

AAV CAPSID VARIANTS AND USES THEREOF

RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 63/274,806 filed on November 2, 2021 and U.S. Provisional Application No. 63/339,711 filed on May 9, 2022; the entire contents of each of which are hereby incorporated by reference in their entirety.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in XML format and is hereby incorporated by reference in its entirety. Said XML copy, created on October 19, 2022, is named V2071-1125PCT_SL.xml and is 5,455,496 bytes in size.

FIELD OF THE DISCLOSURE

[0003] The disclosure relates to compositions and methods for the preparation, use, and/or formulation of adeno-associated virus capsid proteins and variants thereof.

BACKGROUND

[0004] Gene delivery to the adult central nervous system (CNS) remains a significant challenge in gene therapy. Engineered adeno-associated virus (AAV) capsids with improved brain tropism represent an attractive solution to the limitations of CNS delivery.

[0005] AAV-derived vectors are promising tools for clinical gene transfer because of their non-pathogenic nature, their low immunogenic profile, low rate of integration into the host genome and long-term transgene expression in non-dividing cells. However, the transduction efficiency of AAV natural variants in certain organs is too low for clinical applications, and capsid neutralization by pre-existing neutralizing antibodies may prevent treatment of a large proportion of patients. For these reasons, considerable efforts have been devoted to obtaining capsid variants with enhanced properties. Of many approaches tested so far, significant advances have resulted from directed evolution of AAV capsids using *in vitro* or *in vivo* selection of capsid variants created by capsid sequence randomization using either error-prone PCR, shuffling of various parent serotypes, or insertion of fully randomized short peptides at defined positions.

[0006] Attempts at providing AAV capsids with improved properties, e.g., improved tropism to a target cell or tissue upon systemic administration, have met with limited success. As such, there is a need for improved methods of producing AAV capsids and resulting AAV capsids for delivery of a payload of interest to a target cell or tissue, e.g., a CNS cell or tissue, or a muscle cell or tissue.

SUMMARY OF THE DISCLOSURE

[0007] The present disclosure pertains at least in part, to compositions and methods for the production and use of an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid

variant. In some embodiments, the AAV capsid variant has an enhanced tropism for a tissue or a cell, e.g., a CNS tissue or a CNS cell. Said tropism can be useful for delivery of a payload, e.g., a payload described herein to a cell or tissue, for the treatment of a disorder, e.g., a neurological or a neurodegenerative disorder, a muscular or a neuromuscular disorder, or a neuro-oncological disorder.

[0008] Accordingly, in one aspect, the present disclosure provides an AAV capsid variant, comprising an amino acid sequence having the following formula: [N1]-[N2]-[N3], wherein: (i) optionally [N1] comprises X1, X2, and X3, wherein at least one of X1, X2, or X3 is G; (ii) [N2] comprises the amino acid sequence of SPH; (iii) [N3] comprises X4, X5, and X6, wherein at least one of X4, X5, or X6 is a basic amino acid, e.g., a K or R. In some embodiments, position X4 of [N3] is K. In some embodiments, position X5 of [N3] is K. In some embodiments, [N3] is or comprises SKA. In some embodiments [N3] is or comprises KSG. In some embodiments, [N2]-[N3] is present immediately subsequent to position 455, numbered according to SEQ ID NO: 138, 981 or 982. In some embodiments, [N1] is present immediately subsequent to position 452, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138, 981, or 982. In some embodiments, [N1] replaces positions 453- 455 (e.g., G453, S454, and G455), relative to a reference sequence numbered according to SEQ ID NO: 138. In some embodiments, the AAV capsid variant comprises H at position 454 and D at position 455, numbered according to SEQ ID NO: 138 or 982. In some embodiments, the AAV capsid variant comprises S at position 454 and G at position 455, numbered according to SEQ ID NO: 138 or 981. In some embodiments, an insert of 8 amino acids replaces the SG at positions 454-455, numbered according to SEQ ID NO: 138. In some embodiments, an insert of 6 amino acids is present immediately subsequent to position 455, numbered according to SEQ ID NO: 138, 981, or 982.

[0009] In another aspect, the present disclosure provides an AAV capsid variant comprising [A][B] (SEQ ID NO: 4694), wherein: (i) [A] comprises the amino acid sequence of GSGSPH (SEQ ID NO: 4695); and (ii) [B] comprises X1 X2 X3 X4 X5 X6 X7, wherein: (a) position X1 is S, C, F, or V; (b) position X2 is K, L, R, I, E, Y, V, or S; (c) position X3 is A, R, L, G, I, Y, S, F, or W; (d) position X4 is W, Q, R, G, L, V, S, or F; (e) position X5 is N, Y, R, C, K, or L; (f) position X6 is Q, G, K, R, T, L, or Y; and (g) position X7 is Q, L, R, or V.

[0010] In yet another aspect, the present disclosure provides an AAV capsid variant comprising [A][B] (SEQ ID NO: 4699) wherein: (i) [A] comprises X1 X2 X3 X4 X5 X6, wherein (a) position X1 is T, M, A, C, I, R, L, D, F, V, Q, N, or H; (b) position X2 is I, P, E, N, D, S, A, T, M, or Q; (c) position X3 is N, E, G, Y, W, M, T, I, K, Q, F, S, V, A, or L; (d) position X4 is G, D, R, or E; (e) position X5 is H, Q, N, or D; (f) position X6 is D or R; and (ii) [B] comprises SPHKSG (SEQ ID NO: 946).

[0011] In yet another aspect, the present disclosure provides an AAV capsid variant comprising an amino acid sequence having the following formula: [N1]-[N2]-[N3] (SEQ ID NO: 6407), wherein:

(i) [N1] comprises positions X1, X2, and X3, wherein position X2 is S and position X3 is G; (ii) [N2] comprises the amino acid sequence SPH; and (iii) [N3] comprises positions X4, X5, and X6, wherein position X5 is K. In some embodiments, [N1]-[N2]-[N3] is present immediately subsequent to position 452 and replaces positions 453-455, numbered according to SEQ ID NO: 138 or 982. In some embodiments, [N1]-[N2]-[N3] is or comprises GSGSPHKA (SEQ ID NO: 4697).

[0012] In another aspect, the present disclosure provides an AAV capsid variant comprising an amino acid sequence having the following formula: [N1]-[N2]-[N3] (SEQ ID NO: 6408), wherein: (i) [N1] comprises positions X1, X2, and X3, wherein position X2 is an amino acid other than S and position X3 is an amino acid other than G; (ii) [N2] comprises the amino acid sequence SPH; and (iii) [N3] comprises positions X4, X5, and X6, wherein position X4 is K. In some embodiments, [N1]-[N2]-[N3] is present immediately subsequent to position 452 and replaces positions 453-455, numbered according to SEQ ID NO: 138 or 982. In some embodiments, [N1]-[N2]-[N3] is or comprises GHDSPHKSG (SEQ ID NO: 4698).

[0013] In yet another aspect, the present disclosure provides an AAV capsid variant comprising the formula [A]-[B] (SEQ ID NO: 4696), wherein: (i) [A] comprises GSGSPH (SEQ ID NO: 4695); and (ii) [B] comprises X1 X2, X3, X4, and X5, wherein: (a) position X1 is S, I, F, V, C, Y, W, R, P, L, Q, M, K, or G; (b) position X2 is K, M, R, F, V, C, P, Y, L, W, G, N, S, T, I, or A; (c) position X3 is A, Y, L, R, W, C, T, F, H, I, P, M, K, S, V, G, Q, or N; (d) position X4 is Q, M, F, K, H, R, C, W, P, V, L, G, S, Y, I, A, T, D, N, or E; and (e) position X5 is A, N, Y, R, K, L, I, M, Q, S, C, W, F, T, G, V, or P; optionally wherein the AAV capsid variant comprises an amino acid modification, e.g., a conservative substitution, of any of the aforesaid amino acids in (a)-(e). In some, embodiments, [A]-[B] is present immediately subsequent to position 452, and wherein [A]-[B] replaces positions 453-457 (e.g., G453, S454, G455, Q456, N457), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid variant has increased tropism for a liver cell or tissue, relative to the tropism of a reference sequence comprising the amino acid sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid shows preferential transduction in the liver relative to transduction in the brain and/or dorsal root ganglia (DRG), e.g., as compared to SEQ ID NO: 138.

[0014] In another aspect, the present disclosure provides an AAV capsid variant comprising (a) the amino acid sequence of any of the sequences provided in Tables 1, 2A, 2B, 13-19; (b) an amino acid sequence comprising at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or 17, consecutive amino acids from any one of the sequences provided in Tables 1, 2A, 2B, 13-19; (c) an amino acid sequence comprising at least one, two, or three, but no more than four different amino acids, relative to any one of the sequences provided in Tables 1, 2A, 2B, 13-19; or (d) an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of any one of the sequences provided

in Tables 1, 2A, 2B, 13-19. In some embodiments, the amino acid sequence is present in loop IV. In some embodiments, the amino acid sequence is present immediately subsequent to position 448, 452, 453, 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

[0015] In yet another aspect, the present disclosure provides an AAV capsid variant comprising (a) the amino acid sequence of any of SEQ ID NOs: 945-980 or 985-986; (b) an amino acid sequence comprising at least 3, 4, or 5 consecutive amino acids from any one of SEQ ID NOs: 945-980 or 985-986; (c) an amino acid sequence comprising at least one, two, or three but no more than four different amino acids, relative to the amino acid sequence of any one of SEQ ID NOs: 945-980 or 985-986; (d) an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of any one of SEQ ID NOs: 945-980 or 985-986. In some embodiments, the amino acid sequence is present in loop IV. In some embodiments, the amino acid sequence is present immediately subsequent to position 448, 452, 453, 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

[0016] In yet another aspect, the present disclosure provides an AAV capsid variant comprising (a) the amino acid sequence of any of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909; (b) an amino acid sequence comprising at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 consecutive amino acids from any one of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909; (c) an amino acid sequence comprising at least one, two, or three, but no more than four different amino acids, relative to the amino acid sequence of any one of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909; or (d) an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of any one of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909. In some embodiments, the amino acid sequence is present in loop IV. In some embodiments, the amino acid sequence is present immediately subsequent to position 448, 452, 453, 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

[0017] In yet another aspect, the present disclosure provides a polynucleotide encoding an AAV capsid variant described herein. In some embodiments, the polynucleotide comprises (i) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequences of SEQ ID NO: 3 or 942; (ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten different nucleotides, relative to the nucleotide sequences of SEQ ID NO: 3 or 942; or (iii) the nucleotide sequence of SEQ ID NOs: 3 or 942, or nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto.

[0018] In yet another aspect, present disclosure provides an AAV capsid variant comprising an amino acid sequence comprising at least 3, 4, 5, or 6 consecutive amino acids from the amino acid sequence of SPHKA (SEQ ID NO: 941), wherein: (i) the 3 consecutive amino acids comprise SPH; (ii) the 4 consecutive amino acids comprise SPHS (SEQ ID NO: 4700); (iii) the 5 consecutive amino acids comprise SPHSK (SEQ ID NO: 4701); or (iv) the 6 consecutive amino acids comprise SPHKA (SEQ ID NO: 941); wherein the AAV capsid variant comprises: (a) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 138 or SEQ ID NO: 981; (b) a VP2 protein comprising the amino acid sequence of positions 138-736 of SEQ ID NO: 138 or positions 138-742 of SEQ ID NO: 981; (c) a VP3 protein comprising the amino acid sequence of positions 203-736 of SEQ ID NO: 138 or positions 203-742 of SEQ ID NO: 981; or (d) an amino acid sequence with at least 90% (e.g., at least about 95, 96, 97, 98, or 99%) sequence identity to any of the amino acid sequences in (a)-(c). In some embodiments, the amino acid sequence is present immediately subsequent to positions 455, numbered according to SEQ ID NO: 138 or 981.

[0019] In yet another aspect, the present disclosure provides an AAV capsid variant comprising one or two, but no more than three substitutions relative to the amino acid sequence of SPHKA (SEQ ID NO: 941), wherein the AAV capsid variant comprises: (a) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 138 or SEQ ID NO: 981; (b) a VP2 protein comprising the amino acid sequence of positions 138-736 of SEQ ID NO: 138 or positions 138-742 of SEQ ID NO: 981; (c) a VP3 protein comprising the amino acid sequence of positions 203-736 of SEQ ID NO: 138 or positions 203-742 of SEQ ID NO: 981; or (d) an amino acid sequence with at least 90% (e.g., at least about 95, 96, 97, 98, or 99%) sequence identity to any of the amino acid sequences in (a)-(c). In some embodiments, the amino acid sequence is present immediately subsequent to positions 455, numbered according to SEQ ID NO: 138 or 981.

[0020] In another aspect, the present disclosure provides an AAV capsid variant comprising at least 3, 4, 5, or 6 consecutive amino acids from the amino acid sequence of HDSPHK (SEQ ID NO: 2), wherein: (i) the 3 consecutive amino acids comprise HDS; (ii) the 4 consecutive amino acids comprise HDSP (SEQ ID NO: 4702); (iii) the 5 consecutive amino acids comprise HDSPH (SEQ ID NO: 4703); and/or (iv) the 6 consecutive amino acids comprise HDSPHK (SEQ ID NO: 2); wherein the AAV capsid variant comprises: (a) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 138 or SEQ ID NO: 982; (b) a VP2 protein comprising the amino acid sequence of positions 138-736 of SEQ ID NO: 138 or positions 138-742 of SEQ ID NO: 982; (c) a VP3 protein comprising the amino acid sequence of positions 203-736 of SEQ ID NO: 138 or positions 203-742 of SEQ ID NO: 982; or (d) an amino acid sequence with at least 90% (e.g., at least about 95, 96, 97, 98, or 99%) sequence identity to any of the amino acid sequences in (a)-(c). In some embodiments, the amino acid sequence is present immediately subsequent to positions 453, numbered according to SEQ ID NO: 138 or 982.

[0021] In another aspect, the present disclosure provides an AAV capsid variant comprising one or two, but no more than three substitutions relative to the amino acid sequence of HDSPHK (SEQ ID NO: 2), wherein the AAV capsid variant comprises: (a) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 138 or SEQ ID NO: 982; (b) a VP2 protein comprising the amino acid sequence of positions 138-736 of SEQ ID NO: 138 or positions 138-742 of SEQ ID NO: 982; (c) a VP3 protein comprising the amino acid sequence of positions 203-736 of SEQ ID NO: 138 or positions 203-742 of SEQ ID NO: 982; or (d) an amino acid sequence with at least 90% (e.g., at least about 95, 96, 97, 98, or 99%) sequence identity to any of the amino acid sequences in (a)-(c).

[0022] In yet another aspect, the present disclosure provides a peptide comprising: (a) the amino acid sequence of any of the sequences provided in Tables 1, 2A, 2B, 13-19; (b) an amino acid sequence comprising at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or 17 consecutive amino acids from any one of the sequences provided in Tables 1, 2A, 2B, 13-19; (c) an amino acid sequence comprising at least one, two, or three, but no more than four different amino acids relative to the amino acid sequence of any one of the sequences provided in Tables 1, 2A, 2B, 13-19; or (d) an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of any one of the sequences provided in Tables 1, 2A, 2B, 13-19.

[0023] In another aspect, the present disclosure provides a peptide comprising (a) the amino acid sequence of any of SEQ ID NOs: 945-980 or 985-986; (b) an amino acid sequence comprising at least 3, 4, or 5 consecutive amino acids from any one of SEQ ID NOs: 945-980 or 985-986; (c) an amino acid sequence comprising at least one, two, or three, but no more than four different amino acids relative to the amino acid sequence of any one of SEQ ID NOs: 945-980 or 985-986; or (d) an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., substitutions), relative to the amino acid sequence of any one of SEQ ID NOs: 945-980 or 985-986.

[0024] In another aspect, the present disclosure provides a peptide comprising: (a) the amino acid sequence of any of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909; (b) an amino acid sequence comprising at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 consecutive amino acids from any one of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909; or (c) an amino acid sequence comprising at least one, two, or three but no more than four different amino acids relative to the amino acid sequence of any one of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909; or (d) an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (conservative substitutions), relative to the amino acid sequence of any one of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909.

[0025] In yet another aspect, the present disclosure provides a peptide comprising: (i) the amino acid sequence of SPHKA (SEQ ID NO: 941); (ii) an amino acid sequence comprising at least one,

two, or three, but no more than four different amino acids relative to the amino acid sequence of SPHKA (SEQ ID NO: 941); (iii) an amino acid sequence comprising at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of SPHKA (SEQ ID NO: 941); or (iv) at least 3, 4, or 5 consecutive amino acids from the amino acid sequence of SPHKA (SEQ ID NO: 941).

[0026] In yet another aspect, the present disclosure provides a peptide encoded by (i) the nucleotide sequence of SEQ ID NO: 942, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or (ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 942; or (iii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequence of SEQ ID NO: 942.

[0027] In yet another aspect, the present disclosure provides a peptide, wherein the nucleotide sequence encoding the peptide comprises (i) the nucleotide sequence of SEQ ID NO: 942, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; (ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but not more than 10 different nucleotides, relative to the nucleotide sequence of SEQ ID NO: 942; or (iii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequence of SEQ ID NO: 942.

[0028] In another aspect, the present disclosure provides a peptide comprising: (i) the amino acid sequence of HDSPHK (SEQ ID NO: 2); (ii) an amino acid sequence comprising at least one, two, or three, but no more than four different amino acids, relative to the amino acid sequence of HDSPHK (SEQ ID NO: 2); (iii) an amino acid sequence comprising at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of HDSPHK (SEQ ID NO: 2); or (iv) at least 3, 4, or 5 consecutive amino acids from the amino acid sequence of HDSPHK (SEQ ID NO: 2).

[0029] In yet another aspect, the present disclosure provides a peptide encoded by (i) the nucleotide sequence of SEQ ID NO: 3, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; (ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten different nucleotides, relative to the nucleotide sequence of SEQ ID NO: 3; (iii) a nucleotide sequence

comprising at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequence of SEQ ID NO: 3.

[0030] In another aspect, the present disclosure provides a peptide wherein the nucleotide sequence encoding the peptide comprises: (i) the nucleotide sequence of SEQ ID NO: 3, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; (ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 3; or (iii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequence of SEQ ID NO: 3.

[0031] In yet another aspect, the present disclosure provides a polynucleotide encoding an AAV capsid variant comprising: (a) the amino acid sequence of any of the sequences provided in Tables 1, 2A, 2B, 13-19; (b) an amino acid sequence comprising at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or 17 consecutive amino acids from any one of the sequences provided in Tables 1, 2A, 2B, 13-19; (c) an amino acid sequence comprising at least one, two, or three but no more than four different amino acids, relative to the amino acid sequence of any one of the sequences provided in Tables 1, 2A, 2B, 13-19; or (d) an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (conservative substitutions), relative to the amino acid sequence of any one of the sequences provided in Tables 1, 2A, 2B, 13-19. In some embodiments, the amino acid sequence of (a), (b), (c), and/or (d) is present immediately subsequent to position 448, 449, 450, 451, 452, 453, 454, or 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

[0032] In yet another aspect, the present disclosure provides a polynucleotide encoding an AAV capsid variant, wherein the AAV capsid variant comprises: (i) the amino acid sequence of SPHKA (SEQ ID NO: 941); (ii) an amino acid sequence comprising at least one, two, or three, but no more than four different amino acids, relative to the amino acid sequence of SPHKA (SEQ ID NO: 941); (iii) an amino acid sequence comprising at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of SPHKA (SEQ ID NO: 941); or (iv) at least 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of SPHKA (SEQ ID NO: 941). In some embodiments, the amino acid sequence of (i), (ii), (iii), and/or (iv) is present immediately subsequent to position 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

[0033] In another aspect, the present disclosure provides a polynucleotide encoding an AAV capsid variant, wherein the AAV capsid variant comprises: (i) the amino acid sequence of HDSPHK (SEQ ID NO: 2); (ii) an amino acid sequence comprising at least one, two, or three, but no more than four different amino acids, relative to the amino acid sequence of HDSPHK (SEQ ID NO: 2); (iii) an amino acid sequence comprising at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of HDSPHK (SEQ ID NO: 2); or (iv) at least 3, 4, 5, or 6 consecutive amino acids from the amino acid sequence of HDSPHK (SEQ ID NO: 2). In some embodiments, the amino acid sequence of (i), (ii), (iii), and/or (iv) is present immediately subsequent to position 453, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

[0034] In yet another aspect, the present disclosure provides an AAV capsid variant comprising the amino acid sequence of SPH, wherein the amino acid sequence is present immediately subsequent to position 455, numbered according to the amino acid sequence of any one of SEQ ID NOs: 36-59, 138, 981, or 982.

[0035] In yet another aspect, the present disclosure provides an AAV capsid variant comprising the amino acid sequence of SPHKA (SEQ ID NO: 941), wherein the amino acid sequence is present immediately subsequent to position 455, numbered according to the amino acid sequence of SEQ ID NO: 138.

[0036] In yet another aspect, the present disclosure provides an AAV capsid variant comprising the amino acid sequence of SPHKA (SEQ ID NO: 941), wherein the amino acid sequence is present immediately subsequent to position 455, numbered according to the amino acid sequence of SEQ ID NO: 981.

[0037] In yet another aspect, the present disclosure provides an AAV capsid variant comprising the amino acid sequence of HDSPHK (SEQ ID NO: 2), wherein the amino acid sequence is present immediately subsequent to position 453, numbered according to the amino acid sequence of SEQ ID NO: 138.

[0038] In yet another aspect, the present disclosure provides an AAV capsid variant comprising the amino acid sequence of HDSPHK (SEQ ID NO: 2), wherein the amino acid sequence is present immediately subsequent to position 453, numbered according to the amino acid sequence of SEQ ID NO: 982.

[0039] In yet another aspect, the present disclosure provides an AAV capsid variant comprising the amino acid sequence of SPHKA (SEQ ID NO: 941), wherein the amino acid sequence is present in loop IV, relative to a reference sequence of SEQ ID NO: 138. In some embodiments, loop IV comprises positions 449-460, numbered according to SEQ ID NO: 138.

[0040] In yet another aspect, the present disclosure provides an AAV capsid variant comprising the amino acid sequence of HDSPHK (SEQ ID NO: 2), wherein the amino acid sequence is present in loop IV, relative to a reference sequence of SEQ ID NO: 138. In some embodiments, loop IV comprises positions 449-460, numbered according to SEQ ID NO: 138.

[0041] In yet another aspect, the present disclosure provides an AAV particle comprising an AAV capsid variant, described herein. In some embodiments, the AAV particle comprises a nucleic acid sequence encoding a payload. In some embodiments, the AAV particle further comprises a viral genome comprising a promoter operably linked to the nucleic acid encoding the payload.

[0042] In yet another aspect, the present disclosure provides a method of making an AAV particle comprising an AAV capsid variant described herein. The method comprises providing a host cell comprising a viral genome and incubating the host cell under conditions suitable to enclose the viral genome in the AAV capsid variant, e.g., an AAV capsid variant described herein, thereby making the AAV particle.

[0043] In yet another aspect, the present disclosure provides a method of delivering a payload to a cell or tissue (e.g., a CNS cell, a CNS tissue, a liver cell, or a liver tissue). The method comprising administering an effective amount of an AAV particle comprising an AAV capsid variant described herein.

[0044] In yet another aspect, the present disclosure provides a method of treating a subject having or diagnosed with having a genetic disorder, e.g., a monogenic disorder or a polygenic disorder. The method comprising administering to the subject an effective amount an AAV particle comprising an AAV capsid variant described herein.

[0045] In yet another aspect, the present disclosure provides a method of treating a subject having or diagnosed with having neurological, e.g., a neurodegenerative, disorder. The method comprising administering an effective amount of an AAV particle comprising an AAV capsid variant described herein.

[0046] In yet another aspect, the present disclosure provides a method of treating a subject having or diagnosed with having a neuro-oncological disorder. The method comprising administering an effective amount of an AAV particle comprising an AAV capsid variant described herein.

[0047] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following enumerated embodiments.

Enumerated Embodiments

1. An AAV capsid variant, comprising an amino acid sequence having the following formula: [N1]-[N2]-[N3], wherein:

- (i) optionally [N1] comprises X1, X2, and X3, wherein at least one of X1, X2, or X3 is G;
- (ii) [N2] comprises the amino acid sequence of SPH;

(ii) [N3] comprises X4, X5, and X6, wherein at least one of X4, X5, or X6 is a basic amino acid, e.g., a K or R.

2. The AAV capsid variant of embodiment 1, wherein X4, X5, or both of [N3] is a K.

3. The AAV capsid variant of embodiment 1 or 2, wherein X4, X5, or X6 of [N3] is an R.

4. The AAV capsid variant of any one of embodiments 1-3, wherein:

(a) position X4 of [N3] is: K, S, A, V, T, G, F, W, V, N, or R;

(b) position X5 of [N3] is: S, K, T, F, I, L, Y, H, M, or R; and/or

(c) position X6 of [N3] is: G, A, R, M, I, N, T, Y, D, P, V, L, E, W, N, Q, K, or S;

optionally wherein the AAV capsid variant comprises an amino acid modification, e.g., a conservative substitution, of any of the aforesaid amino acids in (a)-(c).

5. The AAV capsid variant of any one of embodiments 1-4, wherein [N3] comprises SK, KA, KS, AR, RM, VK, AS, SR, VK, KR, KK, KN, VR, RS, RK, KT, TS, KF, FG, KI, IG, KL, LG, TT, TY, KY, YG, KD, KP, TR, RG, VR, GA, SL, SS, FL, WK, SA, RA, LR, KW, RR, GK, TK, NK, AK, KV, KG, KH, KM, TG, SE, SV, SW, SN, HG, SQ, LW, MG, MA, or SG.

6. The AAV capsid variant of any one of embodiments 1-5, wherein [N3] is or comprises SKA, KSG, ARM, VKS, ASR, VKI, KKN, VRM, RKA, KTS, KFG, KIG, KLG, KTT, KTY, KYG, SKD, SKP, TRG, VRG, KRG, GAR, KSA, KSR, SKL, SRA, SKR, SLR, SRG, SSR, FLR, SKW, SKS, WKA, VRR, SKV, SKT, SKG, GKA, TKA, NKA, SKL, SKN, AKA, KTG, KSL, KSE, KSV, KSW, KSN, KHG, KSQ, KSK, KLW, WKG, KMG, KMA, or RSG.

7. The AAV capsid variant of any one of embodiments 1-6, wherein [N2]-[N3] comprises SPHSK (SEQ ID NO: 4701), SPHKS (SEQ ID NO: 4704), SPHAR (SEQ ID NO: 4705), SPHVK (SEQ ID NO: 4706), SPHAS (SEQ ID NO: 4707), SPHKK (SEQ ID NO: 4708), SPHVR (SEQ ID NO: 4709), SPHRK (SEQ ID NO: 4710), SPHKT (SEQ ID NO: 4711), SPHKF (SEQ ID NO: 4712), SPHKI (SEQ ID NO: 4713), SPHKL (SEQ ID NO: 4714), SPHKY (SEQ ID NO: 4715), SPHTR (SEQ ID NO: 4716), SPHKR (SEQ ID NO: 4717), SPHGA (SEQ ID NO: 4718), SPHSR (SEQ ID NO: 4719), SPHSL (SEQ ID NO: 4720), SPHSS (SEQ ID NO: 4721), SPHFL (SEQ ID NO: 4722), SPHWK (SEQ ID NO: 4723), SPHGK (SEQ ID NO: 4724), SPHTK (SEQ ID NO: 4725), SPHNK (SEQ ID NO: 4726), SPHAK (SEQ ID NO: 4727), SPHKH (SEQ ID NO: 4728), SPHKM (SEQ ID NO: 4729), or SPHRS (SEQ ID NO: 4730).

8. The AAV capsid variant of any one of embodiments 1-7, wherein [N2]-[N3] is or comprises:

(i) SPHKA (SEQ ID NO: 941), SPHSG (SEQ ID NO: 946), SPHARM (SEQ ID NO: 947), SPHVKS (SEQ ID NO: 948), SPHASR (SEQ ID NO: 949), SPHVKI (SEQ ID NO: 950), SPHKKN (SEQ ID NO: 954), SPHVRM (SEQ ID NO: 955), SPHRKA (SEQ ID NO: 956), SPHKFG (SEQ ID NO: 957), SPHKIG (SEQ ID NO: 958), SPHKLG (SEQ ID NO: 959), SPHKTS (SEQ ID NO: 963), SPHKTT (SEQ ID NO: 964), SPHKTY (SEQ ID NO: 965), SPHKYG (SEQ ID NO: 966), SPHSD (SEQ ID NO: 967), SPHSP (SEQ ID NO: 968), SPHTRG (SEQ ID NO: 972), SPHVRG (SEQ ID NO: 973), SPHGRG (SEQ ID NO: 974), SPHGAR (SEQ ID NO: 975), SPHKA (SEQ ID NO: 977), SPHKS (SEQ ID NO: 951), SPHSL (SEQ ID NO: 960), SPHSRA (SEQ ID NO: 969), SPHKS (SEQ ID NO: 978), SPHSLR (SEQ ID NO: 952), SPHSRG (SEQ ID NO: 961), SPHSSR (SEQ ID NO: 970), SPHFLR (SEQ ID NO: 979), SPHKS (SEQ ID NO: 953), SPHKS (SEQ ID NO: 962), SPHWKA (SEQ ID NO: 971), SPHVRR (SEQ ID NO: 980), SPHKT (SEQ ID NO: 4731), SPHSG (SEQ ID NO: 4732), SPHGKA (SEQ ID NO: 4733), SPHNKA (SEQ ID NO: 4734), SPHKN (SEQ ID NO: 4735), SPHKA (SEQ ID NO: 4736), SPHKS (SEQ ID NO: 4737), SPHKTG (SEQ ID NO: 4738), SPHTKA (SEQ ID NO: 4739), SPHKS (SEQ ID NO: 4740), SPHKS (SEQ ID NO: 4741), SPHKS (SEQ ID NO: 4742), SPHKS (SEQ ID NO: 4743), SPHKS (SEQ ID NO: 4744), SPHKS (SEQ ID NO: 4745), SPHKS (SEQ ID NO: 4746), SPHKS (SEQ ID NO: 4747), SPHKLW (SEQ ID NO: 4748), SPHWKG (SEQ ID NO: 4749), SPHKMG (SEQ ID NO: 4750), SPHKMA (SEQ ID NO: 4751), or SPHRSG (SEQ ID NO: 976);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, or 5 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

9. The AAV capsid variant of any one of embodiments 1-8, which comprises an amino acid other than G at position 453 (e.g., V, R, D, E, M, T, I, S, A, N, L, K, H, P, W, or C), an amino acid other than S at position 454 (V, L, N, D, H, R, P, G, T, I, A, E, Y, M, or Q), and/or a G at position 455 (e.g., C, L, D, E, Y, H, V, A, N, P, or S), numbered according to any one of SEQ ID NOs: 36-59, 138, 981, 982.

10. The AAV capsid variant of any one of embodiments 1-8, which comprises the amino acid G at position 453, the amino acid S at position 454, and the amino acid G at position 455, numbered according to SEQ ID NO: 138 or 981.

11. The AAV capsid variant of any one of embodiments 1-9, which comprises the amino acid G at position 453, the amino acid H at position 454, and the amino acid D at position 455, numbered according to SEQ ID NO: 138 or 982.
12. The AAV capsid variant of any one of embodiments 1-11, wherein [N1] comprises X1, X2, and X3, wherein at least one of X1, X2, or X3 is G.
13. The AAV capsid variant of any one of embodiments 1-12, wherein:
- (a) position X1 of [N1] is: G, V, R, D, E, M, T, I, S, A, N, L, K, H, P, W, or C;
 - (b) position X2 of [N1] is: S, V, L, N, D, H, R, P, G, T, I, A, E, Y, M, or Q; and/or
 - (c) position X3 of [N1] is: G, C, L, D, E, Y, H, V, A, N, P, or S;
- optionally wherein the AAV capsid variant comprises an amino acid modification, e.g., a conservative substitution, of any of the aforesaid amino acids in (a)-(c).
14. The AAV capsid variant of any one of embodiments 1-13, wherein [N1] comprises GS, SG, GH, HD, GQ, QD, VS, CS, GR, RG, QS, SH, MS, RN, TS, IS, GP, ES, SS, GN, AS, NS, LS, GG, KS, GT, PS, RS, GI, WS, DS, ID, GL, DA, DG, ME, EN, KN, KE, AI, NG, PG, TG, SV, IG, LG, AG, EG, SA, YD, HE, HG, RD, ND, PD, MG, QV, DD, HN, HP, GY, GM, GD, or HS.
15. The AAV capsid variant of any one of embodiments 1-14, wherein [N1] is or comprises GSG, GHD, GQD, VSG, CSG, GRG, CSH, GQS, GSH, RVG, GSC, GLL, GDD, GHE, GNY, MSG, RNG, TSG, ISG, GPG, ESG, SSG, GNG, ASG, NSG, LSG, GGG, KSG, HSG, GTG, PSG, GSV, RSG, GIG, WSG, DSG, IDG, GLG, DAG, DGG, MEG, ENG, GSA, KNG, KEG, AIG, GYD, GHG, GRD, GND, GPD, GMG, GQV, GHN, GHP, or GHS.
16. The AAV capsid variant of any one of embodiments 1-15, wherein [N1]-[N2] comprises:
- (i) SGSPH (SEQ ID NO: 4752), HDSPH (SEQ ID NO: 4703), QDSPH (SEQ ID NO: 4753), RGSPH (SEQ ID NO: 4754), SHSPH (SEQ ID NO: 4755), QSSPH (SEQ ID NO: 4756), DDSPH (SEQ ID NO: 4757), HESPH (SEQ ID NO: 4758), NYSPH (SEQ ID NO: 4759), VGSPH (SEQ ID NO: 4760), SCSPH (SEQ ID NO: 4761), LLSPH (SEQ ID NO: 4762), NGSPH (SEQ ID NO: 4763), PGSPH (SEQ ID NO: 4764), GGSPH (SEQ ID NO: 4765), TGSPH (SEQ ID NO: 4766), SVSPH (SEQ ID NO: 4767), IGSPH (SEQ ID NO: 4768), DGSPH (SEQ ID NO: 4769), LGSPH (SEQ ID NO: 4770), AGSPH (SEQ ID NO: 4771), EGSPH (SEQ ID NO: 4772), SASPH (SEQ ID NO: 4773), YDSPH (SEQ ID NO: 4774), HGSPH (SEQ ID NO: 4775), RDSPH (SEQ ID NO: 4776), NDSPH (SEQ ID NO: 4777), PDSPH (SEQ ID NO: 4778), MGSPH (SEQ ID NO: 4779), QVSPH (SEQ ID NO: 4780), HNSPH (SEQ ID NO: 4781), HPSPH (SEQ ID NO: 4782), or HSSPH (SEQ ID NO: 4783);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, or 4 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

17. The AAV capsid variant of any one of embodiments 1-16, wherein [N1]-[N2] is or comprises:

(i) GSGSPH (SEQ ID NO: 4695), GHDSPH (SEQ ID NO: 4784), GQDSPH (SEQ ID NO: 4785), VSGSPH (SEQ ID NO: 4786), CSGSPH (SEQ ID NO: 4787), GRGSPH (SEQ ID NO: 4788), CSHSPH (SEQ ID NO: 4789), GQSSPH (SEQ ID NO: 4790), GSHSPH (SEQ ID NO: 4791), GDDSPH (SEQ ID NO: 4792), GHESPH (SEQ ID NO: 4793), GNYSPH (SEQ ID NO: 4794), RVGSPH (SEQ ID NO: 4795), GSCSPH (SEQ ID NO: 4796), GLLSPH (SEQ ID NO: 4797), MSGSPH (SEQ ID NO: 4798), RNGSPH (SEQ ID NO: 4799), TSGSPH (SEQ ID NO: 4800), ISGSPH (SEQ ID NO: 4801), GPGSPH (SEQ ID NO: 4802), ESGSPH (SEQ ID NO: 4803), SSGSPH (SEQ ID NO: 4804), GNGSPH (SEQ ID NO: 4805), ASGSPH (SEQ ID NO: 4806), NSGSPH (SEQ ID NO: 4807), LSGSPH (SEQ ID NO: 4808), GGGSPH (SEQ ID NO: 4809), KSGSPH (SEQ ID NO: 4810), HSGSPH (SEQ ID NO: 4811), GTGSPH (SEQ ID NO: 4812), PSGSPH (SEQ ID NO: 4813), GSVSPH (SEQ ID NO: 4814), RSGSPH (SEQ ID NO: 4815), GIGSPH (SEQ ID NO: 4816), WSGSPH (SEQ ID NO: 4817), DSGSPH (SEQ ID NO: 4818), IDGSPH (SEQ ID NO: 4819), GLGSPH (SEQ ID NO: 4820), DAGSPH (SEQ ID NO: 4821), DGGSPH (SEQ ID NO: 4822), MEGSPH (SEQ ID NO: 4823), ENGSPH (SEQ ID NO: 4824), GSASPH (SEQ ID NO: 4825), KNGSPH (SEQ ID NO: 4826), KEGSPH (SEQ ID NO: 4827), AIGSPH (SEQ ID NO: 4828), GYDSPH (SEQ ID NO: 4829), GHGSPH (SEQ ID NO: 4830), GRDSPH (SEQ ID NO: 4831), GNDSPH (SEQ ID NO: 4832), GPDSPH (SEQ ID NO: 4833), GMGSPH (SEQ ID NO: 4834), GQVSPH (SEQ ID NO: 4835), GHNSPH (SEQ ID NO: 4836), GHPSPH (SEQ ID NO: 4837), or GHSSPH (SEQ ID NO: 4838);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, or 5 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

18. The AAV capsid variant of any one of embodiments 1-17, wherein [N1]-[N2]-[N3] comprises:

(i) SGSPHSK (SEQ ID NO: 4839), HDSPHSK (SEQ ID NO: 4840), SGSPHAR (SEQ ID NO: 4841), SGSPHVK (SEQ ID NO: 4842), QDSPHSK (SEQ ID NO: 4843), SGSPHKK (SEQ ID NO: 4844), SGSPHVR (SEQ ID NO: 4845), SGSPHAS (SEQ ID NO: 4846), SGSPHRK (SEQ ID NO: 4847), SGSPHKT (SEQ ID NO: 4848), SHSPHSK (SEQ ID NO: 4849), QSSPHRS (SEQ ID NO: 4850), RGSPHAS (SEQ ID NO: 4851), RGSPHSK (SEQ ID NO: 4852), SGSPHKF (SEQ ID NO: 4853), SGSPHKI (SEQ ID NO: 4854), SGSPHKL (SEQ ID NO: 4855), SGSPHKY (SEQ ID NO: 4856), SGSPHTR (SEQ ID NO: 4857), SHSPHKR (SEQ ID NO: 4858), SGSPHGA (SEQ ID NO: 4859), HDSPHKR (SEQ ID NO: 4860), DDSPHKS (SEQ ID NO: 4861), HESPHKS (SEQ ID NO: 4862), NYSPHKI (SEQ ID NO: 4863), SGSPHSR (SEQ ID NO: 4864), SGSPHSL (SEQ ID NO: 4865), SGSPHSS (SEQ ID NO: 4866), VGSPHSK (SEQ ID NO: 4867), SCSPHRK (SEQ ID NO: 4868), SGSPHFL (SEQ ID NO: 4869), LLSPHWK (SEQ ID NO: 4870), NGSPHSK (SEQ ID NO: 4871), PGSPHSK (SEQ ID NO: 4872), GGSPHSK (SEQ ID NO: 4873), TGSPHSK (SEQ ID NO: 4874), SVSPHGK (SEQ ID NO: 4875), SGSPHTK (SEQ ID NO: 4876), IGSPHSK (SEQ ID NO: 4877), DGSPHSK (SEQ ID NO: 4878), SGSPHNK (SEQ ID NO: 4879), LGSPHSK (SEQ ID NO: 4880), AGSPHSK (SEQ ID NO: 4881), EGSPHSK (SEQ ID NO: 4882), SASPHSK (SEQ ID NO: 4883), SGSPHAK (SEQ ID NO: 4884), HDSPHKI (SEQ ID NO: 4885), YDSPHSK (SEQ ID NO: 4886), HDSPHKT (SEQ ID NO: 4887), RGSPHKR (SEQ ID NO: 4888), HGSPHSK (SEQ ID NO: 4889), RDSPHSK (SEQ ID NO: 4890), NDSPHSK (SEQ ID NO: 4891), QDSPHKI (SEQ ID NO: 4892), PDSPHKI (SEQ ID NO: 4893), PDSPHSK (SEQ ID NO: 4894), MGSPHSK (SEQ ID NO: 4895), HDSPHKH (SEQ ID NO: 4896), QVSPHSK (SEQ ID NO: 4897), HNSPHKS (SEQ ID NO: 4898), NGSPHKR (SEQ ID NO: 4899), HDSPHKY (SEQ ID NO: 4900), NDSPHKI (SEQ ID NO: 4901), HDSPHKL (SEQ ID NO: 4902), HPSPHWK (SEQ ID NO: 4903), HDSPHKM (SEQ ID NO: 4904), or HSSPHRS (SEQ ID NO: 4905);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, 5, or 6 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

19. The AAV capsid variant of any one of embodiments 1-18, wherein [N1]-[N2]-[N3] is or comprises:

(i) GSGSPHASKA (SEQ ID NO: 4697), GHDSPHKSG (SEQ ID NO: 4698), GSGSPHARM (SEQ ID NO: 4906), GSGSPHVKS (SEQ ID NO: 4907), GQDSPHKSG (SEQ ID NO: 4908), GSGSPHASR (SEQ ID NO: 4909), GSGSPHVKI (SEQ ID NO: 4910), GSGSPHKKN (SEQ ID NO: 4911), GSGSPHVRM (SEQ ID NO: 4912), VSGSPHASKA (SEQ ID NO: 4913), CSGSPHASKA (SEQ

ID NO: 4914), GSGSPHRKA (SEQ ID NO: 4915), CSGSPHKTS (SEQ ID NO: 4916), CSHSPHKS (SEQ ID NO: 4917), GQSSPHRSG (SEQ ID NO: 4918), GRGSPHASR (SEQ ID NO: 4919), GRGSPHKA (SEQ ID NO: 4920), GSGSPHKFG (SEQ ID NO: 4921), GSGSPHKIG (SEQ ID NO: 4922), GSGSPHKL (SEQ ID NO: 4923), GSGSPHKTS (SEQ ID NO: 4924), GSGSPHKTT (SEQ ID NO: 4925), GSGSPHKTY (SEQ ID NO: 4926), GSGSPHKYG (SEQ ID NO: 4927), GSGSPHSD (SEQ ID NO: 4928), GSGSPHSPK (SEQ ID NO: 4929), GSGSPHTRG (SEQ ID NO: 4930), GSGSPHVRG (SEQ ID NO: 4931), GSHSPHKRG (SEQ ID NO: 4932), GSHSPHKS (SEQ ID NO: 4933), VSGSPHASR (SEQ ID NO: 4934), VSGSPHGR (SEQ ID NO: 4935), VSGSPHKFG (SEQ ID NO: 4936), GHDSPHKRG (SEQ ID NO: 4937), GDDSPHKS (SEQ ID NO: 4938), GHESPHKSA (SEQ ID NO: 4939), GHDSPHKSA (SEQ ID NO: 4940), GNYSPHKIG (SEQ ID NO: 4941), GHDSPHKSR (SEQ ID NO: 4942), GSGSPHSL (SEQ ID NO: 4943), GSGSPHSRA (SEQ ID NO: 4944), GSGSPHSPK (SEQ ID NO: 4945), GSGSPHSLR (SEQ ID NO: 4946), GSGSPHSRG (SEQ ID NO: 4947), GSGSPHSSR (SEQ ID NO: 4948), RVGSPHKA (SEQ ID NO: 4949), GSCSPHRKA (SEQ ID NO: 4950), GSGSPHFLR (SEQ ID NO: 4951), GSGSPHSPK (SEQ ID NO: 4952), GSGSPHSPKS (SEQ ID NO: 4953), GLLSPHWKA (SEQ ID NO: 4954), GSGSPHVRR (SEQ ID NO: 4955), GSGSPHSPKV (SEQ ID NO: 4956), MSGSPHKA (SEQ ID NO: 4957), RNGSPHKA (SEQ ID NO: 4958), TSGSPHKA (SEQ ID NO: 4959), ISGSPHKA (SEQ ID NO: 4960), GPGSPHKA (SEQ ID NO: 4961), GSGSPHSPK (SEQ ID NO: 4962), ESGSPHKA (SEQ ID NO: 4963), SSGSPHKA (SEQ ID NO: 4964), GNGSPHKA (SEQ ID NO: 4965), ASGSPHKA (SEQ ID NO: 4966), NSGSPHKA (SEQ ID NO: 4967), LSGSPHKA (SEQ ID NO: 4968), GGGSPHKA (SEQ ID NO: 4969), KSGSPHKA (SEQ ID NO: 4970), GGGSPHSPKS (SEQ ID NO: 4971), GSGSPHSPKG (SEQ ID NO: 4972), HSGSPHKA (SEQ ID NO: 4973), GTGSPHKA (SEQ ID NO: 4974), PSGSPHKA (SEQ ID NO: 4975), GSVSPHGKA (SEQ ID NO: 4976), RSGSPHKA (SEQ ID NO: 4977), GSGSPHTKA (SEQ ID NO: 4978), GIGSPHKA (SEQ ID NO: 4979), WSGSPHKA (SEQ ID NO: 4980), DSGSPHKA (SEQ ID NO: 4981), IDGSPHKA (SEQ ID NO: 4982), GSGSPHNKA (SEQ ID NO: 4983), GLGSPHSPKS (SEQ ID NO: 4984), DAGSPHKA (SEQ ID NO: 4985), DGGSPHKA (SEQ ID NO: 4986), MEGSPHKA (SEQ ID NO: 4987), ENGSPHKA (SEQ ID NO: 4988), GSASPHKA (SEQ ID NO: 4989), GNGSPHSPKS (SEQ ID NO: 4990), KNGSPHKA (SEQ ID NO: 4991), KEGSPHKA (SEQ ID NO: 4992), AIGSPHKA (SEQ ID NO: 4993), GSGSPHSPKN (SEQ ID NO: 4994), GSGSPHAKA (SEQ ID NO: 4995), GHDSPHKIG (SEQ ID NO: 4996), GYDSPHKS (SEQ ID NO: 4997), GHESPHKS (SEQ ID NO: 4998), GHDSPHKGT (SEQ ID NO: 4999), GRGSPHSPKRG (SEQ ID NO: 5000), GQDSPHKS (SEQ ID NO: 4908), GHDSPHKSL (SEQ ID NO: 5001), GHGSPHKA (SEQ ID NO: 5002), GHDSPHKSE (SEQ ID NO: 5003), VSGSPHKA (SEQ ID NO: 4913), GRDSPHKS (SEQ ID NO: 5004), GNDSPHSPKV (SEQ ID NO: 5005), GQDSPHSPKIG (SEQ ID NO: 5006), GHDSPHSPKV (SEQ ID NO: 5007), GPDSPHSPKIG (SEQ ID NO: 5008), GPDSPHSPKS (SEQ ID NO: 5009), GHDSPHSPKSW (SEQ ID NO: 5010),

GHDSPHKS_N (SEQ ID NO: 5011), GMGSPHKS_T (SEQ ID NO: 5012), GHDSPHKS_{HG} (SEQ ID NO: 5013), GQVSPHKS_G (SEQ ID NO: 5014), GDDSPHKS_V (SEQ ID NO: 5015), GHNSPHKS_G (SEQ ID NO: 5016), GNGSPHKS_R (SEQ ID NO: 5017), GHDSPHKS_{YG} (SEQ ID NO: 5018), GHDSPHKS_{SQ} (SEQ ID NO: 5019), GNDSPHKS_{IG} (SEQ ID NO: 5020), GHDSPHKS_{SK} (SEQ ID NO: 5021), GHDSPHKS_{LW} (SEQ ID NO: 5022), GHPSPHKS_{WG} (SEQ ID NO: 5023), GHDSPHKS_{MG} (SEQ ID NO: 5024), GHDSPHKS_{MA} (SEQ ID NO: 5025), or GHSSPHRS_G (SEQ ID NO: 5026);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, 5, 6, 7, or 8 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

20. The AAV capsid variant of any one of embodiments 1-19, wherein [N3] comprises SK, KA, KS, or SG.

21. The AAV capsid variant of any one of embodiments 1-20, wherein [N3] is or comprises SKA, KSG, or KYG.

22. The AAV capsid variant of any one of embodiments 1-21, wherein [N2]-[N3] comprises SPHKS (SEQ ID NO: 4701), SPHKS (SEQ ID NO: 4704), or SPHKY (SEQ ID NO: 4715).

23. The AAV capsid variant of any one of embodiments 1-22, wherein [N2]-[N3] is or comprises SPHKS_A (SEQ ID NO: 941).

24. The AAV capsid variant of any one of embodiments 1-22, wherein [N2]-[N3] is or comprises SPHKS_G (SEQ ID NO: 946).

25. The AAV capsid variant of any one of embodiments 1-22, wherein [N2]-[N3] is or comprises SPHKY_G (SEQ ID NO: 966).

26. The AAV capsid variant of any one of embodiments 1-25, wherein [N1] comprises GS, SG, GH, or HD.

27. The AAV capsid variant of any one of embodiments 1-26, wherein [N1] is or comprises GSG.

28. The AAV capsid variant of any one of embodiments 1-26, wherein [N1] is or comprises GHD.
29. The AAV capsid variant of any one of embodiments 1-23 or 26-27, wherein [N1]-[N2]-[N3] comprises SGSPHSK (SEQ ID NO: 4839).
30. The AAV capsid variant of any one of embodiments 1-22, 24, 26, or 28, wherein [N1]-[N2]-[N3] comprises HDSPHSK (SEQ ID NO: 4840).
31. The AAV capsid variant of any one of embodiments 1-22 or 25-27, wherein [N1]-[N2]-[N3] comprises SGSPHKEYG (SEQ ID NO: 5027).
32. The AAV capsid variant of any one of embodiments 1-8, 10, 12-23, 26-27, or 29, wherein [N1]-[N2]-[N3] is or comprises GSGSPHKA (SEQ ID NO: 4697).
33. The AAV capsid variant of any one of embodiments 1-9, 11-22, 24, 26, 28, or 30, wherein [N1]-[N2]-[N3] is or comprises GHDSPHKSG (SEQ ID NO: 4698).
34. The AAV capsid variant of any one of embodiments 1-8, 10, 12-22, 25-27, or 31, wherein [N1]-[N2]-[N3] is or comprises GSGSPHKEYG (SEQ ID NO: 4927).
35. The AAV capsid variant of any one of embodiments 1-34, wherein [N1]-[N2]-[N3] replaces positions 453-455, numbered according to the amino acid sequence of SEQ ID NO: 138.
36. The AAV capsid variant of any one of embodiments 1-35, which comprises an amino acid other than Q at position 456 (e.g., W, K, R, G, L, V, S, P, H, K, I, M, A, E, or F), an amino acid other than N at position 457 (e.g., Y, C, K, T, H, R, D, V, S, P, G, W, E, F, A, I, M, Q, or L), an amino acid other than Q at position 458 (e.g., G, K, H, R, T, L, D, A, P, I, F, V, M, W, Y, S, E, N, or Y), and/or an amino acid other than Q at position 459 (e.g., H, L, R, W, K, A, P, E, M, I, S, G, N, Y, C, V, T, D, or V), relative to a reference sequence numbered according to SEQ ID NO: 138.
37. The AAV capsid variant of any one of embodiments 1-36, which comprises an amino acid other than Q at position 462 (e.g., W, K, R, G, L, V, S, P, H, K, I, M, A, E, or F), an amino acid other than N at position 463 (e.g., Y, C, K, T, H, R, D, V, S, P, G, W, E, F, A, I, M, Q, or L), an amino acid other than Q at position 464 (e.g., G, K, H, R, T, L, D, A, P, I, F, V, M, W, Y, S, E, N, or Y), and/or an amino acid other than Q at position 465 (e.g., H, L, R, W, K, A, P, E, M, I, S, G, N, Y, C, V, T, D,

or V), relative to a reference sequence numbered according to SEQ ID NO: 981, 982, 36, 37, 39, 40, 42-46, 48, 49, 50, 52, 53, 56, or 57.

38. The AAV capsid variant of any one of embodiments 1-37, which comprises:

(a) the amino acid Q at position 456, the amino acid N at position 457, the amino acid Q at position 458, and/or the amino acid Q at position 459, relative to a reference sequence numbered according to SEQ ID NO: 138; or

(b) the amino acid Q at position 462, the amino acid N at position 463, the amino acid Q at position 464, and/or the amino acid Q at position 465, relative to a reference sequence numbered according to SEQ ID NO: 981, 982, 36, 37, 39, 40, 42-46, 48, 49, 50, 52, 53, 56, or 57.

39. The AAV capsid variant of any one of embodiments 1-38, which further comprises [N4], wherein [N4] comprises X7 X8 X9 X10, and wherein:

(a) position X7 is: Q, W, K, R, G, L, V, S, P, H, K, I, M, A, E, or F;

(b) position X8 is: N, Y, C, K, T, H, R, D, V, S, P, G, W, E, F, A, I, M, Q, or L;

(c) position X9 is: Q, G, K, H, R, T, L, D, A, P, I, F, V, M, W, Y, S, E, N, or Y; and

(d) position X10 is: Q, H, L, R, W, K, A, P, E, M, I, S, G, N, Y, C, V, T, D, or V;

optionally wherein the AAV capsid variant comprises an amino acid modification, e.g., a conservative substitution, of any of the aforesaid amino acids in (a)-(d).

40. The AAV capsid variant of embodiment 39, wherein:

(a) position X7 of [N4] is Q or R;

(b) position X8 of [N4] is N or R;

(c) position X9 of [N4] is Q or R; and

(d) position X10 of [N4] is Q, L, or R.

41. The AAV capsid variant of embodiment 39 or 40, wherein [N4] is or comprises:

(i) QNQQ (SEQ ID NO: 5028), WNQQ (SEQ ID NO: 5029), QYYV (SEQ ID NO: 5030), RRQQ (SEQ ID NO: 5031), GCGQ (SEQ ID NO: 5032), LRQQ (SEQ ID NO: 5033), RNQQ (SEQ ID NO: 5034), VNQQ (SEQ ID NO: 5035), FRLQ (SEQ ID NO: 5036), FNQQ (SEQ ID NO: 5037), LLQQ (SEQ ID NO: 5038), SNQQ (SEQ ID NO: 5039), RLQQ (SEQ ID NO: 5040), LNQQ (SEQ ID NO: 5041), QRKL (SEQ ID NO: 5042), LRRQ (SEQ ID NO: 5043), QRLR (SEQ ID NO: 5044), QRRL (SEQ ID NO: 5045), RRLQ (SEQ ID NO: 5046), RLRQ (SEQ ID NO: 5047), SKRQ (SEQ ID NO: 5048), QLYR (SEQ ID NO: 5049), QLTV (SEQ ID NO: 5050), QNKQ (SEQ ID NO: 5051), KNQQ (SEQ ID NO: 5052), QKQQ (SEQ ID NO: 5053), QTQQ (SEQ ID NO: 5054), QNHQ (SEQ ID NO: 5055), QHQQ (SEQ ID NO: 5056), QNQH (SEQ ID NO: 5057), QHRQ (SEQ ID NO: 5058), LTQQ (SEQ ID NO: 5059), QNQW (SEQ ID NO: 5060), QNTH (SEQ ID NO: 5061), RRRQ (SEQ

ID NO: 5062), QYQQ (SEQ ID NO: 5063), QNDQ (SEQ ID NO: 5064), QNRH (SEQ ID NO: 5065), RDQQ (SEQ ID NO: 5066), PNLQ (SEQ ID NO: 5067), HVRQ (SEQ ID NO: 5068), PNQH (SEQ ID NO: 5069), HNQQ (SEQ ID NO: 5070), QSQQ (SEQ ID NO: 5071), QPAK (SEQ ID NO: 5072), QNLA (SEQ ID NO: 5073), QNQL (SEQ ID NO: 5074), QGQQ (SEQ ID NO: 5075), LNRQ (SEQ ID NO: 5076), QNPP (SEQ ID NO: 5077), QNLQ (SEQ ID NO: 5078), QDQE (SEQ ID NO: 5079), QDQQ (SEQ ID NO: 5080), HWQQ (SEQ ID NO: 5081), PNQQ (SEQ ID NO: 5082), PEQQ (SEQ ID NO: 5083), QRTM (SEQ ID NO: 5084), LHQH (SEQ ID NO: 5085), QHRI (SEQ ID NO: 5086), QYIH (SEQ ID NO: 5087), QKFE (SEQ ID NO: 5088), QFPS (SEQ ID NO: 5089), QNPL (SEQ ID NO: 5090), QAIK (SEQ ID NO: 5091), QNRQ (SEQ ID NO: 5092), QYQH (SEQ ID NO: 5093), QNPQ (SEQ ID NO: 5094), QHQL (SEQ ID NO: 5095), QSPP (SEQ ID NO: 5096), QAKL (SEQ ID NO: 5097), KSQQ (SEQ ID NO: 5098), QDRP (SEQ ID NO: 5099), QNLG (SEQ ID NO: 5100), QAFH (SEQ ID NO: 5101), QNAQ (SEQ ID NO: 5102), HNQL (SEQ ID NO: 5103), QKLN (SEQ ID NO: 5104), QNVQ (SEQ ID NO: 5105), QAQQ (SEQ ID NO: 5106), QTPP (SEQ ID NO: 5107), QPPA (SEQ ID NO: 5108), QERP (SEQ ID NO: 5109), QDLQ (SEQ ID NO: 5110), QAMH (SEQ ID NO: 5111), QHPS (SEQ ID NO: 5112), PGLQ (SEQ ID NO: 5113), QGIR (SEQ ID NO: 5114), QAPA (SEQ ID NO: 5115), QIPP (SEQ ID NO: 5116), QTQL (SEQ ID NO: 5117), QAPS (SEQ ID NO: 5118), QNTY (SEQ ID NO: 5119), QDKQ (SEQ ID NO: 5120), QNHL (SEQ ID NO: 5121), QIGM (SEQ ID NO: 5122), LNKQ (SEQ ID NO: 5123), PNQL (SEQ ID NO: 5124), QLQQ (SEQ ID NO: 5125), QRMS (SEQ ID NO: 5126), QGIL (SEQ ID NO: 5127), QDRQ (SEQ ID NO: 5128), RDWQ (SEQ ID NO: 5129), QERS (SEQ ID NO: 5130), QNYQ (SEQ ID NO: 5131), QRTC (SEQ ID NO: 5132), QIGH (SEQ ID NO: 5133), QGAI (SEQ ID NO: 5134), QVPP (SEQ ID NO: 5135), QVQQ (SEQ ID NO: 5136), LMRQ (SEQ ID NO: 5137), QYSV (SEQ ID NO: 5138), QAIT (SEQ ID NO: 5139), QKTL (SEQ ID NO: 5140), QLHH (SEQ ID NO: 5141), QNII (SEQ ID NO: 5142), QGGH (SEQ ID NO: 5143), QSKV (SEQ ID NO: 5144), QLPS (SEQ ID NO: 5145), IGKQ (SEQ ID NO: 5146), QAIH (SEQ ID NO: 5147), QHGL (SEQ ID NO: 5148), QFMC (SEQ ID NO: 5149), QNQM (SEQ ID NO: 5150), QHLQ (SEQ ID NO: 5151), QPAR (SEQ ID NO: 5152), QSLQ (SEQ ID NO: 5153), QSQL (SEQ ID NO: 5154), HSQQ (SEQ ID NO: 5155), QMPS (SEQ ID NO: 5156), QGSL (SEQ ID NO: 5157), QVPA (SEQ ID NO: 5158), HYQQ (SEQ ID NO: 5159), QVPS (SEQ ID NO: 5160), RGEQ (SEQ ID NO: 5161), PGQQ (SEQ ID NO: 5162), LEQQ (SEQ ID NO: 5163), QNQS (SEQ ID NO: 5164), QKVI (SEQ ID NO: 5165), QNND (SEQ ID NO: 5166), QSVH (SEQ ID NO: 5167), QPLG (SEQ ID NO: 5168), HNQE (SEQ ID NO: 5169), QIQQ (SEQ ID NO: 5170), QVRN (SEQ ID NO: 5171), PSNQ (SEQ ID NO: 5172), QVGH (SEQ ID NO: 5173), QRDI (SEQ ID NO: 5174), QMPN (SEQ ID NO: 5175), RGLQ (SEQ ID NO: 5176), PSLQ (SEQ ID NO: 5177), QRDQ (SEQ ID NO: 5178), QAKG (SEQ ID NO: 5179), QSAH (SEQ ID NO: 5180), QSTM (SEQ ID NO: 5181), QREM (SEQ ID NO: 5182), QYRA (SEQ ID NO: 5183), QRQQ (SEQ ID NO: 5184), QWQQ (SEQ ID NO: 5185), QRMN (SEQ ID NO: 5186), GDSQ (SEQ ID NO: 5187), QKIS (SEQ ID NO: 5188), PSMQ (SEQ ID NO: 5189), SPRQ (SEQ ID NO: 5190), MEQQ (SEQ ID NO: 5191),

QYQN (SEQ ID NO: 5192), QIRQ (SEQ ID NO: 5193), QSVQ (SEQ ID NO: 5194), RSQQ (SEQ ID NO: 5195), QNKL (SEQ ID NO: 5196), QIQH (SEQ ID NO: 5197), PRQQ (SEQ ID NO: 5198), HTQQ (SEQ ID NO: 5199), QRQH (SEQ ID NO: 5200), RNQE (SEQ ID NO: 5201), QSKQ (SEQ ID NO: 5202), QNQP (SEQ ID NO: 5203), QSPQ (SEQ ID NO: 5204), QTRQ (SEQ ID NO: 5205), QNLH (SEQ ID NO: 5206), QNQE (SEQ ID NO: 5207), LNQP (SEQ ID NO: 5208), QNQD (SEQ ID NO: 5209), QNLL (SEQ ID NO: 5210), QLVI (SEQ ID NO: 5211), RTQE (SEQ ID NO: 5212), QTHQ (SEQ ID NO: 5213), QDQH (SEQ ID NO: 5214), QSQH (SEQ ID NO: 5215), VRQQ (SEQ ID NO: 5216), AWQQ (SEQ ID NO: 5217), QSVP (SEQ ID NO: 5218), QNIQ (SEQ ID NO: 5219), LDQQ (SEQ ID NO: 5220), PDQQ (SEQ ID NO: 5221), ESQQ (SEQ ID NO: 5222), QRQL (SEQ ID NO: 5223), QIIV (SEQ ID NO: 5224), QKQS (SEQ ID NO: 5225), QSHQ (SEQ ID NO: 5226), QFVV (SEQ ID NO: 5227), QSQP (SEQ ID NO: 5228), QNEQ (SEQ ID NO: 5229), INQQ (SEQ ID NO: 5230), RNRQ (SEQ ID NO: 5231), RDQK (SEQ ID NO: 5232), QWKR (SEQ ID NO: 5233), ENRQ (SEQ ID NO: 5234), QTQP (SEQ ID NO: 5235), QKQL (SEQ ID NO: 5236), RNQL (SEQ ID NO: 5237), ISIQ (SEQ ID NO: 5238), QTVC (SEQ ID NO: 5239), QQIM (SEQ ID NO: 5240), LNHQ (SEQ ID NO: 5241), QNQA (SEQ ID NO: 5242), QMIH (SEQ ID NO: 5243), RNHQ (SEQ ID NO: 5244), or QKMN (SEQ ID NO: 5245);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, or 3 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

42. The AAV capsid variant of any one of embodiments 39-41, wherein [N1]-[N2]-[N3]-[N4] is or comprises:

(i) the amino acid sequence of any of SEQ ID NOs: 1800-2241;

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

43. The AAV capsid variant of any one of embodiments 39-42, wherein [N1]-[N2]-[N3]-[N4] is or comprises GSGSPHKAQNQQ (SEQ ID NO: 1801).

44. The AAV capsid variant of any one of embodiments 39-42, wherein [N1]-[N2]-[N3]-[N4] is or comprises GHDSPHKSGQNQQ (SEQ ID NO: 1800).

45. The AAV capsid variant of any one of embodiments 39-42, wherein [N1]-[N2]-[N3]-[N4] is or comprises GSGSPHKYGQNQQ (SEQ ID NO: 910).

46. The AAV capsid variant of any one of embodiments 1-45, which comprises an amino acid other than T at position 450 (e.g., S, Y, M, A, C, I, R, L, D, F, V, Q, N, H, E, or G), an amino acid other than I at position 451 (e.g., M, P, E, N, D, S, A, T, G, Q, F, V, L, C, H, R, W, or L), and/or an amino acid other than N at position 452 (e.g., M, E, G, Y, W, T, I, Q, F, V, A, L, I, P, K, R, H, S, D, or S), relative to a reference sequence numbered according to any one of SEQ ID NOs: 36-59, 138, 981, or 982.

47. The AAV capsid variant of any one of embodiments 1-46, which comprises the amino acid T at position 450, the amino acid I at position 451, and/or the amino acid N at position 452, relative to a reference sequence numbered according to any one of SEQ ID NOs: 138, 981, or 982.

48. The AAV capsid variant of any one of embodiments 1-47, which further comprises [N0], wherein [N0] comprises XA XB and XC, and wherein:

(a) position XA is: T, S, Y, M, A, C, I, R, L, D, F, V, Q, N, H, E, or G;

(b) position XB is: I, M, P, E, N, D, S, A, T, G, Q, F, V, L, C, H, R, W, or L; and

(c) position XC is: N, M, E, G, Y, W, T, I, Q, F, V, A, L, I, P, K, R, H, S, D, or S; and

optionally wherein the AAV capsid variant comprises an amino acid modification, e.g., a conservative substitution, of any of the aforesaid amino acids in (a)-(c).

49. The AAV capsid variant of embodiment 48, wherein [N0] is or comprises TIN, SMN, TIM, YLS, GLS, MPE, MEG, MEY, AEW, CEW, ANN, IPE, ADM, IEY, ADY, IET, MEW, CEY, RIN, MEI, LEY, ADW, IEI, DIM, FEQ, MEF, CDQ, LPE, IEN, MES, AEI, VEY, IIN, TSN, IEV, MEM, AEV, MDA, VEW, AEQ, LEW, MEL, MET, MEA, IES, MEV, CEI, ATN, MDG, QEV, ADQ, NMN, IEM, ISN, TGN, QQQ, HDW, IEG, TII, TFP, TEK, EIN, TVN, TFN, SIN, TER, TSY, ELH, AIN, SVN, TDN, TFH, TVH, TEN, TSS, TID, TCN, NIN, TEH, AEM, AIK, TDK, TFK, SDQ, TEI, NTN, TET, SIK, TEL, TEA, TAN, TIY, TFS, TES, TTN, TED, TNN, EVH, TIS, TVR, TDR, TIK, NHI, TIP, ESD, TDL, TVP, TVI, AEH, NCL, TVK, NAD, TIT, NCV, TIR, NAL, VIN, TIQ, TEF, TRE, QGE, SEK, NVN, GGE, EFV, SDK, TEQ, EVQ, TEY, NCW, TDV, SDI, NSI, NSL, EVV, TEP, SEL, TWQ, TEV, AVN, GVL, TLN, TEG, TRD, NAI, AEN, AET, ETA, NNL, or any dipeptide thereof.

50. The AAV capsid variant of embodiment 48 or 49, wherein [N0]-[N1]-[N2]-[N3]-[N4] is or comprises:
- (i) the amino acid sequence of any one of SEQ ID NOs: 2242-2886;
 - (ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 amino acids, e.g., consecutive amino acids, thereof;
 - (iii) an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the amino acid sequences in (i); or
 - (iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).
51. The AAV capsid variant of any one of embodiments 48-50, wherein [N0]-[N1]-[N2]-[N3]-[N4] is or comprises TINGSGSPHKAQNQQ (SEQ ID NO: 2242).
52. The AAV capsid variant of any one of embodiments 48-50, wherein [N0]-[N1]-[N2]-[N3]-[N4] is or comprises TINGHDSPHKSGQNQQ (SEQ ID NO: 2243).
53. The AAV capsid variant of any one of embodiments 48-52, wherein [N0]-[N1]-[N2]-[N3]-[N4] is or comprises TINGSGSPHKGQNQQ (SEQ ID NO: 5246).
54. The AAV capsid variant of any one of embodiments 1-53, wherein [N1]-[N2]-[N3] is present in loop IV.
55. The AAV capsid variant of any one of embodiments 48-54, wherein [N0] and [N4] are present in loop IV.
56. The AAV capsid variant of any one of embodiments 48-55, wherein [N0] is present immediately subsequent to position 449, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.
57. The AAV capsid variant of any one of embodiments 48-56, wherein [N0] is present immediately subsequent to position 449, relative to a reference sequence numbered according to the amino acid sequence of any one of SEQ ID NOs: 36-59, 981, or 982.

58. The AAV capsid variant of any one of embodiments 48-57, wherein [N0] replaces positions 450, 451, and 452 (e.g., T450, I451, and N452), relative to a reference sequence numbered according to SEQ ID NO: 138.
59. The AAV capsid variant of any one of embodiments 48-58, wherein [N0] replaces positions 450-452 (e.g., T450, I451, and N452), relative to a reference sequence numbered according to any one of SEQ ID NOs: 36-59, 981, or 982.
60. The AAV capsid variant of any one of embodiments 48-59, wherein [N0] corresponds to positions 450-452 of any one of SEQ ID NOs: 36-59, 138, 981 or 982.
61. The AAV capsid variant of any one of embodiments 48-60, wherein [N0] is present immediately subsequent to position 449 and wherein [N0] replaces positions 450-452 (e.g., T450, I451, and N452), relative to a reference sequence numbered according to SEQ ID NO: 138.
62. The AAV capsid variant of any one of embodiments 48-61, wherein [N0] is present immediately subsequent to position 449 and wherein [N0] replaces positions 450-452 (e.g., T450, I451, and N452), relative to a reference sequence numbered according to any one of SEQ ID NOs: 36-59, 981, or 982.
63. The AAV capsid variant of any one of embodiments 1-62, wherein [N1] is present immediately subsequent to position 452, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.
64. The AAV capsid variant of any one of embodiments 1-63, wherein [N1] is present immediately subsequent to position 452, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 981 or 982.
65. The AAV capsid variant of any one of embodiments 1-61, wherein [N1] replaces positions 453-455 (e.g., G453, S454, and G455), relative to a reference sequence numbered according to SEQ ID NO: 138.
66. The AAV capsid variant of any one of embodiments 1-64, wherein [N1] replaces positions 453 (e.g., G453), relative to a reference sequence numbered according to SEQ ID NO: 138.
67. The AAV capsid variant of any one of embodiments 1-65, wherein [N1] replaces positions 453-455 (e.g., G453, S454, and G455), relative to a reference sequence numbered according to SEQ ID NO: 981.

68. The AAV capsid variant of any one of embodiments 1-65 or 67, wherein [N1] replaces positions 453-455, relative to a reference sequence numbered according to SEQ ID NO: 982.

69. The AAV capsid variant of any one of embodiments 1-65, 67, or 68, wherein [N1] is present immediately subsequent to position 452 and wherein [N1] replaces positions 453-455 (e.g., G453, S454, and G455), relative to a reference sequence numbered according to SEQ ID NO: 138.

70. The AAV capsid variant of any one of embodiments 1-64 or 66, wherein [N1] is present immediately subsequent to position 452 and wherein [N1] replaces positions 453 (e.g., G453), relative to a reference sequence numbered according to SEQ ID NO: 138.

71. The AAV capsid variant of any one of embodiments 1-64, 66 or 70, wherein [N1] is present immediately subsequent to position 452 and wherein [N1] replaces positions 453-455, relative to a reference sequence numbered according to SEQ ID NO: 981 or 982.

72. The AAV capsid variant of any one of embodiments 1-71, wherein [N1] corresponds to positions 453-455 of any one of SEQ ID NOs: 36-59, 981 or 982.

73. The AAV capsid variant of any one of embodiment 1-72, which comprises an amino acid other than S at position 454 and/or an amino acid other than G at position 455, numbered according to SEQ ID NO: 138, 981, or 982.

74. The AAV capsid variant of any one of embodiments 1-73, which comprises the amino acid H at position 454 and the amino acid D at position 455, numbered according to SEQ ID NO: 138 or 982.

75. The AAV capsid variant of any one of embodiments 1-74, which comprises a substitution at position 454 (e.g., S454H) and/or a substitution at position 455 (e.g., G455D), numbered according to SEQ ID NO: 138.

76. The AAV capsid variant of any one of embodiments 1-75, which comprises the amino acid H at position 454 and the amino acid D at position 455, and further comprises the amino acid sequence SPHSKA (SEQ ID NO: 941) immediately subsequent to position 455, relative to a reference sequence numbered according to SEQ ID NO: 138.

77. The AAV capsid variant of any one of embodiments 1-76, which comprises the amino acid H at position 454 and the amino acid D at position 455, relative to a reference sequence numbered according to SEQ ID NO: 982.

78. The AAV capsid variant of any one of embodiments 1-77, which comprises the amino acid H at position 454 and the amino acid D at position 455, and further comprises the amino acid sequence SPHKA (SEQ ID NO: 941) immediately subsequent to position 455, relative to a reference sequence numbered according to SEQ ID NO: 982.

79. The AAV capsid variant of any one of embodiments 1-72, which comprises the amino acid S at position 454 and the amino acid G at position 455, relative to a reference sequence numbered according to SEQ ID NO: 138.

80. The AAV capsid variant of any one of embodiments 1-72 or 79, which comprises the amino acid S at position 454 and the amino acid G at position 455, and further comprises the amino acid sequence SPHKA (SEQ ID NO: 941) immediately subsequent to position 455, relative to a reference sequence numbered according to SEQ ID NO: 138.

81. The AAV capsid variant of any one of embodiments 1-72, 79, or 80, which comprises the amino acid S at position 454 and the amino acid G at position 455, relative to a reference sequence numbered according to SEQ ID NO: 981.

82. The AAV capsid variant of any one of embodiments 1-72 or 79-81, which comprises the amino acid S at position 454 and the amino acid G at position 455, and further comprises the amino acid sequence SPHKA (SEQ ID NO: 941) immediately subsequent to position 455, relative to a reference sequence numbered according to SEQ ID NO: 981.

83. The AAV capsid variant of any one of embodiments 1-82, wherein [N2] is present immediately subsequent to position 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

84. The AAV capsid variant of any one of embodiments 1-83, wherein [N2] corresponds to positions 456-458 (e.g., S456, P457, H458) of SEQ ID NO: 981 or 982.

85. The AAV capsid variant of any one of embodiments 1-83, wherein [N2] corresponds to positions 456-458 (e.g., S456, P457, H458) of any one of SEQ ID NOs: 36-59.

86. The AAV capsid variant of any one of embodiments 1-85, wherein [N2]-[N3] is present immediately subsequent to position 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.
87. The AAV capsid variant of any one of embodiments 1-86, wherein [N2] is present immediately subsequent to position 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 981 or 982.
88. The AAV capsid variant of any one of embodiments 1-87, wherein [N2]-[N3] is present immediately subsequent to position 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 981 or 982.
89. The AAV capsid variant of any one of embodiments 1-88, wherein [N2]-[N3] corresponds to positions 456-461 (e.g., S456, P457, H458, S459, K460, A461) of SEQ ID NO: 981.
90. The AAV capsid variant of any one of embodiments 1-88, wherein [N2]-[N3] corresponds to positions 456-461 (e.g., S456, P457, H458, K459, S460, G461) of SEQ ID NO: 982.
91. The AAV capsid variant of any one of embodiments 1-90, wherein [N2] is present immediately subsequent to [N1].
92. The AAV capsid variant of any one of embodiments 1-64, 66, 70, or 71, wherein [N3] is present immediately subsequent to [N2] and replaces positions 454 and 455 (e.g., S454 and G455), numbered according to SEQ ID NO: 138.
93. The AAV capsid variant of any one of embodiments 1-1-64, 66, 70, 71, or 92, wherein [N3] is present immediately subsequent to [N1]-[N2] and replaces positions 454 and 455 (e.g., S454 and G455), numbered according to SEQ ID NO: 138.
94. The AAV capsid variant of any one of embodiments 39-93, wherein [N4] is present immediately subsequent to position 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.
95. The AAV capsid variant of any one of embodiments 39-94, wherein [N4] replaces positions 456-459 (e.g., Q456, N457, Q458, and Q459), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

96. The AAV capsid variant of any one of embodiments 39-95, wherein [N4] corresponds to positions 462-465 (e.g., Q462, N463, Q464, Q465) of SEQ ID NO: 981 or 982.

97. The AAV capsid variant of any one of embodiments 39-96, wherein [N2]-[N3]-[N4] replaces positions 456-459 (e.g., Q456, N457, Q458, and Q459), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

98. The AAV capsid variant of any one of embodiments 39-97, wherein [N2]-[N3]-[N4] is present immediately subsequent to position 455, and wherein [N2]-[N3]-[N4] replaces positions 456-459 (e.g., Q456, N457, Q458, and Q459), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

99. The AAV capsid variant of any one of embodiments 39-98, wherein [N2]-[N3]-[N4] corresponds to positions 456-465 (e.g., S456, P457, H458, S459, K460, A461, Q462, N463, Q464, Q465) of SEQ ID NO: 981.

100. The AAV capsid variant of any one of embodiments 39-98, wherein [N2]-[N3]-[N4] corresponds to positions 456-465 (e.g., S456, P457, H458, K459, S460, G461, Q462, N463, Q464, Q465) of SEQ ID NO: 982.

101. The AAV capsid variant of any one of embodiments 39-98, wherein [N2]-[N3]-[N4] corresponds to positions 456-465 of any one of SEQ ID NOs: 36-59.

102. The AAV capsid variant of any one of embodiments 39-101, wherein [N1]-[N2]-[N3]-[N4] replaces positions 453-459 (e.g., G453, S454, G455, Q456, N457, Q458, and Q459), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

103. The AAV capsid variant of any one of embodiments 39-102, wherein [N1]-[N2]-[N3]-[N4] is present immediately subsequent to position 452, and wherein [N1]-[N2]-[N3]-[N4] replaces positions 453-459 (e.g., G453, S454, G455, Q456, N457, Q458, and Q459), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

104. The AAV capsid variant of any one of embodiments 39-99, 102, 103, wherein [N1]-[N2]-[N3]-[N4] corresponds to positions 453-465 (e.g., G453, S454, G455, S456, P457, H458, S459, K460, A461, Q462, N463, Q464, Q465) of SEQ ID NO: 981.

105. The AAV capsid variant of any one of embodiments 39-98, 100, 102, or 103, wherein [N1]-[N2]-[N3]-[N4] corresponds to positions 453-465 (e.g., G453, H454, D455, S456, P457, H458, K459, S460, G461, Q462, N463, Q464, Q465) of SEQ ID NO: 982.

106. The AAV capsid variant of any one of embodiments 39-98, 102, or 103, wherein [N1]-[N2]-[N3]-[N4] corresponds to positions 453-465 of any one of SEQ ID NOs: 36-59.

107. The AAV capsid variant of any one of embodiments 1-99 or 102-104, wherein [N1]-[N2]-[N3] corresponds to positions 453-461 (e.g., G453, S454, G455, S456, P457, H458, S459, K460, A461) of SEQ ID NO: 981.

108. The AAV capsid variant of any one of embodiments 1-98, 100, 102, 103, or 105, wherein [N1]-[N2]-[N3] corresponds to positions 453-461 (e.g., G453, H454, D455, S456, P457, H458, K459, S460, G461) of SEQ ID NO: 982.

109. The AAV capsid variant of any one of embodiments 39-98, 102, 103, or 106, wherein [N1]-[N2]-[N3] corresponds to positions 453-461 of any one of SEQ ID NOs: 36-59.

110. The AAV capsid variant of any one of embodiments 48-109, wherein [N0]-[N1]-[N2]-[N3]-[N4] replaces positions 450-459 (e.g., T450, I451, N452, G453, S454, G455, Q456, N457, Q458, and Q459), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

111. The AAV capsid variant of any one of embodiments 48-110, wherein [N0]-[N1]-[N2]-[N3]-[N4] is present immediately subsequent to position 449, and wherein [N0]-[N1]-[N2]-[N3]-[N4] replaces positions 450-459 (e.g., T450, I451, N452, G453, S454, G455, Q456, N457, Q458, and Q459), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

112. The AAV capsid variant of any one of embodiments 48-99, 102-104, or 106, wherein [N0]-[N1]-[N2]-[N3]-[N4] corresponds to positions 450-465 (e.g., T450, I451, N452, G453, S454, G455, S456, P457, H458, S459, K460, A461, Q462, N463, Q464, Q465) of SEQ ID NO: 981.

113. The AAV capsid variant of any one of embodiments 48-98, 100, 102, 103, 105, or 108, wherein [N0]-[N1]-[N2]-[N3]-[N4] corresponds to positions 450-465 (e.g., T450, I451, N452, G453, H454, D455, S456, P457, H458, K459, S460, G461, Q462, N463, Q464, Q465) of SEQ ID NO: 982.

114. The AAV capsid variant of any one of embodiments 48-98, 102, 103, 106, or 109, wherein [N0]-[N1]-[N2]-[N3]-[N4] corresponds to positions 450-465 of any one of SEQ ID NOs: 36-59.

115. The AAV capsid variant of any one of embodiments 39-114, wherein [N4] replaces positions 462-465 (e.g., Q462, N463, Q464, and Q465), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 981 or 982.

116. The AAV capsid variant of any one of embodiments 39-115, wherein [N2]-[N3]-[N4] replaces positions 462-465 (e.g., Q462, N463, Q464, and Q465), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 981 or 982.

117. The AAV capsid variant of any one of embodiments 39-116, wherein [N2]-[N3]-[N4] is present immediately subsequent to position 455, and wherein [N2]-[N3]-[N4] replaces positions 462-465 (e.g., Q462, N463, Q464, and Q465), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 981 or 982.

118. The AAV capsid variant of any one of embodiments 1-117, wherein [N3] is present immediately subsequent to [N2].

119. The AAV capsid variant of any one of embodiments 1-118, which comprises from N-terminus to C-terminus, [N2]-[N3].

120. The AAV capsid variant of any one of embodiments 1-119, which comprises from N-terminus to C-terminus, [N1]-[N2]-[N3].

121. The AAV capsid variant of any one of embodiments 48-120, which comprises from N-terminus to C-terminus, [N0]-[N1]-[N2]-[N3].

122. The AAV capsid variant of any one of embodiments 39-121, which comprises from N-terminus to C-terminus, [N1]-[N2]-[N3]-[N4].

123. The AAV capsid variant of any one of embodiments 48-122, which comprises from N-terminus to C-terminus, [N0]-[N1]-[N2]-[N3]-[N4].

124. The AAV capsid variant of any one of the preceding embodiments, which comprises an amino acid other T at position 460 (e.g., N, I, C, H, R, L, D, Y, A, M, Q, I, E, K, P, G or S), numbered according to the amino acid sequence of SEQ ID NO: 138.

125. The AAV capsid variant of any one of the preceding embodiments, which comprises the amino acid N, I, C, H, R, L, D, Y, A, M, Q, I, E, K, P, G or S at position 460, numbered according to the amino acid sequence of SEQ ID NO: 138.

126. The AAV capsid variant of any one of the preceding embodiments, which comprises an amino acid other T at position 466 (e.g., N, I, C, H, R, L, D, Y, A, M, Q, I, E, K, P, G or S), numbered according to the amino acid sequence of any one of SEQ ID NOs: 36-59, 981, or 982.

127. The AAV capsid variant of any one of the preceding embodiments, which comprises the amino acid N, I, C, H, R, L, D, Y, A, M, Q, I, E, K, P, G or S at position 466, numbered according to the amino acid sequence of any one of SEQ ID NOs: 36-59, 981 or 982.

128. The AAV capsid variant of any one of the preceding embodiments, which comprises an amino acid other K at position 449 (e.g., an E, an N, or a T), numbered according to the amino acid sequence of any one of SEQ ID NOs: 36-59, 138, 981, or 982.

129. The AAV capsid variant of any one of the preceding embodiments, which comprises the amino E, N, or T at position 449, numbered according to the amino acid sequence of any one of SEQ ID NOs: 36-59, 138, 981 or 982.

130. An AAV capsid variant, comprising [A][B] (SEQ ID NO: 4694), wherein:

(i) [A] comprises the amino acid sequence of GSGSPH (SEQ ID NO: 4695); and

(ii) [B] comprises X1 X2 X3 X4 X5 X6 X7, wherein:

(a) position X1 is: S, C, F, or V;

(b) position X2 is: K, L, R, I, E, Y, V, or S;

(c) position X3 is: A, R, L, G, I, Y, S, F, or W;

(d) position X4 is: W, Q, R, G, L, V, S, or F;

(e) position X5 is: N, Y, R, C, K, or L;

(f) position X6 is: Q, G, K, R, T, L, or Y; and

(g) position X7 is: Q, L, R, or V;

optionally wherein the AAV capsid variant comprises an amino acid modification, e.g., a conservative substitution, of any of the aforesaid amino acids in (a)-(g).

131. The AAV capsid variant of embodiment 130, wherein

(a) position X1 is S;

(b) position X2 is K or L;

- (c) position X3 is: A, R, or L;
- (d) position X4 is: Q or R;
- (e) position X5 is: N or R;
- (f) position X6 is: Q or R; and
- (g) position X7 is: Q, L, or R.

132. The AAV capsid variant of embodiment 130 or 131, wherein [B] comprises:

(i) SLLWNQQ (SEQ ID NO: 5247), SKAQYYV (SEQ ID NO: 5248), SKLRRQQ (SEQ ID NO: 5249), SIWQNQQ (SEQ ID NO: 5250), SKAGCGQ (SEQ ID NO: 5251), SRAQNQQ (SEQ ID NO: 5252), SKRLRQQ (SEQ ID NO: 5253), SLRRNQQ (SEQ ID NO: 5254), SRGRNQQ (SEQ ID NO: 5255), SEIVNQQ (SEQ ID NO: 5256), SSRRNQQ (SEQ ID NO: 5257), CLLQNQQ (SEQ ID NO: 5258), SKAFRLQ (SEQ ID NO: 5259), CLAQNQQ (SEQ ID NO: 5260), FLRQNQQ (SEQ ID NO: 5261), SLRFNQQ (SEQ ID NO: 5262), SYLRNQQ (SEQ ID NO: 5263), CSLQNQQ (SEQ ID NO: 5264), VLWQNQQ (SEQ ID NO: 5265), SKWLLQQ (SEQ ID NO: 5266), SLWSNQQ (SEQ ID NO: 5267), SKRRLQQ (SEQ ID NO: 5268), SVYLNQQ (SEQ ID NO: 5269), SLWLNQQ (SEQ ID NO: 5270), SKAQRKL (SEQ ID NO: 5271), SKALRRQ (SEQ ID NO: 5272), SKAQRLR (SEQ ID NO: 5273), SKAQNQQ (SEQ ID NO: 5274), SKAQRRL (SEQ ID NO: 5275), SKARRQQ (SEQ ID NO: 5276), SKARRLQ (SEQ ID NO: 5277), SKSRRQQ (SEQ ID NO: 5278), SKARLRQ (SEQ ID NO: 5279), SKASKRQ (SEQ ID NO: 5280), VRRQNQQ (SEQ ID NO: 5281), SKAQLYR (SEQ ID NO: 5282), SLFRNQQ (SEQ ID NO: 5283), SKAQLTV (SEQ ID NO: 5284);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, 5, or 6 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

133. The AAV capsid variant of any one of embodiments 130-132, wherein [A][B] comprises:

(i) GSGSPHSLLNQQ (SEQ ID NO: 5285), GSGSPHKAQYYV (SEQ ID NO: 2060), GSGSPHSLRRQQ (SEQ ID NO: 2061), GSGSPHSIWQNQQ (SEQ ID NO: 5286), GSGSPHSAQCGQ (SEQ ID NO: 2062), GSGSPHSRAQNQQ (SEQ ID NO: 2063), GSGSPHSLRLRQQ (SEQ ID NO: 2064), GSGSPHSLRRNQQ (SEQ ID NO: 2065), GSGSPHSRGRNQQ (SEQ ID NO: 2066), GSGSPHSEIVNQQ (SEQ ID NO: 5287), GSGSPHSSRRNQQ (SEQ ID NO: 2067), GSGSPHCLLNQQ (SEQ ID NO: 5288), GSGSPHSAFRLQ (SEQ ID NO: 2068), GSGSPHCLAQNQQ (SEQ ID NO: 5289), GSGSPHFLRQNQQ (SEQ ID NO: 2070), GSGSPHSLRFNQQ (SEQ ID NO: 2071),

GSGSPHSYLRNQQ (SEQ ID NO: 5290), GSGSPHCSLQNQQ (SEQ ID NO: 5291), GSGSPHVLWQNQQ (SEQ ID NO: 5292), GSGSPHSKWLLQQ (SEQ ID NO: 2072), GSGSPHSLWSNQQ (SEQ ID NO: 5293), GSGSPHSKRRLQQ (SEQ ID NO: 2073), GSGSPHSVYLNQQ (SEQ ID NO: 5294), GSGSPHSLWLNQQ (SEQ ID NO: 5295), GSGSPHKAQRKL (SEQ ID NO: 2074), GSGSPHKAARRQ (SEQ ID NO: 2075), GSGSPHKAQRLR (SEQ ID NO: 2076), GSGSPHKAQNQQ (SEQ ID NO: 1801), GSGSPHKAQRRL (SEQ ID NO: 2077), GSGSPHKAARRQ (SEQ ID NO: 2078), GSGSPHKAARRLQ (SEQ ID NO: 2079), GSGSPHKSRRQ (SEQ ID NO: 2080), GSGSPHKAARRLQ (SEQ ID NO: 2082), GSGSPHKAARRQ (SEQ ID NO: 2083), GSGSPHVRQNQQ (SEQ ID NO: 2084), GSGSPHKAQLYR (SEQ ID NO: 2085), GSGSPHSLFRNQQ (SEQ ID NO: 5296), GSGSPHKAQLTV (SEQ ID NO: 2086);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i)

134. The AAV capsid variant of any one of embodiments 130-133, which further comprises one, two, or all of an amino acid other than T at position 450 (e.g., S, Y, or G), an amino acid other than I at position 451 (e.g., M or L), and/or an amino acid other than N at position 452 (e.g., S), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

135. The AAV capsid variant of any one of embodiments 130-134, which further comprises an S at position 450 and an M at position 451, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

136. The AAV capsid variant of any one of embodiments 130-134, which further comprises a Y at position 450, an L at position 451, and an S at position 452, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

137. The AAV capsid variant of any one of embodiments 130-134, which further comprises a G at position 450, an L at position 451, and an S at position 452, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

138. The AAV capsid variant of any one of embodiments 130-137, wherein [A][B] is present in loop IV.

139. The AAV capsid variant of any one of embodiments 130-138, wherein [A] is present immediately subsequent to position 452, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

140. The AAV capsid variant of any one of embodiments 130-139, wherein [A] replaces positions 453-455 (e.g., G453, S454, G455), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

141. The AAV capsid variant of any one of embodiments 130-140, wherein [A] is present immediately subsequent to position 452, and wherein [A] replaces positions 453-455 (e.g., G453, S454, G455), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

142. The AAV capsid variant of any one of embodiments 130-141, wherein [B] is present immediately subsequent to [A].

143. The AAV capsid variant of any one of embodiments 130-142, wherein [B] replaces positions 456-459 (e.g., Q456, N457, Q458, Q459), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

144. The AAV capsid variant of any one of embodiments 130-143, wherein [A][B] replaces positions 453-459 (e.g., G453, S454, G455, Q456, N457, Q458, Q459), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

145. The AAV capsid variant of any one of embodiments 130-144, wherein [A][B] is present immediately subsequent to position 452, and wherein [A][B] replaces positions 453-459 (e.g., G453, S454, G455, Q456, N457, Q458, Q459), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

146. The AAV capsid variant of any one of embodiments 130-145, which comprises from N-terminus to C-terminus, [A][B].

147. An AAV capsid comprising [A][B] (SEQ ID NO: 4699), wherein:

(i) [A] comprises X1 X2 X3 X4 X5 X6, wherein

- (a) position X1 is T, M, A, C, I, R, L, D, F, V, Q, N, or H;
- (b) position X2 is I, P, E, N, D, S, A, T, M, or Q;
- (c) position X3 is N, E, G, Y, W, M, T, I, K, Q, F, S, V, A, or L;
- (d) position X4 is G, D, R, or E;
- (e) position X5 is H, Q, N, or D;
- (f) position X6 is D or R;

optionally wherein the AAV capsid variant comprises an amino acid modification, e.g., a conservative substitution, of any of the aforesaid amino acids in (a)-(f); and

- (ii) [B] comprises SPHKSG (SEQ ID NO: 946).

148. The AAV capsid of embodiment 147, wherein

- (a) position X1 is: T, M, A, or I;
- (b) position X2 is: E, I or D;
- (c) position X3 is: N, Q, Y, I, M, or V;
- (d) position X4 is G;
- (e) position X5 is H; and
- (f) position X6 is D.

149. The AAV capsid variant of embodiment 147 or 148, wherein [A] comprises:

(i) TINGHD (SEQ ID NO: 5297), MPEGHD (SEQ ID NO: 5298), MEGGHD (SEQ ID NO: 5299), MEYGHGHD (SEQ ID NO: 5300), AEWGHD (SEQ ID NO: 5301), CEWGHD (SEQ ID NO: 5302), ANNGQD (SEQ ID NO: 5303), IPEGHD (SEQ ID NO: 5304), ADMGHD (SEQ ID NO: 5305), IEYGHGHD (SEQ ID NO: 5306), ADYGHGHD (SEQ ID NO: 5307), IETGHGHD (SEQ ID NO: 5308), MEWGHD (SEQ ID NO: 5309), CEYGHGHD (SEQ ID NO: 5310), RINGHD (SEQ ID NO: 5311), MEIGHGHD (SEQ ID NO: 5312), LEYGHGHD (SEQ ID NO: 5313), ADWGHD (SEQ ID NO: 5314), IEIGHGHD (SEQ ID NO: 5315), TIKDND (SEQ ID NO: 5316), DIMGHGHD (SEQ ID NO: 5317), FEQGHGHD (SEQ ID NO: 5318), MEFGHD (SEQ ID NO: 5319), CDQGHGHD (SEQ ID NO: 5320), LPEGHD (SEQ ID NO: 5321), IENGHD (SEQ ID NO: 5322), MESGHGHD (SEQ ID NO: 5323), AEIGHGHD (SEQ ID NO: 5324), VEYGHGHD (SEQ ID NO: 5325), TSNGDD (SEQ ID NO: 5326), IEVGHGHD (SEQ ID NO: 5327), MEMGHGHD (SEQ ID NO: 5328), AEVGHGHD (SEQ ID NO: 5329), MDAGHD (SEQ ID NO: 5330), VEWGHD (SEQ ID NO: 5331), AEQGHGHD (SEQ ID NO: 5332), LEWGHD (SEQ ID NO: 5333), MELGHGHD (SEQ ID NO: 5334), METGHGHD (SEQ ID NO: 5335), MEAGHD (SEQ ID NO: 5336), TINRQR (SEQ ID NO: 5337), IESGHGHD (SEQ ID NO: 5338), TAKDHD (SEQ ID NO: 5339), MEVGHGHD (SEQ ID NO: 5340), CEIGHGHD (SEQ ID NO: 5341), ATNGHD (SEQ ID NO: 5342), MDGGHD (SEQ ID NO: 5343), QEVGHGHD (SEQ ID NO: 5344), ADQGHGHD (SEQ ID NO: 5345), NMNGHD (SEQ ID NO: 5346), TPWEHD (SEQ ID NO: 5347),

IEMGHD (SEQ ID NO: 5348), TANEHD (SEQ ID NO: 5349), QQQGHD (SEQ ID NO: 5350), TPQDHD (SEQ ID NO: 5351), HDWGH (SEQ ID NO: 5352), IEGGHD (SEQ ID NO: 5353)

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, or 5 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

150. The AAV capsid variant of any one of embodiments 147-149, wherein [A][B] comprises:

(i) TINGHDSPHKR (SEQ ID NO: 5354), MPEGHDSPHKS (SEQ ID NO: 5355), MEGGHDSPHKS (SEQ ID NO: 5356), MEYGHDSPHKS (SEQ ID NO: 5357), AEWGHDSPHKS (SEQ ID NO: 5358), CEWGHDSPHKS (SEQ ID NO: 5359), ANNGQDSPHKS (SEQ ID NO: 5360), IPEGHDSPHKS (SEQ ID NO: 5361), ADMGHDSPHKS (SEQ ID NO: 5362), IEYGHDSPHKS (SEQ ID NO: 5363), ADYGHDSPHKS (SEQ ID NO: 5364), IETGHDSPHKS (SEQ ID NO: 5365), MEWGHDSPHKS (SEQ ID NO: 5366), CEYGHDSPHKS (SEQ ID NO: 5367), RINGHDSPHKS (SEQ ID NO: 5368), MEIGHDSPHKS (SEQ ID NO: 5369), LEYGHDSPHKS (SEQ ID NO: 5370), ADWGHDSPHKS (SEQ ID NO: 5371), IEIGHDSPHKS (SEQ ID NO: 5372), TIKDNDSPHKS (SEQ ID NO: 5373), DIMGHDSPHKS (SEQ ID NO: 5374), FEQGHDSPHKS (SEQ ID NO: 5375), MEFGHDSPHKS (SEQ ID NO: 5376), CDQGHDSPHKS (SEQ ID NO: 5377), LPEGHDSPHKS (SEQ ID NO: 5378), IENGHDSPHKS (SEQ ID NO: 5379), MESGHDSPHKS (SEQ ID NO: 5380), AEIGHDSPHKS (SEQ ID NO: 5381), VEYGHDSPHKS (SEQ ID NO: 5382), TSNGDDSPHKS (SEQ ID NO: 5383), IEVGHDSPHKS (SEQ ID NO: 5384), MEMGHDSPHKS (SEQ ID NO: 5385), AEVGHDSPHKS (SEQ ID NO: 5386), MDAGHDSPHKS (SEQ ID NO: 5387), VEWGHDSPHKS (SEQ ID NO: 5388), AEQGHDSPHKS (SEQ ID NO: 5389), LEWGHDSPHKS (SEQ ID NO: 5390), MELGHDSPHKS (SEQ ID NO: 5391), METGHDSPHKS (SEQ ID NO: 5392), MEAGHDSPHKS (SEQ ID NO: 5393), TINRQRSPHKS (SEQ ID NO: 5394), IESGHDSPHKS (SEQ ID NO: 5395), TAKDHDSPHKS (SEQ ID NO: 5396), MEVGHDSPHKS (SEQ ID NO: 5397), CEIGHDSPHKS (SEQ ID NO: 5398), ATNGHDSPHKS (SEQ ID NO: 5399), MDGGHDSPHKS (SEQ ID NO: 5400), QEVGHDSPHKS (SEQ ID NO: 5401), ADQGHDSPHKS (SEQ ID NO: 5402), NMNGHDSPHKS (SEQ ID NO: 5403), TPWEHDSPHKS (SEQ ID NO: 5404), IEMGHDSPHKS (SEQ ID NO: 5405), TANEHDSPHKS (SEQ ID NO: 5406), TINGHDSPHKS (SEQ ID NO: 5407), QQQGHDSPHKS (SEQ ID NO: 5408), TPQDHDSPHKS (SEQ ID NO: 5409), HDWGHDSPHKS (SEQ ID NO: 5410), IEGGHDSPHKS (SEQ ID NO: 5411)

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

151. The AAV capsid variant of any one of embodiments 147-150, which further comprises one, two, three, four, or all of an amino acid other than Q at position 456 (e.g., R or L), N at position 457 (e.g., H, K, or R), Q at position 458 (e.g., R or T), Q at position 459 (H), and/or T at position 460 (N or S), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

152. The AAV capsid variant of any one of embodiments 147-151, which further comprises an R at position 456, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

153. The AAV capsid variant of any one of embodiments 147-151, which further comprises an L at position 456, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

154. The AAV capsid variant of any one of embodiments 147-153, which further comprises an H at position 457 and an R at position 458, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

155. The AAV capsid variant of any one of embodiments 147-153, which further comprises a K at position 457 and an N at position 460, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

156. The AAV capsid variant of any one of embodiments 147-153, which further comprises a T at position 458, an H at position 459, and an S at position 460, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

157. The AAV capsid variant of any one of embodiments 147-151, which further comprises an R at position 456, an R at position 457, and an R at position 458, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

158. The AAV capsid variant of any one of embodiments 147-157, wherein [A][B] is present in loop IV.

159. The AAV capsid variant of any one of embodiments 147-158, wherein [A] is present immediately subsequent to position 449, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

160. The AAV capsid variant of any one of embodiments 147-159, wherein [A] replaces positions 450-453 (e.g., T450, I451, N452, G453), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

161. The AAV capsid variant of any one of embodiments 147-160, wherein [A] is present immediately subsequent to position 449, and wherein [A] replaces positions 450-453 (e.g., T450, I451, N452, G453), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

162. The AAV capsid variant of any one of embodiments 147-161, wherein [A][B] replaces positions 450-455 (e.g., T450, I451, N452, G453, S454, G455), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

163. The AAV capsid variant of any one of embodiments 147-162, wherein [A][B] is present immediately subsequent to position 449, and wherein [A][B] replaces positions 450-455 (e.g., T450, I451, N452, G453, S454, G455), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

164. The AAV capsid variant of any one of embodiments 147-163, wherein [B] is present immediately subsequent [A], and replaces positions 454 and 455 (e.g., S454 and G455), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

165. The AAV capsid variant of any one of embodiments 147-164, wherein [B] is present immediately subsequent to position 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 982.

166. The AAV capsid variant of any one of embodiments 147-165, wherein [B] is present immediately subsequent to [A].

167. The AAV capsid variant of any one of embodiments 147-166, which comprises from N-terminus to C-terminus, [A][B].

168. An AAV capsid variant comprising an amino acid sequence having the following formula: [N1]-[N2]-[N3] (SEQ ID NO: 6407), wherein:

- (i) [N1] comprises positions X1, X2, and X3, wherein position X2 is S and position X3 is G;
- (ii) [N2] comprises the amino acid sequence SPH; and
- (iii) [N3] comprises positions X4, X5, and X6, wherein position X5 is K.

169. The AAV capsid variant of embodiment 168, wherein:

- (i) X4 of [N3] is S, T, N, or A; and
- (ii) X5 of [N3] is A, V, T, S, G, R, L, or N;

optionally wherein the AAV capsid variant comprises an amino acid modification, e.g., a conservative substitution, of any of the aforesaid amino acids in (i) or (ii).

170. The AAV capsid variant of embodiment 168 or 169, wherein X4 is S and/or X5 is A.

171. The AAV capsid variant of any one of embodiments 168-170, wherein [N3] comprises SK, TK, NK, AK, KA, KV, KT, KS, KG, KR, KL, or KN.

172. The AAV capsid variant of any one of embodiments 168-171, wherein [N3] is or comprises SKA, SKV, SKT, SKS, SKG, SKR, TKA, NKA, SKL, SKN, or AKA.

173. The AAV capsid variant of any one of embodiments 168-172, wherein [N3] is or comprises SKA.

174. The AAV capsid variant of any one of embodiments 168-173, wherein [N2]-[N3] comprises SPHSK (SEQ ID NO: 4701), SPHTK (SEQ ID NO: 4725), SPHNK (SEQ ID NO: 4726), or SPHAK (SEQ ID NO: 4727).

175. The AAV capsid variant of any one of embodiments 168-174, wherein [N2]-[N3] is or comprises:

- (i) SPHKA (SEQ ID NO: 941), SPHSKV (SEQ ID NO: 4737), SPHSKT (SEQ ID NO: 4731), SPHSKS (SEQ ID NO: 962), SPHSG (SEQ ID NO: 4732), SPHSKR (SEQ ID NO: 978), SPHTKA (SEQ ID NO: 4739), SPHNKA (SEQ ID NO: 4734), SPHSL (SEQ ID NO: 960), SPHSKN (SEQ ID NO: 4735), or SPHAKA (SEQ ID NO: 4736);
- (ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, or 5 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

176. The AAV capsid variant of any one of embodiments 168-175, wherein [N2]-[N3] is or comprises SPHKA (SEQ ID NO: 941).

177. The AAV capsid variant of any one of embodiments 168-176, which comprises an amino acid other than G at position 453 (e.g., M, T, I, E, S, A, N, V, L, K, H, P, R, W, or D), numbered according to SEQ ID NO: 138 or 981.

178. The AAV capsid variant of any one of embodiments 168-177, which comprises the amino acid G at position 453, numbered according to SEQ ID NO: 138 or 981.

179. The AAV capsid variant of any one of embodiments 168-178, wherein X1 of [N1] is chosen from: G, M, T, I, E, S, A, N, V, L, K, H, P, R, W, or D; optionally wherein the AAV capsid variant comprises an amino acid modification, e.g., a conservative substitution, of any of the aforesaid amino acids.

180. The AAV capsid variant of any one of embodiments 168-179, wherein [N1] comprises SG, GS, MS, TS, IS, ES, SS, AS, NS, VS, LS, KS, HS, PS, RS, WS, or DS.

181. The AAV capsid variant of any one of embodiments 168-180, wherein [N1] is or comprises: GSG, MSG, TSG, ISG, ESG, SSG, ASG, NSG, VSG, LSG, KSG, HSG, PSG, RSG, WSG, or DSG.

182. The AAV capsid variant of any one of embodiments 168-181, wherein [N1] is or comprises GSG.

183. The AAV capsid variant of any one of embodiments 168-182, wherein [N1]-[N2] comprises SGSPH (SEQ ID NO: 4752).

184. The AAV capsid variant of any one of embodiments 168-183, wherein [N1]-[N2] is or comprises:

(i) GSGSPH (SEQ ID NO: 4695), MSGSPH (SEQ ID NO: 4798), TSGSPH (SEQ ID NO: 4800), ISGSPH (SEQ ID NO: 4801), ESGSPH (SEQ ID NO: 4803), SSGSPH (SEQ ID NO: 4804),

ASGSPH (SEQ ID NO: 4806), NSGSPH (SEQ ID NO: 4807), VSGSPH (SEQ ID NO: 4786), LSGSPH (SEQ ID NO: 4808), KSGSPH (SEQ ID NO: 4810), HSGSPH (SEQ ID NO: 4811), PSGSPH (SEQ ID NO: 4813), RSGSPH (SEQ ID NO: 4815), WSGSPH (SEQ ID NO: 4817), DSGSPH (SEQ ID NO: 4818);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, or 5 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

185. The AAV capsid variant of any one of embodiments 168-184, wherein [N1]-[N2]-[N3] is or comprises:

(i) GSGSPHKA (SEQ ID NO: 4697), GSGSPHKA (SEQ ID NO: 4956), MSGSPHKA (SEQ ID NO: 4957), TSGSPHKA (SEQ ID NO: 4959), ISGSPHKA (SEQ ID NO: 4960), GSGSPHKT (SEQ ID NO: 4962), ESGSPHKA (SEQ ID NO: 4963), SSGSPHKA (SEQ ID NO: 4964), GSGSPHKS (SEQ ID NO: 4953), ASGSPHKA (SEQ ID NO: 4966), NSGSPHKA (SEQ ID NO: 4967), VSGSPHKA (SEQ ID NO: 4913), LSGSPHKA (SEQ ID NO: 4968), KSGSPHKA (SEQ ID NO: 4970), GSGSPHKG (SEQ ID NO: 4972), GSGSPHKA (SEQ ID NO: 4945), HSGSPHKA (SEQ ID NO: 4973), PSGSPHKA (SEQ ID NO: 4975), RSGSPHKA (SEQ ID NO: 4977), GSGSPHTKA (SEQ ID NO: 4978), WSGSPHKA (SEQ ID NO: 4980), DSGSPHKA (SEQ ID NO: 4981), GSGSPHKA (SEQ ID NO: 4983), GSGSPHKA (SEQ ID NO: 4943), GSGSPHKA (SEQ ID NO: 4994), or GSGSPHKA (SEQ ID NO: 4995);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, 5, 6, 7, 8, or 9 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

186. The AAV capsid variant of any one of embodiments 168-185, wherein [N1]-[N2]-[N3] is or comprises GSGSPHKA (SEQ ID NO: 4697).

187. The AAV capsid variant of any one of embodiments 168-186, which comprises an amino acid other than Q at position 456 (e.g., R, P, H, L, K, I, G, S, M, or E), an amino acid other than N at

position 457 (e.g., D, V, S, P, T, G, Y, W, E, R, H, K, F, A, I, L, or M), an amino acid other than Q at position 458 (e.g., R, L, A, P, H, T, I, F, K, V, M, G, W, Y, S, E, N, or D), an amino acid other than Q at position 459 (e.g., H, K, A, L, P, E, M, I, S, N, R, Y, C, V, T, W, D, G), and/or an amino acid other than T at position 460 (e.g., I, N, S, H, R, L, D, Y, A, or Q), relative to a reference sequence numbered according to SEQ ID NO: 138.

188. The AAV capsid variant of any one of embodiments 168-187, which comprises an amino acid other than Q at position 462 (e.g., R, P, H, L, K, I, G, S, M, or E), an amino acid other than N at position 463 (e.g., D, V, S, P, T, G, Y, W, E, R, H, K, F, A, I, L, or M), an amino acid other than Q at position 464 (e.g., R, L, A, P, H, T, I, F, K, V, M, G, W, Y, S, E, N, or D), an amino acid other than Q at position 465 (e.g., H, K, A, L, P, E, M, I, S, N, R, Y, C, V, T, W, D, G), and/or an amino acid other than T at position 466 (e.g., I, N, S, H, R, L, D, Y, A, or Q), relative to a reference sequence numbered according to SEQ ID NO: 981.

189. The AAV capsid variant of any one of embodiments 168-188, which comprises the amino acid Q at position 456, the amino acid N at position 457, the amino acid Q at position 458, the amino acid Q at position 459, and/or the amino acid T at position 460, relative to a reference sequence numbered according to SEQ ID NO: 138.

190. The AAV capsid variant of any one of embodiments 168-189, which comprises the amino acid Q at position 462, the amino acid N at position 463, the amino acid Q at position 464, the amino acid Q at position 465, and/or the amino acid T at position 466, numbered according to SEQ ID NO: 981

191. The AAV capsid variant of any one of embodiments 168-190, further comprising [N4] wherein [N4] comprises X7, X8, X9, X10, and X11, wherein:

- (a) X7 is Q, R, P, H, L, K, I, G, S, M, or E;
- (b) X8 is N, D, V, S, P, T, G, Y, W, E, R, H, K, F, A, I, L, or M;
- (c) X9 is Q, R, L, A, P, H, T, I, F, K, V, M, G, W, Y, S, E, N, D;
- (d) X10 is Q, H, K, A, L, P, E, M, I, S, N, R, Y, C, V, T, W, D, G; and
- (e) X11 is T, I, N, S, H, R, L, D, Y, A, Q;

optionally wherein the AAV capsid variant comprises an amino acid modification, e.g., a conservative substitution, of any of the aforesaid amino acids in (a)-(e).

192. The AAV capsid variant of embodiment 191, wherein [N4] is or comprises:

- (i) QNQQT (SEQ ID NO: 5412), QNRHT (SEQ ID NO: 5413), RDQQT (SEQ ID NO: 5414), PNLQT (SEQ ID NO: 5415), HVRQT (SEQ ID NO: 5416), PNQHT (SEQ ID NO: 5417), QSQQT (SEQ ID NO: 5418), QNQQT (SEQ ID NO: 5419), QPAKT (SEQ ID NO: 5420), QTQQN

(SEQ ID NO: 5421), QNLAT (SEQ ID NO: 5422), QNQLT (SEQ ID NO: 5423), QGQQT (SEQ ID NO: 5424), LNRQS (SEQ ID NO: 5425), HNQQT (SEQ ID NO: 5426), QNPPT (SEQ ID NO: 5427), QNLQT (SEQ ID NO: 5428), QYQQT (SEQ ID NO: 5429), QDQET (SEQ ID NO: 5430), QNHQT (SEQ ID NO: 5431), QDQQT (SEQ ID NO: 5432), HWQQT (SEQ ID NO: 5433), PNQQT (SEQ ID NO: 5434), QNQLI (SEQ ID NO: 5435), PEQQT (SEQ ID NO: 5436), QRTMT (SEQ ID NO: 5437), QNQQH (SEQ ID NO: 5438), LHQHT (SEQ ID NO: 5439), QHRIT (SEQ ID NO: 5440), QYIHT (SEQ ID NO: 5441), QKFET (SEQ ID NO: 5442), QFPST (SEQ ID NO: 5443), HNQQR (SEQ ID NO: 5444), QAIKT (SEQ ID NO: 5445), QNRQT (SEQ ID NO: 5446), QYQHT (SEQ ID NO: 5447), QNPQS (SEQ ID NO: 5448), QHQLT (SEQ ID NO: 5449), QSPPT (SEQ ID NO: 5450), QAKLT (SEQ ID NO: 5451), KSQQT (SEQ ID NO: 5452), QDRPT (SEQ ID NO: 5453), QSQQL (SEQ ID NO: 5454), QAFHT (SEQ ID NO: 5455), QKQQT (SEQ ID NO: 5456), QNAQT (SEQ ID NO: 5457), HNQLT (SEQ ID NO: 5458), QNQYQ (SEQ ID NO: 5459), QKLNT (SEQ ID NO: 5460), QNVQT (SEQ ID NO: 5461), QAQQT (SEQ ID NO: 5462), QNLQA (SEQ ID NO: 5463), QTPPT (SEQ ID NO: 5464), QYQHA (SEQ ID NO: 5465), QGQQA (SEQ ID NO: 5466), QPPAT (SEQ ID NO: 5467), QERPT (SEQ ID NO: 5468), QDLQT (SEQ ID NO: 5469), QAMHT (SEQ ID NO: 5470), LNQQT (SEQ ID NO: 5471), QHPST (SEQ ID NO: 5472), PGLQT (SEQ ID NO: 5473), QGIRT (SEQ ID NO: 5474), QAPAT (SEQ ID NO: 5475), QSQQI (SEQ ID NO: 5476), QIPPT (SEQ ID NO: 5477), QTQLT (SEQ ID NO: 5478), QAPST (SEQ ID NO: 5479), QNTYA (SEQ ID NO: 5480), QNQHI (SEQ ID NO: 5481), QNHLT (SEQ ID NO: 5482), QIGMT (SEQ ID NO: 5483), LNKQT (SEQ ID NO: 5484), QLQQT (SEQ ID NO: 5485), QRMST (SEQ ID NO: 5486), QGILT (SEQ ID NO: 5487), QDRQT (SEQ ID NO: 5488), RDWQT (SEQ ID NO: 5489), QNTHD (SEQ ID NO: 5490), PNLQI (SEQ ID NO: 5491), QERST (SEQ ID NO: 5492), QNYQT (SEQ ID NO: 5493), QRTCT (SEQ ID NO: 5494), QIGHT (SEQ ID NO: 5495), QGAIT (SEQ ID NO: 5496), QVPPT (SEQ ID NO: 5497), QVQQI (SEQ ID NO: 5498), LMRQT (SEQ ID NO: 5499), QYSVT (SEQ ID NO: 5500), QAITT (SEQ ID NO: 5501), QKTLT (SEQ ID NO: 5502), QNQWT (SEQ ID NO: 5503), QLHHT (SEQ ID NO: 5504), QNIII (SEQ ID NO: 5505), QGHHT (SEQ ID NO: 5506), QSKVT (SEQ ID NO: 5507), QLPST (SEQ ID NO: 5508), IGKQT (SEQ ID NO: 5509), QAIHT (SEQ ID NO: 5510), QHGLT (SEQ ID NO: 5511), QFMCT (SEQ ID NO: 5512), QHLQT (SEQ ID NO: 5513), QNHQN (SEQ ID NO: 5514), QPART (SEQ ID NO: 5515), QSLQT (SEQ ID NO: 5516), QSQLT (SEQ ID NO: 5517), QDRQS (SEQ ID NO: 5518), QMPST (SEQ ID NO: 5519), QGSLT (SEQ ID NO: 5520), QVPAT (SEQ ID NO: 5521), QDKQT (SEQ ID NO: 5522), HYQQT (SEQ ID NO: 5523), QVPST (SEQ ID NO: 5524), RGEQT (SEQ ID NO: 5525), PGQQT (SEQ ID NO: 5526), QSLQI (SEQ ID NO: 5527), LEQQT (SEQ ID NO: 5528), QNQST (SEQ ID NO: 5529), QKVIT (SEQ ID NO: 5530), QNNDQ (SEQ ID NO: 5531), QSVHT (SEQ ID NO: 5532), QPLGT (SEQ ID NO: 5533), HNQET (SEQ ID NO: 5534), QNLQI (SEQ ID NO: 5535), QIQQT (SEQ ID NO: 5536), QVRNT (SEQ ID NO: 5537), PSNQT (SEQ ID NO: 5538), QVGHT (SEQ ID NO: 5539), QRDIT (SEQ ID NO: 5540), QMPNT (SEQ ID NO: 5541), RGLQT (SEQ ID NO: 5542),

QKQQT (SEQ ID NO: 5543), PSLQT (SEQ ID NO: 5544), QRDQT (SEQ ID NO: 5545), QAKGT (SEQ ID NO: 5546), QSAHT (SEQ ID NO: 5547), QSTMT (SEQ ID NO: 5548), QREMT (SEQ ID NO: 5549), QYRAT (SEQ ID NO: 5550), QWQQT (SEQ ID NO: 5551), QRMNT (SEQ ID NO: 5552), GDSQT (SEQ ID NO: 5553), QKIST (SEQ ID NO: 5554), PSMQT (SEQ ID NO: 5555), SPRQT (SEQ ID NO: 5556), MEQQT (SEQ ID NO: 5557), QYQNT (SEQ ID NO: 5558), QHQQT (SEQ ID NO: 5559), INQQT (SEQ ID NO: 5560), PNQQH (SEQ ID NO: 5561), ENRQT (SEQ ID NO: 5562), QTQQA (SEQ ID NO: 5563), or QNQAT (SEQ ID NO: 5564);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, or 4 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

193. The AAV capsid variant of embodiment 191 or 192, wherein [N1]-[N2]-[N3]-[N4] is or comprises:

(i) the amino acid sequence of any of SEQ ID NOs: 200 or 2887-3076;

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

194. The AAV capsid variant of any one of embodiments 191-193, wherein [N1]-[N2]-[N3]-[N4] is or comprises GSGSPHKAQNQQT (SEQ ID NO: 200).

195. The AAV capsid variant of any one of embodiments 191-193, wherein [N1]-[N2]-[N3]-[N4] is or comprises VSGSPHKAQNQQT (SEQ ID NO: 903).

196. The AAV capsid variant of any one of embodiments 168-195, which comprises an amino acid other than K at position 449 (e.g., T, E, or N), T at position 450 (e.g., S, E, A, N, V, Q, or G), an amino acid other than I at position 451 (e.g., F, E, V, L, D, S, C, T, A, N, H, R, G, or W), and/or an amino acid other than N at position 452 (e.g., I, P, K, R, H, S, M, Q, D, T, L, A, Y, V, F, E, W, or G), relative to a reference sequence numbered according to SEQ ID NO: 138 or 981.

197. The AAV capsid variant of any one of embodiments 168-196, which comprises the amino acid K at position 449, the amino acid T at position 450, the amino acid I at position 451, and/or the amino acid N at position 452, relative to a reference sequence numbered according to SEQ ID NO: 138 or 981.

198. The AAV capsid variant of any one of embodiments 168-197, which further comprises [N0], wherein [N0] comprises X_A, X_B, X_C, and X_D, wherein:

(a) X_A is K, T, E, or N;

(b) X_B is T, S, E, A, N, V, Q, or G;

(c) X_C is I, F, E, V, L, D, S, C, T, A, N, H, R, G, or W; and

(d) X_D is N, I, P, K, R, H, S, M, Q, D, T, L, A, Y, V, F, E, W, or G;

optionally wherein the AAV capsid variant comprises an amino acid modification, e.g., a conservative substitution, of any of the aforesaid amino acids in (a)-(d).

199. The AAV capsid variant of embodiment 198, wherein [N0] is or comprises:

(i) KTII (SEQ ID NO: 5565), KTFP (SEQ ID NO: 5566), KTEK (SEQ ID NO: 5567), KTVN (SEQ ID NO: 5568), KTFN (SEQ ID NO: 5569), KTIN (SEQ ID NO: 5570), TTIN (SEQ ID NO: 5571), KSIN (SEQ ID NO: 5572), KTER (SEQ ID NO: 5573), KELH (SEQ ID NO: 5574), KAIN (SEQ ID NO: 5575), KTDN (SEQ ID NO: 5576), KTFH (SEQ ID NO: 5577), KTSN (SEQ ID NO: 5578), ETIN (SEQ ID NO: 5579), NTIN (SEQ ID NO: 5580), KTEN (SEQ ID NO: 5581), KTSS (SEQ ID NO: 5582), KTCN (SEQ ID NO: 5583), KTEH (SEQ ID NO: 5584), KAEM (SEQ ID NO: 5585), KATN (SEQ ID NO: 5586), KAIK (SEQ ID NO: 5587), KTDK (SEQ ID NO: 5588), KTFK (SEQ ID NO: 5589), KSDQ (SEQ ID NO: 5590), KTEI (SEQ ID NO: 5591), KTID (SEQ ID NO: 5592), KNTN (SEQ ID NO: 5593), KTET (SEQ ID NO: 5594), KTEL (SEQ ID NO: 5595), KNIN (SEQ ID NO: 5596), KTEA (SEQ ID NO: 5597), KTAN (SEQ ID NO: 5598), NTIY (SEQ ID NO: 5599), KTFS (SEQ ID NO: 5600), KTES (SEQ ID NO: 5601), KTTN (SEQ ID NO: 5602), KTED (SEQ ID NO: 5603), KTNN (SEQ ID NO: 5604), KEVH (SEQ ID NO: 5605), KTIS (SEQ ID NO: 5606), KTVR (SEQ ID NO: 5607), KTDR (SEQ ID NO: 5608), ETIK (SEQ ID NO: 5609), KNHI (SEQ ID NO: 5610), KESD (SEQ ID NO: 5611), KTIK (SEQ ID NO: 5612), KTDL (SEQ ID NO: 5613), KTVP (SEQ ID NO: 5614), KTVI (SEQ ID NO: 5615), KAEH (SEQ ID NO: 5616), KNCL (SEQ ID NO: 5617), KTVK (SEQ ID NO: 5618), KNAD (SEQ ID NO: 5619), KTIT (SEQ ID NO: 5620), KNCV (SEQ ID NO: 5621), KNAL (SEQ ID NO: 5622), KVIN (SEQ ID NO: 5623), KTEF (SEQ ID NO: 5624), KTRE (SEQ ID NO: 5625), KQGE (SEQ ID NO: 5626), KSEK (SEQ ID NO: 5627), KNVN (SEQ ID NO: 5628), KGGE (SEQ ID NO: 5629), KEFV (SEQ ID NO: 5630), KSDK (SEQ ID NO: 5631), KTEQ (SEQ ID NO: 5632), KEVQ (SEQ ID NO: 5633), KTEY (SEQ ID NO: 5634), KNCW (SEQ ID NO: 5635), KTDV (SEQ ID NO: 5636), KSDI (SEQ ID NO: 5637), KNSI

(SEQ ID NO: 5638), KNSL (SEQ ID NO: 5639), KEVV (SEQ ID NO: 5640), KTEP (SEQ ID NO: 5641), KSEL (SEQ ID NO: 5642), KTWQ (SEQ ID NO: 5643), KTEV (SEQ ID NO: 5644), KAVN (SEQ ID NO: 5645), KGVV (SEQ ID NO: 5646), KTEG (SEQ ID NO: 5647), KTRD (SEQ ID NO: 5648), KTGN (SEQ ID NO: 5649), KNAI (SEQ ID NO: 5650), KAEN (SEQ ID NO: 5651), KAET (SEQ ID NO: 5652), KTVH (SEQ ID NO: 5653), KETA (SEQ ID NO: 5654), KNNL (SEQ ID NO: 5655), EAIN (SEQ ID NO: 5656), KSLN (SEQ ID NO: 5657), KTIP (SEQ ID NO: 5658), or KTIH (SEQ ID NO: 5659);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, or 3 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

200. The AAV capsid variant of embodiment 198 or 199, wherein [N0]-[N1]-[N2]-[N3]-[N4] is or comprises:

(i) the amino acid sequence of any one of SEQ ID NOs: 3239-3526 or 3591-3605;

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or 17 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

201. The AAV capsid variant of any one of embodiments 198-200, wherein [N0]-[N1]-[N2]-[N3]-[N4] is or comprises KTINGSGSPHKAQNQQT (SEQ ID NO: 5660).

202. The AAV capsid variant of any one of embodiments 198-200, wherein [N0]-[N1]-[N2]-[N3]-[N4] is or comprises KTERVSGSPHKAQNQQT (SEQ ID NO: 3589).

203. An AAV capsid variant comprising an amino acid sequence having the following formula: [N1]-[N2]-[N3] (SEQ ID NO: 6408), wherein:

(i) [N1] comprises positions X1, X2, and X3, wherein position X2 is an amino acid other than S and position X3 is an amino acid other than G;

- (ii) [N2] comprises the amino acid sequence SPH; and
- (iii) [N3] comprises positions X4, X5, and X6, wherein position X4 is K.

204. The AAV capsid variant of embodiment 203, wherein:

- (i) X5 of [N3] is S, I, T, R, H, Y, L, or M; and

- (ii) X6 of [N3] is G, A, L, E, V, R, W, N, Q, or K;

optionally wherein the AAV capsid variant comprises an amino acid modification, e.g., a conservative substitution, of any of the aforesaid amino acids in (i) or (ii).

205. The AAV capsid variant of embodiment 203 or 204, wherein X5 is S and/or X6 is G.

206. The AAV capsid variant of any one of embodiments 203-205, wherein [N3] comprises KS, KI, KT, KR, KH, KY, KL, KM, SG, IG, TG, RG, SA, SL, SE, SV, SR, SW, SN, HG, YG, SQ, IV, SK, LW, MG, or MA.

