEQ ID NO: 2312), GGTCGCGGTTCTTGTTTGTGGAT (SEQ ID NO: 61 of WO2017100671; herein SEQ ID NO: 2313), CGACCTTGAAGCGCATGAACTCCT (SEQ ID NO: 62 of WO2017100671; herein SEQ ID NO: 2314), GTATTCCTTGGTTTTGAACCCAACCGGTCTGCGCCTGTGCMNNMNNNMNNNMNNMNN MNNMNNTTGGGCACTCTGGTGGTTTGTC (SEQ ID NO: 63 of WO2017100671 wherein N may be A, C, T, or G; herein SEQ ID NO: 2315), GTATTCCTTGGTTTTGAACCCAACCGGTCTGCGCMNNMNNMNNAAAAGGCACCGCC AAAGTTTG (SEQ ID NO: 69 of WO2017100671 wherein N may be A, C, T, or G; herein SEQ

ID NO: 2316),
GTATTCCTTGGTTTTGAACCCAACCGGTCTGCGCCTGTGCMNNMNNNMNNCACCGCC AAAGTTTGGGCACT (SEQ ID NO: 70 of WO2017100671 wherein N may be A, C, T, or G; herein SEQ ID NO: 2317),
GTATTCCTTGGTTTTGAACCCAACCGGTCTGCGCCTGTGCCTTAAAMNNMNNMNNC AAAGTTTGGGCACTCTGGTGG (SEQ ID NO: 71 of WO2017100671 wherein N may be A, C, T, or G; herein SEQ ID NO: 2318),
GTATTCCTTGGTTTTGAACCCAACCGGTCTGCGCCTGTGCCTTAAAAGGCACMNNM NNMNNTTGGGCACTCTGGTGGTTTGTG (SEQ ID NO: 72 of WO2017100671 wherein N may be A, C, T, or G; herein SEQ ID NO: 2319), ACTTTGGCGGTGCCTTTTAAG (SEQ ID NO: 74 of WO2017100671; herein SEQ ID NO: 890), AGTGTGAGTAAGCCTTTTTTG (SEQ ID NO: 75 of WO2017100671; herein SEQ ID NO: 891), TTTACGTTGACGACGCCTAAG (SEQ ID NO: 76 of WO2017100671; herein SEQ ID NO: 892),
TATACTTTGTCGCAGGGTTGG (SEQ ID NO: 77 of WO2017100671; herein SEQ ID NO: 898), or CTTGCGAAGGAGCGGCTTTCG (SEQ ID NO: 79 of WO2017100671; herein SEQ ID NO: 2320).

[00196] In one embodiment, the AAV serotype may be, or may have a sequence as described in United States Patent No. US 9624274, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV1 (SEQ ID NO: 181 of US9624274), AAV6 (SEQ ID NO: 182 of US9624274), AAV2 (SEQ ID NO: 183 of US9624274), AAV3b (SEQ ID NO: 184 of US9624274), AAV7 (SEQ ID NO: 185 of US9624274), AAV8 (SEQ ID NO: 186 of US9624274), AAV10 (SEQ ID NO: 187 of US9624274), AAV4 (SEQ ID NO: 188 of US9624274), AAV11 (SEQ ID NO: 189 of US9624274), bAAV (SEQ ID NO: 190 of US9624274), AAV5 (SEQ ID NO: 191 of US9624274), GPV (SEQ ID NO: 192 of US9624274; herein SEQ ID NO: 1862), B19 (SEQ ID NO: 193 of US9624274; herein SEQ ID NO: 1863), MVM (SEQ ID NO: 194 of US9624274; herein SEQ ID NO: 1864), FPV (SEQ ID NO: 195 of US9624274; herein SEQ ID NO: 1865), CPV (SEQ ID NO: 196 of US9624274; herein SEQ ID NO: 1866) or variants thereof. Further, any of the structural protein inserts described in US 9624274, may be inserted into, but not limited to, I-453 and I-587 of any parent AAV serotype, such as, but not limited to, AAV2 (SEQ ID NO: 183 of US9624274). The amino acid insert may be, but is not limited to, any of the following amino acid sequences, VNLTWSRASG (SEQ ID NO: 50 of US9624274; herein SEQ ID NO: 2321), EFCINHRGYWVCGD (SEQ ID NO:55 of US9624274; herein SEQ ID NO: 2322), EDGQVMDVDLS (SEQ ID NO: 85 of US9624274;

herein SEQ ID NO: 2323), EKQRNGTLT (SEQ ID NO: 86 of US9624274; herein SEQ ID NO: 2324), TYQCRVTHPHLPRALMR (SEQ ID NO: 87 of US9624274; herein SEQ ID NO: 2325), RHSTTQPRKTKGSG (SEQ ID NO: 88 of US9624274; herein SEQ ID NO: 2326), DSNPRGVSAYLSR (SEQ ID NO: 89 of US9624274; herein SEQ ID NO: 2327), TITCLWDLAPSK (SEQ ID NO: 90 of US9624274; herein SEQ ID NO: 2328), KTKGSGFFVF (SEQ ID NO: 91 of US9624274; herein SEQ ID NO: 2329), THPHLPRALMRS (SEQ ID NO: 92 of US9624274; herein SEQ ID NO: 2330), GETYQCRVTHPHLPRALMRSTTK (SEQ ID NO: 93 of US9624274; herein SEQ ID NO: 2331), LPRALMRS (SEQ ID NO: 94 of US9624274; herein SEQ ID NO: 2332), INHRGYWV (SEQ ID NO: 95 of US9624274; herein SEQ ID NO: 2333), CDAGSVRTNAPD (SEQ ID NO: 60 of US9624274; herein SEQ ID NO: 2334), AKAVSNLTESRSESLQS (SEQ ID NO: 96 of US9624274; herein SEQ ID NO: 2335), SLTGDEFKKVLET (SEQ ID NO: 97 of US9624274; herein SEQ ID NO: 2336), REAVAYRFEED (SEQ ID NO: 98 of US9624274; herein SEQ ID NO: 2337), INPEIITLDG (SEQ ID NO: 99 of US9624274; herein SEQ ID NO: 2338), DISVTGAPVITATYL (SEQ ID NO: 100 of US9624274; herein SEQ ID NO: 2339), DISVTGAPVITA (SEQ ID NO: 101 of US9624274; herein SEQ ID NO: 2340), PKTVSNLTESSSESVQS (SEQ ID NO: 102 of US9624274; herein SEQ ID NO: 2341), SLMGDEFKAVLET (SEQ ID NO: 103 of US9624274; herein SEQ ID NO: 2342), QHSVAYTFEED (SEQ ID NO: 104 of US9624274; herein SEQ ID NO: 2343), INPEIITRDG (SEQ ID NO: 105 of US9624274; herein SEQ ID NO: 2344), DISLTGDPVITASYL (SEQ ID NO: 106 of US9624274; herein SEQ ID NO: 2345), DISLTGDPVITA (SEQ ID NO: 107 of US9624274; herein SEQ ID NO: 2346), DQSIDFEIDSA (SEQ ID NO: 108 of US9624274; herein SEQ ID NO: 2347), KNVSEDLPLPTFSPTLLGDS (SEQ ID NO: 109 of US9624274; herein SEQ ID NO: 2348), KNVSEDLPLPT (SEQ ID NO: 110 of US9624274; herein SEQ ID NO: 2349), CDSGRVRTDAPD (SEQ ID NO: 111 of US9624274; herein SEQ ID NO: 2350), FPEHLLVDFLQSLS (SEQ ID NO: 112 of US9624274; herein SEQ ID NO: 2351), DAEFRHDSG (SEQ ID NO: 65 of US9624274; herein SEQ ID NO: 2352), HYAAAQWDFGNTMCQL (SEQ ID NO: 113 of US9624274; herein SEQ ID NO: 2353), YAAQWDFGNTMCQ (SEQ ID NO: 114 of US9624274; herein SEQ ID NO: 2354), RSQKEGLHYT (SEQ ID NO: 115 of US9624274; herein SEQ ID NO: 2355), SSRTPSDKPVAHWANPQAE (SEQ ID NO: 116 of US9624274; herein SEQ ID NO: 2356), SRTPSDKPVAHWANP (SEQ ID NO: 117 of US9624274; herein SEQ ID NO: 2357), SSRTPSDKP (SEQ ID NO: 118 of US9624274; herein SEQ ID NO: 2358), NADGNVDYHMNSVP (SEQ ID NO: 119 of US9624274; herein SEQ ID NO: 2359),

DGNVDYHMNSV (SEQ ID NO: 120 of US9624274; herein SEQ ID NO: 2360), RSFKEFLQSSLRALRQ (SEQ ID NO: 121 of US9624274; herein SEQ ID NO: 2361); FKEFLQSSLRA (SEQ ID NO: 122 of US9624274; herein SEQ ID NO: 2362), or QMWAPQWGPD (SEQ ID NO: 123 of US9624274; herein SEQ ID NO: 2363).

[00197] In one embodiment, the AAV serotype may be, or may have a sequence as described in United States Patent No. US 9475845, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV capsid proteins comprising modification of one or more amino acids at amino acid positions 585 to 590 of the native AAV2 capsid protein. Further the modification may result in, but not limited to, the amino acid sequence RGNRQA (SEQ ID NO: 3 of US9475845; herein SEQ ID NO: 2364), SSSTDP (SEQ ID NO: 4 of US9475845; herein SEQ ID NO: 2365), SSNTAP (SEQ ID NO: 5 of US9475845; herein SEQ ID NO: 2366), SNSNLP (SEQ ID NO: 6 of US9475845; herein SEQ ID NO: 2367), SSTTAP (SEQ ID NO: 7 of US9475845; herein SEQ ID NO: 2368), AANTAA (SEQ ID NO: 8 of US9475845; herein SEQ ID NO: 2369), QQNTAP (SEQ ID NO: 9 of US9475845; herein SEQ ID NO: 2370), SAQAQA (SEQ ID NO: 10 of US9475845; herein SEQ ID NO: 2371), QANTGP (SEQ ID NO: 11 of US9475845; herein SEQ ID NO: 2372), NATTAP (SEQ ID NO: 12 of US9475845; herein SEQ ID NO: 2373), SSTAGP (SEQ ID NO: 13 and 20 of US9475845; herein SEQ ID NO: 2374), QQNTAA (SEQ ID NO: 14 of US9475845; herein SEQ ID NO: 2375), PSTAGP (SEQ ID NO: 15 of US9475845; herein SEQ ID NO: 2376), NQNTAP (SEQ ID NO: 16 of US9475845; herein SEQ ID NO: 2377), QAANAP (SEQ ID NO: 17 of US9475845; herein SEQ ID NO: 2378), SIVGLP (SEQ ID NO: 18 of US9475845; herein SEQ ID NO: 2379), AASTAA (SEQ ID NO: 19, and 27 of US9475845; herein SEQ ID NO: 2380), SQNTTA (SEQ ID NO: 21 of US9475845; herein SEQ ID NO: 2381), QQDTAP (SEQ ID NO: 22 of US9475845; herein SEQ ID NO: 2382), QTNTGP (SEQ ID NO: 23 of US9475845; herein SEQ ID NO: 2383), QTNGAP (SEQ ID NO: 24 of US9475845; herein SEQ ID NO: 2384), QQNAAP (SEQ ID NO: 25 of US9475845; herein SEQ ID NO: 2385), or AANTQA (SEQ ID NO: 26 of US9475845; herein SEQ ID NO: 2386). In one embodiment, the amino acid modification is a substitution at amino acid positions 262 through 265 in the native AAV2 capsid protein or the corresponding position in the capsid protein of another AAV with a targeting sequence. The targeting sequence may be, but is not limited to, any of the amino acid sequences, NGRAHA (SEQ ID NO: 38 of US9475845; herein SEQ ID NO: 2387), QPEHSST (SEQ ID NO: 39 and 50 of US9475845; herein SEQ ID NO: 2388), VNTANST (SEQ ID NO: 40 of US9475845; herein SEQ ID NO: 2389), HGPMQKS (SEQ ID NO: 41 of US9475845; herein

SEQ ID NO: 2390), PHKPPLA (SEQ ID NO: 42 of US9475845; herein SEQ ID NO: 2391), IKNNEMW (SEQ ID NO: 43 of US9475845; herein SEQ ID NO: 2392), RNLDTPM (SEQ ID NO: 44 of US9475845; herein SEQ ID NO: 2393), VDSHRQS (SEQ ID NO: 45 of US9475845; herein SEQ ID NO: 2394), YDSKTKT (SEQ ID NO: 46 of US9475845; herein SEQ ID NO: 2395), SQLPHQK (SEQ ID NO: 47 of US9475845; herein SEQ ID NO: 2396), STMQQNT (SEQ ID NO: 48 of US9475845; herein SEQ ID NO: 2397), TERYMTQ (SEQ ID NO: 49 of US9475845; herein SEQ ID NO: 2398), DASLSTS (SEQ ID NO: 51 of US9475845; herein SEQ ID NO: 2399), DLPNKKT (SEQ ID NO: 52 of US9475845; herein SEQ ID NO: 2400), DLTAARL (SEQ ID NO: 53 of US9475845; herein SEQ ID NO: 2401), EPHQFNY (SEQ ID NO: 54 of US9475845; herein SEQ ID NO: 2402), EPQSNHT (SEQ ID NO: 55 of US9475845; herein SEQ ID NO: 2403), MSSWPSQ (SEQ ID NO: 56 of US9475845; herein SEQ ID NO: 2404), NPKHNAT (SEQ ID NO: 57 of US9475845; herein SEQ ID NO: 2405), PDGMRTT (SEQ ID NO: 58 of US9475845; herein SEQ ID NO: 2406), PNNNKTT (SEQ ID NO: 59 of US9475845; herein SEQ ID NO: 2407), QSTTHDS (SEQ ID NO: 60 of US9475845; herein SEQ ID NO: 2408), TGSKQKQ (SEQ ID NO: 61 of US9475845; herein SEQ ID NO: 2409), SLKHQAL (SEQ ID NO: 62 of US9475845; herein SEQ ID NO: 2410), SPIDGEQ (SEQ ID NO: 63 of US9475845; herein SEQ ID NO: 2411), WIFPWIQL (SEQ ID NO: 64 and 112 of US9475845; herein SEQ ID NO: 2412), CDCRGDCFC (SEQ ID NO: 65 of US9475845; herein SEQ ID NO: 2413), CNGRC (SEQ ID NO: 66 of US9475845; herein SEQ ID NO: 2414), CPRECES (SEQ ID NO: 67 of US9475845; herein SEQ ID NO: 2415), CTTHWGFTLC (SEQ ID NO: 68 and 123 of US9475845; herein SEQ ID NO: 2416), CGRRAGGSC (SEQ ID NO: 69 of US9475845; herein SEQ ID NO: 2417), CKGGRAKDC (SEQ ID NO: 70 of US9475845; herein SEQ ID NO: 2418), CVPELGHEC (SEQ ID NO: 71 and 115 of US9475845; herein SEQ ID NO: 2419), CRRETAWAK (SEQ ID NO: 72 of US9475845; herein SEQ ID NO: 2420), VSWFSHRYSPFAVS (SEQ ID NO: 73 of US9475845; herein SEQ ID NO: 2421), GYRDGYAGPILYN (SEQ ID NO: 74 of US9475845; herein SEQ ID NO: 2422), XXXYXXX (SEQ ID NO: 75 of US9475845; herein SEQ ID NO: 2423), YXNW (SEQ ID NO: 76 of US9475845; herein SEQ ID NO: 2424), RPLPPLP (SEQ ID NO: 77 of US9475845; herein SEQ ID NO: 2425), APPLPPR (SEQ ID NO: 78 of US9475845; herein SEQ ID NO: 2426), DVFYPYPYASGS (SEQ ID NO: 79 of US9475845; herein SEQ ID NO: 2427), MYWYPY (SEQ ID NO: 80 of US9475845; herein SEQ ID NO: 2428), DITWDQLWDLMK (SEQ ID NO: 81 of US9475845; herein SEQ ID NO: 2429), CWDDXWLC (SEQ ID NO: 82 of US9475845; herein SEQ ID NO: 2430), EWCEYLGGYLRCYA (SEQ ID NO: 83 of US9475845; herein

SEQ ID NO: 2431), YXCXXGPXTWXCXP (SEQ ID NO: 84 of US9475845; herein SEQ ID NO: 2432), IEGPTLRQWLAARA (SEQ ID NO: 85 of US9475845; herein SEQ ID NO: 2433), LWXXX (SEQ ID NO: 86 of US9475845; herein SEQ ID NO: 2434), XFXXYLW (SEQ ID NO: 87 of US9475845; herein SEQ ID NO: 2435), SSIISHFRWGLCD (SEQ ID NO: 88 of US9475845; herein SEQ ID NO: 2436), MSRPACPPNDKYE (SEQ ID NO: 89 of US9475845; herein SEQ ID NO: 2437), CLRSGRGC (SEQ ID NO: 90 of US9475845; herein SEQ ID NO: 2438), CHWMFSPWC (SEQ ID NO: 91 of US9475845; herein SEQ ID NO: 2439), WXXF (SEQ ID NO: 92 of US9475845; herein SEQ ID NO: 2440), CSSRLDAC (SEQ ID NO: 93 of US9475845; herein SEQ ID NO: 2441), CLPVASC (SEQ ID NO: 94 of US9475845; herein SEQ ID NO: 2442), CGFECVRQCPERC (SEQ ID NO: 95 of US9475845; herein SEQ ID NO: 2443), CVALCREACGEGC (SEQ ID NO: 96 of US9475845; herein SEQ ID NO: 2444), SWCEPGWCR (SEQ ID NO: 97 of US9475845; herein SEQ ID NO: 2445), YSGKWGW (SEQ ID NO: 98 of US9475845; herein SEQ ID NO: 2446), GLSGGRS (SEQ ID NO: 99 of US9475845; herein SEQ ID NO: 2447), LMLPRAD (SEQ ID NO: 100 of US9475845; herein SEQ ID NO: 2448), CSCFRDVCC (SEQ ID NO: 101 of US9475845; herein SEQ ID NO: 2449), CRDVVSVIC (SEQ ID NO: 102 of US9475845; herein SEQ ID NO: 2450), MARSGL (SEQ ID NO: 103 of US9475845; herein SEQ ID NO: 2451), MARAKE (SEQ ID NO: 104 of US9475845; herein SEQ ID NO: 2452), MSRTMS (SEQ ID NO: 105 of US9475845; herein SEQ ID NO: 2453), KCCYSL (SEQ ID NO: 106 of US9475845; herein SEQ ID NO: 2454), MYWGDSHWLQYWYE (SEQ ID NO: 107 of US9475845; herein SEQ ID NO: 2455), MQLPLAT (SEQ ID NO: 108 of US9475845; herein SEQ ID NO: 2456), EWLS (SEQ ID NO: 109 of US9475845; herein SEQ ID NO: 2457), SNEW (SEQ ID NO: 110 of US9475845; herein SEQ ID NO: 2458), TNYL (SEQ ID NO: 111 of US9475845; herein SEQ ID NO: 2459), WDLAWMFRLPVG (SEQ ID NO: 113 of US9475845; herein SEQ ID NO: 2460), CTVALPGGYVRVC (SEQ ID NO: 114 of US9475845; herein SEQ ID NO: 2461), CVAYCIEHHCWTC (SEQ ID NO: 116 of US9475845; herein SEQ ID NO: 2462), CVFAHNYDYLVC (SEQ ID NO: 117 of US9475845; herein SEQ ID NO: 2463), CVFTSNYAFC (SEQ ID NO: 118 of US9475845; herein SEQ ID NO: 2464), VHSPNKK (SEQ ID NO: 119 of US9475845; herein SEQ ID NO: 2465), CRGDGWC (SEQ ID NO: 120 of US9475845; herein SEQ ID NO: 2466), XRGCDX (SEQ ID NO: 121 of US9475845; herein SEQ ID NO: 2467), PXXX (SEQ ID NO: 122 of US9475845; herein SEQ ID NO: 2468), SGKGPRQITAL (SEQ ID NO: 124 of US9475845; herein SEQ ID NO: 2469), AAAAAAAAAXXXXX (SEQ ID NO: 125 of US9475845; herein SEQ ID NO: 2470),

VYMSPF (SEQ ID NO: 126 of US9475845; herein SEQ ID NO: 2471), ATWLPPR (SEQ ID NO: 127 of US9475845; herein SEQ ID NO: 2472), HTMYYHHYQHHL (SEQ ID NO: 128 of US9475845; herein SEQ ID NO: 2473), SEVGCRAGPLQWLCEKYFG (SEQ ID NO: 129 of US9475845; herein SEQ ID NO: 2474), CGLLPVGRPDRNVWRWLC (SEQ ID NO: 130 of US9475845; herein SEQ ID NO: 2475), CKGQCDRFKGLPWEC (SEQ ID NO: 131 of US9475845; herein SEQ ID NO: 2476), SGRSA (SEQ ID NO: 132 of US9475845; herein SEQ ID NO: 2477), WGFP (SEQ ID NO: 133 of US9475845; herein SEQ ID NO: 2478), AEPMPHSLNFSQYLWYT (SEQ ID NO: 134 of US9475845; herein SEQ ID NO: 2479), WAYXSP (SEQ ID NO: 135 of US9475845; herein SEQ ID NO: 2480), IELLQAR (SEQ ID NO: 136 of US9475845; herein SEQ ID NO: 2481), AYTKCSRQWRTCMTTH (SEQ ID NO: 137 of US9475845; herein SEQ ID NO: 2482), PQNSKIPGPTFLDPH (SEQ ID NO: 138 of US9475845; herein SEQ ID NO: 2483), SMEPALPDWWWKMFK (SEQ ID NO: 139 of US9475845; herein SEQ ID NO: 2484), ANTPCGPYTHDCPVKR (SEQ ID NO: 140 of US9475845; herein SEQ ID NO: 2485), TACHQHVRMVRP (SEQ ID NO: 141 of US9475845; herein SEQ ID NO: 2486), VPWMEPAYQRFL (SEQ ID NO: 142 of US9475845; herein SEQ ID NO: 2487), DPRATPGS (SEQ ID NO: 143 of US9475845; herein SEQ ID NO: 2488), FRPNRAQDYNTN (SEQ ID NO: 144 of US9475845; herein SEQ ID NO: 2489), CTKNSYLMC (SEQ ID NO: 145 of US9475845; herein SEQ ID NO: 2490), CXXTXXXGXGC (SEQ ID NO: 146 of US9475845; herein SEQ ID NO: 2491), CPIEDRPMC (SEQ ID NO: 147 of US9475845; herein SEQ ID NO: 2492), HEWSYLAPYPWF (SEQ ID NO: 148 of US9475845; herein SEQ ID NO: 2493), MCPKHPLGC (SEQ ID NO: 149 of US9475845; herein SEQ ID NO: 2494), RMWPSSTVNLSAGRR (SEQ ID NO: 150 of US9475845; herein SEQ ID NO: 2495), SAKTAVSQRVWLPSHRGGEP (SEQ ID NO: 151 of US9475845; herein SEQ ID NO: 2496), KSREHVNNSACPSKRITAAL (SEQ ID NO: 152 of US9475845; herein SEQ ID NO: 2497), EGFR (SEQ ID NO: 153 of US9475845; herein SEQ ID NO: 2498), AGLGVR (SEQ ID NO: 154 of US9475845; herein SEQ ID NO: 2499), GTRQGHTMRLGVSDG (SEQ ID NO: 155 of US9475845; herein SEQ ID NO: 2500), IAGLATPGWSHWLAL (SEQ ID NO: 156 of US9475845; herein SEQ ID NO: 2501), SMSIARL (SEQ ID NO: 157 of US9475845; herein SEQ ID NO: 2502), HTFEPGV (SEQ ID NO: 158 of US9475845; herein SEQ ID NO: 2503), NTSLKRISNKRIRRK (SEQ ID NO: 159 of US9475845; herein SEQ ID NO: 2504), LRIKRKRRKRKKTRK (SEQ ID NO: 160 of US9475845; herein SEQ ID NO: 2505), GGG, GFS, LWS, EGG, LLV, LSP, LBS, AGG, GRR, GGH and GTV.

[00198] In one embodiment, the AAV serotype may be, or may have a sequence as described in United States Publication No. US 20160369298, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, site-specific mutated capsid protein of AAV2 (SEQ ID NO: 97 of US 20160369298; herein SEQ ID NO: 2506) or variants thereof, wherein the specific site is at least one site selected from sites R447, G453, S578, N587, N587+1, S662 of VP1 or fragment thereof.

[00199] Further, any of the mutated sequences described in US 20160369298, may be or may have, but not limited to, any of the following sequences SDSGASN (SEQ ID NO: 1 and SEQ ID NO: 231 of US20160369298; herein SEQ ID NO: 2507), SPSGASN (SEQ ID NO: 2 of US20160369298; herein SEQ ID NO: 2508), SHSGASN (SEQ ID NO: 3 of US20160369298; herein SEQ ID NO: 2509), SRSGASN (SEQ ID NO: 4 of US20160369298; herein SEQ ID NO: 2510), SKSGASN (SEQ ID NO: 5 of US20160369298; herein SEQ ID NO: 2511), SNSGASN (SEQ ID NO: 6 of US20160369298; herein SEQ ID NO: 2512), SGSGASN (SEQ ID NO: 7 of US20160369298; herein SEQ ID NO: 2513), SASGASN (SEQ ID NO: 8, 175, and 221 of US20160369298; herein SEQ ID NO: 2514), SESGTSN (SEQ ID NO: 9 of US20160369298; herein SEQ ID NO: 2515), STTGGSN (SEQ ID NO: 10 of US20160369298; herein SEQ ID NO: 2516), SSAGSTN (SEQ ID NO: 11 of US20160369298; herein SEQ ID NO: 2517), NNDSQA (SEQ ID NO: 12 of US20160369298; herein SEQ ID NO: 2518), NNRNQA (SEQ ID NO: 13 of US20160369298; herein SEQ ID NO: 2519), NNNKQA (SEQ ID NO: 14 of US20160369298; herein SEQ ID NO: 2520), NAKRQA (SEQ ID NO: 15 of US20160369298; herein SEQ ID NO: 2521), NDEHQA (SEQ ID NO: 16 of US20160369298; herein SEQ ID NO: 2522), NTSQKA (SEQ ID NO: 17 of US20160369298; herein SEQ ID NO: 2523), YYLSRTNTPSGTDTQSRLVFSQAGA (SEQ ID NO: 18 of US20160369298; herein SEQ ID NO: 2524), YYLSRTNTDSGTETQSGLDFSQAGA (SEQ ID NO: 19 of US20160369298; herein SEQ ID NO: 2525), YYLSRTNTESGTPTQSALEFSQAGA (SEQ ID NO: 20 of US20160369298; herein SEQ ID NO: 2526), YYLSRTNTHSGTHTQSPLHFSQAGA (SEQ ID NO: 21 of US20160369298; herein SEQ ID NO: 2527), YYLSRTNTSSGTITISHLIFSQAGA (SEQ ID NO: 22 of US20160369298; herein SEQ ID NO: 2528),
YYLSRTNTRSGIMTKSSLMFSQAGA (SEQ ID NO: 23 of US20160369298; herein SEQ ID NO: 2529), YYLSRTNTKSGRKTLSNLSFSQAGA (SEQ ID NO: 24 of US20160369298; herein SEQ ID NO: 2530), YYLSRTNDGSGPVTPSKLRFSQRGA (SEQ ID NO: 25 of US20160369298; herein SEQ ID NO: 2531), YYLSRTNAASGHATHSDLKFSQPGA (SEQ ID NO: 26 of US20160369298; herein SEQ ID NO: 2532),

YYLSRTNGQAGSLTMSELGFSQVGA (SEQ ID NO: 27 of US20160369298; herein SEQ ID NO: 2533), YYLSRTNSTGGNQTTSQLLFSQLSA (SEQ ID NO: 28 of US20160369298; herein SEQ ID NO: 2534), YFLSRTNNNTGLNTNSTLNFSQGRA (SEQ ID NO: 29 of US20160369298; herein SEQ ID NO: 2535), SKTGADNNNSEYSWTG (SEQ ID NO: 30 of US20160369298; herein SEQ ID NO: 2536), SKTDADNNNSEYSWTG (SEQ ID NO: 31 of US20160369298; herein SEQ ID NO: 2537), SKTEADNNNSEYSWTG (SEQ ID NO: 32 of US20160369298; herein SEQ ID NO: 2538), SKTPADNNNSEYSWTG (SEQ ID NO: 33 of US20160369298; herein SEQ ID NO: 2539), SKTHADNNNSEYSWTG (SEQ ID NO: 34 of US20160369298; herein SEQ ID NO: 2540), SKTQADNNNSEYSWTG (SEQ ID NO: 35 of US20160369298; herein SEQ ID NO: 2541), SKTIADNNNSEYSWTG (SEQ ID NO: 36 of US20160369298; herein SEQ ID NO: 2542), SKTMADNNNSEYSWTG (SEQ ID NO: 37 of US20160369298; herein SEQ ID NO: 2543), SKTRADNNNSEYSWTG (SEQ ID NO: 38 of US20160369298; herein SEQ ID NO: 2544), SKTNADNNNSEYSWTG (SEQ ID NO: 39 of US20160369298; herein SEQ ID NO: 2545), SKTVGRNNNSEYSWTG (SEQ ID NO: 40 of US20160369298; herein SEQ ID NO: 2546), SKTADRNNNSEYSWTG (SEQ ID NO: 41 of US20160369298; herein SEQ ID NO: 2547), SKKLSQNNNSKYSWQG (SEQ ID NO: 42 of US20160369298; herein SEQ ID NO: 2548), SKPTTGNNNSDYSWPG (SEQ ID NO: 43 of US20160369298; herein SEQ ID NO: 2549), STQKNENNNSNYSWPG (SEQ ID NO: 44 of US20160369298; herein SEQ ID NO: 2550), HKDDEGKF (SEQ ID NO: 45 of US20160369298; herein SEQ ID NO: 2551), HKDDNRKF (SEQ ID NO: 46 of US20160369298; herein SEQ ID NO: 2552), HKDDTNKF (SEQ ID NO: 47 of US20160369298; herein SEQ ID NO: 2553), HEDSDKNF (SEQ ID NO: 48 of US20160369298; herein SEQ ID NO: 2554), HRDGADSF (SEQ ID NO: 49 of US20160369298; herein SEQ ID NO: 2555), HGDNKSRF (SEQ ID NO: 50 of US20160369298; herein SEQ ID NO: 2556), KQGSEKTNVDFEEV (SEQ ID NO: 51 of US20160369298; herein SEQ ID NO: 2557), KQGSEKTNVDSEEV (SEQ ID NO: 52 of US20160369298; herein SEQ ID NO: 2558), KQGSEKTNVDVEEV (SEQ ID NO: 53 of US20160369298; herein SEQ ID NO: 2559), KQGSDKTNVDDAGV (SEQ ID NO: 54 of US20160369298; herein SEQ ID NO: 2560), KQGSSKTNVDPREV (SEQ ID NO: 55 of US20160369298; herein SEQ ID NO: 2561), KQGSRKTNVDHKQV (SEQ ID NO: 56 of US20160369298; herein SEQ ID NO: 2562), KQGSKGGNVDTNRV (SEQ ID NO: 57 of US20160369298; herein SEQ ID NO: 2563), KQGSGEANVDNGDV (SEQ ID NO: 58 of US20160369298; herein SEQ ID NO: 2564), KQDAAADNIDYDHV (SEQ ID NO: 59 of

US20160369298; herein SEQ ID NO: 2565), KQSGTRSNAAASSV (SEQ ID NO: 60 of US20160369298; herein SEQ ID NO: 2566), KENTNTNDTELTNV (SEQ ID NO: 61 of US20160369298; herein SEQ ID NO: 2567), QRGNNVAATADVNT (SEQ ID NO: 62 of US20160369298; herein SEQ ID NO: 2568), QRGNNEAATADVNT (SEQ ID NO: 63 of US20160369298; herein SEQ ID NO: 2569), QRGNNPAATADVNT (SEQ ID NO: 64 of US20160369298; herein SEQ ID NO: 2570), QRGNNHAATADVNT (SEQ ID NO: 65 of US20160369298; herein SEQ ID NO: 2571), QEENNIAATPGVNT (SEQ ID NO: 66 of US20160369298; herein SEQ ID NO: 2572), QPPNNMAATHEVNT (SEQ ID NO: 67 of US20160369298; herein SEQ ID NO: 2573), QHHNNSAATTIVNT (SEQ ID NO: 68 of US20160369298; herein SEQ ID NO: 2574), QTTNNRAAFNMVET (SEQ ID NO: 69 of US20160369298; herein SEQ ID NO: 2575), QKKNNNAASKKVAT (SEQ ID NO: 70 of US20160369298; herein SEQ ID NO: 2576), QGGNNKAADDAVKT (SEQ ID NO: 71 of US20160369298; herein SEQ ID NO: 2577), QAAKGGAADDAVKT (SEQ ID NO: 72 of US20160369298; herein SEQ ID NO: 2578), QDDRAAAANESVDT (SEQ ID NO: 73 of US20160369298; herein SEQ ID NO: 2579), QQQHDDAAYQRVHT (SEQ ID NO: 74 of US20160369298; herein SEQ ID NO: 2580), QSSSSLAAVSTVQT (SEQ ID NO: 75 of US20160369298; herein SEQ ID NO: 2581), QNNQTTAAIRNVTT (SEQ ID NO: 76 of US20160369298; herein SEQ ID NO: 2582), NYNKKSDNVDFT (SEQ ID NO: 77 of US20160369298; herein SEQ ID NO: 2583), NYNKKSENVDFT (SEQ ID NO: 78 of US20160369298; herein SEQ ID NO: 2584), NYNKKSLNVDFT (SEQ ID NO: 79 of US20160369298; herein SEQ ID NO: 2585), NYNKKSPNVDFT (SEQ ID NO: 80 of US20160369298; herein SEQ ID NO: 2586), NYSKKSHCVDFT (SEQ ID NO: 81 of US20160369298; herein SEQ ID NO: 2587), NYRKTIYVDFT (SEQ ID NO: 82 of US20160369298; herein SEQ ID NO: 2588), NYKEKKDVHFT (SEQ ID NO: 83 of US20160369298; herein SEQ ID NO: 2589), NYGHRAIVQFT (SEQ ID NO: 84 of US20160369298; herein SEQ ID NO: 2590), NYANHQFVVCT (SEQ ID NO: 85 of US20160369298; herein SEQ ID NO: 2591), NYDDDPTGVLLT (SEQ ID NO: 86 of US20160369298; herein SEQ ID NO: 2592), NYDDPTGVLLT (SEQ ID NO: 87 of US20160369298; herein SEQ ID NO: 2593), NFEQQNSVEWT (SEQ ID NO: 88 of US20160369298; herein SEQ ID NO: 2594), SQSGASN (SEQ ID NO: 89 and SEQ ID NO: 241 of US20160369298; herein SEQ ID NO: 2595), NNGSQA (SEQ ID NO: 90 of US20160369298; herein SEQ ID NO: 2596), YYLSRTNTPSGTTTWSRLQFSQAGA (SEQ ID NO: 91 of US20160369298; herein SEQ ID NO: 2597), SKTSADNNNSEYSWTG (SEQ ID NO: 92 of

US20160369298; herein SEQ ID NO: 2598), HKDDEEKF (SEQ ID NO: 93, 209, 214, 219, 224, 234, 239, and 244 of US20160369298; herein SEQ ID NO: 2599), KQGSEKTNVDIEEV (SEQ ID NO: 94 of US20160369298; herein SEQ ID NO: 2600), QRGNNQAATADVNT (SEQ ID NO: 95 of US20160369298; herein SEQ ID NO: 2601), NYNKKSVNVDFT (SEQ ID NO: 96 of US20160369298; herein SEQ ID NO: 2602), SQSGASNYNTPSGTTTQSRLQFSTSADNNNSEYSWTGATKYH (SEQ ID NO: 106 of US20160369298; herein SEQ ID NO: 2603), SASGASNFNSEGGSLTQSSLGFSTDGENNNSDFSWTGATKYH (SEQ ID NO: 107 of US20160369298; herein SEQ ID NO: 2604), SQSGASNYNTPSGTTTQSRLQFSTDGENNNSDFSWTGATKYH (SEQ ID NO: 108 of US20160369298; herein SEQ ID NO: 2605), SASGASNYNTPSGTTTQSRLQFSTSADNNNSEFSWPGATTYH (SEQ ID NO: 109 of US20160369298; herein SEQ ID NO: 2606), SQSGASNFNSEGGSLTQSSLGFSTDGENNNSDFSWTGATKYH (SEQ ID NO: 110 of US20160369298; herein SEQ ID NO: 2607), SASGASNYNTPSGSLTQSSLGFSTDGENNNSDFSWTGATKYH (SEQ ID NO: 111 of US20160369298; herein SEQ ID NO: 2608), SQSGASNYNTPSGTTTQSRLQFSTSADNNNSDFSWTGATKYH (SEQ ID NO: 112 of US20160369298; herein SEQ ID NO: 2609), SGAGASNFNSEGGSLTQSSLGFSTDGENNNSDFSWTGATKYH (SEQ ID NO: 113 of US20160369298; herein SEQ ID NO: 2610), SGAGASN (SEQ ID NO: 176 of US20160369298; herein SEQ ID NO: 2611), NSEGGSLTQSSLGFS (SEQ ID NO: 177, 185, 193 and 202 of US20160369298; herein SEQ ID NO: 2612), TDGENNNSDFS (SEQ ID NO: 178 of US20160369298; herein SEQ ID NO: 2613), SEFSWPGATT (SEQ ID NO: 179 of US20160369298; herein SEQ ID NO: 2614), TSADNNNSDFSWT (SEQ ID NO: 180 of US20160369298; herein SEQ ID NO: 2615), SQSGASNY (SEQ ID NO: 181, 187, and 198 of US20160369298; herein SEQ ID NO: 2616), NTPSGTTTQSRLQFS (SEQ ID NO: 182, 188, 191, and 199 of US20160369298; herein SEQ ID NO: 2617), TSADNNNSEYSWTGATKYH (SEQ ID NO: 183 of US20160369298; herein SEQ ID NO: 2618), SASGASNF (SEQ ID NO: 184 of US20160369298; herein SEQ ID NO: 2619), TDGENNNSDFSWTGATKYH (SEQ ID NO: 186, 189, 194, 197, and 203 of US20160369298; herein SEQ ID NO: 2620), SASGASNY (SEQ ID NO: 190 and SEQ ID NO: 195 of US20160369298; herein SEQ ID NO: 2621), TSADNNNSEFSWPGATTYH (SEQ ID NO: 192 of US20160369298; herein SEQ ID NO:

2622), NTPSGSLTQSSLGFS (SEQ ID NO: 196 of US20160369298; herein SEQ ID NO: 2623), TSADNNNSDFSWTGATKYH (SEQ ID NO: 200 of US20160369298; herein SEQ ID NO: 2624), SGAGASNF (SEQ ID NO: 201 of US20160369298; herein SEQ ID NO: 2625), CTCCAGVVSVVSMRSRVCVNSGCAGCTDHCVVSRNSGTCVMSACACAA (SEQ ID NO: 204 of US20160369298; herein SEQ ID NO: 2626), CTCCAGAGAGGCAACAGACAAGCAGCTACCGCAGATGTCAACACACAA (SEQ ID NO: 205 of US20160369298; herein SEQ ID NO: 2627), SAAGASN (SEQ ID NO: 206 of US20160369298; herein SEQ ID NO: 2628), YFLSRTNTESGSTTQSTLRFSQAG (SEQ ID NO: 207 of US20160369298; herein SEQ ID NO: 2629), SKTSADNNNSDFS (SEQ ID NO: 208, 228, and 253 of US20160369298; herein SEQ ID NO: 2630), KQGSEKTDVDIDKV (SEQ ID NO: 210 of US20160369298; herein SEQ ID NO: 2631), STAGASN (SEQ ID NO: 211 of US20160369298; herein SEQ ID NO: 2632), YFLSRTNTTSGIETQSTLRFSQAG (SEQ ID NO: 212 and SEQ ID NO: 247 of US20160369298; herein SEQ ID NO: 2633), SKTDGENNNSDFS (SEQ ID NO: 213 and SEQ ID NO: 248 of US20160369298; herein SEQ ID NO: 2634), KQGAAADDVEIDGV (SEQ ID NO: 215 and SEQ ID NO: 250 of US20160369298; herein SEQ ID NO: 2635), SEAGASN (SEQ ID NO: 216 of US20160369298; herein SEQ ID NO: 2636), YYLSRTNTPSGTTTQSRLQFSQAG (SEQ ID NO: 217, 232 and 242 of US20160369298; herein SEQ ID NO: 2637), SKTSADNNNSEYS (SEQ ID NO: 218, 233, 238, and 243 of US20160369298; herein SEQ ID NO: 2638), KQGSEKTNVDIEKV (SEQ ID NO: 220, 225 and 245 of US20160369298; herein SEQ ID NO: 2639), YFLSRTNDASGSDTKSTLLFSQAG (SEQ ID NO: 222 of US20160369298; herein SEQ ID NO: 2640), STTPSENNNSEYS (SEQ ID NO: 223 of US20160369298; herein SEQ ID NO: 2641), SAAGATN (SEQ ID NO: 226 and SEQ ID NO: 251 of US20160369298; herein SEQ ID NO: 2642), YFLSRTNGEAGSATLSELRFSQAG (SEQ ID NO: 227 of US20160369298; herein SEQ ID NO: 2643), HGDDADRF (SEQ ID NO: 229 and SEQ ID NO: 254 of US20160369298; herein SEQ ID NO: 2644), KQGAEKSDVEVDRV (SEQ ID NO: 230 and SEQ ID NO: 255 of US20160369298; herein SEQ ID NO: 2645), KQDSGGDNIDIDQV (SEQ ID NO: 235 of US20160369298; herein SEQ ID NO: 2646), SDAGASN (SEQ ID NO: 236 of US20160369298; herein SEQ ID NO: 2647), YFLSRTNTEGGHDTQSTLRFSQAG (SEQ ID NO: 237 of US20160369298; herein SEQ ID NO: 2648), KEDGGGSDVAIDEV (SEQ ID NO: 240 of US20160369298; herein SEQ ID NO: 2649), SNAGASN (SEQ ID NO: 246 of US20160369298; herein SEQ ID NO: 2650), and YFLSRTNGEAGSATLSELRFSQPG (SEQ ID NO: 252 of US20160369298; herein SEQ ID NO: 2651). Non-limiting examples of nucleotide sequences

that may encode the amino acid mutated sites include the following, AGCVVMDCAGGARSCASCAAC (SEQ ID NO: 97 of US20160369298; herein SEQ ID NO: 2652), AACRACRRSMRSMAGGCA (SEQ ID NO: 98 of US20160369298; herein SEQ ID NO: 2653), CACRRGGACRRCRMSRRSARSTTT (SEQ ID NO: 99 of US20160369298; herein SEQ ID NO: 2654), TATTTCTTGAGCAGAACAAACRVCVVSRSCGGAMNCVHSACGMHSTCAVVSCTTVDS TTTTCTCAGSBCRGSGCG (SEQ ID NO: 100 of US20160369298; herein SEQ ID NO: 2655), TCAAMAMMAVNSRVCSRSAACAACAACAGTRASTTCTCGTGGMMAGGA (SEQ ID NO: 101 of US20160369298; herein SEQ ID NO: 2656), AAGSAARRCRSCRVSRVARVCRATRYCGMSNHCRVMVRSGTC (SEQ ID NO: 102 of US20160369298; herein SEQ ID NO: 2657), CAGVVSVVSMRSRVCVNSGCAGCTDHCVVSRNSGTCVMSACA (SEQ ID NO: 103 of US20160369298; herein SEQ ID NO: 2658), AACTWCRVSVASMVSVHSDDTGTGSWSTKSACT (SEQ ID NO: 104 of US20160369298; herein SEQ ID NO: 2659), TTGTTGAACATCACCACGTGACGCACGTTC (SEQ ID NO: 256 of US20160369298; herein SEQ ID NO: 2660), TCCCCGTGGTTCTACTACATAATGTGGCCG (SEQ ID NO: 257 of US20160369298; herein SEQ ID NO: 2661), TTCCACACTCCGTTTTGGATAATGTTGAAC (SEQ ID NO: 258 of US20160369298; herein SEQ ID NO: 2662), AGGGACATCCCCAGCTCCATGCTGTGGTCG (SEQ ID NO: 259 of US20160369298; herein SEQ ID NO: 2663), AGGGACAACCCCTCCGACTCGCCCTAATCC (SEQ ID NO: 260 of US20160369298; herein SEQ ID NO: 2664), TCCTAGTAGAAGACACCCTCTCACTGCCCG (SEQ ID NO: 261 of US20160369298; herein SEQ ID NO: 2665), AGTACCATGTACACCCACTCTCCCAGTGCC (SEQ ID NO: 262 of US20160369298; herein SEQ ID NO: 2666), ATATGGACGTTCATGCTGATCACCATACCG (SEQ ID NO: 263 of US20160369298; herein SEQ ID NO: 2667), AGCAGGAGCTCCTTGGCCTCAGCGTGCGAG (SEQ ID NO: 264 of US20160369298; herein SEQ ID NO: 2668), ACAAGCAGCTTCACTATGACAACCACTGAC (SEQ ID NO: 265 of US20160369298; herein SEQ ID NO: 2669),

CAGCCTAGGAACTGGCTTCCTGGACCCTGTTACCGCCAGCAGAGAGTCTCAAMAMM
AVNSRVCSRSAACAACAACAGTRASTTCTCCTGGMMAGGAGCTACCAAGTACCACC
TCAATGGCAGAGACTCTCTGGTGAATCCCGGACCAGCTATGGCAAGCCACRRGGAC
RRCRMSRRSARSTTTTTTCCTCAGAGCGGGGTTCTCATCTTTGGGAAGSAARRCRSCR

VSRVARVCRATRYCGMSNHCRVMVRSGTCATGATTACAGACGAAGAGGAGATCTGG AC (SEQ ID NO: 266 of US20160369298; herein SEQ ID NO: 2670), TGGGACAATGGCGGTCGTCTCTCAGAGTTKTKKT (SEQ ID NO: 267 of US20160369298; herein SEQ ID NO: 2671), AGAGGACCKKTCCTCGATGGTTCATGGTGGAGTTA (SEQ ID NO: 268 of US20160369298; herein SEQ ID NO: 2672), CCACTTAGGGCCTGGTCGATACCGTTCGGTG (SEQ ID NO: 269 of US20160369298; herein SEQ ID NO: 2673), and TCTCGCCCCAAGAGTAGAAACCCTTCSTTYYG (SEQ ID NO: 270 of US20160369298; herein SEQ ID NO: 2674).

[00200] In some embodiments, the AAV serotype may comprise an ocular cell targeting peptide as described in International Patent Publication WO2016134375, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to SEQ ID NO: 9, and SEQ ID NO:10 of WO2016134375. Further, any of the ocular cell targeting peptides or amino acids described in WO2016134375, may be inserted into any parent AAV serotype, such as, but not limited to, AAV2 (SEQ ID NO:8 of WO2016134375; herein SEQ ID NO: 2675), or AAV9 (SEQ ID NO: 11 of WO2016134375; herein SEQ ID NO: 2676). In some embodiments, modifications, such as insertions are made in AAV2 proteins at P34-A35, T138-A139, A139-P140, G453- T454, N587-R588, and/or R588-Q589. In certain embodiments, insertions are made at D384, G385, 1560, T561, N562, E563, E564, E565, N704, and/or Y705 of AAV9. The ocular cell targeting peptide may be, but is not limited to, any of the following amino acid sequences, GSTPPPM (SEQ ID NO: 1 of WO2016134375; herein SEQ ID NO: 2677), or GETRAPL (SEQ ID NO: 4 of WO2016134375; herein SEQ ID NO: 2678).

[00201] In some embodiments, the AAV serotype may be modified as described in the United States Publication US 20170145405 the contents of which are herein incorporated by reference in their entirety. AAV serotypes may include, modified AAV2(e.g., modifications at Y444F, Y500F, Y730F and/or S662V), modified AAV3 (e.g., modifications at Y705F, Y731F and/or T492V), and modified AAV6 (e.g., modifications at S663V and/or T492V).

[00202] In some embodiments, the AAV serotype may be modified as described in the International Publication WO2017083722 the contents of which are herein incorporated by reference in their entirety. AAV serotypes may include, AAV1 (Y705+731F+T492V), AAV2 (Y444+500+730F+T491V), AAV3 (Y705+731F), AAV5, AAV 5(Y436+693+719F), AAV6 (VP3 variant Y705F/Y731F/T492V), AAV8 (Y733F), AAV9, AAV9 (VP3 variant Y731F), and AAV10 (Y733F).

[00203] In some embodiments, the AAV serotype may comprise, as described in International Patent Publication WO2017015102, the contents of which are herein incorporated by reference in their entirety, an engineered epitope comprising the amino acids SPAKFA (SEQ ID NO: 24 of WO2017015102; herein SEQ ID NO: 2679) or NKDKLN (SEQ ID NO:2 of WO2017015102; herein SEQ ID NO: 2680). The epitope may be inserted in the region of amino acids 665 to 670 based on the numbering of the VP1 capsid of AAV8 (SEQ ID NO:3 of WO2017015102) and/or residues 664 to 668 of AAV3B (SEQ ID NO:3).

[00204] In one embodiment, the AAV serotype may be, or may have a sequence as described in International Patent Publication WO2017058892, the contents of which are herein incorporated by reference in their entirety, such as, but not limited to, AAV variants with capsid proteins that may comprise a substitution at one or more (e.g., 2, 3, 4, 5, 6, or 7) of amino acid residues 262-268, 370- 379, 451 -459, 472-473, 493-500, 528-534, 547-552, 588- 597, 709-710, 716-722 of AAV1, in any combination, or the equivalent amino acid residues in AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12, AAVrh8, AAVrh10, AAVrh32.33, bovine AAV or avian AAV. The amino acid substitution may be, but is not limited to, any of the amino acid sequences described in WO2017058892. In one embodiment, the AAV may comprise an amino acid substitution at residues 256L, 258K, 259Q, 261S, 263A, 264S, 265T, 266G, 272H, 385S, 386Q, S472R, V473D, N500E 547S, 709A, 710N, 716D, 717N, 718N, 720L, A456T, Q457T, N458Q, K459S, T492S, K493A, S586R, S587G, S588N, T589R and/or 722T of AAV1 (SEQ ID NO: 1 of WO2017058892) in any combination, 244N, 246Q, 248R, 249E, 250I, 251K, 252S, 253G, 254S, 255V, 256D, 263Y, 377E, 378N, 453L, 456R, 532Q, 533P, 535N, 536P, 537G, 538T, 539T, 540A, 541T, 542Y, 543L, 546N, 653V, 654P, 656S, 697Q, 698F, 704D, 705S, 706T, 707G, 708E, 709Y and/or 710R of AAV5 (SEQ ID NO:5 of WO2017058892) in any combination, 248R, 316V, 317Q, 318D, 319S, 443N, 530N, 531S, 532Q 533P, 534A, 535N, 540A, 541 T, 542Y, 543L, 545G, 546N, 697Q, 704D, 706T, 708E, 709Yand/or 710R of AAV5 (SEQ ID NO: 5 of WO2017058892) in any combination, 264S, 266G, 269N, 272H, 457Q, 588S and/or 589I of AAV6 (SEQ ID NO:6 WO2017058892) in any combination, 457T, 459N, 496G, 499N, 500N, 589Q, 590N and/or 592A of AAV8 (SEQ ID NO: 8 WO2017058892) in any combination,451I, 452N, 453G, 454S, 455G, 456Q, 457N and/or 458Q of AAV9 (SEQ ID NO: 9 WO2017058892) in any combination.

[00205] In some embodiments, the AAV may include a sequence of amino acids at positions 155, 156 and 157 of VP1 or at positions 17, 18, 19 and 20 of VP2, as described in International Publication No. WO 2017066764, the contents of which are herein incorporated by reference in

their entirety. The sequences of amino acid may be, but not limited to, N-S-S, S-X-S, S-S-Y, N-X-S, N-S-Y, S-X-Y and N-X-Y, where N, X and Y are, but not limited to, independently non-serine, or non-threonine amino acids, wherein the AAV may be, but not limited to AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11 and AAV12. In some embodiments, the AAV may include a deletion of at least one amino acid at positions 156, 157 or 158 of VP1 or at positions 19, 20 or 21 of VP2, wherein the AAV may be, but not limited to AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11 and AAV12.

[00206] In one embodiment, peptides for inclusion in an AAV serotype may be identified using the methods described by Hui et al. (Molecular Therapy – Methods & Clinical Development (2015) 2, 15029 doi:10.1038/mtm.2015.29; the contents of which are herein incorporated by reference in its entirety). As a non-limiting example, the procedure includes isolating human splenocytes, restimulating the splenocytes in vitro using individual peptides spanning the amino acid sequence of the AAV capsid protein, IFN-gamma ELISpot with the individual peptides used for the in vitro restimulation, bioinformatics analysis to determine the HLA restriction of 15-mers identified by IFN-gamma ELISpot, identification of candidate reactive 9-mer epitopes for a given HLA allele, synthesis candidate 9-mers, second IFN-gamma ELISpot screening of splenocytes from subjects carrying the HLA alleles to which identified AAV epitopes are predicted to bind, determine the AAV capsid-reactive CD8+ T cell epitopes and determine the frequency of subjects reacting to a given AAV epitope.

[00207] In one embodiment, the AAV may be a serotype generated by Cre-recombination-based AAV targeted evolution (CREATE) as described by Deverman et al., (Nature Biotechnology 34(2):204-209 (2016)), the contents of which are herein incorporated by reference in their entirety. In one embodiment, AAV serotypes generated in this manner have improved CNS transduction and/or neuronal and astrocytic tropism, as compared to other AAV serotypes. As non-limiting examples, the AAV serotype may be PHP.B, PHP.B2, PHP.B3, PHP.A, G2A12, G2A15. In one embodiment, these AAV serotypes may be AAV9 (SEQ ID NO: 126 and 127) derivatives with a 7-amino acid insert between amino acids 588-589. Non-limiting examples of these 7-amino acid inserts include TLAVPFK (SEQ ID NO: 873), SVSKPFL (SEQ ID NO: 1249), FTLTTPK (SEQ ID NO: 882), YTLSQGW (SEQ ID NO: 888), QAVRTSL (SEQ ID NO: 914) and/or LAKERLS (SEQ ID NO: 915).

[00208] In one embodiment, the AAV serotype may be as described in Jackson et al (Frontiers in Molecular Neuroscience 9:154 (2016)), the contents of which are herein incorporated by

reference in their entirety. In some embodiments, the AAV serotype is PHP.B or AAV9. In some embodiments, the AAV serotype is paired with a synapsin promoter to enhance neuronal transduction, as compared to when more ubiquitous promoters are used (i.e., CBA or CMV).

[00209] In one embodiment, peptides for inclusion in an AAV serotype may be identified by isolating human splenocytes, restimulating the splenocytes in vitro using individual peptides spanning the amino acid sequence of the AAV capsid protein, IFN-gamma ELISpot with the individual peptides used for the in vitro restimulation, bioinformatics analysis to determine the given allele restriction of 15-mers identified by IFN-gamma ELISpot, identification of candidate reactive 9-mer epitopes for a given allele, synthesis candidate 9-mers, second IFN-gamma ELISpot screening of splenocytes from subjects carrying the specific alleles to which identified AAV epitopes are predicted to bind, determine the AAV capsid-reactive CD8+ T cell epitopes and determine the frequency of subjects reacting to a given AAV epitope.

[00210] AAV particles comprising a modulatory polynucleotide encoding the siRNA molecules may be prepared or derived from various serotypes of AAVs, including, but not limited to, AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV9.47, AAV9(hu14), AAV10, AAV11, AAV12, AAVrh8, AAVrh10, AAV-DJ8 and AAV-DJ. In some cases, different serotypes of AAVs may be mixed together or with other types of viruses to produce chimeric AAV particles. As a non-limiting example, the AAV particle is derived from the AAV9 serotype.

Viral Genome

[00211] In one embodiment, as shown in an AAV particle comprises a viral genome with a payload region.

[00212] In one embodiment, the viral genome may comprise the components as shown in FIG. 1. The payload region **110** is located within the viral genome **100**. At the 5' and/or the 3' end of the viral genome **100** there may be at least one inverted terminal repeat (ITR) **120**. Between the 5' ITR **120** and the payload region **110**, there may be a promoter region **130**. In one embodiment, the payload region may comprise at least one modulatory polynucleotide.

[00213] In one embodiment, the viral genome **100** may comprise the components as shown in FIG. 2. The payload region **110** is located within the viral genome **100**. At the 5' and/or the 3' end of the viral genome **100** there may be at least one inverted terminal repeat (ITR) **120**. Between the 5' ITR **120** and the payload region **110**, there may be a promoter region **130**. Between the promoter region **130** and the payload region **110**, there may be an intron region **140**. In one embodiment, the payload region may comprise at least one modulatory polynucleotide.

[00214] In one embodiment, the viral genome **100** may comprise the components as shown in FIG. 3. At the 5' and/or the 3' end of the viral genome **100** there may be at least one inverted terminal repeat (ITR) **120**. Within the viral genome **100**, there may be an enhancer region **150**, a promoter region **130**, an intron region **140**, and a payload region **110**. In one embodiment, the payload region may comprise at least one modulatory polynucleotide.

[00215] In one embodiment, the viral genome **100** may comprise the components as shown in FIG. 4. At the 5' and/or the 3' end of the viral genome **100** there may be at least one inverted terminal repeat (ITR) **120**. Within the viral genome **100**, there may be an enhancer region **150**, a promoter region **130**, an intron region **140**, a payload region **110**, and a polyadenylation signal sequence region **160**. In one embodiment, the payload region may comprise at least one modulatory polynucleotide.

[00216] In one embodiment, the viral genome **100** may comprise the components as shown in FIG. 5. At the 5' and/or the 3' end of the viral genome **100** there may be at least one inverted terminal repeat (ITR) **120**. Within the viral genome **100**, there may be at least one MCS region **170**, an enhancer region **150**, a promoter region **130**, an intron region **140**, a payload region **110**, and a polyadenylation signal sequence region **160**. In one embodiment, the payload region may comprise at least one modulatory polynucleotide.

[00217] In one embodiment, the viral genome **100** may comprise the components as shown in FIG. 6. At the 5' and/or the 3' end of the viral genome **100** there may be at least one inverted terminal repeat (ITR) **120**. Within the viral genome **100**, there may be at least one MCS region **170**, an enhancer region **150**, a promoter region **130**, at least one exon region **180**, at least one intron region **140**, a payload region **110**, and a polyadenylation signal sequence region **160**. In one embodiment, the payload region may comprise at least one modulatory polynucleotide.

[00218] In one embodiment, the viral genome **100** may comprise the components as shown in FIG. 7 and 8. Within the viral genome **100**, there may be at least one promoter region **130**, and a payload region **110**. In one embodiment, the payload region may comprise at least one modulatory polynucleotide.

[00219] In one embodiment, the viral genome **100** may comprise the components as shown in FIG. 9. Within the viral genome **100**, there may be at least one promoter region **130**, a payload region **110**, and a polyadenylation signal sequence region **160**. In one embodiment, the payload region may comprise at least one modulatory polynucleotide.

Viral Genome Size

[00220] In one embodiment, the viral genome which comprises a payload described herein, may be single stranded or double stranded viral genome. The size of the viral genome may be small, medium, large or the maximum size. Additionally, the viral genome may comprise a promoter and a polyA tail.

[00221] In one embodiment, the viral genome which comprises a payload described herein, may be a small single stranded viral genome. A small single stranded viral genome may be 2.7 to 3.5 kb in size such as about 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, and 3.5 kb in size. As a non-limiting example, the small single stranded viral genome may be 3.2 kb in size. Additionally, the viral genome may comprise a promoter and a polyA tail.

[00222] In one embodiment, the viral genome which comprises a payload described herein, may be a small double stranded viral genome. A small double stranded viral genome may be 1.3 to 1.7 kb in size such as about 1.3, 1.4, 1.5, 1.6, and 1.7 kb in size. As a non-limiting example, the small double stranded viral genome may be 1.6 kb in size. Additionally, the viral genome may comprise a promoter and a polyA tail.

[00223] In one embodiment, the viral genome which comprises a payload described herein, may a medium single stranded viral genome. A medium single stranded viral genome may be 3.6 to 4.3 kb in size such as about 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2 and 4.3 kb in size. As a non-limiting example, the medium single stranded viral genome may be 4.0 kb in size. Additionally, the viral genome may comprise a promoter and a polyA tail.

[00224] In one embodiment, the viral genome which comprises a payload described herein, may be a medium double stranded viral genome. A medium double stranded viral genome may be 1.8 to 2.1 kb in size such as about 1.8, 1.9, 2.0, and 2.1 kb in size. As a non-limiting example, the medium double stranded viral genome may be 2.0 kb in size. Additionally, the viral genome may comprise a promoter and a polyA tail.

[00225] In one embodiment, the viral genome which comprises a payload described herein, may be a large single stranded viral genome. A large single stranded viral genome may be 4.4 to 6.0 kb in size such as about 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9 and 6.0 kb in size. As a non-limiting example, the large single stranded viral genome may be 4.7 kb in size. As another non-limiting example, the large single stranded viral genome may be 4.8 kb in size. As yet another non-limiting example, the large single stranded viral genome may be 6.0 kb in size. Additionally, the viral genome may comprise a promoter and a polyA tail.

[00226] In one embodiment, the viral genome which comprises a payload described herein, may be a large double stranded viral genome. A large double stranded viral genome may be 2.2 to 3.0

kb in size such as about 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9 and 3.0 kb in size. As a non-limiting example, the large double stranded viral genome may be 2.4 kb in size. Additionally, the viral genome may comprise a promoter and a polyA tail.

Viral Genome Component: Inverted Terminal Repeats (ITRs)

[00227] The AAV particles of the present invention comprise a viral genome with at least one ITR region and a payload region. In one embodiment the viral genome has two ITRs. These two ITRs flank the payload region at the 5' and 3' ends. The ITRs function as origins of replication comprising recognition sites for replication. ITRs comprise sequence regions which can be complementary and symmetrically arranged. ITRs incorporated into viral genomes of the invention may be comprised of naturally occurring polynucleotide sequences or recombinantly derived polynucleotide sequences.

[00228] The ITRs may be derived from the same serotype as the capsid, selected from any of the serotypes listed in Table 1, or a derivative thereof. The ITR may be of a different serotype from the capsid. In one embodiment the AAV particle has more than one ITR. In a non-limiting example, the AAV particle has a viral genome comprising two ITRs. In one embodiment the ITRs are of the same serotype as one another. In another embodiment the ITRs are of different serotypes. Non-limiting examples include zero, one or both of the ITRs having the same serotype as the capsid. In one embodiment both ITRs of the viral genome of the AAV particle are AAV2 ITRs.

[00229] Independently, each ITR may be about 100 to about 150 nucleotides in length. An ITR may be about 100-105 nucleotides in length, 106-110 nucleotides in length, 111-115 nucleotides in length, 116-120 nucleotides in length, 121-125 nucleotides in length, 126-130 nucleotides in length, 131-135 nucleotides in length, 136-140 nucleotides in length, 141-145 nucleotides in length or 146-150 nucleotides in length. In one embodiment the ITRs are 140-142 nucleotides in length. Non limiting examples of ITR length are 102, 140, 141, 142, 145 nucleotides in length, and those having at least 95% identity thereto.

[00230] In one embodiment, the AAV particle comprises a nucleic acid sequence encoding an siRNA molecule which may be located near the 5' end of the flip ITR in an expression vector. In another embodiment, the AAV particle comprises a nucleic acid sequence encoding an siRNA molecule may be located near the 3' end of the flip ITR in an expression vector. In yet another embodiment, the AAV particle comprises a nucleic acid sequence encoding an siRNA molecule may be located near the 5' end of the flop ITR in an expression vector. In yet another embodiment, the AAV particle comprises a nucleic acid sequence encoding an siRNA molecule

may be located near the 3' end of the flop ITR in an expression vector. In one embodiment, the AAV particle comprises a nucleic acid sequence encoding an siRNA molecule may be located between the 5' end of the flip ITR and the 3' end of the flop ITR in an expression vector. In one embodiment, the AAV particle comprises a nucleic acid sequence encoding an siRNA molecule may be located between (e.g., half-way between the 5' end of the flip ITR and 3' end of the flop ITR or the 3' end of the flop ITR and the 5' end of the flip ITR), the 3' end of the flip ITR and the 5' end of the flip ITR in an expression vector. As a non-limiting example, the AAV particle comprises a nucleic acid sequence encoding an siRNA molecule may be located within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 or more than 30 nucleotides downstream from the 5' or 3' end of an ITR (e.g., Flip or Flop ITR) in an expression vector. As a non-limiting example, the AAV particle comprises a nucleic acid sequence encoding an siRNA molecule may be located within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 or more than 30 nucleotides upstream from the 5' or 3' end of an ITR (e.g., Flip or Flop ITR) in an expression vector. As another non-limiting example, the AAV particle comprises a nucleic acid sequence encoding an siRNA molecule may be located within 1-5, 1-10, 1-15, 1-20, 1-25, 1-30, 5-10, 5-15, 5-20, 5-25, 5-30, 10-15, 10-20, 10-25, 10-30, 15-20, 15-25, 15-30, 20-25, 20-30 or 25-30 nucleotides downstream from the 5' or 3' end of an ITR (e.g., Flip or Flop ITR) in an expression vector. As another non-limiting example, the AAV particle comprises a nucleic acid sequence encoding an siRNA molecule may be located within 1-5, 1-10, 1-15, 1-20, 1-25, 1-30, 5-10, 5-15, 5-20, 5-25, 5-30, 10-15, 10-20, 10-25, 10-30, 15-20, 15-25, 15-30, 20-25, 20-30 or 25-30 upstream from the 5' or 3' end of an ITR (e.g., Flip or Flop ITR) in an expression vector. As a non-limiting example, the AAV particle comprises a nucleic acid sequence encoding an siRNA molecule may be located within the first 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25% or more than 25% of the nucleotides upstream from the 5' or 3' end of an ITR (e.g., Flip or Flop ITR) in an expression vector. As another non-limiting example, the AAV particle comprises a nucleic acid sequence encoding an siRNA molecule may be located with the first 1-5%, 1-10%, 1-15%, 1-20%, 1-25%, 5-10%, 5-15%, 5-20%, 5-25%, 10-15%, 10-20%, 10-25%, 15-20%, 15-25%, or 20-25% downstream from the 5' or 3' end of an ITR (e.g., Flip or Flop ITR) in an expression vector.

Viral Genome Component: Promoters

[00231] In one embodiment, the payload region of the viral genome comprises at least one element to enhance the transgene target specificity and expression (See e.g., Powell et al. Viral

Expression Cassette Elements to Enhance Transgene Target Specificity and Expression in Gene Therapy, 2015; the contents of which are herein incorporated by reference in its entirety). Non-limiting examples of elements to enhance the transgene target specificity and expression include promoters, endogenous miRNAs, post-transcriptional regulatory elements (PREs), polyadenylation (PolyA) signal sequences and upstream enhancers (USEs), CMV enhancers and introns.

[00232] A person skilled in the art may recognize that expression of the polypeptides of the invention in a target cell may require a specific promoter, including but not limited to, a promoter that is species specific, inducible, tissue-specific, or cell cycle-specific (Parr et al., Nat. Med.3:1145-9 (1997); the contents of which are herein incorporated by reference in their entirety).

[00233] In one embodiment, the promoter is deemed to be efficient when it drives expression of the polypeptide(s) encoded in the payload region of the viral genome of the AAV particle.

[00234] In one embodiment, the promoter is a promoter deemed to be efficient to drive the expression of the modulatory polynucleotide.

[00235] In one embodiment, the promoter is a promoter deemed to be efficient when it drives expression in the cell being targeted.

[00236] In one embodiment, the promoter drives expression of the payload for a period of time in targeted tissues. Expression driven by a promoter may be for a period of 1 hour, 2, hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 2 weeks, 15 days, 16 days, 17 days, 18 days, 19 days, 20 days, 3 weeks, 22 days, 23 days, 24 days, 25 days, 26 days, 27 days, 28 days, 29 days, 30 days, 31 days, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 1 year, 13 months, 14 months, 15 months, 16 months, 17 months, 18 months, 19 months, 20 months, 21 months, 22 months, 23 months, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years or more than 10 years. Expression may be for 1-5 hours, 1-12 hours, 1-2 days, 1-5 days, 1-2 weeks, 1-3 weeks, 1-4 weeks, 1-2 months, 1-4 months, 1-6 months, 2-6 months, 3-6 months, 3-9 months, 4-8 months, 6-12 months, 1-2 years, 1-5 years, 2-5 years, 3-6 years, 3-8 years, 4-8 years or 5-10 years.

[00237] In one embodiment, the promoter drives expression of the payload for at least 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months,

11 months, 1 year, 2 years, 3 years 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 11 years, 12 years, 13 years, 14 years, 15 years, 16 years, 17 years, 18 years, 19 years, 20 years, 21 years, 22 years, 23 years, 24 years, 25 years, 26 years, 27 years, 28 years, 29 years, 30 years, 31 years, 32 years, 33 years, 34 years, 35 years, 36 years, 37 years, 38 years, 39 years, 40 years, 41 years, 42 years, 43 years, 44 years, 45 years, 46 years, 47 years, 48 years, 49 years, 50 years, 55 years, 60 years, 65 years, or more than 65 years.

[00238] Promoters may be naturally occurring or non-naturally occurring. Non-limiting examples of promoters include viral promoters, plant promoters and mammalian promoters. In some embodiments, the promoters may be human promoters. In some embodiments, the promoter may be truncated.

[00239] Promoters which drive or promote expression in most tissues include, but are not limited to, human elongation factor 1α-subunit (EF1α), cytomegalovirus (CMV) immediate-early enhancer and/or promoter, chicken β-actin (CBA) and its derivative CAG, β glucuronidase (GUSB), or ubiquitin C (UBC). Tissue-specific expression elements can be used to restrict expression to certain cell types such as, but not limited to, muscle specific promoters, B cell promoters, monocyte promoters, leukocyte promoters, macrophage promoters, pancreatic acinar cell promoters, endothelial cell promoters, lung tissue promoters, astrocyte promoters, or nervous system promoters which can be used to restrict expression to neurons, astrocytes, or oligodendrocytes.

[00240] Non-limiting examples of muscle-specific promoters include mammalian muscle creatine kinase (MCK) promoter, mammalian desmin (DES) promoter, mammalian troponin I (TNNI2) promoter, and mammalian skeletal alpha-actin (ASKA) promoter (see, e.g. U.S. Patent Publication US 20110212529, the contents of which are herein incorporated by reference in their entirety)

[00241] Non-limiting examples of tissue-specific expression elements for neurons include neuron-specific enolase (NSE), platelet-derived growth factor (PDGF), platelet-derived growth factor B-chain (PDGF-β), synapsin (Syn), methyl-CpG binding protein 2 (MeCP2), Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), metabotropic glutamate receptor 2 (mGluR2), neurofilament light (NFL) or heavy (NFH), β-globin minigene nβ2, preproenkephalin (PPE), enkephalin (Enk) and excitatory amino acid transporter 2 (EAAT2) promoters. Non-limiting examples of tissue-specific expression elements for astrocytes include glial fibrillary acidic protein (GFAP) and EAAT2 promoters. A non-limiting example of a tissue-specific expression element for oligodendrocytes includes the myelin basic protein (MBP) promoter.

[00242] In one embodiment, the promoter may be less than 1 kb. The promoter may have a length of 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710, 720, 730, 740, 750, 760, 770, 780, 790, 800 or more than 800 nucleotides. The promoter may have a length between 200-300, 200-400, 200-500, 200-600, 200-700, 200-800, 300-400, 300-500, 300-600, 300-700, 300-800, 400-500, 400-600, 400-700, 400-800, 500-600, 500-700, 500-800, 600-700, 600-800 or 700-800.

[00243] In one embodiment, the promoter may be a combination of two or more components of the same or different starting or parental promoters such as, but not limited to, CMV and CBA. Each component may have a length of 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710, 720, 730, 740, 750, 760, 770, 780, 790, 800 or more than 800. Each component may have a length between 200-300, 200-400, 200-500, 200-600, 200-700, 200-800, 300-400, 300-500, 300-600, 300-700, 300-800, 400-500, 400-600, 400-700, 400-800, 500-600, 500-700, 500-800, 600-700, 600-800 or 700-800. In one embodiment, the promoter is a combination of a 382 nucleotide CMV-enhancer sequence and a 260 nucleotide CBA-promoter sequence.

[00244] In one embodiment, the viral genome comprises a ubiquitous promoter. Non-limiting examples of ubiquitous promoters include CMV, CBA (including derivatives CAG, CBh, etc.), EF-1α, PGK, UBC, GUSB (hGBp), and UCOE (promoter of HNRPA2B1-CBX3).

[00245] Yu et al. (Molecular Pain 2011, 7:63; the contents of which are herein incorporated by reference in their entirety) evaluated the expression of eGFP under the CAG, EFIα, PGK and UBC promoters in rat DRG cells and primary DRG cells using lentiviral vectors and found that UBC showed weaker expression than the other 3 promoters and only 10-12% glial expression was seen for all promoters. Soderblom et al. (E. Neuro 2015; the contents of which are herein incorporated by reference in its entirety) evaluated the expression of eGFP in AAV8 with CMV and UBC promoters and AAV2 with the CMV promoter after injection in the motor cortex. Intranasal administration of a plasmid containing a UBC or EFIα promoter showed a sustained airway expression greater than the expression with the CMV promoter (See e.g., Gill et al., Gene Therapy 2001, Vol. 8, 1539-1546; the contents of which are herein incorporated by reference in their entirety). Husain et al. (Gene Therapy 2009; the contents of which are herein incorporated

by reference in its entirety) evaluated an HβH construct with a hGUSB promoter, a HSV-1LAT promoter and an NSE promoter and found that the HβH construct showed weaker expression than NSE in mouse brain. Passini and Wolfe (J. Virol. 2001, 12382-12392, the contents of which are herein incorporated by reference in its entirety) evaluated the long term effects of the HβH vector following an intraventricular injection in neonatal mice and found that there was sustained expression for at least 1 year. Low expression in all brain regions was found by Xu et al. (Gene Therapy 2001, 8, 1323-1332; the contents of which are herein incorporated by reference in their entirety) when NFL and NFH promoters were used as compared to the CMV-lacZ, CMV-luc, EF, GFAP, hENK, nAChR, PPE, PPE + wpre, NSE (0.3 kb), NSE (1.8 kb) and NSE (1.8 kb + wpre). Xu et al. found that the promoter activity in descending order was NSE (1.8 kb), EF, NSE (0.3 kb), GFAP, CMV, hENK, PPE, NFL and NFH. NFL is a 650 nucleotide promoter and NFH is a 920 nucleotide promoter which are both absent in the liver but NFH is abundant in the sensory proprioceptive neurons, brain and spinal cord and NFH is present in the heart. Scn8a is a 470 nucleotide promoter which expresses throughout the DRG, spinal cord and brain with particularly high expression seen in the hippocampal neurons and cerebellar Purkinje cells, cortex, thalamus and hypothalamus (See e.g., Drews et al. Identification of evolutionary conserved, functional noncoding elements in the promoter region of the sodium channel gene SCN8A, Mamm Genome (2007) 18:723-731; and Raymond et al. Expression of Alternatively Spliced Sodium Channel α-subunit genes, Journal of Biological Chemistry (2004) 279(44) 46234-46241; the contents of each of which are herein incorporated by reference in their entireties).

[00246] Any of promoters taught by the aforementioned Yu, Soderblom, Gill, Husain, Passini, Xu, Drews or Raymond may be used in the present inventions.

[00247] In one embodiment, the promoter is not cell specific.

[00248] In one embodiment, the promoter is an ubiquitin c (UBC) promoter. The UBC promoter may have a size of 300-350 nucleotides. As a non-limiting example, the UBC promoter is 332 nucleotides.

[00249] In one embodiment, the promoter is a β-glucuronidase (GUSB) promoter. The GUSB promoter may have a size of 350-400 nucleotides. As a non-limiting example, the GUSB promoter is 378 nucleotides.

[00250] In one embodiment, the promoter is a neurofilament light (NFL) promoter. The NFL promoter may have a size of 600-700 nucleotides. As a non-limiting example, the NFL promoter is 650 nucleotides. As a non-limiting example, the construct may be AAV-promoter-

CMV/globin intron-modulatory polynucleotide-RBG, where the AAV may be self-complementary and the AAV may be the DJ serotype.

[00251] In one embodiment, the promoter is a neurofilament heavy (NFH) promoter. The NFH promoter may have a size of 900-950 nucleotides. As a non-limiting example, the NFH promoter is 920 nucleotides. As a non-limiting example, the construct may be AAV-promoter-CMV/globin intron-modulatory polynucleotide-RBG, where the AAV may be self-complementary and the AAV may be the DJ serotype.

[00252] In one embodiment, the promoter is a scn8a promoter. The scn8a promoter may have a size of 450-500 nucleotides. As a non-limiting example, the scn8a promoter is 470 nucleotides. As a non-limiting example, the construct may be AAV-promoter-CMV/globin intron-modulatory polynucleotide-RBG, where the AAV may be self-complementary and the AAV may be the DJ serotype

[00253] In one embodiment, the viral genome comprises a Pol III promoter.

[00254] In one embodiment, the viral genome comprises a P1 promoter.

[00255] In one embodiment, the viral genome comprises a FXN promoter.

[00256] In one embodiment, the promoter is a phosphoglycerate kinase 1 (PGK) promoter.

[00257] In one embodiment, the promoter is a chicken β-actin (CBA) promoter.

[00258] In one embodiment, the promoter is a CAG promoter which is a construct comprising the cytomegalovirus (CMV) enhancer fused to the chicken beta-actin (CBA) promoter.

[00259] In one embodiment, the promoter is a cytomegalovirus (CMV) promoter.

[00260] In one embodiment, the viral genome comprises a Pol III promoter, for example, a Pol III type 3 promoter.

[00261] In one embodiment, comprises an U3, U6, U7, 7SK, H1, or MRP, EBER, selenocysteine tRNA, 7SL, adenovirus VA-1, or telomerase gene promoter.

[00262] In one embodiment, the viral genome comprises an H1 promoter.

[00263] In one embodiment, the viral genome comprises a U6 promoter.

[00264] In one embodiment, the promoter is a liver or a skeletal muscle promoter. Non-limiting examples of liver promoters include human α-1-antitrypsin (hAAT) and thyroxine binding globulin (TBG). Non-limiting examples of skeletal muscle promoters include Desmin, MCK or synthetic C5-12.

[00265] In one embodiment, the promoter is a RNA pol III promoter. As a non-limiting example, the RNA pol III promoter is U6. As a non-limiting example, the RNA pol III promoter is H1.

[00266] In one embodiment, the promoter is a RNA Pol II promoter, including, for example, a truncated RNA Pol II promoter.

[00267] In one embodiment, the viral genome comprises two promoters. As a non-limiting example, the promoters are an EF1α promoter and a CMV promoter.

[00268] In one embodiment, the viral genome comprises an enhancer element, a promoter and/or a 5'UTR intron. The enhancer element, also referred to herein as an "enhancer," may be, but is not limited to, a CMV enhancer, the promoter may be, but is not limited to, a CMV, CBA, UBC, GUSB, NSE, Synapsin, MeCP2, and GFAP promoter and the 5'UTR/intron may be, but is not limited to, SV40, and CBA-MVM. As a non-limiting example, the enhancer, promoter and/or intron used in combination may be: (1) CMV enhancer, CMV promoter, SV40 5'UTR intron; (2) CMV enhancer, CBA promoter, SV 40 5'UTR intron; (3) CMV enhancer, CBA promoter, CBA-MVM 5'UTR intron; (4) UBC promoter; (5) GUSB promoter; (6) NSE promoter; (7) Synapsin promoter; (8) MeCP2 promoter, (9) GFAP promoter, (10) H1 promoter; and (11) U6 promoter.

[00269] In one embodiment, the viral genome comprises an engineered promoter.

[00270] In another embodiment the viral genome comprises a promoter from a naturally expressed protein.

Viral Genome Component: Untranslated Regions (UTRs)

[00271] By definition, wild type untranslated regions (UTRs) of a gene are transcribed but not translated. Generally, the 5' UTR starts at the transcription start site and ends at the start codon and the 3' UTR starts immediately following the stop codon and continues until the termination signal for transcription.

[00272] Features typically found in abundantly expressed genes of specific target organs may be engineered into UTRs to enhance the stability and protein production. As a non-limiting example, a 5' UTR from mRNA normally expressed in the liver (e.g., albumin, serum amyloid A, Apolipoprotein A/B/E, transferrin, alpha fetoprotein, erythropoietin, or Factor VIII) may be used in the viral genomes of the AAV particles of the invention to enhance expression in hepatic cell lines or liver.

[00273] While not wishing to be bound by theory, wild-type 5′ untranslated regions (UTRs) include features which play roles in translation initiation. Kozak sequences, which are commonly known to be involved in the process by which the ribosome initiates translation of many genes, are usually included in 5' UTRs. Kozak sequences have the consensus

CCR(A/G)CCAUGG, where R is a purine (adenine or guanine) three bases upstream of the start codon (ATG), which is followed by another 'G'.

[00274] In one embodiment, the 5'UTR in the viral genome includes a Kozak sequence.

[00275] In one embodiment, the 5'UTR in the viral genome does not include a Kozak sequence.

[00276] While not wishing to be bound by theory, wild-type 3′ UTRs are known to have stretches of Adenosines and Uridines embedded therein. These AU rich signatures are particularly prevalent in genes with high rates of turnover. Based on their sequence features and functional properties, the AU rich elements (AREs) can be separated into three classes (Chen et al, 1995, the contents of which are herein incorporated by reference in its entirety): Class I AREs, such as, but not limited to, c-Myc and MyoD, contain several dispersed copies of an AUUUA motif within U-rich regions. Class II AREs, such as, but not limited to, GM-CSF and TNF-a, possess two or more overlapping UUAUUUA(U/A)(U/A) nonamers. Class III ARES, such as, but not limited to, c-Jun and Myogenin, are less well defined. These U rich regions do not contain an AUUUA motif. Most proteins binding to the AREs are known to destabilize the messenger, whereas members of the ELAV family, most notably HuR, have been documented to increase the stability of mRNA. HuR binds to AREs of all the three classes. Engineering the HuR specific binding sites into the 3′ UTR of nucleic acid molecules will lead to HuR binding and thus, stabilization of the message in vivo.

[00277] Introduction, removal or modification of 3′ UTR AU rich elements (AREs) can be used to modulate the stability of polynucleotides. When engineering specific polynucleotides, e.g., payload regions of viral genomes, one or more copies of an ARE can be introduced to make polynucleotides less stable and thereby curtail translation and decrease production of the resultant protein. Likewise, AREs can be identified and removed or mutated to increase the intracellular stability and thus increase translation and production of the resultant protein.

[00278] In one embodiment, the 3' UTR of the viral genome may include an oligo(dT) sequence for templated addition of a poly-A tail.

[00279] In one embodiment, the viral genome may include at least one miRNA seed, binding site or full sequence. microRNAs (or miRNA or miR) are 19-25 nucleotide noncoding RNAs that bind to the sites of nucleic acid targets and down-regulate gene expression either by reducing nucleic acid molecule stability or by inhibiting translation. A microRNA sequence comprises a "seed" region, i.e., a sequence in the region of positions 2-8 of the mature microRNA, which sequence has perfect Watson-Crick complementarity to the miRNA target sequence of the nucleic acid.

[00280] In one embodiment, the viral genome may be engineered to include, alter or remove at least one miRNA binding site, sequence or seed region.

[00281] Any UTR from any gene known in the art may be incorporated into the viral genome of the AAV particle. These UTRs, or portions thereof, may be placed in the same orientation as in the gene from which they were selected or they may be altered in orientation or location. In one embodiment, the UTR used in the viral genome of the AAV particle may be inverted, shortened, lengthened, made with one or more other 5′ UTRs or 3′ UTRs known in the art. As used herein, the term "altered" as it relates to a UTR, means that the UTR has been changed in some way in relation to a reference sequence. For example, a 3′ or 5′ UTR may be altered relative to a wild type or native UTR by the change in orientation or location as taught above or may be altered by the inclusion of additional nucleotides, deletion of nucleotides, swapping or transposition of nucleotides.

[00282] In one embodiment, the viral genome of the AAV particle comprises at least one artificial UTRs which is not a variant of a wild type UTR.

[00283] In one embodiment, the viral genome of the AAV particle comprises UTRs which have been selected from a family of transcripts whose proteins share a common function, structure, feature or property.

Viral Genome Component: Polyadenylation Sequence

[00284] In one embodiment, the viral genome of the AAV particles of the present invention comprise at least one polyadenylation sequence. The viral genome of the AAV particle may comprise a polyadenylation sequence between the 3' end of the payload coding sequence and the 5' end of the 3'ITR.

[00285] In one embodiment, the polyadenylation sequence or "polyA sequence" may range from absent to about 500 nucleotides in length. The polyadenylation sequence may be, but is not limited to, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197,

198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, and 500 nucleotides in length.

[00286] In one embodiment, the polyadenylation sequence is 50-100 nucleotides in length.

[00287] In one embodiment, the polyadenylation sequence is 50-150 nucleotides in length.

[00288] In one embodiment, the polyadenylation sequence is 50-160 nucleotides in length.

[00289] In one embodiment, the polyadenylation sequence is 50-200 nucleotides in length.

[00290] In one embodiment, the polyadenylation sequence is 60-100 nucleotides in length.

[00291] In one embodiment, the polyadenylation sequence is 60-150 nucleotides in length.

[00292] In one embodiment, the polyadenylation sequence is 60-160 nucleotides in length.

[00293] In one embodiment, the polyadenylation sequence is 60-200 nucleotides in length.

[00294] In one embodiment, the polyadenylation sequence is 70-100 nucleotides in length.

[00295] In one embodiment, the polyadenylation sequence is 70-150 nucleotides in length.

[00296] In one embodiment, the polyadenylation sequence is 70-160 nucleotides in length.

[00297] In one embodiment, the polyadenylation sequence is 70-200 nucleotides in length.

[00298] In one embodiment, the polyadenylation sequence is 80-100 nucleotides in length.

[00299] In one embodiment, the polyadenylation sequence is 80-150 nucleotides in length.

[00300] In one embodiment, the polyadenylation sequence is 80-160 nucleotides in length.

[00301] In one embodiment, the polyadenylation sequence is 80-200 nucleotides in length.

[00302] In one embodiment, the polyadenylation sequence is 90-100 nucleotides in length.

[00303] In one embodiment, the polyadenylation sequence is 90-150 nucleotides in length.

[00304] In one embodiment, the polyadenylation sequence is 90-160 nucleotides in length.

[00305] In one embodiment, the polyadenylation sequence is 90-200 nucleotides in length.

[00306] In one embodiment, the AAV particle comprises a nucleic acid sequence encoding an siRNA molecule may be located upstream of the polyadenylation sequence in an expression vector. Further, the AAV particle comprises a nucleic acid sequence encoding an siRNA molecule may be located downstream of a promoter such as, but not limited to, CMV, U6, CAG, CBA or a CBA promoter with a SV40 intron or a human betaglobin intron in an expression vector. As a non-limiting example, the AAV particle comprises a nucleic acid sequence encoding an siRNA molecule may be located within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 or more than 30 nucleotides downstream from the promoter and/or upstream of the polyadenylation sequence in an expression vector. As another non-limiting example, the AAV particle comprises a nucleic acid sequence encoding an siRNA molecule may be located within 1-5, 1-10, 1-15, 1-20, 1-25, 1-30, 5-10, 5-15, 5-20, 5-25, 5-30, 10-15, 10-20, 10-25, 10-30, 15-20, 15-25, 15-30, 20-25, 20-30 or 25-30 nucleotides downstream from the promoter and/or upstream of the polyadenylation sequence in an expression vector. As a non-limiting example, the AAV particle comprises a nucleic acid sequence encoding an siRNA molecule may be located within the first 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25% or more than 25% of the nucleotides downstream from the promoter and/or upstream of the polyadenylation sequence in an expression vector. As another non-limiting example, the AAV particle comprises a nucleic acid sequence encoding an siRNA molecule may be located with the first 1-5%, 1-10%, 1-15%, 1-20%, 1-25%, 5-10%, 5-15%, 5-20%, 5-25%, 10-15%, 10-20%, 10-25%, 15-20%, 15-25%, or 20-25% downstream from the promoter and/or upstream of the polyadenylation sequence in an expression vector.

[00307] In one embodiment, the AAV particle comprises a rabbit globin polyadenylation (polyA) signal sequence.

[00308] In one embodiment, the AAV particle comprises a human growth hormone polyadenylation (polyA) signal sequence.

Viral Genome Component: Introns

[00309] In one embodiment, the payload region comprises at least one element to enhance the expression such as one or more introns or portions thereof. Non-limiting examples of introns include, MVM (67-97 bps), F.IX truncated intron 1 (300 bps), β-globin SD/immunoglobulin

heavy chain splice acceptor (250 bps), adenovirus splice donor/immunoglobin splice acceptor (500 bps), SV40 late splice donor/splice acceptor (19S/16S) (180 bps) and hybrid adenovirus splice donor/IgG splice acceptor (230 bps).

[00310] In one embodiment, the intron or intron portion may be 100-500 nucleotides in length. The intron may have a length of 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490 or 500. The intron may have a length between 80-100, 80-120, 80-140, 80-160, 80-180, 80-200, 80-250, 80-300, 80-350, 80-400, 80-450, 80-500, 200-300, 200-400, 200-500, 300-400, 300-500, or 400-500.

[00311] In one embodiment, the AAV viral genome may comprise a promoter such as, but not limited to, CMV or U6. As a non-limiting example, the promoter for the AAV comprising the nucleic acid sequence for the siRNA molecules of the present invention is a CMV promoter. As another non-limiting example, the promoter for the AAV comprising the nucleic acid sequence for the siRNA molecules of the present invention is a U6 promoter.

[00312] In one embodiment, the AAV viral genome may comprise a CMV promoter.

[00313] In one embodiment, the AAV viral genome may comprise a U6 promoter.

[00314] In one embodiment, the AAV viral genome may comprise a CMV and a U6 promoter.

[00315] In one embodiment, the AAV viral genome may comprise a Pol III promoter.

[00316] In one embodiment, the AAV viral genome may comprise a Pol III type 3 promoter.

[00317] In one embodiment, the AAV viral genome may comprise a H1 promoter.

[00318] In one embodiment, the AAV viral genome may comprise a U6 promoter.

[00319] In one embodiment, the AAV viral genome may comprise a CBA promoter.

[00320] In one embodiment, the encoded siRNA molecule may be located downstream of a promoter in an expression vector such as, but not limited to, CMV, U6, H1, CBA, CAG, or a CBA promoter with an intron such as SV40 or others known in the art. Further, the encoded siRNA molecule may also be located upstream of the polyadenylation sequence in an expression vector. As a non-limiting example, the encoded siRNA molecule may be located within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 or more than 30 nucleotides downstream from the promoter and/or upstream of the polyadenylation sequence in an expression vector. As another non-limiting example, the encoded siRNA molecule may be located within 1-5, 1-10, 1-15, 1-20, 1-25, 1-30, 5-10, 5-15, 5-20, 5-25, 5-30, 10-15, 10-20, 10-25, 10-30, 15-20, 15-25, 15-30, 20-25, 20-30 or 25-30 nucleotides downstream

from the promoter and/or upstream of the polyadenylation sequence in an expression vector. As a non-limiting example, the encoded siRNA molecule may be located within the first 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25% or more than 25% of the nucleotides downstream from the promoter and/or upstream of the polyadenylation sequence in an expression vector. As another non-limiting example, the encoded siRNA molecule may be located with the first 1-5%, 1-10%, 1-15%, 1-20%, 1-25%, 5-10%, 5-15%, 5-20%, 5-25%, 10-15%, 10-20%, 10-25%, 15-20%, 15-25%, or 20-25% downstream from the promoter and/or upstream of the polyadenylation sequence in an expression vector.

Viral Genome Component: Filler Sequence

[00321] In one embodiment, the viral genome comprises one or more filler sequences.

[00322] In one embodiment, the viral genome comprises one or more filler sequences in order to have the length of the viral genome be the optimal size for packaging. As a non-limiting example, the viral genome comprises at least one filler sequence in order to have the length of the viral genome be about 2.3 kb. As a non-limiting example, the viral genome comprises at least one filler sequence in order to have the length of the viral genome be about 4.6 kb.

[00323] In one embodiment, the viral genome comprises one or more filler sequences in order to reduce the likelihood that a hairpin structure of the vector genome (e.g., a modulatory polynucleotide described herein) may be read as an inverted terminal repeat (ITR) during expression and/or packaging. As a non-limiting example, the viral genome comprises at least one filler sequence in order to have the length of the viral genome be about 2.3 kb. As a non-limiting example, the viral genome comprises at least one filler sequence in order to have the length of the viral genome be about 4.6 kb

[00324] In one embodiment, the viral genome is a single stranded (ss) viral genome and comprises one or more filler sequences which have a length about between 0.1 kb - 3.8 kb, such as, but not limited to, 0.1 kb, 0.2 kb, 0.3 kb, 0.4 kb, 0.5 kb, 0.6 kb, 0.7 kb, 0.8 kb, 0.9 kb, 1 kb, 1.1 kb, 1.2 kb, 1.3 kb, 1.4 kb, 1.5 kb, 1.6 kb, 1.7 kb, 1.8 kb, 1.9 kb, 2 kb, 2.1 kb, 2.2 kb, 2.3 kb, 2.4 kb, 2.5 kb, 2.6 kb, 2.7 kb, 2.8 kb, 2.9 kb, 3 kb, 3.1 kb, 3.2 kb, 3.3 kb, 3.4 kb, 3.5 kb, 3.6 kb, 3.7 kb, or 3.8 kb. As a non-limiting example, the total length filler sequence in the vector genome is 3.1 kb. As a non-limiting example, the total length filler sequence in the vector genome is 2.7 kb. As a non-limiting example, the total length filler sequence in the vector genome is 0.8 kb. As a non-limiting example, the total length filler sequence in the vector genome is 0.4 kb. As a non-limiting example, the length of each filler sequence in the vector

genome is 0.8 kb. As a non-limiting example, the length of each filler sequence in the vector genome is 0.4 kb.

[00325] In one embodiment, the viral genome is a self-complementary (sc) viral genome and comprises one or more filler sequences which have a length about between 0.1 kb – 1.5 kb, such as, but not limited to, 0.1 kb, 0.2 kb, 0.3 kb, 0.4 kb, 0.5 kb, 0.6 kb, 0.7 kb, 0.8 kb, 0.9 kb, 1 kb, 1.1 kb, 1.2 kb, 1.3 kb, 1.4 kb, or 1.5 kb. As a non-limiting example, the total length filler sequence in the vector genome is 0.8 kb. As a non-limiting example, the total length filler sequence in the vector genome is 0.4 kb. As a non-limiting example, the length of each filler sequence in the vector genome is 0.8 kb. As a non-limiting example, the length of each filler sequence in the vector genome is 0.4 kb

[00326] In one embodiment, the viral genome comprises any portion of a filler sequence. The viral genome may comprise 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% of a filler sequence.

[00327] In one embodiment, the viral genome is a single stranded (ss) viral genome and comprises one or more filler sequences in order to have the length of the viral genome be about 4.6 kb. As a non-limiting example, the viral genome comprises at least one filler sequence and the filler sequence is located 3’ to the 5’ ITR sequence. As a non-limiting example, the viral genome comprises at least one filler sequence and the filler sequence is located 5’ to a promoter sequence. As a non-limiting example, the viral genome comprises at least one filler sequence and the filler sequence is located 3’ to the polyadenylation signal sequence. As a non-limiting example, the viral genome comprises at least one filler sequence and the filler sequence is located 5’ to the 3’ ITR sequence. As a non-limiting example, the viral genome comprises at least one filler sequence, and the filler sequence is located between two intron sequences. As a non-limiting example, the viral genome comprises at least one filler sequence, and the filler sequence is located within an intron sequence. As a non-limiting example, the viral genome comprises two filler sequences, and the first filler sequence is located 3’ to the 5’ ITR sequence and the second filler sequence is located 3’ to the polyadenylation signal sequence. As a non-limiting example, the viral genome comprises two filler sequences, and the first filler sequence is located 5’ to a promoter sequence and the second filler sequence is located 3’ to the polyadenylation signal sequence. As a non-limiting example, the viral genome comprises two filler sequences, and the first filler sequence is located 3’ to the 5’ ITR sequence and the second filler sequence is located 5’ to the 5’ ITR sequence.

[00328] In one embodiment, the viral genome is a self-complementary (sc) viral genome and comprises one or more filler sequences in order to have the length of the viral genome be about 2.3 kb. As a non-limiting example, the viral genome comprises at least one filler sequence and the filler sequence is located 3' to the 5' ITR sequence. As a non-limiting example, the viral genome comprises at least one filler sequence and the filler sequence is located 5' to a promoter sequence. As a non-limiting example, the viral genome comprises at least one filler sequence and the filler sequence is located 3' to the polyadenylation signal sequence. As a non-limiting example, the viral genome comprises at least one filler sequence and the filler sequence is located 5' to the 3' ITR sequence. As a non-limiting example, the viral genome comprises at least one filler sequence, and the filler sequence is located between two intron sequences. As a non-limiting example, the viral genome comprises at least one filler sequence, and the filler sequence is located within an intron sequence. As a non-limiting example, the viral genome comprises two filler sequences, and the first filler sequence is located 3' to the 5' ITR sequence and the second filler sequence is located 3' to the polyadenylation signal sequence. As a non-limiting example, the viral genome comprises two filler sequences, and the first filler sequence is located 5' to a promoter sequence and the second filler sequence is located 3' to the polyadenylation signal sequence. As a non-limiting example, the viral genome comprises two filler sequences, and the first filler sequence is located 3' to the 5' ITR sequence and the second filler sequence is located 5' to the 5' ITR sequence.

[00329] In one embodiment, the viral genome may comprise one or more filler sequences between one of more regions of the viral genome. In one embodiment, the filler region may be located before a region such as, but not limited to, a payload region, an inverted terminal repeat (ITR), a promoter region, an intron region, an enhancer region, a polyadenylation signal sequence region, a multiple cloning site (MCS) region, and/or an exon region. In one embodiment, the filler region may be located after a region such as, but not limited to, a payload region, an inverted terminal repeat (ITR), a promoter region, an intron region, an enhancer region, a polyadenylation signal sequence region, a multiple cloning site (MCS) region, and/or an exon region. In one embodiment, the filler region may be located before and after a region such as, but not limited to, a payload region, an inverted terminal repeat (ITR), a promoter region, an intron region, an enhancer region, a polyadenylation signal sequence region, a multiple cloning site (MCS) region, and/or an exon region.

[00330] In one embodiment, the viral genome may comprise one or more filler sequences which bifurcates at least one region of the viral genome. The bifurcated region of the viral genome may

comprise 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% of the of the region to the 5' of the filler sequence region. As a non-limiting example, the filler sequence may bifurcate at least one region so that 10% of the region is located 5' to the filler sequence and 90% of the region is located 3' to the filler sequence. As a non-limiting example, the filler sequence may bifurcate at least one region so that 20% of the region is located 5' to the filler sequence and 80% of the region is located 3' to the filler sequence. As a non-limiting example, the filler sequence may bifurcate at least one region so that 30% of the region is located 5' to the filler sequence and 70% of the region is located 3' to the filler sequence. As a non-limiting example, the filler sequence may bifurcate at least one region so that 40% of the region is located 5' to the filler sequence and 60% of the region is located 3' to the filler sequence. As a non-limiting example, the filler sequence may bifurcate at least one region so that 50% of the region is located 5' to the filler sequence and 50% of the region is located 3' to the filler sequence. As a non-limiting example, the filler sequence may bifurcate at least one region so that 60% of the region is located 5' to the filler sequence and 40% of the region is located 3' to the filler sequence. As a non-limiting example, the filler sequence may bifurcate at least one region so that 70% of the region is located 5' to the filler sequence and 30% of the region is located 3' to the filler sequence. As a non-limiting example, the filler sequence may bifurcate at least one region so that 80% of the region is located 5' to the filler sequence and 20% of the region is located 3' to the filler sequence. As a non-limiting example, the filler sequence may bifurcate at least one region so that 90% of the region is located 5' to the filler sequence and 10% of the region is located 3' to the filler sequence.

[00331] In one embodiment, the viral genome comprises a filler sequence after the 5' ITR.

[00332] In one embodiment, the viral genome comprises a filler sequence after the promoter region. In one embodiment, the viral genome comprises a filler sequence after the payload region. In one embodiment, the viral genome comprises a filler sequence after the intron region. In one embodiment, the viral genome comprises a filler sequence after the enhancer region. In one embodiment, the viral genome comprises a filler sequence after the polyadenylation signal sequence region. In one embodiment, the viral genome comprises a filler sequence after the MCS region. In one embodiment, the viral genome comprises a filler sequence after the exon region.

[00333] In one embodiment, the viral genome comprises a filler sequence before the promoter region. In one embodiment, the viral genome comprises a filler sequence before the payload

region. In one embodiment, the viral genome comprises a filler sequence before the intron region. In one embodiment, the viral genome comprises a filler sequence before the enhancer region. In one embodiment, the viral genome comprises a filler sequence before the polyadenylation signal sequence region. In one embodiment, the viral genome comprises a filler sequence before the MCS region. In one embodiment, the viral genome comprises a filler sequence before the exon region.

[00334] In one embodiment, the viral genome comprises a filler sequence before the 3' ITR.

[00335] In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the 5' ITR and the promoter region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the 5' ITR and the payload region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the 5' ITR and the intron region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the 5' ITR and the enhancer region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the 5' ITR and the polyadenylation signal sequence region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the 5' ITR and the MCS region.

[00336] In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the 5' ITR and the exon region.

[00337] In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the promoter region and the payload region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the promoter region and the intron region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the promoter region and the enhancer region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the promoter region and the polyadenylation signal sequence region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the promoter region and the MCS region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the promoter region and the exon region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the promoter region and the 3' ITR.

[00338] In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the payload region and the intron region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the payload region and the

enhancer region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the payload region and the polyadenylation signal sequence region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the payload region and the MCS region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the payload region and the exon region.

[00339] In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the payload region and the 3' ITR.

[00340] In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the intron region and the enhancer region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the intron region and the polyadenylation signal sequence region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the intron region and the MCS region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the intron region and the exon region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the intron region and the 3' ITR. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the enhancer region and the polyadenylation signal sequence region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the enhancer region and the MCS region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the enhancer region and the exon region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the enhancer region and the 3' ITR.

[00341] In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the polyadenylation signal sequence region and the MCS region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the polyadenylation signal sequence region and the exon region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the polyadenylation signal sequence region and the 3' ITR.

[00342] In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the MCS region and the exon region. In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the MCS region and the 3' ITR.

[00343] In one embodiment, a filler sequence may be located between two regions, such as, but not limited to, the exon region and the 3' ITR.

[00344] In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the promoter region and payload region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the promoter region and intron region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the promoter region and enhancer region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the promoter region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the promoter region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the promoter region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the promoter region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the payload region and intron region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the payload region and enhancer region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the payload region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the payload region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the payload region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler

sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the payload region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the intron region and enhancer region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the intron region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the intron region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the intron region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the intron region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the enhancer region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the enhancer region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the enhancer region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence

may be located between the polyadenylation signal sequence region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the MCS region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the MCS region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and promoter region, and the second filler sequence may be located between the exon region and 3' ITR.

[00345] In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the promoter region and payload region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the promoter region and intron region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the promoter region and enhancer region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the promoter region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the promoter region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the promoter region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the promoter region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the payload region and intron region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the payload region and enhancer region. In one embodiment, a viral genome may

comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the payload region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the payload region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the payload region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the intron region and enhancer region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the intron region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the intron region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the intron region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the intron region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the enhancer region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the enhancer region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located

between the enhancer region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the MCS region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the MCS region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and payload region, and the second filler sequence may be located between the exon region and 3' ITR.

[00346] In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the promoter region and payload region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the promoter region and intron region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the promoter region and enhancer region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the promoter region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the promoter region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the promoter region and exon region. In one

embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the promoter region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the payload region and intron region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the payload region and enhancer region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the payload region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the payload region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the payload region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the payload region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the intron region and enhancer region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the intron region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the intron region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the intron region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the intron region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located

between the enhancer region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the enhancer region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the enhancer region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the enhancer region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the MCS region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the MCS region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and intron region, and the second filler sequence may be located between the exon region and 3' ITR.

[00347] In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the promoter region and payload region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the promoter region and intron region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the promoter region and enhancer region. In

one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the promoter region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the promoter region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the promoter region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the promoter region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the payload region and intron region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the payload region and enhancer region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the payload region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the payload region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the payload region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the payload region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the intron region and enhancer region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the intron region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler

sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the intron region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the intron region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the intron region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the enhancer region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the enhancer region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the enhancer region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the MCS region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the MCS region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may

be located between the 5' ITR and enhancer region, and the second filler sequence may be located between the exon region and 3' ITR.

[00348] In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the promoter region and payload region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the promoter region and intron region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the promoter region and enhancer region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the promoter region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the promoter region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the promoter region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the promoter region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the payload region and intron region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the payload region and enhancer region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the payload region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and

the second filler sequence may be located between the payload region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the payload region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the payload region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the intron region and enhancer region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the intron region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the intron region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the intron region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the intron region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the enhancer region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the enhancer region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the enhancer region and 3' ITR. In one embodiment, a viral genome may

comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the MCS region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the MCS region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and polyadenylation signal sequence region, and the second filler sequence may be located between the exon region and 3' ITR.

[00349] In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the promoter region and payload region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the promoter region and intron region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the promoter region and enhancer region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the promoter region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the promoter region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second

filler sequence may be located between the promoter region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the promoter region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the payload region and intron region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the payload region and enhancer region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the payload region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the payload region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the payload region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the payload region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the intron region and enhancer region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the intron region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the intron region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the intron region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the intron region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may

be located between the 5' ITR and MCS region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the enhancer region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the enhancer region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the enhancer region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the MCS region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the MCS region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and MCS region, and the second filler sequence may be located between the exon region and 3' ITR.

[00350] In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the promoter region and payload region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the promoter region and intron region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the

second filler sequence may be located between the promoter region and enhancer region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the promoter region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the promoter region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the promoter region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the promoter region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the payload region and intron region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the payload region and enhancer region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the payload region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the payload region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the payload region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the payload region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the intron region and enhancer region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the intron region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence

may be located between the 5' ITR and exon region, and the second filler sequence may be located between the intron region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the intron region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the intron region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the enhancer region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the enhancer region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the enhancer region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the MCS region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the MCS region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the 5' ITR and exon region, and the second filler sequence may be located between the exon region and 3' ITR.

[00351] In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the payload region and intron region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the payload region and enhancer region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the payload region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the payload region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the payload region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the payload region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the intron region and enhancer region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the intron region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the intron region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the intron region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the intron region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the enhancer region and polyadenylation signal

sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the enhancer region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the enhancer region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the enhancer region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the MCS region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the MCS region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and payload region, and the second filler sequence may be located between the exon region and 3' ITR.

[00352] In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the payload region and intron region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the payload region and enhancer region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the payload region and

polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the payload region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the payload region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the payload region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the intron region and enhancer region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the intron region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the intron region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the intron region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the intron region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the enhancer region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the enhancer region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the enhancer region and 3' ITR. In one

embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the MCS region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the MCS region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and intron region, and the second filler sequence may be located between the exon region and 3' ITR.

[00353] In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the payload region and intron region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the payload region and enhancer region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the payload region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the payload region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the payload region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located

between the payload region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the intron region and enhancer region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the intron region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the intron region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the intron region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the intron region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the enhancer region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the enhancer region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the enhancer region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler

sequence may be located between the polyadenylation signal sequence region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the MCS region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the MCS region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and enhancer region, and the second filler sequence may be located between the exon region and 3' ITR.

[00354] In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the payload region and intron region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the payload region and enhancer region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the payload region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the payload region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the payload region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the payload region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the intron region and enhancer region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between

the intron region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the intron region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the intron region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the intron region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the enhancer region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the enhancer region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the enhancer region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and

polyadenylation signal sequence region, and the second filler sequence may be located between the MCS region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the MCS region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and polyadenylation signal sequence region, and the second filler sequence may be located between the exon region and 3' ITR.

[00355] In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the payload region and intron region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the payload region and enhancer region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the payload region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the payload region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the payload region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the intron region and enhancer region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the intron region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the intron region and MCS region. In one embodiment, a viral genome may

comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the intron region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the intron region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the enhancer region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the enhancer region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the enhancer region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the MCS region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the MCS region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and exon region, and the second filler sequence may be located between the exon region and 3' ITR.

[00356] In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the payload region and intron region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the payload region and enhancer region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the payload region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the promoter region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the payload region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the payload region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the intron region and enhancer region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the intron region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the intron region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the intron region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the intron region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In one

embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the enhancer region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the enhancer region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the MCS region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the MCS region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and MCS region, and the second filler sequence may be located between the exon region and 3' ITR.

[00357] In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the payload region and intron region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the payload region and enhancer region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the payload region and polyadenylation signal

sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the payload region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the payload region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the payload region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the intron region and enhancer region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the intron region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the intron region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the intron region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the intron region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the enhancer region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the enhancer region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the enhancer region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the

promoter region and 3'ITR, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the MCS region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the MCS region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the promoter region and 3'ITR, and the second filler sequence may be located between the exon region and 3' ITR.

[00358] In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and intron region, and the second filler sequence may be located between the intron region and enhancer region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and intron region, and the second filler sequence may be located between the intron region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and intron region, and the second filler sequence may be located between the intron region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and intron region, and the second filler sequence may be located between the intron region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and intron region, and the second filler sequence may be located between the intron region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and intron region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and intron

region, and the second filler sequence may be located between the enhancer region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and intron region, and the second filler sequence may be located between the enhancer region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and intron region, and the second filler sequence may be located between the enhancer region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and intron region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and intron region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and intron region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and intron region, and the second filler sequence may be located between the MCS region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and intron region, and the second filler sequence may be located between the MCS region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and intron region, and the second filler sequence may be located between the exon region and 3' ITR.

[00359] In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and enhancer region, and the second filler sequence may be located between the intron region and enhancer region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and enhancer region, and the second filler sequence may be located between the intron region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and enhancer region, and the second filler sequence may be located between the intron region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and enhancer

region, and the second filler sequence may be located between the intron region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and enhancer region, and the second filler sequence may be located between the intron region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and enhancer region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and enhancer region, and the second filler sequence may be located between the enhancer region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and enhancer region, and the second filler sequence may be located between the enhancer region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and enhancer region, and the second filler sequence may be located between the enhancer region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and enhancer region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and enhancer region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and enhancer region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and enhancer region, and the second filler sequence may be located between the MCS region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and enhancer region, and the second filler sequence may be located between the MCS region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and enhancer region, and the second filler sequence may be located between the exon region and 3' ITR.

[00360] In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and polyadenylation signal sequence region, and the second filler sequence may be located between the intron region and enhancer region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and polyadenylation signal sequence region, and the second filler sequence may be located between the intron region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and polyadenylation signal sequence region, and the second filler sequence may be located between the intron region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and polyadenylation signal sequence region, and the second filler sequence may be located between the intron region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and polyadenylation signal sequence region, and the second filler sequence may be located between the intron region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and polyadenylation signal sequence region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and polyadenylation signal sequence region, and the second filler sequence may be located between the enhancer region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and polyadenylation signal sequence region, and the second filler sequence may be located between the enhancer region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and polyadenylation signal sequence region, and the second filler sequence may be located between the enhancer region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and polyadenylation signal sequence region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and polyadenylation signal sequence region, and the second

filler sequence may be located between the polyadenylation signal sequence region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and polyadenylation signal sequence region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and polyadenylation signal sequence region, and the second filler sequence may be located between the MCS region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and polyadenylation signal sequence region, and the second filler sequence may be located between the MCS region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and polyadenylation signal sequence region, and the second filler sequence may be located between the exon region and 3' ITR.

[00361] In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and MCS region, and the second filler sequence may be located between the intron region and enhancer region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and MCS region, and the second filler sequence may be located between the intron region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and MCS region, and the second filler sequence may be located between the intron region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and MCS region, and the second filler sequence may be located between the intron region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and MCS region, and the second filler sequence may be located between the intron region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and MCS region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and MCS region, and the second filler sequence may be located between the enhancer region and MCS region. In one

embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and MCS region, and the second filler sequence may be located between the enhancer region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and MCS region, and the second filler sequence may be located between the enhancer region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and MCS region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and MCS region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and MCS region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and MCS region, and the second filler sequence may be located between the MCS region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and MCS region, and the second filler sequence may be located between the MCS region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and MCS region, and the second filler sequence may be located between the exon region and 3' ITR.

[00362] In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and exon region, and the second filler sequence may be located between the intron region and enhancer region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and exon region, and the second filler sequence may be located between the intron region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and exon region, and the second filler sequence may be located between the intron region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and exon region, and the second filler sequence may be located between the intron region and exon region. In one embodiment, a

viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and exon region, and the second filler sequence may be located between the intron region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and exon region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and exon region, and the second filler sequence may be located between the enhancer region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and exon region, and the second filler sequence may be located between the enhancer region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and exon region, and the second filler sequence may be located between the enhancer region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and exon region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and exon region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and exon region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and exon region, and the second filler sequence may be located between the MCS region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and exon region, and the second filler sequence may be located between the MCS region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and exon region, and the second filler sequence may be located between the exon region and 3' ITR.

[00363] In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and 3' ITR region, and the second filler sequence may be located between the intron region and enhancer region. In one embodiment, a

viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and 3' ITR region, and the second filler sequence may be located between the intron region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and 3' ITR region, and the second filler sequence may be located between the intron region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and 3' ITR region, and the second filler sequence may be located between the intron region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and 3' ITR region, and the second filler sequence may be located between the intron region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and 3' ITR region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and 3' ITR region, and the second filler sequence may be located between the enhancer region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and 3' ITR region, and the second filler sequence may be located between the enhancer region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and 3' ITR region, and the second filler sequence may be located between the enhancer region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and 3' ITR region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and 3' ITR region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and 3' ITR region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and 3' ITR region, and the second filler sequence may be located between the MCS region and exon region.

In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and 3' ITR region, and the second filler sequence may be located between the MCS region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the payload region and 3' ITR region, and the second filler sequence may be located between the exon region and 3' ITR.