207. The AAV capsid variant of any one of embodiments 203-206, wherein [N3] is or comprises KSG, KIG, KTG, KRG, KSA, KSL, KSE, KSV, KSR, KSW, KSN, KHG, KYG, KSQ, KIV, KSK, KLW, KMG, or KMA.

208. The AAV capsid variant of any one of embodiments 203-207, wherein [N3] is or comprises KSG.

209. The AAV capsid variant of any one of embodiments 203-208, wherein [N2]-[N3] comprises SPHKS (SEQ ID NO: 4704), SPHKI (SEQ ID NO: 4713), SPHKT (SEQ ID NO: 4711), SPHKR (SEQ ID NO: 4717), NPHKS (SEQ ID NO: 5661), SPHKH (SEQ ID NO: 4728), SPHKY (SEQ ID NO: 4715), SPHKL (SEQ ID NO: 4714), or SPHKM (SEQ ID NO: 4729).

210. The AAV capsid variant of any one of embodiments 203-209, wherein [N2]-[N3] is or comprises:

- (i) SPHKSG (SEQ ID NO: 946), SPHKIG (SEQ ID NO: 958), SPHKTG (SEQ ID NO: 4738), SPHKRG (SEQ ID NO: 974), NPHKSG (SEQ ID NO: 5662), SPHKSA (SEQ ID NO: 977), SPHKSL (SEQ ID NO: 4740), SPHKSE (SEQ ID NO: 4741), SPHKSV (SEQ ID NO: 4742), SPHKSR (SEQ ID NO: 951), SPHKSW (SEQ ID NO: 4743), SPHKSN (SEQ ID NO: 4744), SPHKHG (SEQ ID NO: 4745), SPHKYG (SEQ ID NO: 966), SPHKSQ (SEQ ID NO: 4746), SPHKIV (SEQ ID NO: 5663), SPHKSK (SEQ ID NO: 4747), SPHKLW (SEQ ID NO: 4748), SPHKMG (SEQ ID NO: 4750), or SPHKMA (SEQ ID NO: 4751);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, or 5 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

211. The AAV capsid variant of any one of embodiments 203-210, wherein [N2]-[N3] is or comprises SPHKSG (SEQ ID NO: 946).

212. The AAV capsid variant of any one of embodiments 203-211, which comprises an amino acid other than G at position 453 (e.g., A, K, W, R, L, I, M, N, T, E, Q, Y, H, F, or V), numbered according to SEQ ID NO: 138 or 981.

213. The AAV capsid variant of any one of embodiments 203-212, which comprises the amino acid G at position 453, numbered according to SEQ ID NO: 138 or 981.

214. The AAV capsid variant of any one of embodiments 203-214, wherein:

(i) position X1 of [N1] is G, A, K, W, R, L, I, M, N, T, E, Q, Y, H, F, or V;

(ii) position X2 of [N1] is H, Y, R, Q, N, P, or D;

(iii) position X3 of [N1] is D, E, G, V, or N;

optionally wherein the AAV capsid variant comprises an amino acid modification, e.g., a conservative substitution, of any of the aforesaid amino acids in (i), (ii), or (iii).

215. The AAV capsid variant of any one of embodiments 203-214, wherein position X2 of [N1] is H and position X3 of [N1] is D.

216. The AAV capsid variant of any one of embodiments 203-215, wherein position X1 of [N1] is G, position X2 of [N1] is H and position X3 of [N1] is D.

217. The AAV capsid variant of any one of embodiments 203-216, wherein [N1] comprises GH, HD, GY, GR, GQ, AH, GN, KH, GP, WH, RH, LH, IH, MH, GD, NH, TH, EH, QH, YH, HH, FH, VH, YD, HE, RG, QD, RD, ND, PD, QV, DD, HN, or NG

218. The AAV capsid variant of any one of embodiments 203-217, wherein [N1] is or comprises GHD, GYD, GHE, GRG, GQD, GRD, AHD, GND, KHD, GPD, WHD, RHD, LHD, GQV, IHD, MHD, GDD, GHN, NHD, THD, GNG, EHD, QHD, YHD, HHD, FHD, or VHD.

219. The AAV capsid variant of any one of embodiments 203-218, wherein [N1] is or comprises GHD.

220. The AAV capsid variant of any one of embodiments 203-219, wherein [N1]-[N2] comprises HDSPH (SEQ ID NO: 4703).

221. The AAV capsid variant of any one of embodiments 203-220, wherein [N1]-[N2] is or comprises:

(i) GHDSPH (SEQ ID NO: 4784), GYDSPH (SEQ ID NO: 4829), GHESPH (SEQ ID NO: 4793), GRGSPH (SEQ ID NO: 4788), GHDNPH (SEQ ID NO: 5664), GQDSPH (SEQ ID NO: 4785), GRDSPH (SEQ ID NO: 4831), AHDSPH (SEQ ID NO: 5665), GNDSPH (SEQ ID NO: 4832), KHDSPH (SEQ ID NO: 5666), GPDSPH (SEQ ID NO: 4833), WHDSPH (SEQ ID NO: 5667), RHDSPH (SEQ ID NO: 5668), LHDSPH (SEQ ID NO: 5669), GQVSPH (SEQ ID NO: 4835), IHDSPH (SEQ ID NO: 5670), MHDSPH (SEQ ID NO: 5671), GDDSPH (SEQ ID NO: 4792), GHNSPH (SEQ ID NO: 4836), NHDSPH (SEQ ID NO: 5672), THDSPH (SEQ ID NO: 5673), GNGSPH (SEQ ID NO: 4805), EHDSPH (SEQ ID NO: 5674), QHDSPH (SEQ ID NO: 5675), YHDSPH (SEQ ID NO: 5676), HHDSPH (SEQ ID NO: 5677), FHDSPH (SEQ ID NO: 5678), or VHDSPH (SEQ ID NO: 5679);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, or 5 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

222. The AAV capsid variant of any one of embodiments 203-221, wherein [N1]-[N2]-[N3] is or comprises:

(i) GHDSPHKSG (SEQ ID NO: 4698), GHDSPHKIG (SEQ ID NO: 4996), GYDSPHKSG (SEQ ID NO: 4997), GHESPHKSG (SEQ ID NO: 4998), GHDSPHKTG (SEQ ID NO: 4999), GRGSPHKRG (SEQ ID NO: 5000), GHDNPHKSG (SEQ ID NO: 5680), GQDSPHKSG (SEQ ID NO: 4908), GHDSPHKSA (SEQ ID NO: 4940), GHDSPHKSL (SEQ ID NO: 5001), GHDSPHKSE (SEQ ID NO: 5003), GRDSPHKSG (SEQ ID NO: 5004), AHDSPHKSG (SEQ ID NO: 5681),

GNDSPHKSV (SEQ ID NO: 5005), AHDSPHKIG (SEQ ID NO: 5682), GHESPHKSA (SEQ ID NO: 4939), GQDSPHKIG (SEQ ID NO: 5006), GHDSPHKSV (SEQ ID NO: 5007), GHDSPHKSR (SEQ ID NO: 4942), KHDSPHKSG (SEQ ID NO: 5683), GPDSPHKIG (SEQ ID NO: 5008), GPDSPHKSG (SEQ ID NO: 5009), GHDSPHKSW (SEQ ID NO: 5010), WHDSPHKSG (SEQ ID NO: 5684), RHDSPHKSG (SEQ ID NO: 5685), GHDSPHKSN (SEQ ID NO: 5011), GHDSPHKRG (SEQ ID NO: 4937), GHDSPHKHG (SEQ ID NO: 5013), LHDSPHKSG (SEQ ID NO: 5686), GQVSPHKSG (SEQ ID NO: 5014), IHDSPHKSG (SEQ ID NO: 5687), MHDSPHKSG (SEQ ID NO: 5688), GDDSPHKSV (SEQ ID NO: 5015), GHNSPHKSG (SEQ ID NO: 5016), NHDSPHKSG (SEQ ID NO: 5689), THDSPHKSG (SEQ ID NO: 5690), GNGSPHKRG (SEQ ID NO: 5017), EHDSPHKSG (SEQ ID NO: 5691), GHDSPHKYG (SEQ ID NO: 5018), GHDSPHKSQ (SEQ ID NO: 5019), QHDSPHKSG (SEQ ID NO: 5692), RHDSPHKIV (SEQ ID NO: 5693), YHDSPHKSG (SEQ ID NO: 5694), GNDSPHKIG (SEQ ID NO: 5020), HHDSPHKSG (SEQ ID NO: 5695), GHDSPHKSK (SEQ ID NO: 5021), FHDSPHKSG (SEQ ID NO: 5696), GHDSPHKLW (SEQ ID NO: 5022), VHDSPHKSG (SEQ ID NO: 5697), GHDSPHKMG (SEQ ID NO: 5024), GHDSPHKMA (SEQ ID NO: 5025), or GDDSPHKSG (SEQ ID NO: 4938);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, 5, 6, 7, 8, or 9 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

223. The AAV capsid variant of any one of embodiments 203-222, wherein [N1]-[N2]-[N3] is or comprises GHDSPHKSG (SEQ ID NO: 4698).

224. The AAV capsid variant of any one of embodiments 203-223, which comprises an amino acid other than Q at position 456 (e.g., R, P, H, K, L, V, A, E, or I), an amino acid other than N at position 457 (e.g., I, K, S, H, R, T, D, Y, L, W, F, A, Q, or M), an amino acid other than Q at position 458 (e.g., R, V, K, P, Y, H, L, I, E, or M), an amino acid other than Q at position 459 (e.g., H, L, E, P, W, D, I, V, S, K, R, C, M, or N), and/or an amino acid other than T at position 460 (e.g., A, E, K, S, I, P, G, or N), relative to a reference sequence numbered according to SEQ ID NO: 138.

225. The AAV capsid variant of any one of embodiments 203-224, which comprises an amino acid other than Q at position 462 (e.g., R, P, H, K, L, V, A, E, or I), an amino acid other than N at position 463 (e.g., I, K, S, H, R, T, D, Y, L, W, F, A, Q, or M), an amino acid other than Q at position 464 (e.g., R, V, K, P, Y, H, L, I, E, or M), an amino acid other than Q at position 465 (e.g., H, L, E, P, W,

D, I, V, S, K, R, C, M, or N), and/or an amino acid other than T at position 466 (e.g., A, E, K, S, I, P, G, or N), relative to a reference sequence numbered according to SEQ ID NO: 982.

226. The AAV capsid variant of any one of embodiments 203-225, which comprises the amino acid Q at position 456, the amino acid N at position 457, the amino acid Q at position 458, the amino acid Q at position 459, and/or the amino acid T at position 460, relative to a reference sequence numbered according to SEQ ID NO: 138.

227. The AAV capsid variant of any one of embodiments 203-226, which comprises the amino acid Q at position 462, the amino acid N at position 463, the amino acid Q at position 464, the amino acid Q at position 465, and/or the amino acid T at position 466, relative to a reference sequence numbered according to SEQ ID NO: 138.

228. The AAV capsid variant of any one of embodiments 203-227, further comprising [N4] wherein [N4] comprises X7, X8, X9, X10, and X11, wherein:

- (a) X7 is Q, R, P, H, L, K, I, G, S, M, or E;
- (b) X8 is N, D, V, S, P, T, G, Y, W, E, R, H, K, F, A, I, L, or M;
- (c) X9 is Q, R, L, A, P, H, T, I, F, K, V, M, G, W, Y, S, E, N, D;
- (d) X10 is Q, H, K, A, L, P, E, M, I, S, N, R, Y, C, V, T, W, D, G; and
- (e) X11 is T, I, N, S, H, R, L, D, Y, A, Q;

optionally wherein the AAV capsid variant comprises an amino acid modification, e.g., a conservative substitution, of any of the aforesaid amino acids in (a)-(e).

229. The AAV capsid variant of embodiment 228, wherein [N4] is or comprises:

(i) QNQQT (SEQ ID NO: 5412), QIRQT (SEQ ID NO: 5698), QNQHA (SEQ ID NO: 5699), QKQQT (SEQ ID NO: 5543), QSVQT (SEQ ID NO: 5700), RSQQT (SEQ ID NO: 5701), QNKLE (SEQ ID NO: 5702), QNQQK (SEQ ID NO: 5703), QHQQA (SEQ ID NO: 5704), QIQHT (SEQ ID NO: 5705), PRQQT (SEQ ID NO: 5706), HTQQT (SEQ ID NO: 5707), QRQHT (SEQ ID NO: 5708), QSQQT (SEQ ID NO: 5418), QNQQS (SEQ ID NO: 5709), RNQET (SEQ ID NO: 5710), QTQLT (SEQ ID NO: 5478), KNQQT (SEQ ID NO: 5711), QDQQT (SEQ ID NO: 5432), HNQQT (SEQ ID NO: 5426), QNQLT (SEQ ID NO: 5423), QTQQT (SEQ ID NO: 5712), QTQQI (SEQ ID NO: 5713), QSKQA (SEQ ID NO: 5714), QNQPP (SEQ ID NO: 5715), QSPQT (SEQ ID NO: 5716), QNYQT (SEQ ID NO: 5493), QNHQT (SEQ ID NO: 5431), QNRQT (SEQ ID NO: 5446), QNQQG (SEQ ID NO: 5717), QNHLT (SEQ ID NO: 5482), QYQHT (SEQ ID NO: 5447), QNQWT (SEQ ID NO: 5503), QNQHT (SEQ ID NO: 5718), QTRQT (SEQ ID NO: 5719), QNLHT (SEQ ID NO: 5720), LNQQT (SEQ ID NO: 5471), QNQET (SEQ ID NO: 5721), QHLQT (SEQ ID NO: 5513), LNQPT (SEQ ID NO: 5722), QNQDT (SEQ ID NO: 5723), RNQQT (SEQ ID NO: 5724), QNLLT

(SEQ ID NO: 5725), QLVIT (SEQ ID NO: 5726), RTQET (SEQ ID NO: 5727), QTHQT (SEQ ID NO: 5728), QNQPA (SEQ ID NO: 5729), QDQHT (SEQ ID NO: 5730), QSQHT (SEQ ID NO: 5731), RNQOI (SEQ ID NO: 5732), VRQQT (SEQ ID NO: 5733), QNQHS (SEQ ID NO: 5734), AWQQT (SEQ ID NO: 5735), QSVPT (SEQ ID NO: 5736), QNIQP (SEQ ID NO: 5737), QNHLN (SEQ ID NO: 5738), LDQQT (SEQ ID NO: 5739), PDQQS (SEQ ID NO: 5740), ESQQT (SEQ ID NO: 5741), QNKQT (SEQ ID NO: 5742), QRQLT (SEQ ID NO: 5743), QIIVT (SEQ ID NO: 5744), QKQST (SEQ ID NO: 5745), QSHQT (SEQ ID NO: 5746), QFVVT (SEQ ID NO: 5747), QNLQT (SEQ ID NO: 5748), QNQOI (SEQ ID NO: 5749), QSQPT (SEQ ID NO: 5750), QNEQT (SEQ ID NO: 5751), QSLQT (SEQ ID NO: 5752), RNRQT (SEQ ID NO: 5753), QSKQT (SEQ ID NO: 5754), QNPLT (SEQ ID NO: 5755), RDQKT (SEQ ID NO: 5756), HNQQN (SEQ ID NO: 5757), QWKRT (SEQ ID NO: 5758), QSQOI (SEQ ID NO: 5759), QAAQT (SEQ ID NO: 5760), QNHQI (SEQ ID NO: 5761), QNQQA (SEQ ID NO: 5762), QNQLN (SEQ ID NO: 5763), QTQPT (SEQ ID NO: 5764), INQQT (SEQ ID NO: 5765), QKQLT (SEQ ID NO: 5766), RNQLA (SEQ ID NO: 5767), RNQQS (SEQ ID NO: 5768), ISIQT (SEQ ID NO: 5769), QNQQN (SEQ ID NO: 5770), QSQQS (SEQ ID NO: 5771), QTVCT (SEQ ID NO: 5772), QYQQI (SEQ ID NO: 5773), QQIMT (SEQ ID NO: 5774), QNEQS (SEQ ID NO: 5775), LNHQT (SEQ ID NO: 5776), QMIHT (SEQ ID NO: 5777), RNHQS (SEQ ID NO: 5778), QKMNT (SEQ ID NO: 5779), QSQQN (SEQ ID NO: 5780), QYQHA (SEQ ID NO: 5781);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, or 4 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

230. The AAV capsid variant of embodiment 228 or 229, wherein [N1]-[N2]-[N3]-[N4] is or comprises:

(i) the amino acid sequence of any of SEQ ID NOs: 201 or 3160-3237;

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

231. The AAV capsid variant of any one of embodiments 228-230, wherein [N1]-[N2]-[N3]-[N4] is or comprises GHDSPHKSGQNQQT (SEQ ID NO: 201).

232. The AAV capsid variant of any one of embodiments 203-231, which comprises an amino acid other than K at position 449 (e.g., T), T at position 450 (e.g., A, S, I, V, N, E, Y, C, G, W, or Q), an amino acid other than I at position 451 (e.g., E, V, S, T, N, D, C, G, Q, L, P, A), and/or an amino acid other than N at position 452 (e.g., S, Y, I, K, F, T, D, E, G, V, L, A, M, Q, H, P, or R), relative to a reference sequence numbered according to SEQ ID NO: 138 or 982.

233. The AAV capsid variant of any one of embodiments 203-232, which comprises the amino acid K at position 449, the amino acid T at position 450, the amino acid I at position 451, and/or the amino acid N at position 452, relative to a reference sequence numbered according to SEQ ID NO: 138 or 982.

234. The AAV capsid variant of any one of embodiments 203-233, which further comprises [N0], wherein [N0] comprises X_A, X_B, X_C, and X_D, wherein:

(a) X_A is K or T;

(b) X_B is T, A, S, I, V, N, E, Y, C, G, W, or Q;

(c) X_C is I, E, V, S, T, N, D, C, G, Q, L, P, A; and

(d) X_D is N, S, Y, I, K, F, T, D, E, G, V, L, A, M, Q, H, P, or R;

optionally wherein the AAV capsid variant comprises an amino acid modification, e.g., a conservative substitution, of any of the aforesaid amino acids in (a)-(d).

235. The AAV capsid variant of embodiment 234, wherein [N0] is or comprises:

(i) KAIN (SEQ ID NO: 5575), KTIN (SEQ ID NO: 5570), KTES (SEQ ID NO: 5601), TTIN (SEQ ID NO: 5571), KSIN (SEQ ID NO: 5572), KTVN (SEQ ID NO: 5568), KSIY (SEQ ID NO: 5575), KTSN (SEQ ID NO: 5578), KTTN (SEQ ID NO: 5602), KIIN (SEQ ID NO: 5576), KTIS (SEQ ID NO: 5606), KAI (SEQ ID NO: 5577), KTIK (SEQ ID NO: 5612), KTEF (SEQ ID NO: 5624), KTIT (SEQ ID NO: 5620), KTNN (SEQ ID NO: 5604), KTID (SEQ ID NO: 5592), KAIS (SEQ ID NO: 5578), KTVD (SEQ ID NO: 5579), KTIE (SEQ ID NO: 5780), KTEG (SEQ ID NO: 5647), KVIN (SEQ ID NO: 5623), KAVN (SEQ ID NO: 5645), KTIY (SEQ ID NO: 5781), KTDN (SEQ ID NO: 5576), KTCN (SEQ ID NO: 5583), KNVV (SEQ ID NO: 5782), KTEL (SEQ ID NO: 5595), KTDA (SEQ ID NO: 5783), KTEV (SEQ ID NO: 5644), KSEL (SEQ ID NO: 5642), KTEM (SEQ ID NO: 5784), KTEQ (SEQ ID NO: 5632), KTII (SEQ ID NO: 5565), KIVN (SEQ ID NO: 5785), KTEK (SEQ ID NO: 5567), KTEN (SEQ ID NO: 5581), KIGN (SEQ ID NO: 5786), KEVM (SEQ ID NO: 5787), KYQV (SEQ ID NO: 5788), KTEA (SEQ ID NO: 5597), KATN (SEQ ID NO: 5586), KTEH (SEQ ID NO: 5584), KTVE (SEQ ID NO: 5789), KAID (SEQ ID NO: 5790), KTIM

(SEQ ID NO: 5791), KEVG (SEQ ID NO: 5792), KSEM (SEQ ID NO: 5793), KAAQ (SEQ ID NO: 5794), KCGE (SEQ ID NO: 5795), KASN (SEQ ID NO: 5796), KTET (SEQ ID NO: 5594), KTIG (SEQ ID NO: 5797), KTDQ (SEQ ID NO: 5798), KELV (SEQ ID NO: 5799), KELM (SEQ ID NO: 5800), KNEI (SEQ ID NO: 5801), KTPN (SEQ ID NO: 5802), KITN (SEQ ID NO: 5803), KTDI (SEQ ID NO: 5804), KTDQ (SEQ ID NO: 5805), KGIN (SEQ ID NO: 5806), KSEI (SEQ ID NO: 5807), KSEK (SEQ ID NO: 5627), KWSA (SEQ ID NO: 5808), KELA (SEQ ID NO: 5809), KQTQ (SEQ ID NO: 5810), KGAD (SEQ ID NO: 5811), KVGE (SEQ ID NO: 5812), KANE (SEQ ID NO: 5813), KTDI (SEQ ID NO: 5814), KTCI (SEQ ID NO: 5815), KELR (SEQ ID NO: 5816), KCQI (SEQ ID NO: 5817), KGVN (SEQ ID NO: 5818), KACD (SEQ ID NO: 5819), KNEI (SEQ ID NO: 5820), KAAE (SEQ ID NO: 5821), KGQN (SEQ ID NO: 5822), KNEF (SEQ ID NO: 5823), KTSI (SEQ ID NO: 5824), KAEH (SEQ ID NO: 5616), KCDQ (SEQ ID NO: 5825), KEIL (SEQ ID NO: 5826), KTER (SEQ ID NO: 5573), KNAI (SEQ ID NO: 5650), KTDK (SEQ ID NO: 5588), KTPD (SEQ ID NO: 5827), KTIH (SEQ ID NO: 5659), or KTEI (SEQ ID NO: 5591);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, or 3 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

236. The AAV capsid variant of embodiment 234 or 235, wherein [N0]-[N1]-[N2]-[N3]-[N4] is or comprises:

(i) the amino acid sequence of any one of SEQ ID NOs: 3606-3836;

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or 17 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

237. The AAV capsid variant of any one of embodiments 234-236, wherein [N0]-[N1]-[N2]-[N3]-[N4] is or comprises KTINGHDSPHKSGQNQQT (SEQ ID NO: 5828).

238. The AAV capsid variant of any one of embodiments 234-236, wherein [N0]-[N1]-[N2]-[N3]-[N4] is or comprises KAEIGHDSPHKSGQNQQT (SEQ ID NO: 1754).
239. The AAV capsid variant of any one of embodiments 234-236, wherein [N0]-[N1]-[N2]-[N3]-[N4] is or comprises KTEKMSGSPHKAQNQQT (SEQ ID NO: 3241).
240. The AAV capsid variant of any one of embodiments 168-239, wherein [N1]-[N2]-[N3] is present in loop IV.
241. The AAV capsid variant of any one of embodiments 198-202 or 234-240, wherein [N0] and [N4] are present in loop IV.
242. The AAV capsid variant of any one of embodiments 198-202 or 234-241, wherein [N0] is present immediately subsequent to position 448, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138, 981, or 982.
243. The AAV capsid variant of any one of embodiments 198-202 or 234-242, wherein [N0] replaces positions 449-452 (e.g., K449, T450, I451, and N452), relative to a reference sequence numbered according to SEQ ID NO: 138, 981, or 982.
244. The AAV capsid variant of any one of embodiments 198-202 or 234-243, wherein [N0] is present immediately subsequent to position 448 and wherein [N0] replaces positions 449-452 (e.g., K449, T450, I451, and N452), relative to a reference sequence numbered according to SEQ ID NO: 138, 981, or 982.
245. The AAV capsid variant of any one of embodiments 198-202 or 234-244, wherein [N0] corresponds to positions 449-452 (e.g., K449, T450, I451, and N452) of any one of SEQ ID NOs: 138, 981, or 982.
246. The AAV capsid variant of any one of embodiments 168-245, wherein [N1] is present immediately subsequent to position 452, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138, 981, or 982.
247. The AAV capsid variant of any one of embodiments 168-246, wherein [N1] replaces positions 453-455 (e.g., G453, S454, and G455), relative to a reference sequence numbered according to SEQ ID NO: 138, 981, or 982.

248. The AAV capsid variant of any one of embodiments 168-246, wherein [N1] replaces position 453 (e.g., G453), relative to a reference sequence numbered according to SEQ ID NO: 138, 981, or 982.

249. The AAV capsid variant of any one of embodiments 168-177, 179-181, 183-185, 187-193, 195-200, 202, or 240-246, wherein:

- (i) position X1 of [N1] replaces position 453 (e.g., G453);
 - (ii) position X2 of [N1] corresponds to position 454 (e.g., S454); and
 - (iii) position X3 of [N1] corresponds to position 455 (e.g., G455),
- wherein (i), (ii), and (iii) are numbered according to SEQ ID NO: 138 or SEQ ID NO: 981.

250. The AAV capsid variant of any one of embodiments 168-176, 178-201, or 240-246, wherein:

- (i) position X1 of [N1] corresponds to position 453 (e.g., G453);
 - (ii) position X2 of [N1] corresponds to position 454 (e.g., S454); and
 - (iii) position X3 of [N1] corresponds to position 455 (e.g., G455);
- wherein (i), (ii), and (iii) are numbered according to SEQ ID NO: 138 or SEQ ID NO: 981.

251. The AAV capsid variant of any one of embodiments 203-248, wherein:

- (i) position X1 of [N1] corresponds to position 453 (e.g., G453);
 - (ii) position X2 of [N1] replaces position 454 (e.g., S454); and
 - (iii) position X3 of [N1] replaces position 455 (e.g., G455),
- wherein (i), (ii), and (iii) are numbered according to SEQ ID NO: 138 or SEQ ID NO: 982.

252. The AAV capsid variant of any one of embodiments 203-248 or 251, wherein [N1] corresponds to positions 453-455 (e.g., G453, H454, D455) of SEQ ID NO 982.

253. The AAV capsid variant of any one of embodiments 168-176, 178-201, 240-247, or 250, wherein [N1] corresponds to positions 453-455 (e.g., G453, S454, G455) of SEQ ID NO: 138, or 981.

254. The AAV capsid variant of any one of embodiments 168-253, wherein [N2] is present immediately subsequent to position 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138, 981, or 982.

255. The AAV capsid variant of any one of embodiments 168-254, wherein [N2] corresponds to positions 456-458 (e.g., S456, P457, and H458) of SEQ ID NO: 981 or 982.

256. The AAV capsid variant of any one of embodiments 168-254, wherein [N2] corresponds to positions 456-458 (e.g., S456, P457, and H458) of any one of SEQ ID NOs: 36-59.
257. The AAV capsid variant of any one of embodiments 168-256, wherein [N2] is present immediately subsequent to [N1].
258. The AAV capsid variant of any one of embodiments 168-202, 240-247, 249-257, wherein [N3] corresponds to positions 459-460 (e.g., S459, K460, A461) of SEQ ID NO: 981.
259. The AAV capsid variant of any one of embodiments 168-202, 240-247, 249-257, wherein [N3] corresponds to positions 459-460 (e.g., S459, K460, A461) of SEQ ID NO: 36, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 57, or 59.
260. The AAV capsid variant of any one of embodiments 168-259, wherein [N2]-[N3] is present immediately subsequent to position 455, relative to a reference sequence numbered according to the amino acid sequence of any one of SEQ ID NOs: 138, 981, or 982.
261. The AAV capsid variant of any one of embodiments 168-259, wherein [N2]-[N3] is present immediately subsequent to position 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 981.
262. The AAV capsid variant of any one of embodiments 168-261, wherein [N2]-[N3] corresponds to positions 456-461 (e.g., S456, P457, H458, S459, K460, A461) of SEQ ID NO: 981.
263. The AAV capsid variant of any one of embodiments 168-262, wherein [N2]-[N3] corresponds to positions 456-461 (e.g., S456, P457, H458, S459, K460, A461) of any one of SEQ ID NOs: 36, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 57, or 59.
264. The AAV capsid variant of any one of embodiments 203-257 or 259-261, wherein [N3] corresponds to positions 459-460 (e.g., K459, S460, G461) of SEQ ID NO: 982.
265. The AAV capsid variant of any one of embodiments 203-257 or 259-261, wherein [N3] corresponds to positions 459-460 (e.g., K459, S460, G461) of SEQ ID NO: 37.
266. The AAV capsid variant of any one of embodiments 203-265, wherein [N2]-[N3] is present immediately subsequent to position 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 982.

267. The AAV capsid variant of any one of embodiments 203-246, 248, 252, 255, 257, 260, 263-266, wherein [N3] replaces positions 454 and 455 (e.g., S454 and G455), numbered according to SEQ ID NO: 138.

268. The AAV capsid variant of any one of embodiments 203-246, 248, 252, 255, 257, 260, 263-267, wherein [N3] is present immediately subsequent to [N2] and replaces positions 454 and 455 (e.g., S454 and G455), numbered according to SEQ ID NO: 138.

269. The AAV capsid variant of any one of embodiments 203-246, 248, 252, 255, 257, 260, 263-268, wherein [N3] is present immediately subsequent to [N1]-[N2] and replaces positions 454 and 455 (e.g., S454 and G455), numbered according to SEQ ID NO: 138.

270. The AAV capsid variant of any one of embodiments 203-257, 260, 264-269, wherein [N2]-[N3] corresponds to positions 456-461 (e.g., S456, P457, H458, K459, S460, G461) of SEQ ID NO: 982.

271. The AAV capsid variant of any one of embodiments 203-257, 260, 264-270, wherein [N2]-[N3] corresponds to positions 456-461 (e.g., S456, P457, H458, K459, S460, G461) of SEQ ID NO: 37.

272. The AAV capsid variant of any one of embodiments 191-202 or 228-271, wherein [N4] is present immediately subsequent to position 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

273. The AAV capsid variant of any one of embodiments 191-202 or 228-272, wherein [N4] replaces positions 456-460 (e.g., Q456, N457, Q458, Q459, and T460), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

274. The AAV capsid variant of any one of embodiments 191-202 or 228-273, wherein [N4] corresponds to positions 462-466 (e.g., Q462, N463, Q464, Q465, and T466) of SEQ ID NO: 981 or 982.

275. The AAV capsid variant of any one of embodiments 191-202 or 228-273, wherein [N4] corresponds to positions 462-466 of any one of SEQ ID NOs: 36-59.

276. The AAV capsid variant of any one of embodiments 191-202 or 228-274, wherein [N4] corresponds to positions 456-460 (e.g., Q456, N457, Q458, Q459, and T460) of SEQ ID NO: 138.

277. The AAV capsid variant of any one of embodiments 191-202 or 228-276, wherein [N2]-[N3]-[N4] replaces positions 456-460 (e.g., Q456, N457, Q458, Q459, and T460), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

278. The AAV capsid variant of any one of embodiments 191-202 or 228-277, wherein [N2]-[N3]-[N4] is present immediately subsequent to position 455, and wherein [N2]-[N3]-[N4] replaces positions 456-460 (e.g., Q456, N457, Q458, Q459, and T460), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

279. The AAV capsid variant of any one of embodiments 191-202 or 228-278, wherein [N1]-[N2]-[N3]-[N4] replaces positions 453-460 (e.g., G453, S454, G455, Q456, N457, Q458, Q459, and T460), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

280. The AAV capsid variant of any one of embodiments 191-202 or 228-279, wherein [N1]-[N2]-[N3]-[N4] is present immediately subsequent to position 452, and wherein [N1]-[N2]-[N3]-[N4] replaces positions 453-460 (e.g., G453, S454, G455, Q456, N457, Q458, Q459, and T460), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

281. The AAV capsid variant of any one of embodiments 191-202, 240-247, 249, 250, 253-263, 266, or 272-280, wherein [N1]-[N2]-[N3]-[N4] corresponds to positions 453-466 (e.g., G453, S454, G455, S456, P457, H458, S459, K460, A461, Q462, N463, Q464, Q465, and T466) of SEQ ID NO: 981.

282. The AAV capsid variant of any one of embodiments 168-202, 240-247, 249, 250, 253-263, 266, or 272-280, wherein [N1]-[N2]-[N3] corresponds to positions 453-461 (e.g., G453, S454, G455, S456, P457, H458, S459, K460, A461) of SEQ ID NO: 981.

283. The AAV capsid variant of any one of embodiments 228-257, 260, 261, 264-282, wherein [N1]-[N2]-[N3]-[N4] corresponds to positions 453-466 (e.g., G453, H454, D455, S456, P457, H458, K459, S460, G461, Q462, N463, Q464, Q465, T466) of SEQ ID NO: 982.

284. The AAV capsid variant of any one of embodiments 203-257, 260, 261, 264-283, wherein [N1]-[N2]-[N3] corresponds to positions 453-461 (e.g., G453, H454, D455, S456, P457, H458, K459, S460, G461) of SEQ ID NO: 982.

285. The AAV capsid variant of any one of embodiments 228-257, 260, 261, 264-282, wherein [N1]-[N2]-[N3]-[N4] corresponds to positions 453-466 of any one of SEQ ID NOs: 36-59.

286. The AAV capsid variant of any one of embodiments 198-202 or 234-286, wherein [N0]-[N1]-[N2]-[N3]-[N4] replaces positions 449-460 (e.g., K449, T450, I451, N452, G453, S454, G455, Q456, N457, Q458, Q459, and T460), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

287. The AAV capsid variant of any one of embodiments 198-202 or 234-286, wherein [N0]-[N1]-[N2]-[N3]-[N4] is present immediately subsequent to position 449, and wherein [N0]-[N1]-[N2]-[N3]-[N4] replaces positions 449-460 (e.g., K449, T450, I451, N452, G453, S454, G455, Q456, N457, Q458, Q459, and T460), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

288. The AAV capsid variant of any one of embodiments 198-202, 240-247, 249, 250, 253-263, 266, 272-281, 286, or 287, wherein [N0]-[N1]-[N2]-[N3]-[N4] corresponds to positions 449-466 (e.g., K449, T450, I451, N452, G453, S454, G455, S456, P457, H458, S459, K460, A461, Q462, N463, Q464, Q465, T466) of SEQ ID NO: 981.

289. The AAV capsid variant of any one of embodiments 234-257, 260, 261, 264-284, 286, or 287, wherein [N0]-[N1]-[N2]-[N3]-[N4] corresponds to positions 449-466 (e.g., K449, T450, I451, N452, G453, H454, D455, S456, P457, H458, K459, S460, G461, Q462, N463, Q464, Q465, T466) of SEQ ID NO: 982.

290. The AAV capsid variant of any one of embodiments 234-257, 260, 261, 264-284, 286, or 287, wherein [N0]-[N1]-[N2]-[N3]-[N4] corresponds to positions 449-466 of any one of SEQ ID NOs: 36-59.

291. The AAV capsid variant of any one of embodiments 191-202 or 228-290, wherein [N4] is present immediately subsequent to position 461, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 981 or 982.

292. The AAV capsid variant of any one of embodiments 191-202 or 228-291, wherein [N4] replaces positions 462-466 (e.g., Q462, N463, Q464, Q465, and T466), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 981 or 982.

293. The AAV capsid variant of any one of embodiments 191-202 or 228-292, wherein [N2]-[N3]-[N4] replaces positions 462-466 (e.g., Q462, N463, Q464, Q465, and T466), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 981 or 982.

294. The AAV capsid variant of any one of embodiments 191-202 or 228-293, wherein [N2]-[N3]-[N4] is present immediately subsequent to position 455, and wherein [N2]-[N3]-[N4] replaces positions 462-466 (e.g., Q462, N463, Q464, Q465, and T466), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 981 or 982.
295. The AAV capsid variant of any one of embodiments 168-294, which comprises from N-terminus to C-terminus, [N2]-[N3].
296. The AAV capsid variant of any one of embodiments 168-295, which comprises from N-terminus to C-terminus, [N1]-[N2]-[N3].
297. The AAV capsid variant of any one of embodiments 168-296, which comprises from N-terminus to C-terminus, [N0]-[N1]-[N2]-[N3].
298. The AAV capsid variant of any one of embodiments 168-297, which comprises from N-terminus to C-terminus, [N1]-[N2]-[N3]-[N4].
299. The AAV capsid variant of any one of embodiments 168-298, which comprises from N-terminus to C-terminus, [N0]-[N1]-[N2]-[N3]-[N4].
300. An AAV capsid variant comprising the formula [A]-[B] (SEQ ID NO: 4696), wherein:
- (i) [A] comprises GSGSPH (SEQ ID NO: 4695); and
 - (ii) [B] comprises X1 X2, X3, X4, and X5, wherein:
 - (a) position X1 is S, I, F, V, C, Y, W, R, P, L, Q, M, K, or G;
 - (b) position X2 is K, M, R, F, V, C, P, Y, L, W, G, N, S, T, I, or A;
 - (c) position X3 is A, Y, L, R, W, C, T, F, H, I, P, M, K, S, V, G, Q, or N;
 - (d) position X4 is Q, M, F, K, H, R, C, W, P, V, L, G, S, Y, I, A, T, D, N, or E; and
 - (e) position X5 is A, N, Y, R, K, L, I, M, Q, S, C, W, F, T, G, V, or P;optionally wherein the AAV capsid variant comprises an amino acid modification, e.g., a conservative substitution, of any of the aforesaid amino acids in (a)-(e).
301. The AAV capsid variant of embodiment 300, wherein:
- (a) position X1 is S, L, R, V, or P;
 - (b) position X2 is K, C, F, L, P, R, S, or V;
 - (c) position X3 is A, C, F, I, K, L, M, P, R, T, W, or Y;
 - (d) position X4 is Q, R, S, T, C, F, K, L, P or Y; and
 - (e) position X5 is N, R, S, T, K, M, Q or Y;

optionally wherein the AAV capsid variant comprises an amino acid modification, e.g., a conservative substitution, of any of the aforesaid amino acids in (a)-(e).

302. The AAV capsid variant of embodiment 300 or 301, wherein [B] comprises SKA, SMY, SKL, SKR, SKW, SRC, SFT, SKF, IVW, SKY, SCH, FPW, SKI, VYY, SLY, SKP, SRF, SRM, SVK, SWA, SLW, SFR, SKK, SYA, SCS, SGA, SFP, SFF, SMC, SKT, SGK, FYR, CRV, YGI, VNC, SLA, WSY, RWL, PSC, SSW, SKG, VPW, SGC, STT, PKR, SKC, WVP, SFW, RIK, SKM, LRW, LPT, SYM, LLC, RCC, LCV, SYL, QGC, MAF, SFQ, SLC, RPW, RPR, SCP, SVR, SLP, VYH, SYT, LVY, YRY, SWL, CPA, SPP, RWT, PRK, PFV, SKS, WVA, SKV, CAL, SSC, SKN, LCT, STC, SKQ, KSG, SYY, SLT, SCQ, FPF, SVF, GRY, AQA, AQN, YMN, AFY, LKR, RHR, AQK, WRL, CRN, TCN, FFI, AQY, WQN, YFM, ARQ, HQN, IRR, YQN, YWN, AFS, FWN, AQC, MRN, KKN, APN, WKN, ARW, RPN, KVF, AFN, ACS, RLW, SRN, CPN, ACN, FRQ, PFN, FGN, CQN, LFW, TRK, KRN, RQN, VQN, IQN, AQR, PFR, AWN, RSY, LQN, WLN, RRA, AQT, GCT, RYT, TPN, ARM, CFL, PQN, WSN, FKN, KQN, APR, RYN, MIC, TQN, WKS, AAR, LTR, IRG, LVN, FQN, ACQ, WGL, ILR, QIN, ACI, ALR, AHA, CLN, AFV, AQF, RCN, MPC, KTS, PYN, AQS, TRN, LKN, AQM, CTN, PDN, RNY, ACR, CSV, ARI, LPK, SEQ, VRM, NSR, RKR, ARN, QRP, RVV, GQN, YSN, QSN, AKG, CTS, FEN, AKK, KAQ, MYM, KAF, KLF, KRH, KWR, RCR, FTC, KFF, VWQ, KYF, KAR, CHQ, PWQ, KIR, YYQ, LYW, KPK, RFW, RMR, VKK, WAP, LWK, FRP, KKV, YAF, KAC, KRL, CSR, RCP, GAC, KFR, FFG, MCQ, KLF, KTR, GKR, YRQ, RVQ, GIQ, NCQ, KPF, LAW, KRS, SYQ, WLQ, KRR, KGC, KRY, GCQ, FTP, TTC, KRQ, KCF, VPQ, FWS, KFK, IKQ, KAP, FRY, KMI, RWQ, PTQ, KWK, YMR, KAA, LCQ, CCQ, CVQ, KLT, KLC, YLV, AFQ, KWG, KIL, FQI, KAL, KAH, LCL, PRQ, CPQ, VRY, VRC, KMP, KKT, LPY, YHQ, YTR, VYQ, RYQ, WLK, PAQ, MCT, PPD, WTQ, RKQ, KCS, FVQ, KLP, KSE, VAQ, LYQ, KVR, ALQ, SCT, KNS, KRK, CTQ, TCL, YAR, KQR, KRV, SGQ, YYS, LTC, CQS, KAK, KPQ, PFQ, KCT, or VFE.

303. The AAV capsid variant of any one of embodiments 300-302, wherein [B] comprises SKAQ (SEQ ID NO: 5829), SMYM (SEQ ID NO: 5830), SKAF (SEQ ID NO: 5831), SKLK (SEQ ID NO: 5832), SKRH (SEQ ID NO: 5833), SKWR (SEQ ID NO: 5834), SRCR (SEQ ID NO: 5835), SFTC (SEQ ID NO: 5836), SKFF (SEQ ID NO: 5837), IVWQ (SEQ ID NO: 5838), SKYF (SEQ ID NO: 5839), SKAR (SEQ ID NO: 5840), SCHQ (SEQ ID NO: 5841), FPWQ (SEQ ID NO: 5842), SKIR (SEQ ID NO: 5843), VYYQ (SEQ ID NO: 5844), SLYW (SEQ ID NO: 5845), SKPK (SEQ ID NO: 5846), SRFW (SEQ ID NO: 5847), SRMR (SEQ ID NO: 5848), SVKK (SEQ ID NO: 5849), SWAP (SEQ ID NO: 5850), SLWK (SEQ ID NO: 5851), SFRP (SEQ ID NO: 5852), SKKV (SEQ ID NO: 5853), SYAF (SEQ ID NO: 5854), SKAC (SEQ ID NO: 5855), SKRL (SEQ ID NO: 5856), SCSR (SEQ ID NO: 5857), SRCP (SEQ ID NO: 5858), SGAC (SEQ ID NO: 5859), SKFR (SEQ ID NO: 5860), SFPF (SEQ ID NO: 5861), SFFG (SEQ ID NO: 5862), SMCQ (SEQ ID NO: 5863), SKLF

(SEQ ID NO: 5864), SKTR (SEQ ID NO: 5865), SGKR (SEQ ID NO: 5866), FYRQ (SEQ ID NO: 5867), CRVQ (SEQ ID NO: 5868), YGIQ (SEQ ID NO: 5869), VNCQ (SEQ ID NO: 5870), SKPF (SEQ ID NO: 5871), SLAW (SEQ ID NO: 5872), SKRS (SEQ ID NO: 5873), WSYQ (SEQ ID NO: 5874), RWLQ (SEQ ID NO: 5875), PSCQ (SEQ ID NO: 5876), SSWL (SEQ ID NO: 5877), SKRR (SEQ ID NO: 5878), SKGC (SEQ ID NO: 5879), VPWQ (SEQ ID NO: 5880), SKRY (SEQ ID NO: 5881), SGCQ (SEQ ID NO: 5882), SFTP (SEQ ID NO: 5883), STTC (SEQ ID NO: 5884), PKRQ (SEQ ID NO: 5885), SKCF (SEQ ID NO: 5886), WVPQ (SEQ ID NO: 5887), SFWS (SEQ ID NO: 5888), SKFK (SEQ ID NO: 5889), RIKQ (SEQ ID NO: 5890), SKAP (SEQ ID NO: 5891), SFRY (SEQ ID NO: 5892), SKMI (SEQ ID NO: 5893), LRWQ (SEQ ID NO: 5894), LPTQ (SEQ ID NO: 5895), SKWK (SEQ ID NO: 5896), SYMR (SEQ ID NO: 5897), SKAA (SEQ ID NO: 5898), LLCQ (SEQ ID NO: 5899), RCCQ (SEQ ID NO: 5900), LCVQ (SEQ ID NO: 5901), SKLT (SEQ ID NO: 5902), SKLC (SEQ ID NO: 5903), SYLV (SEQ ID NO: 5904), QGCQ (SEQ ID NO: 5905), MAFQ (SEQ ID NO: 5906), SKWG (SEQ ID NO: 5907), SKIL (SEQ ID NO: 5908), SFQI (SEQ ID NO: 5909), SKAL (SEQ ID NO: 5910), SKAH (SEQ ID NO: 5911), SLCL (SEQ ID NO: 5912), RPWQ (SEQ ID NO: 5913), RPRQ (SEQ ID NO: 5914), SCPQ (SEQ ID NO: 5915), SVRY (SEQ ID NO: 5916), SVRC (SEQ ID NO: 5917), SKMP (SEQ ID NO: 5918), SKKT (SEQ ID NO: 5919), SLPY (SEQ ID NO: 5920), VYHQ (SEQ ID NO: 5921), SYTR (SEQ ID NO: 5922), LVYQ (SEQ ID NO: 5923), YRYQ (SEQ ID NO: 5924), SWLK (SEQ ID NO: 5925), CPAQ (SEQ ID NO: 5926), SMCT (SEQ ID NO: 5927), SPPD (SEQ ID NO: 5928), SKRN (SEQ ID NO: 5929), RWTQ (SEQ ID NO: 5930), PRKQ (SEQ ID NO: 5931), SKCS (SEQ ID NO: 5932), PFVQ (SEQ ID NO: 5933), SKLP (SEQ ID NO: 5934), SKSE (SEQ ID NO: 5935), WVAQ (SEQ ID NO: 5936), SLYQ (SEQ ID NO: 5937), SKVR (SEQ ID NO: 5938), CALQ (SEQ ID NO: 5939), SSCT (SEQ ID NO: 5940), SKNS (SEQ ID NO: 5941), SKRK (SEQ ID NO: 5942), LCTQ (SEQ ID NO: 5943), STCL (SEQ ID NO: 5944), SYAR (SEQ ID NO: 5945), SKQR (SEQ ID NO: 5946), SKRV (SEQ ID NO: 5947), KSGQ (SEQ ID NO: 5948), SYYS (SEQ ID NO: 5949), SLTC (SEQ ID NO: 5950), SCQS (SEQ ID NO: 5951), SKAK (SEQ ID NO: 5952), SKPQ (SEQ ID NO: 5953), FPFQ (SEQ ID NO: 5954), SKCT (SEQ ID NO: 5955), SVFE (SEQ ID NO: 5956), GRYQ (SEQ ID NO: 5957), KAQA (SEQ ID NO: 5958), KQAN (SEQ ID NO: 5959), MYMN (SEQ ID NO: 5960), KAFY (SEQ ID NO: 5961), KLKR (SEQ ID NO: 5962), KRHR (SEQ ID NO: 5963), KQK (SEQ ID NO: 5964), KWRL (SEQ ID NO: 5965), RCRN (SEQ ID NO: 5966), FTCN (SEQ ID NO: 5967), KFFI (SEQ ID NO: 5968), KQY (SEQ ID NO: 5969), VWQN (SEQ ID NO: 5970), KYFM (SEQ ID NO: 5971), KARQ (SEQ ID NO: 5972), CHQN (SEQ ID NO: 5973), PWQN (SEQ ID NO: 5974), KIRR (SEQ ID NO: 5975), YYQN (SEQ ID NO: 5976), LYWN (SEQ ID NO: 5977), KPKR (SEQ ID NO: 5978), KAFS (SEQ ID NO: 5979), RFWN (SEQ ID NO: 5980), KQAC (SEQ ID NO: 5981), RMRN (SEQ ID NO: 5982), VKKN (SEQ ID NO: 5983), WAPN (SEQ ID NO: 5984), LWKN (SEQ ID NO: 5985), KARW (SEQ ID NO: 5986), FRPN (SEQ ID NO: 5987), KKVf (SEQ ID NO: 5988), YAFN (SEQ ID NO: 5989), KACS (SEQ ID NO: 5990), KRLW (SEQ ID NO: 5991), CSRN (SEQ ID NO: 5992), RCPN (SEQ ID NO:

5993), GACN (SEQ ID NO: 5994), KFRQ (SEQ ID NO: 5995), FPFN (SEQ ID NO: 5996), FFGN (SEQ ID NO: 5997), MCQN (SEQ ID NO: 5998), KLFW (SEQ ID NO: 5999), KTRK (SEQ ID NO: 6000), GKRN (SEQ ID NO: 6001), YRQN (SEQ ID NO: 6002), RVQN (SEQ ID NO: 6003), GIQN (SEQ ID NO: 6004), KAQR (SEQ ID NO: 6005), NCQN (SEQ ID NO: 6006), KPFR (SEQ ID NO: 6007), LAWN (SEQ ID NO: 6008), KRSY (SEQ ID NO: 6009), SYQN (SEQ ID NO: 6010), WLQN (SEQ ID NO: 6011), SCQN (SEQ ID NO: 6012), SWLN (SEQ ID NO: 6013), KRRR (SEQ ID NO: 6014), KAQT (SEQ ID NO: 6015), KGCT (SEQ ID NO: 6016), KRYT (SEQ ID NO: 6017), GCQN (SEQ ID NO: 6018), FTPN (SEQ ID NO: 6019), TTCN (SEQ ID NO: 6020), KARM (SEQ ID NO: 6021), KRQN (SEQ ID NO: 6022), KCFL (SEQ ID NO: 6023), VPQN (SEQ ID NO: 6024), FWSN (SEQ ID NO: 6025), KFKN (SEQ ID NO: 6026), IKQN (SEQ ID NO: 6027), KAPR (SEQ ID NO: 6028), FRYN (SEQ ID NO: 6029), KMIC (SEQ ID NO: 6030), RWQN (SEQ ID NO: 6031), PTQN (SEQ ID NO: 6032), KWKS (SEQ ID NO: 6033), YMRN (SEQ ID NO: 6034), KAAR (SEQ ID NO: 6035), LCQN (SEQ ID NO: 6036), CCQN (SEQ ID NO: 6037), CVQN (SEQ ID NO: 6038), KLTR (SEQ ID NO: 6039), KLCT (SEQ ID NO: 6040), KIRG (SEQ ID NO: 6041), YLVN (SEQ ID NO: 6042), AFQN (SEQ ID NO: 6043), KACQ (SEQ ID NO: 6044), KWGL (SEQ ID NO: 6045), KILR (SEQ ID NO: 6046), FQIN (SEQ ID NO: 6047), KACI (SEQ ID NO: 6048), KALR (SEQ ID NO: 6049), KAHA (SEQ ID NO: 6050), LCLN (SEQ ID NO: 6051), KAFV (SEQ ID NO: 6052), PRQN (SEQ ID NO: 6053), CPQN (SEQ ID NO: 6054), KAQF (SEQ ID NO: 6055), VRYN (SEQ ID NO: 6056), VRCN (SEQ ID NO: 6057), KMPC (SEQ ID NO: 6058), KKTS (SEQ ID NO: 6059), LPYN (SEQ ID NO: 6060), YHQN (SEQ ID NO: 6061), KACS (SEQ ID NO: 6062), YTRN (SEQ ID NO: 6063), VYQN (SEQ ID NO: 6064), RYQN (SEQ ID NO: 6065), WLKN (SEQ ID NO: 6066), KAAQ (SEQ ID NO: 6067), PAQN (SEQ ID NO: 6068), MCTN (SEQ ID NO: 6069), PPDN (SEQ ID NO: 6070), KRNY (SEQ ID NO: 6071), WTQN (SEQ ID NO: 6072), KACR (SEQ ID NO: 6073), RKQN (SEQ ID NO: 6074), KCSV (SEQ ID NO: 6075), KARI (SEQ ID NO: 6076), FVQN (SEQ ID NO: 6077), KLPK (SEQ ID NO: 6078), KSEQ (SEQ ID NO: 6079), VAQN (SEQ ID NO: 6080), LYQN (SEQ ID NO: 6081), KVRM (SEQ ID NO: 6082), ALQN (SEQ ID NO: 6083), SCTN (SEQ ID NO: 6084), KNSR (SEQ ID NO: 6085), KRKR (SEQ ID NO: 6086), CTQN (SEQ ID NO: 6087), TCLN (SEQ ID NO: 6088), YARN (SEQ ID NO: 6089), KQRP (SEQ ID NO: 6090), KRVV (SEQ ID NO: 6091), SGQN (SEQ ID NO: 6092), YYSN (SEQ ID NO: 6093), LTCN (SEQ ID NO: 6094), CQSN (SEQ ID NO: 6095), KAKG (SEQ ID NO: 6096), KPQN (SEQ ID NO: 6097), PFQN (SEQ ID NO: 6098), KCTS (SEQ ID NO: 6099), VFEN (SEQ ID NO: 6100), or KAKK (SEQ ID NO: 6101).

304. The AAV capsid variant of any one of embodiments 300-303, wherein [B] is or comprises:

(i) SKAQA (SEQ ID NO: 6102), SKAQN (SEQ ID NO: 6103), SMYMN (SEQ ID NO: 6104), SKAFY (SEQ ID NO: 6105), SKLKR (SEQ ID NO: 6106), SKRHR (SEQ ID NO: 6107), SKAQK (SEQ ID NO: 6108), SKWRL (SEQ ID NO: 6109), SRCRN (SEQ ID NO: 6110), SFTCN

(SEQ ID NO: 6111), SKFFI (SEQ ID NO: 6112), SKAQY (SEQ ID NO: 6113), IVWQN (SEQ ID NO: 6114), SKYFM (SEQ ID NO: 6115), SKARQ (SEQ ID NO: 6116), SCHQN (SEQ ID NO: 6117), FPWQN (SEQ ID NO: 6118), SKIRR (SEQ ID NO: 6119), VYYQN (SEQ ID NO: 6120), SLYWN (SEQ ID NO: 6121), SKPKR (SEQ ID NO: 6122), SKAFS (SEQ ID NO: 6123), SRFWN (SEQ ID NO: 6124), SKAQC (SEQ ID NO: 6125), SRMRN (SEQ ID NO: 6126), SVKKN (SEQ ID NO: 6127), SWAPN (SEQ ID NO: 6128), SLWKN (SEQ ID NO: 6129), SKARW (SEQ ID NO: 6130), SFRPN (SEQ ID NO: 6131), SKKVF (SEQ ID NO: 6132), SYAFN (SEQ ID NO: 6133), SKACS (SEQ ID NO: 6134), SKRLW (SEQ ID NO: 6135), SCSRN (SEQ ID NO: 6136), SRCPN (SEQ ID NO: 6137), SGACN (SEQ ID NO: 6138), SKFRQ (SEQ ID NO: 6139), SFPFN (SEQ ID NO: 6140), SFFGN (SEQ ID NO: 6141), SMCQN (SEQ ID NO: 6142), SKLFW (SEQ ID NO: 6143), SKTRK (SEQ ID NO: 6144), SGKRN (SEQ ID NO: 6145), FYRQN (SEQ ID NO: 6146), CRVQN (SEQ ID NO: 6147), YGIQN (SEQ ID NO: 6148), SKAQR (SEQ ID NO: 6149), VNCQN (SEQ ID NO: 6150), SKPFR (SEQ ID NO: 6151), SLAWN (SEQ ID NO: 6152), SKRSY (SEQ ID NO: 6153), WSYQN (SEQ ID NO: 6154), RWLQN (SEQ ID NO: 6155), PSCQN (SEQ ID NO: 6156), SSWLN (SEQ ID NO: 6157), SKRRA (SEQ ID NO: 6158), SKAQT (SEQ ID NO: 6159), SKGCT (SEQ ID NO: 6160), VPWQN (SEQ ID NO: 6161), SKRYT (SEQ ID NO: 6162), SGCQN (SEQ ID NO: 6163), SFTPN (SEQ ID NO: 6164), STTCN (SEQ ID NO: 6165), SKARM (SEQ ID NO: 6166), PKRQN (SEQ ID NO: 6167), SKCFL (SEQ ID NO: 6168), WVPQN (SEQ ID NO: 6169), SFWSN (SEQ ID NO: 6170), SKFKN (SEQ ID NO: 6171), RIKQN (SEQ ID NO: 6172), SKAPR (SEQ ID NO: 6173), SFRYN (SEQ ID NO: 6174), SKMIC (SEQ ID NO: 6175), LRWQN (SEQ ID NO: 6176), LPTQN (SEQ ID NO: 6177), SKWKS (SEQ ID NO: 6178), SYMRN (SEQ ID NO: 6179), SKAAR (SEQ ID NO: 6180), LLCQN (SEQ ID NO: 6181), RCCQN (SEQ ID NO: 6182), LCVQN (SEQ ID NO: 6183), SKLTR (SEQ ID NO: 6184), SKLCT (SEQ ID NO: 6185), SKIRG (SEQ ID NO: 6186), SYLVN (SEQ ID NO: 6187), QGCQN (SEQ ID NO: 6188), MAFQN (SEQ ID NO: 6189), SKACQ (SEQ ID NO: 6190), SKWGL (SEQ ID NO: 6191), SKILR (SEQ ID NO: 6192), SFQIN (SEQ ID NO: 6193), SKACI (SEQ ID NO: 6194), SKALR (SEQ ID NO: 6195), SKAHA (SEQ ID NO: 6196), SLCLN (SEQ ID NO: 6197), SKAFV (SEQ ID NO: 6198), RPWQN (SEQ ID NO: 6199), RPRQN (SEQ ID NO: 6200), SCPQN (SEQ ID NO: 6201), SKAQF (SEQ ID NO: 6202), SVRYN (SEQ ID NO: 6203), SVRCN (SEQ ID NO: 6204), SKMPC (SEQ ID NO: 6205), SKKTS (SEQ ID NO: 6206), SLPYN (SEQ ID NO: 6207), VYHQN (SEQ ID NO: 6208), SKAQS (SEQ ID NO: 6209), SYTRN (SEQ ID NO: 6210), LVYQN (SEQ ID NO: 6211), YRYQN (SEQ ID NO: 6212), SWLKN (SEQ ID NO: 6213), SKAQM (SEQ ID NO: 6214), CPAQN (SEQ ID NO: 6215), SMCTN (SEQ ID NO: 6216), SPPDN (SEQ ID NO: 6217), SKRNY (SEQ ID NO: 6218), RWTQN (SEQ ID NO: 6219), SKACR (SEQ ID NO: 6220), PRKQN (SEQ ID NO: 6221), SKCSV (SEQ ID NO: 6222), SKARI (SEQ ID NO: 6223), PFVQN (SEQ ID NO: 6224), SKLPK (SEQ ID NO: 6225), SKSEQ (SEQ ID NO: 6226), WVAQN (SEQ ID NO: 6227), SLYQN (SEQ ID NO: 6228), SKVRM (SEQ ID NO: 6229), CALQN (SEQ ID NO: 6230), SSCTN (SEQ ID NO: 6231),

SKNSR (SEQ ID NO: 6232), SKRKR (SEQ ID NO: 6233), LCTQN (SEQ ID NO: 6234), STCLN (SEQ ID NO: 6235), SYARN (SEQ ID NO: 6236), SKQRP (SEQ ID NO: 6237), SKRVV (SEQ ID NO: 6238), KSGQN (SEQ ID NO: 6239), SYYSN (SEQ ID NO: 6240), SLTCN (SEQ ID NO: 6241), SCQSN (SEQ ID NO: 6242), SKAKG (SEQ ID NO: 6243), SKPQN (SEQ ID NO: 6244), FPFQN (SEQ ID NO: 6245), SKCTS (SEQ ID NO: 6246), SVFEN (SEQ ID NO: 6247), SKAKK (SEQ ID NO: 6248), or GRYQN (SEQ ID NO: 6249);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, or 4 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

305. The AAV capsid variant of any one of embodiments 300-304, wherein [A]-[B] is or comprises:

(i) GSGSPHKAQA (SEQ ID NO: 6250), GSGSPHKAQN (SEQ ID NO: 6251), GSGSPHSMYMN (SEQ ID NO: 6252), GSGSPHKAIFY (SEQ ID NO: 6253), GSGSPHSLKR (SEQ ID NO: 6254), GSGSPHSCRHR (SEQ ID NO: 6255), GSGSPHKAQK (SEQ ID NO: 6256), GSGSPHKLWRL (SEQ ID NO: 6257), GSGSPHSCRN (SEQ ID NO: 6258), GSGSPHSFTCN (SEQ ID NO: 6259), GSGSPHKKFFI (SEQ ID NO: 6260), GSGSPHKAQY (SEQ ID NO: 6261), GSGSPHIVWQN (SEQ ID NO: 6262), GSGSPHSHYFM (SEQ ID NO: 6263), GSGSPHSHARQ (SEQ ID NO: 6264), GSGSPHSHCHQN (SEQ ID NO: 6265), GSGSPHFPWQN (SEQ ID NO: 6266), GSGSPHSHKIRR (SEQ ID NO: 6267), GSGSPHSHVYYQN (SEQ ID NO: 6268), GSGSPHSHLYWN (SEQ ID NO: 6269), GSGSPHSHKPKR (SEQ ID NO: 6270), GSGSPHSHKAFS (SEQ ID NO: 6271), GSGSPHSHRFWN (SEQ ID NO: 6272), GSGSPHSHKAC (SEQ ID NO: 6273), GSGSPHSHMRN (SEQ ID NO: 6274), GSGSPHSHVKKN (SEQ ID NO: 6275), GSGSPHSHWAPN (SEQ ID NO: 6276), GSGSPHSHLWKN (SEQ ID NO: 6277), GSGSPHSHKARW (SEQ ID NO: 6278), GSGSPHSHFRPN (SEQ ID NO: 6279), GSGSPHSHKKVF (SEQ ID NO: 6280), GSGSPHSHYAFN (SEQ ID NO: 6281), GSGSPHSHKACS (SEQ ID NO: 6282), GSGSPHSHKRLW (SEQ ID NO: 6283), GSGSPHSHCSRN (SEQ ID NO: 6284), GSGSPHSHRCPN (SEQ ID NO: 6285), GSGSPHSHGACN (SEQ ID NO: 6286), GSGSPHSHKFRQ (SEQ ID NO: 6287), GSGSPHSHFPFN (SEQ ID NO: 6288), GSGSPHSHFFGN (SEQ ID NO: 6289), GSGSPHSHMCQN (SEQ ID NO: 6290), GSGSPHSHKLFW (SEQ ID NO: 6291), GSGSPHSHKTRK (SEQ ID NO: 6292), GSGSPHSHGKRN (SEQ ID NO: 6293), GSGSPHSHFYRQN (SEQ ID NO: 6294), GSGSPHSHCRVQN (SEQ ID NO: 6295), GSGSPHSHYGIQN (SEQ ID NO: 6296), GSGSPHSHKAQR (SEQ ID NO: 6297), GSGSPHSHVNCQN (SEQ ID NO: 6298), GSGSPHSHKPFK (SEQ ID NO: 6299), GSGSPHSHLAWN (SEQ ID NO: 6300), GSGSPHSHKRSY (SEQ ID NO: 6301), GSGSPHSHWSYQN (SEQ ID NO: 6302), GSGSPHSHRWLQN (SEQ ID NO: 6303), GSGSPHSHPCQN

(SEQ ID NO: 6304), GSGSPHSSWLN (SEQ ID NO: 6305), GSGSPHSKRRA (SEQ ID NO: 6306), GSGSPHKAQT (SEQ ID NO: 6307), GSGSPHSGCT (SEQ ID NO: 6308), GSGSPHVPWQN (SEQ ID NO: 6309), GSGSPHSKRYT (SEQ ID NO: 6310), GSGSPHSGCQN (SEQ ID NO: 6311), GSGSPHSFTPN (SEQ ID NO: 6312), GSGSPHSTTCN (SEQ ID NO: 6313), GSGSPHSKARM (SEQ ID NO: 6314), GSGSPHPKRQN (SEQ ID NO: 6315), GSGSPHSCFL (SEQ ID NO: 6316), GSGSPHWVPQN (SEQ ID NO: 6317), GSGSPHSFWSN (SEQ ID NO: 6318), GSGSPHSKFKN (SEQ ID NO: 6319), GSGSPHRIKQN (SEQ ID NO: 6320), GSGSPHKAAPR (SEQ ID NO: 6321), GSGSPHSFRYN (SEQ ID NO: 6322), GSGSPHSMIC (SEQ ID NO: 6323), GSGSPHLRWQN (SEQ ID NO: 6324), GSGSPHLPTQN (SEQ ID NO: 6325), GSGSPHKKWS (SEQ ID NO: 6326), GSGSPHSYMRN (SEQ ID NO: 6327), GSGSPHKAAR (SEQ ID NO: 6328), GSGSPHLLCQN (SEQ ID NO: 6329), GSGSPHRCCQN (SEQ ID NO: 6330), GSGSPHLCVQN (SEQ ID NO: 6331), GSGSPHKLTR (SEQ ID NO: 6332), GSGSPHKLCT (SEQ ID NO: 6333), GSGSPHKKIRG (SEQ ID NO: 6334), GSGSPHSYLVN (SEQ ID NO: 6335), GSGSPHQGCQN (SEQ ID NO: 6336), GSGSPHMAFQN (SEQ ID NO: 6337), GSGSPHKKACQ (SEQ ID NO: 6338), GSGSPHKKWGL (SEQ ID NO: 6339), GSGSPHKKILR (SEQ ID NO: 6340), GSGSPHSFQIN (SEQ ID NO: 6341), GSGSPHKKACI (SEQ ID NO: 6342), GSGSPHKKALR (SEQ ID NO: 6343), GSGSPHKKAHA (SEQ ID NO: 6344), GSGSPHSLCLN (SEQ ID NO: 6345), GSGSPHKKAFV (SEQ ID NO: 6346), GSGSPHRPWQN (SEQ ID NO: 6347), GSGSPHRPRQN (SEQ ID NO: 6348), GSGSPHSCPQN (SEQ ID NO: 6349), GSGSPHKAQF (SEQ ID NO: 6350), GSGSPHSVRYN (SEQ ID NO: 6351), GSGSPHSVRCN (SEQ ID NO: 6352), GSGSPHKKMPC (SEQ ID NO: 6353), GSGSPHKKKTS (SEQ ID NO: 6354), GSGSPHSLPYN (SEQ ID NO: 6355), GSGSPHVVYHQN (SEQ ID NO: 6356), GSGSPHKKAQs (SEQ ID NO: 6357), GSGSPHSYTRN (SEQ ID NO: 6358), GSGSPHLVYQN (SEQ ID NO: 6359), GSGSPHYRYQN (SEQ ID NO: 6360), GSGSPHSWLKN (SEQ ID NO: 6361), GSGSPHKKAQM (SEQ ID NO: 6362), GSGSPHCPAQN (SEQ ID NO: 6363), GSGSPHSMCTN (SEQ ID NO: 6364), GSGSPHSPPDN (SEQ ID NO: 6365), GSGSPHKKRNY (SEQ ID NO: 6366), GSGSPHRWTQN (SEQ ID NO: 6367), GSGSPHKKACR (SEQ ID NO: 6368), GSGSPHPRKQN (SEQ ID NO: 6369), GSGSPHKKCSV (SEQ ID NO: 6370), GSGSPHKKARI (SEQ ID NO: 6371), GSGSPHPPFVQN (SEQ ID NO: 6372), GSGSPHKKLPK (SEQ ID NO: 6373), GSGSPHKKSEQ (SEQ ID NO: 6374), GSGSPHWVAQN (SEQ ID NO: 6375), GSGSPHSLYQN (SEQ ID NO: 6376), GSGSPHKKVVM (SEQ ID NO: 6377), GSGSPHCCALQN (SEQ ID NO: 6378), GSGSPHSSCTN (SEQ ID NO: 6379), GSGSPHKKNSR (SEQ ID NO: 6380), GSGSPHKKRKR (SEQ ID NO: 6381), GSGSPHLLCTQN (SEQ ID NO: 6382), GSGSPHSTCLN (SEQ ID NO: 6383), GSGSPHSYARN (SEQ ID NO: 6384), GSGSPHKKQRP (SEQ ID NO: 6385), GSGSPHKKRVV (SEQ ID NO: 6386), GSGSPHKKSGQN (SEQ ID NO: 6387), GSGSPHSYYSN (SEQ ID NO: 6388), GSGSPHSLTCN (SEQ ID NO: 6389), GSGSPHSCQSN (SEQ ID NO: 6390), GSGSPHKKAKG (SEQ ID NO: 6391), GSGSPHKKPQN (SEQ ID NO: 6392), GSGSPHPPFQN (SEQ ID NO: 6393), GSGSPHKKCTS

(SEQ ID NO: 6394), GSGSPHSVFEN (SEQ ID NO: 6395), GSGSPHSKAKK (SEQ ID NO: 6396), or GSGSPHGRYQN (SEQ ID NO: 6397);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i)

306. The AAV capsid of any one of embodiments 300-305, wherein [A]-[B] does not comprise the amino acid sequence of GSGSPHKAQN (SEQ ID NO: 6251).

307. The AAV capsid variant of any one of embodiments 300-306, which comprises one, two, or all of an amino acid other than Q at position 458 (e.g., R, C, S, W, L, F, Y, H, I, V, A, or P), an amino acid other than Q at position 459 (e.g., K, I, R, L or S), and/or an amino acid other than T at position 460 (e.g., R), numbered relative to SEQ ID NO: 138.

308. The AAV capsid variant of any one of embodiments 300-307, which comprises:

- (i) the amino acid R at position 458;
- (ii) the amino acid W at position 458;
- (iii) the amino acid Y at position 458;
- (iv) the amino acid F at position 458;
- (v) the amino acid S at position 458;
- (vi) the amino acid C at position 458;
- (vii) the amino acid I at position 458;
- (viii) the amino acid L at position 458;
- (ix) the amino acid P at position 458;
- (x) the amino acid I at position 459;
- (xi) the amino acid H at position 458; or
- (xii) the amino acid V at position 458;

wherein (i)-(xii) are numbered according to SEQ ID NO: 138.

309. The AAV capsid variant of any one of embodiments 300-307, which comprises:

- (i) the amino acid R at position 458 and the amino acid K at position 459;
- (ii) the amino acid C at position 458 and the amino acid I at position 459;
- (iii) the amino acid S at position 458 and the amino acid R at position 459;

- (iv) the amino acid L at position 458 and the amino acid K at position 459;
 - (v) the amino acid F at position 458 and the amino acid K at position 459;
 - (vi) the amino acid C at position 458 and the amino acid R at position 459;
 - (vii) the amino acid H at position 458 and the amino acid R at position 459;
 - (viii) the amino acid I at position 458 and the amino acid L at position 459;
 - (ix) the amino acid V at position 458 and the amino acid R at position 459;
 - (x) the amino acid A at position 458 and the amino acid K at position 459;
 - (xi) the amino acid I at position 458 and the amino acid K at position 459;
 - (xii) the amino acid C at position 458 and the amino acid S at position 459; or
 - (xiii) the amino acid C at position 458 and the amino acid L at position 459
- wherein (i)-(xiii) are numbered according to SEQ ID NO: 138.

310. The AAV capsid variant of any one of embodiments 300-307, which comprises the amino acid F at position 458, the amino acid K at position 459, and the amino acid R at position 460, numbered relative to SEQ ID NO: 138.

311. The AAV capsid variant of any one of embodiments 300-310, which comprises one, two, or all of an amino acid other than T at position 450 (e.g., Y, P, W, R, K, S, or F), an amino acid other than I at position 451 (e.g., R, S, Y, L, V, H, P, A, or F), and/or an amino acid other than N at position 452 (e.g., V, W, A, T, F, Y, L, R, H, S, or M), numbered relative to SEQ ID NO: 138.

312. The AAV capsid variant of any one of embodiments 300-311, which comprises the amino acid V at position 452, numbered according to SEQ ID NO: 138.

313. The AAV capsid variant of any one of embodiments 300-312, which comprises the amino acid Y at position 450 and the amino acid V at position 452, numbered according to SEQ ID NO: 138.

314. The AAV capsid variant of any one of embodiments 300-312, which comprises the amino acid R at position 450 and the amino acid Y at position 451, numbered according to SEQ ID NO: 138.

315. The AAV capsid variant of any one of embodiments 300-311, which comprises:

(i) the amino acid P at position 450, the amino acid R at position 451, and the amino acid W at position 452;

(ii) the amino acid Y at position 450, the amino acid S at position 451, and the amino acid A at position 452;

(iii) the amino acid Y at position 450, the amino acid Y at position 451, and the amino acid T at position 452;

(iv) the amino acid P at position 450, the amino acid R at position 451, and the amino acid F at position 452;

(v) the amino acid W at position 450, the amino acid L at position 451, and the amino acid T at position 452;

(vi) the amino acid R at position 450, the amino acid S at position 451, and the amino acid Y at position 452;

(vii) the amino acid Y at position 450, the amino acid V at position 451, and the amino acid F at position 452;

(viii) the amino acid K at position 450, the amino acid H at position 451, and the amino acid L at position 452;

(ix) the amino acid P at position 450, the amino acid P at position 451, and the amino acid L at position 452;

(x) the amino acid P at position 450, the amino acid A at position 451, and the amino acid R at position 452;

(xi) the amino acid S at position 450, the amino acid R at position 451, and the amino acid R at position 452;

(xii) the amino acid F at position 450, the amino acid F at position 451, and the amino acid H at position 452;

(xiii) the amino acid R at position 450, the amino acid F at position 451, and the amino acid S at position 452;

(xiv) the amino acid Y at position 450, the amino acid S at position 451, and the amino acid M at position 452; or

(xv) the amino acid P at position 450, the amino acid F at position 451, and the amino acid L at position 452;

wherein (i)-(xv) is numbered according to SEQ ID NO: 138.

316. The AAV capsid variant of any one of embodiments 300-315, which comprises:

(i) the amino acid sequence of any one of SEQ ID NOs: 3849-3982, 2984-4010, 4681-4693;

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or 17 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

317. The AAV capsid variant of any one of embodiments 300-316, which does not comprise the amino acid sequence of GSGSPHKAQNQQ (SEQ ID NO: 1801) or GSGSPHKAQNQQT (SEQ ID NO: 200).

318. The AAV capsid variant of any one of embodiments 300-317, wherein [A]-[B] is present in loop IV.

319. The AAV capsid variant of any one of embodiments 300-318, wherein [A] is present immediately subsequent to position 452, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138 or 981.

320. The AAV capsid variant of any one of embodiments 300-319, wherein [A] replaces positions 453-455 (e.g., G453, S454, G455), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138 or 981.

321. The AAV capsid variant of any one of embodiments 300-320, wherein [A] is present immediately subsequent to position 452, and wherein [A] replaces positions 453-455 (e.g., G453, S454, G455), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138 or 981.

322. The AAV capsid variant of any one of embodiments 300-321, wherein [B] is present immediately subsequent to [A].

323. The AAV capsid variant of any one of embodiments 300-322, wherein [B] replaces positions 456 and 457 (e.g., Q456, N457), numbered relative to SEQ ID NO: 138.

324. The AAV capsid variant of any one of embodiments 300-323, wherein [A]-[B] replaces positions 453-457 (e.g., G453, S454, G455, Q456, N457), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

325. The AAV capsid variant of any one of embodiments 300-324, wherein [A]-[B] is present immediately subsequent to position 452, and wherein [A]-[B] replaces positions 453-457 (e.g., G453, S454, G455, Q456, N457), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

326. The AAV capsid variant of any one of embodiments 300-325, which comprises from N-terminus to C-terminus, [A][B].

327. The AAV capsid variant of any one of the preceding embodiments, which comprises at least one, two, three or four (e.g., from 1-4 to 1-5) charged amino acid residues (e.g., acidic and/or basic amino acid residues) relative to SEQ ID NO: 138, which is present N-terminal to the amino acid sequence of SPH (e.g., within 1, 2, 3, 4, 5, or 6 amino acids from the start of the SPH amino acid sequence (e.g., within positions 450-455 numbered according to SEQ ID NO: 138)), optionally wherein the amino acid sequence of SPH is present at positions 456-458 numbered according to any one of SEQ ID NOs: 36-59, 981, or 982.

328. The AAV capsid variant of embodiment 327, wherein the amino acid sequence of SPH is present at positions 456-458 numbered according to any one of SEQ ID NOs: 36-59, 981, or 982.

329. The AAV capsid variant of embodiment 327 or 328, which comprises less than four, less than three, less than two (e.g., two or one) charged amino acid residues (e.g., acidic and/or basic amino acid residues) relative to SEQ ID NO: 138.

330. The AAV capsid variant of any one of embodiments 327-329, which comprises one charged amino acid residues (e.g., an acidic or basic amino acid residue) relative to SEQ ID NO: 138, optionally at any one of positions 450-455 numbered relative to SEQ ID NO: 138.

331. The AAV capsid variant of any one of embodiments 327-330, wherein the charged amino acid residue is an acidic amino acid (e.g., D or E).

332. The AAV capsid variant of any one of embodiments 327-331, wherein the charged amino acid residue is a negatively charged amino acid (e.g., D or E).

333. The AAV capsid variant of any one of embodiments 327-332, wherein the charged amino acid residue is D.

334. The AAV capsid variant of any one of embodiments 327-333, wherein the charged amino acid residue is E.

335. The AAV capsid variant of any one of embodiments 327-334, wherein the charged amino acid residue is a basic amino acid (e.g., K, R, or H).

336. The AAV capsid variant of any one of embodiments 327-335, wherein the charged amino acid residue is a positively charged amino acid (e.g., K, R, or H).

337. The AAV capsid variant of any one of embodiments 327-336, wherein the charged amino acid residue is H.

338. The AAV capsid variant of any one of embodiments 327-337, wherein the charged amino acid residue is R.

339. The AAV capsid variant of any one of embodiments 327-338, wherein the charged amino acid residue is K.

340. The AAV capsid variant of any one of embodiments 327-339, wherein the AAV capsid variant comprises an acidic amino acid (e.g., E or D) and a basic amino acid (e.g., R, K, or H).

341. The AAV capsid variant of any one of embodiments 327-340, at least one, two, three or four charged amino acid residues is present within 1, 2, 3, 4, 5, or 6 (e.g., 1-6) amino acids from the start of the SPH amino acid sequence.

342. The AAV capsid variant of any one of embodiments 327-341, which comprises two charged amino acid residue immediately preceding the amino acid sequence of SPH (e.g., at positions 454 and 455, numbered according to SEQ ID NO: 138 or SEQ ID NO: 982).

343. The AAV capsid variant of any one of embodiments 327-342, which comprises a charged amino acid residue (e.g., E) within 1, 2, 3, 4, 5 (e.g., 5) amino acids from the start of the SPH amino acid sequence.

344. The AAV capsid variant of any one of embodiments 327-343, which comprises a charged amino acid residue (e.g., E) at position 451, numbered according to any one of SEQ ID NO: 138, 981, or 982.

345. The AAV capsid variant of any one of embodiments 327-344, which comprises E at position 451, numbered according to any one of SEQ ID NOs: 138, 981, or 982.

346. The AAV capsid variant of any one of embodiments 327-345, which comprises a charged amino acid residue (e.g., R or K) at position 452, numbered according to any one of SEQ ID NOs: 138, 981, or 982.

347. The AAV capsid variant of any one of embodiments 327-346, which comprises R at position 452, numbered according to SEQ ID NO: 138 or SEQ ID NO: 982.

348. The AAV capsid variant of any one of embodiments 327-347, which comprises E at position 451 and R at position 452, numbered according to SEQ ID NO: 138 or SEQ ID NO: 982.

349. The AAV capsid variant of any one of embodiments 327-348, which has decreased tropism for a liver cell or tissue, relative to the tropism of a reference sequence comprising the amino acid sequence of SEQ ID NO: 138 or SEQ ID NO: 981.

350. The AAV capsid variant of any one of the preceding embodiments, which comprises at least one, two, three or four (e.g., from 1-4 to 1-5) charged amino acid residues (e.g., basic amino acid residues) relative to SEQ ID NO: 138, which is present C-terminal to the amino acid sequence of SPH (e.g., within 1, 2, 3, 4, 5, 6, or 7 amino acids from the end of the SPH amino acid sequence (e.g., within positions 459-465 numbered according to any one of SEQ ID NOs: 36-59, or 981)), optionally wherein the amino acid sequence of SPH is present at positions 456-458 numbered according to any one of SEQ ID NOs: 36-59, 981, or 982.

351. The AAV capsid variant of embodiment 350, wherein the amino acid sequence of SPH is present at positions 456-458 numbered according to any one of SEQ ID NOs: 36-59, 981, or 982.

352. The AAV capsid variant of embodiment 350 or 351, which comprises less than four, less than three, less than two (e.g., two or one) charged amino acid residues (e.g., basic amino acid residues) relative to SEQ ID NO: 138.

353. The AAV capsid variant of any one of embodiments 350-352, which comprises one charged amino acid residues (e.g., an basic amino acid residue) relative to SEQ ID NO: 138, optionally at any one of positions 456-460 numbered relative to SEQ ID NO: 138 or at positions 462-466 numbered according to any one of SEQ ID NOs: 36-59, 981, or 982.

354. The AAV capsid variant of any one of embodiments 350-353, wherein the charged amino acid residue is a basic amino acid (e.g., R or K).

355. The AAV capsid variant of any one of embodiments 350-354, wherein the charged amino acid residue is a positively charged amino acid (e.g., R or K).

356. The AAV capsid variant of any one of embodiments 350-355, wherein the charged amino acid residue is R.

357. The AAV capsid variant of any one of embodiments 350-355, wherein the charged amino acid residue is K.

358. The AAV capsid variant of any one of embodiments 350-357, at least one, two, three or four charged amino acid residues is present within 1, 2, 3, 4, 5, 6, 7 (e.g., 1-7) amino acids from the end of the SPH amino acid sequence.

359. The AAV capsid variant of any one of embodiments 350-358, which comprises a charged amino acid residue (e.g., K or R) immediately after the SPH sequence (e.g., at position 459 numbered according to SEQ ID NO: 981).

360. The AAV capsid variant of any one of embodiments 350-359, which comprises a charged amino acid residue (e.g., K or R) at position 459, numbered according to SEQ ID NO: 138 or SEQ ID NO: 982.

361. The AAV capsid variant of any one of embodiments 350-360, which comprises K at position 459, numbered according to SEQ ID NO: 981.

362. The AAV capsid variant of any one of embodiments 350-360, which comprises R at position 459, numbered according to SEQ ID NO: 981.

363. The AAV capsid variant of any one of embodiments 350-362, which comprises a charged amino acid residue (e.g., R or K) at one, two three, four, five, or all of positions 460, 461, 462, 463, 464, and/or 465, numbered according to SEQ ID NO: 138 or 981.

364. The AAV capsid variant of any one of embodiments 300-326 or 350-363, which has increased tropism for a liver cell or tissue, relative to the tropism of a reference sequence comprising the amino acid sequence of SEQ ID NO: 138.

365. The AAV capsid variant of any one of embodiments 300-326 or 350-364, which is enriched at least about 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 150, 160, 170, 180, 190, or 200-fold, in the liver compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay as described in Example 4.

366. The AAV capsid variant of any one of embodiments 300-326, 364, or 365, which has reduced tropism for a CNS cell or tissue, e.g., a brain cell, brain tissue, spinal cord cell, or spinal cord tissue, relative to the tropism of a reference sequence comprising the amino acid sequence of SEQ ID NO: 138.

367. The AAV capsid variant of any one of embodiments 300-326 or 364-366, which shows preferential transduction in a liver region relative to the transduction in the brain and/or dorsal root ganglia (DRG).

368. The AAV capsid variant of any one of embodiments 300-326 or 364-367, which shows preferential transduction in a liver region relative to the transduction in the heart and/or muscle (e.g., quadriceps).

369. An AAV capsid variant comprising:

- (a) the amino acid sequence of any of the sequences provided in Tables 1, 2A, 2B, 13-19;
- (b) an amino acid sequence comprising at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or 17 consecutive amino acids from any one of the sequences provided in Tables 1, 2A, 2B, 13-19; or
- (c) an amino acid sequence comprising at least one, two, or three but no more than four different amino acids, relative to any one of the sequences provided in Tables 1, 2A, 2B, 13-19; or
- (d) an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of any one of the sequences provided in Tables 1, 2A, 2B, 13-19.

370. An AAV capsid variant comprising:

- (a) the amino acid sequence of any of SEQ ID NOs: 945-980 or 985-986;
- (b) an amino acid sequence comprising at least 3, 4, or 5 consecutive amino acids from any one of SEQ ID NOs: 945-980 or 985-986; or
- (c) an amino acid sequence comprising at least one, two, or three but no more than four different amino acids, relative to the amino acid sequence of any one of SEQ ID NOs: 945-980 or 985-986;
- (d) an amino sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of any one of SEQ ID NOs: 945-980 or 985-986.

371. An AAV capsid variant comprising:

- (a) the amino acid sequence of any of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909;

(b) an amino acid sequence comprising at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 consecutive amino acids from any one of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909;

(c) an amino acid sequence comprising at least one, two, or three but no more than four different amino acids, relative to the amino acid sequence of any one of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909; or

(d) an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of any one of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909.

372. An AAV capsid variant comprising:

(a) the amino acid sequence of any of SEQ ID NOs: 3849-4051 or 4681-4693;

(b) an amino acid sequence comprising at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16 or 17 consecutive amino acids from any one of SEQ ID NOs: 3849-4051 or 4681-4693;

(c) an amino acid sequence comprising at least one, two, or three but no more than four different amino acids, relative to the amino acid sequence of any one of SEQ ID NOs: 3849-4051 or 4681-4693; or

(d) an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of any one of SEQ ID NOs: 3849-4051 or 4681-4693.

373. An AAV capsid variant comprising:

(a) the amino acid sequence of any of SEQ ID NOs: 4052-4092;

(b) an amino acid sequence comprising at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16 or 17 consecutive amino acids from any one of SEQ ID NOs: 4052-4092;

(c) an amino acid sequence comprising at least one, two, or three but no more than four different amino acids, relative to the amino acid sequence of any one of SEQ ID NOs: 4052-4092; or

(d) an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of any one of SEQ ID NOs: 4052-4092.

374. An AAV capsid variant comprising:

(a) the amino acid sequence of any of SEQ ID NOs: 4056, 4058, 4059, 4062-4064, 4066, 4067, 4080, 4084, 4090, or 4095-4097;

(b) an amino acid sequence comprising at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16 or 17 consecutive amino acids from any one of SEQ ID NOs: 4056, 4058, 4059, 4062-4064, 4066, 4067, 4080, 4084, 4090, or 4095-4097;

(c) an amino acid sequence comprising at least one, two, or three but no more than four different amino acids, relative to the amino acid sequence of any one of SEQ ID NOs: 4056, 4058, 4059, 4062-4064, 4066, 4067, 4080, 4084, 4090, or 4095-4097; or

(d) an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of any one of SEQ ID NOs: 4056, 4058, 4059, 4062-4064, 4066, 4067, 4080, 4084, 4090, or 4095-4097.

375. The AAV capsid variant of embodiment 369 or 371, comprising an amino acid sequence comprising at least 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 consecutive amino acids from any one of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909.

376. The AAV capsid variant of any one of embodiments 369-375, wherein the 3 consecutive amino acids comprise SPH.

377. The AAV capsid variant of any one of embodiments 369-371 or 376, wherein the 4 consecutive amino acids comprise SPHS (SEQ ID NO: 4700).

378. The AAV capsid variant of any one of embodiments 369-371, 376, or 377, wherein the 5 consecutive amino acids comprise SPHSK (SEQ ID NO: 4701).

379. The AAV capsid variant of any one of embodiments 369-371 or 376-378, wherein the 6 consecutive amino acids comprise SPHKA (SEQ ID NO: 941).

380. The AAV capsid variant of embodiment 369-371, wherein the 3 consecutive amino acids comprise HDS.

381. The AAV capsid variant of any one of embodiments 369-371 or 380, wherein the 4 consecutive amino acids comprise HDSP (SEQ ID NO: 4702).

382. The AAV capsid variant of any one of embodiments 369-371, 380, or 381, wherein the 5 consecutive amino acids comprise HDSPH (SEQ ID NO: 4703).

383. The AAV capsid variant of any one of embodiments 369-371 or 380-382, wherein the 6 consecutive amino acids comprise HDSPHK (SEQ ID NO: 2).

384. The AAV capsid variant of any one of embodiments 369-371, wherein:

(i) the 3 consecutive amino acids comprise SPH; (ii) the 4 consecutive amino acids comprise SPHK (SEQ ID NO: 6398);

(iii) the 5 consecutive amino acids comprise SPHKY (SEQ ID NO: 4715); and/or

(iv) the 6 consecutive amino acids comprise SPHKYG (SEQ ID NO: 966).

385. The AAV capsid variant of embodiment 369 or 371, which comprises an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of any one of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909.

386. The AAV capsid variant of any one of embodiments 369, 371, or 385, which comprises an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of SPHKA (SEQ ID NO: 941).

387. The AAV capsid variant of any one of embodiments 369, 371, or 385, which comprises an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of HDSPHK (SEQ ID NO: 2).

388. The AAV capsid variant of any one of embodiments 369-371, 384, or 385, which comprises an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of SPHKYG (SEQ ID NO: 966).

389. The AAV capsid variant of embodiment 370, which comprises:

(i) an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of KTERVSGSPHKAQNQQT (SEQ ID NO: 3589);

(ii) an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of KAEIGHDSPHKGQNQQT (SEQ ID NO: 1754)

(iii) an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of KTEKMSGSPHKAQNQQT (SEQ ID NO: 3241);

(iv) an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of KTINGHDSPHSKAQNLQT (SEQ ID NO: 4100); or

(v) an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of KTVNGHDSPHSKAQNQQT (SEQ ID NO: 4062).

390. The AAV capsid variant of embodiment 369 or 371, which comprises an amino acid sequence comprising at least one, two, or three but no more than four different amino acids relative to the amino acid sequence of any one of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909.

391. The AAV capsid variant of any one of embodiments 369, 371, or 390, which comprises an amino acid sequence comprising at least one, two, or three but no more than four different amino acids relative to the amino acid sequence of SPHKA (SEQ ID NO: 941).

392. The AAV capsid variant of any one of embodiments 369, 371, or 390, which comprises an amino acid sequence comprising at least one, two, or three but no more than four different amino acids relative to the amino acid sequence of HDSPHK (SEQ ID NO: 2).

393. The AAV capsid variant of any one of embodiments 369, 371, 384, or 390, which comprises an amino acid sequence comprising at least one, two, or three but no more than four different amino acids relative to the amino acid sequence of SPHKEYG (SEQ ID NO: 966).

394. The AAV capsid variant of embodiment 369, which comprises:

(i) an amino acid sequence comprising at least one, two, or three but no more than four different amino acids relative to the amino acid sequence of KTERVSGSPHKAQNQQT (SEQ ID NO: 3589);

(ii) an amino acid sequence comprising at least one, two, or three but no more than four different amino acids relative to the amino acid sequence of KAEIGHDSPHKSGQNQQT (SEQ ID NO: 1754);

(iii) an amino acid sequence comprising at least one, two, or three but no more than four different amino acids relative to the amino acid sequence of KTEKMSGSPHKAQNQQT (SEQ ID NO: 3241);

(iv) an amino acid sequence comprising at least one, two, or three but no more than four different amino acids relative to the amino acid sequence of KTINGHDSPHSKAQNLQT (SEQ ID NO: 4100); or

(v) an amino acid sequence comprising at least one, two, or three but no more than four different amino acids relative to the amino acid sequence of KTVNGHDSPHSKAQNQQT (SEQ ID NO: 4062).

395. The AAV capsid variant of any one of embodiments 1-129, 269, 271, 375-388, or 390-394, which comprises the amino acid sequence of any of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909.

396. The AAV capsid variant of any one of embodiments 295-297, 301-305, 313, 314, 318, 319, or 323, which comprises the amino acid sequence of ERVSGSPHKA (SEQ ID NO: 6399), optionally wherein the amino acid sequence is present immediately subsequent to position 450 and replaces positions 451-455 (e.g., I451, N542, G453, S454, G455), numbered according to SEQ ID NO: 138.

397. The AAV capsid variant of any one of embodiments 369-371, 375-379, 385, 386, 389-391, or 394-396, which comprises the amino acid sequence of KTERVSGSPHKAQNQQT (SEQ ID NO: 3589), optionally wherein the amino acid sequence is present immediately subsequent to position 448 and replaces positions 449-460 (e.g., K449, T450, I451, N452, G453, S454, G455, Q456, N457, Q458, Q459, T460), numbered according to SEQ ID NO: 138.

398. The AAV capsid variant of any one of embodiments 269-371, 375, 380-383, 385, 387, 389, 390, 393, or 394, which comprises the amino acid sequence of AEIGHDSPHKSG (SEQ ID NO: 6400), optionally wherein the amino acid sequence is present immediately subsequent to position 449 and replaces positions 450-455 (e.g., T450, I451, N452, G453, S454, G455), numbered according to SEQ ID NO: 138.

399. The AAV capsid variant of any one of embodiments 369-371, 375, 380-383, 385, 387, 389, 390, 393, 394, or 398, which comprises the amino acid sequence of KAEIGHDSPHKSGQNQQT (SEQ ID NO: 1754), optionally wherein the amino acid sequence is present immediately subsequent to position 448 and replaces positions 449-460 (e.g., K449, T450, I451, N452, G453, S454, G455, Q456, N457, Q458, Q459, T460), numbered according to SEQ ID NO: 138.

400. The AAV capsid variant of any one of embodiments 369-371, 375-379, 390, 391, or 395, which comprises the amino acid sequence of EKMSGSPHKA (SEQ ID NO: 6401), optionally wherein the amino acid sequence is present immediately subsequent to position 450 and replaces positions 451-455 (e.g., I451, N452, G453, S454, G455), numbered according to SEQ ID NO: 138.

401. The AAV capsid variant of any one of embodiments 369-371, 375-379, 390, 391, or 395, which comprises the amino acid sequence of KTEKMSGSPHKAQNQQT (SEQ ID NO: 3241), optionally wherein the amino acid sequence is present immediately subsequent to position 448 and replaces positions 449-460 (e.g., K449, T450, I451, N452, G453, S454, G455, Q456, N457, Q458, Q459, T460), numbered according to SEQ ID NO: 138.

402. The AAV capsid variant of any one of embodiments 369-371, 375-379, 390, 391, or 395, which comprises the amino acid sequence of HDSPHKAQNL (SEQ ID NO: 6402), optionally wherein the amino acid sequence is present immediately subsequent to position 453 and replaces positions 456-458 (e.g., Q456, N457, Q458), numbered according to SEQ ID NO: 138.

403. The AAV capsid variant of any one of embodiments 369-371, 375-379, 390, 391, or 395, which comprises the amino acid sequence of KTINGHDSPHKAQNLQT (SEQ ID NO: 4100), optionally wherein the amino acid sequence is present immediately subsequent to position 448 and replaces positions 449-460 (e.g., K449, T450, I451, N452, G453, S454, G455, Q456, N457, Q458, Q459, T460), numbered according to SEQ ID NO: 138.

404. The AAV capsid variant of any one of embodiments 369-371, 375-379, 390, 391, or 395, which comprises the amino acid sequence of VNGHDSPHKA (SEQ ID NO: 6403), optionally wherein the amino acid sequence is present immediately subsequent to position 450 and replaces positions 451-455 (e.g., I451, N452, G453, S454, G455), numbered according to SEQ ID NO: 138.

405. The AAV capsid variant of any one of embodiments 369-371, 375-379, 390, 391, or 395, which comprises the amino acid sequence of KTVNGHDSPHKAQNQQT (SEQ ID NO: 4062), optionally wherein the amino acid sequence is present immediately subsequent to position 448 and replaces positions 449-460 (e.g., K449, T450, I451, N452, G453, S454, G455, Q456, N457, Q458, Q459, T460), numbered according to SEQ ID NO: 138.

406. The AAV capsid variant of any one of embodiments 1-23, 26-29, 32, 35-43, 46-51, 54-72, 69-89, 91, 94-99, 102-104, 107, 110-112, 115-129, 168-202, 02, 240-247, 249, 250, 253-263, 266, 272-281, 286, 288, 291-299, 327-363, 369-371, 375-379, 385, 386, 390, 391, or 395, comprising an amino acid sequence encoded by: the nucleotide sequence of SEQ ID NO: 942; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequence of SEQ ID NO: 942; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 942.

407. The AAV capsid variant of any one of embodiments 1-9, 11, 12-22, 24, 26, 28, 30, 33, 35-42, 44, 46-50, 52, 54-77, 83-88, 90-97, 100-103, 105, 110, 111, 113-129, 203-248, 251, 252, 254-257, 260, 261, 264-280, 283-287, 289-299, 327-363, 369, 369, 371, 380-383, 385, 386, 390, 392, or 395, comprising an amino acid sequence encoded by: the nucleotide sequence of SEQ ID NO: 3; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequence of SEQ ID NO: 3; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 3.

408. The AAV capsid variant of any one of embodiments 1-23, 26-29, 32, 35-43, 46-51, 54-72, 69-89, 91, 94-99, 102-104, 107, 110-112, 115-129, 168-202, 02, 240-247, 249, 250, 253-263, 266, 272-281, 286, 288, 291-299, 327-363, 369-371, 375-379, 385, 386, 390, 391, 395, or 406, wherein the nucleotide sequence encoding the capsid variant comprises the nucleotide sequence of SEQ ID NO: 942; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequence of SEQ ID NO: 942; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 942.

409. The AAV capsid variant of any one of embodiments 1-9, 11, 12-22, 24, 26, 28, 30, 33, 35-42, 44, 46-50, 52, 54-77, 83-88, 90-97, 100-103, 105, 110, 111, 113-129, 203-248, 251, 252, 254-257, 260, 261, 264-280, 283-287, 289-299, 327-363, 369, 369, 371, 380-383, 385, 386, 390, 392, 395, or 407, wherein the nucleotide sequence encoding the capsid variant comprises the nucleotide sequence of SEQ ID NO: 3; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequence of SEQ ID NO: 3; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 3.

410. The AAV capsid variant of any one of embodiments 369-409, wherein the amino acid sequence is present in loop IV.

411. The AAV capsid variant of any one of embodiments 369-410, wherein the amino acid sequence is present immediately subsequent to position 448, 449, 450, 451, 452, 453, 454, or 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

412. The AAV capsid variant of any one of embodiments 369-411, wherein the amino acid sequence replaces amino acids 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, and/or 460 (e.g., K449, T450, I451, N452, G453, S454, G455, Q456, N457, Q458, Q459, and/or T460), numbered according to the amino acid sequence of SEQ ID NO: 138.

413. The AAV capsid variant of any one of embodiments 369-412, wherein the amino acid sequence is present immediately subsequent to position 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

414. The AAV capsid variant of any one of embodiments 369-413, wherein the amino acid sequence is present immediately subsequent to position 453, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

415. The AAV capsid variant of any one of embodiments 1-23, 26-29, 32, 35-43, 46-51, 54-72, 69-89, 91, 94-99, 102-104, 107, 110-112, 115-129, 168-202, 02, 240-247, 249, 250, 253-263, 266, 272-281, 286, 288, 291-299, 327-363, 369-371, 375-379, 385, 386, 390, 391, 395, 406, 408, or 410-413, comprising the amino acid sequence of SPHKA (SEQ ID NO: 941), wherein the amino acid sequence is present immediately subsequent to position 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

416. The AAV capsid variant of any one of embodiments 1-23, 26-29, 32, 35-43, 46-51, 54-72, 69-89, 91, 94-99, 102-104, 107, 110-112, 115-129, 168-202, 02, 240-247, 249, 250, 253-263, 266, 272-281, 286, 288, 291-299, 327-363, 369-371, 375-379, 385, 386, 390, 391, 395, 406, 408, 410-413, or 415, comprising the amino acid sequence of SPHKA (SEQ ID NO: 941), wherein the amino acid sequence is present immediately subsequent to position 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 981.

417. The AAV capsid variant of embodiment 415 or 416, which further comprises an amino acid other than I at position 451, an amino acid other than N at position 452, and an amino acid other than G at position 453, numbered according to any one of SEQ ID NOs: 36, 138, or 981.

418. The AAV capsid variant of any one of embodiments 415-417, which further comprises E at position 451, R at position 452, and V at position 453, numbered according to any one of SEQ ID NOs: 36, 138, or 981.

419. The AAV capsid variant of any one of embodiments 415-418, which further comprises the substitutions I451E, N452R, and G453V, numbered according to any one of SEQ ID NOs: 36, 138, or 981.

420. The AAV capsid variant of any one of embodiments 415-419, which comprises:

(i) E at position 451, R at position 452, and V at position 453, numbered according to any one of SEQ ID NOs: 36, 138, or 981; and

(ii) the amino acid sequence of SPHSKA (SEQ ID NO: 941), wherein the amino acid sequence is present immediately subsequent to position 455, numbered according to any one of SEQ ID NOs: 36, 138, or 981.

421. The AAV capsid variant of embodiment 415 or 416, which further comprises an amino acid other than I at position 451, an amino acid other than N at position 452, and/or G at position 453, numbered according to SEQ ID NO: 39 or 138.

422. The AAV capsid variant of any one of embodiments 415, 416, or 421, which further comprises E at position 451, K at position 452, and/or M at position 453, numbered according to SEQ ID NO: 138 or 39.

423. The AAV capsid variant of any one of embodiments 415, 416, 421, or 422, which further comprises the substitutions I451E, N452K, and G453M, numbered according to SEQ ID NO: 39 or 138.

424. The AAV capsid variant of any one of embodiments 415, 416, or 421-423, which comprises:

(i) E at position 451, K at position 452, and M at position 453, numbered according to SEQ ID NO: 39 or 138; and

(ii) the amino acid sequence of SPHSKA (SEQ ID NO: 941), wherein the amino acid sequence is present immediately subsequent to position 455, numbered according to SEQ ID NO: 39 or 138.

425. The AAV capsid variant of embodiment 415 or 416, which further comprises an amino acid other than S at position 454, an amino acid other than G at position 455, and/or Q at position 458, numbered according to SEQ ID NO: 138.

426. The AAV capsid variant of any one of embodiments 415, 416, or 425, which further comprises H at position 454, D at position 455, and/or L at position 458, numbered according to SEQ ID NO: 138.

427. The AAV capsid variant of any one of embodiments 415, 416, 425, or 426, which further comprises the substitutions S454H, G455D, and Q458L, numbered according to SEQ ID NO: 138.

428. The AAV capsid variant of any one of embodiments 415, 416, or 425-427, which comprises:

(i) H at position 454, D at position 455, and/or L at position 458, numbered according to SEQ ID NO: 138; and

(ii) the amino acid sequence of SPHSKA (SEQ ID NO: 941), wherein the amino acid sequence is present immediately subsequent to position 455, numbered according to SEQ ID NO: 138.

429. The AAV capsid variant of embodiment 415 or 416, which further comprises an amino acid other than I at position 451, an amino acid other than S at position 454, and/or an amino acid other than G at position 455, numbered according to SEQ ID NO: 52 or 138.

430. The AAV capsid variant of any one of embodiments 415, 416, or 429, which further comprises V at position 451, H at position 454, and/or D at position 455, numbered according to SEQ ID NO: 52 or 138.

431. The AAV capsid variant of any one of embodiments 415, 416, 429, or 430, which further comprises the substitutions I451V, S454H, and/or G455D, numbered according to SEQ ID NO: 52 or 138.

432. The AAV capsid variant of any one of embodiments 415, 416, or 429-431, which comprises:

(i) V at position 451, H at position 454, and/or D at position 455, numbered according to SEQ ID NO: 52 or 138; and

(ii) the amino acid sequence of SPHSKA (SEQ ID NO: 941), wherein the amino acid sequence is present immediately subsequent to position 455, numbered according to SEQ ID NO: 52 or 138.

433. The AAV capsid variant of any one of embodiments 1-9, 11, 12-22, 24, 26, 28, 30, 33, 35-42, 44, 46-50, 52, 54-77, 83-88, 90-97, 100-103, 105, 110, 111, 113-129, 203-248, 251, 252, 254-257, 260, 261, 264-280, 283-287, 289-299, 327-363, 369, 369, 371, 380-383, 385, 386, 390, 392, 395, 407, 409-412, or 414, comprising the amino acid sequence of HDSPHK (SEQ ID NO: 2), wherein the amino acid sequence is present immediately subsequent to position 453, numbered according to the amino acid sequence of SEQ ID NO: 138.

434. The AAV capsid variant of any one of embodiments 1-9, 11, 12-22, 24, 26, 28, 30, 33, 35-42, 44, 46-50, 52, 54-77, 83-88, 90-97, 100-103, 105, 110, 111, 113-129, 203-248, 251, 252, 254-257, 260, 261, 264-280, 283-287, 289-299, 327-363, 369, 369, 371, 380-383, 385, 386, 390, 392, 395, 407, 409-412, 414, or 433, comprising the amino acid sequence of HDSPHK (SEQ ID NO: 2), wherein the amino acid sequence is present immediately subsequent to position 453, numbered according to the amino acid sequence of SEQ ID NO: 982.

435. The AAV capsid variant of any one of embodiments 1-9, 11, 12-22, 24, 26, 28, 30, 33, 35-42, 44, 46-50, 52, 54-77, 83-88, 90-97, 100-103, 105, 110, 111, 113-129, 203-248, 251, 252, 254-257, 260, 261, 264-280, 283-287, 289-299, 327-363, 369, 369, 371, 380-383, 385, 386, 390, 392, 395, 407, 409-412, 414, 433, or 434, comprising the amino acid sequence of SPHKSG (SEQ ID NO: 946), wherein the amino acid sequence is present immediately subsequent to position 455, numbered relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 982.

436. The AAV capsid variant of any one of embodiments 369-435, which comprises:

(i) the amino acid sequence of HDSPHKA (SEQ ID NO: 4486), which is present immediately subsequent to position 453; and

(ii) a deletion of amino acids SG at position 454 and 455;

wherein (i) and (ii) are numbered according to SEQ ID NO: 138.

437. The AAV capsid variant of any one of embodiments 369-436, which comprises the amino acids HD at position 454 and 455, and further comprises the amino acid sequence of SPHKA (SEQ ID NO: 941), which is present immediately subsequent to position 455, numbered relative to SEQ ID NO: 138.

438. The AAV capsid variant of any one of embodiments 433-435, which further comprises an amino acid other than T at position 450, an amino acid other than I at position 451, and an amino acid other than N at position 452, numbered according to SEQ ID NO: 138 or 982.

439. The AAV capsid variant of any one of embodiments 433-435 or 438, which further comprises A at position 450, E at position 451, and I at position 452, numbered according to SEQ ID NO: 138 or 982.

440. The AAV capsid variant of any one of embodiments 433-435, 438, or 439, which further comprises the substitutions T450A, I451E, and N452I, numbered according to SEQ ID NO: 138 or 982.

441. The AAV capsid variant of any one of embodiments 433, 434, or 438-440, which comprises:

(i) A at position 450, E at position 451, and I at position 452, numbered according to SEQ ID NO: 138 or 982; and

(ii) the amino acid sequence of HDSPHK (SEQ ID NO: 2), which is present immediately subsequent to positions 453, numbered according to SEQ ID NO: 138 or 982.

442. The AAV capsid variant of any one of embodiments 1-22, 25-27, 31, 34-42, 45-50, 53-63, 69, 79, 83-86, 91-98, 102, 103, 110, 111, 118-129, 369-371, 384, 385, 390, 393, 395, 410-413, comprising the amino acid sequence of SPHKYG (SEQ ID NO: 966), wherein the amino acid sequence is present immediately subsequent to position 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

443. An AAV capsid variant comprising the amino acid sequence of HDSPHK (SEQ ID NO: 2), wherein the amino acid sequence is present immediately subsequent to position 453, numbered according to the amino acid sequence of SEQ ID NO: 982.

444. An AAV capsid variant comprising the amino acid sequence of SPHKA (SEQ ID NO: 941), wherein the amino acid sequence is present immediately subsequent to position 455, numbered according to the amino acid sequence of SEQ ID NO: 981.

445. An AAV capsid variant comprising the amino acid sequence of HDSPHK (SEQ ID NO: 2), wherein the amino acid sequence is present immediately subsequent to position 453, numbered according to the amino acid sequence of SEQ ID NO: 37, and optionally further comprising:

(i) one, two, or all of an amino acid other than T at position 450, an amino acid other than I at position 541, and/or an amino acid other than N at position 452, numbered according to SEQ ID NO: 138 or 37;

(ii) one, two, or all of A at position 450, E at position 451, and/or I at position 452, numbered according to SEQ ID NO: 138 or 37.

446. An AAV capsid variant comprising the amino acid sequence of SPHKA (SEQ ID NO: 941), wherein the amino acid sequence is present immediately subsequent to position 455, numbered according to the amino acid sequence of any one of SEQ ID NO: 36, 38-55, 57, or 59.

447. The AAV capsid variant of any one of the preceding embodiments, which further comprises:

(i) a modification, e.g., an insertion, substitution (e.g., conservative substitution), and/or deletion, in loop I, II, VI and/or VIII; and/or

(ii) a substitution at position K449, e.g., a K449R substitution, numbered according to SEQ ID NO: 138.

448. The AAV capsid variant of any one of the preceding embodiments, which comprises an amino acid sequence comprising at least one, two or three modifications, e.g., substitutions (e.g., conservative substitutions), but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of SEQ ID NO: 138.

449. The AAV capsid variant of any one of the preceding embodiments, which comprises an amino acid sequence comprising at least one, two or three, but no more than 30, 20 or 10 different amino acids relative to the amino acid sequence of SEQ ID NO: 138.

450. The AAV capsid variant of any one of the preceding embodiments, which comprises the amino acid sequence of SEQ ID NO: 138, or an amino acid sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto.

451. The AAV capsid variant of any one of the preceding embodiments, which comprises the amino acid sequence of SEQ ID NO: 138.

452. The AAV capsid variant of any one of the preceding embodiments, which comprises an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 137, or a sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto.

453. The AAV capsid variant of any one of the preceding embodiments, wherein the nucleotide sequence encoding the capsid variant comprises the nucleotide sequence of SEQ ID NO: 137, or a sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto.

454. The AAV capsid variant of any one of the preceding embodiments, which comprises a VP1 protein, a VP2 protein, a VP3 protein, or a combination thereof.

455. The AAV capsid variant of any one of embodiments 1-454, which comprises the amino acid sequence corresponding to positions 138-742, e.g., a VP2, of SEQ ID NO: 981 or 982, or a sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto.

456. The AAV capsid variant of any one of embodiments 1-455, which comprises the amino acid sequence corresponding to positions 203-742, e.g., a VP3, of SEQ ID NO: 981 or 982, or a sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto.

457. The AAV capsid variant of any one of embodiments 1-456, which comprises the amino acid sequence corresponding to positions 138-736, e.g., a VP2, of SEQ ID NO: 138, or a sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto.

458. The AAV capsid variant of any one of embodiments 1-457, which comprises the amino acid sequence corresponding to positions 203-736, e.g., a VP3, of SEQ ID NO: 138, or a sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto.

459. The AAV capsid variant of any one of embodiments 1-23, 26-29, 32, 35-43, 46-51, 54-72, 69-89, 91, 94-99, 102-104, 107, 110-112, 115-129, 168-202, 02, 240-247, 249, 250, 253-263, 266, 272-281, 286, 288, 291-299, 327-363, 369-371, 375-379, 385, 386, 390, 391, 395, 406, 408, 410-413, 415-432, 444, or 446-458, comprising an amino acid sequence comprising at least 3, 4, 5, or 6 consecutive amino acids from the amino acid sequence of SPHKA (SEQ ID NO: 941), wherein:

- (i) the 3 consecutive amino acids comprise SPH;
- (ii) the 4 consecutive amino acids comprise SPHS (SEQ ID NO: 4700);
- (iii) the 5 consecutive amino acids comprise SPHKA (SEQ ID NO: 4701); or
- (iv) the 6 consecutive amino acids comprise SPHKA (SEQ ID NO: 941);

wherein the AAV capsid variant comprises: (a) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 138 or SEQ ID NO: 981; (b) a VP2 protein comprising the amino acid sequence of positions 138-736 of SEQ ID NO: 138 or positions 138-742 of SEQ ID NO: 981; (c) a VP3 protein comprising the amino acid sequence of positions 203-736 of SEQ ID NO: 138 or positions 203-742 of SEQ ID NO: 981; or (d) an amino acid sequence with at least 90% (e.g., at least about 95, 96, 97, 98, or 99%) sequence identity to any of the amino acid sequences in (a)-(c).

460. The AAV capsid variant of any one of embodiments 1-23, 26-29, 32, 35-43, 46-51, 54-72, 69-89, 91, 94-99, 102-104, 107, 110-112, 115-129, 168-202, 02, 240-247, 249, 250, 253-263, 266, 272-281, 286, 288, 291-299, 327-363, 369-371, 375-379, 385, 386, 390, 391, 395, 406, 408, 410-413, 415-432, 444, or 446-459, comprising an amino acid sequence comprising at least 3, 4, 5, or 6 consecutive amino acids from the amino acid sequence of SPHKA (SEQ ID NO: 941), wherein:

- (i) the 3 consecutive amino acids comprise SPH;
- (ii) the 4 consecutive amino acids comprise SPHS (SEQ ID NO: 4700);
- (iii) the 5 consecutive amino acids comprise SPHKA (SEQ ID NO: 4701); or
- (iv) the 6 consecutive amino acids comprise SPHKA (SEQ ID NO: 941);

wherein the AAV capsid variant comprises an amino acid sequence at least 90% (e.g., at least about 95, 96, 97, 98, or 99%) identical to the amino acid sequence of SEQ ID NO: 981.

461. The AAV capsid variant of any one of embodiments 1-23, 26-29, 32, 35-43, 46-51, 54-72, 69-89, 91, 94-99, 102-104, 107, 110-112, 115-129, 168-202, 02, 240-247, 249, 250, 253-263, 266, 272-281, 286, 288, 291-299, 327-363, 369-371, 375-379, 385, 386, 390, 391, 395, 406, 408, 410-413, 415-432, 444, or 446-460, comprising one or two, but no more than three substitutions relative to the amino acid sequence of SPHKA (SEQ ID NO: 941), wherein the AAV capsid variant comprises:

(a) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 138 or SEQ ID NO: 981;

(b) a VP2 protein comprising the amino acid sequence of positions 138-736 of SEQ ID NO: 138 or positions 138-742 of SEQ ID NO: 981;

(c) a VP3 protein comprising the amino acid sequence of positions 203-736 of SEQ ID NO: 138 or positions 203-742 of SEQ ID NO: 981; or

(d) an amino acid sequence with at least 90% (e.g., at least about 95, 96, 97, 98, or 99%) sequence identity to any of the amino acid sequences in (a)-(c).

462. The AAV capsid variant of any one of embodiments 1-23, 26-29, 32, 35-43, 46-51, 54-72, 69-89, 91, 94-99, 102-104, 107, 110-112, 115-129, 168-202, 02, 240-247, 249, 250, 253-263, 266, 272-281, 286, 288, 291-299, 327-363, 369-371, 375-379, 385, 386, 390, 391, 395, 406, 408, 410-413, 415-432, 444, or 446-461, comprising one or two, but no more than three substitutions relative to the amino acid sequence of SPHKA (SEQ ID NO: 941), wherein the AAV capsid variant comprises an amino acid sequence at least 90% (e.g., at least about 95, 96, 97, 98, or 99%) identical to the amino acid sequence of SEQ ID NO: 138 or SEQ ID NO: 981.

463. The AAV capsid variant of any one of embodiments 459-462, wherein the amino acid sequence is present immediately subsequent to position 455, numbered according to SEQ ID NO: 138 or 981.

464. The AAV capsid variant of any one of embodiments 1-9, 11, 12-22, 24, 26, 28, 30, 33, 35-42, 44, 46-50, 52, 54-77, 83-88, 90-97, 100-103, 105, 110, 111, 113-129, 203-248, 251, 252, 254-257, 260, 261, 264-280, 283-287, 289-299, 327-363, 369, 369, 371, 380-383, 385, 386, 390, 392, 395, 407, 409-412, 414, 433-435, 438-441, 443, 445, or 447-458, comprising an amino acid sequence comprising at least 3, 4, 5, or 6 consecutive amino acids from the amino acid sequence of HDSPHK (SEQ ID NO: 2), wherein:

(i) the 3 consecutive amino acids comprise HDS;

(ii) the 4 consecutive amino acids comprise HDSP (SEQ ID NO: 4702);

(iii) the 5 consecutive amino acids comprise HDSPH (SEQ ID NO: 4703); or

(iv) the 6 consecutive amino acids comprise HDSPHK (SEQ ID NO: 2);

wherein the AAV capsid variant comprises: (a) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 138 or SEQ ID NO: 982; (b) a VP2 protein comprising the amino acid sequence of positions 138-736 of SEQ ID NO: 138 or positions 138-742 of SEQ ID NO: 982; (c) a VP3 protein comprising the amino acid sequence of positions 203-736 of SEQ ID NO: 138 or positions 203-742 of SEQ ID NO: 982; or (d) an amino acid sequence with at least 90% (e.g., at least about 95, 96, 97, 98, or 99%) sequence identity to any of the amino acid sequences in (a)-(c).

465. The AAV capsid variant of any one of embodiments 1-9, 11, 12-22, 24, 26, 28, 30, 33, 35-42, 44, 46-50, 52, 54-77, 83-88, 90-97, 100-103, 105, 110, 111, 113-129, 203-248, 251, 252, 254-257, 260, 261, 264-280, 283-287, 289-299, 327-363, 369, 369, 371, 380-383, 385, 386, 390, 392, 395, 407, 409-412, 414, 433-435, 438-441, 443, 445, 447-458, or 464, comprising an amino acid sequence comprising at least 3, 4, 5, or 6 consecutive amino acids from the amino acid sequence of HDSPHK (SEQ ID NO: 2), wherein:

- (i) the 3 consecutive amino acids comprise HDS;
- (ii) the 4 consecutive amino acids comprise HDSP (SEQ ID NO: 4702);
- (iii) the 5 consecutive amino acids comprise HDSPH (SEQ ID NO: 4703); or
- (iv) the 6 consecutive amino acids comprise HDSPHK (SEQ ID NO: 2);

wherein the AAV capsid variant comprises an amino acid sequence at least 90% (e.g., at least about 95, 96, 97, 98, or 99%) identical to the amino acid sequence of SEQ ID NO: 982.

466. The AAV capsid variant of any one of embodiments 1-9, 11, 12-22, 24, 26, 28, 30, 33, 35-42, 44, 46-50, 52, 54-77, 83-88, 90-97, 100-103, 105, 110, 111, 113-129, 203-248, 251, 252, 254-257, 260, 261, 264-280, 283-287, 289-299, 327-363, 369, 369, 371, 380-383, 385, 386, 390, 392, 395, 407, 409-412, 414, 433-435, 438-441, 443, 445, 447-458, 464, or 465, comprising one or two, but no more than three substitutions relative to the amino acid sequence of HDSPHK (SEQ ID NO: 2), wherein the AAV capsid variant comprises:

- (a) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 138 or SEQ ID NO: 982;
- (b) a VP2 protein comprising the amino acid sequence of positions 138-736 of SEQ ID NO: 138 or positions 138-742 of SEQ ID NO: 982;
- (c) a VP3 protein comprising the amino acid sequence of positions 203-736 of SEQ ID NO: 138 or positions 203-742 of SEQ ID NO: 982; or
- (d) an amino acid sequence with at least 90% (e.g., at least about 95, 96, 97, 98, or 99%) sequence identity to any of the amino acid sequences in (a)-(c).

467. The AAV capsid variant of any one of embodiments 1-9, 11, 12-22, 24, 26, 28, 30, 33, 35-42, 44, 46-50, 52, 54-77, 83-88, 90-97, 100-103, 105, 110, 111, 113-129, 203-248, 251, 252, 254-257, 260, 261, 264-280, 283-287, 289-299, 327-363, 369, 369, 371, 380-383, 385, 386, 390, 392, 395, 407, 409-412, 414, 433-435, 438-441, 443, 445, 447-458, or 464-466, comprising one or two, but no more than three substitutions relative to the amino acid sequence of HDSPHK (SEQ ID NO: 2), wherein the AAV capsid variant comprises an amino acid sequence at least 90% (e.g., at least about 95, 96, 97, 98, or 99%) identical to the amino acid sequence of SEQ ID NO: 982.

468. The AAV capsid variant of any one of embodiments 464-468, wherein the amino acid sequence is present immediately subsequent to position 453, numbered according to SEQ ID NO: 138 or 982.

469. The AAV capsid variant of any one of embodiments 1-468, which comprises the amino acid sequence of any one of SEQ ID NO: 981 or 982, or an amino acid sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto.

470. The AAV capsid variant of any one of embodiments 1-469, which comprises an amino acid sequence comprising at least one, two or three modifications, e.g., substitutions (e.g., conservative substitutions), but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of SEQ ID NO: 981 or 982.

471. The AAV capsid variant of any one of embodiments, 1-470, which comprises an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids, relative to the amino acid sequence of SEQ ID NO: 981 or 982.

472. The AAV capsid variant of any one of embodiments 1-23, 26-29, 32, 35-43, 46-51, 54-72, 69-89, 91, 94-99, 102-104, 107, 110-112, 115-129, 168-202, 02, 240-247, 249, 250, 253-263, 266, 272-281, 286, 288, 291-299, 327-363, 369-371, 375-379, 385, 386, 390, 391, 395, 406, 408, 410-413, 415-432, 444, 446-463, or 469-471, which comprises the amino acid sequence of SEQ ID NO: 981, or an amino acid sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto.

473. The AAV capsid variant of any one of embodiments 1-23, 26-29, 32, 35-43, 46-51, 54-72, 69-89, 91, 94-99, 102-104, 107, 110-112, 115-129, 168-202, 02, 240-247, 249, 250, 253-263, 266, 272-281, 286, 288, 291-299, 327-363, 369-371, 375-379, 385, 386, 390, 391, 395, 406, 408, 410-413, 415-432, 444, 446-463, or 469-472, which comprises an amino acid sequence comprising at least one, two or three modifications, e.g., substitutions (e.g., conservative substitutions), but not more than 30, 20 or

10 modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of SEQ ID NO: 981.

474. The AAV capsid variant of any one of embodiments 1-23, 26-29, 32, 35-43, 46-51, 54-72, 69-89, 91, 94-99, 102-104, 107, 110-112, 115-129, 168-202, 02, 240-247, 249, 250, 253-263, 266, 272-281, 286, 288, 291-299, 327-363, 369-371, 375-379, 385, 386, 390, 391, 395, 406, 408, 410-413, 415-432, 444, 446-463, or 469-473, which comprises an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids, relative to the amino acid sequence of SEQ ID NO: 981.

475. The AAV capsid variant of any one of embodiments 1-9, 11, 12-22, 24, 26, 28, 30, 33, 35-42, 44, 46-50, 52, 54-77, 83-88, 90-97, 100-103, 105, 110, 111, 113-129, 203-248, 251, 252, 254-257, 260, 261, 264-280, 283-287, 289-299, 327-363, 369, 369, 371, 380-383, 385, 386, 390, 392, 395, 407, 409-412, 414, 433-435, 438-441, 443, 445, 447-458, or 464-471, which comprises the amino acid sequence of SEQ ID NO: 982, or an amino acid sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto.

476. The AAV capsid variant of any one of embodiments 1-9, 11, 12-22, 24, 26, 28, 30, 33, 35-42, 44, 46-50, 52, 54-77, 83-88, 90-97, 100-103, 105, 110, 111, 113-129, 203-248, 251, 252, 254-257, 260, 261, 264-280, 283-287, 289-299, 327-363, 369, 369, 371, 380-383, 385, 386, 390, 392, 395, 407, 409-412, 414, 433-435, 438-441, 443, 445, 447-458, 464-471, or 475, which comprises an amino acid sequence comprising at least one, two or three modifications, e.g., substitutions (e.g., conservative substitutions), but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of SEQ ID NO: 982.

477. The AAV capsid variant of any one of embodiments 1-9, 11, 12-22, 24, 26, 28, 30, 33, 35-42, 44, 46-50, 52, 54-77, 83-88, 90-97, 100-103, 105, 110, 111, 113-129, 203-248, 251, 252, 254-257, 260, 261, 264-280, 283-287, 289-299, 327-363, 369, 369, 371, 380-383, 385, 386, 390, 392, 395, 407, 409-412, 414, 433-435, 438-441, 443, 445, 447-458, 464-471, 475, or 476, which comprises an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids, relative to the amino acid sequence of SEQ ID NO: 982.

478. The AAV capsid variant of any one of embodiments 1-477, which comprises an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 983 or 984, or a nucleotide sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto.

479. The AAV capsid variant of any one of the preceding embodiments 1-478, wherein the nucleotide sequence encoding the capsid variant comprises the nucleotide sequence of SEQ ID NOs: 983 or 984, or a nucleotide sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto.

480. The AAV capsid variant of any one of the preceding embodiments 1-23, 26-29, 32, 35-43, 46-51, 54-72, 69-89, 91, 94-99, 102-104, 107, 110-112, 115-129, 168-202, 02, 240-247, 249, 250, 253-263, 266, 272-281, 286, 288, 291-299, 327-363, 369-371, 375-379, 385, 386, 390, 391, 395, 406, 408, 410-413, 415-432, 444, 446-463, 469-474, 478, or 479, wherein the nucleotide sequence encoding the capsid variant comprises the nucleotide sequence of SEQ ID NO: 983, or a nucleotide sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto.

481. The AAV capsid variant of any one of the preceding embodiments 1-9, 11, 12-22, 24, 26, 28, 30, 33, 35-42, 44, 46-50, 52, 54-77, 83-88, 90-97, 100-103, 105, 110, 111, 113-129, 203-248, 251, 252, 254-257, 260, 261, 264-280, 283-287, 289-299, 327-363, 369, 369, 371, 380-383, 385, 386, 390, 392, 395, 407, 409-412, 414, 433-435, 438-441, 443, 445, 447-458, 464-471, or 475-479, wherein the nucleotide sequence encoding the capsid variant comprises the nucleotide sequence of SEQ ID NO: 984, or a nucleotide sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto.

482. The AAV capsid variant of any one of the preceding embodiments, wherein the nucleotide sequence encoding the capsid variant is codon optimized.

483. An AAV capsid variant, comprising the amino acid sequence of any one of embodiments 1-23, 26-29, 32, 35-43, 46-51, 54-72, 69-89, 91, 94-99, 102-104, 107, 110-112, 115-129, 168-202, 02, 240-247, 249, 250, 253-263, 266, 272-281, 286, 288, 291-299, 327-363, 369-371, 375-379, 385, 386, 390, 391, 395, 406, 408, 410-413, 415-432, 444, 446-463, 469-474, 478-480, or 482, and further comprising an amino acid sequence at least 95% identical to SEQ ID NO: 981.

484. An AAV capsid variant comprising the amino acid sequence of SEQ ID NO: 981.

485. The AAV capsid variant of embodiment 483 or 484, wherein the nucleotide sequence encoding the AAV capsid variant comprises the nucleotide sequence of SEQ ID NO: 983, or a nucleotide sequence at least 90%, 95%, or 99% identical thereto.

486. An AAV capsid variant, comprising the amino acid sequence of any one of embodiments 1-9, 11, 12-22, 24, 26, 28, 30, 33, 35-42, 44, 46-50, 52, 54-77, 83-88, 90-97, 100-103, 105, 110, 111, 113-

129, 203-248, 251, 252, 254-257, 260, 261, 264-280, 283-287, 289-299, 327-363, 369, 369, 371, 380-383, 385, 386, 390, 392, 395, 407, 409-412, 414, 433-435, 438-441, 443, 445, 447-458, 464-471, 475-479, 481, or 482, and further comprising an amino acid sequence at least 95% identical to SEQ ID NO: 982.

487. An AAV capsid variant comprising the amino acid sequence of SEQ ID NO: 982.

488. The AAV capsid variant of embodiment 486 or 487, wherein the nucleotide sequence encoding the AAV capsid variant comprises the nucleotide sequence of SEQ ID NO: 984, or a nucleotide sequence at least 90%, 95%, or 99% identical thereto.

489. An AAV capsid variant comprising an amino acid sequence encoded by the nucleotide sequence of SEQ ID NOs: 983 or 984, or a nucleotide sequence at least 95% identical thereto.

490. An AAV capsid variant comprising the amino acid sequence of any one of SEQ ID NOs: 36-59.

491. An AAV capsid variant comprising an amino acid sequence encoded by the nucleotide sequence of any one of SEQ ID NOs: 12-35, or a nucleotide sequence at least 95% identical thereto.

492. The AAV capsid variant of 490 or 491, wherein the nucleotide sequence encoding the AAV capsid variant comprises the nucleotide sequence of any one of SEQ ID NOs: 12-35, or a nucleotide sequence at least 95% identical thereto.

493. The AAV capsid variant of any one of embodiments 1-299, 369-371, or 375-492, which has an increased tropism for a CNS cell or tissue, e.g., a brain cell, brain tissue, spinal cord cell, or spinal cord tissue, relative to the tropism of a reference sequence comprising the amino acid sequence of SEQ ID NO: 138.

494. The AAV capsid variant of any one of embodiments 1-129, 168-299, 369-371, or 375-493, which transduces a brain region, e.g., a midbrain region (e.g., the hippocampus, or thalamus) or the brain stem, optionally wherein the level of transduction is at least 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, or 65-fold greater as compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay, e.g., an immunohistochemistry assay or a qPCR assay, e.g., as described in Example 2.

495. The AAV capsid variant of any one of embodiments 1-129, 168-299, 369-371, or 375-494, which transduces a brain region, e.g., a midbrain region (e.g., the hippocampus, or thalamus) or the brain stem, optionally wherein the level of transduction is at least 30, 35, 40, 45, 50, 55, 60, or 65-fold

greater as compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay, e.g., an immunohistochemistry assay or a qPCR assay, e.g., as described in Example 2.

496. The AAV capsid variant of any one of embodiments 1-129, 168-299, 369-371, or 375-495, which is enriched at least about 3, 4, 5, 6, 7, 8, 9, or 10-fold, in the brain compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay as described in Example 1.

497. The AAV capsid variant of any one of embodiments 1-129, 168-299, 369-371, or 375-496, which is enriched at least about 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80 or 85-fold, in the brain compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay as described in Example 1.

498. The AAV capsid variant of any one of embodiments 1-129, 168-299, 369-371, or 375-497, which is enriched in the brain of at least two to three species, e.g., a non-human primate and rodent (e.g., mouse), e.g., as compared to a reference sequence of SEQ ID NO: 138.

499. The AAV capsid variant of any one of embodiments 1-129, 168-299, 369-371, or 375-498, which is enriched at least about 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 190, 200, 205, or 210-fold, in the brain of at least two to three species, e.g., a non-human primate and rodent (e.g., mouse), compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay as described in Example 1 or 5.

500. The AAV capsid variant of embodiment 498 or 499, wherein the at least two to three species are *Macaca fascicularis*, *Chlorocebus sabaeus*, *Callithrix jacchus*, and/or mouse (e.g., BALB/c mice, C57Bl/6 mice, and/or CD-1 outbred mice).

501. The AAV capsid variant of any one of embodiments 130-146, 369, 410-414, 447-454, 457, 458, 482, or 493, which is enriched at least about 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, or 8-fold, in the brain compared to a reference sequence of SEQ ID NO: 981, e.g., when measured by an assay as described in Example 3.

502. The AAV capsid variant of any one of embodiments 147-167, 369, 410-414, 447-454, 457, 458, 482, or 493, which is enriched at least about 2, 2.5, 3, 3.5, 4, 4.5, 5, or 5.5-fold, in the brain compared to a reference sequence of SEQ ID NO: 982, e.g., when measured by an assay as described in Example 3.

503. The AAV capsid variant of any one of embodiments 1-129, 168-299, 369-371, or 375-500, which delivers an increased level of a payload to a brain region, optionally wherein the level of the payload is increased by at least 10, 12, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, or 70-fold, as compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay, e.g., a qRT-PCR or a qPCR assay (e.g., as described in Example 2 or 8).

504. The AAV capsid variant of any one of embodiments 1-129, 168-299, 369-371, 375-500, or 503, which delivers an increased level of viral genomes to a brain region, optionally wherein the level of viral genomes is increased by at least 5, 10, 15, 17, 18, 19, 20, 25, 30, 35, 40, 45, or 50-fold, as compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay, e.g., a qRT-PCR or a qPCR assay (e.g., as described in Example 2 or 8).

505. The AAV capsid variant of embodiment 504 or 504, wherein the brain region is a midbrain region (e.g., the hippocampus or thalamus), frontal cortex, temporal cortex, motor cortex, cerebral cortex, caudate, putamen, dentate nucleus, substantia nigra, or the brainstem.

506. The AAV capsid variant of any one of embodiments 1-129, 168-299, 369-371, 375-500, or 503-505, which is enriched at least about 4, 5, 10, 15, 20, 25, 30, or 35-fold, in the spinal cord compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay as described in Example 1 or 8, optionally wherein the region of the spinal cord is a thoracic spinal cord region, cervical spinal cord region, C5 ventral horn region, lumbar spinal cord region, or L5 ventral horn region.

507. The AAV capsid variant of any one of embodiments 1-129, 168-299, 369-371, 375-500, or 503-506, which shows preferential transduction in a brain region relative to the transduction in the dorsal root ganglia (DRG).

508. The AAV capsid variant of any one of embodiments 1-129, 168-299, 369-371, 375-500, or 503-507, which shows preferential transduction in a brain region relative to the liver.

509. The AAV capsid variant of any one of embodiments 1-129, 168-299, 369-371, 375-500, or 503-508, which shows preferential transduction in a brain region relative to the transduction in the heart.

510. The AAV capsid variant of any one of embodiments 1-129, 168-299, 369-371, 375-500, or 503-509, which shows preferential transduction in a brain region relative to the transduction in the dorsal root ganglia (DRG) and the heart.

511. The AAV capsid variant of any one of the preceding embodiments, which is capable of transducing non-neuronal cells, e.g., glial cells (e.g., oligodendrocytes or astrocytes).
512. The AAV capsid variant of embodiment 511, wherein the non-neuronal cells comprise glial cells, oligodendrocytes (e.g., Olig2 positive oligodendrocytes), or astrocytes (e.g., Olig2 positive astrocytes).
513. The AAV capsid variant of any one of the preceding embodiments, which is capable of transducing Olig2 positive cells, e.g., Olig2 positive astrocytes or Olig2 positive oligodendrocytes.
514. The AAV capsid variant of any one of embodiments 369, 373, 447-454, 457, 458, or 482, which has increased tropism for a heart cell or tissue, e.g., a heart ventricle or heart atrium, relative to the tropism of a reference sequence of SEQ ID NO: 138.
515. The AAV capsid variant of any one of embodiments 369, 373, 447-454, 457, 458, 482, or 514, which is enriched at least about 4, 5, 8, 10, 11, 12, 13, 14, 18, 19, 20, 21, 22, 24, 25, 27, 31, 33, or 34-fold, in the heart compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay as described in Example 4.
516. The AAV capsid variant of any one of embodiments 369, 374, 447-454, 457, 458, 482, which has an increased tropism for a muscle cell or tissue (e.g., a quadriceps cell or a quadriceps tissue), relative to the tropism of a reference sequence comprising the amino acid sequence of SEQ ID NO: 138.
517. The AAV capsid variant of any one of embodiments 369, 374, 447-454, 457, 458, 482, which is enriched at least about 4, 5, 8, 12, 17, 18, 20, 26, 27, 28, 30, or 36-fold, in the muscle compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay as described in Example 4.
518. The AAV capsid variant of embodiment 516 or 517, wherein the muscle cell or tissue is a heart muscle (e.g., a heart ventricle or a heart atrium, or both), a quadriceps muscle, or both.
519. The AAV capsid variant of any one of the preceding embodiments, which is isolated, e.g., recombinant.
520. A polynucleotide encoding the AAV capsid variant of any one of embodiments 1-519.
521. The polynucleotide of embodiment 520, which comprises:

(i) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequences of SEQ ID NO: 3 or 942;

(ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten different nucleotides, relative to the nucleotide sequences of SEQ ID NO: 3 or 942; or

(iii) the nucleotide sequence of SEQ ID NOs: 3 or 942, or nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto.

522. The polynucleotide of embodiment 520 or 521, which comprises the nucleotide sequence of SEQ ID NO: 983 or 984, or a nucleotide sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto.

523. The polynucleotide of any one of embodiments 520-522, which comprises a nucleotide sequence that is codon optimized.

524. A peptide comprising an amino acid sequence having the following formula: [N1]-[N2]-[N3] according to any one of embodiments 1-8, 12-35, 39-45, 48-53, 91, or 118-123.

525. A peptide comprising an amino acid sequence having the following formula: [A][B] according to any one of embodiments 130-133, 142, or 146.

526. A peptide comprising an amino acid sequence having the following formula: [A][B] according to any one of embodiments 147-150, 166, or 167.

527. A peptide comprising an amino acid sequence having the following formula: [N1]-[N2]-[N3] according to any one of embodiments 168-176, 179-186, 191-195, 198-202, or 295-299.

528. A peptide comprising an amino acid sequence having the following formula: [N1]-[N2]-[N3] according to any one of embodiments 203-211, 214-223, 228-231, 234-239, or 295-299.

529. A peptide comprising an amino acid sequence having the following formula: [A]-[B], according to any one of embodiments 300-306, 316, 317, 322, or 326.

530. A peptide comprising:

(a) the amino acid sequence of any of the sequences provided in Tables 1, 2A, 2B, 13-19;

(b) an amino acid sequence comprising at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or 17 consecutive amino acids from any one of the sequences provided in Tables 1, 2A, 2B, 13-19;

(c) an amino acid sequence comprising at least one, two, or three but no more than four different amino acids relative to the amino acid sequence of any one of the sequences provided in Tables 1, 2A, 2B, 13-19; or

(d) an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of any one of the sequences provided in Tables 1, 2A, 2B, 13-19.

531. A peptide comprising:

(a) the amino acid sequence of any of SEQ ID NOs: 3849-4051 or 4681-4693;

(b) an amino acid sequence comprising at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or 17 consecutive amino acids from any one of SEQ ID NOs: 3849-4051 or 4681-4693;

(c) an amino acid sequence comprising at least one, two, or three but no more than four different amino acids relative to the amino acid sequence of any one of SEQ ID NOs: 3849-4051 or 4681-4693; or

(d) an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of any one of SEQ ID NOs: 3849-4051 or 4681-4693.

532. A peptide comprising:

(a) the amino acid sequence of any of SEQ ID NOs: 4052-4092;

(b) an amino acid sequence comprising at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or 17 consecutive amino acids from any one of SEQ ID NOs: 4052-4092;

(c) an amino acid sequence comprising at least one, two, or three but no more than four different amino acids relative to the amino acid sequence of any one of SEQ ID NOs: 4052-4092; or

(d) an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of any one of SEQ ID NOs: 4052-4092.

533. A peptide comprising:

(a) the amino acid sequence of any of SEQ ID NOs: 4056, 4058, 4059, 4062-4064, 4066, 4067, 4080, 4084, 4090, or 4095-4097;

(b) an amino acid sequence comprising at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or 17 consecutive amino acids from any one of SEQ ID NOs: 4056, 4058, 4059, 4062-4064, 4066, 4067, 4080, 4084, 4090, or 4095-4097;

(c) an amino acid sequence comprising at least one, two, or three but no more than four different amino acids relative to the amino acid sequence of any one of SEQ ID NOs: 4056, 4058, 4059, 4062-4064, 4066, 4067, 4080, 4084, 4090, or 4095-4097; or

(d) an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of any one of SEQ ID NOs: 4056, 4058, 4059, 4062-4064, 4066, 4067, 4080, 4084, 4090, or 4095-4097.

534. A peptide comprising:

(a) the amino acid sequence of any of SEQ ID NOs: 945-980 or 985-986;

(b) an amino acid sequence comprising at least 3, 4, or 5 consecutive amino acids from any one of SEQ ID NOs: 945-980 or 985-986;

(c) an amino acid sequence comprising at least one, two, or three but no more than four different amino acids relative to the amino acid sequence of any one of SEQ ID NOs: 945-980 or 985-986; or

(d) an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of any one of SEQ ID NOs: 945-980 or 985-986.

535. A peptide comprising:

(a) the amino acid sequence of any of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909;

(b) an amino acid sequence comprising at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 consecutive amino acids from any one of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909;

(c) an amino acid sequence comprising at least one, two, or three but no more than four different amino acids relative to the amino acid sequence of any one of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909; or

(d) an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of any one of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909.

536. A peptide comprising:

(i) the amino acid sequence of SPHSKA (SEQ ID NO: 941);

(ii) an amino acid sequence comprising at least one, two, or three, but no more than four different amino acids relative to the amino acid sequence of SPHSKA (SEQ ID NO: 941);

(iii) an amino acid sequence comprising at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), but no more than four modifications, e.g., substitutions

(e.g., conservative substitutions), relative to the amino acid sequence of SPHKA (SEQ ID NO: 941);
or

(iv) at least 3, 4, or 5 consecutive amino acids from the amino acid sequence of SPHKA (SEQ ID NO: 941).

537. A peptide encoded by:

(i) the nucleotide sequence of SEQ ID NO: 942, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto;

(ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 942; or

(iii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequence of SEQ ID NO: 942.

538. A peptide wherein the nucleotide sequence encoding the peptide comprises:

(i) the nucleotide sequence of SEQ ID NO: 942, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto;

(ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but not more than 10 different nucleotides, relative to the nucleotide sequence of SEQ ID NO: 942; or

(iii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequence of SEQ ID NO: 942.

539. A peptide comprising:

(i) the amino acid sequence of HDSPHK (SEQ ID NO: 2);

(ii) an amino acid sequence comprising at least one, two, or three, but no more than four different amino acids, relative to the amino acid sequence of HDSPHK (SEQ ID NO: 2);

(iii) an amino acid sequence comprising at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of HDSPHK (SEQ ID NO: 2);
or

(iv) at least 3, 4, or 5 consecutive amino acids from the amino acid sequence of HDSPHK (SEQ ID NO: 2).

540. A peptide encoded by:

(i) the nucleotide sequence of SEQ ID NO: 3, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or

(ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten different nucleotides, relative to the nucleotide sequence of SEQ ID NO: 3

(iii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequence of SEQ ID NO: 3.

541. A peptide wherein the nucleotide sequence encoding the peptide comprises:

(i) the nucleotide sequence of SEQ ID NO: 3, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto;

(ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 3; or

(iii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequence of SEQ ID NO: 3.

542. A peptide comprising:

(i) the amino acid sequence of KTERVSGSPHKAQNQQT (SEQ ID NO: 3589);

(ii) an amino acid sequence comprising at least one, two, or three, but no more than four different amino acids, relative to the amino acid sequence of KTERVSGSPHKAQNQQT (SEQ ID NO: 3589);

(iii) an amino acid sequence comprising at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of KTERVSGSPHKAQNQQT (SEQ ID NO: 3589); or

(iv) at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16 or 17 consecutive amino acids from the amino acid sequence of KTERVSGSPHKAQNQQT (SEQ ID NO: 3589).

543. A peptide comprising:

(i) the amino acid sequence of KAEIGHDSPHKSGQNQQT (SEQ ID NO: 1754);

(ii) an amino acid sequence comprising at least one, two, or three, but no more than four different amino acids, relative to the amino acid sequence of KAEIGHDSPHKSGQNQQT (SEQ ID NO: 1754);

(iii) an amino acid sequence comprising at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of KAEIGHDSPHKSGQNQQT (SEQ ID NO: 1754); or

(iv) at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16 or 17 consecutive amino acids from the amino acid sequence of KAEIGHDSPHKSGQNQQT (SEQ ID NO: 1754).

544. The peptide of any one of embodiments 524-543, which is fused or coupled, e.g., conjugated, to an active agent, e.g., a therapeutic agent or a diagnostic agent.

545. The peptide of any one of embodiments 524-544, wherein at least 1-5, e.g., at least 1, 2, 3, 4, or 5, peptides are fused or coupled, e.g., conjugated, to an active agent, e.g., a therapeutic agent or a diagnostic agent.

546. The peptide of embodiment 545, wherein the at least 1-5, e.g., at least 1, 2, 3, 4, or 5, peptides comprise the same amino acid sequence.

547. The peptide of embodiment 545, wherein the at least 1-5, e.g., at least 1, 2, 3, 4, or 5, peptides comprise different amino acid sequences.

548. The peptide of any one of embodiments 545-547, wherein the at least 1-5, e.g., at least 1, 2, 3, 4, or 5, peptides are present in tandem (e.g., connected directly or indirectly via a linker) or in a multimeric configuration.

549. The peptide of any one of embodiments 524-548, wherein the peptide comprises an amino acid sequence of at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 15, 20, 25, 30, or 35 amino acids in length.

550. The peptide of any one of embodiments 544-549, wherein the active agent is or comprises a therapeutic agent chosen from a protein (e.g., an enzyme), an antibody molecule, a nucleic acid molecule (e.g., an RNAi agent), or a small molecule.

551. The peptide of any one of embodiments 544-549, wherein the active agent is or comprises a ribonucleic acid complex (e.g., a Cas9/gRNA complex), a plasmid, a closed-end DNA, a circ-RNA, or an mRNA.

552. The peptide of any one of embodiments 544-549, wherein the active agent is an RNAi agent.

553. The peptide of embodiment 552, wherein the RNAi agent is a dsRNA, a siRNA, a shRNA, a pre-miRNA, a pri-miRNA, a miRNA, a stRNA, a lncRNA, a piRNA, an antisense oligonucleotide agent (ASO), or a snoRNA, optionally wherein the RNAi agent is an siRNA or an ASO, which further optionally comprises at least one modified nucleotide.

554. The peptide of any one of embodiments 544-553, wherein the active agent modulates, e.g., inhibits, decreases or increases, expression of, a CNS related gene, mRNA, and/or protein.

555. The peptide of any one of embodiments 544-549, wherein the active agent is a diagnostic agent is or comprises an imaging agent (e.g., a protein or small molecule compound coupled to a detectable moiety).

556. The peptide of any one of embodiments 544-555, wherein the peptide covalently linked, e.g., directly or indirectly via a linker, to the active agent.

557. The peptide of any one of embodiments 544-556, wherein the peptide is conjugated to the active agent via a linker.

558. The peptide of embodiment 557, wherein the linker is a cleavable linker or a non-cleavable linker.

559. The peptide of embodiment 558, wherein the cleavable linker is a pH sensitive linker or an enzyme sensitive linker.

560. The peptide of embodiment 558 or 559, wherein:

- (i) the pH sensitive linker comprises a hydrazine/hydrazone linker or a disulfide linker;
- (ii) the enzyme sensitive linker comprises a peptide based linker, e.g., a peptide linker sensitive to a protease (e.g., a lysosomal protease); or a beta-glucuronide linker; or
- (iii) the non-cleavable linker is a linker comprising a thioether group or a maleimidocaproyl group.

561. The peptide of any one of embodiments 544-560, wherein:

- (i) the peptide and the active agent are fused or coupled post-translationally, e.g., using click chemistry; or
- (ii) the peptide and the active agent are fused or couple via chemically induced dimerization.

562. The peptide of any one of embodiments 544-561, wherein the peptide is present N-terminal relative to the active agent.

563. The peptide of any one of embodiments 544-561, wherein the peptide is present C-terminal relative to the active agent.

564. The peptide of any one of embodiment 544-549, 554, or 556-563, wherein the peptide is present or coupled to a carrier, e.g., an exosome, a microvesicle, or a lipid nanoparticle (LNP), optionally, wherein the carrier comprises a therapeutic agent (e.g., an RNAi agent (e.g., an dsRNA, a siRNA, a shRNA, a pre-miRNA, a pri-miRNA, a miRNA, a stRNA, a lncRNA, a piRNA, an antisense oligonucleotide agent (ASO), or a snoRNA), an mRNA, a ribonucleoprotein complex (e.g., a Cas9/gRNA complex), or a circRNA).

565. The peptide of embodiment 564, wherein the peptide is present on the surface of the carrier, optionally wherein at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, or 80% of the surface of the carrier comprises at least 1-5, e.g., at least 1, 2, 3, 4, or 5 peptides according to any one of embodiments 422-436.

566. An AAV capsid variant, comprising the peptide of any one of embodiments 524-543.

567. A polynucleotide encoding an AAV capsid variant comprising:

- (a) the amino acid sequence of any of the sequences provided in Tables 1, 2A, 2B, 13-19;
 - (b) an amino acid sequence comprising at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or 17 consecutive amino acids from any one of the sequences provided in Tables 1, 2A, 2B, 13-19;
 - (c) an amino a sequence comprising at least one, two, or three but no more than four different amino acids, relative to the amino acid sequence of any one of the sequences provided in Tables 1, 2A, 2B, 13-19; or
 - (d) an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (conservative substitutions), relative to the amino acid sequence of any one of the sequences provided in Tables 1, 2A, 2B, 13-19;
- optionally wherein the amino acid sequence of (a), (b), (c), and/or (d) is present immediately subsequent to position 448, 449, 450, 451, 452, 453, 454, or 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138, 981, or 982.

568. A polynucleotide encoding an AAV capsid variant, wherein the AAV capsid variant comprises:

- (i) the amino acid sequence of SPHSKA (SEQ ID NO: 941);

- (ii) an amino acid sequence comprising at least one, two, or three, but no more than four different amino acids, relative to the amino acid sequence of SPHKA (SEQ ID NO: 941);
 - (iii) an amino acid sequence comprising at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of SPHKA (SEQ ID NO: 941);
- or
- (iv) at least 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of SPHKA (SEQ ID NO: 941);
- optionally wherein the amino acid sequence of (i), (ii), (iii), and/or (iv) is present immediately subsequent to position 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

569. The polynucleotide of embodiment 567 or 568, which comprises:

- (i) the nucleotide sequence of SEQ ID NO: 942, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto;
- (ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequence of SEQ ID NO: 942;
- (iii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequence of SEQ ID NO: 942.

570. A polynucleotide encoding an AAV capsid variant, wherein the AAV capsid variant comprises:

- (i) the amino acid sequence of HDSPHK (SEQ ID NO: 2);
 - (ii) an amino acid sequence comprising at least one, two, or three, but no more than four different amino acids, relative to the amino acid sequence of HDSPHK (SEQ ID NO: 2);
 - (iii) an amino acid sequence comprising at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of HDSPHK (SEQ ID NO: 2);
- or
- (iv) at least 3, 4, or 5 consecutive amino acids from the amino acid sequence of HDSPHK (SEQ ID NO: 2);

optionally wherein the amino acid sequence of (i), (ii), (iii), and/or (iv) is present immediately subsequent to position 453, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

571. The polynucleotide of any one of embodiments 567 or 570, which comprises:

(i) the nucleotide sequence of SEQ ID NO: 3, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto;

(ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten different nucleotides, relative to the nucleotide sequence of SEQ ID NO: 3; or

(iii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequence of SEQ ID NO: 3.

572. The polynucleotide of any one of embodiments 567-571, wherein the AAV capsid variant comprises:

(i) the amino acid sequence of SEQ ID NO: 981 or 982, or an amino acid sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto;

(ii) an amino acid sequence having at least one, two or three, but no more than four different amino acids, relative to the amino acid sequence of SEQ ID NO: 981 or 982; or

(iii) an amino acid sequence having at least one, two or three modifications, e.g., substitutions (e.g., conservative substitutions), but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of SEQ ID NO: 981 or 982.

573. The polynucleotide of any one of embodiments 567-572, comprising the nucleotide sequence of SEQ ID NO: 983 or 984, or a nucleotide sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto.

574. The polynucleotide, peptide, or AAV capsid variant, of any one of embodiments 1-573, which is isolated, e.g., recombinant.

575. An AAV particle comprising the AAV capsid variant of any one of embodiments 1-519, 566, or 574.

576. The AAV particle of embodiment 575, which comprises a nucleotide sequence encoding a payload.

577. The AAV particle of embodiment 576, wherein the encoded payload comprises a therapeutic protein or functional variant thereof; an antibody or antibody fragment; an enzyme; a component of a gene editing system; an RNAi agent (e.g., a dsRNA, siRNA, shRNA, pre-miRNA, pri-miRNA, miRNA, stRNA, lncRNA, piRNA, or snoRNA); or a combination thereof.

578. The AAV particle of embodiment 577, wherein the therapeutic protein or functional variant thereof, e.g., a recombinant protein, is associated with (e.g., aberrantly expressed in) a neurological or neurodegenerative disorder, a muscular or neuromuscular disorder, or a neuro-oncological disorder.

579. The AAV particle of embodiment 577 or 578, the therapeutic protein or functional variant thereof is chosen from apolipoprotein E (APOE) (e.g., ApoE2, ApoE3 and/or ApoE4); human survival of motor neuron (SMN) 1 or SMN2; glucocerebrosidase (GBA1); aromatic L-amino acid decarboxylase (AADC); aspartoacylase (ASPA); tripeptidyl peptidase I (CLN2); beta-galactosidase (GLB1); N-sulphoglucosamine sulphohydrolase (SGSH); N-acetyl-alpha-glucosaminidase (NAGLU); iduronate 2-sulfatase (IDS); intracellular cholesterol transporter (NPC1); gigaxonin (GAN); or a combination thereof.

580. The AAV particle of embodiment 577, wherein the antibody or antibody binding fragment binds to:

(i) a CNS related target, e.g., an antigen associated with a neurological or neurodegenerative disorder, e.g., β -amyloid, APOE, tau, SOD1, TDP-43, huntingtin (HTT), and/or synuclein;

(ii) a muscular or neuromuscular related target, e.g., an antigen associated with a muscular or neuromuscular disorder; or

(iii) a neuro-oncology related target, e.g., an antigen associated with a neuro-oncological disorder, e.g., HER2, or EGFR (e.g., EGFRvIII).

581. The AAV particle of embodiment 577, wherein the enzyme comprises a meganuclease, a zinc finger nuclease, a TALEN, a recombinase, integrase, a base editor, a Cas9, or a fragment thereof.

582. The AAV particle of embodiment 577, wherein the component of a gene editing system comprises one or more components of a CRISPR-Cas system.

583. The AAV particle of embodiment 582, wherein the one or more components of the CRISPR-Cas system comprises a Cas9, e.g., a Cas9 ortholog or a Cpf1, and a single guide RNA (sgRNA), optionally wherein:

(i) the sgRNA is located upstream (5') of the cas9 enzyme; or

(ii) the sgRNA is located downstream (3') of the cas9 enzyme.

584. The AAV particle of embodiment 577, wherein the RNAi agent (e.g., a dsRNA, siRNA, shRNA, pre-miRNA, pri-miRNA, miRNA, stRNA, lncRNA, piRNA, or snoRNA), modulates, e.g., inhibits, expression of, a CNS related gene, mRNA, and/or protein.

585. The AAV particle of embodiment 584, wherein the CNS related gene is chosen from SOD1, MAPT, APOE, HTT, C9ORF72, TDP-43, APP, BACE, SNCA, ATXN1, ATXN3, ATXN7, SCN1A-SCN5A, SCN8A-SCN11A, or a combination thereof.

586. The AAV particle of any one of embodiments 575-585, which comprises a viral genome comprising a promoter operably linked to the nucleic acid sequence encoding the payload.

587. The AAV particle of embodiment 586, wherein the promoter is chosen from human elongation factor 1 α -subunit (EF1 α), cytomegalovirus (CMV) immediate-early enhancer and/or promoter, chicken β -actin (CBA) and its derivative CAG, β glucuronidase (GUSB), or ubiquitin C (UBC), neuron-specific enolase (NSE), platelet-derived growth factor (PDGF), platelet-derived growth factor B-chain (PDGF- β), intercellular adhesion molecule 2 (ICAM-2), synapsin (Syn), methyl-CpG binding protein 2 (MeCP2), Ca²⁺/calmodulin-dependent protein kinase II (CaMKII), metabotropic glutamate receptor 2 (mGluR2), neurofilament light (NFL) or heavy (NFH), β -globin minigene n β 2, preproenkephalin (PPE), enkephalin (Enk) and excitatory amino acid transporter 2 (EAAT2), glial fibrillary acidic protein (GFAP), myelin basic protein (MBP), a cardiovascular promoter (e.g., α MHC, cTnT, and CMV-MLC2k), a liver promoter (e.g., hAAT, TBG), a skeletal muscle promoter (e.g., desmin, MCK, C512) or a fragment, e.g., a truncation, or a functional variant thereof.

588. The AAV particle of embodiment 586 or 587, wherein the promoter is an EF-1 α promoter variant, e.g., a truncated EF-1 α promoter.

589. The AAV particle of any one of embodiments 586-588, wherein the promoter comprises the nucleotide sequence of any one of SEQ ID NOs: 987, 988, 990, 991, 995, 996, 998-1007 or any one of the sequences provided in Table 8, a nucleotide sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequence of SEQ ID NOs: 987, 988, 990, 991, 995, 996, 998-1007 or any one of the sequences provided in Table 8, or a nucleotide sequence with at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, or 99%) sequence identity to any one of SEQ ID NOs: 987, 988, 990, 991, 995, 996, 998-1007 or any one of the sequences provided in Table 8.

590. The AAV particle of any one of embodiments 586-589 wherein the viral genome further comprises a polyA signal sequence.
591. The AAV particle of any one of embodiments 586-590, wherein the viral genome further comprises an inverted terminal repeat (ITR) sequence.
592. The AAV particle of any one of embodiments 586-591, wherein the viral genome comprises an ITR sequence positioned 5' relative to the encoded payload.
593. The AAV particle of any one of embodiments 586-592, wherein the viral genome comprises an ITR sequence positioned 3' relative to the encoded payload.
594. The AAV particle of any one of embodiments 586-593, wherein the viral genome comprises an ITR sequence positioned 5' relative to the encoded payload and an ITR sequence positioned 3' relative to the encoded payload.
595. The AAV particle of any one of embodiments 586-594, wherein the viral genome further comprises an enhancer, a Kozak sequence, an intron region, and/or an exon region.
596. The AAV particle of any one of embodiments 586-594, wherein the viral genome further comprises a nucleotide sequence encoding a miR binding site, e.g., a miR binding site that modulates, e.g., reduces, expression of the antibody molecule encoded by the viral genome in a cell or tissue where the corresponding miRNA is expressed.
597. The AAV particle of embodiment 596, wherein the encoded miRNA binding site is complementary, e.g., fully complementary or partially complementary, to a miRNA expressed in a cell or tissue of the DRG, liver, heart, hematopoietic, or a combination thereof.
598. The AAV particle of embodiment 596 or 597, wherein the encoded miR binding site modulates, e.g., reduces, expression of the encoded antibody molecule in a cell or tissue of the DRG, liver, heart, hematopoietic lineage, or a combination thereof.
599. The AAV particle of any one of embodiments 586-598, wherein the viral genome comprises at least 1-5 copies of the encoded miR binding site, e.g., at least 1, 2, 3, 4, or 5 copies.

600. The AAV particle of any one of embodiments 586-599, wherein the viral genome comprises at least 3 copies of an encoded miR binding sites, optionally wherein all three copies comprise the same miR binding site, or at least one, two, three, or all of the copies comprise a different miR binding site.

601. The AAV particle of embodiment 600, wherein the 3 copies of the encoded miR binding sites are continuous (e.g., not separated by a spacer), or are separated by a spacer, optionally wherein the spacer comprises the nucleotide sequence of GATAGTTA, or a nucleotide sequence having at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequence of GATAGTTA.

602. The AAV particle of any one of embodiments 586-601, wherein the viral genome comprises at least 4 copies of an encoded miR binding site, optionally wherein all four copies comprise the same miR binding site, or at least one, two, three, or all of the copies comprise a different miR binding site.

603. The AAV particle of embodiment 602, wherein the 4 copies of the encoded miR binding sites are continuous (e.g., not separated by a spacer), or are separated by a spacer, optionally wherein the spacer comprises the nucleotide sequence of GATAGTTA, or a nucleotide sequence having at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequence of GATAGTTA.

604. The AAV particle of any one of embodiments 596-603, wherein the encoded miR binding site comprises a miR122 binding site, a miR183 binding site, a miR-1 binding site, a miR-142-3p, or a combination thereof, optionally wherein:

(i) the encoded miR122 binding site comprises the nucleotide sequence of SEQ ID NO: 4673, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or a nucleotide sequence having at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to SEQ ID NO: 4673;

(ii) the encoded miR183 binding site comprises the nucleotide sequence of SEQ ID NO: 4676, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or a nucleotide sequence having at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to SEQ ID NO: 4676;

(iii) the encoded miR-1 binding site comprises the nucleotide sequence of SEQ ID NO: 4679, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or a nucleotide sequence having at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to SEQ ID NO: 4679; and/or

(iv) the encoded miR-142-3p binding site comprises the nucleotide sequence of SEQ ID NO: 4675, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or a nucleotide sequence having at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to SEQ ID NO: 4675.

605. The AAV particle of any one of embodiments 586-604, wherein the viral genome comprises an encoded miR122 binding site.

606. The AAV particle of any one of embodiments 586-605, wherein the viral genome comprises at least 1-5 copies, e.g., 1, 2, or 3 copies of a miR122 binding site, optionally wherein each copy is continuous (e.g., not separated by a spacer), or each copy is separated by a spacer, optionally wherein the spacer comprises the nucleotide sequence of GATAGTTA, or a nucleotide sequence having at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequence of GATAGTTA.

607. The AAV particle of embodiment 605 or 606, wherein the encoded miR122 binding site comprises the nucleotide sequence of SEQ ID NO: 4673, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or a nucleotide sequence having at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to SEQ ID NO: 4673.

608. The AAV particle of any one of embodiments 586-607, wherein the viral genome comprises:
(A) (i) a first encoded miR122 binding site comprising the nucleotide sequence of SEQ ID NO: 4673, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or a nucleotide sequence having at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative

substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to SEQ ID NO: 4673;

(ii) a first spacer comprising the nucleotide sequence of GATAGTTA, or a nucleotide sequence having at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequence of GATAGTTA; and

(iii) a second encoded miR122 binding site comprising the nucleotide sequence of SEQ ID NO: 4673, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or a nucleotide sequence having at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to SEQ ID NO: 4673; or

(B) (i) a first encoded miR122 binding site comprising the nucleotide sequence of SEQ ID NO: 4673, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or a nucleotide sequence having at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to SEQ ID NO: 4673;

(ii) a first spacer comprising the nucleotide sequence of GATAGTTA, or a nucleotide sequence having at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequence of GATAGTTA;

(iii) a second encoded miR122 binding site comprising the nucleotide sequence of SEQ ID NO: 4673, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or a nucleotide sequence having at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to SEQ ID NO: 4673;

(iv) a second spacer comprising the nucleotide sequence of GATAGTTA, or a nucleotide sequence having at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequence of GATAGTTA; and

(v) a third encoded miR122 binding site comprising the nucleotide sequence of SEQ ID NO: 4673, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or a nucleotide sequence having at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative

substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to SEQ ID NO: 4673.

609. The AAV particle of any one of embodiments 586-608, wherein the viral genome comprises an encoded miR183 binding site.

610. The AAV particle of any one of embodiments 586-609, wherein the viral genome comprises at least 1-5 copies, e.g., 1, 2, or 3 copies of a miR183 binding site, optionally wherein each copy is continuous (e.g., not separated by a spacer), or each copy is separated by a spacer, optionally wherein the spacer comprises the nucleotide sequence of GATAGTTA, or a nucleotide sequence having at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequence of GATAGTTA.

611. The AAV particle of embodiment 609 or 610, wherein the encoded miR183 binding site comprises the nucleotide sequence of SEQ ID NO: 4673, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or a nucleotide sequence having at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to SEQ ID NO: 4673.

612. The AAV particle of any one of embodiments 586-611, wherein the viral genome comprises:
(A) (i) a first encoded miR183 binding site comprising the nucleotide sequence of SEQ ID NO: 4676, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or a nucleotide sequence having at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to SEQ ID NO: 4676;

(ii) a first spacer comprising the nucleotide sequence of GATAGTTA, or a nucleotide sequence having at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequence of GATAGTTA; and

(iii) a second encoded miR183 binding site comprising the nucleotide sequence of SEQ ID NO: 4676, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or a nucleotide sequence having at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative

substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to SEQ ID NO: 4676; or

(B) (i) a first encoded miR183 binding site comprising the nucleotide sequence of SEQ ID NO: 4676, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or a nucleotide sequence having at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to SEQ ID NO: 4676;

(ii) a first spacer comprising the nucleotide sequence of GATAGTTA, or a nucleotide sequence having at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to GATAGTTA;

(iii) a second encoded miR183 binding site comprising the nucleotide sequence of SEQ ID NO: 4676, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or a nucleotide sequence having at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to SEQ ID NO: 4676;

(iv) a second spacer comprising the nucleotide sequence of GATAGTTA, or a nucleotide sequence having at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequence of GATAGTTA; and

(v) a third encoded miR183 binding site comprising the nucleotide sequence of SEQ ID NO: 4676, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or a nucleotide sequence having at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to SEQ ID NO: 4676.

613. The AAV particle of any one of embodiments 586-612, wherein the viral genome comprises an encoded miR122 binding site and a miR-1 binding site.

614. The AAV particle of any one of embodiments 586-613, wherein the viral genome is single stranded.

615. The AAV particle of any one of embodiments 586-613, wherein the viral genome self-complementary.

616. The AAV particle of any one of embodiments 586-615, wherein the viral genome further comprises a nucleotide sequence encoding a Rep protein, e.g., a non-structural protein, wherein the Rep protein comprises a Rep78 protein, a Rep68, Rep52 protein, and/or a Rep40 protein (e.g., a Rep78 and a Rep52 protein).

617. The AAV particle of any one of embodiments 586-615, wherein the AAV particle further comprises a nucleotide sequence encoding a Rep protein, e.g., a non-structural protein, wherein the Rep protein comprises a Rep78 protein, a Rep68, Rep52 protein, and/or a Rep40 protein (e.g., a Rep78 and a Rep52 protein).

618. The AAV particle of embodiment 616 or 617, wherein the Rep78 protein, the Rep68 protein, the Rep52 protein, and/or the Rep40 protein are encoded by at least one Rep gene.

619. The AAV particle of any one of embodiments 586-618, wherein the viral genome further comprises a nucleic acid sequence encoding the AAV capsid variant of any one of embodiments 1-519, 566, or 574.

620. The AAV particle of any one of embodiments 575-519, which is isolated, e.g., recombinant.

621. A vector comprising a polynucleotide encoding the AAV capsid variant of any one of embodiments 1-519, 566, or 574, the polynucleotide of any one of embodiments 520-523 or 567-574, or a polynucleotide encoding the peptide of any one of embodiments 524-543 or 574.

622. A cell, e.g., a host cell, comprising the AAV capsid variant of any one of embodiments 1-519, 566, or 574, the polynucleotide of any one of embodiments 520-523 or 567-574, the peptide of any one of embodiments 524-565 or 574, the AAV particle of any one of embodiments 575-620, or the vector of embodiment 621.

623. The cell of embodiment 622, wherein the cell is a mammalian cell or an insect cell.

624. The cell of embodiment 622 or 623, wherein the cell is a cell of a brain region or a spinal cord region, optionally a cell of the brain stem, hippocampus, or thalamus.

625. The cell of any one of embodiments 622-624, wherein the cell is a neuron, a sensory neuron, a motor neuron, an astrocyte, a glial cell, oligodendrocyte, or a muscle cell (e.g., a cell of the heart, diaphragm, or quadriceps).

626. The cell of embodiment 622 or 623, wherein the cell is a liver cell.

627. A method of making an AAV particle, comprising

(i) providing a host cell comprising a viral genome; and

(ii) incubating the host cell under conditions suitable to enclose the viral genome in the AAV capsid variant of any one of embodiments 1-519, 566, or 574 or an AAV capsid variant encoded by the polynucleotide of any one of embodiments 520-523 or 567-574;

thereby making the AAV particle.

628. The method of embodiment 627, further comprising, prior to step (i), introducing a first nucleic acid molecule comprising the viral genome into the host cell.

629. The method of embodiment 628, wherein the host cell comprises a second nucleic acid encoding the capsid variant.

630. The method of embodiment 629, wherein the second nucleic acid molecule is introduced into the host cell prior to, concurrently with, or after the first nucleic acid molecule.

631. A pharmaceutical composition comprising the AAV particle of any one of embodiments 575-620, an AAV particle comprising the capsid variant of any one of embodiments 1-519, 566, or 574, an AAV particle comprising the peptide of any one of embodiments 524-543 or 574, and a pharmaceutically acceptable excipient.

632. A method of delivering a payload to a cell or tissue (e.g., a CNS cell, CNS tissue, a liver cell, or a liver tissue), comprising administering an effective amount of the pharmaceutical composition of embodiment 631, the AAV particle of any one of embodiments 575-620, an AAV particle comprising the capsid variant of any one of embodiments 1-519, 566, or 574, or an AAV particle comprising the peptide of any one of embodiments 524-543 or 574.

633. The method of embodiment 632, wherein the cell is a cell of a brain region or a spinal cord region, optionally a cell of the frontal cortex, sensory cortex, motor cortex, caudate, cerebellar cortex, cerebral cortex, brain stem, hippocampus, or thalamus.

634. The method of embodiment 632 or 633, wherein the cell is a neuron, a sensory neuron, a motor neuron, an astrocyte, a glial cell, or an oligodendrocyte.

635. The method of embodiment 632, wherein the cell is a liver cell.

636. The method of any one of embodiments 632-635, wherein the cell or tissue is within a subject.

637. The method of embodiment 636, wherein the subject has, has been diagnosed with having, or is at risk of having a genetic disorder, e.g., a monogenic disorder or a polygenic disorder.

638. The method of embodiment 636 or 637, wherein the subject has, has been diagnosed with having, or is at risk of having a neurological, e.g., a neurodegenerative disorder.

639. The method of embodiment 636 or 637, wherein the subject has, has been diagnosed with having, or is at risk of having a neuro-oncological disorder.

640. The method of embodiment 636 or 637, wherein the subject has, has been diagnosed with having, or is at risk of having a muscular disorder or a neuromuscular disorder.

641. A method of treating a subject having or diagnosed with having a genetic disorder, e.g., a monogenic disorder or a polygenic disorder, comprising administering to the subject an effective amount of the pharmaceutical composition of embodiment 631, the AAV particle of any one of embodiments 575-620, an AAV particle comprising the capsid variant of any one of embodiments 1-519, 566, or 574, or an AAV particle comprising the peptide of any one of embodiments 524-543 or 574.

642. A method of treating a subject having or diagnosed with having a neurological disorder, e.g., a neurodegenerative disorder, comprising administering to the subject an effective amount of the pharmaceutical composition of embodiment 631, the AAV particle of any one of embodiments 575-620, an AAV particle comprising the capsid variant of any one of embodiments 1-519, 566, or 574, or an AAV particle comprising the peptide of any one of embodiments 524-543 or 574.

643. A method of treating a subject having or diagnosed with having a muscular disorder or a neuromuscular disorder, comprising administering to the subject an effective amount of the pharmaceutical composition of embodiment 631, the AAV particle of any one of embodiments 575-620, an AAV particle comprising the capsid variant of any one of embodiments 1-519, 566, or 574, or an AAV particle comprising the peptide of any one of embodiments 524-543 or 574.

644. A method of treating a subject having or diagnosed with having a neuro-oncological disorder, comprising administering to the subject an effective amount of the pharmaceutical composition of embodiment 631, the AAV particle of any one of embodiments 575-620, an AAV particle comprising

the capsid variant of any one of embodiments 1-519, 566, or 574, or an AAV particle comprising the peptide of any one of embodiments 524-543 or 574.

645. The method of any one of embodiments 637-645, wherein the genetic disorder, neurological disorder, neurodegenerative disorder, muscular disorder, neuromuscular disorder, or neuro-oncological disorder is Huntington's Disease, Amyotrophic Lateral Sclerosis (ALS), Gaucher Disease, Dementia with Lewy Bodies, Parkinson's disease, Spinal Muscular Atrophy, Alzheimer's Disease, a leukodystrophy (e.g., Alexander disease, autosomal dominant leukodystrophy with autonomic diseases (ADLD), Canavan disease, cerebrotendinous xanthomatosis (CTX), metachromatic leukodystrophy (MLD), Pelizaeus-Merzbacher disease, or Refsum disease), or a cancer (e.g., a HER2/neu positive cancer or a glioblastoma).

646. The method of any one of embodiments 641-645, where treating comprises prevention of progression of the disease or disorder in the subject.

647. The method of embodiment 636-646, wherein the subject is a human.

648. The method of any one of embodiments 636-647, wherein the AAV particle is administered to the subject intravenously, via intra-cisterna magna injection (ICM), intracerebrally, intrathecally, intracerebroventricularly, via intraparenchymal administration, intraarterially, or intramuscularly.

649. The method of any one of embodiments 636-648, wherein the AAV particle is administered to the subject via focused ultrasound (FUS), e.g., coupled with the intravenous administration of microbubbles (FUS-MB), or MRI-guided FUS coupled with intravenous administration.

650. The method of any one of embodiments 636-649, wherein the AAV particle is administered to the subject intravenously.

651. The method of any one of embodiments 636-650, wherein the AAV particle is administered to the subject via intra-cisterna magna injection (ICM).

652. The method of any one of embodiments 636-651, wherein the AAV particle is administered to the subject intraarterially.

653. The method of any one of embodiments 648-652, wherein administration of the AAV particle results in a decreased presence, level, and/or activity of a gene, mRNA, protein, or combination thereof.

654. The method of any one of embodiments 648-652, wherein administration of the AAV particle results in an increased presence, level, and/or activity of a gene, mRNA, protein, or a combination thereof.

655. The pharmaceutical composition of embodiment 631, the AAV particle of any one of embodiments 575-620, an AAV particle comprising the capsid variant of any one of embodiments 1-519, 566, or 574, or an AAV particle comprising the peptide of any one of embodiments 524-543 or 574, for use in a method of delivering a payload to a cell or tissue.

656. The pharmaceutical composition of embodiment 631, the AAV particle of any one of embodiments 575-620, an AAV particle comprising the capsid variant of any one of embodiments 1-519, 566, or 574, or an AAV particle comprising the peptide of any one of embodiments 524-543 or 574, for use in a method of treating a genetic disorder, a neurological disorder, a neurodegenerative disorder, a muscular disorder, a neuromuscular disorder, or a neuro-oncological disorder.

657. The pharmaceutical composition of embodiment 631, the AAV particle of any one of embodiments 575-620, an AAV particle comprising the capsid variant of any one of embodiments 1-519, 566, or 574, or an AAV particle comprising the peptide of any one of embodiments 524-543 or 574, for use in the manufacture of a medicament.

658. Use of the pharmaceutical composition of embodiment 631, the AAV particle of any one of embodiments 575-620, an AAV particle comprising the capsid variant of any one of embodiments 1-519, 566, or 574, or an AAV particle comprising the peptide of any one of embodiments 524-543 or 574, in the manufacture of a medicament.

659. Use of the pharmaceutical composition of embodiment 631, the AAV particle of any one of embodiments 575-620, an AAV particle comprising the capsid variant of any one of embodiments 1-519, 566, or 574, or an AAV particle comprising the peptide of any one of embodiments 524-543 or 574, in the manufacture of a medicament for treating a genetic disorder, a neurological disorder, a neurodegenerative disorder, a muscular disorder, a neuromuscular disorder, or a neuro-oncological disorder.

[0048] The details of one or more embodiments of the disclosure are set forth in the accompanying description below. Other features, objects and advantages of the disclosure will be apparent from the description. In the description, the singular forms also include the plural unless the context clearly dictates otherwise. Certain terms are defined in the Definition section and throughout.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0049] Described herein, *inter alia*, are compositions comprising an AAV capsid variant, e.g., an AAV capsid variant described herein, and methods of making and using the same. Generally, the AAV capsid variant has enhanced tropism for a cell or tissue, e.g., for the delivery of a payload to said cell or tissue, for example a CNS tissue or a CNS cell or a liver cell or liver tissue.

[0050] As demonstrated in the Examples herein below, certain AAV capsid variants described herein show multiple advantages over wild-type AAV9, including (i) increased penetrance through the blood brain barrier following intravenous administration, (ii) wider distribution throughout the multiple brain regions, e.g., frontal cortex, sensory cortex, motor cortex, putamen, thalamus, cerebellar cortex, dentate nucleus, caudate, and/or hippocampus, and/or (iii) elevated payload expression in multiple brain regions. Without wishing to be bound by theory, it is believed that these advantages may be due, in part, to the dissemination of the AAV capsid variants through the brain vasculature. In some embodiments, the AAV capsids described herein enhance the delivery of a payload to multiple regions of the brain including for example, the frontal cortex, sensory cortex, motor cortex, putamen, thalamus, cerebellar cortex, dentate nucleus, caudate, and/or hippocampus.

[0051] Several approaches have been used previously to produce AAV capsids with enhanced tropism for a cell or tissue, e.g., a CNS cell or tissue. One approach used co-infection of cultured cells (Grimm et al. In vitro and in vivo gene therapy vector evolution via multispecies interbreeding and retargeting of adeno-associated viruses. J. Virol. 2008 June 82(12):5887–5911, the contents of which are herein incorporated by reference in its entirety) or *in situ* animal tissue (Lisowski et al. Selection and evaluation of clinically relevant AAV variants in a xenograft liver model. Nature 2014 506:382–386, the contents of which are herein incorporated by reference in its entirety) with adenovirus, in order to trigger exponential replication of infectious AAV DNA. Another approach involved the use of cell-specific CRE transgenic mice (Deverman et al. Cre-dependent selection yields AAV variants for widespread gene transfer to the adult brain. Nat Biotechnol. 2016 Feb. 34(2)204–209; the contents of which are herein incorporated by reference in its entirety) allowing viral DNA recombination specifically in astrocytes, followed by recovery of CRE-recombined capsid variants. Other approaches apply high throughput DNA synthesis, multiplexing, sequencing technologies, and machine learning to evaluate sequencing reads of viral DNA in different tissues to engineer variant capsids. These approaches are different from the approach disclosed herein.

[0052] There are some limitations to the art-known capsid generation methods. For example, the transgenic CRE system used by Deverman et al. (2016) has limited tractability in other animal species and AAV variants selected by directed evolution in mouse tissue do not show similar properties in large animals. Previously described transduction-specific approaches are not amenable to large animal studies because: 1) many tissues of interest (e.g., CNS) are not readily accessible to adenovirus co-infection, 2) the specific adenovirus tropism itself would bias the library distribution, and 3) large

animals are typically not amenable to transgenesis or genetic engineering to express CRE recombinase in defined cell types.

[0053] To address these limitations, a broadly-applicable functional AAV capsid library screening platform for cell type-specific biopanning in non-transgenic animals has been developed and is described in the appended Examples. In the TRACER (Tropism Redirection of AAV by Cell type-specific Expression of RNA) platform system, the capsid gene is placed under the control of a cell type-specific promoter to drive capsid mRNA expression in the absence of helper virus co-infection. Without wishing to be bound by theory, it is believed that this RNA-driven screen increases the selective pressure in favor of capsid variants which transduce a specific cell type. The TRACER platform allows for generation of AAV capsid libraries whereby specific recovery and subcloning of capsid mRNA expressed in transduced cells is achieved with no need for transgenic animals or helper virus co-infection. Without wishing to be bound by theory, it is believed that since mRNA transcription is a hallmark of full transduction, the methods disclosed herein allow identification of fully infectious AAV capsid mutants, and in addition to its higher stringency, this method allows identification of capsids with high tropism for particular cell types using libraries designed to express CAP mRNA under the control of any cell-specific promoter such as, but not limited to, synapsin-1 promoter (neurons), GFAP promoter (astrocytes), TBG promoter (liver), CAMK promoter (skeletal muscle), MYH6 promoter (cardiomyocytes). Described herein are novel AAV capsid variants generated using the TRACER method which demonstrate enhance tropism in for example a CNS cell, a CNS tissue, a liver cell, a liver tissue, a muscle cell, or a muscle tissue.

[0054] In some embodiments, an AAV capsid variant disclosed herein comprises a modification in loop IV of AAV9, e.g., at positions between 449-460, e.g., at position 454 and/or 455, numbered relative to SEQ ID NO: 138, 981, or 982. In some embodiments, loop (e.g., loop IV) is used interchangeably herein with the term variable region (e.g., variable region IV), or VR (e.g., VR-IV). In some embodiments loop IV comprises positions 449-475 (e.g., amino acids KTINGSGQNQQTLKFSVAGPSNMAVQG (SEQ ID NO: 6404)), numbered according to SEQ ID NO: 138. In some embodiments loop IV comprises positions 449-460 (e.g., amino acids KTINGSGQNQQT (SEQ ID NO: 6405)), numbered according to SEQ ID NO: 138. In some embodiments, loop IV or variable region IV (VR-IV) is as described in DiMattia et al. “Structural Insights into the Unique Properties of the Adeno-Associated Virus Serotype 9,” *Journal of Virology*, 12(86):6947-6958 (the contents of which are hereby incorporated by reference in their entirety), e.g., comprising positions 452-460 (e.g., NGSQGNQQT (SEQ ID NO: 4487)), numbered according to SEQ ID NO: 138.

[0055] The AAV particles and payloads of the disclosure may be delivered to one or more target cells, tissues, organs, or organisms. In some embodiments, the AAV particles of the disclosure demonstrate enhanced tropism for a target cell type, tissue or organ. As a non-limiting example, the

AAV particle may have enhanced tropism for cells and tissues of the central or peripheral nervous systems (CNS and PNS, respectively). In some embodiments, an AAV particle of the disclosure may, in addition, or alternatively, have decreased tropism for a cell-type, tissue or organ.

[0056] In some embodiments, an AAV comprises a small non-enveloped icosahedral capsid virus of the Parvoviridae family and is characterized by a single stranded DNA viral genome. Parvoviridae family viruses consist of two subfamilies: Parvovirinae, which infect vertebrates, and Densovirinae, which infect invertebrates. The Parvoviridae family comprises the Dependovirus genus which includes AAV, capable of replication in vertebrate hosts including, but not limited to, human, primate, bovine, canine, equine, and ovine species.

[0057] 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.

[0058] In some embodiments, AAV are used as a biological tool due to a relatively simple structure, their ability to infect a wide range of cells (including quiescent and dividing cells) without integration into the host genome and without replicating, and their relatively benign immunogenic profile. The genome of the virus may be manipulated to contain a minimum of components for the assembly of a functional recombinant virus, or viral particle, which is loaded with or engineered to target a particular tissue and express or deliver a desired payload.

[0059] In some embodiments, the AAV, is a naturally occurring (e.g., wild-type) AAV or a recombinant AAV. In some embodiments, the wild-type AAV vector genome is a linear, single-stranded DNA (ssDNA) molecule approximately 5,000 nucleotides (nt) in length. In some embodiments, inverted terminal repeats (ITRs) cap the viral genome at both the 5' and the 3' end, providing origins of replication for the viral genome. In some embodiments, an AAV viral genome typically comprises two ITR sequences. These ITRs have a characteristic T-shaped hairpin structure defined by a self-complementary region (145nt in wild-type AAV) at 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.

[0060] In some embodiments, the wild-type AAV viral genome further comprises nucleotide sequences for two open reading frames, one for the four non-structural Rep proteins (Rep78, Rep68, Rep52, Rep40, encoded by Rep genes) and one for the three capsid, or structural, proteins (VP1, VP2, VP3, encoded by capsid genes or Cap genes). The Rep proteins are used for replication and packaging, while the capsid proteins are assembled to create the protein shell of the AAV, or AAV capsid polypeptide, e.g., an AAV capsid variant. Alternative splicing and alternate initiation codons and promoters result in the generation of four different Rep proteins from a single open reading frame and the generation of three capsid proteins from a single open reading frame. Though it varies by

AAV serotype, as a non-limiting example, for AAV9/hu.14 (SEQ ID NO: 123 of US 7,906,111, the contents of which are herein incorporated by reference in their entirety) VP1 refers to amino acids 1-736, VP2 refers to amino acids 138-736, and VP3 refers to amino acids 203-736. In some embodiments, for any one of the amino acid sequences of SEQ ID NO: 981 or 982, VP1 comprises amino acids 1-742, VP2 comprises amino acids 138-742, and VP3 comprises amino acids 203-742. In other words, VP1 is the full-length capsid sequence, while VP2 and VP3 are shorter components of the whole. As a result, changes in the sequence in the VP3 region, are also changes to VP1 and VP2, however, the percent difference as compared to the parent sequence will be greatest for VP3 since it is the shortest sequence of the three. Though described here in relation to the amino acid sequence, the nucleic acid sequence encoding these proteins can be similarly described. Together, the three capsid proteins assemble to create the AAV capsid protein. While not wishing to be bound by theory, the AAV capsid protein typically comprises a molar ratio of 1:1:10 of VP1:VP2:VP3.

[0061] AAV vectors of the present disclosure may be produced recombinantly and may be based on adeno-associated virus (AAV) reference sequences. In addition to single stranded AAV viral genomes (e.g., ssAAVs), the present disclosure also provides for self-complementary AAV (scAAVs) viral genomes. scAAV vector genomes contain DNA strands which anneal together to form double stranded DNA. By skipping second strand synthesis, scAAVs allow for rapid expression in the transduced cell. In some embodiments, the AAV particle of the present disclosure is an scAAV. In some embodiments, the AAV particle of the present disclosure is an ssAAV.

[0062] 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; WO2005005610; and WO2005072364, the content of each of which is incorporated herein by reference in its entirety).

[0063] As described herein, the AAV particles of the disclosure comprising an AAV capsid variant, and a viral genome, have enhanced tropism for a cell-type or a tissue, e.g., a CNS cell-type, region, or tissue.

Peptides

[0064] Disclosed herein are peptides, and associated AAV particles comprising an AAV capsid variant and a peptide for enhanced or improved transduction of a target tissue (e.g., cells of the CNS or PNS). In some, embodiments, the peptide is an isolated, e.g., recombinant, peptide. In some embodiments, the nucleic acid encoding the peptide, is an isolated, e.g., recombinant nucleic acid.

[0065] In some embodiments, the peptide may increase distribution of an AAV particle to a cell, region, or tissue of the CNS. The cell of the CNS may be, but is not limited to, neurons (e.g., excitatory, inhibitory, motor, sensory, autonomic, sympathetic, parasympathetic, Purkinje, Betz, etc.), glial cells (e.g., microglia, astrocytes, oligodendrocytes) and/or supporting cells of the brain such as immune cells (e.g., T cells). The tissue of the CNS may be, but is not limited to, the cortex (e.g.,

frontal, parietal, occipital, and/or temporal), thalamus, hypothalamus, striatum, putamen, caudate nucleus, hippocampus, entorhinal cortex, basal ganglia, or deep cerebellar nuclei.

[0066] In some embodiments, the peptide may increase distribution of an AAV particle to a cell, region, or tissue of the PNS. The cell or tissue of the PNS may be, but is not limited to, a dorsal root ganglion (DRG).

[0067] In some embodiments, the peptide may increase distribution of an AAV particle to the CNS (e.g., the cortex) after intravenous administration. In some embodiments, the peptide may increase distribution of an AAV particle to the CNS (e.g., the cortex) following focused ultrasound (FUS), e.g., coupled with the intravenous administration of microbubbles (FUS-MB), or MRI-guided FUS coupled with intravenous administration.

[0068] In some embodiments, the peptide may increase distribution of an AAV particle to the PNS (e.g., DRG) after intravenous administration. In some embodiments, the peptide may increase distribution of an AAV particle to the PNS (e.g., DRG) following focused ultrasound (FUS), e.g., coupled with the intravenous administration of microbubbles (FUS-MB), or MRI-guided FUS coupled with intravenous administration.

[0069] In some embodiments, the peptide may increase distribution of an AAV particle to a cell, region, or tissue of a muscle. In some embodiments, the muscle is a heart muscle, e.g., a heart atrium or a heart ventricle. In some embodiments, the peptide may direct an AAV particle to a muscle cell, region, or tissue after intravenous administration.

[0070] In some embodiments, the peptide may increase distribution of an AAV particle to a cell, region, or tissue of the liver.

[0071] A peptide may vary in length. In some embodiments, the peptide is about 3 to about 20 amino acids in length. As non-limiting examples, the peptide may be 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or 3-5, 3-8, 3-10, 3-12, 3-15, 3-18, 3-20, 5-10, 5-15, 5-20, 10-12, 10-15, 10-20, 12-20, or 15-20 amino acids in length. In some embodiments, a peptide comprises about 6 to 12 amino acids in length, e.g., about 9 amino acids in length. In some embodiments, a peptide comprises about 5 to 10 amino acids in length, e.g., about 7 amino acids in length. In some embodiments, a peptide comprises about 7 to 11 amino acids in length, e.g., about 8 amino acids in length. In some embodiments, a peptide comprises about 4 to 9 amino acids in length, e.g., about 6 amino acids in length.

[0072] In some embodiments a peptide may comprise a sequence as set forth in Table 1 (e.g., comprising the amino acid sequence of any one of SEQ ID NOs: 200-940, 1800-2241, 2242-2886, or 2887-3076). In some embodiments a peptide may comprise a sequence as set forth in Table 2A or 2B. In some embodiments, the peptide may comprise a sequence set forth in Table 13 or 14. In some embodiments, the peptide may comprise a sequence as set forth in Table 15. In some embodiments, the peptide may comprise a sequence as set forth in Table 16. In some embodiments, the peptide may

comprise a sequence as set forth in Table 17. In some embodiments, the peptide may comprise a sequence as set forth in Table 18. In some embodiments, the peptide may comprise a sequence as set forth in Table 19. In some embodiments, the peptide is isolated, e.g., recombinant.

Table 1. Exemplary Peptide Sequences

Peptide Sequence	SEQ ID NO:	Peptide Sequence	SEQ ID NO:	Peptide Sequence	SEQ ID NO:	Peptide Sequence	SEQ ID NO:
GSGSPHKAQN QQT	200	GSLHHDNHGQN QQT	385	GSVFGVPSG QNQQT	570	GSIAMTSHG QNQQT	755
GHDSPHKSGQN QQT	201	GIMARDSSGQN QQT	386	GSGLPDRNL QNQQT	571	GSPGVSPSG QNQQT	756
GSGSPHARMQN QQT	202	GVVHITNSGQN QQT	387	GSGTHNSAIQ QNQQT	572	GSGQNQQTG SSSRV	757
GSGSPHVKSQN QQT	203	GSGQNQHSAFP NQT	388	GSGMIASMQ QNQQT	573	GSGQHLPLL GNQQT	758
GQDSPHKSGQN QQT	204	GSGQTSGLKQN QQT	389	GGITWTD SG QNQQT	574	GSDHSHRGG QNQQT	759
GSGSPHASRQN QQT	205	GSGQNQQTSLS NTA	390	GSGQNQQAS GRQQT	575	GSGIVTKLG QNQQT	760
GSGSPHASRQN KQT	206	GSGQNQAVHNK SQT	391	GSGQNQQPH LKSLT	576	GSGQDVTKT GNQQT	761
GSGSPHVKIQNQ QT	207	GVHTHLPSGQN QQT	392	GPPQHMTSG QNQQT	577	GSGQNQQSH GRIGT	762
GSGSPHSAKN QQT	208	GHLTMHNSGQN HQT	393	GSGQNQQAS LPSRT	578	GSGQNQQIN HRSPT	763
GSGSPHKKNQN QQT	209	GSGSSSRPYQNQ QT	394	GSGQIVSTQT NQQT	579	GSGDDSRVG QNQQT	764
GSGSPHVRMQN QQT	210	GILLATPSGQNQ QT	395	GSGKGHSAG QNQQT	580	GSGQSTLKRI NQQT	765
GSGSPHASRQK QQT	211	GSGQNAGSFPN QQT	396	GSGQNTRLQ LGQQT	581	GSGSQHKA QNQQT	766
GHSSPHRSGQN QQT	212	GSRDGHTVGQN QQT	397	GSVGSRPVG QNQQT	582	GSGQNQQHA SSNNT	767
GMRTYHLSGQN QQT	213	GSLLISTSGQNQ QT	398	GSSHTLALG QNQQT	583	GSRTYQVSG QNQQT	768
GSGSPHTRGQN QQT	214	GSGAMP SHGQN QQT	399	GMYEYSQSG QNQQT	584	GSGQNQGLL SSPQT	769
GSGIIPVSSQNQ QT	215	GALVSPISGQNQ QT	400	GNGQNQQHS ILHGT	585	GSGGGLQHN QNQQT	770
GSEYGHKSGQN QQT	216	GSLSSHGVGQN QQT	401	GSGYNQPHL QNQQT	586	GSGQNQQTT AATRM	771
GRGQNVSSVHR QQT	217	GSGQNQQASLA MRT	402	GPLVNASSG QNQQT	587	GSGQNQRAS ILVQT	772
GSSHRFYGGQN QQT	218	GPGLGSHSGQN QQT	403	GSGQNQQVL TTART	588	GSGQNLGLL GAQQT	773
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GSVLHSHAAQN QQT	220	GSGTLTSATQN QQT	405	GAGLIMHSG QNQQT	590	GNSQVKVSG QNQQT	775
GSGDLVVSTQN QQT	221	GSGQVVAHVGN QQT	406	GMGRHSASG QNQQT	591	GSSGSHQYG QNQQT	776
GSYGMAASGQN QQT	222	GSGLRMTTQN QQT	407	GSHSQSGHG QNQQT	592	GSGQNQQQR DGTLT	777
GLNHFGASGQN QQT	223	GSGQVGRLLQN QQT	408	GSSTTIVSGQ NHQT	593	GRGQHVSVN NQQT	778

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GLAGHTVSGQN QQT	225	GSGDRYQTLQN QQT	410	GSGQNQQHA NLNQT	595	GSGQNQQHS LSSQT	780
GILGASSGQNQ QT	226	GSGQNQQLKSS AQT	411	GSGSTHKA QNQQT	596	GSLMDVHRG QNQQT	781
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GSLVSVQTGQN QQT	228	GSGERLHLTON QQT	413	GSGQVHNPT QNQQT	598	GLGSKNPSG QNQQT	783
GQSSPHRSGQN QQT	229	GSGHNQQVRTA PNT	414	GSGQNQQIP HVHQT	599	GSGQLVLTL QNQQT	784
GREYGHKSGQN QQT	230	GGLSHVMSGQN QQT	415	GSLHAGLSG QNQQT	600	GSGQNQQTS QPLPG	785
GHTLTLSSGQN QQT	231	GSGQSHRDVLN QQT	416	GPAQHGTSG QNQQT	601	GSGQNQQNL GKLNT	786
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GERHTVLSGQN QQT	237	GSGQNQQTSQT TNC	422	GSGQMOPHV QNQQT	607	GSGQNPIRG AMQQT	792
GSGMPQSHIQN QQT	238	GMTSHSVSGQN QQT	423	GSGQNQQVA GLNNT	608	GSGYVITGS QNQQT	793
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GSDFLGTHGQN QQT	242	GSGQNQQTALG VKC	427	GSSRVPVSG QNQQT	612	GNVTTQKSG QNQQT	797
GQIVQNPSGQN QQT	243	GAMVSHSSGQN QQT	428	GSGQNQQTN LGHTT	613	GSGNPVSHL QNQQT	798
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GGGDLGRSSQN QQT	251	GSGQYANHGIN QQT	436	GSGQNQQGT GVSH	621	GSGQNQQYA GKILT	806
GGGTKMDSGQN QQT	252	GSRSTGPSGQN QQT	437	GSRTVPVYG QNQQT	622	GSGNPHVRN QNQQT	807

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GNIAGSVSGQN QQT	261	GSSHTQALGQN QQT	446	GSSHTLALG QNKQT	631	GSGQNQQTV QSNLV	816
GSGSHRDVSQN QQT	262	GSGVHGVSSQN QQT	447	GSGQNQHSL PAHRT	632	GSGQNQQLG SRQCT	817
GGLGSMSSGQN QQT	263	GSSGRDMGGQN QQT	448	GSGQNQGTV YPNQT	633	GSGQNQYLR LELQT	818
GSGHLPQSAQN QQT	264	GERAFPTSGQN QQT	449	GSGQNQQPS LRQST	634	GSGQNQQTS PRLQT	819
GGVLVGSGGQN QQT	265	GGRIVLSGQNN QT	450	GSGQNARLK DNQQT	635	GSGQNQQTT SSNMT	820
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GSGQNQQTSPH NHT	268	GSGPQSHTGQN QQT	453	GSGASESHR QNQQT	638	GSGQSHLHT GNQQT	823
GSGTLYPQSQN QQT	269	GSGQNQQLSRD AST	454	GVGVTSSGQ NQQT	639	GVKGVGHSG QNQQT	824
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GGQVAPSSGQN QQT	284	GHPSPHVSGQN QQT	469	GSGTSGKTG KNQQT	654	GSGQNNKIL TLDQT	839
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GSVSTHSSGQN QQT	338	GSGLLHRAQQN QQT	523	GRLSNAHGG QNQQT	708	GSGQNQGRA HPMQT	893
GSGQNQHSLGN YQT	339	GSGQNAQAAAA QQT	524	GSGQNQRAV LNDQT	709	GSGQLIASV VNQQT	894

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GSGLDYSQRQN QQT	362	GSGQLSVPYDN QQT	547	GSGQNQQMP GLSST	732	GSGSPHKFG KNQQT	917
GSGQSSGRLINK QT	363	GSGRNPQTQPL QQT	548	GSGQNQQTV GGKNL	733	GSGSPHASR QNQHT	918
GSSVSPSSGQNQ QT	364	GSGQPYSTGLN QQT	549	GSSREFHSGQ NQQT	734	GSHSPHKS QNQQT	919
GSGQVVGLSGN QQT	365	GSGQNQQTHGG LRD	550	GSGQNQQTV PSNLV	735	GSGQNQQRR MSPST	920
GSNMGVPLGQN QQT	366	GAYGMVSSGQN QQT	551	GSGQNAYSS QAQQT	736	GSGSPHSPK QNQQT	921
GSFYPSSTGQNQ QT	367	GSGIQSSYSQNQ QT	552	GSGQNKDHS TRRQT	737	GSGSPHKFG QKQQT	922
GSGQNQQTRLT DLT	368	GPRLSDQSGQN QQT	553	GQLGSVSG QDQQT	738	VSGSPHGAR QNQQT	923

GPTNGRSSGQN QQT	369	GSGQNQQTHPS PCT	554	GSGQHAAPG HNQQT	739	GSGSPHKA QKQQT	924
GSGLLHGKLQN QQT	370	GSGQSFQMHTN QQT	555	GSGQNQQTS QSPPT	740	GSHSPHKRG QNQQT	925
GANMGHVSGQ NQQT	371	GSGQNQQTGNP KHT	556	GSGNYRDHE QNQQT	741	GSGQNRQRL KGLET	926
GSGQNQQSGRG DLT	372	GFSSAVHSGQN QQT	557	GSGQHSNQH VNQQT	742	GSGSPHKL GQNQQT	927
GSHGHYASGQK QQT	373	GSGQNQQTSMS NAT	558	GSGQTARNG INQQT	743	GSGSPHKTS KNQQT	928
GSGDLRISPQN QQT	374	GSGQDMKQHH NQQT	559	GSGQNQQHY GSQGT	744	GSGSPHKIG QNQQT	929
GSGMPVILGQN QQT	375	GLRLSTPSGQN QQT	560	GSGSPQASR QNQQT	745	GSGQDSPHV RNQQT	930
GRGVITSSGQN QQT	376	GSGQNQQTSVY MNT	561	GSGFSHSMG KNQQT	746	GSGSPHKTS QNQQT	931
GSGHSVSGPQN QQT	377	GSGQNQYSQSS MQT	562	GSGQSHSLET NQQT	747	GSGSPHASR KNQQT	932
GSRNGHTVGRN QQT	378	GSGQNQQSMAD HTT	563	GTEQTRQSG QNQQT	748	GSHSPHKS GQKQQT	933
GAGVHVMVSGQ NQQT	379	GWERSFVSGQN QQT	564	GSGRHLASV QNQQT	749	GSGSPHKTS QKQQT	934
GSGQNHHRPSV LQQT	380	GLLAGKSSGQN QQT	565	GLGSKNHSG QNQQT	750	GSGSPHVRG QNKQT	935
GSGSPRDSIQN QQT	381	GKSFVPQSGQN QQT	566	GSGQNQQTS HFPSA	751	GSGSPHKTT QNQQT	936
GSGQGIHSSVN QQT	382	GSGQMQSAGSN QQT	567	GSGQLSGTP QNQQT	752	GSGPVRALR QNQQT	937
GSGQQLSITPN QQT	383	GSDQNQRLTSS MQT	568	GSGQNQQAP HKKET	753	GSGSPHVRG QKQQT	938
GGYHSQTSGQN QQT	384	GESRAVLSGQN QQT	569	GSGQNQQTL RGSLE	754	CSGSPHKTS QNQQT	939
CSHSPHKSQGN QQT	940	DAGSPHKAQN QQ	1909	GSGSPHASR QNQQ	2019	GNDSPHKSV QNQQ	2129
GHDSPHKSGQN QQ	1800	GSGSPHKSQGN QQ	1910	GSGSPHASR QNKQ	2020	GHDSPHKSA QNYQ	2130
GSGSPHKAQN QQ	1801	DGGSPHKAQN QQ	1911	GSGSPHVKI QNKQ	2021	GSASPHKA LNQQ	2131
GSGSPHKAQN RH	1802	ASGSPHKAHN QQ	1912	GSGSPHKA KNQQ	2022	GHESPHKSA QNRQ	2132
GSGSPHKSQVN QQ	1803	GSGSPHKAQN TY	1913	GSGSPHKKN QNQQ	2023	GQDSPHKIG QNQQ	2133
MSGSPHKAQN QQ	1804	GSGSPHKSQVN QH	1914	GSGSPHVRM QNQQ	2024	GHDSPHKSG QNLH	2134
GRGSPHKAQN QQ	1805	GGGSPHKAQD KQ	1915	GSGSPHASR QKQQT	2025	GHDSPHKSG QYQH	2135
RNGSPHKAQN QQ	1806	GSGSPHKAQN HL	1916	GHSSPHRSG QNQQ	2026	GNDSPHKSV QNHQ	2136
GSGSPHKAQN QQ	1807	GSGSPHKAQIG M	1917	GSGSPHTRG QNQQ	2027	GHDSPHKSG QNQW	2137
GSGSPHKAQN Q	1808	GSGSPHKAQN KQ	1918	CSGSPHKA QNQQ	2028	GHDSPHKSV QNHQ	2138
TSGSPHKAQN QQ	1809	GGGSPHKAQN PQ	1919	GSGSPHKA QNQQ	2029	GHDSPHKSG QNHQ	2139
GSGSPHKAHV RQ	1810	GTGSPHKAQN QL	1920	GSGSPHKA QNKQ	2030	GHDSPHKSG QTRQ	2140
GSGSPHKAQN H	1811	GSGSPHKAQN Q	1921	GSGSPHKA QTQQ	2031	GHDSPHKSG QNLH	2141

ISGSPHKAQNNQ Q	1812	GGGSPHKAQY QQ	1922	CSGSPHKTSQ NQ	2032	GHDSPHKSA QNQE	2142
GPGSPHKAHN QQ	1813	GGGSPHKAQH QQ	1923	CSHSPHKSG QNQQ	2033	GHDSPHKSG QHLQ	2143
GSGSPHKTQSQ Q	1814	GSGSPHKAQR MS	1924	GQSSPHRSG QNQQ	2034	GHDSPHKSR LNQP	2144
ESGSPHKAQN QQ	1815	GSGSPHKAQGI L	1925	GRGSPHASR QNQQ	2035	GQDSPHKSG QNQD	2145
GSGSPHKAQPA K	1816	GSGSPHKAQD RQ	1926	GSGSPHASR KNQQ	2036	GHDSPHKSG RNQQ	2146
SSGSPHKAQNNQ Q	1817	GSGSPHKAARD WQ	1927	GSGSPHASR QNQH	2037	GHDSPHKSG QNLL	2147
GNGSPHKAQN QQ	1818	GSGSPHKAQN TH	1928	GSGSPHKFG KNQQ	2038	GHDSPHKSG QLVI	2148
GSGSPHKSQTQ Q	1819	GSGSPHKAQE RS	1929	GSGSPHKFG QKQQ	2039	GHDSPHKSR QSQQ	2149
ASGSPHKAQN QQ	1820	GSGSPHKAQN YQ	1930	GSGSPHKFG QNQQ	2040	GHDSPHKSG RTQE	2150
GSGSPHKAQN LA	1821	GSGSPHKAQR TC	1931	GSGSPHKIGQ NQ	2041	GHDSPHKSV QTHQ	2151
GSGSPHKSQNQ L	1822	GSGSPHKAQIG H	1932	GSGSPHKLQ QNQQ	2042	GHDSPHKSG QNQP	2152
NSGSPHKAQN QQ	1823	GSGSPHKAQG AI	1933	GSGSPHKTSK NQ	2043	GHDSPHKSG QTQQ	2153
GSGSPHKAQG QQ	1824	GSGSPHKAQV PP	1934	GSGSPHKTSQ KQQ	2044	GPDSPHKIGQ NQ	2154
VSGSPHKAQN QQ	1825	GSGSPHKAQV QQ	1935	GSGSPHKTSQ NQ	2045	GHDSPHKSV QNQQ	2155
GSGSPHKAALNR Q	1826	GSGSPHKAALM RQ	1936	GSGSPHKTT QNQQ	2046	GHDSPHKSR QDQH	2156
LSGSPHKAQN QQ	1827	GSGSPHKAQY SV	1937	GSGSPHKTY QNQQ	2047	GPDSPHKSG QKQQ	2157
GSGSPHKAHN QQ	1828	GSGSPHKAQVNL Q	1938	GSGSPHKYQ QNQQ	2048	GHDSPHKSR QSQH	2158
GSGSPHKTQN QQ	1829	GSGSPHKAQAI T	1939	GSGSPHKA QHQQ	2049	GHDSPHKSV QNQL	2159
GGGSPHKAQT QQ	1830	GSGSPHKAQK TL	1940	GSGSPHKAQ QNQQ	2050	GYDSPHKAQ QYQH	2160
GSGSPHKAQNP P	1831	GSGSPHKAQ QW	1941	GSGSPHKAQ NQ	2051	GHDSPHKSR QNQQ	2161
GSGSPHKAQN LQ	1832	GSGSPHKAQL HH	1942	GSGSPHVRG QKQQ	2052	GHDSPHKSW VRQQ	2162
GGGSPHKAQN QQ	1833	GSGSPHKAQNI I	1943	GSGSPHVRG QNKQ	2053	GHDSPHKSG QNQH	2163
GSGSPHKAQY QQ	1834	MEGSPHKAQN QQ	1944	GSHSPHKG QNQQ	2054	GHDSPHKIG HNQQ	2164
GGGSPHKAQN KQ	1835	GSGSPHKAQG HH	1945	GSHSPHKG QKQQ	2055	GHDSPHKSN AWQQ	2165
GSGSPHKAQD QE	1836	GSGSPHKAQS KV	1946	GSHSPHKG QNQQ	2056	GHDSPHKSG QSVQ	2166
KSGSPHKAQN QQ	1837	GSGSPHKAQLP S	1947	VSGSPHASR QNQQ	2057	GHDSPHKSG QNIQ	2167
GGGSPHKAQN QL	1838	GSGSPHKAIGK Q	1948	VSGSPHGAR QNQQ	2058	GHDSPHKSV QNHL	2168
GSGSPHKAQN HQ	1839	GGGSPHKSQN QQ	1949	VSGSPHKFG QNQQ	2059	GHDSPHKIG LDQQ	2169
GSGSPHKAQD QQ	1840	GSGSPHKAQAI H	1950	ASGSPHKA QYQV	2060	ASGSPHKA QHQQ	2170

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GNGSPHKAQN KQ	1842	GSGSPHKAQF MC	1952	GSGSPHKA GCGQ	2062	GMGSPHKT QNQQ	2172
GSGSPHSGHW QQ	1843	VSGSPHKAQG QQ	1953	GSGSPHRA QNQQ	2063	GHDSPHSG ESQQ	2173
GSGSPHKAQNP Q	1844	GGGSPHKAQN QM	1954	GSGSPHSLR RQQ	2064	GHDSPHKG QNHQ	2174
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GSGSPHKAQH RI	1853	GSGSPHKAQG SL	1963	GSGSPHKS LQQ	2073	GDDSPHKS QNQQ	2183
GSGSPHKAQYI H	1854	GSGSPHKSQN QQ	1964	GSGSPHKA QRKL	2074	GHDSPHKS QSHQ	2184
GGGSPHKAHN QQ	1855	GNGSPHKSQN QQ	1965	GSGSPHKA RRQ	2075	GHDSPHSG QFVV	2185
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ESGSPHKAQN HQ	1857	GNGSPHKAQN LQ	1967	GSGSPHKA QRRL	2077	GHNSPHKS QNQE	2187
GSGSPHKAQFP S	1858	GSGSPHKAQD KQ	1968	GSGSPHKA RRQQ	2078	GHDSPHKS QSQP	2188
PSGSPHKAQNP Q	1859	GSGSPHKAHY QQ	1969	GSGSPHKA RRLQ	2079	GHNSPHKS QNEQ	2189
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GGGSPHKAQS QQ	1861	GGGSPHKAQN HQ	1971	GLLSPHKA QNQQ	2081	GHDSPHKA QNLL	2191
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GSGSPHKAQS Q	1864	GSGSPHKAQ QQ	1974	GSGSPHVR QNQQ	2084	GHDSPHKS QSLQ	2194
GSVSPHKAQN QL	1865	KNGSPHKAQN QQ	1975	GSGSPHKA QLYR	2085	GHDSPHKA QNHQ	2195
ASGSPHKAQN QL	1866	GSGSPHKSRL Q	1976	GSGSPHKA QLTV	2086	GHDSPHKS RNRQ	2196
RSGSPHKAQN QQ	1867	GSGSPHKAQN QS	1977	GHDSPHKG QHRQ	2087	GHDSPHKG QNEQ	2197
GSGSPHKAQY QH	1868	GSGSPHKAQK VI	1978	GHDSPHKS QKQQ	2088	GNGSPHKA PNLQ	2198
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GNGSPHKAQN HQ	1882	GSGSPHKLQK QQ	1992	GYDSPHSG QKQQ	2102	GHDSPHKSK QNQQ	2212
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GSGSPHKAQN HQ	1892	GSGSPHKAQR EM	2002	GHDSPHKSG HTQQ	2112	GHDSPHKSGI SIQ	2222
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GSGSPHKAQER P	1894	GSGSPHKAQY RA	2004	GSGSPHTKA QNQQ	2114	GHDSPHKMA HNQQ	2224
GSGSPHKAQD LQ	1895	GGGSPHKAQR QQ	2005	GHDSPHKSA QSQQ	2115	GHDSPHKHG QNQQ	2225
GGGSPHKAQN PP	1896	GSGSPHKNQW QQ	2006	GHESPHKSG QNQQ	2116	GHDSPHKSV QSQQ	2226
GSGSPHKAQA MH	1897	GSGSPHKAQR MN	2007	GHDSPHKSL QNQQ	2117	GHDSPHKSG QTVQ	2227
GSGSPHKAQN QQ	1898	GSGSPHKAQN HQ	2008	GHGSPHKA QNPQ	2118	GQDSPHSG QYQQ	2228

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GLGSPHKSQNQQ	1900	GSGSPHKLKLSQQ	2010	GHDSPHKSGQTQL	2120	GHDSPHKSRQNEQ	2230
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GSGSPHKAAPGLQ	1902	GSGSPHKAAPSMQ	2012	GRDSPHKSGQDQQ	2122	GYDSPHKSGQNQQ	2232
GSGSPHKAQGI R	1903	GSGSPHKAASPRQ	2013	GHDSPHKTGHNQQ	2123	GHDSPHKSGQNLQ	2233
GSGSPHKAQAP A	1904	GSGSPHKS RMEQQ	2014	GYDSPHKSGQTQQ	2124	GHDSPHKSRQDQQ	2234
GSGSPHKSQSQQ	1905	GSGSPHKAQYQN	2015	GHESPHKSGQTQQ	2125	GDDSPHKSGQKQL	2235
GSGSPHKAQIP P	1906	GSGSPHARMQNQQ	2016	GHDSPHKSGQSKQ	2126	GSGSPHKAQNQA	2236
GSGSPHKAQTQL	1907	GSGSPHVKSQNQQ	2017	GHDSPHKTGQNQP	2127	GDDSPHKSGHNQQ	2237
GSGSPHKAQAP S	1908	GQDSPHKSGQNQQ	2018	GHDSPHKSGQSPQ	2128	GHDSPHKSGQMIH	2238
GHDSPHKSGRN HQ	2239	GHDSPHKSVQN RQ	2240	GHDSPHKSGQKMN	2241	TINGHDSPHKSRLNQP	2728
TINGSGSPHKAQNQQ	2242	TDRGSGSPHKAQNQQ	2404	TINGSGSPHKAQSTM	2566	TVDGHDSPHKSGQKQQ	2729
TINGHDSPHKSGQNQQ	2243	TINGSGSPHKAQIPP	2405	TVNASGSPHKAQNQL	2567	TINGQDSPHKSQNQD	2730
TIIGSGSPHKAQNRH	2244	TVKGSGSPHKAQDQQ	2406	TINGSGSPHKAQREM	2568	TIEGHDSPHKSGRNQQ	2731
TFPGSGSPHKS VQNQQ	2245	NADGSGSPHKAQNQQ	2407	TVHSGSPHKAQSQQ	2569	TTNGHDSPHKSGQNLL	2732
TEKMSGSPHKAQNQQ	2246	TDKVSGSPHKAQNQQ	2408	TINGGGSPHKSQNRRQ	2570	TINGHDSPHKSGQLVI	2733
EINGRGSPHKAQNQQ	2247	TITGSGSPHKAQTQL	2409	TINGSGSPHKAQYRA	2571	TVNGHDSPHKSRQSQQ	2734
TVNRNGSPHKAQNQQ	2248	TINGSGSPHKAQAPS	2410	TINGGGSPHKAQROQ	2572	TINGHDSPHKSGRTQE	2735
TVNGSGSPHKAARDQQ	2249	NCVSGSGSPHKAQNQQ	2411	TEPMGSPHKAQNQQ	2573	TINGHDSPHKSVQTHQ	2736
TFNGSGSPHKA PNLQ	2250	TIRDAGSPHKAQNQQ	2412	TINGSGSPHKNQWQQ	2574	TSNGHDSPHKSGQNQP	2737
TEKTSGSPHKAQNQQ	2251	TVKDSGSPHKAQNQQ	2413	ETAGSGSPHKAQNQQ	2575	VINGHDSPHKSGQTQQ	2738
TINGSGSPHKAHVRQ	2252	NALGSGSPHKAQNQQ	2414	TINGSGSPHKAQRMN	2576	TINGPDSPHKIGQNQQ	2739
TVNGSGSPHKAAPNQH	2253	VINGSGSPHKSQNQQ	2415	NNLGSGSPHKAQNQQ	2577	AVNGHDSPHKSVQNQQ	2740
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SINESGSPHKAQNQQ	2257	TSNASGSPHKAHNQQ	2419	TINGSGSPHKLKSQQ	2581	TIYGHDSPHKSVQNQL	2744
TERTSGSPHKAQNQQ	2258	TINGSGSPHKAQNTY	2420	TINGSGSPHKAQKIS	2582	TVNGHDSPHKSGQNLL	2745
TINGSGSPHKAQPAK	2259	TINGSGSPHKSQNQH	2421	TEYNSGSPHKAQNQQ	2583	TENKSGSPHKAQNQQ	2746

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TEKGSGSPHKA QNQQ	2262	TVNGSGSPHSK AQNHL	2424	TINGSGSPHS KASPRQ	2586	TIDGHDSPH KSGRNQQ	2749
TINGSGSPHSKS QTQQ	2263	TREISGSPHKA QNQQ	2425	TINGSGSPHS KRMEQQ	2587	TINGYDSPH KSGQYQH	2750
TERISGSPHKA QNQQ	2264	TINGSGSPHKA QIGM	2426	TINGSGSPHS KAQYQN	2588	TDNGHDSPH KSRQNQQ	2751
TERASGSPHKA QNQQ	2265	TIDGSGSPHKA LNKQ	2427	TINGSGSPHS KAQYYV	2589	TINGHDSPH KSWVRQQ	2752
ELHGSGLPHSKA QNQQ	2266	TIIGGGSPHKA QNPQ	2428	TINGSGSPHS KLRRQQ	2590	TINGHESPHK SGQNQH	2753
AINSGSPHKA QNLA	2267	QGEGLSPHSK AQNQQ	2429	TINGSGSPHS KAGCGQ	2591	TVNGHDSPH KIGHNQQ	2754
TVNGSGSPHSKS QNQL	2268	TINGTGSPHKA PNQL	2430	SMNGSGSPH SRAQNQQ	2592	TCNGHDSPH KSGRNQQ	2755
TERNSGSPHKA QNQQ	2269	TVNGSGSPHSK AQLQQ	2431	TINGSGSPHS KRLRQQ	2593	TINGNGSPHS KAQNHQ	2756
SVNGNGSPHSK AQNQQ	2270	TFNGGGSPHSK AQYQQ	2432	TINGSGSPHS LRRNQQ	2594	NVVGHDSPH KSGQNQQ	2757
TFNGSGSPHKA QGQQ	2271	SINGSGSPHKT QSQQ	2433	TINGSGSPHS RGRNQQ	2595	TINGHDSPH KSNAWQQ	2758
TERVSGSPHKA QNQQ	2272	TVNGGGSPHSK AQHQQ	2434	TINGSGSPHS SRRNQQ	2596	TDAGHDSPH KSGQNQQ	2759
TINGSGSPHKA LNRQ	2273	SEKSGSPHKA QNQQ	2435	TINGSGSPHS KAFRLQ	2597	TEVGHDSPH KSGQNQQ	2760
TERLSGSPHKA QNQQ	2274	NVNGSGSPHSK AQNQQ	2436	TINGSCSPHR KAQNQQ	2598	SELGHDSPH KSGQNQQ	2761
TDNGSGSPHSK AHNQQ	2275	GGEGLSPHSK AQNQQ	2437	TINGSGSPHF LRQNQQ	2599	TINGHDSPH KSGQSV	2762
TFHGSGLPHSKT QNQQ	2276	TINGSGSPHKA QRMS	2438	TINGSGSPHS LRFNQQ	2600	TINGHESPHK SGQNIQ	2763
TINGGGSPHKA QTQQ	2277	TINGSGSPHKA QGIL	2439	TINGSGSPHS KWLLQQ	2601	TINGHDSPH KSVQNL	2764
TSNGSGSPHKA QNPP	2278	EFVSGSPHKA QNQQ	2440	TINGSGSPHS KRRLQQ	2602	TINGHDSPH KIGLDQQ	2765
TINGSGSPHKA QNLQ	2279	TIIGSGSPHKAQ DRQ	2441	TINGSGSPHS KAQRKL	2603	TSNASGSPHS KAQHQQ	2766
TVHGNGLPHSK AQNQQ	2280	SDKGSGSPHSK AQNQQ	2442	TINGSGSPHS KALRRQ	2604	TINGHDSPH KRGPDQQ	2767
TINGGGSPHKA QNQQ	2281	TEQVSGSPHKA QNQQ	2443	TINGSGSPHS KAQRLR	2605	TINGMGSPH SKTQNQQ	2768
TENMSGSPHSK AQNQQ	2282	TEHVSGSPHKA QNQQ	2444	YLSGSGSPHS KAQNQQ	2606	TIKGHDSPH KSGESQQ	2769
TENVSGSPHKA QNQQ	2283	TINGSGSPHKA RDWQ	2445	TINGSGSPHS KAQRRL	2607	TINGHDSPH KHGQNHQ	2770
TSSGSGSPHKA QYQQ	2284	TENASGSPHKA QNQQ	2446	TINGSGSPHS KARRQQ	2608	TVNGTGSPH SKAQNL	2771
TIDGGGSPHKA QNKQ	2285	EVQGSGLPHSK AQNQQ	2447	TINGSGSPHS KARRLQ	2609	TIIGHDSPH SGQYQH	2772
TEKVSGSPHKA QNQQ	2286	TINGSGSPHKA QNTN	2448	TINGSGSPHS KSRRQQ	2610	TSNGHDSPH KSVQNKQ	2773
AINSGSPHKA QDQE	2287	TINGSGSPHKA PNLQ	2449	TINGLLSPHW KAQNQQ	2611	IVNGQVSPH KSGQNQQ	2774
TCNKSGSPHKA QNQQ	2288	TINGSGSPHKA QERS	2450	TINGSGSPHS KARLRQ	2612	TVNGHDSPH KSGQRQL	2775

TINGGGSPHKA QNQL	2289	TSNGSGSPHKA QNYQ	2451	TINGSGSPHS KASKRQ	2613	TVNGHDSPH KIGQNQL	2776
NINGGGSPHKA QNQQ	2290	TEYISGSPHKA QNQQ	2452	TINGSGSPHV RRQNQQ	2614	TINGHDSPH KSGQIIV	2777
TEHLSGSPHKA QNQQ	2291	TINGSGSPHKA QRTC	2453	TINGSGSPHS KAQLYR	2615	IGNGHESPH KSGQNQQ	2778
AEMGSGSPHKA AQNQQ	2292	TINGSGSPHKA QIGH	2454	GLSGSGSPHS KAQNQQ	2616	EVMGHDSPH KSGQNQQ	2779
ATNGSGSPHKA AQNHQ	2293	NCWGS SPHKA AQNQQ	2455	TINGSGSPHS KAQLTV	2617	TINGYDSPH KSGQKQS	2780
AIKGS SPHKA QDQQ	2294	TINGSGSPHKA QGAI	2456	TINGHDSPHK RGQHRQ	2618	TIHNGSPHS KAQNE	2781
TINGGGSPHKS QNQL	2295	TDVNSGSPHKA AQNQQ	2457	MPEGHDSPH KSGQNQQ	2619	YQVGHDSPH KSGQNQQ	2782
TVNGNGSPHKA AQNKQ	2296	SDIGSGSPHKA QNQQ	2458	MEGGHDSPH KSGQNQQ	2620	TIKGDDSPH KSVQNQQ	2783
TINGSGSPHKA HWQQ	2297	TINGSGSPHKA QVPP	2459	MEYGHDSPH KSGQNQQ	2621	TINGHDSPH KSVQSHQ	2784
TDKTS SPHKA QNQQ	2298	TINGSGSPHKA QVQQ	2460	AEWGHDSPH KSGQNQQ	2622	TINGHDSPH KSGQFVV	2785
TFKGS SPHKA PNQQ	2299	TINGSGSPHKA LMRQ	2461	CEWGHDSPH KSGQNQQ	2623	TVNGHDSPH KSRQNLQ	2786
TVNGSGSPHKA AQNQL	2300	TINGSGSPHKA QYSV	2462	ANNGQDSPH KSGQNQQ	2624	ATNGHNSPH KSGQNE	2787
TINGSGSPHKA PEQQ	2301	NSIGSGSPHKA QNQQ	2463	IPEGHDSPHK SGQNQQ	2625	AINGHDSPH KSAQNQQ	2788
TINGSGSPHKA QRTM	2302	TINGSGSPHKA PNLQ	2464	ADMGHDSPH KSGQNQQ	2626	TEHGHDSPH KSGQNQQ	2789
TEKASGSPHKA QNQQ	2303	AINSGSPHKA QSQQ	2465	IEYGHDSPHK SGQNQQ	2627	TIYGHDSPH KSGQSQP	2790
SDQGS SPHKA QNQQ	2304	TINGSGSPHKA QAIT	2466	ADYGHDSPH KSGQNQQ	2628	TISGHESPHK SGQNEQ	2791
TEITSGSPHKA QNQQ	2305	TINGSGSPHKA QKTL	2467	IETGHDSPHK SGQNQQ	2629	AIIGHDSPHK SAQNQQ	2792
TDKSSGSPHKA QNQQ	2306	TVNGSGSPHKA AQNQW	2468	MEWGHDSPH KSGQNQQ	2630	AIDGHDSPH KSGQNQL	2793
TIDGS SPHKA QNQQ	2307	TINGSGSPHKA QLHH	2469	CEYGHDSPH KSGQNQQ	2631	TIMGHDSPH KSVQNQQ	2794
TVNGNGSPHKA AQNQH	2308	TEQTS SPHKA QNQQ	2470	RINGHDSPHK SGQKQQ	2632	EVGGHDSPH KSGQNQQ	2795
NTNGSGSPHKA AQNQQ	2309	TINGSGSPHKA QNII	2471	MEIGHDSPH KSGQNQQ	2633	TINGHDSPH KSAQNLL	2796
TETHSGSPHKA QNQQ	2310	NSLGS SPHKA QNQQ	2472	LEYGHDSPH KSGQNQQ	2634	TINASGSPHS KAINQQ	2797
TINGGGSPHKA LNQQ	2311	TIPMEGSPHKA QNQQ	2473	ADWGHDSPH KSGQNQQ	2635	AINGNGSPH KRGQNQQ	2798
TINGSGSPHKA LHQH	2312	TINGSGSPHKA QGHH	2474	IEIGHDSPHK SGQNQQ	2636	SEMGHDSPH KSGQNQQ	2799
TINGTSPHKA QNHQ	2313	TDRTSGSPHKA QNQQ	2475	DIMGHDSPH KSGQNQQ	2637	AQQGHDSPH KSGQNQQ	2800
TINGSGSPHKA QHRI	2314	TINGSGSPHKA QSKV	2476	FEQGHDSPH KSGQNQQ	2638	AINGHDSPH KSGQSLQ	2801
TINGSGSPHKA QYIH	2315	EVVGS SPHKA AQNQQ	2477	MEFGHDSPH KSGQNQQ	2639	TINGSGSPHS KAPNQQ	2802
TENISGSPHKA QNQQ	2316	TINGSGSPHKA QLPS	2478	CDQGHDSPH KSGQNQQ	2640	CGEGHDSPH KSGQNQQ	2803
TIIGGS SPHKA HNQQ	2317	TINGSGSPHKA GKQ	2479	LPEGHDSPH KSGQNQQ	2641	TVNGHDSPH KSAQNHQ	2804

TINGSGSPHKA QKFE	2318	TEPTSGSPHKA QNQQ	2480	IENGHDSPHK SGQNQQ	2642	TVNGHDSPH KSGQTQL	2805
TSNESGSPHKA QNHQ	2319	TVNGGGSPHKA SQNQQ	2481	MESGHDSPH KSGQNQQ	2643	TNNGHDSPH KSGRNRQ	2806
TINGSGSPHKA QFPS	2320	TINGSGSPHKA QAIH	2482	AEIGHDSPHK SGQNQQ	2644	TINGHDSPH KYGQNEQ	2807
TERPSGSPHKA QNQQ	2321	TINGSGSPHKA QHGL	2483	VEYGHDSPH KSGQNQQ	2645	TINGNGSPHS KAPNLQ	2808
TINGNGSPHKA QNPL	2322	SELGSGSPHKA QNQQ	2484	IINGHDSPHK SGLTQQ	2646	SINGHDSPHK SQQNQQ	2809
SIKGNGSPHKA QNQQ	2323	TINGSGSPHKA QFMC	2485	TSNGDDSPH KSGRNRQ	2647	TIGGHDSPH KSGQNQQ	2810
TERMSGSPHKA AQNQQ	2324	TINVSGSPHKA QGQQ	2486	IEVGHDSPHK SGQNQQ	2648	TINGHDSPH KSVQSKQ	2811
TERSSGSPHKA QNQQ	2325	TINGGGSPHKA QNQM	2487	MEMGHDSPH KSGQNQQ	2649	ELVGHDSPH KSGQNQQ	2812
TELHSGSPHKA QNQQ	2326	TVNGSGSPHKA AQHLQ	2488	AEVGHDSPH KSGQNQQ	2650	ELMGHDSPH KSGQNQQ	2813
TELTSGSPHKA QNQQ	2327	TIRENGSPHKA QNQQ	2489	MDAGHDSPH KSGQNQQ	2651	TINGNDSPH KIGHNQQ	2814
TINGSGSPHKA HNQQ	2328	TINGSGSPHKA QNHQ	2490	VEWGHDSPH KSGQNQQ	2652	TIKGGSPHS KAQDQQ	2815
TINGGGSPHKA QSQQ	2329	TINGSGSPHKA QPAR	2491	AEQGHDSPH KSGQNQQ	2653	TVNGHDSPH KSGQTQQ	2816
TINGSGSPHKA QAIK	2330	TVNGSGSPHKA AQSLQ	2492	LEWGHDSPH KSGQNQQ	2654	TINGQDSPH KSGQNPL	2817
TENTSGSPHKA QNQQ	2331	TINGSGSPHKA QSQL	2493	MELGHDSPH KSGQNQQ	2655	TVNASGSPH SKAQNHO	2818
TIDGSGSPHKA QNRQ	2332	TINGSASPHKA HSQQ	2494	METGHDSPH KSGQNQQ	2656	TINGHDSPH KSGRDQK	2819
NINGSGSPHKA QSQQ	2333	TWQNSGSPHKA AQNQQ	2495	MEAGHDSPH KSGQNQQ	2657	TINGHDSPH KSVHNQQ	2820
TINGSVSPHKA QNQL	2334	TINGSGSPHKA QDRQ	2496	IESGHDSPHK SGQNQQ	2658	TINGHDSPH KSGQWKR	2821
TSNASGSPHKA QNQL	2335	TINGSGSPHKA QMPS	2497	MEVGHDSPH KSGQNQQ	2659	TIDGSGSPHS KAENRQ	2822
TEARSGSPHKA QNQQ	2336	TNNGGGSPHKA AQNLQ	2498	CEIGHDSPHK SGQNQQ	2660	NEIGHDSPH KSGQNQQ	2823
TEKNSGSPHKA QNQQ	2337	TINGSGSPHKA QGSL	2499	ATNGHDSPH KSGLNQQ	2661	AINGHDSPH KSGQSQQ	2824
TANGSGSPHKA AQYQQ	2338	TEVTSGSPHKA QNQQ	2500	MDGGHDSPH KSGQNQQ	2662	IINGHDSPHK SRQAQQ	2825
TVNGSGSPHKA AQYQH	2339	SINGGGSPHKA QYQQ	2501	QEVGHDSPH KSGQNQQ	2663	TPNGHDSPH KSGQNQQ	2826
TINGSGSPHTKA QNPQ	2340	TVIGSGSPHKA QNQQ	2502	ADQGHDSPH KSGQNQQ	2664	ITNGHDSPH KSGQTQQ	2827
TINGSGSPHKA QNPP	2341	AVNVSGSPHKA AQNQQ	2503	TINGHESPHK SAQNHQ	2665	TINGHDSPH KSVQNHQ	2828
TIIGSGSPHKA QHQL	2342	TVNGNGSPHKA SQNQQ	2504	TINGHDSPHK SAQNQW	2666	TINGHDSPH KSKQNQQ	2829
TINGSGSPHKA QSPP	2343	TDRNSGSPHKA AQNQQ	2505	NMNGHDSPH KSGQNTN	2667	TINGHDSPH KSAQNQL	2830
TIYGSGSPHKA QNQQ	2344	TINGSGSPHKA QVPA	2506	IEMGHDSPH KSGQNQQ	2668	TVNGHDSPH KSGQTQP	2831
TINGSGSPHKA QAKL	2345	GVLGSGSPHKA AQNQQ	2507	TINGHDSPHK SGRRRQ	2669	TDQGHDSPH KSGQNQQ	2832
TDKNSGSPHKA AQNQQ	2346	TLNGNGSPHKA AQNLQ	2508	ISNGHDSPHK SAQNQQ	2670	TINGHDSPH KLWINQQ	2833

TINGSGSPHST KSQQ	2347	AINSGSPHST QDKQ	2509	TGNHDSPH KSGYQQ	2671	GINGDPSHK SGQNQQ	2834
TINGSGSPHST QDRP	2348	TSNGSGSPHST HYQQ	2510	TINGNYSPHK IGQNQQ	2672	SEIGHDSPHK SGQNQQ	2835
TINGIGSPHST QNLG	2349	TINGSGSPHST QVPS	2511	TINGHDSPHK SRQNDQ	2673	TINGHDSPH KSVQKQL	2836
TINGSGSPHST QSQQ	2350	TELRSRSPHST QNQQ	2512	QQQGHDSPH KSGQNQQ	2674	TINGHPSPH WKGQNQQ	2837
TENLSRSPHST QNQQ	2351	NINGSGSPHST QNHQ	2513	HDWGHDSPH KSGQNQQ	2675	TVNGHDSPH KSGRNQL	2838
TINGSGSPHST QAFH	2352	TVNGGSPHST AQNHQ	2514	IEGGHDSPHK SGQNQQ	2676	TIKSGSPHS KVQDQQ	2839
TINGSGSPHST QKQQ	2353	TINGSGSPHST RGEQ	2515	TFNRSGSPHS KAQNQQ	2677	SEKGHDSPH KSGQNQQ	2840
TFSRSGSPHST QNLQ	2354	TINGGSPHST QYQH	2516	AINGHDSPH KSGQIRQ	2678	WSAGHDSPH KSGQNQQ	2841
AINSGSPHST QNAQ	2355	TEDLSRSPHST QNQQ	2517	TINGHDSPHK IGQNHQ	2679	ELAGHDSPH KSGQNQQ	2842
TESWSPHST QNQQ	2356	TINGSGSPHST PGQQ	2518	AINGYDSPH KSGQKQQ	2680	TINGHDSPH KMGRNQ	2843
TTNGSGSPHST HNQL	2357	TIPKNGSPHST QNQQ	2519	TESGHDSPH KSGQNQQ	2681	TINGHDSPH KSGISIQ	2844
TVNGNGSPHST AQNHQ	2358	TINGSGSPHST QSLQ	2520	TINGHDSPHK SGQSVQ	2682	TSNGHDSPH KSVQNLQ	2845
TEDKSGSPHST QNQQ	2359	TINGSGSPHST LEQQ	2521	TINGHDSPHK SGRSQQ	2683	QTQGHDSPH KSGQNQQ	2846
TESASGSPHST QNQQ	2360	TERGSGSPHST QNQQ	2522	TINGHDSPHK SGQNKL	2684	TINGHDSPH KMAHNQQ	2847
TNNGSGSPHST AQNQ	2361	TVNGSGSPHST APNQ	2523	TINGHDSPHK TGQNQQ	2685	AINSGSPHS KAQTQQ	2848
TSNGGSPHST AQNLQ	2362	TSNGSGSPHST QNQS	2524	TINGRSPHST RGQNQQ	2686	TINGHDSPH KHGQNQQ	2849
TDKMSGSPHST AQNQ	2363	TINGSGSPHST QKVI	2525	TINGSGSPHT KAQNPP	2687	GADGHDSPH KSGQNQQ	2850
EVHSGSPHST AQNQ	2364	TEGISGSPHST QNQQ	2526	TINGQDSPHK SGQHQQ	2688	VGEHDSPH KSGQNQQ	2851
TINGSGSPHST QKLN	2365	TINGSGSPHST QNND	2527	SINGHDSPHK SGQIQH	2689	ANEGHDSPH KSGQNQQ	2852
TINGGSPHST QNQH	2366	TINGSGSPHST QSVH	2528	AINGHDSPH KSGPRQQ	2690	TEAKSGSPHS KAQNQQ	2853
TVNGGSPHST AQSQ	2367	TINGSGSPHST QPLG	2529	TVNGHDSPH KSGHTQQ	2691	TINGHDSPH KSVQSQ	2854
TTNGSGSPHST QYQH	2368	TINKEGSPHST QNQQ	2530	SINGHDSPHK SGQRQH	2692	TIPSGSPHS KAQNLQ	2855
TISGSGSPHST QYQH	2369	TCNASGSPHST AQNQ	2531	SLNGSGSPHT KAQNQQ	2693	TINGHDSPH KSGQTV	2856
TESTSGSPHST QNQQ	2370	AINSGSPHST HNQE	2532	AINGHDSPH KSAQSQ	2694	ELRGHDSPH KSGQNQQ	2857
TINGSGSPHST QNVQ	2371	TEGLSGSPHST QNQQ	2533	SIYGHDSPHK SGQNQQ	2695	CQIGHDSPH KSGQNQQ	2858
SINGSGSPHST QAQQ	2372	TRDASGSPHST AQNQ	2534	TVNGHDSPH KSLQNQQ	2696	GVMGHDSPH KSGQNQQ	2859
TVNGSGSPHST AQNLQ	2373	TSNGSGSPHST QNLQ	2535	TINGHDSPH KAQNPQ	2697	ACDGHDSPH KSGQNQQ	2860
TVRDSGSPHST AQNQ	2374	TGNNGSGSPHST AQIQ	2536	TSNGYDSPH KSGQKQQ	2698	TINGQDSPH KSGYQQ	2861
TFNASGSPHST PNQQ	2375	TVNGGSPHST AQNLQ	2537	TVNGHDSPH KSGRNQE	2699	TINGHDSPH KSGQQIM	2862

TDRMSGSPHSK AQNOQ	2376	TDRSSGSPHSKA QNOQ	2538	TTNGHDSPH KSGQTQL	2700	TINGHDSPH KSRQNEQ	2863
TINGSGSPHSKA QTPP	2377	TINGSGSPHSKA QVRN	2539	AINGHDSPH KSEKNQO	2701	ASNGHDSPH KSGLNHQ	2864
TIKSGSPHSKA QNOQ	2378	TINGSGSPHSKA PSNO	2540	IINGRDSPHK SGQDOO	2702	TVNGHDSPH KSGQSQP	2865
NHIGSGSPHSKA QNOQ	2379	TINGSGSPHSKA QVGH	2541	TISGHDSPHK TGHNOO	2703	NELGHDSPH KSGQNOO	2866
TINGSGSPHSKA QYQH	2380	NAIGSGSPHSKA QNOO	2542	SINGYDSPHK SGQTQO	2704	AAEGHDSPH KSGQNOO	2867
TIPIDGSPHSKAQ NOO	2381	AENGSGSPHSK AQNOO	2543	TINGHESPHK SGQTQO	2705	GQNGHDSPH KSGQNOO	2868
TINGSGSPHSKA QGOO	2382	TINGSGSPHSKA QRDI	2544	TINGHDSPHK SGQSKO	2706	NEFGHDSPH KSGQNOO	2869
TFNGSGSPHNK AQNHQ	2383	TINGSGSPHSKA QMPN	2545	AIIGHESPHK SGQNOO	2707	TSIGYDSPHK SGQNOO	2870
ESDGS SPHSKA QNOO	2384	TVNGSGSPHSKS QNOO	2546	TINGHDSPHK TGQNOO	2708	TDNGHDSPH KSGQNLQ	2871
TINGSGSPHSKA QPPA	2385	TIPAI GSPHSKAQ NOO	2547	AINGHDSPH KSGQSPQ	2709	TITGHDSPHK SRQDOO	2872
TINGSGSPHSKA QERP	2386	TINGSGSPHSKA RGLQ	2548	TIKGNDSPHK SVQNOO	2710	AEHGHDSPH KSGQNOO	2873
TIKSGSPHSKA QDLQ	2387	TELGSGSPHSKA QNOO	2549	TEFGHDSPH KSGQNOO	2711	TINGDDSPH KSGQKQL	2874
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TINGGGSPHSKA QNPP	2389	TINGSGSPHSKL QKQO	2551	TFNGSASPHS KALNOO	2713	TIHSGSPHS KAQNOA	2876
TINGSGSPHSKA QAMH	2390	TINGSGSPHSKA PSLQ	2552	TINGHESPHK SAQNRQ	2714	AINGDDSPH KSGHNQO	2877
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TVIGSGSPHSKA LNQO	2392	TDVGS SPHSK AQNOO	2554	TIKGQDSPHK IGQNOO	2716	TINGHDSPH KSGQMIH	2879
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TINGTGSPHSKA QNOO	2395	TINGSGSPHSKA QAKG	2557	TINGNDSPHK SVQNHQ	2719	TITGHDSPHK SVQNRQ	2882
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TESHSGSPHSKA QNOO	2398	TINGSGSPHSKA QSAH	2560	TIDGHDSPHK SGQNHQ	2722	TEIGHDSPHK SGQNOO	2885
TINGSGSPHSKA QAPA	2399	TINGNGSPHSKS QNQH	2561	TVNGHDSPH KSGQTRQ	2723	TINGHDSPH KSGQYQH	2886
TINGSGSPHSKS QSQQ	2400	TVPTSGSPHSKA QNOO	2562	TVNGHDSPH KSGQNLH	2724	NCLGSGSPH SKAQNOO	2403
AEHGS SPHSK AQNOO	2401	TIDGSGSPHSKS QNHQ	2563	ASGHDSPHK SGLNOO	2725	AINRSGSPHS KAQDOO	2565
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GSGSPHSKAQN RHT	2887	GSGSPHSKAQS QQT	2936	GSGSPHSKA QRMST	2985	GSGSPHSKA QNNDQ	3034
GSGSPHSKVQN QQT	2888	ASGSPHSKAQN QLT	2937	GSGSPHSKA QGILT	2986	GSGSPHSKA QSVHT	3035

MSGSPHSAQN QQT	2889	RSGSPHSAQN QQT	2938	GSGSPHSA QDRQT	2987	GSGSPHSA QPLGT	3036
GSGSPHSAKARD QQT	2890	GSGSPHSAQY QHT	2939	GSGSPHSA RDWQT	2988	GSGSPHSA HNQET	3037
GSGSPHSAKAPNL QT	2891	GSGSPHTKAQN PQS	2940	GSGSPHSA QNTHD	2989	GSGSPHSA QNLQI	3038
TSGSPHSAQN QQT	2892	GSGSPHSAQGN PPT	2941	GSGSPHSA NLQI	2990	GSGSPHSA QIQQT	3039
GSGSPHSAHV RQT	2893	GSGSPHSAQH QLT	2942	GSGSPHSA QERST	2991	GSGSPHSA QVRNT	3040
GSGSPHSAKAPNQ HT	2894	GSGSPHSAQSP PT	2943	GSGSPHSA QNYQT	2992	GSGSPHSA PSNQT	3041
ISGSPHSAQNNQ QT	2895	GSGSPHSAQA KLT	2944	GSGSPHSA QRTCT	2993	GSGSPHSA QVGHT	3042
GSGSPHSAKTSQ QT	2896	GSGSPHSAKTSQ QT	2945	GSGSPHSA QIGHT	2994	GSGSPHSA QRDIT	3043
GSGSPHSAQN QST	3032	GSGSPHSAQD RPT	2946	GSGSPHSA QGAIT	2995	GSGSPHSA QMPNT	3044
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GSGSPHSAQPA KT	2899	GSGSPHSAQA FHT	2948	GSGSPHSA QVQQI	2997	GSGSPHSA QKQQT	3046
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KSGSPHSAQN QQT	2916	GSGSPHSAQE RPT	2965	VSGSPHSA QGQQT	3014	GSGSPHSA PSMQT	3063
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KTINGSGSPHSK AVRWQT	4169	KAINGHDSPHKS GQNLRS	4265	KTINGHDSPH SKALSLQT	4361	KTINGSGSPH SKLQRQQT	4457
KTINGSGSPHSK AYTRQT	4170	KAINGHDSPHKS GQNLSS	4266	KTINGHDSPH SKAQGQQT	4362	KTINGSGSPH SKMLRQQT	4458
KTINGSGSPHSK CQSQQT	4171	KAINGHDSPHKS GQNSLG	4267	KTINGHDSPH SKAQHQQT	4363	KTINGSGSPH SKSSIKQT	4459
KTINGSGSPHSK FLRQQT	4172	KAINGHDSPHKS GQNTLQ	4268	KTINGHDSPH SKAQIQQT	4364	KTINGSGSPH SKVRFQQT	4460
KTINGSGSPHSK FRFQQT	4173	KAINGHDSPHKS GQNTSL	4269	KTINGHDSPH SKAQKQQT	4365	KTINGSGSPH SVVWNQQT	4461
KTINGSGSPHSK FRLQQT	4174	KAINGHDSPHKS GQRLGT	4270	KTINGHDSPH SKAQNLS	4366	KTINGSTSPH KLAQNQQP	4462
KTINGSGSPHSK FRRQQT	4175	KAINGHDSPHKS GQRNYT	4271	KTINGHDSPH SKAQNQQT	4367	KTINRHDSPH KSGQRPST	4463
KTINGSGSPHSK GMKQQT	4176	KAINGHDSPHKS GQRPST	4272	KTINGHDSPH SKAQNQET	4368	KTINRIMSPH SKAQNQQT	4464
KTINGSGSPHSK KLRQQT	4177	KAINGHDSPHKS GQRPVT	4273	KTINGHDSPH SKAQNQHT	4369	KTINTARSPH SKAQNQQT	4465
KTINGSGSPHSK KRPPQT	4178	KAINGHDSPHKS GQVPST	4274	KTINGHDSPH SKAQNQLT	4370	KTISGHDSPH SKAQNQQT	4466
KTINGSGSPHSK KSRQQT	4179	KAINGHDSPHKS LSNQQT	4275	KTINGHDSPH SKAQNQPT	4371	KTISGSGSPH KSGQNQQT	4467
KTINGSGSPHSK LYRQQT	4180	KAINGHDSPHKS VLSQQT	4276	KTINGHDSPH SKAQNQQA	4372	KTITGHDSPH KSGQRLGT	4468
KTINGSGSPHSK LYWQQT	4181	KAINGHDSPHKT LQNQQT	4277	KTINGHDSPH SKAQNTGS	4373	KTITGSGSPH KSGQNQQT	4469
KTINGSGSPHSK PRMQQT	4182	KAINGHNSPHSK AQNQQT	4278	KTINGHDSPH SKAQSQQT	4374	KTIYGHDSH HKSGQRLGT	4470
KTINGSGSPHSK RFPQQT	4183	KAINGLDSPHSK AQNQQT	4279	KTINGHDSPH SKAQTQQT	4375	KTLNGHDSH HKSGQNLFL	4471
KTINGSGSPHSK RFRQQT	4184	KAINGSGSPHSK GQNQQT	4280	KTINGHDSPH SKAQYQQT	4376	KTLNGHDSH HKSGQNLSS	4472
KTINGSGSPHSK RPYQQT	4185	KAINGSGSPHSK AQGQQT	4281	KTINGHDSPH SKARNQQT	4377	KTLSFHDSH KSGQNQQS	4473
KTINGSGSPHSK RRMQQT	4186	KAINGSGSPHSK AQLSGT	4282	KTINGHDSPH SKLPGQQT	4378	KTSNGSGSP HKAQNTMT	4474
KTINGSGSPHSK RSKQQT	4187	KAINGSGSPHSK AQNGSL	4283	KTINGHDSPH SKSPNQQT	4379	KTTNGHDSH HKAQNQQT	4475

KTINGSGSPHSK RSRQQT	4188	KAINGSGSPHSK AQNSSL	4284	KTINGHESPH KSGQNAFL	4380	KTVNNGGSP HSAQNQQT	4476
KTINGSGSPHSK RTMQQT	4189	KAINGSGSPHSK AVGLQT	4285	KTINGIGSPH SKAPNEQT	4381	KTVNGHDSP HKSQNVSL	4477
KTINGSGSPHSK RTRQQT	4190	KAINGSGSPHSK SLLQQT	4286	KTINGQDSPH KSGQNLHM	4382	KTVNGHDSP HKSQRPST	4478
KTINGSGSPHSK RVRQQT	4191	KAINGSGSPHSK SLPQQT	4287	KTINGRGSPH SKAQIGMT	4383	KTVNGHDSP HKSQTQQA	4479
KTINGSGSPHSK RYIQQT	4192	KAINGSGSPHSK STFQQT	4288	KTINGRGSPH SKAQNVL	4384	KTVNGHESP HSAQNQQT	4480
KTINGSGSPHSK RYNQQT	4193	KAITGHDSPHSK AQNQQT	4289	KTINGRGSPH SKAQSPPT	4385	KTVNNGGSP HSAQGLST	4481
KTINGSGSPHSK RYPQQT	4194	KDVMGSGSPHS KAQNQQT	4290	KTINGRGSPH SKATSFQT	4386	KTVNNGGSP HSAQNVTS	4482
KTINGSGSPHSK RYSQQT	4195	KEIVGSGSPHSK AQNQQT	4291	KTINGSGSPH FVVQNQQT	4387	KTVPASGSP HSAQNQQT	4483
NTINGSGSPHSK AHNQQT	4484	TTINGGGSPHSK AQNQQT	4485				

Table 2A. Exemplary Peptide Sequences

SEQ ID NO:	Amino Acid Sequence	SEQ ID NO:	Nucleotide Sequence
941	SPHKA	942	AGCCACACAGCAAAGCA
943	HDSPHKS	944	CACGACAGCCACACAAAAGCGGA
2	HDSPHK	3	CACGACAGCCACACAAA

Table 2B. Exemplary Peptide Sequences

Amino Acid Sequence	SEQ ID NO:	Amino Acid Sequence	SEQ ID NO:	Amino Acid Sequence	SEQ ID NO:	Amino Acid Sequence	SEQ ID NO:
SPHKA	945	SPHKKN	954	SPHKTS	963	SPHTRG	972
SPHKS	946	SPHVRM	955	SPHKTT	964	SPHVRG	973
SPHARM	947	SPHRKA	956	SPHKTY	965	SPHKRG	974
SPHVKS	948	SPHKFG	957	SPHKYG	966	SPHGAR	975
SPHASR	949	SPHKIG	958	SPHSD	967	SPHRSG	976
SPHVKI	950	SPHKL	959	SPHSPK	968	SPHKA	977
SPHKSR	951	SPHSL	960	SPHSRA	969	SPHKS	978
SPHSLR	952	SPHSRG	961	SPHSSR	970	SPHFLR	979
SPHSLW	953	SPHSS	962	SPHWKA	971	SPHVRR	980
STHASR	985	SQHKSG	986	HDSPHK	2	HDSPHKA	4486

[0073] In some embodiments, the peptide comprises an amino acid sequence having the formula [N1]-[N2]-[N3], wherein [N2] comprises the amino acid sequence of SPH and [N3] comprises X4, X5, and X6, wherein at least one of X4, X5, or X6 is a basic amino acid, e.g., a K or R. In some embodiments, position X4 of [N2] is K. In some embodiments, position X5 of [N2] is K.