[00364] In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and enhancer region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and enhancer region, and the second filler sequence may be located between the enhancer region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and enhancer region, and the second filler sequence may be located between the enhancer region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and enhancer region, and the second filler sequence may be located between the enhancer region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and enhancer region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and enhancer region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and enhancer region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and enhancer region, and the second filler sequence may be located between the MCS region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and enhancer region, and the second filler sequence may be located between the MCS region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may

be located between the intron region and enhancer region, and the second filler sequence may be located between the exon region and 3' ITR.

[00365] In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and polyadenylation signal sequence region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and polyadenylation signal sequence region, and the second filler sequence may be located between the enhancer region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and polyadenylation signal sequence region, and the second filler sequence may be located between the enhancer region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and polyadenylation signal sequence region, and the second filler sequence may be located between the enhancer region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and polyadenylation signal sequence region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and polyadenylation signal sequence region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and polyadenylation signal sequence region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and polyadenylation signal sequence region, and the second filler sequence may be located between the MCS region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and polyadenylation signal sequence region, and the second filler sequence may be located between the MCS region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and polyadenylation signal sequence region, and the second filler sequence may be located between the exon region and 3' ITR.

[00366] In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and MCS region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and MCS region, and the second filler sequence may be located between the enhancer region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and MCS region, and the second filler sequence may be located between the enhancer region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and MCS region, and the second filler sequence may be located between the enhancer region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and MCS region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and MCS region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and MCS region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and MCS region, and the second filler sequence may be located between the MCS region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and MCS region, and the second filler sequences, the first filler sequence may be located between the intron region and MCS region, and the second filler sequence may be located between the MCS region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and MCS region, and the second filler sequence may be located between the exon region and 3' ITR.

[00367] In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and exon region, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and exon region, and the second filler

sequence may be located between the enhancer region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and exon region, and the second filler sequence may be located between the enhancer region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and exon region, and the second filler sequence may be located between the enhancer region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and exon region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and exon region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and exon region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and exon region, and the second filler sequence may be located between the MCS region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and exon region, and the second filler sequence may be located between the MCS region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and exon region, and the second filler sequence may be located between the exon region and 3' ITR.

[00368] In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and 3'ITR, and the second filler sequence may be located between the enhancer region and polyadenylation signal sequence region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and 3'ITR, and the second filler sequence may be located between the enhancer region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and 3'ITR, and the second filler sequence may be located between the enhancer region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and 3'ITR, and the second filler sequence

may be located between the enhancer region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and 3'ITR, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and 3'ITR, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and 3'ITR, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and 3'ITR, and the second filler sequence may be located between the MCS region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and 3'ITR, and the second filler sequence may be located between the MCS region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the intron region and 3'ITR, and the second filler sequence may be located between the exon region and 3' ITR.

[00369] In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and polyadenylation signal sequence region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and polyadenylation signal sequence region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and polyadenylation signal sequence region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and polyadenylation signal sequence region, and the second filler sequence may be located between the MCS region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and polyadenylation signal sequence region, and the second filler sequence may be located between the MCS region and 3' ITR. In one embodiment, a viral genome may comprise

two filler sequences, the first filler sequence may be located between the enhancer region and polyadenylation signal sequence region, and the second filler sequence may be located between the exon region and 3' ITR.

[00370] In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and MCS region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and MCS region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and MCS region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and MCS region, and the second filler sequence may be located between the MCS region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and MCS region, and the second filler sequence may be located between the MCS region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and MCS region, and the second filler sequence may be located between the exon region and 3' ITR.

[00371] In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and exon region, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and exon region, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and exon region, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and exon region, and the second filler sequence may be located between the MCS region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and exon region,

and the second filler sequence may be located between the MCS region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and exon region, and the second filler sequence may be located between the exon region and 3' ITR.

[00372] In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and 3' ITR, and the second filler sequence may be located between the polyadenylation signal sequence region and MCS region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and 3' ITR, and the second filler sequence may be located between the polyadenylation signal sequence region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and 3' ITR, and the second filler sequence may be located between the enhancer region and 3' ITR, and the second filler sequence may be located between the polyadenylation signal sequence region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and 3' ITR, and the second filler sequence may be located between the MCS region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and 3' ITR, and the second filler sequence may be located between the MCS region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the enhancer region and 3' ITR, and the second filler sequence may be located between the exon region and 3' ITR.

[00373] In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the polyadenylation signal sequence region and MCS region, and the second filler sequence may be located between the MCS region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the polyadenylation signal sequence region and MCS region, and the second filler sequence may be located between the MCS region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the polyadenylation signal sequence region and MCS region, and the second filler sequence may be located between the exon region and 3' ITR.

[00374] In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the polyadenylation signal sequence region and exon region, and the second filler sequence may be located between the MCS region and exon region. In one

embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the polyadenylation signal sequence region and exon region, and the second filler sequence may be located between the MCS region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the polyadenylation signal sequence region and exon region, and the second filler sequence may be located between the exon region and 3' ITR.

[00375] In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the polyadenylation signal sequence region and 3' ITR, and the second filler sequence may be located between the MCS region and exon region. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the polyadenylation signal sequence region and 3' ITR, and the second filler sequence may be located between the MCS region and 3' ITR. In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the polyadenylation signal sequence region and 3' ITR, and the second filler sequence may be located between the exon region and 3' ITR.

[00376] In one embodiment, a viral genome may comprise two filler sequences, the first filler sequence may be located between the MCS region and exon region, and the second filler sequence may be located between the exon region and 3' ITR.

Payloads of the Invention

[00377] The AAV particles of the present disclosure comprise at least one payload region. As used herein, "payload" or "payload region" refers to one or more polynucleotides or polynucleotide regions encoded by or within a viral genome or an expression product of such polynucleotide or polynucleotide region, e.g., a transgene, a polynucleotide encoding a polypeptide or multi-polypeptide or a modulatory nucleic acid or regulatory nucleic acid. Payloads of the present invention typically encode modulatory polynucleotides or fragments or variants thereof.

[00378] The payload region may be constructed in such a way as to reflect a region similar to or mirroring the natural organization of an mRNA.

[00379] The payload region may comprise a combination of coding and non-coding nucleic acid sequences.

[00380] In some embodiments, the AAV payload region may encode a coding or non-coding RNA.

[00381] In one embodiment, the AAV particle comprises a viral genome with a payload region comprising nucleic acid sequences encoding a siRNA, miRNA or other RNAi agent. In such an embodiment, a viral genome encoding more than one polypeptide may be replicated and packaged into a viral particle. A target cell transduced with a viral particle may express the encoded siRNA, miRNA or other RNAi agent inside a single cell.

Modulatory Polynucleotides

[00382] In one embodiment, modulatory polynucleotides, e.g., RNA or DNA molecules, may be used to treat at least one neurodegenerative disease. As used herein, a "modulatory polynucleotide" is any nucleic acid sequence(s) which functions to modulate (either increase or decrease) the level or amount of a target gene, e.g., mRNA or protein levels.

[00383] In one embodiment, the modulatory polynucleotides may comprise at least one nucleic acid sequence encoding at least one siRNA molecule. The nucleic acids may, independently if there is more than one, encode 1, 2, 3, 4, 5, 6, 7, 8, 9, or more than 9 siRNA molecules.

[00384] In one embodiment, the molecular scaffold may be located downstream of a CMV promoter, fragment or variant thereof.

[00385] In one embodiment, the molecular scaffold may be located downstream of a CBA promoter, fragment or variant thereof.

[00386] In one embodiment, the molecular scaffold may be a natural pri-miRNA scaffold located downstream of a CMV promoter. As a non-limiting example, the natural pri-miRNA scaffold is derived from the human miR155 scaffold.

[00387] In one embodiment, the molecular scaffold may be a natural pri-miRNA scaffold located downstream of a CBA promoter.

[00388] In one embodiment, the selection of a molecular scaffold and modulatory polynucleotide is determined by a method of comparing modulatory polynucleotides in pri-miRNA (see e.g., the method described by Miniarikova et al. Design, Characterization, and Lead Selection of Therapeutic miRNAs Targeting Huntingtin for Development of Gene Therapy for Huntington's Disease. Molecular Therapy-Nucleic Acids (2016) 5, e297 and International Publication No. WO2016102664; the contents of each of which are herein incorporated by reference in their entireties). To evaluate the activities of the modulatory polynucleotides, the molecular scaffold used which may be used is a human pri-miRNA scaffold (e.g., miR155 scaffold) and the promoter may be CMV. The activity may be determined in vitro using HEK293T cells and a reporter (e.g., Luciferase).

[00389] In order to evaluate the optimal molecular scaffold for the modulatory polynucleotide, the modulatory polynucleotide is used in pri-miRNA scaffolds with a CAG promoter. The constructs are co-transfected with a reporter (e.g., luciferase reporter) at 50 ng. Constructs with greater than 80% knockdown at 50 ng co-transfection are considered efficient. In one aspect, the constructs with strong guide-strand activity are preferred. The molecular scaffolds can be processed in HEK293T cells by NGS to determine guide-passenger ratios, and processing variability.

[00390] In one embodiment, the disease to be treated is HD and the modulatory polynucleotide may, but it not limited to, targeting exon 1, CAG repeats, SNP rs362331 in exon 50 and/or SNP rs362307 in exon 67. For exon 1 targeting, the modulatory polynucleotide is determined to be efficient at HTT knockdown if the knockdown is 80% or greater. For CAG targeting, the modulatory polynucleotide is determined to be efficient at HTT knockdown if the knockdown is at least 60%. For SNP targeting, the modulatory polynucleotide is determined to be efficient at HTT knockdown if the knockdown is at least 60%. For allele selectivity for CAG repeats or SNP targeting the modulatory polynucleotides may comprise at least 1 substitution in order to improve allele selectivity. As a non-limiting example, substitution may be a G or C replaced with a T or corresponding U and A or T/U replaced by a C.

[00391] To evaluate the molecular scaffolds and modulatory polynucleotides in vivo the molecular scaffolds comprising the modulatory polynucleotides are packaged in AAV (e.g., the serotype may be AAV5 (see e.g., the method and constructs described in WO2015060722, the contents of which are herein incorporated by reference in their entirety)) and administered to an in vivo model (e.g., For HD, a Hu128/21 HD mouse may be used) and the guide-passenger ratios, 5' and 3' end processing, reversal of guide and passenger strands, and knockdown can be determined in different areas of the model.

[00392] In one embodiment, the selection of a molecular scaffold and modulatory polynucleotide is determined by a method of comparing modulatory polynucleotides in natural pri-miRNA and synthetic pri-miRNA. The modulatory polynucleotide may, but it not limited to, targeting an exon other than exon 1. To evaluate the activities of the modulatory polynucleotides, the molecular scaffold is used with a CBA promoter. In one aspect, the activity may be determined in vitro using HEK293T cells, HeLa cell and a reporter (e.g., Luciferase) and knockdown efficient modulatory polynucleotides showed the gene of interest knockdown of at least 80% in the cell tested. Additionally, the modulatory polynucleotides which are considered most efficient showed low to no significant passenger strand (p-strand) activity. In another

aspect, the endogenous gene of interest knockdown efficacy is evaluated by transfection in vitro using HEK293T cells, HeLa cell and a reporter. Efficient modulatory polynucleotides show greater than 50% endogenous gene of interest knockdown. In yet another aspect, the endogenous gene of interest knockdown efficacy is evaluated in different cell types (e.g., HEK293, HeLa, primary astrocytes, U251 astrocytes, SH-SY5Y neuron cells and fibroblasts from subjects with the disease to be treated) by infection (e.g., AAV2). Efficient modulatory polynucleotides show greater than 60% endogenous gene of interest knockdown.

[00393] To evaluate the molecular scaffolds and modulatory polynucleotides in vivo the molecular scaffolds comprising the modulatory polynucleotides are packaged in AAV and administered to an in vivo model (e.g., For treating HD, a YAC128 HD mouse model may be used) and the guide-passenger ratios, 5' and 3' end processing, ratio of guide to passenger strands, and knockdown can be determined in different areas of the model (e.g., tissue regions). The molecular scaffolds can be processed from in vivo samples by NGS to determine guide-passenger ratios, and processing variability.

[00394] In one embodiment, the modulatory polynucleotide is designed using at least one of the following properties: loop variant, seed mismatch/bulge/wobble variant, stem mismatch, loop variant and vassal stem mismatch variant, seed mismatch and basal stem mismatch variant, stem mismatch and basal stem mismatch variant, seed wobble and basal stem wobble variant, or a stem sequence variant.

siRNA Molecules

[00395] The present invention relates to RNA interference (RNAi) induced inhibition of gene expression for treating neurodegenerative disorders. Provided herein are siRNA duplexes or encoded dsRNA that target the gene of interest (referred to herein collectively as "siRNA molecules"). Such siRNA duplexes or encoded dsRNA can reduce or silence gene expression in cells, such as but not limited to, medium spiny neurons, cortical neurons and/or astrocytes.

[00396] RNAi (also known as post-transcriptional gene silencing (PTGS), quelling, or co-suppression) is a post-transcriptional gene silencing process in which RNA molecules, in a sequence specific manner, inhibit gene expression, typically by causing the destruction of specific mRNA molecules. The active components of RNAi are short/small double stranded RNAs (dsRNAs), called small interfering RNAs (siRNAs), that typically contain 15-30 nucleotides (e.g., 19 to 25, 19 to 24 or 19-21 nucleotides) and 2 nucleotide 3' overhangs and that match the nucleic acid sequence of the target gene. These short RNA species may be naturally

produced in vivo by Dicer-mediated cleavage of larger dsRNAs and they are functional in mammalian cells.

[00397] Naturally expressed small RNA molecules, named microRNAs (miRNAs), elicit gene silencing by regulating the expression of mRNAs. The miRNAs containing RNA Induced Silencing Complex (RISC) targets mRNAs presenting a perfect sequence complementarity with nucleotides 2-7 in the 5' region of the miRNA which is called the seed region, and other base pairs with its 3' region. miRNA mediated down regulation of gene expression may be caused by cleavage of the target mRNAs, translational inhibition of the target mRNAs, or mRNA decay. miRNA targeting sequences are usually located in the 3'-UTR of the target mRNAs. A single miRNA may target more than 100 transcripts from various genes, and one mRNA may be targeted by different miRNAs.

[00398] siRNA duplexes or dsRNA targeting a specific mRNA may be designed and synthesized in vitro and introduced into cells for activating RNAi processes. Elbashir et al. demonstrated that 21-nucleotide siRNA duplexes (termed small interfering RNAs) were capable of effecting potent and specific gene knockdown without inducing immune response in mammalian cells (Elbashir SM et al., Nature, 2001, 411, 494-498). Since this initial report, post-transcriptional gene silencing by siRNAs quickly emerged as a powerful tool for genetic analysis in mammalian cells and has the potential to produce novel therapeutics.

[00399] RNAi molecules which were designed to target against a nucleic acid sequence that encodes poly-glutamine repeat proteins which cause poly-glutamine expansion diseases such as Huntington's Disease, are described in US Patent No. 9,169,483 and 9,181,544 and International Patent Publication No. WO2015179525, the content of each of which is herein incorporated by reference in their entirety. US Patent Nos. 9,169,483 and 9,181,544 and International Patent Publication No. WO2015179525 each provide isolated RNA duplexes comprising a first strand of RNA (e.g., 15 contiguous nucleotides) and second strand of RNA (e.g., complementary to at least 12 contiguous nucleotides of the first strand) where the RNA duplex is about 15 to 30 base pairs in length. The first strand of RNA and second strand of RNA may be operably linked by an RNA loop (~4 to 50 nucleotides) to form a hairpin structure which may be inserted into an expression cassette. Non-limiting examples of loop portions include SEQ ID NO: 9-14 of US Patent No. 9,169,483, the content of which is herein incorporated by reference in its entirety. Non-limiting examples of strands of RNA which may be used, either full sequence or part of the sequence, to form RNA duplexes include SEQ ID NO: 1-8 of US Patent No. 9,169,483 and SEQ ID NO: 1-11, 33-59, 208-210, 213-215 and 218-221 of US Patent No. 9,181,544, the contents of

each of which is herein incorporated by reference in its entirety. Non-limiting examples of RNAi molecules include SEQ ID NOs: 1-8 of US Patent No. 9,169,483, SEQ ID NOs: 1-11, 33-59, 208-210, 213-215 and 218-221 of US Patent No. 9,181,544 and SEQ ID NOs: 1, 6, 7, and 35-38 of International Patent Publication No. WO2015179525, the contents of each of which is herein incorporated by reference in their entirety.

[00400] In vitro synthetized siRNA molecules may be introduced into cells in order to activate RNAi. An exogenous siRNA duplex, when it is introduced into cells, similar to the endogenous dsRNAs, can be assembled to form the RNA Induced Silencing Complex (RISC), a multiunit complex that interacts with RNA sequences that are complementary to one of the two strands of the siRNA duplex (i.e., the antisense strand). During the process, the sense strand (or passenger strand) of the siRNA is lost from the complex, while the antisense strand (or guide strand) of the siRNA is matched with its complementary RNA. In particular, the targets of siRNA containing RISC complexes are mRNAs presenting a perfect sequence complementarity. Then, siRNA mediated gene silencing occurs by cleaving, releasing and degrading the target.

[00401] The siRNA duplex comprised of a sense strand homologous to the target mRNA and an antisense strand that is complementary to the target mRNA offers much more advantage in terms of efficiency for target RNA destruction compared to the use of the single strand (ss)-siRNAs (e.g. antisense strand RNA or antisense oligonucleotides). In many cases, it requires higher concentration of the ss-siRNA to achieve the effective gene silencing potency of the corresponding duplex.

[00402] Any of the foregoing molecules may be encoded by a viral genome.

Design and Sequences of siRNA duplexes targeting gene of interest

[00403] The present invention provides small interfering RNA (siRNA) duplexes (and modulatory polynucleotides encoding them) that target mRNA to interfere with gene expression and/or protein production.

[00404] The encoded siRNA duplex of the present invention contains an antisense strand and a sense strand hybridized together forming a duplex structure, wherein the antisense strand is complementary to the nucleic acid sequence of the targeted gene, and wherein the sense strand is homologous to the nucleic acid sequence of the targeted gene. In some aspects, the 5' end of the antisense strand has a 5' phosphate group and the 3' end of the sense strand contains a 3'hydroxyl group. In other aspects, there are none, one or 2 nucleotide overhangs at the 3'end of each strand.

[00405] Some guidelines for designing siRNAs have been proposed in the art. These guidelines generally recommend generating a 19-nucleotide duplexed region, symmetric 2-3 nucleotide 3'overhangs, 5'- phosphate and 3'- hydroxyl groups targeting a region in the gene to be silenced. Other rules that may govern siRNA sequence preference include, but are not limited to, (i) A/U at the 5′ end of the antisense strand; (ii) G/C at the 5′ end of the sense strand; (iii) at least five A/U residues in the 5′ terminal one-third of the antisense strand; and (iv) the absence of any GC stretch of more than 9 nucleotides in length. In accordance with such consideration, together with the specific sequence of a target gene, highly effective siRNA molecules essential for suppressing mammalian target gene expression may be readily designed.

[00406] According to the present invention, siRNA molecules (e.g., siRNA duplexes or encoded dsRNA) that target the gene of interest are designed. Such siRNA molecules can specifically, suppress gene expression and protein production. In some aspects, the siRNA molecules are designed and used to selectively "knock out" gene variants in cells, i.e., mutated transcripts. In some aspects, the siRNA molecules are designed and used to selectively "knock down" gene variants in cells. In other aspects, the siRNA molecules are able to inhibit or suppress both the wild type and mutated version of the gene of interest.

[00407] In one embodiment, an siRNA molecule of the present invention comprises a sense strand and a complementary antisense strand in which both strands are hybridized together to form a duplex structure. The antisense strand has sufficient complementarity to the target mRNA sequence to direct target-specific RNAi, i.e., the siRNA molecule has a sequence sufficient to trigger the destruction of the target mRNA by the RNAi machinery or process.

[00408] In one embodiment, an siRNA molecule of the present invention comprises a sense strand and a complementary antisense strand in which both strands are hybridized together to form a duplex structure and where the start site of the hybridization to the mRNA is between nucleotide 10 and 7000 on the mRNA sequence. As a non-limiting example, the start site may be between nucleotide 10-20, 20-30, 30-40, 40-50, 60-70, 70-80, 80-90, 90-100, 100-150, 150-200, 200-250, 250-300, 300-350, 350-400, 400-450, 450-500, 500-550, 550-600, 600-650, 650-700, 700-70, 750-800, 800-850, 850-900, 900-950, 950-1000, 1000-1050, 1050-1100, 1100-1150, 1150-1200, 1200-1250, 1250-1300, 1300-1350, 1350-1400, 1400-1450, 1450-1500, 1500-1550, 1550-1600, 1600-1650, 1650-1700, 1700-1750, 1750-1800, 1800-1850, 1850-1900, 1900-1950, 1950-2000, 2000-2050, 2050-2100, 2100-2150, 2150-2200, 2200-2250, 2250-2300, 2300-2350, 2350-2400, 2400-2450, 2450-2500, 2500-2550, 2550-2600, 2600-2650, 2650-2700, 2700-2750, 2750-2800, 2800-2850, 2850-2900, 2900-2950, 2950-3000, 3000-3050, 3050-3100, 3100-3150,

3150-3200, 3200-3250, 3250-3300, 3300-3350, 3350-3400, 3400-3450, 3450-3500, 3500-3550, 3550-3600, 3600-3650, 3650-3700, 3700-3750, 3750-3800, 3800-3850, 3850-3900, 3900-3950, 3950-4000, 4000-4050, 4050-4100, 4100-4150, 4150-4200, 4200-4250, 4250-4300, 4300-4350, 4350-4400, 4400-4450, 4450-4500, 4500-4550, 4550-4600, 4600-4650, 4650-4700, 4700-4750, 4750-4800, 4800-4850, 4850-4900, 4900-4950, 4950-5000, 5000-5050, 5050-5100, 5100-5150, 5150-5200, 5200-5250, 5250-5300, 5300-5350, 5350-5400, 5400-5450, 5450-5500, 5500-5550, 5550-5600, 5600-5650, 5650-5700, 5700-5750, 5750-5800, 5800-5850, 5850-5900, 5900-5950, 5950-6000, 6000-6050, 6050-6100, 6100-6150, 6150-6200, 6200-6250, 6250-6300, 6300-6350, 6350-6400, 6400-6450, 6450-6500, 6500-6550, 6550-6600, 6600-6650, 6650-6700, 6700-6750, 6750-6800, 6800-6850, 6850-6900, 6900-6950, 6950-7000, 7000-7050, 7050-7100, 7100-7150, 7150-7200, 7200-7250, 7250-7300, 7300-7350, 7350-7400, 7400-7450, 7450-7500, 7500-7550, 7550-7600, 7600-7650, 7650-7700, 7700-7750, 7750-7800, 7800-7850, 7850-7900, 7900-7950, 7950-8000, 8000-8050, 8050-8100, 8100-8150, 8150-8200, 8200-8250, 8250-8300, 8300-8350, 8350-8400, 8400-8450, 8450-8500, 8500-8550, 8550-8600, 8600-8650, 8650-8700, 8700-8750, 8750-8800, 8800-8850, 8850-8900, 8900-8950, 8950-9000, 9000-9050, 9050-9100, 9100-9150, 9150-9200, 9200-9250, 9250-9300, 9300-9350, 9350-9400, 9400-9450, 9450-9500, 9500-9550, 9550-9600, 9600-9650, 9650-9700, 9700-9750, 9750-9800, 9800-9850, 9850-9900, 9900-9950, 9950-10000, 10000-10050, 10050-10100, 10100-10150, 10150-10200, 10200-10250, 10250-10300, 10300-10350, 10350-10400, 10400-10450, 10450-10500, 10500-10550, 10550-10600, 10600-10650, 10650-10700, 10700-10750, 10750-10800, 10800-10850, 10850-10900, 10900-10950, 10950-11000, 11050-11100, 11100-11150, 11150-11200, 11200-11250, 11250-11300, 11300-11350, 11350-11400, 11400-11450, 11450-11500, 11500-11550, 11550-11600, 11600-11650, 11650-11700, 11700-11750, 11750-11800, 11800-11850, 11850-11900, 11900-11950, 11950-12000, 12000-12050, 12050-12100, 12100-12150, 12150-12200, 12200-12250, 12250-12300, 12300-12350, 12350-12400, 12400-12450, 12450-12500, 12500-12550, 12550-12600, 12600-12650, 12650-12700, 12700-12750, 12750-12800, 12800-12850, 12850-12900, 12900-12950, 12950-13000, 13050-13100, 13100-13150, 13150-13200, 13200-13250, 13250-13300, 13300-13350, 13350-13400, 13400-13450, and 13450-13500 on the target mRNA sequence. As yet another non-limiting example, the start site may be nucleotide 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115,

116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, 500, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, 511, 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 526, 527, 528, 529, 530, 531, 532, 533, 534, 535, 536, 537, 538, 539, 540, 541, 542, 543, 544, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 572, 573, 574, 575, 576, 577, 578, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 593, 594, 595, 596, 597, 598, 599, 600, 601, 602, 603, 604, 605, 606, 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 619, 620, 621, 622, 623, 624, 625, 626, 627, 628, 629, 630, 631, 632, 633, 634, 635, 636, 637, 638, 639, 640, 641, 642, 643, 644, 645, 646, 647, 648, 649, 650, 651, 652, 653, 654, 655, 656, 657, 658, 659, 660, 661, 662, 663, 664, 665, 666, 667, 668, 669, 670, 671, 672, 673, 674, 675, 676, 677, 678, 679, 680, 681, 682, 683, 684, 685, 686, 687, 688, 689, 690, 691, 692, 693, 694, 695, 696, 697, 698, 699, 700, 701, 702, 703, 704, 705, 706, 707, 708, 709, 710, 711, 712, 713, 714, 715, 716, 717, 718, 719, 720, 721, 722, 723, 724, 725, 726, 727, 728, 729, 730, 731, 732, 733, 734, 735, 736, 737, 738, 739, 740, 741, 742,

743, 744, 745, 746, 747, 748, 749, 750, 751, 752, 753, 754, 755, 756, 757, 758, 759, 760, 761, 762, 763, 764, 765, 766, 767, 768, 769, 770, 771, 772, 773, 774, 775, 776, 777, 778, 779, 780, 781, 782, 783, 784, 785, 786, 787, 788, 789, 790, 791, 792, 793, 794, 795, 796, 797, 798, 799, 800, 801, 802, 803, 804, 805, 806, 807, 808, 809, 810, 811, 812, 813, 814, 815, 816, 817, 818, 819, 820, 821, 822, 823, 824, 825, 826, 827, 828, 829, 830, 831, 832, 833, 834, 835, 836, 837, 838, 839, 840, 841, 842, 843, 844, 845, 846, 847, 848, 849, 850, 851, 852, 853, 854, 855, 856, 857, 858, 859, 860, 861, 862, 863, 864, 865, 866, 867, 868, 869, 870, 871, 872, 873, 874, 875, 876, 877, 878, 879, 880, 881, 882, 883, 884, 885, 886, 887, 888, 889, 890, 891, 892, 893, 894, 895, 896, 897, 898, 899, 900, 901, 902, 903, 904, 905, 906, 907, 908, 909, 910, 911, 912, 913, 914, 915, 916, 917, 918, 919, 920, 921, 922, 923, 924, 925, 926, 927, 928, 929, 930, 931, 932, 933, 934, 935, 936, 937, 938, 939, 940, 941, 942, 943, 944, 945, 946, 947, 948, 949, 950, 951, 952, 953, 954, 955, 956, 957, 958, 959, 960, 961, 962, 963, 964, 965, 966, 967, 968, 969, 970, 971, 972, 973, 974, 975, 976, 977, 978, 979, 980, 981, 982, 983, 984, 985, 986, 987, 988, 989, 990, 991, 992, 993, 994, 995, 996, 997, 998, 999, 1000, 1375, 1376, 1377, 1378, 1379, 1380, 1381, 1382, 1383, 1384, 1385, 1386, 1387, 1388, 1389, 1390, 1391, 1392, 1393, 1394, 1395, 1396, 1397, 1398, 1399, 1400, 1401, 1402, 1403, 1404, 1405, 1406, 1407, 1408, 1409, 1410, 1411, 1412, 1413, 1414, 1415, 1416, 1417, 1418, 1419, 1420, 1421, 1422, 1423, 1424, 1425, 1426, 1427, 1428, 1429, 1430, 1431, 1432, 1433, 1434, 1435, 1436, 1437, 1438, 1439, 1440, 1441, 1442, 1443, 1444, 1445, 1446, 1447, 1448, 1449, 1450, 1660, 1661, 1662, 1663, 1664, 1665, 1666, 1667, 1668, 1669, 1670, 1671, 1672, 1673, 1674, 1675, 2050, 2051, 2052, 2053, 2054, 2055, 2056, 2057, 2058, 2059, 2060, 2061, 2062, 2063, 2064, 2065, 2066, 2067, 2068, 2069, 2070, 2071, 2072, 2073, 2074, 2075, 2076, 2077, 2078, 2079, 2080, 2081, 2082, 2083, 2084, 2085, 2086, 2087, 2088, 2089, 2090, 2091, 2092, 2093, 2094, 2095, 2096, 2097, 2098, 2099, 2100, 2580, 2581, 2582, 2583, 2584, 2585, 2586, 2587, 2588, 2589, 2590, 2591, 2592, 2593, 2594, 2595, 2596, 2597, 2598, 2599, 2600, 2601, 2602, 2603, 2604, 2605, 4525, 4526, 4527, 4528, 4529, 4530, 4531, 4532, 4533, 4534, 4535, 4536, 4537, 4538, 4539, 4540, 4541, 4542, 4543, 4544, 4545, 4546, 4547, 4548, 4549, 4550, 4575, 4576, 4577, 4578, 4579, 4580, 4581, 4582, 4583, 4584, 4585, 4586, 4587, 4588, 4589, 4590, 4591, 4592, 4593, 4594, 4595, 4596, 4597, 4598, 4599, 4600, 4850, 4851, 4852, 4853, 4854, 4855, 4856, 4857, 4858, 4859, 4860, 4861, 4862, 4863, 4864, 4865, 4866, 4867, 4868, 4869, 4870, 4871, 4872, 4873, 4874, 4875, 4876, 4877, 4878, 4879, 4880, 4881, 4882, 4883, 4884, 4885, 4886, 4887, 4888, 4889, 4890, 4891, 4892, 4893, 4894, 4895, 4896, 4897, 4898, 4899, 4900, 5460, 5461, 5462, 5463, 5464, 5465, 5466, 5467, 5468, 5469, 5470, 5471, 5472, 5473, 5474, 5475, 5476, 5477, 5478,

5479, 5480, 6175, 6176, 6177, 6178, 6179, 6180, 6181, 6182, 6183, 6184, 6185, 6186, 6187, 6188, 6189, 6190, 6191, 6192, 6193, 6194, 6195, 6196, 6197, 6198, 6199, 6200, 6315, 6316, 6317, 6318, 6319, 6320, 6321, 6322, 6323, 6324, 6325, 6326, 6327, 6328, 6329, 6330, 6331, 6332, 6333, 6334, 6335, 6336, 6337, 6338, 6339, 6340, 6341, 6342, 6343, 6344, 6345, 6600, 6601, 6602, 6603, 6604, 6605, 6606, 6607, 6608, 6609, 6610, 6611, 6612, 6613, 6614, 6615, 6725, 6726, 6727, 6728, 6729, 6730, 6731, 6732, 6733, 6734, 6735, 6736, 6737, 6738, 6739, 6740, 6741, 6742, 6743, 6744, 6745, 6746, 6747, 6748, 6749, 6750, 6751, 6752, 6753, 6754, 6755, 6756, 6757, 6758, 6759, 6760, 6761, 6762, 6763, 6764, 6765, 6766, 6767, 6768, 6769, 6770, 6771, 6772, 6773, 6774, 6775, 7655, 7656, 7657, 7658, 7659, 7660, 7661, 7662, 7663, 7664, 7665, 7666, 7667, 7668, 7669, 7670, 7671, 7672, 8510, 8511, 8512, 8513, 8514, 8515, 8516, 8715, 8716, 8717, 8718, 8719, 8720, 8721, 8722, 8723, 8724, 8725, 8726, 8727, 8728, 8729, 8730, 8731, 8732, 8733, 8734, 8735, 8736, 8737, 8738, 8739, 8740, 8741, 8742, 8743, 8744, 8745, 9250, 9251, 9252, 9253, 9254, 9255, 9256, 9257, 9258, 9259, 9260, 9261, 9262, 9263, 9264, 9265, 9266, 9267, 9268, 9269, 9270, 9480, 9481, 9482, 9483, 9484, 9485, 9486, 9487, 9488, 9489, 9490, 9491, 9492, 9493, 9494, 9495, 9496, 9497, 9498, 9499, 9500, 9575, 9576, 9577, 9578, 9579, 9580, 9581, 9582, 9583, 9584, 9585, 9586, 9587, 9588, 9589, 9590, 10525, 10526, 10527, 10528, 10529, 10530, 10531, 10532, 10533, 10534, 10535, 10536, 10537, 10538, 10539, 10540, 11545, 11546, 11547, 11548, 11549, 11550, 11551, 11552, 11553, 11554, 11555, 11556, 11557, 11558, 11559, 11560, 11875, 11876, 11877, 11878, 11879, 11880, 11881, 11882, 11883, 11884, 11885, 11886, 11887, 11888, 11889, 11890, 11891, 11892, 11893, 11894, 11895, 11896, 11897, 11898, 11899, 11900, 11915, 11916, 11917, 11918, 11919, 11920, 11921, 11922, 11923, 11924, 11925, 11926, 11927, 11928, 11929, 11930, 11931, 11932, 11933, 11934, 11935, 11936, 11937, 11938, 11939, 11940, 13375, 13376, 13377, 13378, 13379, 13380, 13381, 13382, 13383, 13384, 13385, 13386, 13387, 13388, 13389 and 13390 on the target mRNA sequence.

[00409] In some embodiments, the antisense strand and target mRNA sequences have 100% complementarity. The antisense strand may be complementary to any part of the target mRNA sequence.

[00410] In other embodiments, the antisense strand and target mRNA sequences comprise at least one mismatch. As a non-limiting example, the antisense strand and the target mRNA sequence have at least 30%, 40%, 50%, 60%, 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-99%, 30-40%, 30-50%, 30-

60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-99%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-99%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-99%, 60-70%, 60-80%, 60-90%, 60-95%, 60-99%, 70-80%, 70-90%, 70-95%, 70-99%, 80-90%, 80-95%, 80-99%, 90-95%, 90-99% or 95-99% complementarity.

[00411] In one embodiment, an siRNA or dsRNA includes at least two sequences that are complementary to each other.

[00412] According to the present invention, the siRNA molecule has a length from about 10-50 or more nucleotides, i.e., each strand comprising 10-50 nucleotides (or nucleotide analogs). Preferably, the siRNA molecule has a length from about 15-30, e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in each strand, wherein one of the strands is sufficiently complementarity to a target region. In one embodiment, each strand of the siRNA molecule has a length from about 19 to 25, 19 to 24 or 19 to 21 nucleotides. In one embodiment, at least one strand of the siRNA molecule is 19 nucleotides in length. In one embodiment, at least one strand of the siRNA molecule is 20 nucleotides in length. In one embodiment, at least one strand of the siRNA molecule is 21 nucleotides in length. In one embodiment, at least one strand of the siRNA molecule is 22 nucleotides in length. In one embodiment, at least one strand of the siRNA molecule is 23 nucleotides in length. In one embodiment, at least one strand of the siRNA molecule is 24 nucleotides in length. In one embodiment, at least one strand of the siRNA molecule is 25 nucleotides in length.\

[00413] In some embodiments, the siRNA molecules of the present invention can be synthetic RNA duplexes comprising about 19 nucleotides to about 25 nucleotides, and two overhanging nucleotides at the 3'-end. In some aspects, the siRNA molecules may be unmodified RNA molecules. In other aspects, the siRNA molecules may contain at least one modified nucleotide, such as base, sugar or backbone modifications.

[00414] In one embodiment, the siRNA molecules of the present invention may comprise an antisense sequence and a sense sequence, or a fragment or variant thereof. As a non-limiting example, the antisense sequence and the sense sequence have at least 30%, 40%, 50%, 60%, 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-99%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-99%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-99%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-99%, 60-70%, 60-80%, 60-90%, 60-95%, 60-99%, 70-80%, 70-90%, 70-95%, 70-99%, 80-90%, 80-95%, 80-99%, 90-95%, 90-99% or 95-99% complementarity.

[00415] In other embodiments, the siRNA molecules of the present invention can be encoded in plasmid vectors, AAV particles, viral genome or other nucleic acid expression vectors for delivery to a cell.

[00416] DNA expression plasmids can be used to stably express the siRNA duplexes or dsRNA of the present invention in cells and achieve long-term inhibition of the target gene expression. In one aspect, the sense and antisense strands of a siRNA duplex are typically linked by a short spacer sequence leading to the expression of a stem-loop structure termed short hairpin RNA (shRNA). The hairpin is recognized and cleaved by Dicer, thus generating mature siRNA molecules.

[00417] According to the present invention, AAV particles comprising the nucleic acids encoding the siRNA molecules targeting the mRNA are produced, the AAV serotypes may be any of the serotypes listed in Table 1. Non-limiting examples of the AAV serotypes include, AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV9.47, AAV9(hu14), AAV10, AAV11, AAV12, AAVrh8, AAVrh10, AAV-DJ8, AAV-DJ, AAV-PHP.A, and/or AAV-PHP.B, AAVPHP.B2, AAVPHP.B3, AAVPHP.N/PHP.B-DGT, AAVPHP.B-EST, AAVPHP.B-GGT, AAVPHP.B-ATP, AAVPHP.B-ATT-T, AAVPHP.B-DGT-T, AAVPHP.B-GGT-T, AAVPHP.B-SGS, AAVPHP.B-AQP, AAVPHP.B-QQP, AAVPHP.B-SNP(3), AAVPHP.B-SNP, AAVPHP.B-QGT, AAVPHP.B-NQT, AAVPHP.B-EGS, AAVPHP.B-SGN, AAVPHP.B-EGT, AAVPHP.B-DST, AAVPHP.B-DST, AAVPHP.B-STP, AAVPHP.B-PQP, AAVPHP.B-SQP, AAVPHP.B-QLP, AAVPHP.B-TMP, AAVPHP.B-TTP, AAVPHP.S/G2A12, AAVG2A15/G2A3, AAVG2B4, AAVG2B5 and variants thereof.

[00418] In some embodiments, the siRNA duplexes or encoded dsRNA of the present invention suppress (or degrade) the target mRNA. Accordingly, the siRNA duplexes or encoded dsRNA can be used to substantially inhibit the gene expression in a cell, for example a neuron. In some aspects, the inhibition of the gene expression refers to an inhibition by at least about 20%, preferably by at least about 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95% and 100%, or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% or 95-100%. Accordingly, the protein product of the targeted gene may be inhibited by at least about 20%, preferably by at least about 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95% and 100%, or at least 20-30%, 20-40%, 20-50%, 20-

60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% or 95-100%.

[00419] In one embodiment, the siRNA molecules comprise a miRNA seed match for the target located in the guide strand. In another embodiment, the siRNA molecules comprise a miRNA seed match for the target located in the passenger strand. In yet another embodiment, the siRNA duplexes or encoded dsRNA targeting the gene of interest do not comprise a seed match for the target located in the guide or passenger strand.

[00420] In one embodiment, the siRNA duplexes or encoded dsRNA targeting the gene of interest may have almost no significant full-length off target effects for the guide strand. In another embodiment, the siRNA duplexes or encoded dsRNA targeting the gene of interest may have almost no significant full-length off target effects for the passenger strand. The siRNA duplexes or encoded dsRNA targeting the gene of interest may have less than 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%,11%, 12%, 13%, 14%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 1-5%, 2-6%, 3-7%, 4-8%, 5-9%, 5-10%, 6-10%, 5-15%, 5-20%, 5-25% 5-30%, 10-20%, 10-30%, 10-40%, 10-50%, 15-30%, 15-40%, 15-45%, 20-40%, 20-50%, 25-50%, 30-40%, 30-50%, 35-50%, 40-50%, 45-50% full-length off target effects for the passenger strand. In yet another embodiment, the siRNA duplexes or encoded dsRNA targeting the gene of interest may have almost no significant full-length off target effects for the guide strand or the passenger strand. The siRNA duplexes or encoded dsRNA targeting the gene of interest may have less than 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%,11%, 12%, 13%, 14%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 1-5%, 2-6%, 3-7%, 4-8%, 5-9%, 5-10%, 6-10%, 5-15%, 5-20%, 5-25% 5-30%, 10-20%, 10-30%, 10-40%, 10-50%, 15-30%, 15-40%, 15-45%, 20-40%, 20-50%, 25-50%, 30-40%, 30-50%, 35-50%, 40-50%, 45-50% full-length off target effects for the guide or passenger strand.

[00421] In one embodiment, the siRNA duplexes or encoded dsRNA targeting the gene of interest may have high activity in vitro. In another embodiment, the siRNA molecules may have low activity in vitro. In yet another embodiment, the siRNA duplexes or dsRNA targeting the gene of interest may have high guide strand activity and low passenger strand activity in vitro.

[00422] In one embodiment, the siRNA molecules have a high guide strand activity and low passenger strand activity in vitro. The target knock-down (KD) by the guide strand may be at

least 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, 99.5% or 100%. The target knock-down by the guide strand may be 40-50%, 45-50%, 50-55%, 50-60%, 60-65%, 60-70%, 60-75%, 60-80%, 60-85%, 60-90%, 60-95%, 60-99%, 60-99.5%, 60-100%, 65-70%, 65-75%, 65-80%, 65-85%, 65-90%, 65-95%, 65-99%, 65-99.5%, 65-100%, 70-75%, 70-80%, 70-85%, 70-90%, 70-95%, 70-99%, 70-99.5%, 70-100%, 75-80%, 75-85%, 75-90%, 75-95%, 75-99%, 75-99.5%, 75-100%, 80-85%, 80-90%, 80-95%, 80-99%, 80-99.5%, 80-100%, 85-90%, 85-95%, 85-99%, 85-99.5%, 85-100%, 90-95%, 90-99%, 90-99.5%, 90-100%, 95-99%, 95-99.5%, 95-100%, 99-99.5%, 99-100% or 99.5-100%. As a non-limiting example, the target knock-down (KD) by the guide strand is greater than 70%. As a non-limiting example, the target knock-down (KD) by the guide strand is greater than 60%.

[00423] In one embodiment, the siRNA duplex is designed so there is no miRNA seed match for the sense or antisense sequence to the non-gene of interest sequence.

[00424] In one embodiment, the IC_{50} of the guide strand for the nearest off target is greater than 100 multiplied by the IC_{50} of the guide strand for the on-target gene. As a non-limiting example, if the IC_{50} of the guide strand for the nearest off target is greater than 100 multiplied by the IC_{50} of the guide strand for the target then the siRNA molecule is said to have high guide strand selectivity for inhibiting the gene of interest in vitro.

[00425] In one embodiment, the 5' processing of the guide strand has a correct start (n) at the 5' end at least 75%, 80%, 85%, 90%, 95%, 99% or 100% of the time in vitro or in vivo. As a non-limiting example, the 5' processing of the guide strand is precise and has a correct start (n) at the 5' end at least 99% of the time in vitro. As a non-limiting example, the 5' processing of the guide strand is precise and has a correct start (n) at the 5' end at least 99% of the time in vivo. As a non-limiting example, the 5' processing of the guide strand is precise and has a correct start (n) at the 5' end at least 90% of the time in vitro. As a non-limiting example, the 5' processing of the guide strand is precise and has a correct start (n) at the 5' end at least 90% of the time in vivo. As a non-limiting example, the 5' processing of the guide strand is precise and has a correct start (n) at the 5' end at least 85% of the time in vitro. As a non-limiting example, the 5' processing of the guide strand is precise and has a correct start (n) at the 5' end at least 85% of the time in vivo.

[00426] In one embodiment, the guide to passenger (G:P) (also referred to as the antisense to sense) strand ratio expressed is 1:10, 1:9, 1:8, 1:7, 1:6, 1:5, 1:4, 1:3, 1:2, 1;1, 2:10, 2:9, 2:8, 2:7, 2:6, 2:5, 2:4, 2:3, 2:2, 2:1, 3:10, 3:9, 3:8, 3:7, 3:6, 3:5, 3:4, 3:3, 3:2, 3:1, 4:10, 4:9, 4:8, 4:7, 4:6, 4:5, 4:4, 4:3, 4:2, 4:1, 5:10, 5:9, 5:8, 5:7, 5:6, 5:5, 5:4, 5:3, 5:2, 5:1, 6:10, 6:9, 6:8, 6:7, 6:6, 6:5, 6:4, 6:3, 6:2, 6:1, 7:10, 7:9, 7:8, 7:7, 7:6, 7:5, 7:4, 7:3, 7:2, 7:1, 8:10, 8:9, 8:8, 8:7, 8:6, 8:5, 8:4,

8:3, 8:2, 8:1, 9:10, 9:9, 9:8, 9:7, 9:6, 9:5, 9:4, 9:3, 9:2, 9:1, 10:10, 10:9, 10:8, 10:7, 10:6, 10:5, 10:4, 10:3, 10:2, 10:1, 1:99, 5:95, 10:90, 15:85, 20:80, 25:75, 30:70, 35:65, 40:60, 45:55, 50:50, 55:45, 60:40, 65:35, 70:30, 75:25, 80:20, 85:15, 90:10, 95:5, or 99:1 in vitro or in vivo. The guide to passenger ratio refers to the ratio of the guide strands to the passenger strands after intracellular processing of the pri-microRNA. For example, a 80:20 of guide-to-passenger ratio would have 8 guide strands to every 2 passenger strands processed from the precursor. As a non-limiting example, the guide-to-passenger strand ratio is 8:2 in vitro. As a non-limiting example, the guide-to-passenger strand ratio is 8:2 in vivo. As a non-limiting example, the guide-to-passenger strand ratio is 9:1 in vitro. As a non-limiting example, the guide-to-passenger strand ratio is 9:1 in vivo.

[00427] In one embodiment, the guide to passenger (G:P) (also referred to as the antisense to sense) strand ratio expressed is greater than 1.

[00428] In one embodiment, the guide to passenger (G:P) (also referred to as the antisense to sense) strand ratio expressed is greater than 2.

[00429] In one embodiment, the guide to passenger (G:P) (also referred to as the antisense to sense) strand ratio expressed is greater than 5.

[00430] In one embodiment, the guide to passenger (G:P) (also referred to as the antisense to sense) strand ratio expressed is greater than 10.

[00431] In one embodiment, the guide to passenger (G:P) (also referred to as the antisense to sense) strand ratio expressed is greater than 20.

[00432] In one embodiment, the guide to passenger (G:P) (also referred to as the antisense to sense) strand ratio expressed is greater than 50.

[00433] In one embodiment, the guide to passenger (G:P) (also referred to as the antisense to sense) strand ratio expressed is at least 3:1.

[00434] In one embodiment, the guide to passenger (G:P) (also referred to as the antisense to sense) strand ratio expressed is at least 5:1.

[00435] In one embodiment, the guide to passenger (G:P) (also referred to as the antisense to sense) strand ratio expressed is at least 10:1.

[00436] In one embodiment, the guide to passenger (G:P) (also referred to as the antisense to sense) strand ratio expressed is at least 20:1.

[00437] In one embodiment, the guide to passenger (G:P) (also referred to as the antisense to sense) strand ratio expressed is at least 50:1.

[00438] In one embodiment, the passenger to guide (P:G) (also referred to as the sense to antisense) strand ratio expressed is 1:10, 1:9, 1:8, 1:7, 1:6, 1:5, 1:4, 1:3, 1:2, 1;1, 2:10, 2:9, 2:8, 2:7, 2:6, 2:5, 2:4, 2:3, 2:2, 2:1, 3:10, 3:9, 3:8, 3:7, 3:6, 3:5, 3:4, 3:3, 3:2, 3:1, 4:10, 4:9, 4:8, 4:7, 4:6, 4:5, 4:4, 4:3, 4:2, 4:1, 5:10, 5:9, 5:8, 5:7, 5:6, 5:5, 5:4, 5:3, 5:2, 5:1, 6:10, 6:9, 6:8, 6:7, 6:6, 6:5, 6:4, 6:3, 6:2, 6:1, 7:10, 7:9, 7:8, 7:7, 7:6, 7:5, 7:4, 7:3, 7:2, 7:1, 8:10, 8:9, 8:8, 8:7, 8:6, 8:5, 8:4, 8:3, 8:2, 8:1, 9:10, 9:9, 9:8, 9:7, 9:6, 9:5, 9:4, 9:3, 9:2, 9:1, 10:10, 10:9, 10:8, 10:7, 10:6, 10:5, 10:4, 10:3, 10:2, 10:1, 1:99, 5:95, 10:90, 15:85, 20:80, 25:75, 30:70, 35:65, 40:60, 45:55, 50:50, 55:45, 60:40, 65:35, 70:30, 75:25, 80:20, 85:15, 90:10, 95:5, or 99:1 in vitro or in vivo. The passenger to guide ratio refers to the ratio of the passenger strands to the guide strands after the intracellular processing of the pri-microRNA. For example, a 80:20 passenger-to-guide ratio would have 8 passenger strands to every 2 guide strands processed from the precursor. As a non-limiting example, the passenger-to-guide strand ratio is 80:20 in vitro. As a non-limiting example, the passenger-to-guide strand ratio is 80:20 in vivo. As a non-limiting example, the passenger-to-guide strand ratio is 8:2 in vitro. As a non-limiting example, the passenger-to-guide strand ratio is 8:2 in vivo. As a non-limiting example, the passenger-to-guide strand ratio is 9:1 in vitro. As a non-limiting example, the passenger-to-guide strand ratio is 9:1 in vivo.

[00439] In one embodiment, the passenger to guide (P:G) (also referred to as the sense to antisense) strand ratio expressed is greater than 1.

[00440] In one embodiment, the passenger to guide (P:G) (also referred to as the sense to antisense) strand ratio expressed is greater than 2.

[00441] In one embodiment, the passenger to guide (P:G) (also referred to as the sense to antisense) strand ratio expressed is greater than 5.

[00442] In one embodiment, the passenger to guide (P:G) (also referred to as the sense to antisense) strand ratio expressed is greater than 10.

[00443] In one embodiment, the passenger to guide (P:G) (also referred to as the sense to antisense) strand ratio expressed is greater than 20.

[00444] In one embodiment, the passenger to guide (P:G) (also referred to as the sense to antisense) strand ratio expressed is greater than 50.

[00445] In one embodiment, the passenger to guide (P:G) (also referred to as the sense to antisense) strand ratio expressed is at least 3:1.

[00446] In one embodiment, the passenger to guide (P:G) (also referred to as the sense to antisense) strand ratio expressed is at least 5:1.

[00447] In one embodiment, the passenger to guide (P:G) (also referred to as the sense to antisense) strand ratio expressed is at least 10:1.

[00448] In one embodiment, the passenger to guide (P:G) (also referred to as the sense to antisense) strand ratio expressed is at least 20:1.

[00449] In one embodiment, the passenger to guide (P:G) (also referred to as the sense to antisense) strand ratio expressed is at least 50:1.

[00450] In one embodiment, a passenger-guide strand duplex is considered effective when the pri- or pre-microRNAs demonstrate, but methods known in the art and described herein, greater than 2-fold guide to passenger strand ratio when processing is measured. As a non-limiting examples, the pri- or pre-microRNAs demonstrate great than 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, 11-fold, 12-fold, 13-fold, 14-fold, 15-fold, or 2 to 5-fold, 2 to 10-fold, 2 to 15-fold, 3 to 5-fold, 3 to 10-fold, 3 to 15-fold, 4 to 5-fold, 4 to 10-fold, 4 to 15-fold, 5 to 10-fold, 5 to 15-fold, 6 to 10-fold, 6 to 15-fold, 7 to 10-fold, 7 to 15-fold, 8 to 10-fold, 8 to 15-fold, 9 to 10-fold, 9 to 15-fold, 10 to 15-fold, 11 to 15-fold, 12 to 15-fold, 13 to 15-fold, or 14 to 15-fold guide to passenger strand ratio when processing is measured.

[00451] In one embodiment, the vector genome encoding the dsRNA comprises a sequence which is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99% or more than 99% of the full length of the construct. As a non-limiting example, the vector genome comprises a sequence which is at least 80% of the full length sequence of the construct.

[00452] In one embodiment, the siRNA molecules may be used to silence wild type or mutant version of the gene of interest by targeting at least one exon on the gene of interest sequence. The exon may be exon 1, exon 2, exon 3, exon 4, exon 5, exon 6, exon 7, exon 8, exon 9, exon 10, exon 11, exon 12, exon 13, exon 14, exon 15, exon 16, exon 17, exon 18, exon 19, exon 20, exon 21, exon 22, exon 23, exon 24, exon 25, exon 26, exon 27, exon 28, exon 29, exon 30, exon 31, exon 32, exon 33, exon 34, exon 35, exon 36, exon 37, exon 38, exon 39, exon 40, exon 41, exon 42, exon 43, exon 44, exon 45, exon 46, exon 47, exon 48, exon 49, exon 50, exon 51, exon 52, exon 53, exon 54, exon 55, exon 56, exon 57, exon 58, exon 59, exon 60, exon 61, exon 62, exon 63, exon 64, exon 65, exon 66, and/or exon 67.

Design and Sequences of siRNA duplexes targeting HTT gene

[00453] The present invention provides small interfering RNA (siRNA) duplexes (and modulatory polynucleotides encoding them) that target HTT mRNA to interfere with HTT gene expression and/or HTT protein production.

[00454] The encoded siRNA duplex of the present invention contains an antisense strand and a sense strand hybridized together forming a duplex structure, wherein the antisense strand is complementary to the nucleic acid sequence of the targeted HTT gene, and wherein the sense strand is homologous to the nucleic acid sequence of the targeted HTT gene. In some aspects, the 5'end of the antisense strand has a 5' phosphate group and the 3'end of the sense strand contains a 3'hydroxyl group. In other aspects, there are none, one or 2 nucleotide overhangs at the 3'end of each strand.

[00455] Some guidelines for designing siRNAs have been proposed in the art. These guidelines generally recommend generating a 19-nucleotide duplexed region, symmetric 2-3 nucleotide 3'overhangs, 5'- phosphate and 3'- hydroxyl groups targeting a region in the gene to be silenced. Other rules that may govern siRNA sequence preference include, but are not limited to, (i) A/U at the 5′ end of the antisense strand; (ii) G/C at the 5′ end of the sense strand; (iii) at least five A/U residues in the 5′ terminal one-third of the antisense strand; and (iv) the absence of any GC stretch of more than 9 nucleotides in length. In accordance with such consideration, together with the specific sequence of a target gene, highly effective siRNA molecules essential for suppressing the Htt gene expression may be readily designed.

[00456] According to the present invention, siRNA molecules (e.g., siRNA duplexes or encoded dsRNA) that target the HTT gene are designed. Such siRNA molecules can specifically, suppress HTT gene expression and protein production. In some aspects, the siRNA molecules are designed and used to selectively "knock out" HTT gene variants in cells, i.e., mutated HTT transcripts that are identified in patients with HD disease. In some aspects, the siRNA molecules are designed and used to selectively "knock down" HTT gene variants in cells. In other aspects, the siRNA molecules are able to inhibit or suppress both the wild type and mutated HTT gene.

[00457] In one embodiment, an siRNA molecule of the present invention comprises a sense strand and a complementary antisense strand in which both strands are hybridized together to form a duplex structure. The antisense strand has sufficient complementarity to the HTT mRNA sequence to direct target-specific RNAi, i.e., the siRNA molecule has a sequence sufficient to trigger the destruction of the target mRNA by the RNAi machinery or process.