[0074] In some embodiments, [N1] comprises X1, X2, and X3, wherein at least one of X1, X2, or X3 is G. In some embodiments, position X1 of [N1] is G, V, R, D, E, M, T, I, S, A, N, L, K, H, P, W, or C. In some embodiments, position X2 of [N1] is: S, V, L, N, D, H, R, P, G, T, I, A, E, Y, M, or Q. In some embodiments, position X3 of [N1] is: G, C, L, D, E, Y, H, V, A, N, P, or S. In some

embodiments, [N1] comprises GS, SG, GH, HD, GQ, QD, VS, CS, GR, RG, QS, SH, MS, RN, TS, IS, GP, ES, SS, GN, AS, NS, LS, GG, KS, GT, PS, RS, GI, WS, DS, ID, GL, DA, DG, ME, EN, KN, KE, AI, NG, PG, TG, SV, IG, LG, AG, EG, SA, YD, HE, HG, RD, ND, PD, MG, QV, DD, HN, HP, GY, GM, GD, or HS. In some embodiments, [N1] comprises GS, SG, GH, or HD. In some embodiments [N1] is or comprises GSG, GHD, GQD, VSG, CSG, GRG, CSH, GQS, GSH, RVG, GSC, GLL, GDD, GHE, GNY, MSG, RNG, TSG, ISG, GPG, ESG, SSG, GNG, ASG, NSG, LSG, GGG, KSG, HSG, GTG, PSG, GSV, RSG, GIG, WSG, DSG, IDG, GLG, DAG, DGG, MEG, ENG, GSA, KNG, KEG, AIG, GYD, GHG, GRD, GND, GPD, GMG, GQV, GHN, GHP, or GHS. In some embodiments, [N1] is or comprises GSG. In some embodiments, [N1] is or comprises GHD. In some embodiments, [N1]-[N2] comprises SGSPH (SEQ ID NO: 4752), HDSPH (SEQ ID NO: 4703), QDSPH (SEQ ID NO: 4753), RGSPH (SEQ ID NO: 4754), SHSPH (SEQ ID NO: 4755), QSSPH (SEQ ID NO: 4756), DDSPH (SEQ ID NO: 4757), HESPH (SEQ ID NO: 4758), NYSPH (SEQ ID NO: 4759), VGSPH (SEQ ID NO: 4760), SCSPH (SEQ ID NO: 4761), LLSPH (SEQ ID NO: 4762), NGSPH (SEQ ID NO: 4763), PGSPH (SEQ ID NO: 4764), GGSPH (SEQ ID NO: 4765), TGSPH (SEQ ID NO: 4766), SVSPH (SEQ ID NO: 4767), IGSPH (SEQ ID NO: 4768), DGSPH (SEQ ID NO: 4769), LGSPH (SEQ ID NO: 4770), AGSPH (SEQ ID NO: 4771), EGSPH (SEQ ID NO: 4772), SASPH (SEQ ID NO: 4773), YDSPH (SEQ ID NO: 4774), HGSPH (SEQ ID NO: 4775), RDSPH (SEQ ID NO: 4776), NDSPH (SEQ ID NO: 4777), PDSPH (SEQ ID NO: 4778), MGSPH (SEQ ID NO: 4779), QVSPH (SEQ ID NO: 4780), HNSPH (SEQ ID NO: 4781), HPSPH (SEQ ID NO: 4782), or HSSPH (SEQ ID NO: 4783); an amino acid sequence comprising any portion of any of the aforesaid amino acid sequences (e.g., any 2, 3, or 4 amino acids, e.g., consecutive amino acids) thereof; an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the aforesaid amino acid sequences; or an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the aforesaid amino acid sequences. In some embodiments, [N1]-[N2] is or comprises GSGSPH (SEQ ID NO: 4695), GHDSPH (SEQ ID NO: 4784), GQDSPH (SEQ ID NO: 4785), VGSPH (SEQ ID NO: 4786), CSGSPH (SEQ ID NO: 4787), GRGSPH (SEQ ID NO: 4788), CSHSPH (SEQ ID NO: 4789), GQSSPH (SEQ ID NO: 4790), GSHSPH (SEQ ID NO: 4791), GDDSPH (SEQ ID NO: 4792), GHESPH (SEQ ID NO: 4793), GNYSPH (SEQ ID NO: 4794), RVGSPH (SEQ ID NO: 4795), GSCSPH (SEQ ID NO: 4796), GLLSPH (SEQ ID NO: 4797), MSGSPH (SEQ ID NO: 4798), RNGSPH (SEQ ID NO: 4799), TSGSPH (SEQ ID NO: 4800), ISGSPH (SEQ ID NO: 4801), GPGSPH (SEQ ID NO: 4802), ESGSPH (SEQ ID NO: 4803), SSGSPH (SEQ ID NO: 4804), GNGSPH (SEQ ID NO: 4805), ASGSPH (SEQ ID NO: 4806), NSGSPH (SEQ ID NO: 4807), LSGSPH (SEQ ID NO: 4808), GGGSPH (SEQ ID NO: 4809), KSGSPH (SEQ ID NO: 4810), HSGSPH (SEQ ID NO: 4811), GTGSPH (SEQ ID NO: 4812), PSGSPH (SEQ ID NO: 4813), GSVSPH (SEQ ID NO: 4814), RSGSPH (SEQ ID NO: 4815), GIGSPH (SEQ ID NO: 4816), WSGSPH (SEQ ID NO: 4817),

DSGSPH (SEQ ID NO: 4818), IDGSPH (SEQ ID NO: 4819), GLGSPH (SEQ ID NO: 4820), DAGSPH (SEQ ID NO: 4821), DGGSPH (SEQ ID NO: 4822), MEGSPH (SEQ ID NO: 4823), ENGSPH (SEQ ID NO: 4824), GSASPH (SEQ ID NO: 4825), KNGSPH (SEQ ID NO: 4826), KEGSPH (SEQ ID NO: 4827), AIGSPH (SEQ ID NO: 4828), GYDSPH (SEQ ID NO: 4829), GHGSPH (SEQ ID NO: 4830), GRDSPH (SEQ ID NO: 4831), GNDSPH (SEQ ID NO: 4832), GPDSPH (SEQ ID NO: 4833), GMGSPH (SEQ ID NO: 4834), GQVSPH (SEQ ID NO: 4835), GHNSPH (SEQ ID NO: 4836), GHPSPH (SEQ ID NO: 4837), or GHSSPH (SEQ ID NO: 4838); an amino acid sequence comprising any portion of any of the aforesaid amino acid sequences (e.g., any 2, 3, 4, or 5 amino acids, e.g., consecutive amino acids) thereof; an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the aforesaid amino acid sequences; or an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the aforesaid amino acid sequences. In some embodiments, [N1]-[N2] is or comprises GSGSPH (SEQ ID NO: 4695). In some embodiments, [N1]-[N2] is or comprises GHDSPH (SEQ ID NO: 4784).

[0075] In some embodiments, X4, X5, or both of [N3] are K. In some embodiments, X4, X5, or X6 of [N3] is R. In some embodiments, position X4 of [N3] is: A, K, V, S, T, G, F, W, V, N, or R. In some embodiments, position X5 of [N3] is: S, K, T, F, I, L, Y, H, M, or R. In some embodiments, position X6 of [N3] is: G, R, A, M, I, N, T, Y, D, P, V, L, E, W, N, Q, K, or S. In some embodiments, [N3] comprises SK, KA, KS, AR, RM, VK, AS, SR, VK, KR, KK, KN, VR, RS, RK, KT, TS, KF, FG, KI, IG, KL, LG, TT, TY, KY, YG, KD, KP, TR, RG, VR, GA, SL, SS, FL, WK, SA, RA, LR, KW, RR, GK, TK, NK, AK, KV, KG, KH, KM, TG, SE, SV, SW, SN, HG, SQ, LW, MG, MA, or SG. In some embodiments, [N3] comprises SK, KA, KS, or SG. In some embodiments, [N3] is or comprises SKA, KSG, ARM, VKS, ASR, VKI, KKN, VRM, RKA, KTS, KFG, KIG, KLG, KTT, KTY, KYG, SKD, SKP, TRG, VRG, KRG, GAR, KSA, KSR, SKL, SRA, SKR, SLR, SRG, SSR, FLR, SKW, SKS, WKA, VRR, SKV, SKT, SKG, GKA, TKA, NKA, SKL, SKN, AKA, KTG, KSL, KSE, KSV, KSW, KSN, KHG, KSQ, KSK, KLW, WKG, KMG, KMA, or RSG. In some embodiments, [N3] is or comprises SKA. In some embodiments, [N3] is or comprises KSG. In some embodiments, [N2]-[N3] comprises SPHSPH (SEQ ID NO: 4701), SPHKS (SEQ ID NO: 4704), SPHAR (SEQ ID NO: 4705), SPHVK (SEQ ID NO: 4706), SPHAS (SEQ ID NO: 4707), SPHKK (SEQ ID NO: 4708), SPHVR (SEQ ID NO: 4709), SPHRK (SEQ ID NO: 4710), SPHKT (SEQ ID NO: 4711), SPHKF (SEQ ID NO: 4712), SPHKI (SEQ ID NO: 4713), SPHKL (SEQ ID NO: 4714), SPHKY (SEQ ID NO: 4715), SPHTR (SEQ ID NO: 4716), SPHKR (SEQ ID NO: 4717), SPHGA (SEQ ID NO: 4718), SPHSR (SEQ ID NO: 4719), SPHSL (SEQ ID NO: 4720), SPHSS (SEQ ID NO: 4721), SPHFL (SEQ ID NO: 4722), SPHWK (SEQ ID NO: 4723), SPHGK (SEQ ID NO: 4724), SPHTK (SEQ ID NO: 4725), SPHNK (SEQ ID NO: 4726), SPHAK (SEQ ID NO: 4727), SPHKH (SEQ ID NO: 4728), SPHKM (SEQ ID NO: 4729), or SPHRS (SEQ ID NO: 4730). In some

embodiments [N2]-[N3] comprises SPHKS (SEQ ID NO: 4701) or SPHKS (SEQ ID NO: 4704). In some embodiments, [N2]-[N3] is or comprises SPHKA (SEQ ID NO: 941), SPHKS (SEQ ID NO: 946), SPHARM (SEQ ID NO: 947), SPHVKS (SEQ ID NO: 948), SPHASR (SEQ ID NO: 949), SPHVKI (SEQ ID NO: 950), SPHKKN (SEQ ID NO: 954), SPHVRM (SEQ ID NO: 955), SPHRKA (SEQ ID NO: 956), SPHKFG (SEQ ID NO: 957), SPHKIG (SEQ ID NO: 958), SPHKLG (SEQ ID NO: 959), SPHKTS (SEQ ID NO: 963), SPHKTT (SEQ ID NO: 964), SPHKTY (SEQ ID NO: 965), SPHKYG (SEQ ID NO: 966), SPHSD (SEQ ID NO: 967), SPHSDP (SEQ ID NO: 968), SPHTRG (SEQ ID NO: 972), SPHVRG (SEQ ID NO: 973), SPHKRG (SEQ ID NO: 974), SPHGAR (SEQ ID NO: 975), SPHKA (SEQ ID NO: 977), SPHKS (SEQ ID NO: 951), SPHSL (SEQ ID NO: 960), SPHSRA (SEQ ID NO: 969), SPHKS (SEQ ID NO: 978), SPHSLR (SEQ ID NO: 952), SPHSRG (SEQ ID NO: 961), SPHSS (SEQ ID NO: 970), SPHFLR (SEQ ID NO: 979), SPHKS (SEQ ID NO: 953), SPHKS (SEQ ID NO: 962), SPHWKA (SEQ ID NO: 971), SPHVRR (SEQ ID NO: 980), SPHKT (SEQ ID NO: 4731), SPHKS (SEQ ID NO: 4732), SPHGKA (SEQ ID NO: 4733), SPHNKA (SEQ ID NO: 4734), SPHKN (SEQ ID NO: 4735), SPHKA (SEQ ID NO: 4736), SPHKS (SEQ ID NO: 4737), SPHKTG (SEQ ID NO: 4738), SPHTKA (SEQ ID NO: 4739), SPHKS (SEQ ID NO: 4740), SPHKS (SEQ ID NO: 4741), SPHKS (SEQ ID NO: 4742), SPHKS (SEQ ID NO: 4743), SPHKS (SEQ ID NO: 4744), SPHKS (SEQ ID NO: 4745), SPHKS (SEQ ID NO: 4746), SPHKS (SEQ ID NO: 4747), SPHKLW (SEQ ID NO: 4748), SPHWKG (SEQ ID NO: 4749), SPHKMG (SEQ ID NO: 4750), SPHKMA (SEQ ID NO: 4751), or SPHRS (SEQ ID NO: 976). In some embodiments, [N2]-[N3] is or comprises SPHKA (SEQ ID NO: 941). In some embodiments, [N2]-[N3] is or comprises SPHKS (SEQ ID NO: 946).

[0076] In some embodiments, [N1]-[N2]-[N3] comprises SGSPHKS (SEQ ID NO: 4839), HDSPHKS (SEQ ID NO: 4840), SGSPHAR (SEQ ID NO: 4841), SGSPHVK (SEQ ID NO: 4842), QDSPHKS (SEQ ID NO: 4843), SGSPHKK (SEQ ID NO: 4844), SGSPHVR (SEQ ID NO: 4845), SGSPHAS (SEQ ID NO: 4846), SGSPHRK (SEQ ID NO: 4847), SGSPHKT (SEQ ID NO: 4848), SHSPHKS (SEQ ID NO: 4849), QSSPHRS (SEQ ID NO: 4850), RGSPHAS (SEQ ID NO: 4851), RGSPHKS (SEQ ID NO: 4852), SGSPHKF (SEQ ID NO: 4853), SGSPHKI (SEQ ID NO: 4854), SGSPHKL (SEQ ID NO: 4855), SGSPHKY (SEQ ID NO: 4856), SGSPHTR (SEQ ID NO: 4857), SHSPHKS (SEQ ID NO: 4858), SGSPHGA (SEQ ID NO: 4859), HDSPHKS (SEQ ID NO: 4860), DDSPHKS (SEQ ID NO: 4861), HESPHKS (SEQ ID NO: 4862), NYSPHKI (SEQ ID NO: 4863), SGSPHSR (SEQ ID NO: 4864), SGSPHSL (SEQ ID NO: 4865), SGSPHSS (SEQ ID NO: 4866), VGSPHKS (SEQ ID NO: 4867), SCSPHRK (SEQ ID NO: 4868), SGSPHFL (SEQ ID NO: 4869), LLSPHWK (SEQ ID NO: 4870), NGSPHKS (SEQ ID NO: 4871), PGSPHKS (SEQ ID NO: 4872), GGSPHKS (SEQ ID NO: 4873), TGSPHKS (SEQ ID NO: 4874), SVSPHGK (SEQ ID NO: 4875), SGSPHTK (SEQ ID NO: 4876), IGSPHKS (SEQ ID NO: 4877), DGSPHKS (SEQ ID NO: 4878), SGSPHNS (SEQ ID NO: 4879), LGSPHKS (SEQ ID NO: 4880), AGSPHKS (SEQ ID NO: 4881), EGSPHKS (SEQ ID NO: 4882), SASPHKS (SEQ ID NO: 4883), SGSPHAK (SEQ ID NO: 4884),

HDSPHKI (SEQ ID NO: 4885), YDSPHKS (SEQ ID NO: 4886), HDSPHKT (SEQ ID NO: 4887), RGSPHKR (SEQ ID NO: 4888), HGSPHSK (SEQ ID NO: 4889), RDSPHKS (SEQ ID NO: 4890), NDSPHKS (SEQ ID NO: 4891), QDSPHKI (SEQ ID NO: 4892), PDSPHKI (SEQ ID NO: 4893), PDSPHKS (SEQ ID NO: 4894), MGSPHSK (SEQ ID NO: 4895), HDSPHKH (SEQ ID NO: 4896), QVSPHKS (SEQ ID NO: 4897), HNSPHKS (SEQ ID NO: 4898), NGSPHKR (SEQ ID NO: 4899), HDSPHKY (SEQ ID NO: 4900), NDSPHKI (SEQ ID NO: 4901), HDSPHKL (SEQ ID NO: 4902), HPSPHWK (SEQ ID NO: 4903), HDSPHKM (SEQ ID NO: 4904), or HSSPHRS (SEQ ID NO: 4905). In some embodiments, [N1]-[N2]-[N3] is GSGSPHKA (SEQ ID NO: 4697), GHDSPHKSG (SEQ ID NO: 4698), GSGSPHARM (SEQ ID NO: 4906), GSGSPHVKS (SEQ ID NO: 4907), GQDSPHKSG (SEQ ID NO: 4908), GSGSPHASR (SEQ ID NO: 4909), GSGSPHVKI (SEQ ID NO: 4910), GSGSPHKKN (SEQ ID NO: 4911), GSGSPHVRM (SEQ ID NO: 4912), VSGSPHKA (SEQ ID NO: 4913), CSGSPHKA (SEQ ID NO: 4914), GSGSPHRKA (SEQ ID NO: 4915), CSGSPHKTS (SEQ ID NO: 4916), CSHSPHKSG (SEQ ID NO: 4917), GQSSPHRSG (SEQ ID NO: 4918), GRGSPHASR (SEQ ID NO: 4919), GRGSPHKA (SEQ ID NO: 4920), GSGSPHKFG (SEQ ID NO: 4921), GSGSPHKIG (SEQ ID NO: 4922), GSGSPHKLK (SEQ ID NO: 4923), GSGSPHKTS (SEQ ID NO: 4924), GSGSPHKTT (SEQ ID NO: 4925), GSGSPHKTY (SEQ ID NO: 4926), GSGSPHKYG (SEQ ID NO: 4927), GSGSPHSD (SEQ ID NO: 4928), GSGSPHSP (SEQ ID NO: 4929), GSGSPHTRG (SEQ ID NO: 4930), GSGSPHVRG (SEQ ID NO: 4931), GSHSPHKRG (SEQ ID NO: 4932), GSHSPHKSG (SEQ ID NO: 4933), VSGSPHASR (SEQ ID NO: 4934), VSGSPHGAR (SEQ ID NO: 4935), VSGSPHKFG (SEQ ID NO: 4936), GHDSPHKRG (SEQ ID NO: 4937), GDDSPHKSG (SEQ ID NO: 4938), GHESPHKSA (SEQ ID NO: 4939), GHDSPHKSA (SEQ ID NO: 4940), GNYSPHKIG (SEQ ID NO: 4941), GHDSPHKSR (SEQ ID NO: 4942), GSGSPHKL (SEQ ID NO: 4943), GSGSPHSRA (SEQ ID NO: 4944), GSGSPHSP (SEQ ID NO: 4945), GSGSPHSLR (SEQ ID NO: 4946), GSGSPHSRG (SEQ ID NO: 4947), GSGSPHSSR (SEQ ID NO: 4948), RVGSPHKA (SEQ ID NO: 4949), GSCSPHRKA (SEQ ID NO: 4950), GSGSPHFLR (SEQ ID NO: 4951), GSGSPHSP (SEQ ID NO: 4952), GSGSPHSP (SEQ ID NO: 4953), GLLSPHWKA (SEQ ID NO: 4954), GSGSPHVRR (SEQ ID NO: 4955), GSGSPHSP (SEQ ID NO: 4956), MSGSPHKA (SEQ ID NO: 4957), RNGSPHKA (SEQ ID NO: 4958), TSGSPHKA (SEQ ID NO: 4959), ISGSPHKA (SEQ ID NO: 4960), GPGSPHKA (SEQ ID NO: 4961), GSGSPHSP (SEQ ID NO: 4962), ESGSPHKA (SEQ ID NO: 4963), SSGSPHKA (SEQ ID NO: 4964), GNGSPHKA (SEQ ID NO: 4965), ASGSPHKA (SEQ ID NO: 4966), NSGSPHKA (SEQ ID NO: 4967), LSGSPHKA (SEQ ID NO: 4968), GGGSPHKA (SEQ ID NO: 4969), KSGSPHKA (SEQ ID NO: 4970), GGGSPHSP (SEQ ID NO: 4971), GSGSPHSP (SEQ ID NO: 4972), HSGSPHKA (SEQ ID NO: 4973), GTGSPHKA (SEQ ID NO: 4974), PSGSPHKA (SEQ ID NO: 4975), GSVSPHGKA (SEQ ID NO: 4976), RSGSPHKA (SEQ ID NO: 4977), GSGSPHTKA (SEQ ID NO: 4978), GIGSPHKA (SEQ ID NO: 4979), WSGSPHKA (SEQ ID NO: 4980), DSGSPHKA (SEQ ID NO: 4981), IDGSPHKA (SEQ ID NO: 4982),

GSGSPHNKA (SEQ ID NO: 4983), GLGSPHSKS (SEQ ID NO: 4984), DAGSPHKA (SEQ ID NO: 4985), DGGSPHKA (SEQ ID NO: 4986), MEGSPHKA (SEQ ID NO: 4987), ENGSPHKA (SEQ ID NO: 4988), GSASPHKA (SEQ ID NO: 4989), GNGSPHSKS (SEQ ID NO: 4990), KNGSPHKA (SEQ ID NO: 4991), KEGSPHKA (SEQ ID NO: 4992), AIGSPHKA (SEQ ID NO: 4993), GSGSPHSKN (SEQ ID NO: 4994), GSGSPHAKA (SEQ ID NO: 4995), GHDSPHKIG (SEQ ID NO: 4996), GYDSPHKS (SEQ ID NO: 4997), GHESPHKS (SEQ ID NO: 4998), GHDSPHKTG (SEQ ID NO: 4999), GRGSPHKRG (SEQ ID NO: 5000), GQDSPHKS (SEQ ID NO: 4908), GHDSPHKSL (SEQ ID NO: 5001), GHGSPHKA (SEQ ID NO: 5002), GHDSPHKSE (SEQ ID NO: 5003), VSGSPHKA (SEQ ID NO: 4913), GRDSPHKS (SEQ ID NO: 5004), GNDSPHKS (SEQ ID NO: 5005), GQDSPHKIG (SEQ ID NO: 5006), GHDSPHKS (SEQ ID NO: 5007), GPDSPHKIG (SEQ ID NO: 5008), GPDSPHKS (SEQ ID NO: 5009), GHDSPHKS (SEQ ID NO: 5010), GHDSPHKS (SEQ ID NO: 5011), GMGSPHKS (SEQ ID NO: 5012), GHDSPHKS (SEQ ID NO: 5013), GQVSPHKS (SEQ ID NO: 5014), GDDSPHKS (SEQ ID NO: 5015), GHNSPHKS (SEQ ID NO: 5016), GNGSPHKS (SEQ ID NO: 5017), GHDSPHKS (SEQ ID NO: 5018), GHDSPHKS (SEQ ID NO: 5019), GNDSPHKS (SEQ ID NO: 5020), GHDSPHKS (SEQ ID NO: 5021), GHDSPHKS (SEQ ID NO: 5022), GHSPHWS (SEQ ID NO: 5023), GHDSPHKS (SEQ ID NO: 5024), GHDSPHKS (SEQ ID NO: 5025), or GHSSPHRS (SEQ ID NO: 5026); an amino acid sequence comprising any portion of any of the aforesaid amino acid sequences (e.g., any 2, 3, 4, 5, 6, 7, or 8 amino acids, e.g., consecutive amino acids) thereof; an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the aforesaid amino acid sequences; or an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the aforesaid amino acid sequences. In some embodiments, [N1]-[N2]-[N3] is or comprises GSGSPHKA (SEQ ID NO: 4697). In some embodiments, [N1]-[N2]-[N3] is or comprises GHDSPHKS (SEQ ID NO: 4698).

[0077] In some embodiments, the peptide comprising an amino acid sequence having the formula [N1]-[N2]-[N3], further comprises [N4] which comprises X7 X8 X9 X10. In some embodiments, position X7 of [N4] is W, Q, K, R, G, L, V, S, P, H, K, I, M, A, E, or F. In some embodiments, position X8 of [N4] is N, Y, C, K, T, H, R, D, V, S, P, G, W, E, F, A, I, M, Q, or L. In some embodiments, position X9 of [N4] is Q, G, K, H, R, T, L, D, A, P, I, F, V, M, W, Y, S, E, N, or Y. In some embodiments, position X10 of [N4] is Q, H, L, R, W, K, A, P, E, M, I, S, G, N, Y, C, V, T, D, or V. In some embodiments [N4] is or comprises QNQQ (SEQ ID NO: 5028), WNQQ (SEQ ID NO: 5029), QYYV (SEQ ID NO: 5030), RRQQ (SEQ ID NO: 5031), QNQQ (SEQ ID NO: 5028), GCGQ (SEQ ID NO: 5032), LRQQ (SEQ ID NO: 5033), RNQQ (SEQ ID NO: 5034), VNQQ (SEQ ID NO: 5035), FRLQ (SEQ ID NO: 5036), FNQQ (SEQ ID NO: 5037), LLQQ (SEQ ID NO: 5038), SNQQ (SEQ ID NO: 5039), RLQQ (SEQ ID NO: 5040), LNQQ (SEQ ID NO: 5041), QRKL (SEQ ID NO: 5042), LRRQ (SEQ ID NO: 5043), QRLR (SEQ ID NO: 5044), QRRL (SEQ ID NO: 5045), RRLQ

(SEQ ID NO: 5046), RLRQ (SEQ ID NO: 5047), SKRQ (SEQ ID NO: 5048), QLYR (SEQ ID NO: 5049), QLTV (SEQ ID NO: 5050), QNKQ (SEQ ID NO: 5051), KNQQ (SEQ ID NO: 5052), QKQQ (SEQ ID NO: 5053), QTQQ (SEQ ID NO: 5054), QNHQ (SEQ ID NO: 5055), QHQQ (SEQ ID NO: 5056), QNQH (SEQ ID NO: 5057), QHRQ (SEQ ID NO: 5058), LTQQ (SEQ ID NO: 5059), QNQW (SEQ ID NO: 5060), QNTH (SEQ ID NO: 5061), RRRQ (SEQ ID NO: 5062), QYQQ (SEQ ID NO: 5063), QNDQ (SEQ ID NO: 5064), QNRH (SEQ ID NO: 5065), RDQQ (SEQ ID NO: 5066), PNLQ (SEQ ID NO: 5067), HVRQ (SEQ ID NO: 5068), PNQH (SEQ ID NO: 5069), HNQQ (SEQ ID NO: 5070), QSQQ (SEQ ID NO: 5071), QPAK (SEQ ID NO: 5072), QNLA (SEQ ID NO: 5073), QNQL (SEQ ID NO: 5074), QGQQ (SEQ ID NO: 5075), LNRQ (SEQ ID NO: 5076), QNPP (SEQ ID NO: 5077), QNLQ (SEQ ID NO: 5078), QDQE (SEQ ID NO: 5079), QDQQ (SEQ ID NO: 5080), HWQQ (SEQ ID NO: 5081), PNQQ (SEQ ID NO: 5082), PEQQ (SEQ ID NO: 5083), QRTM (SEQ ID NO: 5084), LHQH (SEQ ID NO: 5085), QHRI (SEQ ID NO: 5086), QYIH (SEQ ID NO: 5087), QKFE (SEQ ID NO: 5088), QFPS (SEQ ID NO: 5089), QNPL (SEQ ID NO: 5090), QAIK (SEQ ID NO: 5091), QNRQ (SEQ ID NO: 5092), QYQH (SEQ ID NO: 5093), QNPQ (SEQ ID NO: 5094), QHQL (SEQ ID NO: 5095), QSPP (SEQ ID NO: 5096), QAKL (SEQ ID NO: 5097), KSQQ (SEQ ID NO: 5098), QDRP (SEQ ID NO: 5099), QNLG (SEQ ID NO: 5100), QAFH (SEQ ID NO: 5101), QNAQ (SEQ ID NO: 5102), HNQL (SEQ ID NO: 5103), QKLN (SEQ ID NO: 5104), QNVQ (SEQ ID NO: 5105), QAAQ (SEQ ID NO: 5106), QTPP (SEQ ID NO: 5107), QPPA (SEQ ID NO: 5108), QERP (SEQ ID NO: 5109), QDLQ (SEQ ID NO: 5110), QAMH (SEQ ID NO: 5111), QHPS (SEQ ID NO: 5112), PGLQ (SEQ ID NO: 5113), QGIR (SEQ ID NO: 5114), QAPA (SEQ ID NO: 5115), QIPP (SEQ ID NO: 5116), QTQL (SEQ ID NO: 5117), QAPS (SEQ ID NO: 5118), QNTY (SEQ ID NO: 5119), QDKQ (SEQ ID NO: 5120), QNHL (SEQ ID NO: 5121), QIGM (SEQ ID NO: 5122), LNKQ (SEQ ID NO: 5123), PNQL (SEQ ID NO: 5124), QLQQ (SEQ ID NO: 5125), QRMS (SEQ ID NO: 5126), QGIL (SEQ ID NO: 5127), QDRQ (SEQ ID NO: 5128), RDWQ (SEQ ID NO: 5129), QERS (SEQ ID NO: 5130), QNYQ (SEQ ID NO: 5131), QRTC (SEQ ID NO: 5132), QIGH (SEQ ID NO: 5133), QGAI (SEQ ID NO: 5134), QVPP (SEQ ID NO: 5135), QVQQ (SEQ ID NO: 5136), LMRQ (SEQ ID NO: 5137), QYSV (SEQ ID NO: 5138), QAIT (SEQ ID NO: 5139), QKTL (SEQ ID NO: 5140), QLHH (SEQ ID NO: 5141), QNII (SEQ ID NO: 5142), QGHH (SEQ ID NO: 5143), QSKV (SEQ ID NO: 5144), QLPS (SEQ ID NO: 5145), IGKQ (SEQ ID NO: 5146), QAIH (SEQ ID NO: 5147), QHGL (SEQ ID NO: 5148), QFMC (SEQ ID NO: 5149), QNQM (SEQ ID NO: 5150), QHLQ (SEQ ID NO: 5151), QPAR (SEQ ID NO: 5152), QSLQ (SEQ ID NO: 5153), QSQL (SEQ ID NO: 5154), HSQQ (SEQ ID NO: 5155), QMPS (SEQ ID NO: 5156), QGSL (SEQ ID NO: 5157), QVPA (SEQ ID NO: 5158), HYQQ (SEQ ID NO: 5159), QVPS (SEQ ID NO: 5160), RGEQ (SEQ ID NO: 5161), PGQQ (SEQ ID NO: 5162), LEQQ (SEQ ID NO: 5163), QNQS (SEQ ID NO: 5164), QKVI (SEQ ID NO: 5165), QNND (SEQ ID NO: 5166), QSVH (SEQ ID NO: 5167), QPLG (SEQ ID NO: 5168), HNQE (SEQ ID NO: 5169), QIQQ (SEQ ID NO: 5170), QVRN (SEQ ID NO: 5171), PSNQ (SEQ ID NO: 5172), QVGH (SEQ ID NO: 5173), QRDI (SEQ ID NO: 5174), QMPN (SEQ

ID NO: 5175), RGLQ (SEQ ID NO: 5176), PSLQ (SEQ ID NO: 5177), QRDQ (SEQ ID NO: 5178), QAKG (SEQ ID NO: 5179), QSAH (SEQ ID NO: 5180), QSTM (SEQ ID NO: 5181), QREM (SEQ ID NO: 5182), QYRA (SEQ ID NO: 5183), QRQQ (SEQ ID NO: 5184), QWQQ (SEQ ID NO: 5185), QRMN (SEQ ID NO: 5186), GDSQ (SEQ ID NO: 5187), QKIS (SEQ ID NO: 5188), PSMQ (SEQ ID NO: 5189), SPRQ (SEQ ID NO: 5190), MEQQ (SEQ ID NO: 5191), QYQN (SEQ ID NO: 5192), QIRQ (SEQ ID NO: 5193), QSVQ (SEQ ID NO: 5194), RSQQ (SEQ ID NO: 5195), QNKL (SEQ ID NO: 5196), QIQH (SEQ ID NO: 5197), PRQQ (SEQ ID NO: 5198), HTQQ (SEQ ID NO: 5199), QRQH (SEQ ID NO: 5200), RNQE (SEQ ID NO: 5201), QSKQ (SEQ ID NO: 5202), QNQP (SEQ ID NO: 5203), QSPQ (SEQ ID NO: 5204), QTRQ (SEQ ID NO: 5205), QNLH (SEQ ID NO: 5206), QNQE (SEQ ID NO: 5207), LNQP (SEQ ID NO: 5208), QNQD (SEQ ID NO: 5209), QNLL (SEQ ID NO: 5210), QLVI (SEQ ID NO: 5211), RTQE (SEQ ID NO: 5212), QTHQ (SEQ ID NO: 5213), QDQH (SEQ ID NO: 5214), QSQH (SEQ ID NO: 5215), VRQQ (SEQ ID NO: 5216), AWQQ (SEQ ID NO: 5217), QSVQ (SEQ ID NO: 5218), QNIQ (SEQ ID NO: 5219), LDQQ (SEQ ID NO: 5220), PDQQ (SEQ ID NO: 5221), ESQQ (SEQ ID NO: 5222), QRQL (SEQ ID NO: 5223), QIIV (SEQ ID NO: 5224), QKQS (SEQ ID NO: 5225), QSHQ (SEQ ID NO: 5226), QFVV (SEQ ID NO: 5227), QSQP (SEQ ID NO: 5228), QNEQ (SEQ ID NO: 5229), INQQ (SEQ ID NO: 5230), RNRQ (SEQ ID NO: 5231), RDQK (SEQ ID NO: 5232), QWKR (SEQ ID NO: 5233), ENRQ (SEQ ID NO: 5234), QTQP (SEQ ID NO: 5235), QKQL (SEQ ID NO: 5236), RNQL (SEQ ID NO: 5237), ISIQ (SEQ ID NO: 5238), QTVC (SEQ ID NO: 5239), QQIM (SEQ ID NO: 5240), LNHQ (SEQ ID NO: 5241), QNQA (SEQ ID NO: 5242), QMIH (SEQ ID NO: 5243), RNHQ (SEQ ID NO: 5244), or QKMN (SEQ ID NO: 5245), or any dipeptide or tripeptide thereof. In some embodiments, [N1]-[N2]-[N3]-[N4] is or comprises: the amino acid sequence of any of SEQ ID NOs: 1800-2241; an amino acid sequence comprising any portion of any of the aforesaid amino acid sequences (e.g., any 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 amino acids, e.g., consecutive amino acids) thereof; an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the aforesaid amino acid sequences; or an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the aforesaid amino acid sequences. In some embodiments, [N1]-[N2]-[N3]-[N4] is or comprises GSGSPHKAQNQQ (SEQ ID NO: 1801). In some embodiments, [N1]-[N2]-[N3]-[N4] is or comprises GHDSPHKSGQNQQ (SEQ ID NO: 1800).

[0078] In some embodiments, the peptide comprising an amino acid sequence having the formula [N1]-[N2]-[N3], further comprises [N0], which comprises XA XB and XC. In some embodiments, XA of [N0] is T, S, Y, M, A, C, I, R, L, D, F, V, Q, N, H, E, or G. In some embodiments, XB of [N0] is I, M, P, E, N, D, S, A, T, G, Q, F, V, L, C, H, R, W, or L. In some embodiments, XC of [N0] is N, M, E, G, Y, W, T, I, Q, F, V, A, L, I, P, K, R, H, S, D, or S. In some embodiments, [N0] is or comprises TIN, SMN, TIM, YLS, GLS, MPE, MEG, MEY, AEW, CEW, ANN, IPE, ADM, IEY, ADY, IET, MEW, CEY, RIN, MEI, LEY, ADW, IEI, DIM, FEQ, MEF, CDQ, LPE, IEN, MES, AEI,

VEY, IIN, TSN, IEV, MEM, AEV, MDA, VEW, AEQ, LEW, MEL, MET, MEA, IES, MEV, CEI, ATN, MDG, QEV, ADQ, NMN, IEM, ISN, TGN, QQQ, HDW, IEG, TII, TFP, TEK, EIN, TVN, TFN, SIN, TER, TSY, ELH, AIN, SVN, TDN, TFH, TVH, TEN, TSS, TID, TCN, NIN, TEH, AEM, AIK, TDK, TFK, SDQ, TEL, NTN, TET, SIK, TEL, TEA, TAN, TIY, TFS, TES, TTN, TED, TNN, EVH, TIS, TVR, TDR, TIK, NHI, TIP, ESD, TDL, TVP, TVI, AEH, NCL, TVK, NAD, TIT, NCV, TIR, NAL, VIN, TIQ, TEF, TRE, QGE, SEK, NVN, GGE, EFV, SDK, TEQ, EVQ, TEY, NCW, TDV, SDI, NSI, NSL, EVV, TEP, SEL, TWQ, TEV, AVN, GVL, TLN, TEG, TRD, NAI, AEN, AET, ETA, NNL, or any dipeptide thereof. In some embodiments, [N0]-[N1]-[N2]-[N3]-[N4] is or comprises the amino acid sequence of any one of SEQ ID NOs: 2242-2886; an amino acid sequence comprising any portion of any of the aforesaid amino acid sequences (e.g., any 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 amino acids, e.g., consecutive amino acids) thereof; an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the aforesaid amino acid sequences; or an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the aforesaid amino acid sequences. In some embodiments, [N0]-[N1]-[N2]-[N3]-[N4] is or comprises TINGSGSPHKAQNQQ (SEQ ID NO: 2242). In some embodiments, [N0]-[N1]-[N2]-[N3]-[N4] is or comprises TINGHDSPHKSGQNQQ (SEQ ID NO: 2243).

[0079] In some embodiments, [N3] is present immediately subsequent to [N2]. In some embodiments, the peptide comprises from N-terminus to C-terminus, [N2]-[N3]. In some embodiments, the peptide comprises from N-terminus to C-terminus, [N1]-[N2]-[N3]. In some embodiments, the peptide comprises from N-terminus to C-terminus, [N1]-[N2]-[N3]-[N4]. In some embodiments, the peptide comprises from N-terminus to C-terminus, [N0]-[N1]-[N2]-[N3]. In some embodiments, the peptide comprises from N-terminus to C-terminus, [N0]-[N1]-[N2]-[N3]-[N4].

[0080] In some embodiments, the peptide comprises an amino acid sequence having the formula [A][B] (SEQ ID NO: 4694), wherein [A] comprises the amino acid sequence of GSGSPH (SEQ ID NO: 4695) and [B] comprises X1 X2 X3 X4 X5 X6 X7. In some embodiments, position X1 of [B] is S, C, F, or V. In some embodiments, position X2 of [B] is K, L, R, I, E, Y, V, or S. In some embodiments, X3 of [B] is A, R, L, G, I, Y, S, F, or W. In some embodiments X4 of [B] is W, Q, R, G, L, V, S, or F. In some embodiments, position X5 of [B] is N, Y, R, C, K, or L. In some embodiments, position X6 of [B] is Q, G, K, R, T, L, or Y. In some embodiment, position X7 of [B] is Q, L, R, or V. In some embodiments, [B] comprises S LLWNQQ (SEQ ID NO: 5247), SKAQYYV (SEQ ID NO: 5248), SKLRRQQ (SEQ ID NO: 5249), SIWQNQQ (SEQ ID NO: 5250), SKAGCGQ (SEQ ID NO: 5251), SRAQNQQ (SEQ ID NO: 5252), SKRLRQQ (SEQ ID NO: 5253), SLRRNQQ (SEQ ID NO: 5254), SRGRNQQ (SEQ ID NO: 5255), SEIVNQQ (SEQ ID NO: 5256), SSRRNQQ (SEQ ID NO: 5257), CLLQNQQ (SEQ ID NO: 5258), SKAFRLQ (SEQ ID NO: 5259),

CLAQNQQ (SEQ ID NO: 5260), FLRQNQQ (SEQ ID NO: 5261), SLRFNQQ (SEQ ID NO: 5262), SYLRNQQ (SEQ ID NO: 5263), CSLQNQQ (SEQ ID NO: 5264), VLWQNQQ (SEQ ID NO: 5265), SKWLLQQ (SEQ ID NO: 5266), SLWSNQQ (SEQ ID NO: 5267), SKRRLQQ (SEQ ID NO: 5268), SVYLNQQ (SEQ ID NO: 5269), SLWLNQQ (SEQ ID NO: 5270), SKAQRKL (SEQ ID NO: 5271), SKALRRQ (SEQ ID NO: 5272), SKAQRLR (SEQ ID NO: 5273), SKAQNQQ (SEQ ID NO: 5274), SKAQRRQ (SEQ ID NO: 5275), SKARRQQ (SEQ ID NO: 5276), SKARRLQ (SEQ ID NO: 5277), SKSRRQQ (SEQ ID NO: 5278), SKARLRQ (SEQ ID NO: 5279), SKASKRQ (SEQ ID NO: 5280), VRRQNQQ (SEQ ID NO: 5281), SKAQLYR (SEQ ID NO: 5282), SLFRNQQ (SEQ ID NO: 5283), SKAQLTV (SEQ ID NO: 5284), or any dipeptide, tripeptide, tetrapeptide, pentapeptide, or hexapeptide thereof. In some embodiments, [A][B] comprises GSGSPHSLLWNQQ (SEQ ID NO: 5285), GSGSPHKAQYYV (SEQ ID NO: 2060), GSGSPHSLRRQQ (SEQ ID NO: 2061), GSGSPHSIWQNQQ (SEQ ID NO: 5286), GSGSPHSGAGCGQ (SEQ ID NO: 2062), GSGSPHSRAQNQQ (SEQ ID NO: 2063), GSGSPHSLRRQQ (SEQ ID NO: 2064), GSGSPHSLRRNQQ (SEQ ID NO: 2065), GSGSPHSRGRNQQ (SEQ ID NO: 2066), GSGSPHSEIVNQQ (SEQ ID NO: 5287), GSGSPHSSRRNQQ (SEQ ID NO: 2067), GSGSPHCLLNQQ (SEQ ID NO: 5288), GSGSPHKAFLRQ (SEQ ID NO: 2068), GSGSPHCLAQNQQ (SEQ ID NO: 5289), GSGSPHFLRQNQQ (SEQ ID NO: 2070), GSGSPHSLRFNQQ (SEQ ID NO: 2071), GSGSPHSYLRNQQ (SEQ ID NO: 5290), GSGSPHCSLNQQ (SEQ ID NO: 5291), GSGSPHVLWQNQQ (SEQ ID NO: 5292), GSGSPHSLWLLQQ (SEQ ID NO: 2072), GSGSPHSLWSNQQ (SEQ ID NO: 5293), GSGSPHSLRRQQ (SEQ ID NO: 2073), GSGSPHSVYLNQQ (SEQ ID NO: 5294), GSGSPHSLWLNQQ (SEQ ID NO: 5295), GSGSPHKAQRKL (SEQ ID NO: 2074), GSGSPHSLRRQ (SEQ ID NO: 2075), GSGSPHKAQRLR (SEQ ID NO: 2076), GSGSPHKAQNQQ (SEQ ID NO: 1801), GSGSPHKAQRRQ (SEQ ID NO: 2077), GSGSPHSLRRQQ (SEQ ID NO: 2078), GSGSPHSLRRQ (SEQ ID NO: 2079), GSGSPHSLRRQQ (SEQ ID NO: 2080), GSGSPHSLRRQ (SEQ ID NO: 2082), GSGSPHSLRRQ (SEQ ID NO: 2083), GSGSPHSLRRQ (SEQ ID NO: 2084), GSGSPHSLRRQ (SEQ ID NO: 2085), GSGSPHSLRRQ (SEQ ID NO: 5296), GSGSPHSLRRQ (SEQ ID NO: 2086), or any portion thereof, e.g., any 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 amino acids, e.g., consecutive amino acids, thereof. In some embodiments, [B] is present immediately subsequent to [A]. In some embodiments, the peptide comprises from N-terminus to C-terminus, [A][B].

[0081] In some embodiments, the peptide comprises an amino acid sequence having the formula [A][B] (SEQ ID NO: 4699), wherein [A] comprises X1 X2 X3 X4 X5 X6 and [B] comprises SPHKSG (SEQ ID NO: 946). In some embodiments, position X1 of [A] is T, M, A, C, I, R, L, D, F, V, Q, N, or H. In some embodiments, position X2 of [A] is I, P, E, N, D, S, A, T, M, or Q. In some embodiments, position X3 of [A] is N, E, G, Y, W, M, T, I, K, Q, F, S, V, A, or L. In some

embodiments, position X4 of [A] is G, D, R, or E. In some embodiments, position X5 of [A] is H, Q, N, or D. In some embodiments, position X6 of [A] is D or R. In some embodiments, [A] comprises TINGHD (SEQ ID NO: 5297), MPEGHD (SEQ ID NO: 5298), MEGGHD (SEQ ID NO: 5299), MEYGHHD (SEQ ID NO: 5300), AEWGHD (SEQ ID NO: 5301), CEWGHD (SEQ ID NO: 5302), ANNGQD (SEQ ID NO: 5303), IPEGHD (SEQ ID NO: 5304), ADMGHD (SEQ ID NO: 5305), IEYGHHD (SEQ ID NO: 5306), ADYGHHD (SEQ ID NO: 5307), IETGHHD (SEQ ID NO: 5308), MEWGHD (SEQ ID NO: 5309), CEYGHHD (SEQ ID NO: 5310), RINGHD (SEQ ID NO: 5311), MEIGHHD (SEQ ID NO: 5312), LEYGHHD (SEQ ID NO: 5313), ADWGHHD (SEQ ID NO: 5314), IEIGHHD (SEQ ID NO: 5315), TIKDND (SEQ ID NO: 5316), DIMGHHD (SEQ ID NO: 5317), FEQGHHD (SEQ ID NO: 5318), MEFGHHD (SEQ ID NO: 5319), CDQGHHD (SEQ ID NO: 5320), LPEGHD (SEQ ID NO: 5321), IENGHD (SEQ ID NO: 5322), MESGHHD (SEQ ID NO: 5323), AEIGHHD (SEQ ID NO: 5324), VEYGHHD (SEQ ID NO: 5325), TSNGDD (SEQ ID NO: 5326), IEVGHHD (SEQ ID NO: 5327), MEMGHHD (SEQ ID NO: 5328), AEVGHHD (SEQ ID NO: 5329), MDAGHD (SEQ ID NO: 5330), VEWGHHD (SEQ ID NO: 5331), AEQGHHD (SEQ ID NO: 5332), LEWGHHD (SEQ ID NO: 5333), MELGHHD (SEQ ID NO: 5334), METGHHD (SEQ ID NO: 5335), MEAGHD (SEQ ID NO: 5336), TINRQR (SEQ ID NO: 5337), IESGHHD (SEQ ID NO: 5338), TAKDHD (SEQ ID NO: 5339), MEVGHHD (SEQ ID NO: 5340), CEIGHHD (SEQ ID NO: 5341), ATNGHD (SEQ ID NO: 5342), MDGGHD (SEQ ID NO: 5343), QEVGHHD (SEQ ID NO: 5344), ADQGHHD (SEQ ID NO: 5345), NMNGHD (SEQ ID NO: 5346), TPWEHD (SEQ ID NO: 5347), IEMGHHD (SEQ ID NO: 5348), TANEHD (SEQ ID NO: 5349), QQQGHHD (SEQ ID NO: 5350), TPQDHD (SEQ ID NO: 5351), HDWGHHD (SEQ ID NO: 5352), IEGGHHD (SEQ ID NO: 5353), or any dipeptide, tripeptide, tetrapeptide, or pentapeptide thereof. In some embodiments, [A][B] comprises TINGHDSPHKR (SEQ ID NO: 5354), MPEGHDSPHKS (SEQ ID NO: 5355), MEGGHDSPHKS (SEQ ID NO: 5356), MEYGHDSPHKS (SEQ ID NO: 5357), AEWGHDSPHKS (SEQ ID NO: 5358), CEWGHDSPHKS (SEQ ID NO: 5359), ANNGQDSPHKS (SEQ ID NO: 5360), IPEGHDSPHKS (SEQ ID NO: 5361), ADMGHDSPHKS (SEQ ID NO: 5362), IEYGHDSPHKS (SEQ ID NO: 5363), ADYGHDSPHKS (SEQ ID NO: 5364), IETGHDSPHKS (SEQ ID NO: 5365), MEWGHDSPHKS (SEQ ID NO: 5366), CEYGHDSPHKS (SEQ ID NO: 5367), RINGHDSPHKS (SEQ ID NO: 5368), MEIGHDSPHKS (SEQ ID NO: 5369), LEYGHDSPHKS (SEQ ID NO: 5370), ADWGHDSPHKS (SEQ ID NO: 5371), IEIGHDSPHKS (SEQ ID NO: 5372), TIKDNDSPHKS (SEQ ID NO: 5373), DIMGHDSPHKS (SEQ ID NO: 5374), FEQGHDSPHKS (SEQ ID NO: 5375), MEFGHDSPHKS (SEQ ID NO: 5376), CDQGHDSPHKS (SEQ ID NO: 5377), LPEGHDSPHKS (SEQ ID NO: 5378), IENGHDSPHKS (SEQ ID NO: 5379), MESGHDSPHKS (SEQ ID NO: 5380), AEIGHDSPHKS (SEQ ID NO: 5381), VEYGHDSPHKS (SEQ ID NO: 5382), TSNGDDSPHKS (SEQ ID NO: 5383), IEVGHDSPHKS (SEQ ID NO: 5384), MEMGHDSPHKS (SEQ ID NO: 5385), AEVGHDSPHKS (SEQ ID NO: 5386), MDAGHDSPHKS (SEQ ID NO: 5387), VEWGHDSPHKS (SEQ ID NO: 5388), AEQGHDSPHKS (SEQ ID NO: 5389), LEWGHDSPHKS (SEQ ID NO: 5390),

MELGHDSPHKS (SEQ ID NO: 5391), METGHDSPHKS (SEQ ID NO: 5392), MEAGHDSPHKS (SEQ ID NO: 5393), TINRQRSPHKS (SEQ ID NO: 5394), IESGHDSPHKS (SEQ ID NO: 5395), TAKDHDSPHKS (SEQ ID NO: 5396), MEVGHDSPHKS (SEQ ID NO: 5397), CEIGHDSPHKS (SEQ ID NO: 5398), ATNGHDSPHKS (SEQ ID NO: 5399), MDGGHDSPHKS (SEQ ID NO: 5400), QEVGHDSPHKS (SEQ ID NO: 5401), ADQGHDSPHKS (SEQ ID NO: 5402), NMNGHDSPHKS (SEQ ID NO: 5403), TPWEHDSPHKS (SEQ ID NO: 5404), IEMGHDSPHKS (SEQ ID NO: 5405), TANEHDSPHKS (SEQ ID NO: 5406), TINGHDSPHKS (SEQ ID NO: 5407), QQQGHDSPHKS (SEQ ID NO: 5408), TPQDHDSPHKS (SEQ ID NO: 5409), HDWGHDSPHKS (SEQ ID NO: 5410), IEGGHDSPHKS (SEQ ID NO: 5411), or any portion thereof, e.g., any 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 amino acids, e.g., consecutive amino acids, thereof. In some embodiments, [B] is present immediately subsequent to [A]. In some embodiments, the peptide comprises from N-terminus to C-terminus, [A][B].

[0082] In some embodiments, the peptide comprises an amino acid sequence comprising at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or 17 consecutive amino acids from any one of the sequences provided in Tables 1, 2A, 2B, 13-19. In some embodiments, the peptide comprises an amino acid sequence comprising at least 3, 4, or 5 consecutive amino acids from any one of SEQ ID NOs: 945-980 or 985-986. In some embodiments, the peptide comprises an amino acid sequence comprising at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 consecutive amino acids from any one of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909.

[0083] In some embodiments, the 3 consecutive amino acids comprise SPH. In some embodiments, the 4 consecutive amino acids comprise SPHS (SEQ ID NO: 4700). In some embodiments, the 5 consecutive amino acids comprise SPHSK (SEQ ID NO: 4701). In some embodiments, the 6 consecutive amino acids comprise SPHKA (SEQ ID NO: 941).

[0084] In some embodiments, 3 consecutive amino acids comprise HDS. In some embodiments, the 4 consecutive amino acids comprise HDSP (SEQ ID NO: 4702). In some embodiments, the 5 consecutive amino acids comprise HDSPH (SEQ ID NO: 4703). In some embodiments, the 6 consecutive amino acids comprise HDSPHK (SEQ ID NO: 2).

[0085] In some embodiments, the 3 consecutive amino acids comprise SPH. In some embodiments, the 4 consecutive amino acids comprise SPHK (SEQ ID NO: 6398). In some embodiments, the 5 consecutive amino acids comprise SPHKY (SEQ ID NO: 4715). In some embodiments, the 6 consecutive amino acids comprise SPHKYG (SEQ ID NO: 966).

[0086] In some embodiments, the peptide comprises an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the amino acid sequence of any one of the sequences provided in Tables 1, 2A, 2B, 13-19. In some embodiments, the peptide comprises an amino acid sequence comprising at least one, two, or three but no more than four different amino acids, relative to

the amino acid sequence of any one of the sequences provided in Tables 1, 2A, 2B, 13-19. In some embodiments, the peptide comprises an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the amino acid sequence of any one of SEQ ID NOs: 945-980 or 985-986. In some embodiments, the peptide comprises an amino acid sequence comprising at least one, two, or three but no more than four different amino acids, relative to the amino acid sequence of any one of SEQ ID NOs: 945-980 or 985-986. In some embodiments, the peptide comprises an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the amino acid sequence of any one of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909. In some embodiments, the peptide comprises an amino acid sequence comprising at least one, two, or three but no more than four different amino acids relative to the amino acid sequence of any one of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909. In some embodiments, the peptide comprises an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the amino acid sequence of SEQ ID NO: 3589. In some embodiments, the peptide comprises an amino acid sequence comprising at least one, two, or three but no more than four different amino acids relative to the amino acid sequence of SEQ ID NO: 3589. In some embodiments, the peptide comprises an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the amino acid sequence of SEQ ID NO: 1754. In some embodiments, the peptide comprises an amino acid sequence comprising at least one, two, or three but no more than four different amino acids relative to the amino acid sequence of SEQ ID NO: 1754.

[0087] In some embodiments, the peptide comprises an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the amino acid sequence of SPHSKA (SEQ ID NO: 941). In some embodiments, the peptide comprises an amino acid sequence comprising at least one, two, or three but no more than four different amino acids relative to the amino acid sequence of SPHSKA (SEQ ID NO: 941).

[0088] In some embodiments, the peptide comprises an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the amino acid sequence of HDSPHK (SEQ ID NO: 2). In some embodiments, the peptide comprises an amino acid sequence comprising at least one, two, or three but no more than four different amino acids relative to the amino acid sequence of HDSPHK (SEQ ID NO: 2).

[0089] In some embodiments, the peptide comprises an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the amino acid sequence of SPHKYG (SEQ ID NO: 966). In some embodiments, the peptide comprises an amino acid sequence comprising at least one, two, or three but no more than four different amino acids relative to the amino acid sequence of SPHKYG (SEQ ID NO: 966).

[0090] In some embodiments, the peptide comprises the amino acid sequence of any of the sequences provided in Tables 1, 2A, 2B, 13-19. In some embodiments, the peptide comprises the amino acid sequence of any of SEQ ID NOs: 945-980 or 985-986. In some embodiments, the peptide comprises the amino acid sequence of any of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909. In some embodiments, the peptide comprises the amino acid sequence of SEQ ID NO: 941. In some embodiments, the peptide comprises the amino acid sequence of SEQ ID NO: 943. In some embodiments, the peptide comprises the amino acid sequence of SEQ ID NO: 2. In some embodiments, the peptide comprises the amino acid sequence of SEQ ID NO: 3589. In some embodiments, the peptide comprises the amino acid sequence of SEQ ID NO: 1754. In some embodiments, the peptide comprises the amino acid sequence of SEQ ID NO: 3241. In some embodiments, the peptide comprises the amino acid sequence of SEQ ID NO: 4100. In some embodiments, the peptide comprises the amino acid sequence of SEQ ID NO: 4062. In some embodiments, the peptide comprises the amino acid sequence of SEQ ID NO: 4486.

[0091] In some embodiments, the peptide comprises an amino acid sequence encoded by a nucleotide sequence described herein, e.g., a nucleotide sequence of Table 2A. In some embodiments, the peptide comprises an amino acid sequence encoded by a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the nucleotide sequence of SEQ ID NO: 942. In some embodiments, the peptide comprises an amino acid sequence encoded by a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten different nucleotides, relative to the nucleotide sequence of SEQ ID NO: 942. In some embodiments, the peptide comprises an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 942, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto. In some embodiments, the peptide comprises an amino acid sequence encoded by a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the nucleotide sequence of SEQ ID NO: 944. In some embodiments, the peptide comprises an amino acid sequence encoded by a

nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten different nucleotides, relative to the nucleotide sequence of SEQ ID NO: 944. In some embodiments, the peptide comprises an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 944, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto.

[0092] In some embodiments, the nucleotide sequence encoding a peptide described herein comprises a nucleotide sequence described herein, e.g., as described in Table 2A. In some embodiments, the nucleotide sequence encoding a peptide described herein is codon optimized. In some embodiments, the nucleotide sequence encoding a peptide described herein is isolated, e.g., recombinant.

[0093] In some embodiments the nucleotide sequence encoding a peptide described herein comprises the nucleotide sequence of SEQ ID NO: 942, or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the nucleotide sequence of SEQ ID NO: 942. In some embodiments, the nucleotide sequence encoding a peptide described herein comprises a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten different nucleotides, relative to the nucleotide sequence of SEQ ID NO: 942. In some embodiments the nucleic acid sequence encoding a peptide described herein comprises a nucleotide sequence comprising the nucleotide sequence of SEQ ID NO: 942, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto.

[0094] In some embodiments, the nucleic acid encoding a peptide described herein comprises the nucleotide sequence of SEQ ID NO: 3, or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the nucleotide sequence of SEQ ID NO: 3. In some embodiments, the nucleotide sequence encoding a peptide described herein comprises a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten different nucleotides, relative to the nucleotide sequence of SEQ ID NO: 3. In some embodiments the nucleic acid encoding a peptide described herein comprises a nucleotide sequence comprising the nucleotide sequence of SEQ ID NO: 3, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto.

[0095] In some embodiments, the nucleic acid encoding a peptide described herein comprises the nucleotide sequence of SEQ ID NO: 944, or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), insertions,

or deletions, but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the nucleotide sequence of SEQ ID NO: 944. In some embodiments, the nucleotide sequence encoding a peptide described herein comprises a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten different nucleotides, relative to the nucleotide sequence of SEQ ID NO: 944. In some embodiments the nucleic acid encoding a peptide described herein comprises a nucleotide sequence comprising the nucleotide sequence of SEQ ID NO: 944, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto.

[0096] In some embodiments, a peptide described herein is fused or coupled, e.g., conjugated, to an active agent. In some embodiments, the active agent is a therapeutic agent. In some embodiments, the agent is a therapeutic agent. In some embodiments, the active agent comprises a therapeutic protein, an antibody molecule, an enzyme, one or more components of a genome editing system, an Fc polypeptide fused or coupled (e.g., covalently or non covalently) to a therapeutic agent, and/or an RNAi agent (e.g., a dsRNA, antisense oligonucleotide (ASO), siRNA, shRNA, pre-miRNA, pri-miRNA, miRNA, stRNA, lncRNA, piRNA, or snoRNA). In some embodiments, the therapeutic agent is an antibody. In some embodiments, the peptide is fused or coupled, e.g., conjugated (e.g., directly or indirectly) to the Fc region of the antibody, e.g., at the C-terminus of the Fc region or the N-terminus of the Fc region. In some embodiments, the therapeutic agent is an RNAi agent. In some embodiments, the RNAi agent is a siRNA or an ASO. In some embodiments, the ASO or siRNA comprises at least one (e.g., one or more or all) modified nucleotides. In some embodiments, the peptide is fused or coupled, e.g., conjugated (e.g., directly or indirectly via a linker), to at least one strand of the RNAi agent. In some embodiments, the peptide is conjugated, e.g., directly or indirectly via a linker, to the C-terminus of at least one strand of the RNAi agent. In some embodiments, the peptide is conjugated, e.g., directly or indirectly via a linker, to an internal nucleotide of at least one strand of the RNAi agent. In some embodiments, the at least one strand is the sense strand. In some embodiments, the therapeutic agent modulates, e.g., inhibits, decreases, or increases, expression of, a CNS related gene, mRNA, and/or protein.

[0097] In some embodiments, the active agent is a diagnostic agent. In some embodiments, the diagnostic agent is or comprises an imaging agent (e.g., a protein or small molecule compound coupled to a detectable moiety). In some embodiments, the imaging agent comprises a PET or MRI ligand, or an antibody molecule coupled to a detectable moiety. In some embodiments, the detectable moiety is or comprises a radiolabel, a fluorophore, a chromophore, or an affinity tag. In some embodiments, the radiolabel is or comprises tc99m, iodine-123, a spin label, iodine-131, indium-111, fluorine-19, carbon-13, nitrogen-15, oxygen-17, gadolinium, manganese, or iron. In some embodiments, the active agent is a small molecule. In some embodiments, the active agent is a ribonucleic acid complex (e.g., a Cas9/gRNA complex), a plasmid, a closed-end DNA, a circ-RNA, or an mRNA.

[0098] In some embodiments, at least 1-5, e.g., at least 1, 2, 3, 4, or 5, peptides are fused or coupled, e.g., conjugated, to an active agent, e.g., a therapeutic agent or a diagnostic agent. In some embodiments, the at least 1-5, e.g., at least 1, 2, 3, 4, or 5, peptides comprise the same amino acid sequence. In some embodiments, the at least 1-5, e.g., at least 1, 2, 3, 4, or 5, peptides comprise different amino acid sequences. In some embodiments, the at least 1-5, e.g., at least 1, 2, 3, 4, or 5, peptides are present in tandem (e.g., connected directly or indirectly via a linker) or in a multimeric configuration. In some embodiments, the peptide comprises an amino acid sequence of at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 15, 20, 25, 30, or 35 amino acids in length.

[0099] In some embodiments, the peptide covalently linked, e.g., directly or indirectly via a linker, to the active agent. In some embodiments, the peptide is conjugated to the active agent via a linker. In some embodiments, the linker is a cleavable linker or a non-cleavable linker. In some embodiments, the cleavable linker is a pH sensitive linker or an enzyme sensitive linker. In some embodiments, the pH sensitive linker comprises a hydrazine/hydrazone linker or a disulfide linker. In some embodiments, the enzyme sensitive linker comprises a peptide based linker, e.g., a peptide linker sensitive to a protease (e.g., a lysosomal protease); or a beta-glucuronide linker. In some embodiments, the non-cleavable linker is a linker comprising a thioether group or a maleimidocaproyl group. In some embodiments, the peptide and the active agent are fused or coupled post-translationally, e.g., using click chemistry. In some embodiments, the peptide and the active agent are fused or couple via chemically induced dimerization. In some embodiments, the peptide is present N-terminal relative to the active agent. In some embodiments, the peptide is present C-terminal relative to the active agent.

[0100] In some embodiments, the peptide is present or coupled to a carrier. In some embodiments, the carrier comprises an exosome, a microvesicle, or a lipid nanoparticle (LNP). In some embodiments, the carrier comprises a therapeutic agent (e.g., an RNAi agent (e.g., an dsRNA, a siRNA, a shRNA, a pre-miRNA, a pri-miRNA, a miRNA, a stRNA, a lncRNA, a piRNA, an antisense oligonucleotide agent (ASO), or a snoRNA), an mRNA, a ribonucleoprotein complex (e.g., a Cas9/gRNA complex), or a circRNA). In some embodiments, the peptide is present on the surface of the carrier. In some embodiments, at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, or 80% of the surface of the carrier comprises at least 1-5, e.g., at least 1, 2, 3, 4, or 5 peptides described herein.

[0101] The present disclosure also provides a nucleic acid or polynucleotide encoding any of the peptides described herein and AAV capsid variants, AAV particles, vectors, and cells comprising the same.

AAV Capsid Variant

[0102] In some embodiments, an AAV particle described herein comprises an AAV capsid variant, e.g., an AAV capsid variant described herein (e.g., an AAV capsid variant comprising a

peptide described herein). In some embodiments, an AAV capsid variant comprises a peptide as set forth in any of Tables 1, 2A, 2B, 13-19.

[0103] In some embodiments, an AAV capsid variant described herein comprises an amino acid sequence having the formula [N1]-[N2]-[N3], wherein [N2] comprises the amino acid sequence of SPH and [N3] comprises X4, X5, and X6, wherein at least one of X4, X5, or X6 is a basic amino acid, e.g., a K or R. In some embodiments, position X4 of [N2] is K. In some embodiments, position X5 of [N2] is K.

[0104] In some embodiments, [N1] comprises X1, X2, and X3, wherein at least one of X1, X2, or X3 is G. In some embodiments, position X1 of [N1] is G, V, R, D, E, M, T, I, S, A, N, L, K, H, P, W, or C. In some embodiments, position X2 of [N1] is: S, V, L, N, D, H, R, P, G, T, I, A, E, Y, M, or Q. In some embodiments, position X3 of [N1] is: G, C, L, D, E, Y, H, V, A, N, P, or S. In some embodiments, [N1] comprises GS, SG, GH, HD, GQ, QD, VS, CS, GR, RG, QS, SH, MS, RN, TS, IS, GP, ES, SS, GN, AS, NS, LS, GG, KS, GT, PS, RS, GI, WS, DS, ID, GL, DA, DG, ME, EN, KN, KE, AI, NG, PG, TG, SV, IG, LG, AG, EG, SA, YD, HE, HG, RD, ND, PD, MG, QV, DD, HN, HP, GY, GM, GD, or HS. In some embodiments, [N1] comprises GS, SG, GH, or HD. In some embodiments [N1] is or comprises GSG, GHD, GQD, VSG, CSG, CSH, GQS, GRG, GSH, RVG, GSC, GLL, GDD, GHE, GNY, MSG, RNG, TSG, ISG, GPG, ESG, SSG, GNG, ASG, NSG, LSG, GGG, KSG, HSG, GTG, PSG, GSV, RSG, GIG, WSG, DSG, IDG, GLG, DAG, DGG, MEG, ENG, GSA, KNG, KEG, AIG, GYD, GHG, GRD, GND, GPD, GMG, GQV, GHN, GHP, or GHS. In some embodiments, [N1] is or comprises GSG. In some embodiments, [N1] is or comprises GHD. In some embodiments, [N1]-[N2] comprises SGSPH (SEQ ID NO: 4752), HDSPH (SEQ ID NO: 4703), QDSPH (SEQ ID NO: 4753), RGSPH (SEQ ID NO: 4754), SHSPH (SEQ ID NO: 4755), QSSPH (SEQ ID NO: 4756), DDSPH (SEQ ID NO: 4757), HESPH (SEQ ID NO: 4758), NYSPH (SEQ ID NO: 4759), VGSPH (SEQ ID NO: 4760), SCSPH (SEQ ID NO: 4761), LLSPH (SEQ ID NO: 4762), NGSPH (SEQ ID NO: 4763), PGSPH (SEQ ID NO: 4764), GGSPH (SEQ ID NO: 4765), TGSPH (SEQ ID NO: 4766), SVSPH (SEQ ID NO: 4767), IGSPH (SEQ ID NO: 4768), DGSPH (SEQ ID NO: 4769), LGSPH (SEQ ID NO: 4770), AGSPH (SEQ ID NO: 4771), EGSPH (SEQ ID NO: 4772), SASPH (SEQ ID NO: 4773), YDSPH (SEQ ID NO: 4774), HGSPH (SEQ ID NO: 4775), RDSPH (SEQ ID NO: 4776), NDSPH (SEQ ID NO: 4777), PDSPH (SEQ ID NO: 4778), MGSPH (SEQ ID NO: 4779), QVSPH (SEQ ID NO: 4780), HNSPH (SEQ ID NO: 4781), HPSPH (SEQ ID NO: 4782), or HSSPH (SEQ ID NO: 4783); an amino acid sequence comprising any portion of any of the aforesaid amino acid sequences (e.g., any 2, 3, or 4 amino acids, e.g., consecutive amino acids) thereof; an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the aforesaid amino acid sequences; or an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the aforesaid amino acid sequences. In some embodiments, [N1]-[N2] is or comprises GSGSPH (SEQ ID NO: 4695), GHDSPH (SEQ ID NO:

4784), GQDSPH (SEQ ID NO: 4785), VSGSPH (SEQ ID NO: 4786), CSGSPH (SEQ ID NO: 4787), GRGSPH (SEQ ID NO: 4788), CSHSPH (SEQ ID NO: 4789), GQSSPH (SEQ ID NO: 4790), GSHSPH (SEQ ID NO: 4791), GDDSPH (SEQ ID NO: 4792), GHESPH (SEQ ID NO: 4793), GNYSPH (SEQ ID NO: 4794), RVGSPH (SEQ ID NO: 4795), GSCSPH (SEQ ID NO: 4796), GLLSPH (SEQ ID NO: 4797), MSGSPH (SEQ ID NO: 4798), RNGSPH (SEQ ID NO: 4799), TSGSPH (SEQ ID NO: 4800), ISGSPH (SEQ ID NO: 4801), GPGSPH (SEQ ID NO: 4802), ESGSPH (SEQ ID NO: 4803), SSGSPH (SEQ ID NO: 4804), GNGSPH (SEQ ID NO: 4805), ASGSPH (SEQ ID NO: 4806), NSGSPH (SEQ ID NO: 4807), LSGSPH (SEQ ID NO: 4808), GGGSPH (SEQ ID NO: 4809), KSGSPH (SEQ ID NO: 4810), HSGSPH (SEQ ID NO: 4811), GTGSPH (SEQ ID NO: 4812), PSGSPH (SEQ ID NO: 4813), GSVSPH (SEQ ID NO: 4814), RSGSPH (SEQ ID NO: 4815), GIGSPH (SEQ ID NO: 4816), WSGSPH (SEQ ID NO: 4817), DSGSPH (SEQ ID NO: 4818), IDGSPH (SEQ ID NO: 4819), GLGSPH (SEQ ID NO: 4820), DAGSPH (SEQ ID NO: 4821), DGGSPH (SEQ ID NO: 4822), MEGSPH (SEQ ID NO: 4823), ENGSPH (SEQ ID NO: 4824), GSASPH (SEQ ID NO: 4825), KNGSPH (SEQ ID NO: 4826), KEGSPH (SEQ ID NO: 4827), AIGSPH (SEQ ID NO: 4828), GYDSPH (SEQ ID NO: 4829), GHGSPH (SEQ ID NO: 4830), GRDSPH (SEQ ID NO: 4831), GNDSPH (SEQ ID NO: 4832), GPDSPH (SEQ ID NO: 4833), GMGSPH (SEQ ID NO: 4834), GQVSPH (SEQ ID NO: 4835), GHNSPH (SEQ ID NO: 4836), GHPSPH (SEQ ID NO: 4837), or GHSSPH (SEQ ID NO: 4838); an amino acid sequence comprising any portion of any of the aforesaid amino acid sequences (e.g., any 2, 3, 4, or 5 amino acids, e.g., consecutive amino acids) thereof; an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the aforesaid amino acid sequences; or an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the aforesaid amino acid sequences. In some embodiments, [N1]-[N2] is or comprises GSGSPH (SEQ ID NO: 4695). In some embodiments, [N1]-[N2] is or comprises GHDSPH (SEQ ID NO: 4784).

[0105] In some embodiments, X4, X5, or both of [N3] are K. In some embodiments, X4, X5, or X6 of [N3] is R. In some embodiments, position X4 of [N3] is: A, K, V, S, T, G, F, W, V, N, or R. In some embodiments, position X5 of [N3] is: S, K, T, F, I, L, Y, H, M, or R. In some embodiments, position X6 of [N3] is: G, R, A, M, I, N, T, Y, D, P, V, L, E, W, N, Q, K, or S. In some embodiments, [N3] comprises SK, KA, KS, AR, RM, VK, AS, SR, VK, KR, KK, KN, VR, RS, RK, KT, TS, KF, FG, KI, IG, KL, LG, TT, TY, KY, YG, KD, KP, TR, RG, VR, GA, SL, SS, FL, WK, SA, RA, LR, KW, RR, GK, TK, NK, AK, KV, KG, KH, KM, TG, SE, SV, SW, SN, HG, SQ, LW, MG, MA, or SG. In some embodiments, [N3] comprises SK, KA, KS, or SG. In some embodiments, [N3] is or comprises SKA, KSG, ARM, VKS, ASR, VKI, KKN, VRM, RKA, KTS, KFG, KIG, KLG, KTT, KTY, KYG, SKD, SKP, TRG, VRG, KRG, GAR, KSA, KSR, SKL, SRA, SKR, SLR, SRG, SSR, FLR, SKW, SKS, WKA, VRR, SKV, SKT, SKG, GKA, TKA, NKA, SKL, SKN, AKA, KTG,

KSL, KSE, KSV, KSW, KSN, KHG, KSQ, KSK, KLW, WKG, KMG, KMA, or RSG. In some embodiments, [N3] is or comprises SKA. In some embodiments, [N3] is or comprises KSG. In some embodiments, [N2]-[N3] comprises SPHSK (SEQ ID NO: 4701), SPHKS (SEQ ID NO: 4704), SPHAR (SEQ ID NO: 4705), SPHVK (SEQ ID NO: 4706), SPHAS (SEQ ID NO: 4707), SPHKK (SEQ ID NO: 4708), SPHVR (SEQ ID NO: 4709), SPHRK (SEQ ID NO: 4710), SPHKT (SEQ ID NO: 4711), SPHKF (SEQ ID NO: 4712), SPHKI (SEQ ID NO: 4713), SPHKL (SEQ ID NO: 4714), SPHKY (SEQ ID NO: 4715), SPHTR (SEQ ID NO: 4716), SPHKR (SEQ ID NO: 4717), SPHGA (SEQ ID NO: 4718), SPHSR (SEQ ID NO: 4719), SPHSL (SEQ ID NO: 4720), SPHSS (SEQ ID NO: 4721), SPHFL (SEQ ID NO: 4722), SPHWK (SEQ ID NO: 4723), SPHGK (SEQ ID NO: 4724), SPHTK (SEQ ID NO: 4725), SPHNK (SEQ ID NO: 4726), SPHAK (SEQ ID NO: 4727), SPHKH (SEQ ID NO: 4728), SPHKM (SEQ ID NO: 4729), or SPHRS (SEQ ID NO: 4730). In some embodiments [N2]-[N3] comprises SPHSK (SEQ ID NO: 4701) or SPHKS (SEQ ID NO: 4704). In some embodiments, [N2]-[N3] is or comprises SPHKA (SEQ ID NO: 941), SPHKSG (SEQ ID NO: 946), SPHARM (SEQ ID NO: 947), SPHVKS (SEQ ID NO: 948), SPHASR (SEQ ID NO: 949), SPHVKI (SEQ ID NO: 950), SPHKKN (SEQ ID NO: 954), SPHVRM (SEQ ID NO: 955), SPHRKA (SEQ ID NO: 956), SPHKFG (SEQ ID NO: 957), SPHKIG (SEQ ID NO: 958), SPHKLK (SEQ ID NO: 959), SPHKTS (SEQ ID NO: 963), SPHKTT (SEQ ID NO: 964), SPHKTY (SEQ ID NO: 965), SPHKYG (SEQ ID NO: 966), SPHSD (SEQ ID NO: 967), SPHSP (SEQ ID NO: 968), SPHTRG (SEQ ID NO: 972), SPHVRG (SEQ ID NO: 973), SPHKRG (SEQ ID NO: 974), SPHGAR (SEQ ID NO: 975), SPHKSA (SEQ ID NO: 977), SPHKS (SEQ ID NO: 951), SPHSL (SEQ ID NO: 960), SPHSRA (SEQ ID NO: 969), SPHKS (SEQ ID NO: 978), SPHSLR (SEQ ID NO: 952), SPHSRG (SEQ ID NO: 961), SPHSSR (SEQ ID NO: 970), SPHFLR (SEQ ID NO: 979), SPHKS (SEQ ID NO: 953), SPHKS (SEQ ID NO: 962), SPHWKA (SEQ ID NO: 971), SPHVRR (SEQ ID NO: 980), SPHKT (SEQ ID NO: 4731), SPHKS (SEQ ID NO: 4732), SPHGKA (SEQ ID NO: 4733), SPHNKA (SEQ ID NO: 4734), SPHKN (SEQ ID NO: 4735), SPHKA (SEQ ID NO: 4736), SPHKS (SEQ ID NO: 4737), SPHKTG (SEQ ID NO: 4738), SPHTKA (SEQ ID NO: 4739), SPHKS (SEQ ID NO: 4740), SPHKS (SEQ ID NO: 4741), SPHKS (SEQ ID NO: 4742), SPHKS (SEQ ID NO: 4743), SPHKS (SEQ ID NO: 4744), SPHKS (SEQ ID NO: 4745), SPHKS (SEQ ID NO: 4746), SPHKS (SEQ ID NO: 4747), SPHKLW (SEQ ID NO: 4748), SPHWKG (SEQ ID NO: 4749), SPHKMG (SEQ ID NO: 4750), SPHKMA (SEQ ID NO: 4751), or SPHRS (SEQ ID NO: 976). In some embodiments, [N2]-[N3] is SPHKA (SEQ ID NO: 941). In some embodiments, [N2]-[N3] is or comprises SPHKSG (SEQ ID NO: 946).

[0106] In some embodiments, [N1]-[N2]-[N3] comprises SGSPHSK (SEQ ID NO: 4839), HDSPHSK (SEQ ID NO: 4840), SGSPHAR (SEQ ID NO: 4841), SGSPHVK (SEQ ID NO: 4842), QDSPHSK (SEQ ID NO: 4843), SGSPHKK (SEQ ID NO: 4844), SGSPHVR (SEQ ID NO: 4845), SGSPHAS (SEQ ID NO: 4846), SGSPHRK (SEQ ID NO: 4847), SGSPHKT (SEQ ID NO: 4848), SHSPHSK (SEQ ID NO: 4849), QSSPHRS (SEQ ID NO: 4850), RGSPHAS (SEQ ID NO: 4851),

RGSPHSK (SEQ ID NO: 4852), SGSPHKF (SEQ ID NO: 4853), SGSPHKI (SEQ ID NO: 4854), SGSPHKL (SEQ ID NO: 4855), SGSPHKY (SEQ ID NO: 4856), SGSPHTR (SEQ ID NO: 4857), SHSPHKR (SEQ ID NO: 4858), SGSPHGA (SEQ ID NO: 4859), HDSPHKR (SEQ ID NO: 4860), DDSPHKS (SEQ ID NO: 4861), HESPHKS (SEQ ID NO: 4862), NYSPHKI (SEQ ID NO: 4863), SGSPHSR (SEQ ID NO: 4864), SGSPHSL (SEQ ID NO: 4865), SGSPHSS (SEQ ID NO: 4866), VGSPHSK (SEQ ID NO: 4867), SCSPHRK (SEQ ID NO: 4868), SGSPHFL (SEQ ID NO: 4869), LLSPHWK (SEQ ID NO: 4870), NGSPHSK (SEQ ID NO: 4871), PGSPHSK (SEQ ID NO: 4872), GGSPHSK (SEQ ID NO: 4873), TGSPHSK (SEQ ID NO: 4874), SVSPHGK (SEQ ID NO: 4875), SGSPHTK (SEQ ID NO: 4876), IGSPHSK (SEQ ID NO: 4877), DGSPHSK (SEQ ID NO: 4878), SGSPHNK (SEQ ID NO: 4879), LGSPHSK (SEQ ID NO: 4880), AGSPHSK (SEQ ID NO: 4881), EGSPHSK (SEQ ID NO: 4882), SASPHSK (SEQ ID NO: 4883), SGSPHAK (SEQ ID NO: 4884), HDSPHKI (SEQ ID NO: 4885), YDSPHSK (SEQ ID NO: 4886), HDSPHKT (SEQ ID NO: 4887), RGSPHKR (SEQ ID NO: 4888), HGSPHSK (SEQ ID NO: 4889), RDSPHSK (SEQ ID NO: 4890), NDSPHSK (SEQ ID NO: 4891), QDSPHKI (SEQ ID NO: 4892), PDSPHKI (SEQ ID NO: 4893), PDSPHSK (SEQ ID NO: 4894), MGSPHSK (SEQ ID NO: 4895), HDSPHKH (SEQ ID NO: 4896), QVSPHSK (SEQ ID NO: 4897), HNSPHKS (SEQ ID NO: 4898), NGSPHKR (SEQ ID NO: 4899), HDSPHKY (SEQ ID NO: 4900), NDSPHKI (SEQ ID NO: 4901), HDSPHKL (SEQ ID NO: 4902), HPSPHWK (SEQ ID NO: 4903), HDSPHKM (SEQ ID NO: 4904), or HSSPHRS (SEQ ID NO: 4905). In some embodiments, [N1]-[N2]-[N3] is GSGSPHKA (SEQ ID NO: 4697), GHDSPHKSG (SEQ ID NO: 4698), GSGSPHARM (SEQ ID NO: 4906), GSGSPHVKS (SEQ ID NO: 4907), GQDSPHKSG (SEQ ID NO: 4908), GSGSPHASR (SEQ ID NO: 4909), GSGSPHVKI (SEQ ID NO: 4910), GSGSPHKKN (SEQ ID NO: 4911), GSGSPHVRM (SEQ ID NO: 4912), VSGSPHKA (SEQ ID NO: 4913), CSGSPHKA (SEQ ID NO: 4914), GSGSPHRKA (SEQ ID NO: 4915), CSGSPHKTS (SEQ ID NO: 4916), CSHSPHKSG (SEQ ID NO: 4917), GQSSPHRSG (SEQ ID NO: 4918), GRGSPHASR (SEQ ID NO: 4919), GRGSPHKA (SEQ ID NO: 4920), GSGSPHKFG (SEQ ID NO: 4921), GSGSPHKIG (SEQ ID NO: 4922), GSGSPHKLK (SEQ ID NO: 4923), GSGSPHKTS (SEQ ID NO: 4924), GSGSPHKTT (SEQ ID NO: 4925), GSGSPHKTY (SEQ ID NO: 4926), GSGSPHKYG (SEQ ID NO: 4927), GSGSPHSD (SEQ ID NO: 4928), GSGSPHSP (SEQ ID NO: 4929), GSGSPHTRG (SEQ ID NO: 4930), GSGSPHVRG (SEQ ID NO: 4931), GSHSPHKRG (SEQ ID NO: 4932), GSHSPHKSG (SEQ ID NO: 4933), VSGSPHASR (SEQ ID NO: 4934), VSGSPHGAR (SEQ ID NO: 4935), VSGSPHKFG (SEQ ID NO: 4936), GHDSPHKRG (SEQ ID NO: 4937), GDDSPHKSG (SEQ ID NO: 4938), GHESPHKSA (SEQ ID NO: 4939), GHDSPHKSA (SEQ ID NO: 4940), GNYSPHKIG (SEQ ID NO: 4941), GHDSPHKSR (SEQ ID NO: 4942), GSGSPHSL (SEQ ID NO: 4943), GSGSPHSRA (SEQ ID NO: 4944), GSGSPHSP (SEQ ID NO: 4945), GSGSPHSLR (SEQ ID NO: 4946), GSGSPHSRG (SEQ ID NO: 4947), GSGSPHSSR (SEQ ID NO: 4948), RVGSPHKA (SEQ ID NO: 4949), GSCSPHRKA (SEQ ID NO: 4950), GSGSPHFLR (SEQ ID NO: 4951), GSGSPHSP (SEQ ID NO: 4952), GSGSPHSP (SEQ ID NO: 4953), GSGSPHSP (SEQ ID NO: 4954), GSGSPHSP (SEQ ID NO: 4955), GSGSPHSP (SEQ ID NO: 4956), GSGSPHSP (SEQ ID NO: 4957), GSGSPHSP (SEQ ID NO: 4958), GSGSPHSP (SEQ ID NO: 4959), GSGSPHSP (SEQ ID NO: 4960), GSGSPHSP (SEQ ID NO: 4961), GSGSPHSP (SEQ ID NO: 4962), GSGSPHSP (SEQ ID NO: 4963), GSGSPHSP (SEQ ID NO: 4964), GSGSPHSP (SEQ ID NO: 4965), GSGSPHSP (SEQ ID NO: 4966), GSGSPHSP (SEQ ID NO: 4967), GSGSPHSP (SEQ ID NO: 4968), GSGSPHSP (SEQ ID NO: 4969), GSGSPHSP (SEQ ID NO: 4970), GSGSPHSP (SEQ ID NO: 4971), GSGSPHSP (SEQ ID NO: 4972), GSGSPHSP (SEQ ID NO: 4973), GSGSPHSP (SEQ ID NO: 4974), GSGSPHSP (SEQ ID NO: 4975), GSGSPHSP (SEQ ID NO: 4976), GSGSPHSP (SEQ ID NO: 4977), GSGSPHSP (SEQ ID NO: 4978), GSGSPHSP (SEQ ID NO: 4979), GSGSPHSP (SEQ ID NO: 4980), GSGSPHSP (SEQ ID NO: 4981), GSGSPHSP (SEQ ID NO: 4982), GSGSPHSP (SEQ ID NO: 4983), GSGSPHSP (SEQ ID NO: 4984), GSGSPHSP (SEQ ID NO: 4985), GSGSPHSP (SEQ ID NO: 4986), GSGSPHSP (SEQ ID NO: 4987), GSGSPHSP (SEQ ID NO: 4988), GSGSPHSP (SEQ ID NO: 4989), GSGSPHSP (SEQ ID NO: 4990), GSGSPHSP (SEQ ID NO: 4991), GSGSPHSP (SEQ ID NO: 4992), GSGSPHSP (SEQ ID NO: 4993), GSGSPHSP (SEQ ID NO: 4994), GSGSPHSP (SEQ ID NO: 4995), GSGSPHSP (SEQ ID NO: 4996), GSGSPHSP (SEQ ID NO: 4997), GSGSPHSP (SEQ ID NO: 4998), GSGSPHSP (SEQ ID NO: 4999), GSGSPHSP (SEQ ID NO: 5000).

4953), GLLSPHWKA (SEQ ID NO: 4954), GSGSPHVRR (SEQ ID NO: 4955), GSGSPHSKV (SEQ ID NO: 4956), MSGSPHKA (SEQ ID NO: 4957), RNGSPHKA (SEQ ID NO: 4958), TSGSPHKA (SEQ ID NO: 4959), ISGSPHKA (SEQ ID NO: 4960), GPGSPHKA (SEQ ID NO: 4961), GSGSPHKT (SEQ ID NO: 4962), ESGSPHKA (SEQ ID NO: 4963), SSGSPHKA (SEQ ID NO: 4964), GNGSPHKA (SEQ ID NO: 4965), ASGSPHKA (SEQ ID NO: 4966), NSGSPHKA (SEQ ID NO: 4967), LSGSPHKA (SEQ ID NO: 4968), GGGSPHKA (SEQ ID NO: 4969), KSGSPHKA (SEQ ID NO: 4970), GGGSPHKS (SEQ ID NO: 4971), GSGSPHKG (SEQ ID NO: 4972), HSGSPHKA (SEQ ID NO: 4973), GTGSPHKA (SEQ ID NO: 4974), PSGSPHKA (SEQ ID NO: 4975), GSVSPHGKA (SEQ ID NO: 4976), RSGSPHKA (SEQ ID NO: 4977), GSGSPHTKA (SEQ ID NO: 4978), GIGSPHKA (SEQ ID NO: 4979), WSGSPHKA (SEQ ID NO: 4980), DSGSPHKA (SEQ ID NO: 4981), IDGSPHKA (SEQ ID NO: 4982), GSGSPHNKA (SEQ ID NO: 4983), GLGSPHKS (SEQ ID NO: 4984), DAGSPHKA (SEQ ID NO: 4985), DGGSPHKA (SEQ ID NO: 4986), MEGSPHKA (SEQ ID NO: 4987), ENGSPHKA (SEQ ID NO: 4988), GSASPHKA (SEQ ID NO: 4989), GNGSPHKS (SEQ ID NO: 4990), KNGSPHKA (SEQ ID NO: 4991), KEGSPHKA (SEQ ID NO: 4992), AIGSPHKA (SEQ ID NO: 4993), GSGSPHKN (SEQ ID NO: 4994), GSGSPHAKA (SEQ ID NO: 4995), GHDSPHKIG (SEQ ID NO: 4996), GYDSPHKSG (SEQ ID NO: 4997), GHESPHKSG (SEQ ID NO: 4998), GHDSPHKTG (SEQ ID NO: 4999), GRGSPHKRG (SEQ ID NO: 5000), GQDSPHKSG (SEQ ID NO: 4908), GHDSPHKSL (SEQ ID NO: 5001), GHGSPHKA (SEQ ID NO: 5002), GHDSPHKSE (SEQ ID NO: 5003), VSGSPHKA (SEQ ID NO: 4913), GRDSPHKSG (SEQ ID NO: 5004), GNDSPHKSV (SEQ ID NO: 5005), GQDSPHKIG (SEQ ID NO: 5006), GHDSPHKSV (SEQ ID NO: 5007), GPDSPHKIG (SEQ ID NO: 5008), GPDSPHKSG (SEQ ID NO: 5009), GHDSPHKSW (SEQ ID NO: 5010), GHDSPHKSN (SEQ ID NO: 5011), GMGSPHKT (SEQ ID NO: 5012), GHDSPHKHG (SEQ ID NO: 5013), GQVSPHKSG (SEQ ID NO: 5014), GDDSPHKSV (SEQ ID NO: 5015), GHNSPHKSG (SEQ ID NO: 5016), GNGSPHKRG (SEQ ID NO: 5017), GHDSPHKYG (SEQ ID NO: 5018), GHDSPHKSQ (SEQ ID NO: 5019), GNDSPHKIG (SEQ ID NO: 5020), GHDSPHKSK (SEQ ID NO: 5021), GHDSPHKLW (SEQ ID NO: 5022), GHSPSPHWKG (SEQ ID NO: 5023), GHDSPHKMG (SEQ ID NO: 5024), GHDSPHKMA (SEQ ID NO: 5025), or GHSSPHRSG (SEQ ID NO: 5026); an amino acid sequence comprising any portion of any of the aforesaid amino acid sequences (e.g., any 2, 3, 4, 5, 6, 7, or 8 amino acids, e.g., consecutive amino acids) thereof; an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the aforesaid amino acid sequences; or an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the aforesaid amino acid sequences. In some embodiments, [N1]-[N2]-[N3] is or comprises GSGSPHKA (SEQ ID NO: 4697). In some embodiments, [N1]-[N2]-[N3] is or comprises GHDSPHKSG (SEQ ID NO: 4698).

[0107] In some embodiments, the AAV capsid variant comprising an amino acid sequence having the formula [N1]-[N2]-[N3], further comprises [N4], wherein [N4] comprises X7 X8 X9 X10. In some embodiments, position X7 of [N4] is W, Q, K, R, G, L, V, S, P, H, K, I, M, A, E, or F. In some embodiments, position X8 of [N4] is N, Y, C, K, T, H, R, D, V, S, P, G, W, E, F, A, I, M, Q, or L. In some embodiments, position X9 of [N4] is Q, G, K, H, R, T, L, D, A, P, I, F, V, M, W, Y, S, E, N, or Y. In some embodiments, position X10 of [N4] is Q, H, L, R, W, K, A, P, E, M, I, S, G, N, Y, C, V, T, D, or V. In some embodiments [N4] comprises QNQQ (SEQ ID NO: 5028), WNQQ (SEQ ID NO: 5029), QYYV (SEQ ID NO: 5030), RRQQ (SEQ ID NO: 5031), GCGQ (SEQ ID NO: 5032), LRQQ (SEQ ID NO: 5033), RNQQ (SEQ ID NO: 5034), VNQQ (SEQ ID NO: 5035), FRLQ (SEQ ID NO: 5036), FNQQ (SEQ ID NO: 5037), LLQQ (SEQ ID NO: 5038), SNQQ (SEQ ID NO: 5039), RLQQ (SEQ ID NO: 5040), LNQQ (SEQ ID NO: 5041), QRKL (SEQ ID NO: 5042), LRRQ (SEQ ID NO: 5043), QRLR (SEQ ID NO: 5044), QRRL (SEQ ID NO: 5045), RRLQ (SEQ ID NO: 5046), RLRQ (SEQ ID NO: 5047), SKRQ (SEQ ID NO: 5048), QLYR (SEQ ID NO: 5049), QLTV (SEQ ID NO: 5050), QNKQ (SEQ ID NO: 5051), KNQQ (SEQ ID NO: 5052), QKQQ (SEQ ID NO: 5053), QTQQ (SEQ ID NO: 5054), QNHQ (SEQ ID NO: 5055), QHQQ (SEQ ID NO: 5056), QNQH (SEQ ID NO: 5057), QHRQ (SEQ ID NO: 5058), LTQQ (SEQ ID NO: 5059), QNQW (SEQ ID NO: 5060), QNTH (SEQ ID NO: 5061), RRRQ (SEQ ID NO: 5062), QYQQ (SEQ ID NO: 5063), QNDQ (SEQ ID NO: 5064), QNRH (SEQ ID NO: 5065), RDQQ (SEQ ID NO: 5066), PNLQ (SEQ ID NO: 5067), HVRQ (SEQ ID NO: 5068), PNQH (SEQ ID NO: 5069), HNQQ (SEQ ID NO: 5070), QSQQ (SEQ ID NO: 5071), QPAK (SEQ ID NO: 5072), QNLA (SEQ ID NO: 5073), QNQL (SEQ ID NO: 5074), QGQQ (SEQ ID NO: 5075), LNRQ (SEQ ID NO: 5076), QNPP (SEQ ID NO: 5077), QNLQ (SEQ ID NO: 5078), QDQE (SEQ ID NO: 5079), QDQQ (SEQ ID NO: 5080), HWQQ (SEQ ID NO: 5081), PNQQ (SEQ ID NO: 5082), PEQQ (SEQ ID NO: 5083), QRTM (SEQ ID NO: 5084), LHQH (SEQ ID NO: 5085), QHRI (SEQ ID NO: 5086), QYIH (SEQ ID NO: 5087), QKFE (SEQ ID NO: 5088), QFPS (SEQ ID NO: 5089), QNPL (SEQ ID NO: 5090), QAIK (SEQ ID NO: 5091), QNRQ (SEQ ID NO: 5092), QYQH (SEQ ID NO: 5093), QNPQ (SEQ ID NO: 5094), QHQL (SEQ ID NO: 5095), QSPP (SEQ ID NO: 5096), QAKL (SEQ ID NO: 5097), KSQQ (SEQ ID NO: 5098), QDRP (SEQ ID NO: 5099), QNLG (SEQ ID NO: 5100), QAFH (SEQ ID NO: 5101), QNAQ (SEQ ID NO: 5102), HNQL (SEQ ID NO: 5103), QKLN (SEQ ID NO: 5104), QNVQ (SEQ ID NO: 5105), QAAQ (SEQ ID NO: 5106), QTPP (SEQ ID NO: 5107), QPPA (SEQ ID NO: 5108), QERP (SEQ ID NO: 5109), QDLQ (SEQ ID NO: 5110), QAMH (SEQ ID NO: 5111), QHPS (SEQ ID NO: 5112), PGLQ (SEQ ID NO: 5113), QGIR (SEQ ID NO: 5114), QAPA (SEQ ID NO: 5115), QIPP (SEQ ID NO: 5116), QTQL (SEQ ID NO: 5117), QAPS (SEQ ID NO: 5118), QNTY (SEQ ID NO: 5119), QDKQ (SEQ ID NO: 5120), QNHL (SEQ ID NO: 5121), QIGM (SEQ ID NO: 5122), LNKQ (SEQ ID NO: 5123), PNQL (SEQ ID NO: 5124), QLQQ (SEQ ID NO: 5125), QRMS (SEQ ID NO: 5126), QGIL (SEQ ID NO: 5127), QDRQ (SEQ ID NO: 5128), RDWQ (SEQ ID NO: 5129), QERS (SEQ ID NO: 5130), QNYQ (SEQ ID NO: 5131), QRTC (SEQ ID NO: 5132), QIGH (SEQ ID NO: 5133), QGAI (SEQ ID NO:

5134), QVPP (SEQ ID NO: 5135), QVQQ (SEQ ID NO: 5136), LMRQ (SEQ ID NO: 5137), QYSV (SEQ ID NO: 5138), QAIT (SEQ ID NO: 5139), QKTL (SEQ ID NO: 5140), QLHH (SEQ ID NO: 5141), QNII (SEQ ID NO: 5142), QGHH (SEQ ID NO: 5143), QSKV (SEQ ID NO: 5144), QLPS (SEQ ID NO: 5145), IGKQ (SEQ ID NO: 5146), QAIH (SEQ ID NO: 5147), QHGL (SEQ ID NO: 5148), QFMC (SEQ ID NO: 5149), QNQM (SEQ ID NO: 5150), QHLQ (SEQ ID NO: 5151), QPAR (SEQ ID NO: 5152), QSLQ (SEQ ID NO: 5153), QSQL (SEQ ID NO: 5154), HSQQ (SEQ ID NO: 5155), QMPS (SEQ ID NO: 5156), QGSL (SEQ ID NO: 5157), QVPA (SEQ ID NO: 5158), HYQQ (SEQ ID NO: 5159), QVPS (SEQ ID NO: 5160), RGEQ (SEQ ID NO: 5161), PGQQ (SEQ ID NO: 5162), LEQQ (SEQ ID NO: 5163), QNQS (SEQ ID NO: 5164), QKVI (SEQ ID NO: 5165), QNND (SEQ ID NO: 5166), QSVH (SEQ ID NO: 5167), QPLG (SEQ ID NO: 5168), HNQE (SEQ ID NO: 5169), QIQQ (SEQ ID NO: 5170), QVRN (SEQ ID NO: 5171), PSNQ (SEQ ID NO: 5172), QVGH (SEQ ID NO: 5173), QRDI (SEQ ID NO: 5174), QMPN (SEQ ID NO: 5175), RGLQ (SEQ ID NO: 5176), PSLQ (SEQ ID NO: 5177), QRDQ (SEQ ID NO: 5178), QAKG (SEQ ID NO: 5179), QSAH (SEQ ID NO: 5180), QSTM (SEQ ID NO: 5181), QREM (SEQ ID NO: 5182), QYRA (SEQ ID NO: 5183), QRQQ (SEQ ID NO: 5184), QWQQ (SEQ ID NO: 5185), QRMN (SEQ ID NO: 5186), GDSQ (SEQ ID NO: 5187), QKIS (SEQ ID NO: 5188), PSMQ (SEQ ID NO: 5189), SPRQ (SEQ ID NO: 5190), MEQQ (SEQ ID NO: 5191), QYQN (SEQ ID NO: 5192), QIRQ (SEQ ID NO: 5193), QSVQ (SEQ ID NO: 5194), RSQQ (SEQ ID NO: 5195), QNKL (SEQ ID NO: 5196), QIQH (SEQ ID NO: 5197), PRQQ (SEQ ID NO: 5198), HTQQ (SEQ ID NO: 5199), QRQH (SEQ ID NO: 5200), RNQE (SEQ ID NO: 5201), QSKQ (SEQ ID NO: 5202), QNQP (SEQ ID NO: 5203), QSPQ (SEQ ID NO: 5204), QTRQ (SEQ ID NO: 5205), QNLH (SEQ ID NO: 5206), QNQE (SEQ ID NO: 5207), LNQP (SEQ ID NO: 5208), QNQD (SEQ ID NO: 5209), QNLL (SEQ ID NO: 5210), QLVI (SEQ ID NO: 5211), RTQE (SEQ ID NO: 5212), QTHQ (SEQ ID NO: 5213), QDQH (SEQ ID NO: 5214), QSQH (SEQ ID NO: 5215), VRQQ (SEQ ID NO: 5216), AWQQ (SEQ ID NO: 5217), QSVP (SEQ ID NO: 5218), QNIQ (SEQ ID NO: 5219), LDQQ (SEQ ID NO: 5220), PDQQ (SEQ ID NO: 5221), ESQQ (SEQ ID NO: 5222), QRQL (SEQ ID NO: 5223), QIIV (SEQ ID NO: 5224), QKQS (SEQ ID NO: 5225), QSHQ (SEQ ID NO: 5226), QFVV (SEQ ID NO: 5227), QSQP (SEQ ID NO: 5228), QNEQ (SEQ ID NO: 5229), INQQ (SEQ ID NO: 5230), RNRQ (SEQ ID NO: 5231), RDQK (SEQ ID NO: 5232), QWKR (SEQ ID NO: 5233), ENRQ (SEQ ID NO: 5234), QTQP (SEQ ID NO: 5235), QKQL (SEQ ID NO: 5236), RNQL (SEQ ID NO: 5237), ISIQ (SEQ ID NO: 5238), QTVC (SEQ ID NO: 5239), QQIM (SEQ ID NO: 5240), LNHQ (SEQ ID NO: 5241), QNQA (SEQ ID NO: 5242), QMIH (SEQ ID NO: 5243), RNHQ (SEQ ID NO: 5244), or QKMN (SEQ ID NO: 5245), or any dipeptide or tripeptide thereof. In some embodiments, [N1]-[N2]-[N3]-[N4] is or comprises: the amino acid sequence of any of SEQ ID NOs: 1800-2241; an amino acid sequence comprising any portion of any of the aforesaid amino acid sequences (e.g., any 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 amino acids, e.g., consecutive amino acids) thereof; an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions,

relative to any of the aforesaid amino acid sequences; or an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the aforesaid amino acid sequences. In some embodiments, [N1]-[N2]-[N3]-[N4] is or comprises GSGSPHKAQNQQ (SEQ ID NO: 1801). In some embodiments, [N1]-[N2]-[N3]-[N4] is or comprises GHDSPHKSGQNQQ (SEQ ID NO: 1800).

[0108] In some embodiments, the AAV capsid variant comprising an amino acid sequence having the formula [N1]-[N2]-[N3], further comprises [N0], wherein [N0] comprises XA XB and XC. In some embodiments, XA of [N0] is T, S, Y, M, A, C, I, R, L, D, F, V, Q, N, H, E, or G. In some embodiments, XB of [N0] is I, M, P, E, N, D, S, A, T, G, Q, F, V, L, C, H, R, W, or L. In some embodiments, XC of [N0] is N, M, E, G, Y, W, T, I, Q, F, V, A, L, I, P, K, R, H, S, D, or S. In some embodiments, [N0] comprises TIN, SMN, TIM, YLS, GLS, MPE, MEG, MEY, AEW, CEW, ANN, IPE, ADM, IEY, ADY, IET, MEW, CEY, RIN, MEI, LEY, ADW, IEL, DIM, FEQ, MEF, CDQ, LPE, IEN, MES, AEI, VEY, IIN, TSN, IEV, MEM, AEV, MDA, VEW, AEQ, LEW, MEL, MET, MEA, IES, MEV, CEI, ATN, MDG, QEV, ADQ, NMN, IEM, ISN, TGN, QQQ, HDW, IEG, TII, TFP, TEK, EIN, TVN, TFN, SIN, TER, TSY, ELH, AIN, SVN, TDN, TFH, TVH, TEN, TSS, TID, TCN, NIN, TEH, AEM, AIK, TDK, TFK, SDQ, TEI, NTN, TET, SIK, TEL, TEA, TAN, TIY, TFS, TES, TTN, TED, TNN, EVH, TIS, TVR, TDR, TIK, NHI, TIP, ESD, TDL, TVP, TVI, AEH, NCL, TVK, NAD, TIT, NCV, TIR, NAL, VIN, TIQ, TEF, TRE, QGE, SEK, NVN, GGE, EFV, SDK, TEQ, EVQ, TEY, NCW, TDV, SDI, NSI, NSL, EVV, TEP, SEL, TWQ, TEV, AVN, GVL, TLN, TEG, TRD, NAI, AEN, AET, ETA,>NNL, or any dipeptide thereof. In some embodiments, [N0]-[N1]-[N2]-[N3]-[N4] is or comprises the amino acid sequence of any one of SEQ ID NOs: 2242-2886; an amino acid sequence comprising any portion of any of the aforesaid amino acid sequences (e.g., any 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 amino acids, e.g., consecutive amino acids) thereof; an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the aforesaid amino acid sequences; or an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the aforesaid amino acid sequences. In some embodiments, [N0]-[N1]-[N2]-[N3]-[N4] is or comprises TINGSGSPHKAQNQQ (SEQ ID NO: 2242). In some embodiments, [N0]-[N1]-[N2]-[N3]-[N4] is or comprises TINGHDSPHKSGQNQQ (SEQ ID NO: 2243).

[0109] In some embodiments, [N1]-[N2]-[N3] is present in loop IV of the AAV capsid variant. In some embodiments [N0] and [N4] are present in loop IV of the AAV capsid variant. In some embodiments, [N0]-[N1]-[N2]-[N3]-[N4] is present in loop IV of the AAV capsid variant. In some embodiments, [N0] is present immediately subsequent to position 449, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, wherein [N0] is present immediately subsequent to position 449, relative to a reference

sequence numbered according to the amino acid sequence of SEQ ID NO: 981 or 982. In some embodiments, [N0] replaces positions 450, 451, and 452 (e.g., amino acids T450, I451, and N452), relative to a reference sequence numbered according to SEQ ID NO: 138, 981, or 982. wherein [N0] is present immediately subsequent to position 449 and wherein [N0] replaces positions 450-452 (e.g., T450, I451, and N452), relative to a reference sequence numbered according to SEQ ID NO: 138, 981, or 982. In some embodiments, [N1] is present immediately subsequent to position 452, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138, 981 or 982. In some embodiments, wherein [N1] replaces positions 453- 455 (e.g., G453, S454, and G455), relative to a reference sequence numbered according to SEQ ID NO: 138, 981, or 982. In some embodiments, [N1] is present immediately subsequent to position 452 and wherein [N1] replaces positions 453-455 (e.g., G453, S454, and G455), relative to a reference sequence numbered according to SEQ ID NO: 138, 981, or 982. In some embodiments, [N2] is present immediately subsequent to position 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138, 981, or 982. In some embodiments, [N2]-[N3] is present immediately subsequent to position 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138, 981, or 982. In some embodiments [N1]-[N2]-[N3] is present immediately subsequent to position 452, numbered relative to SEQ ID NO: 138, 981, or 982. In some embodiments, [N1]-[N2]-[N3] replaces positions 453-455 (e.g., G453, S454, and G455), relative to a reference sequence numbered according to SEQ ID NO: 138, 981, or 982. In some embodiments, [N1] is present immediately subsequent to position 452 and wherein [N1]-[N2]-[N3] replaces positions 453-455 (e.g., G453, S454, and G455), relative to a reference sequence numbered according to SEQ ID NO: 138, 981, or 982. In some embodiments, [N4] is present immediately subsequent to position 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, [N4] replaces positions 456-459 (e.g., Q456, N457, Q458, and Q459), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, [N4] is present immediately subsequent to position 455, and [N4] replaces positions 456-459 (e.g., Q456, N457, Q458, and Q459), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, [N2]-[N3]-[N4] replaces positions 456-459 (e.g., Q456, N457, Q458, and Q459), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, [N2]-[N3]-[N4] is present immediately subsequent to position 455, and wherein [N2]-[N3]-[N4] replaces positions 456-459 (e.g., Q456, N457, Q458, and Q459), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, [N1]-[N2]-[N3]-[N4] replaces positions 453-459 (e.g., G453, S454, G455, Q456, N457, Q458, and Q459), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, [N1]-[N2]-[N3]-[N4] is present immediately subsequent to position 452, and wherein [N1]-[N2]-[N3]-[N4] replaces positions 453-459 (e.g., G453, S454, G455, Q456, N457, Q458, and

Q459), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, [N0]-[N1]-[N2]-[N3]-[N4] replaces positions 450-456 (e.g., T450, I451, N452, G453, S454, G455, Q456, N457, Q458, and Q459), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, [N0]-[N1]-[N2]-[N3]-[N4] is present immediately subsequent to position 449, and wherein [N0]-[N1]-[N2]-[N3]-[N4] replaces positions 450-456 (e.g., T450, I451, N452, G453, S454, G455, Q456, N457, Q458, and Q459), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

[0110] In some embodiments, [N3] is present immediately subsequent to [N2].

[0111] In some embodiments, the AAV capsid variant comprises from N-terminus to C-terminus, [N2]-[N3]. In some embodiments, the AAV capsid variant comprises from N-terminus to C-terminus, [N1]-[N2]-[N3]. In some embodiments, the AAV capsid variant comprises from N-terminus to C-terminus, [N1]-[N2]-[N3]-[N4]. In some embodiments, the AAV capsid variant comprises from N-terminus to C-terminus, [N0]-[N1]-[N2]-[N3]. In some embodiments, the AAV capsid variant comprises from N-terminus to C-terminus, [N0]-[N1]-[N2]-[N3]-[N4].

[0112] In some embodiments, an AAV capsid variant described herein comprises an amino acid sequence having the formula [A][B] (SEQ ID NO: 4694), wherein [A] comprises the amino acid sequence of GSGSPH (SEQ ID NO: 4695) and [B] comprises X1 X2 X3 X4 X5 X6 X7. In some embodiments, position X1 of [B] is S, C, F, or V. In some embodiments, position X2 of [B] is K, L, R, I, E, Y, V, or S. In some embodiments, X3 of [B] is A, R, L, G, I, Y, S, F, or W. In some embodiments X4 of [B] is W, Q, R, G, L, V, S, or F. In some embodiments, position X5 of [B] is N, Y, R, C, K, or L. In some embodiments, position X6 of [B] is Q, G, K, R, T, L, or Y. In some embodiment, position X7 of [B] is Q, L, R, or V. In some embodiments, [B] comprises S LLWNQQ (SEQ ID NO: 5247), SKAQYYV (SEQ ID NO: 5248), SKLRRQQ (SEQ ID NO: 5249), SIWQNQQ (SEQ ID NO: 5250), SKAGCGQ (SEQ ID NO: 5251), SRAQNQQ (SEQ ID NO: 5252), SKRLRQQ (SEQ ID NO: 5253), SLRRNQQ (SEQ ID NO: 5254), SRGRNQQ (SEQ ID NO: 5255), SEIVNQQ (SEQ ID NO: 5256), SSRRNQQ (SEQ ID NO: 5257), CLLQNQQ (SEQ ID NO: 5258), SKAFRLQ (SEQ ID NO: 5259), CLAQNQQ (SEQ ID NO: 5260), FLRQNQQ (SEQ ID NO: 5261), SLRFNQQ (SEQ ID NO: 5262), SYLRNQQ (SEQ ID NO: 5263), CSLQNQQ (SEQ ID NO: 5264), VLWQNQQ (SEQ ID NO: 5265), SKWLLQQ (SEQ ID NO: 5266), SLWSNQQ (SEQ ID NO: 5267), SKRRLQQ (SEQ ID NO: 5268), SVYLNQQ (SEQ ID NO: 5269), SLWLNQQ (SEQ ID NO: 5270), SKAQRKL (SEQ ID NO: 5271), SKALRRQ (SEQ ID NO: 5272), SKAQRLR (SEQ ID NO: 5273), SKAQNQQ (SEQ ID NO: 5274), SKAQRRQ (SEQ ID NO: 5275), SKARRQQ (SEQ ID NO: 5276), SKARRLQ (SEQ ID NO: 5277), SKSRRQQ (SEQ ID NO: 5278), SKARLRQ (SEQ ID NO: 5279), SKASKRQ (SEQ ID NO: 5280), VRRQNQQ (SEQ ID NO: 5281), SKAQLYR (SEQ ID NO: 5282), SLFRNQQ (SEQ ID NO: 5283), SKAQLTV (SEQ ID NO: 5284), or any dipeptide, tripeptide, tetrapeptide,

pentapeptide, or hexapeptide thereof. In some embodiments, [A][B] comprises GSGSPHSLLNQQ (SEQ ID NO: 5285), GSGSPHKAQYYV (SEQ ID NO: 2060), GSGSPHSLRRQQ (SEQ ID NO: 2061), GSGSPHSIWQNNQ (SEQ ID NO: 5286), GSGSPHKAAGCGQ (SEQ ID NO: 2062), GSGSPHSRAQNNQ (SEQ ID NO: 2063), GSGSPHSLRRQQ (SEQ ID NO: 2064), GSGSPHSLRRNNQ (SEQ ID NO: 2065), GSGSPHSRGRNNQ (SEQ ID NO: 2066), GSGSPHSEIVNNQ (SEQ ID NO: 5287), GSGSPHSSRRNNQ (SEQ ID NO: 2067), GSGSPHCLLNQQ (SEQ ID NO: 5288), GSGSPHKAFLRQ (SEQ ID NO: 2068), GSGSPHCLAQNNQ (SEQ ID NO: 5289), GSGSPHFLRQNNQ (SEQ ID NO: 2070), GSGSPHSLRFNNQ (SEQ ID NO: 2071), GSGSPHSYLRNNQ (SEQ ID NO: 5290), GSGSPHCSLQNNQ (SEQ ID NO: 5291), GSGSPHVLWQNNQ (SEQ ID NO: 5292), GSGSPHSLWLLQ (SEQ ID NO: 2072), GSGSPHSLWSNNQ (SEQ ID NO: 5293), GSGSPHSLRRQQ (SEQ ID NO: 2073), GSGSPHSVYLRNNQ (SEQ ID NO: 5294), GSGSPHSLWLNQQ (SEQ ID NO: 5295), GSGSPHKAQRKL (SEQ ID NO: 2074), GSGSPHSLRRQ (SEQ ID NO: 2075), GSGSPHKAQRLR (SEQ ID NO: 2076), GSGSPHKAQNNQ (SEQ ID NO: 1801), GSGSPHKAQRRL (SEQ ID NO: 2077), GSGSPHSLRRQ (SEQ ID NO: 2078), GSGSPHSLRRQ (SEQ ID NO: 2079), GSGSPHSLRRQ (SEQ ID NO: 2080), GSGSPHSLRRQ (SEQ ID NO: 2082), GSGSPHSLRRQ (SEQ ID NO: 2083), GSGSPHSLRRQ (SEQ ID NO: 2084), GSGSPHSLRRQ (SEQ ID NO: 2085), GSGSPHSLRRQ (SEQ ID NO: 5296), GSGSPHSLRRQ (SEQ ID NO: 2086), or any portion thereof, e.g., any 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 amino acids, e.g., consecutive amino acids, thereof.

[0113] In some embodiments, [A][B] is present in loop IV of the AAV capsid variant. In some embodiments, [A] is present immediately subsequent to position 452, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, [A] replaces positions 453-455 (e.g., G453, S454, G455), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, [A] is present immediately subsequent to position 452, and wherein [A] replaces positions 453-455 (e.g., G453, S454, G455), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, [B] is present immediately subsequent to [A]. In some embodiments, [B] replaces positions 456-459 (e.g., Q456, N457, Q458, Q459), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, [A][B] replaces positions 453-459 (e.g., G453, S454, G455, Q456, N457, Q458, Q459), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, [A][B] is present immediately subsequent to position 452, and wherein [A][B] replaces positions 453-459 (e.g., G453, S454, G455, Q456, N457, Q458, Q459), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid variant comprises from N-terminus to C-terminus, [A][B].

[0114] In some embodiments, an AAV capsid variant described herein comprises an amino acid sequence having the formula [A][B] (SEQ ID NO: 4699), wherein [A] comprises X1 X2 X3 X4 X5 X6 and [B] comprises SPHKSG (SEQ ID NO: 946). In some embodiments, position X1 of [A] is T, M, A, C, I, R, L, D, F, V, Q, N, or H. In some embodiments, position X2 of [A] is I, P, E, N, D, S, A, T, M, or Q. In some embodiments, position X3 of [A] is N, E, G, Y, W, M, T, I, K, Q, F, S, V, A, or L. In some embodiments, position X4 of [A] is G, D, R, or E. In some embodiments, position X5 of [A] is H, Q, N, or D. In some embodiments, position X6 of [A] is D or R. In some embodiments, [A] comprises TINGHD (SEQ ID NO: 5297), MPEGHD (SEQ ID NO: 5298), MEGGHD (SEQ ID NO: 5299), MEYGH (SEQ ID NO: 5300), AEWGHD (SEQ ID NO: 5301), CEWGHD (SEQ ID NO: 5302), ANNGQD (SEQ ID NO: 5303), IPEGHD (SEQ ID NO: 5304), ADMGHD (SEQ ID NO: 5305), IEYGH (SEQ ID NO: 5306), ADYGH (SEQ ID NO: 5307), IETGH (SEQ ID NO: 5308), MEWGH (SEQ ID NO: 5309), CEYGH (SEQ ID NO: 5310), RINGHD (SEQ ID NO: 5311), MEIGH (SEQ ID NO: 5312), LEYGH (SEQ ID NO: 5313), ADWGH (SEQ ID NO: 5314), IEIGH (SEQ ID NO: 5315), TIKDND (SEQ ID NO: 5316), DIMGH (SEQ ID NO: 5317), FEQGH (SEQ ID NO: 5318), MEFGH (SEQ ID NO: 5319), CDQGH (SEQ ID NO: 5320), LPEGHD (SEQ ID NO: 5321), IENGHD (SEQ ID NO: 5322), MESGH (SEQ ID NO: 5323), AEIGH (SEQ ID NO: 5324), VEYGH (SEQ ID NO: 5325), TSNGDD (SEQ ID NO: 5326), IEVGH (SEQ ID NO: 5327), MEMGH (SEQ ID NO: 5328), AEVGH (SEQ ID NO: 5329), MDAGHD (SEQ ID NO: 5330), VEWGH (SEQ ID NO: 5331), AEQGH (SEQ ID NO: 5332), LEWGH (SEQ ID NO: 5333), MELGH (SEQ ID NO: 5334), METGH (SEQ ID NO: 5335), MEAGHD (SEQ ID NO: 5336), TINRQR (SEQ ID NO: 5337), IESGH (SEQ ID NO: 5338), TAKDHD (SEQ ID NO: 5339), MEVGH (SEQ ID NO: 5340), CEIGH (SEQ ID NO: 5341), ATNGHD (SEQ ID NO: 5342), MDGGHD (SEQ ID NO: 5343), QEVGH (SEQ ID NO: 5344), ADQGH (SEQ ID NO: 5345), NMNGHD (SEQ ID NO: 5346), TPWEHD (SEQ ID NO: 5347), IEMGH (SEQ ID NO: 5348), TANEHD (SEQ ID NO: 5349), QQQGH (SEQ ID NO: 5350), TPQDHD (SEQ ID NO: 5351), HDWGH (SEQ ID NO: 5352), IEGGH (SEQ ID NO: 5353), or any dipeptide, tripeptide, tetrapeptide, or pentapeptide thereof. In some embodiments, [A][B] comprises TINGHDSPHKR (SEQ ID NO: 5354), MPEGHDSPHKS (SEQ ID NO: 5355), MEGGHDSPHKS (SEQ ID NO: 5356), MEYGHDSPHKS (SEQ ID NO: 5357), AEWGHDSPHKS (SEQ ID NO: 5358), CEWGHDSPHKS (SEQ ID NO: 5359), ANNGQDSPHKS (SEQ ID NO: 5360), IPEGHDSPHKS (SEQ ID NO: 5361), ADMGHDSPHKS (SEQ ID NO: 5362), IEYGHDSPHKS (SEQ ID NO: 5363), ADYGHDSPHKS (SEQ ID NO: 5364), IETGHDSPHKS (SEQ ID NO: 5365), MEWGHDSPHKS (SEQ ID NO: 5366), CEYGHDSPHKS (SEQ ID NO: 5367), RINGHDSPHKS (SEQ ID NO: 5368), MEIGHDSPHKS (SEQ ID NO: 5369), LEYGHDSPHKS (SEQ ID NO: 5370), ADWGHDSPHKS (SEQ ID NO: 5371), IEIGHDSPHKS (SEQ ID NO: 5372), TIKDNDSPHKS (SEQ ID NO: 5373), DIMGHDSPHKS (SEQ ID NO: 5374), FEQGHDSPHKS (SEQ ID NO: 5375), MEFGHDSPHKS (SEQ ID NO: 5376), CDQGHDSPHKS (SEQ ID NO: 5377), LPEGHDSPHKS

(SEQ ID NO: 5378), IENGHDSPHKS (SEQ ID NO: 5379), MESGHDSPHKS (SEQ ID NO: 5380), AEIGHDSPHKS (SEQ ID NO: 5381), VEYGHDSPHKS (SEQ ID NO: 5382), TSNGDDSPHKS (SEQ ID NO: 5383), IEVGHDSPHKS (SEQ ID NO: 5384), MEMGHDSPHKS (SEQ ID NO: 5385), AEVGHDSPHKS (SEQ ID NO: 5386), MDAGHDSPHKS (SEQ ID NO: 5387), VEWGHDSPHKS (SEQ ID NO: 5388), AEQGHDSPHKS (SEQ ID NO: 5389), LEWGHDSPHKS (SEQ ID NO: 5390), MELGHDSPHKS (SEQ ID NO: 5391), METGHDSPHKS (SEQ ID NO: 5392), MEAGHDSPHKS (SEQ ID NO: 5393), TINRQRSPHKS (SEQ ID NO: 5394), IESGHDSPHKS (SEQ ID NO: 5395), TAKDHDSPHKS (SEQ ID NO: 5396), MEVGHDSPHKS (SEQ ID NO: 5397), CEIGHDSPHKS (SEQ ID NO: 5398), ATNGHDSPHKS (SEQ ID NO: 5399), MDGGHDSPHKS (SEQ ID NO: 5400), QEVGHDSPHKS (SEQ ID NO: 5401), ADQGHDSPHKS (SEQ ID NO: 5402), NMNGHDSPHKS (SEQ ID NO: 5403), TPWEHDSPHKS (SEQ ID NO: 5404), IEMGHDSPHKS (SEQ ID NO: 5405), TANEHDSPHKS (SEQ ID NO: 5406), TINGHDSPHKS (SEQ ID NO: 5407), QQQGHDSPHKS (SEQ ID NO: 5408), TPQDHDSPHKS (SEQ ID NO: 5409), HDWGHDSPHKS (SEQ ID NO: 5410), IEGGHDSPHKS (SEQ ID NO: 5411), or any portion thereof, e.g., any 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 amino acids, e.g., consecutive amino acids, thereof.

[0115] In some embodiments, [A][B] is present in loop IV of the AAV capsid variant. In some embodiments, [A] is present immediately subsequent to position 449, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, [A] replaces positions 450-455 (e.g., T450, I451, N452, G453, S454, G455), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, [A] is present immediately subsequent to position 449, and wherein [A] replaces positions 450-455 (e.g., T450, I451, N452, G453, S454, G455), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, [B] is present immediately subsequent to [A]. In some embodiments, [A][B] replaces positions 450-455 (e.g., T450, I451, N452, G453, S454, G455), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, [A][B] is present immediately subsequent to position 449, and wherein [A][B] replaces positions 450-455 (e.g., T450, I451, N452, G453, S454, G455), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, the peptide comprises from N-terminus to C-terminus, [A][B].

[0116] In some embodiments, an AAV capsid variant described herein comprises an amino acid sequence comprising at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 16, or 17 consecutive amino acids from any one of the sequences provided in Tables 1, 2A, 2B, 13-19. In some embodiments, the AAV capsid variant comprises an amino acid sequence comprising at least 3, 4, or 5 consecutive amino acids from any one of SEQ ID NOs: 945-980 or 985-986. In some embodiments, the AAV capsid variant comprises an amino acid sequence comprising at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 consecutive amino acids from any one of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-

909. In some embodiments, the amino acid sequence is present in loop IV. In some embodiments, the amino acid sequence is present immediately subsequent to position 448, 452, 453, 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138, 981, or 982. In some embodiments, the amino acid sequence is present immediately subsequent to position 455, numbered according to SEQ ID NO: 982. In some embodiments, the amino acid sequence is present immediately subsequent to position 455, numbered according to SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to position 453, numbered according to SEQ ID NO: 981. In some embodiments, the amino acid sequence is present immediately subsequent to position 453, numbered according to SEQ ID NO: 138. In some embodiments, the amino acid sequence replaces 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or all of positions 499 (e.g., K499), 450 (e.g., T450), 451 (e.g., I451), 452 (e.g., N452), 453 (e.g., G453), 454 (e.g., S454), 455 (e.g., G455), 456 (e.g., Q456), 457 (e.g., N457), 458 (e.g., Q458), 459 (e.g., Q459), and 460 (e.g., T460), numbered according to SEQ ID NO: 138. In some embodiments, the AAV capsid variant comprises one or more amino acid substitutions at positions 499 (e.g., K499), 450 (e.g., T450), 451 (e.g., I451), 452 (e.g., N452), 453 (e.g., G453), 454 (e.g., S454), 455 (e.g., G455), 456 (e.g., Q456), 457 (e.g., N457), 458 (e.g., Q458), 459 (e.g., Q459), and/or 460 (e.g., T460), numbered according to SEQ ID NO: 138.

[0117] In some embodiments, the 3 consecutive amino acids comprise SPH. In some embodiments, the 4 consecutive amino acids comprise SPHS (SEQ ID NO: 4700). In some embodiments, the 5 consecutive amino acids comprise SPHSK (SEQ ID NO: 4701). In some embodiments, the 6 consecutive amino acids comprise SPHKA (SEQ ID NO: 941).

[0118] In some embodiments, 3 consecutive amino acids comprise HDS. In some embodiments, the 4 consecutive amino acids comprise HDSP (SEQ ID NO: 4702). In some embodiments, the 5 consecutive amino acids comprise HDSPH (SEQ ID NO: 4703). In some embodiments, the 6 consecutive amino acids comprise HDSPHK (SEQ ID NO: 2).

[0119] In some embodiments, an AAV capsid variant described herein comprises an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the amino acid sequence of any one of the sequences provided in Tables 1, 2A, 2B, 13-19. In some embodiments, the AAV capsid variant comprises an amino acid sequence comprising at least one, two, or three but no more than four different amino acids, relative to the amino acid sequence of any one of the sequences provided in Tables 1, 2A, 2B, 13-19. In some embodiments, the AAV capsid variant comprises an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the amino acid sequence of any one of SEQ ID NOs: 945-980 or 985-986. In some embodiments, the AAV capsid variant comprises an amino acid sequence comprising at least one, two, or three but no more than four different amino

acids, relative to the amino acid sequence of any one of SEQ ID NOs: 945-980 or 985-986. In some embodiments, the AAV capsid variant comprises an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the amino acid sequence of any one of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909. In some embodiments, the AAV capsid variant comprises an amino acid sequence comprising at least one, two, or three but no more than four different amino acids, from the amino acid sequence of any one of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909. In some embodiments, the amino acid sequence is present in loop IV. In some embodiments, the amino acid sequence is present immediately subsequent to position 448, 452, 453, 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138, 981, or 982. In some embodiments, the amino acid sequence is present immediately subsequent to position 455, numbered according to SEQ ID NO: 982. In some embodiments, the amino acid sequence is present immediately subsequent to position 455, numbered according to SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to position 453, numbered according to SEQ ID NO: 981. In some embodiments, the amino acid sequence is present immediately subsequent to position 453, numbered according to SEQ ID NO: 138. In some embodiments, the amino acid sequence replaces 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or all of positions 499 (e.g., K499), 450 (e.g., T450), 451 (e.g., I451), 452 (e.g., N452), 453 (e.g., G453), 454 (e.g., S454), 455 (e.g., G455), 456 (e.g., Q456), 457 (e.g., N457), 458 (e.g., Q458), 459 (e.g., Q459), and 460 (e.g., T460), numbered according to SEQ ID NO: 138.

[0120] In some embodiments, the AAV capsid variant comprises an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the amino acid sequence of SPHKA (SEQ ID NO: 941). In some embodiments, the AAV capsid variant comprises an amino acid sequence comprising at least one, two, or three, but no more than four different amino acids from the amino acid sequence of SPHKA (SEQ ID NO: 941).

[0121] In some embodiments, the AAV capsid variant comprises an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the amino acid sequence of HDSPHK (SEQ ID NO: 2). In some embodiments, the AAV capsid variant comprises an amino acid sequence comprising at least one, two, or three, but no more than four different amino acids that relative to the amino acid sequence of HDSPHK (SEQ ID NO: 2).