[00458] In one embodiment, an siRNA molecule of the present invention comprises a sense strand and a complementary antisense strand in which both strands are hybridized together to form a duplex structure and where the start site of the hybridization to the HTT

mRNA is between nucleotide 100 and 7000 on the HTT mRNA sequence. As a non-limiting example, the start site may be between nucleotide 100-150, 150-200, 200-250, 250-300, 300-350, 350-400, 400-450, 450-500, 500-550, 550-600, 600-650, 650-700, 700-70, 750-800, 800-850, 850-900, 900-950, 950-1000, 1000-1050, 1050-1100, 1100-1150, 1150-1200, 1200-1250, 1250-1300, 1300-1350, 1350-1400, 1400-1450, 1450-1500, 1500-1550, 1550-1600, 1600-1650, 1650-1700, 1700-1750, 1750-1800, 1800-1850, 1850-1900, 1900-1950, 1950-2000, 2000-2050, 2050-2100, 2100-2150, 2150-2200, 2200-2250, 2250-2300, 2300-2350, 2350-2400, 2400-2450, 2450-2500, 2500-2550, 2550-2600, 2600-2650, 2650-2700, 2700-2750, 2750-2800, 2800-2850, 2850-2900, 2900-2950, 2950-3000, 3000-3050, 3050-3100, 3100-3150, 3150-3200, 3200-3250, 3250-3300, 3300-3350, 3350-3400, 3400-3450, 3450-3500, 3500-3550, 3550-3600, 3600-3650, 3650-3700, 3700-3750, 3750-3800, 3800-3850, 3850-3900, 3900-3950, 3950-4000, 4000-4050, 4050-4100, 4100-4150, 4150-4200, 4200-4250, 4250-4300, 4300-4350, 4350-4400, 4400-4450, 4450-4500, 4500-4550, 4550-4600, 4600-4650, 4650-4700, 4700-4750, 4750-4800, 4800-4850, 4850-4900, 4900-4950, 4950-5000, 5000-5050, 5050-5100, 5100-5150, 5150-5200, 5200-5250, 5250-5300, 5300-5350, 5350-5400, 5400-5450, 5450-5500, 5500-5550, 5550-5600, 5600-5650, 5650-5700, 5700-5750, 5750-5800, 5800-5850, 5850-5900, 5900-5950, 5950-6000, 6000-6050, 6050-6100, 6100-6150, 6150-6200, 6200-6250, 6250-6300, 6300-6350, 6350-6400, 6400-6450, 6450-6500, 6500-6550, 6550-6600, 6600-6650, 6650-6700, 6700-6750, 6750-6800, 6800-6850, 6850-6900, 6900-6950, 6950-7000, 7000-7050, 7050-7100, 7100-7150, 7150-7200, 7200-7250, 7250-7300, 7300-7350, 7350-7400, 7400-7450, 7450-7500, 7500-7550, 7550-7600, 7600-7650, 7650-7700, 7700-7750, 7750-7800, 7800-7850, 7850-7900, 7900-7950, 7950-8000, 8000-8050, 8050-8100, 8100-8150, 8150-8200, 8200-8250, 8250-8300, 8300-8350, 8350-8400, 8400-8450, 8450-8500, 8500-8550, 8550-8600, 8600-8650, 8650-8700, 8700-8750, 8750-8800, 8800-8850, 8850-8900, 8900-8950, 8950-9000, 9000-9050, 9050-9100, 9100-9150, 9150-9200, 9200-9250, 9250-9300, 9300-9350, 9350-9400, 9400-9450, 9450-9500, 9500-9550, 9550-9600, 9600-9650, 9650-9700, 9700-9750, 9750-9800, 9800-9850, 9850-9900, 9900-9950, 9950-10000, 10000-10050, 10050-10100, 10100-10150, 10150-10200, 10200-10250, 10250-10300, 10300-10350, 10350-10400, 10400-10450, 10450-10500, 10500-10550, 10550-10600, 10600-10650, 10650-10700, 10700-10750, 10750-10800, 10800-10850, 10850-10900, 10900-10950, 10950-11000, 11050-11100, 11100-11150, 11150-11200, 11200-11250, 11250-11300, 11300-11350, 11350-11400, 11400-11450, 11450-11500, 11500-11550, 11550-11600, 11600-11650, 11650-11700,

11700-11750, 11750-11800, 11800-11850, 11850-11900, 11900-11950, 11950-12000, 12000-12050, 12050-12100, 12100-12150, 12150-12200, 12200-12250, 12250-12300, 12300-12350, 12350-12400, 12400-12450, 12450-12500, 12500-12550, 12550-12600, 12600-12650, 12650-12700, 12700-12750, 12750-12800, 12800-12850, 12850-12900, 12900-12950, 12950-13000, 13050-13100, 13100-13150, 13150-13200, 13200-13250, 13250-13300, 13300-13350, 13350-13400, 13400-13450, and 13450-13500 on the HTT mRNA sequence. As yet another non-limiting example, the start site may be nucleotide 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 595, 596, 597, 598, 599, 600, 601, 602, 603, 604, 605, 606, 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 619, 620, 621, 622, 623, 624, 625, 715, 716, 717, 718, 719, 720, 721, 722, 723, 724, 725, 875, 876, 877, 878, 879, 880, 881, 882, 883, 884, 885, 886, 887, 888, 889, 890, 891, 892, 893, 894, 895, 896, 897, 898, 899, 900, 1375, 1376, 1377, 1378, 1379, 1380, 1381, 1382, 1383, 1384, 1385, 1386, 1387, 1388, 1389, 1390, 1391, 1392, 1393, 1394, 1395, 1396, 1397, 1398, 1399, 1400, 1401, 1402, 1403, 1404, 1405, 1406, 1407, 1408, 1409, 1410, 1411, 1412, 1413, 1414, 1415, 1416, 1417, 1418, 1419, 1420, 1421, 1422, 1423, 1424, 1425, 1426, 1427, 1428, 1429, 1430, 1431, 1432, 1433, 1434, 1435, 1436, 1437, 1438, 1439, 1440, 1441, 1442, 1443, 1444, 1445, 1446, 1447, 1448, 1449, 1450, 1660, 1661, 1662, 1663, 1664, 1665, 1666, 1667, 1668, 1669, 1670, 1671, 1672, 1673, 1674, 1675, 2050, 2051, 2052, 2053, 2054, 2055, 2056, 2057, 2058, 2059, 2060, 2061, 2062, 2063, 2064, 2065, 2066, 2067, 2068, 2069, 2070, 2071, 2072, 2073, 2074, 2075, 2076, 2077, 2078, 2079, 2080, 2081, 2082, 2083, 2084, 2085, 2086, 2087, 2088, 2089, 2090, 2091, 2092, 2093, 2094, 2095, 2096, 2097, 2098, 2099, 2100, 2580, 2581, 2582, 2583, 2584, 2585, 2586, 2587, 2588, 2589, 2590, 2591, 2592, 2593, 2594, 2595, 2596, 2597, 2598, 2599, 2600, 2601, 2602, 2603, 2604, 2605, 4525, 4526, 4527, 4528, 4529, 4530, 4531, 4532, 4533, 4534, 4535, 4536, 4537, 4538, 4539, 4540, 4541, 4542, 4543, 4544, 4545, 4546, 4547, 4548, 4549, 4550, 4575, 4576, 4577, 4578, 4579, 4580, 4581, 4582, 4583, 4584, 4585, 4586, 4587, 4588, 4589, 4590, 4591, 4592, 4593, 4594, 4595, 4596, 4597, 4598, 4599, 4600, 4850, 4851, 4852, 4853, 4854, 4855, 4856, 4857, 4858, 4859, 4860, 4861, 4862, 4863, 4864, 4865, 4866, 4867, 4868, 4869, 4870, 4871, 4872, 4873, 4874, 4875, 4876, 4877, 4878, 4879, 4880, 4881, 4882, 4883, 4884, 4885, 4886, 4887, 4888, 4889, 4890, 4891, 4892, 4893, 4894, 4895, 4896, 4897, 4898, 4899, 4900, 5460, 5461, 5462, 5463, 5464, 5465, 5466, 5467, 5468, 5469, 5470, 5471, 5472, 5473, 5474, 5475, 5476, 5477, 5478, 5479, 5480, 6175, 6176, 6177, 6178, 6179, 6180, 6181, 6182, 6183, 6184, 6185,

6186, 6187, 6188, 6189, 6190, 6191, 6192, 6193, 6194, 6195, 6196, 6197, 6198, 6199, 6200, 6315, 6316, 6317, 6318, 6319, 6320, 6321, 6322, 6323, 6324, 6325, 6326, 6327, 6328, 6329, 6330, 6331, 6332, 6333, 6334, 6335, 6336, 6337, 6338, 6339, 6340, 6341, 6342, 6343, 6344, 6345, 6600, 6601, 6602, 6603, 6604, 6605, 6606, 6607, 6608, 6609, 6610, 6611, 6612, 6613, 6614, 6615, 6725, 6726, 6727, 6728, 6729, 6730, 6731, 6732, 6733, 6734, 6735, 6736, 6737, 6738, 6739, 6740, 6741, 6742, 6743, 6744, 6745, 6746, 6747, 6748, 6749, 6750, 6751, 6752, 6753, 6754, 6755, 6756, 6757, 6758, 6759, 6760, 6761, 6762, 6763, 6764, 6765, 6766, 6767, 6768, 6769, 6770, 6771, 6772, 6773, 6774, 6775, 7655, 7656, 7657, 7658, 7659, 7660, 7661, 7662, 7663, 7664, 7665, 7666, 7667, 7668, 7669, 7670, 7671, 7672, 8510, 8511, 8512, 8513, 8514, 8515, 8516, 8715, 8716, 8717, 8718, 8719, 8720, 8721, 8722, 8723, 8724, 8725, 8726, 8727, 8728, 8729, 8730, 8731, 8732, 8733, 8734, 8735, 8736, 8737, 8738, 8739, 8740, 8741, 8742, 8743, 8744, 8745, 9250, 9251, 9252, 9253, 9254, 9255, 9256, 9257, 9258, 9259, 9260, 9261, 9262, 9263, 9264, 9265, 9266, 9267, 9268, 9269, 9270, 9480, 9481, 9482, 9483, 9484, 9485, 9486, 9487, 9488, 9489, 9490, 9491, 9492, 9493, 9494, 9495, 9496, 9497, 9498, 9499, 9500, 9575, 9576, 9577, 9578, 9579, 9580, 9581, 9582, 9583, 9584, 9585, 9586, 9587, 9588, 9589, 9590, 10525, 10526, 10527, 10528, 10529, 10530, 10531, 10532, 10533, 10534, 10535, 10536, 10537, 10538, 10539, 10540, 11545, 11546, 11547, 11548, 11549, 11550, 11551, 11552, 11553, 11554, 11555, 11556, 11557, 11558, 11559, 11560, 11875, 11876, 11877, 11878, 11879, 11880, 11881, 11882, 11883, 11884, 11885, 11886, 11887, 11888, 11889, 11890, 11891, 11892, 11893, 11894, 11895, 11896, 11897, 11898, 11899, 11900, 11915, 11916, 11917, 11918, 11919, 11920, 11921, 11922, 11923, 11924, 11925, 11926, 11927, 11928, 11929, 11930, 11931, 11932, 11933, 11934, 11935, 11936, 11937, 11938, 11939, 11940, 13375, 13376, 13377, 13378, 13379, 13380, 13381, 13382, 13383, 13384, 13385, 13386, 13387, 13388, 13389 and 13390 on the HTT mRNA sequence.

[00459] In some embodiments, the antisense strand and target Htt mRNA sequences have 100% complementarity. The antisense strand may be complementary to any part of the target Htt mRNA sequence.

[00460] In other embodiments, the antisense strand and target Htt mRNA sequences comprise at least one mismatch. As a non-limiting example, the antisense strand and the target Htt mRNA sequence have at least 30%, 40%, 50%, 60%, 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-99%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-99%, 40-50%, 40-

60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-99%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-99%, 60-70%, 60-80%, 60-90%, 60-95%, 60-99%, 70-80%, 70-90%, 70-95%, 70-99%, 80-90%, 80-95%, 80-99%, 90-95%, 90-99% or 95-99% complementarity.

[00461] In one embodiment, an siRNA or dsRNA targeting Htt includes at least two sequences that are complementary to each other.

[00462] According to the present invention, the siRNA molecule targeting Htt has a length from about 10-50 or more nucleotides, i.e., each strand comprising 10-50 nucleotides (or nucleotide analogs). Preferably, the siRNA molecule has a length from about 15-30, e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in each strand, wherein one of the strands is sufficiently complementarity to a target region. In one embodiment, each strand of the siRNA molecule has a length from about 19 to 25, 19 to 24 or 19 to 21 nucleotides. In one embodiment, at least one strand of the siRNA molecule is 19 nucleotides in length. In one embodiment, at least one strand of the siRNA molecule is 20 nucleotides in length. In one embodiment, at least one strand of the siRNA molecule is 21 nucleotides in length. In one embodiment, at least one strand of the siRNA molecule is 22 nucleotides in length. In one embodiment, at least one strand of the siRNA molecule is 23 nucleotides in length. In one embodiment, at least one strand of the siRNA molecule is 24 nucleotides in length. In one embodiment, at least one strand of the siRNA molecule is 25 nucleotides in length.

[00463] In some embodiments, the siRNA molecules of the present invention targeting Htt can be synthetic RNA duplexes comprising about 19 nucleotides to about 25 nucleotides, and two overhanging nucleotides at the 3'-end. In some aspects, the siRNA molecules may be unmodified RNA molecules. In other aspects, the siRNA molecules may contain at least one modified nucleotide, such as base, sugar or backbone modifications.

[00464] In one embodiment, the siRNA molecules of the present invention targeting Htt may comprise a nucleotide sequence such as, but not limited to, the antisense (guide) sequences in Table 2 or a fragment or variant thereof. As a non-limiting example, the antisense sequence used in the siRNA molecule of the present invention is at least 30%, 40%, 50%, 60%, 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-99%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-99%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-99%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-99%, 60-70%, 60-80%, 60-90%, 60-95%, 60-

99%, 70-80%, 70-90%, 70-95%, 70-99%, 80-90%, 80-95%, 80-99%, 90-95%, 90-99% or 95-99% of a nucleotide sequence in Table 2. As another non-limiting example, the antisense sequence used in the siRNA molecule of the present invention comprises at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21 or more than 21 consecutive nucleotides of a nucleotide sequence in Table 2. As yet another non-limiting example, the antisense sequence used in the siRNA molecule of the present invention comprises nucleotides 1 to 22, 1 to 21, 1 to 20, 1 to 19, 1 to 18, 1 to 17, 1 to 16, 1 to 15, 1 to 14, 1 to 13, 1 to 12, 1 to 11, 1 to 10, 1 to 9, 1 to 8, 2 to 22, 2 to 21, 2 to 20, 2 to 19, 2 to 18, 2 to 17, 2 to 16, 2 to 15, 2 to 14, 2 to 13, 2 to 12, 2 to 11, 2 to 10, 2 to 9, 2 to 8, 3 to 22, 3 to 21, 3 to 20, 3 to 19, 3 to 18, 3 to 17, 3 to 16, 3 to 15, 3 to 14, 3 to 13, 3 to 12, 3 to 11, 3 to 10, 3 to 9, 3 to 8, 4 to 22, 4 to 21, 4 to 20, 4 to 19, 4 to 18, 4 to 17, 4 to 16, 4 to 15, 4 to 14, 4 to 13, 4 to 12, 4 to 11, 4 to 10, 4 to 9, 4 to 8, 5 to 22, 5 to 21, 5 to 20, 5 to 19, 5 to 18, 5 to 17, 5 to 16, 5 to 15, 5 to 14, 5 to 13, 5 to 12, 5 to 11, 5 to 10, 5 to 9, 5 to 8, 6 to 22, 6 to 21, 6 to 20, 6 to 19, 6 to 18, 6 to 17, 6 to 16, 6 to 15, 6 to 14, 6 to 13, 6 to 12, 6 to 11, 6 to 10, 7 to 22, 7 to 21, 7 to 20, 7 to 19, 7 to 18, 7 to 17, 7 to 16, 7 to 15, 7 to 14, 7 to 13, 7 to 12, 8 to 22, 8 to 21, 8 to 20, 8 to 19, 8 to 18, 8 to 17, 8 to 16, 8 to 15, 8 to 14, 8 to 13, 8 to 12, 9 to 22, 9 to 21, 9 to 20, 9 to 19, 9 to 18, 9 to 17, 9 to 16, 9 to 15, 9 to 14, 10 to 22, 10 to 21, 10 to 20, 10 to 19, 10 to 18, 10 to 17, 10 to 16, 10 to 15, 10 to 14, 11 to 22, 11 to 21, 11 to 20, 11 to 19, 11 to 18, 11 to 17, 11 to 16, 11 to 15, 11 to 14, 12 to 22, 12 to 21, 12 to 20, 12 to 19, 12 to 18, 12 to 17, 12 to 16, 13 to 22, 13 to 21, 13 to 20, 13 to 19, 13 to 18, 13 to 17, 13 to 16, 14 to 22, 14 to 21, 14 to 20, 14 to 19, 14 to 18, 14 to 17, 15 to 22, 15 to 21, 15 to 20, 15 to 19, 15 to 18, 16 to 22, 16 to 21, 16 to 20, 17 to 22, 17 to 21, or 18 to 22 of the sequences in Table 2.

Table 2. Antisense Sequences

Antisense ID	Sequence	SEQ ID NO
A-2000	UUAACGUCAGUUCAUAAACUU	916
A-2000dt	UUAACGUCAGUUCAUAAACdTdT	917
A-2001	UGUCGGUACCGUCUAACACUU	918
A-2001dt	UGUCGGUACCGUCUAACACdTdT	919
A-2002	UAAGCAUGGAGCUAGCAGGUU	920

A-2002dt	UAAGCAUGGAGCUAGCAGGdTdT	921
A-2003	UACAACGAGACUGAAUUGCUU	922
A-2003dt	UACAACGAGACUGAAUUGCdTdT	923
A-2004	UUCAGUUCAUAAACCUGGAUU	924
A-2004dt	UUCAGUUCAUAAACCUGGAdTdT	925
A-2005	UAACGUCAGUUCAUAAACCUU	926
A-2005dt	UAACGUCAGUUCAUAAACCdTdT	927
A-2006	UCCGGUCACAACAUUGUGGUU	928
A-2006dt	UCCGGUCACAACAUUGUGGdTdT	929
A-2007	UUGCACGGUUCUUUGUGACUU	930
A-2007dt	UUGCACGGUUCUUUGUGACdTdT	931
A-2008	UUUUAUAACAAGAGGUUCAUU	932
A-2008dt	UUUUAUAACAAGAGGUUCAdTdT	933
A-2009	UCCAAAUACUGGUUGUCGGUU	934
A-2009dt	UCCAAAUACUGGUUGUCGGdTdT	935
A-2010	UAUUUUAGGAAUUCCAAUGUU	936
A-2010dt	UAUUUUAGGAAUUCCAAUGdTdT	937
A-2011	UUUAGGAAUUCCAAUGAUCUU	938
A-2011dt	UUUAGGAAUUCCAAUGAUCdTdT	939
A-2012dt	UUAAUCUCUUUACUGAUAUdTdT	940
A-2013dt	GAUUUUAGGAAUUCCAAUGdTdT	941
A-2014	UAAGCAUGGAGCUAGCAGGCUU	942
A-2015	UAAGCAUGGAGCUAGCAGGGU	943

A-2016	AAGGACUUGAGGGACUCGAAGU	944
A-2017	AAGGACUUGAGGGACUCGAAG	945
A-2018	AAGGACUUGAGGGACUCGA	946
A-2019	AGGACUUGAGGGACUCGAAGU	947
A-2020	GAGGACUUGAGGGACUCGAAGU	948
A-2021	AAGGACUUGAGGGACUCGAAGU	949
A-2022	AAGGACUUGAGGGACUCGAAGUU	950
A-2023	AAGGACUUGAGGGACUCGAAG	951
A-2024	AAGGACUUGAGGGACUCGA	952
A-2025	AAGGACUUGAGGGACUCGAAGG	953
A-2026	AAGGACUUGAGGGACUCGAAU	954
A-2027	AAGGACUUGAGGGACUCGAAGA	955
A-2028	AAGGACUUGAGGGACUCGAAGG	956
A-2029	AAGGACUUGAGGGACUCGAAGGU	957
A-2030	AAGGACUUGAGGGACUCGAAGGA	958
A-2031	AAGGACUUGAGGGACUCGAAG	959
A-2032	AAGGACUUGAGGGACUCGAAGU	960
A-2033	AAGGACUUGAGGGACUCGA	961
A-2034	AAGGACUUGAGGGACUCGAAGGA	962
A-2035	AAGGACUUGAGGGACUCGAAGG	963
A-2036	AAGGACUUGAGGGACUCGAAGGAU	964
A-2037	AAGGACUUGAGGGACUCGAAGGAUU	965
A-2038	AAGGACUUGAGGGACUCGAAG	966

A-2039	AAGGACUUGAGGGACUCGAAGGAA	967
A-2040	GAUGAAGUGCACACAUUGGAUGA	968
A-2041	GAUGAACUGCACACAUUGGAUG	969
A-2042	GAUGAAUUGCACACAGUAGAUGA	970
A-2043	AAGGACUUGAGGGACUCGAAGGUU	971
A-2044	AAGGACUUGAGGGACUCGAAGGUUU	972
A-2045	AAGGACUUGAGGGACUCGAAGGU	973
A-2046	AAGGACUUGAGGGACUCGAAGGUUUU	974
A-2047	AAGGACUUGAGGGACUCGAAGGUUUUU	975
A-2048	AAGGACUUGAGGGACUCGAAGG	976
A-2049	UAAGGACUUGAGGGACUCGAAG	977
A-2050	AAGGACUUGAGGGACUCGAAG	978
A-2051	AAGGACUUGAGGGACUCGAAGU	979
A-2052	AAGGACUUGAGGGACUCGAAGACGAGUCCC	980
A-2053	AAGGACUUGAGGGACUCGAAGACGAGUCCCA	981
A-2054	AAGGACUUGAGGGACUCGAAGACGAGUCCCU	982
A-2055	GAUGAAGUGCACACAUUGGAUAC	983
A-2056	GAUGAAGUGCACACAUUGGAUACA	984
A-2057	GAUGAAGUGCACACAUUGGAUACAAUGUGU	985
A-2058	GAUGAAGUGCACACAUUGGAU	986
A-2059	GAUGAAGUGCACACAUUGGAUA	987
A-2060	GAUGAAUUGCACACAGUAGAUAU	988
A-2061	GAUGAAUUGCACACAGUAGAUAUAC	989

A-2062	GAUGAAUUGCACACAGUAGAUAUACUGUGU	990
A-2063	GAUGAAUUGCACACAGUAGAUAUA	991
A-2064	AUGAAUUGCACACAGUAGAUAUAC	992
A-2065	GAUGAAUUGCACACAGUAGAUA	993
A-2066	GAUGAAUUGCACACAGUAGAUAUACUGUGU	994
A-2067	UACAACGAGACUGAAUUGCU	995
A-2068	ACAACGAGACUGAAUUGCUU	996
A-2069	UCCGGUCACAACAUUGUGGUUC	997
A-2070	UCCGGUCACAACAUUGUGGU	998
A-2071	UCCGGUCACAACAUUGUG	999
A-2072	CCGGUCACAACAUUGUGGUU	1000
A-2073	UUUUAUAACAAGAGGUUCAU	1001
A-2074	UUUAUAACAAGAGGUUCAUU	1002
A-2075	UAAGCAUGGAGCUAGCAGGU	1003
A-2076	AAGCAUGGAGCUAGCAGGUU	1004
A-2077	CCAAAUACUGGUUGUCGGUU	1005
A-2078	UACAACGAGACUGAAUUGCUUU	1006
A-2079	UAACGUCAGUUCAUAAACCUUU	1007
A-2080	GUCCGGUCACAACAUUGUGGUU	1008
A-2081	UCCGGUCACAACAUUGUGGUUUG	1009
A-2082	UCCGGUCACAACAUUGUGGUUU	1010
A-2083	UCCGGUCACAACAUUGUGG	1011
A-2084	UAAGCAUGGAGCUAGCAGGUUU	1012

A-2085	AAGCAUGGAGCUAGCAGGUUU	1013
A-2086	UCCAAAUACUGGUUGUCGGUUU	1014
A-2087	CCAAAUACUGGUUGUCGGUUU	1015

[00465] In one embodiment, the siRNA molecules of the present invention targeting Htt may comprise a nucleotide sequence such as, but not limited to, the sense (passenger) sequences in Table 3 or a fragment or variant thereof. As a non-limiting example, the sense sequence used in the siRNA molecule of the present invention is at least 30%, 40%, 50%, 60%, 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-99%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-99%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-99%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-99%, 60-70%, 60-80%, 60-90%, 60-95%, 60-99%, 70-80%, 70-90%, 70-95%, 70-99%, 80-90%, 80-95%, 80-99%, 90-95%, 90-99% or 95-99% of a nucleotide sequence in Table 3. As another non-limiting example, the sense sequence used in the siRNA molecule of the present invention comprises at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21 or more than 21 consecutive nucleotides of a nucleotide sequence in Table 3. As yet another non-limiting example, the sense sequence used in the siRNA molecule of the present invention comprises nucleotides 1 to 22, 1 to 21, 1 to 20, 1 to 19, 1 to 18, 1 to 17, 1 to 16, 1 to 15, 1 to 14, 1 to 13, 1 to 12, 1 to 11, 1 to 10, 1 to 9, 1 to 8, 2 to 22, 2 to 21, 2 to 20, 2 to 19, 2 to 18, 2 to 17, 2 to 16, 2 to 15, 2 to 14, 2 to 13, 2 to 12, 2 to 11, 2 to 10, 2 to 9, 2 to 8, 3 to 22, 3 to 21, 3 to 20, 3 to 19, 3 to 18, 3 to 17, 3 to 16, 3 to 15, 3 to 14, 3 to 13, 3 to 12, 3 to 11, 3 to 10, 3 to 9, 3 to 8, 4 to 22, 4 to 21, 4 to 20, 4 to 19, 4 to 18, 4 to 17, 4 to 16, 4 to 15, 4 to 14, 4 to 13, 4 to 12, 4 to 11, 4 to 10, 4 to 9, 4 to 8, 5 to 22, 5 to 21, 5 to 20, 5 to 19, 5 to 18, 5 to 17, 5 to 16, 5 to 15, 5 to 14, 5 to 13, 5 to 12, 5 to 11, 5 to 10, 5 to 9, 5 to 8, 6 to 22, 6 to 21, 6 to 20, 6 to 19, 6 to 18, 6 to 17, 6 to 16, 6 to 15, 6 to 14, 6 to 13, 6 to 12, 6 to 11, 6 to 10, 7 to 22, 7 to 21, 7 to 20, 7 to 19, 7 to 18, 7 to 17, 7 to 16, 7 to 15, 7 to 14, 7 to 13, 7 to 12, 8 to 22, 8 to 21, 8 to 20, 8 to 19, 8 to 18, 8 to 17, 8 to 16, 8 to 15, 8 to 14, 8 to 13, 8 to 12, 9 to 22, 9 to 21, 9 to 20, 9 to 19, 9 to 18, 9 to 17, 9 to 16, 9 to 15, 9 to 14, 10 to 22, 10 to 21, 10 to 20, 10 to 19, 10 to 18, 10 to 17, 10 to 16, 10 to 15, 10 to 14, 11 to 22, 11 to 21, 11 to 20, 11 to 19, 11 to 18, 11 to 17, 11 to 16, 11 to 15, 11 to 14, 12 to 22, 12 to 21, 12 to 20, 12 to 19, 12 to 18, 12 to 17, 12 to 16, 13 to 22, 13 to 21, 13 to

20, 13 to 19, 13 to 18, 13 to 17, 13 to 16, 14 to 22, 14 to 21, 14 to 20, 14 to 19, 14 to 18, 14 to 17, 15 to 22, 15 to 21, 15 to 20, 15 to 19, 15 to 18, 16 to 22, 16 to 21, 16 to 20, 17 to 22, 17 to 21, or 18 to 22 of the sequences in Table 3.

Table 3. Sense Sequences

Sense ID	Sequence	SEQ ID NO
S-1000	GUUUAUGAACUGAUCUUACCC	1016
S-1001	GUGUUAGACGGUACUGAUCCC	1017
S-1002	CCUGCUAGCUCCAUGCUUCCC	1018
S-1003	GUUUAUGAACUGAUCUUAGCC	1019
S-1004	GUGUUAGACGGUACUGAUGCC	1020
S-1005	CCUGCUAGCUCCAUGCUUGCC	1021
S-1006	GUUUAUGAAGUGAUCUUAACC	1022
S-1007	GUGUUAGACCGUACUGAUACC	1023
S-1008	CCUGCUAGCACCAUGCUUACC	1024
S-1009	GUUUAUGAACUGAUCUUAACC	1025
S-1010	GUGUUAGACGGUACUGAUACC	1026
S-1011	CCUGCUAGCUCCAUGCUUACC	1027
S-1011dt	CCUGCUAGCUCCAUGCUUAdTdT	1028
S-1012	GUUUAUGAACUGAUCUUGCCC	1029
S-1013	GUUUAUGAACUGAUCUUGGCC	1030
S-1014	GUUUAUGAACUGAUCUUGACC	1031
S-1015	GCAAUUCAGUCUCGUUGUCCC	1032
S-1016	UCCAGGUUUAUGAACUGACCC	1033
S-1017	GGUUUAUGAACUGACGUUCCC	1034
S-1018	CCACAAUGUUGUGACUGGCCC	1035
S-1019	GUCACAAAGAACCGUGUACCC	1036
S-1020	UGAACCUCUUGUUAUAAACCC	1037
S-1021	CCGACAACCAGUAUUUGGCCC	1038
S-1022	GCAAUUCAGUCUCGUUGUGCC	1039
S-1023	UCCAGGUUUAUGAACUGAGCC	1040
S-1024	GGUUUAUGAACUGACGUUGCC	1041
S-1025	CCACAAUGUUGUGACUGGGCC	1042

S-1026	GUCACAAAGAACCGUGUAGCC	1043
S-1027	UGAACCUCUUGUUAUAAAGCC	1044
S-1028	CCGACAACCAGUAUUUGGGCC	1045
S-1029	GCAAUUCAGUCUCGUUGUACC	1046
S-1029dt	GCAAUUCAGUCUCGUUGUAdTdT	1047
S-1030	UCCAGGUUUAUGAACUGAACC	1048
S-1030dt	UCCAGGUUUAUGAACUGAAdTdT	1049
S-1031	GGUUUAUGAACUGACGUUACC	1050
S-1032	CCACAAUGUUGUGACUGGACC	1051
S-1033	GUCACAAAGAACCGUGUAACC	1052
S-1034	UGAACCUCUUGUUAUAAAACC	1053
S-1034dt	UGAACCUCUUGUUAUAAAAdTdT	1054
S-1035	CCGACAACCAGUAUUUGGACC	1055
S-1035dt	CCGACAACCAGUAUUUGGAdTdT	1056
S-1036	GCAAUUCAGACUCGUUGUACC	1057
S-1037	UCCAGGUUUUUGAACUGAACC	1058
S-1038	GGUUUAUGAUCUGACGUUACC	1059
S-1039	CCACAAUGUAGUGACUGGACC	1060
S-1040	GUCACAAAGUACCGUGUAACC	1061
S-1041	UGAACCUCUAGUUAUAAAACC	1062
S-1042	CCGACAACCUGUAUUUGGACC	1063
S-1043	CAUUGGAAUUCCUAAAAUUCC	1064
S-1044	GAUCAUUGGAAUUCCUAAUCC	1065
S-1045	CAUUGGAAUUCCUAAAAUGCC	1066
S-1046	GAUCAUUGGAAUUCCUAAGCC	1067
S-1047	CAUUGGAAUUCCUAAAAUACC	1068
S-1047dt	CAUUGGAAUUCCUAAAAUAdTdT	1069
S-1048	GAUCAUUGGAAUUCCUAAACC	1070
S-1048dt	GAUCAUUGGAAUUCCUAAAdTdT	1071
S-1049	CAUUGGAAUACCUAAAAUACC	1072
S-1050	GAUCAUUGGUAUUCCUAAACC	1073
S-1051dt	GUUUAUGAACUGACGUUAAdTdT	1074

S-1052dt	GUGUUAGACGGUACCGACAdTdT	1075
S-1053dt	AUAUCAGUAAAGAGAUUAAdTdT	1076
S-1054dt	GGUUUAUGAACUGACGUUAdTdT	1077
S-1055dt	CCACAAUGUUGUGACCGGAdTdT	1078
S-1056dt	GUCACAAAGAACCGUGCAAdTdT	1079
S-1057dt	CAUUGGAAUUCCUAAAAUCdTdT	1080
S-1058	CCUGCUAGCUCCAUGCUUGCU	1081
S-1059	CCUGCUAGCUCCAUGCUUGAU	1082
S-1060	CCUGCUAGCUCCAUGCUUAUU	1083
S-1061	CCUGCUAGCUCCAUGCUUGUU	1084
S-1062	UUCGAGUCCCUCAAGUAGCU	1085
S-1063	UUCGAGUCCCUCAAGUAGCUUU	1086
S-1064	UCGAGUCCCUCAAGUCCAUUCU	1087
S-1065	UUCCAGUCCAUCAAGUCAAUU	1088
S-1066	UUCCGAGUCUAAAAGUCCUUGG	1089
S-1067	UUCCGAGUCUAAAAGUCCUUGGC	1090
S-1068	CUUCCGAGUCUAAAAGUCCUUGG	1091
S-1069	UUCCGAGUCUAAAAGUCCUUGGU	1092
S-1070	UUCCGAGUCUAAAAGUCCUUGGCU	1093
S-1071	UCCAAUGUGAAACUUCAUCGGCU	1094
S-1072	UCCAAUGUGAAACUUCAUCGGC	1095
S-1073	AUCCAAUGUGAAACUUCAUCGU	1096
S-1074	AUCCAAUGUGAAACUUCAUCGGU	1097
S-1075	UCCAAUGUGAAACUUCAUCGGU	1098
S-1076	UCCAAUGUGAAACUUCAUCGGCUU	1099
S-1077	AUCUACUGUGAAAAUUCAUCGG	1100
S-1078	UCUACUGUGAAAAUUCAUCGG	1101
S-1079	UCUACUGUGAAAAUUCAUCGGC	1102
S-1080	AUCUACUGUGAAAAUUCAUCGGU	1103
S-1081	UCUACUGUGAAAAUUCAUCGGU	1104
S-1082	UCUACUGUGAAAAUUCAUCGGCU	1105
S-1083	CCUUCGGUCCUCAAGUCCUUCA	1106

S-1084	UUCGAGUCCAUCAAAUCCUAUAGU	1107
S-1085	UACAAUGUGUGCACUUCAUAU	1108
S-1086	UAUACUGUGUGCAAUUCAUUUCU	1109
S-1087	GCAAUUCAGUCUCGUUGUCC	1110
S-1088	GCAAUUCAGUCUCGUUGUC	1111
S-1089	CAAUUCAGUCUCGUUGUCCC	1112
S-1090	CAAUUCAGUCUCGUUGUCC	1113
S-1091	GCAAUUCAGUCUCGUUGUGC	1114
S-1092	CAAUUCAGUCUCGUUGUGCC	1115
S-1093	CCACAAUGUUGUGACUGGGCCU	1116
S-1094	CCACAAUGUUGUGACUGGGC	1117
S-1095	CACAAUGUUGUGACUGGGCC	1118
S-1096	UGAACCUCUUGUUAUAAAGCCU	1119
S-1097	UGAACCUCUUGUUAUAAAGC	1120
S-1098	GAACCUCUUGUUAUAAAGCC	1121
S-1099	CCUGCUAGCUCCAUGCUUGCCU	1122
S-1100	CCUGCUAGCUCCAUGCUUGC	1123
S-1101	CCUGCUAGCUCCAUGCUUG	1124
S-1102	CUGCUAGCUCCAUGCUUGCC	1125
S-1103	CCGACAACCAGUAUUUGGGCCU	1126
S-1104	CCGACAACCAGUAUUUGGGC	1127
S-1105	CCGACAACCAGUAUUUGGG	1128
S-1106	CGACAACCAGUAUUUGGGCC	1129
S-1107	CGACAACCAGUAUUUGGGC	1130
S-1108	GCAAUUCAGUCUCGUUGUACCU	1131
S-1109	GCAAUUCAGUCUCGUUGUAC	1132
S-1110	GCAAUUCAGUCUCGUUGUA	1133
S-1111	CAAUUCAGUCUCGUUGUACC	1134
S-1112	GCAAUUCAGACUCGUUGUACCU	1135
S-1113	GCAAUUCAGACUCGUUGUAC	1136
S-1114	GCAAUUCAGACUCGUUGUA	1137
S-1115	CAAUUCAGACUCGUUGUACC	1138

S-1116	AGCAAUUCAGUCUCGUUGUACC	1139
S-1117	AGCAAUUCAGUCUCGUUGUAC	1140
S-1118	AGGUUUAUGAACUGACGUUAC	1141
S-1119	AGGUUUAUGAACUGACGUUACC	1142
S-1120	ACCACAAUGUUGUGACUGGAC	1143
S-1121	ACCACAAUGUUGUGACUGGACC	1144
S-1122	CCACAAUGUUGUGACUGGACCGU	1145
S-1123	CCACAAUGUUGUGACUGGACCG	1146
S-1124	CCACAAUGUUGUGACUGGAC	1147
S-1125	CACAAUGUUGUGACUGGACC	1148
S-1126	ACCUGCUAGCUCCAUGCUUCCC	1149
S-1127	ACCUGCUAGCUCCAUGCUUCC	1150
S-1128	ACCUGCUAGCUCCAUGCUUC	1151
S-1129	CCUGCUAGCUCCAUGCUUCC	1152
S-1130	CCUGCUAGCUCCAUGCUUC	1153
S-1131	CUGCUAGCUCCAUGCUUCCC	1154
S-1132	CUGCUAGCUCCAUGCUUCC	1155
S-1133	ACCGACAACCAGUAUUUGGACC	1156
S-1134	ACCGACAACCAGUAUUUGGAC	1157
S-1135	CCGACAACCAGUAUUUGGACCGU	1158
S-1136	CCGACAACCAGUAUUUGGACCGU	1159
S-1137	CCGACAACCAGUAUUUGGAC	1160
S-1138	CGACAACCAGUAUUUGGACC	1161
S-1139	CCUGCUAGCACCGUGCUUACC	1162

[00466] In one embodiment, the siRNA molecules of the present invention targeting Htt may comprise an antisense sequence from Table 2 and a sense sequence from Table 3, or a fragment or variant thereof. As a non-limiting example, the antisense sequence and the sense sequence have at least 30%, 40%, 50%, 60%, 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-99%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-99%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-99%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-99%, 60-

70%, 60-80%, 60-90%, 60-95%, 60-99%, 70-80%, 70-90%, 70-95%, 70-99%, 80-90%, 80-95%, 80-99%, 90-95%, 90-99% or 95-99% complementarity.

[00467] In one embodiment, the siRNA molecules of the present invention targeting Htt may comprise the sense and antisense siRNA duplex as described in Tables 4-6. As a non-limiting example, these siRNA duplexes may be tested for in vitro inhibitory activity on endogenous HTT gene expression. The start site for the sense and antisense sequence is compared to HTT gene sequence known as NM_002111.7 (SEQ ID NO: 1163) from NCBI.

Table 4. Sense and antisense strand sequences of HTT dsRNA

siRNA Duplex ID	SS ID	Start SS	Sense Strand Sequence (5'-3')	SS SEQ ID	AS ID	Start AS	Antisense Strand Sequence (5'-3')	AS SEQ ID
D-3566	S-1058	6751	CCUGCUAGCUCCAUGCUUGCU	1081	A-2002	6751	UAAGCAUGGAGCUAGCAGGUU	920
D-3567	S-1058	6751	CCUGCUAGCUCCAUGCUUGCU	1081	A-2014	6748	UAAGCAUGGAGCUAGCAGGCUU	942
D-3568	S-1059	6751	CCUGCUAGCUCCAUGCUUGAU	1082	A-2002	6751	UAAGCAUGGAGCUAGCAGGUU	920
D-3569	S-1060	6751	CCUGCUAGCUCCAUGCUUAUU	1083	A-2015	6751	UAAGCAUGGAGCUAGCAGGGU	943
D-3570	S-1061	6751	CCUGCUAGCUCCAUGCUUGUU	1084	A-2002	6751	UAAGCAUGGAGCUAGCAGGUU	920
D-3500	S-1016	1386	UCCAGGUUUAUGAACUGACCC	1033	A-2004	1386	UUCAGUUCAUAAACCUGGAUU	924
D-3501	S-1023	1386	UCCAGGUUUAUGAACUGAGCC	1040	A-2004	1386	UUCAGUUCAUAAACCUGGAUU	924
D-3502	S-1030	1386	UCCAGGUUUAUGAACUGAACC	1048	A-2004	1386	UUCAGUUCAUAAACCUGGAUU	924
D-3503	S-1037	1386	UCCAGGUUUUUGAACUGAACC	1058	A-2004	1386	UUCAGUUCAUAAACCUGGAUU	924
D-3504	S-1030	1386	UCCAGGUUUAUGAACUGAACC	1048	A-2001	2066	UGUCGGUACCGUCUAACACUU	918
D-3505	S-1017	1390	GGUUUAUGAACUGACGUUCCC	1034	A-2005	1389	UAACGUCAGUUCAUAAACCUU	926
D-3506	S-1024	1390	GGUUUAUGAACUGACGUUGCC	1041	A-2005	1389	UAACGUCAGUUCAUAAACCUU	926
D-3507	S-1031	1390	GGUUUAUGAACUGACGUUACC	1050	A-2005	1389	UAACGUCAGUUCAUAAACCUU	926
D-3508	S-1038	1390	GGUUUAUGAUCUGACGUUACC	1059	A-2005	1389	UAACGUCAGUUCAUAAACCUU	926
D-3509	S-1000	1391	GUUUAUGAACUGAUCUUACCC	1016	A-2000	1391	UUAACGUCAGUUCAUAAACUU	916
D-3510	S-1003	1391	GUUUAUGAACUGAUCUUAGCC	1019	A-2000	1391	UUAACGUCAGUUCAUAAACUU	916
D-3511	S-1006	1391	GUUUAUGAAGUGAUCUUAACC	1022	A-2000	1391	UUAACGUCAGUUCAUAAACUU	916
D-3512	S-1009	1391	GUUUAUGAACUGAUCUUAACC	1025	A-2000	1391	UUAACGUCAGUUCAUAAACUU	916
D-3513	S-1012	1391	GUUUAUGAACUGAUCUUGCCC	1029	A-2000	1391	UUAACGUCAGUUCAUAAACUU	916

D-3514	S-1013	1391	GUUUAUGAACUGAUCUUGGCC	1030	A-2000	1391	UUAACGUCAGUUCAUAAACUU	916
D-3515	S-1014	1391	GUUUAUGAACUGAUCUUGACC	1031	A-2000	1391	UUAACGUCAGUUCAUAAACUU	916
D-3516	S-1018	1429	CCACAAUGUUGUGACUGGCCC	1035	A-2006	1428	UCCGGUCACAACAUUGUGGUU	928
D-3517	S-1025	1429	CCACAAUGUUGUGACUGGGCC	1042	A-2006	1428	UCCGGUCACAACAUUGUGGUU	928
D-3518	S-1032	1429	CCACAAUGUUGUGACUGGACC	1051	A-2006	1428	UCCGGUCACAACAUUGUGGUU	928
D-3519	S-1039	1429	CCACAAUGUAGUGACUGGACC	1060	A-2006	1428	UCCGGUCACAACAUUGUGGUU	928
D-3520	S-1001	2066	GUGUUAGACGGUACUGAUCCC	1017	A-2001	2066	UGUCGGUACCGUCUAACACUU	918
D-3521	S-1004	2066	GUGUUAGACGGUACUGAUGCC	1020	A-2001	2066	UGUCGGUACCGUCUAACACUU	918
D-3522	S-1007	2066	GUGUUAGACCGUACUGAUACC	1023	A-2001	2066	UGUCGGUACCGUCUAACACUU	918
D-3523	S-1010	2066	GUGUUAGACGGUACUGAUACC	1026	A-2001	2066	UGUCGGUACCGUCUAACACUU	918
D-3524	S-1021	2079	CCGACAACCAGUAUUUGGCCC	1038	A-2009	2078	UCCAAAUACUGGUUGUCGGUU	934
D-3525	S-1028	2079	CCGACAACCAGUAUUUGGGCC	1045	A-2009	2078	UCCAAAUACUGGUUGUCGGUU	934
D-3526	S-1035	2079	CCGACAACCAGUAUUUGGACC	1055	A-2009	2078	UCCAAAUACUGGUUGUCGGUU	934
D-3527	S-1042	2079	CCGACAACCUGUAUUUGGACC	1063	A-2009	2078	UCCAAAUACUGGUUGUCGGUU	934
D-3528	S-1019	4544	GUCACAAAGAACCGUGUACCC	1036	A-2007	4544	UUGCACGGUUCUUUGUGACUU	930
D-3529	S-1026	4544	GUCACAAAGAACCGUGUAGCC	1043	A-2007	4544	UUGCACGGUUCUUUGUGACUU	930
D-3530	S-1033	4544	GUCACAAAGAACCGUGUAACC	1052	A-2007	4544	UUGCACGGUUCUUUGUGACUU	930
D-3531	S-1040	4544	GUCACAAAGUACCGUGUAACC	1061	A-2007	4544	UUGCACGGUUCUUUGUGACUU	930
D-3532	S-1020	4597	UGAACCUCUUGUUAUAAACCC	1037	A-2008	4597	UUUUAUAACAAGAGGUUCAUU	932
D-3533	S-1027	4597	UGAACCUCUUGUUAUAAAGCC	1044	A-2008	4597	UUUUAUAACAAGAGGUUCAUU	932
D-3534	S-1034	4597	UGAACCUCUUGUUAUAAAACC	1053	A-2008	4597	UUUUAUAACAAGAGGUUCAUU	932
D-3535	S-1041	4597	UGAACCUCUAGUUAUAAAACC	1062	A-2008	4597	UUUUAUAACAAGAGGUUCAUU	932
D-3536	S-1044	4861	GAUCAUUGGAAUUCCUAAUCC	1065	A-2011	4860	UUUAGGAAUUCCAAUGAUCUU	938
D-3537	S-1046	4861	GAUCAUUGGAAUUCCUAAGCC	1067	A-2011	4860	UUUAGGAAUUCCAAUGAUCUU	938
D-3538	S-1048	4861	GAUCAUUGGAAUUCCUAAACC	1070	A-2011	4860	UUUAGGAAUUCCAAUGAUCUU	938
D-3539	S-1050	4861	GAUCAUUGGUAUUCCUAAACC	1073	A-2011	4860	UUUAGGAAUUCCAAUGAUCUU	938
D-3540	S-1043	4864	CAUUGGAAUUCCUAAAAUUCC	1064	A-2010	4864	UAUUUUAGGAAUUCCAAUGUU	936

D-3541	S-1045	4864	CAUUGGAAUUCCUAAAAUGCC	1066	A-2010	4864	UAUUUUAGGAAUUCCAAUGUU	936
D-3542	S-1047	4864	CAUUGGAAUUCCUAAAAUACC	1068	A-2010	4864	UAUUUUAGGAAUUCCAAUGUU	936
D-3543	S-1049	4864	CAUUGGAAUACCUAAAAUACC	1072	A-2010	4864	UAUUUUAGGAAUUCCAAUGUU	936
D-3544	S-1015	6188	GCAAUUCAGUCUCGUUGUCCC	1032	A-2003	6188	UACAACGAGACUGAAUUGCUU	922
D-3545	S-1022	6188	GCAAUUCAGUCUCGUUGUGCC	1039	A-2003	6188	UACAACGAGACUGAAUUGCUU	922
D-3546	S-1029	6188	GCAAUUCAGUCUCGUUGUACC	1046	A-2003	6188	UACAACGAGACUGAAUUGCUU	922
D-3547	S-1036	6188	GCAAUUCAGACUCGUUGUACC	1057	A-2003	6188	UACAACGAGACUGAAUUGCUU	922
D-3548	S-1002	6751	CCUGCUAGCUCCAUGCUUCCC	1018	A-2002	6751	UAAGCAUGGAGCUAGCAGGUU	920
D-3549	S-1005	6751	CCUGCUAGCUCCAUGCUUGCC	1021	A-2002	6751	UAAGCAUGGAGCUAGCAGGUU	920
D-3550	S-1008	6751	CCUGCUAGCACCAUGCUUACC	1024	A-2002	6751	UAAGCAUGGAGCUAGCAGGUU	920
D-3551	S-1011	6751	CCUGCUAGCUCCAUGCUUACC	1027	A-2002	6751	UAAGCAUGGAGCUAGCAGGUU	920

Table 5. Sense and antisense strand sequences of HTT dsRNA

siRNA Duplex ID	SS ID	Start SS	Sense Strand Sequence (5'-3')	SS SEQ ID	AS ID	Start AS	Antisense Strand Sequence (5'-3')	AS SEQ ID
D-3552	S-1051dt	1391	GUUUAUGAACUGACGUUAAdTdT	1074	A-2000dt	1391	UUAACGUCAGUUCAUAAACdTdT	917
D-3553	S-1052dt	2066	GUGUUAGACGGUACCGACAdTdT	1075	A-2001dt	2066	UGUCGGUACCGUCUAACACdTdT	919
D-3554	S-1011dt	6751	CCUGCUAGCUCCAUGCUUAdTdT	1028	A-2002dt	6751	UAAGCAUGGAGCUAGCAGGdTdT	921
D-3555	S-1053dt	10322	AUAUCAGUAAAGAGAUUAAdTdT	1076	A-2012dt	10322	UUAAUCUCUUUACUGAUAUdTdT	940
D-3556	S-1030dt	1386	UCCAGGUUUAUGAACUGAAdTdT	1049	A-2004dt	1386	UUCAGUUCAUAAACCUGGAdTdT	925
D-3557	S-1054dt	1390	GGUUUAUGAACUGACGUUAdTdT	1077	A-2005dt	1390	UAACGUCAGUUCAUAAACCdTdT	927
D-3558	S-1055dt	1429	CCACAAUGUUGUGACCGGAdTdT	1078	A-2006dt	1429	UCCGGUCACAACAUUGUGGdTdT	929
D-3559	S-1035dt	2079	CCGACAACCAGUAUUUGGAdTdT	1056	A-2009dt	2079	UCCAAAUACUGGUUGUCGGdTdT	935
D-3560	S-1056dt	4544	GUCACAAAGAACCGUGCAAdTdT	1079	A-2007dt	4544	UUGCACGGUUCUUUGUGACdTdT	931
D-3561	S-1034dt	4597	UGAACCUCUUGUUAUAAAAdTdT	1054	A-2008dt	4597	UUUUAUAACAAGAGGUUCAdTdT	933
D-3562	S-1029dt	6188	GCAAUUCAGUCUCGUUGUAdTdT	1047	A-2003dt	6188	UACAACGAGACUGAAUUGCdTdT	923
D-3563	S-1047dt	4864	CAUUGGAAUUCCUAAAAUAdTdT	1069	A-2010dt	4864	UAUUUUAGGAAUUCCAAUGdTdT	937
D-3564	S-1048dt	4861	GAUCAUUGGAAUUCCUAAAdTdT	1071	A-2011dt	4861	UUUAGGAAUUCCAAUGAUCdTdT	939

D-3565	S-1057dt	4864	CAUUGGAAUUCCUA AAAUCdTdT	1080	A-2013dt	4864	GAUUUUAGGAAUU CCAAUGdTdT	941

Table 6. Antisense and Sense strand sequences of HTT dsRNA

siRNA Duplex ID	AS ID	Start AS	Antisense Strand Sequence (5'-3')	AS SEQ ID	SS ID	Start SS	Sense Strand Sequence (5'-3')	SS SEQ ID
D-3569	S-1060	6751	CCUGCUAGCUCCA UGCUUAUU	1083	A-2015	6751	UAAGCAUGGAGCU AGCAGGGU	943
D-3570	S-1061	6751	CCUGCUAGCUCCA UGCUUGUU	1084	A-2002	6751	UAAGCAUGGAGCU AGCAGGUU	920

[00468] In other embodiments, the siRNA molecules of the present invention targeting Htt can be encoded in plasmid vectors, AAV particles, viral genome or other nucleic acid expression vectors for delivery to a cell.

[00469] DNA expression plasmids can be used to stably express the siRNA duplexes or dsRNA of the present invention targeting Htt in cells and achieve long-term inhibition of the target gene expression. In one aspect, the sense and antisense strands of a siRNA duplex are typically linked by a short spacer sequence leading to the expression of a stem-loop structure termed short hairpin RNA (shRNA). The hairpin is recognized and cleaved by Dicer, thus generating mature siRNA molecules.

[00470] According to the present invention, AAV particles comprising the nucleic acids encoding the siRNA molecules targeting HTT mRNA are produced, the AAV serotypes may be any of the serotypes listed in Table 1. Non-limiting examples of the AAV serotypes include, AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV9.47, AAV9(hu14), AAV10, AAV11, AAV12, AAVrh8, AAVrh10, AAV-DJ8, AAV-DJ, AAV-PHP.A, and/or AAV-PHP.B, and variants thereof.

[00471] In some embodiments, the siRNA duplexes or encoded dsRNA of the present invention suppress (or degrade) HTT mRNA. Accordingly, the siRNA duplexes or encoded dsRNA can be used to substantially inhibit HTT gene expression in a cell, for example a neuron. In some aspects, the inhibition of HTT gene expression refers to an inhibition by at least about 20%, preferably by at least about 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95% and 100%, or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% or 95-100%. Accordingly,

the protein product of the targeted gene may be inhibited by at least about 20%, preferably by at least about 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95% and 100%, or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% or 95-100%.

[00472] According to the present invention, the siRNA molecules are designed and tested for their ability in reducing HTT mRNA levels in cultured cells. Such siRNA molecules may form a duplex such as, but not limited to, include those listed in Table 4, Table 5 or Table 6. As a non-limiting example, the siRNA duplexes may be siRNA duplex IDs: D-3500 to D-3570.

[00473] In one embodiment, the siRNA molecules comprise a miRNA seed match for HTT located in the guide strand. In another embodiment, the siRNA molecules comprise a miRNA seed match for HTT located in the passenger strand. In yet another embodiment, the siRNA duplexes or encoded dsRNA targeting HTT gene do not comprise a seed match for HTT located in the guide or passenger strand.

[00474] In one embodiment, the siRNA duplexes or encoded dsRNA targeting HTT gene may have almost no significant full-length off target effects for the guide strand. In another embodiment, the siRNA duplexes or encoded dsRNA targeting HTT gene may have almost no significant full-length off target effects for the passenger strand. The siRNA duplexes or encoded dsRNA targeting HTT gene may have less than 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%,11%, 12%, 13%, 14%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 1-5%, 2-6%, 3-7%, 4-8%, 5-9%, 5-10%, 6-10%, 5-15%, 5-20%, 5-25% 5-30%, 10-20%, 10-30%, 10-40%, 10-50%, 15-30%, 15-40%, 15-45%, 20-40%, 20-50%, 25-50%, 30-40%, 30-50%, 35-50%, 40-50%, 45-50% full-length off target effects for the passenger strand. In yet another embodiment, the siRNA duplexes or encoded dsRNA targeting HTT gene may have almost no significant full-length off target effects for the guide strand or the passenger strand. The siRNA duplexes or encoded dsRNA targeting HTT gene may have less than 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%,11%, 12%, 13%, 14%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 1-5%, 2-6%, 3-7%, 4-8%, 5-9%, 5-10%, 6-10%, 5-15%, 5-20%, 5-25% 5-30%, 10-20%, 10-30%, 10-40%, 10-50%, 15-30%, 15-40%, 15-45%, 20-40%, 20-50%, 25-50%, 30-40%, 30-50%, 35-50%, 40-50%, 45-50% full-length off target effects for the guide or passenger strand.

[00475] In one embodiment, the siRNA duplexes or encoded dsRNA targeting HTT gene may have high activity in vitro. In another embodiment, the siRNA molecules may have low activity in vitro. In yet another embodiment, the siRNA duplexes or dsRNA targeting the HTT gene may have high guide strand activity and low passenger strand activity in vitro.

[00476] In one embodiment, the siRNA molecules targeting HTT have a high guide strand activity and low passenger strand activity in vitro. The target knock-down (KD) by the guide strand may be at least 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, 99.5% or 100%. The target knock-down by the guide strand may be 40-50%, 45-50%, 50-55%, 50-60%, 60-65%, 60-70%, 60-75%, 60-80%, 60-85%, 60-90%, 60-95%, 60-99%, 60-99.5%, 60-100%, 65-70%, 65-75%, 65-80%, 65-85%, 65-90%, 65-95%, 65-99%, 65-99.5%, 65-100%, 70-75%, 70-80%, 70-85%, 70-90%, 70-95%, 70-99%, 70-99.5%, 70-100%, 75-80%, 75-85%, 75-90%, 75-95%, 75-99%, 75-99.5%, 75-100%, 80-85%, 80-90%, 80-95%, 80-99%, 80-99.5%, 80-100%, 85-90%, 85-95%, 85-99%, 85-99.5%, 85-100%, 90-95%, 90-99%, 90-99.5%, 90-100%, 95-99%, 95-99.5%, 95-100%, 99-99.5%, 99-100% or 99.5-100%. As a non-limiting example, the target knock-down (KD) by the guide strand is greater than 70%. As a non-limiting example, the target knock-down (KD) by the guide strand is greater than 60%.

[00477] In one embodiment, the siRNA duplex target HTT is designed so there is no miRNA seed match for the sense or antisense sequence to the non-Htt sequence.

[00478] In one embodiment, the IC_{50} of the guide strand in the siRNA duplex targeting HTT for the nearest off target is greater than 100 multiplied by the IC_{50} of the guide strand for the on-target gene, Htt. As a non-limiting example, if the IC_{50} of the guide strand for the nearest off target is greater than 100 multiplied by the IC_{50} of the guide strand for the target then the siRNA molecule is said to have high guide strand selectivity for inhibiting Htt in vitro.

[00479] In one embodiment, the 5' processing of the guide strand of the siRNA duplex targeting HTT has a correct start (n) at the 5' end at least 75%, 80%, 85%, 90%, 95%, 99% or 100% of the time in vitro or in vivo. As a non-limiting example, the 5' processing of the guide strand is precise and has a correct start (n) at the 5' end at least 99% of the time in vitro. As a non-limiting example, the 5' processing of the guide strand is precise and has a correct start (n) at the 5' end at least 99% of the time in vivo. As a non-limiting example, the 5' processing of the guide strand is precise and has a correct start (n) at the 5' end at least 90% of the time in vitro. As a non-limiting example, the 5' processing of the guide strand is precise and has a correct start (n) at the 5' end at least 90% of the time in vivo. As a non-limiting example, the 5' processing of the guide strand is precise and has a correct start (n) at the 5' end at least 85% of the time in vitro. As a

non-limiting example, the 5' processing of the guide strand is precise and has a correct start (n) at the 5' end at least 85% of the time in vivo.

[00480] In one embodiment, a passenger-guide strand duplex for HTT is considered effective when the pri- or pre-microRNAs demonstrate, by methods known in the art and described herein, greater than 2-fold guide to passenger strand ratio when processing is measured. As a non-limiting examples, the pri- or pre-microRNAs demonstrate great than 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, 11-fold, 12-fold, 13-fold, 14-fold, 15-fold, or 2 to 5-fold, 2 to 10-fold, 2 to 15-fold, 3 to 5-fold, 3 to 10-fold, 3 to 15-fold, 4 to 5-fold, 4 to 10-fold, 4 to 15-fold, 5 to 10-fold, 5 to 15-fold, 6 to 10-fold, 6 to 15-fold, 7 to 10-fold, 7 to 15-fold, 8 to 10-fold, 8 to 15-fold, 9 to 10-fold, 9 to 15-fold, 10 to 15-fold, 11 to 15-fold, 12 to 15-fold, 13 to 15-fold, or 14 to 15-fold guide to passenger strand ratio when processing is measured.

[00481] In one embodiment, the siRNA molecules may be used to silence wild type or mutant HTT by targeting at least one exon on the htt sequence. The exon may be exon 1, exon 2, exon 3, exon 4, exon 5, exon 6, exon 7, exon 8, exon 9, exon 10, exon 11, exon 12, exon 13, exon 14, exon 15, exon 16, exon 17, exon 18, exon 19, exon 20, exon 21, exon 22, exon 23, exon 24, exon 25, exon 26, exon 27, exon 28, exon 29, exon 30, exon 31, exon 32, exon 33, exon 34, exon 35, exon 36, exon 37, exon 38, exon 39, exon 40, exon 41, exon 42, exon 43, exon 44, exon 45, exon 46, exon 47, exon 48, exon 49, exon 50, exon 51, exon 52, exon 53, exon 54, exon 55, exon 56, exon 57, exon 58, exon 59, exon 60, exon 61, exon 62, exon 63, exon 64, exon 65, exon 66, and/or exon 67. As a non-limiting example, the siRNA molecules may be used to silence wild type or mutant HTT by targeting exon 1. As another non-limiting example, the siRNA molecules may be used to silence wild type or mutant HTT by targeting an exon other than exon 1. As another non-limiting example, the siRNA molecules may be used to silence wild type or mutant HTT by targeting exon 50. As another non-limiting example, the siRNA molecules may be used to silence wild type or mutant HTT by targeting exon 67.

[00482] In one embodiment, the siRNA molecules may be used to silence wild type and/or mutant HTT by targeting at least one exon on the htt sequence. The exon may be exon 1, exon 2, exon 3, exon 4, exon 5, exon 6, exon 7, exon 8, exon 9, exon 10, exon 11, exon 12, exon 13, exon 14, exon 15, exon 16, exon 17, exon 18, exon 19, exon 20, exon 21, exon 22, exon 23, exon 24, exon 25, exon 26, exon 27, exon 28, exon 29, exon 30, exon 31, exon 32, exon 33, exon 34, exon 35, exon 36, exon 37, exon 38, exon 39, exon 40, exon 41, exon 42, exon 43, exon 44, exon 45, exon 46, exon 47, exon 48, exon 49, exon 50, exon 51, exon 52, exon 53, exon 54, exon 55, exon 56, exon 57, exon 58, exon 59, exon 60, exon 61, exon 62, exon 63, exon 64, exon 65, exon

66, and/or exon 67. As a non-limiting example, the siRNA molecules may be used to silence wild type and/or mutant HTT by targeting exon 1. As another non-limiting example, the siRNA molecules may be used to silence wild type and/or mutant HTT by targeting an exon other than exon 1. As another non-limiting example, the siRNA molecules may be used to silence wild type and/or mutant HTT by targeting exon 50. As another non-limiting example, the siRNA molecules may be used to silence wild type and/or mutant HTT by targeting exon 67.

Design and Sequences of siRNA duplexes targeting SOD1 gene

[00483] The present invention provides small interfering RNA (siRNA) duplexes (and modulatory polynucleotides encoding them) that target SOD1 mRNA to interfere with SOD1 gene expression and/or SOD1 protein production.

[00484] The encoded siRNA duplex of the present invention contains an antisense strand and a sense strand hybridized together forming a duplex structure, wherein the antisense strand is complementary to the nucleic acid sequence of the targeted SOD1 gene, and wherein the sense strand is homologous to the nucleic acid sequence of the targeted SOD1 gene. In some aspects, the 5'end of the antisense strand has a 5' phosphate group and the 3'end of the sense strand contains a 3'hydroxyl group. In other aspects, there are none, one or 2 nucleotide overhangs at the 3'end of each strand.

[00485] Some guidelines for designing siRNAs have been proposed in the art. These guidelines generally recommend generating a 19-nucleotide duplexed region, symmetric 2-3 nucleotide 3'overhangs, 5'- phosphate and 3'- hydroxyl groups targeting a region in the gene to be silenced. Other rules that may govern siRNA sequence preference include, but are not limited to, (i) A/U at the 5′ end of the antisense strand; (ii) G/C at the 5′ end of the sense strand; (iii) at least five A/U residues in the 5′ terminal one-third of the antisense strand; and (iv) the absence of any GC stretch of more than 9 nucleotides in length. In accordance with such consideration, together with the specific sequence of a target gene, highly effective siRNA molecules essential for suppressing the SOD1 gene expression may be readily designed.

[00486] According to the present invention, siRNA molecules (e.g., siRNA duplexes or encoded dsRNA) that target the SOD1 gene are designed. Such siRNA molecules can specifically, suppress SOD1 gene expression and protein production. In some aspects, the siRNA molecules are designed and used to selectively "knock out" SOD1 gene variants in cells, i.e., mutated SOD1 transcripts that are identified in patients with ALS disease. In some aspects, the siRNA molecules are designed and used to selectively "knock down" SOD1

gene variants in cells. In other aspects, the siRNA molecules are able to inhibit or suppress both the wild type and mutated SOD1 gene.

[00487] In one embodiment, an siRNA molecule of the present invention comprises a sense strand and a complementary antisense strand in which both strands are hybridized together to form a duplex structure. The antisense strand has sufficient complementarity to the SOD1 mRNA sequence to direct target-specific RNAi, i.e., the siRNA molecule has a sequence sufficient to trigger the destruction of the target mRNA by the RNAi machinery or process.

[00488] In one embodiment, an siRNA molecule of the present invention comprises a sense strand and a complementary antisense strand in which both strands are hybridized together to form a duplex structure and where the start site of the hybridization to the SOD1 mRNA is between nucleotide 15 and 1000 on the SOD1 mRNA sequence. As a non-limiting example, the start site may be between nucleotide 15-25, 15-50, 15-75, 15-100, 100-150, 150-200, 200-250, 250-300, 300-350, 350-400, 400-450, 450-500, 500-550, 550-600, 600-650, 650-700, 700-70, 750-800, 800-850, 850-900, 900-950, and 950-1000 on the SOD1 mRNA sequence. As yet another non-limiting example, the start site may be nucleotide 26, 27, 28, 29, 30, 32, 33, 34, 35, 36, 37, 74, 76, 77, 78, 149, 153, 157, 160, 177, 192, 193, 195, 196, 197, 198, 199, 206, 209, 210, 239, 241, 261, 263, 264, 268, 269, 276, 278, 281, 284, 290, 291, 295, 296, 316, 317, 329, 330, 337, 350, 351, 352, 354, 357, 358, 364, 375, 378, 383, 384, 390, 392, 395, 404, 406, 417, 418, 469, 470, 475, 476, 480, 487, 494, 496, 497, 501, 504, 515, 518, 522, 523, 524, 552, 554, 555, 562, 576, 577, 578, 579, 581, 583, 584, 585, 587, 588, 589, 593, 594, 595, 596, 597, 598, 599, 602, 607, 608, 609, 610, 611, 612, 613, 616, 621, 633, 635, 636, 639, 640, 641, 642, 643, 644, 645, 654, 660, 661, 666, 667, 668, 669, 673, 677, 692, 698, 699, 700, 701, 706, 749, 770, 772, 775, 781, 800, 804, 819, 829, 832, 833, 851, 854, 855, 857, 858, 859, 861, 869, 891, 892, 906, 907, 912, 913, 934, 944, and 947 on the SOD1 mRNA sequence.

[00489] In some embodiments, the antisense strand and target SOD1 mRNA sequences have 100% complementarity. The antisense strand may be complementary to any part of the target SOD1 mRNA sequence.

[00490] In other embodiments, the antisense strand and target SOD1 mRNA sequences comprise at least one mismatch. As a non-limiting example, the antisense strand and the target SOD1 mRNA sequence have at least 30%, 40%, 50%, 60%, 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%

or 99% or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-99%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-99%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-99%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-99%, 60-70%, 60-80%, 60-90%, 60-95%, 60-99%, 70-80%, 70-90%, 70-95%, 70-99%, 80-90%, 80-95%, 80-99%, 90-95%, 90-99% or 95-99% complementarity.

[00491] In one embodiment, an siRNA or dsRNA targeting SOD1 includes at least two sequences that are complementary to each other.

[00492] According to the present invention, the siRNA molecule targeting SOD1 has a length from about 10-50 or more nucleotides, i.e., each strand comprising 10-50 nucleotides (or nucleotide analogs). Preferably, the siRNA molecule has a length from about 15-30, e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in each strand, wherein one of the strands is sufficiently complementarity to a target region. In one embodiment, each strand of the siRNA molecule has a length from about 19 to 25, 19 to 24 or 19 to 21 nucleotides. In one embodiment, at least one strand of the siRNA molecule is 19 nucleotides in length. In one embodiment, at least one strand of the siRNA molecule is 20 nucleotides in length. In one embodiment, at least one strand of the siRNA molecule is 21 nucleotides in length. In one embodiment, at least one strand of the siRNA molecule is 22 nucleotides in length. In one embodiment, at least one strand of the siRNA molecule is 23 nucleotides in length. In one embodiment, at least one strand of the siRNA molecule is 24 nucleotides in length. In one embodiment, at least one strand of the siRNA molecule is 25 nucleotides in length.

[00493] In some embodiments, the siRNA molecules of the present invention targeting SOD1 can be synthetic RNA duplexes comprising about 19 nucleotides to about 25 nucleotides, and two overhanging nucleotides at the 3'-end. In some aspects, the siRNA molecules may be unmodified RNA molecules. In other aspects, the siRNA molecules may contain at least one modified nucleotide, such as base, sugar or backbone modifications.

[00494] In one embodiment, the siRNA molecules of the present invention targeting SOD1 may comprise a nucleotide sequence such as, but not limited to, the antisense (guide) sequences in Table 7 or a fragment or variant thereof. As a non-limiting example, the antisense sequence used in the siRNA molecule of the present invention is at least 30%, 40%, 50%, 60%, 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-99%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-

90%, 30-95%, 30-99%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-99%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-99%, 60-70%, 60-80%, 60-90%, 60-95%, 60-99%, 70-80%, 70-90%, 70-95%, 70-99%, 80-90%, 80-95%, 80-99%, 90-95%, 90-99% or 95-99% of a nucleotide sequence in Table 7. As another non-limiting example, the antisense sequence used in the siRNA molecule of the present invention comprises at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21 or more than 21 consecutive nucleotides of a nucleotide sequence in Table 7. As yet another non-limiting example, the antisense sequence used in the siRNA molecule of the present invention comprises nucleotides 1 to 22, 1 to 21, 1 to 20, 1 to 19, 1 to 18, 1 to 17, 1 to 16, 1 to 15, 1 to 14, 1 to 13, 1 to 12, 1 to 11, 1 to 10, 1 to 9, 1 to 8, 2 to 22, 2 to 21, 2 to 20, 2 to 19, 2 to 18, 2 to 17, 2 to 16, 2 to 15, 2 to 14, 2 to 13, 2 to 12, 2 to 11, 2 to 10, 2 to 9, 2 to 8, 3 to 22, 3 to 21, 3 to 20, 3 to 19, 3 to 18, 3 to 17, 3 to 16, 3 to 15, 3 to 14, 3 to 13, 3 to 12, 3 to 11, 3 to 10, 3 to 9, 3 to 8, 4 to 22, 4 to 21, 4 to 20, 4 to 19, 4 to 18, 4 to 17, 4 to 16, 4 to 15, 4 to 14, 4 to 13, 4 to 12, 4 to 11, 4 to 10, 4 to 9, 4 to 8, 5 to 22, 5 to 21, 5 to 20, 5 to 19, 5 to 18, 5 to 17, 5 to 16, 5 to 15, 5 to 14, 5 to 13, 5 to 12, 5 to 11, 5 to 10, 5 to 9, 5 to 8, 6 to 22, 6 to 21, 6 to 20, 6 to 19, 6 to 18, 6 to 17, 6 to 16, 6 to 15, 6 to 14, 6 to 13, 6 to 12, 6 to 11, 6 to 10, 7 to 22, 7 to 21, 7 to 20, 7 to 19, 7 to 18, 7 to 17, 7 to 16, 7 to 15, 7 to 14, 7 to 13, 7 to 12, 8 to 22, 8 to 21, 8 to 20, 8 to 19, 8 to 18, 8 to 17, 8 to 16, 8 to 15, 8 to 14, 8 to 13, 8 to 12, 9 to 22, 9 to 21, 9 to 20, 9 to 19, 9 to 18, 9 to 17, 9 to 16, 9 to 15, 9 to 14, 10 to 22, 10 to 21, 10 to 20, 10 to 19, 10 to 18, 10 to 17, 10 to 16, 10 to 15, 10 to 14, 11 to 22, 11 to 21, 11 to 20, 11 to 19, 11 to 18, 11 to 17, 11 to 16, 11 to 15, 11 to 14, 12 to 22, 12 to 21, 12 to 20, 12 to 19, 12 to 18, 12 to 17, 12 to 16, 13 to 22, 13 to 21, 13 to 20, 13 to 19, 13 to 18, 13 to 17, 13 to 16, 14 to 22, 14 to 21, 14 to 20, 14 to 19, 14 to 18, 14 to 17, 15 to 22, 15 to 21, 15 to 20, 15 to 19, 15 to 18, 16 to 22, 16 to 21, 16 to 20, 17 to 22, 17 to 21, or 18 to 22 of the sequences in Table 7.

Table 7. Antisense Sequences

Antisense ID	Sequence	SEQ ID NO
A-3000	UUUAUAGGCCAGACCUCCGdTdT	1164
A-3001	UUUUAUAGGCCAGACCUCCdTdT	1165
A-3002	UCUUUAUAGGCCAGACCUCdTdT	1166
A-3003	UACUUUAUAGGCCAGACCUdTdT	1167

A-3004	UUACUUUAUAGGCCAGACCdTdT	1168
A-3005	UACUACUUUAUAGGCCAGAdTdT	1169
A-3006	UGACUACUUUAUAGGCCAGdTdT	1170
A-3007	UCGACUACUUUAUAGGCCAdTdT	1171
A-3008	UGCGACUACUUUAUAGGCCdTdT	1172
A-3009	UCGCGACUACUUUAUAGGCdTdT	1173
A-3010	UCCGCGACUACUUUAUAGGdTdT	1174
A-3011	UGCUGCAGGAGACUACGACdTdT	1175
A-3012	UACGCUGCAGGAGACUACGdTdT	1176
A-3013	UGACGCUGCAGGAGACUACdTdT	1177
A-3014	UAGACGCUGCAGGAGACUAdTdT	1178
A-3015	UCACGGCCUUCGUCGCCAUdTdT	1179
A-3016	UCGCACACGGCCUUCGUCGdTdT	1180
A-3017	UAGCACGCACACGGCCUUCdTdT	1181
A-3018	UUUCAGCACGCACACGGCCdTdT	1182
A-3019	UGCACUGGGCCGUCGCCCUdTdT	1183
A-3020	UAAUUGAUGAUGCCCUGCAdTdT	1184
A-3021	UAAAUUGAUGAUGCCCUGCdTdT	1185
A-3022	UCGAAAUUGAUGAUGCCCUdTdT	1186
A-3023	UUCGAAAUUGAUGAUGCCCdTdT	1187
A-3024	UCUCGAAAUUGAUGAUGCCdTdT	1188
A-3025	UGCUCGAAAUUGAUGAUGCdTdT	1189
A-3026	UUGCUCGAAAUUGAUGAUGdTdT	1190

A-3027	UUUCCUUCUGCUCGAAAUUdTdT	1191
A-3028	UACUUUCCUUCUGCUCGAAdTdT	1192
A-3029	UUACUUUCCUUCUGCUCGAdTdT	1193
A-3030	UAAUGCUUCCCCACACCUUdTdT	1194
A-3031	UUUAAUGCUUCCCCACACCdTdT	1195
A-3032	UGCAGGCCUUCAGUCAGUCdTdT	1196
A-3033	UAUGCAGGCCUUCAGUCAGdTdT	1197
A-3034	UCAUGCAGGCCUUCAGUCAdTdT	1198
A-3035	UAAUCCAUGCAGGCCUUCAdTdT	1199
A-3036	UGAAUCCAUGCAGGCCUUCdTdT	1200
A-3037	UGAACAUGGAAUCCAUGCAdTdT	1201
A-3038	UAUGAACAUGGAAUCCAUGdTdT	1202
A-3039	UCUCAUGAACAUGGAAUCCdTdT	1203
A-3040	UAAACUCAUGAACAUGGAAdTdT	1204
A-3041	UAUCUCCAAACUCAUGAACdTdT	1205
A-3042	UUAUCUCCAAACUCAUGAAdTdT	1206
A-3043	UGUAUUAUCUCCAAACUCAdTdT	1207
A-3044	UUGUAUUAUCUCCAAACUCdTdT	1208
A-3045	UCCUGCACUGGUACAGCCUdTdT	1209
A-3046	UACCUGCACUGGUACAGCCdTdT	1210
A-3047	UAUUAAAGUGAGGACCUGCdTdT	1211
A-3048	UGAUUAAAGUGAGGACCUGdTdT	1212
A-3049	UGAUAGAGGAUUAAAGUGAdTdT	1213

A-3050	UACCGUGUUUUCUGGAUAGdTdT	1214
A-3051	UCACCGUGUUUUCUGGAUAdTdT	1215
A-3052	UCCACCGUGUUUUCUGGAUdTdT	1216
A-3053	UGCCCACCGUGUUUUCUGGdTdT	1217
A-3054	UUUGGCCCACCGUGUUUUCdTdT	1218
A-3055	UUUUGGCCCACCGUGUUUUdTdT	1219
A-3056	UUCAUCCUUUGGCCCACCGdTdT	1220
A-3057	UCAUGCCUCUCUUCAUCCUdTdT	1221
A-3058	UCAACAUGCCUCUCUUCAUdTdT	1222
A-3059	UGUCUCCAACAUGCCUCUCdTdT	1223
A-3060	UAGUCUCCAACAUGCCUCUdTdT	1224
A-3061	UUGCCCAAGUCUCCAACAUdTdT	1225
A-3062	UAUUGCCCAAGUCUCCAACdTdT	1226
A-3063	UCACAUUGCCCAAGUCUCCdTdT	1227
A-3064	UGUCAGCAGUCACAUUGCCdTdT	1228
A-3065	UUUGUCAGCAGUCACAUUGdTdT	1229
A-3066	UCCACACCAUCUUUGUCAGdTdT	1230
A-3067	UGCCACACCAUCUUUGUCAdTdT	1231
A-3068	UAUGCAAUGGUCUCCUGAGdTdT	1232
A-3069	UGAUGCAAUGGUCUCCUGAdTdT	1233
A-3070	UCCAAUGAUGCAAUGGUCUdTdT	1234
A-3071	UGCCAAUGAUGCAAUGGUCdTdT	1235
A-3072	UUGCGGCCAAUGAUGCAAUdTdT	1236

A-3073	UACCAGUGUGCGGCCAAUGdTdT	1237
A-3074	UAUGGACCACCAGUGUGCGdTdT	1238
A-3075	UUCAUGGACCACCAGUGUGdTdT	1239
A-3076	UUUCAUGGACCACCAGUGUdTdT	1240
A-3077	UCUUUUUCAUGGACCACCAdTdT	1241
A-3078	UCUGCUUUUUCAUGGACCAdTdT	1242
A-3079	UGCCCAAGUCAUCUGCUUUdTdT	1243
A-3080	UUUUGCCCAAGUCAUCUGCdTdT	1244
A-3081	UCACCUUUGCCCAAGUCAUdTdT	1245
A-3082	UCCACCUUUGCCCAAGUCAdTdT	1246
A-3083	UUCCACCUUUGCCCAAGUCdTdT	1247
A-3084	UCGUUUCCUGUCUUUGUACdTdT	1248
A-3085	UAGCGUUUCCUGUCUUUGUdTdT	1249
A-3086	UCAGCGUUUCCUGUCUUUGdTdT	1250
A-3087	UCGACUUCCAGCGUUUCCUdTdT	1251
A-3088	UCACCACAAGCCAAACGACdTdT	1252
A-3089	UACACCACAAGCCAAACGAdTdT	1253
A-3090	UUACACCACAAGCCAAACGdTdT	1254
A-3091	UUUACACCACAAGCCAAACdTdT	1255
A-3092	UAAUUACACCACAAGCCAAdTdT	1256
A-3093	UCCAAUUACACCACAAGCCdTdT	1257
A-3094	UCCCAAUUACACCACAAGCdTdT	1258
A-3095	UUCCCAAUUACACCACAAGdTdT	1259

A-3096	UGAUCCCAAUUACACCACAdTdT	1260
A-3097	UCGAUCCCAAUUACACCACdTdT	1261
A-3098	UGCGAUCCCAAUUACACCAdTdT	1262
A-3099	UUUGGGCGAUCCCAAUUACdTdT	1263
A-3100	UAUUGGGCGAUCCCAAUUAdTdT	1264
A-3101	UUAUUGGGCGAUCCCAAUUdTdT	1265
A-3102	UUUAUUGGGCGAUCCCAAUdTdT	1266
A-3103	UUUUAUUGGGCGAUCCCAAdTdT	1267
A-3104	UGUUUAUUGGGCGAUCCCAdTdT	1268
A-3105	UUGUUUAUUGGGCGAUCCCdTdT	1269
A-3106	UGAAUGUUUAUUGGGCGAUdTdT	1270
A-3107	UCAAGGGAAUGUUUAUUGGdTdT	1271
A-3108	UCCAAGGGAAUGUUUAUUGdTdT	1272
A-3109	UUCCAAGGGAAUGUUUAUUdTdT	1273
A-3110	UAUCCAAGGGAAUGUUUAUdTdT	1274
A-3111	UCAUCCAAGGGAAUGUUUAdTdT	1275
A-3112	UACAUCCAAGGGAAUGUUUdTdT	1276
A-3113	UUACAUCCAAGGGAAUGUUdTdT	1277
A-3114	UGACUACAUCCAAGGGAAUdTdT	1278
A-3115	UCCUCAGACUACAUCCAAGdTdT	1279
A-3116	UUGAGUUAAGGGGCCUCAGdTdT	1280
A-3117	UGAUGAGUUAAGGGGCCUCdTdT	1281
A-3118	UAGAUGAGUUAAGGGGCCUdTdT	1282

A-3119	UAACAGAUGAGUUAAGGGGdTdT	1283
A-3120	UUAACAGAUGAGUUAAGGGdTdT	1284
A-3121	UAUAACAGAUGAGUUAAGGdTdT	1285
A-3122	UGAUAACAGAUGAGUUAAGdTdT	1286
A-3123	UGGAUAACAGAUGAGUUAAdTdT	1287
A-3124	UAGGAUAACAGAUGAGUUAdTdT	1288
A-3125	UCAGGAUAACAGAUGAGUUdTdT	1289
A-3126	UUACAGCUAGCAGGAUAACdTdT	1290
A-3127	UCAUUUCUACAGCUAGCAGdTdT	1291
A-3128	UACAUUUCUACAGCUAGCAdTdT	1292
A-3129	UAGGAUACAUUUCUACAGCdTdT	1293
A-3130	UCAGGAUACAUUUCUACAGdTdT	1294
A-3131	UUCAGGAUACAUUUCUACAdTdT	1295
A-3132	UAUCAGGAUACAUUUCUACdTdT	1296
A-3133	UGUUUAUCAGGAUACAUUUdTdT	1297
A-3134	UUAAUGUUUAUCAGGAUACdTdT	1298
A-3135	UUAAGAUUACAGUGUUUAAdTdT	1299
A-3136	UCACUUUUAAGAUUACAGUdTdT	1300
A-3137	UACACUUUUAAGAUUACAGdTdT	1301
A-3138	UUACACUUUUAAGAUUACAdTdT	1302
A-3139	UUUACACUUUUAAGAUUACdTdT	1303
A-3140	UCACAAUUACACUUUUAAGdTdT	1304
A-3141	UAGUUUCUCACUACAGGUAdTdT	1305

A-3142	UUCUUCCAAGUGAUCAUAAdTdT	1306
A-3143	UAAUCUUCCAAGUGAUCAUdTdT	1307
A-3144	UACAAAUCUUCCAAGUGAUdTdT	1308
A-3145	UAACUAUACAAAUCUUCCAdTdT	1309
A-3146	UUUUUAACUGAGUUUUAUAdTdT	1310
A-3147	UGACAUUUUAACUGAGUUUdTdT	1311
A-3148	UCAGGUCAUUGAAACAGACdTdT	1312
A-3149	UUGGCAAAAUACAGGUCAUdTdT	1313
A-3150	UGUCUGGCAAAAUACAGGUdTdT	1314
A-3151	UAGUCUGGCAAAAUACAGGdTdT	1315
A-3152	UAUACCCAUCUGUGAUUUAdTdT	1316
A-3153	UUUAAUACCCAUCUGUGAUdTdT	1317
A-3154	UUUUAAUACCCAUCUGUGAdTdT	1318
A-3155	UAGUUUAAUACCCAUCUGUdTdT	1319
A-3156	UAAGUUUAAUACCCAUCUGdTdT	1320
A-3157	UCAAGUUUAAUACCCAUCUdTdT	1321
A-3158	UGACAAGUUUAAUACCCAUdTdT	1322
A-3159	UGAAAUUCUGACAAGUUUAdTdT	1323
A-3160	UAUUCACAGGCUUGAAUGAdTdT	1324
A-3161	UUAUUCACAGGCUUGAAUGdTdT	1325
A-3162	UCCAUACAGGGUUUUUAUUdTdT	1326
A-3163	UGCCAUACAGGGUUUUUAUdTdT	1327
A-3164	UUAAGUGCCAUACAGGGUUdTdT	1328

A-3165	UAUAAGUGCCAUACAGGGUdTdT	1329
A-3166	UGAUUCUUUUAAUAGCCUCdTdT	1330
A-3167	UUUUGAAUUUGGAUUCUUUdTdT	1331
A-3168	UUAGUUUGAAUUUGGAUUCdTdT	1332

[00495] In one embodiment, the siRNA molecules of the present invention targeting SOD1 may comprise a nucleotide sequence such as, but not limited to, the sense (passenger) sequences in Table 8 or a fragment or variant thereof. As a non-limiting example, the sense sequence used in the siRNA molecule of the present invention is at least 30%, 40%, 50%, 60%, 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-99%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-99%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-99%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-99%, 60-70%, 60-80%, 60-90%, 60-95%, 60-99%, 70-80%, 70-90%, 70-95%, 70-99%, 80-90%, 80-95%, 80-99%, 90-95%, 90-99% or 95-99% of a nucleotide sequence in Table 8. As another non-limiting example, the sense sequence used in the siRNA molecule of the present invention comprises at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21 or more than 21 consecutive nucleotides of a nucleotide sequence in Table 8. As yet another non-limiting example, the sense sequence used in the siRNA molecule of the present invention comprises nucleotides 1 to 22, 1 to 21, 1 to 20, 1 to 19, 1 to 18, 1 to 17, 1 to 16, 1 to 15, 1 to 14, 1 to 13, 1 to 12, 1 to 11, 1 to 10, 1 to 9, 1 to 8, 2 to 22, 2 to 21, 2 to 20, 2 to 19, 2 to 18, 2 to 17, 2 to 16, 2 to 15, 2 to 14, 2 to 13, 2 to 12, 2 to 11, 2 to 10, 2 to 9, 2 to 8, 3 to 22, 3 to 21, 3 to 20, 3 to 19, 3 to 18, 3 to 17, 3 to 16, 3 to 15, 3 to 14, 3 to 13, 3 to 12, 3 to 11, 3 to 10, 3 to 9, 3 to 8, 4 to 22, 4 to 21, 4 to 20, 4 to 19, 4 to 18, 4 to 17, 4 to 16, 4 to 15, 4 to 14, 4 to 13, 4 to 12, 4 to 11, 4 to 10, 4 to 9, 4 to 8, 5 to 22, 5 to 21, 5 to 20, 5 to 19, 5 to 18, 5 to 17, 5 to 16, 5 to 15, 5 to 14, 5 to 13, 5 to 12, 5 to 11, 5 to 10, 5 to 9, 5 to 8, 6 to 22, 6 to 21, 6 to 20, 6 to 19, 6 to 18, 6 to 17, 6 to 16, 6 to 15, 6 to 14, 6 to 13, 6 to 12, 6 to 11, 6 to 10, 7 to 22, 7 to 21, 7 to 20, 7 to 19, 7 to 18, 7 to 17, 7 to 16, 7 to 15, 7 to 14, 7 to 13, 7 to 12, 8 to 22, 8 to 21, 8 to 20, 8 to 19, 8 to 18, 8 to 17, 8 to 16, 8 to 15, 8 to 14, 8 to 13, 8 to 12, 9 to 22, 9 to 21, 9 to 20, 9 to 19, 9 to 18, 9 to 17, 9 to 16, 9 to 15, 9 to 14, 10 to 22, 10 to 21, 10 to 20, 10 to 19, 10 to 18, 10 to 17, 10 to 16, 10 to 15, 10

to 14, 11 to 22, 11 to 21, 11 to 20, 11 to 19, 11 to 18, 11 to 17, 11 to 16, 11 to 15, 11 to 14, 12 to 22, 12 to 21, 12 to 20, 12 to 19, 12 to 18, 12 to 17, 12 to 16, 13 to 22, 13 to 21, 13 to 20, 13 to 19, 13 to 18, 13 to 17, 13 to 16, 14 to 22, 14 to 21, 14 to 20, 14 to 19, 14 to 18, 14 to 17, 15 to 22, 15 to 21, 15 to 20, 15 to 19, 15 to 18, 16 to 22, 16 to 21, 16 to 20, 17 to 22, 17 to 21, or 18 to 22 of the sequences in Table 8.

Table 8. Sense Sequences

Sense ID	Sequence	SEQ ID NO
S-3000	CGGAGGUCUGGCCUAUAACdTdT	1333
S-3001	GGAGGUCUGGCCUAUAAACdTdT	1334
S-3002	GAGGUCUGGCCUAUAAAGCdTdT	1335
S-3003	AGGUCUGGCCUAUAAAGUCdTdT	1336
S-3004	GGUCUGGCCUAUAAAGUACdTdT	1337
S-3005	UCUGGCCUAUAAAGUAGUCdTdT	1338
S-3006	CUGGCCUAUAAAGUAGUCCdTdT	1339
S-3007	UGGCCUAUAAAGUAGUCGCdTdT	1340
S-3008	GGCCUAUAAAGUAGUCGCCdTdT	1341
S-3009	GCCUAUAAAGUAGUCGCGCdTdT	1342
S-3010	CCUAUAAAGUAGUCGCGGCdTdT	1343

S-3011	GUCGUAGUCUCCUGCAGCCdTdT	1344
S-3012	CGUAGUCUCCUGCAGCGUCdTdT	1345
S-3013	GUAGUCUCCUGCAGCGUCCdTdT	1346
S-3014	UAGUCUCCUGCAGCGUCUCdTdT	1347
S-3015	AUGGCGACGAAGGCCGUGCdTdT	1348
S-3016	CGACGAAGGCCGUGUGCGCdTdT	1349
S-3017	GAAGGCCGUGUGCGUGCUCdTdT	1350
S-3018	GGCCGUGUGCGUGCUGAACdTdT	1351
S-3019	AGGGCGACGGCCCAGUGCCdTdT	1352
S-3020	UGCAGGGCAUCAUCAAUUCdTdT	1353
S-3021	GCAGGGCAUCAUCAAUUUCdTdT	1354
S-3022	AGGGCAUCAUCAAUUUCGCdTdT	1355
S-3023	GGGCAUCAUCAAUUUCGACdTdT	1356
S-3024	GGCAUCAUCAAUUUCGAGCdTdT	1357

S-3025	GCAUCAUCAAUUUCGAGCCdTdT	1358
S-3026	CAUCAUCAAUUUCGAGCACdTdT	1359
S-3027	AAUUUCGAGCAGAAGGAACdTdT	1360
S-3028	UUCGAGCAGAAGGAAAGUCdTdT	1361
S-3029	UCGAGCAGAAGGAAAGUACdTdT	1362
S-3030	AAGGUGUGGGGAAGCAUUCdTdT	1363
S-3031	GGUGUGGGGAAGCAUUAACdTdT	1364
S-3032	GACUGACUGAAGGCCUGCCdTdT	1365
S-3033	CUGACUGAAGGCCUGCAUCdTdT	1366
S-3034	UGACUGAAGGCCUGCAUGCdTdT	1367
S-3035	UGAAGGCCUGCAUGGAUUCdTdT	1368
S-3036	GAAGGCCUGCAUGGAUUCCdTdT	1369
S-3037	UGCAUGGAUUCCAUGUUCCdTdT	1370
S-3038	CAUGGAUUCCAUGUUCAUCdTdT	1371

S-3039	GGAUUCCAUGUUCAUGAGCdTdT	1372
S-3040	UUCCAUGUUCAUGAGUUUCdTdT	1373
S-3041	GUUCAUGAGUUUGGAGAUCdTdT	1374
S-3042	UUCAUGAGUUUGGAGAUACdTdT	1375
S-3043	UGAGUUUGGAGAUAAUACCdTdT	1376
S-3044	GAGUUUGGAGAUAAUACACdTdT	1377
S-3045	AGGCUGUACCAGUGCAGGCdTdT	1378
S-3046	GGCUGUACCAGUGCAGGUCdTdT	1379
S-3047	GCAGGUCCUCACUUUAAUCdTdT	1380
S-3048	CAGGUCCUCACUUUAAUCCdTdT	1381
S-3049	UCACUUUAAUCCUCUAUCCdTdT	1382
S-3050	CUAUCCAGAAAACACGGUCdTdT	1383
S-3051	UAUCCAGAAAACACGGUGCdTdT	1384
S-3052	AUCCAGAAAACACGGUGGCdTdT	1385

S-3053	CCAGAAAACACGGUGGGCCdTdT	1386
S-3054	GAAAACACGGUGGGCCAACdTdT	1387
S-3055	AAAACACGGUGGGCCAAACdTdT	1388
S-3056	CGGUGGGCCAAAGGAUGACdTdT	1389
S-3057	AGGAUGAAGAGAGGCAUGCdTdT	1390
S-3058	AUGAAGAGAGGCAUGUUGCdTdT	1391
S-3059	GAGAGGCAUGUUGGAGACCdTdT	1392
S-3060	AGAGGCAUGUUGGAGACUCdTdT	1393
S-3061	AUGUUGGAGACUUGGGCACdTdT	1394
S-3062	GUUGGAGACUUGGGCAAUCdTdT	1395
S-3063	GGAGACUUGGGCAAUGUGCdTdT	1396
S-3064	GGCAAUGUGACUGCUGACCdTdT	1397
S-3065	CAAUGUGACUGCUGACAACdTdT	1398
S-3066	CUGACAAAGAUGGUGUGGCdTdT	1399

S-3067	UGACAAAGAUGGUGUGGCCdTdT	1400
S-3068	CUCAGGAGACCAUUGCAUCdTdT	1401
S-3069	UCAGGAGACCAUUGCAUCCdTdT	1402
S-3070	AGACCAUUGCAUCAUUGGCdTdT	1403
S-3071	GACCAUUGCAUCAUUGGCCdTdT	1404
S-3072	AUUGCAUCAUUGGCCGCACdTdT	1405
S-3073	CAUUGGCCGCACACUGGUCdTdT	1406
S-3074	CGCACACUGGUGGUCCAUCdTdT	1407
S-3075	CACACUGGUGGUCCAUGACdTdT	1408
S-3076	ACACUGGUGGUCCAUGAACdTdT	1409
S-3077	UGGUGGUCCAUGAAAAAGCdTdT	1410
S-3078	UGGUCCAUGAAAAAGCAGCdTdT	1411
S-3079	AAAGCAGAUGACUUGGGCCdTdT	1412
S-3080	GCAGAUGACUUGGGCAAACdTdT	1413

S-3081	AUGACUUGGGCAAAGGUGCdTdT	1414
S-3082	UGACUUGGGCAAAGGUGGCdTdT	1415
S-3083	GACUUGGGCAAAGGUGGACdTdT	1416
S-3084	GUACAAAGACAGGAAACGCdTdT	1417
S-3085	ACAAAGACAGGAAACGCUCdTdT	1418
S-3086	CAAAGACAGGAAACGCUGCdTdT	1419
S-3087	AGGAAACGCUGGAAGUCGCdTdT	1420
S-3088	GUCGUUUGGCUUGUGGUGCdTdT	1421
S-3089	UCGUUUGGCUUGUGGUGUCdTdT	1422
S-3090	CGUUUGGCUUGUGGUGUACdTdT	1423
S-3091	GUUUGGCUUGUGGUGUAACdTdT	1424
S-3092	UUGGCUUGUGGUGUAAUUCdTdT	1425
S-3093	GGCUUGUGGUGUAAUUGGCdTdT	1426
S-3094	GCUUGUGGUGUAAUUGGGCdTdT	1427

S-3095	CUUGUGGUGUAAUUGGGACdTdT	1428
S-3096	UGUGGUGUAAUUGGGAUCCdTdT	1429
S-3097	GUGGUGUAAUUGGGAUCGCdTdT	1430
S-3098	UGGUGUAAUUGGGAUCGCCdTdT	1431
S-3099	GUAAUUGGGAUCGCCCAACdTdT	1432
S-3100	UAAUUGGGAUCGCCCAAUCdTdT	1433
S-3101	AAUUGGGAUCGCCCAAUACdTdT	1434
S-3102	AUUGGGAUCGCCCAAUAACdTdT	1435
S-3103	UUGGGAUCGCCCAAUAAACdTdT	1436
S-3104	UGGGAUCGCCCAAUAAACCdTdT	1437
S-3105	GGGAUCGCCCAAUAAACACdTdT	1438
S-3106	AUCGCCCAAUAAACAUUCCdTdT	1439
S-3107	CCAAUAAACAUUCCCUUGCdTdT	1440
S-3108	CAAUAAACAUUCCCUUGGCdTdT	1441

S-3109	AAUAAACAUUCCCUUGGACdTdT	1442
S-3110	AUAAACAUUCCCUUGGAUCdTdT	1443
S-3111	UAAACAUUCCCUUGGAUGCdTdT	1444
S-3112	AAACAUUCCCUUGGAUGUCdTdT	1445
S-3113	AACAUUCCCUUGGAUGUACdTdT	1446
S-3114	AUUCCCUUGGAUGUAGUCCdTdT	1447
S-3115	CUUGGAUGUAGUCUGAGGCdTdT	1448
S-3116	CUGAGGCCCCUUAACUCACdTdT	1449
S-3117	GAGGCCCCUUAACUCAUCCdTdT	1450
S-3118	AGGCCCCUUAACUCAUCUCdTdT	1451
S-3119	CCCCUUAACUCAUCUGUUCdTdT	1452
S-3120	CCCUUAACUCAUCUGUUACdTdT	1453
S-3121	CCUUAACUCAUCUGUUAUCdTdT	1454
S-3122	CUUAACUCAUCUGUUAUCCdTdT	1455

S-3123	UUAACUCAUCUGUUAUCCCdTdT	1456
S-3124	UAACUCAUCUGUUAUCCUCdTdT	1457
S-3125	AACUCAUCUGUUAUCCUGCdTdT	1458
S-3126	GUUAUCCUGCUAGCUGUACdTdT	1459
S-3127	CUGCUAGCUGUAGAAAUGCdTdT	1460
S-3128	UGCUAGCUGUAGAAAUGUCdTdT	1461
S-3129	GCUGUAGAAAUGUAUCCUCdTdT	1462
S-3130	CUGUAGAAAUGUAUCCUGCdTdT	1463
S-3131	UGUAGAAAUGUAUCCUGACdTdT	1464
S-3132	GUAGAAAUGUAUCCUGAUCdTdT	1465
S-3133	AAAUGUAUCCUGAUAAACCdTdT	1466
S-3134	GUAUCCUGAUAAACAUUACdTdT	1467
S-3135	UUAAACACUGUAAUCUUACdTdT	1468
S-3136	ACUGUAAUCUUAAAAGUGCdTdT	1469

S-3137	CUGUAAUCUUAAAAGUGUCdTdT	1470
S-3138	UGUAAUCUUAAAAGUGUACdTdT	1471
S-3139	GUAAUCUUAAAAGUGUAACdTdT	1472
S-3140	CUUAAAAGUGUAAUUGUGCdTdT	1473
S-3141	UACCUGUAGUGAGAAACUCdTdT	1474
S-3142	UUAUGAUCACUUGGAAGACdTdT	1475
S-3143	AUGAUCACUUGGAAGAUUCdTdT	1476
S-3144	AUCACUUGGAAGAUUUGUCdTdT	1477
S-3145	UGGAAGAUUUGUAUAGUUCdTdT	1478
S-3146	UAUAAAACUCAGUUAAAACdTdT	1479
S-3147	AAACUCAGUUAAAAUGUCCdTdT	1480
S-3148	GUCUGUUUCAAUGACCUGCdTdT	1481
S-3149	AUGACCUGUAUUUUGCCACdTdT	1482
S-3150	ACCUGUAUUUUGCCAGACCdTdT	1483

S-3151	CCUGUAUUUUGCCAGACUCdTdT	1484
S-3152	UAAAUCACAGAUGGGUAUCdTdT	1485
S-3153	AUCACAGAUGGGUAUUAACdTdT	1486
S-3154	UCACAGAUGGGUAUUAAACdTdT	1487
S-3155	ACAGAUGGGUAUUAAACUCdTdT	1488
S-3156	CAGAUGGGUAUUAAACUUCdTdT	1489
S-3157	AGAUGGGUAUUAAACUUGCdTdT	1490
S-3158	AUGGGUAUUAAACUUGUCCdTdT	1491
S-3159	UAAACUUGUCAGAAUUUCCdTdT	1492
S-3160	UCAUUCAAGCCUGUGAAUCdTdT	1493
S-3161	CAUUCAAGCCUGUGAAUACdTdT	1494
S-3162	AAUAAAAACCCUGUAUGGCdTdT	1495
S-3163	AUAAAAACCCUGUAUGGCCdTdT	1496
S-3164	AACCCUGUAUGGCACUUACdTdT	1497

S-3165	ACCCUGUAUGGCACUUAUCdTdT	1498
S-3166	GAGGCUAUUAAAAGAAUCCdTdT	1499
S-3167	AAAGAAUCCAAAUUCAAACdTdT	1500
S-3168	GAAUCCAAAUUCAAACUACdTdT	1501

[00496] In one embodiment, the siRNA molecules of the present invention targeting SOD1 may comprise an antisense sequence from Table 7 and a sense sequence from Table 8, or a fragment or variant thereof. As a non-limiting example, the antisense sequence and the sense sequence have at least 30%, 40%, 50%, 60%, 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-99%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-99%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-99%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-99%, 60-70%, 60-80%, 60-90%, 60-95%, 60-99%, 70-80%, 70-90%, 70-95%, 70-99%, 80-90%, 80-95%, 80-99%, 90-95%, 90-99% or 95-99% complementarity.

[00497] In one embodiment, the siRNA molecules of the present invention targeting SOD1 may comprise the sense and antisense siRNA duplex as described in Table 9. As a non-limiting example, these siRNA duplexes may be tested for in vitro inhibitory activity on endogenous SOD1 gene expression. The start site for the sense and antisense sequence is compared to SOD1 gene sequence known as NM_000454.4 (SEQ ID NO: 1502) from NCBI.

Table 9. Sense and antisense strand sequences of SOD1 dsRNA

siRNA Duplex ID	SS ID	Sense Strand Sequence (5'-3')	SS SEQ ID	AS ID	Antisense Strand Sequence (5'-3')	AS SEQ ID
D-2741	S-3000	CGGAGGUCUGGCCUAUAACdTdT	1333	A-3000	UUUAUAGGCCAGACCUCCGdTdT	1164
D-2742	S-3001	GGAGGUCUGGCCUAUAAACdTdT	1334	A-3001	UUUUAUAGGCCAGACCUCCdTdT	1165
D-2743	S-3002	GAGGUCUGGCCUAUAAAGCdTdT	1335	A-3002	UCUUUAUAGGCCAGACCUCdTdT	1166
D-2744	S-3003	AGGUCUGGCCUAUAAAGUCdTdT	1336	A-3003	UACUUUAUAGGCCAGACCUdTdT	1167

D-2745	S-3004	GGUCUGGCCUAUAAAGUACdTdT	1337	A-3004	UUACUUUAUAGGCCAGACCdTdT	1168
D-2746	S-3005	UCUGGCCUAUAAAGUAGUCdTdT	1338	A-3005	UACUACUUUAUAGGCCAGAdTdT	1169
D-2747	S-3006	CUGGCCUAUAAAGUAGUCCdTdT	1339	A-3006	UGACUACUUUAUAGGCCAGdTdT	1170
D-2748	S-3007	UGGCCUAUAAAGUAGUCGCdTdT	1340	A-3007	UCGACUACUUUAUAGGCCAdTdT	1171
D-2749	S-3008	GGCCUAUAAAGUAGUCGCCdTdT	1341	A-3008	UGCGACUACUUUAUAGGCCdTdT	1172
D-2750	S-3009	GCCUAUAAAGUAGUCGCGCdTdT	1342	A-3009	UCGCGACUACUUUAUAGGCdTdT	1173
D-2751	S-3010	CCUAUAAAGUAGUCGCGGCdTdT	1343	A-3010	UCCGCGACUACUUUAUAGGdTdT	1174
D-2752	S-3011	GUCGUAGUCUCCUGCAGCCdTdT	1344	A-3011	UGCUGCAGGAGACUACGACdTdT	1175
D-2753	S-3012	CGUAGUCUCCUGCAGCGUCdTdT	1345	A-3012	UACGCUGCAGGAGACUACGdTdT	1176
D-2754	S-3013	GUAGUCUCCUGCAGCGUCCdTdT	1346	A-3013	UGACGCUGCAGGAGACUACdTdT	1177
D-2755	S-3014	UAGUCUCCUGCAGCGUCUCdTdT	1347	A-3014	UAGACGCUGCAGGAGACUAdTdT	1178
D-2756	S-3015	AUGGCGACGAAGGCCGUGCdTdT	1348	A-3015	UCACGGCCUUCGUCGCCAUdTdT	1179
D-2757	S-3016	CGACGAAGGCCGUGUGCGCdTdT	1349	A-3016	UCGCACACGGCCUUCGUCGdTdT	1180
D-2758	S-3017	GAAGGCCGUGUGCGUGCUCdTdT	1350	A-3017	UAGCACGCACACGGCCUUCdTdT	1181
D-2759	S-3018	GGCCGUGUGCGUGCUGAACdTdT	1351	A-3018	UUUCAGCACGCACACGGCCdTdT	1182
D-2760	S-3019	AGGGCGACGGCCCAGUGCCdTdT	1352	A-3019	UGCACUGGGCCGUCGCCCUdTdT	1183
D-2761	S-3020	UGCAGGGCAUCAUCAAUUCdTdT	1353	A-3020	UAAUUGAUGAUGCCCUGCAdTdT	1184
D-2762	S-3021	GCAGGGCAUCAUCAAUUUCdTdT	1354	A-3021	UAAAUUGAUGAUGCCCUGCdTdT	1185
D-2763	S-3022	AGGGCAUCAUCAAUUUCGCdTdT	1355	A-3022	UCGAAAUUGAUGAUGCCCUdTdT	1186
D-2764	S-3023	GGGCAUCAUCAAUUUCGACdTdT	1356	A-3023	UUCGAAAUUGAUGAUGCCCdTdT	1187
D-2765	S-3024	GGCAUCAUCAAUUUCGAGCdTdT	1357	A-3024	UCUCGAAAUUGAUGAUGCCdTdT	1188
D-2766	S-3025	GCAUCAUCAAUUUCGAGCCdTdT	1358	A-3025	UGCUCGAAAUUGAUGAUGCdTdT	1189
D-2767	S-3026	CAUCAUCAAUUUCGAGCACdTdT	1359	A-3026	UUGCUCGAAAUUGAUGAUGdTdT	1190
D-2768	S-3027	AAUUUCGAGCAGAAGGAACdTdT	1360	A-3027	UUUCCUUCUGCUCGAAAUUdTdT	1191
D-2769	S-3028	UUCGAGCAGAAGGAAAGUCdTdT	1361	A-3028	UACUUUCCUUCUGCUCGAAdTdT	1192
D-2770	S-3029	UCGAGCAGAAGGAAAGUACdTdT	1362	A-3029	UUACUUUCCUUCUGCUCGAdTdT	1193
D-2771	S-3030	AAGGUGUGGGGAAGCAUUCdTdT	1363	A-3030	UAAUGCUUCCCCACACCUUdTdT	1194

D-2772	S-3031	GGUGUGGGGAAGCAUUAACdTdT	1364	A-3031	UUUAAUGCUUCCCCACACCdTdT	1195
D-2773	S-3032	GACUGACUGAAGGCCUGCCdTdT	1365	A-3032	UGCAGGCCUUCAGUCAGUCdTdT	1196
D-2774	S-3033	CUGACUGAAGGCCUGCAUCdTdT	1366	A-3033	UAUGCAGGCCUUCAGUCAGdTdT	1197
D-2775	S-3034	UGACUGAAGGCCUGCAUGCdTdT	1367	A-3034	UCAUGCAGGCCUUCAGUCAdTdT	1198
D-2776	S-3035	UGAAGGCCUGCAUGGAUUCdTdT	1368	A-3035	UAAUCCAUGCAGGCCUUCAdTdT	1199
D-2777	S-3036	GAAGGCCUGCAUGGAUUCCdTdT	1369	A-3036	UGAAUCCAUGCAGGCCUUCdTdT	1200
D-2778	S-3037	UGCAUGGAUUCCAUGUUCCdTdT	1370	A-3037	UGAACAUGGAAUCCAUGCAdTdT	1201
D-2779	S-3038	CAUGGAUUCCAUGUUCAUCdTdT	1371	A-3038	UAUGAACAUGGAAUCCAUGdTdT	1202
D-2780	S-3039	GGAUUCCAUGUUCAUGAGCdTdT	1372	A-3039	UCUCAUGAACAUGGAAUCCdTdT	1203
D-2781	S-3040	UUCCAUGUUCAUGAGUUUCdTdT	1373	A-3040	UAAACUCAUGAACAUGGAAdTdT	1204
D-2782	S-3041	GUUCAUGAGUUUGGAGAUCdTdT	1374	A-3041	UAUCUCCAAACUCAUGAACdTdT	1205
D-2783	S-3042	UUCAUGAGUUUGGAGAUACdTdT	1375	A-3042	UUAUCUCCAAACUCAUGAAdTdT	1206
D-2784	S-3043	UGAGUUUGGAGAUAAUACCdTdT	1376	A-3043	UGUAUUAUCUCCAAACUCAdTdT	1207
D-2785	S-3044	GAGUUUGGAGAUAAUACACdTdT	1377	A-3044	UUGUAUUAUCUCCAAACUCdTdT	1208
D-2786	S-3045	AGGCUGUACCAGUGCAGGCdTdT	1378	A-3045	UCCUGCACUGGUACAGCCUdTdT	1209
D-2787	S-3046	GGCUGUACCAGUGCAGGUCdTdT	1379	A-3046	UACCUGCACUGGUACAGCCdTdT	1210
D-2788	S-3047	GCAGGUCCUCACUUUAAUCdTdT	1380	A-3047	UAUUAAAGUGAGGACCUGCdTdT	1211
D-2789	S-3048	CAGGUCCUCACUUUAAUCCdTdT	1381	A-3048	UGAUUAAAGUGAGGACCUGdTdT	1212
D-2790	S-3049	UCACUUUAAUCCUCUAUCCdTdT	1382	A-3049	UGAUAGAGGAUUAAAGUGAdTdT	1213
D-2791	S-3050	CUAUCCAGAAAACACGGUCdTdT	1383	A-3050	UACCGUGUUUUCUGGAUAGdTdT	1214
D-2792	S-3051	UAUCCAGAAAACACGGUGCdTdT	1384	A-3051	UCACCGUGUUUUCUGGAUAdTdT	1215
D-2793	S-3052	AUCCAGAAAACACGGUGGCdTdT	1385	A-3052	UCCACCGUGUUUUCUGGAUdTdT	1216
D-2794	S-3053	CCAGAAAACACGGUGGGCCdTdT	1386	A-3053	UGCCCACCGUGUUUUCUGGdTdT	1217
D-2795	S-3054	GAAAACACGGUGGGCCAACdTdT	1387	A-3054	UUUGGCCCACCGUGUUUUCdTdT	1218
D-2796	S-3055	AAAACACGGUGGGCCAAACdTdT	1388	A-3055	UUUUGGCCCACCGUGUUUUdTdT	1219
D-2797	S-3056	CGGUGGGCCAAAGGAUGACdTdT	1389	A-3056	UUCAUCCUUUGGCCCACCGdTdT	1220
D-2798	S-3057	AGGAUGAAGAGAGGCAUGCdTdT	1390	A-3057	UCAUGCCUCUCUUCAUCCUdTdT	1221

D-2799	S-3058	AUGAAGAGAGGCAUGUUGCdTdT	1391	A-3058	UCAACAUGCCUCUCUUCAUdTdT	1222
D-2800	S-3059	GAGAGGCAUGUUGGAGACCdTdT	1392	A-3059	UGUCUCCAACAUGCCUCUCdTdT	1223
D-2801	S-3060	AGAGGCAUGUUGGAGACUCdTdT	1393	A-3060	UAGUCUCCAACAUGCCUCUdTdT	1224
D-2802	S-3061	AUGUUGGAGACUUGGGCACdTdT	1394	A-3061	UUGCCCAAGUCUCCAACAUdTdT	1225
D-2803	S-3062	GUUGGAGACUUGGGCAAUCdTdT	1395	A-3062	UAUUGCCCAAGUCUCCAACdTdT	1226
D-2804	S-3063	GGAGACUUGGGCAAUGUGCdTdT	1396	A-3063	UCACAUUGCCCAAGUCUCCdTdT	1227
D-2805	S-3064	GGCAAUGUGACUGCUGACCdTdT	1397	A-3064	UGUCAGCAGUCACAUUGCCdTdT	1228
D-2806	S-3065	CAAUGUGACUGCUGACAACdTdT	1398	A-3065	UUUGUCAGCAGUCACAUUGdTdT	1229
D-2807	S-3066	CUGACAAAGAUGGUGUGGCdTdT	1399	A-3066	UCCACACCAUCUUUGUCAGdTdT	1230
D-2808	S-3067	UGACAAAGAUGGUGUGGCCdTdT	1400	A-3067	UGCCACACCAUCUUUGUCAdTdT	1231
D-2809	S-3068	CUCAGGAGACCAUUGCAUCdTdT	1401	A-3068	UAUGCAAUGGUCUCCUGAGdTdT	1232
D-2810	S-3069	UCAGGAGACCAUUGCAUCCdTdT	1402	A-3069	UGAUGCAAUGGUCUCCUGAdTdT	1233
D-2811	S-3070	AGACCAUUGCAUCAUUGGCdTdT	1403	A-3070	UCCAAUGAUGCAAUGGUCUdTdT	1234
D-2812	S-3071	GACCAUUGCAUCAUUGGCCdTdT	1404	A-3071	UGCCAAUGAUGCAAUGGUCdTdT	1235
D-2813	S-3072	AUUGCAUCAUUGGCCGCACdTdT	1405	A-3072	UUGCGGCCAAUGAUGCAAUdTdT	1236
D-2814	S-3073	CAUUGGCCGCACACUGGUCdTdT	1406	A-3073	UACCAGUGUGCGGCCAAUGdTdT	1237
D-2815	S-3074	CGCACACUGGUGGUCCAUCdTdT	1407	A-3074	UAUGGACCACCAGUGUGCGdTdT	1238
D-2816	S-3075	CACACUGGUGGUCCAUGACdTdT	1408	A-3075	UUCAUGGACCACCAGUGUGdTdT	1239
D-2817	S-3076	ACACUGGUGGUCCAUGAACdTdT	1409	A-3076	UUUCAUGGACCACCAGUGUdTdT	1240
D-2818	S-3077	UGGUGGUCCAUGAAAAAGCdTdT	1410	A-3077	UCUUUUUCAUGGACCACCAdTdT	1241
D-2819	S-3078	UGGUCCAUGAAAAAGCAGCdTdT	1411	A-3078	UCUGCUUUUUCAUGGACCAdTdT	1242
D-2820	S-3079	AAAGCAGAUGACUUGGGCCdTdT	1412	A-3079	UGCCCAAGUCAUCUGCUUUdTdT	1243
D-2821	S-3080	GCAGAUGACUUGGGCAAACdTdT	1413	A-3080	UUUUGCCCAAGUCAUCUGCdTdT	1244
D-2822	S-3081	AUGACUUGGGCAAAGGUGCdTdT	1414	A-3081	UCACCUUUGCCCAAGUCAUdTdT	1245
D-2823	S-3082	UGACUUGGGCAAAGGUGGCdTdT	1415	A-3082	UCCACCUUUGCCCAAGUCAdTdT	1246
D-2824	S-3083	GACUUGGGCAAAGGUGGACdTdT	1416	A-3083	UUCCACCUUUGCCCAAGUCdTdT	1247
D-2825	S-3084	GUACAAAGACAGGAAACGCdTdT	1417	A-3084	UCGUUUCCUGUCUUUGUACdTdT	1248