[0122] In some embodiments, the AAV capsid variant, comprises the amino acid sequence of any of the sequences provided in Tables 1, 2A, 2B, 13-19. In some embodiments, the peptide comprises the amino acid sequence of any of SEQ ID NOs: 945-980 or 985-986. In some embodiments, the AAV capsid variant comprises the amino acid sequence of any of SEQ ID NOs: 2, 200, 201, 941, 943,

204, 208, 404, or 903-909. In some embodiments, the AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 941. In some embodiments, the AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 2. In some embodiments, the AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 943. In some embodiments, the AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 3589. In some embodiments, the AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 1754. In some embodiments, the amino acid sequence is present in loop IV. In some embodiments, the amino acid sequence is present immediately subsequent to position 448, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, the amino acid sequence replaces positions 449-460 (e.g., K449, T450, I451, N452, G453, S454, G455, Q456, N457, Q458, Q459, and T460), numbered relative to SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to position 448 and replaces positions 449-460 (e.g., K449, T450, I451, N452, G453, S454, G455, Q456, N457, Q458, Q459, and T460), numbered relative to SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to position 449, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, the amino acid sequence replaces positions 450-460 (e.g., T450, I451, N452, G453, S454, G455, Q456, N457, Q458, Q459, and T460), numbered relative to SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to position 449, and replaces positions 450-460 (e.g., T450, I451, N452, G453, S454, G455, Q456, N457, Q458, Q459, and T460), numbered relative to SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to position 450, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, the amino acid sequence replaces positions 451-460 (e.g., I451, N452, G453, S454, G455, Q456, N457, Q458, Q459, and T460), numbered relative to SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to position 450 and replaces positions 451-460 (e.g., I451, N452, G453, S454, G455, Q456, N457, Q458, Q459, and T460), numbered relative to SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to position 451, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, the amino acid sequence replaces positions 452-460 (e.g., N452, G453, S454, G455, Q456, N457, Q458, Q459, and T460), numbered relative to SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to position 451 and replaces positions 452-460 (e.g., N452, G453, S454, G455, Q456, N457, Q458, Q459, and T460), numbered relative to SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to position 452, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, the amino acid sequence replaces positions 453-460 (e.g., G453, S454, G455, Q456, N457, Q458, Q459, and T460), numbered relative to SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately

subsequent to position 452, and replaces positions 453-460 (e.g., G453, S454, G455, Q456, N457, Q458, Q459, and T460), numbered relative to SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to position 453, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, the amino acid sequence replaces positions 454 and 455 (e.g., S454 and G455), numbered according to SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to position 453, and replaces positions 454 and 455 (e.g., S454 and G455), numbered according to SEQ ID NO: 138. In some embodiments, the amino acid sequence replaces positions 454-460 (e.g., S454, G455, Q456, N457, Q458, Q459, and T460), numbered relative to SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to position 453, and replaces positions 454-460 (e.g., S454, G455, Q456, N457, Q458, Q459, and T460), numbered relative to SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to position 454, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to position 454, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 981. In some embodiments, the amino acid sequence replaces positions 455-460 (e.g., positions G455, Q456, N457, Q458, Q459, and T460), numbered relative to SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to positions 454, and replaces positions 455-460 (e.g., positions G455, Q456, N457, Q458, Q459, and T460), numbered relative to SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to position 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to position 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 982. In some embodiments, the amino acid sequence replaces positions 456-460 (e.g., Q456, N457, Q458, Q459, and T460), numbered relative to SEQ ID NO: 138. In some embodiments, the amino acid sequence is present immediately subsequent to position 455, and replaces positions 456-460 (e.g., Q456, N457, Q458, Q459, and T460), numbered relative to SEQ ID NO: 138.

[0123] In some embodiments, the AAV capsid variant (e.g., an AAV capsid variant described herein), comprises an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 942 or 944, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto. In some embodiments, the AAV capsid variant described herein, comprises an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 3 or 942, or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the nucleotide sequence of SEQ ID NO: 3 or 942. In some

embodiments, the AAV capsid variant comprises an amino acid sequence encoded by a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 3 or 942.

[0124] In some embodiments, the nucleotide sequence encoding the AAV capsid variant (e.g., an AAV capsid variant described herein), comprises the nucleotide sequence of SEQ ID NO: 942, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto. In some embodiments, the nucleic acid sequence encoding the AAV capsid variant comprises a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the nucleotide sequences of SEQ ID NO: 942. In some embodiments, the nucleotide sequence encoding an AAV capsid variant described herein comprises a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten different nucleotides, relative to the nucleotide sequence of SEQ ID NO: 942.

[0125] In some embodiments, the nucleotide sequence encoding the AAV capsid variant (e.g., an AAV capsid variant described herein), comprises the nucleotide sequence of SEQ ID NO: 3, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto. In some embodiments, the nucleic acid sequence encoding the AAV capsid variant comprises a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the nucleotide sequences of SEQ ID NO: 3. In some embodiments, the nucleotide sequence encoding an AAV capsid variant described herein comprises a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 3.

[0126] In some embodiments, an AAV capsid variant described herein comprises the amino acid sequence of SPHKA (SEQ ID NO: 941), wherein the amino acid sequence is present immediately subsequent to position 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, an AAV capsid variant described herein comprises the amino acid sequence of SPHKA (SEQ ID NO: 941), wherein the amino acid sequence is present immediately subsequent to position 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 981.

[0127] In some embodiments, an AAV capsid variant described herein comprises the amino acid sequence of HDSPHK (SEQ ID NO: 2), wherein the amino acid sequence is present immediately subsequent to position 453, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, an AAV capsid variant described herein

comprises the amino acid sequence of HDSPHK (SEQ ID NO: 2), wherein the amino acid sequence is present immediately subsequent to position 453, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 982.

[0128] In some embodiments, an AAV capsid variant described herein comprises (i) the amino acid sequence of HDSPHKA (SEQ ID NO: 4486), which is present immediately subsequent to position 453; and (ii) a deletion of amino acids SG at position 454 and 455; wherein (i) and (ii) are numbered according to SEQ ID NO: 138.

[0129] In some embodiments, an AAV capsid variant described herein comprises an amino acid other than S at position 454 and/or an amino acid other than G at position 455, numbered according to SEQ ID NO: 138. In some embodiments, the AAV capsid variant comprises the amino acid H at position 454 and the amino acid D at position 455, numbered according to SEQ ID NO: 138. In some embodiments, the AAV capsid variant further comprises the amino acid sequence of SPHKA (SEQ ID NO: 941). In some embodiments, the AAV capsid variant comprises: (i) the amino acid H at position 454 and the amino acid D at position 455, and (ii) the amino acid sequence SPHKA (SEQ ID NO: 941), wherein the amino acid sequence of SPHKSG (SEQ ID NO: 946) is present immediately subsequent to position 455, wherein (i) and (ii) are numbered according to SEQ ID NO: 138.

[0130] In some embodiments, an AAV capsid variant described herein comprises a modification, e.g., substitution, relative to SEQ ID NO: 138. In some embodiments, the AAV capsid variant comprises a modification, e.g., substitution, at position S454 and/or G455, numbered relative to SEQ ID NO: 138. In some embodiments, the AAV capsid variant comprises a S454H substitution and/or G455D substitution, numbered relative to SEQ ID NO: 138. In some embodiments, the AAV capsid variant comprises a S454H substitution and a G455D substitution, numbered relative to SEQ ID NO: 138. In some embodiments, the AAV capsid variant further comprises the amino acid sequence of SPHKA (SEQ ID NO: 941). In some embodiments, the AAV capsid variant comprises: (i) a S454H substitution and a G455D substitution, and (ii) the amino acid sequence SPHKSG (SEQ ID NO: 946), wherein the amino acid sequence of SPHKA (SEQ ID NO: 941) is present immediately subsequent to position 455, wherein (i) and (ii) are numbered according to SEQ ID NO: 138.

[0131] In some embodiments, the AAV capsid variant further comprises one, two, or all of an amino acid other than T at position 450 (e.g., S, Y, or G), an amino acid other than I at position 451 (e.g., M or L), and/or an amino acid other than N at position 452 (e.g., S), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid variant further comprises an S at position 450 and an M at position 451, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid variant further comprises a Y at position 450, an L at position 451, and an S at position 452, relative to a reference sequence numbered according to the

amino acid sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid variant further comprises a G at position 450, an L at position 451, and an S at position 452, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

[0132] In some embodiments, the AAV capsid variant further comprises one, two, three, four, or all of an amino acid other than Q at position 456 (e.g., R or L), N at position 457 (e.g., H, K, or R), Q at position 458 (e.g., R or T), Q at position 459 (H), and/or T at position 460 (N or S), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid variant further comprises an R at position 456, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid variant further comprises an L at position 456, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid variant further comprises an H at position 457 and an R at position 458, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid variant further comprises a K at position 457 and an N at position 460, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid variant further comprises a T at position 458, an H at position 459, and an S at position 460, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid variant further comprises an R at position 456, an R at position 457, and an R at position 458, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138.

[0133] In some embodiments, an AAV capsid variant described herein comprises an amino acid other than I at position 451, an amino acid other than N at position 452, and an amino acid other than G at position 453, numbered according to SEQ ID NO: 138 or 981. In some embodiments, the AAV capsid variant comprises E at position 451, R at position 452, and V at position 453, numbered according to SEQ ID NO: 138 or 981. In some embodiments, the AAV capsid variant comprises the substitutions I451E, N452R, and G453V, numbered according to SEQ ID NO: 138 or 981.

[0134] In some embodiments, the AAV capsid variant comprises the amino acid sequence of SPHska (SEQ ID NO: 941), wherein the amino acid sequence is present immediately subsequent to position 455 and wherein the AAV capsid variant comprises the E at position 451, R at position 452, and V at position 453, numbered according to the amino acid sequence of SEQ ID NO: 138 or 981. In some embodiments, the AAV capsid variant comprises the substitutions I451E, N452R, and G453V, and further comprises the amino acid sequence of SPHska (SEQ ID NO: 941), wherein the amino acid sequence is present immediately subsequent to position 455, all numbered according to SEQ ID NO: 138 or 981. In some embodiments, the AAV capsid variant comprises the amino acid sequence of ERVSGSPHska (SEQ ID NO: 6399), and wherein the amino acid sequence is present immediately subsequent to position 449 and replaces positions 450-455, numbered according to SEQ

ID NO: 138. In some embodiments, the AAV capsid variant comprises the amino acid sequence of KTERVSGSPHKAQNQQT (SEQ ID NO: 3589), wherein the amino acid sequence is present immediately subsequent to position 448 and replaces positions 449-460, numbered according to SEQ ID NO: 138.

[0135] In some embodiments, an AAV capsid variant described herein comprises an amino acid other than T at position 450, an amino acid other than I at position 451, and an amino acid other than N at position 452, numbered according to SEQ ID NO: 138 or 982. In some embodiments, the AAV capsid variant comprises A at position 450, E at position 451, and I at position 452, numbered according to SEQ ID NO: 138 or 982. In some embodiments, the AAV capsid variant comprises the substitutions T450A, I451E, and N452I, numbered according to SEQ ID NO: 138 or 982.

[0136] In some embodiments, the AAV capsid variant comprises the amino acid sequence of HDSPHK (SEQ ID NO: 2), which is present immediately subsequent to positions 453, and further comprises A at position 450, E at position 451, and I at position 452, all numbered according to SEQ ID NO: 138 or 982. In some embodiments, the AAV capsid variant comprises the substitutions T450A, I451E, and N452I, and further comprises the amino acid sequence HDSPHK (SEQ ID NO: 2) present immediately subsequent to position 453, all numbered according to SEQ ID NO: 138 or 982. In some embodiments, the AAV capsid variant comprises the amino acid sequence of AEIGHDSPHKSG (SEQ ID NO: 6400), wherein the amino acid sequence is present immediately subsequent to position 449 and replaces positions 450-455, numbered according to SEQ ID NO: 138. In some embodiments, the AAV capsid variant comprises the amino acid sequence of KAEIGHDSPHKSGQNQQT (SEQ ID NO: 1754), wherein the amino acid sequence is present immediately subsequent to position 448 and replaces positions 449-460, numbered according to SEQ ID NO: 138.

[0137] In some embodiments, the AAV capsid variant, further comprises a substitution at position K449, e.g., a K449R substitution, numbered according to SEQ ID NO: 138. In some embodiments, the AAV capsid variant, further comprises an amino acid other than K at position 449 (e.g., R), relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid variant comprises an R at position 449, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid variant further comprises a modification, e.g., an insertion, substitution, and/or deletion in loop I, II, VI, and/or VIII.

[0138] In some embodiments, the AAV capsid variant, further comprises an amino acid sequence comprising at least one, two or three modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, of the amino acid sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid variant, further comprises an amino acid sequence

comprising at least one, two or three, but not more than 30, 20 or 10 amino acids that differ from the amino acid sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid variant further comprises the amino acid sequence of SEQ ID NO: 138, or an amino acid sequence with at least 70% (e.g., at least about 80, 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto.

[0139] In some embodiments, the AAV capsid variant further comprises (a) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 138, 981, or 982; (b) a VP2 protein comprising the amino acid sequence of positions 138-736 of SEQ ID NO: 138 or positions 138-742 of SEQ ID NO: 981 or 982; (c) a VP3 protein comprising the amino acid sequence of positions 203-736 of SEQ ID NO: 138 or positions 203-742 of SEQ ID NO: 981 or 982; or (d) an amino acid sequence with at least 70% (e.g., at least about 80, 85, 90, 95, 96, 97, 98, or 99%) sequence identity to any of the amino acid sequences in (a)-(c), an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids relative to any of the amino acid sequences in (a)-(c), or an amino acid sequence comprising at least one, two or three modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the amino acid sequences in (a)-(c).

[0140] In some embodiments, the AAV capsid variant further comprises an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 137, or a sequence with at least 70% (e.g., at least about 80, 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto. In some embodiments, the AAV capsid variant further comprises an amino acid sequence encoded by a nucleotide sequence comprising at least one, two or three modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the nucleotide sequence of SEQ ID NO: 137. In some embodiments, the AAV capsid variant further comprises an amino acid sequence encoded by a nucleotide sequence comprising at least one, two or three, but not more than 30, 20 or 10 different nucleotides, relative to the amino acid sequence of SEQ ID NO: 137.

[0141] In some embodiments, the nucleotide sequence encoding the AAV capsid variant further comprises the nucleotide sequence of SEQ ID NO: 137, or a sequence with at least 70% (e.g., at least about 80, 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto. In some embodiments, the nucleotide sequence encoding the AAV capsid variant further comprises a nucleotide sequence comprising at least one, two or three modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the nucleotide sequence of SEQ ID NO: 137. In some embodiments, the nucleotide sequence encoding the AAV capsid variant further comprises a nucleotide sequence comprising at least one, two or three, but not more than 30, 20 or 10 different nucleotides, relative to the amino acid sequence of SEQ ID NO: 137.

[0142] In some embodiments, an AAV capsid variant of the present disclosure comprises an amino acid sequence as described herein, e.g., an amino acid sequence of an AAV capsid variant of TTM-001 or TTM-002, e.g., as described in Tables 3 and 4. In some embodiments, an AAV capsid variant of the present disclosure comprises an amino acid sequence as described herein, e.g., an amino acid sequence of an AAV capsid variant of TTM-003, TTM-004, TTM-005, TTM-006, TTM-007, TTM-008, TTM-009, TTM-010, TTM-011, TTM-012, TTM-013, TTM-014, TTM-015, TTM-016, TTM-017, TTM-018, TTM-019, TTM-020, TTM-021, TTM-022, TTM-023, TTM-024, TTM-025, or TTM-026, e.g., as described in Table 4.

[0143] In some embodiments, an AAV capsid variant described herein comprises a VP1, VP2, and/or VP3 protein comprising an amino acid sequence described herein, e.g., an amino acid sequence of an AAV capsid variant of TTM-001 or TTM-002, e.g., as described in Tables 3 and 4. In some embodiments, an AAV capsid variant described herein comprises a VP1, VP2, and/or VP3 protein comprising an amino acid sequence described herein, e.g., an amino acid sequence of an AAV capsid variant of TTM-003, TTM-004, TTM-005, TTM-006, TTM-007, TTM-008, TTM-009, TTM-010, TTM-011, TTM-012, TTM-013, TTM-014, TTM-015, TTM-016, TTM-017, TTM-018, TTM-019, TTM-020, TTM-021, TTM-022, TTM-023, TTM-024, TTM-025, or TTM-026, e.g., as described in Table 4.

[0144] In some embodiments, an AAV capsid variant described herein comprises an amino acid sequence encoded by a nucleotide sequence as described herein, e.g., a nucleotide sequence of an AAV capsid variant of TTM-001 or TTM-002, e.g., as described in Tables 3 and 5. In some embodiments, an AAV capsid variant described herein comprises an amino acid sequence encoded by a nucleotide sequence as described herein, e.g., a nucleotide sequence of an AAV capsid variant of TTM-003, TTM-004, TTM-005, TTM-006, TTM-007, TTM-008, TTM-009, TTM-010, TTM-011, TTM-012, TTM-013, TTM-014, TTM-015, TTM-016, TTM-017, TTM-018, TTM-019, TTM-020, TTM-021, TTM-022, TTM-023, TTM-024, TTM-025, or TTM-026, e.g., as described in Table 5.

[0145] In some embodiments, a polynucleotide or nucleic acid encoding an AAV capsid variant, of the present disclosure comprises a nucleotide sequence described herein, e.g., a nucleotide sequence of an AAV capsid variant of TTM-001 or TTM-002, e.g., as described in Tables 3 and 5. In some embodiments, a polynucleotide or nucleic acid encoding an AAV capsid variant, of the present disclosure comprises a nucleotide sequence described herein, e.g., a nucleotide sequence of an AAV capsid variant of TTM-003, TTM-004, TTM-005, TTM-006, TTM-007, TTM-008, TTM-009, TTM-010, TTM-011, TTM-012, TTM-013, TTM-014, TTM-015, TTM-016, TTM-017, TTM-018, TTM-019, TTM-020, TTM-021, TTM-022, TTM-023, TTM-024, TTM-025, or TTM-026, e.g., as described in Table 5.

Table 3. Exemplary full length capsid sequences

Name	VP1 DNA SEQ ID NO:	VP1 (amino acid) SEQ ID NO:	Peptide (amino acid) SEQ ID NO:	Peptide DNA SEQ ID NO:
TTM-001	983	981	941	942
TTM-002	984	982	2	3

Table 4. Exemplary full length capsid amino acid sequences

Name and Annotation	SEQ ID NO:	Amino Acid Sequence
TTM-001 6mer peptide underlined, starts at position 456 (immediately subsequent to position 455); 742 aa	981	MAADGYLPDWLEDNLSEGIREWALKPGAPQPKANQQHQDNARGLVLPGYKYLPGP NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADADEFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVPDPQPIGEPPAAPSGVGS LTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGD RVITTTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDENRFHCHFS PRDWQRLINNNWGFPRKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVF TDSYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLT LNDGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENV PFHSSYAHSQSLDRLMNPLIDQYLYYLS KTINGSG SPHSKA QNQQTLKF SVAGPSNMAVQGRNYIPGPSYRQQRVSTT VTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGVQVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGP I WAKI PHTDGNFHPSPLMGGFGMKHPPPPQILIKNT PVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENS KRWNPEIQYTSNYKSSNNVEFAVNTEGVYS EPRPIGTRYLTRNL
TTM-002 6mer peptide underlined, starts at position 454 (immediately subsequent to position 453); 742 aa	982	MAADGYLPDWLEDNLSEGIREWALKPGAPQPKANQQHQDNARGLVLPGYKYLPGP NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADADEFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVPDPQPIGEPPAAPSGVGS LTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGD RVITTTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDENRFHCHFS PRDWQRLINNNWGFPRKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVF TDSYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLT LNDGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENV PFHSSYAHSQSLDRLMNPLIDQYLYYLS KTING HDS SPHSKA SGQNQQTLKF SVAGPSNMAVQGRNYIPGPSYRQQRVSTT VTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGVQVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGP I WAKI PHTDGNFHPSPLMGGFGMKHPPPPQILIKNT PVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENS KRWNPEIQYTSNYKSSNNVEFAVNTEGVYS EPRPIGTRYLTRNL
TTM-003 6mer peptide underlined, starts at position 456 (immediately subsequent to position 455); modifications at positions 451, 452, and 453 underlined; 742 aa	36	MAADGYLPDWLEDNLSEGIREWALKPGAPQPKANQQHQDNARGLVLPGYKYLPGP NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADADEFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVPDPQPIGEPPAAPSGVGS LTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGD RVITTTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDENRFHCHFS PRDWQRLINNNWGFPRKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVF TDSYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLT LNDGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENV PFHSSYAHSQSLDRLMNPLIDQYLYYLS K T ERV SG SPHSKA QNQQTLKF SVAGPSNMAVQGRNYIPGPSYRQQRVSTT VTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGVQVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGP I WAKI PHTDGNFHPSPLMGGFGMKHPPPPQILIKNT PVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENS KRWNPEIQYTSNYKSSNNVEFAVNTEGVYS EPRPIGTRYLTRNL
TTM-004 6mer peptide underlined, starts at position 454	37	MAADGYLPDWLEDNLSEGIREWALKPGAPQPKANQQHQDNARGLVLPGYKYLPGP NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADADEFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVPDPQPIGEPPAAPSGVGS LTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGD RVITTTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP

(immediately subsequent to position 453); modifications at positions 450, 451, and 452 underlined; 742 aa		WGYFDNFRFHCHFS PRDWQRLINNNWGFPRKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVFVTDSDYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLDNGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSSQLDRLMNPPLIDQYLYYLS <u>KAEI</u> <u>GHDSPHK</u> SGQNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYQGVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGPWIWAKIPHTDGNFHPSPLMGGFGMKHPPQILIKNTVPVADPPTAFNKDK LNSLITQYSTGQVSVEIEWELQKENS KRWNPEIQYTSNYYSNNVEFAVNTGEGVYS EPRPIGTRYLTRNL
TTM-005 6mer peptide underlined, starts at position 456 (immediately subsequent to position 455); modifications at positions 452, 464, and 465 underlined; 742 aa	38	MAADGYLPDWLEDNLSEGI REWWALKPGAPQPKANQQHQDNARGVLVPGYKYLGP NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADA EFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVPDPQPIGEPPAAPSGVGS LTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGD RVITTTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDNFRFHCHFS PRDWQRLINNNWGFPRKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVFVTDSDYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLDNGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSSQLDRLMNPPLIDQYLYYLS KT <u>I</u> SGS <u>SPH</u> <u>SKA</u> <u>QNRH</u> TLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYQGVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGPWIWAKIPHTDGNFHPSPLMGGFGMKHPPQILIKNTVPVADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENS KRWNPEIQYTSNYYSNNVEFAVNTGEGVYS EPRPIGTRYLTRNL
TTM-006 6mer peptide underlined, starts at position 456 (immediately subsequent to position 455); modifications at positions 451, 452, and 453 underlined; 742 aa	39	MAADGYLPDWLEDNLSEGI REWWALKPGAPQPKANQQHQDNARGVLVPGYKYLGP NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADA EFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVPDPQPIGEPPAAPSGVGS LTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGD RVITTTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDNFRFHCHFS PRDWQRLINNNWGFPRKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVFVTDSDYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLDNGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSSQLDRLMNPPLIDQYLYYLS KT <u>EKM</u> SGS <u>SPH</u> <u>SKA</u> <u>QNRH</u> TLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYQGVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGPWIWAKIPHTDGNFHPSPLMGGFGMKHPPQILIKNTVPVADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENS KRWNPEIQYTSNYYSNNVEFAVNTGEGVYS EPRPIGTRYLTRNL
TTM-007 6mer peptide underlined, starts at position 456 (immediately subsequent to position 455); modifications at positions 450 and 454 underlined; 742 aa	40	MAADGYLPDWLEDNLSEGI REWWALKPGAPQPKANQQHQDNARGVLVPGYKYLGP NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADA EFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVPDPQPIGEPPAAPSGVGS LTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGD RVITTTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDNFRFHCHFS PRDWQRLINNNWGFPRKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVFVTDSDYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLDNGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSSQLDRLMNPPLIDQYLYYLS <u>KE</u> ING <u>R</u> GS <u>SPH</u> <u>SKA</u> <u>QNRH</u> TLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYQGVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGPWIWAKIPHTDGNFHPSPLMGGFGMKHPPQILIKNTVPVADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENS KRWNPEIQYTSNYYSNNVEFAVNTGEGVYS EPRPIGTRYLTRNL
TTM-008 6mer peptide underlined, starts at position 456 (immediately subsequent to position 455); modifications at positions 451,	41	MAADGYLPDWLEDNLSEGI REWWALKPGAPQPKANQQHQDNARGVLVPGYKYLGP NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADA EFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVPDPQPIGEPPAAPSGVGS LTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGD RVITTTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDNFRFHCHFS PRDWQRLINNNWGFPRKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVFVTDSDYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLDNGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSSQLDRLMNPPLIDQYLYYLS KT <u>F</u> NGSG <u>SPH</u> <u>SKA</u> <u>PN</u> <u>L</u> QTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD

462, and 464 underlined; 742 aa		ADKVMITNEEEIKTTNPVATESYQVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGPWAKIPHTDGNFHPSPLMGGFGMKHPPQILIKNTVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENS KRWNPEIQYTSNYYSNNVEFAVNTGEGVYS EPRPIGTRYLTRNL
TTM-009 6mer peptide underlined, starts at position 456 (immediately subsequent to position 455); modifications at positions 451, 452, and 453 underlined; 742 aa	42	MAADGYLPDWLEDNLSEGI REWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGP NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADA EFQERLKEDTSFGG NLGRAVFQAKKRLLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTE SVDPDQPIGEPPAAPSGVGS LTMA SGGGAPVADNNEGADGVGSS SGNWHCDSQWL GDRVITTTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDENRFHCHFS PRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIAN NLSTSTVQVFTDSYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLDNGSQAVGRS SFYCLEYFSPQMLRTGNNFQFSYEFENVPFHSSYAHSSQLDRLMNP LIDQYLYYLS KT EKTSGSPHSA QNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYQVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGPWAKIPHTDGNFHPSPLMGGFGMKHPPQILIKNTVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENS KRWNPEIQYTSNYYSNNVEFAVNTGEGVYS EPRPIGTRYLTRNL
TTM-010 6mer peptide underlined, starts at position 456 (immediately subsequent to position 455); modifications at positions 451, 454, and 455 underlined; 742 aa	43	MAADGYLPDWLEDNLSEGI REWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGP NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADA EFQERLKEDTSFGG NLGRAVFQAKKRLLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTE SVDPDQPIGEPPAAPSGVGS LTMA SGGGAPVADNNEGADGVGSS SGNWHCDSQWL GDRVITTTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDENRFHCHFS PRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIAN NLSTSTVQVFTDSYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLDNGSQAVGRS SFYCLEYFSPQMLRTGNNFQFSYEFENVPFHSSYAHSSQLDRLMNP LIDQYLYYLS KT MNGHDSPHSA QNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYQVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGPWAKIPHTDGNFHPSPLMGGFGMKHPPQILIKNTVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENS KRWNPEIQYTSNYYSNNVEFAVNTGEGVYS EPRPIGTRYLTRNL
TTM-011 6mer peptide underlined, starts at position 456 (immediately subsequent to position 455); modifications at positions 452, 454, and 455 underlined; 742 aa	44	MAADGYLPDWLEDNLSEGI REWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGP NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADA EFQERLKEDTSFGG NLGRAVFQAKKRLLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTE SVDPDQPIGEPPAAPSGVGS LTMA SGGGAPVADNNEGADGVGSS SGNWHCDSQWL GDRVITTTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDENRFHCHFS PRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIAN NLSTSTVQVFTDSYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLDNGSQAVGRS SFYCLEYFSPQMLRTGNNFQFSYEFENVPFHSSYAHSSQLDRLMNP LIDQYLYYLS KT IDGHDSPHSA QNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYQVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGPWAKIPHTDGNFHPSPLMGGFGMKHPPQILIKNTVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENS KRWNPEIQYTSNYYSNNVEFAVNTGEGVYS EPRPIGTRYLTRNL
TTM-012 6mer peptide underlined, starts at position 456 (immediately subsequent to position 455); modifications at positions 452, 454, and 455 underlined; 742 aa	45	MAADGYLPDWLEDNLSEGI REWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGP NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADA EFQERLKEDTSFGG NLGRAVFQAKKRLLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTE SVDPDQPIGEPPAAPSGVGS LTMA SGGGAPVADNNEGADGVGSS SGNWHCDSQWL GDRVITTTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDENRFHCHFS PRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIAN NLSTSTVQVFTDSYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLDNGSQAVGRS SFYCLEYFSPQMLRTGNNFQFSYEFENVPFHSSYAHSSQLDRLMNP LIDQYLYYLS KT NNGHDSPHSA QNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYQVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGPWAKIPHTDGNFHPSPLMGGFGMKHPPQILIKNTVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENS KRWNPEIQYTSNYYSNNVEFAVNTGEGVYS EPRPIGTRYLTRNL

TTM-013 6mer peptide underlined, starts at position 456 (immediately subsequent to position 455); modifications at positions 451, 452, and 453 underlined; 742 aa	46	MAADGYLPDWLEDNLSEGI REWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGP NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADA EFQERLKEDTSFGG NLGRAVFQAKKRLLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVDPDQPIGEPPAAPSGVGS LTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGD RVITTTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDENRFHCHFS PRDWQRLINNNWGFPRKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVFTDSYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLT LNDGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSSQSLDRLMNP LIDQYLYYLS KT <u>QRKSGSPHSKA</u> QNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTT VQTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGVATNHQSAQAQAQTGWVQNQGI LPGMVWQDR DVYLQGP I WAKI PHTDGNFHPSPLMGGFGMKHPPQILIKNT PVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENS KRWNPEIQYTSNYKSNNV EFAVNT EGVYS EPRPIGTRYLTRNL
TTM-014 6mer peptide underlined, starts at position 456 (immediately subsequent to position 455); modifications at positions 463, 464, and 465 underlined; 742 aa	47	MAADGYLPDWLEDNLSEGI REWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGP NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADA EFQERLKEDTSFGG NLGRAVFQAKKRLLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVDPDQPIGEPPAAPSGVGS LTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGD RVITTTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDENRFHCHFS PRDWQRLINNNWGFPRKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVFTDSYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLT LNDGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSSQSLDRLMNP LIDQYLYYLS KT <u>INGSGSPHSKA</u> QARKTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTT VQTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGVATNHQSAQAQAQTGWVQNQGI LPGMVWQDR DVYLQGP I WAKI PHTDGNFHPSPLMGGFGMKHPPQILIKNT PVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENS KRWNPEIQYTSNYKSNNV EFAVNT EGVYS EPRPIGTRYLTRNL
TTM-015 6mer peptide underlined, starts at position 456 (immediately subsequent to position 455); modifications at positions 450 and 452 underlined; 742 aa	48	MAADGYLPDWLEDNLSEGI REWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGP NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADA EFQERLKEDTSFGG NLGRAVFQAKKRLLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVDPDQPIGEPPAAPSGVGS LTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGD RVITTTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDENRFHCHFS PRDWQRLINNNWGFPRKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVFTDSYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLT LNDGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSSQSLDRLMNP LIDQYLYYLS <u>KYIV</u> SGSGSPHSKAQNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTT VQTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGVATNHQSAQAQAQTGWVQNQGI LPGMVWQDR DVYLQGP I WAKI PHTDGNFHPSPLMGGFGMKHPPQILIKNT PVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENS KRWNPEIQYTSNYKSNNV EFAVNT EGVYS EPRPIGTRYLTRNL
TTM-016 6mer peptide underlined, starts at position 456 (immediately subsequent to position 455); modifications at positions 452, 453, and 454 underlined; 742 aa	49	MAADGYLPDWLEDNLSEGI REWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGP NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADA EFQERLKEDTSFGG NLGRAVFQAKKRLLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVDPDQPIGEPPAAPSGVGS LTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGD RVITTTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDENRFHCHFS PRDWQRLINNNWGFPRKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVFTDSYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLT LNDGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSSQSLDRLMNP LIDQYLYYLS KTI <u>SKRSGSPHSKA</u> QNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTT VQTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGVATNHQSAQAQAQTGWVQNQGI LPGMVWQDR DVYLQGP I WAKI PHTDGNFHPSPLMGGFGMKHPPQILIKNT PVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENS KRWNPEIQYTSNYKSNNV EFAVNT EGVYS EPRPIGTRYLTRNL
TTM-017 6mer peptide underlined, starts at position 456	50	MAADGYLPDWLEDNLSEGI REWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGP NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADA EFQERLKEDTSFGG NLGRAVFQAKKRLLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVDPDQPIGEPPAAPSGVGS LTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGD RVITTTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP

(immediately subsequent to position 455); modifications at positions 450, 451, and 452 underlined; 742 aa		WGYFDNFRFHCHFS PRDWQRLINNNWGFPRKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVF TDSYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLDNGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSSQLDRLMNP LIDQYLYYLS <u>KGLGSGSPHSA</u> QNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGP I WAKI PHTDGNFHPSPLMGGFGMKHPPQILIKNT PVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENS KRWNPEIQYTSNYYSNNVEFAVNTGEGVYS EPRPIGTRYLTRNL
TTM-018 6mer peptide underlined, starts at position 456 (immediately subsequent to position 455); modifications at positions 454, 455, and 464 underlined; 742 aa	51	MAADGYLPDWLEDNLSEGI REWWALKPGAPQPKANQQHQDNARGVLVPGYKYLGP NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLYKNHADA EFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGD TESVPDPQPIGEPPAAPSGVGS LTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWL GDRVITTTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDNFRFHCHFS PRDWQRLINNNWGFPRKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVF TDSYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLDNGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSSQLDRLMNP LIDQYLYYLS KTING <u>HDSPHSKA</u> QNQLTKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGP I WAKI PHTDGNFHPSPLMGGFGMKHPPQILIKNT PVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENS KRWNPEIQYTSNYYSNNVEFAVNTGEGVYS EPRPIGTRYLTRNL
TTM-019 6mer peptide underlined, starts at position 456 (immediately subsequent to position 455); modifications at positions 451, 454, and 455 underlined; 742 aa	52	MAADGYLPDWLEDNLSEGI REWWALKPGAPQPKANQQHQDNARGVLVPGYKYLGP NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLYKNHADA EFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGD TESVPDPQPIGEPPAAPSGVGS LTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWL GDRVITTTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDNFRFHCHFS PRDWQRLINNNWGFPRKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVF TDSYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLDNGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSSQLDRLMNP LIDQYLYYLS KT <u>VNGHDSPHSKA</u> QNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGP I WAKI PHTDGNFHPSPLMGGFGMKHPPQILIKNT PVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENS KRWNPEIQYTSNYYSNNVEFAVNTGEGVYS EPRPIGTRYLTRNL
TTM-020 6mer peptide underlined, starts at position 456 (immediately subsequent to position 455); modifications at positions 454, 455, and 462 underlined; 742 aa	53	MAADGYLPDWLEDNLSEGI REWWALKPGAPQPKANQQHQDNARGVLVPGYKYLGP NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLYKNHADA EFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGD TESVPDPQPIGEPPAAPSGVGS LTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWL GDRVITTTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDNFRFHCHFS PRDWQRLINNNWGFPRKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVF TDSYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLDNGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSSQLDRLMNP LIDQYLYYLS KTING <u>HDSPHSKAL</u> NQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGP I WAKI PHTDGNFHPSPLMGGFGMKHPPQILIKNT PVPADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENS KRWNPEIQYTSNYYSNNVEFAVNTGEGVYS EPRPIGTRYLTRNL
TTM-021 6mer peptide underlined, starts at position 456 (immediately subsequent to position 455); modifications at positions 454,	54	MAADGYLPDWLEDNLSEGI REWWALKPGAPQPKANQQHQDNARGVLVPGYKYLGP NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLYKNHADA EFQERLKEDTSFGG NLGRAVFQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGD TESVPDPQPIGEPPAAPSGVGS LTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWL GDRVITTTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDNFRFHCHFS PRDWQRLINNNWGFPRKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVF TDSYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLDNGSQAVGRS SFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSSQLDRLMNP LIDQYLYYLS KTING <u>HDSPHSKA</u> QNQQSLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD

455, and 466 underlined; 742 aa		ADKVMITNEEEIKTTNPVATESYGVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGGPIWAKIPHTDGNFHPSPLMGGFGMKHPPQILIKNTVPVADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENS KRWNPEIQYTSNYYSNNVEFAVNTTEGVYS EPRPIGTRYLTRNL
TTM-022 6mer peptide underlined, starts at position 456 (immediately subsequent to position 455); modifications at positions 454, 455, and 466 underlined; 742 aa	55	MAADGYLPDWLEDNLSEGIREWALKPGAPQPKANQQHQDNARGLVLPGYKYLPGP NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADADEFQERLKEDTSFGG NLGRAVFQAKKRLLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTEVPDPQPIGEPPAAPSGVGS LTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGD RVITTTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDENRFHCHFS PRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIAN NLSTSTVQVFTDSYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLDNGSQAVGRS SFYCLEYFPPS QMLRTGNNFQFSYEFENVPFHSSYAHSSQLDRLMNP LIDQYLYYLS KTING HDS PHSKA Q NQ Q I LKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGGPIWAKIPHTDGNFHPSPLMGGFGMKHPPQILIKNTVPVADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENS KRWNPEIQYTSNYYSNNVEFAVNTTEGVYS EPRPIGTRYLTRNL
TTM-023 6mer peptide underlined, starts at position 456 (immediately subsequent to position 455); 742 aa	56	MAADGYLPDWLEDNLSEGIREWALKPGAPQPKANQQHQDNARGLVLPGYKYLPGP NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADADEFQERLKEDTSFGG NLGRAVFQAKKRLLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTEVPDPQPIGEPPAAPSGVGS LTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGD RVITTTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDENRFHCHFS PRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIAN NLSTSTVQVFTDSYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLDNGSQAVGRS SFYCLEYFPPS QMLRTGNNFQFSYEFENVPFHSSYAHSSQLDRLMNP LIDQYLYYLS KTINGSG SPHFTR Q NQ Q T LKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGGPIWAKIPHTDGNFHPSPLMGGFGMKHPPQILIKNTVPVADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENS KRWNPEIQYTSNYYSNNVEFAVNTTEGVYS EPRPIGTRYLTRNL
TTM-024 6mer peptide underlined, starts at position 456 (immediately subsequent to position 455); modifications at positions 451, 454, and 455 underlined; 742 aa	57	MAADGYLPDWLEDNLSEGIREWALKPGAPQPKANQQHQDNARGLVLPGYKYLPGP NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADADEFQERLKEDTSFGG NLGRAVFQAKKRLLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTEVPDPQPIGEPPAAPSGVGS LTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGD RVITTTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDENRFHCHFS PRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIAN NLSTSTVQVFTDSYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLDNGSQAVGRS SFYCLEYFPPS QMLRTGNNFQFSYEFENVPFHSSYAHSSQLDRLMNP LIDQYLYYLS KT NG HDS PHSKA Q NQ Q T LKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGGPIWAKIPHTDGNFHPSPLMGGFGMKHPPQILIKNTVPVADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENS KRWNPEIQYTSNYYSNNVEFAVNTTEGVYS EPRPIGTRYLTRNL
TTM-025 6mer peptide underlined, starts at position 456 (immediately subsequent to position 455); modification at position 462 underlined; 742 aa	58	MAADGYLPDWLEDNLSEGIREWALKPGAPQPKANQQHQDNARGLVLPGYKYLPGP NGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADADEFQERLKEDTSFGG NLGRAVFQAKKRLLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTEVPDPQPIGEPPAAPSGVGS LTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGD RVITTTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTP WGYFDENRFHCHFS PRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIAN NLSTSTVQVFTDSYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLDNGSQAVGRS SFYCLEYFPPS QMLRTGNNFQFSYEFENVPFHSSYAHSSQLDRLMNP LIDQYLYYLS KTINGSG SPHSLPW N Q Q T LKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYGVATNHQSAQAQAQTGWVQNQGILPGMVWQDR DVYLQGGPIWAKIPHTDGNFHPSPLMGGFGMKHPPQILIKNTVPVADPPTAFNKDK LNSFITQYSTGQVSVEIEWELQKENS KRWNPEIQYTSNYYSNNVEFAVNTTEGVYS EPRPIGTRYLTRNL

TTM-026 6mer peptide underlined, starts at position 456 (immediately subsequent to position 455); modification at positions 454, 455, and 464 underlined; 742 aa	59	MAADGYLPDWLEDNLSEGIREWALKPGAPQPKANQQHQDNARGLVLPGYKYLGP NGLDKGEFVNAADAAALEHDKAYDQQLKAGDNPYLYNHADADEFQERLKEDTSFGG NLGRAVFQAKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAK KRLNFGQTGDTESVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSS SGNWHCDSQWLGDVRVITSTRTWALPTYNNHLYKQISNSTSGSSNDNAYFGYSTP WGYFDENRFHCHFSRDLWQRLINNNWGFPRKRLNFKLFNIQVKEVTDNNGVKTIAN NLTSTVQVFTSDYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLNDGSQAVGRS SFYCLEYFPSQMLRTGNFQFSYEFENVFPHSSYAHSSQLDRLMNPIDQYLYYLS KTING <u>HDS</u> <u>PHSKA</u> <u>QNH</u> QTLKFSVAGPSNMAVQGRNYIPGPSYRQVRVSTTVTQNNN SEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVD ADKVMITNEEEIKTTNPVATESYQVATNHQSAQAQAQTGWVQNGILPGMVWQDR DVLQGPWAKIPHTDGNFHPSPLMGGFGMKHPPQILIKNTFPVADPPTAFNKKDK LNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYKSNNVFAVNTGEGVYS EPRPIGTRYLTRNL
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Table 5. Exemplary full length capsid nucleic acid sequences

Name and Annotation	SEQ ID NO:	NT Sequence
TTM-001 9mer peptide underlined	983	ATGGCTGCCGATGGTTATCTTCCAGAttggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGTATTGGCAAATCGGGTGCACAGCCCGCTAAA AAGAGACTCAATTTTCGGTCAGACTGGCGACACAGAGTCAGTCCAGACCCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACCTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAAGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTACGGACTCAGACTATCAGCTCCCGTACGT GCTCGGGTCCGGCTCACGAGGGCTGCCTCCCGCCGTTCCAGCGGACGTTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGCGGTGGGTCTGTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAAGCGGGTAACAATT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGACCAATACTTGTAAtTActTgagt AAaACaATTAACGGAAGCGGAAGCCACACAGCAAAGCAAAAAACACAGACCTT gAAgTTtctcgTAgCtGgTcCtAGCAACATGGCTGTCCAGGGAAGAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAGAAGGAGAGGACCGTTTTCTTTC CTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAAGTGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAACCTACTAACCCGGTAGC AACGGAGTCTTATGGACAAGtgccacaaaccaccagagtGCCCAAGCACAGGCGC AGaccggctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCTTCTCCGCTGATGGGAGGGTTTGAATGAAGACCCGCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCAACGGCCTTCAACAAGGACAAG CTGAACCTTTTCATCACCCAGTATTTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAAActTaTAA

TTM-002 7mer peptide underlined	984	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGGCGGCCCTCGAGCA CGACAAGGCCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGACAGCCCCGTAAA AAGAGACTCAATTTTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCCTACTTCGGGTACAGCACCCTC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACCTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTATCAGCTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCACGCGGACGTTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCTTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACCT CCAGTTCAGCTACGAGTTTGAGAAGCTACCTTTCCATAGCAGTACGCTCAGAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGACCAATACTTGTATtActTgagt AAaACaATTAACGGACACGACAGCCACACAAAAGCGGACAAAACACAGACcT gAAgTtTtcgGTaGcTGGtCCTAGCAACATGGCTGTCCAGGGAAAGAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAGAAGGAGGACCGTTTTCTTTC CTTTGTCTGGATCTTTAATTTTTTGGCAAAACAAGGAAGTGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAACCTACTAACCCGGTAGC AACGGAGTCTATGGACAAGtggccacaaaccaccagagtGCCAAGCACAGGCGC AGaccggtctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCCTTCTCCGCTGATGGGAGGGTTTGAATGAAGCACCAGCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACCTTTTCATCACCAGTATTTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAAcTtTaTAA
TTM-023	12	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGGCGGCCCTCGAGCA CGACAAGGCCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGACAGCCCCGTAAA AAGAGACTCAATTTTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCCTACTTCGGGTACAGCACCCTC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACCTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTATCAGTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCACGCGGACGTTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCTTCG

		TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCAgTAtcTGTAAtActTgagt AAGACGGAGCGTGTGTCTGGTTCTCCGCATTCTAAGGCGCAGAATCAGCAGACgT gAAgTtTtcgGTaGcTGGtCctAGcAAcATGGCTGTCCAGGGAAGAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTC CTTTGTCTGGATCTTTAATTTTTTGGCAAACAAGGAAGTGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAACTACTAACCCGGTAGC AACGGAGTCTTATGGACAAGtgccacaaaccaccagagtGCCCCAGCACAGGCGC AGaccggtggtgttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCCTTCTCCGCTGATGGGAGGGTTTGAATGAAGCACCCGCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACCTTTTATCACCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAAcTta
TTM-004	13	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCGGAGTTCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCCGACTCCTCCGCGGTATTGGCAAATCGGGTGACAGCCCCGTAAA AAGAGACTCAATTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGGCTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACCTGGGGATTCCGGCCTAAGCGACTCAACTCAAGCTCT TCAACATTCAAGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTACGGACTCAGACTATCAGCTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCACAGCGGACGTTTTTATGA TTCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCGGTGGGTCTGTTCCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAAGCGGTTAAACAATT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCAgTAtcTGTAAtActTgagt AAGGCGGAGATTGGTCATGATTCTCCGCATAAGTCTGGTCAGAATCAGCAGACgT gAAgTtTtcgGTaGcTGGtCctAGcAAcATGGCTGTCCAGGGAAGAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTC CTTTGTCTGGATCTTTAATTTTTTGGCAAACAAGGAAGTGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAACTACTAACCCGGTAGC AACGGAGTCTTATGGACAAGtgccacaaaccaccagagtGCCCCAGCACAGGCGC AGaccggtggtgttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCCTTCTCCGCTGATGGGAGGGTTTGAATGAAGCACCCGCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACCTTTAATCACCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAAcTta
TTM-005	14	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCCTCAACCCAAGGCAAATCAACAAC

		ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCA CGACAAGGCTTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGG AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGACAGCCCCGTAAA AAGAGACTCAATTTCCGTGAGCTGGCGACACAGAGTCAGTCCCAGACCCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGAATTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTACGGACTCAGACTATCAGCTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCCAGCGGACGTTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCTGTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCAGAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGATCAGTATcTGTATtActTgagt AAGACGATTATTGGTTCTGGTTCTCCGATTCTAAGGCGCAGAATCGTCATACGtT gAAgTtttcgGTaGctGgtCctAGCAACATGGCTGTCCAGGGAAGAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTTCTTTC CTTTGTCTGGATCTTTAATTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAACTACTAACCCGGTAGC AACGGAGTCCCTATGGACAAGTggccacaaaccaccagagtGCCCAAGCACAGGCGC AGaccggtcggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCCTTCTCCGCTGATGGGAGGGTTTGAATGAAGCACCCGCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACCTCTTTCATCACCAGTATTCTACTGGCCAAGTCAGCTGGAGATCGATG GGAGCTGCAGAAGGAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAActTa
TTM-006	15	ATGGCTGCCGATGGTTATCTTCCAGAttggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCCTCAACCCAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCA CGACAAGGCCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGG AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGACAGCCCCGTAAA AAGAGACTCAATTTCCGTGAGCTGGCGACACAGAGTCAGTCCCAGACCCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGAATTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTACGGACTCAGACTATCAGCTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCCAGCGGACGTTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCTGTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCAGAGCC

		AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCagTAtcTGTAtTAActTgagt AAGACGGAGAAGATGTCTGGTTCTCCGCATTCTAAGGCGCAGAATCAGCAGACgT gAAgTtTtcgGTaGctGGtCctAGCAACATGGCTGTCCAGGGAGAAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTC CTTTGTCTGGATCTTTAATTTTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAACTACTAACCCGGTAGC AACGGAGTCTATGGACAAGtgggccacaaaccaccagagtGCCCCAAGCACAGGCGC AGaccggtctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCTTCTCCGCTGATGGGAGGGTTTGAATGAAGCACCCGCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACCTTTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAAcTta
TTM-007	16	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGGCGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGTATTGGCAAATCGGGTGCACAGCCCGCTAAA AAGAGACTCAATTTCCGTGAGACTGGCGACACAGAGTCAGTCCAGACCCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCCACAG CACCCGAACCTGGGCCCTGCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCCGTACAGCACCCCT TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAAGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTACGGACTCAGACTACGTCCCGTACGT GCTCGGGTCCGCTCACGAGGGCTGCCTCCCGCGTTCACGCGGACGTTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCTGTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTT CCAGTTCAGCTACGAGTTTGAGAAGCTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCagTAtcTGTAtTAActTgagt AAGGAGATTAATGGTCTGGTTCTCCGCATTCTAAGGCGCAGAATCAGCAGACgT gAAgTtTtcgGTaGctGGtCctAGCAACATGGCTGTCCAGGGAGAAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTC CTTTGTCTGGATCTTTAATTTTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAACTACTAACCCGGTAGC AACGGAGTCTATGGACAAGtgggccacaaaccaccagagtGCCCCAAGCACAGGCGC AGaccggtctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCTTCTCCGCTGATGGGAGGGTTTGAATGAAGCACCCGCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACCTTTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAAcTta
TTM-008	17	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGGCGCCCTCGAGCA

		CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGCCAGCCCCGTAAA AAGAGACTCAATTTTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACCTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAAGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTACGAGTCAAGTATCAGCTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCACGCGGACGTTTTTCATGA TTCCTTCTAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCTGTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAAACAACCT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCAgTAtcTGTAAtTAActTgagt AAGACGTTAATGGTTCTGGTTCTCCGCATTCTAAGGCGCCGAATCTGCAGACGtT gAAgTtTtcgGTaGctGGtCctAGCAACATGGCTGTCCAGGGAAGAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAGAAGGAGAGGACCGTTTTCTTTC CTTTGTCTGGATCTTTAATTTTGGCAAACAAGGAAGTGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAACCTACTAACCCTGAGC AACGGAGTCTATGGACAAGtgggccacaaaccaccagagtGCCCAAGCACAGGCCG AGaccggtctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTGGCAGGACAGA GATGTGTACTTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCTTCTCCGCTGATGGGAGGGTTTGAATGAAGACCCGCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACCTTTTCATACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTAACTAGCAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAAActTa
TTM-009	18	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGGCTTCGAGCA CGACAAGGCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGCCAGCCCCGTAAA AAGAGACTCAATTTTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACCTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAAGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTACGGACTCAGACTATCAGCTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCACGCGGACGTTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCTGTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAAACAACCT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCAgTAtcTGTAAtTAActTgagt AAGACGGAGAAGACGTCTGGTTCTCCGCATTCTAAGGCGCAGAATCAGCAGACGtT

		gAAgTtttcgGTaGcTgGtCctAGCAACATGGCTGTCCAGGGAAGAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTC CTTTGTCTGGATCTTTAATTTTTTGGCAAACAAGGAAGTGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAATACTACTAACCCGGTAGC AACGGAGTCCATGGACAAGtgGCCacaaaccaccagagtGCCCAAGCACAGGCGC AGaccggtctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCCTTCTCCGCTGATGGGAGGGTTTGAATGAAGCACCCGCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACCTTTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAActTa
TTM-010	19	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGCTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAGAAGAGGCCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGCACAGCCCGTAAA AAGAGACTCAATTTCCGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTCGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAAGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTACGGACTCAGACTATCAGTCCCGTACGT GCTCGGGTCCGCTCACGAGGGCTGCCTCCCGCCGTCCAGCGGACGTTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGTCCGTTCC TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACCTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGATCAgTAtcTGTAtTAActTgagt AAGACGATGAATGGTCATGATTCTCCGCATTCTAAGGCGCAGAATCAGCAGACgT gAAgTtttcgGTaGcTgGtCctAGCAACATGGCTGTCCAGGGAAGAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTC CTTTGTCTGGATCTTTAATTTTTTGGCAAACAAGGAAGTGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAATACTACTAACCCGGTAGC AACGGAGTCCATATGGACAAGtgGCCacaaaccaccagagtGCCCAAGCACAGGCGC AGaccggtctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCCTTCTCCGCTGATGGGAGGGTTTGAATGAAGCACCCGCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACCTTTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAActTa
TTM-011	20	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGCTCTTTTGGGGGC

		AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGACAGCCCCGTAAA AAGAGACTCAATTTTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCCTACTTCGGGTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAAGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTCACGACTCAGACTATCAGCTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCACGCGGACGTTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCTTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTT CCAGTTCAGCTACGAGTTTGAGAAGCTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCagTAtcTGtAtTActTgagt AAGACGATTGATGGTCATGATTCTCCGCATTCTAAGGCGCAGAATCAGCAGACgT gAAgTtTtcgGTaGctGGtCctAGCAACATGGCTGTCCAGGGAAGAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAGAAGGAGAGGACCGTTTTCTTTC CTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAACCTGGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAACCTACTAACCCGGTAGC AACGGAGTCTATGGACAAGtgcccaaaaccaccagagtGCCCAAGCACAGGCGC AGaccggtggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCCTTCTCCGCTGATGGGAGGGTTTGAATGAAGACCCGCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCCTTCAACAAGGACAAG CTGAACCTTTTCATCACCAGTATTTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTATAACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACGcGgTAttTAACgaGgAAcTta
TTM-012	21	ATGGCTGCCGATGGTTATCTTCCAGAttggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCCTCAACCCAAGGCAAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGACAGCCCCGTAAA AAGAGACTCAATTTTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAAGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTACGGAATCAGACTATCAGTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCACGCGGACGTTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCTTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTT CCAGTTCAGCTACGAGTTTGAGAAGCTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCagTAtcTGtAtTActTgagt AAGACGAATAATGGTCATGATTCTCCGCATTCTAAGGCGCAGAATCAGCAGACgT gAAgTtTtcgGTaGctGGtCctAGCAACATGGCTGTCCAGGGAAGAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC

		AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTC CTTTGTCTGGATCTTTAATTTTTTGGCAAACAAGGAAGTGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAATACTACTAACCCGGTAGC AACGGAGTCTTATGGACAAGtggccacaaaccaccagagtGCCCAAGCACAGGCGC AGaccggtctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCCTTCTCCGCTGATGGGAGGGTTTGAATGAAGCACCCGCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACCTTTTCATCAGCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTAAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAActTa
TTM-013	22	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCCTCAACCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCCGACTCCTCCGCGGTATTGGCAAATCGGGTGACAGCCCGCTAAA AAGAGACTCAATTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTACGGACTCAGACTATCAGTCCCCTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCACAGCGGACGTTTTTATGA TTCTCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCTGTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAAACACTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGATCAgTatcTGTAActTgagt AAGACGCAGCGTAAGTCTGGTTCTCCGATTCTAAGGCGCAGAATCAGCAGACGtT gAAgTtttcgGTaGctGgtCctAGCAACATGGCTGTCCAGGGAGAAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTC CTTTGTCTGGATCTTTAATTTTTTGGCAAACAAGGAAGTGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAATACTACTAACCCGGTAGC AACGGAGTCTTATGGACAAGtggccacaaaccaccagagtGCCCAAGCACAGGCGC AGaccggtctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCCTTCTCCGCTGATGGGAGGGTTTGAATGAAGCACCCGCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACCTTTTCATCAGCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTAAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAActTa
TTM-014	23	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCCTCAACCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAGAAGAGGCCTGTAGAGCAGTCTC

		CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGACAGCCCCGTAAA AAGAGACTCAATTTTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGGTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTATCAGCTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCCAGCGGACGTTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCTTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACCTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCAGAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCAgTAtcTGTAAtActTgagt AAGACGATTAATGGTTCTGGTTCTCCGCATTCTAAGGCGCAGGCGCGTAAGACGtT gAAgTtttcgGTaGcTgGtCctAGCAACATGGCTGTCCAGGGAAGAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTTCTTTC CTTTGTCTGGATCTTTAATTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAACTACTAACCCGGTAGC AACGGAGTCTTATGGACAAGtgccacaaaccaccagagtGCCCCAAGCACAGGCGC AGaccggtctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCCTTCTCCGCTGATGGGAGGGTTTGAATGAAGCACCCGCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACCTTTTATCACCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAAcTta
TTM-015	24	ATGGCTGCCGATGGTTATCTTCCAGAttggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGACAGCCCCGTAAA AAGAGACTCAATTTTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTATCAGCTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCCAGCGGACGTTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCTTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACCTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCAGAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCAgTAtcTGTAAtActTgagt AAGTATATTGTGGGTTCTGGTTCTCCGCATTCTAAGGCGCAGAAATCAGCAGACGtT gAAgTtttcgGTaGcTgGtCctAGCAACATGGCTGTCCAGGGAAGAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTTCTTTC

		CTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAAGTGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAACCTACTAACCCGGTAGC AACGGAGTCTATGGACAAGTggccacaaaccaccagagtGCCCAAGCACAGGCGC AGaccggtgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCCTTCTCCGCTGATGGGAGGGTTTGAATGAAGCACCCGCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACCTTTTCATCACCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAAcTta
TTM-016	25	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCCTCAACCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGTATTGGCAAATCGGGTGCACAGCCCGCTAAA AAGAGACTCAATTTTCGTGAGTGGCGACACAGAGTCAGTCCAGACCCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACAG CACCCGAACCTGGGCCCTGCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAAGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTACGGACTCAGACTATCAGTCCCGTACGT GCTCGGGTTCGGCTCACGAGGGCTGCCCTCCGCGCTTCCAGCGGACGTTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCTGTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCagTAtcTGtAtTAActTgagt AAGACGATTTCTAAGCGTGGTTCTCCGATTCTAAGGCGCAGAAATCAGCAGAGCgt gAAgTtTtcgGTaGctGGtCctAGCAACATGGCTGTCCAGGGAAGAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTTCTTTC CTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAAGTGAAGAGACAACCTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAACCTACTAACCCTGATG AACGGAGTCTATGGACAAGTggccacaaaccaccagagtGCCCAAGCACAGGCGC AGaccggtgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCCTTCTCCGCTGATGGGAGGGTTTGAATGAAGCACCCGCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACCTTTTCATCACCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAAcTta
TTM-017	26	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCCTCAACCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGTATTGGCAAATCGGGTGCACAGCCCGCTAAA AAGAGACTCAATTTTCGTGAGTGGCGACACAGAGTCAGTCCAGACCCCTCAACC

		AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGAATTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACCTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAAGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTACGAGCTCAGACTATCAGCTCCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCACGCGGACGTTTTTCATGA TTCTCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCTGTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACCT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCAgTAtcTGTAAtActTgagt AAGGGTCTGGGTGGTTCGTGTTCTCCGCATTCTAAGGCGCAGAATCAGCAGACGtT gAAgTtTtcgGTaGcTGGtCctAGCAACATGGCTGTCCAGGGAAGAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAGAAGGAGAGGACCGTTTTCTTTC CTTTGTCTGGATCTTTAATTTTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAAACTACTAACCCGGTAGC AACGGAGTCTTATGGACAAGtgggccacaaaccaccagagtGCCCCAGCACAGGCGC AGaccggtctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGGACGGCAACTT TCACCCCTTCTCCGCTGATGGGAGGGTTTGAATGAAGCACCCGCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACCTTTTCATCAGCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACGcGgTAttTAACGaGgAAcTtTa
TTM-018	27	ATGGCTGCCGATGGTTATCTTCCAGAttggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGGCCCTCGAGCA CGACAAGGCTACGACCAGCAGCTCAAGGCCGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGCTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTC CTCAGGAACCCGACTCCTCCGCGGGTATTGGCAAATCGGGTGACAGCCCGCTAAA AAGAGACTCAATTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGAGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGAATTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACCTGGGGATTCCGGCCTAAGCGACTCACTTCAAGCTCT TCAACATTCAAGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTACGGACTCAGACTATCAGCTCCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCACGCGGACGTTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCTGTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACCTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCAgTAtcTGTAAtActTgagt AAGACGATTAATGGTCATGATTCTCCGCATTCTAAGGCGCAGAATCTGCAGACGtT gAAgTtTtcgGTaGcTGGtCctAGCAACATGGCTGTCCAGGGAAGAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAGAAGGAGAGGACCGTTTTCTTTC CTTTGTCTGGATCTTTAATTTTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAAACTACTAACCCGGTAGC

		AACGGAGTCCTATGGACAAGtggccacaaaccaccagagtGCCCAAGCACAGGCGC AGaccggctggggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCTTCTCCGCTGATGGGAGGGTTTGAATGAAGCACCCGCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACCTCTTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACGaGgAActTa
TTM-019	28	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGCTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAGAAGAGGCCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGCACAGCCCGTAAA AAGAGACTCAATTTGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTCGCAATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGGTACAGCACCCTC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAAGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTCCAGGACTCAGACTATCAGTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCACGCGGACGTTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCGTGGGTCTTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACCTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGATCAgTatcTGTAAtTgagt AAGACGGTGAATGGTCATGATTCTCCGCATTCTAAGGCGCAGAATCAGCAGACgT gAAgTtttcgGTaGctGgtCctAGCAACATGGCTGTCCAGGGAAGAAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTTCTTC CTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAACTACTAACCCGGTAGC AACGGAGTCCTATGGACAAGtggccacaaaccaccagagtGCCCAAGCACAGGCGC AGaccggctggggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCTTCTCCGCTGATGGGAGGGTTTGAATGAAGCACCCGCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACCTCTTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACGaGgAActTa
TTM-020	29	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGCTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAGAAGAGGCCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGCACAGCCCGCTAAA AAGAGACTCAATTTGGTCAGACTGGCGACACAGAGTCAGTCCAGACCCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC

		TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCCTACTTCGGGTACAGCACCCTC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTATCAGCTCCCCTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCACAGCGGACGTTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCTTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACCTT CCAGTTCAGCTACGAGTTTGAGAAGCTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGATCAGTAtcTGTAtTAActTgagt AAGACGATTAATGGTCATGATTCTCCGCTTCTAAGGCGCTGAATCAGCAGACGtT gAAgTtTtcgGTaGcTGGtCCtAGCAACATGGCTGTCCAGGGAAGAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCTGGAGCTTCTTCTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTTCTTTC CTTTGTCTGGATCTTTAATTTTTTGGCAAACAAGGAAGTGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAACCTACTAACCCGGTAGC AACGGAGTCTATGGACAAGtgcccaaaaccaccagagtGCCCCAGCACAGGCGC AGaccggtgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCCTTCTCCGCTGATGGGAGGGTTTGAATGAAGACCCGCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACCTTTTCATCACCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACGcGgTAttTAACgaGgAAcTtA
TTM-021	30	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCTCAACCCAAGGCAAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGCGGCCCTCGAGCA CGACAAGGCCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCAGGAGCGGCTCAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAGAGGCCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGTATTGGCAAATCGGGTGACAGCCCGCTAAA AAGAGACTCAATTTTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCTCAACC AATCGGAGAACCTCCCCGAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACAG CACCCGAACCTGGGCCCTGCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCCTACTTCGGCTACAGCACCCTC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAAGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTACGGACTCAGACTATCAGTCCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCACAGCGGACGTTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCTTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACCTT CCAGTTCAGCTACGAGTTTGAGAAGCTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGATCAGTAtcTGTAtTAActTgagt AAGACGATTAATGGTCATGATTCTCCGCTTCTAAGGCGCAGAATCAGCAGTCTtT gAAgTtTtcgGTaGcTGGtCCtAGCAACATGGCTGTCCAGGGAAGAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCTGGAGCTTCTTCTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTTCTTTC CTTTGTCTGGATCTTTAATTTTTTGGCAAACAAGGAAGTGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAACCTACTAACCCGGTAGC AACGGAGTCTATGGACAAGtgcccaaaaccaccagagtGCCCCAGCACAGGCGC AGaccggtgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA

		GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCCTTCTCCGCTGATGGGAGGGTTTGAATGAAGCACCCGCTCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACCTTTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTAAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAAcTta
TTM-022	31	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGG AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAGAGAGGCTTAGAGCAGTCTC CTCAGGAACCCGACTCCTCCGCGGTATTGGCAAATCGGGTGACAGCCCCGTAAA AAGAGACTCAATTTCCGTGAGCTGGCGACACAGAGTCAGTCCCAGACCCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCCTACTTCCGGTACAGCACCCCC TGGGGGTATTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACCTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGTCTC TCAACATTGAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTACGGACTCAGACTATCAGTCCCCTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCACAGCGGACGTTTTTATGA TTCTCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCTGTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCagTAtcTGTAtTActTgagt AAGACGATTAATGGTCATGATTCTCCGATTCTAAGGCGCAGAATCAGCAGATTtT gAAgTtTtcgGTaGctGgtCctAGCAACATGGCTGTCCAGGGAGAAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAGAAGGAGAGGACCGTTTTCTTTC CTTTGTCTGGATCTTTAATTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAACCTACTAACCCGGTAGC AACGGAGTCTATGGACAAGtgccacaaaccacagagtGCCCAAGCACAGGCGC AGaccggtctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCCTTCTCCGCTGATGGGAGGGTTTGAATGAAGCACCCGCTCTCAGTACC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACCTTTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAAcTta
TTM-023	32	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCCTCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGG AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAGAAGAGGCTGTAGAGCAGTCTC CTCAGGAACCCGACTCCTCCGCGGTATTGGCAAATCGGGTGACAGCCCCGTAAA AAGAGACTCAATTTCCGTGAGCTGGCGACACAGAGTCAGTCCCAGACCCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCACCTACAACAATCACCTCTACAAGCAAATCTCCA

		ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTATCAGCTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCAGCGGACGTTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCGTTTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACCTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCAgTAtcTGTATtActTgagt AAGACGATTAATGGTTCTGGTTCTCCGCATTTTACGCGTCAGAATCAGCAGACGtT gAAgTtttcgGTaGcTGGtCctAGCAACATGGCTGTCCAGGGAAGAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTC CTTTGTCTGGATCTTTAATTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAACTACTAACCCGGTAGC AACGGAGTCCCTATGGACAAGtgccacaaaccaccagagtGCCCAAGCACAGGCGC AGaccggtcggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCCTTCTCCGCTGATGGGAGGGTTTGAATGAAGCACCCGCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACCTTTTCATCACCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAAcTta
TTM-024	33	ATGGCTGCCGATGGTTATCTTCCAGAttggcTCGAGGACAACCTTAGTGAAGGAAT TCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCCAACCCAAGGCAAATCAACAAC ATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTACAAATACCTTGGACCCGGC AACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCA CGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACA ACCACGCCGACGCCGAGTTCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAGAGGCTTCTTGAACCTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAGAAGAGGCCCTGTAGAGCAGTCTC CTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGACAGCCCGCTAA AAGAGACTCAATTTCCGTCAGACTGGCGACACAGAGTCAGTCCAGACCCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAG GTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAG CACCCGAACCTGGGCCCTGCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACGCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTATCAGCTCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCAGCGGACGTTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCGTTTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACCTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCAgTAtcTGTATtActTgagt AAGACGTCTAATGGTCATGATTCTCCGCATTTCTAAGGCGCAGAATCAGCAGACGtT gAAgTtttcgGTaGcTGGtCctAGCAACATGGCTGTCCAGGGAAGAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTC CTTTGTCTGGATCTTTAATTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAACTACTAACCCGGTAGC AACGGAGTCCCTATGGACAAGtgccacaaaccaccagagtGCCCAAGCACAGGCGC AGaccggtcggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCCTTCTCCGCTGATGGGAGGGTTTGAATGAAGCACCCGCTCCTCAGATCC

		TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAGCTGAACCTTTTCATCACCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTGGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGTGAACCCCGCCCCATTGGCACGcGgTAttTAACGaGgAAcTta
TTM-025	34	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAATTCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCCTCAACCCAAGGCAAATCAACAACATCAAGACAACGCTCGAGGTCTTGCTTCCGGGTACAAATACCTTGGACCCGGCAACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGGCGGCCCTCGAGCAGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACAACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGCAACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCTGGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTCTCAGGAACCGGACTCCTCCGCGGTATTGGCAAATCGGGTGACAGCCCCGTAAA AAGAGACTCAATTTTCGTGACTGGCGACACAGAGTCAGTCCCAGACCCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAGGTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACACAGCACCCGAACCTGGGCCCTGCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA GCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAAGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAA TAACTTACCAGCACGGTCCAGGTCTTACGGAAGTCAAGACTCAGACTCAGCTCCCGTACGT GCTCGGGTCCGGCTCAGGAGGCTGCCCTCCGCGCTTCCAGCGGACGTTTTTCATGA TTCTCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCTGTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTT CCAGTTCAGCTACGAGTTTGAGAAGCTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCagTAtcTGtAtTActTgagt AAGACGATTAATGGTTCTGGTTCTCGCATTCTCTGCCGTGGAATCAGCAGACGtT gAAgTtttcgGTaGctGGtCctAGCAACATGGCTGTCCAGGGAAGAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAACAACAAC AGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTTCTTTC TTTGTCTGGATCTTTAATTTTGGCAAACAAGGAAGTGAAGAGACAACAGTGGAT GCGGACAAAGTCATGATAACCAACGAGAAGAAATTAAACTACTAACCCTGATAGC AACGGAGTCTATGGACAAGtgggccacaaaccaccagagtGCCCCAGCACAGGCGC AGaccggtgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCTTCTCCGCTGATGGGAGGTTTGAATGAAGCACCCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACCTTTTCATCACCAGTATTCTACTGGCCAAGTCAGCTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACGcGgTAttTAACGaGgAAcTta
TTM-026	35	ATGGCTGCCGATGGTTATCTTCCAGattggcTCGAGGACAACCTTAGTGAAGGAATTCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCCTCAACCCAAGGCAAATCAACAACATCAAGACAACGCTCGAGGTCTTGCTTCCGGGTACAAATACCTTGGACCCGGCAACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGGCGGCCCTCGAGCAGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACAACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGCAACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCTGGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTCTCAGGAACCGGACTCCTCCGCGGTATTGGCAAATCGGGTGACAGCCCCGTAAA AAGAGACTCAATTTTCGTGACTGGCGACACAGAGTCAGTCCCAGACCCCTCAACC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAGGTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCC TCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACAGCACCCGAACCTGGGCCCTGCCACCTACAACAATCACCTCTACAAGCAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCA

	GCGACTCATCAACAACAACCTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCT TCAACATTCAAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAAT AACCTTACCAGCACGGTCCAGGTCTTACGGACTCAGACTATCAGCTCCCCGTACGT GCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCCAGCGGACGTTTTTCATGA TTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCTGTCG TCCTTTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACCTT CCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCC AAAGCCTGGACCGACTAATGAATCCACTCATCGAtCAgTAtcTGTAAtActTgagt AAGACGATTAATGGTCATGATTCTCCGCATTCTAAGGCGCAGAAATCATCAGACGtT gAAgTtTtcgGTaGcTGGtCCtAGCAACATGGCTGTCCAGGGAAGAAACTACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAAC AGCGAATTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTC CTTTGTCTGGATCTTTAATTTTTTGGCAAACAAGGAAGTGAAGAGACAACGTGGAT GCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAATACTACTAACCCGGTAGC AACGGAGTCTTATGGACAAGtgccacaaaccaccagagtGCCCCAGCACAGGCGC AGaccggtctgggttcaaaaccaAGGAATACTTCCGGGTATGGTTTGGCAGGACAGA GATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTT TCACCCTTCTCCGCTGATGGGAGGGTTTGAATGAAGCACCCGCTCCTCAGATCC TCATCAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAG CTGAACCTTTTCATACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTG GGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCA ACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGT GAACCCCGCCCCATTGGCACgcGgTAttTAACgaGgAAcTtA
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[0146] In some embodiments, the polynucleotide encoding an AAV capsid variant, described herein comprises the nucleotide sequence of SEQ ID NO: 983 or 984, or a nucleotide sequence with at least 70% (e.g., at least about 80, 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto.

[0147] In some embodiments, the polynucleotide encoding an AAV capsid variant, described herein comprises the nucleotide sequence of any one of SEQ ID NOs: 12-35, or a nucleotide sequence with at least 70% (e.g., at least about 80, 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto.

[0148] In some embodiments, the polynucleotide encoding an AAV capsid variant described herein comprises the nucleotide sequence of SEQ ID NO: 983, or a nucleotide sequence with at least 70% (e.g., at least about 80, 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto. In some embodiments, the nucleotide sequence encoding an AAV capsid variant described herein, comprises a nucleotide sequence comprising at least one, two or three modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the nucleotide sequence of SEQ ID NO: 983. In some embodiments, the nucleotide sequence encoding an AAV capsid variant described herein, comprises a nucleotide sequence comprising at least one, two or three, but not more than 30, 20 or 10 different nucleotides relative to the amino acid sequence of SEQ ID NO: 983. In some embodiments, the nucleic acid sequence encoding an AAV capsid variant described herein is codon optimized.

[0149] In some embodiments, the polynucleotide encoding an AAV capsid variant described herein comprises the nucleotide sequence of SEQ ID NO: 984, or a nucleotide sequence with at least 70% (e.g., at least about 80, 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto. In some

embodiments, the nucleotide sequence encoding an AAV capsid variant described herein, comprises a nucleotide sequence comprising at least one, two or three modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the nucleotide sequence of SEQ ID NO: 984. In some embodiments, the nucleotide sequence encoding an AAV capsid variant described herein, comprises a nucleotide sequence comprising at least one, two or three, but not more than 30, 20 or 10 different nucleotides, relative to the amino acid sequence of SEQ ID NO: 984. In some embodiments, the nucleic acid sequence encoding an AAV capsid variant described herein is codon optimized.

[0150] In some embodiments, an AAV capsid variant described herein comprises the amino acid sequence of any one of SEQ ID NOs: 36-59, 981, or 982, or an amino acid sequence with at least 70% (e.g., at least about 80, 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto. In some embodiments, an AAV capsid variant described herein comprises an amino acid sequence comprising at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the amino acid sequence of SEQ ID NO: 36-59, 981, or 982. In some embodiments, the AAV capsid variant, comprises an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids, relative to the amino acid sequence of SEQ ID NO: 36-59, 981, or 982.

[0151] In some embodiments, an AAV capsid variant described herein, comprises the amino acid sequence of SEQ ID NO: 981, or an amino acid sequence with at least 70% (e.g., at least about 80, 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto. In some embodiments, an AAV capsid variant described herein comprises an amino acid sequence comprising at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the amino acid sequence of SEQ ID NO: 981. In some embodiments, an AAV capsid variant described herein comprises an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids, relative to the amino acid sequence of SEQ ID NO: 981.

[0152] In some embodiments, an AAV capsid variant described herein comprises the amino acid sequence of SEQ ID NO: 982, or an amino acid sequence with at least 70% (e.g., at least about 80, 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto. In some embodiments, an AAV capsid variant described herein comprises an amino acid sequence comprising at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the amino acid sequence of SEQ ID NO: 982. In some embodiments, the AAV

capsid variant, comprises an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids, relative to the amino acid sequence of SEQ ID NO: 982.

[0153] In some embodiments, an AAV capsid variant described herein comprises the amino acid sequence of SEQ ID NO: 36, or an amino acid sequence with at least 70% (e.g., at least about 80, 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto. In some embodiments, an AAV capsid variant described herein comprises an amino acid sequence comprising at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the amino acid sequence of SEQ ID NO: 36. In some embodiments, the AAV capsid variant, comprises an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids, relative to the amino acid sequence of SEQ ID NO: 36.

[0154] In some embodiments, an AAV capsid variant described herein comprises the amino acid sequence of SEQ ID NO: 39, or an amino acid sequence with at least 70% (e.g., at least about 80, 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto. In some embodiments, an AAV capsid variant described herein comprises an amino acid sequence comprising at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the amino acid sequence of SEQ ID NO: 39. In some embodiments, the AAV capsid variant, comprises an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids, relative to the amino acid sequence of SEQ ID NO: 39.

[0155] In some embodiments, an AAV capsid variant described herein comprises the amino acid sequence of SEQ ID NO: 51, or an amino acid sequence with at least 70% (e.g., at least about 80, 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto. In some embodiments, an AAV capsid variant described herein comprises an amino acid sequence comprising at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the amino acid sequence of SEQ ID NO: 51. In some embodiments, the AAV capsid variant, comprises an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids, relative to the amino acid sequence of SEQ ID NO: 51.

[0156] In some embodiments, an AAV capsid variant described herein comprises the amino acid sequence of SEQ ID NO: 52, or an amino acid sequence with at least 70% (e.g., at least about 80, 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto. In some embodiments, an AAV capsid variant described herein comprises an amino acid sequence comprising at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the amino acid sequence of SEQ ID NO: 52. In some embodiments, the AAV

capsid variant, comprises an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids, relative to the amino acid sequence of SEQ ID NO: 52.

[0157] In some embodiments, an AAV capsid variant described herein comprises an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 983 or 984, or a nucleotide sequence with at least 70% (e.g., at least about 80, 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto. In some embodiments, an AAV capsid variant described herein comprises an amino acid sequence encoded by a nucleotide sequence comprising at least one, two or three, but not more than 30, 20 or 10 different nucleotides, relative to the amino acid sequence of SEQ ID NO: 983 or 984. In some embodiments, an AAV capsid variant described herein comprises an amino acid sequence encoded by a nucleotide sequence comprising at least one, two or three modifications, e.g., substitutions, insertions, or deletions, but not more than 30, 20 or 10 modifications, e.g., substitutions, insertions, or deletions, relative to the nucleotide sequence of SEQ ID NO: 983 or 984.

[0158] In some embodiments, an AAV capsid variant described herein comprises an amino acid sequence encoded by the nucleotide sequence of any one of SEQ ID NOs: 12-35, or a nucleotide sequence with at least 70% (e.g., at least about 80, 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto. In some embodiments, an AAV capsid variant described herein comprises an amino acid sequence encoded by a nucleotide sequence comprising at least one, two or three, but not more than 30, 20 or 10 different nucleotides, relative to the amino acid sequence of any one of SEQ ID NOs: 12-35. In some embodiments, an AAV capsid variant described herein comprises an amino acid sequence encoded by a nucleotide sequence comprising at least one, two or three modifications, e.g., substitutions, insertions, or deletions, but not more than 30, 20 or 10 modifications, e.g., substitutions, insertions, or deletions, relative to the nucleotide sequence of any one of SEQ ID NOs: 12-35.

[0159] In some embodiments, an AAV capsid variant described herein comprises a VP1, VP2, VP3 protein, or a combination thereof. In some embodiments, an AAV capsid variant comprises the amino acid sequence corresponding to positions 138-742, e.g., a VP2, of SEQ ID NO: 981 or 982, or a sequence with at least 70% (e.g., at least about 80, 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto. In some embodiments, the AAV capsid protein comprises the amino acid sequence corresponding to positions 203-742, e.g., a VP3, of SEQ ID NO: 981 or 982, or a sequence with at least 70% (e.g., at least about 80, 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto. In some embodiments, the AAV capsid variant comprises the amino acid sequence corresponding to positions 1-742, e.g., a VP1, of SEQ ID NO: 981 or 982, or an amino acid sequence with at least 70% (e.g., at least about 80, 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto.

[0160] In some embodiments, an AAV capsid variant described herein comprises a VP1, VP2, VP3 protein, or a combination thereof. In some embodiments, an AAV capsid variant comprises the amino acid sequence corresponding to positions 138-742, e.g., a VP2, of any one of SEQ ID NOs: 36-59, or a sequence with at least 70% (e.g., at least about 80, 85, 90, 95, 96, 97, 98, or 99%) sequence

identity thereto. In some embodiments, the AAV capsid protein comprises the amino acid sequence corresponding to positions 203-742, e.g., a VP3, of any one of SEQ ID NOs: 36-59, or a sequence with at least 70% (e.g., at least about 80, 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto. In some embodiments, the AAV capsid variant comprises the amino acid sequence corresponding to positions 1-742, e.g., a VP1, of any one of SEQ ID NOs: 36-59, or an amino acid sequence with at least 70% (e.g., at least about 80, 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto.

[0161] In some embodiments, an AAV capsid variant, described herein has an increased tropism for a CNS cell or tissue, e.g., a brain cell, brain tissue, spinal cord cell, or spinal cord tissue, relative to the tropism of a reference sequence comprising the amino acid sequence of SEQ ID NO: 138.

[0162] In some embodiments, an AAV capsid variant described herein transduces a brain region, e.g., a midbrain region (e.g., the hippocampus, or thalamus) or the brain stem. In some embodiments, the level of transduction is at least 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, or 65-fold greater as compared to a reference sequence of SEQ ID NO: 138. In some embodiments, the level of transduction is at least 30, 35, 40, 45, 50, 55, 60, or 65-fold greater as compared to a reference sequence of SEQ ID NO: 138.

[0163] In some embodiments, an AAV capsid variant described herein is enriched at least about 3, 4, 5, 6, 7, 8, 9, or 10-fold in the brain compared to a reference sequence of SEQ ID NO: 138. In some embodiments, an AAV capsid variant described herein is enriched at least about 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80 or 85-fold in the brain compared to a reference sequence of SEQ ID NO: 138.

[0164] In some embodiments, an AAV capsid variant described herein is enriched in the brain of at least two to three species, e.g., a non-human primate and rodent (e.g., mouse) species, compared to a reference sequence of SEQ ID NO: 138. In some embodiments, an AAV capsid variant described herein is enriched at least about 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100-fold in the brain of at least two to three species, e.g., a non-human primate and rodent (e.g., mouse) species, compared to a reference sequence of SEQ ID NO: 138. In some embodiments, the at least two to three species are *Macaca fascicularis*, *Chlorocebus sabaeus*, *Callithrix jacchus*, and/or mouse (e.g., BALB/c mice, C57Bl/6 mice, and/or CD-1 outbred mice).

[0165] In some embodiments, an AAV capsid variant described herein is enriched at least about 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, or 8-fold, in the brain compared to a reference sequence of SEQ ID NO: 981. In some embodiments, an AAV capsid variant described herein is enriched about 2, 2.5, 3, 3.5, 4, 4.5, 5, or 5.5-fold, in the brain compared to a reference sequence of SEQ ID NO: 982.

[0166] In some embodiments, an AAV capsid variant described herein delivers an increased level of viral genomes to a brain region. In some embodiments, the level of viral genomes is increased by at least 20, 25, 30, 35, 40, 45, or 50-fold, as compared to a reference sequence of SEQ ID NO: 138.

In some embodiments, the brain region comprises a midbrain region (e.g., the hippocampus or thalamus) and/or the brainstem.

[0167] In some embodiments, an AAV capsid variant described herein delivers an increased level of a payload to a brain region. In some embodiments, the level of the payload is increased by at least 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, or 70-fold, as compared to a reference sequence of SEQ ID NO: 138. In some embodiments, the brain region comprises a midbrain region (e.g., the hippocampus or thalamus) and/or the brainstem.

[0168] In some embodiments, an AAV capsid variant described herein is enriched at least about 5, 10, 15, 20, 25, 30, or 35-fold, in the spinal cord compared to a reference sequence of SEQ ID NO: 138.

[0169] In some embodiments, an AAV capsid variant described herein shows preferential transduction in a brain region relative to the transduction in the dorsal root ganglia (DRG). In some embodiments, the AAV capsid variant shows preferential transduction in a brain region relative to the transduction in the liver. In some embodiments, the AAV capsid variant shows preferential transduction in a brain region relative to the transduction in the liver and the DRG. In some embodiments, the AAV capsid variant shows preferential transduction in a brain region relative to the transduction in the heart. In some embodiments, the AAV capsid variant shows preferential transduction in a brain region relative to the transduction in the heart and DRG. In some embodiments, the AAV capsid variant shows preferential transduction in a brain region relative to the transduction in the heart, DRG, and liver. In some embodiments, the AAV capsid variant shows preferential transduction in a brain region and/or a heart region relative to the transduction in the liver and DRG.

[0170] In some embodiments, an AAV capsid variant described herein is capable of transducing non-neuronal cells, e.g., glial cells (e.g., oligodendrocytes or astrocytes). In some embodiments, the AAV capsid variant described herein is capable of transducing neuronal cells and non-neuronal cells, e.g., glial cells (e.g., oligodendrocytes or astrocytes). In some embodiments, the non-neuronal cells are glial cells, oligodendrocytes (e.g., Olig2 positive oligodendrocytes), or astrocytes (e.g., Olig2 positive astrocytes). In some embodiments, the AAV capsid variant is capable of transducing Olig2 positive cells, e.g., Olig2 positive astrocytes or Olig2 positive oligodendrocytes.

[0171] In some embodiments, an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein has an increased tropism for a muscle cell or tissue, e.g., a heart or quadriceps cell or tissue, relative to the tropism of a reference sequence comprising the amino acid sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid variant is enriched at least about 4, 5, 8, 12, 17, 18, 20, 26, 27, 28, 30, or 36-fold, in the muscle compared to a reference sequence of SEQ ID NO: 138. In some embodiments, the muscle region comprises a quadriceps muscle, heart muscle, and/or a

diaphragm muscle region. In some embodiments, the muscle region comprises a heart muscle region, e.g., a heart atrium muscle region or a heart ventricle muscle region.

[0172] In some embodiments, an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein has an increased tropism for a heart cell or heart tissue. In some embodiments, the AAV capsid variant is enriched at least about 4, 5, 8, 10, 11, 12, 13, 14, 18, 19, 20, 21, 22, 24, 25, 27, 31, 33, or 34-fold, in the heart compared to a reference sequence of SEQ ID NO: 138.

[0173] In some embodiments, an AAV capsid variant described herein has increased tropism for a liver cell or tissue, relative to the tropism of a reference sequence comprising the amino acid sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid variant is enriched at least about 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 150, 160, 170, 180, 190, or 200-fold, in the liver compared to a reference sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid variant has reduced tropism for a CNS cell or tissue, e.g., a brain cell, brain tissue, spinal cord cell, or spinal cord tissue, relative to the tropism of a reference sequence comprising the amino acid sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid variant shows preferential transduction in a liver region relative to the transduction in the brain and/or dorsal root ganglia (DRG). In some embodiments, the AAV capsid variant shows preferential transduction in a liver region relative to the transduction in the heart and/or muscle (e.g., quadriceps).

[0174] In some embodiments, an AAV capsid variant of the present disclosure has decreased tropism for the liver. In some embodiments, an AAV capsid variant comprises a modification, e.g., substitution (e.g., conservative substitution), insertion, or deletion, that results in reduced tropism (e.g., de-targeting) and/or activity in the liver. In some embodiments, the reduced tropism in the liver is compared to an otherwise similar capsid that does not comprise the modification, e.g., a wild-type capsid. In some embodiments, an AAV capsid variant described herein comprises a modification, e.g., substitution (e.g., conservative substitution), insertion, or deletion that results in one or more of the following properties: (1) reduced tropism in the liver; (2) reduced, e.g., de-targeted, expression in the liver; (3) reduced activity in the liver; and/or (4) reduced binding to galactose. In some embodiments, the reduction in any one, or all of properties (1)-(3) is compared to an otherwise similar AAV capsid variant that does not comprise the modification. Exemplary modifications are provided in WO 2018/119330; Pulicherla et al. (2011) *Mol. Ther.* 19(6): 1070-1078; Adachi et al. (2014) *Nature Communications* 5(3075), DOI: 10.1038/ncomms4075; and Bell et al. (2012) *J. Virol.* 86(13): 7326-33; the contents of which are hereby incorporated by reference in their entirety. In some embodiments, the AAV capsid variant comprises a modification e.g., substitution (e.g., conservative substitution), insertion, or deletion, at position N470 (e.g., N470A), D271 (e.g., D271A), N272 (e.g., N297A), Y446 (e.g., Y446A), N498 (e.g., N498Y or N498I), W503 (e.g., W530R or W530A), L620 (e.g., L620F), or a combination thereof, relative to a reference sequence numbered according to SEQ

ID NO: 138. In some embodiments, the AAV capsid variant comprises one, two, three, four, five or all of an amino acid other than N at position 470 (e.g., A), an amino acid other than D at position 271 (e.g., A), an amino acid other than N at position 272 (e.g., A), an amino acid other than Y at position 446 (e.g., A), and amino acid other than N at position 498/ (e.g., Y or I), and amino acid other than W at position 503 (e.g., R or A), and amino acid other than L at position 620 (e.g., F), relative to a reference sequence numbered according to SEQ ID NO: 138. In some embodiments, the AAV capsid variant comprises a modification e.g., substitution (e.g., conservative substitution), insertion, or deletion, at position N470 (e.g., N470A), D271 (e.g., D271A), N272 (e.g., N297A), Y446 (e.g., Y446A), and W503 (e.g., W530R or W530A), relative to a reference sequence numbered according to SEQ ID NO: 138. In some embodiments, the AAV capsid variant comprises a modification e.g., substitution (e.g., conservative substitution), insertion, or deletion, at N498 (e.g., N498Y) and L620 (e.g., L620F).

[0175] In some embodiments, an AAV capsid variant comprised herein comprises a modification as described in Adachi et al. (2014) *Nature Communications* 5(3075), DOI: 10.1038/ncomms4075, the contents of which are hereby incorporated by reference in its entirety. Exemplary modifications that alter or do not alter tissue transduction in at least the brain, liver, heart, lung, and/or kidney can be found in Supplementary Data 2 showing the AAV Barcode-Seq data obtained with AAV9-AA-VBCLib of Adachi et al. (*supra*), the contents of which are hereby incorporated by reference in its entirety.

[0176] In some embodiments, an AAV capsid variant of the present disclosure is isolated, e.g., recombinant. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, of the present disclosure is isolated, e.g., recombinant.

[0177] Also provided herein are polynucleotide sequences encoding any of the AAV capsid variants described above and AAV particles, vectors, and cells comprising the same.

AAV serotypes and capsids

[0178] In some embodiments, an AAV particle of the present disclosure may comprise a capsid protein or variant thereof any natural or recombinant AAV serotype. AAV serotypes may differ in characteristics such as, but not limited to, packaging, tropism, transduction and immunogenic profiles. While not wishing to be bound by theory, it is believed in some embodiments, that the AAV capsid protein, e.g., an AAV capsid variant, can modulate, e.g., direct, AAV particle tropism to a particular tissue.

[0179] In some embodiments, an AAV capsid variant described herein allows for blood brain barrier penetration following intravenous administration. In some embodiments, the AAV capsid variant allows for blood brain barrier penetration following intravenous administration, focused ultrasound (FUS), e.g., coupled with the intravenous administration of microbubbles (FUS-MB), or MRI-guided FUS coupled with intravenous administration. In some embodiments the AAV capsid

variant allows for increased distribution to a brain region. In some embodiments, the brain region comprises a frontal cortex, sensory cortex, motor cortex, caudate, dentate nucleus, cerebellar cortex, cerebral cortex, brain stem, hippocampus, thalamus, putamen, or a combination thereof. In some embodiments, the AAV capsid variant allows for preferential transduction in a brain region relative to the transduction in the dorsal root ganglia (DRG). In some embodiments, the AAV capsid variant allows for transduction in a non-neuronal cell, e.g., a glial cell (e.g., an astrocyte, an oligodendrocyte, or a combination thereof).

[0180] In some embodiments, an AAV capsid variant allows for increased distribution to a spinal cord region. In some embodiments, the spinal region comprises a cervical spinal cord region, thoracic spinal cord region, and/or lumbar spinal cord region.

[0181] In some embodiments, the AAV capsid variant, is suitable for intramuscular administration and/or transduction of muscle fibers. In some embodiments the AAV capsid variant, allows for increased distribution to a muscle region. In some embodiments, the muscle region comprises a heart muscle, quadriceps muscle, a diaphragm muscle region, or a combination thereof. In some embodiments, the muscle region comprises a heart muscle region, e.g., a heart atrium muscle region or a heart ventricle muscle region.

[0182] In some embodiments, the initiation codon for translation of the AAV VP1 capsid protein, e.g., a capsid variant, described herein may be CTG, TTG, or GTG as described in US Patent No. US8163543, the contents of which are herein incorporated by reference in its entirety.

[0183] The present disclosure refers to structural capsid proteins (including VP1, VP2 and VP3) which are encoded by capsid (Cap) genes. These capsid proteins form an outer protein structural shell (e.g., capsid) of a viral vector such as AAV. VP capsid proteins synthesized from Cap polynucleotides generally include a methionine as the first amino acid in the peptide sequence (Met1), which is associated with the start codon (AUG or ATG) in the corresponding Cap nucleotide sequence. However, it is common for a first-methionine (Met1) residue or generally any first amino acid (AA1) to be cleaved off after or during polypeptide synthesis by protein processing enzymes such as Met-aminopeptidases. This “Met/AA-clipping” process often correlates with a corresponding acetylation of the second amino acid in the polypeptide sequence (e.g., alanine, valine, serine, threonine, etc.). Met-clipping commonly occurs with VP1 and VP3 capsid proteins but can also occur with VP2 capsid proteins.

[0184] Where the Met/AA-clipping is incomplete, a mixture of one or more (one, two or three) VP capsid proteins comprising the viral capsid may be produced, some of which may include a Met1/AA1 amino acid (Met+/AA+) and some of which may lack a Met1/AA1 amino acid as a result of Met/AA-clipping (Met-/AA-). For further discussion regarding Met/AA-clipping in capsid proteins, see Jin, et al. Direct Liquid Chromatography/Mass Spectrometry Analysis for Complete Characterization of Recombinant Adeno-Associated Virus Capsid Proteins. *Hum Gene Ther Methods*.

2017 Oct. 28(5):255-267; Hwang, et al. N-Terminal Acetylation of Cellular Proteins Creates Specific Degradation Signals. *Science*. 2010 February 19. 327(5968): 973-977; the contents of which are each incorporated herein by reference in its entirety.

[0185] According to the present disclosure, references to capsid proteins, e.g., AAV capsid variants, is not limited to either clipped (Met-/AA-) or unclipped (Met+/AA+) and may, in context, refer to independent capsid proteins, viral capsids comprised of a mixture of capsid proteins, and/or polynucleotide sequences (or fragments thereof) which encode, describe, produce or result in capsid proteins of the present disclosure. A direct reference to a capsid protein or capsid polypeptide (such as VP1, VP2 or VP2) may also comprise VP capsid proteins which include a Met1/AA1 amino acid (Met+/AA+) as well as corresponding VP capsid proteins which lack the Met1/AA1 amino acid as a result of Met/AA-clipping (Met-/AA-).

[0186] Further according to the present disclosure, a reference to a specific SEQ ID NO: (whether a protein or nucleic acid) which comprises or encodes, respectively, one or more capsid proteins which include a Met1/AA1 amino acid (Met+/AA+) should be understood to teach the VP capsid proteins which lack the Met1/AA1 amino acid as upon review of the sequence, it is readily apparent any sequence which merely lacks the first listed amino acid (whether or not Met1/AA1).

[0187] As a non-limiting example, reference to a VP1 polypeptide sequence which is 736 amino acids in length, and which includes a "Met1" amino acid (Met+) encoded by the AUG/ATG start codon may also be understood to teach a VP1 polypeptide sequence which is 735 amino acids in length, and which does not include the "Met1" amino acid (Met-) of the 736 amino acid Met+ sequence. As a second non-limiting example, reference to a VP1 polypeptide sequence which is 736 amino acids in length, and which includes an "AA1" amino acid (AA1+) encoded by any NNN initiator codon may also be understood to teach a VP1 polypeptide sequence which is 735 amino acids in length, and which does not include the "AA1" amino acid (AA1-) of the 736 amino acid AA1+ sequence.

[0188] References to viral capsids formed from VP capsid proteins (such as reference to specific AAV capsid serotypes), can incorporate VP capsid proteins which include a Met1/AA1 amino acid (Met+/AA1+), corresponding VP capsid proteins which lack the Met1/AA1 amino acid as a result of Met/AA1-clipping (Met-/AA1-), and combinations thereof (Met+/AA1+ and Met-/AA1-).

[0189] As a non-limiting example, an AAV capsid serotype can include VP1 (Met+/AA1+), VP1 (Met-/AA1-), or a combination of VP1 (Met+/AA1+) and VP1 (Met-/AA1-). An AAV capsid serotype can also include VP3 (Met+/AA1+), VP3 (Met-/AA1-), or a combination of VP3 (Met+/AA1+) and VP3 (Met-/AA1-); and can also include similar optional combinations of VP2 (Met+/AA1) and VP2 (Met-/AA1-).

Additional AAV Sequences

[0190] In some embodiments, the AAV capsid variant, comprises immediately subsequent to position 448, 449, 452, 453, 455, numbered relative to SEQ ID NO: 138 or corresponding to equivalent positions in any other AAV serotype (e.g., AAV1, AAV2, AAV3, AAV3b, AAV4, AAV5, AAV6, AAV7, AAV8, AAVrh8, AAVrh10, AAVrh32.33, AAVrh74, SEQ ID NO: 1, SEQ ID NO: 11, PHP.N, PHP.B, or an AAV serotype as provided in Table 6 of WO 2021/230987 (the contents of which are hereby incorporated by reference in their entirety)), at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 consecutive amino acids of any of amino acid sequence provided in Tables 1, 2A, 2B, 13-19. In some embodiments, the at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 consecutive amino acids of any of amino acid sequence provided in Tables 1, 2A, 2B, 13-19 replaces at least one, two, three, four, five, six, seven, eight, nine, ten, or all of positions K449, T450, I451, N452, G453, S454, G455, Q456, N457, Q458, and/or Q459, numbered according to SEQ ID NO: 138 or corresponding to equivalent positions in any other AAV serotype (e.g., AAV1, AAV2, AAV3, AAV3b, AAV4, AAV5, AAV6, AAV7, AAV8, AAVrh8, AAVrh10, AAVrh32.33, AAVrh74, SEQ ID NO: 1, SEQ ID NO: 11, PHP.N, PHP.B, or an AAV serotype as provided in Table 6 of WO 2021/230987 (the contents of which are hereby incorporated by reference in their entirety)). In some embodiments, the at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 consecutive amino acids of any of amino acid sequence provided in Tables 1, 2A, 2B, 13-19 replaces positions S454, G455, or both positions S454 and G455, numbered according to SEQ ID NO: 138 or corresponding to equivalent positions in any other AAV serotype (e.g., AAV1, AAV2, AAV3, AAV3b, AAV4, AAV5, AAV6, AAV7, AAV8, AAVrh8, AAVrh10, AAVrh32.33, AAVrh74, SEQ ID NO: 1, SEQ ID NO: 11, PHP.N, PHP.B, or an AAV serotype as provided in Table 6 of WO 2021/230987 (the contents of which are hereby incorporated by reference in their entirety)). In some embodiments, the AAV capsid variant comprises an amino acid other than the wild-type, e.g., native, amino acid, at one, two, three, four, five, six, seven, eight, nine or all of positions T450, I451, N452, G453, S454, G455, Q456, N457, Q458, and/or Q459, numbered according to SEQ ID NO: 138 or corresponding to equivalent positions in any other AAV serotype (e.g., AAV1, AAV2, AAV3, AAV3b, AAV4, AAV5, AAV6, AAV7, AAV8, AAVrh8, AAVrh10, AAVrh32.33, AAVrh74, SEQ ID NO: 1, SEQ ID NO: 11, PHP.N, PHP.B, or an AAV serotype as provided in Table 6 of WO 2021/230987 (the contents of which are hereby incorporated by reference in their entirety)). In some embodiments, the AAV capsid variant comprises an amino acid other than the wild-type, e.g., native, amino acid, at position S454, G455, or both positions S454 and G455, numbered according to SEQ ID NO: 138 or corresponding to equivalent positions in any other AAV serotype (e.g., AAV1, AAV2, AAV3, AAV3b, AAV4, AAV5, AAV6, AAV7, AAV8, AAVrh8, AAVrh10, AAVrh32.33, AAVrh74, SEQ ID NO: 1, SEQ ID NO: 11, PHP.N, PHP.B, or an AAV serotype as provided in Table 6 of WO 2021/230987 (the contents of which are hereby incorporated by reference in their entirety)). In some embodiments, the AAV capsid variant comprises a modification, e.g., substitution, at one, two, three, four, five, six, seven, eight, nine, ten or all of

positions K449, T450, I451, N452, G453, S454, G455, Q456, N457, Q458, and/or Q459, numbered according to SEQ ID NO: 138 or corresponding to equivalent positions in any other AAV serotype (e.g., AAV1, AAV2, AAV3, AAV3b, AAV4, AAV5, AAV6, AAV7, AAV8, AAVrh8, AAVrh10, AAVrh32.33, AAVrh74, SEQ ID NO: 1, SEQ ID NO: 11, PHP.N, PHP.B, or an AAV serotype as provided in Table 6 of WO 2021/230987 (the contents of which are hereby incorporated by reference in their entirety). In some embodiments, the AAV capsid variant comprises a modification, e.g., substitution, at position S454, G455, or both positions S454 and G455, numbered according to SEQ ID NO: 138 or corresponding to equivalent positions in any other AAV serotype (e.g., AAV1, AAV2, AAV3, AAV3b, AAV4, AAV5, AAV6, AAV7, AAV8, AAVrh8, AAVrh10, AAVrh32.33, AAVrh74, SEQ ID NO: 1, SEQ ID NO: 11, PHP.N, PHP.B, or an AAV serotype as provided in Table 6 of WO 2021/230987 (the contents of which are hereby incorporated by reference in their entirety).

[0191] In some embodiments, an AAV capsid polypeptide or AAV capsid variant described herein may comprise a VOY101 capsid polypeptide, an AAVPHP.B (PHP.B) capsid polypeptide, a AAVPHP.N (PHP.N) capsid polypeptide, an AAV1 capsid polypeptide, an AAV2 capsid polypeptide, an AAV5 capsid polypeptide, an AAV9 capsid polypeptide, an AAV9 K449R capsid polypeptide, an AAVrh10 capsid polypeptide, or a functional variant thereof. In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, comprises an amino acid sequence of any of the AAV capsid polypeptides in Table 6, or an amino acid sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto. In some embodiments, the nucleotide sequence encoding the AAV capsid polypeptide comprises any one of the nucleotide sequences in Table 6, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto.

[0192] In some embodiments, an AAV capsid polypeptide or an AAV capsid variant described herein comprises the amino acid sequence of SEQ ID NO: 138 or an amino acid sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto. In some embodiments the AAV capsid polypeptide or the AAV capsid variant, comprises an amino acid sequence comprising at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), but no more than 30, 20, or 10 modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid polypeptide or the AAV capsid variant, comprises an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 137 or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto. In some embodiments, the nucleotide sequence encoding the AAV capsid polypeptide or the AAV capsid variant comprises the nucleotide sequence of SEQ ID NO: 137 or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto. In some embodiments, the AAV

capsid polypeptide or the AAV capsid variant, comprises substitution at position K449, e.g., a K449R substitution, numbered according to SEQ ID NO: 138.

[0193] In some embodiments, the AAV capsid polypeptide or the AAV capsid variant, comprises a peptide comprising the amino acid sequence of TLAVPFK (SEQ ID NO: 4680). In some embodiments, the peptide is present immediately subsequent to position 588, relative to a reference sequence numbered according to SEQ ID NO: 138. In some embodiments, the capsid polypeptide comprises the amino acid substitutions of A587D and Q588G, numbered according to SEQ ID NO: 138.

[0194] In some embodiments, the AAV capsid polypeptide or the AAV capsid variant comprises the amino acid substitution of K449R, numbered according to SEQ ID NO: 138; and a peptide comprising the amino acid sequence of TLAVPFK (SEQ ID NO: 4680), wherein the peptide is present immediately subsequent to position 588, relative to a reference sequence numbered according to SEQ ID NO: 138.

[0195] In some embodiments, the AAV capsid polypeptide or the AAV capsid variant comprises the amino acid substitution of K449R, numbered according to SEQ ID NO: 138; an peptide comprising the amino acid sequence of TLAVPFK (SEQ ID NO: 4680), wherein the insert is present immediately subsequent to position 588, relative to a reference sequence numbered according to SEQ ID NO: 138; and the amino acid substitutions of A587D and Q588G, numbered according to SEQ ID NO: 138.

[0196] In some embodiments, the AAV capsid polypeptide or the AAV capsid variant comprises a peptide comprising the amino acid sequence of TLAVPFK (SEQ ID NO: 4680), wherein the insert is present immediately subsequent to position 588, relative to a reference sequence numbered according to SEQ ID NO: 138; and the amino acid substitutions of A587D and Q588G, numbered according to SEQ ID NO: 138.

[0197] In some embodiments, the AAV capsid polypeptide or the AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 11 or an amino acid sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto. In some embodiments the AAV capsid polypeptide or the AAV capsid variant, comprises an amino acid sequence comprising at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), but no more than 30, 20, or 10 modifications, e.g., substitutions (conservative substitutions), relative to the amino acid sequence of SEQ ID NO: 11, optionally wherein position 449 is not R.

[0198] In some embodiments, the AAV capsid polypeptide or AAV capsid variant, comprises the amino acid sequence of SEQ ID NO: 1 or an amino acid sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto. In some embodiments the AAV capsid polypeptide or the AAV capsid variant, comprises an amino acid

sequence comprising at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), but no more than 30, 20, or 10 modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of SEQ ID NO: 1.

Table 6. AAV Sequences

Serotype	SEQ ID NO:	Sequence
VOY101	1	MAADGYLPDWLEDNLSEGIREWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPNGGLD KGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADADEFQERLKEDTSFGGNLGRAVFQ AKKRLLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAKKRLNFGQTGDTE SVPDPQPIGEPPAAPSGVGSMTASGGGAPVADNNEGADGVGSSSGNWHCDSQLGDRVI TTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWGYDFNRFHCHFSRDPWQR LINNNWGFPRKRLNFKLFNIQVKEVTDNNGVKTIANNNLTSTVQVFTDSDYQLPYVLGSAH EGCLPPFPADVFMIPQYGYLTLNDGSQAVGRSSFYCLEYFPSQMLRTGNNFQFSYEFENV PFHSSYAHSQSLDRLMNPLIDQYLYLSKTINGSGQNQOTLKFSVAGPSNMAVQGRNYIP GPSYRQQRVSTTVTQNNNSEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGS LIFGKQGTGRDNVDADKVMITNEEEIKTTNPVATESYQGVATNHQSDGTLAVPFKAQAQT GWVQNGQILPGMVWQDRDVYLQGPWAKIPHTDGNFHPSPMLGGFGMKHPPQILIKNTP VPADPPTAFNKDKLNSFITQYSTGQVSVEIEWELQKENS KRWNPEIQYTSNYYKSNNVEF AVNTEGVYSEPRPIGTRYLTRNL
AAV9/hu.1 4 K449R	11	MAADGYLPDWLEDNLSEGIREWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPNGGLD KGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADADEFQERLKEDTSFGGNLGRAVFQ AKKRLLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAKKRLNFGQTGDTE SVPDPQPIGEPPAAPSGVGSMTASGGGAPVADNNEGADGVGSSSGNWHCDSQLGDRVI TTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWGYDFNRFHCHFSRDPWQR LINNNWGFPRKRLNFKLFNIQVKEVTDNNGVKTIANNNLTSTVQVFTDSDYQLPYVLGSAH EGCLPPFPADVFMIPQYGYLTLNDGSQAVGRSSFYCLEYFPSQMLRTGNNFQFSYEFENV PFHSSYAHSQSLDRLMNPLIDQYLYLSRTINGSGQNQOTLKFSVAGPSNMAVQGRNYIP GPSYRQQRVSTTVTQNNNSEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGS LIFGKQGTGRDNVDADKVMITNEEEIKTTNPVATESYQGVATNHQSAQAQAQTGWVQNGQ ILPGMVWQDRDVYLQGPWAKIPHTDGNFHPSPMLGGFGMKHPPQILIKNTPVPADPPT AFNKDKLNSFITQYSTGQVSVEIEWELQKENS KRWNPEIQYTSNYYKSNNVEFAVNTEGV YSEPRPIGTRYLTRNL
AAV9/hu.1 4 WT (amino acid)	138	MAADGYLPDWLEDNLSEGIREWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPNGGLD KGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADADEFQERLKEDTSFGGNLGRAVFQ AKKRLLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAKKRLNFGQTGDTE SVPDPQPIGEPPAAPSGVGSMTASGGGAPVADNNEGADGVGSSSGNWHCDSQLGDRVI TTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWGYDFNRFHCHFSRDPWQR LINNNWGFPRKRLNFKLFNIQVKEVTDNNGVKTIANNNLTSTVQVFTDSDYQLPYVLGSAH EGCLPPFPADVFMIPQYGYLTLNDGSQAVGRSSFYCLEYFPSQMLRTGNNFQFSYEFENV PFHSSYAHSQSLDRLMNPLIDQYLYLSKTINGSGQNQOTLKFSVAGPSNMAVQGRNYIP GPSYRQQRVSTTVTQNNNSEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGS LIFGKQGTGRDNVDADKVMITNEEEIKTTNPVATESYQGVATNHQSAQAQAQTGWVQNGQ ILPGMVWQDRDVYLQGPWAKIPHTDGNFHPSPMLGGFGMKHPPQILIKNTPVPADPPT AFNKDKLNSFITQYSTGQVSVEIEWELQKENS KRWNPEIQYTSNYYKSNNVEFAVNTEGV YSEPRPIGTRYLTRNL
AAV9/hu.1 4 WT (DNA)	137	ATGGCTGCCGATGGTTATCTTCCAGATTGGCTCGAGGACAACCTTAGTGAAGGAATTCGC GAGTGGTGGGCTTTGAAACCTGGAGCCCCTCAACCAAGGCAATCAACAACATCAAGAC AACGCTCGAGGTCTTGTGCTTCCGGGTACAAATACCTTGGACCGGCAACGGACTCGAC AAGGGGAGCCGGTCAACGCAGCAGACGCGCGGCCCTCGAGCAGACAAGGCCTACGAC CAGCAGCTCAAGGCCGAGACAACCCGTACCTCAAGTACAACCACGCCGACGCCGAGTTC CAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGCAACCTCGGGCGAGCAGTCTTCCAG GCCAAAAGAGGGCTTCTGAACCTCTTGGTCTGGTTGAGGAAGCGGCTAAGACGGCTCCT GGAAAGAAGAGGCCTGTAGAGCAGTCTCCTCAGGAACCGGACTCCTCCGCGGGTATTGGC AAATCGGGTGACAGCCCGCTAAAAAGAGACTCAATTTCTGGTCTGAGTGGCGACACAGAG TCAGTCCCAGACCCTCAACCAATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCT CTTACAATGGCTTCAGGTGGTGGCGACCACTGGCAGACAATAACGAAGGTGCCGATGGA GTGGGTAGTTCCTCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATC

	ACCACCAGCACCCGAACCTGGGCCCTGCCACCTACAACAATCACCTCTACAAGCAAATC TCCAACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCC TGGGGGTATTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCAGCGA CTCATCAACAACAACCTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCTTCAACATT CAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAATAACCTTACCAGC ACGGTCCAGGTCTTCACGACTCAGACTATCAGCTCCCGTACGTGCTCGGGTCGGCTCAC GAGGGCTGCCTCCCGCGGTTCCAGCGGACGTTTTCATGATTCTCAGTACGGGTATCTG ACGCTTAATGATGGAAGCCAGGCCGTGGGTCTGTCCTTTTACTGCCTGGAATATTTT CCGTCGCAAATGCTAAGAACGGGTAAACAACCTCCAGTTTACGTACGAGTTTGAAGACGTA CCTTTCCATAGCAGCTACGCTCACAGCCAAAGCCTGGACCGACTAATGAATCCACTCATC GACCAATACTTGTACTATCTCTCAAAGACTATTAACGGTTCTGGACAGAATCAACAAACG CTAAAATTCAAGTGTGGCCGGACCCAGCAACATGGCTGTCCAGGGAAGAACTACATACCT GGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAACAGCGAA TTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTTGATGAATCCT GGACCTGCTATGGCCAGCCACAAAGAGGAGAGGACCGTTTCTTCTTCTTGTCTGGATCT TTAATTTTGGCAAACAAGGAAGTGAAGAGACAACGTGGATGCGGACAAAGTCATGATA ACCAACGAAGAAGAAATTAACCTACTAACCCTGGTAGCAACGGAGTCTTATGGACAAGTG GCCACAAACCACAGAGTGGCCAAAGCACAGGCGCAGACCGGCTGGGTTCAAAACCAAGGA ATACTTCCGGGTATGGTTGGCAGGACAGAGATGTGTACCTGCAAGGACCCATTTGGGCC AAAATTCCTCACACGGACGGCAACTTTCACCTTCTCCGCTGATGGGAGGGTTTGAATG AAGCACCCGCCTCTCAGATCCTCATCAAAAACACACCTGTACCTGCGGATCTCCAACG GCCTTCAACAAGGACAAGCTGAACCTTTTCATCACCCAGTATTCTACTGGCCAAGTCAGC GTGGAGATCGAGTGGGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAG TACACTTCCAACATATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTA TATAGTGAACCCCGCCCCATTGGCACCAGATACCTGACTCGTAATCTGTAA
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Viral Genome of the AAV particle

[0199] In some embodiments, an AAV particle as described herein comprising an AAV capsid variant described herein, may be used for the delivery of a viral genome to a tissue (e.g., CNS, DRG, and/or muscle). In some embodiments, an AAV particle comprising an AAV capsid variant described herein can be used for delivery of a viral genome to a tissue or cell, e.g., CNS, DRG, or muscle cell or tissue. In some embodiments, an AAV particle of the present disclosure is a recombinant AAV particle. In some embodiments, an AAV particle of the present disclosure is an isolated AAV particle.

[0200] The viral genome may encode any payload, such as but not limited to a polypeptide (e.g., a therapeutic polypeptide), an antibody, an enzyme, an RNAi agent and/or components of a gene editing system. In one embodiment, the AAV particles described herein are used to deliver a payload to cells of the CNS, after intravenous delivery. In another embodiment, the AAV particles described herein are used to deliver a payload to cells of the DRG, after intravenous delivery. In some embodiments, the AAV particles described herein are used to deliver a payload to cells of a muscle, e.g., a heart muscle, after intravenous delivery.

[0201] In some embodiments, a viral genome of an AAV particle comprising an AAV capsid variant, as described herein, comprises a nucleotide sequence comprising a transgene encoding a payload. In some embodiments, the viral genome comprises an inverted terminal repeat sequence (ITR). In some embodiments, the viral genome comprises two ITR sequences, one at the 5' end of the viral genome (e.g., 5' relative to the encoded payload) and one at the 3' end of the viral genome (e.g., 3' relative to the encoded payload). In some embodiments, a viral genome of an AAV particle, e.g.,

an AAV particle comprising an AAV capsid variant described herein, may comprise a regulatory element (e.g., promoter), untranslated regions (UTR), a miR binding site, a polyadenylation sequence (polyA), a filler or stuffer sequence, an intron, and/or a linker sequence, e.g., for enhancing transgene expression.

[0202] In some embodiments, the viral genome components are selected and/or engineered for expression of the payload in a target tissue (e.g., CNS, muscle, or DRG).

Viral Genome Component: Inverted Terminal Repeats (ITRs)

[0203] In some embodiments, the AAV particle comprising an AAV capsid variant described herein comprises a viral genome comprising an ITR and a transgene encoding a payload. In some embodiments, the viral genome comprises two ITRs. In some embodiments, the two ITRs flank the nucleotide sequence encoding the payload at the 5' and 3' ends. In some embodiments, the ITRs function as origins of replication comprising recognition sites for replication. In some embodiments, the ITRs comprise sequence regions which can be complementary and symmetrically arranged. In some embodiments, the ITRs incorporated into viral genomes as described herein may be comprised of naturally occurring polynucleotide sequences or recombinantly derived polynucleotide sequences.

[0204] In some embodiments, the ITR may be from the same serotype as the capsid polypeptide, e.g., capsid variant, selected from any of the known serotypes, or a variant thereof. In some embodiments, the ITR may be of a different serotype than the capsid. In some embodiments, the viral genome comprises two ITR sequence regions, wherein the ITRs are of the same serotype as one another. In some embodiments, the viral genome comprises two ITR sequence regions, wherein 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.

[0205] 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, 105, 130, 140, 141, 142, 145 nucleotides in length.

Viral Genome Component: Promoters

[0206] In some embodiments, viral genome of an AAV particle described herein comprises at least one element to enhance the payload 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 their entirety). Non-limiting examples of elements to enhance payload 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.

[0207] In some embodiments, an AAV particle comprising an AAV capsid variant described herein comprises a viral genome comprising a nucleic acid comprising a transgene encoding a payload, wherein the transgene is operably linked to a promoter. In some embodiments, the promoter is a species specific promoter, an inducible promoter, a tissue-specific promoter, or a cell cycle-specific promoter (e.g., a promoter as described in Parr et al., *Nat. Med.* 3:1145-9 (1997); the contents of which are herein incorporated by reference in their entirety).

[0208] In some embodiments, the Promoter may be naturally occurring or non-naturally occurring. Non-limiting examples of promoters include those derived from viruses, plants, mammals, or humans. In some embodiments, the promoters may be those derived from human cells or systems. In some embodiments, the promoter may be truncated or mutated, e.g., a promoter variant.

[0209] In some embodiments, the promoter is a ubiquitous promoter, e.g., capable of expression in multiple tissues. In some embodiments the promoter is an human elongation factor 1 α -subunit (EF1 α) promoter, the cytomegalovirus (CMV) immediate-early enhancer and/or promoter, the chicken β -actin (CBA) promoter and its derivative CAG, β glucuronidase (GUSB) promoter, or ubiquitin C (UBC) promoter. In some embodiments, the promoter is a cell or tissue specific promoter, e.g., capable of expression in tissues or cells of the central or peripheral nervous systems, targeted regions within (e.g., frontal cortex), and/or sub-sets of cells therein (e.g., excitatory neurons). In some embodiments, the promoter is a cell-type specific promoters capable of expression of a payload in excitatory neurons (e.g., glutamatergic), inhibitory neurons (e.g., GABA-ergic), neurons of the sympathetic or parasympathetic nervous system, sensory neurons, neurons of the dorsal root ganglia, motor neurons, or supportive cells of the nervous systems such as microglia, glial cells, astrocytes, oligodendrocytes, and/or Schwann cells.

[0210] In some embodiments, the promoter is a liver specific promoter (e.g., hAAT, TBG), skeletal muscle specific promoter (e.g., desmin, MCK, C512), B cell promoter, monocyte promoter, leukocyte promoter, macrophage promoter, pancreatic acinar cell promoter, endothelial cell promoter, lung tissue promoter, and/or cardiac or cardiovascular promoter (e.g., α MHC, cTnT, and CMV-MLC2k).

[0211] In some embodiments, the promoter is a tissue-specific promoter for payload expression in a tissue or cell of the central nervous system. In some embodiments, the promoter is a synapsin (Syn) promoter, glutamate vesicular transporter (VGLUT) promoter, vesicular GABA transporter (VGAT) promoter, parvalbumin (PV) promoter, sodium channel Na_v 1.8 promoter, tyrosine hydroxylase (TH) promoter, choline acetyltransferase (ChAT) promoter, methyl-CpG binding protein 2 (MeCP2) promoter, Ca²⁺/calmodulin-dependent protein kinase II (CaMKII) promoter, metabotropic glutamate receptor 2 (mGluR2) promoter, neurofilament light (NFL) or heavy (NFH) promoter, neuron-specific

enolase (NSE) promoter, β -globin minigene β 2 promoter, preproenkephalin (PPE) promoter, enkephalin (Enk) promoter, and excitatory amino acid transporter 2 (EAAT2) promoter, or a fragment thereof. In some embodiments, the promoter is a cell-type specific promoter capable of expression in an astrocyte, e.g., a glial fibrillary acidic protein (GFAP) promoter and a EAAT2 promoter, or a fragment thereof. In some embodiments, the promoter is a cell-type specific promoter capable of expression in an oligodendrocyte, e.g., a myelin basic protein (MBP) promoter or a fragment thereof.

[0212] In some embodiments, the promoter is a GFAP promoter. In some embodiments, the promoter is a synapsin (syn or syn1) promoter, or a fragment thereof.

[0213] In some embodiments, the promoter comprises an insulin promoter or a fragment thereof.

[0214] In some embodiments, the promoter of the viral genome described herein (e.g., comprised within an AAV particle comprising an AAV capsid variant described herein) comprises an EF-1 α promoter or variant thereof, e.g., as provided in Table 8. In some embodiments, the EF-1 α promoter comprises the nucleotide sequence of any one of SEQ ID NOs: 987, 988, 990, 991, 995, 996, 998-1007 or any one of the sequences provided in Table 8, a nucleotide sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions, relative to the nucleotide sequence of SEQ ID NOs: 987, 988, 990, 991, 995, 996, 998-1007 or any one of the sequences provided in Table 8, or a nucleotide sequence with at least 70% (e.g., 80, 85%, 90%, 95%, 96%, 97%, 98%, or 99%) sequence identity to any one of SEQ ID NOs: 987, 988, 990, 991, 995, 996, 998-1007 or any one of the sequences provided in Table 8.

Table 8. Exemplary Promoter Variants

Description	Sequences	SEQ ID NO:
EF1a Promoter (intron underlined)	CGTGAGGCTCCGGTGCCCGTCAGTGGGCAGAGCGCACATCGCCACAGTCCCCGA GAAGTTGGGGGAGGGGTCGGCAATTGAACCGGTGCCTAGAGAAGGTGGCGCGGG GTAAACTGGGAAAGTGATGTCTGTACTGGCTCCGCCTTTTCCCGAGGGTGGGG GAGAACCGTATATAAGTGCAGTAGTGCCTGTAACGTTCTTTTCGCAACGGGTT TGCCGCGCAGAACACAGGTAAGTGCCGTGTGTGGTTCCCGCGGGCCTGGCCTCTTT ACGGGTTATGGCCCTTGCGTGCCCTGAATTACTTCCACCTGGCTGCAGTACGTGA TTCTTGATCCCGAGCTTCGGGTTGGAAGTGGGTGGGAGAGTTCGAGGCCCTTGC GC TTAAGGAGCCCCCTTCGCCTCGTGTGAGTTGAGGCCTGGCCTGGGCGCTGGGGC CGCCGCGTGCGAATCTGGTGGCACCTTCGCGCCTGTCTCGCTGCTTTCGATAAGT CTCTAGCCATTTAAATTTTTGATGACCTGCTGCGACGCTTTTTTCTGGCAAGA TAGTCTTGTAATGCGGGCCAAGATCTGCACACTGGTATTTCCGGTTTTTGGGGCC GCGGGCGGCGACGGGGCCCGTGCCTCCAGCGCACATGTTCCGGCAGGCGGGGCC TGCGAGCGCGGCCACCGAGAATCGGACGGGGGTAGTCTCAAGCTGGCCGCGCTGC TCTGGTGCCTGGCCTCGCGCGCCGCTGTATCGCCCCGCCCTGGGCGGCAAGGCTG GCGCGGTGCGGCACCACTTGCCTGAGCGGAAAGATGGCCGCTTCCCGGCCCTGCTG CAGGGAGCTCAAAATGGAGGACGCGCGCTCGGGAGAGCGGGCGGGTGAGTCACC CACACAAAGGAAAAGGGCCTTTCCGTCTCAGCCGTGCTTCATGTGACTCCACG GAGTACCGGGCGCCGTCCAGGCACCTCGATTAGTTCTCGAGCTTTTGGAGTACGT CGTCTTTAGGTTGGGGGAGGGTTTTATGCGATGGAGTTTCCCCACACTGAGTG GGTGGAGACTGAAGTTAGGCCAGCTTGGCACTTGATGTAATTCTCCTTGAATTT GCCCTTTTGTAGTTTGGATCTTGGTTCATTCTCAAGCCTCAGACAGTGGTTCAA GTTTTTTCTTCCATTTCAAGTGTGCTGA	987
miniEF1a	GCGCGTCAGTGGGCAGAGCGCACATCGCCACAGTCCCCGAGAAGTTGGGGGGAG GGGTCGGCAATTGAACCGGTGCCTAGAGAAGGTGGCGCGGGTAAACTGGGAAAG TGATGTGCTGTACTGGCTCCGCCTTTTCCCGAGGGTGGGGGAGAACCCTATATA	988

	AGTGCAGTAGTCGCCGTGAACGTTCTTTTTTCGCAACGGGTTTGCCGCCAGAACACGCGTAAAG	
Promoter Variant 1	GCATG	
Promoter Variant 2	GGTGGAGAAGAGCATG	990
Promoter Variant 3	GTCATCACTGAGGTGGAGAAGAGCATG	991
Promoter Variant 4	CGTGAG	
Promoter Variant 5	GT	
Promoter Variant 6	GCTCCGGT	
Promoter Variant 19	GCCCGTCAGTGGGCAGAGCGCACATCGCCACAGTCCCCGAGAAGTTGGGGGGAGGGTTCGGCAATTGAACCGGTGCCTAGAGAAGGTGGCGCGGGGTAACTGGGAAAGTGATGTCGTGTACTGGCTCCGCCTTTTTCCCGAGGGTGGGGGAGAACCGTATATAAGTGCAGTAGTCGCCGTGAACGTTCTTTTTTCGCAACGGGTTTGCCGCCAGAACACAG	995
Promoter Variant 20	GCCCGTCAGTGGGCAGAGCGCACATCGCCACAGTCCCCGAGAAGTTGGGGGGAGGGTTCGGCAATTGAACCGGTGCCTAGAGAAGGTGGCGCGGGGTAACTGGGAAAGTGATGTCGTGTACTGGCTCCGCCTTTTTCCCGAGGGTGGGGGAGAACCGTATATAAGTGCAGTAGTCGCCGTGAACGTTCTTTTTTCGCAACGGGTTTGCCGCCAGAACACGC	996
Promoter Variant 7	GTAAG	
Promoter Variant 8	GTGCCCGTCAGTGGGCAGAGCGCACATCGCCACAGTCCCCGAGAAGTTGGGGGGAGGGGTTCGGCAATTGAACCGGTGCCTAGAGAAGGTGGCGCGGGGTAACTGGGAAAGTGATGTCGTGTACTGGCTCCGCCTTTTTCCCGAGGGTGGGGGAGAACCGTATATAAGTGCAGTAGTCGCCGTGAACGTTCTTTTTTCGCAACGGGTTTGCCGCCAGAACACGCGTAAAG	998
Promoter Variant 9	GCTCCGGTGCCCGTCAGTGGGCAGAGCGCACATCGCCACAGTCCCCGAGAAGTTGGGGGGAGGGGTTCGGCAATTGAACCGGTGCCTAGAGAAGGTGGCGCGGGGTAAACTGGGAAAGTGATGTCGTGTACTGGCTCCGCCTTTTTCCCGAGGGTGGGGGAGAACCGTATATAAGTGCAGTAGTCGCCGTGAACGTTCTTTTTTCGCAACGGGTTTGCCGCCAGAACACGCGTAAAG	999
Promoter Variant 10	CGTGAGGCTCCGGTGCCCGTCAGTGGGCAGAGCGCACATCGCCACAGTCCCCGAGAAGTTGGGGGGAGGGGTTCGGCAATTGAACCGGTGCCTAGAGAAGGTGGCGCGGGGTAAACTGGGAAAGTGATGTCGTGTACTGGCTCCGCCTTTTTCCCGAGGGTGGGGGAGAACCGTATATAAGTGCAGTAGTCGCCGTGAACGTTCTTTTTTCGCAACGGGTTTGCCGCCAGAACACGCGTAAAG	1000
Promoter Variant 11	CGTGAGGCTCCGGTGCCCGTCAGTGGGCAGAGCGCACATCGCCACAGTCCCCGAGAAGTTGGGGGGAGGGGTTCGGCAATTGAACCGGTGCCTAGAGAAGGTGGCGCGGGGTAAACTGGGAAAGTGATGTCGTGTACTGGCTCCGCCTTTTTCCCGAGGGTGGGGGAGAACCGTATATAAGTGCAGTAGTCGCCGTGAACGTTCTTTTTTCGCAACGGGTTTGCCGCCAGAACACAG	1001
Promoter Variant 12	GCATGCGTGAGGCTCCGGTGCCCGTCAGTGGGCAGAGCGCACATCGCCACAGTCCCCGAGAAGTTGGGGGGAGGGGTTCGGCAATTGAACCGGTGCCTAGAGAAGGTGGCGCGGGGTAAACTGGGAAAGTGATGTCGTGTACTGGCTCCGCCTTTTTCCCGAGGGTGGGGGAGAACCGTATATAAGTGCAGTAGTCGCCGTGAACGTTCTTTTTTCGCAACGGGTTTGCCGCCAGAACACGCGTAAAG	1002
Promoter Variant 13	GCATGCGTGAGGCTCCGGTGCCCGTCAGTGGGCAGAGCGCACATCGCCACAGTCCCCGAGAAGTTGGGGGGAGGGGTTCGGCAATTGAACCGGTGCCTAGAGAAGGTGGCGCGGGGTAAACTGGGAAAGTGATGTCGTGTACTGGCTCCGCCTTTTTCCCGAGGGTGGGGGAGAACCGTATATAAGTGCAGTAGTCGCCGTGAACGTTCTTTTTTCGCAACGGGTTTGCCGCCAGAACACAG	1003
Promoter Variant 14	GGTGGAGAAGAGCATGCGTGAGGCTCCGGTGCCCGTCAGTGGGCAGAGCGCACATCGCCACAGTCCCCGAGAAGTTGGGGGGAGGGGTTCGGCAATTGAACCGGTGCCTAGAGAAGGTGGCGCGGGGTAAACTGGGAAAGTGATGTCGTGTACTGGCTCCGCCTTTTTCCCGAGGGTGGGGGAGAACCGTATATAAGTGCAGTAGTCGCCGTGAACGTTCTTTTTTCGCAACGGGTTTGCCGCCAGAACACGCGTAAAG	1004

	TTTCCCGAGGGTGGGGGAGAACCGTATATAAGTGCAGTAGTCGCCGTGAACGTTCTTTTCGCAACGGGTTTGCCGCCAGAACACGCGTAAG	
Promoter Variant 15	GGTGGAGAAGAGCATGCGTGAGGCTCCGGTGCCCGTCAGTGGGCAGAGCGCACATCGCCCCACAGTCCCCGAGAAGTTGGGGGGAGGGGTCGGCAATTGAACCGGTGCCTAGAGAAGGTGGCGCGGGGTAAACTGGGAAAGTGATGTCGTGTACTGGCTCCGCCTTTTCCCGAGGGTGGGGGAGAACCGTATATAAGTGCAGTAGTCGCCGTGAACGTTCTTTTCGCAACGGGTTTGCCGCCAGAACACAG	1005
Promoter Variant 16	GTCATCACTGAGGTGGAGAAGAGCATGCGTGAGGCTCCGGTGCCCGTCAGTGGGCAGAGCGCACATCGCCCCACAGTCCCCGAGAAGTTGGGGGGAGGGGTCGGCAATTGAACCGGTGCCTAGAGAAGGTGGCGCGGGGTAAACTGGGAAAGTGATGTCGTGTACTGGCTCCGCCTTTTCCCGAGGGTGGGGGAGAACCGTATATAAGTGCAGTAGTCGCGCTGAACGTTCTTTTCGCAACGGGTTTGCCGCCAGAACACGCGTAAG	1006
Promoter Variant 18	GTCATCACTGAGGTGGAGAAGAGCATGCGTGAGGCTCCGGTGCCCGTCAGTGGGCAGAGCGCACATCGCCCCACAGTCCCCGAGAAGTTGGGGGGAGGGGTCGGCAATTGAACCGGTGCCTAGAGAAGGTGGCGCGGGGTAAACTGGGAAAGTGATGTCGTGTACTGGCTCCGCCTTTTCCCGAGGGTGGGGGAGAACCGTATATAAGTGCAGTAGTCGCGCTGAACGTTCTTTTCGCAACGGGTTTGCCGCCAGAACACAG	1007

Viral Genome Component: Untranslated Regions (UTRs)

[0215] In some embodiments, 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.

[0216] Features typically found in abundantly expressed genes of specific target organs (e.g., CNS tissue, muscle, or DRG) may be engineered into UTRs to enhance stability and protein production. As a non-limiting example, a 5' UTR from mRNA normally expressed in the brain (e.g., huntingtin) may be used in the viral genomes of the AAV particles described herein to enhance expression in neuronal cells or other cells of the central nervous system.

[0217] 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'.

[0218] In one embodiment, the 5'UTR in the viral genome includes a Kozak sequence.

[0219] In one embodiment, the 5'UTR in the viral genome does not include a Kozak sequence.

[0220] 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- α , possess two or more overlapping

UUUUUA(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*.

[0221] Introduction, removal or modification of 3' UTR AU rich elements (ARES) can be used to modulate the stability of a polynucleotide. 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.

[0222] In one embodiment, the 3' UTR of the viral genome may include an oligo(dT) sequence for templated addition of a poly-A tail.

[0223] 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. In some embodiments, a microRNA sequence comprises a seed region, e.g., a sequence in the region of positions 2-8 of the mature microRNA, which has Watson-Crick sequence fully or partially complementarity to the miRNA target sequence of the nucleic acid.

[0224] In one embodiment, the viral genome may be engineered to include, alter or remove at least one miRNA binding site, full sequence or seed region.

[0225] 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.

[0226] In one embodiment, the viral genome of the AAV particle comprises at least one artificial UTR which is not a variant of a wild type UTR.

[0227] 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

[0228] The viral genome of the AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant, described herein) may comprise a polyadenylation sequence. In some embodiments, the viral genome of the AAV particle (e.g., an AAV particle comprising an AAV capsid variant, described herein) comprises a polyadenylation sequence between the 3' end of the nucleotide sequence encoding the payload and the 5' end of the 3'ITR.

Viral Genome Component: Introns

[0229] In some embodiments, the viral genome of the AAV particle as described herein (e.g., an AAV particle comprising an AAV capsid variant), comprises an element to enhance the payload target specificity and expression (See e.g., Powell et al. *Viral Expression Cassette Elements to Enhance Transgene Target Specificity and Expression in Gene Therapy*, Discov. Med, 2015, 19(102): 49-57; the contents of which are herein incorporated by reference in their entirety), such as an intron. 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/immunoglobulin splice acceptor (500 bps), SV40 late splice donor/splice acceptor (19S/16S) (180 bps) and hybrid adenovirus splice donor/IgG splice acceptor (230 bps).

Viral Genome Component: Stuffer sequences

[0230] In some embodiments, the viral genome of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant), comprises an element to improve packaging efficiency and expression, such as a stuffer or filler sequence. Non-limiting examples of stuffer sequences include albumin and/or alpha-1 antitrypsin. Any known viral, mammalian, or plant sequence may be manipulated for use as a stuffer sequence.

[0231] In one embodiment, the stuffer or filler sequence may be from about 100-3500 nucleotides in length. The stuffer sequence may have a length of about 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, 2000, 2100, 2200, 2300, 2400, 2500, 2600, 2700, 2800, 2900 or 3000 nucleotides.

Viral Genome Component: miRNA

[0232] In one embodiment, the viral genome comprises a sequence encoding a miRNA to reduce the expression of the payload in a tissue or cell, e.g., the DRG (dorsal root ganglion), or neurons of other ganglia, such as those of the sympathetic or parasympathetic nervous system. In some embodiments, a miRNA, e.g., a miR183, a miR182, and/or miR96, may be encoded in the viral

genome to modulate, e.g., reduce the expression, of the viral genome in a DRG neuron. As another non-limiting example, a miR-122 miRNA may be encoded in the viral genome to modulate, e.g., reduce, the expression of the viral genome in the liver. In some embodiments, a miRNA, e.g., a miR-142-3p, may be encoded in the viral genome to modulate, e.g., reduce, the expression, of the viral genome in a cell or tissue of the hematopoietic lineage, including for example immune cells (e.g., antigen presenting cells or APC, including dendritic cells (DCs), macrophages, and B-lymphocytes). In some embodiments, a miRNA, e.g., a miR-1, may be encoded in the viral genome to modulate, e.g., reduce, the expression, of the viral genome in a cell or tissue of the heart.

Viral Genome Component: miR Binding Site

[0233] Tissue- or cell-specific expression of the AAV viral particles disclosed herein can be enhanced by introducing tissue- or cell-specific regulatory sequences, e.g., promoters, enhancers, microRNA binding sites, e.g., a detargeting site. Without wishing to be bound by theory, it is believed that an encoded miR binding site can modulate, e.g., prevent, suppress, or otherwise inhibit, the expression of a gene of interest on the viral genome disclosed herein, based on the expression of the corresponding endogenous microRNA (miRNA) or a corresponding controlled exogenous miRNA in a tissue or cell, e.g., a non-targeting cell or tissue. In some embodiments, a miR binding site modulates, e.g., reduces, expression of the payload encoded by a viral genome of an AAV particle described herein in a cell or tissue where the corresponding mRNA is expressed.

[0234] In some embodiments, the viral genome of an AAV particle described herein comprises a nucleotide sequence encoding a microRNA binding site, e.g., a detargeting site. In some embodiments, the viral genome of an AAV particle described herein comprises a nucleotide sequence encoding a miR binding site, a microRNA binding site series (miR BSs), or a reverse complement thereof.

[0235] In some embodiments, the nucleotide sequence encoding the miR binding site series or the miR binding site is located in the 3'-UTR region of the viral genome (e.g., 3' relative to the nucleotide sequence encoding a payload), e.g., before the polyA sequence, 5'-UTR region of the viral genome (e.g., 5' relative to the nucleotide sequence encoding a payload), or both.

[0236] In some embodiments, the encoded miR binding site series comprise at least 1-5 copies, e.g., at least 1-3, 2-4, 3-5, 1, 2, 3, 4, 5 or more copies of a miR binding site (miR BS). In some embodiments, all copies are identical, e.g., comprise the same miR binding site. In some embodiments, the miR binding sites within the encoded miR binding site series are continuous and not separated by a spacer. In some embodiments, the miR binding sites within an encoded miR binding site series are separated by a spacer, e.g., a non-coding sequence. In some embodiments, the spacer is about 1 to 6 nucleotides or about 5 to 10 nucleotides, e.g., about 7-8 nucleotides, nucleotides in length. In some embodiments, the spacer coding sequence or reverse complement thereof comprises one or more of (i) GGAT; (ii) CACGTG; (iii) GCATGC, or a repeat of one or more of (i)-

(iii). In some embodiments, the spacer comprises the nucleotide sequence of GATAGTTA, or a nucleotide sequence having at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions relative to the nucleotide sequence of GATAGTTA.

[0237] In some embodiments, the encoded miR binding site series comprise at least 1-5 copies, e.g., at least 1-3, 2-4, 3-5, 1, 2, 3, 4, 5 or more copies of a miR binding site (miR BS). In some embodiments, at least 1, 2, 3, 4, 5, or all of the copies are different, e.g., comprise a different miR binding site. In some embodiments, the miR binding sites within the encoded miR binding site series are continuous and not separated by a spacer. In some embodiments, the miR binding sites within an encoded miR binding site series are separated by a spacer, e.g., a non-coding sequence. In some embodiments, the spacer is about 1 to 6 nucleotides or about 5 to 10 nucleotides, e.g., about 7-8 nucleotides, in length. In some embodiments, the spacer comprises one or more of (i) GGAT; (ii) CACGTG; (iii) GCATGC, or a repeat of one or more of (i)-(iii). In some embodiments, the spacer comprises the nucleotide sequence of GATAGTTA, or a nucleotide sequence having at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), insertions, but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions relative to the nucleotide sequence of GATAGTTA.

[0238] In some embodiments, the encoded miR binding site is substantially identical (e.g., at least 70%, 75%, 80%, 85%, 90%, 95%, 99% or 100% identical), to the miR in the host cell. In some embodiments, the encoded miR binding site comprises at least 1, 2, 3, 4, or 5 mismatches or no more than 6, 7, 8, 9, or 10 mismatches to a miR in the host cell. In some embodiments, the mismatched nucleotides are contiguous. In some embodiments, the mismatched nucleotides are non-contiguous. In some embodiments, the mismatched nucleotides occur outside the seed region-binding sequence of the miR binding site, such as at one or both ends of the miR binding site. In some embodiments, the miR binding site is 100% identical to the miR in the host cell.

[0239] In some embodiments, the nucleotide sequence encoding the miR binding site is substantially complementary (e.g., at least 70%, 75%, 80%, 85%, 90%, 95%, 99% or 100% complementary), to the miR in the host cell. In some embodiments, the complementary sequence of the nucleotide sequence encoding the miR binding site comprises at least 1, 2, 3, 4, or 5 mismatches or no more than 6, 7, 8, 9, or 10 mismatches to a miR in the host cell. In some embodiments, the mismatched nucleotides are contiguous. In some embodiments, the mismatched nucleotides are non-contiguous. In some embodiments, the mismatched nucleotides occur outside the seed region-binding sequence of the miR binding site, such as at one or both ends of the miR binding site. In some embodiments, the encoded miR binding site is 100% complementary to the miR in the host cell.

[0240] In some embodiments, an encoded miR binding site or sequence region is at least about 10 to about 125 nucleotides in length, e.g., at least about 10 to 50 nucleotides, 10 to 100 nucleotides, 50 to 100 nucleotides, 50 to 125 nucleotides, or 100 to 125 nucleotides in length. In some embodiments, an encoded miR binding site or sequence region is at least about 7 to about 28 nucleotides in length, e.g., at least about 8-28 nucleotides, 7-28 nucleotides, 8-18 nucleotides, 12-28 nucleotides, 20-26 nucleotides, 22 nucleotides, 24 nucleotides, or 26 nucleotides in length, and optionally comprises at least one consecutive region (e.g., 7 or 8 nucleotides) complementary (e.g., fully or partially complementary) to the seed sequence of a miRNA (e.g., a miR122, a miR142, a miR183, or a miR1).

[0241] In some embodiments, the encoded miR binding site is complementary (e.g., fully or partially complementary) to a miR expressed in liver or hepatocytes, such as miR122. In some embodiments, the encoded miR binding site or encoded miR binding site series comprises a miR122 binding site sequence. In some embodiments, the encoded miR122 binding site comprises the nucleotide sequence of ACAAACACCATTGTCACACTCCA (SEQ ID NO: 4673), or a nucleotide sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, at least 95%, at least 99%, or 100% sequence identity, or having at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but no more than ten modifications, e.g., insertions, deletions, or substitutions (e.g., conservative substitutions), relative to the nucleotide sequence of SEQ ID NO: 4673, e.g., wherein the modification can result in a mismatch between the encoded miR binding site and the corresponding miRNA. In some embodiments, the viral genome comprises at least 2, 3, 4, or 5 copies of the encoded miR122 binding site, e.g., an encoded miR122 binding site series, optionally wherein the encoded miR122 binding site series comprises the nucleotide sequence of:

ACAAACACCATTGTCACACTCCACACAAACACCATTGTCACACTCCACACAAACACCATTGTCACACTCCA (SEQ ID NO: 4674), or a nucleotide sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, at least 95%, at least 99%, or 100% sequence identity, or having at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the nucleotide sequence of SEQ ID NO: 4674, e.g., wherein the modification can result in a mismatch between the encoded miR binding site and the corresponding miRNA. In some embodiments, at least two of the encoded miR122 binding sites are connected directly, e.g., without a spacer. In other embodiments, at least two of the encoded miR122 binding sites are separated by a spacer, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides in length, which is located between two or more consecutive encoded miR122 binding site sequences. In some embodiments, the spacer is about 1 to 6 nucleotides or about 5 to 10 nucleotides, e.g., about 7-8, in length. In some embodiments, the spacer coding sequence or reverse complement thereof comprises one or more of (i) GGAT; (ii) CACGTG; (iii) GCATGC, or a repeat of one or more of (i)-(iii). In

some embodiments, an encoded miR binding site series comprises at least 3-5 copies (e.g., 4 copies) of a miR122 binding site, with or without a spacer, wherein the spacer is about 1 to 6 nucleotides or about 5 to 10 nucleotides, e.g., about 7-8 nucleotides or about 8 nucleotides, in length. In some embodiments, the spacer comprises the nucleotide sequence of GATAGTTA, or a nucleotide sequence having at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions relative to the nucleotide sequence of GATAGTTA.

[0242] In some embodiments, the encoded miR binding site is complementary (e.g., fully or partially complementary) to a miR expressed in the heart. In embodiments, the encoded miR binding site or encoded miR binding site series comprises a miR-1 binding site. In some embodiments, the encoded miR-1 binding site comprises the nucleotide sequence of ATACATACTTCTTTACATTCCA (SEQ ID NO: 4679), a nucleotide sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, at least 95%, at least 99%, or 100% sequence identity, or having at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the nucleotide sequence of SEQ ID NO: 4679, e.g., wherein the modification can result in a mismatch between the encoded miR binding site and the corresponding miRNA. In some embodiments, the viral genome comprises at least 2, 3, 4, or 5 copies of the encoded miR-1 binding site, e.g., an encoded miR-1 binding site series. In some embodiments, the at least 2, 3, 4, or 5 copies (e.g., 2 or 3 copies) of the encoded miR-1 binding site are continuous (e.g., not separated by a spacer) or separated by a spacer. In some embodiments, the spacer is about 1 to 6 nucleotides or about 5 to 10 nucleotides, e.g., about 7-8 nucleotides or about 8 nucleotides, in length. In some embodiments, the spacer sequence comprises one or more of (i) GGAT; (ii) CACGTG; (iii) GCATGC, or a repeat of one or more of (i)-(iii). In some embodiments, the spacer comprises the nucleotide sequence of GATAGTTA, or a nucleotide sequence having at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the nucleotide sequence of GATAGTTA.

[0243] In some embodiments, the encoded miR binding site is complementary (e.g., fully or partially complementary) to a miR expressed in hematopoietic lineage, including immune cells (e.g., antigen presenting cells or APC, including dendritic cells (DCs), macrophages, and B-lymphocytes). In some embodiments, the encoded miR binding site complementary to a miR expressed in hematopoietic lineage comprises a nucleotide sequence disclosed, e.g., in US 2018/0066279, the contents of which are incorporated by reference herein in its entirety.

[0244] In embodiments, the encoded miR binding site or encoded miR binding site series comprises a miR-142-3p binding site sequence. In some embodiments, the encoded miR-142-3p binding site comprises the nucleotide sequence of TCCATAAAGTAGGAAACACTACA (SEQ ID NO: 4675), a nucleotide sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, at least 95%, at least 99%, or 100% sequence identity, or having at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the nucleotide sequence of SEQ ID NO: 4675, e.g., wherein the modification can result in a mismatch between the encoded miR binding site and the corresponding miRNA. In some embodiments, the viral genome comprises at least 2, 3, 4, or 5 copies of the encoded miR-142-3p binding site, e.g., an encoded miR-142-3p binding site series. In some embodiments, the at least 2, 3, 4, or 5 copies (e.g., 2 or 3 copies) of the encoded miR-142-3p binding site are continuous (e.g., not separated by a spacer) or separated by a spacer. In some embodiments, the spacer is about 1 to 6 nucleotides or about 5 to 10 nucleotides, e.g., about 7-8 nucleotides or about 8 nucleotides, in length. In some embodiments, the spacer sequence comprises one or more of (i) GGAT; (ii) CACGTG; (iii) GCATGC, or a repeat of one or more of (i)-(iii). In some embodiments, the spacer comprises the nucleotide sequence of GATAGTTA, or a nucleotide sequence having at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the nucleotide sequence of GATAGTTA.

[0245] In some embodiments, the encoded miR binding site is complementary (e.g., fully complementary or partially complementary) to a miR expressed in a DRG (dorsal root ganglion) neuron, e.g., a miR183, a miR182, and/or miR96 binding site. In some embodiments, the encoded miR binding site is complementary to a miR expressed in a DRG neuron comprises a nucleotide sequence disclosed, e.g., in WO2020/132455, the contents of which are incorporated by reference herein in its entirety.

[0246] In some embodiments, the encoded miR binding site or encoded miR binding site series comprises a miR183 binding site sequence. In some embodiments, the encoded miR183 binding site comprises the nucleotide sequence of AGTGAATTCTACCAGTGCCATA (SEQ ID NO: 4676), or a nucleotide sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, at least 95%, at least 99%, or 100% sequence identity, or having at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the nucleotide sequence of SEQ ID NO: 4676, e.g., wherein the modification can result in a mismatch between the encoded miR binding site and the corresponding miRNA. In some embodiments, the sequence complementary to the seed sequence corresponds to the double underlined

of the encoded miR-183 binding site sequence. In some embodiments, the viral genome comprises at least comprises at least 2, 3, 4, or 5 copies (e.g., at least 2 or 3 copies) of the encoded miR183 binding site, e.g., an encoded miR183 binding site. In some embodiments, the at least 2, 3, 4, or 5 copies (e.g., 2 or 3 copies) of the encoded miR183 binding site are continuous (e.g., not separated by a spacer) or separated by a spacer. In some embodiments, the spacer is about 1 to 6 nucleotides or about 5 to 10 nucleotides, e.g., about 7-8 nucleotides or about 8 nucleotides, in length. In some embodiments, the spacer comprises the nucleotide sequence of GATAGTTA, or a nucleotide sequence having at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the nucleotide sequence of GATAGTTA. In some embodiments, the spacer sequence comprises one or more of (i) GGAT; (ii) CACGTG; (iii) GCATGC, or a repeat of one or more of (i)-(iii).

[0247] In some embodiments, the encoded miR binding site or the encoded miR binding site series comprises a miR182 binding site sequence. In some embodiments, the encoded miR182 binding site comprises, the nucleotide sequence of AGTGTGAGTTCTACCATTGCCAAA (SEQ ID NO: 4677), a sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, at least 95%, at least 99%, or 100% sequence identity, or having at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the nucleotide sequence of SEQ ID NO: 4677, e.g., wherein the modification can result in a mismatch between the encoded miR binding site and the corresponding miRNA. In some embodiments, the viral genome comprises at least 2, 3, 4, or 5 copies of the encoded miR182 binding site, e.g., an encoded miR182 binding site series. In some embodiments, the at least 2, 3, 4, or 5 copies (e.g., 2 or 3 copies) of the encoded miR182 binding site are continuous (e.g., not separated by a spacer) or separated by a spacer. In some embodiments, the spacer is about 1 to 6 nucleotides or about 5 to 10 nucleotides, e.g., about 7-8 nucleotides or about 8 nucleotides, in length. In some embodiments, the spacer comprises the nucleotide sequence of GATAGTTA, or a nucleotide sequence having at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the nucleotide sequence of GATAGTTA. In some embodiments, the spacer sequence comprises one or more of (i) GGAT; (ii) CACGTG; (iii) GCATGC, or a repeat of one or more of (i)-(iii).

[0248] In certain embodiments, the encoded miR binding site or the encoded miR binding site series comprises a miR96 binding site sequence. In some embodiments, the encoded miR96 binding site comprises the nucleotide sequence of AGCAAAAATGTGCTAGTGCCAAA (SEQ ID NO: 4678), a sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, at least 95%, at least

99%, or 100% sequence identity, or having at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the nucleotide sequence of SEQ ID NO: 4678, e.g., wherein the modification can result in a mismatch between the encoded miR binding site and the corresponding miRNA. In some embodiments, the viral genome comprises at least 2, 3, 4, or 5 copies of the encoded miR96 binding site, e.g., an encoded miR96 binding site series. In some embodiments, the at least 2, 3, 4, or 5 copies (e.g., 2 or 3 copies) of the encoded miR96 binding site are continuous (e.g., not separated by a spacer) or separated by a spacer. In some embodiments, the spacer is about 1 to 6 nucleotides or about 5 to 10 nucleotides, e.g., about 7-8 nucleotides or about 8 nucleotides, in length. In some embodiments, the spacer comprises the nucleotide sequence of GATAGTTA, or a nucleotide sequence having at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the nucleotide sequence of GATAGTTA. In some embodiments, the spacer sequence comprises one or more of (i) GGAT; (ii) CACGTG; (iii) GCATGC, or a repeat of one or more of (i)-(iii).

[0249] In some embodiments, the encoded miR binding site series comprises a miR122 binding site, a miR-1, a miR142 binding site, a miR183 binding site, a miR182 binding site, a miR 96 binding site, or a combination thereof. In some embodiments, the encoded miR binding site series comprises at least 2, 3, 4, or 5 copies of a miR122 binding site, a miR142 binding site, a miR183 binding site, a miR182 binding site, a miR 96 binding site, or a combination thereof. In some embodiments, at least two of the encoded miR binding sites are connected directly, e.g., without a spacer. In other embodiments, at least two of the encoded miR binding sites are separated by a spacer, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides in length, which is located between two or more consecutive encoded miR binding site sequences. In embodiments, the spacer is at least about 5 to 10 nucleotides, e.g., about 7-8 nucleotides or about 8 nucleotides, in length. In some embodiments, the spacer coding sequence or reverse complement thereof comprises one or more of (i) GGAT; (ii) CACGTG; (iii) GCATGC, or a repeat of one or more of (i)-(iii). In some embodiments, the spacer comprises the nucleotide sequence of GATAGTTA, or a nucleotide sequence having at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the nucleotide sequence of GATAGTTA.

[0250] In some embodiments, an encoded miR binding site series comprises at least 2-5 copies (e.g., 2 or 3 copies) of a combination of at least two, three, four, five, or all of a miR-1, miR122 binding site, a miR142 binding site, a miR183 binding site, a miR182 binding site, a miR96 binding site, wherein each of the miR binding sites within the series are continuous (e.g., not separated by a spacer) or are separated by a spacer. In some embodiments, the spacer is about 1 to 6 nucleotides or

about 5 to 10 nucleotides, e.g., about 7-8 nucleotides or about 8 nucleotides, in length. In some embodiments, the spacer sequence comprises one or more of (i) GGAT; (ii) CACGTG; (iii) GCATGC, or a repeat of one or more of (i)-(iii). In some embodiments, the spacer comprises the nucleotide sequence of GATAGTTA, or a nucleotide sequence having at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the nucleotide sequence of GATAGTTA.

[0251] In some embodiments, an encoded miR binding site series comprises at least 2-5 copies (e.g., 2 or 3 copies) of a combination of a miR-122 binding site and a miR-1 binding site, wherein each of the miR binding sites within the series are continuous (e.g., not separated by a spacer) or are separated by a spacer. In some embodiments, the spacer is about 1 to 6 nucleotides or about 5 to 10 nucleotides, e.g., about 7-8 nucleotides or about 8 nucleotides, in length. In some embodiments, the spacer sequence comprises one or more of (i) GGAT; (ii) CACGTG; (iii) GCATGC, or a repeat of one or more of (i)-(iii). In some embodiments, the spacer comprises the nucleotide sequence of GATAGTTA, or a nucleotide sequence having at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the nucleotide sequence of GATAGTTA.

Genome Size

[0252] In one embodiment, the AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant), may comprise a single-stranded or double-stranded viral genome. The size of the viral genome may be small, medium, large or the maximum size. As described above, the viral genome may comprise a promoter and a polyA tail.

[0253] In one embodiment, the viral genome may be a small single stranded viral genome. A small single stranded viral genome may be 2.1 to 3.5 kb in size such as, but not limited to, about 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, and 3.5 kb in size.

[0254] In one embodiment, the viral genome 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, but not limited to, about 1.3, 1.4, 1.5, 1.6, and 1.7 kb in size.

[0255] In one embodiment, the viral genome may be a medium single stranded viral genome. A medium single stranded viral genome may be 3.6 to 4.3 kb in size such as, but not limited to, about 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2 and 4.3 kb in size.

[0256] In one embodiment, the viral genome 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, but not limited to, about 1.8, 1.9, 2.0, and 2.1 kb in size.

[0257] In one embodiment, the viral genome 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, but not limited to, 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.

[0258] In one embodiment, the viral genome 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, but not limited to, about 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9 and 3.0 kb in size.

Payloads

[0259] In some embodiments, an AAV particle of the present disclosure (e.g. an AAV particle comprising an AAV capsid variant described herein) comprises a viral genome comprising a nucleic acid encoding a payload. In some embodiments, the encoded payload is an RNAi agent or a polypeptide. A payload of the present disclosure may be, but is not limited to, a peptide, a polypeptide, a protein, an antibody, an RNAi agent, etc.

[0260] In some embodiments, the nucleotide sequence encoding a payload may comprise a combination of coding and non-coding nucleic acid sequences. In some embodiments, the nucleotide sequence encoding the payload may encode a coding or non-coding RNA.

[0261] In some embodiments, the AAV particles described herein, e.g., an AAV particle comprising an AAV capsid variant, comprises a nucleic acid encoding a payload. In some embodiments, the encoded payload comprises a therapeutic protein, an antibody, an enzyme, one or more components of a genome editing system, and/or an RNAi agent (e.g., a dsRNA, siRNA, shRNA, pre-miRNA, pri-miRNA, miRNA, stRNA, lncRNA, piRNA, or snoRNA). In some embodiments, the encoded payload modulates, e.g., increases or decreases, the presence, level, and/or activity of a gene, mRNA, protein, or a combination thereof, e.g., in a cell or a tissue.

Polypeptides

[0262] In some embodiments, the encoded payload of AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein comprises a polypeptide, protein, or peptide, e.g., a polypeptide, protein, or peptide described herein. The nucleic acid encoding the payload, may encode a product of any known gene and/or a recombinant version thereof. In some embodiments, the nucleic acid encoding the payload may encode at least one allele of apolipoprotein E (APOE) such as, but not limited to ApoE2, ApoE3 and/or ApoE4. In one embodiment, the nucleic acid encoding the payload encodes ApoE2 (cys112, cys158) protein or a fragment or variant thereof. In one embodiment, the nucleic acid encoding the payload encodes an ApoE3 (cys112, arg158) protein or fragment or variant thereof. In one embodiment, the nucleic acid encoding the payload encodes ApoE4 (arg112, arg158). As another non-limiting example, the encoded payload comprises an aromatic L-amin acid decarboxylase (AADC) protein. As another non-limiting example, the encoded payload comprises an antibody, or a fragment thereof. As another non-limiting example, the

encoded payload comprises a human survival of motor neuron (SMN) 1 or SMN2 protein, or fragments or variants thereof. As another non-limiting example, the encoded payload region comprises a glucocerebrosidase (GBA1) protein, or a fragment or variant thereof. As another non-limiting example, the encoded payload comprises a granulin precursor or progranulin (GRN) protein, or a fragment or variant thereof. As another non-limiting example, the encoded payload comprises an aspartoacylase (ASPA) protein, or a fragment or variant thereof. As another non-limiting example, the encoded payload comprises a tripeptidyl peptidase I (CLN2) protein, or a fragment or variant thereof. As another non-limiting example, the encoded payload comprises a beta-galactosidase (GLB1) protein, or a fragment or variant thereof. As another non-limiting example, the encoded payload comprises a N-sulphoglucosamine sulphohydrolase (SGSH) protein, or a fragment or variant thereof. As another non-limiting example, the encoded payload comprises an N-acetyl-alpha-glucosaminidase (NAGLU) protein, or a fragment or variant thereof. As another non-limiting example, the encoded payload comprises a iduronate 2-sulfatase (IDS) protein, or a fragment or variant thereof. As another non-limiting example, the encoded payload comprises an intracellular cholesterol transporter (NPC1) protein, or a fragment or variant thereof. As another non-limiting example, the encoded payload comprises a gigaxonin (GAN) protein, or a fragment or variant thereof. The AAV viral genomes encoding polypeptides 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.

[0263] Amino acid sequences of a payload polypeptide encoded by a viral genome described herein, may be translated as a whole polypeptide, a plurality of polypeptides or fragments of polypeptides, which independently may be encoded by one or more nucleic acids, fragments of nucleic acids or variants of any of the aforementioned.

Antibodies and Antibody Binding Fragments

[0264] In some embodiments, the encoded payload of AAV particle comprising an AAV capsid variant described herein comprises an antibody or antibody binding fragment. In some embodiments, the antibody may be a full antibody, a fragment, or any functional variant thereof. As non-limiting examples, an antibody may be a native antibody (e.g., with two heavy and two light chains), a heavy chain variable region, a light chain variable region, a heavy chain constant region, a light chain constant region, Fab, Fab', F(ab')₂, Fv, or scFv fragments, a diabody, a linear antibody, a single-chain antibody, a multi-specific antibody, an intrabody, one or more heavy chain complementarity determining regions (CDR), one or more light chain CDRs, a bi-specific antibody, a monoclonal antibody, a polyclonal antibody, a humanized antibody, an antibody mimetic, an antibody variant, a miniaturized antibody, a unibody, a maxibody, and/or a chimeric antigen receptor. The encoded antibody or antibody binding fragment may be useful in the treatment of a neurological disease, a

neurodegenerative disorder, a muscular disease, a neuromuscular disorder, a neuro-oncological disorder, or any disorder associated with the central and/or peripheral nervous systems.

[0265] In some embodiments, the viral genome of the AAV particle (e.g., an AAV particle comprising an AAV capsid variant described herein) may comprise a nucleic acid which has been engineered to enable or enhance the expression of an antibody, or antibody binding fragment thereof.

[0266] In some embodiments, the encoded antibody of the payload of an AAV particle comprising an AAV capsid variant, described herein comprises at least one immunoglobulin variable domain sequence. An antibody may include, for example, full-length, mature antibodies and antigen-binding fragments of an antibody. For example, an antibody can include a heavy (H) chain variable domain sequence (VH), and a light (L) chain variable domain sequence (VL). In another example, an antibody includes two heavy (H) chain variable domain sequences and two light (L) chain variable domain sequence, thereby forming two antigen binding sites, such as Fab, Fab', F(ab')₂, Fc, Fd, Fd', Fv, single chain antibodies (scFv for example), single variable domain antibodies, diabodies (Dab) (bivalent and bispecific), and chimeric (e.g., humanized) antibodies, which may be produced by the modification of whole antibodies or those synthesized de novo using recombinant DNA technologies. These functional antibody fragments, e.g., an antibody binding fragments, retain the ability to selectively bind with their respective antigen or receptor.

[0267] In some embodiments, the antibody binding fragment comprises at least one portion of an intact antibody, or recombinant variants thereof, and refers to the antigen binding domain, for example, an antigenic determining variable region of an intact antibody, that is sufficient to confer recognition and specific binding of the antibody fragment to a target, such as an antigen. Examples of antigen binding fragments include: (i) a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; (ii) a F(ab')₂ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the VH and CH1 domains; (iv) a Fv fragment consisting of the VL and VH domains of a single arm of an antibody, (v) a diabody (dAb) fragment, which consists of a VH domain; (vi) a camelid or camelized variable domain; (vii) a single chain Fv (scFv), see e.g., Bird et al. (1988) Science 242:423-426; and Huston et al. (1988) Proc. Natl. Acad. Sci. USA 85:5879-5883; and (viii) a single domain antibody. These antibody fragments are obtained using conventional techniques known to those with skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies. An antibody fragment can also be incorporated into single domain antibodies, maxibodies, minibodies, nanobodies, intrabodies, diabodies, triabodies, tetrabodies, v-NAR and bis-scFv (see, for example, Hollinger and Hudson, Nature Biotechnology 23:1126-1136, 2005).

[0268] In some embodiments, the encoded antibody of the payload of an AAV particle described herein comprises a multispecific antibody, e.g., it comprises a plurality of immunoglobulin variable domains sequences, wherein a first immunoglobulin variable domain sequence of the plurality has

binding specificity for a first epitope and a second immunoglobulin variable domain sequence of the plurality has binding specificity for a second epitope. In some embodiments, the first and second epitopes are on the same antigen, e.g., the same protein (or subunit of a multimeric protein). In some embodiments, the first and second epitopes overlap. In some embodiments, the first and second epitopes do not overlap. In some embodiments, the first and second epitopes are on different antigens, e.g., the different proteins (or different subunits of a multimeric protein). In some embodiments, a multispecific antibody comprises a third, fourth or fifth immunoglobulin variable domain. In some embodiments, a multispecific antibody is a bispecific antibody, a trispecific antibody, or tetraspecific antibody.

[0269] In some embodiments, an encoded multispecific antibody of the payload of an AAV particle described herein is an encoded bispecific antibody. A bispecific antibody has specificity for no more than two antigens. A bispecific antibody is characterized by a first immunoglobulin variable domain sequence which has binding specificity for a first epitope and a second immunoglobulin variable domain sequence that has binding specificity for a second epitope. In some embodiments, the first and second epitopes are on the same antigen, e.g., the same protein (or subunit of a multimeric protein). In some embodiments, the first and second epitopes overlap. In some embodiments, the first and second epitopes do not overlap. In some embodiments, the first and second epitopes are on different antigens, e.g., the different proteins (or different subunits of a multimeric protein).

[0270] An antibody or an antibody binding fragment encoded by a viral genome of an AAV particle described herein, may be, but is not limited to, an antibody or antibody fragment that binds to β -amyloid, APOE, tau, SOD1, TDP-43, huntingtin, and/or synuclein. In some embodiments, the encoded payload comprises an antibody or antibody fragment that binds to a neuro-oncology related target, e.g., HER2, EGFR (e.g., EGFRvIII). In some embodiments, the encoded payload comprises an antibody that binds to HER2/neu. In some embodiments, the encoded payload comprises an antibody that binds to β -amyloid. In some embodiments, the encoded payload comprises an antibody that binds to tau.

Gene Editing System

[0271] In some embodiments, the encoded payload of AAV particle comprising an AAV capsid variant described herein comprises a gene editing system or one or more components thereof. In some embodiments, the gene editing system comprises nucleic acid sequences that encode proteins having enzymatic activity to (i) selectively induce double or single stranded breaks in a DNA or RNA sequence, or (ii) substitute, insert or delete a particular base or set of bases of a DNA or RNA sequence in the absence of a double or single stranded break in the DNA or RNA. In some embodiments, the gene editing system includes, but is not limited to a CRISPR-Cas system (including different Cas or Cas-related nucleases), a Zinc finger nuclease, a meganuclease, a TALEN or a base

editors. In some embodiments, the gene editing system comprises a chromosomal integration of a transgene, e.g., introduced by a parvovirus vector in the absence of an exogenous nuclease or an enzymatic entity.

RNAi agents

[0272] In some embodiments, the encoded payload of AAV particle comprising an AAV capsid variant described herein comprises an RNAi agent, e.g., an RNAi agent described herein. In some embodiments, the encoded payload of a viral genome of an AAV particle comprising an AAV capsid variant described herein comprises a dsRNA, a siRNA, a shRNA, a pre-miRNA, a pri-miRNA, a miRNA, a stRNA, a lncRNA, a piRNA, or a snoRNA. In some embodiments, the encoded payload comprises an RNAi agent for inhibiting expression of a SOD1, MAPT, APOE, HTT, C9ORF72, TDP-43, APP, BACE, SNCA, ATXN1, ATXN3, ATXN7, SCN1A-SCN5A, or SCN8A-SCN11A gene, protein, and/or mRNA. In some embodiments, the RNAi agent encoded by a viral genome described herein inhibits SOD1, MAPT, APOE, HTT, C9ORF72, TDP-43, APP, BACE, SNCA, ATXN1, ATXN3, ATXN7, SCN1A-SCN5A, or SCN8A-SCN11A.

[0273] An AAV particle comprising an AAV capsid variant described herein may comprise a viral genome encoding an RNAi agent, which targets the mRNA of a gene to modulate, e.g., interfere with gene expression and/or protein production.

[0274] In some embodiments, the RNAi agent may target a gene at the location of a single-nucleotide polymorphism (SNP) or variant within the nucleotide sequence of the gene.

[0275] The RNAi agent may be an siRNA duplex, wherein the siRNA duplex contains an antisense strand (guide strand) and a sense strand (passenger 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.

[0276] Each strand of an siRNA duplex targeting a gene of interest may be about 19 to 25, 19 to 24 or 19 to 21 nucleotides in length, preferably about 19 nucleotides, 20 nucleotides, 21 nucleotides, 22 nucleotides, 23 nucleotides, 24 nucleotides, or 25 nucleotides in length.

[0277] In one embodiment, an siRNA or dsRNA includes at least two sequences that are complementary to each other. The dsRNA includes a sense strand having a first sequence and an antisense strand having a second sequence. The antisense strand includes a nucleotide sequence that is substantially complementary to at least part of an mRNA encoding the target gene, and the region of complementarity is 30 nucleotides or less, and at least 15 nucleotides in length. Generally, the dsRNA is 19 to 25, 19 to 24 or 19 to 21 nucleotides in length. In some embodiments, the dsRNA is from about 15 to about 25 nucleotides in length, and in other embodiments the dsRNA is from about

25 to about 30 nucleotides in length. In some embodiments, the dsRNA is about 15 nucleotides in length, 16 nucleotides in length, 17 nucleotides in length, 18 nucleotides in length, 19 nucleotides, 20 nucleotides, 21 nucleotides, 22 nucleotides, 23 nucleotides, 24 nucleotides, 25 nucleotides in length, 26 nucleotides in length, 27 nucleotides in length, 28 nucleotides in length, 29 nucleotides in length, or 30 nucleotides in length.

[0278] In some embodiments, the encoded RNAi agent is an siRNA.

[0279] In some embodiments, the RNAi agent, e.g., an RNAi agent described herein inhibits the expression of the gene, mRNA, and/or protein by at least 10%, at least 20%, at least 25%, at least 30%, at least 35% or at least 40% or more, such as when assayed by a method known in the art. In some embodiments, the RNAi agent inhibits expression of a gene, mRNA, and protein by 50-100%, e.g., by 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95% and 100%.

[0280] In some embodiments, the AAV particle described herein, comprising a viral genome encoding an RNAi agent targeting a gene of interest is administered to a subject in need for treating and/or ameliorating a disease, e.g., a neurological disorder of any disease associated with the central or peripheral nervous systems.

Design of siRNA

[0281] An AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant described herein) may comprise a viral genome encoding a siRNA molecule (e.g., siRNA duplex or encoded dsRNA) that target a gene of interest and suppress target gene expression, mRNA expression, and protein production. In some aspects, the siRNA molecules are designed and used to knock out target gene variants in cells, e.g., transcripts that are identified in neurological disease. In some aspects, the siRNA molecules are designed and used to knock down target gene variants in cells.

[0282] Some guidelines for designing siRNAs (for insertion into a viral genome of the AAV particles described herein) 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 considerations, together with the specific sequence of a target gene, highly effective siRNA molecules essential for suppressing mammalian target gene expression may be readily designed.

[0283] In one embodiment, the sense and/or antisense strand is designed based on the method and rules outlined in European Patent Publication No. EP1752536, the contents of which are herein incorporated by reference in their entirety. As a non-limiting example, the 3'-terminal base of the sequence is adenine, thymine or uracil. As a non-limiting example, the 5'-terminal base of the

sequence is guanine or cytosine. As a non-limiting example, the 3'-terminal sequence comprises seven bases rich in one or more bases of adenine, thymine and uracil.

[0284] In one embodiment, an siRNA molecule 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, e.g., the siRNA molecule has a sequence sufficient to trigger the destruction of the target mRNA by the RNAi machinery or process.

[0285] 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. Neither the identity of the sense sequence nor the homology of the antisense sequence need be 100% complementary to the target.

[0286] 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 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% complementary.

[0287] The siRNA molecule may have a length from about 10-50 or more nucleotides, e.g., 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 complementary to a target region. In one embodiment, the siRNA molecule has a length from about 19 to 25, 19 to 24 or 19 to 21 nucleotides.

[0288] In some embodiments, the siRNA molecule can be a synthetic RNA duplex comprising about 19 nucleotides to about 25 nucleotides, and two overhanging nucleotides at the 3'-end.

[0289] The siRNA molecule 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 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% complementary.

[0290] 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% complementary across independently at least 50, 60, 70, 80, 85, 90, 95, or 99% of the length of the strands.

[0291] In some embodiments, the sense and antisense strands of a siRNA duplex are 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.

[0292] In some embodiments, the siRNA molecules, as well as associated spacer and/or flanking regions once designed, can be encoded by the viral genome of the AAV particles described herein, for delivery to a cell.

Molecular Scaffold

[0293] In some embodiments, the siRNA molecules may be encoded in a modulatory polynucleotide which also comprises a molecular scaffold.

[0294] In some embodiments, the modulatory polynucleotide which comprises the payload (e.g., siRNA, miRNA or other RNAi agent described herein) includes a molecular scaffold which comprises a 5' flanking sequence, a loop region, and/or a 3' flanking region. In some embodiments a 5' or 3' flanking region may be of any length and may a wild type microRNA sequence or a portion thereof, or may be completely artificial. A 3' flanking sequence may mirror the 5' flanking sequence in size and origin. Either flanking sequence may be absent. In one embodiment, both the 5' and 3' flanking sequences are absent. The 3' flanking sequence may optionally contain one or more CNNC motifs, where "N" represents any nucleotide. In some embodiments, the loop comprises at least one UGUG motif. In some embodiments, the UGUG motif is located at the 5' terminus of the loop. In some embodiments the 5' and 3' flanking sequences are the same sequence. In some embodiments they differ by 2%, 3%, 4%, 5%, 10%, 20% or more than 30% when aligned to each other.

[0295] In some embodiments, modulatory polynucleotide comprises a stem loop structure. In some embodiments, the modulatory polynucleotide comprises in 5' to 3' order: a 5' flanking sequence, a guide strand sequence, a loop region, a passenger strand sequence, and a 3' flanking sequence. In some embodiments, the modulatory polynucleotide comprises in 5' to 3' order: a 5' flanking sequence, a passenger strand sequence, a loop region, a guide strand sequence, and a 3' flanking sequence.

[0296] In one embodiment, the molecular scaffold comprises a dual-function targeting modulatory polynucleotide.

[0297] 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.

[0298] 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 basal 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.

AAV production

[0299] Viral production disclosed herein describes processes and methods for producing AAV particles (with enhanced, improved and/or increased tropism for a target tissue), e.g., an AAV particle comprising an AAV capsid variant that may be used to contact a target cell to deliver a payload.

[0300] In some embodiments, disclosed herein is a method of making AAV particle of the present disclosure, e.g., an AAV particle comprising an AAV capsid variant the method comprising: (i) providing a host cell comprising a viral genome described herein and (ii) incubating the host cell under conditions suitable to enclose the viral genome in an AAV capsid variant, e.g., an AAV capsid variant described herein (e.g., an AAV capsid variant listed in Tables 3, 4, or 5), thereby making the AAV particle. In some embodiments, the method comprises prior to step (i), introducing a first nucleic acid comprising the viral genome into a cell. In some embodiments, the host cell comprises a second nucleic acid encoding the AAV capsid variant. In some embodiments, the second nucleic acid is introduced into the host cell prior to, concurrently with, or after the first nucleic acid molecule. In some embodiments, the AAV particle described herein is an isolated AAV particle. In some embodiments, the AAV particle described herein is a recombinant AAV particle.

[0301] Any method known in the art may be used for the preparation of AAV particles. In some embodiments, AAV particles are produced in mammalian cells (e.g., HEK293). In another embodiment, AAV particles are produced in insect cells (e.g., Sf9).

[0302] Methods of making AAV particles are well known in the art and are described in e.g., U.S. Patent Nos. US6204059, US5756283, US6258595, US6261551, US6270996, US6281010, US6365394, US6475769, US6482634, US6485966, US6943019, US6953690, US7022519, US7238526, US7291498 and US7491508, US5064764, US6194191, US6566118, US8137948; or International Publication Nos. WO1996039530, WO1998010088, WO1999014354, WO1999015685, WO1999047691, WO2000055342, WO2000075353 and WO2001023597; Methods In Molecular Biology, ed. Richard, Humana Press, NJ (1995); O'Reilly et al., *Baculovirus Expression Vectors*, A Laboratory Manual, Oxford Univ. Press (1994); Samulski et al., *J. Vir.* 63:3822-8 (1989); Kajigaya et al., *Proc. Nat'l. Acad. Sci. USA* 88: 4646-50 (1991); Ruffing et al., *J. Vir.* 66:6922-30 (1992); Kimbauer et al., *Vir.*, 219:37-44 (1996); Zhao et al., *Vir.* 272:382-93 (2000); the contents of each of which are herein incorporated by reference in their entirety. In some embodiments, the AAV particles are made using the methods described in International Patent Publication WO2015191508, the contents of which are herein incorporated by reference in their entirety.

Therapeutic Applications

[0303] The present disclosure provides a method for treating a disease, disorder and/or condition in a subject, including a human subject, comprising administering to the subject an AAV particle described herein, e.g., an AAV particle comprising an AAV capsid variant (e.g., an AAV capsid

variant described herein), or administering to the subject any of the described compositions, including a pharmaceutical composition, described herein.

[0304] In some embodiments, the AAV particle (e.g., an AAV particle comprising an AAV capsid variant) is administered to a subject prophylactically, to prevent on-set of disease. In another embodiment, the AAV particle (e.g., an AAV particle comprising an AAV capsid variant) is administered to treat (e.g., lessen the effects of) a disease or symptoms thereof. In yet another embodiment, the AAV particle (e.g., an AAV particle comprising an AAV capsid variant) is administered to cure (eliminate) a disease. In another embodiment, the AAV particle (e.g., an AAV particle comprising an AAV capsid variant) of the present disclosure is administered to prevent or slow progression of disease. In yet another embodiment, the AAV particle (e.g., an AAV particle comprising an AAV capsid variant) of the present disclosure are used to reverse the deleterious effects of a disease. Disease status and/or progression may be determined or monitored by standard methods known in the art.

[0305] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for treatment, prophylaxis, palliation or amelioration of a genetic disorder, e.g., an autosomal dominant genetic disorder, an autosomal recessive disorder, X-linked dominant genetic disorder, an X-linked recessive genetic disorder, or a Y-linked genetic disorder. In some embodiments, the genetic disorder is a monogenetic disorder or a polygenic disorder. In some embodiments, treatment of a genetic disorder, e.g., a monogenic disorder, comprises the use of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant described herein) for a gene replacement therapy.

[0306] In some embodiments, provided herein is method for treating a neurological disorder and/or neurodegenerative disorder in a subject, comprising administering to the subject an effective amount of a pharmaceutical composition described herein or an AAV particle, e.g., a plurality of particles, comprising an AAV capsid variant described herein. In some embodiments, treatment of a neurological disorder and/or neurodegenerative disorder comprises prevention of said neurological disorder and/or neurological disorder.

[0307] In some embodiments, the AAV particle (e.g., an AAV particle comprising an AAV capsid variant) of the disclosure is useful for the treatment, prophylaxis, palliation or amelioration of neurological diseases and/or disorders. In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for the treatment, prophylaxis, palliation or amelioration of tauopathy.

[0308] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is for the treatment, prophylaxis, palliation or amelioration of Alzheimer's Disease. In some embodiments, treatment of Alzheimer's Disease comprises the use of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant described

herein) for a gene replacement therapy. In some embodiments, the payload encoded by an AAV particle comprising a capsid variant described herein comprises an ApoE2 protein, ApoE4 protein, an ApoE3 protein, BDNF protein, CYP46A1 protein, Klotho protein, fractalkine (FKN) protein, neprilysin protein (NEP), CD74 protein, caveolin-1, or a combination or variant thereof. In some embodiments, treatment of Alzheimer's Disease comprises the use of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant described herein) for a reduction in the expression of a tau gene and/or protein, a synuclein gene and/or protein, or a combination or variant thereof. In some embodiments, the payload encoded by an AAV particle comprising a capsid variant described herein comprises an antibody that binds to tau or synuclein, an RNAi agent for inhibiting tau or synuclein, a gene editing system (e.g., a CRISPR-Cas system) for altering tau or synuclein expression, or a combination thereof.

[0309] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful the treatment, prophylaxis, palliation or amelioration of Friedrich's ataxia, or any disease stemming from a loss or partial loss of frataxin protein.

[0310] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is for the treatment, prophylaxis, palliation or amelioration of frontal temporal dementia. In some embodiments, treatment of frontal temporal dementia comprises the use of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant described herein) for a gene replacement therapy. In some embodiments, the payload encoded by an AAV particle comprising a capsid variant described herein comprises a progranulin protein or variant thereof.

[0311] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for the treatment, prophylaxis, palliation or amelioration of Parkinson's Disease. In some embodiments, treatment of Parkinson's disease comprises the use of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant described herein) for a gene replacement therapy. In some embodiments, the payload encoded by an AAV particle comprising a capsid variant described herein comprises an AADC protein, GAD protein, GDNF protein, TH-GCH1 protein, GBA protein, AIMP2-DX2 protein, or a combination or variant thereof. In some embodiments, treatment of Parkinson's disease comprises the use of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant described herein) for a gene knock-down therapy or a gene editing therapy (e.g., knock-out, repression, or correction). In some embodiments, the payload encoded by an AAV particle comprising a capsid variant described herein comprises a modulator, e.g., an RNAi agent or a CRISPR-Cas system, for altering expression of an alpha-synuclein gene, mRNA, and/or protein, or variant thereof. In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for the treatment, prophylaxis, palliation or amelioration of an AADC deficiency. In some embodiments,

treatment of AADC deficiency comprises the use of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant described herein) for a gene replacement therapy. In some embodiments, the payload encoded by an AAV particle comprising a capsid variant described herein comprises an AADC protein or variant thereof.

[0312] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for the treatment, prophylaxis, palliation or amelioration of Amyotrophic lateral sclerosis. In some embodiments, treatment of ALS comprises the use of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant described herein) for a gene replacement therapy. In some embodiments, the payload encoded by an AAV particle comprising a capsid variant described herein comprises a TDP-43 protein, UPF1 protein, C9orf72 protein, CCNF protein, HSF1 protein, Factor H protein, NGF protein, ADAR2 protein, GDNF protein, VEGF protein, HGF protein, NRTN protein, AIMP2-DX2 protein, or a combination or variant thereof. In some embodiments, treatment of ALS comprises the use of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant described herein) for a gene knock-down therapy or a gene editing therapy (e.g., knock-out, repression, or correction). In some embodiments, the payload encoded by an AAV particle comprising a capsid variant described herein comprises a modulator, e.g., an RNAi agent or a CRISPR-Cas system, for altering expression of a SOD1 or C9ORF72 gene, mRNA, and/or protein, or a combination or variant thereof.

[0313] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for the treatment, prophylaxis, palliation or amelioration of Huntington's Disease. In some embodiments, treatment of ALS comprises the use of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant described herein) for a gene knock-down (e.g., knock-out) therapy or a gene editing therapy (e.g., knock-out, repression, or correction). In some embodiments, the payload encoded by an AAV particle comprising a capsid variant described herein comprises a modulator, e.g., an RNAi agent or a CRISPR-Cas system, for altering expression of an HTT gene, mRNA, and/or protein, or a variant thereof.

[0314] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for the treatment, prophylaxis, palliation or amelioration of spinal muscular atrophy. In some embodiments, treatment of spinal muscular atrophy comprises the use of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant described herein) for a gene replacement therapy. In some embodiments, the payload encoded by an AAV particle comprising a capsid variant described herein comprises an SMN1 protein, an SMN2 protein, or a combination or variant thereof.

[0315] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for the treatment, prophylaxis, palliation or amelioration

of multiple system atrophy. In some embodiments, treatment of multiple system atrophy comprises the use of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant described herein) for a gene replacement therapy.

[0316] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for the treatment, prophylaxis, palliation or amelioration of Gaucher disease (GD) (e.g., Type 1 GD, Type 2 GD, or Type 3 GD). In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for the treatment, prophylaxis, palliation or amelioration of Parkinson's disease associated with a GBA mutation. In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for the treatment, prophylaxis, palliation or amelioration of dementia with Lewy Bodies (DLB).

[0317] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for treatment, prophylaxis, palliation or amelioration of a leukodystrophy, e.g., Alexander disease, autosomal dominant leukodystrophy with autonomic diseases (ADLD), Canavan disease, cerebrotendinous xanthomatosis (CTX), metachromatic leukodystrophy (MLD), Pelizaeus-Merzbacher disease, or Refsum disease. In some embodiments, treatment of MLD comprises the use of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant described herein) for a gene replacement therapy. In some embodiments, the payload encoded by an AAV particle comprising a capsid variant described herein comprises an ARSA protein or variant thereof. In some embodiments, treatment of ALD comprises the use of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant described herein) for a gene replacement therapy. In some embodiments, the payload encoded by an AAV particle comprising a capsid variant described herein comprises an ABCD-1 protein or variant thereof.

[0318] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for the treatment, prophylaxis, palliation, or amelioration of megalencephalic leukoencephalopathy (MLC). In some embodiments, treatment of MLC comprises the use of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant described herein) for a gene replacement therapy. In some embodiments, the payload encoded by an AAV particle comprising a capsid variant described herein comprises an MLC1 protein or variant thereof.

[0319] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for the treatment, prophylaxis, palliation, or amelioration of Krabbe disease. In some embodiments, treatment of Krabbe disease comprises the use of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant described herein)

for a gene replacement therapy. In some embodiments, the payload encoded by an AAV particle comprising a capsid variant described herein comprises a GALC protein or variant thereof.

[0320] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for the treatment, prophylaxis, palliation, or amelioration of Mucopolysaccharidosis, e.g., a Type I (MPS I), Type II (MPS II), Type IIIA (MPS IIIA), Type IIIB (MPS IIIB), or Type IIIC (MPS IIIC). In some embodiments, treatment of Mucopolysaccharidosis comprises the use of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant described herein) for a gene replacement therapy or a gene editing therapy (e.g., enhancement or correction). In some embodiments, the payload encoded or corrected by an AAV particle comprising a capsid variant described herein comprises an IDUA protein, IDS protein, SGSH protein, NAGLU protein, HGSNAT protein, or a combination or variant thereof.

[0321] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for the treatment, prophylaxis, palliation, or amelioration of Batten/NCL. In some embodiments, treatment of Batten/NCL comprises the use of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant described herein) for a gene replacement therapy. In some embodiments, the payload encoded by an AAV particle comprising a capsid variant described herein comprises a CLN1 protein, CLN2 protein, CLN3 protein, CLN5 protein, CLN6 protein, CLN7 protein, CLN8 protein, or a combination or variant thereof.

[0322] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for the treatment, prophylaxis, palliation or amelioration of Rett Syndrome. In some embodiments, treatment of Rett Syndrome comprises the use of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant described herein) for a gene replacement therapy. In some embodiments, the payload encoded by an AAV particle comprising a capsid variant described herein comprises an MeCP2 protein or variant thereof.

[0323] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for the treatment, prophylaxis, palliation, or amelioration of Angelman Syndrome. In some embodiments, treatment of Angelman Syndrome comprises the use of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant described herein) for a gene replacement therapy. In some embodiments, the payload encoded by an AAV particle comprising a capsid variant described herein comprises a UBE3A protein or variant thereof.

[0324] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for the treatment, prophylaxis, palliation, or amelioration of Fragile X Syndrome. In some embodiments, treatment of Fragile X Syndrome comprises the use of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant

described herein) for a gene replacement therapy. In some embodiments, the payload encoded by an AAV particle comprising a capsid variant described herein comprises a Reelin protein, a DgkK protein, a FMR1 protein, or a combination or variant thereof.

[0325] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for the treatment, prophylaxis, palliation, or amelioration of Canavan Disease. In some embodiments, treatment of Canavan Disease comprises the use of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant described herein) for a gene replacement therapy. In some embodiments, the payload encoded by an AAV particle comprising a capsid variant described herein comprises an ASPA protein or variant thereof.

[0326] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for the treatment, prophylaxis, palliation, or amelioration of a Gangliosidosis, e.g., a GM1 Gangliosidosis or a GM2 Gangliosidosis (e.g., Tay Sachs Sandhoff). In some embodiments, treatment of a Gangliosidosis, e.g., a GM1 Gangliosidosis or a GM2 Gangliosidosis (e.g., Tay Sachs Sandhoff), comprises the use of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant described herein) for a gene replacement therapy. In some embodiments, the payload encoded by an AAV particle comprising a capsid variant described herein comprises a GLB1 protein, a HEXA protein, a HEXB protein, a GM2A protein, or a combination or variant thereof.

[0327] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for the treatment, prophylaxis, palliation, or amelioration of GM3 Synthase Deficiency. In some embodiments, treatment of GM3 Synthase Deficiency comprises the use of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant described herein) for a gene replacement therapy. In some embodiments, the payload encoded by an AAV particle comprising a capsid variant described herein comprises an ST3GAL5 protein or variant thereof.

[0328] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for the treatment, prophylaxis, palliation, or amelioration of a Niemann-Pick disorder, e.g., a Niemann-Pick A or a Niemann-Pick C1 (NPC-1). In some embodiments, treatment of a Niemann-Pick disorder, e.g., a Niemann-Pick A or a Niemann-Pick C1 (NPC-1) comprises the use of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant described herein) for a gene replacement therapy. In some embodiments, the payload encoded by an AAV particle comprising a capsid variant described herein comprises an ASM protein, an NPC1 protein, or variant thereof.

[0329] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for the treatment, prophylaxis, palliation, or amelioration of Schwannoma (e.g., Neuroma). In some embodiments, treatment of Schwannoma (e.g., Neuroma)

comprises the use of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant described herein) for a gene replacement therapy. In some embodiments, the payload encoded by an AAV particle comprising a capsid variant described herein comprises a Caspase-1 protein or variant thereof.

[0330] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for the treatment, prophylaxis, palliation, or amelioration of a Tuberous Sclerosis, e.g., Tuberous Sclerosis Type 1 or Tuberous Sclerosis Type 2. In some embodiments, treatment of Tuberous Sclerosis, e.g., Tuberous Sclerosis Type 1 or Tuberous Sclerosis Type 2 comprises the use of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant described herein) for a gene replacement therapy. In some embodiments, the payload encoded by an AAV particle comprising a capsid variant described herein comprises a TSC1 protein, a TSC2 protein, or variant thereof.

[0331] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for the treatment, prophylaxis, palliation, or amelioration of a CDKL5 Deficiency. In some embodiments, treatment of a CDKL5 Deficiency comprises the use of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant described herein) for a gene replacement therapy. In some embodiments, the payload encoded by an AAV particle comprising a capsid variant described herein comprises a CDKL5 protein or variant thereof.

[0332] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for the treatment, prophylaxis, palliation, or amelioration of a Charcot-Marie-Tooth disorder, e.g., a Charcot-Marie-Tooth Type 1X (CMT1X) disorder, a Charcot-Marie-Tooth Type 2A (CMT2A) disorder, or a Charcot-Marie-Tooth Type 4J (CMT4J) disorder. In some embodiments, treatment of a Charcot-Marie-Tooth disorder, e.g., a Charcot-Marie-Tooth Type 1X (CMT1X) disorder, a Charcot-Marie-Tooth Type 2A (CMT2A) disorder, or a Charcot-Marie-Tooth Type 4J (CMT4J) disorder, comprises the use of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant described herein) for a gene replacement therapy. In some embodiments, the payload encoded by an AAV particle comprising a capsid variant described herein comprises a GJB1 protein, a MFN2 protein, a FIG4 protein, or variant thereof.

[0333] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for the treatment, prophylaxis, palliation, or amelioration of an Aspartylglucosaminuria (AGU). In some embodiments, treatment of an AGU comprises the use of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant described herein) for a gene replacement therapy. In some embodiments, the payload encoded by an

AAV particle comprising a capsid variant described herein comprises an AGA protein or variant thereof.

[0334] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for the treatment, prophylaxis, palliation, or amelioration of a Leigh Syndrome. In some embodiments, treatment of a Leigh Syndrome comprises the use of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant described herein) for a gene replacement therapy. In some embodiments, the payload encoded by an AAV particle comprising a capsid variant described herein comprises a SURF1 protein or variant thereof.

[0335] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for the treatment, prophylaxis, palliation, or amelioration of epilepsy. In some embodiments, treatment of epilepsy comprises the use of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant described herein) for a gene replacement therapy. In some embodiments, the payload encoded by an AAV particle comprising a capsid variant described herein comprises an NPY/Y2 protein, a Galanin protein, a Dynorphin protein, an AIMP2-DX2 protein, an SLC6A1 protein, an SLC13A5 protein, a KCNQ2 protein, or variant thereof.

[0336] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for the treatment, prophylaxis, palliation, or amelioration of a Dravet Syndrome. In some embodiments, treatment of Dravet Syndrome comprises the use of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant described herein) for a gene replacement therapy. In some embodiments, the payload encoded by an AAV particle comprising a capsid variant described herein comprises an SCN1a protein, or variant thereof.

[0337] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for the treatment, prophylaxis, palliation, or amelioration of a Duchenne muscular dystrophy (DMD). In some embodiments, treatment of DMD comprises the use of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant described herein) for a gene replacement therapy or enhancement (e.g., correction of exon-skipping), or a gene editing therapy (e.g., enhancement or correction). In some embodiments, the payload encoded or corrected by an AAV particle comprising a capsid variant described herein comprises a Dystrophin gene and/or protein, a Utrophin gene and/or protein, or a GALGT2 gene and/or protein, or a Follistatin gene and/or protein, or a combination or variant thereof.

[0338] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for the treatment, prophylaxis, palliation, or amelioration of Pompe Disease. In some embodiments, treatment of Pompe Disease comprises the use of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant described herein)

for a gene replacement therapy. In some embodiments, the payload encoded by an AAV particle comprising a capsid variant described herein comprises a GAA protein, or variant thereof.

[0339] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for the treatment, prophylaxis, palliation, or amelioration of Limb-Girdle Muscular Dystrophy (LGMD2A). In some embodiments, treatment of LGMD2A comprises the use of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant described herein) for a gene replacement therapy. In some embodiments, the payload encoded by an AAV particle comprising a capsid variant described herein comprises a CAPN-3 protein, DYSF protein, a SGCG protein, a SGCA protein, a SGCB protein, a FKR1P protein, a ANO5 protein, or a combination or variant thereof.

[0340] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for the treatment, prophylaxis, palliation or amelioration of chronic or neuropathic pain.

[0341] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising AAV capsid variant) is useful for treatment, prophylaxis, palliation or amelioration of a disease associated with the central nervous system.

[0342] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for treatment, prophylaxis, palliation or amelioration of a disease associated with the peripheral nervous system.

[0343] In some embodiments, provided herein is a method for treating a neuro-oncological disorder in a subject, comprising administering to the subject an effective amount of a pharmaceutical composition described herein or an AAV particle, e.g., a plurality of particles, comprising an AAV capsid variant described herein. In some embodiments, treatment of a neuro-oncological disorder comprises prevention of said neuro-oncological disorder. In some embodiments, a neuro-oncological disorder comprises a cancer of a primary CNS origin (e.g., a CNS cell, a tissue, or a region), or a metastatic cancer in a CNS cell, tissue, or region. Examples of primary CNS cancers could be gliomas (which may include glioblastoma (also known as glioblastoma multiforme), astrocytomas, oligodendrogliomas, and ependymomas, and mixed gliomas), meningiomas, medulloblastomas, neuromas, and primary CNS lymphoma (in the brain, spinal cord, or meninges), among others. Examples of metastatic cancers include those originating in another tissue or organ, e.g., breast, lung, lymphoma, leukemia, melanoma (skin cancer), colon, kidney, prostate, or other types that metastasize to brain.

[0344] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for the treatment, prophylaxis, palliation or amelioration of a disease associated with expression of HER2, e.g., a disease associated with overexpression of HER2. In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising

an AAV capsid variant) is useful for the treatment, prophylaxis, palliation or amelioration of a HER2-positive cancer. In some embodiments, the HER2-positive cancer is a HER2-positive solid tumor. Additionally, or alternatively, the HER2-positive cancer may be a locally advanced or metastatic HER2-positive cancer. In some instances, the HER2-positive cancer is a HER2-positive breast cancer or a HER2-positive gastric cancer. In some embodiments, the HER2-positive cancer is selected from the group consisting of a HER2-positive gastroesophageal junction cancer, a HER2-positive colorectal cancer, a HER2-positive lung cancer (e.g., a HER2-positive non-small cell lung carcinoma), a HER2-positive pancreatic cancer, a HER2-positive colorectal cancer, a HER2-positive bladder cancer, a HER2-positive salivary duct cancer, a HER2-positive ovarian cancer (e.g., a HER2-positive epithelial ovarian cancer), or a HER2-positive endometrial cancer. In some instances, the HER2-positive cancer is prostate cancer. In some embodiments, the HER2-positive cancer has metastasized to the central nervous system (CNS). In some instances, the metastasized HER2-cancer has formed CNS neoplasms.

[0345] In some embodiments, the AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) is administered to a subject having at least one of the diseases or symptoms described herein. In some embodiments, an AAV particle of the present disclosure is administered to a subject having or diagnosed with having a disease or disorder described herein.

[0346] In some embodiments, provided herein is a method for treating a muscular disorder and/or neuromuscular disorder in a subject, comprising administering to the subject an effective amount of a pharmaceutical composition described herein or an AAV particle, e.g., a plurality of particles, comprising an AAV capsid variant described herein. In some embodiments, treatment of a muscular disorder and/or neuromuscular disorder comprises prevention of said muscular disorder and/or neuromuscular disorder.

[0347] In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for treatment, prophylaxis, palliation or amelioration of a cardiac disease or heart disease and/or method of improving (e.g., enhancing) cardiac function in a subject. In some embodiments, the cardiac disease is a cardiomyopathy (e.g., arrhythmogenic right ventricular cardiomyopathy, dilated cardiomyopathy, or hypertrophic cardiomyopathy), congestive heart failure, tachycardia (e.g., catecholaminergic polymorphic ventricular tachycardia), ischemic heart disease, and/or myocardial infarction. In some embodiments, the cardiac disease is a disease associated with expression, e.g., aberrant expression, of LAMP2B, MYBPC3, TNNI3, LMNA, BAG3, DWORF, PKP2, Cx43, TAZ, CASQ2, SERCA2a, I-1c, S100A1 and/or ARC, S100A1, ASCL1, miR133, Mydelta3, Sav, or a combination or variant thereof. In some embodiments, treatment of a cardiac disorder described herein comprises the use of an AAV particle described

herein (e.g., an AAV particle comprising an AAV capsid variant described herein) for a gene replacement therapy.

[0348] In some embodiments, the cardiac disease is a genetic disorder, e.g., an autosomal dominant genetic disorder, an autosomal recessive disorder, or an X-linked recessive genetic disorder. In some embodiments, the cardiomyopathy is a genetic disorder, e.g., a genetic disorder associated with an abnormality (e.g., mutation, insertion, rearrangement and/or deletion) in a gene chosen from TTN, LMNA, MYH7, MYH6, SCN5A, TNNT2, RBM20, TNNI3, MYL2, MYL3, PKP2, DSP, DSG2, DSC2, JUP, or a combination thereof. In some embodiments, the cardiac disorder is a dilated cardiomyopathy, e.g., a dilated cardiomyopathy associated with an abnormality (e.g., mutation, insertion, rearrangement and/or deletion) in a gene chosen from TTN, LMNA, MYH7, BAG3, MIPN, TNNT2, SCN5A, RBM20, TNPO, LAMA4, VCL, LDB3, TCAP, PSEN1/2, ACTN2, CRYAB, TPM1, ABCC9, ACTC1, PDLIM3, ILK, TNNC1, TNNI3, PLN, DES, SGCD, CSRP3, MYH6, EYA4, ANKRD1, DMD, GATAD1, TAZ/G4.5, or combination thereof. In some embodiments, the cardiac disorder is a hypertrophic cardiomyopathy, e.g., a hypertrophic cardiomyopathy associated with an abnormality (e.g., mutation, insertion, rearrangement and/or deletion) in a gene chosen from MYH7, TNNT2, TNNI3, TPM1, MYL2, MYL3, ACTC1, CSRP3, TTN, ACTN2, MYH6, TCAP, TNNC1, or a combination thereof. In some embodiments, the cardiac disorder is an arrhythmogenic ventricular cardiomyopathy, e.g., an arrhythmogenic ventricular cardiomyopathy associated with an abnormality (e.g., mutation, insertion, rearrangement and/or deletion) in a gene chosen from PKP2, DSG2, DSP, RYR2, DSC2, TGFB3, TMEM43, DES, TTN, LMNA, or a combination thereof.

[0349] In some embodiments, the AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) is administered to a subject having at least one of the diseases or symptoms described herein. In some embodiments, an AAV particle of the present disclosure is administered to a subject having or diagnosed with having a disease or disorder described herein.

[0350] Any neurological disease or disorder, neurodegenerative disorder, muscular disorder, neuromuscular disorder, and/or neuro-oncological disorder may be treated with the AAV particles of the disclosure, or pharmaceutical compositions thereof.

Pharmaceutical Composition and Formulations

[0351] According to the present disclosure, an AAV particle comprising an AAV capsid variant described herein may be prepared as a pharmaceutical composition. In some embodiments, the pharmaceutical composition comprises at least one active ingredients. In some embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable excipient.

[0352] In some embodiments, an AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) can be formulated using an excipient to: (1) increase stability; (2) increase cell transfection or transduction; (3) permit the

sustained or delayed expression of the payload; (4) alter the biodistribution (e.g., target the viral particle to specific tissues or cell types); (5) increase the translation of encoded protein; (6) alter the release profile of encoded protein; and/or (7) allow for regulatable expression of the payload.

Formulations of the present disclosure can include, without limitation, saline, liposomes, lipid nanoparticles, polymers, peptides, proteins, cells transfected with viral vectors (e.g., for transfer or transplantation into a subject) and combinations thereof.

[0353] In some embodiments, the relative amount of the active ingredient (e.g. an AAV particle comprising an AAV capsid variant described herein), a pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition in accordance with the present disclosure may vary, depending upon the identity, size, and/or condition of the subject being treated and further depending upon the route by which the composition is to be administered. For example, the composition may comprise between 0.1% and 99% (w/w) of the active ingredient. By way of example, the composition may comprise between 0.1% and 100%, e.g., between .5 and 50%, between 1-30%, between 5-80%, at least 80% (w/w) active ingredient.

[0354] In some embodiments, the pharmaceutical composition comprising an AAV particle described herein may comprise an AAV capsid variant and a viral genome encoding a payload, e.g., a payload described herein, with or without a pharmaceutically acceptable excipient.

[0355] The present disclosure also provides in some embodiments, a pharmaceutical composition suitable for administration to a subject, e.g., a human. In some embodiments, the pharmaceutical composition is administered to a subject, e.g., a human.

Administration

[0356] In some embodiments, an AAV particle disclosed herein (e.g., an AAV particle comprising an AAV capsid variant) may be administered to a subject by a delivery route, e.g., a localized delivery route or a systemic delivery route.

[0357] In some embodiments, an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant) may be administered via such a route that it is able to cross the blood-brain barrier, vascular barrier, or other epithelial barrier. In some embodiments, an AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid variant) may be administered in any suitable form, either as a liquid solution or suspension, as a solid form suitable for liquid solution or suspension in a liquid solution. In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid variant) may be formulated with any appropriate and pharmaceutically acceptable excipient.

[0358] In some embodiments, the AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant) is administered intramuscularly, intravenously, intracerebrally, intrathecally, intratumorally, intracerebroventricularly, via intraparenchymal administration, or via intra-cisterna magna injection (ICM). In some embodiments, the AAV particle described herein (e.g.,

an AAV particle comprising an AAV capsid variant) is administered intravenously. In some embodiments, the AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant) is administered via intra-cisterna magna injection (ICM). In some embodiments, the AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant) is administered intratumorally. In some embodiments, the AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant) is administered intraarterially.

[0359] In some embodiments, an AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid variant) may be delivered to a subject via a single route administration. In some embodiments, an AAV particle of the present disclosure may be delivered to a subject via a multi-site route of administration. In some embodiments, a subject may be administered at 2, 3, 4, 5, or more than 5 sites.

[0360] In some embodiments, an AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid variant) is administered via a bolus infusion. In some embodiments, an AAV particle of the present disclosure is administered via sustained delivery over a period of minutes, hours, or days. In some embodiments, the infusion rate may be changed depending on the subject, distribution, formulation, and/or another delivery parameter. In some embodiments, an AAV particle of the present disclosure is administered using a controlled release. In some embodiments, an AAV particle of the present disclosure is administered using a sustained release, e.g., a release profile that conforms to a release rate over a specific period of time.

[0361] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid variant) may be delivered by more than one route of administration. As non-limiting examples of combination administrations, an AAV particle may be delivered by intrathecal and intracerebroventricular, or by intravenous and intraparenchymal administration.

Intravenous administration

[0362] In some embodiments, an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant) may be administered to a subject by systemic administration. In some embodiments, the systemic administration is intravenous administration. In another embodiment, the systemic administration is intraarterial administration. In some embodiments, an AAV particle of the present disclosure may be administered to a subject by intravenous administration. In some embodiments, the intravenous administration may be achieved by subcutaneous delivery. In some embodiments, the AAV particle is administered to the subject via focused ultrasound (FUS), e.g., coupled with the intravenous administration of microbubbles (FUS-MB) or MRI-guided FUS coupled with intravenous administration, e.g., as described in Terstappen et al. (Nat Rev Drug Discovery, doi.org/10.1038/s41573-021-00139-y (2021)), the contents of which are incorporated herein by reference in its entirety. In some embodiments, the AAV particle is administered to the subject intravenously. In some embodiments, the subject is a human.

Administration to the CNS

[0363] In some embodiments, an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant) may be delivered by direct injection into the brain. As a non-limiting example, the brain delivery may be by intrahippocampal administration. In some embodiments, an AAV particle of the present disclosure may be administered to a subject by intraparenchymal administration. In some embodiments, the intraparenchymal administration is to tissue of the central nervous system. In some embodiments, an AAV particle of the present disclosure may be administered to a subject by intracranial delivery (See, e.g., US Pat. No. 8119611; the content of which is incorporated herein by reference in its entirety). In some embodiments, an AAV particle described herein may be delivered by injection into the CSF pathway. Non-limiting examples of delivery to the CSF pathway include intrathecal and intracerebroventricular administration. In some embodiments, an AAV particle described herein may be administered via intracisternal magna (ICM) injection.

[0364] In some embodiments, an AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid variant) may be delivered to the brain by systemic delivery. As a non-limiting example, the systemic delivery may be by intravascular administration. As a non-limiting example, the systemic or intravascular administration may be intravenous.

[0365] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid variant) of the present disclosure may be delivered by an intraocular delivery route. A non-limiting example of an intraocular administration includes an intravitreal injection.

Intramuscular administration

[0366] In some embodiments, an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant) may be delivered by intramuscular administration. Without wishing to be bound by theory, it is believed in some embodiments, that the multi-nucleated nature of muscle cells provides an advantage to gene transduction subsequent to AAV delivery. In some embodiments, cells of the muscle are capable of expressing recombinant proteins with the appropriate post-translational modifications. Without wishing to be bound by theory, it is believed in some embodiments, the enrichment of muscle tissue with vascular structures allows for transfer to the blood stream and whole-body delivery. Examples of intramuscular administration include systemic (e.g., intravenous), subcutaneous or directly into the muscle. In some embodiments, more than one injection is administered. In some embodiments, an AAV particle of the present disclosure may be delivered by an intramuscular delivery route. (See, e.g., U. S. Pat. No. 6506379; the content of which is incorporated herein by reference in its entirety). Non-limiting examples of intramuscular administration include an intravenous injection or a subcutaneous injection.

[0367] In some embodiments, an AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid variant) is administered to a subject and transduces the muscle of a subject. As a non-limiting example, an AAV particle is administered by intramuscular administration. In some embodiments, an AAV particle of the present disclosure may be administered to a subject by subcutaneous administration. In some embodiments, the intramuscular administration is via systemic delivery. In some embodiments, the intramuscular administration is via intravenous delivery. In some embodiments, the intramuscular administration is via direct injection to the muscle.

[0368] In some embodiments, the muscle is transduced by administration, e.g., intramuscular administration. In some embodiments, an intramuscular delivery comprises administration at one site. In some embodiments, an intramuscular delivery comprises administration at more than one site. In some embodiments, an intramuscular delivery comprises administration at two, three, four, or more sites. In some embodiments, intramuscular delivery is combined with at least one other method of administration.

[0369] In some embodiments, an AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid variant) may be administered to a subject by peripheral injections. Non-limiting examples of peripheral injections include intraperitoneal, intramuscular, intravenous, conjunctival, or joint injection. It was disclosed in the art that the peripheral administration of AAV vectors can be transported to the central nervous system, for example, to the motor neurons (e.g., U. S. Patent Publication Nos. US20100240739 and US20100130594; the content of each of which is incorporated herein by reference in their entirety).

[0370] In some embodiments, an AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid variant) may be administered to a subject by intraparenchymal administration. In some embodiments, the intraparenchymal administration is to muscle tissue. In some embodiments, an AAV particle of the present disclosure is delivered as described in Bright et al 2015 (Neurobiol Aging. 36(2):693-709), the contents of which are herein incorporated by reference in their entirety. In some embodiments, an AAV particle of the present disclosure is administered to the gastrocnemius muscle of a subject. In some embodiments, an AAV particle of the present disclosure is administered to the bicep femorii of the subject. In some embodiments, an AAV particles of the present disclosure is administered to the tibialis anterior muscles. In some embodiments, an AAV particle of the present disclosure is administered to the soleus muscle.

Depot administration

[0371] In some embodiments, a pharmaceutical composition and/or an AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid variant) are formulated in depots for extended release. Generally, specific organs or tissues are targeted for administration.

[0372] In some embodiments, a pharmaceutical composition and/or an AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid variant) are spatially retained

within or proximal to target tissues. Provided are methods of providing a pharmaceutical composition, an AAV particle, to target tissues of mammalian subjects by contacting target tissues (which comprise one or more target cells) with the pharmaceutical composition and/or the AAV particle, under conditions such that they are substantially retained in target tissues, e.g., such that at least 10, 20, 30, 40, 50, 60, 70, 80, 85, 90, 95, 96, 97, 98, 99, 99.9, 99.99 or greater than 99.99% of the composition is retained in the target tissues. In some embodiments, retention is determined by measuring the amount of pharmaceutical composition and/or AAV particle, that enter a target cell or a plurality of target cells. For example, at least 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.9%, 99.99%, or greater than 99.99% of a pharmaceutical composition and/or an AAV particle, administered to a subject are present intracellularly at a period of time following administration. For example, intramuscular injection to a subject may be performed using aqueous compositions comprising a pharmaceutical composition and/or an AAV particle of the present disclosure and a transfection reagent, and retention is determined by measuring the amount of the pharmaceutical composition and/or the AAV particle, present in the muscle cell or plurality of muscle cells.

[0373] In some embodiments, disclosed herein are methods of providing a pharmaceutical composition and/or an AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid variant) to a tissue of a subject, by contacting the tissue (comprising a cell, e.g., a plurality of cells) with the pharmaceutical composition and/or the AAV particle under conditions such that they are substantially retained in the tissue. In some embodiments, a pharmaceutical composition and/or AAV particle described herein comprise a sufficient amount of an active ingredient such that the effect of interest is produced in at least one cell. In some embodiments, a pharmaceutical composition and/or an AAV particle generally comprise one or more cell penetration agents. In some embodiments, the disclosure provides a naked formulations (such as without cell penetration agents or other agents), with or without pharmaceutically acceptable carriers.

Methods of Treatment

[0374] Provided in the present disclosure are methods for introducing (e.g., delivering) an AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid variant) into cells. In some embodiments, the method comprises introducing into said cells an AAV particle or vector described herein in an amount sufficient to modulate, e.g., increase, the production of a target gene, mRNA, and/or protein. In some embodiments, the method comprises introducing into said cells an AAV particle or vector described herein in an amount sufficient to modulate, e.g., decrease, expression of a target gene, mRNA, and/or protein. In some aspects, the cells may be neurons such as but not limited to, motor, hippocampal, entorhinal, thalamic, cortical, sensory, sympathetic, or parasympathetic neurons, and glial cells such as astrocytes, microglia, and/or oligodendrocytes. In other aspects, the cells may be a muscle cell, e.g., a cell of a diaphragm, a quadriceps, or a heart (e.g.,

a heart atrium or a heart ventricle). In other embodiments, the cells may be a muscle cell (e.g., a cell of a diaphragm, a quadriceps, or a heart (e.g., a heart atrium or a heart ventricle)) or a liver cell. In some embodiments, the cell may be a heart cell (e.g., a cell of a heart atrium or a cell of a heart ventricle).

[0375] Disclosed in the present disclosure are methods for treating a neurological disease/disorder or a neurodegenerative disorder, a muscular or neuromuscular disorder, or a neurooncological disorder associated with aberrant, e.g., insufficient or increased, function/presence of a protein, e.g., a target protein in a subject in need of treatment.

[0376] In some embodiments, the method comprises administering to the subject a therapeutically effective amount of a composition comprising AAV particles of the present disclosure. As a non-limiting example, the AAV particles can increase target gene expression, increase target protein production, and thus reduce one or more symptoms of neurological disease in the subject such that the subject is therapeutically treated.

[0377] In other embodiments, the method comprises administering to the subject a therapeutically effective amount of a composition comprising AAV particles (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules. As a non-limiting example, the siRNA molecules can silence target gene expression, inhibit target protein production, and reduce one or more symptoms of neurological disease in the subject such that the subject is therapeutically treated.

[0378] In some embodiments, the composition comprising the AAV particles of the present disclosure (e.g., an AAV particle comprising an AAV capsid variant described herein) is administered to the central nervous system of the subject via systemic administration. In some embodiments, the systemic administration is intravenous (IV) injection. In some embodiments, the AAV particle described herein or a pharmaceutical composition comprising an AAV particle described herein is administered by focused ultrasound (FUS), e.g., coupled with the intravenous administration of microbubbles (FUS-MB) or MRI-guided FUS coupled with intravenous administration.

[0379] In some embodiments, the composition comprising the AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid variant) is administered to the central nervous system of the subject via intraventricular administration. In some embodiments, the composition comprising the AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid variant) is administered via intra-cisterna magna injection (ICM).

[0380] In some embodiments, the composition comprising an AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid variant) is administered to the central nervous system of the subject via intraventricular injection and intravenous injection.

[0381] In some embodiments, the composition comprising the AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid variant) is administered to the central

nervous system of the subject via ICM injection and intravenous injection at a specific dose per subject. As a non-limiting example, the AAV particles are administered via ICM injection at a dose of 1×10^4 VG per subject. As a non-limiting example, the AAV particles are administered via IV injection at a dose of 2×10^{13} VG per subject.

[0382] In some embodiments, the composition comprising the AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid variant) is administered to the central nervous system of the subject. In other embodiments, the composition comprising the AAV particles of the present disclosure is administered to a CNS tissue of a subject (e.g., putamen, hippocampus, thalamus, or cortex of the subject).

[0383] In some embodiments, the composition comprising the AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid variant) is administered to the central nervous system of the subject via intraparenchymal injection. Non-limiting examples of intraparenchymal injections include intraputamenal, intracortical, intrathalamic, intrastriatal, intrahippocampal or into the entorhinal cortex.

[0384] In some embodiments, the composition comprising the AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid variant) is administered to the central nervous system of the subject via intraparenchymal injection and intravenous injection.

[0385] In some embodiments, the composition comprising the AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid variant) is administered to the central nervous system of the subject via intraventricular injection, intraparenchymal injection and intravenous injection.

[0386] In some embodiments, the composition comprising an AAV particle (e.g., an AAV particle comprising an AAV capsid variant) of a plurality of particles of the present disclosure is administered to a muscle of the subject via intravenous injection. In some embodiments, the composition comprising an AAV particle of a plurality of particles of the present disclosure is administered to a muscle of the subject via intramuscular injection.

[0387] In some embodiments, an AAV particle of the present disclosure (e.g., an AAV particle comprising an AAV capsid variant) may be delivered into specific types of cells, including, but not limited to, thalamic, hippocampal, entorhinal, cortical, motor, sensory, excitatory, inhibitory, sympathetic, or parasympathetic neurons; glial cells including oligodendrocytes, astrocytes and microglia; and/or other cells surrounding neurons such as T cells. In some embodiments, an AAV particle of the present disclosure may be delivered into a muscle cell, e.g., a cell of the quadriceps, diaphragm, liver, and/or heart (e.g., heart atrium or heart ventricle).

[0388] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant), e.g., a plurality of particles, of the present disclosure may be delivered to a cell or region of the midbrain. In some embodiments, an AAV particle (e.g., an

AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant), e.g., a plurality of particles, of the present disclosure may be delivered to a cell or region of the brains stem.

[0389] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant), e.g., a plurality of particles, of the present disclosure may be delivered to neurons in the putamen, hippocampus, thalamus and/or cortex.

[0390] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid variant), e.g., a plurality of particles, of the present disclosure may be used as a therapy for a genetic disorder, e.g., an autosomal dominant genetic disorder, an autosomal recessive disorder, X-linked dominant genetic disorder, an X-linked recessive genetic disorder, or a Y-linked genetic disorder. In some embodiments, the genetic disorder is a monogenetic disorder or a polygenic disorder. In some embodiments, treatment of a genetic disorder, e.g., a monogenic disorder, comprises the use of an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant described herein) for a gene replacement therapy.

[0391] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid variant), e.g., a plurality of particles, of the present disclosure may be used as a therapy for a neurological disease.

[0392] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid variant), e.g., a plurality of particles, of the present disclosure may be used as a therapy for tauopathies.

[0393] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid variant), e.g., a plurality of particles, of the present disclosure may be used as a therapy for Alzheimer's Disease.

[0394] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid variant), e.g., a plurality of particles, of the present disclosure may be used as a therapy for Amyotrophic Lateral Sclerosis.

[0395] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid variant), e.g., a plurality of particles, of the present disclosure may be used as a therapy for Huntington's Disease.

[0396] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid variant), e.g., a plurality of particles, of the present disclosure may be used as a therapy for Parkinson's Disease.

[0397] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid variant), e.g., a plurality of particles, of the present disclosure may be used as a therapy for Gaucher disease (GD) (e.g., Type 1 GD, Type 2 GD, or Type 3 GD). In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid variant), e.g., a plurality of particles, of the present disclosure may be used as a therapy for Parkinson's disease associated with a GBA mutation. In some

embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid variant), e.g., a plurality of particles, of the present disclosure may be used as a therapy for dementia with Lewy Bodies (DLB).

[0398] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid variant), e.g., a plurality of particles, of the present disclosure may be used as a therapy for spinal muscular atrophy.

[0399] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid variant), e.g., a plurality of particles, of the present disclosure may be used as a therapy for a leukodystrophy, e.g., Alexander disease, autosomal dominant leukodystrophy with autonomic diseases (ADLD), Canavan disease, cerebrotendinous xanthomatosis (CTX), metachromatic leukodystrophy (MLD), Pelizaeus-Merzbacher disease, or Refsum disease.

[0400] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid variant), e.g., a plurality of particles, of the present disclosure may be used as a therapy for Friedreich's Ataxia.

[0401] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid variant), e.g., a plurality of particles, of the present disclosure may be used as a therapy for chronic or neuropathic pain.

[0402] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid variant), e.g., a plurality of particles, of the present disclosure may be used as a therapy for a muscular disorder or a neuromuscular disorder.

[0403] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid variant), e.g., a plurality of particles, of the present disclosure may be used as a therapy for a cardiac disease or heart disease and/or method of improving (e.g., enhancing) cardiac function in a subject. In some embodiments, the cardiac disease is a cardiomyopathy (e.g., arrhythmogenic right ventricular cardiomyopathy, dilated cardiomyopathy, or hypertrophic cardiomyopathy), congestive heart failure, tachycardia (e.g., catecholaminergic polymorphic ventricular tachycardia), ischemic heart disease, and/or myocardial infarction.

[0404] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid variant), e.g., a plurality of particles, of the present disclosure may be used as a therapy for a disease associated with expression of HER2, e.g., a disease associated with overexpression of HER2. In some embodiments, the AAV particle of the disclosure (e.g., an AAV particle comprising an AAV capsid variant) is useful for the treatment, prophylaxis, palliation or amelioration of a HER2-positive cancer. In some embodiments, the HER2-positive cancer is a HER2-positive solid tumor. Additionally, or alternatively, the HER2-positive cancer may be a locally advanced or metastatic HER2-positive cancer. In some instances, the HER2-positive cancer is a HER2-positive breast cancer or a HER2-positive gastric cancer. In some embodiments, the HER2-positive cancer is selected from the group

consisting of a HER2- positive gastroesophageal junction cancer, a HER2-positive colorectal cancer, a HER2-positive lung cancer (e.g., a HER2-positive non-small cell lung carcinoma), a HER2-positive pancreatic cancer, a HER2-positive colorectal cancer, a HER2-positive bladder cancer, a HER2-positive salivary duct cancer, a HER2-positive ovarian cancer (e.g., a HER2-positive epithelial ovarian cancer), or a HER2-positive endometrial cancer. In some instances, the HER2-positive cancer is prostate cancer. In some embodiments, the HER2-positive cancer has metastasized to the central nervous system (CNS). In some instances, the metastasized HER2-cancer has formed CNS neoplasms.

[0405] In some embodiments, an AAV particle (e.g., an AAV particle comprising an AAV capsid variant) e.g., a plurality of particles, of the present disclosure may be used as a therapy for a neuro-oncological disorder. In some embodiments, the neuro-oncological disorder is a cancer of primary CNS origin (e.g., a cancer of a CNS cell and/or CNS tissue). In some embodiments, the neuro-oncological disorder is metastatic cancer in a CNS cell, CNS region, and/or a CNS tissue. Examples of primary CNS cancers could be gliomas (which may include glioblastoma (also known as glioblastoma multiforme), astrocytomas, oligodendrogliomas, and ependymomas, and mixed gliomas), meningiomas, medulloblastomas, neuromas, and primary CNS lymphoma (in the brain, spinal cord, or meninges), among others. Examples of metastatic cancers include those originating in another tissue or organ, e.g., breast, lung, lymphoma, leukemia, melanoma (skin cancer), colon, kidney, prostate, or other types that metastasize to brain.

[0406] In some embodiments, administration of the AAV particle described herein (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) to a subject may increase target gene, mRNA, and/or protein levels in a subject, relative to a control, e.g., the gene, mRNA, and/or mRNA levels in the subject prior to receiving AAV particle. The target gene, mRNA, and/or protein levels may be increased by 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% in a subject such as, but not limited to, the CNS, a region of the CNS, or a specific cell of the CNS, or a muscle, a region of a muscle, or a cell of a muscle, of a subject. In some embodiments, cell of the CNS comprises an astrocyte, microglia, cortical neuron, hippocampal neuron, DRG and/or sympathetic neuron, sensory neuron, oligodendrocyte, motor neuron, or combination thereof. As a non-limiting example, the AAV particles may increase the gene, mRNA, and/or protein levels of a target protein by fold increases over baseline. In some embodiments, AAV particles lead to 5-6 times higher levels of a target gene, mRNA, or protein.

[0407] In some embodiments, administration of the AAV particle described herein (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant), e.g., an AAV particle comprising a nucleic acid encoding a siRNA molecule, to a subject may decrease target gene, mRNA, and/or protein levels in a subject, relative to a control, e.g., the gene, mRNA, and/or mRNA levels in the subject prior to receiving AAV particle. The target gene, mRNA, and/or protein levels may be decreased by 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% in a subject such as, but not limited to, the CNS, a region of the CNS, or a specific cell of the CNS, or a muscle, a region of a muscle, or a cell of a muscle, of a subject. In some embodiments, cell of the CNS comprises an astrocyte, microglia, cortical neuron, hippocampal neuron, DRG and/or sympathetic neuron, sensory neuron, oligodendrocyte, motor neuron, or combination thereof. As a non-limiting example, the AAV particles may decrease the gene, mRNA, and/or protein levels of a target protein by fold decreases over baseline.

[0408] In some embodiments, the AAV particles of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) may be used to increase target protein and reduce symptoms of neurological disease in a subject. In some embodiments, the AAV particles of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) may be used to decrease target protein and reduce symptoms of neurological disease in a subject.

[0409] In some embodiments, the AAV particles of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) may be used to reduce the decline of functional capacity and activities of daily living as measured by a standard evaluation system such as, but not limited to, the total functional capacity (TFC) scale.

[0410] In some embodiments, the AAV particles of the present disclosure (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) may be used to improve performance on any assessment used to measure symptoms of neurological disease. Such assessments include, but are not limited to ADAS-cog (Alzheimer Disease Assessment Scale – cognitive), MMSE (Mini-Mental State Examination), GDS (Geriatric Depression Scale), FAQ (Functional Activities Questionnaire), ADL (Activities of Daily Living), GPCOG (General Practitioner Assessment of Cognition), Mini-Cog, AMTS (Abbreviated Mental Test Score), Clock-drawing test, 6-CIT (6-item Cognitive Impairment Test), TYM (Test Your Memory), MoCa (Montreal Cognitive Assessment), ACE-R (Addenbrookes Cognitive Assessment), MIS (Memory Impairment Screen), BADLS (Bristol Activities of Daily Living Scale), Barthel Index, Functional

Independence Measure, Instrumental Activities of Daily Living, IQCODE (Informant Questionnaire on Cognitive Decline in the Elderly), Neuropsychiatric Inventory, The Cohen-Mansfield Agitation Inventory, BEHAVE-AD, EuroQoL, Short Form-36 and/or MBR Caregiver Strain Instrument, or any of the other tests as described in Sheehan B (Ther Adv Neurol Disord. 5(6):349-358 (2012)), the contents of which are herein incorporated by reference in their entirety.

[0411] In some embodiments, the present composition is administered as a solo therapeutic or as combination therapeutic for the treatment of a neurological disease/disorder or a neurodegenerative disorder, a muscular disorder or neuromuscular disorder, and/or a neuro-oncological disorder.

[0412] The AAV particles (e.g., an AAV particle comprising an AAV capsid variant) encoding the target protein may be used in combination with one or more other therapeutic agents. In some embodiments, compositions can be administered concurrently with, prior to, or subsequent to, additional therapeutic or medical procedures. In general, each agent will be administered at a dose and/or on a time schedule determined for that agent.

[0413] Therapeutic agents that may be used in combination with the AAV particles of the present disclosure (e.g., an AAV particle comprising an AAV capsid variant) can be small molecule compounds which are antioxidants, anti-inflammatory agents, anti-apoptosis agents, calcium regulators, anti-glutamatergic agents, structural protein inhibitors, compounds involved in muscle function, and compounds involved in metal ion regulation. As a non-limiting example, the combination therapy may be in combination with one or more neuroprotective agents such as small molecule compounds, growth factors and hormones which have been tested for their neuroprotective effect on motor neuron degeneration.

[0414] Compounds tested for treating neurological disease which may be used in combination with the AAV particles described herein include, but are not limited to, cholinesterase inhibitors (donepezil, rivastigmine, galantamine), NMDA receptor antagonists such as memantine, anti-psychotics, anti-depressants, anti-convulsants (e.g., sodium valproate and levetiracetam for myoclonus), secretase inhibitors, amyloid aggregation inhibitors, copper or zinc modulators, BACE inhibitors, inhibitors of tau aggregation, such as Methylene blue, phenothiazines, anthraquinones, n-phenylamines or rhodamines, microtubule stabilizers such as NAP, taxol or paclitaxel, kinase or phosphatase inhibitors such as those targeting GSK3 β (lithium) or PP2A, immunization with A β peptides or tau phospho-epitopes, anti-tau or anti-amyloid antibodies, dopamine-depleting agents (e.g., tetrabenazine for chorea), benzodiazepines (e.g., clonazepam for myoclonus, chorea, dystonia, rigidity, and/or spasticity), amino acid precursors of dopamine (e.g., levodopa for rigidity), skeletal muscle relaxants (e.g., baclofen, tizanidine for rigidity and/or spasticity), inhibitors for acetylcholine release at the neuromuscular junction to cause muscle paralysis (e.g., botulinum toxin for bruxism and/or dystonia), atypical neuroleptics (e.g., olanzapine and quetiapine for psychosis and/or irritability, risperidone, sulpiride and haloperidol for psychosis, chorea and/or irritability, clozapine

for treatment-resistant psychosis, aripiprazole for psychosis with prominent negative symptoms), selective serotonin reuptake inhibitors (SSRIs) (e.g., citalopram, fluoxetine, paroxetine, sertraline, mirtazapine, venlafaxine for depression, anxiety, obsessive compulsive behavior and/or irritability), hypnotics (e.g., xopiclone and/or zolpidem for altered sleep-wake cycle), anticonvulsants (e.g., sodium valproate and carbamazepine for mania or hypomania) and mood stabilizers (e.g., lithium for mania or hypomania).

[0415] Neurotrophic factors may be used in combination therapy with the AAV particles of the present disclosure (e.g., an AAV particle comprising an AAV capsid variant) for treating neurological disease. Generally, a neurotrophic factor is defined as a substance that promotes survival, growth, differentiation, proliferation and/or maturation of a neuron, or stimulates increased activity of a neuron. In some embodiments, the present methods further comprise delivery of one or more trophic factors into the subject in need of treatment. Trophic factors may include, but are not limited to, IGF-I, GDNF, BDNF, CTNF, VEGF, Colivelin, Xaliproden, Thyrotrophin-releasing hormone and ADNF, and variants thereof.

[0416] In one aspect, the AAV particle described herein (e.g., an AAV particle comprising an AAV capsid variant) may be co-administered with AAV particles expressing neurotrophic factors such as AAV-IGF-I (See e.g., Vincent et al., *Neuromolecular medicine*, 2004, 6, 79-85; the contents of which are incorporated herein by reference in their entirety) and AAV-GDNF (See e.g., Wang et al., *J Neurosci.*, 2002, 22, 6920-6928; the contents of which are incorporated herein by reference in their entirety).

[0417] In some embodiments, administration of the AAV particles (e.g., an AAV particle comprising an AAV capsid variant) to a subject will modulate, e.g., increase or decrease, the expression of a target protein in a subject and the modulation, e.g., increase or decrease of the presence, level, activity, and/or expression of the target protein will reduce the effects and/or symptoms of a neurological disease/disorder or a neurodegenerative disorder, a muscular disorder or neuromuscular disorder, and/or a neuro-oncological disorder in a subject.

DEFINITIONS

[0418] 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 the invention pertains.

[0419] Articles such as “a,” “an,” and “the” may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include “or” between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The disclosure includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given

product or process. The disclosure includes embodiments in which more than one, or the entire group members are present in, employed in, or otherwise relevant to a given product or process.

[0420] It is also noted that the term “comprising” is intended to be open and permits but does not require the inclusion of additional elements or steps. When the term “comprising” is used herein, the term “consisting of” and “consisting essentially thereof” is thus also encompassed and disclosed.

[0421] Where ranges are given, endpoints are included. Furthermore, it is to be understood that unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or subrange within the stated ranges in different embodiments of the disclosure, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[0422] *Adeno-associated virus*: As used herein, the term “adeno-associated virus” or “AAV” refers to members of the dependovirus genus or a variant, e.g., a functional variant, thereof. In some embodiments, the AAV is wildtype, or naturally occurring. In some embodiments, the AAV is recombinant.

[0423] *AAV Particle*: As used herein, an “AAV particle” refers to a particle or a virion comprising an AAV capsid, e.g., an AAV capsid variant, and a polynucleotide, e.g., a viral genome or a vector genome. In some embodiments, the viral genome of the AAV particle comprises at least one payload region and at least one ITR. In some embodiments, an AAV particle of the disclosure is an AAV particle comprising an AAV variant. In some embodiments, the AAV particle is capable of delivering a nucleic acid, e.g., a payload region, encoding a payload to cells, typically, mammalian, e.g., human, cells. In some embodiments, an AAV particle of the present disclosure may be produced recombinantly. In some embodiments, an AAV particle may be derived from any serotype, described herein or known in the art, including combinations of serotypes (e.g., “pseudotyped” AAV) or from various genomes (e.g., single stranded or self-complementary). In some embodiments, the AAV particle may be replication defective and/or targeted. It is to be understood that reference to the AAV particle of the disclosure also includes pharmaceutical compositions thereof, even if not explicitly recited.

[0424] *Administering*: As used herein, the term “administering” refers to providing a pharmaceutical agent or composition to a subject.

[0425] *Amelioration*: As used herein, the term “amelioration” or “ameliorating” refers to a lessening of severity of at least one indicator of a condition or disease. For example, in the context of neurodegeneration disorder, amelioration includes the reduction of neuron loss.

[0426] *Amplicon*: As used herein, “amplicon” may refer to any piece of RNA or DNA formed as the product of amplification events, e.g. PCR. In some embodiments, full-length capsid amplicons may be used as templates for next generation sequencing (NGS) library generation. Full-length capsid

amplicons may be used for cloning into a DNA library for any number of additional rounds of AAV selection as described herein.

[0427] *Animal*: As used herein, the term “animal” refers to any member of the animal kingdom. In some embodiments, “animal” refers to humans at any stage of development. In some embodiments, “animal” refers to non-human animals at any stage of development. In certain embodiments, the non-human animal is a mammal (e.g., a rodent, a mouse, a rat, a rabbit, a monkey, a dog, a cat, a sheep, cattle, a primate, or a pig). In some embodiments, animals include, but are not limited to, mammals, birds, reptiles, amphibians, fish, and worms. In some embodiments, the animal is a transgenic animal, genetically engineered animal, or a clone.

[0428] *Antisense strand*: As used herein, the term “the antisense strand” or “the first strand” or “the guide strand” of a siRNA molecule refers to a strand that is substantially complementary to a section of about 10-50 nucleotides, e.g., about 15-30, 16-25, 18-23 or 19-22 nucleotides of the mRNA of a gene targeted for silencing. The antisense strand or first strand has sequence sufficiently complementary to the desired target mRNA sequence to direct target-specific silencing, e.g., complementarity sufficient to trigger the destruction of the desired target mRNA by the RNAi machinery or process.

[0429] *Approximately*: As used herein, the term “approximately” or “about,” as applied to one or more values of interest, refers to a value that is similar to a stated reference value. In certain embodiments, the term “approximately” or “about” refers to a range of values that fall within 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less in either direction (greater than or less than) of the stated reference value unless otherwise stated or otherwise evident from the context (except where such number would exceed 100% of a possible value).

[0430] *Biopanning*: As used herein, the term “biopanning” refers to an AAV capsid library selection process comprising administration of an AAV particle with enhanced tissue- and/or cell type-specific transduction to a cell and/or subject; extraction of nucleotides encoded by said AAV particle from said transduced tissue- and/or cell type-specific; and, use of the extracted nucleotides for cloning into a nucleotide library for the generation of AAV particles for subsequent rounds of the same.

[0431] *Capsid*: As used herein, the term “capsid” refers to the exterior, e.g., a protein shell, of a virus particle, e.g., an AAV particle, that is substantially (e.g., >50%, >60%, >70%, >80%, >90%, >95%, >99%, or 100%) protein. In some embodiments, the capsid is an AAV capsid comprising an AAV capsid protein described herein, e.g., a VP1, VP2, and/or VP3 polypeptide. The AAV capsid protein can be a wild-type AAV capsid protein or a variant, e.g., a structural and/or functional variant from a wild-type or a reference capsid protein, referred to herein as an “AAV capsid variant.” In some embodiments, the AAV capsid variant described herein has the ability to enclose, e.g.,

encapsulate, a viral genome and/or is capable of entry into a cell, e.g., a mammalian cell. In some embodiments, the AAV capsid variant described herein may have modified tropism compared to that of a wild-type AAV capsid, e.g., the corresponding wild-type capsid.

[0432] *Complementary and substantially complementary:* As used herein, the term “complementary” refers to the ability of polynucleotides to form base pairs with one another. Base pairs are typically formed by hydrogen bonds between nucleotide units in antiparallel polynucleotide strands. Complementary polynucleotide strands can form base pairs in the Watson-Crick manner (e.g., A to T, A to U, C to G), or in any other manner that allows for the formation of duplexes. As persons skilled in the art are aware, when using RNA as opposed to DNA, uracil rather than thymine is the base that is considered to be complementary to adenine. However, when a U is denoted in the context of the present disclosure, the ability to substitute a T is implied, unless otherwise stated. Perfect complementarity or 100% complementarity refers to the situation in which each nucleotide unit of one polynucleotide strand can form a hydrogen bond with a nucleotide unit of a second polynucleotide strand. Less than perfect complementarity refers to the situation in which some, but not all, nucleotide units of two strands can form hydrogen bond with each other. For example, for two 20-mers, if only two base pairs on each strand can form a hydrogen bond with each other, the polynucleotide strands exhibit 10% complementarity. In the same example, if 18 base pairs on each strand can form hydrogen bonds with each other, the polynucleotide strands exhibit 90% complementarity. The term “complementary” as used herein can encompass fully complementary, partially complementary, or substantially complementary. As used herein, the term “substantially complementary” means that the siRNA has a sequence (e.g., in the antisense strand) which is sufficient to bind the desired target mRNA, and to trigger the RNA silencing of the target mRNA. “Fully complementary”, “perfect complementarity”, or “100% complementarity” refers to the situation in which each nucleotide unit of one polynucleotide or oligonucleotide strand can base-pair with a nucleotide unit of a second polynucleotide or oligonucleotide strand.

[0433] *Control Elements:* As used herein, “control elements”, “regulatory control elements” or “regulatory sequences” refers to promoter regions, polyadenylation signals, transcription termination sequences, upstream regulatory domains, origins of replication, internal ribosome entry sites (“IRES”), enhancers, and the like, which provide for the replication, transcription and translation of a coding sequence in a recipient cell. Not all of these control elements need always be present as long as the selected coding sequence is capable of being replicated, transcribed and/or translated in an appropriate host cell.

[0434] *Delivery:* As used herein, “delivery” refers to the act or manner of delivering an AAV particle, a compound, substance, entity, moiety, cargo or payload.

[0435] *Element*: As used herein, the term “element” refers to a distinct portion of an entity. In some embodiments, an element may be a polynucleotide sequence with a specific purpose, incorporated into a longer polynucleotide sequence.

[0436] *Encapsulate*: As used herein, the term “encapsulate” means to enclose, surround or encase. As an example, a capsid protein, e.g., an AAV capsid variant, often encapsulates a viral genome. In some embodiments, encapsulate within a capsid, e.g., an AAV capsid variant, encompasses 100% coverage by a capsid, as well as less than 100% coverage, e.g., 95%, 90%, 85%, 80%, 70%, 60% or less. For example, gaps or discontinuities may be present in the capsid so long as the viral genome is retained in the capsid, e.g., prior to entry into a cell.

[0437] *Effective Amount*: As used herein, the term “effective amount” of an agent is that amount sufficient to effect beneficial or desired results, for example, clinical results, and, as such, an “effective amount” depends upon the context in which it is being applied. For example, in the context of administering an agent that treats cancer, an effective amount of an agent is, for example, an amount sufficient to achieve treatment, as defined herein, of cancer, as compared to the response obtained without administration of the agent.

[0438] *Expression*: As used herein, “expression” of a nucleic acid sequence refers to one or more of the following events: (1) production of an RNA template from a DNA sequence (e.g., by transcription); (2) processing of an RNA transcript (e.g., by splicing, editing, 5' cap formation, and/or 3' end processing); (3) translation of an RNA into a polypeptide or protein; and (4) post-translational modification of a polypeptide or protein.

[0439] *Formulation*: As used herein, a “formulation” includes at least one AAV particle (active ingredient) and an excipient, and/or an inactive ingredient.

[0440] *Fragment*: A “fragment,” as used herein, refers to a portion. For example, an antibody fragment may comprise a CDR, or a heavy chain variable region, or a scFv, etc.

[0441] *Homology*: As used herein, the term “homology” refers to the overall relatedness between polymeric molecules, e.g. between polynucleotide molecules (e.g. DNA molecules and/or RNA molecules) and/or between polypeptide molecules. In some embodiments, polymeric molecules are considered to be “homologous” to one another if their sequences are at least 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% identical or similar. The term “homologous” necessarily refers to a comparison between at least two sequences (polynucleotide or polypeptide sequences). In accordance with the disclosure, two polynucleotide sequences are considered to be homologous if the polypeptides they encode are at least about 50%, 60%, 70%, 80%, 90%, 95%, or even 99% for at least one stretch of at least about 20 amino acids. In some embodiments, homologous polynucleotide sequences are characterized by the ability to encode a stretch of at least 4–5 uniquely specified amino acids. For polynucleotide sequences less than 60 nucleotides in length, homology is determined by the ability to encode a stretch of at least 4–5

uniquely specified amino acids. In accordance with the disclosure, two protein sequences are considered to be homologous if the proteins are at least about 50%, 60%, 70%, 80%, or 90% identical for at least one stretch of at least about 20 amino acids.

[0442] *Identity.* As used herein, the term “identity” refers to the overall relatedness between polymeric molecules, *e.g.*, between polynucleotide molecules (*e.g.* DNA molecules and/or RNA molecules) and/or between polypeptide molecules. Calculation of the percent identity of two polynucleotide sequences, for example, can be performed by aligning the two sequences for optimal comparison purposes (*e.g.*, gaps can be introduced in one or both of a first and a second nucleic acid sequences for optimal alignment and non-identical sequences can be disregarded for comparison purposes). In certain embodiments, the length of a sequence aligned for comparison purposes is at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or 100% of the length of the reference sequence. The nucleotides at corresponding nucleotide positions are then compared. When a position in the first sequence is occupied by the same nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which needs to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. For example, the percent identity between two nucleotide sequences can be determined using methods such as those described in Computational Molecular Biology, Lesk, A. M., ed., Oxford University Press, New York, 1988; Biocomputing: Informatics and Genome Projects, Smith, D. W., ed., Academic Press, New York, 1993; Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press, 1987; Computer Analysis of Sequence Data, Part I, Griffin, A. M., and Griffin, H. G., eds., Humana Press, New Jersey, 1994; and Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991; the contents of each of which are incorporated herein by reference in their entirety. For example, the percent identity between two nucleotide sequences can be determined using the algorithm of Meyers and Miller (CABIOS, 1989, 4:11-17), which has been incorporated into the ALIGN program (version 2.0) using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. The percent identity between two nucleotide sequences can, alternatively, be determined using the GAP program in the GCG software package using an NWSgapdna.CMP matrix. Methods commonly employed to determine percent identity between sequences include, but are not limited to those disclosed in Carillo, H., and Lipman, D., SIAM J Applied Math., 48:1073 (1988); incorporated herein by reference. Techniques for determining identity are codified in publicly available computer programs. Exemplary computer software to determine homology between two sequences include, but are not limited to, GCG program package, Devereux, J., *et al.*, *Nucleic Acids Research*, 12(1), 387 (1984)), BLASTP, BLASTN, and FASTA Altschul, S. F. *et al.*, *J. Molec. Biol.*, 215, 403 (1990)).

[0443] *Inhibit expression of a gene:* As used herein, the phrase “inhibit expression of a gene” means to cause a reduction in the amount of an expression product of the gene. The expression product can be an RNA transcribed from the gene (e.g., an mRNA) or a polypeptide translated from an mRNA transcribed from the gene. Typically, a reduction in the level of an mRNA results in a reduction in the level of a polypeptide translated therefrom. The level of expression may be determined using standard techniques for measuring mRNA or protein.

[0444] *Inverted terminal repeat:* As used herein, the term “inverted terminal repeat” or “ITR” refers to a cis-regulatory element for the packaging of polynucleotide sequences into viral capsids.

[0445] *Isolated:* As used herein, the term “isolated” refers to a substance or entity that is altered or removed from the natural state, e.g., altered or removed from at least some of component with which it is associated in the natural state. For example, a nucleic acid or a peptide naturally present in a living animal is not “isolated,” but the same nucleic acid or peptide partially or completely separated from the coexisting materials of its natural state is “isolated.” An isolated nucleic acid or protein can exist in substantially purified form, or can exist in a non-native environment such as, for example, a host cell. Such polynucleotides could be part of a vector and/or such polynucleotides or polypeptides could be part of a composition, and still be isolated in that such vector or composition is not part of the environment in which it is found in nature. In some embodiments, an isolated nucleic acid is recombinant, e.g., incorporated into a vector.

[0446] *Library:* As used herein, the term “library” refers to a diverse collection of linear polypeptides, polynucleotides, viral particles, or viral vectors. As examples, a library may be a DNA library or an AAV capsid library.

[0447] *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.

[0448] *Neurological disease:* As used herein, a “neurological disease” is any disease associated with the central or peripheral nervous system and components thereof (e.g., neurons).

[0449] *Orthogonal evolution:* As used herein, the term “orthogonal evolution” refers to a method wherein AAV particles are administered for a first round of AAV selection as described herein across a set of any number of cell- and/or subject-types that may be from different species and/or strains, and wherein any number of additional, i.e., subsequent, AAV selection rounds are performed either across a set of any number of cell- and/or subject-types that may be from different species and/or strains, or across a set of any number of cell- and/or subject-types that may be from the same species and/or strain.

[0450] *Open reading frame:* As used herein, “open reading frame” or “ORF” refers to a sequence which does not contain a stop codon in a given reading frame.

[0451] *Particle*: As used herein, a “particle” is a virus comprised of at least two components, a protein capsid and a polynucleotide sequence enclosed within the capsid.

[0452] *Payload region*: As used herein, a “payload region” is any nucleic acid sequence (e.g., within the viral genome) which encodes one or more “payloads” of the disclosure. As non-limiting examples, a payload region may be a nucleic acid sequence within the viral genome of an AAV particle, which encodes a payload, wherein the payload is an RNAi agent or a polypeptide. Payloads of the present disclosure may be, but are not limited to, peptides, polypeptides, proteins, antibodies, RNAi agents, etc.

[0453] *Polypeptide*: As used herein, “polypeptide” means a polymer of amino acid residues (natural or unnatural) linked together most often by peptide bonds. The term, as used herein, refers to proteins, polypeptides, and peptides of any size, structure, or function. In some instances, the polypeptide encoded is smaller than about 50 amino acids and the polypeptide is then termed a peptide. If the polypeptide is a peptide, it will be at least about 2, 3, 4, or at least 5 amino acid residues long. Thus, polypeptides include gene products, naturally occurring polypeptides, synthetic polypeptides, homologs, orthologs, paralogs, fragments and other equivalents, variants, and analogs of the foregoing. A polypeptide may be a single molecule or may be a multi-molecular complex such as a dimer, trimer or tetramer. They may also comprise single chain or multichain polypeptides and may be associated or linked. The term polypeptide may also apply to amino acid polymers in which one or more amino acid residues are an artificial chemical analogue of a corresponding naturally occurring amino acid.

[0454] *Polypeptide variant*: The term “polypeptide variant” refers to molecules which differ in their amino acid sequence from a native or reference sequence. The amino acid sequence variants may possess substitutions, deletions, and/or insertions at certain positions within the amino acid sequence, as compared to a native or reference sequence. In some embodiments, a variant comprises a sequence having at least about 50%, at least about 80%, or at least about 90%, identical (homologous) to a native or a reference sequence.

[0455] *Peptide*: As used herein, “peptide” is less than or equal to 50 amino acids long, e.g., about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 amino acids long.

[0456] *Pharmaceutically acceptable*: The phrase “pharmaceutically acceptable” is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0457] *Preventing*: As used herein, the term “preventing” or “prevention” refers to partially or completely delaying onset of an infection, disease, disorder and/or condition; partially or completely delaying onset of one or more symptoms, features, or clinical manifestations of a particular infection,

disease, disorder, and/or condition; partially or completely delaying onset of one or more symptoms, features, or manifestations of a particular infection, disease, disorder, and/or condition; partially or completely delaying progression from an infection, a particular disease, disorder and/or condition; and/or decreasing the risk of developing pathology associated with the infection, the disease, disorder, and/or condition.

[0458] *Prophylactic*: As used herein, “prophylactic” refers to a therapeutic or course of action used to prevent the spread of disease.

[0459] *Prophylaxis*: As used herein, a “prophylaxis” refers to a measure taken to maintain health and prevent the spread of disease.

[0460] *Region*: As used herein, the term “region” refers to a zone or general area. In some embodiments, when referring to a protein or protein module, a region may comprise a linear sequence of amino acids along the protein or protein module or may comprise a three-dimensional area, an epitope and/or a cluster of epitopes. In some embodiments, regions comprise terminal regions. As used herein, the term “terminal region” refers to regions located at the ends or termini of a given agent. When referring to proteins, terminal regions may comprise N- and/or C-termini.

[0461] In some embodiments, when referring to a polynucleotide, a region may comprise a linear sequence of nucleic acids along the polynucleotide or may comprise a three-dimensional area, secondary structure, or tertiary structure. In some embodiments, regions comprise terminal regions. As used herein, the term “terminal region” refers to regions located at the ends or termini of a given agent. When referring to polynucleotides, terminal regions may comprise 5' and/or 3' termini.

[0462] *RNA or RNA molecule*: As used herein, the term “RNA” or “RNA molecule” or “ribonucleic acid molecule” refers to a polymer of ribonucleotides; the term “DNA” or “DNA molecule” or “deoxyribonucleic acid molecule” refers to a polymer of deoxyribonucleotides. DNA and RNA can be synthesized naturally, e.g., by DNA replication and transcription of DNA, respectively; or be chemically synthesized. DNA and RNA can be single-stranded (i.e., ssRNA or ssDNA, respectively) or multi-stranded (e.g., double stranded, i.e., dsRNA and dsDNA, respectively). The term “mRNA” or “messenger RNA”, as used herein, refers to a single stranded RNA that encodes the amino acid sequence of one or more polypeptide chains.

[0463] *RNA interfering or RNAi*: As used herein, the term “RNA interfering” or “RNAi” refers to a sequence specific regulatory mechanism mediated by RNA molecules which results in the inhibition or interfering or “silencing” of the expression of a corresponding protein-coding gene. RNAi has been observed in many types of organisms, including plants, animals and fungi. RNAi occurs in cells naturally to remove foreign RNAs (e.g., viral RNAs). Natural RNAi proceeds via fragments cleaved from free dsRNA which direct the degradative mechanism to other similar RNA sequences. RNAi is controlled by the RNA-induced silencing complex (RISC) and is initiated by short/small dsRNA molecules in cell cytoplasm, where they interact with the catalytic RISC component argonaute. The

dsRNA molecules can be introduced into cells exogenously. Exogenous dsRNA initiates RNAi by activating the ribonuclease protein Dicer, which binds and cleaves dsRNAs to produce double-stranded fragments of 21-25 base pairs with a few unpaired overhang bases on each end. These short double stranded fragments are called small interfering RNAs (siRNAs).

[0464] *RNAi agent*: As used herein, the term “RNAi agent” refers to an RNA molecule, or its derivative, that can induce inhibition, interfering, or “silencing” of the expression of a target gene and/or its protein product. An RNAi agent may knock-out (virtually eliminate or eliminate) expression, or knock-down (lessen or decrease) expression. The RNAi agent may be, but is not limited to, dsRNA, siRNA, shRNA, pre-miRNA, pri-miRNA, miRNA, stRNA, lncRNA, piRNA, or snoRNA.

[0465] *miR binding site*: As used herein, a “miR binding site” comprises a nucleic acid sequence (whether RNA or DNA, e.g., differ by “U” of RNA or “T” in DNA) that is capable of binding, or binds, in whole or in part to a microRNA (miR) through complete or partial hybridization. Typically, such binding occurs between the miR and the miR binding site in the reverse complement orientation. In some embodiments, the miR binding site is transcribed from the AAV vector genome encoding the miR binding site.

[0466] In some embodiments, a miR binding site may be encoded or transcribed in series. Such a “miR binding site series” or “miR BSs” may include two or more miR binding sites having the same or different nucleic acid sequence.

[0467] *Spacer*: As used here, a “spacer” is generally any selected nucleic acid sequence of, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides in length, which is located between two or more consecutive miR binding site sequences. Spacers may also be more than 10 nucleotides in length, e.g., 20, 30, 40, or 50 or more than 50 nucleotides.

[0468] *Sample*: As used herein, the term “sample” or “biological sample” refers to a subset of its tissues, cells, nucleic acids, or component parts (e.g. body fluids, including but not limited to blood, serum, mucus, lymphatic fluid, synovial fluid, cerebrospinal fluid, saliva, amniotic fluid, amniotic cord blood, urine, vaginal fluid and semen).

[0469] *Self-complementary viral particle*: As used herein, a “self-complementary viral particle” is a particle comprised of at least two components, a protein capsid and a self-complementary viral genome enclosed within the capsid.

[0470] *Sense Strand*: As used herein, the term “the sense strand” or “the second strand” or “the passenger strand” of a siRNA molecule refers to a strand that is complementary to the antisense strand or first strand. The antisense and sense strands of a siRNA molecule are hybridized to form a duplex structure. As used herein, a “siRNA duplex” includes a siRNA strand having sufficient complementarity to a section of about 10-50 nucleotides of the mRNA of the gene targeted for

silencing and a siRNA strand having sufficient complementarity to form a duplex with the other siRNA strand.

[0471] *Similarity:* As used herein, the term “similarity” refers to the overall relatedness between polymeric molecules, *e.g.* between polynucleotide molecules (*e.g.* DNA molecules and/or RNA molecules) and/or between polypeptide molecules. Calculation of percent similarity of polymeric molecules to one another can be performed in the same manner as a calculation of percent identity, except that calculation of percent similarity takes into account conservative substitutions as is understood in the art.