D-2826	S-3085	ACAAAGACAGGAAACGCUCdTdT	1418	A-3085	UAGCGUUUCCUGUCUUUGUdTdT	1249
D-2827	S-3086	CAAAGACAGGAAACGCUGCdTdT	1419	A-3086	UCAGCGUUUCCUGUCUUUGdTdT	1250
D-2828	S-3087	AGGAAACGCUGGAAGUCGCdTdT	1420	A-3087	UCGACUUCCAGCGUUUCCUdTdT	1251
D-2829	S-3088	GUCGUUUGGCUUGUGGUGCdTdT	1421	A-3088	UCACCACAAGCCAAACGACdTdT	1252
D-2830	S-3089	UCGUUUGGCUUGUGGUGUCdTdT	1422	A-3089	UACACCACAAGCCAAACGAdTdT	1253
D-2831	S-3090	CGUUUGGCUUGUGGUGUACdTdT	1423	A-3090	UUACACCACAAGCCAAACGdTdT	1254
D-2832	S-3091	GUUUGGCUUGUGGUGUAACdTdT	1424	A-3091	UUUACACCACAAGCCAAACdTdT	1255
D-2833	S-3092	UUGGCUUGUGGUGUAAUUCdTdT	1425	A-3092	UAAUUACACCACAAGCCAAdTdT	1256
D-2834	S-3093	GGCUUGUGGUGUAAUUGGCdTdT	1426	A-3093	UCCAAUUACACCACAAGCCdTdT	1257
D-2835	S-3094	GCUUGUGGUGUAAUUGGGCdTdT	1427	A-3094	UCCCAAUUACACCACAAGCdTdT	1258
D-2836	S-3095	CUUGUGGUGUAAUUGGGACdTdT	1428	A-3095	UUCCCAAUUACACCACAAGdTdT	1259
D-2837	S-3096	UGUGGUGUAAUUGGGAUCCdTdT	1429	A-3096	UGAUCCCAAUUACACCACAdTdT	1260
D-2838	S-3097	GUGGUGUAAUUGGGAUCGCdTdT	1430	A-3097	UCGAUCCCAAUUACACCACdTdT	1261
D-2839	S-3098	UGGUGUAAUUGGGAUCGCCdTdT	1431	A-3098	UGCGAUCCCAAUUACACCAdTdT	1262
D-2840	S-3099	GUAAUUGGGAUCGCCCAACdTdT	1432	A-3099	UUUGGGCGAUCCCAAUUACdTdT	1263
D-2841	S-3100	UAAUUGGGAUCGCCCAAUCdTdT	1433	A-3100	UAUUGGGCGAUCCCAAUUAdTdT	1264
D-2842	S-3101	AAUUGGGAUCGCCCAAUACdTdT	1434	A-3101	UUAUUGGGCGAUCCCAAUUdTdT	1265
D-2843	S-3102	AUUGGGAUCGCCCAAUAACdTdT	1435	A-3102	UUUAUUGGGCGAUCCCAAUdTdT	1266
D-2844	S-3103	UUGGGAUCGCCCAAUAAACdTdT	1436	A-3103	UUUUAUUGGGCGAUCCCAAdTdT	1267
D-2845	S-3104	UGGGAUCGCCCAAUAAACCdTdT	1437	A-3104	UGUUUAUUGGGCGAUCCCAdTdT	1268
D-2846	S-3105	GGGAUCGCCCAAUAAACACdTdT	1438	A-3105	UUGUUUAUUGGGCGAUCCCdTdT	1269
D-2847	S-3106	AUCGCCCAAUAAACAUUCCdTdT	1439	A-3106	UGAAUGUUUAUUGGGCGAUdTdT	1270
D-2848	S-3107	CCAAUAAACAUUCCCUUGCdTdT	1440	A-3107	UCAAGGGAAUGUUAUUGGdTdT	1271
D-2849	S-3108	CAAUAAACAUUCCCUUGGCdTdT	1441	A-3108	UCCAAGGGAAUGUUUAUUGdTdT	1272
D-2850	S-3109	AAUAAACAUUCCCUUGGACdTdT	1442	A-3109	UUCCAAGGGAAUGUUUAUUdTdT	1273
D-2851	S-3110	AUAAACAUUCCCUUGGAUCdTdT	1443	A-3110	UAUCCAAGGGAAUGUUUAUdTdT	1274
D-2852	S-3111	UAAACAUUCCCUUGGAUGCdTdT	1444	A-3111	UCAUCCAAGGGAAUGUUUAdTdT	1275

D-2853	S-3112	AAACAUUCCCUUGGAUGUCdTdT	1445	A-3112	UACAUCCAAGGGAAUGUUUdTdT	1276
D-2854	S-3113	AACAUUCCCUUGGAUGUACdTdT	1446	A-3113	UUACAUCCAAGGGAAUGUUdTdT	1277
D-2855	S-3114	AUUCCCUUGGAUGUAGUCCdTdT	1447	A-3114	UGACUACAUCCAAGGGAAUdTdT	1278
D-2856	S-3115	CUUGGAUGUAGUCUGAGGCdTdT	1448	A-3115	UCCUCAGACUACAUCCAAGdTdT	1279
D-2857	S-3116	CUGAGGCCCCUUAACUCACdTdT	1449	A-3116	UUGAGUUAAGGGGCCUCAGdTdT	1280
D-2858	S-3117	GAGGCCCCUUAACUCAUCCdTdT	1450	A-3117	UGAUGAGUUAAGGGGCCUCdTdT	1281
D-2859	S-3118	AGGCCCCUUAACUCAUCUCdTdT	1451	A-3118	UAGAUGAGUUAAGGGGCCUdTdT	1282
D-2860	S-3119	CCCCUUAACUCAUCUGUUCdTdT	1452	A-3119	UAACAGAUGAGUUAAGGGGdTdT	1283
D-2861	S-3120	CCCUUAACUCAUCUGUUACdTdT	1453	A-3120	UUAACAGAUGAGUUAAGGGdTdT	1284
D-2862	S-3121	CCUUAACUCAUCUGUUAUCdTdT	1454	A-3121	UAUAACAGAUGAGUUAAGGdTdT	1285
D-2863	S-3122	CUUAACUCAUCUGUUAUCCdTdT	1455	A-3122	UGAUAACAGAUGAGUUAAGdTdT	1286
D-2864	S-3123	UUAACUCAUCUGUUAUCCCdTdT	1456	A-3123	UGGAUAACAGAUGAGUUAAdTdT	1287
D-2865	S-3124	UAACUCAUCUGUUAUCCUCdTdT	1457	A-3124	UAGGAUAACAGAUGAGUUAdTdT	1288
D-2866	S-3125	AACUCAUCUGUUAUCCUGCdTdT	1458	A-3125	UCAGGAUAACAGAUGAGUUdTdT	1289
D-2867	S-3126	GUUAUCCUGCUAGCUGUACdTdT	1459	A-3126	UUACAGCUAGCAGGAUAACdTdT	1290
D-2868	S-3127	CUGCUAGCUGUAGAAAUGCdTdT	1460	A-3127	UCAUUUCUACAGCUAGCAGdTdT	1291
D-2869	S-3128	UGCUAGCUGUAGAAAUGUCdTdT	1461	A-3128	UACAUUUCUACAGCUAGCAdTdT	1292
D-2870	S-3129	GCUGUAGAAAUGUAUCCUCdTdT	1462	A-3129	UAGGAUACAUUUCUACAGCdTdT	1293
D-2871	S-3130	CUGUAGAAAUGUAUCCUGCdTdT	1463	A-3130	UCAGGAUACAUUUCUACAGdTdT	1294
D-2872	S-3131	UGUAGAAAUGUAUCCUGACdTdT	1464	A-3131	UUCAGGAUACAUUUCUACAdTdT	1295
D-2873	S-3132	GUAGAAAUGUAUCCUGAUCdTdT	1465	A-3132	UAUCAGGAUACAUUUCUACdTdT	1296
D-2874	S-3133	AAAUGUAUCCUGAUAAACCdTdT	1466	A-3133	UGUUUAUCAGGAUACAUUUdTdT	1297
D-2875	S-3134	GUAUCCUGAUAAACAUUACdTdT	1467	A-3134	UUAAUGUUUAUCAGGAUACdTdT	1298
D-2876	S-3135	UUAAACACUGUAAUCUUACdTdT	1468	A-3135	UUAAGAUUACAGUGUUUAAdTdT	1299
D-2877	S-3136	ACUGUAAUCUUAAAAGUGCdTdT	1469	A-3136	UCACUUUUAAGAUUACAGUdTdT	1300
D-2878	S-3137	CUGUAAUCUUAAAAGUGUCdTdT	1470	A-3137	UACACUUUUAAGAUUACAGdTdT	1301
D-2879	S-3138	UGUAAUCUUAAAAGUGUACdTdT	1471	A-3138	UUACACUUUUAAGAUUACAdTdT	1302

D-2880	S-3139	GUAAUCUUAAAAGUGUAACdTdT	1472	A-3139	UUUACACUUUUAAGAUUACdTdT	1303
D-2881	S-3140	CUUAAAAGUGUAAUUGUGCdTdT	1473	A-3140	UCACAAUUACACUUUUAAGdTdT	1304
D-2882	S-3141	UACCUGUAGUGAGAAACUCdTdT	1474	A-3141	UAGUUUCUCACUACAGGUAdTdT	1305
D-2883	S-3142	UUAUGAUCACUUGGAAGACdTdT	1475	A-3142	UUCUUCCAAGUGAUCAUAAdTdT	1306
D-2884	S-3143	AUGAUCACUUGGAAGAUUCdTdT	1476	A-3143	UAAUCUUCCAAGUGAUCAUdTdT	1307
D-2885	S-3144	AUCACUUGGAAGAUUUGUCdTdT	1477	A-3144	UACAAAUCUUCCAAGUGAUdTdT	1308
D-2886	S-3145	UGGAAGAUUUGUAUAGUUCdTdT	1478	A-3145	UAACUAUACAAAUCUUCCAdTdT	1309
D-2887	S-3146	UAUAAAACUCAGUUAAAACdTdT	1479	A-3146	UUUUUAACUGAGUUUUAUAdTdT	1310
D-2888	S-3147	AAACUCAGUUAAAAUGUCCdTdT	1480	A-3147	UGACAUUUUAACUGAGUUUdTdT	1311
D-2889	S-3148	GUCUGUUUCAAUGACCUGCdTdT	1481	A-3148	UCAGGUCAUUGAAACAGACdTdT	1312
D-2890	S-3149	AUGACCUGUAUUUUGCCACdTdT	1482	A-3149	UUGGCAAAAUACAGGUCAUdTdT	1313
D-2891	S-3150	ACCUGUAUUUUGCCAGACCdTdT	1483	A-3150	UGUCUGGCAAAAUACAGGUdTdT	1314
D-2892	S-3151	CCUGUAUUUUGCCAGACUCdTdT	1484	A-3151	UAGUCUGGCAAAAUACAGGdTdT	1315
D-2893	S-3152	UAAAUCACAGAUGGGUAUCdTdT	1485	A-3152	UAUACCCAUCUGUGAUUUAdTdT	1316
D-2894	S-3153	AUCACAGAUGGGUAUUAACdTdT	1486	A-3153	UUUAAUACCCAUCUGUGAUdTdT	1317
D-2895	S-3154	UCACAGAUGGGUAUUAAACdTdT	1487	A-3154	UUUUAAUACCCAUCUGUGAdTdT	1318
D-2896	S-3155	ACAGAUGGGUAUUAAACUCdTdT	1488	A-3155	UAGUUUAAUACCCAUCUGUdTdT	1319
D-2897	S-3156	CAGAUGGGUAUUAAACUUCdTdT	1489	A-3156	UAAGUUUAAUACCCAUCUGdTdT	1320
D-2898	S-3157	AGAUGGGUAUUAAACUUGCdTdT	1490	A-3157	UCAAGUUUAAUACCCAUCUdTdT	1321
D-2899	S-3158	AUGGGUAUUAAACUUGUCCdTdT	1491	A-3158	UGACAAGUUUAAUACCCAUdTdT	1322
D-2900	S-3159	UAAACUUGUCAGAAUUUCCdTdT	1492	A-3159	UGAAAUUCUGACAAGUUUAdTdT	1323
D-2901	S-3160	UCAUUCAAGCCUGUGAAUCdTdT	1493	A-3160	UAUUCACAGGCUUGAAUGAdTdT	1324
D-2902	S-3161	CAUUCAAGCCUGUGAAUACdTdT	1494	A-3161	UUAUUCACAGGCUUGAAUGdTdT	1325
D-2903	S-3162	AAUAAAAACCCUGUAUGGCdTdT	1495	A-3162	UCCAUACAGGGUUUUUAUUdTdT	1326
D-2904	S-3163	AUAAAAACCCUGUAUGGCCdTdT	1496	A-3163	UGCCAUACAGGGUUUUUAUdTdT	1327
D-2905	S-3164	AACCCUGUAUGGCACUUACdTdT	1497	A-3164	UUAAGUGCCAUACAGGGUUdTdT	1328
D-2906	S-3165	ACCCUGUAUGGCACUUAUCdTdT	1498	A-3165	UAUAAGUGCCAUACAGGGUdTdT	1329

D-2907	S-3166	GAGGCUAUUAAAAG AAUCCdTdT	1499	A-3166	UGAUUCUUUUAAU AGCCUCdTdT	1330
D-2908	S-3167	AAAGAAUCCAAAUUC AAACdTdT	1500	A-3167	UUUUGAAUUUGGA UUCUUUdTdT	1331
D-2909	S-3168	GAAUCCAAAUUCAAA CUACdTdT	1501	A-3168	UUAGUUUGAAUUU GGAUUCdTdT	1332

[00498] In other embodiments, the siRNA molecules of the present invention targeting SOD1 can be encoded in plasmid vectors, AAV particles, viral genome or other nucleic acid expression vectors for delivery to a cell.

[00499] DNA expression plasmids can be used to stably express the siRNA duplexes or dsRNA of the present invention targeting SOD1 in cells and achieve long-term inhibition of the target gene expression. In one aspect, the sense and antisense strands of a siRNA duplex are typically linked by a short spacer sequence leading to the expression of a stem-loop structure termed short hairpin RNA (shRNA). The hairpin is recognized and cleaved by Dicer, thus generating mature siRNA molecules.

[00500] According to the present invention, AAV particles comprising the nucleic acids encoding the siRNA molecules targeting SOD1 mRNA are produced, the AAV serotypes may be any of the serotypes listed in Table 1. Non-limiting examples of the AAV serotypes include, AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV9.47, AAV9(hu14), AAV10, AAV11, AAV12, AAVrh8, AAVrh10, AAV-DJ8, AAV-DJ, AAV-PHP.A, AAV-PHP.B, AAVPHP.B2, AAVPHP.B3, AAVPHP.N/PHP.B-DGT, AAVPHP.B-EST, AAVPHP.B-GGT, AAVPHP.B-ATP, AAVPHP.B-ATT-T, AAVPHP.B-DGT-T, AAVPHP.B-GGT-T, AAVPHP.B-SGS, AAVPHP.B-AQP, AAVPHP.B-QQP, AAVPHP.B-SNP(3), AAVPHP.B-SNP, AAVPHP.B-QGT, AAVPHP.B-NQT, AAVPHP.B-EGS, AAVPHP.B-SGN, AAVPHP.B-EGT, AAVPHP.B-DST, AAVPHP.B-DST, AAVPHP.B-STP, AAVPHP.B-PQP, AAVPHP.B-SQP, AAVPHP.B-QLP, AAVPHP.B-TMP, AAVPHP.B-TTP, AAVPHP.S/G2A12, AAVG2A15/G2A3, AAVG2B4, AAVG2B5 and variants thereof.

[00501] In some embodiments, the siRNA duplexes or encoded dsRNA of the present invention suppress (or degrade) SOD1 mRNA. Accordingly, the siRNA duplexes or encoded dsRNA can be used to substantially inhibit SOD1 gene expression in a cell. In some aspects, the inhibition of SOD1 gene expression refers to an inhibition by at least about 20%, preferably by at least about 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95% and 100%, or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%, 40-60%,

40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% or 95-100%. Accordingly, the protein product of the targeted gene may be inhibited by at least about 20%, preferably by at least about 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95% and 100%, or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% or 95-100%.

[00502] According to the present invention, the siRNA molecules are designed and tested for their ability in reducing SOD1 mRNA levels in cultured cells. Such siRNA molecules may form a duplex such as, but not limited to, include those listed in Table 9. As a non-limiting example, the siRNA duplexes may be siRNA duplex IDs: D-2741 to D-2909.

[00503] In one embodiment, the siRNA molecules comprise a miRNA seed match for SOD1 located in the guide strand. In another embodiment, the siRNA molecules comprise a miRNA seed match for SOD1 located in the passenger strand. In yet another embodiment, the siRNA duplexes or encoded dsRNA targeting SOD1 gene do not comprise a seed match for SOD1 located in the guide or passenger strand.

[00504] In one embodiment, the siRNA duplexes or encoded dsRNA targeting SOD1 gene may have almost no significant full-length off target effects for the guide strand. In another embodiment, the siRNA duplexes or encoded dsRNA targeting SOD1 gene may have almost no significant full-length off target effects for the passenger strand. The siRNA duplexes or encoded dsRNA targeting SOD1 gene may have less than 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%,11%, 12%, 13%, 14%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 1-5%, 2-6%, 3-7%, 4-8%, 5-9%, 5-10%, 6-10%, 5-15%, 5-20%, 5-25% 5-30%, 10-20%, 10-30%, 10-40%, 10-50%, 15-30%, 15-40%, 15-45%, 20-40%, 20-50%, 25-50%, 30-40%, 30-50%, 35-50%, 40-50%, 45-50% full-length off target effects for the passenger strand. In yet another embodiment, the siRNA duplexes or encoded dsRNA targeting SOD1 gene may have almost no significant full-length off target effects for the guide strand or the passenger strand. The siRNA duplexes or encoded dsRNA targeting SOD1 gene may have less than 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%,11%, 12%, 13%, 14%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 1-5%, 2-6%, 3-7%, 4-8%, 5-9%, 5-10%, 6-10%, 5-15%, 5-20%, 5-25% 5-30%, 10-20%, 10-30%, 10-40%, 10-

50%, 15-30%, 15-40%, 15-45%, 20-40%, 20-50%, 25-50%, 30-40%, 30-50%, 35-50%, 40-50%, 45-50% full-length off target effects for the guide or passenger strand.

[00505] In one embodiment, the siRNA duplexes or encoded dsRNA targeting SOD1 gene may have high activity in vitro. In another embodiment, the siRNA molecules may have low activity in vitro. In yet another embodiment, the siRNA duplexes or dsRNA targeting the SOD1 gene may have high guide strand activity and low passenger strand activity in vitro.

[00506] In one embodiment, the siRNA molecules targeting SOD1 have a high guide strand activity and low passenger strand activity in vitro. The target knock-down (KD) by the guide strand may be at least 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, 99.5% or 100%. The target knock-down by the guide strand may be 40-50%, 45-50%, 50-55%, 50-60%, 60-65%, 60-70%, 60-75%, 60-80%, 60-85%, 60-90%, 60-95%, 60-99%, 60-99.5%, 60-100%, 65-70%, 65-75%, 65-80%, 65-85%, 65-90%, 65-95%, 65-99%, 65-99.5%, 65-100%, 70-75%, 70-80%, 70-85%, 70-90%, 70-95%, 70-99%, 70-99.5%, 70-100%, 75-80%, 75-85%, 75-90%, 75-95%, 75-99%, 75-99.5%, 75-100%, 80-85%, 80-90%, 80-95%, 80-99%, 80-99.5%, 80-100%, 85-90%, 85-95%, 85-99%, 85-99.5%, 85-100%, 90-95%, 90-99%, 90-99.5%, 90-100%, 95-99%, 95-99.5%, 95-100%, 99-99.5%, 99-100% or 99.5-100%. As a non-limiting example, the target knock-down (KD) by the guide strand is greater than 70%. As a non-limiting example, the target knock-down (KD) by the guide strand is greater than 60%.

[00507] In one embodiment, the siRNA duplex target SOD1 is designed so there is no miRNA seed match for the sense or antisense sequence to the non-SOD1 sequence.

[00508] In one embodiment, the IC_{50} of the guide strand in the siRNA duplex targeting SOD1 for the nearest off target is greater than 100 multiplied by the IC_{50} of the guide strand for the on-target gene, SOD1. As a non-limiting example, if the IC_{50} of the guide strand for the nearest off target is greater than 100 multiplied by the IC_{50} of the guide strand for the target then the siRNA molecule is said to have high guide strand selectivity for inhibiting SOD1 in vitro.

[00509] In one embodiment, the 5' processing of the guide strand of the siRNA duplex targeting SOD1 has a correct start (n) at the 5' end at least 75%, 80%, 85%, 90%, 95%, 99% or 100% of the time in vitro or in vivo. As a non-limiting example, the 5' processing of the guide strand is precise and has a correct start (n) at the 5' end at least 99% of the time in vitro. As a non-limiting example, the 5' processing of the guide strand is precise and has a correct start (n) at the 5' end at least 99% of the time in vivo. As a non-limiting example, the 5' processing of the guide strand is precise and has a correct start (n) at the 5' end at least 90% of the time in vitro. As a non-limiting example, the 5' processing of the guide strand is precise and has a correct start (n) at the

5' end at least 90% of the time in vivo. As a non-limiting example, the 5' processing of the guide strand is precise and has a correct start (n) at the 5' end at least 85% of the time in vitro. As a non-limiting example, the 5' processing of the guide strand is precise and has a correct start (n) at the 5' end at least 85% of the time in vivo.

[00510] In one embodiment, a passenger-guide strand duplex for SOD1 is considered effective when the pri- or pre-microRNAs demonstrate, by methods known in the art and described herein, greater than 2-fold guide to passenger strand ratio when processing is measured. As a non-limiting examples, the pri- or pre-microRNAs demonstrate great than 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, 11-fold, 12-fold, 13-fold, 14-fold, 15-fold, or 2 to 5-fold, 2 to 10-fold, 2 to 15-fold, 3 to 5-fold, 3 to 10-fold, 3 to 15-fold, 4 to 5-fold, 4 to 10-fold, 4 to 15-fold, 5 to 10-fold, 5 to 15-fold, 6 to 10-fold, 6 to 15-fold, 7 to 10-fold, 7 to 15-fold, 8 to 10-fold, 8 to 15-fold, 9 to 10-fold, 9 to 15-fold, 10 to 15-fold, 11 to 15-fold, 12 to 15-fold, 13 to 15-fold, or 14 to 15-fold guide to passenger strand ratio when processing is measured.

[00511] In one embodiment, the siRNA molecules may be used to silence wild type or mutant SOD1 by targeting at least one exon on the SOD1 sequence. The exon may be exon 1, exon 2, exon 3, exon 4, exon 5, exon 6, exon 7, exon 8, exon 9, exon 10, exon 11, exon 12, exon 13, exon 14, exon 15, exon 16, exon 17, exon 18, exon 19, exon 20, exon 21, exon 22, exon 23, exon 24, exon 25, exon 26, exon 27, exon 28, exon 29, exon 30, exon 31, exon 32, exon 33, exon 34, exon 35, exon 36, exon 37, exon 38, exon 39, exon 40, exon 41, exon 42, exon 43, exon 44, exon 45, exon 46, exon 47, exon 48, exon 49, exon 50, exon 51, exon 52, exon 53, exon 54, exon 55, exon 56, exon 57, exon 58, exon 59, exon 60, exon 61, exon 62, exon 63, exon 64, exon 65, exon 66, and/or exon 67.

siRNA modification

[00512] In some embodiments, the siRNA molecules of the present invention, when not delivered as a precursor or DNA, may be chemically modified to modulate some features of RNA molecules, such as, but not limited to, increasing the stability of siRNAs in vivo. The chemically modified siRNA molecules can be used in human therapeutic applications, and are improved without compromising the RNAi activity of the siRNA molecules. As a non-limiting example, the siRNA molecules modified at both the 3′ and the 5′ end of both the sense strand and the antisense strand.

[00513] In some aspects, the siRNA duplexes of the present invention may contain one or more modified nucleotides such as, but not limited to, sugar modified nucleotides, nucleobase modifications and/or backbone modifications. In some aspects, the siRNA

molecule may contain combined modifications, for example, combined nucleobase and backbone modifications.

[00514] In one embodiment, the modified nucleotide may be a sugar-modified nucleotide. Sugar modified nucleotides include, but are not limited to 2′-fluoro, 2′-amino and 2′-thio modified ribonucleotides, e.g. 2′-fluoro modified ribonucleotides. Modified nucleotides may be modified on the sugar moiety, as well as nucleotides having sugars or analogs thereof that are not ribosyl. For example, the sugar moieties may be, or be based on, mannoses, arabinoses, glucopyranoses, galactopyranoses, 4′-thioribose, and other sugars, heterocycles, or carbocycles.

[00515] In one embodiment, the modified nucleotide may be a nucleobase-modified nucleotide.

[00516] In one embodiment, the modified nucleotide may be a backbone-modified nucleotide. In some embodiments, the siRNA duplexes of the present invention may further comprise other modifications on the backbone. A normal “backbone”, as used herein, refers to the repeating alternating sugar-phosphate sequences in a DNA or RNA molecule. The deoxyribose/ribose sugars are joined at both the 3'-hydroxyl and 5'-hydroxyl groups to phosphate groups in ester links, also known as "phosphodiester" bonds/linker (PO linkage). The PO backbones may be modified as “phosphorothioate backbone (PS linkage). In some cases, the natural phosphodiester bonds may be replaced by amide bonds but the four atoms between two sugar units are kept. Such amide modifications can facilitate the solid phase synthesis of oligonucleotides and increase the thermodynamic stability of a duplex formed with siRNA complement. See e.g. Mesmaeker et al., Pure & Appl. Chem., 1997, 3, 437-440; the content of which is incorporated herein by reference in its entirety.

[00517] Modified bases refer to nucleotide bases such as, for example, adenine, guanine, cytosine, thymine, uracil, xanthine, inosine, and queuosine that have been modified by the replacement or addition of one or more atoms or groups. Some examples of modifications on the nucleobase moieties include, but are not limited to, alkylated, halogenated, thiolated, aminated, amidated, or acetylated bases, individually or in combination. More specific examples include, for example, 5-propynyluridine, 5-propynylcytidine, 6-methyladenine, 6-methylguanine, N,N,-dimethyladenine, 2-propyladenine, 2-propylguanine, 2-aminoadenine, 1-methylinosine, 3-methyluridine, 5-methylcytidine, 5-methyluridine and other nucleotides having a modification at the 5 position, 5-(2-amino)propyl uridine, 5-halocytidine, 5-halouridine, 4-acetylcytidine, 1-methyladenosine, 2-methyladenosine, 3-methylcytidine, 6-

methyluridine, 2-methylguanosine, 7-methylguanosine, 2,2-dimethylguanosine, 5-methylaminoethyluridine, 5-methyloxyuridine, deazanucleotides such as 7-deaza-adenosine, 6-azouridine, 6-azocytidine, 6-azothymidine, 5-methyl-2-thiouridine, other thio bases such as 2-thiouridine and 4-thiouridine and 2-thiocytidine, dihydrouridine, pseudouridine, queuosine, archaeosine, naphthyl and substituted naphthyl groups, any O- and N-alkylated purines and pyrimidines such as N6-methyladenosine, 5-methylcarbonylmethyluridine, uridine 5-oxyacetic acid, pyridine-4-one, pyridine-2-one, phenyl and modified phenyl groups such as aminophenol or 2,4,6-trimethoxy benzene, modified cytosines that act as G-clamp nucleotides, 8-substituted adenines and guanines, 5-substituted uracils and thymines, azapyrimidines, carboxyhydroxyalkyl nucleotides, carboxyalkylaminoalkyl nucleotides, and alkylcarbonylalkylated nucleotides.

[00518] In one embodiment, the modified nucleotides may be on just the sense strand.

[00519] In another embodiment, the modified nucleotides may be on just the antisense strand.

[00520] In some embodiments, the modified nucleotides may be in both the sense and antisense strands.

[00521] In some embodiments, the chemically modified nucleotide does not affect the ability of the antisense strand to pair with the target mRNA sequence.

[00522] In one embodiment, the AAV particle comprising a nucleic acid sequence encoding the siRNA molecules of the present invention may encode siRNA molecules which are polycistronic molecules. The siRNA molecules may additionally comprise one or more linkers between regions of the siRNA molecules.

Molecular Scaffold

[00523] In one embodiment, the siRNA molecules may be encoded in a modulatory polynucleotide which also comprises a molecular scaffold. As used herein a “molecular scaffold” is a framework or starting molecule that forms the sequence or structural basis against which to design or make a subsequent molecule.

[00524] In one embodiment, the molecular scaffold comprises at least one 5’ flanking region. As a non-limiting example, the 5’ flanking region may comprise a 5’ flanking sequence which may be of any length and may be derived in whole or in part from wild type microRNA sequence or be a completely artificial sequence.

[00525] In one embodiment, the molecular scaffold comprises at least one 3’ flanking region. As a non-limiting example, the 3’ flanking region may comprise a 3’ flanking sequence which

may be of any length and may be derived in whole or in part from wild type microRNA sequence or be a completely artificial sequence.

[00526] In one embodiment, the molecular scaffold comprises at least one loop motif region. As a non-limiting example, the loop motif region may comprise a sequence which may be of any length.

[00527] In one embodiment, the molecular scaffold comprises a 5' flanking region, a loop motif region and/or a 3' flanking region.

[00528] In one embodiment, at least one siRNA, miRNA or other RNAi agent described herein, may be encoded by a modulatory polynucleotide which may also comprise at least one molecular scaffold. The molecular scaffold may comprise a 5' flanking sequence which may be of any length and may be derived in whole or in part from wild type microRNA sequence or be completely artificial. The 3' flanking sequence may mirror the 5' flanking sequence and/or a 3' flanking sequence in size and origin. Either flanking sequence may be absent. The 3' flanking sequence may optionally contain one or more CNNC motifs, where "N" represents any nucleotide.

[00529] Forming the stem of a stem loop structure is a minimum of the modulatory polynucleotide encoding at least one siRNA, miRNA or other RNAi agent described herein. In some embodiments, the siRNA, miRNA or other RNAi agent described herein comprises at least one nucleic acid sequence which is in part complementary or will hybridize to a target sequence. In some embodiments the payload is an siRNA molecule or fragment of an siRNA molecule.

[00530] In some embodiments, the 5' arm of the stem loop structure of the modulatory polynucleotide comprises a nucleic acid sequence encoding a sense sequence. Non-limiting examples of sense sequences, or fragments or variants thereof, which may be encoded by the modulatory polynucleotide are described in Table 3 and Table 8.

[00531] In some embodiments, the 3' arm of the stem loop of the modulatory polynucleotide comprises a nucleic acid sequence encoding an antisense sequence. The antisense sequence, in some instances, comprises a "G" nucleotide at the 5' most end. Non-limiting examples of antisense sequences, or fragments or variants thereof, which may be encoded by the modulatory polynucleotide are described in Table 2 and Table 7.

[00532] In other embodiments, the sense sequence may reside on the 3' arm while the antisense sequence resides on the 5' arm of the stem of the stem loop structure of the modulatory polynucleotide. Non-limiting examples of sense and antisense sequences which may be encoded by the modulatory polynucleotide are described in Tables 2, 3, 7, and 8.

[00533] In one embodiment, the sense and antisense sequences may be completely complementary across a substantial portion of their length. In other embodiments the sense sequence and antisense sequence may be at least 70, 80, 90, 95 or 99% complementarity across independently at least 50, 60, 70, 80, 85, 90, 95, or 99 % of the length of the strands.

[00534] Neither the identity of the sense sequence nor the homology of the antisense sequence need to be 100% complementarity to the target sequence.

[00535] In one embodiment, separating the sense and antisense sequence of the stem loop structure of the modulatory polynucleotide is a loop sequence (also known as a loop motif, linker or linker motif). The loop sequence may be of any length, between 4-30 nucleotides, between 4-20 nucleotides, between 4-15 nucleotides, between 5-15 nucleotides, between 6-12 nucleotides, 6 nucleotides, 7 nucleotides, 8 nucleotides, 9 nucleotides, 10 nucleotides, 11 nucleotides, 12 nucleotides, 13 nucleotides, 14 nucleotides, and/or 15 nucleotides.

[00536] In some embodiments, the loop sequence comprises a nucleic acid sequence encoding at least one UGUG motif. In some embodiments, the nucleic acid sequence encoding the UGUG motif is located at the 5' terminus of the loop sequence.

[00537] In one embodiment, spacer regions may be present in the modulatory polynucleotide to separate one or more modules (e.g., 5' flanking region, loop motif region, 3' flanking region, sense sequence, antisense sequence) from one another. There may be one or more such spacer regions present.

[00538] In one embodiment, a spacer region of between 8-20, i.e., 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 nucleotides may be present between the sense sequence and a flanking region sequence.

[00539] In one embodiment, the length of the spacer region is 13 nucleotides and is located between the 5' terminus of the sense sequence and the 3' terminus of the flanking sequence. In one embodiment, a spacer is of sufficient length to form approximately one helical turn of the sequence.

[00540] In one embodiment, a spacer region of between 8-20, i.e., 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 nucleotides may be present between the antisense sequence and a flanking sequence.

[00541] In one embodiment, the spacer sequence is between 10-13, i.e., 10, 11, 12 or 13 nucleotides and is located between the 3' terminus of the antisense sequence and the 5' terminus of a flanking sequence. In one embodiment, a spacer is of sufficient length to form approximately one helical turn of the sequence.

[00542] In one embodiment, the molecular scaffold of the modulatory polynucleotide comprises in the 5' to 3' direction, a 5' flanking sequence, a 5' arm, a loop motif, a 3' arm and a 3' flanking sequence. As a non-limiting example, the 5' arm may comprise a nucleic acid sequence encoding a sense sequence and the 3' arm comprises a nucleic acid sequence encoding the antisense sequence. In another non-limiting example, the 5' arm comprises a nucleic acid sequence encoding the antisense sequence and the 3' arm comprises a nucleic acid sequence encoding the sense sequence.

[00543] In one embodiment, the 5' arm, sense and/or antisense sequence, loop motif and/or 3' arm sequence may be altered (e.g., substituting 1 or more nucleotides, adding nucleotides and/or deleting nucleotides). The alteration may cause a beneficial change in the function of the construct (e.g., increase knock-down of the target sequence, reduce degradation of the construct, reduce off target effect, increase efficiency of the payload, and reduce degradation of the payload).

[00544] In one embodiment, the molecular scaffold of the modulatory polynucleotides is aligned in order to have the rate of excision of the guide strand (also referred to herein as the antisense strand) be greater than the rate of excision of the passenger strand (also referred to herein as the sense strand). The rate of excision of the guide or passenger strand may be, independently, 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99% or more than 99%. As a non-limiting example, the rate of excision of the guide strand is at least 80%. As another non-limiting example, the rate of excision of the guide strand is at least 90%.

[00545] In one embodiment, the rate of excision of the guide strand is greater than the rate of excision of the passenger strand. In one aspect, the rate of excision of the guide strand may be at least 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99% or more than 99% greater than the passenger strand.

[00546] In one embodiment, the efficiency of excision of the guide strand is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99% or more than 99%. As a non-limiting example, the efficiency of the excision of the guide strand is greater than 80%.

[00547] In one embodiment, the efficiency of the excision of the guide strand is greater than the excision of the passenger strand from the molecular scaffold. The excision of the guide strand may be 2, 3, 4, 5, 6, 7, 8, 9, 10 or more than 10 times more efficient than the excision of the passenger strand from the molecular scaffold.

[00548] In one embodiment, the molecular scaffold comprises a dual-function targeting modulatory polynucleotide. As used herein, a "dual-function targeting" modulatory polynucleotide is a polynucleotide where both the guide and passenger strands knock down the same target or the guide and passenger strands knock down different targets.

[00549] In one embodiment, the molecular scaffold of the modulatory polynucleotides described herein may comprise a 5' flanking region, a loop motif region and a 3' flanking region. Non-limiting examples of the sequences for the 5' flanking region, loop motif region (may also be referred to as a linker region) and the 3' flanking region which may be used, or fragments thereof used, in the modulatory polynucleotides described herein are shown in Tables 10 – 12.

Table 10. 5' Flanking Regions for Molecular Scaffold

5' Flanking Region Name	5' Flanking Region Sequence	5' Flanking Region SEQ ID
5F3	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCTCCACGGAA	1503
5F1	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCTCTTCGGAA	1504
5F2	GAAGCAAAGAAGGGGCAGAGGGAGCCCGTGAGCTGAGTGGGCCAGGGACTGGGAGAAGGAGTGAGGAGGCAGGGCCGGCATGCCTCTGCTGCTGGCCAGA	1505
5F4	GGGCCCTCCCGCAGAACACCATGCGCTCCACGGAA	1506
5F5	CTCCCGCAGAACACCATGCGCTCCACGGAA	1507
5F6	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCTCCACGGAAG	1508
5F7	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCTCCTCGGAA	1509

5F8	TTTATGCCTCATCCTCTGAGTGCTGAAGGCTTGCTGTAGGCTGTATGCTG	1692
5F9	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCTCTTCGGGA	1782

Table 11. Loop Motif Regions for Molecular Scaffold

Loop Motif Region Name	Loop Motif Region Sequence	Loop Motif Region SEQ ID
L5	GTGGCCACTGAGAAG	1510
L1	TGTGACCTGG	1511
L2	TGTGATTTGG	1512
L3	GTCTGCACCTGTCACTAG	1513
L4	GTGACCCAAG	1514
L6	GTGACCCAAT	1515
L7	GTGACCCAAC	1516
L8	GTGGCCACTGAGAAA	1517
L9	TATAATTTGG	1693
L10	CCTGACCCAGT	1694

Table 12. 3' Flanking Regions for Molecular Scaffold

3' Flanking Region Name	3' Flanking Region Sequence	3' Flanking Region SEQ ID
3F1	CTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTCAGTGA	1518
3F2	CTGTGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTCAGTGA	1519
3F3	TGGCCGTGTAGTGCTACCCAGCGCTGGCTGCCTCCTCAGCATTGCAATTCCTCTCCCATCTGGGCACCAGTCAGCTACCCTGGTGGGAATCTGGGTAGCC	1520

3F4	CTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCC	1521
3F5	CTGCGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTCAGTGA	1522
3F6	AGTGTATGATGCCTGTTACTAGCATTCACATGGAACAAATTGCTGCCGTG	1695
3F7	TCCTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTCAGTGA	1783

[00550] In one embodiment, the molecular scaffold may comprise at least one 5' flanking region, fragment or variant thereof listed in Table 10. As a non-limiting example, the 5' flanking region may be 5F1, 5F2, 5F3, 5F4, 5F5, 5F6, 5F7, 5F8, or 5F9.

[00551] In one embodiment, the molecular scaffold may comprise at least one 5F1 flanking region.

[00552] In one embodiment, the molecular scaffold may comprise at least one 5F2 flanking region.

[00553] In one embodiment, the molecular scaffold may comprise at least one 5F3 flanking region.

[00554] In one embodiment, the molecular scaffold may comprise at least one 5F4 flanking region.

[00555] In one embodiment, the molecular scaffold may comprise at least one 5F5 flanking region.

[00556] In one embodiment, the molecular scaffold may comprise at least one 5F6 flanking region.

[00557] In one embodiment, the molecular scaffold may comprise at least one 5F7 flanking region.

[00558] In one embodiment, the molecular scaffold may comprise at least one 5F8 flanking region.

[00559] In one embodiment, the molecular scaffold may comprise at least one 5F9 flanking region.

[00560] In one embodiment, the molecular scaffold may comprise at least one loop motif region, fragment or variant thereof listed in Table 11. As a non-limiting example, the loop motif region may be L1, L2, L3, L4, L5, L6, L7, L8, L9, or L10.

[00561] In one embodiment, the molecular scaffold may comprise at least one L1 loop motif region.

[00562] In one embodiment, the molecular scaffold may comprise at least one L2 loop motif region.

[00563] In one embodiment, the molecular scaffold may comprise at least one L3 loop motif region.

[00564] In one embodiment, the molecular scaffold may comprise at least one L4 loop motif region.

[00565] In one embodiment, the molecular scaffold may comprise at least one L5 loop motif region.

[00566] In one embodiment, the molecular scaffold may comprise at least one L6 loop motif region.

[00567] In one embodiment, the molecular scaffold may comprise at least one L7 loop motif region.

[00568] In one embodiment, the molecular scaffold may comprise at least one L8 loop motif region.

[00569] In one embodiment, the molecular scaffold may comprise at least one L9 loop motif region.

[00570] In one embodiment, the molecular scaffold may comprise at least one L10 loop motif region.

[00571] In one embodiment, the molecular scaffold may comprise at least one 3' flanking region, fragment or variant thereof listed in Table 12. As a non-limiting example, the 3' flanking region may be 3F1, 3F2, 3F3, 3F4, 3F5, 3F6, or 3F7.

[00572] In one embodiment, the molecular scaffold may comprise at least one 3F1 flanking region.

[00573] In one embodiment, the molecular scaffold may comprise at least one 3F2 flanking region.

[00574] In one embodiment, the molecular scaffold may comprise at least one 3F3 flanking region.

[00575] In one embodiment, the molecular scaffold may comprise at least one 3F4 flanking region.

[00576] In one embodiment, the molecular scaffold may comprise at least one 3F5 flanking region.

[00577] In one embodiment, the molecular scaffold may comprise at least one 3F6 flanking region.

[00578] In one embodiment, the molecular scaffold may comprise at least one 3F7 flanking region.

[00579] In one embodiment, the molecular scaffold may comprise at least one 5' flanking region, fragment or variant thereof, and at least one loop motif region, fragment or variant thereof, as described in Tables 10 and 11. As a non-limiting example, the 5' flanking region and the loop motif region may be 5F1 and L1, 5F1 and L2, 5F1 and L3, 5F1 and L4, 5F1 and L5, 5F1 and L6, 5F1 and L7, 5F1 and L8, 5F1 and L9, 5F1 and L10, 5F2 and L1, 5F2 and L2, 5F2 and L3, 5F2 and L4, 5F2 and L5, 5F2 and L6, 5F2 and L7, 5F2 and L8, 5F2 and L9, 5F2 and L10, 5F3 and L1, 5F3 and L2, 5F3 and L3, 5F3 and L4, 5F3 and L5, 5F3 and L6, 5F3 and L7, 5F3 and L8, 5F3 and L9, 5F3 and L10, 5F4 and L1, 5F4 and L2, 5F4 and L3, 5F4 and L4, 5F4 and L5, 5F4 and L6, 5F4 and L7, 5F4 and L8, 5F4 and L9, 5F4 and L10, 5F5 and L1, 5F5 and L2, 5F5 and L3, 5F5 and L4, 5F5 and L5, 5F5 and L6, 5F5 and L7, 5F5 and L8, 5F5 and L9, 5F5 and L10, 5F6 and L1, 5F6 and L2, 5F6 and L3, 5F6 and L4, 5F6 and L5, 5F6 and L6, 5F6 and L7, 5F6 and L8, 5F6 and L9, 5F6 and L10, 5F7 and L1, 5F7 and L2, 5F7 and L3, 5F7 and L4, 5F7 and L5, 5F7 and L6, 5F7 and L7, 5F7 and L8, 5F7 and L9, 5F7 and L10, 5F8 and L1, 5F8 and L2, 5F8 and L3, 5F8 and L4, 5F8 and L5, 5F8 and L6, 5F8 and L7, 5F8 and L8, 5F8 and L9, 5F8 and L10, 5F9 and L1, 5F9 and L2, 5F9 and L3, 5F9 and L4, 5F9 and L5, 5F9 and L6, 5F9 and L7, 5F9 and L8, 5F9 and L9, and 5F9 and L10.

[00580] In one embodiment, the molecular scaffold may comprise at least one 5F2 flanking region and at least one L1 loop motif region.

[00581] In one embodiment, the molecular scaffold may comprise at least one 5F1 flanking region and at least one L4 loop motif region.

[00582] In one embodiment, the molecular scaffold may comprise at least one 5F7 flanking region and at least one L8 loop motif region.

[00583] In one embodiment, the molecular scaffold may comprise at least one 5F3 flanking region and at least one L4 loop motif region.

[00584] In one embodiment, the molecular scaffold may comprise at least one 5F3 flanking region and at least one L5 loop motif region.

[00585] In one embodiment, the molecular scaffold may comprise at least one 5F4 flanking region and at least one L4 loop motif region.

[00586] In one embodiment, the molecular scaffold may comprise at least one 5F3 flanking region and at least one L7 loop motif region.

[00587] In one embodiment, the molecular scaffold may comprise at least one 5F5 flanking region and at least one L4 loop motif region.

[00588] In one embodiment, the molecular scaffold may comprise at least one 5F6 flanking region and at least one L4 loop motif region.

[00589] In one embodiment, the molecular scaffold may comprise at least one 5F3 flanking region and at least one L6 loop motif region.

[00590] In one embodiment, the molecular scaffold may comprise at least one 5F7 flanking region and at least one L4 loop motif region.

[00591] In one embodiment, the molecular scaffold may comprise at least one 5F2 flanking region and at least one L2 loop motif region.

[00592] In one embodiment, the molecular scaffold may comprise at least one 5F1 flanking region and at least one L1 loop motif region.

[00593] In one embodiment, the molecular scaffold may comprise at least one 5F1 flanking region and at least one L2 loop motif region.

[00594] In one embodiment, the molecular scaffold may comprise at least one 3' flanking region, fragment or variant thereof, and at least one motif region, fragment or variant thereof, as described in Tables 11 and 12. As a non-limiting example, the 3' flanking region and the loop motif region may be 3F1 and L1, 3F1 and L2, 3F1 and L3, 3F1 and L4, 3F1 and L5, 3F1 and L6, 3F1 and L7, 3F1 and L8, 3F1 and L9, 3F1 and L10, 3F2 and L1, 3F2 and L2, 3F2 and L3, 3F2 and L4, 3F2 and L5, 3F2 and L6, 3F2 and L7, 3F2 and L8, 3F2 and L9, 3F2 and L10, 3F3 and L1, 3F3 and L2, 3F3 and L3, 3F3 and L4, 3F3 and L5, 3F3 and L6, 3F3 and L7, 3F3 and L8, 3F3 and L9, 3F3 and L10, 3F4 and L1, 3F4 and L2, 3F4 and L3, 3F4 and L4, 3F4 and L5, 3F4 and L6, 3F4 and L7, 3F4 and L8, 3F4 and L9, 3F4 and L10, 3F5 and L1, 3F5 and L2, 3F5 and L3, 3F5 and L4, 3F5 and L5, 3F5 and L6, 3F5 and L7, 3F5 and L8, 3F5 and L9, 3F5 and L10, 3F6 and L1, 3F6 and L2, 3F6 and L3, 3F6 and L4, 3F6 and L5, 3F6 and L6, 3F6 and L7, 3F6 and L8, 3F6 and L9, 3F6 and L10, 3F7 and L1, 3F7 and L2, 3F7 and L3, 3F7 and L4, 3F7 and L5, 3F7 and L6, 3F7 and L7, 3F7 and L8, 3F7 and L9, and 3F7 and L10.

[00595] In one embodiment, the molecular scaffold may comprise at least one L1 loop motif region and at least one 3F2 flanking region.

[00596] In one embodiment, the molecular scaffold may comprise at least one L4 loop motif region and at least one 3F1 flanking region.

[00597] In one embodiment, the molecular scaffold may comprise at least one L8 loop motif region and at least one 3F5 flanking region.

[00598] In one embodiment, the molecular scaffold may comprise at least one L5 loop motif region and at least 3F1 flanking region.

[00599] In one embodiment, the molecular scaffold may comprise at least one L4 loop motif region and at least one 3F4 flanking region.

[00600] In one embodiment, the molecular scaffold may comprise at least one L7 loop motif region and at least one 3F1 flanking region.

[00601] In one embodiment, the molecular scaffold may comprise at least one L6 loop motif region and at least one 3F1 flanking region.

[00602] In one embodiment, the molecular scaffold may comprise at least one L4 loop motif region and at least one 3F5 flanking region.

[00603] In one embodiment, the molecular scaffold may comprise at least one L2 loop motif region and at least one 3F2 flanking region.

[00604] In one embodiment, the molecular scaffold may comprise at least one L1 loop motif region and at least one 3F3 flanking region.

[00605] In one embodiment, the molecular scaffold may comprise at least one L5 loop motif region and at least one 3F4 flanking region.

[00606] In one embodiment, the molecular scaffold may comprise at least one L1 loop motif region and at least one 3F1 flanking region.

[00607] In one embodiment, the molecular scaffold may comprise at least one L2 loop motif region and at least one 3F1 flanking region.

[00608] In one embodiment, the molecular scaffold may comprise at least one 5' flanking region, fragment or variant thereof, and at least one 3' flanking region, fragment or variant thereof, as described in Tables 10 and 12. As a non-limiting example, the flanking regions may be 5F1 and 3F1, 5F1 and 3F2, 5F1 and 3F3, 5F1 and 3F4, 5F1 and 3F5, 5F1 and 3F6, 5F1 and 3F7, 5F2 and 3F1, 5F2 and 3F2, 5F2 and 3F3, 5F2 and 3F4, 5F2 and 3F5, 5F2 and 3F6, 5F2 and 3F7, 5F3 and 3F1, 5F3 and 3F2, 5F3 and 3F3, 5F3 and 3F4, 5F3 and 3F5, 5F3 and 3F6, 5F3 and 3F7, 5F4 and 3F1, 5F4 and 3F2, 5F4 and 3F3, 5F4 and 3F4, 5F4 and 3F5, 5F4 and 3F6, 5F4 and

3F7, 5F5 and 3F1, 5F5 and 3F2, 5F5 and 3F3, 5F5 and 3F4, 5F5 and 3F5, 5F5 and 3F6, 5F5 and 3F7, 5F6 and 3F1, 5F6 and 3F2, 5F6 and 3F3, 5F6 and 3F4, 5F6 and 3F5, 5F6 and 3F6, 5F6 and 3F7, 5F7 and 3F1, 5F7 and 3F2, 5F7 and 3F3, 5F7 and 3F4, 5F7 and 3F5, 5F7 and 3F6, 5F7 and 3F7, 5F8 and 3F1, 5F8 and 3F2, 5F8 and 3F3, 5F8 and 3F4, 5F8 and 3F5, 5F8 and 3F6, and 5F8 and 3F7. 5F9 and 3F1, 5F9 and 3F2, 5F9 and 3F3, 5F9 and 3F4, 5F9 and 3F5, 5F9 and 3F6, and 5F9 and 3F7

[00609] In one embodiment, the molecular scaffold may comprise at least one 5F2 5' flanking region and at least one 3F2 3' flanking region.

[00610] In one embodiment, the molecular scaffold may comprise at least one 5F1 5' flanking region and at least one 3F1 3' flanking region.

[00611] In one embodiment, the molecular scaffold may comprise at least one 5F7 5' flanking region and at least one 3F5 3' flanking region.

[00612] In one embodiment, the molecular scaffold may comprise at least one 5F3 5' flanking region and at least one 3F1 3' flanking region.

[00613] In one embodiment, the molecular scaffold may comprise at least one 5F4 5' flanking region and at least one 3F4 3' flanking region.

[00614] In one embodiment, the molecular scaffold may comprise at least one 5F5 5' flanking region and at least one 3F4 3' flanking region.

[00615] In one embodiment, the molecular scaffold may comprise at least one 5F6 5' flanking region and at least one 3F1 3' flanking region.

[00616] In one embodiment, the molecular scaffold may comprise at least one 5F2 5' flanking region and at least one 3F3 3' flanking region.

[00617] In one embodiment, the molecular scaffold may comprise at least one 5F3 5' flanking region and at least one 3F4 3' flanking region.

[00618] In one embodiment, the molecular scaffold may comprise at least one 5F1 5' flanking region and at least one 3F2 3' flanking region.