[0472] *Short interfering RNA or siRNA:* As used herein, the terms “short interfering RNA,” “small interfering RNA” or “siRNA” refer to an RNA molecule (or RNA analog) comprising between about 5-60 nucleotides (or nucleotide analogs) which is capable of directing or mediating RNAi. Preferably, a siRNA molecule comprises between about 15-30 nucleotides or nucleotide analogs, such as between about 16-25 nucleotides (or nucleotide analogs), between about 18-23 nucleotides (or nucleotide analogs), between about 19-22 nucleotides (or nucleotide analogs) (*e.g.*, 19, 20, 21 or 22 nucleotides or nucleotide analogs), between about 19-25 nucleotides (or nucleotide analogs), and between about 19-24 nucleotides (or nucleotide analogs). The term “short” siRNA refers to a siRNA comprising 5-23 nucleotides, preferably 21 nucleotides (or nucleotide analogs), for example, 19, 20, 21 or 22 nucleotides. The term “long” siRNA refers to a siRNA comprising 24-60 nucleotides, preferably about 24-25 nucleotides, for example, 23, 24, 25 or 26 nucleotides. Short siRNAs may, in some instances, include fewer than 19 nucleotides, *e.g.*, 16, 17 or 18 nucleotides, or as few as 5 nucleotides, provided that the shorter siRNA retains the ability to mediate RNAi. Likewise, long siRNAs may, in some instances, include more than 26 nucleotides, *e.g.*, 27, 28, 29, 30, 35, 40, 45, 50, 55, or even 60 nucleotides, provided that the longer siRNA retains the ability to mediate RNAi or translational repression absent further processing, *e.g.*, enzymatic processing, to a short siRNA. siRNAs can be single stranded RNA molecules (ss-siRNAs) or double stranded RNA molecules (ds-siRNAs) comprising a sense strand and an antisense strand which hybridized to form a duplex structure called an siRNA duplex.

[0473] *Subject:* As used herein, the term “subject” or “patient” refers to any organism to which a composition in accordance with the disclosure may be administered, *e.g.*, for experimental, diagnostic, prophylactic, and/or therapeutic purposes. Typical subjects include animals (*e.g.*, mammals such as mice, rats, rabbits, non-human primates, and humans) and/or plants.

[0474] *Substantially:* As used herein, the term “substantially” refers to the qualitative condition of exhibiting total or near-total extent or degree of a characteristic or property of interest. One of ordinary skill in the biological arts will understand that biological and chemical phenomena rarely, if ever, go to completion and/or proceed to completeness or achieve or avoid an absolute result. The

term “substantially” is therefore used herein to capture the potential lack of completeness inherent in many biological and chemical phenomena.

[0475]

[0476] *Target Cells:* As used herein, “target cells” or “target tissue” refers to any one or more cells of interest. The cells may be found *in vitro*, *in vivo*, *in situ* or in the tissue or organ of an organism. The organism may be an animal, preferably a mammal, more preferably a human and most preferably a patient.

[0477] *Therapeutic Agent:* The term “therapeutic agent” refers to any agent that, when administered to a subject, has a therapeutic, diagnostic, and/or prophylactic effect and/or elicits a desired biological and/or pharmacological effect.

[0478] *Therapeutically effective amount:* As used herein, the term “therapeutically effective amount” means an amount of an agent to be delivered (*e.g.*, nucleic acid, drug, therapeutic agent, diagnostic agent, prophylactic agent, *etc.*) that is sufficient, when administered to a subject suffering from or susceptible to an infection, disease, disorder, and/or condition, to treat, improve symptoms of, diagnose, prevent, and/or delay the onset of the infection, disease, disorder, and/or condition. In some embodiments, a therapeutically effective amount is provided in a single dose.

[0479] *Therapeutically effective outcome:* As used herein, the term “therapeutically effective outcome” means an outcome that is sufficient in a subject suffering from or susceptible to an infection, disease, disorder, and/or condition, to treat, improve symptoms of, diagnose, prevent, and/or delay the onset of the infection, disease, disorder, and/or condition.

[0480] *Treating:* As used herein, the term “treating” refers to partially or completely alleviating, ameliorating, improving, relieving, delaying onset of, inhibiting progression of, reducing severity of, and/or reducing incidence of one or more symptoms or features of a particular infection, disease, disorder, and/or condition. For example, “treating” cancer may refer to inhibiting survival, growth, and/or spread of a tumor. Treatment may be administered to a subject who does not exhibit signs of a disease, disorder, and/or condition and/or to a subject who exhibits only early signs of a disease, disorder, and/or condition for the purpose of decreasing the risk of developing pathology associated with the disease, disorder, and/or condition.

[0481] *Conservative amino acid substitution:* As used herein, a “conservative amino acid substitution” is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains

(e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine).

[0482] *Variant*: As used herein, the term “variant” refers to a polypeptide or polynucleotide that has an amino acid or a nucleotide sequence that is substantially identical, e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% or 99% sequence identity to a reference sequence. In some embodiments, the variant is a functional variant.

[0483] *Functional Variant*: As used herein, the term “functional variant” refers to a polypeptide variant or a polynucleotide variant that has at least one activity of the reference sequence.

[0484] *Insertional Variant*: “Insertional variants” when referring to polypeptides are those with one or more amino acids inserted, e.g., immediately adjacent or subsequent, to a position in an amino acid sequence. “Immediately adjacent” or “immediately subsequent” to an amino acid means connected to either the alpha-carboxy or alpha-amino functional group of the amino acid.

[0485] *Deletional Variant*: “Deletional variants” when referring to polypeptides, are those with one or more amino acids in deleted from a reference protein.

[0486] *Vector*: As used herein, the term “vector” refers to any molecule or moiety which transports, transduces or otherwise acts as a carrier of a heterologous molecule. In some embodiments, vectors may be plasmids. In some embodiments, vectors may be viruses. An AAV particle is an example of a vector. Vectors of the present disclosure may be produced recombinantly and may be based on and/or may comprise adeno-associated virus (AAV) parent or reference sequences. The heterologous molecule may be a polynucleotide and/or a polypeptide.

[0487] *Viral Genome*: As used herein, the terms “viral genome” or “vector genome” refer to the nucleic acid sequence(s) encapsulated in an AAV particle. A viral genome comprises a nucleic acid sequence with at least one payload region encoding a payload and at least one ITR.

Equivalents and Scope

[0488] The disclosures of each and every patent, patent application, and publication cited herein are hereby incorporated herein by reference in their entirety. While this invention has been disclosed with reference to certain embodiments, it is apparent that further embodiments and variations of this invention may be devised by others skilled in the art without departing from the true spirit and scope of the invention. The appended claims are intended to be construed to include all such embodiments and equivalent variations.

[0489] The present disclosure is further illustrated by the following non-limiting examples.

EXAMPLES

Example 1. High-throughput screen of TRACER AAV library in NHP and Mice

[0490] A TRACER based method as described in WO2020072683, WO 2021/202651, and WO2021230987, the contents of which are herein incorporated by reference in their entirety, was

used to generate the AAV capsid variants described herein. An orthogonal evolution approach was combined with a high throughput screening by NGS. Briefly, the library of AAV capsid variants was generated using a sliding window approach, where 6 amino acid sequences were inserted into 8 different positions across loop IV of AAV9, including immediately subsequent to positions 453, 454, 455, 456, 457, 458, 459, and 460, relative to a reference sequence numbered according to SEQ ID NO: 138. The initial library was passed twice through non-human primates (NHP, 2-4 years of age). After the second passage (e.g., 28 days post injection into two NHPs), RNA was extracted from six brain regions. Following RNA recovery and RT-PCR amplification, a systematic NGS enrichment analysis was performed to calculate fold enrichment relative to an AAV9 wild-type control. Following these two passages, approximately 21195 variants were identified with an average fold change greater than wild-type. Of the 21195 variants, 1558 demonstrated a fold-change of greater than 6 compared to wild-type and were detected across all brain regions investigated. Of these 1558, approximately 1470 variants were selected for constructing a synthetic library and a third passage through two NHPs. Within the 1470 variants selected for further characterization and investigation, there was a relatively even distribution for each insertion position of the sliding window used to generate the initial library.

[0491] After creation of the synthetic library with the sub-selected variants, the synthetic library was screened (passage 3) in two NHPs (2-4 years of age) and two strains of mice, BALB/c (n=3, 6-8 weeks of age) and C57Bl/6 mice (n=3, 6-8 weeks of age), in a first cross-species evolution screen. The animals were injected intravenously with the synthetic library. After a period *in vivo*, (e.g., 28-days) RNA was extracted from nervous tissue, e.g., brain, spinal cord, and DRG of the NHPs and the brains of mice. Following RNA recovery and RT-PCR amplification, a systematic NGS enrichment analysis was performed, and the peptides comprised within the variants were identified and the capsid enrichment ratio for each variant compared to the wild-type AAV9 control was calculated (fold enrichment relative to wild-type AAV9) (**Table 9**). Values above 1 indicate an increase in expression relative to AAV9. All animals were dosed intravenously at 2-3 VG/kg across the screen.

[0492] As shown in Table 9, approximately 700 variants demonstrated an increase in expression relative to AAV9, and several variants demonstrated a greater than 10-fold enrichment relative to AAV9 in the brain of NHPs. Further, the variants demonstrating the greatest fold enrichment in the brain also demonstrated the greatest fold enrichment in the spinal cord relative to AAV9 in NHPs. These variants also demonstrated de-targeting in the DRG (data not shown). For instance, the variant comprising GSGSPHKAQNQQT (SEQ ID NO: 200) demonstrated a 76.6 fold enrichment in the brain, a 29.4 fold enrichment in the spinal cord, and 0.4 fold enrichment in the DRG of NHPs relative to AAV9; and GHDSPHKSGQNQQT (SEQ ID NO: 201) demonstrated a 62.6 fold enrichment in the brain, a 15.6 fold enrichment in the spinal cord, and 0.0 fold enrichment in the DRG of NHPs relative to AAV9. Also, across the peptides comprised within the AAV capsid variants with the greatest fold-enrichment in the NHP brain relative wild-type AAV9, it was observed that each of these peptides

comprised an SPH motif in the same position (e.g., immediately subsequent to position 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138), regardless of the insertion position within the variant capsid, as well as a positive amino acid (e.g., K or R) in one of the next three residues subsequent to the SPH motif.

[0493] Those variants with the greatest fold enrichment in the brains of NHPs also had the greatest fold enrichment in the brains of both mouse species. Also, when comparing the fold enrichment relative to wild-type for each variant between the two species of mice investigated (C57Bl/6 and BALB/c mice), they were highly correlated ($R^2 = 0.8591$).

Table 9. NGS fold-enrichment of AAV capsid variants in NHPs and mice

Peptide Sequence	SEQ ID NO:	Fold enrichment over AAV9 in the brain of NHPs	Fold enrichment over AAV9 in the spinal cord of NHPs	Fold enrichment over AAV9 in the brain of Mice (C57Bl/6)	Fold enrichment over AAV9 in the brain of Mice (BALB/c)
GSGSPHKAQNQQT	200	73.615	29.402	25.293	41.304
GHDSPHKSGQNQQT	201	62.612	15.641	63.993	49.760
GSGSPHARMQNQQT	202	56.138	22.690	7.795	4.164
GSGSPHVKSQNQQT	203	37.551	13.649	8.069	15.861
GQDSPHKSGQNQQT	204	24.569	3.548	57.344	42.615
GSGSPHASRQNQQT	205	18.265	7.804	28.028	36.577
GSGSPHASRQNKQT	206	17.520	35.029	13.096	18.114
GSGSPHVKIQNQQT	207	16.854	9.068	2.173	2.227
GSGSPHSAKNQQT	208	14.458	0.049	21.494	23.556
GSGSPHKKQNQQT	209	12.991	0.379	25.958	7.415
GSGSPHVRMQNQQT	210	11.574	6.764	9.121	10.076
GSGSPHASRQKQQT	211	11.417	0.005	7.413	12.400
GHSSPHRSGQNQQT	212	10.357	1.887	23.197	25.442
GMRTYHLSGQNQQT	213	9.241	1.939	2.033	1.586
GSGSPHTRGQNQQT	214	7.092	3.815	10.801	6.240
GSGIIPVSSQNQQT	215	6.352	0.000	0.642	0.253
GSEYGHKSGQNQQT	216	6.308	2.750	5.198	5.332
GRGQNVSSVHRQQT	217	5.404	0.000	1.206	0.691
GSSHRFYGGQNQQT	218	4.732	0.000	0.787	0.110
GYFVAAWSGQNQQT	219	4.488	0.000	0.071	0.175
GSVLHSHAAQNQQT	220	4.150	6.448	0.675	0.423
GSGDLVVSTQNQQT	221	3.874	1.177	0.411	0.273
GSYGMAASGQNQQT	222	3.817	10.052	1.274	0.829
GLNHFGASGQNQQT	223	3.802	3.188	0.774	0.579
GSTGSHSAGQNQHT	224	3.717	0.285	1.190	0.850
GLAGHTVSGQNQQT	225	3.632	0.229	0.972	0.202
GIILGASSGQNQQT	226	3.630	4.868	1.378	0.865
GSGVSTYNIQNQQT	227	3.609	2.912	0.769	0.520
GSLVSVQTGQNQQT	228	3.534	6.043	0.903	0.469
GQSSPHRSGQNQQT	229	3.496	2.142	12.352	19.366
GREYGHKSGQNQQT	230	3.453	0.000	1.422	0.959
GHTLTLLSSGQNQQT	231	3.405	5.648	0.648	0.606
GSITLIPSGQNQQT	232	3.361	3.917	0.326	0.435
GSGFTALGQNQQT	233	3.361	2.663	0.830	0.332
GSGHSSHSVQNQQT	234	3.339	3.318	0.942	0.424

GSGIPQSRSGKNQQT	235	3.331	0.000	1.418	1.685
GSGDTLHMLQNNQQT	236	3.317	1.174	0.393	0.482
GERHTVLSGQNNQQT	237	3.289	3.008	1.027	0.607
GSGMPQSHIQNNQQT	238	3.289	11.609	0.514	0.334
GSGQLSGIGGNQQT	239	3.266	0.287	0.993	0.626
GSGQNRKPASFAQT	240	3.204	0.000	0.892	1.061
GSGSVSQLGQNNQQT	241	3.184	2.307	0.596	0.375
GSDFLGTHGQNNQQT	242	3.171	0.348	1.038	0.750
GQIVQNPSGQNNQQT	243	3.133	0.406	1.446	0.635
GSGTQIPSQNNQQT	244	3.112	1.224	0.470	0.151
GSGQNNQQSAREGLT	245	3.111	5.632	1.221	1.104
GSGGLMSTGQNNQQT	246	3.110	5.499	0.458	0.660
GSGLPVLSGQNNQQT	247	3.100	4.149	0.631	0.210
GSGHSIRTDQNNQQT	248	3.074	15.600	0.229	0.148
GSGQSVQTVVNQQT	249	3.057	5.441	0.582	0.240
GSGQNRAQSRFQQT	250	3.043	0.000	0.619	1.788
GGGDLGRSSQNNQQT	251	3.036	4.830	0.916	0.539
GGGTKMDSGQNNQQT	252	3.034	0.000	0.733	0.297
GSGSPHPSRQNNQQT	253	3.017	1.993	1.869	0.975
GSGQFTNAGMNQQT	254	2.969	0.936	0.565	0.418
GGRNGHTVGQNNQQT	255	2.965	3.732	1.105	1.003
GSGFGPQTGQNNQQT	256	2.964	2.861	1.280	0.849
GRTDSHTSGQNNQQT	257	2.913	1.510	1.299	0.704
GYEVLGSSGQNNQQT	258	2.891	0.000	2.459	0.319
GSVHLSVTGQNNQQT	259	2.882	1.157	0.741	0.282
GFMSYKSGGQNNQQT	260	2.865	0.209	1.808	0.569
GNIAGSVSGQNNQQT	261	2.849	1.187	0.446	0.257
GSGSHRDVSGQNNQQT	262	2.843	4.022	0.626	0.550
GGLGSMSSGQNNQQT	263	2.812	1.405	1.802	0.822
GSGHLPQSAQNNQQT	264	2.803	7.828	0.826	0.496
GGVLVGSGGQNNQQT	265	2.778	0.178	1.527	0.688
GTHPYTSSGQNNQQT	266	2.775	1.684	0.758	0.471
GSGQNNQLKENRST	267	2.765	0.062	1.149	1.118
GSGQNNQQTSPHNHT	268	2.761	3.132	1.524	0.845
GSGTLYPQSQNNQQT	269	2.761	5.558	0.324	0.160
GSGQNNQQSNWITKT	270	2.711	0.000	0.540	0.634
GSGYTSLFLQNNQQT	271	2.710	0.010	0.490	1.044
GSGVMTHVLQNNQQT	272	2.692	0.347	0.370	0.533
GSVSDVRAGQNNQQT	273	2.661	1.647	0.267	0.747
GSGQSHMATLNQQT	274	2.657	0.724	1.173	0.504
GSGLSVHLAQNNQQT	275	2.657	1.234	0.806	0.508
GSGLSHATQNNQQT	276	2.640	7.819	1.111	0.638
GSGLSVQSGQNNQQT	277	2.637	2.929	1.695	1.005
GSGHMTYREKNQQT	278	2.633	5.267	1.257	0.540
GSKGVPTPGQNNQQT	279	2.625	1.292	1.452	0.459
GSGLLPLSSQNNQQT	280	2.612	1.130	0.501	0.293
GNGLYAVSGQNNQQT	281	2.611	9.148	0.322	0.213
GFNGSPSSGQNNQQT	282	2.609	12.197	2.338	0.924
GSGQIRHSDQNNQQT	283	2.600	12.884	1.170	0.320
GGQVAPSSGQNNQQT	284	2.581	2.427	1.433	0.709
GSFSMHTHGQNNQQT	285	2.535	0.118	1.027	0.693
GSGQNNQQVIQGSNT	286	2.521	8.778	0.935	0.810
GRVLHSHAGQNNQQT	287	2.513	0.826	1.294	0.908

GSGQNQQTSLQDOT	288	2.505	0.500	0.315	0.968
GSGLGRAPVQNQQT	289	2.503	2.214	0.841	0.383
GNGFSSASGQNQQT	290	2.493	0.772	0.240	0.182
GSGQMASRESNQQT	291	2.492	0.300	0.341	0.288
GPGLPNHSGQNQQT	292	2.486	1.992	1.197	0.659
GNIQWQSGQNQQT	293	2.468	6.266	1.182	0.837
GMSAHMSSGQNQQT	294	2.456	5.255	1.310	0.947
GHSFVNRSQNQQT	295	2.447	11.148	1.305	0.756
GRAVMDHSGQNQQT	296	2.408	3.209	0.728	0.283
GALTVMQSGQNQQT	297	2.381	0.430	0.246	0.199
GSGQRSPVLPNQQT	298	2.369	6.230	0.434	0.526
GSGQNGHLSLKQQT	299	2.362	1.896	0.718	0.270
GSLPRGTSQDNQQT	300	2.362	0.000	0.453	0.495
GVAGSLVSGQNQQT	301	2.358	7.670	1.321	1.160
GRGGIPQSGQNQQT	302	2.352	8.683	1.639	1.181
GSGQYASSIPNQQT	303	2.346	3.321	1.022	0.489
GTDFGRQSSQNQQT	304	2.346	3.196	1.021	0.797
GIFMQTPSGQNQQT	305	2.344	6.198	0.938	0.252
GSGQNQQTRLVDLT	306	2.342	9.348	1.268	0.490
GTEMPLSGQNQQT	307	2.339	2.830	1.436	0.538
GSRLVHVHGQNQQT	308	2.334	1.174	1.277	0.934
GSGRLVPNGPNQQT	309	2.314	3.925	0.639	0.411
GSGYLRESPQNQQT	310	2.311	0.878	0.331	0.677
GARIQNASGQKQQT	311	2.300	2.103	1.220	1.039
GLSNPMPSSGQNQQT	312	2.280	6.033	1.190	0.829
GSTVQDTRGQNQQT	313	2.270	4.979	0.576	0.473
GPFGMPSSGQNQQT	314	2.260	2.700	0.727	0.560
GSGQNHGVLNQQT	315	2.254	1.603	1.113	0.701
GSGYSMSQAQNQQT	316	2.250	4.479	0.519	0.329
GSGMLTHTLQNQQT	317	2.246	2.272	0.496	0.199
GRGSPHASRQNQQT	318	2.241	0.000	5.050	5.856
GLSWPSTSGQNQQT	319	2.238	0.000	0.910	0.610
GNSMERTSGQNQQT	320	2.221	4.177	1.047	0.935
GSGMSPSTLQNQQT	321	2.216	3.053	0.318	0.153
GSGHGQVLSQNQQT	322	2.213	12.133	1.880	0.661
GRGQIYSTGGNQQT	323	2.210	11.629	1.329	0.743
GVVAAHNSGQNQQT	324	2.202	1.301	1.196	1.336
GDSSLRHSGQNQQT	325	2.194	0.000	0.662	0.412
GSLVSQGAGQNQQT	326	2.188	4.414	1.436	1.246
GSLLOAHSGQNQQT	327	2.182	1.008	0.575	0.748
GSGHIYVGIQNQQT	328	2.178	6.428	0.989	0.337
GHHTTVQSGQNQQT	329	2.177	6.245	0.851	0.755
GSRQSKRNELNQQT	330	2.177	0.000	1.325	0.232
GSGQNQQHVSSPRT	331	2.176	1.279	1.847	0.938
GSSKELLWGQNQQT	332	2.163	0.000	0.506	0.883
GSLSTPSSGQNQQT	333	2.159	1.279	1.094	0.669
GSIGYAGQGQNQQT	334	2.157	4.951	1.604	0.712
GSGQNQRVSNQQT	335	2.146	0.492	1.086	0.985
GSGYASHVQQNQQT	336	2.146	3.038	1.157	0.758
GSGEYSRSGQNQQT	337	2.145	0.745	0.617	0.205
GSVSTHSSGQNQQT	338	2.145	3.446	1.198	0.918
GSGQNQHSLGNYQT	339	2.143	1.896	1.077	0.606
GSGGLDTRGQNQQT	340	2.139	6.216	0.236	0.197

GNILHATSGQNQQT	341	2.136	0.125	1.159	0.424
GSGQSYTMTQNQQT	342	2.136	6.755	0.297	0.231
GSGQNQHSAFNSQT	343	2.134	4.143	1.187	0.731
GSGQNQQTMDHNRT	344	2.130	4.944	0.642	0.440
GSNGGVGTGQNQQT	345	2.130	0.788	1.191	1.087
GAGSIIPSGQNQQT	346	2.129	7.164	0.595	0.249
GSGQTHGGQHNQQT	347	2.125	12.251	1.448	1.098
GSNLSFQSGQNQQT	348	2.122	5.853	1.087	0.719
GATLQVHSGQNQQT	349	2.122	2.219	0.623	0.545
GSGFNQRSEQNQQT	350	2.121	4.491	1.770	0.758
GSGSLRDFDQNQQT	351	2.120	6.846	0.586	0.272
GSGDSITGKQNQQT	352	2.112	1.295	0.793	0.306
GSGQDRNIVQNQQT	353	2.112	0.229	0.454	0.632
GSGLSHSHQQNQQT	354	2.109	5.852	1.256	0.592
GSGQNQQTGMSSVK	355	2.109	4.544	1.451	0.679
GSVTHGISGQNQQT	356	2.105	4.542	1.135	0.789
GVVAHQPSGQNQQT	357	2.103	0.152	0.910	2.267
GSGPILGQLQNQQT	358	2.097	2.058	0.470	0.123
GSGHVPNSGLNQQT	359	2.091	0.653	1.636	1.154
GDAGVRSSGQNQQT	360	2.068	3.918	1.033	1.193
GSGSQLMSLQNQQT	361	2.065	3.559	0.563	0.172
GSGLDYSQRQNQQT	362	2.056	0.837	0.484	0.217
GSGQSSGRLINKQT	363	2.055	28.135	0.543	0.277
GSSVSPSSGQNQQT	364	2.054	0.579	1.064	0.787
GSGQVVGLSGNQQT	365	2.052	7.212	0.785	0.881
GSNMGVPLGQNQQT	366	2.049	2.448	0.334	0.420
GSFYPPSTGQNQQT	367	2.047	2.374	0.420	0.277
GSGQNQQTRLTDLT	368	2.046	8.470	0.910	0.776
GPTNGRSSGQNQQT	369	2.034	8.903	0.936	1.308
GSGLLHGKLNQQT	370	2.032	2.521	1.068	0.917
GANMGHVSQVNQQT	371	2.020	0.810	1.302	1.138
GSGQNQQSGRGDLT	372	2.019	6.919	0.524	1.152
GSHGHYASGQKQQT	373	2.016	0.000	0.895	0.685
GSGDLRISPQNQQT	374	2.012	16.207	0.620	0.237
GSGMPVILGQNQQT	375	2.005	0.150	0.840	0.287
GRGVITSSGQNHQT	376	2.004	0.864	1.656	0.669
GSGHSVSGPQNQQT	377	1.993	6.259	1.370	0.619
GSRNGHTVGRNQQT	378	1.993	0.000	1.162	0.367
GAGVHMOVSGQNQQT	379	1.987	6.488	1.055	0.791
GSGQNHRPSVLQQT	380	1.983	5.582	0.433	0.582
GSGSPRDSIQNQQT	381	1.981	4.914	0.171	0.446
GSGQGIHSSVNQQT	382	1.981	4.873	0.632	0.634
GSGQQLSITPNQQT	383	1.979	10.280	0.845	0.201
GGYHSQTSQVNQQT	384	1.978	2.642	1.740	1.525
GSLHHDNHGQNQQT	385	1.976	0.980	0.968	0.463
GIMARDSSGQNQQT	386	1.972	3.486	1.320	0.904
GVVHITNSGQNQQT	387	1.969	0.504	0.794	0.846
GSGQNQHSAFNFQT	388	1.969	0.499	0.759	0.870
GSGQTSGLKQNQQT	389	1.968	3.927	0.394	0.334
GSGQNQQTSLSNTA	390	1.959	1.186	1.567	1.182
GSGQNQAQVHNKSQT	391	1.956	3.791	1.465	1.083
GVHHTHLPSSGQNQQT	392	1.952	1.364	1.414	0.796
GHLTMHNSGQNHQT	393	1.938	1.798	1.030	0.586

GSGSSSRPYQNQQT	394	1.934	3.823	0.962	0.496
GILLATPSGQNQQT	395	1.931	8.205	1.341	0.288
GSGQNAGSFNQQT	396	1.928	12.575	1.091	0.286
GSRDGHTVGQNQQT	397	1.928	7.089	0.495	0.661
GSLLISTSGQNQQT	398	1.919	5.763	1.488	0.808
GSGAMP SHGQNQQT	399	1.915	0.000	1.142	0.912
GALVSPISGQNQQT	400	1.912	1.051	0.640	0.347
GSLSSHGVGQNQQT	401	1.911	7.498	1.218	0.804
GSGQNQQASLAMRT	402	1.910	3.577	2.066	1.638
GPGLGSHSGQNQQT	403	1.906	14.563	0.880	1.195
GHDSQHKSQNQQT	404	1.904	6.988	1.154	0.869
GSGLTLSATQNQQT	405	1.901	0.193	0.708	0.340
GSGQVVAHVGNQQT	406	1.901	0.833	0.800	0.321
GSGLRMTTQNQQT	407	1.900	8.939	0.838	0.594
GSGQVGRLLQNQQT	408	1.899	1.762	0.773	0.748
GSGQLSHQSVNQQT	409	1.898	4.032	0.720	0.695
GSGDRYQTLQNQQT	410	1.897	1.075	0.645	0.318
GSGQNQQLKSSAQT	411	1.891	1.197	0.908	0.716
GSGQNQYSIPVAQT	412	1.891	1.194	0.511	0.297
GSGERLHLTQNQQT	413	1.885	1.456	0.387	0.245
GSGHNQQVRTAPNT	414	1.885	1.022	1.006	0.580
GGLSHVMSGQNQQT	415	1.875	0.403	0.885	0.378
GSGQSHRDVLNQQT	416	1.872	15.082	0.138	0.280
GSGQNLAGRMDQQT	417	1.864	0.085	0.362	0.295
GSGQNQQTNRGNPM	418	1.860	3.402	1.349	1.098
GSGQSYQRDHNQQT	419	1.859	8.013	0.779	0.323
GSLLSAGMGQNQHT	420	1.856	6.168	0.589	0.342
GSGQNQQTAIYRNI	421	1.854	2.207	0.818	1.437
GSGQNQQTSGETTNC	422	1.854	8.161	1.040	0.806
GMTSHSVSGQNQQT	423	1.850	2.732	0.220	0.154
GSSQSTGYQPNQQT	424	1.847	3.388	0.522	0.577
GSLKPTTLGQNQQT	425	1.840	0.476	0.175	0.220
GRMFSLGSGQNQQT	426	1.836	8.429	1.630	1.174
GSGQNQQTALGVKC	427	1.835	1.343	1.378	1.014
GAMVSHSSGQNQQT	428	1.833	8.999	0.739	0.868
GSGQNQQRNSDSVT	429	1.829	0.000	1.238	0.842
GSGQSMTLHLNQQT	430	1.827	0.991	0.721	0.248
GSGQVHQAEVNQQT	431	1.825	0.152	0.436	0.287
GSGQNQSQNHLQQT	432	1.825	0.600	1.063	0.772
GSLLTASGQNQQT	433	1.822	0.780	0.938	0.635
GSGLIRTAQNQQT	434	1.822	8.339	0.808	0.998
GSGQNQQTVSRQST	435	1.820	0.472	1.330	0.796
GSGQYANHGINQQT	436	1.820	5.717	0.906	0.701
GSRSTGPSGQNQQT	437	1.819	2.479	0.440	0.466
GRGVQQKLQQNQQT	438	1.817	0.000	1.974	0.823
GSGQNQQVHLSTGT	439	1.811	0.266	1.011	0.455
GSGQNQQLSAKSST	440	1.809	1.567	1.224	1.115
GSGYKAARPQNQQT	441	1.803	0.000	1.418	0.337
GSAGISPSGQNQQT	442	1.797	1.812	0.784	0.622
GSGQNRAHAFLOQT	443	1.795	0.000	1.200	1.271
GSGLSGITMQNQQT	444	1.792	14.796	0.862	0.496
GPMSAHSSGQNQQT	445	1.785	4.392	1.099	0.872
GSSHTQALGQNQQT	446	1.784	0.143	0.882	0.874

GSGVHGVSSQNQQT	447	1.781	4.519	1.504	0.951
GSSGRDMGGQNQQT	448	1.778	2.177	1.052	0.595
GERAFPTSGQNQQT	449	1.775	6.515	0.972	0.362
GGRIVSLSGQNQQT	450	1.766	4.936	1.161	0.847
GSGQNSYSHTSQQT	451	1.765	2.262	1.130	0.658
GLGYPGSSGQNQQT	452	1.763	7.090	0.929	0.577
GSGPQSHTGQNQQT	453	1.757	9.490	0.958	0.447
GSGQNQQLSRDAST	454	1.754	3.716	1.877	0.611
GSGQILHVSVPNQQT	455	1.752	1.316	0.398	0.240
GSGFHTDSRQNQQT	456	1.748	4.384	7.344	0.575
GSGQSHSLATNQQT	457	1.745	2.711	1.021	0.343
GSGQNQQTLSKPWT	458	1.743	0.253	0.845	0.733
GSGHAAISQQNQQT	459	1.742	2.373	1.211	0.520
GSGQNQQQIGGNST	460	1.741	6.169	0.877	0.576
GGGPMAGSGQNQQT	461	1.735	2.815	1.049	0.372
GMRMEYQSGQNQQT	462	1.729	3.695	0.644	0.632
GSGQNQQGTLHQT	463	1.728	2.065	1.347	1.303
GSGQNQRSSGGVQT	464	1.723	2.056	1.805	1.165
GSGQNQRGALATQT	465	1.722	1.117	0.899	0.891
GSGTVHAATQNQQT	466	1.721	1.676	0.563	0.476
GSRMTQQFGQNQQT	467	1.720	25.798	1.233	0.976
GSSSPGASGQNQQT	468	1.717	1.244	1.378	0.660
GHPSPHVSGQNQQT	469	1.713	0.416	0.551	0.488
GSGSHHASRQNQQT	470	1.712	0.451	3.073	0.584
GAVGHSYSGQNQQT	471	1.706	0.808	0.306	0.536
GSRSQYDIGQNQQT	472	1.706	0.112	0.528	0.193
GSGQGPQERGNQQT	473	1.702	1.269	0.846	0.313
GSLAHVGTGQNQQT	474	1.696	1.264	0.837	1.045
GSGQNQQKQNHGNT	475	1.695	5.349	1.538	1.340
GSGQNQQALGSQRT	476	1.695	1.934	1.419	0.562
GSGAITHMPQNQQT	477	1.695	1.681	0.647	0.411
GSGQRNPLLLNQQT	478	1.693	0.144	0.662	0.740
GSSGIPVSHQNQQT	479	1.690	3.384	0.820	0.333
GVHSLTPSGQNQQT	480	1.687	4.104	0.475	0.215
GVIVLHGSGQNQQT	481	1.682	14.166	1.074	1.098
GGTRVVDGSGQNQQT	482	1.676	9.735	0.676	0.370
GSGGVITYQSGQNQQT	483	1.673	7.283	0.649	0.181
GSGQNQAGHGPQT	484	1.670	2.861	1.040	0.887
GSGQLVTSGPNQQT	485	1.669	5.271	0.964	0.433
GSGIAAQRTQNQQT	486	1.665	2.691	1.062	0.754
GSTPAGVGGQNQQT	487	1.663	2.733	0.593	0.477
GSGQNQQTSTGVHS	488	1.660	8.271	1.039	1.075
GSGQIRQLVDNQQT	489	1.657	5.529	0.314	0.272
GSLIGMQSGQNQQT	490	1.656	6.783	0.797	0.392
GSGQIKGKMDNQQT	491	1.654	2.601	1.065	1.012
GSGSDMSSWQNQQT	492	1.651	0.175	0.281	0.303
GRGQNQQHTGLATT	493	1.650	6.174	1.134	0.691
GSGQNQQTLYSSNT	494	1.642	1.044	0.664	0.368
GSGQTQVLKSNQQT	495	1.640	3.031	1.599	0.975
GSRTLSNVGQNQQT	496	1.640	3.219	0.617	0.542
GSGVQHSLPQNQQT	497	1.639	0.764	0.440	0.387
GNYLHQASGQNQQT	498	1.635	1.454	0.816	0.181
GSGGTSVHQQNQQT	499	1.629	0.000	0.585	0.195

GMDHSRPSGQNQQT	500	1.627	3.976	0.918	0.648
GSGQNQQSMGTFTT	501	1.625	0.000	1.792	0.399
GSGQNQQTPLRPPT	502	1.624	0.352	0.874	0.472
GSGQNQHHSVSQQT	503	1.623	3.700	0.605	0.334
GSGQLRSLSTNQQT	504	1.622	6.855	1.310	0.382
GSGSPRQLSQNQQT	505	1.621	0.873	0.520	0.273
GSGQNQQTTASSHT	506	1.618	7.404	0.745	0.678
GRGQVVSTHQNQQT	507	1.607	3.318	0.931	0.561
GSAQVSMVGQNQQT	508	1.601	1.332	0.500	0.285
GSSTLVTIGKNQQT	509	1.592	4.316	0.917	0.819
GFAHQASSGQNQQT	510	1.587	1.852	1.638	1.080
GSGQPVLISISNQQT	511	1.586	2.695	0.390	0.282
GSGQSHRSELNQQT	512	1.585	11.974	0.668	0.256
GSSVGSPIGQNQQT	513	1.584	3.574	1.059	0.706
GSGMPIRNVQNQQT	514	1.584	0.138	0.684	0.631
GSSTRVDSGQNQQT	515	1.584	2.774	0.704	0.660
GSGQNQQTAMRSTT	516	1.581	2.588	0.656	0.665
GSGQNQQHSSSHLT	517	1.581	2.782	1.091	0.859
GSRNGHAVGQNQQT	518	1.574	2.688	0.434	0.939
GLGAYQSSGQNQQT	519	1.574	0.696	1.407	0.688
GPGLSGHSGQNQQT	520	1.571	1.603	1.154	1.297
GSTGIVSSGQNQQT	521	1.570	0.927	2.141	1.046
GSRTTQVIGQNQQT	522	1.570	1.838	0.773	0.564
GSGLLHRAQQNQQT	523	1.569	0.724	1.583	0.646
GSGQNAQQAAAQQT	524	1.568	4.239	0.937	0.604
GSGQNQQSALRTQT	525	1.568	1.913	1.581	1.421
GSGFLSDTRQNQQT	526	1.566	45.953	0.473	0.575
GSGLLYHDQQNQQT	527	1.565	2.760	0.405	0.107
GSGQNQHYSLHKQT	528	1.563	3.399	1.485	1.273
GSGHSPLPQQNQQT	529	1.562	0.556	0.387	0.247
GNGHSMRPNQNQQT	530	1.560	2.341	0.693	0.376
GSGLKWSTLQNQQT	531	1.556	0.000	1.134	2.442
GSGQMGRQAVNQQT	532	1.554	1.529	0.535	0.411
GSGQNQQTSGLVTL	533	1.553	0.000	1.104	0.782
GSGQNQQALHNPHT	534	1.553	0.664	0.638	0.213
GSGQNQQVIPNSKT	535	1.548	1.036	0.844	0.376
GSPLQDRVGQNQQT	536	1.548	0.753	0.469	0.391
GSGQNQYSSSTNPQT	537	1.542	2.251	0.544	0.535
GAMTVTISGQNQQT	538	1.542	6.249	0.443	0.257
GSGQNQQQLQTLIRT	539	1.538	1.425	0.813	0.514
GSGLRQTSQQNQQT	540	1.537	2.067	0.978	0.705
GSGQNQQTGLRQQT	541	1.533	2.120	1.217	1.103
GSGQTRQMKDNQQT	542	1.530	11.079	0.841	0.214
GSGQNHLQSGQQT	543	1.530	4.960	0.938	0.779
GSGQSHRQPENQQT	544	1.529	2.153	0.209	0.159
GSGQDRHIVQNQQT	545	1.527	11.068	0.285	0.162
GSGQNQQLPHSNLT	546	1.521	1.838	0.442	0.283
GSGQLSVPYDNQQT	547	1.521	0.000	0.622	0.111
GSGRNPQTQPLQQT	548	1.519	0.040	0.733	0.573
GSGQPYSTGLNQQT	549	1.519	1.403	0.612	0.376
GSGQNQQTHGGLRD	550	1.519	6.487	1.913	1.298
GAYGMVSSGQNQQT	551	1.518	3.469	0.732	0.773
GSGIQSSYSQNQQT	552	1.517	15.978	1.032	0.684

GPRLSDQSGQNQQT	553	1.511	0.364	0.640	0.579
GSGQNQQTHPS PCT	554	1.510	1.003	1.120	0.546
GSGQSFQMHTNQQT	555	1.504	9.770	0.503	0.325
GSGQNQQTGPNKHT	556	1.504	5.973	1.391	1.139
GFSSAVHSGQNQQT	557	1.502	1.234	0.218	0.210
GSGQNQQTSMSNAT	558	1.501	6.766	1.605	0.745
GSGQDMKQHNNQQT	559	1.501	1.638	0.358	0.239
GLRLSTPSGQNQQT	560	1.498	4.334	0.804	0.522
GSGQNQQTSVYMNT	561	1.498	0.613	0.640	0.983
GSGQNQYSQSSMQT	562	1.494	4.278	0.375	0.309
GSGQNQQSMADHTT	563	1.494	1.728	0.428	0.215
GWERSFVSGQNQQT	564	1.492	0.943	0.490	0.538
GLLAGKSSGQNQQT	565	1.491	2.981	0.999	0.946
GKS FVPQSGQNQQT	566	1.489	2.502	1.798	0.430
GSGQM QSAGSNQQT	567	1.482	0.116	1.034	1.128
GSDQNQR LTSSMQT	568	1.479	0.164	0.875	0.670
GESRAVLSGQNQQT	569	1.476	0.938	0.789	0.368
GSVFGVPSGQNQQT	570	1.474	1.248	0.685	0.213
GSGLPDRNLQNQQT	571	1.471	7.306	1.136	0.611
GSGTHNSAIQNQQT	572	1.469	0.570	0.762	0.574
GSGMIIASMQNQQT	573	1.469	6.722	1.135	0.415
GGITWTD SGQNQQT	574	1.462	4.535	1.472	0.468
GSGQNQQASGRQQT	575	1.458	3.179	0.943	0.991
GSGQNQQPHLKS LT	576	1.457	5.016	1.096	0.740
GPPQHMTSGQNQQT	577	1.457	1.547	0.509	0.677
GSGQNQQASLP SRT	578	1.456	0.389	0.930	0.673
GSGQIVSTQTNQQT	579	1.456	1.103	0.453	0.512
GSGKGHSAGQNQQT	580	1.453	0.936	1.035	1.173
GSGQNTRLQLGQQT	581	1.452	1.747	0.181	0.234
GSVGSRPVGQNQQT	582	1.442	11.363	1.182	0.716
GSSHTLALGQNQQT	583	1.441	7.071	0.851	0.406
GMYEYSQSGQNQQT	584	1.438	0.000	1.410	0.448
GNGQNQQHSILHGT	585	1.435	0.000	0.777	0.415
GSGYNQPHLQNQQT	586	1.435	4.512	0.711	0.395
GPLVNASSGQNQQT	587	1.434	5.239	0.831	0.343
GSGQNQQVLT TART	588	1.434	4.142	1.071	0.948
GSGQNQHSVHNDQT	589	1.428	0.000	0.521	0.515
GAGLIMHSGQNQQT	590	1.425	1.408	0.565	0.511
GMGRHSASGQNQQT	591	1.417	6.500	0.470	0.389
GSHSQSGHGQNQQT	592	1.413	1.240	0.696	0.318
GSSTTIVSGQNHQT	593	1.411	0.000	0.993	0.672
GRHLVTASGQNQQT	594	1.411	2.885	0.648	0.404
GSGQNQQHANLNQT	595	1.410	0.094	0.416	0.544
GSGSTHSKAQNQQT	596	1.410	0.515	0.921	0.801
GSGQNQKMLSGNTT	597	1.410	2.219	1.074	0.404
GSGQVHNPTQNQQT	598	1.410	2.488	1.021	0.542
GSGQNQQIPHVHQT	599	1.409	0.768	0.576	0.218
GSLHAGLSGQNQQT	600	1.408	1.739	1.286	0.936
GPAQHGTSGQNQQT	601	1.407	0.866	1.030	0.615
GEKAVTSSGQNQQT	602	1.402	0.998	0.558	0.327
GSGQNQQTMANGQR	603	1.394	0.216	1.169	1.230
GSGSPHSDKQNQQT	604	1.394	0.000	2.041	4.680
GSFSMGYGGQNQQT	605	1.393	18.476	1.908	1.030

GSGTHLVSLQNQQT	606	1.392	0.000	0.715	1.167
GSGQMOPHVQNQQT	607	1.389	9.381	0.387	0.153
GSGQNQQVAGLNNT	608	1.386	3.218	0.449	0.492
GSSQNQQHDMRLRT	609	1.386	2.645	0.669	0.552
GPASLPISGQNQQT	610	1.386	9.008	0.312	0.155
GSGQNQQPPLATRT	611	1.386	2.295	0.593	0.287
GSSRVPVSGQNQQT	612	1.385	13.191	0.870	0.485
GSGQNQQTNLGHTT	613	1.383	1.523	1.343	1.281
GSGQNQQLVSRVQT	614	1.381	1.195	0.656	0.466
GPNSYPVSGQKQQT	615	1.381	4.040	0.736	0.834
GHAHYQASGQNQQT	616	1.377	7.299	0.803	0.745
GSGQALLSTGNQQT	617	1.377	0.847	0.536	0.370
GSGQLPRQMTNQQT	618	1.376	3.550	0.400	0.562
GSGFPKSTEQNQQT	619	1.376	2.058	0.610	0.194
GSRETSLSGQNQQT	620	1.373	5.193	1.364	0.203
GSGQNQQGTGVSH	621	1.371	4.295	1.417	0.749
GSRTVPVYGQNQQT	622	1.371	0.363	1.226	0.969
GSNAQSAHGQNQQT	623	1.371	0.888	0.976	0.245
GAFLAASGQNQQT	624	1.369	18.165	0.994	0.775
GSGQYRSSSDNQQT	625	1.369	6.209	0.681	0.409
GSGQVYISTPNQQT	626	1.367	0.000	0.859	0.282
GSGVSTQLLNQQT	627	1.367	2.467	0.928	0.509
GSGQLGLSVTNQQT	628	1.364	6.906	1.395	0.376
GSGSNMRLSQNQQT	629	1.363	0.588	0.962	0.730
GSGQNLHSGLPQQT	630	1.363	1.594	1.054	0.592
GSSHTLALGQNKQT	631	1.362	2.160	0.838	0.643
GSGQNQHSLPAHRT	632	1.361	0.700	0.911	0.742
GSGQNQGTVPYNT	633	1.358	7.648	0.835	0.815
GSGQNQQPSLRQST	634	1.356	2.905	1.315	0.554
GSGQNARLKDQQT	635	1.354	2.395	0.580	0.938
GHAGSTGSGQNQQT	636	1.352	2.829	1.332	1.233
GSGQALSSSGNQQT	637	1.351	6.860	0.894	0.931
GSGASESHRQNQQT	638	1.350	0.850	0.325	0.313
GVGVITSSGQNQQT	639	1.348	0.918	1.296	0.777
GSLYGQSLGQNQQT	640	1.348	11.248	0.894	0.843
GSGQMSDVHGNQQT	641	1.346	7.172	0.408	0.548
GSGQNQQHSSKATT	642	1.345	12.248	1.350	1.401
GSGQNQQTSVSQQT	643	1.342	1.614	1.030	0.913
GSGQKMWKLDNQQT	644	1.341	0.000	0.990	1.418
GSGQNVSMQVNQQT	645	1.341	0.000	0.357	0.251
GSGQNQRATLSNQ	646	1.339	1.084	0.947	0.723
GSGQASSKSANQQT	647	1.339	1.138	0.500	0.175
GSGKNQTPIPKGQT	648	1.339	5.077	1.306	1.154
GSGQNQQTRQEGST	649	1.339	0.000	0.645	0.718
GASSLATSGQNQQT	650	1.337	0.703	0.423	0.217
GSGQRGSLTENQQT	651	1.337	2.482	0.300	0.567
GSEQTRQRGQNQQT	652	1.333	2.172	0.574	0.815
GSGQNQQTLTASKE	653	1.333	1.152	0.981	1.172
GSGTSGKTGKNQQT	654	1.333	4.033	0.358	0.676
GQLVTFSTSGQNQQT	655	1.331	11.282	0.819	0.294
GSGQNQQSANKILT	656	1.331	3.789	0.894	1.236
GSGQNQQHSSHTT	657	1.328	2.158	0.957	0.452
GSGQNQKGMQPNQT	658	1.326	3.139	0.775	1.059

GSGQLVSGLYNQQT	659	1.325	0.000	0.842	0.733
GSSVGVPSTGQNTQT	660	1.322	4.867	0.336	1.157
GSGQNTQWDSRRQT	661	1.321	0.531	1.059	0.825
GSEQTRQSGQNTQT	662	1.321	0.514	0.734	0.900
GSGIGSHIPQNTQT	663	1.319	0.173	0.822	0.597
GSGQNTQRLHGVDTQT	664	1.318	4.655	0.459	0.341
GEVSRVLSGQNTQT	665	1.318	0.437	1.150	0.440
GSGQNTQKVSPLLT	666	1.314	1.602	0.755	0.806
GSGLALERSQNTQT	667	1.311	0.486	0.618	0.096
GPDRIGSSGQNTQT	668	1.308	0.426	0.654	0.342
GSGQNTQDHQNKQQT	669	1.308	1.470	0.510	0.761
GSGQNTQTALYNNT	670	1.307	0.862	0.660	0.726
GSGAVHLTAQNTQT	671	1.306	1.668	0.541	0.466
GSLVSTQSGQNTQT	672	1.305	1.293	1.282	0.650
GSGVSARMVQNTQT	673	1.299	0.624	0.870	0.697
GSGQTRMPLAQNTQT	674	1.296	0.790	0.447	0.273
GSGISSRNMQNTQT	675	1.291	6.328	1.671	0.560
GSGEKVHSGQNTQT	676	1.289	0.062	0.862	0.671
GSGQNTQKLSSMST	677	1.286	1.586	1.160	1.052
GSGQNTQTGHMRV	678	1.286	4.161	1.839	1.635
GSGMIHTTAQNTQT	679	1.285	0.105	0.678	0.276
GSGQNTWPALKGQQT	680	1.284	2.031	1.101	1.222
GASHMSISGQNTQT	681	1.284	0.462	0.404	0.374
GSDQNTQLGYSKQT	682	1.283	0.000	0.853	0.660
GIPSIRESGQNTQT	683	1.282	0.166	0.484	0.254
GSGIPSVKFQNTQT	684	1.281	0.061	0.364	0.561
GSGQNTQTSVSNV	685	1.281	0.750	0.788	0.715
GSGQNTQIGESRMT	686	1.279	0.103	0.890	0.453
GSGSSMSFQNTQT	687	1.279	0.540	0.466	0.095
GSGQKQERAVSKQT	688	1.277	0.000	1.174	0.732
GCTTRLNSGQNTQT	689	1.276	0.000	0.184	0.618
GSGQNTQIISTKIT	690	1.275	0.000	0.951	0.710
GSGQNTQKSLNGNT	691	1.275	8.573	0.586	0.851
GSGIPAPRLQNTQT	692	1.273	4.162	0.583	0.396
GSGQIRESMGNTQT	693	1.270	1.676	0.833	0.523
GSGQNTSGVHFNTQT	694	1.268	0.587	0.871	0.377
GSGQNTIGHSLPQQT	695	1.264	6.183	0.740	0.478
GSGERSISVQNTQT	696	1.264	1.619	0.598	0.173
GSGLPKNVLQNTQT	697	1.263	0.975	0.701	0.268
GSGQVAYAQNTQT	698	1.259	1.309	0.734	0.313
GSGQSSYSGNTQT	699	1.257	1.686	1.161	0.456
GSGQNTQAMTHGDTQT	700	1.257	1.878	0.357	0.259
GSGQNTQALVSMGQT	701	1.255	1.876	0.987	0.560
GSGQNTQPSFMRGQQT	702	1.252	1.454	1.293	1.094
GSGQNTQQSHLRTNT	703	1.251	4.583	1.022	0.718
GYTRLETSGQNTQT	704	1.250	1.323	0.841	0.297
GSGQSYDMRGNTQT	705	1.248	0.567	0.588	0.368
GSRTTQDIGQNTQT	706	1.247	0.000	0.685	0.280
GSGHPYKAAQNTQT	707	1.246	0.000	0.872	0.507
GRLSNAHGGQNTQT	708	1.245	0.839	1.036	0.725
GSGQNTQRAVLNDQT	709	1.242	3.023	0.556	0.259
GGSHTYGGGQNTQT	710	1.241	13.065	0.982	0.730

GSSVNSMIGQNQQT	711	1.239	0.000	0.976	0.580
GNSSMMGSGQNQQT	712	1.239	3.856	0.656	0.364
GNRDRPSSGQNQQT	713	1.239	3.947	0.298	0.178
GSGNMHASRQNQQT	714	1.238	3.878	0.782	0.687
GFI FPKVSGQNQQT	715	1.237	0.000	1.764	0.692
GSGQNQQLKNSTST	716	1.235	1.703	1.063	0.538
GSGQNQQSQYMPRT	717	1.234	0.401	0.549	0.520
GSGQRMADIGNQQT	718	1.233	2.539	0.352	0.427
GSGQNQSHYPSQQT	719	1.228	4.315	0.644	0.402
GSDGKMHRGQNQQT	720	1.227	0.000	1.826	0.776
GSGSVGFIGQNQQT	721	1.227	8.261	0.689	0.445
GLHGMTLSGQNQQT	722	1.226	3.552	0.470	0.338
GSDQSKRGDSNQQT	723	1.225	0.639	0.479	0.267
GSLFLATGGQNQQT	724	1.220	0.000	0.775	0.485
GSGQNQQPSAFSKT	725	1.220	4.906	1.309	0.754
GSGQLPQSGLNQQT	726	1.218	1.504	0.641	0.318
GSGSKQNALQNQQT	727	1.216	2.010	0.941	0.594
GSGQRRELSQNQQT	728	1.215	1.791	0.622	0.396
GSGQREP KASNQQT	729	1.214	2.793	0.399	0.520
GSGQNQQHPSTQQT	730	1.205	1.552	1.017	0.680
GSQSTLGLGQNQQT	731	1.204	3.246	0.594	0.400
GSGQNQQMPGLSST	732	1.204	1.887	0.234	0.181
GSGQNQQTVGGKNL	733	1.203	0.128	0.777	1.051
GSSREFHSGQNQQT	734	1.203	1.591	0.688	0.474
GSGQNQQTVPSNLV	735	1.201	0.791	0.434	0.281
GSGQNAYSSQAQQT	736	1.201	12.096	0.629	0.216
GSGQNKDHS TRRQT	737	1.197	0.000	0.384	0.477
GQLGSVSGSQDQQT	738	1.196	0.000	1.020	0.437
GSGQHAAPGHNQQT	739	1.195	5.999	0.600	0.199
GSGQNQQTSQSPPT	740	1.194	1.208	0.851	0.478
GSGNYRDHEQNQQT	741	1.193	7.389	0.287	0.222
GSGQHSNQHVQNQQT	742	1.192	1.453	0.955	0.558
GSGQTARNGINQQT	743	1.192	2.030	1.002	0.472
GSGQNQQHYGSQGT	744	1.189	0.453	1.345	0.379
GSGSPQASRQNQQT	745	1.189	6.782	0.923	0.542
GSGFHSMSGKNQQT	746	1.188	9.809	1.381	0.611
GSGQSHSLETNQQT	747	1.188	1.319	0.520	0.363
GTEQTRQSGQNQQT	748	1.188	0.132	0.756	0.756
GSGRHLASVQNQQT	749	1.187	1.024	0.654	0.606
GLGSKNHS GQNQQT	750	1.187	5.046	0.825	0.224
GSGQNQQTSHFP SA	751	1.185	0.325	0.969	0.907
GSGQLSGTPQNQQT	752	1.185	1.382	1.025	0.643
GSGQNQQAPHKKET	753	1.180	0.598	0.994	0.689
GSGQNQQTLRGSLE	754	1.179	1.812	0.853	0.354
GSIAMTSHGQNQQT	755	1.178	1.435	0.551	0.438
GSPGVSPSGQNQQT	756	1.178	3.006	0.853	1.160
GSGQNQQTGSSSRV	757	1.176	0.580	0.995	1.128
GSGQHLPLLGQNQQT	758	1.175	1.739	0.519	0.347
GSDHSHRGGQNQQT	759	1.174	0.504	0.818	0.331
GSGIVTKLGQNQQT	760	1.174	10.571	0.599	0.242
GSGQDVTKTGNQQT	761	1.173	4.523	0.531	0.035
GSGQNQQSHGRIGT	762	1.173	5.117	0.607	0.455
GSGQNQQINHRSP T	763	1.173	0.748	0.259	0.220

GSGDDSRVGQNQQT	764	1.172	0.191	0.466	0.156
GSGQSTLKRINQQT	765	1.168	13.442	0.534	1.184
GSGSQHSKAQNQQT	766	1.168	0.312	0.638	0.916
GSGQNQQHASSNNT	767	1.166	7.155	0.789	0.896
GSRTYQVSGQNQQT	768	1.164	1.853	0.638	0.641
GSGQNQGLLSSPQT	769	1.164	0.000	0.707	0.417
GSGGGLQHNQNQQT	770	1.163	4.098	1.137	0.778
GSGQNQQTTAATRM	771	1.163	3.925	0.947	1.005
GSGQNQRASILVQT	772	1.162	3.632	0.531	0.569
GSGQNGLLGAQQT	773	1.161	1.458	0.524	0.226
GSLDLGRSGQNQQT	774	1.160	3.283	1.002	0.505
GNSQVKVSGQNQQT	775	1.158	4.930	1.422	0.728
GSSGSHQYGNQQT	776	1.155	0.000	1.129	0.794
GSGQNQQQRDGTLT	777	1.152	0.387	0.760	0.730
GRGQHVS VANNQQT	778	1.152	1.896	1.032	0.589
GDSSSRISGNQQT	779	1.151	3.787	0.916	0.348
GSGQNQQHSLSSQT	780	1.150	3.844	0.700	0.730
GSLMDVHRGNQQT	781	1.150	0.387	1.009	0.238
GSIQYQSSGNQQT	782	1.147	2.601	1.074	1.191
GLGSKNP SGQNQQT	783	1.147	1.629	1.184	0.424
GSGQLVLT LQNQQT	784	1.143	0.000	0.336	0.336
GSGQNQQTSQPLPG	785	1.141	0.080	0.748	0.530
GSGQNQQNLGKLNT	786	1.141	0.000	0.919	0.687
GTTAHQPSGNQQT	787	1.138	0.211	0.726	0.275
GSGQNRAQIGTQQT	788	1.138	0.469	0.776	0.654
GSGQYVHVSSNQQT	789	1.137	1.803	0.739	0.366
GSGQNQQTAHAFNI	790	1.132	3.404	0.699	0.729
GSGQNQR TMVATQT	791	1.130	1.122	0.649	0.554
GSGQNPIRGAMQQT	792	1.126	1.327	1.296	0.427
GSGYVITGSQNQQT	793	1.125	6.271	0.971	0.248
GRGPKQSNIQNQQT	794	1.125	0.737	0.771	2.490
GSGQNQQTMLGKPC	795	1.125	0.047	1.090	0.992
GSGQNQQVGSTVRT	796	1.124	2.040	0.918	0.614
GNVTTQKSGQNQQT	797	1.122	2.546	1.215	0.922
GSGNPFVSHLQNQQT	798	1.121	1.037	0.583	0.310
GSLSHMESGNQQT	799	1.120	0.829	0.489	0.265
GRAPTNLSGQNQQT	800	1.118	0.687	0.757	0.169
GSGQNQQTVMTARA	801	1.117	1.535	0.995	0.843
GSGMPASRLQNQQT	802	1.117	1.689	0.790	0.372
GVVRNHQSGQNQQT	803	1.116	5.801	0.899	0.868
GSGQNQHSVQVRQT	804	1.116	1.909	0.782	0.916
GSGQNTGHLTMQQT	805	1.114	0.078	1.026	0.595
GSGQNQQYAGKILT	806	1.112	0.300	1.078	0.431
GSGNPHVRNQNQQT	807	1.112	0.873	0.732	0.755
GSGQNGGSSNRQQT	808	1.109	2.594	1.255	0.844
GSGQRLSQGVNHQT	809	1.108	3.394	0.931	1.141
GSGQNAHAKEGQQT	810	1.108	0.000	0.875	1.179
GSSPAPNSGNQQT	811	1.106	2.229	0.719	0.368
GLAHKTSSGNQQT	812	1.106	0.915	0.427	0.690
GSGQNQQTPGAHKT	813	1.105	3.827	0.957	0.277
GSGQNQQSLSGSFT	814	1.105	0.735	0.745	0.883
GSGQNQQSTGTSRT	815	1.103	4.054	1.209	0.935
GSGQNQQTVQSNLV	816	1.103	2.350	0.577	0.698

GSGQNQQLGSRQCT	817	1.102	0.183	0.987	0.407
GSGQNQYLRLELQT	818	1.101	0.000	0.416	0.839
GSGQNQQTSPRLQT	819	1.100	0.795	1.156	1.091
GSGQNQQTSSNMT	820	1.099	0.569	0.638	0.698
GTASTYNSGQNQQT	821	1.099	2.560	0.250	0.625
GSGQNQQTMPQHKE	822	1.097	2.394	0.479	0.197
GSGQSHLHTGNQQT	823	1.096	2.584	0.721	0.295
GVKGVGHSGQNQQT	824	1.096	2.485	0.994	0.783
GSGKVTKQSQNQQT	825	1.095	0.000	0.928	1.035
GSGQNQQTALEKSL	826	1.092	0.000	0.625	0.702
GSGYKDTYGQNQQT	827	1.091	0.854	0.717	0.448
GSGQNQQSGTFLST	828	1.090	5.673	1.021	0.742
GSGQNTGQHMMQQT	829	1.090	1.058	1.147	0.917
GSGKNQQRPGLDQT	830	1.089	1.557	0.583	0.385
GSGQSREISLNQQT	831	1.088	6.954	0.594	0.282
GTPTSPSSGQNQQT	832	1.086	4.558	0.833	0.662
GKPAGGLSGQNQQT	833	1.085	2.805	0.708	0.739
GSGQNHRSDMQQT	834	1.084	12.001	0.417	0.212
GSGQNQQTLPLSL	835	1.084	1.758	0.527	0.175
GSPYMGATGQNQQT	836	1.083	5.364	0.918	0.254
GSGHAKAVGQNQQT	837	1.081	4.357	0.703	0.824
GHMKGVTSGQNQQT	838	1.081	2.814	0.807	0.413
GSGQNQQKILTLDT	839	1.080	0.371	0.291	0.314
GSGQNQQTKVGHSA	840	1.079	1.256	0.669	1.019
GIARTTISGQNQQT	841	1.078	1.783	0.819	0.330
GSGQNQQTSVGFRT	842	1.077	3.737	0.648	0.534
GSGQNQQTMLANIR	843	1.076	0.000	0.379	0.458
GDMTRSSSGQNQQT	844	1.075	0.802	1.145	1.038
GSGHMSDLRQNQQT	845	1.073	4.291	0.555	0.328
GRGAVMASGQNQQT	846	1.072	0.923	0.783	0.605
GSGQNQQLSGKSVT	847	1.070	1.524	1.276	0.930
GSHTLVVSGQNQQT	848	1.069	1.535	0.671	0.748
GSGPWSAGLQNQQT	849	1.067	0.947	0.700	0.539
GSGQHSFHALNQQT	850	1.064	1.412	0.885	0.573
GSGQNQQPNSSGSM	851	1.064	0.925	0.588	0.339
GSGLAHLGGQNQQT	852	1.064	2.191	0.749	0.794
GSSVRYEPKQNQQT	853	1.063	1.564	0.450	0.501
GSGQNQQARPLELT	854	1.061	0.059	0.389	0.252
GSGQPRSTGINQQT	855	1.061	0.693	0.650	0.542
GSGQNQANWVKVQT	856	1.059	0.126	0.683	0.532
GSGHLFQSGQNQQT	857	1.057	0.615	0.751	0.386
GSGQNRGISISQQT	858	1.057	2.166	0.686	0.566
GSGTHYDNRQNQQT	859	1.054	0.072	0.612	0.486
GSGQNQQTSTTPLP	860	1.052	2.823	0.828	0.741
GSGQVHASQVNQKT	861	1.049	0.503	0.855	0.767
GSSGHRESGQNQQT	862	1.048	4.398	0.641	0.691
GLSAEKSSGQNQQT	863	1.047	7.203	0.629	0.303
GSGQEHRSLSANQQT	864	1.046	0.000	0.507	0.344
GSGQTVVRIANQQT	865	1.046	4.156	0.661	0.390
GSGQNVS SVHRQQT	866	1.045	0.712	0.383	0.271
GSGASRMSIQNQQT	867	1.045	0.111	0.801	0.417
GVAFIGSSGQNQQT	868	1.043	0.000	0.744	0.648
GSGQNQQTVPTROT	869	1.040	1.207	0.629	0.138

GSGQAAKSSQNQQT	870	1.036	0.681	0.778	0.737
GSGQNQQVAIRTST	871	1.035	2.447	0.963	0.370
GSVHMQNAGQNQQT	872	1.034	3.608	1.004	0.625
GSGMRQAGVQNQQT	873	1.032	0.811	0.736	0.775
GSGQNQQVGGKTVT	874	1.032	6.195	1.094	0.821
GVHDMRVSGQNQQT	875	1.032	8.083	1.171	0.818
GSGQHVSVANNNQQT	876	1.029	5.734	0.974	0.577
GSAAMSVRGQNQQT	877	1.029	2.386	0.202	0.287
GVSRGGPSGQNQQT	878	1.028	1.611	0.750	0.591
GSGQMVTIGNQQT	879	1.026	1.328	0.406	0.430
GRGGSMAETQNQQT	880	1.024	2.853	0.799	0.669
GSGHTNPTRQNQQT	881	1.021	0.688	0.726	0.807
GSGEAARYEQNQQT	882	1.020	0.000	0.107	0.125
GSGQNERHLVLQQT	883	1.019	5.354	0.416	0.150
GSGQNQQSKQQVLT	884	1.019	1.494	1.428	1.256
GSGQARAHRGQNQQT	885	1.017	0.000	0.254	0.386
GSGQNQQPLDTSRT	886	1.015	0.775	0.491	0.376
GSGQNQQLANMVT	887	1.014	1.739	1.253	0.987
GSGQMKDLHRNQQT	888	1.014	1.068	0.587	0.506
GSGQNQHLSFVQT	889	1.013	0.110	1.090	0.364
GSGQNQQPSSRVTT	890	1.012	2.179	0.784	0.504
GSGQNQQLAITLGT	891	1.011	0.000	0.877	0.143
GSGQNQQTVGNPAT	892	1.008	3.014	0.856	0.395
GSGQNQGRAHPMQT	893	1.007	2.364	0.684	0.453
GSGQLIASVVNNQQT	894	1.005	0.086	0.197	0.359
GSSVRSVLVGQNQQT	895	1.004	3.840	0.412	0.608
GGAGSAHSGQNQQT	896	1.003	6.108	0.474	1.092
GSDQNQQTMSSTRT	897	1.003	2.428	1.306	0.835
GSGQNQQMAGAFRT	898	1.003	1.784	1.307	0.762
GSLGNLQRGQNQQT	899	1.003	0.895	0.947	0.385
GSGPSISHGQNQQT	900	1.000	0.000	0.614	0.665
GSGQNQQT	6406	1.000	1.000	1.000	1.000
GSGQNQQSSFNVT	901	0.998	0.000	1.307	0.675
GSGQNQQTGQATHN	902	0.996	2.199	0.877	0.527

[0494] A second cross-species evolution screen was performed using an AAV capsid variant library with a modification in loop IV introduced as described above and passaging it once through NHPs (passage 1) and then subsequently injected it into two different strains of mice (passage 2), C57Bl/6 and BALB/c. The fold-enrichment for each variant in the brain of each mouse species was calculated by systematic NGS enrichment analysis following RNA recovery and RT-PCR amplification. The fold enrichment values in the second passage in mice were compared to those fold enrichment values from the second pass that was performed in NHPs as described above. As shown in **Table 10**, when comparing the second pass fold enrichment values in the mice versus NHPs, 12 variants were identified that had a fold-enrichment value greater than 10 in all three animal groups. Further, 10 of these 12 variants comprised the SPH motif and a positive residue in one of the next three subsequent residues (**Table 10**).

Table 10. NGS fold-enrichment of AAV capsid variants from a second passage (P2) in NHPs or mice (C57Bl/6 or BALB/c) following a first passage in NHPs

Peptide Sequence	SEQ ID NO:	Fold enrichment over AAV9 in NHP P2	Fold enrichment over AAV9 in BALB/c P2	Fold enrichment over AAV9 in C57Bl/6 P2
VSGSPHKAQNQQT	903	99.76	92.99	34.29
CSGSPHKAQNQQT	904	85.1	66.74	22.19
GSGSPHKAQNQQT	200	56.33	44.58	14.48
GSGSPHRKAQNQQT	905	46.39	42.47	14.11
GRGSPHKAQNQQT	906	43.68	59.65	28.13
GHDSPHKSGQNQQT	201	33.96	59.14	27.15
GSGSPHSAKKNQQT	208	31.27	41.51	14
GSGSPHKAQNKQT	907	29.52	44.1	13.69
GSGSPHKAQTQQT	908	24.27	41.75	18
GQDSPHKSGQNQQT	204	22.7	32.37	16.02
GSGSTHASRQNQQT	909	11.04	23.71	10.67
GHDSQHKSGQNQQT	404	10.36	21.3	13.55

[0495] Following the second passage in mice, a synthetic library was generated using those variants that demonstrated a fold-change in enrichment relative to wild-type AAV9 that was above 10 in the brain of either strain of mice, as measured by systematic NGS enrichment analysis following RNA recovery and RT-PCR amplification. There were approximately 500 variants in this synthetic library. This synthetic library was then injected back into both strains of mice (C57Bl/6 and BALB/c; passage 3). RNA was recovered from the mouse brains, RT-PCR amplification was performed, and fold-enrichment relative to wild-type AAV9 was calculated by NGS analysis, which is provided in **Table 11**. As shown in **Table 11**, the variants with the greatest fold-enrichment in the brain in each strain, were highly correlated across strains ($R^2=0.8458$).

Table 11. NGS fold-enrichment of AAV capsid variants in the brain from a third passage (P3) in mice (C57Bl/6 or BALB/c) following a first and second passage in mice

Peptide Sequence	SEQ ID NO:	Fold enrichment over AAV9 in BALB/c	Fold enrichment over AAV9 in C57Bl/6	Average
GSGSPHKEYGQNQQT	910	150.445	103.488	126.966
GSGSPHKFGQNQQT	911	73.364	60.304	66.834
GHDSPHKSGQNQQT	201	82.460	51.125	66.792
GSGSPHKAQNQQT	200	60.312	65.853	63.083
VSGSPHKFGQNQQT	912	60.186	59.142	59.664
GSGSPHKAQNHQT	913	63.486	51.647	57.566
VSGSPHKAQNQQT	903	73.555	37.429	55.492
GQDSPHKSGQNQQT	204	63.898	43.752	53.825
GSGSPHKAQHQQT	914	45.309	45.600	45.454
GSGSPHKTYQNQQT	915	50.283	35.460	42.871
GSGSPHKAQTQQT	908	43.120	39.098	41.109
VSGSPHASRQNQQT	916	46.572	32.480	39.526
GSGSPHKAQNKQT	907	39.848	35.596	37.722

GSGSPHKFGKNQQT	917	31.948	34.899	33.423
GSGSPHASRQNQHT	918	28.145	30.928	29.537
GSHSPHKSGQNQQT	919	22.948	35.412	29.180
GSGQNQQRMSPT	920	4.576	53.520	29.048
GSGSPHASRQNQQT	205	28.866	29.139	29.003
GSGSPHSKPQNQQT	921	26.958	28.599	27.779
GSGSPHKFGQKQQT	922	39.597	14.927	27.262
VSGSPHGARQNQQT	923	30.985	22.634	26.810
GSGSPHSAQKQQT	924	25.052	27.459	26.256
GHSSPHRSGQNQQT	212	16.982	35.081	26.032
GSGSPHSAKNQQT	208	21.069	25.711	23.390
GSHSPHKGQNQQT	925	24.054	20.262	22.158
GRGSPHSAQNQQT	906	20.939	22.720	21.830
GQSSPHRSGQNQQT	229	9.916	26.608	18.262
GSGQNRQRLKGLT	926	3.937	31.022	17.480
GSGSPHKLGNQQT	927	18.905	14.732	16.818
GSGSPHKTSKNQQT	928	14.654	17.606	16.130
GSGSPHKIGQNQQT	929	16.999	14.794	15.897
GSGSPHKKNQNQQT	209	25.633	5.605	15.619
GSGSPHASRQNKQT	206	10.738	20.347	15.542
GSGSPHTRGQNQQT	214	16.899	13.869	15.384
GSGQDSPHVRNQQT	930	15.340	14.646	14.993
GSGSPHKTSQNQQT	931	20.428	8.818	14.623
GSGSPHASRKNQQT	932	13.799	12.749	13.274
GSGSPHASRQKQQT	211	13.624	11.188	12.406
GSHSPHKSGQKQQT	933	6.700	17.736	12.218
GSGSPHKTSQKQQT	934	12.621	11.720	12.170
GSGSPHVRGQNKQT	935	13.174	11.017	12.095
GSGSPHKTTQNQQT	936	9.722	13.381	11.552
CSGSPHSAQNQQT	904	11.772	9.447	10.610
GSGPVRLRQNQQT	937	3.369	17.431	10.400
GSGSPHVRGQKQQT	938	7.573	12.498	10.036
GSGSPHRKAQNQQT	905	12.308	7.349	9.828
GRGSPHASRQNQQT	318	11.903	6.780	9.342
CSGSPHKTSQNQQT	939	11.167	6.631	8.899
CSHSPHKSGQNQQT	940	11.356	6.304	8.830
GSGSPHSDKQNQQT	604	3.492	10.236	6.864

[0496] Taken together, these results demonstrate that after 3 rounds of screening of this AAV9 variant library with loop IV modifications in NHP and mice, many AAV capsid variants outperformed the wild-type AAV9, for example, in penetration of the blood brain barrier (BBB) and spinal cord expression. These capsid variants were able to cross-species, evidenced by expression and tropism in the NHP brain/spinal cord as well as in the brain of two different mouse species.

Example 2. Individual Capsid Characterization in Mice

[0497] The goal of these experiments was to determine the transduction level, tropism, ability to cross the blood brain barrier, and overall spatial distribution in the central nervous system (CNS) of 2

capsid variants selected from the study described in Example 1 relative to AAV9 following intravenous injection in mice. The 2 capsid variants were TTM-001 (SEQ ID NO: 981 (amino acid) and 983 (DNA), comprising SEQ ID NO: 941) and TTM-002 (SEQ ID NO: 982 (amino acid) and 984 (DNA), comprising SEQ ID NO: 2), as outlined in Table 3 above. The amino acid and DNA sequences of TTM-001 and TTM-002 are provided, e.g., in Tables 4 and 5, respectively.

[0498] AAV particles were generated with each of these capsid variants encapsulating a luciferase-EGFP transgene driven by a CMV/chicken beta actin promoter in a single stranded viral genome. Each capsid variant and AAV9 control were tested by intravenously administering by tail vein injection, the AAV particle formulation at 5×10^{11} VG/dose (2.5×10^{13} vg/kg) to three female BALB/c mice. The in-life period was 28 days and then various CNS and peripheral tissues were collected for measuring transgene mRNA, transgene protein, and viral DNA (biodistribution).

[0499] At 28 days post-injection of the AAV particles encapsulated in the TTM-001 capsid variant (AAV_TTM-001), mice were injected with luciferin and their brains were harvested for IVIS imaging. Robust luciferase signal was observed in mice injected with AAV particles encapsulated in the TTM-001 capsid variant, and this was greatly increased relative to AAV particles encapsulated in the wild-type AAV9 control capsid.

[0500] The brains isolated from mice injected with the AAV particles encapsulated in the TTM-001 capsid variant (AAV_TTM-001) or the TTM-002 capsid variant (AAV_TTM-002) were assayed by qPCR for the presence of transgene RNA as a measure of transgene expression, and the presence of viral DNA as a measure of viral genome levels. Data were provided as fold over AAV9 (**Table 12**). As shown in **Table 12**, when compared to the wild-type AAV9 capsid control, TTM-001 and TTM-002 demonstrated a 30-fold and 66-fold increase, respectively, in transgene mRNA levels and expression in the brain, indicative of enhanced payload delivery. This correlated with a 32-fold (TTM-001) and 47-fold (TTM-002) increase, respectively, in viral genome (DNA) concentrations in the brain relative to the AAV9 capsid control, which is indicative of enhanced CNS tropism and transduction (**Table 12**).

Table 12. Transgene mRNA and viral genome levels (DNA) in mice relative to the AAV9 control

Measure	Tissue	AAV9	TTM-001	TTM-002
mRNA (transgene expression)	Brain	1.0	30.4503	66.2161
DNA (viral genome quantification)	Brain	1.0	32.0315	47.2810
mRNA (transgene expression)	Liver	1.0	1.2356	0.2016
DNA (viral genome quantification)	Liver	1.0	0.4802	0.0277

[0501] The brain tissues and spinal cords of the mice were also subjected to anti-GFP immunohistochemistry staining to evaluate overall CNS tropism and biodistribution. Immunohistochemical staining correlated with the qPCR analysis, as TTM-001 and TTM-002 showed significantly stronger staining and payload expression in the brain and spinal cord, as compared to the AAV9 control. More specifically, TTM-001 and TTM-02 demonstrated localization and strong

payload expression and transduction in the mid-brain region, with increased staining observed in the hippocampus and thalamus, as well as in the brain stem, compared to AAV9. Less staining was observed in the cortical regions of the brain compared to the midbrain. However, staining in these cortical regions was stronger for TTM-001 and TTM-002 compared to the AAV9 control. It also appeared that the TTM-001 and TTM-002 capsid variants were able to transduce non-neuronal cells, including glial cells and oligodendrocytes. With respect to the spinal cord, staining and payload expression for TTM-01 and TTM-002 were localized to the ventral horns of the grey matter.

[0502] Peripheral tissues were also isolated from the mice intravenously injected with the AAV particles encapsulated in the TTM-001 capsid variant or the TTM-002 capsid variant for analysis by qPCR and/or GFP immunohistochemical staining. Transgene mRNA levels and viral genome DNA levels were quantified in the liver by qPCR and the fold over AAV9 was calculated for each capsid variant (**Table 12**). TTM-001 resulted in similar levels of payload expression (mRNA levels) as compared to wild-type AAV9, but only half as much viral genome DNA was quantified in the liver compared to AAV9. TTM-002 demonstrated greatly reduced mRNA and viral genome DNA levels in the liver compared to AAV9. GFP immunohistochemical staining of the spleen, heart, skeletal muscle, kidneys, and lungs of mice injected with AAV particles encapsulated in the TTM-001 capsid variant or the TTM-002 capsid variant showed similar levels of payload expression as compared to those mice injected with AAV particles encapsulated in the wild-type AAV9 control capsid.

[0503] Taken together, these data demonstrate that TTM-001 and TTM-002 are enhanced CNS tropic capsids in mice that can infect non-neuronal cells. Additionally, these capsid variants were able to successfully penetrate the blood brain barrier following intravenous injection.

Example 3. Maturation of TTM-001 and TTM-002 Capsid in Mice

[0504] This Example describes maturation of the TTM-001 (SEQ ID NO: 981 (amino acid) and 983 (DNA), comprising SEQ ID NO: 941) and TTM-002 (SEQ ID NO: 982 (amino acid) and 984 (DNA), comprising SEQ ID NO: 2) capsid variants to further enhance their transduction and biodistribution in the central nervous system and evolve the AAV capsid variants to provide further cross-species compatibility. Two approaches were used to mature the TTM-001 and TTM-002 capsid sequences in order to randomize and mutate within and around the peptide insert comprised within loop IV of the capsid variant. As many of the AAV capsid variants that demonstrated the greatest fold-enrichment in the NHP brain relative wild-type AAV9 comprised an SPH motif in the same position (e.g., immediately subsequent to position 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138) (see **Example 1**), the SPH motif was not mutated in either approach to mature the TTM-001 and TTM-002 capsid variants. In the first maturation approach, sets of three contiguous amino acids were randomized across the mutagenesis region in the TTM-001 and TTM-002 sequences, which spanned from position 450 to position 466, numbered according to SEQ ID NO: 981 and 982. In the second maturation approach, mutagenic

primers were used to introduce point mutations at a low frequency, scattered across the mutagenesis region in the TTM-001 and TTM-002 sequences ranging from position 449 to position 466, numbered according to SEQ ID NO: 981 and 982. AAV capsid variants arising from each maturation approach for TTM-001 were pooled together and AAV capsid variants arising from each maturation approach for TTM-002 were also pooled together, for subsequent testing and characterization in mice.

[0505] The library of pooled matured AAV capsid variants generated from TTM-001 or library of pooled matured AAV capsid variants generated from the TTM-002 matured AAV capsid variant each were intravenously injected into the tail vein of three female CD-1 Outbred mice (Charles River) at a dose of 1.0×10^{12} VG/dose. After 14-days in life, the brains of the mice were isolated and RNA was extracted. Following RNA recovery and RT-PCR amplification, a systematic NGS enrichment analysis was performed to calculate the fold enrichment ratio relative to the corresponding TTM-001 or TTM-002 control, and the peptides comprised within the variants were identified. The data for the TTM-001 matured capsid variants is provided in **Table 13** and the data for the TTM-002 matured capsid variants is provided in **Table 14**.

[0506] As shown in **Table 13**, approximately 714 TTM-001 matured capsid variants demonstrated at least a 2-fold increase in expression relative to the non-matured TTM-001 control, and several variants demonstrated greater than a four-fold enrichment relative to the non-matured TTM-001 control. Also, across the peptides comprised within the TTM-001 matured capsid variants with the greatest fold-enrichment relative to the non-matured TTM-001 capsid in the brain, it was observed that the modifications in the variant sequences appeared in the region C-terminal to the SPH motif present within the capsid variant. This indicates that modifications that appeared to improve TTM-001 capsid tropism in the CNS of mice were skewed to the C-terminal portion of the peptide insertion in loop IV of the sequence. Additionally, a number of these C-terminal modifications were the incorporation of an arginine (R) or leucine (L) residue.

Table 13. NGS fold-enrichment of TTM-001 matured AAV capsid variants in the brain of CD-1 Outbred mice

Peptide Sequence	SEQ ID NO:	Fold enrichment over TTM-001	Peptide Sequence	SEQ ID NO:	Fold enrichment over TTM-001
KTINGSGSPHSLLNQQT	1008	7.983	KTINGRPSPHVKAQNQQT	1365	2.419
KTINGSGSPHKAQYYVT	1009	6.283	KTINGSGSPHSMFPNQQT	1366	2.419
KTINGSGSPHSLRRQQT	1010	6.231	KTINGMKSPHKAQNQQT	1367	2.413
KTINGSGSPHSIWQNQQT	1011	5.883	KTINGSGSPHSAVRAQQT	1368	2.412
KTINGSSSPHCTAQNQQT	1012	5.607	KGLVGSGSPHKAQNQQT	1369	2.412
KTINGSGSPHSAKAGCGQT	1013	5.341	KTINGSRSPHVRAQNQQT	1370	2.412
KSMNGSGSPHSRAQNQQT	1014	5.145	KTIRLRGSPHKAQNQQT	1371	2.408
KTINGSGSPHSLRLRQQT	1015	5.034	KPRLGSGSPHKAQNQQT	1372	2.406
KTINGSGSPHSLRRNQQT	1016	4.985	KTINGSGSPHSAWYPQT	1373	2.406
KTINGSGSPHSRGRNQQT	1017	4.961	KTINGSCSPHVRAQNQQT	1374	2.406
KTINGSGSPHSEIVNQQT	1018	4.931	KTINGSGSPHSAKRVQQT	1375	2.404

KTINGS SGSPHSSRRNQQT	1019	4.920	KTINGS SGSPHSKRGLQQT	1376	2.402
KTINGS SGSPHCLLQNQQT	1020	4.898	KTINGS SGSPHSKRLAQQT	1377	2.397
KTIMRVGSPHSKAQNQQT	1021	4.875	KTINGS SGSPHSKVTRQQT	1378	2.397
KTINGS SGSPHSAFRLQQT	1022	4.849	KTINGS SGSPHTWLQNQQT	1379	2.397
KTINGS SGSPHCLAQNQQT	1023	4.847	KTINGS SGSPHSKQRSQQT	1380	2.395
KTINGS SCSPHRKAQNQQT	1024	4.801	KTINGS SGSPHSAQRCST	1381	2.393
KTINGS SGSPHFLRQNQQT	1025	4.777	KTINGS PPSPHYLAQNQQT	1382	2.391
KTINGS SGSPHSLRFNQQT	1026	4.765	KTINGRRSPHLKAQNQQT	1383	2.391
KTINGS SGSPHSYLRNQQT	1027	4.566	KTINGS SGSPHWSLQNQQT	1384	2.389
KTINGS SGSPHCSLQNQQT	1028	4.540	KTINGVTS PHWKAQNQQT	1385	2.387
KTINGS SGSPHVLWQNQQT	1029	4.533	KTINGS SGSPHSAQTTRT	1386	2.385
KTINGS SGSPHSKWLLQQT	1030	4.521	KTINGS SGSPHSAQLFKT	1387	2.385
KTINGS SGSPHSLWSNQQT	1031	4.467	KTINGS SGSPHSKARSYQT	1388	2.382
KTINGS SGSPHSKRRLQQT	1032	4.451	KTINGS SGSPHSKLSRQQT	1389	2.380
KTINGS SGSPHSVYLNQQT	1033	4.426	KTINGS SGSPHLVFQNQQT	1390	2.376
KTINGS SGSPHSLWLNQQT	1034	4.412	KTINGS SGSPHSAQLVKT	1391	2.376
KTINGS SGSPHSAQRKLT	1035	4.339	KTINGS SGSPHSAQTGRT	1392	2.371
KTINGS SGSPHSAKALRRQT	1036	4.330	KTINGS SGSPHSKARYSQT	1393	2.369
KTINGS SGSPHSAQRLRT	1037	4.322	KTINGRHSPHLKAQNQQT	1394	2.369
KYLSGSGSPHSAQNQQT	1038	4.264	KTINGS SGSPHSFARNQQT	1395	2.367
KTINGS SGSPHSAQRRLT	1039	4.227	KTINGS SGSPHSSCQNQQT	1396	2.365
KTINGS SGSPHSAKARRQT	1040	4.218	KTINGS SGSPHSLFANQQT	1397	2.365
KTINGS SGSPHSAKARRLQT	1041	4.210	KTINGS SGSPHSKRLTQQT	1398	2.363
KTINGS SGSPHSAKARRQQT	1042	4.175	KTINGS SGSPHSAQTART	1399	2.363
KTINGLLSPHWAQNQQT	1043	4.173	KTINGS SGSPHFLNQNQQT	1400	2.359
KTINGS SGSPHSAKARLQQT	1044	4.155	KTINGS SGSPHSAQLILT	1401	2.358
KTINGS SGSPHSAKASKRQT	1045	4.117	KEVGGSGSPHSAQNQQT	1402	2.358
KTINGS SGSPHVRQNQQT	1046	4.114	KTINGS RSPHIRAQNQQT	1403	2.356
KTINGS SGSPHSAQLYRT	1047	4.108	KTINGS SGSPHSSWLNQQT	1404	2.354
KGLSGSGSPHSAQNQQT	1048	4.056	KTINGS MSPHLYAQNQQT	1405	2.354
KTINGS SGSPHSLFRNQQT	1049	4.037	KTINGMSSPHRKAQNQQT	1406	2.352
KTINGS SGSPHSAQLTVT	1050	4.026	KTINGS SGSPHSKPRPQQT	1407	2.352
KTINGS RSPHTRAQNQQT	1051	3.989	KTINGS SGSPHSGLWNQQT	1408	2.350
KTINGS SGSPHSAKALRQT	1052	3.976	KTINGS SGSPHRWAQNQQT	1409	2.350
KTINGS SGSPHSAKLIRQQT	1053	3.968	KTINGS SGSPHSKIRLQQT	1410	2.348
KTINGS SGSPHSAKALRFQT	1054	3.894	KTINGS SGSPHSAKFSQQT	1411	2.348
KTINGS SGSPHSAKRTFQQT	1055	3.879	KTINGS SGSPHSAKSCAQQT	1412	2.348
KTINGS SGSPHSAQAQKRLT	1056	3.872	KTINGS SGSPHSAKRLMQQT	1413	2.345
KTINGS SGSPHSLWSQNQQT	1057	3.857	KT SRC SGSPHSAQNQQT	1414	2.345
KTINGS SGSPHLLWQNQQT	1058	3.855	KTINGS SGSPHSLLNQQT	1415	2.341
KTINGS SGSPHSRLRNQQT	1059	3.851	KTINGS SGSPHCSAQNQQT	1416	2.339
KTINGS SGSPHSAKRAAQQT	1060	3.838	KTINGS SGSPHSAQAQPSKT	1417	2.339
KTINGS SGSPHSAKRSWQQT	1061	3.838	KTINGS SGSPHSYVRNQQT	1418	2.339
KTINGS SGSPHSAQAQLRRT	1062	3.825	KTINGS SGSPHSAQAQSRT	1419	2.337
KTINGS SGSPHYLVQNQQT	1063	3.819	KTINGS SGSPHSFVVNQQT	1420	2.335
KTINGS SGSPHSAKLFRQQT	1064	3.806	KTINGFRSPHSAQNQQT	1421	2.333
KTINGS SGSPHSAKRAMQQT	1065	3.801	KTINGS SGSPHSAKWLQQT	1422	2.333
KTINGS SGSPHSAKTLRQQT	1066	3.788	KTINGS SGSPHSAKRTAQQT	1423	2.331
KTINGS SGSPHSAKSRNQQT	1067	3.784	KTINGLFS PHRKAQNQQT	1424	2.331
KTINGS SGSPHSAKRRNQQT	1068	3.754	KTINTIESPHSAQNQQT	1425	2.331
KTINGS SGSPHSAKTCQLQQT	1069	3.717	KRLFGSGSPHSAQNQQT	1426	2.330
KTINGS SGSPHSAKSRWQQT	1070	3.698	KTINGS SGSPHSAKAPNHLT	1427	2.324
KTINGS SGSPHSAKFRQNQQT	1071	3.698	KTINGS SGSPHSAKFRQNQQT	1428	2.324

KTINGLRSPHRKAQNQQT	1072	3.676	KTINGSGSPHASKASRHQT	1429	2.324
KTRSRSGSPHASKAQNQQT	1073	3.669	KTINGSGSPHASKLSWQQT	1430	2.322
KTINGSGSPHASKAQLVVT	1074	3.654	KETAGSGSPHASKAQNQQT	1431	2.320
KTINGSGSPHSRKLNQQT	1075	3.646	KTINGHRSPHLKAQNQQT	1432	2.320
KTINGSGSPHSLLCNQQT	1076	3.644	KTINGSGSPHASKGCLQQT	1433	2.320
KTINGKRSPHASKAQNQQT	1077	3.611	KTINGSGSPHASKAQLIT	1434	2.317
KTINGSRSPHLFAQNQQT	1078	3.601	KTINGSGSPHASKLRSQQT	1435	2.309
KSINGSGSPHASKAHDQQT	1079	3.592	KTINGTLSPHRKAQNQQT	1436	2.307
KTINGSGSPHASKAQRST	1080	3.585	KTINGSGSPHSTWTNQQT	1437	2.307
KTINGSGSPHSTWLNQQT	1081	3.583	KTINGSGSPHASKAQCLT	1438	2.304
KTINGSGSPHASKASRRQT	1082	3.577	KTINNLRSPHASKAQNQQT	1439	2.302
KTINGSGSPHASKRSMQQT	1083	3.561	KTINGSGSPHASKARANQT	1440	2.300
KTINGSGSPHASKLQNQQT	1084	3.559	KTINGRQSPHTKAQNQQT	1441	2.294
KTINGSGSPHASKRLWQQT	1085	3.529	KTINSARSPHASKAQNQQT	1442	2.292
KTINGSGSPHASKWLSNQQT	1086	3.495	KTINGCSSPHRKAQNQQT	1443	2.291
KTINGSGSPHLRRQNQQT	1087	3.493	KTINGSVSPHFMAQNQQT	1444	2.287
KTINGSGSPHASKARRSQT	1088	3.493	KTINGSGSPHASKLCQNQQT	1445	2.285
KTINGSGSPHASKHLRQQT	1089	3.438	KTINGSLSPHLFAQNQQT	1446	2.285
KTINGSGSPHASKSQNQQT	1090	3.428	KTINGSGSPHASKACPLQT	1447	2.285
KTINGSGSPHASKSFRQQT	1091	3.426	KTINGRTSPHRKAQNQQT	1448	2.285
KTINGSGSPHLCLQNQQT	1092	3.425	KTINGSGSPHASKRATQQT	1449	2.283
KTINGSGSPHASKAQTST	1093	3.421	KTINGSGSPHASKARIMQT	1450	2.283
KTINGSGSPHASKLCSNQQT	1094	3.413	KTINGSGSPHVTWQNQQT	1451	2.281
KTINGSRSPHLRAQNQQT	1095	3.410	KTINGSGSPHASKRLPQQT	1452	2.279
KTINGSGSPHASKAQVSKT	1096	3.406	KTINGSGSPHASKAQGFRT	1453	2.279
KTINGSGSPHASKAQRHVT	1097	3.404	KTINGSGSPHLYGQNQQT	1454	2.277
KTINGSSSPHLCAQNQQT	1098	3.402	KTINGSGSPHASKLCQNQQT	1455	2.277
KTINGSGSPHASKFLRNQQT	1099	3.384	KTINGSGSPHASKAQFTLT	1456	2.277
KTINGSGSPHASKFVLNQQT	1100	3.382	KTINGSRSPHFKAQNQQT	1457	2.277
KTINGSGSPHASKMRAQQT	1101	3.382	KTINGRPSPHASKAQNQQT	1458	2.276
KTINGSGSPHRPRQNQQT	1102	3.380	KTINGFSSPHRKAQNQQT	1459	2.276
KTINGSGSPHASKCLLQQT	1103	3.374	KTINGRASPHVKAQNQQT	1460	2.272
KTINGSGSPHASKAQRRT	1104	3.372	KTINGSGSPHASKAQNVEH	1461	2.272
KTINGSGSPHASKRWQNQQT	1105	3.372	KTINGSGSPHASKRSLQQT	1462	2.270
KYSVSGSPHASKAQNQQT	1106	3.365	KTINGSGSPHASKSRQNQQT	1463	2.270
KTINGSGSPHASKRFLQQT	1107	3.359	KPPTGSGSPHASKAQNQQT	1464	2.270
KTINGSGSPHASKLFLNQQT	1108	3.358	KTINGSGSPHASKAARTQT	1465	2.266
KTINGSGSPHASKAYLRQT	1109	3.356	KTINGSGSPHASKSWANQQT	1466	2.264
KTINGSGSPHASKRNGQQT	1110	3.350	KTINGSGSPHASKAQRHAT	1467	2.264
KTINGSGSPHSTRQNQQT	1111	3.350	KTINSRPSPHASKAQNQQT	1468	2.264
KTINGSGSPHASKPRLQQT	1112	3.337	KTINGSGSPHASKSERQQT	1469	2.263
KTINFLRSPHASKAQNQQT	1113	3.331	KTINGSGSPHALFQNQQT	1470	2.261
KTINGSGSPHLLCQNQQT	1114	3.328	KTINGSGSPHASKAQCYVT	1471	2.261
KTINGSGSPHASKARIVQT	1115	3.287	KTINGVASPHRKAQNQQT	1472	2.261
KTINGSKSPHFKAQNQQT	1116	3.285	KTINGSGSPHASKALWNQQT	1473	2.261
KTINGSGSPHASKAQIRLT	1117	3.279	KTINGSGSPHASKSVRQQT	1474	2.259
KTINGSSSPHWVAQNQQT	1118	3.277	KTINGSGSPHASKSHMENQQT	1475	2.259
KTINGSGSPHASKATRRQT	1119	3.277	KTINGSGTPHASKAQNQQT	1476	2.259
KTINGSLSPHASKAQNQQT	1120	3.268	KTINGSGSPHASKTGRQQT	1477	2.259
KTINGSGSPHASKLYLNQQT	1121	3.264	KTINGSGSPHASKAQANRT	1478	2.255
KTINGSGSPHASKVGRQQT	1122	3.255	KTINGSGSPHASKARFSQT	1479	2.253
KTINGSGSPHASKRRLNQQT	1123	3.251	KYLLGSGSPHASKAQNQQT	1480	2.253
KTINGSGSPHASKAQHSRT	1124	3.227	KTINGSGSPHASKSSQNQQT	1481	2.253

KTINGSKSPHSAFPRQT	1125	3.220	KTINGSMSPHRKAQNQQT	1482	2.251
KTINGSKSPHRRANQQT	1126	3.216	KTINGNLSPHRKAQNQQT	1483	2.250
KTINGSKSPHRSKRNQQT	1127	3.210	KEVAGSGSPHSAQNQQT	1484	2.250
KTINGSKSPHSPTRQQT	1128	3.201	KTINLSRSPHSAQNQQT	1485	2.246
KTINGSKSPHSLWLQQT	1129	3.199	KTINGSKSPHSAKARQQT	1486	2.244
KTINGSKSPHSLANQQT	1130	3.192	KTINGTPSPHSAQNQQT	1487	2.244
KTINGSKSPHSTRQQT	1131	3.190	KTINGSKSPHSAKFLQQT	1488	2.244
KTINGSKSPHSLNKQQT	1132	3.181	KTINGSKSPHSAKALLQQT	1489	2.240
KTINGSKSPHSSLWNQQT	1133	3.179	KTINGLRSPPHSAQNQQT	1490	2.238
KTINGSKSPHSAQITLT	1134	3.177	KTINGRLSPHSAQNQQT	1491	2.238
KTINGSKSPHSAKFLQQT	1135	3.173	KTINGSKSPHSAKFAQNQQT	1492	2.238
KTINGSKSPHSAKRTQQT	1136	3.169	KDLRGSGSPHSAQNQQT	1493	2.238
KTINGSKSPHSAKNSRR	1137	3.168	KTINGSKSPHSAKLAQT	1494	2.238
KTINGSKSPHSAKLNQQT	1138	3.156	KTINGSKSPHSAKPRSQQT	1495	2.235
KTINGSKSPHSAKLLNQQT	1139	3.127	KTINGSKSPHSAKMSQQT	1496	2.235
KTINGSKSPHSAKLYQNQQT	1140	3.117	KTINGSKSPHSAKQIVT	1497	2.235
KTINGSKSPHSAKPSQQT	1141	3.114	KTINGSKSPHSAKARFTQT	1498	2.233
KTINGSKSPHSAKLRNQQT	1142	3.112	KTINGSKSPHSAKPLFQNQQT	1499	2.233
KTINGSKSPHSAKLNWQQT	1143	3.112	KTINGSKSPHSAKQRGMT	1500	2.231
KTINGSKSPHSAKQVNQQT	1144	3.106	KTINGSKSPHSAKQNLRR	1501	2.231
KTINGSKSPHSAKRPQQT	1145	3.095	KTINGSKSPHSAKQFRVT	1502	2.231
KTINGSKSPHSAKRNQQT	1146	3.089	KTINGSKSPHSAKAFVQQT	1503	2.225
KTINGSKSPHSAKPLAQQT	1147	3.086	KTINGSKSPHSAKARLTQT	1504	2.223
KTINGSKSPHSAKAFARQT	1148	3.082	KTINGSKSPHSAKRFQVNQQT	1505	2.223
KTINGSKSPHSAKALRYQT	1149	3.076	KTINGSKSPHSAKQETQQT	1506	2.223
KTINGSKSPHSAKALNQQT	1150	3.073	KTINGSKSPHSAKTRAQQT	1507	2.223
KTINGSKSPHSAKALNQQT	1151	3.073	KTINGSKSPHSAKSVWNQQT	1508	2.223
KTINGSKSPHSAKALNQQT	1152	3.061	KTINGSKSPHSAKTKWQVNQQT	1509	2.222
KTINGSKSPHSAKALNQQT	1153	3.054	KTINGSKSPHSAKQVNQQT	1510	2.218
KTINGSKSPHSAKARPYQT	1154	3.050	KTINGSKSPHSAKQNKRS	1511	2.214
KTINGSKSPHSAKRVQQT	1155	3.048	KTINGSKSPHSAKSTRQVNQQT	1512	2.212
KTINGSKSPHSAKSWQVNQQT	1156	3.047	KTINGSKSPHSAKQVNQQT	1513	2.203
KTINGSKSPHSAKQVNQQT	1157	3.035	KTINGSKSPHSAKVLQVNQQT	1514	2.203
KTINGSKSPHSAKQVNQQT	1158	3.034	KTINGSKSPHSAKQVNQQT	1515	2.203
KTINGSKSPHSAKQVNQQT	1159	3.026	KTINGSKSPHSAKQVNQQT	1516	2.203
KTINGSKSPHSAKQVNQQT	1160	2.998	KTINGSKSPHSAKQVNQQT	1517	2.201
KTINGSKSPHSAKQVNQQT	1161	2.994	KTINGSKSPHSAKQVNQQT	1518	2.199
KTINGSKSPHSAKQVNQQT	1162	2.993	KTINGSKSPHSAKQVNQQT	1519	2.199
KTINGSKSPHSAKQVNQQT	1163	2.989	KTINGSKSPHSAKQVNQQT	1520	2.197
KTINGSKSPHSAKQVNQQT	1164	2.985	KTINGSKSPHSAKQVNQQT	1521	2.197
KTINGSKSPHSAKQVNQQT	1165	2.985	KTINGSKSPHSAKQVNQQT	1522	2.196
KTINGSKSPHSAKQVNQQT	1166	2.983	KTINGSKSPHSAKQVNQQT	1523	2.196
KTINGSKSPHSAKQVNQQT	1167	2.981	KTINGSKSPHSAKQVNQQT	1524	2.196
KTINGSKSPHSAKQVNQQT	1168	2.980	KTINGSKSPHSAKQVNQQT	1525	2.194
KTINGSKSPHSAKQVNQQT	1169	2.978	KTINGSKSPHSAKQVNQQT	1526	2.194
KTINGSKSPHSAKQVNQQT	1170	2.972	KTINGSKSPHSAKQVNQQT	1527	2.190
KTINGSKSPHSAKQVNQQT	1171	2.965	KTINGSKSPHSAKQVNQQT	1528	2.190
KTINGSKSPHSAKQVNQQT	1172	2.950	KTINGSKSPHSAKQVNQQT	1529	2.188
KTINGSKSPHSAKQVNQQT	1173	2.937	KTINGSKSPHSAKQVNQQT	1530	2.186
KTINGSKSPHSAKQVNQQT	1174	2.931	KTINGSKSPHSAKQVNQQT	1531	2.186
KTINGSKSPHSAKQVNQQT	1175	2.924	KTINGSKSPHSAKQVNQQT	1532	2.186
KTINGSKSPHSAKQVNQQT	1176	2.920	KTINGSKSPHSAKQVNQQT	1533	2.186
KTINGSKSPHSAKQVNQQT	1177	2.916	KTINGSKSPHSAKQVNQQT	1534	2.184

KTINGSKSPHSGARLWQT	1178	2.914	KTINGSKSPHSGKASRGQT	1535	2.182
KTINGSKSPHSGSRTRNQQT	1179	2.912	KTINGSKSPHSGKAQVCLT	1536	2.182
KTINGSKSPHSGKRSNQQT	1180	2.886	KTINGSKSPHSGKARGVQT	1537	2.181
KTINGSKSPHSGSWAQNQQT	1181	2.885	KTINGSKSPHSGHLWQNQQT	1538	2.181
KTINGSKSPHSGHYKAQNQQT	1182	2.879	KTINGSKSPHSGKAQVWFT	1539	2.181
KTINRHSKSPHSGKAQNQQT	1183	2.877	KTINGSKSPHSGKAQVTLT	1540	2.179
KTINGSKSPHSGKRRNQQT	1184	2.877	KTINGSKSPHSGKAQLRIT	1541	2.179
KTINGSKSPHSGKAKHLQT	1185	2.870	KDSLKSGSPHSGKAQNQQT	1542	2.175
KTINGSKSPHSGKRTYQQT	1186	2.870	KTINGSKSPHSGKRSQQT	1543	2.173
KTINGVLSKSPHSGKAQNQQT	1187	2.868	KTINGSKSPHSGKSRINQQT	1544	2.173
KTINGSKSPHSGFITNQQT	1188	2.868	KTINGSKSPHSGKASKNQQT	1545	2.171
KTINGSKSPHSGSTRLNQQT	1189	2.860	KTINGSKSPHSGKAQLPWT	1546	2.169
KTINGSKSPHSGKRTSQQT	1190	2.857	KTINGSKSPHSGSKLTRQQT	1547	2.169
KTINGSKSPHSGRRSNQQT	1191	2.851	KTINGSKSPHSGSKTNRQQT	1548	2.169
KTINGHLSKSPHSGKAQNQQT	1192	2.851	KTINRVISKSPHSGKAQNQQT	1549	2.169
KTINGSKSPHSGKAQFSRT	1193	2.847	KTINGSKSPHSGHTLWQNQQT	1550	2.168
KTINGSKSPHSGKAQTFRT	1194	2.847	KTINGSKSPHSGRRQNQQT	1551	2.166
KTINGSKSPHSGKPLRQQT	1195	2.844	KTINGSKSPHSGKGRQQT	1552	2.164
KTINGSKSPHSGKASCRT	1196	2.840	KTINGSKSPHSGKASQNQQT	1553	2.164
KTINGSKSPHSGKILWQQT	1197	2.838	KTINGSKSPHSGSRPRNQQT	1554	2.164
KTINGSKSPHSGKALKRQT	1198	2.836	KTINGSKSPHSGSRKQNQQT	1555	2.162
KTINGSKSPHSGKAHRSQT	1199	2.819	KTINGSKSPHSGKAQEELT	1556	2.162
KTINGSKSPHSGSMLYNQQT	1200	2.808	KTINGWRSKSPHSGKAQNQQT	1557	2.160
KTINGSKSPHSGKCTLQQT	1201	2.808	KTINGSKSPHSGSLLYNQQT	1558	2.158
KTINGSKSPHSGKQNRMR	1202	2.804	KTINGSKSPHSGSFRLNQQT	1559	2.158
KTINGSKSPHSGSKLVRQQT	1203	2.801	KTINGSKSPHSGKAQFLRT	1560	2.156
KTINGSKSPHSGSKRILQQT	1204	2.801	KTINGSKSPHSGKQSRQQT	1561	2.156
KTINGSKSPHSGKAQWLRT	1205	2.795	KTINGSKSPHSGKASQNQRQT	1562	2.155
KTINGSKSPHSGSLTCNQQT	1206	2.795	KTINGRPSKPHIKAQNQQT	1563	2.155
KTINGIRSPHTKAQNQQT	1207	2.793	KTINGSKSPHSGSKRLVQQT	1564	2.151
KTINGSKSPHSGKAQRWLT	1208	2.788	KGHEGSGSPHSGKAQNQQT	1565	2.151
KTINGSKSPHSGKAQLSIT	1209	2.784	KTINGSKSPHSGKAQKRST	1566	2.151
KTINGSKSPHSGHIYRQNQQT	1210	2.782	KTINGSKSPHSGSYLLNQQT	1567	2.147
KTINGSKSPHSGSLRSNQQT	1211	2.778	KTINGSKSPHSGSKPRGQQT	1568	2.147
KTINGSKSPHSGKVKPQQT	1212	2.778	KTINGSKSPHSGSKTRLQQT	1569	2.145
KTINGSKSPHSGKATRHQT	1213	2.777	KTINGSKSPHSGSKSHRQQT	1570	2.145
KTINGSKSPHSGKLCANQQT	1214	2.775	KEIKGSGSPHSGKAQNQQT	1571	2.140
KTINGSKSPHSGKACASQT	1215	2.775	KTINGSKSPHSGKARGIQT	1572	2.140
KWSPGSGSPHSGKAQNQQT	1216	2.764	KTINGYRSKSPHSGKAQNQQT	1573	2.140
KTINGYLSKSPHSGKAQNQQT	1217	2.762	KTINGSKSPHSGSKLWTQQT	1574	2.140
KTINGSKSPHSGKVIRQQT	1218	2.760	KTINGSKSPHSGSKPWLQQT	1575	2.138
KTINGSKSPHSGFLLQNQQT	1219	2.758	KTINGSKSPHSGHWSVQNQQT	1576	2.138
KTINGSKSPHSGKARSQQT	1220	2.758	KTINGSKSPHSGSKVARQQT	1577	2.136
KTINGVPSKPHWKAQNQQT	1221	2.758	KTINGSKSPHSGHTLFQNQQT	1578	2.136
KTINGSKSPHSGKATRNT	1222	2.756	KTINGSCSPHSLAQNQQT	1579	2.134
KTINGSKSPHSGKACSAQT	1223	2.754	KTINGSKSPHSGSKTSRQQT	1580	2.132
KTINGSKSPHSGKARYVQT	1224	2.749	KTINGSKSPHSGKAQNARH	1581	2.127
KTINGSKSPHSGKARQNQQT	1225	2.745	KTINGSKSPHSGKAQLKLT	1582	2.125
KTINGSKSPHSGKAQHLRT	1226	2.741	KTINGSKSPHSGKAQNWRT	1583	2.125
KTINGSKSPHSGKAKSRQT	1227	2.739	KTINGSKSPHSGHFLPQNQQT	1584	2.123
KTINGSKSPHSGKIGRQQT	1228	2.739	KTINGSKSPHSGSKNVRQQT	1585	2.123
KTINGLASKSPHSGKAQNQQT	1229	2.737	KTINGSKSPHSGHMRQNQQT	1586	2.123
KTINGSKSPHSGKARTRQT	1230	2.737	KTINGSKSPHSGHWAQNQQT	1587	2.121

KTINGSGSPHKSIRQQT	1231	2.728	KTINGSGSPHFHLQNNQQT	1588	2.121
KTINGSGSPHSKRLYQQT	1232	2.721	KTINGSASPHWSAQNNQQT	1589	2.121
KTINGLPSPHRKAQNNQQT	1233	2.719	KTINGSSSPHWSAQNNQQT	1590	2.119
KTINGSLSPHRRKAQNNQQT	1234	2.717	KTINGSGSPHSKAHRQQT	1591	2.117
KTINGKTSPhGKAQNNQQT	1235	2.717	KTINGSGSPHSKQRVQQT	1592	2.117
KTINGSRSPHRLAQNNQQT	1236	2.698	KTLRRSGSPHSKAQNNQQT	1593	2.117
KTINGSGSPHSLTWNQQT	1237	2.698	KTINGSGSPHSGVRQQT	1594	2.115
KTINGSKSPHRKAQNNQQT	1238	2.696	KTINGSLSPHTWAQNNQQT	1595	2.115
KTINGSGSPHSKAQLRKT	1239	2.689	KTINGSGSPHSKRALQQT	1596	2.114
KTINGSGSPHSKSRHQQT	1240	2.685	KTINGSGSPHCLSQNNQQT	1597	2.114
KTINRRLSPHKAQNNQQT	1241	2.678	KTINGSGSPHKAQSLKT	1598	2.110
KTINGSGSPHSRRVNQQT	1242	2.676	KTINGSGSPHSFVRNQQT	1599	2.110
KTINGSGSPHSHWQNNQQT	1243	2.676	KTINGSGSPHSIFSNNQQT	1600	2.110
KTTHCSGSPHKAQNNQQT	1244	2.672	KTINGSGSPHSKVSQQT	1601	2.108
KTINGSGSPHSLWLNQQT	1245	2.665	KTINGSGSPHSKARNKQT	1602	2.108
KTINGSTSPHYLAQNNQQT	1246	2.665	KTINASGSPHKAQGGQQT	1603	2.108
KTINGLTSPHRKAQNNQQT	1247	2.663	KTINGSGSPHSKLRMQQT	1604	2.106
KTINGSGSPHSKRLLQQT	1248	2.659	KTINGSWSPHMLAQNNQQT	1605	2.106
KTINGSGSPHSKLCVQQT	1249	2.659	KTINGSGSPHSLFPNQQT	1606	2.106
KTINGFLSPHRKAQNNQQT	1250	2.654	KPPLGSGSPHKAQNNQQT	1607	2.102
KTINGSGSPHSKMRPQQT	1251	2.652	KTINGIASPHRKAQNNQQT	1608	2.099
KTINGSGSPHSKQTRQQT	1252	2.650	KTINGSCSPHSLAQNNQQT	1609	2.099
KTINGSGSPHSYLINQQT	1253	2.650	KTINGRLSPHFKAQNNQQT	1610	2.097
KTINGSGSPHSKALRSQT	1254	2.648	KTINGSGSPHSKARMTQT	1611	2.091
KTINGMLSPHRKAQNNQQT	1255	2.646	KTINGSGSPHSKARLQQT	1612	2.089
KTINGSGSPHSKCLTQQT	1256	2.644	KTINGSGSPHSKWVSQQT	1613	2.089
KTINGSGSPHKAQLTLT	1257	2.641	KTINGSGSPHSKKVSQQT	1614	2.088
KTINGHSSPHRKAQNNQQT	1258	2.639	KTINGSGSPHKAQSYRT	1615	2.088
KTINGSGSPHLTWQNNQQT	1259	2.637	KAFNGSGSPHKAQNNQQT	1616	2.088
KTINGSGSPHKAQYCLT	1260	2.628	KTINGSGSPHKAQYRLT	1617	2.088
KTINGSGSPHSFLVNQQT	1261	2.624	KTINGSWSPHLVAQNNQQT	1618	2.084
KTINMSRSPHKAQNNQQT	1262	2.622	KTINGSGSPHSWTQNNQQT	1619	2.084
KTINGSGSPHKAQLHRT	1263	2.618	KTINGSGSPHKAQSHRT	1620	2.084
KTINGSGSPHLYMQNNQQT	1264	2.615	KGINGSGSPHGKAQNNQQT	1621	2.084
KTINGSRSPHRRKAQNNQQT	1265	2.615	KTINGSGSPHKAQNRKL	1622	2.084
KTINGSGSPHKAQNRRS	1266	2.613	KTINGRYSPhKAQNNQQT	1623	2.080
KTINLRFSPHKAQNNQQT	1267	2.611	KTINGSGSPHSGRSQQT	1624	2.080
KTINGSGSPHKAQRLWT	1268	2.611	KTINGSGSPHCVAQNNQQT	1625	2.080
KTINGSGSPHSGRAQQT	1269	2.607	KTINGSGSPHSKIROPQT	1626	2.080
KTINGSGSPHSLSCNQQT	1270	2.605	KTINGSGSPHKAQSSKT	1627	2.078
KTINGLVSPHCKAQNNQQT	1271	2.605	KTINGSGSPHSKRPFQQT	1628	2.076
KTINGSSSPHLWAQNNQQT	1272	2.605	KTINGSSSPHCLAQNNQQT	1629	2.074
KTINGSGSPHKAHRLQT	1273	2.603	KTINGTRSPHAKAQNNQQT	1630	2.071
KTINGSGSPHPYAQNNQQT	1274	2.598	KTINGSGSPHLLFQNNQQT	1631	2.069
KTINGSGSPHSTRPNQQT	1275	2.598	KTINGRRSPHTKAQNNQQT	1632	2.069
KTINGRSSPHPKAQNNQQT	1276	2.596	KTINGSGSPHSKASKQQT	1633	2.069
KTINGSGSPHKAQSWRT	1277	2.596	KTINGSGSPHKAQLGRT	1634	2.069
KTINGQSPHVKAQNNQQT	1278	2.596	KTINGSGSPHVSFLNQQT	1635	2.069
KTINGSGSPHKAQFVRT	1279	2.596	KTINGSGSPHKSARQQT	1636	2.067
KTINGSGSPHSKCLNQQT	1280	2.594	KTINGSGSPHSKLRLQQT	1637	2.065
KTINGSGSPHSSLCNQQT	1281	2.592	KTRKSSGSPHKAQNNQQT	1638	2.065
KTINGQSPHKAQNNQQT	1282	2.590	KTINGFRSPHLAQNNQQT	1639	2.063
KTINGSGSPHSLSWNQQT	1283	2.588	KTINGSGSPHSKRSIQQT	1640	2.063

KTINGSKSPHSSRKNQQT	1284	2.585	KTINGSKSPHSGRIQQT	1641	2.061
KTINGSKSPHSKRTLQQT	1285	2.583	KTINGSRSPHRPAQNQQT	1642	2.061
KTINGSKSPHCLAQNQQT	1286	2.577	KTINGSKSPHSLRPQQT	1643	2.060
KTINGSKSPHKAQSSRT	1287	2.575	KTINGSKSPHMYAQNQQT	1644	2.060
KTINGSKSPHKLKRNQQT	1288	2.564	KTINGRTSPHAKAQNQQT	1645	2.060
KTINGSKSPHSKARMQQT	1289	2.564	KTINGSKSPHSKAGRGQT	1646	2.058
KTINGSKSPHKAQVKLT	1290	2.564	KTINGSKSPHSKLMRQQT	1647	2.056
KTINGSKSPHSKLPRQQT	1291	2.562	KTINGSKSPHSKANKSQT	1648	2.056
KTINGSKSPHSKLCLQQT	1292	2.562	KTINGSKSPHSKAVRQQT	1649	2.052
KTINGSKSPHSPHPLWNQQT	1293	2.562	KTINGSKSPHSKCLSQQT	1650	2.052
KTINGSKSPHSPHWAQNQQT	1294	2.562	KTINGSKSPHKAQWVLT	1651	2.052
KTIRSKGSPHKAQNQQT	1295	2.559	KTINGSKSPHKAQFWVT	1652	2.050
KTINGSRSPHSPHWAQNQQT	1296	2.559	KTINGSKSPHSKALCRQT	1653	2.048
KTINGSKSPHSKILRQQT	1297	2.557	KEVMGSGSPHKAQNQQT	1654	2.047
KTINGRQSPHVKANQQT	1298	2.557	KTINGSKSPHSKNTRQQT	1655	2.047
KTINGSKSPHKAQSIKT	1299	2.555	KTINGSKSPHTWTQNQQT	1656	2.045
KTINGSKSPHKAQASKT	1300	2.546	KTINGSTSPHWSAQNQQT	1657	2.043
KTINGSKSPHSPHRLFNQQT	1301	2.542	KTINGNVSPHRKAQNQQT	1658	2.043
KTINGSKSPHSPHLYLQNNQQT	1302	2.542	KTINGSTSPHPLFAQNQQT	1659	2.041
KTINGSKSPHSPHSPHVRNQQT	1303	2.540	KTINGSKSPHKAQNYRA	1660	2.039
KTINGSKSPHSPHKAQVRAQT	1304	2.538	KTINGSKSPHSPHKAQKQQT	1661	2.039
KTINGSKSPHSPHKAQPARQQT	1305	2.538	KTINGSKSPHSPHKAQNRIR	1662	2.039
KTINGSKSPHSPHSPHRYSNQQT	1306	2.536	KTINGSKSPHSPHKAQWTLQQT	1663	2.039
KTINGSRSPHSPHKAQNNQQT	1307	2.536	KTINGSKSPHSPHKAQMKCT	1664	2.039
KTINGSKSPHSPHSPHIAQNQQT	1308	2.536	KTINGSKSPHSPHSLWQNNQQT	1665	2.037
KTINGSKSPHSPHSPHSPHVPVRQQT	1309	2.529	KTINGSKSPHSPHKAQQLSKT	1666	2.035
KTINGMRSPHSPHKAQNNQQT	1310	2.527	KTINLIWSPHKAQNNQQT	1667	2.035
KTINGSKSPHSPHKAQKITQT	1311	2.525	KTINGSKSPHSPHSPHKAQVLRQQT	1668	2.035
KTINGSKSPHSPHSPHSPHSLNQQT	1312	2.523	KTINGSKSPHSPHSPHKAQVVRQQT	1669	2.034
KTINTSRSPHKAQNNQQT	1313	2.520	KTINSRSPHKAQNNQQT	1670	2.032
KTINGSKSPHKAQFTRQQT	1314	2.518	KRSKSGSPHKAQNNQQT	1671	2.030
KTINGSKSPHKAQVRNQT	1315	2.516	KTINGSKSPHRRRLQNNQQT	1672	2.030
KTINGSKSPHKAQTNRT	1316	2.510	KTINGSKSPHSPHKAQNNQQT	1673	2.030
KTINGSKSPHKAQNRMQT	1317	2.508	KTINGPLSPHKAQNNQQT	1674	2.028
KTINGSKSPHKAQQLVLT	1318	2.508	KTINGSKSPHSPHLYAQNQQT	1675	2.028
KTINGSKSPHKAQKTRQQT	1319	2.505	KTINGRISPHLKAQNNQQT	1676	2.028
KTINGSKSPHKAQKARGTQT	1320	2.505	KTINGSHSPHKAQNNQQT	1677	2.028
KTINGSKSPHKAQQWSVT	1321	2.501	KTINGSKSPHKAQVSIT	1678	2.028
KTINGSKSPHKAQWLIQT	1322	2.499	KTINGSKSPHSPHKAQNNQQT	1679	2.028
KTINGSKSPHKAQFRPQT	1323	2.499	KTINGRQSPHKAQNNQQT	1680	2.026
KTINGSKSPHRRSQNNQQT	1324	2.497	KTINGSKSPHKAQVVRQQT	1681	2.026
KTINGSKSPHSPHSGIRQQT	1325	2.497	KQPLGSGSPHKAQNNQQT	1682	2.024
KTINGSKSPHSPHCTLQNNQQT	1326	2.497	KTINGSKSPHKAQNVKL	1683	2.024
KPLPGSGSPHKAQNNQQT	1327	2.495	KTINGSKSPHSPHKAQKRGQT	1684	2.022
KTINGSKSPHSPHSPHLCQNNQQT	1328	2.493	KTINGSKSPHSPHSPHLYAQNQQT	1685	2.022
KTINGSKSPHSPHKAQKRGYQT	1329	2.492	KTINGSKSPHSPHSPHKAQNLQQT	1686	2.022
KTINGRISPHGKAQNNQQT	1330	2.492	KTINGSKSPHKAQAFRT	1687	2.022
KTINGSKSPHSPHSPHKAQNNQQT	1331	2.490	KTINGSKSPHSPHKAQKSNQQT	1688	2.020
KTINGSKSPHSPHKAQKARMAQT	1332	2.488	KELVSGSGSPHKAQNNQQT	1689	2.019
KPLDGSKSPHKAQNNQQT	1333	2.488	KTINGSKSPHSPHSPHKAQNNQQT	1690	2.019
KPLRSGSGSPHKAQNNQQT	1334	2.486	KTINGSKSPHKAQATRT	1691	2.019
KTINGSKSPHKAQNAKL	1335	2.486	KTINGTSPHKAQNNQQT	1692	2.017
KTINGSKSPHSPHKAQKSKQQT	1336	2.482	KTINGSKSPHKAQKALWRQT	1693	2.015

KTINGSGSPHSEKARNGQT	1337	2.482	KTINGSGSPHSEKAFSVT	1694	2.015
KTINGSGSPHSEKARRQT	1338	2.479	KTINGSGSPHSEKLYMQQT	1695	2.015
KTINGSGSPHSEKWPQQQT	1339	2.477	KTINGSLSPHYMAQNQQT	1696	2.015
KTINGSGSPHSEKFLQNQQT	1340	2.475	KTINGSGSPHSEKAWLMQT	1697	2.015
KTINGILSPHSEKQNQQT	1341	2.475	KTINGSGSPHSEKSLKQQT	1698	2.013
KTINGSGSPHSEKSNQQT	1342	2.473	KTINGSGSPHSEKQNTRR	1699	2.013
KTINGSGSPHSEKCLNQQT	1343	2.471	KTINGSGSPHYLLQNQQT	1700	2.011
KTINGSGSPHSEKQSVKT	1344	2.464	KTINGSGSPHTWSQNQQT	1701	2.011
KTINGSGSPHSEKRYNQQT	1345	2.462	KTINGSGSPHSEKTRMQQT	1702	2.011
KTINGSGSPHSEKARKLQT	1346	2.458	KTINTRPSPHSEKQNQQT	1703	2.011
KHRSGSGSPHSEKQNQQT	1347	2.456	KTINGSGSPHSEKQILVT	1704	2.009
KTINGSGSPHSEKWSLQQT	1348	2.453	KTINGSGSPHSEKQNAKS	1705	2.009
KTINGSGSPHSEKQTMRT	1349	2.453	KTINGSGSPHSEKTYNQQT	1706	2.009
KTINGSGSPHSEKTIKQQT	1350	2.453	KTINGSGSPHSEKKGQQT	1707	2.009
KTINGKLSPHSEKQNQQT	1351	2.449	KTINGYSSPHSEKQNQQT	1708	2.007
KTINGSGSPHSEKARPFQT	1352	2.443	KTINGSGSPHSEKWSQNQQT	1709	2.007
KTINGSGSPHSEKPRVQQT	1353	2.441	KTINGSGSPHSEKARLAQT	1710	2.007
KTINGSGSPHSEKQVVLVT	1354	2.438	KTINGMCSPHSEKQNQQT	1711	2.006
KTRRSSGSPHSEKQNQQT	1355	2.438	KTINGSGSPHSEKSNKQQT	1712	2.006
KTINGSGSPHSEKPSRQQT	1356	2.438	KTINGSGSPHSEKQFVLT	1713	2.006
KTINGSGSPHSEKSYRNQQT	1357	2.432	KTINGSLSPHSEKQNQQT	1714	2.006
KTINGSGSPHSEKTCQQT	1358	2.430	KTINGSGSPHSEKRMQNQQT	1715	2.004
KTINGSPSPHSEKQNQQT	1359	2.430	KTINGSGSPHSEKAWILQT	1716	2.004
KTINGRSSPHSEKQNQQT	1360	2.428	KTINGSGSPHSEKQGVKT	1717	2.002
KTINGSGSPHSEKQMVRT	1361	2.426	KTINGSGSPHSEKQFSLT	1718	2.000
KTINGSRSPHSEKQNQQT	1362	2.426	KTINMLRSPHSEKQNQQT	1719	2.000
KTINGSCSPHSEKQNQQT	1363	2.423	KTINGSGSPHSEKQLGKT	1720	2.000
KTINGSGSPHSEKQCLFT	1364	2.421	KTINGSGSPHSEKMYLNQQT	1721	2.000

[0507] As shown in **Table 14**, approximately 72 TTM-002 matured capsid variants demonstrated at least a 2-fold increase in expression relative to the non-matured TTM-002 control, with a few variants demonstrating greater than a three- to five-fold enrichment relative to the non-matured TTM-002 control. Also, across the peptides comprised within the TTM-002 matured capsid variants with the greatest fold-enrichment relative to the non-matured TTM-002 capsid in the brain, it was observed that the modifications in the variant sequences appeared in the region N-terminal to the SPH motif present within the capsid variant. This indicates that modifications that appeared to improve TTM-002 capsid tropism in the CNS of mice were skewed to the N-terminal portion of the peptide insertion in loop IV of the sequence. Additionally, a number of these N-terminal modifications that were incorporated into the matured TTM-002 capsid variants were negatively charged amino acids (particularly glutamic acid (E)).