[00619] In one embodiment, the molecular scaffold may comprise at least one 5' flanking region, fragment or variant thereof, at least one loop motif region, fragment or variant thereof, and at least one 3' flanking region as described in Tables 10 – 12. As a non-limiting example, the flanking and loop motif regions may be 5F1, L1 and 3F1; 5F1, L1 and 3F2; 5F1, L1 and 3F3; 5F1, L1 and 3F4; 5F1, L1 and 3F5; 5F1, L1 and 3F6; 5F1, L1 and 3F7; 5F2, L1 and 3F1; 5F2, L1 and 3F2; 5F2, L1 and 3F3; 5F2, L1 and 3F4; 5F2, L1 and 3F5; 5F2, L1 and 3F6; 5F2, L1 and 3F7; 5F3, L1 and 3F1; 5F3, L1 and 3F2; 5F3, L1 and 3F3; 5F3, L1 and 3F4; 5F3, L1 and 3F5;

5F3, L1 and 3F6; 5F3, L1 and 3F7; 5F4, L1 and 3F1; 5F4, L1 and 3F2; 5F4, L1 and 3F3; 5F4, L1 and 3F4; 5F4, L1 and 3F5; 5F4, L1 and 3F6; 5F4, L1 and 3F7; 5F5, L1 and 3F1; 5F5, L1 and 3F2; 5F5, L1 and 3F3; 5F5, L1 and 3F4; 5F5, L1 and 3F5; 5F5, L1 and 3F6; 5F5, L1 and 3F7; 5F6, L1 and 3F1; 5F6, L1 and 3F2; 5F6, L1 and 3F3; 5F6, L1 and 3F4; 5F6, L1 and 3F5; 5F6, L1 and 3F6; 5F6, L1 and 3F7; 5F7, L1 and 3F1; 5F7, L1 and 3F2; 5F7, L1 and 3F3; 5F7, L1 and 3F4; 5F7, L1 and 3F5; 5F7, L1 and 3F6; 5F7, L1 and 3F7; 5F8, L1 and 3F1; 5F8, L1 and 3F2; 5F8, L1 and 3F3; 5F8, L1 and 3F4; 5F8, L1 and 3F5; 5F8, L1 and 3F6; 5F8, L1 and 3F7; 5F9, L1 and 3F1; 5F9, L1 and 3F2; 5F9, L1 and 3F3; 5F9, L1 and 3F4; 5F9, L1 and 3F5; 5F9, L1 and 3F6; 5F9, L1 and 3F7; 5F1, L2 and 3F1; 5F1, L2 and 3F2; 5F1, L2 and 3F3; 5F1, L2 and 3F4; 5F1, L2 and 3F5; 5F1, L2 and 3F6; 5F1, L2 and 3F7; 5F2, L2 and 3F1; 5F2, L2 and 3F2; 5F2, L2 and 3F3; 5F2, L2 and 3F4; 5F2, L2 and 3F5; 5F2, L2 and 3F6; 5F2, L2 and 3F7; 5F3, L2 and 3F1; 5F3, L2 and 3F2; 5F3, L2 and 3F3; 5F3, L2 and 3F4; 5F3, L2 and 3F5; 5F3, L2 and 3F6; 5F3, L2 and 3F7; 5F4, L2 and 3F1; 5F4, L2 and 3F2; 5F4, L2 and 3F3; 5F4, L2 and 3F4; 5F4, L2 and 3F5; 5F4, L2 and 3F6; 5F4, L2 and 3F7; 5F5, L2 and 3F1; 5F5, L2 and 3F2; 5F5, L2 and 3F3; 5F5, L2 and 3F4; 5F5, L2 and 3F5; 5F5, L2 and 3F6; 5F5, L2 and 3F7; 5F6, L2 and 3F1; 5F6, L2 and 3F2; 5F6, L2 and 3F3; 5F6, L2 and 3F4; 5F6, L2 and 3F5; 5F6, L2 and 3F6; 5F6, L2 and 3F7; 5F7, L2 and 3F1; 5F7, L2 and 3F2; 5F7, L2 and 3F3; 5F7, L2 and 3F4; 5F7, L2 and 3F5; 5F7, L2 and 3F6; 5F7, L2 and 3F7; 5F8, L2 and 3F1; 5F8, L2 and 3F2; 5F8, L2 and 3F3; 5F8, L2 and 3F4; 5F8, L2 and 3F5; 5F8, L2 and 3F6; 5F8, L2 and 3F7; 5F9, L2 and 3F1; 5F9, L2 and 3F2; 5F9, L2 and 3F3; 5F9, L2 and 3F4; 5F9, L2 and 3F5; 5F9, L2 and 3F6; 5F9, L2 and 3F7; 5F1, L3 and 3F1; 5F1, L3 and 3F2; 5F1, L3 and 3F3; 5F1, L3 and 3F4; 5F1, L3 and 3F5; 5F1, L3 and 3F6; 5F1, L3 and 3F7; 5F2, L3 and 3F1; 5F2, L3 and 3F2; 5F2, L3 and 3F3; 5F2, L3 and 3F4; 5F2, L3 and 3F5; 5F2, L3 and 3F6; 5F2, L3 and 3F7; 5F3, L3 and 3F1; 5F3, L3 and 3F2; 5F3, L3 and 3F3; 5F3, L3 and 3F4; 5F3, L3 and 3F5; 5F3, L3 and 3F6; 5F3, L3 and 3F7; 5F4, L3 and 3F1; 5F4, L3 and 3F2; 5F4, L3 and 3F3; 5F4, L3 and 3F4; 5F4, L3 and 3F5; 5F4, L3 and 3F6; 5F4, L3 and 3F7; 5F5, L3 and 3F1; 5F5, L3 and 3F2; 5F5, L3 and 3F3; 5F5, L3 and 3F4; 5F5, L3 and 3F5; 5F5, L3 and 3F6; 5F5, L3 and 3F7; 5F6, L3 and 3F1; 5F6, L3 and 3F2; 5F6, L3 and 3F3; 5F6, L3 and 3F4; 5F6, L3 and 3F5; 5F6, L3 and 3F6; 5F6, L3 and 3F7; 5F7, L3 and 3F1; 5F7, L3 and 3F2; 5F7, L3 and 3F3; 5F7, L3 and 3F4; 5F7, L3 and 3F5; 5F7, L3 and 3F6; 5F7, L3 and 3F7; 5F8, L3 and 3F1; 5F8, L3 and 3F2; 5F8, L3 and 3F3; 5F8, L3 and 3F4; 5F8, L3 and 3F5; 5F8, L3 and 3F6; 5F8, L3 and 3F7; 5F9, L3 and 3F1; 5F9, L3 and 3F2; 5F9, L3 and 3F3; 5F9, L3 and 3F4; 5F9, L3 and 3F5; 5F9, L3 and 3F6; 5F9, L3 and 3F7; 5F1, L4 and 3F1; 5F1, L4 and 3F2; 5F1, L4 and 3F3; 5F1, L4 and 3F4; 5F1, L4 and 3F5; 5F1, L4 and 3F6;

5F1, L4 and 3F7; 5F2, L4 and 3F1; 5F2, L4 and 3F2; 5F2, L4 and 3F3; 5F2, L4 and 3F4; 5F2, L4 and 3F5; 5F2, L4 and 3F6; 5F2, L4 and 3F7; 5F3, L4 and 3F1; 5F3, L4 and 3F2; 5F3, L4 and 3F3; 5F3, L4 and 3F4; 5F3, L4 and 3F5; 5F3, L4 and 3F6; 5F3, L4 and 3F7; 5F4, L4 and 3F1; 5F4, L4 and 3F2; 5F4, L4 and 3F3; 5F4, L4 and 3F4; 5F4, L4 and 3F5; 5F4, L4 and 3F6; 5F4, L4 and 3F7; 5F5, L4 and 3F1; 5F5, L4 and 3F2; 5F5, L4 and 3F3; 5F5, L4 and 3F4; 5F5, L4 and 3F5; 5F5, L4 and 3F6; 5F5, L4 and 3F7; 5F6, L4 and 3F1; 5F6, L4 and 3F2; 5F6, L4 and 3F3; 5F6, L4 and 3F4; 5F6, L4 and 3F5; 5F6, L4 and 3F6; 5F6, L4 and 3F7; 5F7, L4 and 3F1; 5F7, L4 and 3F2; 5F7, L4 and 3F3; 5F7, L4 and 3F4; 5F7, L4 and 3F5; 5F7, L4 and 3F6; 5F7, L4 and 3F7; 5F8, L4 and 3F1; 5F8, L4 and 3F2; 5F8, L4 and 3F3; 5F8, L4 and 3F4; 5F8, L4 and 3F5; 5F8, L4 and 3F6; 5F8, L4 and 3F7; 5F9, L4 and 3F1; 5F9, L4 and 3F2; 5F9, L4 and 3F3; 5F9, L4 and 3F4; 5F9, L4 and 3F5; 5F9, L4 and 3F6; 5F9, L4 and 3F7; 5F1, L5 and 3F1; 5F1, L5 and 3F2; 5F1, L5 and 3F3; 5F1, L5 and 3F4; 5F1, L5 and 3F5; 5F1, L5 and 3F6; 5F1, L5 and 3F7; 5F2, L5 and 3F1; 5F2, L5 and 3F2; 5F2, L5 and 3F3; 5F2, L5 and 3F4; 5F2, L5 and 3F5; 5F2, L5 and 3F6; 5F2, L5 and 3F7; 5F3, L5 and 3F1; 5F3, L5 and 3F2; 5F3, L5 and 3F3; 5F3, L5 and 3F4; 5F3, L5 and 3F5; 5F3, L5 and 3F6; 5F3, L5 and 3F7; 5F4, L5 and 3F1; 5F4, L5 and 3F2; 5F4, L5 and 3F3; 5F4, L5 and 3F4; 5F4, L5 and 3F5; 5F4, L5 and 3F6; 5F4, L5 and 3F7; 5F5, L5 and 3F1; 5F5, L5 and 3F2; 5F5, L5 and 3F3; 5F5, L5 and 3F4; 5F5, L5 and 3F5; 5F5, L5 and 3F6; 5F5, L5 and 3F7; 5F6, L5 and 3F1; 5F6, L5 and 3F2; 5F6, L5 and 3F3; 5F6, L5 and 3F4; 5F6, L5 and 3F5; 5F6, L5 and 3F6; 5F6, L5 and 3F7; 5F7, L5 and 3F1; 5F7, L5 and 3F2; 5F7, L5 and 3F3; 5F7, L5 and 3F4; 5F7, L5 and 3F5; 5F7, L5 and 3F6; 5F7, L5 and 3F7; 5F8, L5 and 3F1; 5F8, L5 and 3F2; 5F8, L5 and 3F3; 5F8, L5 and 3F4; 5F8, L5 and 3F5; 5F8, L5 and 3F6; 5F8, L5 and 3F7; 5F9, L5 and 3F1; 5F9, L5 and 3F2; 5F9, L5 and 3F3; 5F9, L5 and 3F4; 5F9, L5 and 3F5; 5F9, L5 and 3F6; 5F9, L5 and 3F7; 5F1, L6 and 3F1; 5F1, L6 and 3F2; 5F1, L6 and 3F3; 5F1, L6 and 3F4; 5F1, L6 and 3F5; 5F1, L6 and 3F6; 5F1, L6 and 3F7; 5F2, L6 and 3F1; 5F2, L6 and 3F2; 5F2, L6 and 3F3; 5F2, L6 and 3F4; 5F2, L6 and 3F5; 5F2, L6 and 3F6; 5F2, L6 and 3F7; 5F3, L6 and 3F1; 5F3, L6 and 3F2; 5F3, L6 and 3F3; 5F3, L6 and 3F4; 5F3, L6 and 3F5; 5F3, L6 and 3F6; 5F3, L6 and 3F7; 5F4, L6 and 3F1; 5F4, L6 and 3F2; 5F4, L6 and 3F3; 5F4, L6 and 3F4; 5F4, L6 and 3F5; 5F4, L6 and 3F6; 5F4, L6 and 3F7; 5F5, L6 and 3F1; 5F5, L6 and 3F2; 5F5, L6 and 3F3; 5F5, L6 and 3F4; 5F5, L6 and 3F5; 5F5, L6 and 3F6; 5F5, L6 and 3F7; 5F6, L6 and 3F1; 5F6, L6 and 3F2; 5F6, L6 and 3F3; 5F6, L6 and 3F4; 5F6, L6 and 3F5; 5F6, L6 and 3F6; 5F6, L6 and 3F7; 5F7, L6 and 3F1; 5F7, L6 and 3F2; 5F7, L6 and 3F3; 5F7, L6 and 3F4; 5F7, L6 and 3F5; 5F7, L6 and 3F6; 5F7, L6 and 3F7; 5F8, L6 and 3F1; 5F8, L6 and 3F2; 5F8, L6 and 3F3; 5F8, L6 and 3F4; 5F8, L6 and 3F5; 5F8, L6 and 3F6; 5F8, L6 and 3F7;

5F9, L6 and 3F1; 5F9, L6 and 3F2; 5F9, L6 and 3F3; 5F9, L6 and 3F4; 5F9, L6 and 3F5; 5F9, L6 and 3F6; 5F9, L6 and 3F7; 5F1, L7 and 3F1; 5F1, L7 and 3F2; 5F1, L7 and 3F3; 5F1, L7 and 3F4; 5F1, L7 and 3F5; 5F1, L7 and 3F6; 5F1, L7 and 3F7; 5F2, L7 and 3F1; 5F2, L7 and 3F2; 5F2, L7 and 3F3; 5F2, L7 and 3F4; 5F2, L7 and 3F5; 5F2, L7 and 3F6; 5F2, L7 and 3F7; 5F3, L7 and 3F1; 5F3, L7 and 3F2; 5F3, L7 and 3F3; 5F3, L7 and 3F4; 5F3, L7 and 3F5; 5F3, L7 and 3F6; 5F3, L7 and 3F7; 5F4, L7 and 3F1; 5F4, L7 and 3F2; 5F4, L7 and 3F3; 5F4, L7 and 3F4; 5F4, L7 and 3F5; 5F4, L7 and 3F6; 5F4, L7 and 3F7; 5F5, L7 and 3F1; 5F5, L7 and 3F2; 5F5, L7 and 3F3; 5F5, L7 and 3F4; 5F5, L7 and 3F5; 5F5, L7 and 3F6; 5F5, L7 and 3F7; 5F6, L7 and 3F1; 5F6, L7 and 3F2; 5F6, L7 and 3F3; 5F6, L7 and 3F4; 5F6, L7 and 3F5; 5F6, L7 and 3F6; 5F6, L7 and 3F7; 5F7, L7 and 3F1; 5F7, L7 and 3F2; 5F7, L7 and 3F3; 5F7, L7 and 3F4; 5F7, L7 and 3F5; 5F7, L7 and 3F6; 5F7, L7 and 3F7; 5F8, L7 and 3F1; 5F8, L7 and 3F2; 5F8, L7 and 3F3; 5F8, L7 and 3F4; 5F8, L7 and 3F5; 5F8, L7 and 3F6; 5F8, L7 and 3F7; ; 5F9, L7 and 3F1; 5F9, L7 and 3F2; 5F9, L7 and 3F3; 5F9, L7 and 3F4; 5F9, L7 and 3F5; 5F9, L7 and 3F6; 5F9, L7 and 3F7; 5F1, L8 and 3F1; 5F1, L8 and 3F2; 5F1, L8 and 3F3; 5F1, L8 and 3F4; 5F1, L8 and 3F5; 5F1, L8 and 3F6; 5F1, L8 and 3F7; 5F2, L8 and 3F1; 5F2, L8 and 3F2; 5F2, L8 and 3F3; 5F2, L8 and 3F4; 5F2, L8 and 3F5; 5F2, L8 and 3F6; 5F2, L8 and 3F7; 5F3, L8 and 3F1; 5F3, L8 and 3F2; 5F3, L8 and 3F3; 5F3, L8 and 3F4; 5F3, L8 and 3F5; 5F3, L8 and 3F6; 5F3, L8 and 3F7; 5F4, L8 and 3F1; 5F4, L8 and 3F2; 5F4, L8 and 3F3; 5F4, L8 and 3F4; 5F4, L8 and 3F5; 5F4, L8 and 3F6; 5F4, L8 and 3F7; 5F5, L8 and 3F1; 5F5, L8 and 3F2; 5F5, L8 and 3F3; 5F5, L8 and 3F4; 5F5, L8 and 3F5; 5F5, L8 and 3F6; 5F5, L8 and 3F7; 5F6, L8 and 3F1; 5F6, L8 and 3F2; 5F6, L8 and 3F3; 5F6, L8 and 3F4; 5F6, L8 and 3F5; 5F6, L8 and 3F6; 5F6, L8 and 3F7; 5F7, L8 and 3F1; 5F7, L8 and 3F2; 5F7, L8 and 3F3; 5F7, L8 and 3F4; 5F7, L8 and 3F5; 5F7, L8 and 3F6; 5F7, L8 and 3F7; 5F8, L8 and 3F1; 5F8, L8 and 3F2; 5F8, L8 and 3F3; 5F8, L8 and 3F4; 5F8, L8 and 3F5; 5F8, L8 and 3F6; 5F8, L8 and 3F7; 5F9, L8 and 3F1; 5F9, L8 and 3F2; 5F9, L8 and 3F3; 5F9, L8 and 3F4; 5F9, L8 and 3F5; 5F9, L8 and 3F6; 5F9, L8 and 3F7; 5F1, L9 and 3F1; 5F1, L9 and 3F2; 5F1, L9 and 3F3; 5F1, L9 and 3F4; 5F1, L9 and 3F5; 5F1, L9 and 3F6; 5F1, L9 and 3F7; 5F2, L9 and 3F1; 5F2, L9 and 3F2; 5F2, L9 and 3F3; 5F2, L9 and 3F4; 5F2, L9 and 3F5; 5F2, L9 and 3F6; 5F2, L9 and 3F7; 5F3, L9 and 3F1; 5F3, L9 and 3F2; 5F3, L9 and 3F3; 5F3, L9 and 3F4; 5F3, L9 and 3F5; 5F3, L9 and 3F6; 5F3, L9 and 3F7; 5F4, L9 and 3F1; 5F4, L9 and 3F2; 5F4, L9 and 3F3; 5F4, L9 and 3F4; 5F4, L9 and 3F5; 5F4, L9 and 3F6; 5F4, L9 and 3F7; 5F5, L9 and 3F1; 5F5, L9 and 3F2; 5F5, L9 and 3F3; 5F5, L9 and 3F4; 5F5, L9 and 3F5; 5F5, L9 and 3F6; 5F5, L9 and 3F7; 5F6, L9 and 3F1; 5F6, L9 and 3F2; 5F6, L9 and 3F3; 5F6, L9 and 3F4; 5F6, L9 and 3F5; 5F6, L9 and 3F6; 5F6, L9 and 3F7; 5F7, L9 and 3F1;

5F7, L9 and 3F2; 5F7, L9 and 3F3; 5F7, L9 and 3F4; 5F7, L9 and 3F5; 5F7, L9 and 3F6; 5F7, L9 and 3F7; 5F8, L9 and 3F1; 5F8, L9 and 3F2; 5F8, L9 and 3F3; 5F8, L9 and 3F4; 5F8, L9 and 3F5; 5F8, L9 and 3F6; 5F8, L9 and 3F7; 5F9, L9 and 3F1; 5F9, L9 and 3F2; 5F9, L9 and 3F3; 5F9, L9 and 3F4; 5F9, L9 and 3F5; 5F9, L9 and 3F6; 5F9, L9 and 3F7; 5F1, L10 and 3F1; 5F1, L10 and 3F2; 5F1, L10 and 3F3; 5F1, L10 and 3F4; 5F1, L10 and 3F5; 5F1, L10 and 3F6; 5F1, L10 and 3F7; 5F2, L10 and 3F1; 5F2, L10 and 3F2; 5F2, L10 and 3F3; 5F2, L10 and 3F4; 5F2, L10 and 3F5; 5F2, L10 and 3F6; 5F2, L10 and 3F7; 5F3, L10 and 3F1; 5F3, L10 and 3F2; 5F3, L10 and 3F3; 5F3, L10 and 3F4; 5F3, L10 and 3F5; 5F3, L10 and 3F6; 5F3, L10 and 3F7; 5F4, L10 and 3F1; 5F4, L10 and 3F2; 5F4, L10 and 3F3; 5F4, L10 and 3F4; 5F4, L10 and 3F5; 5F4, L10 and 3F6; 5F4, L10 and 3F7; 5F5, L10 and 3F1; 5F5, L10 and 3F2; 5F5, L10 and 3F3; 5F5, L10 and 3F4; 5F5, L10 and 3F5; 5F5, L10 and 3F6; 5F5, L10 and 3F7; 5F6, L10 and 3F1; 5F6, L10 and 3F2; 5F6, L10 and 3F3; 5F6, L10 and 3F4; 5F6, L10 and 3F5; 5F6, L10 and 3F6; 5F6, L10 and 3F7; 5F7, L10 and 3F1; 5F7, L10 and 3F2; 5F7, L10 and 3F3; 5F7, L10 and 3F4; 5F7, L10 and 3F5; 5F7, L10 and 3F6; 5F7, L10 and 3F7; 5F8, L10 and 3F1; 5F8, L10 and 3F2; 5F8, L10 and 3F3; 5F8, L10 and 3F4; 5F8, L10 and 3F5; 5F8, L10 and 3F6; 5F8, L10 and 3F7; 5F9, L10 and 3F1; 5F9, L10 and 3F2; 5F9, L10 and 3F3; 5F9, L10 and 3F4; 5F9, L10 and 3F5; 5F9, L10 and 3F6; and 5F9, L10 and 3F7.

[00620] In one embodiment, the molecular scaffold may comprise at least one 5F2 5' flanking region, at least one L1 loop motif region, and at least one 3F2 3' flanking region.

[00621] In one embodiment, the molecular scaffold may comprise at least one 5F1 5' flanking region, at least one L4 loop motif region, and at least one 3F1 3' flanking region.

[00622] In one embodiment, the molecular scaffold may comprise at least one 5F7 5' flanking region, at least one L8 loop motif region, and at least one 3F5 3' flanking region.

[00623] In one embodiment, the molecular scaffold may comprise at least one 5F3 5' flanking region, at least one L4 loop motif region, and at least one 3F1 3' flanking region.

[00624] In one embodiment, the molecular scaffold may comprise at least one 5F3 5' flanking region, at least one L5 loop motif region, and at least one 3F1 3' flanking region.

[00625] In one embodiment, the molecular scaffold may comprise at least one 5F4 5' flanking region, at least one L4 loop motif region, and at least one 3F4 3' flanking region.

[00626] In one embodiment, the molecular scaffold may comprise at least one 5F3 5' flanking region, at least one L7 loop motif region, and at least one 3F1 3' flanking region.

[00627] In one embodiment, the molecular scaffold may comprise at least one 5F5 5' flanking region, at least one L4 loop motif region, and at least one 3F4 3' flanking region.

[00628] In one embodiment, the molecular scaffold may comprise at least one 5F6 5' flanking region, at least one L4 loop motif region, and at least one 3F1 3' flanking region.

[00629] In one embodiment, the molecular scaffold may comprise at least one 5F3 5' flanking region, at least one L6 loop motif region, and at least one 3F1 3' flanking region.

[00630] In one embodiment, the molecular scaffold may comprise at least one 5F7 5' flanking region, at least one L4 loop motif region, and at least one 3F5 3' flanking region.

[00631] In one embodiment, the molecular scaffold may comprise at least one 5F2 5' flanking region, at least one L2 loop motif region, and at least one 3F2 3' flanking region.

[00632] In one embodiment, the molecular scaffold may comprise at least one 5F2 5' flanking region, at least one L1 loop motif region, and at least one 3F3 3' flanking region.

[00633] In one embodiment, the molecular scaffold may comprise at least one 5F3 5' flanking region, at least one L5 loop motif region, and at least one 3F4 3' flanking region.

[00634] In one embodiment, the molecular scaffold may comprise at least one 5F1 5' flanking region, at least one L1 loop motif region, and at least one 3F1 3' flanking region.

[00635] In one embodiment, the molecular scaffold may comprise at least one 5F1 5' flanking region, at least one L2 loop motif region, and at least one 3F1 3' flanking region.

[00636] In one embodiment, the molecular scaffold may comprise at least one 5F1 5' flanking region, at least one L1 loop motif region, and at least one 3F2 3' flanking region.

[00637] In one embodiment, the molecular scaffold may comprise at least one 5F2 5' flanking region, at least one L3 loop motif region, and at least one 3F3 3' flanking region.

[00638] In one embodiment, the molecular scaffold may be a natural pri-miRNA scaffold. As a non-limiting example, the molecular scaffold may be a scaffold derived from the human miR155 scaffold.

[00639] In one embodiment, the molecular scaffold may comprise one or more linkers known in the art. The linkers may separate regions or one molecular scaffold from another. As a non-limiting example, the molecular scaffold may be polycistronic.

Modulatory Polynucleotide Comprising Molecular Scaffold and siRNA Molecules Targeting HTT

[00640] In one embodiment, the modulatory polynucleotide may comprise 5' and 3' flanking regions, loop motif region, and nucleic acid sequences encoding sense sequence and antisense sequence as described in Tables 13 and 14. In Tables 13 and 14, the DNA sequence identifier for the passenger and guide strands are described as well as the 5' and 3' Flanking Regions and the Loop region (also referred to as the linker region). In Tables 13 and 14, the "miR" component of

the name of the sequence does not necessarily correspond to the sequence numbering of miRNA genes (e.g., VOYHTmiR-102 is the name of the sequence and does not necessarily mean that miR-102 is part of the sequence).

Table 13. HTT Modulatory Polynucleotide Sequence Regions (5' to 3')

Modulatory Polynucleotide Construct Name	5' Flanking to 3' Flanking SEQ ID NO	5' Flanking SEQ ID NO	Passenger SEQ ID NO	Loop SEQ ID NO	Guide SEQ ID NO	3' Flanking SEQ ID NO
VOYHTmiR-102.214	1523	1504	1636	1511	1677	1518
VOYHTmiR-104.214	1524	1504	1643	1511	1677	1518
VOYHTmiR-109.214	1525	1504	1650	1512	1677	1518
VOYHTmiR-114.214	1526	1504	1657	1511	1677	1519
VOYHTmiR-116.214	1527	1504	1650	1511	1677	1519
VOYHTmiR-127.214	1528	1505	1650	1513	1674	1520
VOYHTmiR-102.218	1529	1504	1637	1511	1678	1518
VOYHTmiR-104.218	1530	1504	1644	1511	1678	1518
VOYHTmiR-109.218	1531	1504	1651	1512	1678	1518
VOYHTmiR-114.218	1532	1504	1658	1511	1678	1519
VOYHTmiR-116.218	1533	1504	1651	1511	1678	1519
VOYHTmiR-127.218	1534	1505	1651	1513	1678	1520
VOYHTmiR-102.219.o	1535	1504	1620	1511	1673	1518
VOYHTmiR-104.219.o	1536	1504	1623	1511	1673	1518
VOYHTmiR-109.219.o	1537	1504	1620	1512	1673	1518

VOYHTmiR-114.219	153 8	150 4	1 626	15 11	673	151 9
VOYHTmiR-116.219.o	153 9	150 4	1 629	15 11	673	151 9
VOYHTmiR-127.219.o	154 0	150 5	1 620	15 13	673	152 0
VOYHTmiR-102.219.n	154 1	150 4	1 632	15 11	673	151 8
VOYHTmiR-104.219.n	154 2	150 4	1 633	15 11	673	151 8
VOYHTmiR-109.219.n	154 3	150 4	1 632	15 12	673	151 8
VOYHTmiR-116.219.n	154 4	150 4	1 634	15 11	673	151 9
VOYHTmiR-127.219.n	154 5	150 5	1 632	15 13	673	152 0
VOYHTmiR-102.257	154 6	150 4	1 638	15 11	679	151 8
VOYHTmiR-104.257	154 7	150 4	1 645	15 11	679	151 8
VOYHTmiR-109.257	154 8	150 4	1 652	15 12	679	151 8
VOYHTmiR-114.257	154 9	150 4	1 659	15 11	679	151 9
VOYHTmiR-116.257	155 0	150 4	1 652	15 11	679	151 9
VOYHTmiR-127.257	155 1	150 5	1 652	15 13	679	152 0
VOYHTmiR-102.894	155 2	150 4	1 621	15 11	674	151 8
VOYHTmiR-104.894	155 3	150 4	1 624	15 11	674	151 8
VOYHTmiR-109.894	155 4	150 4	1 621	15 12	674	151 8
VOYHTmiR-114.894	155 5	150 4	1 627	15 11	674	151 9
VOYHTmiR-116.894	155 6	150 4	1 630	15 11	674	151 9

VOYHTmiR-127.894	1557	1505	1621	1513	674	1520
VOYHTmiR-102.907	1558	1504	1641	1511	682	1518
VOYHTmiR-104.907	1559	1504	1648	1511	682	1518
VOYHTmiR-109.907	1560	1504	1655	1512	682	1518
VOYHTmiR-114.907	1561	1504	1662	1511	682	1519
VOYHTmiR-116.907	1562	1504	1655	1511	682	1519
VOYHTmiR-127.907	1563	1505	1655	1513	682	1520
VOYHTmiR-102.372	1564	1504	1639	1511	680	1518
VOYHTmiR-104.372	1565	1504	1646	1511	680	1518
VOYHTmiR-109.372	1566	1504	1653	1512	680	1518
VOYHTmiR-114.372	1567	1504	1660	1511	680	1519
VOYHTmiR-116.372	1568	1504	1653	1511	680	1519
VOYHTmiR-127.372	1569	1505	1653	1513	680	1520
VOYHTmiR-102.425	1570	1504	1640	1511	681	1518
VOYHTmiR-104.425	1571	1504	1647	1511	681	1518
VOYHTmiR-109.425	1572	1504	1654	1512	681	1518
VOYHTmiR-114.425	1573	1504	1661	1511	681	1519
VOYHTmiR-116.425	1574	1504	1654	1511	681	1519
VOYHTmiR-127.425	1575	1505	1654	1513	681	1520

VOYHTmiR-102.032	157 6	150 4	1 664	15 11	684	151 8
VOYHTmiR-104.032	157 7	150 4	1 666	15 11	684	151 8
VOYHTmiR-109.032	157 8	150 4	1 668	15 12	684	151 8
VOYHTmiR-114.032	157 9	150 4	1 670	15 11	684	151 9
VOYHTmiR-116.032	158 0	150 4	1 668	15 11	684	151 9
VOYHTmiR-127.032	158 1	150 5	1 668	15 13	684	152 0
VOYHTmiR-102.020	158 2	150 4	1 663	15 11	683	151 8
VOYHTmiR-104.020	158 3	150 4	1 665	15 11	683	151 8
VOYHTmiR-109.020	158 4	150 4	1 667	15 12	683	151 8
VOYHTmiR-114.020	158 5	150 4	1 669	15 11	683	151 9
VOYHTmiR-116.020	158 6	150 4	1 667	15 11	683	151 9
VOYHTmiR-127.020	158 7	150 5	1 667	15 13	683	152 0
VOYHTmiR-102.016	158 8	150 4	1 635	15 11	676	151 8
VOYHTmiR-104.016	158 9	150 4	1 642	15 11	676	151 8
VOYHTmiR-109.016	159 0	150 4	1 649	15 12	676	151 8
VOYHTmiR-114.016	159 1	150 4	1 656	15 11	676	151 9
VOYHTmiR-116.016	159 2	150 4	1 649	15 11	676	151 9
VOYHTmiR-127.016	159 3	150 5	1 649	15 13	676	152 0
VOYHTmiR-102.579	159 4	150 4	1 622	15 11	675	151 8

VOYHTmiR-104.579	1595	1504	1625	1511	675	1518
VOYHTmiR-109.579	1596	1504	1622	1512	675	1518
VOYHTmiR-114.579	1597	1504	1628	1511	675	1519
VOYHTmiR-116.579	1598	1504	1631	1511	675	1519
VOYHTmiR-127.579	1599	1505	1622	1513	675	1520
VOYHTmiR-104.579.1	1600	1504	1671	1514	675	1518
VOYHTmiR-104.579.2	1601	1503	1671	1514	675	1518
VOYHTmiR-104.579.3	1602	1503	1671	1510	675	1518
VOYHTmiR-104.579.4	1603	1506	1671	1514	675	1521
VOYHTmiR-104.579.6	1604	1507	1671	1514	675	1521
VOYHTmiR-104.579.7	1605	1508	1671	1514	685	1518
VOYHTmiR-104.579.8	1606	1503	1672	1515	675	1518
VOYHTmiR-104.579.9	1607	1509	1671	1514	675	1522
VOYHTmiR-102.020	1608	1504	1663	1511	683	1518
VOYHTmiR-102.032	1609	1504	1664	1511	684	1518
VOYHTmiR-104.020	1610	1504	1665	1511	683	1518
VOYHTmiR-104.032	1611	1504	1666	1511	684	1518
VOYHTmiR-109.020	1612	1504	1667	1512	683	1518
VOYHTmiR-109.032	1613	1504	1668	1512	684	1518

VOYHTmiR-114.020	1614	1504	1669	1511	683	1519
VOYHTmiR-114.032	1615	1504	1670	1511	684	1519
VOYHTmiR-116.020	1616	1504	1667	1511	683	1519
VOYHTmiR-116.032	1617	1504	1668	1511	684	1519
VOYHTmiR-127.020	1618	1505	1667	1513	683	1520
VOYHTmiR-127.032	1619	1505	1668	1513	684	1520

Table 14. HTT Modulatory Polynucleotide Sequence Region (5' to 3')

Name	5' Flanking to 3' Flanking SEQ ID NO	5' Flanking SEQ ID NO	Passenger SEQ ID NO	Loop SEQ ID NO	Guide SEQ ID NO	3' Flanking SEQ ID NO
VOYHTmiR-104.579.5	1686	1503	1688	1516	1690	1518
VOYHTmiR-104.579.10	1687	1509	1689	1517	1691	1532

Modulatory Polynucleotide Comprising Molecular Scaffold and siRNA Molecules Targeting SOD1

[00641] In one embodiment, the modulatory polynucleotide may comprise 5' and 3' flanking regions, loop motif region, and nucleic acid sequences encoding sense sequence and antisense sequence as described in Tables 15 and 16. In Tables 15 and 16, the DNA sequence identifier for the passenger and guide strands are described as well as the 5' and 3' Flanking Regions and the Loop region (also referred to as the linker region). In Tables 15 and 16, the "miR" component of the name of the sequence does not necessarily correspond to the sequence numbering of miRNA genes (e.g., VOYSOD1miR-102 is the name of the sequence and does not necessarily mean that miR-102 is part of the sequence).

Table 15. SOD1 Modulatory Polynucleotide Sequence Regions (5' to 3')

Modulatory Polynucleotide Construct Name	5' Flanking to 3' Flanking SEQ ID NO	5' Flanking SEQ ID NO	Passenger SEQ ID NO	Loop SEQ ID NO	uide SEQ ID NO	3' Flanking SEQ ID NO
VOYSOD1miR-101	1696	1692	1746	1510	1747	1695
VOYSOD1miR-102	1697	1503	1746	1510	1747	1518
VOYSOD1miR-103	1698	1503	1748	1510	1747	1518
VOYSOD1miR-104	1699	1503	1749	1510	1747	1518
VOYSOD1miR-105	1700	1503	1750	1510	1747	1518
VOYSOD1miR-106	1701	1503	1751	1510	1747	1518
VOYSOD1miR-107	1702	1503	1752	1510	1747	1518
VOYSOD1miR-108	1703	1503	1754	1510	1747	1518
VOYSOD1miR-109	1704	1503	1746	1511	1747	1518
VOYSOD1miR-110	1705	1503	1746	1693	1747	1518
VOYSOD1miR-111	1706	1503	1753	1694	1747	1518
VOYSOD1miR-112	1707	1503	1746	1510	1747	1519
VOYSOD1miR-113	1708	1503	1748	1510	1747	1519
VOYSOD1miR-114	1709	1503	1751	1510	1747	1519
VOYSOD1miR-115	1710	1503	1753	1694	1747	1519
VOYSOD1miR-116	1711	1503	1749	1510	1747	1519

VOYSOD1miR-117	1712	1503	1755	1510	756	1518
VOYSOD1miR-118	1713	1503	1757	1510	758	1518
VOYSOD1miR-119	1714	1503	1759	1510	760	1518
VOYSOD1miR-127	1715	1504	1746	1512	747	1520
VOYSOD1miR-102.860	1716	1503	1761	1510	762	1518
VOYSOD1miR-102.861	1717	1503	1763	1510	764	1518
VOYSOD1miR-102.866	1718	1503	1765	1510	760	1518
VOYSOD1miR-102.870	1719	1503	1766	1510	767	1518
VOYSOD1miR-102.823	1720	1503	1768	1510	758	1518
VOYSOD1miR-104.860	1721	1503	1769	1510	762	1518
VOYSOD1miR-104.861	1722	1503	1770	1510	764	1518
VOYSOD1miR-104.866	1723	1503	1771	1510	760	1518
VOYSOD1miR-104.870	1724	1503	1772	1510	767	1518
VOYSOD1miR-104.823	1725	1503	1773	1510	758	1518
VOYSOD1miR-109.860	1726	1503	1761	1511	762	1518
VOYSOD1miR-104.861	1727	1503	1763	1511	764	1518
VOYSOD1miR-104.866	1728	1503	1765	1511	760	1518
VOYSOD1miR-109.870	1729	1503	1766	1511	767	1518
VOYSOD1miR-109.823	1730	1503	1768	1511	758	1518

VOYSOD1miR-114.860	1731	1503	1774	1510	762	1519
VOYSOD1miR-114.861	1732	1503	1775	1510	764	1519
VOYSOD1miR-114.866	1733	1503	1776	1510	760	1519
VOYSOD1miR-114.870	1734	1503	1777	1510	767	1519
VOYSOD1miR-114.823	1735	1503	1778	1510	758	1519
VOYSOD1miR-116.860	1736	1503	1769	1510	762	1519
VOYSOD1miR-116.861	1737	1503	1770	1510	764	1519
VOYSOD1miR-116.866	1738	1503	1779	1510	760	1519
VOYSOD1miR-116.870	1739	1503	1772	1510	767	1519
VOYSOD1miR-116.823	1740	1503	1773	1510	758	1519
VOYSOD1miR-127.860	1741	1504	1780	1512	762	1520
VOYSOD1miR-127.861	1742	1504	1763	1512	764	1520
VOYSOD1miR-127.866	1743	1504	1765	1512	760	1520
VOYSOD1miR-127.870	1744	1504	1766	1512	767	1520
VOYSOD1miR-127.823	1745	1504	1781	1512	758	1520

Table 16. SOD1 Modulatory Polynucleotide Sequence Region (5’ to 3’)

Name	5’ Flanking to 3’ Flanking SEQ ID NO	5’ Flanking SEQ ID NO	Passenger SEQ ID NO	Loop SEQ ID NO	Guide SEQ ID NO	3’ Flanking SEQ ID NO

VOYSOD1	1	1	17	15	1	1783
miR-120	784	782	85	11	786	

AAV Particles Comprising Modulatory Polynucleotides

[00642] In one embodiment, the AAV particle comprises a viral genome with a payload region comprising a modulatory polynucleotide sequences. In such an embodiment, a viral genome encoding more than one polypeptide may be replicated and packaged into a viral particle. A target cell transduced with a viral particle comprising a modulatory polynucleotide may express the encoded sense and/or antisense sequences in a single cell.

[00643] In some embodiments, the AAV particles are useful in the field of medicine for the treatment, prophylaxis, palliation or amelioration of neurological diseases and/or disorders.

[00644] In one embodiment, the AAV particles comprising modulatory polynucleotide sequence which comprises a nucleic acid sequence encoding at least one siRNA molecule may be introduced into mammalian cells.

[00645] Where the AAV particle payload region comprises a modulatory polynucleotide, the modulatory polynucleotide may comprise sense and/or antisense sequences to knock down a target gene. The AAV viral genomes encoding modulatory polynucleotides described herein may be useful in the fields of human disease, viruses, infections veterinary applications and a variety of in vivo and in vitro settings.

[00646] In one embodiment, the AAV particle viral genome may comprise at least one inverted terminal repeat (ITR) region. The ITR region(s) may, independently, have a length such as, but not limited to, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, and 175 nucleotides. The length of the ITR region for the viral genome may be 75-80, 75-85, 75-100, 80-85, 80-90, 80-105, 85-90, 85-95, 85-110, 90-95, 90-100, 90-115, 95-100, 95-105, 95-120, 100-105, 100-110, 100-125, 105-110, 105-115, 105-130, 110-115, 110-120, 110-135, 115-120, 115-125, 115-140, 120-125, 120-130, 120-145, 125-130, 125-135, 125-150, 130-135, 130-140, 130-155, 135-140, 135-145, 135-160, 140-145, 140-150, 140-165, 145-150, 145-155, 145-170, 150-155, 150-160, 150-175, 155-160, 155-165, 160-165, 160-170, 165-170, 165-175, and 170-175 nucleotides. As a non-limiting example, the viral genome comprises an ITR that is

about 105 nucleotides in length. As a non-limiting example, the viral genome comprises an ITR that is about 141 nucleotides in length. As a non-limiting example, the viral genome comprises an ITR that is about 130 nucleotides in length.

[00647] In one embodiment, the AAV particle viral genome may comprises two inverted terminal repeat (ITR) regions. Each of the ITR regions may independently have a length such as, but not limited to, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, and 175 nucleotides. The length of the ITR regions for the viral genome may be 75-80, 75-85, 75-100, 80-85, 80-90, 80-105, 85-90, 85-95, 85-110, 90-95, 90-100, 90-115, 95-100, 95-105, 95-120, 100-105, 100-110, 100-125, 105-110, 105-115, 105-130, 110-115, 110-120, 110-135, 115-120, 115-125, 115-140, 120-125, 120-130, 120-145, 125-130, 125-135, 125-150, 130-135, 130-140, 130-155, 135-140, 135-145, 135-160, 140-145, 140-150, 140-165, 145-150, 145-155, 145-170, 150-155, 150-160, 150-175, 155-160, 155-165, 160-165, 160-170, 165-170, 165-175, and 170-175 nucleotides. As a non-limiting example, the viral genome comprises an ITR that is about 105 nucleotides in length and 141 nucleotides in length. As a non-limiting example, the viral genome comprises an ITR that is about 105 nucleotides in length and 130 nucleotides in length. As a non-limiting example, the viral genome comprises an ITR that is about 130 nucleotides in length and 141 nucleotides in length.

[00648] In one embodiment, the AAV particle viral genome may comprise at least one sequence region as described in Tables 17-24. The regions may be located before or after any of the other sequence regions described herein.

[00649] In one embodiment, the AAV particle viral genome comprises at least one inverted terminal repeat (ITR) sequence region. Non-limiting examples of ITR sequence regions are described in Table 17.

Table 17. Inverted Terminal Repeat (ITR) Sequence Regions

Sequence Region Name	SEQ ID NO
ITR1	1787
ITR2	1788
ITR3	1789
ITR4	1790

[00650] In one embodiment, the AAV particle viral genome comprises two ITR sequence regions. In one embodiment, the ITR sequence regions are the ITR1 sequence region and the

ITR3 sequence region. In one embodiment, the ITR sequence regions are the ITR1 sequence region and the ITR4 sequence region. In one embodiment, the ITR sequence regions are the ITR2 sequence region and the ITR3 sequence region. In one embodiment, the ITR sequence regions are the ITR2 sequence region and the ITR4 sequence region.

[00651] In one embodiment, the AAV particle viral genome may comprise at least one multiple cloning site (MCS) sequence region. The MCS region(s) may, independently, have a length such as, but not limited to, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, and 150 nucleotides. The length of the MCS region for the viral genome may be 2-10, 5-10, 5-15, 10-20, 10-30, 10-40, 15-20, 15-25, 20-30, 20-40, 20-50, 25-30, 25-35, 30-40, 30-50, 30-60, 35-40, 35-45, 40-50, 40-60, 40-70, 45-50, 45-55, 50-60, 50-70, 50-80, 55-60, 55-65, 60-70, 60-80, 60-90, 65-70, 65-75, 70-80, 70-90, 70-100, 75-80, 75-85, 80-90, 80-100, 80-110, 85-90, 85-95, 90-100, 90-110, 90-120, 95-100, 95-105, 100-110, 100-120, 100-130, 105-110, 105-115, 110-120, 110-130, 110-140, 115-120, 115-125, 120-130, 120-140, 120-150, 125-130, 125-135, 130-140, 130-150, 135-140, 135-145, 140-150, and 145-150 nucleotides. As a non-limiting example, the viral genome comprises a MCS region that is about 5 nucleotides in length. As a non-limiting example, the viral genome comprises a MCS region that is about 10 nucleotides in length. As a non-limiting example, the viral genome comprises a MCS region that is about 14 nucleotides in length. As a non-limiting example, the viral genome comprises a MCS region that is about 18 nucleotides in length. As a non-limiting example, the viral genome comprises a MCS region that is about 73 nucleotides in length. As a non-limiting example, the viral genome comprises a MCS region that is about 121 nucleotides in length.

[00652] In one embodiment, the AAV particle viral genome comprises at least one multiple cloning site (MCS) sequence regions. Non-limiting examples of MCS sequence regions are described in Table 18.

Table 18. Multiple Cloning Site (MCS) Sequence Regions

Sequence Region Name	SEQ ID NO or Sequence
MCS1	1791
MCS2	1792

MCS3	1793
MCS4	1794
MCS5	TCGAG
MCS6	1795

[00653] In one embodiment, the AAV particle viral genome comprises one MCS sequence region. In one embodiment, the MCS sequence region is the MCS1 sequence region. In one embodiment, the MCS sequence region is the MCS2 sequence region. In one embodiment, the MCS sequence region is the MCS3 sequence region. In one embodiment, the MCS sequence region is the MCS4 sequence region. In one embodiment, the MCS sequence region is the MCS5 sequence region. In one embodiment, the MCS sequence region is the MCS6 sequence region.

[00654] In one embodiment, the AAV particle viral genome comprises two MCS sequence regions. In one embodiment, the two MCS sequence regions are the MCS1 sequence region and the MCS2 sequence region. In one embodiment, the two MCS sequence regions are the MCS1 sequence region and the MCS3 sequence region. In one embodiment, the two MCS sequence regions are the MCS1 sequence region and the MCS4 sequence region. In one embodiment, the two MCS sequence regions are the MCS1 sequence region and the MCS5 sequence region. In one embodiment, the two MCS sequence regions are the MCS1 sequence region and the MCS6 sequence region. In one embodiment, the two MCS sequence regions are the MCS2 sequence region and the MCS3 sequence region. In one embodiment, the two MCS sequence regions are the MCS2 sequence region and the MCS4 sequence region. In one embodiment, the two MCS sequence regions are the MCS2 sequence region and the MCS5 sequence region. In one embodiment, the two MCS sequence regions are the MCS2 sequence region and the MCS6 sequence region. In one embodiment, the two MCS sequence regions are the MCS3 sequence region and the MCS4 sequence region. In one embodiment, the two MCS sequence regions are the MCS3 sequence region and the MCS5 sequence region. In one embodiment, the two MCS sequence regions are the MCS3 sequence region and the MCS6 sequence region. In one embodiment, the two MCS sequence regions are the MCS4 sequence region and the MCS5 sequence region. In one embodiment, the two MCS sequence regions are the MCS4 sequence region and the MCS6 sequence region. In one embodiment, the two MCS sequence regions are the MCS5 sequence region and the MCS6 sequence region.

[00655] In one embodiment, the AAV particle viral genome comprises two or more MCS sequence regions.

[00656] In one embodiment, the AAV particle viral genome comprises three MCS sequence regions. In one embodiment, the three MCS sequence regions are the MCS1 sequence region, the MCS2 sequence region, and the MCS3 sequence region. In one embodiment, the three MCS

sequence regions are the MCS1 sequence region, the MCS2 sequence region, and the MCS4 sequence region. In one embodiment, the three MCS sequence regions are the MCS1 sequence region, the MCS2 sequence region, and the MCS5 sequence region. In one embodiment, the three MCS sequence regions are the MCS1 sequence region, the MCS2 sequence region, and the MCS6 sequence region. In one embodiment, the three MCS sequence regions are the MCS1 sequence region, the MCS3 sequence region, and the MCS4 sequence region. In one embodiment, the three MCS sequence regions are the MCS1 sequence region, the MCS3 sequence region, and the MCS5 sequence region. In one embodiment, the three MCS sequence regions are the MCS1 sequence region, the MCS3 sequence region, and the MCS6 sequence region. In one embodiment, the three MCS sequence regions are the MCS1 sequence region, the MCS4 sequence region, and the MCS5 sequence region. In one embodiment, the three MCS sequence regions are the MCS1 sequence region, the MCS4 sequence region, and the MCS6 sequence region. In one embodiment, the three MCS sequence regions are the MCS1 sequence region, the MCS5 sequence region, and the MCS6 sequence region. In one embodiment, the three MCS sequence regions are the MCS2 sequence region, the MCS3 sequence region, and the MCS4 sequence region. In one embodiment, the three MCS sequence regions are the MCS2 sequence region, the MCS3 sequence region, and the MCS5 sequence region. In one embodiment, the three MCS sequence regions are the MCS2 sequence region, the MCS3 sequence region, and the MCS6 sequence region. In one embodiment, the three MCS sequence regions are the MCS2 sequence region, the MCS4 sequence region, and the MCS5 sequence region. In one embodiment, the three MCS sequence regions are the MCS2 sequence region, the MCS4 sequence region, and the MCS6 sequence region. In one embodiment, the three MCS sequence regions are the MCS2 sequence region, the MCS5 sequence region, and the MCS6 sequence region. In one embodiment, the three MCS sequence regions are the MCS3 sequence region, the MCS4 sequence region, and the MCS5 sequence region. In one embodiment, the three MCS sequence regions are the MCS3 sequence region, the MCS4 sequence region, and the MCS6 sequence region. In one embodiment, the three MCS sequence regions are the MCS3 sequence region, the MCS5 sequence region, and the MCS6 sequence region. In one embodiment, the three MCS sequence regions are the MCS4 sequence region, the MCS5 sequence region, and the MCS6 sequence region.

[00657] In one embodiment, the AAV particle viral genome may comprise at least one multiple filler sequence region. The filler region(s) may, independently, have a length such as, but not limited to, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72,

73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, 500, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, 511, 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 526, 527, 528, 529, 530, 531, 532, 533, 534, 535, 536, 537, 538, 539, 540, 541, 542, 543, 544, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 572, 573, 574, 575, 576, 577, 578, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 593, 594, 595, 596, 597, 598, 599, 600, 601, 602, 603, 604, 605, 606, 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 619, 620, 621, 622, 623, 624, 625, 626, 627, 628, 629, 630, 631, 632, 633, 634, 635, 636, 637, 638, 639, 640, 641, 642, 643, 644, 645, 646, 647, 648, 649, 650, 651, 652, 653, 654, 655, 656, 657, 658, 659, 660, 661, 662, 663, 664, 665, 666, 667, 668, 669, 670, 671, 672, 673, 674, 675, 676, 677, 678, 679, 680, 681, 682, 683, 684, 685, 686, 687, 688, 689, 690, 691, 692, 693, 694, 695, 696, 697, 698, 699, 700, 701, 702, 703, 704, 705, 706,

707, 708, 709, 710, 711, 712, 713, 714, 715, 716, 717, 718, 719, 720, 721, 722, 723, 724, 725, 726, 727, 728, 729, 730, 731, 732, 733, 734, 735, 736, 737, 738, 739, 740, 741, 742, 743, 744, 745, 746, 747, 748, 749, 750, 751, 752, 753, 754, 755, 756, 757, 758, 759, 760, 761, 762, 763, 764, 765, 766, 767, 768, 769, 770, 771, 772, 773, 774, 775, 776, 777, 778, 779, 780, 781, 782, 783, 784, 785, 786, 787, 788, 789, 790, 791, 792, 793, 794, 795, 796, 797, 798, 799, 800, 801, 802, 803, 804, 805, 806, 807, 808, 809, 810, 811, 812, 813, 814, 815, 816, 817, 818, 819, 820, 821, 822, 823, 824, 825, 826, 827, 828, 829, 830, 831, 832, 833, 834, 835, 836, 837, 838, 839, 840, 841, 842, 843, 844, 845, 846, 847, 848, 849, 850, 851, 852, 853, 854, 855, 856, 857, 858, 859, 860, 861, 862, 863, 864, 865, 866, 867, 868, 869, 870, 871, 872, 873, 874, 875, 876, 877, 878, 879, 880, 881, 882, 883, 884, 885, 886, 887, 888, 889, 890, 891, 892, 893, 894, 895, 896, 897, 898, 899, 900, 901, 902, 903, 904, 905, 906, 907, 908, 909, 910, 911, 912, 913, 914, 915, 916, 917, 918, 919, 920, 921, 922, 923, 924, 925, 926, 927, 928, 929, 930, 931, 932, 933, 934, 935, 936, 937, 938, 939, 940, 941, 942, 943, 944, 945, 946, 947, 948, 949, 950, 951, 952, 953, 954, 955, 956, 957, 958, 959, 960, 961, 962, 963, 964, 965, 966, 967, 968, 969, 970, 971, 972, 973, 974, 975, 976, 977, 978, 979, 980, 981, 982, 983, 984, 985, 986, 987, 988, 989, 990, 991, 992, 993, 994, 995, 996, 997, 998, 999, 1000, 1001, 1002, 1003, 1004, 1005, 1006, 1007, 1008, 1009, 1010, 1011, 1012, 1013, 1014, 1015, 1016, 1017, 1018, 1019, 1020, 1021, 1022, 1023, 1024, 1025, 1026, 1027, 1028, 1029, 1030, 1031, 1032, 1033, 1034, 1035, 1036, 1037, 1038, 1039, 1040, 1041, 1042, 1043, 1044, 1045, 1046, 1047, 1048, 1049, 1050, 1051, 1052, 1053, 1054, 1055, 1056, 1057, 1058, 1059, 1060, 1061, 1062, 1063, 1064, 1065, 1066, 1067, 1068, 1069, 1070, 1071, 1072, 1073, 1074, 1075, 1076, 1077, 1078, 1079, 1080, 1081, 1082, 1083, 1084, 1085, 1086, 1087, 1088, 1089, 1090, 1091, 1092, 1093, 1094, 1095, 1096, 1097, 1098, 1099, 1100, 1101, 1102, 1103, 1104, 1105, 1106, 1107, 1108, 1109, 1110, 1111, 1112, 1113, 1114, 1115, 1116, 1117, 1118, 1119, 1120, 1121, 1122, 1123, 1124, 1125, 1126, 1127, 1128, 1129, 1130, 1131, 1132, 1133, 1134, 1135, 1136, 1137, 1138, 1139, 1140, 1141, 1142, 1143, 1144, 1145, 1146, 1147, 1148, 1149, 1150, 1151, 1152, 1153, 1154, 1155, 1156, 1157, 1158, 1159, 1160, 1161, 1162, 1163, 1164, 1165, 1166, 1167, 1168, 1169, 1170, 1171, 1172, 1173, 1174, 1175, 1176, 1177, 1178, 1179, 1180, 1181, 1182, 1183, 1184, 1185, 1186, 1187, 1188, 1189, 1190, 1191, 1192, 1193, 1194, 1195, 1196, 1197, 1198, 1199, 1200, 1201, 1202, 1203, 1204, 1205, 1206, 1207, 1208, 1209, 1210, 1211, 1212, 1213, 1214, 1215, 1216, 1217, 1218, 1219, 1220, 1221, 1222, 1223, 1224, 1225, 1226, 1227, 1228, 1229, 1230, 1231, 1232, 1233, 1234, 1235, 1236, 1237, 1238, 1239, 1240, 1241, 1242, 1243, 1244, 1245, 1246, 1247, 1248, 1249, 1250, 1251, 1252, 1253, 1254, 1255, 1256, 1257, 1258, 1259, 1260, 1261, 1262, 1263,

1264, 1265, 1266, 1267, 1268, 1269, 1270, 1271, 1272, 1273, 1274, 1275, 1276, 1277, 1278, 1279, 1280, 1281, 1282, 1283, 1284, 1285, 1286, 1287, 1288, 1289, 1290, 1291, 1292, 1293, 1294, 1295, 1296, 1297, 1298, 1299, 1300, 1301, 1302, 1303, 1304, 1305, 1306, 1307, 1308, 1309, 1310, 1311, 1312, 1313, 1314, 1315, 1316, 1317, 1318, 1319, 1320, 1321, 1322, 1323, 1324, 1325, 1326, 1327, 1328, 1329, 1330, 1331, 1332, 1333, 1334, 1335, 1336, 1337, 1338, 1339, 1340, 1341, 1342, 1343, 1344, 1345, 1346, 1347, 1348, 1349, 1350, 1351, 1352, 1353, 1354, 1355, 1356, 1357, 1358, 1359, 1360, 1361, 1362, 1363, 1364, 1365, 1366, 1367, 1368, 1369, 1370, 1371, 1372, 1373, 1374, 1375, 1376, 1377, 1378, 1379, 1380, 1381, 1382, 1383, 1384, 1385, 1386, 1387, 1388, 1389, 1390, 1391, 1392, 1393, 1394, 1395, 1396, 1397, 1398, 1399, 1400, 1401, 1402, 1403, 1404, 1405, 1406, 1407, 1408, 1409, 1410, 1411, 1412, 1413, 1414, 1415, 1416, 1417, 1418, 1419, 1420, 1421, 1422, 1423, 1424, 1425, 1426, 1427, 1428, 1429, 1430, 1431, 1432, 1433, 1434, 1435, 1436, 1437, 1438, 1439, 1440, 1441, 1442, 1443, 1444, 1445, 1446, 1447, 1448, 1449, 1450, 1451, 1452, 1453, 1454, 1455, 1456, 1457, 1458, 1459, 1460, 1461, 1462, 1463, 1464, 1465, 1466, 1467, 1468, 1469, 1470, 1471, 1472, 1473, 1474, 1475, 1476, 1477, 1478, 1479, 1480, 1481, 1482, 1483, 1484, 1485, 1486, 1487, 1488, 1489, 1490, 1491, 1492, 1493, 1494, 1495, 1496, 1497, 1498, 1499, 1500, 1501, 1502, 1503, 1504, 1505, 1506, 1507, 1508, 1509, 1510, 1511, 1512, 1513, 1514, 1515, 1516, 1517, 1518, 1519, 1520, 1521, 1522, 1523, 1524, 1525, 1526, 1527, 1528, 1529, 1530, 1531, 1532, 1533, 1534, 1535, 1536, 1537, 1538, 1539, 1540, 1541, 1542, 1543, 1544, 1545, 1546, 1547, 1548, 1549, 1550, 1551, 1552, 1553, 1554, 1555, 1556, 1557, 1558, 1559, 1560, 1561, 1562, 1563, 1564, 1565, 1566, 1567, 1568, 1569, 1570, 1571, 1572, 1573, 1574, 1575, 1576, 1577, 1578, 1579, 1580, 1581, 1582, 1583, 1584, 1585, 1586, 1587, 1588, 1589, 1590, 1591, 1592, 1593, 1594, 1595, 1596, 1597, 1598, 1599, 1600, 1601, 1602, 1603, 1604, 1605, 1606, 1607, 1608, 1609, 1610, 1611, 1612, 1613, 1614, 1615, 1616, 1617, 1618, 1619, 1620, 1621, 1622, 1623, 1624, 1625, 1626, 1627, 1628, 1629, 1630, 1631, 1632, 1633, 1634, 1635, 1636, 1637, 1638, 1639, 1640, 1641, 1642, 1643, 1644, 1645, 1646, 1647, 1648, 1649, 1650, 1651, 1652, 1653, 1654, 1655, 1656, 1657, 1658, 1659, 1660, 1661, 1662, 1663, 1664, 1665, 1666, 1667, 1668, 1669, 1670, 1671, 1672, 1673, 1674, 1675, 1676, 1677, 1678, 1679, 1680, 1681, 1682, 1683, 1684, 1685, 1686, 1687, 1688, 1689, 1690, 1691, 1692, 1693, 1694, 1695, 1696, 1697, 1698, 1699, 1700, 1701, 1702, 1703, 1704, 1705, 1706, 1707, 1708, 1709, 1710, 1711, 1712, 1713, 1714, 1715, 1716, 1717, 1718, 1719, 1720, 1721, 1722, 1723, 1724, 1725, 1726, 1727, 1728, 1729, 1730, 1731, 1732, 1733, 1734, 1735, 1736, 1737, 1738, 1739, 1740, 1741, 1742, 1743, 1744, 1745, 1746, 1747, 1748, 1749, 1750, 1751, 1752, 1753, 1754, 1755, 1756, 1757, 1758,

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2254, 2255, 2256, 2257, 2258, 2259, 2260, 2261, 2262, 2263, 2264, 2265, 2266, 2267, 2268, 2269, 2270, 2271, 2272, 2273, 2274, 2275, 2276, 2277, 2278, 2279, 2280, 2281, 2282, 2283, 2284, 2285, 2286, 2287, 2288, 2289, 2290, 2291, 2292, 2293, 2294, 2295, 2296, 2297, 2298, 2299, 2300, 2301, 2302, 2303, 2304, 2305, 2306, 2307, 2308, 2309, 2310, 2311, 2312, 2313, 2314, 2315, 2316, 2317, 2318, 2319, 2320, 2321, 2322, 2323, 2324, 2325, 2326, 2327, 2328, 2329, 2330, 2331, 2332, 2333, 2334, 2335, 2336, 2337, 2338, 2339, 2340, 2341, 2342, 2343, 2344, 2345, 2346, 2347, 2348, 2349, 2350, 2351, 2352, 2353, 2354, 2355, 2356, 2357, 2358, 2359, 2360, 2361, 2362, 2363, 2364, 2365, 2366, 2367, 2368, 2369, 2370, 2371, 2372, 2373, 2374, 2375, 2376, 2377, 2378, 2379, 2380, 2381, 2382, 2383, 2384, 2385, 2386, 2387, 2388, 2389, 2390, 2391, 2392, 2393, 2394, 2395, 2396, 2397, 2398, 2399, 2400, 2401, 2402, 2403, 2404, 2405, 2406, 2407, 2408, 2409, 2410, 2411, 2412, 2413, 2414, 2415, 2416, 2417, 2418, 2419, 2420, 2421, 2422, 2423, 2424, 2425, 2426, 2427, 2428, 2429, 2430, 2431, 2432, 2433, 2434, 2435, 2436, 2437, 2438, 2439, 2440, 2441, 2442, 2443, 2444, 2445, 2446, 2447, 2448, 2449, 2450, 2451, 2452, 2453, 2454, 2455, 2456, 2457, 2458, 2459, 2460, 2461, 2462, 2463, 2464, 2465, 2466, 2467, 2468, 2469, 2470, 2471, 2472, 2473, 2474, 2475, 2476, 2477, 2478, 2479, 2480, 2481, 2482, 2483, 2484, 2485, 2486, 2487, 2488, 2489, 2490, 2491, 2492, 2493, 2494, 2495, 2496, 2497, 2498, 2499, 2500, 2501, 2502, 2503, 2504, 2505, 2506, 2507, 2508, 2509, 2510, 2511, 2512, 2513, 2514, 2515, 2516, 2517, 2518, 2519, 2520, 2521, 2522, 2523, 2524, 2525, 2526, 2527, 2528, 2529, 2530, 2531, 2532, 2533, 2534, 2535, 2536, 2537, 2538, 2539, 2540, 2541, 2542, 2543, 2544, 2545, 2546, 2547, 2548, 2549, 2550, 2551, 2552, 2553, 2554, 2555, 2556, 2557, 2558, 2559, 2560, 2561, 2562, 2563, 2564, 2565, 2566, 2567, 2568, 2569, 2570, 2571, 2572, 2573, 2574, 2575, 2576, 2577, 2578, 2579, 2580, 2581, 2582, 2583, 2584, 2585, 2586, 2587, 2588, 2589, 2590, 2591, 2592, 2593, 2594, 2595, 2596, 2597, 2598, 2599, 2600, 2601, 2602, 2603, 2604, 2605, 2606, 2607, 2608, 2609, 2610, 2611, 2612, 2613, 2614, 2615, 2616, 2617, 2618, 2619, 2620, 2621, 2622, 2623, 2624, 2625, 2626, 2627, 2628, 2629, 2630, 2631, 2632, 2633, 2634, 2635, 2636, 2637, 2638, 2639, 2640, 2641, 2642, 2643, 2644, 2645, 2646, 2647, 2648, 2649, 2650, 2651, 2652, 2653, 2654, 2655, 2656, 2657, 2658, 2659, 2660, 2661, 2662, 2663, 2664, 2665, 2666, 2667, 2668, 2669, 2670, 2671, 2672, 2673, 2674, 2675, 2676, 2677, 2678, 2679, 2680, 2681, 2682, 2683, 2684, 2685, 2686, 2687, 2688, 2689, 2690, 2691, 2692, 2693, 2694, 2695, 2696, 2697, 2698, 2699, 2700, 2701, 2702, 2703, 2704, 2705, 2706, 2707, 2708, 2709, 2710, 2711, 2712, 2713, 2714, 2715, 2716, 2717, 2718, 2719, 2720, 2721, 2722, 2723, 2724, 2725, 2726, 2727, 2728, 2729, 2730, 2731, 2732, 2733, 2734, 2735, 2736, 2737, 2738, 2739, 2740, 2741, 2742, 2743, 2744, 2745, 2746, 2747, 2748,

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3244, 3245, 3246, 3247, 3248, 3249, and 3250 nucleotides. The length of any filler region for the viral genome may be 50-100, 100-150, 150-200, 200-250, 250-300, 300-350, 350-400, 400-450, 450-500, 500-550, 550-600, 600-650, 650-700, 700-750, 750-800, 800-850, 850-900, 900-950, 950-1000, 1000-1050, 1050-1100, 1100-1150, 1150-1200, 1200-1250, 1250-1300, 1300-1350, 1350-1400, 1400-1450, 1450-1500, 1500-1550, 1550-1600, 1600-1650, 1650-1700, 1700-1750, 1750-1800, 1800-1850, 1850-1900, 1900-1950, 1950-2000, 2000-2050, 2050-2100, 2100-2150, 2150-2200, 2200-2250, 2250-2300, 2300-2350, 2350-2400, 2400-2450, 2450-2500, 2500-2550, 2550-2600, 2600-2650, 2650-2700, 2700-2750, 2750-2800, 2800-2850, 2850-2900, 2900-2950, 2950-3000, 3000-3050, 3050-3100, 3100-3150, 3150-3200, and 3200-3250 nucleotides. As a non-limiting example, the viral genome comprises a filler region that is about 55 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 56 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 97 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 103 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 105 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 357 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 363 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 712 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 714 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 1203 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 1209 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 1512 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 1519 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 2395 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 2403 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 2405 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 3013 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 3021 nucleotides in length.

[00658] In one embodiment, the AAV particle viral genome may comprise at least one multiple filler sequence region. The filler region(s) may, independently, have a length such as, but not limited to, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72,

73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, 500, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, 511, 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 526, 527, 528, 529, 530, 531, 532, 533, 534, 535, 536, 537, 538, 539, 540, 541, 542, 543, 544, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 572, 573, 574, 575, 576, 577, 578, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 593, 594, 595, 596, 597, 598, 599, 600, 601, 602, 603, 604, 605, 606, 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 619, 620, 621, 622, 623, 624, 625, 626, 627, 628, 629, 630, 631, 632, 633, 634, 635, 636, 637, 638, 639, 640, 641, 642, 643, 644, 645, 646, 647, 648, 649, 650, 651, 652, 653, 654, 655, 656, 657, 658, 659, 660, 661, 662, 663, 664, 665, 666, 667, 668, 669, 670, 671, 672, 673, 674, 675, 676, 677, 678, 679, 680, 681, 682, 683, 684, 685, 686, 687, 688, 689, 690, 691, 692, 693, 694, 695, 696, 697, 698, 699, 700, 701, 702, 703, 704, 705, 706,

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1759, 1760, 1761, 1762, 1763, 1764, 1765, 1766, 1767, 1768, 1769, 1770, 1771, 1772, 1773, 1774, 1775, 1776, 1777, 1778, 1779, 1780, 1781, 1782, 1783, 1784, 1785, 1786, 1787, 1788, 1789, 1790, 1791, 1792, 1793, 1794, 1795, 1796, 1797, 1798, 1799, 1800, 1801, 1802, 1803, 1804, 1805, 1806, 1807, 1808, 1809, 1810, 1811, 1812, 1813, 1814, 1815, 1816, 1817, 1818, 1819, 1820, 1821, 1822, 1823, 1824, 1825, 1826, 1827, 1828, 1829, 1830, 1831, 1832, 1833, 1834, 1835, 1836, 1837, 1838, 1839, 1840, 1841, 1842, 1843, 1844, 1845, 1846, 1847, 1848, 1849, 1850, 1851, 1852, 1853, 1854, 1855, 1856, 1857, 1858, 1859, 1860, 1861, 1862, 1863, 1864, 1865, 1866, 1867, 1868, 1869, 1870, 1871, 1872, 1873, 1874, 1875, 1876, 1877, 1878, 1879, 1880, 1881, 1882, 1883, 1884, 1885, 1886, 1887, 1888, 1889, 1890, 1891, 1892, 1893, 1894, 1895, 1896, 1897, 1898, 1899, 1900, 1901, 1902, 1903, 1904, 1905, 1906, 1907, 1908, 1909, 1910, 1911, 1912, 1913, 1914, 1915, 1916, 1917, 1918, 1919, 1920, 1921, 1922, 1923, 1924, 1925, 1926, 1927, 1928, 1929, 1930, 1931, 1932, 1933, 1934, 1935, 1936, 1937, 1938, 1939, 1940, 1941, 1942, 1943, 1944, 1945, 1946, 1947, 1948, 1949, 1950, 1951, 1952, 1953, 1954, 1955, 1956, 1957, 1958, 1959, 1960, 1961, 1962, 1963, 1964, 1965, 1966, 1967, 1968, 1969, 1970, 1971, 1972, 1973, 1974, 1975, 1976, 1977, 1978, 1979, 1980, 1981, 1982, 1983, 1984, 1985, 1986, 1987, 1988, 1989, 1990, 1991, 1992, 1993, 1994, 1995, 1996, 1997, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016, 2017, 2018, 2019, 2020, 2021, 2022, 2023, 2024, 2025, 2026, 2027, 2028, 2029, 2030, 2031, 2032, 2033, 2034, 2035, 2036, 2037, 2038, 2039, 2040, 2041, 2042, 2043, 2044, 2045, 2046, 2047, 2048, 2049, 2050, 2051, 2052, 2053, 2054, 2055, 2056, 2057, 2058, 2059, 2060, 2061, 2062, 2063, 2064, 2065, 2066, 2067, 2068, 2069, 2070, 2071, 2072, 2073, 2074, 2075, 2076, 2077, 2078, 2079, 2080, 2081, 2082, 2083, 2084, 2085, 2086, 2087, 2088, 2089, 2090, 2091, 2092, 2093, 2094, 2095, 2096, 2097, 2098, 2099, 2100, 2101, 2102, 2103, 2104, 2105, 2106, 2107, 2108, 2109, 2110, 2111, 2112, 2113, 2114, 2115, 2116, 2117, 2118, 2119, 2120, 2121, 2122, 2123, 2124, 2125, 2126, 2127, 2128, 2129, 2130, 2131, 2132, 2133, 2134, 2135, 2136, 2137, 2138, 2139, 2140, 2141, 2142, 2143, 2144, 2145, 2146, 2147, 2148, 2149, 2150, 2151, 2152, 2153, 2154, 2155, 2156, 2157, 2158, 2159, 2160, 2161, 2162, 2163, 2164, 2165, 2166, 2167, 2168, 2169, 2170, 2171, 2172, 2173, 2174, 2175, 2176, 2177, 2178, 2179, 2180, 2181, 2182, 2183, 2184, 2185, 2186, 2187, 2188, 2189, 2190, 2191, 2192, 2193, 2194, 2195, 2196, 2197, 2198, 2199, 2200, 2201, 2202, 2203, 2204, 2205, 2206, 2207, 2208, 2209, 2210, 2211, 2212, 2213, 2214, 2215, 2216, 2217, 2218, 2219, 2220, 2221, 2222, 2223, 2224, 2225, 2226, 2227, 2228, 2229, 2230, 2231, 2232, 2233, 2234, 2235, 2236, 2237, 2238, 2239, 2240, 2241, 2242, 2243, 2244, 2245, 2246, 2247, 2248, 2249, 2250, 2251, 2252, 2253,

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2749, 2750, 2751, 2752, 2753, 2754, 2755, 2756, 2757, 2758, 2759, 2760, 2761, 2762, 2763, 2764, 2765, 2766, 2767, 2768, 2769, 2770, 2771, 2772, 2773, 2774, 2775, 2776, 2777, 2778, 2779, 2780, 2781, 2782, 2783, 2784, 2785, 2786, 2787, 2788, 2789, 2790, 2791, 2792, 2793, 2794, 2795, 2796, 2797, 2798, 2799, 2800, 2801, 2802, 2803, 2804, 2805, 2806, 2807, 2808, 2809, 2810, 2811, 2812, 2813, 2814, 2815, 2816, 2817, 2818, 2819, 2820, 2821, 2822, 2823, 2824, 2825, 2826, 2827, 2828, 2829, 2830, 2831, 2832, 2833, 2834, 2835, 2836, 2837, 2838, 2839, 2840, 2841, 2842, 2843, 2844, 2845, 2846, 2847, 2848, 2849, 2850, 2851, 2852, 2853, 2854, 2855, 2856, 2857, 2858, 2859, 2860, 2861, 2862, 2863, 2864, 2865, 2866, 2867, 2868, 2869, 2870, 2871, 2872, 2873, 2874, 2875, 2876, 2877, 2878, 2879, 2880, 2881, 2882, 2883, 2884, 2885, 2886, 2887, 2888, 2889, 2890, 2891, 2892, 2893, 2894, 2895, 2896, 2897, 2898, 2899, 2900, 2901, 2902, 2903, 2904, 2905, 2906, 2907, 2908, 2909, 2910, 2911, 2912, 2913, 2914, 2915, 2916, 2917, 2918, 2919, 2920, 2921, 2922, 2923, 2924, 2925, 2926, 2927, 2928, 2929, 2930, 2931, 2932, 2933, 2934, 2935, 2936, 2937, 2938, 2939, 2940, 2941, 2942, 2943, 2944, 2945, 2946, 2947, 2948, 2949, 2950, 2951, 2952, 2953, 2954, 2955, 2956, 2957, 2958, 2959, 2960, 2961, 2962, 2963, 2964, 2965, 2966, 2967, 2968, 2969, 2970, 2971, 2972, 2973, 2974, 2975, 2976, 2977, 2978, 2979, 2980, 2981, 2982, 2983, 2984, 2985, 2986, 2987, 2988, 2989, 2990, 2991, 2992, 2993, 2994, 2995, 2996, 2997, 2998, 2999, 3000, 3001, 3002, 3003, 3004, 3005, 3006, 3007, 3008, 3009, 3010, 3011, 3012, 3013, 3014, 3015, 3016, 3017, 3018, 3019, 3020, 3021, 3022, 3023, 3024, 3025, 3026, 3027, 3028, 3029, 3030, 3031, 3032, 3033, 3034, 3035, 3036, 3037, 3038, 3039, 3040, 3041, 3042, 3043, 3044, 3045, 3046, 3047, 3048, 3049, 3050, 3051, 3052, 3053, 3054, 3055, 3056, 3057, 3058, 3059, 3060, 3061, 3062, 3063, 3064, 3065, 3066, 3067, 3068, 3069, 3070, 3071, 3072, 3073, 3074, 3075, 3076, 3077, 3078, 3079, 3080, 3081, 3082, 3083, 3084, 3085, 3086, 3087, 3088, 3089, 3090, 3091, 3092, 3093, 3094, 3095, 3096, 3097, 3098, 3099, 3100, 3101, 3102, 3103, 3104, 3105, 3106, 3107, 3108, 3109, 3110, 3111, 3112, 3113, 3114, 3115, 3116, 3117, 3118, 3119, 3120, 3121, 3122, 3123, 3124, 3125, 3126, 3127, 3128, 3129, 3130, 3131, 3132, 3133, 3134, 3135, 3136, 3137, 3138, 3139, 3140, 3141, 3142, 3143, 3144, 3145, 3146, 3147, 3148, 3149, 3150, 3151, 3152, 3153, 3154, 3155, 3156, 3157, 3158, 3159, 3160, 3161, 3162, 3163, 3164, 3165, 3166, 3167, 3168, 3169, 3170, 3171, 3172, 3173, 3174, 3175, 3176, 3177, 3178, 3179, 3180, 3181, 3182, 3183, 3184, 3185, 3186, 3187, 3188, 3189, 3190, 3191, 3192, 3193, 3194, 3195, 3196, 3197, 3198, 3199, 3200, 3201, 3202, 3203, 3204, 3205, 3206, 3207, 3208, 3209, 3210, 3211, 3212, 3213, 3214, 3215, 3216, 3217, 3218, 3219, 3220, 3221, 3222, 3223, 3224, 3225, 3226, 3227, 3228, 3229, 3230, 3231, 3232, 3233, 3234, 3235, 3236, 3237, 3238, 3239, 3240, 3241, 3242, 3243,

3244, 3245, 3246, 3247, 3248, 3249, and 3250 nucleotides. The length of any filler region for the viral genome may be 50-100, 100-150, 150-200, 200-250, 250-300, 300-350, 350-400, 400-450, 450-500, 500-550, 550-600, 600-650, 650-700, 700-750, 750-800, 800-850, 850-900, 900-950, 950-1000, 1000-1050, 1050-1100, 1100-1150, 1150-1200, 1200-1250, 1250-1300, 1300-1350, 1350-1400, 1400-1450, 1450-1500, 1500-1550, 1550-1600, 1600-1650, 1650-1700, 1700-1750, 1750-1800, 1800-1850, 1850-1900, 1900-1950, 1950-2000, 2000-2050, 2050-2100, 2100-2150, 2150-2200, 2200-2250, 2250-2300, 2300-2350, 2350-2400, 2400-2450, 2450-2500, 2500-2550, 2550-2600, 2600-2650, 2650-2700, 2700-2750, 2750-2800, 2800-2850, 2850-2900, 2900-2950, 2950-3000, 3000-3050, 3050-3100, 3100-3150, 3150-3200, and 3200-3250 nucleotides. As a non-limiting example, the viral genome comprises a filler region that is about 55 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 56 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 97 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 103 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 105 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 357 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 363 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 712 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 714 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 1203 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 1209 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 1512 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 1519 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 2395 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 2403 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 2405 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 3013 nucleotides in length. As a non-limiting example, the viral genome comprises a filler region that is about 3021 nucleotides in length.

[00659] In one embodiment, the AAV particle viral genome comprises at least one filler sequence regions. Non-limiting examples of filler sequence regions are described in Table 19.

Table 19. Filler Sequence Regions

Sequence Region Name	SEQ ID NO
FILL1	1796
FILL2	1797
FILL3	1798
FILL4	1799
FILL5	1800
FILL6	1801
FILL7	1802
FILL8	1803
FILL9	1804
FILL10	1805
FILL11	1806
FILL12	1807
FILL13	1808
FILL14	1809
FILL15	1810
FILL16	1811
FILL17	1812
FILL18	1813

[00660] In one embodiment, the AAV particle viral genome comprises one filler sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region. In one embodiment, the filler sequence region is the FILL2 sequence region. In one embodiment, the filler sequence region is the FILL3 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region. In one embodiment, the filler sequence region is the FILL5 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region. In one embodiment, the filler sequence region is the FILL11 sequence region. In one embodiment, the filler sequence region is the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL18 sequence region.

[00661] In one embodiment, the AAV particle viral genome comprises two filler sequence regions. In one embodiment, the two filler sequence regions are the FILL1 sequence region, and the FILL2 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, and the FILL3 sequence region. In one embodiment, the filler sequence region

is the FILL1 sequence region, and the FILL4 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, and the FILL5 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, and the FILL6 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, and the FILL7 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, and the FILL8 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, and the FILL9 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, and the FILL10 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, and the FILL11 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL1 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL2 sequence region, and the FILL3 sequence region. In one embodiment, the filler sequence region is the FILL3 sequence region, and the FILL4 sequence region. In one embodiment, the filler sequence region is the FILL3 sequence region, and the FILL5 sequence region. In one embodiment, the filler sequence region is the FILL3 sequence region, and the FILL6 sequence region. In one embodiment, the filler sequence region is the FILL3 sequence region, and the FILL7 sequence region. In one embodiment, the filler sequence region is the FILL3 sequence region, and the FILL8 sequence region. In one embodiment, the filler sequence region is the FILL3 sequence region, and the FILL9 sequence region. In one embodiment, the filler sequence region is the FILL3 sequence region, and the FILL10 sequence region. In one embodiment, the filler sequence region is the FILL3 sequence region, and the FILL11 sequence region. In one embodiment, the filler sequence region is the FILL3 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL3 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL3 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL3 sequence region, and the FILL15 sequence region. In one embodiment, the filler

sequence region is the FILL3 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL3 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL3 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, and the FILL5 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, and the FILL6 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, and the FILL7 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, and the FILL8 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, and the FILL9 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, and the FILL10 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, and the FILL11 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL4 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL5 sequence region, and the FILL6 sequence region. In one embodiment, the filler sequence region is the FILL5 sequence region, and the FILL7 sequence region. In one embodiment, the filler sequence region is the FILL5 sequence region, and the FILL8 sequence region. In one embodiment, the filler sequence region is the FILL5 sequence region, and the FILL9 sequence region. In one embodiment, the filler sequence region is the FILL5 sequence region, and the FILL10 sequence region. In one embodiment, the filler sequence region is the FILL5 sequence region, and the FILL11 sequence region. In one embodiment, the filler sequence region is the FILL5 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL5 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL5 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL5 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL5 sequence region, and the FILL16 sequence region. In one

embodiment, the filler sequence region is the FILL5 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL5 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, and the FILL7 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, and the FILL8 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, and the FILL9 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, and the FILL10 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, and the FILL11 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL6 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, and the FILL8 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, and the FILL9 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, and the FILL10 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, and the FILL11 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL7 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, and the FILL9 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, and the FILL10 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, and the FILL11 sequence region. In one

embodiment, the filler sequence region is the FILL8 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL8 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, and the FILL10 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, and the FILL11 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL9 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, and the FILL11 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL10 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL11 sequence region, and the FILL12 sequence region. In one embodiment, the filler sequence region is the FILL11 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL11 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL11 sequence

region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL11 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL11 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL11 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL12 sequence region, and the FILL13 sequence region. In one embodiment, the filler sequence region is the FILL12 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL12 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL12 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL12 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL12 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL13 sequence region, and the FILL14 sequence region. In one embodiment, the filler sequence region is the FILL13 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL13 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL13 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL13 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL14 sequence region, and the FILL15 sequence region. In one embodiment, the filler sequence region is the FILL14 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL14 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL14 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL15 sequence region, and the FILL16 sequence region. In one embodiment, the filler sequence region is the FILL15 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL15 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL16 sequence region, and the FILL17 sequence region. In one embodiment, the filler sequence region is the FILL16 sequence region, and the FILL18 sequence region. In one embodiment, the filler sequence region is the FILL17 sequence region, and the FILL18 sequence region.

[00662] In one embodiment, the AAV particle viral genome comprises three filler sequence regions. In one embodiment, the two filler sequence regions are the FILL1 sequence region, the FILL2 sequence region, and the FILL3 sequence region. In one embodiment, the filler sequence

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CLAIMS

We claim:

1. An adeno-associated viral (AAV) viral genome comprising a nucleic acid sequence positioned between two inverted terminal repeats (ITRs), wherein said nucleic acid when expressed inhibits or suppresses the expression of a target gene in a cell, wherein said nucleic acid sequence comprises, in a 5' to 3' order: a first region encoding a first sense strand sequence, a second region encoding a first antisense strand sequence, a third region encoding a second sense strand, and a fourth region encoding a second antisense strand sequence, wherein the first and second sense strand sequences comprise at least 15 contiguous nucleotides and the first and second antisense strand sequences are complementary to an mRNA produced by the target gene and comprise at least 15 contiguous nucleotides, and wherein said first sense strand sequence and first antisense strand sequence share a region of complementarity of at least four nucleotides in length and said second sense strand sequence and second antisense strand sequence share a region of complementarity of at least four nucleotides in length.

2. An adeno-associated viral (AAV) viral genome comprising a nucleic acid sequence positioned between two inverted terminal repeats (ITRs), wherein said nucleic acid when expressed inhibits or suppresses the expression of a first target gene and a second target gene in a cell, wherein said nucleic acid sequence comprises, in a 5' to 3' order: a first region encoding a first sense strand sequence, a second region encoding a first antisense strand sequence, a third region encoding a second sense strand, and a fourth region encoding a second antisense strand sequence, wherein the first and second sense strand sequences comprise at least 15 contiguous nucleotides and the first antisense strand sequence is complementary to an mRNA produced by the first target gene and the second antisense strand sequence is complementary to an mRNA produced by the second target gene and comprise at least 15 contiguous nucleotides, and wherein said first sense strand sequence and first antisense strand sequence share a region of complementarity of at least four nucleotides in length and said second sense strand sequence and second antisense strand sequence share a region of complementarity of at least four nucleotides in length.

3. The AAV viral genome of claim 2, further comprising, in a 5' to 3' order, a fifth region encoding a third sense strand sequence and a sixth region encoding a third antisense strand sequence, wherein the third sense strand sequence comprises at least 15 contiguous nucleotides and the third antisense strand sequence is complementary to an mRNA produced by a third target gene and comprises at least 15 contiguous nucleotides, and wherein said third sense strand sequence and third antisense strand sequence share a region of complementarity of at least four nucleotides.

4. The AAV viral genome of claim 3, further comprising, in a 5' to 3' order, a seventh region encoding a fourth sense strand sequence and a eighth region encoding a fourth antisense strand sequence, wherein the fourth sense strand sequence comprises at least 15 contiguous nucleotides and the fourth antisense strand sequence is complementary to an mRNA produced by a fourth target gene and comprises at least 15 contiguous nucleotides, and wherein said fourth sense strand sequence and fourth antisense strand sequence share a region of complementarity of at least four nucleotides.

5. The AAV viral genome of claim 2, wherein the first target gene is the same as the second target gene.

6. The AAV viral genome of claim 3, wherein the third target gene is the same as the first target gene.

7. The AAV viral genome of claim 3, wherein the third target gene is the same as the second target gene.

8. The AAV viral genome of claim 3, wherein the first target gene, the second target gene and the third target gene are the same.

9. The AAV viral genome of claim 4, wherein the fourth target gene is the same as the first target gene.

10. The AAV viral genome of claim 4, wherein the fourth target gene is the same as the second target gene.

11. The AAV viral genome of claim 4, wherein the fourth target gene is the same as the third target gene.

12. The AAV viral genome of claim 4, wherein the fourth target gene is the same as the first target gene and the second target gene.

13. The AAV viral genome of claim 4, wherein the fourth target gene is the same as the second target gene and the third target gene.

14. The AAV viral genome of claim 4, wherein the fourth target gene is the same as the first target gene, the second target gene and the third target gene.

15. The AAV viral genome of any one of claims 1-14 wherein the first target gene, the second target gene, the third target gene and/or the fourth target gene is Huntingtin.

16. The AAV viral genome of any one of claims 1-14 wherein the first target gene, the second target gene, the third target gene and/or the fourth target gene is SOD1.

17. The AAV viral genome of any one of claims 1-14 wherein the first target gene, the second target gene, the third target gene and/or the fourth target gene is Huntingtin or SOD1.

18. The AAV viral genome of claim 1 or 2, wherein the region of complementarity between the first sense strand and the first antisense strand is at least 12 nucleotides in length.

19. The AAV viral genome of claim 18, wherein the region of complementarity between the first sense strand and the first antisense strand is between 14 and 21 nucleotides in length.

20. The AAV viral genome of claim 19, wherein the region of complementarity between the first sense strand and the first antisense strand is 19 nucleotides in length.

21. The AAV viral genome of claim 1 or 2, wherein the region of complementarity between the second sense strand and the second antisense strand is at least 12 nucleotides in length.

22. The AAV viral genome of claim 21, wherein the region of complementarity between the second sense strand and the second antisense strand is between 14 and 21 nucleotides in length.

23. The AAV viral genome of claim 22, wherein the region of complementarity between the second sense strand and the second antisense strand is 19 nucleotides in length.

24. The AAV viral genome of claim 3, wherein the region of complementarity between the third sense strand and the third antisense strand is at least 12 nucleotides in length.

25. The AAV viral genome of claim 24, wherein the region of complementarity between the third sense strand and the third antisense strand is between 14 and 21 nucleotides in length.

26. The AAV viral genome of claim 25, wherein the region of complementarity between the third sense strand and the third antisense strand is 19 nucleotides in length.

27. The AAV viral genome of claim 4, wherein the region of complementarity between the fourth sense strand and the fourth antisense strand is at least 12 nucleotides in length.

28. The AAV viral genome of claim 27, wherein the region of complementarity between the fourth sense strand and the fourth antisense strand is between 14 and 21 nucleotides in length.

29. The AAV viral genome of claim 25, wherein the region of complementarity between the fourth sense strand and the fourth antisense strand is 19 nucleotides in length.

30. The AAV viral genome of claim 1 or 2, wherein the first sense strand sequence, the second sense strand sequence, the first antisense strand sequence, and the second antisense strand sequence are, independently, 30 nucleotides or less.

31. The AAV viral genome of claim 3, wherein the first sense strand sequence, the second sense strand sequence, the third sense strand sequence, the first antisense strand sequence,

the second antisense strand sequence and the third antisense strand sequence, are, independently, 30 nucleotides or less.

32. The AAV viral genome of claim 4 wherein the first sense strand sequence, the second sense strand sequence, the third sense strand sequence, the fourth sense strand sequence, the first antisense strand sequence, the second antisense strand sequence, the third antisense strand sequence and the fourth antisense strand sequence, are, independently, 30 nucleotides or less.

33. The AAV viral genome of claim 1 or 2, wherein at least one of the first sense strand sequence and the first antisense strand sequence or the second sense strand sequence and the second antisense strand sequence comprise a 3' overhang of at least 1 nucleotide.

34. The AAV viral genome of claim 1 or 2, wherein at least one of the first sense strand sequence and the first antisense strand sequence or the second sense strand sequence and the second antisense strand sequence comprise a 3' overhang of at least 2 nucleotides.

35. The AAV viral genome of claim 3, wherein the third sense strand sequence and the third antisense strand sequence comprise a 3' overhang of at least 1 nucleotide.

36. The AAV viral genome of claim 3, wherein the third sense strand sequence and the third antisense strand sequence comprise a 3' overhang of at least 2 nucleotides.

37. The AAV viral genome of claim 4 wherein the fourth sense strand sequence and the fourth antisense strand sequence comprise a 3' overhang of at least 1 nucleotide.

38. The AAV viral genome of claim 4 wherein the fourth sense strand sequence and the fourth antisense strand sequence comprise a 3' overhang of at least 2 nucleotides.

39. The AAV viral genome of any one of claims 1-38, wherein the first region comprises, a promoter 5' of the first sense strand sequence followed by the first sense strand sequence, and the second region comprises the first antisense strand sequence followed by a promoter terminator 3' of the first antisense strand sequence; or the third region comprises a promoter

5’ of the second sense strand sequence followed by the second sense strand sequence, and the fourth region comprises the second antisense strand sequence followed by a promoter terminator 3’ of the second antisense strand sequence.

40. The AAV viral genome of any one of claims 1-38, wherein the first region comprises, a promoter 5’ of the first sense strand sequence followed by the first sense strand sequence, and the second region comprises the first antisense strand sequence followed by a promoter terminator 3’ of the first antisense strand sequence; and the third region comprises a promoter 5’ of the second sense strand sequence followed by the second sense strand sequence, and the fourth region comprises the second antisense strand sequence followed by a promoter terminator 3’ of the second antisense strand sequence.

41. The AAV viral genome of any one of claims 3-40, wherein the fifth region comprises a promoter 5’ of the third sense strand sequence followed by the third sense strand sequence and the sixth region comprises the third antisense strand sequence followed by a promoter terminator 3’ of the third antisense strand sequence.

42. The AAV viral genome of any one of claims 4-41 wherein the seventh region comprises a promoter 5’ of the fourth sense strand sequence followed by the fourth sense strand sequence and the eighth region comprises the fourth antisense strand sequence followed by a promoter terminator 3’ of the fourth antisense strand sequence.

43. The AAV viral genome of claim 3, wherein the fifth region is 3’ of the fourth region.

44. The AAV viral genome of claim 4, wherein the seventh region is 3’ of the sixth region.

45. The AAV viral genome of any one of claims 39-44 wherein a promoter is a Pol III promoter and the promoter terminator is a Pol III promoter terminator.

46. The AAV viral genome of claim 45, wherein the Pol III promoter is a U3, U6, U7, 7SK, H1, or MRP, EBER, seleno-cysteine tRNA, 7SL, adenovirus VA-1, or telomerase gene promoter, and the Pol III promoter terminator is a U3, U6, U7, 7SK, H1, or MRP, EBER,

seleno-cysteine tRNA, 7SL, adenovirus VA-1, or telomerase gene promoter terminator, respectively.

47. The AAV viral genome of claim 46, wherein the Pol III promoter is an H1 promoter and the Pol III promoter terminator is an H1 promoter terminator.

48. The AAV viral genome of any one of claims 1-47, wherein the AAV viral genome is a monospecific polycistronic AAV viral genome.

49 The AAV viral genome of any one of claims 1-47, wherein the AAV viral genome is a bispecific polycistronic AAV viral genome.

50. The AAV viral genome of claim 1 or 2, wherein the first region and the second region encode a first siRNA molecule, and the third region and the fourth region encode a second siRNA molecule, wherein the first and the second siRNA molecules target a different target gene.

51. The AAV viral genome of claim 3, wherein the fifth region and the sixth region encode a third siRNA molecule, wherein the first siRNA molecule, the second siRNA molecule and the third siRNA molecule each target a different target gene.

52. The AAV viral genome of claim 4, wherein the seventh region and the eighth region encode a fourth siRNA molecule, wherein the first siRNA molecule, the second siRNA molecule, the third siRNA molecule and the fourth siRNA molecule each target a different target gene.

53. An adeno-associated viral (AAV) viral genome comprising a nucleic acid sequence positioned between two inverted terminal repeats (ITRs), wherein said nucleic acid sequence comprises a first molecular scaffold region and a second molecular scaffold region, wherein said first molecular scaffold region comprises a first molecular scaffold nucleic acid sequence encoding:

(f) a first stem and loop to form a first stem-loop structure, the sequence of said first

stem-loop structure from 5’ to 3’ comprising:

x. a first UG motif at or near the base of the first 5’ stem of the first stem-loop structure;

xi. a first 5’ stem arm comprising a first sense strand and optional first 5’ spacer region, wherein said first 5’ spacer region, when present, is located between said first UG motif and said first sense strand;

xii. a first loop region comprising a first UGUG motif at the 5’ end of said first loop region;

xiii. a first 3’ stem arm comprising a first antisense strand and optionally a first 3’ spacer region, wherein a uridine is present at the 5’ end of said first antisense strand and wherein said first 3’ spacer region, when present, has a length sufficient to form one helical turn;

(g) a first 5’ flanking region located 5’ to said first stem-loop structure; and

(h) a first 3’ flanking region located 3’ to said first stem-loop structure, said first 3’ flanking region comprising a CNNC motif, and

a second molecular scaffold region comprising a second molecular scaffold nucleic acid sequence encoding

(i) a second stem and loop to form a second stem-loop structure, the sequence of said second stem-loop structure from 5’ to 3’ comprising:

xiv. a second UG motif at or near the base of the second 5’ stem of the second stem-loop structure;

xv. a second 5’ stem arm comprising a second sense strand and optional second 5’ spacer region, wherein said second 5’ spacer region, when present, is located between said second UG motif and said second sense strand;

xvi. a second loop region comprising a second UGUG motif at the 5’ end of said second loop region;

xvii. a second 3’ stem arm comprising a second antisense strand and optionally a second 3’ spacer region, wherein a uridine is present at the 5’ end of said second antisense strand and wherein said second 3’ spacer region, when present, has a length sufficient to form one helical turn;

(j) a second 5’ flanking region located 5’ to said second stem-loop structure; and

(k) a second 3’ flanking region located 3’ to said second stem-loop structure, said second 3’ flanking region comprising a CNNC motif, and

wherein said first antisense strand and said first sense strand form a first siRNA duplex and said second antisense strand and said second sense strand form a second siRNA duplex, where the first siRNA duplex, when expressed, inhibits or suppresses the expression of a first target gene in a cell, and the second siRNA duplex, when expressed, inhibits or suppresses the expression of a second target gene in a cell, wherein the first and second sense strand sequences comprise at least 15 nucleotides, the first antisense strand sequence is complementary to an mRNA produced by the first target gene and second antisense strand sequences is complementary to an mRNA produced by the second target gene, and wherein said first sense strand sequence and first antisense strand sequence share a region of complementarity of at least four nucleotides in length and said second sense strand sequence and second antisense strand sequence share a region of complementarity of at least four nucleotides in length.

54. An adeno-associated viral (AAV) viral genome comprising a nucleic acid sequence positioned between two inverted terminal repeats (ITRs), wherein said nucleic acid sequence comprises a first molecular scaffold region and a second molecular scaffold region, wherein said first molecular scaffold region comprises a first molecular scaffold nucleic acid sequence encoding:

(m) a first stem and loop to form a first stem-loop structure, the sequence of said first stem-loop structure from 5’ to 3’ comprising:

xvii. a first UG motif at or near the base of the first 5’ stem of the first stem-loop structure;

xviii. a first 5’ stem arm comprising a first antisense strand and optional first 5’ spacer region, wherein said first 5’ spacer region, when present, is located between said first UG motif and said first antisense strand;

xix. a first loop region comprising a first UGUG motif at the 5’ end of said first loop region;

xx. a first 3’ stem arm comprising a first sense strand and optionally a first 3’ spacer region, wherein a uridine is present at the 5’ end of said first sense strand and wherein said first 3’ spacer region, when present, has a length sufficient to form one helical turn;

(n) a first 5’ flanking region located 5’ to said first stem-loop structure; and

(o) a first 3’ flanking region located 3’ to said first stem-loop structure, said first 3’

flanking region comprising a CNNC motif, and

a second molecular scaffold region comprising a second molecular scaffold nucleic acid sequence encoding

(p) a second stem and loop to form a second stem-loop structure, the sequence of said second stem-loop structure from 5' to 3' comprising:

xxi. a second UG motif at or near the base of the second 5' stem of the second stem-loop structure;

xxii. a second 5' stem arm comprising a second antisense strand and optional second 5' spacer region, wherein said second 5' spacer region, when present, is located between said second UG motif and said second antisense strand;

xxiii. a second loop region comprising a second UGUG motif at the 5' end of said second loop region;

xxiv. a second 3' stem arm comprising a second sense strand and optionally a second 3' spacer region, wherein a uridine is present at the 5' end of said second sense strand and wherein said second 3' spacer region, when present, has a length sufficient to form one helical turn;

(q) a second 5' flanking region located 5' to said second stem-loop structure; and

(r) a second 3' flanking region located 3' to said second stem-loop structure, said second 3' flanking region comprising a CNNC motif, and

wherein said first antisense strand and said first sense strand form a first siRNA duplex and said second antisense strand and said second sense strand form a second siRNA duplex, where the first siRNA duplex, when expressed, inhibits or suppresses the expression of a first target gene in a cell, and the second siRNA duplex, when expressed, inhibits or suppresses the expression of a second target gene in a cell, wherein the first and second sense strand sequences comprise at least 15 nucleotides, the first antisense strand sequence is complementary to an mRNA produced by the first target gene and second antisense strand sequences is complementary to an mRNA produced by the second target gene, and wherein said first sense strand sequence and first antisense strand sequence share a region of complementarity of at least four nucleotides in length and said second sense strand sequence and second antisense strand sequence share a region of complementarity of at least four nucleotides in length.

55. The AAV viral genome of claim 53 or 54, wherein the first antisense strand sequence or the second antisense strand sequence inhibits or suppresses the expression of Huntingtin.

56. The AAV viral genome of claim 53 or 54, wherein the first antisense strand sequence and the second antisense sequence strand inhibits or suppresses the expression of Huntingtin.

57. The AAV viral genome of claim 53 or 54, wherein the first antisense strand sequence or the second antisense strand sequence inhibits or suppresses the expression of SOD1.

58. The AAV viral genome of claim 53 or 54, wherein the first antisense strand sequence and the second antisense strand sequence inhibits or suppresses the expression of SOD1.

59. The AAV viral genome of claim 53 or 54, wherein the first 5' flanking region is selected from the sequences listed in Table 10.

60. The AAV viral genome of claim 53 or 54, wherein the second 5' flanking region is selected from the sequences listed in Table 10.

61. The AAV viral genome of claim 59, wherein the second 5' flanking region is selected from the sequences listed in Table 10.

62. The AAV viral genome of claim 53 or 54, wherein the first loop region is selected from the sequences listed in Table 11.

63. The AAV viral genome of claim 53 or 54, wherein the second loop region is selected from the sequences listed in Table 11.

64. The AAV viral genome of claim 62, wherein the second loop region is selected from the sequences listed in Table 11.

65. The AAV viral genome of claim 53 or 54, wherein the first 3' flanking region is selected from the sequences listed in Table 12.

66. The AAV viral genome of claim 53 or 54, wherein the second 3' flanking region is selected from the sequences listed in Table 12.

67. The AAV viral genome of claim 65, wherein the second 3' flanking region is selected from the sequences listed in Table 12.

68. The AAV viral genome of claim 53 or 54, wherein the nucleic acid sequence comprises a promoter sequence between the first molecular scaffold nucleic acid sequence and the second molecular scaffold nucleic acid sequence.

69. The AAV viral genome of claim 53 or 54, further comprising, in (b), a promoter 5' of the first 5' flanking region followed by the first 5' flanking region and in (c) the first 3' flanking region followed by a promoter terminator 3' of the first '3 flanking region, and in (d), a promoter 5' of the second 5' flanking region followed by the second 5' flanking region and in (e) the second 3' flanking region followed by a promoter terminator 3' of the second 3' flanking region.

70. The AAV viral genome of claim 69, wherein the promoter is a Pol III promoter.

71. The AAV viral genome of claim 70, wherein the Pol III promoter sequence is a U3, U6, U7, 7SK, H1, or MRP, EBER, seleno-cysteine tRNA, 7SL, adenovirus VA-1, or telomerase gene promoter.

72. The AAV viral genome of claim 71, wherein the Pol III promoter is an H1 promoter.

73. The AAV viral genome of claim 53, wherein the nucleic acid sequence further comprises a third molecular scaffold region comprising a third molecular scaffold nucleic acid sequence encoding:

(s) a third stem and loop to form a third stem-loop structure, the sequence of said third stem-loop structure from 5' to 3' comprising:

xxv. a third UG motif at or near the base of the third 5' stem of the third stem-loop structure;

xxvi. a third 5' stem arm comprising a third sense strand and optional third 5'

spacer region, wherein said third 5’ spacer region, when present, is located between said third UG motif and said third sense strand;

xxvii. a third loop region comprising a third UGUG motif at the 5’ end of said third loop region;

xxviii. a third 3’ stem arm comprising a third antisense strand and optionally a third 3’ spacer region, wherein a uridine is present at the 5’ end of said third antisense strand and wherein said third 3’ spacer region, when present, has a length sufficient to form one helical turn;

(t) a third 5’ flanking region located 5’ to said third stem-loop structure; and

(u) a third 3’ flanking region located 3’ to said third stem-loop structure, said third 3’ flanking region comprising a CNNC motif, and

wherein said third antisense strand and said third sense strand form a third siRNA duplex, wherein the third siRNA duplex, when expressed, inhibits or suppresses the expression of a third target gene in a cell, wherein the third sense strand sequence comprises at least 15 nucleotides, the third antisense strand sequence is complementary to an mRNA produced by the third target gene, and wherein said third sense strand sequence and third antisense strand sequence share a region of complementarity of at least four nucleotides in length.

74. The AAV viral genome of claim 73, further comprising, in (h), a promoter 5’ of the third 5’ flanking region followed by the third 5’ flanking region, and in (i) the third 3’ flanking region followed by a promoter terminator 3’ of the third ‘3 flanking region.

75. The AAV viral genome of claim 74, wherein the promoter is a Pol III promoter.

76. The AAV viral genome of claim 75, wherein the Pol III promoter sequence is a U3, U6, U7, 7SK, H1, or MRP, EBER, seleno-cysteine tRNA, 7SL, adenovirus VA-1, or telomerase gene promoter.

77. The AAV viral genome of claim 76, wherein the Pol III promoter is an H1 promoter.

78. The AAV viral genome of claim 73, wherein the nucleic acid sequence further comprises a fourth molecular scaffold region comprising a fourth molecular scaffold nucleic acid sequence encoding

(v) a fourth stem and loop to form a fourth stem-loop structure, the sequence of said fourth stem-loop structure from 5' to 3' comprising:

xxix. a fourth UG motif at or near the base of the fourth 5' stem of the fourth stem-loop structure;

xxx. a fourth 5' stem arm comprising a fourth sense strand and optional fourth 5' spacer region, wherein said fourth 5' spacer region, when present, is located between said fourth UG motif and said fourth sense strand;

xxxi. a fourth loop region comprising a fourth UGUG motif at the 5' end of said fourth loop region;

xxxii. a fourth 3' stem arm comprising a fourth antisense strand and optionally a fourth 3' spacer region, wherein a uridine is present at the 5' end of said fourth antisense strand and wherein said fourth 3' spacer region, when present, has a length sufficient to form one helical turn;

(w) a fourth 5' flanking region located 5' to said fourth stem-loop structure; and

(x) a fourth 3' flanking region located 3' to said fourth stem-loop structure, said fourth 3' flanking region comprising a CNNC motif, and

wherein said fourth antisense strand and said fourth sense strand form a fourth siRNA duplex, wherein the fourth siRNA duplex, when expressed, inhibits or suppresses the expression of a fourth target gene in a cell, wherein the fourth sense strand sequence comprises at least 15 nucleotides, the fourth antisense strand sequence is complementary to an mRNA produced by the fourth target gene, and wherein said fourth sense strand sequence and fourth antisense strand sequence share a region of complementarity of at least four nucleotides in length.

79. The AAV viral genome of claim 78, further comprising, in (k), a promoter 5' of the fourth 5' flanking region followed by the fourth 5' flanking region, and in (l) the fourth 3' flanking region followed by a promoter terminator 3' of the fourth '3 flanking region.

80. The AAV viral genome of claim 79, wherein the promoter is a Pol III promoter.

81. The AAV viral genome of claim 80, wherein the Pol III promoter sequence is a U3, U6, U7, 7SK, H1, or MRP, EBER, seleno-cysteine tRNA, 7SL, adenovirus VA-1, or telomerase gene promoter.

82. The AAV viral genome of claim 81, wherein the Pol III promoter is an H1 promoter.

83. The AAV viral genome of any one of claims 53-82, wherein the first target gene is the same as the second target gene.

84. The AAV viral genome of any one of claims 53-82, wherein the third target gene is the same as the first target gene.

85. The AAV viral genome of any one of claims 53-82, wherein the third target gene is the same as the second target gene.

86. The AAV viral genome of any one of claims 53-82, wherein the first target gene, the second target gene and the third target gene are the same.

87. The AAV viral genome of any one of claims 53-82, wherein the fourth target gene is the same as the first target gene.

88. The AAV viral genome of any one of claims 53-82, wherein the fourth target gene is the same as the second target gene.

89. The AAV viral genome of any one of claims 53-82, wherein the fourth target gene is the same as the third target gene.

90. The AAV viral genome of any one of claims 53-82, wherein the fourth target gene is the same as the first target gene and the second target gene.

91. The AAV viral genome of claim 53-82, wherein the fourth target gene is the same as the second target gene and the third target gene.

92. The AAV viral genome of claim 53-82, wherein the fourth target gene is the same as the first target gene and the third target gene.

93. The AAV viral genome of any one of claims 53-82, wherein the fourth target gene is the same as the first target gene, the second target gene and the third target gene.

94. The AAV viral genome of any one of claims 53-93 wherein the first target gene, the second target gene, the third target gene and/or the fourth target gene is Huntingtin.

95. The AAV viral genome of any one of claims 53-93 wherein the first target gene, the second target gene, the third target gene and/or the fourth target gene is SOD1.

96. The AAV viral genome of any one of claims 53-93 wherein the first target gene, the second target gene, the third target gene and/or the fourth target gene is Huntingtin or SOD1.

97. A method for inhibiting the expression of a gene of a target gene in a cell comprising administering to the cell a composition comprising an AAV viral genome of any one of claims 1-96.

98. The method of claim 97, wherein the cell is a mammalian cell.

99. The method of claim 98, wherein the mammalian cell is a medium spiny neuron.

100. The method of claim 98, wherein the mammalian cell is a cortical neuron.

101. The method of claim 98, wherein the mammalian cell is a motor neuron.

102. The method of claim 98, wherein the mammalian cell is an astrocyte.

103. A method for treating a disease and/or disorder in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a composition comprising an AAV viral genome of any one of claims 1-96.

104. The method of claim 103, wherein the expression of a target gene is inhibited or suppressed.

105. The method of claim 104, wherein the expression of a target gene of interest is inhibited or suppressed by about 30% to about 70%.

106. The method of claim 104, wherein the expression of a target gene is inhibited or suppressed by about 50% to about 90%.

107. A method for inhibiting the expression of a target gene in a cell wherein the target gene causes a gain of function effect inside the cell, comprising administering to the cell a composition comprising an AAV viral genome of any one of claims 1-96.

108. The method of claim 107, wherein the cell is a mammalian cell.

109. The method of claim 108, wherein the mammalian cell is a medium spiny neuron.

110. The method of claim 108, wherein the mammalian cell is a cortical neuron.

111. The method of claim 108, wherein the mammalian cell is a motor neuron.

112. The method of claim 108, wherein the mammalian cell is an astrocyte.

FIG. 1

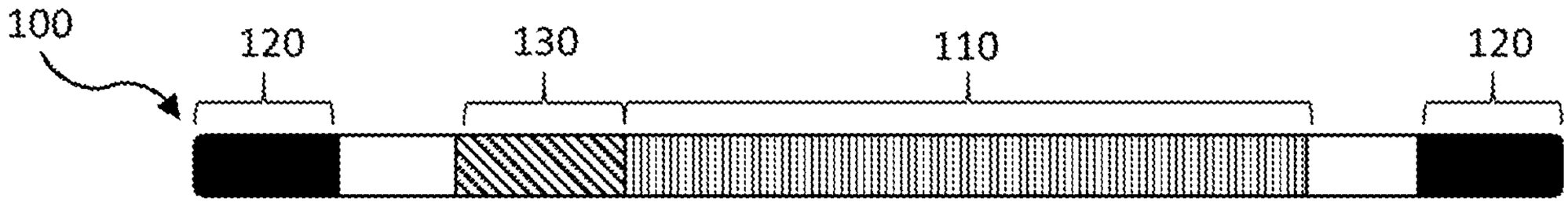


FIG. 2

FIG. 3

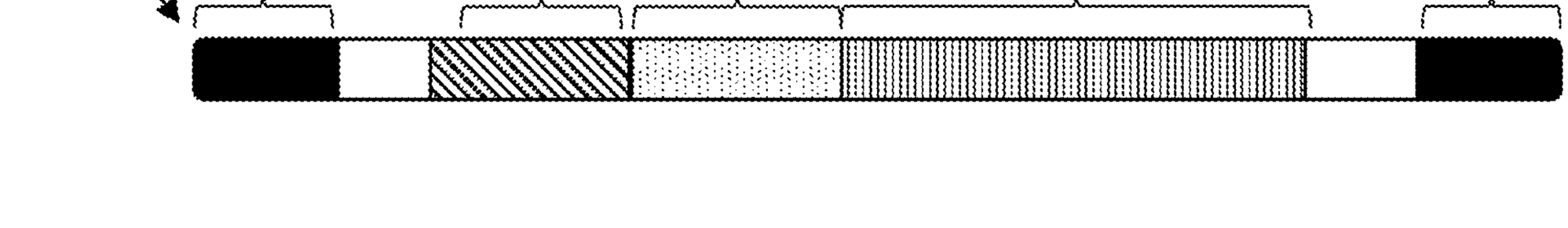


FIG. 4

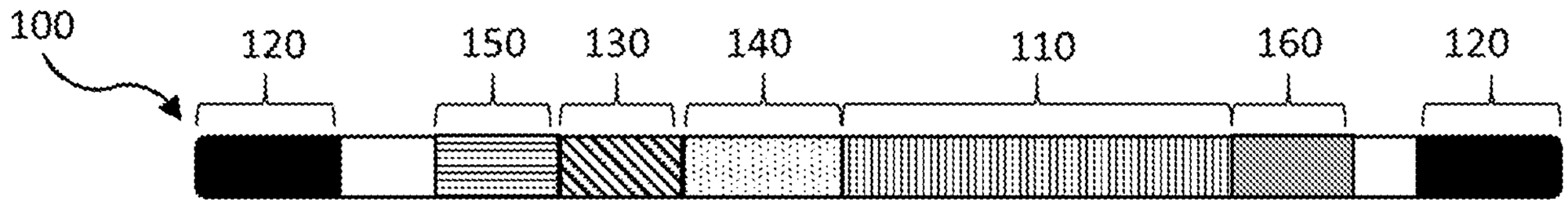


FIG. 5

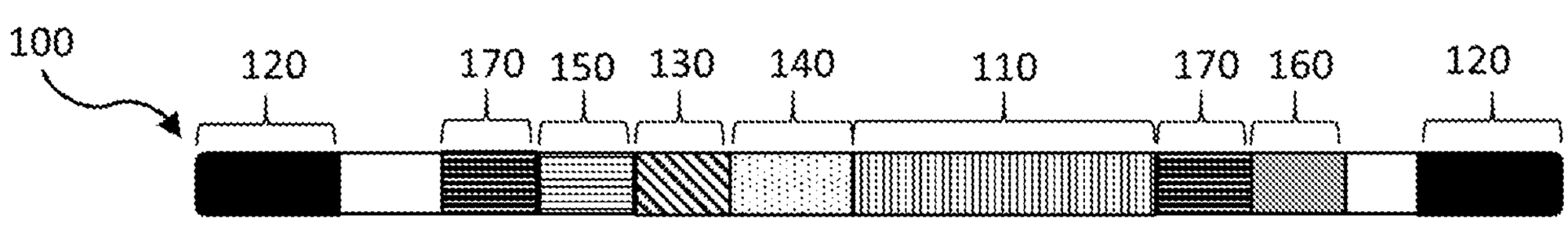
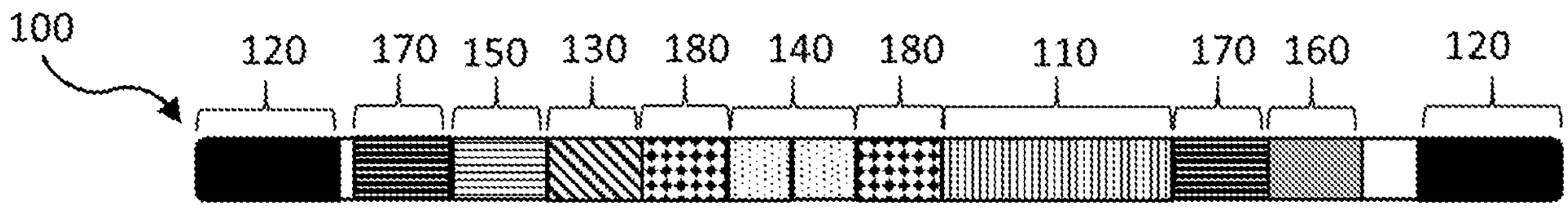


FIG. 6



3/3

FIG. 7

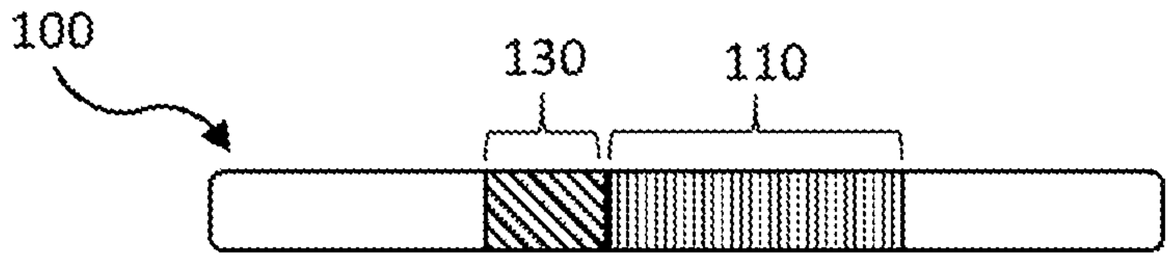


FIG. 8

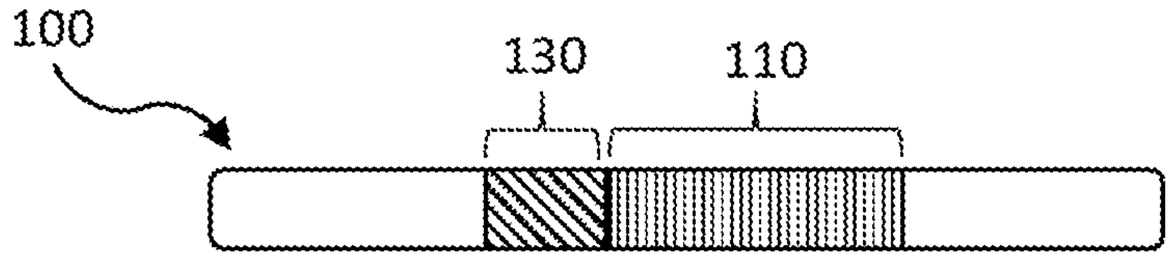


FIG. 9

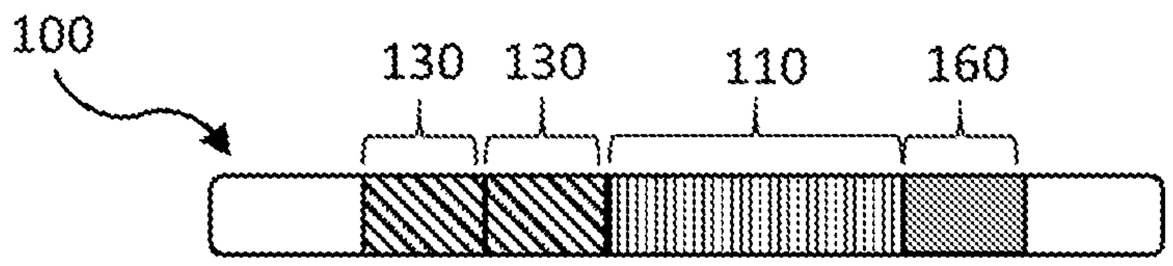


FIG. 1