Table 14. NGS fold-enrichment of TTM-002 matured AAV capsid variants in the brain of CD-1 Outbred mice

Peptide Sequence	SEQ ID NO:	Fold enrichment over TTM-002	Peptide Sequence	SEQ ID NO:	Fold enrichment over TTM-002
KTINGHDSPHVTDQNQQT	1722	5.20	KAEVGHDSPHKSGQNQQT	1760	2.15
KTINGHDSPHKRGQHRQT	1723	4.20	KMDAGHDSPHKSGQNQQT	1761	2.15
KMEPEGHDSPHKSGQNQQT	1724	3.18	KVEWGHDSPHKSGQNQQT	1762	2.15
KMEGGHDSPHKSGQNQQT	1725	2.72	KAEQGHDSPHKSGQNQQT	1763	2.14
KMEYGHDSPHKSGQNQQT	1726	2.71	KLEWGHDSPHKSGQNQQT	1764	2.14
KAEWGHDSPHKSGQNQQT	1727	2.69	KTINGHPSPHYLGQNQQT	1765	2.14
KCEWGHDSPHKSGQNQQT	1728	2.68	KTINGHLSPHYYGQNQQT	1766	2.13
KANNGQDSPHKSGQNQQT	1729	2.67	KMELGHDSPHKSGQNQQT	1767	2.13
KTINGHDSPHLCGQNQQT	1730	2.59	KMETGHDSPHKSGQNQQT	1768	2.12
KIPEGHDSPHKSGQNQQT	1731	2.54	KMEAGHDSPHKSGQNQQT	1769	2.12
KADMGHDSPHKSGQNQQT	1732	2.48	KTINGHDSPHLLWQNQQT	1770	2.12
KTINGHLSPHYFGQNQQT	1733	2.41	KTINRQRSPHKSGQNQQT	1771	2.11
KIEYGHDSPHKSGQNQQT	1734	2.41	KIESGHDSPHKSGQNQQT	1772	2.11
KADYGHDSPHKSGQNQQT	1735	2.40	KTAKDHDSPHKSGQNQQT	1773	2.11
KIETGHDSPHKSGQNQQT	1736	2.38	KMEVGHDSPHKSGQNQQT	1774	2.11
KTINGHDSPHTNGQKQQT	1737	2.38	KCEIGHDSPHKSGQNQQT	1775	2.10
KMEWGHDSPHKSGQNQQT	1738	2.38	KATNGHDSPHKSGLNQQT	1776	2.10
KTINGHDSPHWLLQNQQT	1739	2.37	KMDGGHDSPHKSGQNQQT	1777	2.09
KCEYGHDSPHKSGQNQQT	1740	2.36	KQEVGHDSPHKSGQNQQT	1778	2.07
KRINGHDSPHKSGQKQQN	1741	2.34	KADQGHDSPHKSGQNQQT	1779	2.07
KMEIGHDSPHKSGQNQQT	1742	2.34	KTINGHESPHKSAQNHQT	1780	2.07
KLEYGHDSPHKSGQNQQT	1743	2.33	KTINGHDSPHKSAQNQWT	1781	2.07
KADWGHDSPHKSGQNQQT	1744	2.32	KNMNGHDSPHKSGQNTHS	1782	2.06
KIEIGHDSPHKSGQNQQT	1745	2.30	KTPWEHDSPHKSGQNQQT	1783	2.05
KTIKDNDSPHKSGQNQQT	1746	2.27	KTINGHSSPHYFGQNQQT	1784	2.05
KDIMGHDSPHKSGQNQQT	1747	2.23	KIEMGHDSPHKSGQNQQT	1785	2.05
KFEQGHDSPHKSGQNQQT	1748	2.22	KTANEHDSPHKSGQNQQT	1786	2.05
KMEFGHDSPHKSGQNQQT	1749	2.21	KTINGHDSPHKSGRRRQT	1787	2.04
KCDQGHDSPHKSGQNQQT	1750	2.21	KISNGHDSPHKSAQNQQT	1788	2.03
KLPEGHDSPHKSGQNQQT	1751	2.19	KTGNGHDSPHKSGQYQQT	1789	2.03
KIENGHDSPHKSGQNQQT	1752	2.19	KTINGHYSPhLFGQNQQT	1790	2.02
KMESGHDSPHKSGQNQQT	1753	2.18	KTINGNYSPhKIGQNQQT	1791	2.02
KAELGHDSPHKSGQNQQT	1754	2.17	KTINGHDSPHKSRQNDQT	1792	2.01
KVEYGHDSPHKSGQNQQT	1755	2.17	KQQQGHDSPHKSGQNQQT	1793	2.01
KIINGHDSPHKSGLTQQT	1756	2.17	KTPQDHDSPHKSGQNQQT	1794	2.00
KTSNGDDSPHKSGRNQQT	1757	2.17	KHDWGHDSPHKSGQNQQT	1795	2.00
KIEVGHDSPHKSGQNQQT	1758	2.16	KIEGGHDSPHKSGQNQQT	1796	2.00
KMEMGHDSPHKSGQNQQT	1759	2.16			

[0508] These data demonstrate that following two maturation approaches, matured TTM-001 and TTM-002 capsid variants with loop IV modifications were generated with significantly enhanced CNS tropism in mice compared to the corresponding non-matured TTM-001 and TTM-002 capsid variants, which already exhibited a significant fold enrichment over AAV9 in the mouse brain.

Example 4. Maturation of TTM-001 and TTM-002 Capsid in NHPs

[0509] This Example describes maturation of the AAV9 capsid variants, TTM-001 (SEQ ID NO: 981 (amino acid) and 983 (DNA), comprising SEQ ID NO: 941 (encoded by SEQ ID NO: 942)) and TTM-002 (SEQ ID NO: 982 (amino acid) and 984 (DNA), comprising SEQ ID NO: 2 (encoded by SEQ ID NO: 3)) in NHPs to further enhance their transduction and biodistribution in the central nervous system as well as other tissues, and evolve the AAV capsid variants to provide further cross-species compatibility. Two approaches were used to mature the TTM-001 and TTM-002 capsid sequences in order to randomize and mutate within and around the peptide insert comprised within loop IV of the capsid variant. As many of the AAV capsid variants that demonstrated the greatest fold-enrichment in the NHP brain relative wild-type AAV9 comprised an SPH motif in the same position (e.g., immediately subsequent to position 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138) (see **Example 1**), the SPH motif was not mutated in either approach to mature the TTM-001 and TTM-002 capsid variants. In the first maturation approach, sets of three contiguous amino acids were randomized across the mutagenesis region in the TTM-001 and TTM-002 sequences, which spanned from position 450 to position 466, numbered according to SEQ ID NO: 981 and 982. In the second maturation approach, mutagenic primers were used to introduce point mutations at a low frequency, scattered across the mutagenesis region in the TTM-001 and TTM-002 sequences ranging from position 449 to position 466, numbered according to SEQ ID NO: 981 and 982. AAV capsid variants arising from each maturation approach for TTM-001 and TTM-002 were pooled together, for subsequent testing and characterization in NHPs.

[0510] The library of pooled matured AAV capsid variants generated using the first maturation approach and the second maturation approach for the TTM-001 and TTM-002 AAV capsid variants were injected into two NHPs. After a period in life, the brains, heart, liver, muscle, and DRG of the NHPs were isolated and RNA was extracted. Following RNA recovery and RT-PCR amplification, a systematic NGS enrichment analysis was performed to calculate the fold enrichment ratio relative to an AAV9 control, and the peptides comprised within the variants were identified.

[0511] Following the RNA recovery and NGS analysis from the second maturation approach, approximately 680,000 capsid variants were identified. The 680,000 matured capsid variants were then filtered based on samples with a raw virus count greater than 10 and a coefficient of variance (CV) of less than 1, which was calculated for each peptide across the brain samples taken from the two NHPs. Those that had a CV value <1 were identified, as these were the peptides that were reliably detected in the majority of samples isolated from the brains of the two NHPs. Using this filtering criteria, this led to approximately 64,000 matured capsid variants.

[0512] **Table 15** provides the peptide sequences of the matured capsid variants having a raw virus count greater than 10, a CV of less than 1 for the brain samples isolated, and that also demonstrated a

50-fold or greater fold-increase in expression in the brain relative to the AAV9 control in both mice and NHPs. The matured variants in **Table 15**, were also those variants that had a fold-change in expression that was less than 2 relative to the AAV9 control in the liver and the DRG. Applying these criteria, approximately 350 matured capsid variants were identified that demonstrated high transduction in the brain in NHPs and mice, cross-species compatibility in mice and NHPs, and were de-targeted in the liver and DRG, relative to the AAV9 control. Several variants as shown in **Table 15**, led to greater than 100-fold increase in expression relative to AAV9 in the NHP and/or mouse brain, with one variant resulting in a greater than 200-fold increase in expression relative to AAV9 in both species.

[0513] Fold-change in expression for the TTM-001 and TTM-002 matured variants in **Table 15** that showed increased expression in the brain of the NHPs and mice, were also calculated for the DRG, muscle, liver (RNA and DNA), and heart of the NHPs following each maturation approach. As shown in **Table 15**, many variants were de-targeted in the peripheral tissues with a lower fold-change in expression relative to the AAV9 control, demonstrating CNS-specific tropism and a preferential transduction of the brain and CNS. Some variants demonstrated increased expression to AAV9 in multiple tissues, including the brain and peripheral tissues, demonstrating pan-tropism.

Table 15. NGS fold-enrichment of TTM-001 and TTM-002 matured AAV capsid variants in the brain of NHPs and mice

Sequence	SEQ ID NO:	Fold Enrichment relative to AAV9						
		Brain (NHP)	DRG (NHP)	Heart (NHP)	Muscle (NHP)	Liver RNA (NHP)	Liver DNA (NHP)	Brain (Mouse)
KTIIIGSGSPHASKAQNRRHT	3239	217.176	0.000	0.000	0.000	0.000	0.000	210.515
KTFPGSGSPHASKVQNQQT	3240	199.720	0.000	0.000	0.000	0.000	0.967	97.703
KTEKMSGSPHASKAQNQQT	3241	169.461	0.523	0.000	0.000	0.000	0.158	109.161
KEINGRSGSPHASKAQNQQT	3527	134.390	0.239	0.000	0.000	0.000	0.232	52.311
KTVNRNGSPHASKAQNQQT	3528	133.016	0.000	0.416	0.000	0.000	0.000	85.361
KTVNGSGSPHASKARDQQT	3242	124.789	0.123	0.039	0.312	0.569	0.454	132.137
KTFNGSGSPHASKAPNLQT	3243	121.436	0.000	0.167	0.000	0.000	0.015	168.920
KTEKTSGSPHASKAQNQQT	3244	120.337	0.000	0.355	0.000	0.000	0.119	101.467
KTINGSGSPHASKAHVRQT	3245	119.798	0.000	0.000	0.262	0.694	1.039	165.590
KTVNGSGSPHASKAPNQHT	3246	117.207	0.000	0.109	0.000	0.000	0.074	51.008
KTEKISGSPHASKAQNQQT	3247	116.603	0.000	0.000	0.000	0.000	0.426	102.978
KTINGPGSPHASKAHNQQT	3529	115.742	0.146	0.000	0.235	0.000	0.513	52.508
KTVNGSGSPHASKTQSQQT	3248	115.086	0.000	0.726	0.000	0.000	0.340	63.248
TTINGSGSPHASKAQNQQT	3249	114.856	1.340	14.856	0.827	1.281	0.957	72.058
KSINESGSPHASKAQNQQI	3250	113.833	0.000	0.000	0.000	0.000	0.000	67.649
KTERTSGSPHASKAQNQQT	3251	112.957	0.000	0.009	0.000	1.128	0.207	117.374
KTINGSGSPHASKAQPACT	3252	111.472	0.331	0.000	1.089	0.044	1.796	215.275
KTEKSSGSPHASKAQNQQT	3253	107.470	0.000	0.016	0.014	0.977	0.179	100.177
KTSYNGSGSPHASKAQNQQT	3530	105.937	0.000	0.000	0.000	0.000	0.114	105.894
KTEKSGSGSPHASKAQNQQT	3254	105.614	0.053	0.031	0.000	0.586	0.169	84.653
KTINGSGSPHASKSQTQQN	3255	104.474	0.000	0.131	0.000	0.084	0.038	54.021
KTERISGSPHASKAQNQQT	3256	103.692	0.000	0.000	0.000	0.062	0.370	89.637
KTERASGSPHASKAQNQQT	3257	103.669	0.000	0.000	0.000	0.127	0.070	115.550
KELHSGSGSPHASKAQNQQT	3258	102.680	0.000	0.000	0.000	1.634	0.592	96.554

KAINGSGSPHKAQNLAT	3259	101.954	0.000	10.954	8.655	0.298	0.239	116.685
KTVNGSGSPHKSQNQLT	3260	101.327	0.000	0.035	0.000	0.000	0.025	80.716
KTERNSGSPHKAQNQQT	3261	99.892	0.000	0.000	0.000	0.000	0.107	87.392
KSVNNGSGSPHKAQNQQT	3531	99.385	0.000	1.329	0.000	0.359	0.079	51.016
KTFNGSGSPHKAQGGQT	3262	99.253	0.000	0.208	0.000	0.128	0.099	81.459
KTINGSGSPHGWVQNQQT	3532	97.122	0.000	0.000	0.000	1.240	1.975	290.720
KTERVSGSPHKAQNQQT	3263	96.943	0.000	0.000	0.000	0.000	0.144	135.438
KTINGSGSPHKAQNRQS	3264	96.843	0.136	0.532	0.000	0.042	0.178	55.945
KTERLSGSPHKAQNQQT	3265	95.857	0.000	0.004	0.005	0.126	0.260	102.372
KTDNGSGSPHKAHNQQT	3266	95.164	0.000	0.000	0.000	0.000	0.027	55.313
KTFHSGSGSPHKTQNQQT	3267	94.714	0.000	0.210	0.120	0.000	0.000	51.119
KTINGGGSPHKAQTQQI	3533	92.345	0.000	0.000	0.000	0.000	0.023	54.199
KTSNGSGSPHKAQNPPPT	3268	91.528	0.000	0.000	0.000	0.000	0.039	51.541
ETINGSGSPHKAQNLQT	3269	90.969	0.221	1.023	0.197	0.179	0.813	107.216
KTVHNGSGSPHKAQNQQT	3534	90.073	0.000	0.000	0.000	0.000	0.304	97.003
NTINGSGSPHKAQNQQT	3270	90.017	1.712	1.261	1.171	0.923	0.540	55.179
KTINGGGSPHKAQNQQC	3535	89.301	0.219	0.000	0.000	0.287	0.319	53.840
KTENMSGSPHKAQNQQT	3271	89.247	0.000	0.000	0.000	0.000	0.260	130.568
KTENVSGSPHKAQNQQT	3272	88.506	0.000	0.000	0.000	0.964	0.112	108.591
KTSSGSGSPHKAQYQQT	3273	87.304	0.000	0.000	0.000	0.000	0.299	58.143
KTIDGGSGSPHKAQNKQT	3536	85.019	0.000	0.000	0.000	0.000	0.477	55.517
KTEKVSOGSPHKAQNQQT	3274	84.558	0.000	0.022	0.000	0.873	0.424	112.185
KAINGSGSPHKAQDQET	3275	84.080	0.000	0.000	0.000	0.194	0.027	87.637
KTCNKSGSPHKAQNQQT	3276	83.992	0.000	0.000	0.165	0.283	0.000	119.496
KTINGGGSPHKAQNLQI	3537	83.881	0.000	0.000	0.000	0.046	0.387	78.383
KNINGGGSPHKAQNQQT	3538	83.083	0.000	0.042	0.000	0.000	0.000	75.913
KTEHLSGSPHKAQNQQT	3277	83.080	0.000	0.000	0.012	0.021	0.189	69.494
KAEMGSGSPHKAQNQQT	3278	83.049	0.000	0.020	0.000	0.768	0.112	135.019
KATNGSGSPHKAQNHQT	3279	82.627	0.000	0.176	0.000	0.155	0.057	66.207
KAIKGSGSPHKAQDQQT	3280	82.258	0.000	0.000	0.000	0.108	0.000	85.178
KTINGGGSPHKSQNQLT	3539	82.231	0.000	0.070	0.000	0.000	0.498	126.986
KTVNNGSGSPHKAQNKQT	3540	81.481	0.000	0.000	0.000	0.000	0.122	69.455
KTINGSGSPHSGHWWQT	3281	81.434	0.000	0.000	0.000	0.000	1.011	65.252
KTDKTSOGSPHKAQNQQT	3282	81.430	0.000	0.000	0.000	1.362	0.291	169.515
KTFKSGSGSPHKAQNQQT	3283	80.890	0.000	0.000	0.000	0.000	0.017	71.144
KTVNNGSGSPHKAQNLQI	3284	80.509	0.000	0.000	0.000	0.000	0.166	71.156
KTINGSGSPHKAQRPEQT	3285	80.418	0.000	0.013	0.000	0.149	0.361	50.319
KTINGSGSPHKAQRTMT	3286	80.388	0.000	0.022	0.170	1.812	1.025	100.248
KTEKASGSPHKAQNQQT	3287	80.285	0.000	0.041	0.000	0.000	0.261	90.390
KSDQSGSGSPHKAQNQQT	3288	80.076	0.000	0.000	0.000	0.993	0.124	151.911
KTEITSGSPHKAQNQQT	3289	79.620	0.000	0.163	0.000	0.332	0.074	76.686
KTDKSSGSPHKAQNQQT	3290	79.470	0.055	0.012	0.000	1.437	0.367	141.351
KTIDGSGSPHKAQNQQH	3291	79.090	0.000	0.000	0.000	0.136	0.049	57.914
KTVNNGSGSPHKAQNHQT	3541	78.849	0.000	0.000	0.000	0.000	0.045	54.086
KNTNGSGSPHKAQNQQT	3292	78.445	0.000	0.000	0.000	0.571	0.177	89.719
KTETHSGSPHKAQNQQT	3293	77.974	0.000	0.067	0.000	0.000	0.512	57.287
KTINGGGSPHKAQNLQI	3542	77.822	0.000	0.131	0.000	0.000	0.274	69.884
KTINGSGSPHKAQHQT	3294	77.502	0.000	0.052	0.041	0.000	0.188	68.196
KTINGTSGSPHKAQNHQI	3543	77.089	0.171	0.000	0.000	0.000	0.166	54.281
KTINGSGSPHKAQHRIT	3295	76.849	0.105	0.499	0.170	1.424	0.214	127.000
KTINGSGSPHKAQYIHT	3296	76.170	0.000	0.014	0.033	1.523	0.168	59.649
KTENISGSPHKAQNQQT	3297	76.072	0.000	0.000	0.000	0.115	0.132	83.118
KTIIGSGSPHKAHNQQT	3544	75.872	0.000	0.050	0.000	0.000	0.235	65.492
KTINGSGSPHKAQKFET	3298	75.788	0.000	0.000	0.028	0.108	0.093	65.588
KTSNESGSPHKAQNHQT	3299	75.720	0.000	0.000	0.000	0.169	0.217	70.590
KTINGSGSPHKAQFPST	3300	75.677	0.000	0.004	0.000	0.849	0.127	119.712
KTERPSGSPHKAQNQQT	3301	75.669	0.000	0.029	0.000	0.000	0.156	73.894
KTINGNGSPHKAQNPLT	3545	75.269	0.000	0.000	0.000	0.366	0.000	53.583

KSIKNGSGSPHKAQNQQT	3546	75.196	0.000	0.000	0.000	0.000	0.000	90.251
KTERMSGSPHKAQNQQT	3302	74.910	0.000	0.000	0.000	0.100	0.151	122.812
KTERSSGSPHKAQNQQT	3303	74.853	0.000	0.071	0.000	1.036	0.056	125.538
KTELHSGSPHKAQNQQT	3304	74.620	0.000	0.000	0.000	0.021	0.089	53.124
KTELTSGSPHKAQNQQT	3305	74.548	0.000	0.000	0.000	0.537	0.421	100.311
KTINGSGSPHKAHNQQR	3306	74.272	0.562	0.486	0.047	0.956	0.057	107.301
KTINGGGSPHKAQSQQI	3547	74.264	0.000	0.000	0.000	0.000	0.235	67.651
KTINGSGSPHKAQAIKT	3307	74.261	0.255	0.000	0.000	0.186	0.132	73.560
KTENTSGSPHKAQNQQT	3308	74.061	0.000	0.000	0.218	0.233	0.730	96.249
KTIDGSGSPHSGQNRQT	3309	73.930	0.000	0.000	0.000	0.106	0.091	63.626
KNINGSGSPHKAQSQQT	3310	73.757	0.000	0.000	0.000	0.000	0.041	57.432
KTINGSVSPHGAQNQLT	3548	73.525	0.000	0.061	0.067	0.000	0.053	51.358
KTSNASGSPHKAQNQLT	3311	73.501	0.000	0.000	0.297	0.000	0.313	150.401
KTEARSGSPHKAQNQQT	3312	73.349	0.000	0.000	0.000	0.695	0.118	62.903
KTEKNSGSPHKAQNQQT	3313	73.347	0.000	0.000	0.044	0.159	0.021	74.393
KTANGSGSPHKAQYQQT	3314	73.038	0.000	0.000	0.000	0.153	0.160	139.451
KTVNGSGSPHKAQYQHT	3315	72.847	0.000	0.000	0.000	0.000	0.130	54.158
KTINGSGSPHTKAQNPQS	3316	72.594	0.000	0.000	0.000	0.000	0.130	62.508
KTINGSGSPHSGQNPPT	3317	72.339	0.000	0.206	0.000	0.000	0.041	134.808
KTIIGSGSPHKAQHQLT	3318	72.291	0.000	0.000	0.000	0.000	0.000	100.144
KTINGSGSPHKAQS PPT	3319	71.632	0.069	0.047	0.274	0.179	0.425	97.111
NTIYGSGSPHKAQNQQT	3320	71.267	1.739	0.000	273.69	0.000	0.209	59.707
KTINGSGSPHKAQAKLT	3321	71.154	0.000	0.273	0.017	1.591	0.777	130.132
KTDKNSGSPHKAQNQQT	3322	70.964	0.000	0.000	0.000	0.070	0.123	62.932
KTINGSGSPHSKTKSQQT	3323	70.891	0.000	0.568	0.045	0.418	0.496	83.923
KTINGSGSPHKAQDRPT	3324	70.831	0.132	0.006	0.000	0.039	0.379	66.800
KTINGIGSPHKAQNLGT	3549	70.543	0.000	0.071	0.000	0.000	0.135	104.769
KTINGSGSPHKAQSQQQL	3325	70.539	0.000	0.000	0.000	0.000	0.041	51.126
KTENLSGSPHKAQNQQT	3326	70.303	0.070	0.000	0.000	0.395	0.470	107.385
KTINGSGSPHKAQAFHT	3327	70.159	0.033	0.000	0.058	0.762	0.119	86.268
KTINGSGSPHKAQKQQT	3328	70.116	0.000	0.024	0.000	0.064	0.083	110.196
KTFSGSGSPHKAQNLQT	3329	70.035	0.000	0.327	0.303	0.000	0.228	70.917
KAINGSGSPHKAQNAQT	3330	69.651	0.000	0.000	0.000	0.023	0.142	72.160
KTESWSGSPHKAQNQQT	3331	69.144	0.000	0.000	0.000	0.000	0.019	67.699
KTTNGSGSPHKAHNQLT	3332	69.062	0.000	0.000	0.000	0.708	0.000	65.505
KTVNGNGSPHKAQNHQT	3550	68.889	0.000	0.000	0.000	0.000	0.030	52.482
KTEDKSGSPHKAQNQQT	3333	68.813	0.000	0.000	0.000	0.000	0.000	70.071
KTESASGSPHKAQNQQT	3334	68.651	0.000	0.000	0.000	0.274	0.084	80.500
KTNNGSGSPHKAQNQQY	3335	68.530	0.000	0.040	0.000	0.000	0.059	82.656
KTSGNGSGSPHKAQNLQT	3551	68.311	0.000	0.052	0.000	0.000	0.000	124.871
KTDKMSGSPHKAQNQQT	3336	68.167	0.000	0.000	0.000	0.017	0.205	88.234
KEVHSGSGSPHKAQNQQT	3337	67.901	0.000	0.000	0.000	0.727	0.000	100.111
KTINGSGSPHKAQKLNT	3338	67.782	0.073	0.092	0.000	1.232	0.201	68.637
KTINGGGSPHKSQNQHT	3552	67.773	0.000	0.057	0.000	0.000	0.220	100.748
KTVNGGGSPHKAQSQQT	3553	67.634	0.000	0.055	0.000	0.000	0.210	160.711
KTTNGSGSPHKAQYQHT	3339	67.325	0.000	0.000	0.000	1.378	0.080	83.337
KTISGSGSPHKAQYQHT	3340	66.739	0.000	0.000	0.000	0.000	0.191	59.822
KTESTSGSPHKAQNQQT	3341	66.649	0.000	0.009	0.000	1.688	0.176	95.861
KTINGSGSPHKSQNVTQT	3342	66.627	0.000	0.190	0.000	0.202	0.188	56.672
KSINGSGSPHKAQAQQT	3343	66.464	0.000	0.711	0.000	0.148	0.111	78.451
KTVNGSGSPHKAQNLQA	3344	66.379	0.000	0.000	0.000	0.000	0.132	50.934
KTVRDSGSPHKAQNQQT	3345	66.056	0.000	0.025	0.000	0.129	0.461	142.600
KTFNASGSPHKAQNPQT	3346	65.392	0.208	0.000	0.000	0.215	0.156	66.275
KTDMSGSPHKAQNQQT	3347	65.143	0.000	0.000	0.000	0.332	0.103	104.890
KTINGSGSPHKAQTPPT	3348	64.657	0.010	0.015	0.014	0.200	0.207	54.179
ETIKSGSPHKAQNQQT	3349	64.609	0.000	0.000	0.144	0.000	0.024	67.201
KNHIGSGSPHKAQNQQT	3350	64.535	0.000	0.000	0.000	1.253	0.187	70.356
KTINGSGSPHKAQYQHA	3351	64.435	0.000	0.000	0.024	0.993	0.097	57.278

KTIPIDGSPHSAQNQQT	3354	64.421	0.000	0.047	0.000	0.234	0.936	76.826
KTINGSGSPHSAQGQQA	3352	64.128	0.000	0.185	0.000	0.063	0.195	64.116
KTFNGSGSPHNKAQNHQT	3353	64.060	0.000	0.000	0.035	0.094	0.317	67.757
KESDGS GSPHSAQNQQT	3354	63.766	0.000	0.000	0.000	0.567	0.146	115.231
KTINGSGSPHSAQPPAT	3355	63.510	0.048	0.030	0.031	0.126	0.302	117.453
KTINGSGSPHSAQERPT	3356	63.460	0.000	0.011	0.000	0.810	0.173	57.506
KTIKSGSPHSAQDLQT	3357	63.260	0.000	0.000	0.000	0.000	0.218	58.576
KTDLKS GSPHSAQNQQT	3358	63.152	0.000	0.000	0.012	0.285	0.377	62.687
KTINGSGSPHSAQNPPT	3555	63.041	0.000	0.082	0.000	0.000	0.057	64.045
KTINGSGSPHSAQAMHT	3359	62.756	0.000	0.000	0.010	0.976	0.393	84.056
KTVPN SGSPHSAQNQQT	3360	62.540	0.000	0.000	0.011	0.202	0.161	93.793
KTVIGSGSPHSAQNQQT	3361	62.358	0.000	0.310	0.000	0.062	0.245	60.369
KTINGSGSPHSAQHPST	3362	62.255	0.000	0.044	0.000	1.345	0.301	101.103
KTINGL SGSPHSAQNQQT	3556	62.170	0.000	0.157	0.000	0.146	0.107	64.139
KTINGTSGSPHSAQNQQT	3557	62.151	0.000	0.000	0.000	0.000	0.000	62.376
KTINGSGSPHSAQGLQT	3363	62.043	0.007	0.000	0.005	0.651	0.210	144.610
KTINGSGSPHSAQGIPT	3364	61.952	0.041	0.000	0.012	0.897	0.502	155.013
KTESHSGSPHSAQNQQT	3365	61.947	0.000	0.000	0.000	1.480	0.106	52.506
KTINGSGSPHSAQAPAT	3366	61.934	0.000	0.169	0.015	0.696	0.197	127.420
KTINGSGSPHSAQSQSI	3367	61.870	0.000	0.000	0.000	0.200	0.175	64.027
KAEHSGSGSPHSAQNQQT	3368	61.830	0.000	0.000	0.000	0.772	0.184	116.201
KTEDRSGSPHSAQNQQT	3369	61.756	0.000	0.000	0.000	1.004	0.408	66.887
KNCLSGSGSPHSAQNQQT	3370	61.442	0.000	0.036	0.000	1.849	0.026	82.488
KTD RSGSGSPHSAQNQQT	3371	61.419	0.000	0.004	0.000	0.211	0.316	74.256
KTINGSGSPHSAQIPPT	3372	61.258	0.000	0.000	0.000	0.758	0.115	87.661
KTVKSGSGSPHSAQDQQT	3373	61.175	0.000	0.041	0.000	0.432	0.090	58.114
KNADSGSGSPHSAQNQQT	3374	60.944	0.000	0.000	0.000	1.239	0.085	104.503
KTDKVS GSPHSAQNQQT	3375	60.935	0.000	0.015	0.000	0.765	0.128	146.657
KTITGSGSPHSAQTLT	3376	60.846	0.160	8.992	0.000	0.000	0.000	55.640
KTINGSGSPHSAQAPST	3377	60.696	0.200	0.005	0.000	0.751	0.263	115.528
KNCVSGSGSPHSAQNQQT	3378	60.535	0.000	0.000	0.000	0.018	0.282	96.175
KTIRDAGSPHSAQNQQT	3558	60.346	0.000	0.000	0.000	0.141	0.251	113.179
KTVKDS GSPHSAQNQQT	3379	60.216	0.000	0.019	0.000	0.443	0.251	87.334
KNALSGSGSPHSAQNQQT	3380	60.014	0.000	0.003	0.000	0.682	0.213	137.222
KVINGSGSPHSAQGNQQT	3381	60.001	0.000	0.000	0.031	0.264	0.157	68.532
KTVNGSGSPHSAQNQQT	3559	59.871	0.062	0.020	0.000	0.080	0.185	61.847
KTIQDGS GSPHSAQNQQT	3560	59.865	0.000	0.000	0.116	1.435	0.789	87.522
KTISGGSGSPHSAQNQQT	3561	59.801	0.000	0.000	0.000	0.722	0.039	87.761
KTSNAGSGSPHSAHNQQT	3382	59.607	0.000	0.078	0.067	0.031	0.050	67.967
KTINGSGSPHSAQNQTYA	3383	59.603	0.000	0.000	0.000	0.425	0.346	101.715
KTINGSGSPHSAQNHQI	3384	59.438	0.000	0.099	0.000	0.111	0.108	76.025
KTINGGGSPHSAQDKQT	3562	59.322	0.000	0.000	0.000	0.000	0.093	50.764
KTEFVS GSPHSAQNQQT	3385	59.306	0.000	0.000	0.000	0.196	0.276	69.788
KTVNGSGSPHSAQNHLT	3386	59.239	0.133	0.034	0.000	0.000	0.156	70.786
KTREIS GSPHSAQNQQT	3387	59.027	0.000	0.042	0.224	0.356	0.269	51.696
KTINGSGSPHSAQIGMT	3388	59.013	0.081	106.528	0.000	1.003	0.248	134.585
KTIDSGSGSPHSAQNLKQT	3389	58.992	0.000	0.267	0.000	0.000	0.056	74.626
KTIIGSGSPHSAQNQQT	3563	58.924	0.000	0.202	0.000	0.000	0.126	53.992
KQEGSGSGSPHSAQNQQT	3390	58.752	0.000	0.000	0.000	0.000	0.151	135.300
KTINGTSGSPHSAQNLQT	3564	58.738	0.000	0.000	0.000	0.229	0.035	86.939
KTVNGSGSPHSAQLQQT	3391	58.681	0.315	0.465	0.045	0.529	0.333	81.201
KTFNGSGSPHSAQYQQT	3565	58.609	0.000	0.000	0.000	0.163	0.045	72.618
KSINGSGSPHSAQTSQQT	3392	58.608	0.000	3.017	0.000	0.155	0.017	71.397
KTVNGSGSPHSAQHQQT	3566	58.602	0.729	0.000	0.000	0.000	0.043	138.544
KSEKSGSGSPHSAQNQQT	3393	58.566	0.000	0.010	0.011	1.601	0.059	158.931
KNVNGSGSPHSAQNQQT	3394	58.481	0.000	0.000	0.000	0.917	0.166	53.379
KGEGSGSGSPHSAQNQQT	3395	58.472	0.000	0.034	0.000	0.037	0.066	91.023
KTINGSGSPHSAQRMST	3396	58.435	0.192	0.037	0.000	1.707	0.882	53.414

KTINGSGSPHKAQGILT	3397	58.418	0.000	0.005	0.010	0.569	0.192	102.631
KEFVGSGSPHKAQNQQT	3398	58.374	0.000	0.046	0.000	0.088	0.326	128.675
KTIIGSGSPHKAQDRQT	3399	58.258	1.393	0.230	0.219	0.000	0.045	53.981
KSDKSGSPHKAQNQQT	3400	58.248	0.000	0.000	0.000	0.076	0.166	146.566
KTEQVSGSPHKAQNQQT	3401	58.247	0.000	0.000	0.000	0.000	0.081	88.487
KTEHVS GSPHKAQNQQT	3402	58.228	0.000	0.024	0.000	0.433	0.141	71.410
KTINGS GSPHKAQDRQT	3403	58.216	0.000	0.005	0.000	0.800	0.259	120.704
KTENAS GSPHKAQNQQT	3404	58.187	0.000	0.038	0.000	0.371	0.129	88.439
KEVQSGSGSPHKAQNQQT	3405	58.125	0.000	0.000	0.000	0.657	0.000	168.220
KTINGS GSPHKAQNTHD	3406	58.108	0.000	0.027	0.000	0.410	0.126	81.189
KTINGS GSPHKAQNLQI	3407	58.022	0.000	0.044	0.000	1.548	0.243	55.714
KTINGS GSPHKAQERST	3408	58.021	0.000	0.011	0.005	0.829	0.409	87.656
KTSNGSGSPHKAQNQQT	3409	57.894	0.000	0.082	0.000	0.000	0.110	63.681
KTEYIS GSPHKAQNQQT	3410	57.891	0.000	0.000	0.000	0.076	0.075	57.620
KTINGS GSPHKAQRTCT	3411	57.863	0.000	0.140	0.129	1.855	1.716	90.146
KTINGS GSPHKAQIGHT	3412	57.769	0.024	0.000	0.000	0.281	0.154	99.262
KNCWGS GSPHKAQNQQT	3413	57.756	0.000	0.000	0.000	0.000	0.092	59.888
KTINGS GSPHKAQGAIT	3414	57.627	0.000	0.000	0.000	0.594	0.161	95.696
KTDVNS GSPHKAQNQQT	3415	57.593	0.000	0.000	0.000	0.000	0.331	66.127
KSDIGSGSPHKAQNQQT	3416	57.592	0.000	0.000	0.000	0.844	0.128	107.342
KTINGS GSPHKAQVPPT	3417	57.316	0.000	0.012	0.000	0.257	0.200	90.220
KTINGS GSPHKAQVQOI	3418	57.308	0.000	1.113	0.000	0.000	0.113	61.957
KTINGS GSPHKAQMRQT	3419	57.234	0.060	0.036	0.100	1.798	0.517	81.332
KTINGS GSPHKAQYSVT	3420	57.130	0.000	0.093	0.000	1.235	0.302	60.023
KNSIGSGSPHKAQNQQT	3421	57.101	0.000	0.052	0.000	0.083	0.074	97.381
KTINGS GSPHKAQVNLQT	3422	57.046	0.000	0.029	0.000	0.459	0.082	50.474
KAINGS GSPHKAQSQQI	3423	56.976	0.000	0.000	0.000	0.000	0.000	57.052
KTINGS GSPHKAQAITT	3424	56.924	0.000	0.000	0.000	1.239	0.438	75.250
KTINGS GSPHKAQKTLT	3425	56.844	0.000	0.017	0.009	1.800	1.400	66.415
KTVNGSGSPHKAQNQWT	3426	56.823	0.000	0.000	0.299	0.000	0.219	69.906
KTINGS GSPHKAQLHHT	3427	56.815	0.025	0.000	0.010	0.712	0.368	58.418
KTEQTS GSPHKAQNQQT	3428	56.683	0.000	0.045	0.000	0.792	0.430	59.360
KTINGS GSPHKAQNIIL	3429	56.630	0.000	0.062	0.123	0.099	0.056	76.742
KNSLGS GSPHKAQNQQT	3430	56.621	0.000	0.028	0.000	0.308	0.162	101.942
KTIPTMGSPHKAQNQQT	3567	56.560	0.000	0.000	0.000	1.824	0.371	89.951
KTINGS GSPHKAQGHHT	3431	56.559	0.000	0.000	0.000	0.632	0.117	71.050
KTDRTSGSPHKAQNQQT	3432	56.466	0.000	0.000	0.000	0.062	0.160	148.498
KTINGS GSPHKAQSKVT	3433	56.373	0.000	0.050	0.014	1.021	0.390	76.115
KEVVGSGSPHKAQNQQT	3434	56.371	0.000	0.000	0.000	0.000	0.323	116.964
KTINGS GSPHKAQLPST	3435	56.238	0.005	4.258	0.001	1.040	0.185	84.918
KTINGS GSPHKAQIGQT	3436	56.158	0.000	0.000	0.000	0.887	0.088	110.132
KTEPTSGSPHKAQNQQT	3437	56.134	0.000	0.000	0.000	0.061	0.527	143.397
KTVNGGSGSPHKSQNQQT	3568	56.114	0.116	0.000	0.000	0.000	0.040	170.548
KTINGS GSPHKAQAIHT	3438	56.047	0.000	0.000	212.32	0.887	0.890	81.908
KTINGS GSPHKAQHGLT	3439	55.999	0.000	0.000	0.101	1.913	0.244	117.191
KSELGS GSPHKAQNQQT	3440	55.997	0.000	0.005	0.000	0.881	0.239	120.521
KTINGS GSPHKAQFMCT	3441	55.916	0.000	0.000	0.000	0.078	0.448	81.959
KTINVS GSPHKAQGQQT	3442	55.870	0.000	0.191	0.000	0.592	0.040	87.211
KTINGGSGSPHKAQNQMT	3569	55.778	0.000	0.000	0.000	0.866	0.012	73.177
KTVNGSGSPHKAQHLQT	3443	55.739	0.091	0.036	0.000	0.062	0.409	62.743
KTIRENGSPHKAQNQQT	3570	55.605	0.000	0.000	0.016	0.131	0.257	95.931
KTINGS GSPHKSQTQNHQN	3444	55.551	0.000	0.048	0.000	0.000	0.099	64.846
KTINGS GSPHKAQPART	3445	55.513	0.000	0.000	0.328	1.294	0.991	127.301
KTVNGSGSPHKAQSLQT	3446	55.497	0.000	0.060	0.000	0.000	0.143	69.033
KTINGS GSPHKSQSQT	3447	55.430	0.000	0.035	0.000	0.050	0.013	125.577
KTINGSASPHKAHSQQT	3571	55.293	0.000	0.000	0.000	0.000	0.166	66.252
KTWQNS GSPHKAQNQQT	3448	55.245	0.000	0.000	0.000	0.111	0.265	114.258
KTINGS GSPHKAQDRQS	3449	55.137	1.146	0.016	0.106	0.644	0.086	55.701

KTINGSGSPHSAQMPST	3450	54.986	1.691	0.039	0.028	0.450	0.202	114.331
KTNNGGSPHSAQNLT	3572	54.963	0.000	0.000	0.000	0.000	0.089	80.506
KTINGSGSPHSAQGLT	3451	54.717	0.000	0.006	0.013	0.480	0.298	142.786
KTEVTSGSPHSAQNQQT	3452	54.663	0.000	0.000	0.000	0.323	0.185	81.482
KSINGGSPHSAQYQQT	3573	54.612	0.000	0.000	0.000	0.105	0.010	65.952
KTVIGSGSPHSAQNQQT	3453	54.603	0.000	0.000	0.000	0.000	0.106	69.121
KAVNVSGSPHSAQNQQT	3454	54.586	0.000	0.000	0.000	0.000	0.023	57.835
KTVNGSGSPHSAQNQQT	3574	54.586	0.000	0.000	0.000	0.256	0.168	95.384
KTDNRSGSPHSAQNQQT	3455	54.495	0.000	0.000	0.000	0.823	0.241	85.823
KTINGSGSPHSAQVPAT	3456	54.475	0.000	0.002	0.000	0.782	0.223	137.743
KGVLSGSPHSAQNQQT	3457	54.472	0.000	0.007	0.027	0.359	0.189	145.740
KTNGSGSPHSAQNLT	3575	54.458	0.668	0.000	0.000	0.161	0.172	159.134
KAINGSGSPHSAQDKQT	3458	54.452	0.000	0.000	0.057	0.044	0.223	56.004
KTSNGSGSPHSAHYQQT	3459	54.414	0.000	0.251	0.000	0.249	0.204	54.162
KTINGSGSPHSAQVPST	3460	54.366	0.000	1.001	0.000	0.202	0.139	117.223
KTINGSGSSHSAQNQQT	3576	54.292	1.709	1.870	1.287	1.075	0.458	67.731
KTELRSRSGSPHSAQNQQT	3461	54.289	0.000	0.007	0.040	0.790	0.239	57.814
KNINGSGSPHSAQNHQT	3462	54.248	0.000	0.034	0.000	0.340	0.075	74.979
KTVNGGSPHSAQNHQT	3577	54.246	0.375	0.024	0.000	0.000	0.146	67.188
KTINGSGSPHSAKARGEQT	3463	54.207	0.025	0.006	0.005	0.309	0.327	128.098
KTINGGSPHSAQYQHT	3578	54.188	0.000	0.000	0.000	0.000	0.223	82.256
KTEDLSGSPHSAQNQQT	3464	54.156	0.000	0.000	0.000	1.193	0.132	70.198
KTINGSGSPHSAKPGQQT	3465	54.071	0.065	0.000	0.004	0.542	0.179	73.440
KTIPKNGSPHSAQNQQT	3579	53.824	0.000	0.032	0.000	0.115	0.178	77.458
KTINGSGSPHSAQSLQI	3466	53.778	0.000	0.186	0.000	0.022	0.047	51.543
KTINGSGSPHSAKRLEQQT	3467	53.512	0.000	0.118	0.003	0.161	0.292	71.704
KTERGSGSPHSAQNQQT	3468	53.475	0.000	0.030	0.000	1.416	0.175	85.368
KTVNGSGSPHSAKPNQQT	3469	53.444	0.833	2.206	0.006	0.156	0.178	58.080
KTSNGSGSPHSAQNQST	3470	53.353	0.000	0.000	0.000	0.000	0.014	120.897
KTINGSGSPHSAQKVIT	3471	53.273	0.000	0.000	0.000	0.357	0.402	95.147
KTEGISGSPHSAQNQQT	3472	53.270	0.000	0.000	0.000	0.000	0.010	78.303
KTINGSGSPHSAQNNDQ	3473	53.226	0.000	0.000	0.000	0.593	0.046	59.664
KTINGSGSPHSAQSVHT	3474	53.226	0.000	0.004	0.000	0.446	0.217	76.110
KTINGSGSPHSAQPLGT	3475	53.049	0.015	0.004	0.001	0.515	0.222	68.656
KTINKEGSPHSAQNQQT	3580	53.006	0.000	0.029	0.000	0.177	0.111	64.520
KTCNASGSPHSAQNQQT	3476	52.998	0.000	0.011	0.000	0.897	0.141	67.934
KAINGSGSPHSAKHNET	3477	52.973	0.000	0.030	0.000	0.035	0.058	71.809
KTEGLSGSPHSAQNQQT	3478	52.891	0.000	0.000	0.020	0.104	0.155	104.529
KTRDASGSPHSAQNQQT	3479	52.861	0.000	0.000	0.010	1.062	0.402	52.089
KTSNGSGSPHSAQNLT	3480	52.843	0.000	0.000	1.605	0.178	0.214	74.823
KTNGSGSPHSAQIQQT	3481	52.809	0.000	0.000	0.000	0.000	0.012	98.291
KTVNGGSPHSAQNLT	3581	52.788	0.000	0.031	0.000	0.000	0.165	83.215
KTDRSSGSPHSAQNQQT	3482	52.737	0.000	0.000	0.000	0.995	0.085	123.421
KTINGSGSPHSAQVRNT	3483	52.735	0.000	0.101	0.011	0.230	0.423	68.893
KTINGSGSPHSAKPSNQT	3484	52.680	1.494	4.762	0.003	0.330	0.208	87.951
KTINGSGSPHSAQVGHT	3485	52.624	0.000	0.000	0.006	0.535	0.192	106.448
KNAIGSGSPHSAQNQQT	3486	52.516	0.000	0.000	0.000	0.165	0.198	117.939
KAENGSGSPHSAQNQQT	3487	52.487	0.000	0.157	0.029	0.000	0.242	120.256
KTINGSGSPHSAQRDIT	3488	52.415	0.098	0.000	0.008	1.784	0.605	88.122
KTINGSGSPHSAQMPNT	3489	52.408	0.084	0.036	0.025	0.057	0.359	66.040
KTVNGSGSPHSAQNQQT	3490	52.395	0.033	0.077	0.013	0.105	0.175	58.000
KTIPAIGSPHSAQNQQT	3582	52.346	0.000	0.009	0.000	0.034	0.134	51.949
KTINGSGSPHSAKARGLQT	3491	52.275	0.000	0.000	0.036	1.235	1.425	169.881
KTELGSGSPHSAQNQQT	3492	52.232	0.000	0.007	0.006	0.532	0.088	87.314
KAETGSGSPHSAQNQQT	3493	52.219	0.000	0.047	0.581	0.009	0.188	132.940
KTINGSGSPHSAKLQKQQT	3494	52.144	0.615	0.477	1.071	1.113	0.429	61.833
KTINGSGSPHSAKPSLQT	3495	52.137	0.041	1.614	0.002	0.902	0.222	70.363
KTINGSGSPHSAQRDQT	3496	51.897	0.069	0.014	0.040	0.867	0.554	102.317

KTDVSGSPHPSKAQNQQT	3497	51.849	0.000	0.007	0.000	0.385	0.560	115.774
KTINGSGSPHPSKNRDQQT	3498	51.830	0.000	0.008	0.000	0.480	0.138	100.300
KSINGSGSPHPSKAPNLQT	3499	51.812	0.000	0.256	0.000	0.085	0.139	59.270
KTINGSGSPHPSKAQAKGT	3500	51.727	0.048	0.016	0.000	0.271	0.525	104.917
KTVNGSGSPHPSKAQDKQT	3501	51.580	0.428	0.000	0.069	0.041	0.063	69.225
KTINGGGSPHPSKAQNPQA	3583	51.574	0.000	0.000	0.000	0.192	0.000	102.792
KTINGSGSPHPSKAQSAHT	3502	51.569	0.068	0.070	0.000	0.589	0.249	79.498
KTINGNGSPHPSKSQNHQT	3584	51.379	0.000	0.054	0.000	0.000	0.082	56.614
KTVPTSGSPHPSKAQNQQT	3503	51.348	0.013	0.000	0.000	1.017	0.338	102.651
KTIDGSGSPHPSKSQNHQT	3504	51.307	0.000	0.000	0.000	0.000	0.269	63.174
KTDVKSQSPHPSKAQNQQT	3505	51.296	0.000	0.000	0.000	0.515	0.224	53.601
KAINRSGSPHPSKAQDQQT	3506	51.262	0.000	0.000	0.000	0.000	0.036	54.631
KTINGSGSPHPSKAQSTMT	3507	51.249	0.018	0.002	0.002	0.321	0.341	73.213
KTVNASGSPHPSKAQNQLT	3508	51.249	0.000	0.000	0.000	0.000	0.268	99.559
KTINGSGSPHPSKAQREMT	3509	51.076	0.000	24.900	143.49	1.564	0.476	70.961
KTIVHSGSPHPSKAQSQQT	3510	51.057	0.000	0.000	0.000	0.143	0.146	54.185
KTINGGGSPHPSKSQNRQT	3585	51.017	0.000	0.000	0.000	0.000	0.421	149.370
KTINGSGSPHPSKAQYRAT	3511	51.008	0.000	0.158	0.000	0.690	0.120	50.650
KTINGGGSPHPSKAQRQQT	3586	50.998	0.000	0.041	0.000	0.991	0.142	147.942
KTEPMMSGSPHPSKAQNQQT	3512	50.960	0.203	0.000	0.000	1.816	0.415	126.322
KTINGSGSPHPSKQWQQT	3513	50.800	0.000	0.044	0.047	0.111	0.324	65.506
KETAGSGSPHPSKAQNQQT	3514	50.762	0.000	0.027	0.000	1.706	0.054	212.795
KTINGSGSPHPSKAQRMNT	3515	50.686	0.000	108.747	0.019	0.943	0.264	97.975
KNNLGGSPHPSKAQNQQT	3516	50.670	0.000	0.019	0.000	0.406	0.121	102.408
KTINGSGSPHPSKAQNHQT	3517	50.667	0.211	0.140	0.051	0.101	0.090	80.603
KTIIKNGSPHPSKAQNQQT	3587	50.587	0.000	0.000	0.000	0.000	0.751	75.547
KTINGSGSPHPSYHVNQQT	3588	50.486	0.000	0.056	0.059	0.528	0.275	179.489
KTINGSGSPHPSKAGDSQT	3518	50.457	0.614	0.236	0.008	1.062	0.071	74.355
KTINGSGSPHPSKLSQQT	3519	50.368	0.000	0.296	0.000	1.796	1.096	95.240
KTINGSGSPHPSKAQKIST	3520	50.285	0.000	0.000	0.088	0.108	0.302	51.115
KTEYNSGSPHPSKAQNQQT	3521	50.256	0.000	0.000	0.000	0.000	0.009	62.679
KTINGSGSPHPSKAPSMQT	3522	50.249	0.000	0.000	0.004	0.941	0.460	75.504
EAINSGSPHPSKAQNQQT	3523	50.243	0.629	0.094	0.000	0.057	1.519	117.305
KTINGSGSPHPSKASPRQT	3524	50.227	0.088	0.005	0.068	1.761	0.530	67.241
KTINGSGSPHPSKRMEQQT	3525	50.177	0.000	0.000	0.000	1.327	0.208	81.769
KTINGSGSPHPSKAQYQNT	3526	50.099	0.000	0.008	0.000	0.017	0.119	71.846
KTERVSGSPHPSKAQNQQT	3589	96.943	0.000	0.000	0.000	0.000	0.144	135.438
KAEIGHDSPHPSKSGQNQQT	1754	63.249	0.000	0.000	0.000	0.060	0.024	27.173

[0514] Table 16 provides the peptide sequence of 341 matured capsid variants, and the fold enrichment of these matured capsid variants relative to the AAV9 control that demonstrated a 75-fold or greater increase in expression in the brain of NHPs relative to the AAV9 control and had a fold-change in expression that was less than 2 relative to the AAV9 control in the liver and the DRG.

Table 16. NGS fold-enrichment of TTM-001 and TTM-002 matured AAV capsid variants in the brain of NHPs

Sequence	SEQ ID NO:	Fold Enrichment relative to AAV9						
		Brain (NHP)	DRG (NHP)	Heart (NHP)	Muscle (NHP)	Liver RNA (NHP)	Liver DNA (NHP)	Brain (Mouse)
KTFNRSQSPHPSKAQNQQI	3591	86.359	0.000	113.67	0.000	0.000	0.092	25.568
KTIIIGSGSPHPSKAQNRHT	3239	217.176	0.000	0.000	0.000	0.000	0.000	210.515
KTFPGSGSPHPSKVQNQQT	3240	199.720	0.000	0.000	0.000	0.000	0.967	97.703
KTEKMSGSPHPSKAQNQQT	3241	169.461	0.523	0.000	0.000	0.000	0.158	109.161
KAINGHDSQPHPSKSGQIRQT	3606	108.510	0.000	23.908	0.000	0.132	0.261	8.862

KTINGHDSPHKIGQNQHA	3607	77.321	0.000	18.836	0.028	0.220	0.132	7.578
KEINGRGSPhSKAQNQQT	3527	134.390	0.239	0.000	0.000	0.000	0.232	52.311
KTVNRNGSPHSKAQNQQT	3528	133.016	0.000	0.416	0.000	0.000	0.000	85.361
KAINGYDSPHKSQGKQQT	3608	83.803	0.041	9.491	0.000	0.031	0.150	13.057
KTVNGSGSPHSKARDQQT	3242	124.789	0.123	0.039	0.312	0.569	0.454	132.137
KTESGHDSPHKSGQNQQT	3609	86.513	0.000	7.414	0.000	0.000	0.038	13.163
KTINGHDSPHKSGQSVQT	3610	75.748	0.010	6.808	0.000	0.165	0.058	9.321
KTFNNGSGSPHSKAPNLQT	3243	121.436	0.000	0.167	0.000	0.000	0.015	168.920
KTEKTSGSPHSKAQNQQT	3244	120.337	0.000	0.355	0.000	0.000	0.119	101.467
TTINGHDSPHKSGQNQQT	3611	108.963	1.512	3.445	0.869	0.659	1.109	14.788
KTINGHESPHKSGRSQQT	3612	97.106	0.000	3.329	0.022	0.000	0.181	9.378
KTINGSGSPHSKAHVRQT	3245	119.798	0.000	0.000	0.262	0.694	1.039	165.590
KTVNGSGSPHSKAPNQHT	3246	117.207	0.000	0.109	0.000	0.000	0.074	51.008
KTEKISGSPHSKAQNQQT	3247	116.603	0.000	0.000	0.000	0.000	0.426	102.978
KTINGPGSPHSKAHNQQT	3529	115.742	0.146	0.000	0.235	0.000	0.513	52.508
KTINGHDSPHKSGQNKLE	3613	76.204	0.000	1.430	0.000	0.015	0.031	12.419
KTVNGSGSPHSKTQSQQT	3248	115.086	0.000	0.726	0.000	0.000	0.340	63.248
TTINGSGSPHSKAQNQQT	3249	114.856	1.340	14.856	0.827	1.281	0.957	72.058
KSINESGSPHSKAQNQQT	3250	113.833	0.000	0.000	0.000	0.000	0.000	67.649
KTINGHDSPHKTGQNQQT	3614	77.562	0.000	1.056	0.000	0.000	0.000	6.379
KTERTSGSPHSKAQNQQT	3251	112.957	0.000	0.009	0.000	1.128	0.207	117.374
KTINGSGSPHSKAQPAKT	3252	111.472	0.331	0.000	1.089	0.044	1.796	215.275
KTINGRGSPhKRGQNQQT	3837	120.889	0.100	0.814	0.434	0.458	0.614	13.988
KTINGSGSPHTKAQNPPT	3592	147.061	0.000	0.727	0.000	0.000	0.000	34.425
KTEKSSGSPHSKAQNQQT	3253	107.470	0.000	0.016	0.014	0.977	0.179	100.177
KAINGHDNPHKSGQNQQT	3615	88.906	0.297	0.721	0.482	0.222	0.130	9.702
KTSYNGSGSPHSKAQNQQT	3530	105.937	0.000	0.000	0.000	0.000	0.114	105.894
KTINGQDSPHKSQGHHQA	3616	85.657	1.127	0.579	0.000	0.193	0.557	5.582
KTEKSGSGSPHSKAQNQQT	3254	105.614	0.053	0.031	0.000	0.586	0.169	84.653
KTINGSGSPHKSQTQQN	3255	104.474	0.000	0.131	0.000	0.084	0.038	54.021
KTERISGSPHSKAQNQQT	3256	103.692	0.000	0.000	0.000	0.062	0.370	89.637
KTERASGSPHSKAQNQQT	3257	103.669	0.000	0.000	0.000	0.127	0.070	115.550
KSINGHDSPHKSGQIQHT	3617	87.598	0.000	0.480	0.000	0.714	0.347	13.872
KELHSGSGSPHSKAQNQQT	3258	102.680	0.000	0.000	0.000	1.634	0.592	96.554
KAINGSGSPHSKAQNLAT	3259	101.954	0.000	10.954	8.655	0.298	0.239	116.685
KTVNGSGSPHKSQNQLT	3260	101.327	0.000	0.035	0.000	0.000	0.025	80.716
KAINGHDSPHKSGPRQQT	3618	145.142	0.000	0.408	0.000	0.000	0.000	8.259
KTVNGHDSPHKSGHTQQT	3619	82.246	0.000	0.378	1.142	0.000	0.123	6.160
KSINGHDSPHKSGQRQHT	3620	80.132	0.000	0.357	0.000	0.000	0.000	9.851
KTERNSGSPHSKAQNQQT	3261	99.892	0.000	0.000	0.000	0.000	0.107	87.392
KSLNGSGSPHTKAQNQQT	3593	81.515	0.197	0.333	0.000	0.000	0.085	45.140
KSVNNGSGSPHSKAQNQQT	3531	99.385	0.000	1.329	0.000	0.359	0.079	51.016
KAINGHDSPHKSAQSQQT	3621	95.204	0.146	0.310	0.000	0.699	0.058	14.595
KSIYGHESPHKSGQNQQS	3622	90.947	0.817	0.310	0.000	0.000	0.243	8.064
KTENGSGSPHSKAQGQQT	3262	99.253	0.000	0.208	0.000	0.128	0.099	81.459
KTVNGHDSPHKSLQNQQT	3623	112.925	0.000	0.301	0.059	0.000	0.322	16.726
KTINGSGSPHGWVQNQQT	3532	97.122	0.000	0.000	0.000	1.240	1.975	290.720
KTINGHGSPhSKAQNPQT	3838	83.478	0.000	0.288	0.219	0.000	0.260	11.001
KTSNGYDSPHKSQGKQQT	3624	77.001	0.032	0.286	0.000	0.000	0.016	8.813
KTVNGHDSPHKSGRNQET	3625	102.695	0.000	0.286	0.000	0.000	0.027	11.958
KTTNGHDSPHKSGQTQLT	3626	115.637	0.000	0.283	0.000	0.052	0.321	17.885
KAINGHDSPHKSEKNQQT	3627	77.103	0.000	0.274	0.000	0.000	0.000	26.868
KTERVSGSPHSKAQNQQT	3263	96.943	0.000	0.000	0.000	0.000	0.144	135.438
KTINGSGSPHSKALNRQS	3264	96.843	0.136	0.532	0.000	0.042	0.178	55.945
KTERLSGSPHSKAQNQQT	3265	95.857	0.000	0.004	0.005	0.126	0.260	102.372
KIINGRDSPhKSGQDQQT	3628	78.773	0.000	0.254	0.000	0.000	0.156	16.132
KTDNGSGSPHSKAHNQQT	3266	95.164	0.000	0.000	0.000	0.000	0.027	55.313
KTFHSGSGSPHKTQNQQT	3267	94.714	0.000	0.210	0.120	0.000	0.000	51.119

KTISGHDSPHKTGHNQQT	3629	92.490	0.000	0.233	0.057	0.730	0.000	8.823
KTVNAHDSPHKSGQNQLT	3630	79.137	0.000	0.233	0.178	0.753	0.045	29.254
KTINGGGSPHKSQAQTQQI	3533	92.345	0.000	0.000	0.000	0.000	0.023	54.199
KSINGYDSPHKSGQTQQT	3631	79.227	1.817	0.226	0.000	0.000	1.148	4.497
KTINGHESPHKSGQTQQI	3632	86.089	0.000	0.222	0.000	0.000	0.024	3.989
KTINGHDSPHKSGQSKQA	3633	101.460	0.000	0.222	0.000	0.185	0.114	7.510
KTSSNGSGSPHKSQAQNPPT	3268	91.528	0.000	0.000	0.000	0.000	0.039	51.541
ETINGSGSPHKSQAQNLQT	3269	90.969	0.221	1.023	0.197	0.179	0.813	107.216
KTVHNGSPHKSQAQNNQT	3534	90.073	0.000	0.000	0.000	0.000	0.304	97.003
NTINGSGSPHKSQAQNNQT	3270	90.017	1.712	1.261	1.171	0.923	0.540	55.179
KTINGGGSPHKSQAQNNQC	3535	89.301	0.219	0.000	0.000	0.287	0.319	53.840
KTENMSGSPHKSQAQNNQT	3271	89.247	0.000	0.000	0.000	0.000	0.260	130.568
KTENVSGSPHKSQAQNNQT	3272	88.506	0.000	0.000	0.000	0.964	0.112	108.591
KTSSSGSGSPHKSQAQYQQT	3273	87.304	0.000	0.000	0.000	0.000	0.299	58.143
KTIDGGSPHKSQAQNKQT	3536	85.019	0.000	0.000	0.000	0.000	0.477	55.517
KTEKVSOGSPHKSQAQNNQT	3274	84.558	0.000	0.022	0.000	0.873	0.424	112.185
KAINGSGSPHKSQAQNDQET	3275	84.080	0.000	0.000	0.000	0.194	0.027	87.637
KTCNKSGSPHKSQAQNNQT	3276	83.992	0.000	0.000	0.165	0.283	0.000	119.496
KTINGGGSPHKSQAQNNQLI	3537	83.881	0.000	0.000	0.000	0.046	0.387	78.383
KNINGGGSPHKSQAQNNQT	3538	83.083	0.000	0.042	0.000	0.000	0.000	75.913
KTEHLSGSPHKSQAQNNQT	3277	83.080	0.000	0.000	0.012	0.021	0.189	69.494
KAIIGHESPHKSGQNQQT	3634	88.563	0.000	0.150	0.000	0.062	0.145	8.530
KTINGHDSPHKGTGQNQPP	3635	77.357	0.000	0.149	0.000	0.000	0.096	8.865
KAINGHDSPHKSGQSPQT	3636	75.734	0.095	0.148	0.000	0.000	0.238	14.195
KAEMSGSGSPHKSQAQNNQT	3278	83.049	0.000	0.020	0.000	0.768	0.112	135.019
KATNGSGSPHKSQAQNHQT	3279	82.627	0.000	0.176	0.000	0.155	0.057	66.207
KTIKGNDSPHKSVQNNQT	3637	85.986	0.000	0.135	0.000	0.263	0.000	8.603
KAIKGSGSPHKSQAQDQQT	3280	82.258	0.000	0.000	0.000	0.108	0.000	85.178
KTINGGGSPHKSQNNQLT	3539	82.231	0.000	0.070	0.000	0.000	0.498	126.986
KTEFGHDSPHKSGQNQQT	3638	77.245	0.000	0.124	0.000	0.561	0.063	16.337
KTINGHDSPHKSQAQNYQT	3639	130.375	0.000	0.124	0.000	0.097	0.123	19.443
KTFNGSASPHKSALNNQT	3839	84.258	0.000	0.122	0.000	0.104	0.037	31.855
KTINGCGSPHASGQNQQT	3840	132.540	0.000	0.121	0.042	0.000	0.059	1.857
KTINAHDSPHKIGQNNHQT	3640	106.832	0.000	0.121	0.000	0.000	0.231	5.074
KTVNGNGSPHKSQAQNKQT	3540	81.481	0.000	0.000	0.000	0.000	0.122	69.455
KTINGHESPHKSQAQNRQT	3641	95.531	0.000	0.113	0.000	0.130	0.082	4.815
KTINGSGSPHKSQGHWQQT	3281	81.434	0.000	0.000	0.000	0.000	1.011	65.252
KTTNGHDSPHKSGQNQQG	3642	85.113	0.000	0.107	0.000	0.000	0.017	10.555
KTIKGQDSPHKIGQNNQQT	3643	110.357	0.000	0.103	0.058	0.166	0.135	11.829
KTDKTSOGSPHKSQAQNNQT	3282	81.430	0.000	0.000	0.000	1.362	0.291	169.515
KTVNGHDSPHKSGQNNHLT	3644	81.516	0.000	0.100	0.017	0.000	0.028	16.096
KTFKSGSPHKSAPNNQQT	3283	80.890	0.000	0.000	0.000	0.000	0.017	71.144
KSINGHDSPHKSGQYQHT	3645	88.195	0.000	0.099	0.000	0.000	0.149	14.485
KTINGNDSPHKSVQNNHQT	3646	120.002	0.000	0.099	0.788	0.000	0.000	7.920
KTVNGSGSPHKSQAQNNQLI	3284	80.509	0.000	0.000	0.000	0.000	0.166	71.156
KTINGSGSPHKSQRPEQQT	3285	80.418	0.000	0.013	0.000	0.149	0.361	50.319
KTINGSGSPHKSQAQRMTT	3286	80.388	0.000	0.022	0.170	1.812	1.025	100.248
KTITGHDSPHKSGQNNQWT	3647	81.658	0.000	0.090	0.000	0.936	0.000	7.744
KTNNGHDSPHKSVQNNQHT	3648	115.172	0.000	0.083	0.000	0.000	0.062	7.934
KTEKASGSPHKSQAQNNQQT	3287	80.285	0.000	0.041	0.000	0.000	0.261	90.390
KTIDGHDSPHKSGQNNQHA	3649	91.058	0.000	0.082	0.000	0.000	0.000	10.781
KSDQSGSGSPHKSQAQNNQQT	3288	80.076	0.000	0.000	0.000	0.993	0.124	151.911
KTVNGHDSPHKSGQTRQT	3650	133.276	0.251	0.080	0.093	0.034	0.129	7.174
KTVNGHDSPHKSGQNNLHT	3651	88.080	0.000	0.080	0.000	0.000	0.039	11.363
KAISGHDSPHKSGLNQQT	3652	78.846	0.000	0.079	0.000	0.000	0.015	11.045
KTEITSGSPHKSQAQNNQQT	3289	79.620	0.000	0.163	0.000	0.332	0.074	76.686
KTDKSSGSPHKSQAQNNQQT	3290	79.470	0.055	0.012	0.000	1.437	0.367	141.351
KAINGHDSPHKSQAQNDQET	3653	90.402	0.000	0.073	0.000	0.746	0.000	10.674

KTITGHDSPHKSGQHLQT	3654	137.945	0.000	0.072	0.000	0.000	0.000	4.187
KTIDGSGSPHKAQNQQH	3291	79.090	0.000	0.000	0.000	0.136	0.049	57.914
KTVNGNGSPHKAQNQHT	3541	78.849	0.000	0.000	0.000	0.000	0.045	54.086
KNTNGSGSPHKAQNQQT	3292	78.445	0.000	0.000	0.000	0.571	0.177	89.719
KTINGHDSPHKSRNLNPT	3655	92.883	0.000	0.070	0.050	0.904	1.075	5.598
KTETHSGSPHKAQNQQT	3293	77.974	0.000	0.067	0.000	0.000	0.512	57.287
KTVDGHDSPHKSGQKQQT	3656	78.802	0.000	0.069	0.000	0.157	0.342	7.200
KTINGQDSPHKSGQNQDT	3657	82.075	0.000	0.067	0.000	0.225	0.144	9.626
KTINGGSGSPHKSALNQON	3542	77.822	0.000	0.131	0.000	0.000	0.274	69.884
KTIEGHDSPHKSGRNQQT	3658	75.838	0.000	0.065	0.017	0.000	0.079	7.818
KTTNGHDSPHKSGQNLLT	3659	77.738	0.130	0.064	0.185	0.424	0.326	15.192
KTINGHDSPHKSGQLVIT	3660	76.781	0.089	0.064	0.000	0.338	0.475	11.323
KTVNGHDSPHKSRQSQQT	3661	76.458	0.000	0.063	0.000	0.000	0.021	8.136
KTINGSGSPHKSALHQHT	3294	77.502	0.000	0.052	0.041	0.000	0.188	68.196
KTINGHDSPHKSGRTQET	3662	81.599	0.000	0.062	0.000	0.000	0.137	7.270
KTINGHDSPHKSVQTHQT	3663	77.309	0.237	0.062	0.000	0.000	0.116	7.519
KTINGTSGSPHKAQNHQI	3543	77.089	0.171	0.000	0.000	0.000	0.166	54.281
KTINGSGSPHKAQHRTIT	3295	76.849	0.105	0.499	0.170	1.424	0.214	127.000
KTINGSGSPHKAQYIHT	3296	76.170	0.000	0.014	0.033	1.523	0.168	59.649
KTSNGHDSPHKSGQNQPA	3664	75.834	0.000	0.056	0.000	0.000	0.000	8.501
KTEGKHDSPHKSGQNQQT	3665	98.384	0.000	0.056	0.000	0.000	0.000	10.345
KTENISGSPHKAQNQQT	3297	76.072	0.000	0.000	0.000	0.115	0.132	83.118
KVINGHDSPHKSGQTQQT	3666	91.665	0.000	0.055	1.526	0.311	0.000	7.391
KTIIIGGSGSPHKAHNQQT	3544	75.872	0.000	0.050	0.000	0.000	0.235	65.492
KTINGPDSPHKIGQNQQS	3667	85.726	0.000	0.055	0.171	0.000	0.063	10.055
KTINGSGSPHKAQKFET	3298	75.788	0.000	0.000	0.028	0.108	0.093	65.588
KTSNESGSPHKAQNHQT	3299	75.720	0.000	0.000	0.000	0.169	0.217	70.590
KTINGSGSPHKAQFPST	3300	75.677	0.000	0.004	0.000	0.849	0.127	119.712
KTERPSGSPHKAQNQQT	3301	75.669	0.000	0.029	0.000	0.000	0.156	73.894
KAVNGHDSPHKSVQNQQT	3668	81.051	0.448	0.051	0.000	0.665	0.091	11.288
KTINGNGSPHKAQNPLT	3545	75.269	0.000	0.000	0.000	0.366	0.000	53.583
KSIKNGSPHKAQNQQT	3546	75.196	0.000	0.000	0.000	0.000	0.000	90.251
KTINGHDSPHKSRQDQHT	3669	75.595	0.000	0.049	0.118	0.030	0.045	8.540
KAINGPDSPHKSGQKQQT	3670	78.213	0.464	0.047	0.000	0.323	0.162	10.395
KTINGHDSPHKSRQSQHT	3671	88.544	0.499	0.046	0.000	0.059	0.032	8.324
KTIYGHDSPHKSVQNQLT	3672	92.381	0.000	0.043	0.000	0.103	0.016	12.323
KTVNGHDSPHKSGQNLLT	3673	83.969	0.114	0.040	0.023	0.000	0.035	18.894
KTESAHDSPHKSGQNQQT	3674	80.810	0.000	0.039	0.000	0.000	0.000	13.338
KTENKSGSPHKAQNQQT	3594	103.854	0.000	0.037	0.000	0.000	0.119	31.182
KTTNGQDSPHKSGQNQQS	3675	92.419	0.000	0.037	0.043	0.000	0.079	7.592
KTDKSGSPHKAQNQQT	3595	94.572	0.000	0.037	0.000	0.951	0.367	47.888
KTIDGHDSPHKSGRNQQI	3676	80.240	0.000	0.037	0.000	0.040	0.144	10.363
KTINGYDSPHKSGQYQHT	3677	81.534	0.000	0.036	0.000	0.000	0.000	10.524
KTDNGHDSPHKSRQNQQT	3678	105.312	0.000	0.033	0.000	0.000	0.018	7.931
KTINGHDSPHKSWVRQQT	3679	125.537	0.000	0.033	0.000	0.291	0.174	11.687
KTINGHESPHKSGQNQHS	3680	92.248	0.000	0.032	0.012	0.090	0.088	9.720
KTVNGHDSPHKIGHNQQT	3681	120.985	0.000	0.029	0.000	0.000	0.009	10.167
KTCNGHDSPHKSGRNQQT	3682	94.616	0.000	0.025	0.000	0.000	0.128	12.496
KTINGNGSPHKAQNHQA	3841	88.274	0.000	0.024	0.000	0.000	0.041	36.754
KNVVGHDSPHKSGQNQQT	3683	75.330	0.000	0.024	0.000	0.063	0.049	8.077
KTELWHDSPHKSGQNQQT	3684	85.323	0.057	0.020	0.000	0.000	0.243	9.915
KTELRRHDSPHKSGQNQQT	3685	98.098	0.000	0.019	0.000	0.000	0.007	6.588
KTINGHDSPHKSNWQQT	3686	84.825	0.000	0.016	0.000	0.000	0.132	15.788
KTDAGHDSPHKSGQNQQT	3687	88.924	0.000	0.013	0.000	1.076	0.070	18.107
KTEVGHDSPHKSGQNQQT	3688	112.457	0.000	0.011	0.000	0.000	0.138	13.125
KTESRHDSPHKSGQNQQT	3689	81.766	0.000	0.011	0.000	0.052	0.036	6.975
KSELGHDSPHKSGQNQQT	3690	107.059	0.000	0.005	0.000	0.000	0.055	13.285
KTINGHDSPHKSGQSVPT	3691	77.840	0.000	0.003	0.000	0.136	0.061	6.768

KTINGHESPHKSGQNIQP	3692	253.840	0.000	0.000	0.000	0.000	0.000	14.042
KTEMKHDSPHKSGQNQQT	3693	240.075	0.000	0.000	0.000	0.000	0.000	3.183
KTINGHDSPHKSVQNHNLN	3694	196.758	0.000	0.000	0.000	0.000	0.000	14.557
KTINGHDSPHKIGLDQQT	3695	165.627	0.000	0.000	0.000	1.942	0.000	5.469
KTSNASGSPHKAQHQQT	3596	165.206	0.000	0.000	0.000	0.000	0.082	40.558
KTINGHDSPHKRGPDQQS	3696	160.084	0.000	0.000	0.000	0.000	0.000	2.923
KTINGMGSPHKSQTQNNQT	3842	158.728	0.000	0.000	0.000	0.000	0.638	47.809
KTIKGHDSPHKSGESQQT	3697	142.264	0.000	0.000	0.000	0.000	0.218	4.176
KTEGWHDSPHKSGQNQQT	3698	142.064	0.000	0.000	0.000	0.000	0.264	11.785
KTINGHDSPHKHGQNHQT	3699	141.405	0.191	0.000	0.000	0.000	0.000	10.214
KTEQLHDSPHKSGQNQQT	3700	138.345	0.000	0.000	0.000	0.000	0.000	12.606
KTVNGTGSPHKAQNQLT	3843	137.639	0.000	0.000	0.000	0.000	0.277	48.950
KTIIGHDSPHKSGQYQHT	3701	131.825	0.000	0.000	0.000	0.000	0.211	5.762
KTSNGHDSPHKSVQNKQT	3702	130.640	0.000	0.000	0.000	0.172	0.039	11.850
KIVNGQVSPHKSGQNQQT	3703	129.649	0.000	0.000	0.000	0.000	0.031	16.942
KTVNGHDSPHKSGQRQLT	3704	129.641	0.000	0.000	0.000	0.000	0.487	20.145
KTVNGHDSPHKIGQNQLT	3705	128.582	0.000	0.000	0.499	0.027	0.199	20.957
KTINGHDSPHKSGQIIVT	3706	125.245	0.000	0.000	0.151	0.000	0.379	6.808
KTEKIHDSPHKSGQNQQT	3707	125.178	0.000	0.000	0.000	0.000	0.000	17.604
KTENAHDSPHKSGQNQQT	3708	124.477	0.000	0.000	0.000	0.000	0.062	15.805
KIGNGHESPHKSGQNQQT	3709	123.324	0.000	0.000	0.000	0.000	0.000	11.198
KEVMGHDSPHKSGQNQQT	3710	121.107	0.000	0.000	0.000	0.000	0.000	17.191
KTEVKHDSPHKSGQNQQT	3711	119.733	0.000	0.000	0.000	0.000	0.000	5.550
KTINGYDSPHKSGQKQST	3712	119.615	0.000	0.000	0.000	0.000	0.000	7.970
KTIHNGSPHKAQNQET	3844	117.388	0.000	0.000	0.000	0.000	0.000	38.874
KYQVGHDSPHKSGQNQQT	3713	112.797	0.000	0.000	0.000	0.000	0.542	9.335
KTEAMHDSPHKSGQNQQT	3714	111.765	0.000	0.000	0.000	0.000	0.000	16.142
KTIKGDDSPHKSVQNQQT	3715	109.397	0.000	0.000	0.000	0.000	0.000	19.125
KTINGHDSPHKSVQSHQT	3716	109.375	0.107	0.000	0.319	0.000	0.547	12.617
KTINGHDSPHKSGQFVVT	3717	108.725	0.000	0.000	0.000	0.124	0.406	10.179
KTVNGHDSPHKSRQNLQT	3718	107.496	0.205	0.000	0.000	1.934	0.062	8.616
KATNGHNSPHKSGQNQET	3719	106.806	0.000	0.000	0.000	0.000	0.000	10.566
KAINGHDSPHKSAQNQOI	3720	106.539	0.000	0.000	0.000	0.000	0.113	21.786
KTEHGHDSPHKSGQNQQT	3721	106.486	0.000	0.000	0.000	0.000	0.006	14.956
KTVENHDSPHKSGQNQQT	3722	106.468	0.000	0.000	0.000	0.000	0.156	9.246
KTIYGHDSPHKSGQSQPT	3723	106.431	0.000	0.000	0.000	0.155	0.137	6.562
KTISGHESPHKSGQNEQT	3724	105.740	0.000	0.000	0.000	0.378	1.384	9.156
KAIIGHDSPHKSAQNQQT	3725	105.292	0.000	0.000	0.000	0.000	0.553	16.793
KAIDGHDSPHKSGQNQLT	3726	104.701	0.331	0.000	0.000	0.201	0.638	16.109
KTIMGHDSPHKSVQNQQT	3727	104.683	0.000	0.000	0.000	0.000	0.000	8.029
KEVGGHDSPHKSGQNQQT	3728	103.896	0.000	0.000	0.000	0.000	0.000	16.899
KTINGHDSPHKSAQNLLT	3729	103.332	0.000	0.000	0.256	0.194	0.000	15.722
KTEFTHDSPHKSGQNQQT	3730	102.052	0.062	0.000	0.000	0.439	0.047	12.527
KTINASGSPHKAQNNQQT	3597	101.122	0.233	0.000	0.000	0.000	0.145	47.196
KAINGNGSPHKGQNQQT	3845	100.925	0.000	0.000	0.000	0.000	0.159	10.011
KSEMGHDSPHKSGQNQQT	3731	100.539	0.000	0.000	0.000	0.000	0.000	18.356
KAQQGHDSPHKSGQNQQT	3732	100.395	0.000	0.000	0.000	0.000	0.057	3.954
KTEVMHDSPHKSGQNQQT	3733	99.473	0.000	0.000	0.000	0.000	0.000	12.400
KAINGHDSPHKSGQSLQT	3734	99.310	0.058	0.000	1.439	0.254	0.056	17.323
KTINGSGSPHKAQNNQQT	3598	99.300	0.252	0.000	0.000	0.000	0.038	39.297
KCGEGHDSPHKSGQNQQT	3735	99.298	0.000	0.000	0.000	0.000	0.000	13.147
KTVNGHDSPHKSAQNHQT	3736	99.257	0.000	0.000	0.078	0.000	0.027	17.639
KTVNGHDSPHKSGQTQLT	3737	98.524	0.000	0.000	0.313	0.183	0.172	14.883
KTNNGHDSPHKSGRNQQT	3738	98.307	0.000	0.000	0.124	0.000	0.037	5.840
KTCNEHDSPHKSGQNQQT	3739	97.092	0.000	0.000	0.000	0.000	0.000	8.364
KTINGHDSPHKYGQNEQT	3740	96.960	0.000	0.000	0.000	0.000	0.000	4.613
KASNRHDSPHKSGHNQQT	3741	96.283	0.000	0.000	0.000	0.000	0.675	8.045
KTINGNGSPHKAQNNLQT	3846	95.963	0.000	0.000	0.000	0.000	0.247	36.341

KTETKHDSPHKSGQNQQT	3742	95.121	0.000	0.000	0.000	0.000	0.083	4.831
KSINGHDSPHKSQQNQQT	3743	94.479	0.000	0.000	0.000	0.000	1.696	9.633
KTIGGHDSPHKSGQNQQT	3744	94.420	0.000	0.000	0.000	0.000	0.333	19.324
KTDPQHDSPHKSGQNQQT	3745	93.931	0.000	0.000	0.000	0.906	0.019	11.749
KTINRHDSPHKIVQNQQT	3746	93.409	0.000	0.000	0.000	0.000	0.000	3.064
KTEQYHDSPHKSGQNQQT	3747	93.065	0.000	0.000	0.000	0.000	0.047	15.190
KTINGHDSPHKSVQSKQT	3748	92.445	0.000	0.000	0.078	0.000	0.047	4.263
KELVGHDSPHKSGQNQQT	3749	92.262	0.000	0.000	0.000	0.594	0.000	14.890
KTENRHDSPHKSGQNQQT	3750	91.675	0.000	0.000	0.000	0.000	0.000	13.282
KELMGHDSPHKSGQNQQT	3751	91.191	0.000	0.000	0.000	0.000	0.000	14.032
KTINGNDSPHKIGHNQQT	3752	91.183	0.000	0.000	0.117	0.000	0.270	11.095
KTIKGGSPHKSQAQDQQT	3847	91.172	0.000	0.000	0.000	0.064	0.085	49.580
KTEGHDSPHKSGQNQQT	3753	89.922	0.000	0.000	0.000	0.000	0.000	23.929
KTEGYHDSPHKSGQNQQT	3754	89.891	0.000	0.000	0.000	0.000	0.000	15.116
KTVNGHDSPHKSGQTQQT	3755	89.801	0.000	0.000	0.657	0.000	0.542	11.543
KTINGQDSPHKSGQNPLT	3756	89.726	0.000	0.000	0.000	0.363	0.000	15.561
KTVNASGSPHKSQAQNHQT	3599	89.467	0.091	0.000	0.000	0.045	0.252	39.024
KTINGHDSPHKSGRDQKT	3757	88.871	0.000	0.000	0.000	0.350	0.181	12.117
KTINGHDSPHKSVHNQQN	3758	88.715	0.089	0.000	0.081	0.000	0.143	10.787
KTINGHDSPHKSGQWKRT	3759	88.633	0.000	0.000	0.000	0.202	0.094	5.186
KTIDGSGSPHKSQAENRQT	3600	87.993	0.092	0.000	0.000	0.139	0.054	40.629
KNEIGHDSPHKSGQNQQT	3760	87.758	0.000	0.000	0.000	0.000	0.055	14.110
KAINGHDSPHKSGQSQQI	3761	87.585	0.000	0.000	5.310	0.000	0.000	12.864
KIINGHDSPHKSRQAQQT	3762	86.966	0.000	0.000	0.000	0.000	0.000	9.193
KTPNGHDSPHKSGQNQQT	3763	86.683	0.000	0.000	0.000	0.000	0.109	21.278
KITNGHDSPHKSGQTQQT	3764	86.443	0.000	0.000	0.000	0.192	0.190	17.479
KTINGHDSPHKSVQNHQI	3765	86.395	0.000	0.000	0.000	0.000	0.000	9.148
KTINGHDSPHKSKQNQQA	3766	86.265	0.000	0.000	0.000	0.123	0.041	5.768
KTINGHDSPHKSAQNQLN	3767	86.153	0.000	0.000	0.000	0.050	0.019	15.587
KTDITHDSPHKSGQNQQT	3768	85.876	0.000	0.000	0.000	0.000	0.013	9.076
KTVNGHDSPHKSGQTQPT	3769	85.680	0.000	0.000	1.301	1.064	0.000	8.067
KTEKFHDSPHKSGQNQQT	3770	85.358	0.000	0.000	0.000	0.000	0.026	7.229
KTDQGHDSPHKSGQNQQT	3771	85.267	0.000	0.000	0.000	0.000	0.000	16.042
KTINGHDSPHKLWINQQT	3772	85.132	0.000	0.000	1.154	0.000	0.017	12.704
KGINGPDSPHKSGQNQQT	3773	85.080	0.000	0.000	0.084	0.000	0.054	13.750
KSEIGHDSPHKSGQNQQT	3774	84.789	0.000	0.000	0.000	0.000	0.013	15.955
KTINGHDSPHKSVQKQLT	3775	84.351	0.000	0.000	0.000	0.038	0.103	11.890
KTINGHPSPHWKQNQQT	3848	84.153	0.000	0.000	0.000	0.000	0.058	3.280
KTVNGHDSPHKSGRNQLA	3776	83.858	0.000	0.000	0.000	0.000	0.132	21.252
KTNNVHDSPHKSGQNQQS	3777	83.697	0.000	0.000	0.000	0.176	0.000	7.117
KTIKGSGSPHKSQVQDQQT	3601	83.077	0.000	0.000	0.034	0.000	0.107	21.001
KSEKGHDSPHKSGQNQQT	3778	82.982	0.000	0.000	0.000	0.000	0.105	16.662
KWSAGHDSPHKSGQNQQT	3779	82.949	0.000	0.000	0.000	0.000	0.211	12.499
KELAGHDSPHKSGQNQQT	3780	82.876	0.000	0.000	0.000	0.000	0.093	18.063
KTINGHDSPHKMGRNQQS	3781	82.787	0.000	0.000	0.000	0.000	0.000	6.467
KTDQAHDSPHKSGQNQQT	3782	82.402	0.000	0.000	0.141	0.000	0.000	13.397
KTETQHDSPHKSGQNQQT	3783	82.316	0.000	0.000	0.000	0.000	0.198	10.823
KTEMTHDSPHKSGQNQQT	3784	82.221	0.000	0.000	0.000	0.000	0.000	8.431
KTINGHDSPHKSGISIQT	3785	82.019	0.000	0.000	0.000	0.191	0.044	7.310
KTDAVHDSPHKSGQNQQT	3786	81.968	0.000	0.000	0.000	0.297	0.107	13.596
KTSNGHDSPHKSVQNLQT	3787	81.921	0.000	0.000	0.072	0.000	0.330	11.544
KTEKYHDSPHKSGQNQQT	3788	81.637	0.000	0.000	0.000	0.000	0.013	7.580
KQTQGHDSPHKSGQNQQT	3789	81.581	0.000	0.000	0.000	0.000	0.133	15.225
KTINGHDSPHKMAHNQQT	3790	81.329	0.000	0.000	0.000	0.000	0.094	15.949
KAINGSGSPHKSQAQTQQA	3602	81.207	0.000	0.000	0.000	0.000	0.016	40.435
KTINGHDSPHKHGQNQQN	3791	81.065	0.000	0.000	0.000	0.000	0.000	4.110
KGADGHDSPHKSGQNQQT	3792	80.981	0.000	0.000	0.000	0.000	0.074	11.423
KVGEHDSPHKSGQNQQT	3793	80.775	0.084	0.000	0.000	0.000	0.019	16.378

KANEGHDSPHKSGQNQQT	3794	80.470	0.000	0.000	0.000	0.000	0.000	12.818
KTDTHMDSPHKSGQNQQT	3795	80.364	0.000	0.000	0.000	0.000	0.000	13.166
KTEAKSGSPHKAQNQQT	3603	80.088	0.192	0.000	0.000	0.000	0.613	47.130
KTINGHDSPHKSVQSQQS	3796	80.000	0.000	0.000	0.000	1.055	0.082	17.620
KTI PGSGSPHKAQNLQT	3604	79.973	0.871	0.000	0.000	0.000	0.000	32.693
KTCIAHDSPHKSGQNQQT	3797	79.857	0.000	0.000	0.066	0.000	0.093	1.930
KETINGHDSPHKSGQTVCT	3798	79.730	0.000	0.000	0.000	0.050	0.030	7.873
KELRGHDSPHKSGQNQQT	3799	79.596	0.000	0.000	0.000	0.000	0.006	22.001
KCQIGHDSPHKSGQNQQT	3800	79.359	0.000	0.000	0.000	0.000	0.000	2.614
KGVMGHDSPHKSGQNQQT	3801	79.170	0.000	0.000	0.000	0.138	0.086	17.287
KACDGHDSPHKSGQNQQT	3802	78.648	0.000	0.000	0.000	0.000	0.128	17.767
KTINGQDSPHKSGQYQOI	3803	78.585	0.000	0.000	0.000	0.286	0.672	5.664
KTINGHDSPHKSGQQIMT	3804	78.534	0.000	0.000	0.000	0.000	0.058	7.067
KTINGHDSPHKSRQNEQS	3805	78.534	0.000	0.000	0.000	0.112	0.188	13.388
KASNGHDSPHKSGLNHQT	3806	78.451	0.000	0.000	0.000	0.000	0.000	17.975
KTVNGHDSPHKSGQSQPT	3807	78.309	0.000	0.000	0.000	0.000	0.231	10.627
KNELGHDSPHKSGQNQQT	3808	78.135	0.000	0.000	0.000	0.000	0.182	17.457
KTETFDHDSPHKSGQNQQT	3809	78.070	0.000	0.000	0.000	0.782	0.007	4.693
KAAEGHDSPHKSGQNQQT	3810	77.793	0.000	0.000	0.000	0.000	0.060	13.552
KGQNGHDSPHKSGQNQQT	3811	77.770	0.000	0.000	0.000	0.107	0.056	13.618
KNEFGHDSPHKSGQNQQT	3812	77.740	0.000	0.000	0.000	0.000	0.029	16.318
KTSIGYDSPHKSGQNQQT	3813	77.730	0.000	0.000	0.000	0.057	0.178	4.831
KTDNGHDSPHKSGQNLQT	3814	77.565	0.504	0.000	0.000	0.000	0.000	16.184
KTEGQHDSPHKSGQNQQT	3815	77.423	0.000	0.000	0.000	0.000	0.748	20.310
KTITGHDSPHKSRQDQQT	3816	77.127	0.000	0.000	0.000	0.000	0.000	6.250
KAEHGHDSPHKSGQNQQT	3817	77.026	0.000	0.000	0.000	0.000	0.017	20.937
KTINGDDSPHKSGQKQLT	3818	76.968	0.000	0.000	0.000	0.163	0.014	15.820
KCDQGHDSPHKSGQNQQT	3819	76.887	0.000	0.000	0.000	0.193	0.013	27.317
KEILGHDSPHKSGQNQQT	3820	76.770	0.000	0.000	0.000	0.804	0.009	10.771
KTIHGSGSPHKAQNQAT	3605	76.765	0.000	0.000	0.000	0.000	0.215	43.969
KTERNHDSPHKSGQNQQT	3821	76.751	0.000	0.000	0.000	0.000	0.000	14.979
KAINGDDSPHKSGHNQQT	3822	76.578	0.000	0.000	0.000	0.032	0.059	17.755
KTSNGHNSPHKSGQNQET	3823	76.515	0.000	0.000	0.000	0.000	0.000	4.764
KTINGHDSPHKSGQMIHT	3824	76.364	0.000	0.000	0.000	0.000	0.000	9.486
KNAIGHDSPHKSGQNQQT	3825	76.289	0.000	0.000	0.000	0.009	0.072	15.178
KTDKFHDSPHKSGQNQQT	3826	76.204	0.000	0.000	0.000	0.000	0.000	7.096
KTEGFHDSPHKSGQNQQT	3827	76.191	0.000	0.000	0.000	0.000	0.080	13.163
KVINGHDSPHKSGRNHQS	3828	75.961	0.000	0.000	0.000	0.000	0.000	13.568
KTITGHDSPHKSVQNRQT	3829	75.940	0.000	0.000	0.000	0.621	0.000	4.310
KTPDMHDSPHKSGQNQQT	3830	75.871	0.659	0.000	0.000	0.000	0.048	11.277
KTINGHDSPHKSGQKMNT	3831	75.820	0.000	0.000	0.000	0.000	0.167	6.373
KTELQHDSPHKSGQNQQT	3832	75.814	0.000	0.000	0.000	0.105	0.000	11.798
KTIHGHDSPHKSGQSQQN	3833	75.777	0.000	0.000	0.059	0.000	0.166	7.426
KTEIGHDSPHKSGQNQQT	3834	75.525	0.000	0.000	0.016	0.012	0.000	9.593
KTINGHDSPHKSGQYQHA	3835	75.308	0.000	0.000	0.000	0.000	0.017	17.081
KTELYHDSPHKSGQNQQT	3836	75.235	0.000	0.000	0.000	0.000	0.042	10.354

[0515] Table 17 provides the sequences of 216 matured capsid variants having a CV of less than 1 for the liver RNA samples isolated and a 10-fold or greater increase in expression relative to AAV9 in the liver of NHPs. These matured variants showed preferential transduction of the liver over other tissues as shown by a low value for fold-enrichment relative to AAV9 in the other tissues investigated including the brain, DRG, heart and muscle. As such, Table 17 provides TTM-001 and TTM-002 matured AAV capsid variants with liver-specific tropism. Across the peptides within the matured

capsid variants in Table 17, approximately 175 of them comprised the sequence GSGSPH (SEQ ID NO: 4695) and further comprised additional modifications in the C-terminal region of the sequence.

Table 17. NGS fold-enrichment of TTM-001 and TTM-002 matured AAV capsid variants in the liver of NHPs

Sequence	SEQ ID NO:	Fold Enrichment relative to AAV9					
		Liver RNA (NHP)	Liver DNA (NHP)	Brain (NHP)	DRG (NHP)	Heart (NHP)	Muscle (NHP)
KTQRKSGSPHSKAQNQQT	4011	119.659	1.439	0.000	0.000	0.000	0.000
KTINGSGSPHSKAQARKT	4681	96.557	3.644	0.000	0.000	0.000	0.000
KYIVGSGSPHSKAQNQQT	4682	94.721	4.480	0.000	0.000	0.000	0.000
KTINGSGSPHSMYMNQQT	4683	81.106	5.840	0.000	0.000	0.000	0.000
KTINGSGSPHSKAFYRQT	4684	77.541	3.577	0.000	0.000	0.000	0.000
KTINGSGSPHSKLKRQQT	4685	76.103	6.884	0.000	0.000	0.000	0.000
KTINGSGSPHSKRHRQQT	4686	73.225	4.648	0.000	0.000	0.000	0.000
KTINGSGSPHSKAQKCIT	4687	69.547	1.887	0.000	0.000	0.000	0.000
KTINGSGSPHSKWRLQQT	4688	68.083	2.037	0.000	0.000	0.000	0.000
KTINGSGSPHSCRNQQT	4689	64.416	5.150	0.000	0.000	0.000	0.000
KTINGSGSPHSFTCNQQT	4690	63.936	2.155	0.000	0.000	0.000	271.289
KTINGSGSPHSKFFIQQT	4691	63.255	6.916	0.000	0.000	0.000	0.000
KTINGSYSPHCLAQNQQT	4012	62.942	0.309	0.000	0.000	0.000	0.000
KTINGSGSPHSKAQYSRT	4692	60.119	0.956	0.000	0.000	0.000	0.000
KTINGSGSPHIVWQNQQT	3849	58.021	6.056	0.000	0.000	0.000	0.000
KTINGSGSPHSKYFMQQT	3850	57.350	2.993	0.000	0.000	0.000	0.000
KTINGSGSPHSKARQQT	3851	56.775	2.205	0.000	0.000	0.000	0.000
KTINGSGSPHSHQNQQT	3852	56.242	8.562	0.000	0.000	0.000	0.000
KTINGSGSPHFPWQNQQT	3853	53.587	1.731	0.000	0.000	0.000	0.000
KTINGSGSPHSKIIRQQT	3854	53.528	1.388	0.000	0.000	0.000	0.000
KTINGSGSPHVVYQNQQT	3855	53.294	2.173	0.944	0.000	0.246	5.268
KTINGSGSPHSLYWNQQT	3856	53.262	0.000	0.000	0.000	0.000	0.000
KTINGSGSPHSPKPRQQT	3857	52.881	2.832	0.000	0.000	0.000	0.000
KPRWGSGSPHSKAQNQQT	3858	51.637	0.386	0.000	0.000	375.537	0.000
KTINGSGSPHSKAFSWQT	3859	51.304	1.805	0.000	0.000	0.000	0.000
KTINGSGSPHSRFWNQQT	3860	51.225	6.955	0.000	0.000	0.000	0.000
KTINGSGSPHSKAQCLKT	3861	49.565	1.453	0.000	0.000	0.000	0.000
KTINGSGSPHSRMRNQQT	3862	48.902	2.816	0.000	0.000	0.000	0.000
KTINGSGSPHSVKKNQQT	3863	48.475	3.908	0.000	0.000	0.000	0.000
KTINGSGSPHSWAPNQQT	3864	47.897	1.789	0.000	0.000	0.000	0.000
KTINGSGSPHSLWKNQQT	3865	45.796	4.010	0.000	0.000	0.000	0.000
KTINGSGSPHSKARWQQT	3866	45.017	2.377	0.000	0.000	0.000	0.000
KTINGSGSPHSFRPNQQT	3867	44.801	9.191	0.000	0.000	0.000	0.000
KTINGSGSPHSKKVQQT	3868	43.747	4.480	0.000	0.000	0.000	0.000
KTINGSLSPHFWAQNQQT	4013	43.190	2.041	0.000	0.000	0.000	0.000
KTINGSGSPHSYAFNQQT	3869	43.037	1.742	0.000	0.000	0.000	0.000
KTINHRI SPHSKAQNQQT	4014	42.998	1.876	0.000	0.000	0.000	0.000
KTINGSGSPHSKACSRQT	3870	42.696	2.468	0.000	0.000	0.000	0.000
KTRRPSGSPHSKAQNQQT	4015	42.374	2.384	0.000	0.000	0.000	0.000
KYSAGSGSPHSKAQNQQT	3871	41.310	1.824	0.000	0.000	0.000	0.000
KTINGAYSPHRKAQNQQT	4016	40.969	1.283	0.000	0.000	0.000	0.000
KTINGSGSPHSKRLWQQT	3872	40.932	4.801	0.000	0.000	0.000	0.000
KTINGSGSPHSCSRNQQT	3873	40.372	4.293	0.000	0.000	0.000	0.000
KTINGSGSPHSRCPNQQT	3874	39.529	4.890	0.000	0.000	0.000	0.000
KTINGSGSPHSGACNQQT	3875	39.163	3.215	0.000	0.000	0.000	4733.916
KYYTSGSPHSKAQNQQT	3876	38.777	1.199	0.000	0.000	0.000	0.000
KTINGSGSPHSKFRQQT	3877	38.665	3.260	0.000	0.000	0.000	0.000

KTINGSGSPHSFPFNQQT	3878	38.584	4.693	0.000	0.000	0.000	0.000
KTINGSGSPHSFFGNQQT	3879	38.088	6.101	0.000	0.000	0.000	0.000
KTINGRRSPHGKAQNQQT	4017	37.728	3.259	0.000	0.000	0.000	0.000
KTINGSGSPHSMCQNQQT	3880	37.209	1.348	0.000	0.000	0.000	0.000
KTINGSGSPHSKLFWQQT	3881	37.022	4.178	0.000	0.000	0.000	0.000
KTINGSGSPHSKTRKQQT	3882	36.010	2.858	0.000	0.000	0.000	0.000
KTINGRTSPHRKAQNQQT	4018	35.792	5.682	0.000	0.000	0.000	0.000
KTINGSGSPHSGKRNQQT	3883	35.120	5.396	0.000	0.000	0.000	0.000
KTINGSGSPHСКАQNFRR	3884	32.291	0.964	0.000	0.000	0.000	0.000
KTINGSGSPHFYRQNQQT	3885	31.724	9.342	0.000	0.000	0.000	0.000
KTINGSRSPHAWAQNQQT	4019	31.146	6.838	0.000	0.000	0.000	0.000
KTINGSGSPHCRVQNQQT	3886	31.043	1.203	0.000	0.000	0.000	0.000
KTINGSGSPHYGIQNQQT	3887	30.908	1.076	0.000	0.000	0.000	0.000
KTINKCLSPHСКАQNNQQT	4020	30.667	5.097	0.000	0.000	0.000	0.000
KTINGSGSPHСКАQRFKT	3888	30.363	0.139	0.000	0.000	0.000	0.000
KTINGSGSPHVNCQNQQT	3889	30.010	6.122	0.000	0.000	0.000	0.000
KTINGSGSPHSPFRQQT	3890	29.842	8.700	0.000	0.000	0.000	0.000
KTINGSGSPHSLAWNQQT	3891	29.015	4.746	0.000	0.000	0.000	0.000
KTINGSGSPHRSYQQT	3892	28.973	2.116	0.000	0.000	0.000	0.000
KTINGSSSPHRCAQNQQT	4021	28.887	1.829	0.000	0.000	0.000	0.000
KTINGSGSPHWSYQNQQT	3893	28.607	3.751	0.000	0.000	0.000	0.000
KTINCRTPHСКАQNNQQT	4022	28.301	1.117	0.000	0.000	0.000	0.000
KTINGSGSPHRWLQNQQT	3894	28.147	6.882	0.000	0.000	0.000	0.000
KTIFDCGSPHСКАQNNQQT	4023	27.844	1.602	0.000	0.000	0.000	0.000
KTINGSGSPHSPSCQNQQT	3895	27.796	2.790	0.000	0.000	0.000	0.000
KTINGSGSPHSSWLNQQT	3896	27.318	3.271	0.000	0.000	0.000	0.000
KTINSRSPHСКАQNNQQT	4024	27.240	1.554	0.000	0.000	0.000	0.000
KPRFGSGSPHСКАQNNQQT	3897	27.203	0.657	0.000	0.000	0.000	0.000
KWLTGSGSPHСКАQNNQQT	3898	26.975	2.388	0.364	0.000	0.000	2578.486
KTINGSGSPHSKRRAQQT	3899	26.523	5.906	0.000	0.000	0.000	0.000
KTINGSGSPHСКАQTCRT	3900	26.472	6.369	0.000	0.000	0.000	0.000
KTINGLDSPHRSRQNQQT	4025	26.403	0.321	0.000	0.000	0.000	0.000
KTINGSGSPHSGCTQQT	3901	26.068	0.529	0.000	0.000	0.000	0.000
KTRTRSGSPHСКАQNNQQT	4026	25.852	6.894	0.000	0.000	0.000	0.000
KTINGSGSPHVPWQNQQT	3902	25.294	3.435	0.000	0.000	0.000	0.000
KTINGSGSPHSKRYTQQT	3903	25.267	9.412	0.000	0.000	0.000	0.000
KTINGSISPHCPAQNNQQT	4027	24.932	0.556	0.000	0.000	0.000	0.000
KTINGSGSPHSGCQNQQT	3904	24.818	1.981	0.000	0.000	0.000	0.000
KTINGSGSPHSFTPNNQQT	3905	24.227	1.036	0.000	0.000	0.000	0.000
KTINGSGSPHSTTCNQQT	3906	23.771	3.315	0.000	0.000	0.000	0.000
KTINGSGSPHSKARMYQT	3907	23.424	0.313	0.000	0.000	0.000	0.000
KTINGLVSPHRKAQNQQT	4028	23.417	2.739	0.000	0.000	0.000	0.000
KTINGSGSPHPRQNQQT	3908	23.055	2.355	0.000	0.000	0.000	0.000
KTINGSGSPHSKCFLQQT	3909	22.987	1.434	0.000	0.000	0.000	0.000
KTINGSGSPHWVPQNQQT	3910	22.907	3.219	0.000	0.000	0.000	0.000
KTINGSGSPHSFWSNQQT	3911	22.857	1.345	0.000	0.000	0.000	0.000
KRSYSGSPHСКАQNNQQT	3912	22.474	2.841	0.000	0.000	0.000	0.000
KYVFGSGSPHСКАQNNQQT	3913	22.232	2.346	0.000	0.000	0.000	0.000
KTINGSGSPHSPKFNQQT	3914	21.951	1.074	0.000	0.000	0.000	0.000
KTINGSGSPHRIKQNQQT	3915	21.720	3.064	0.000	0.000	0.000	0.000
KTINGSGSPHSKAPRRQT	3916	21.645	3.940	0.000	0.000	0.000	0.000
KTINGSGSPHSFRYNQQT	3917	21.097	4.148	0.000	0.000	0.000	0.000
KTINGSGSPHSMICQQT	3918	21.036	0.144	0.000	0.000	0.000	0.000
KTINGSGSPHLRWQNQQT	3919	21.014	9.649	0.000	0.000	0.000	0.000
KTINGSGSPHLPTQNQQT	3920	20.704	3.127	0.000	0.000	0.000	0.000
KTINGSGSPHSKWKSQQT	3921	20.390	1.239	0.000	0.000	4.904	0.163
KTINALRSPHСКАQNNQQT	4029	20.053	1.655	0.000	0.000	0.000	0.000
KTINGSGSPHSYMRNQQT	3922	20.007	2.293	0.000	0.000	0.000	0.000

KTINGSGSPHKAARRQT	3923	19.998	6.633	0.000	0.000	0.000	0.000
KTINGSGSPHLLCQNQQT	3924	19.796	3.484	0.673	0.000	0.000	1.309
KTINGSGSPHRCCQNQQT	3925	19.084	2.213	0.000	0.000	0.000	0.000
KTINGSGSPHLCVQNQQT	3926	19.030	1.428	0.000	0.000	0.000	0.000
KTINGSGSPHSLTRQQT	3927	19.004	2.712	0.000	0.000	0.000	0.000
KTICGRGSPHKAQNQQT	4030	18.923	2.171	0.000	0.000	0.000	0.000
KTTRKSGSPHKAQNQQT	4031	18.849	2.617	0.000	0.000	0.000	0.000
KTINGSGSPHSLCTQQT	3928	18.674	1.269	0.000	0.000	0.000	0.000
KKHLGSGSPHKAQNQQT	3929	18.521	0.658	0.000	0.000	0.000	0.000
KTINGSGSPHSKIRGQQT	3930	18.150	1.584	0.000	0.000	0.000	0.000
KTMQRSGSPHKAQNQQT	4032	18.020	3.159	0.000	0.000	0.000	0.000
KTINGSGSPHSLVNQQT	3931	17.766	1.267	0.000	0.000	0.000	0.000
KTINGSGSPHQGCQNQQT	3932	17.676	1.037	0.000	0.000	0.000	0.000
KTINGSGSPHMAFQNQQT	3933	17.644	0.542	0.000	0.000	0.000	0.000
KTINGSGSPHAKACQFQT	3934	17.640	8.562	0.000	0.000	0.000	9.605
KTINGSGSPHSLKWGLQQT	3935	17.543	2.639	0.000	0.000	0.000	0.000
KTINGSGSPHSLKLRQQT	3936	17.419	2.546	0.000	0.000	0.000	0.000
KTINGSGSPHSLFQINQQT	3937	17.418	0.269	0.308	0.000	1.568	0.000
KTINGSGSPHSLKACISQT	3938	17.371	0.240	0.000	0.000	0.000	0.000
KTINGSGSPHSLKAQTHRT	3939	17.290	2.917	0.000	0.000	0.000	0.000
KTINGSGSPHSLKALRQQT	3940	17.283	1.892	0.000	0.000	0.000	0.000
KTINGSGSPHSLKAFYIQT	3941	17.172	0.239	0.000	0.000	0.000	0.000
KTINGSGSPHSLKAHARQT	3942	17.075	1.800	0.000	0.000	0.000	0.000
KTINGSGSPHSLCLNQQT	3943	17.028	1.790	0.000	0.000	0.000	0.000
KTINGSGSPHSLKAFVRQT	3944	16.935	1.985	0.000	0.000	0.000	0.000
KPPLGSGSPHKAQNQQT	3945	16.897	0.805	0.000	0.000	0.000	0.000
KTINGSGSPHSLRPWQNQQT	3946	16.869	4.936	0.000	0.000	0.000	0.000
KPARGSGSPHKAQNQQT	3947	16.793	1.391	0.000	0.000	0.000	0.000
KTINGSGSPHSLRPRQNQQT	3948	16.784	5.206	0.000	0.000	0.000	0.000
KTINGSGSPHSLSCPQNQQT	3949	16.701	1.776	0.000	0.000	0.000	0.000
KTINGSGSPHSLKAQFILT	3950	16.650	4.208	0.000	0.000	0.000	0.000
KTINGSGSPHSLWMAQNQQT	4033	16.635	2.390	0.000	0.000	0.000	0.000
KTRKRSRSPHKAQNQQT	4034	16.603	2.075	0.000	0.000	0.000	0.000
KTINGSGSPHSLSVRYNQQT	3951	16.390	1.413	0.000	0.000	0.000	0.000
KSRRGSGSPHKAQNQQT	3952	16.131	1.446	0.000	0.000	0.000	0.000
KTINGSGSPHSLSVRCNQQT	3953	15.860	3.912	0.000	0.000	0.000	0.000
KFFHSGSGSPHKAQNQQT	3954	15.412	0.897	0.000	0.000	0.000	0.000
KTINGSGSPHSLKMPCCQQT	3955	15.343	1.063	0.000	0.000	0.000	0.000
KTINGSGSPHSLKSKTSQQT	3956	15.244	1.344	0.000	0.000	0.000	0.000
KRYNGSGSPHKAQNQQT	3957	15.160	0.806	0.000	0.000	0.000	0.000
KTINFTRSPHKAQNQQT	4035	14.908	3.751	0.000	0.000	0.000	0.000
KTINGSGSPHSLPYNQQT	3958	14.792	2.048	0.000	0.000	0.000	0.000
KTINGSGSPHSLVYHQNQQT	3959	14.770	1.733	0.000	0.000	0.000	0.000
KTINGSGSPHSLKAQSRKT	3960	14.589	2.715	0.000	0.000	0.000	0.000
KTINGSGSPHSLSYTRNQQT	3961	14.535	1.986	0.000	0.000	0.000	0.000
KTINNLRSPHKAQNQQT	4036	14.514	1.354	0.000	0.000	0.000	0.000
KTINGRPSPHGKAQNQQT	4037	14.442	0.705	0.000	0.000	0.000	0.000
KTINWRSRSPHKAQNQQT	4038	14.399	5.624	0.000	0.000	0.000	0.000
KTINGSGSPHSLVYQNQQT	3962	14.196	1.045	0.000	0.000	0.000	0.000
KTINGTRSPHKKQNQQT	4039	14.173	1.152	0.700	0.225	0.052	4.082
KTINGSGSPHSLKALRWQT	3963	14.118	5.252	0.000	0.000	0.000	0.000
KTINGSGSPHSLHYRYQNQQT	3964	14.107	1.027	0.000	0.000	0.000	0.000
KTINGSGSPHSLKLNQQT	3965	13.995	0.603	0.000	0.000	0.000	0.000
KTINGSGSPHSLKAQMQIT	3966	13.990	0.371	0.000	0.000	0.000	0.000
KTINGSVSPHCTAQNQQT	4040	13.502	2.955	0.000	0.000	0.000	0.000
KTINGSGSPHSLCPAQNQQT	3967	13.359	1.409	0.000	0.000	0.000	0.000
KTINGSGSPHSLMCTNQQT	3968	13.114	0.392	0.000	0.000	0.000	0.000
KTINGSGSPHSLPPDNQQT	3969	12.973	0.033	0.000	0.000	0.000	0.000

KTINGSGSPHSKRNYQQT	3970	12.781	5.528	0.000	0.000	0.000	0.000
KTTRCSGSPHСКАQNNQQT	4041	12.639	8.168	0.000	0.000	0.000	0.000
KTKLCGSPHСКАQNNQQT	4042	12.570	2.139	0.000	0.000	0.000	0.000
KTINLGCSPHСКАQNNQQT	4043	12.564	0.654	0.000	0.000	0.000	0.000
KTINGSGSPHRWTQNQQT	3971	12.490	0.844	0.000	0.000	0.000	0.000
KTISGHDSPHISGQYQQT	4044	12.395	0.420	0.000	0.000	0.074	1214.588
KTINGSGSPHSKACRLQT	3972	12.297	6.537	0.000	0.000	0.000	0.000
KTINGSGSPHPRKQNQQT	3973	12.249	3.248	0.000	0.000	0.000	0.000
KTINGSGSPHSKCSVQQT	3974	12.246	1.465	0.000	0.000	0.000	0.000
KTINGSGSPHСКАQYVRT	3975	12.239	3.275	0.000	0.000	0.000	0.000
KTINGSGSPHSKARISQT	3976	12.142	1.565	0.000	0.000	0.000	0.000
KTINGRRSPHМКАQNNQQT	4045	12.136	3.510	0.000	0.000	0.000	0.000
KTINGPWSPHRKAQNNQQT	4046	12.103	0.434	0.000	0.000	0.000	0.000
KTINGSGSPHPFVQNQQT	3977	12.091	1.286	0.000	0.000	0.000	0.000
KTINGSGSPHSKLPKQQT	3978	11.856	0.274	0.000	0.000	0.000	0.000
KTINSCFSPHСКАQNNQQT	4047	11.847	1.016	0.000	0.000	0.000	0.000
KTINGSGSPHSKNSEQQQT	3979	11.785	1.769	0.000	0.000	0.000	0.000
KTINGSGSPHWVAQNQQT	3980	11.703	3.634	0.000	0.000	0.000	0.000
KTINGSGSPHSLYQNQQT	3981	11.590	1.503	0.000	0.000	0.000	0.000
KTINGSGSPHSKVRMQQT	3982	11.572	1.835	0.000	0.000	0.000	0.000
KTINYTRSPHСКАQNNQQT	3983	11.514	0.431	0.000	0.000	0.000	0.000
KTIKRYGSPHСКАQNNQQT	4048	11.461	2.022	0.000	0.000	0.000	0.000
KTINGSGSPHСALQNQQT	4693	11.404	3.867	0.000	0.000	0.000	0.000
KTINGSGSPHSSCTNQQT	3984	11.382	3.363	0.000	0.000	0.000	0.000
KTINGSGSPHSKNSRQQT	3985	11.280	1.093	0.000	0.000	0.000	0.000
KTINGSGSPHSKRKRQQT	3986	11.215	3.027	0.000	0.000	0.000	0.000
KTINGSGSPHLCTQNQQT	3987	11.176	2.489	0.000	0.000	0.000	0.000
KTINGSGSPHСКАQSAKT	3988	11.162	4.200	0.000	0.000	0.000	0.000
KTINGSGSPHSTCLNQQT	3989	11.132	4.762	0.000	0.000	0.000	0.000
KTINGSGSPHSYARNQQT	3990	11.131	0.996	0.000	0.000	0.000	0.000
KTINGSGSPHSKQRPQQT	3991	11.130	2.347	0.000	0.000	0.000	0.000
KTINGSGSPHSKRVVQQT	3992	11.094	1.639	0.000	0.000	0.000	0.000
KRFSGSGSPHСКАQNNQQT	3993	11.024	1.358	0.000	0.000	0.000	0.000
KTINGSGSPHKSQNQQT	3994	11.014	11.790	0.000	0.000	0.000	0.000
KTINRYSSPHСКАQNNQQT	4049	10.926	1.544	0.000	0.000	0.000	0.000
KTTGRSGSPHСКАQNNQQT	4050	10.863	0.126	0.000	0.000	0.000	0.000
KTINGSGSPHSKALRHQT	3995	10.774	4.532	0.000	0.000	0.000	0.000
KTINGSGSPHSYYSNQQT	3996	10.680	2.856	0.000	0.000	0.000	0.000
KTINGSGSPHSLTCNQQT	3997	10.658	2.214	0.490	0.000	0.163	1.398
KTINGSGSPHSCQSNQQT	3998	10.631	1.468	0.000	0.000	0.000	0.000
KTINGSGSPHСКАQSIKT	3999	10.544	1.355	0.000	0.000	0.000	0.000
KYSMSGSPHСКАQNNQQT	4000	10.478	1.587	0.000	0.000	0.000	0.000
KTINGSGSPHСКАKGWQT	4001	10.450	1.827	0.000	0.000	0.000	0.000
KTIVGSGSPHSKPQNQQT	4002	10.381	0.894	0.000	0.000	0.000	0.000
KTINGSGSPHFPPQNQQT	4003	10.322	3.715	0.000	0.000	0.000	0.000
KPFLGSGSPHСКАQNNQQT	4004	10.318	1.328	0.000	0.000	0.000	0.000
KTINGSGSPHSKTQSQQT	4005	10.311	5.821	0.493	0.232	1.413	2.353
KTINRQFSPHСКАQNNQQT	4051	10.275	4.480	0.000	0.000	0.000	0.000
KTINGSGSPHSHVFENQQT	4006	10.218	0.224	0.000	0.000	0.000	0.000
KTINGSGSPHСКАKQVQT	4007	10.102	3.974	0.000	0.000	0.000	0.000
KTINGSGSPHСКАQRCST	4008	10.084	0.762	0.000	0.000	0.000	0.000
KTINGSGSPHСКАQFCLT	4009	10.065	3.371	0.000	0.000	0.000	0.000
KTINGSGSPHGRYQNQQT	4010	10.028	0.778	0.000	0.000	0.000	0.000

[0516] Table 18 provides the peptide sequences of 43 matured capsid variants having a raw virus count greater than 10, a CV of less than 1 for the heart samples isolated, and that also demonstrated a

4-fold or greater fold-increase in expression in the heart relative to the AAV9 control. A number of the matured variants shown in **Table 18** also demonstrated increased expression in other tissues isolated from the NHPs, including the brain, muscle, and/or liver, and are therefore pan-tropic.

Table 18. NGS fold-enrichment of TTM-001 and TTM-002 matured AAV capsid variants in the heart of NHPs

Sequence	SEQ ID NO:	Fold Enrichment relative to AAV9						
		Heart (NHP)	Brain (NHP)	DRG (NHP)	Muscle (NHP)	Liver RNA (NHP)	Liver DNA (NHP)	Brain (Mouse)
KTITGHDSPHSKAQNNQQT	4052	34.375	230.437	4.338	1.378	19.165	5.672	0.000
KTINGSGSPHKSGQYQQT	4053	33.208	851.414	8.704	17.754	17.342	9.915	12.911
KTINGSGSPHKSGQDQQT	4054	31.166	218.057	34.358	33.372	27.081	8.836	24.849
KTINGSGSPHKSGQIQQT	4055	27.293	201.467	48.033	12.706	17.874	13.192	10.912
KTINGSGSPHKSGRNQQT	4056	27.283	313.826	8.723	36.593	15.252	12.352	21.595
KTINGSGSPHKSGKNQQT	4057	25.992	230.621	6.343	97.671	15.369	7.226	31.282
KTIYGHDSPHSKAQNNQQT	4058	25.673	269.879	3.694	8.391	11.895	6.197	0.000
KTINGSGSPHKSGQNNQQS	4059	24.783	244.030	16.675	26.058	18.059	9.809	29.751
KTINGSGSPHKSGQNLQQT	4060	24.464	392.519	15.629	0.371	29.977	18.332	30.446
KAINGHDSPHSKAQNNQQT	4061	22.460	640.466	7.358	9.986	9.358	8.490	0.000
KTVNGHDSPHSKAQNNQQT	4062	21.066	614.034	3.392	30.908	21.560	11.933	121.235
KTIKGHDSPHSKAQNNQQT	4063	20.803	213.564	24.646	12.361	15.379	6.551	13.319
KSINGHDSPHSKAQNNQQT	4064	20.698	246.819	7.592	28.235	11.773	6.888	280.630
KTINGSGSPHKSGQTQQT	4065	19.925	466.459	55.454	15.485	15.473	6.446	15.179
KTINGSGSPHKSGHNQQT	4066	19.548	287.922	12.159	20.851	17.821	10.084	21.011
KTFNGHDSPHSKAQNNQQT	4067	19.301	239.922	9.109	17.215	12.193	6.413	30.747
KTINGSGSPHKSGQLNQQT	4068	19.136	319.093	3.083	4.096	14.009	7.446	9.340
KTINGHDSPHSKALNQQT	4069	18.542	605.641	13.375	1.902	12.621	7.054	51.283
KTINGSGSPHKSGQNLQQT	4070	18.454	317.452	33.967	28.952	18.533	8.992	36.272
KTLNGHDSPHSKAQNNQQT	4071	18.236	195.734	19.341	9.266	25.732	13.333	0.000
KTINGSGSPHKSGQNNQHT	4072	14.269	313.837	7.125	39.273	29.714	7.797	25.119
KTIDGHDSPHSKAQNNQQT	4073	13.836	242.100	1.731	12.555	17.223	7.439	0.000
KTNNGHDSPHSKAQNNQQT	4074	12.872	134.488	0.504	3.877	17.044	5.982	22.358
KTINGSGSPHKSGQKQQT	4075	12.357	323.373	10.936	1172.3	12.604	7.970	48.699
KTINGSGSPHKSGQNRQQT	4076	11.563	145.363	36.865	3.855	11.403	7.667	16.860
KTINGSGSPHKSGQNNQQA	4077	11.507	156.385	582.38	8.559	9.273	7.668	18.138
KTINGSGSPHKSGQNNQQA	4078	11.313	135.164	12.425	12.699	9.714	6.077	17.265
KTINGHDSPHSKAHNNQQT	4079	10.024	236.106	19.495	5.258	2.406	3.316	45.691
KTINGHDSPHSKAQNNQQT	4080	8.954	186.839	9.457	5.507	5.929	3.651	31.453
KTINGSGSPHKSGQNNQQT	4081	8.744	261.947	43.435	10.217	6.468	4.265	19.828
KTINGHDSPHCKAQNNQQT	4082	8.417	15.165	0.887	2.368	3.328	0.771	148.172
KTINGHDSPHSKAQNNQQS	4083	5.678	603.027	7.280	0.670	4.301	4.307	65.271
KTINGSGSPHKSGQNNQQT	4084	5.586	115.994	28.397	4.326	5.307	3.569	24.908
KTINGHDSPHDKSGQNNQQT	4085	5.569	30.854	4.934	1.112	0.671	0.781	14.499
KPINGHDSPHKSGQNNQQT	4086	5.203	36.266	0.000	0.258	4.478	0.521	28.786
KTSNGSGSPHKSGQNNQQT	4087	4.746	197.282	4.177	4.466	3.972	7.425	75.623
KTVNGSGSPHKSGQNNQQT	4088	4.610	200.076	2.739	2.873	2.725	3.478	43.548
KTINGHDSHKSNGHNQQT	4089	4.369	27.630	2.883	1.302	0.421	0.176	12.973
KTINGHDSPHSKAQNNQQA	4090	4.271	319.610	1.163	5.173	3.406	4.995	50.220
KTIYSGSGSPHKSGQNNQQT	4091	4.140	110.329	2.603	2.545	4.488	4.110	29.293
KTINGLDSPHKSGQNNQQT	4092	4.055	12.958	3.240	3.205	0.645	0.296	5.608

[0517] Table 19 provides the peptide sequences of 14 matured capsid variants having a raw virus count greater than 10, a CV of less than 1 for the muscle samples isolated (e.g., quadriceps), and that

also demonstrated a 4-fold or greater fold-increase in expression in the muscle relative to the AAV9 control. A number of the matured variants shown in **Table 19** also demonstrated increased expression in other tissues isolated from the NHPs, including the brain, heart, and/or liver, and are therefore pan-tropic.

Table 19. NGS fold-enrichment of TTM-001 and TTM-002 matured AAV capsid variants in the muscle (e.g., quadriceps) of NHPs

Sequence	SEQ ID NO:	Fold Enrichment relative to AAV9						
		Muscle (NHP)	Brain (NHP)	DRG (NHP)	Heart (NHP)	Liver RNA (NHP)	Liver DNA (NHP)	Brain (Mouse)
KTINGSGSPHKSGRNQQT	4056	36.593	313.826	8.723	27.283	15.252	12.352	21.595
KTIIGHDSEPHSKAQNQQT	4095	27.271	341.528	5.423	26.154	18.305	6.293	0.000
KTIYGHDSPEHKAQNQQT	4058	8.391	269.879	3.694	25.673	11.895	6.197	0.000
KTINGSGSPHKSGQNQQS	4059	26.058	244.030	16.675	24.783	18.059	9.809	29.751
KTVNGHDSPEHKAQNQQT	4062	30.908	614.034	3.392	21.066	21.560	11.933	121.235
KTIKGHDSPEHKAQNQQT	4063	12.361	213.564	24.646	20.803	15.379	6.551	13.319
KSINGHDSPEHKAQNQQT	4064	28.235	246.819	7.592	20.698	11.773	6.888	280.630
KTINGSGSPHKSGHNQQT	4066	20.851	287.922	12.159	19.548	17.821	10.084	21.011
KTFNGHDSPEHKAQNQQT	4067	17.215	239.922	9.109	19.301	12.193	6.413	30.747
KTSNGHDSPEHKAQNQQT	4096	18.580	507.189	7.777	17.770	21.537	8.789	70.219
KTINGHDSPEHKAQNQQT	4080	5.507	186.839	9.457	8.954	5.929	3.651	31.453
KTINGSGSPHKSGQNQQT	4084	4.326	115.994	28.397	5.586	5.307	3.569	24.908
KTINGHDSPEHKAQNQQN	4090	5.173	319.610	1.163	4.271	3.406	4.995	50.220
KTINGSGSPHKSAQNRRR	4097	4.237	8.348	0.291	0.636	1.597	5.396	158.853

[0518] Additional variants were identified following generation and screening in NHPs that had the following properties. TTM-001 and TTM-002 capsid variants comprising the amino acid sequence of SEQ ID NOs: 4253, 4281, 4290-4295, 4304, 4305, 4320, 4328-4335, 4337-4340, 4353, 4355, 4369, 4387, 4421, 4424-4428, 4430, 4432, 4433, 4435, 4436-4449, 4452, 4455, 4476, 4483, or 4484 had a raw virus count 10 or greater, a CV of less than 1 for the brain samples isolated from the NHPs, demonstrated a 50-fold or greater increase in expression in the brain of mice and NHPs relative to AAV9, and demonstrated 2-fold or less expression in the liver and DRG of NHPs relative to AAV9. TTM-001 and TTM-002 capsid variants comprising the amino acid sequence of SEQ ID NOs: 4098-4105, 4254-4280, 4282-4289, 4296-4303, 4306-4327, 4336, 4341-4352, 4354, 4356-4420, 4422, 4423, 4425, 4429, 4431, 4434, 4444, 4450, 4451, 4453, 4454, 4456-4475, 4477-4482, or 4485 had a CV of less than 1 in across the brain samples isolated from the NHPs and demonstrated a 100-fold or greater increase in expression in the brain of NHPs relative to AAV9. TTM-001 and TTM-002 capsid variants comprising the amino acid sequence of SEQ ID NOs: 4102 and 4106-4252 had normalized virus counts of greater than or equal to 0.01, a CV of less than 1 across the liver RNA samples isolated from the NHPs, and demonstrated a 20-fold or greater increase in expression in the liver of NHPs relative to AAV9. TM-001 and TTM-002 capsid variants comprising the amino acid sequence of SEQ ID NO: 4105 had a raw virus count 9.9 or greater, a CV of less than 1 across the muscle samples isolated from the NHPs, and 5-fold or greater increase in expression in the muscle of

the NHPs relative to AAV9. TTM-001 and TTM-002 capsid variants comprising the amino acid sequence of SEQ ID NO: 4105 also had a raw virus count 9.9 or greater, a CV of less than 1 across the samples isolated from the heart of the NHPs, and 5-fold or greater increase in expression in the heart of the NHPs relative to AAV9.

[0519] These data demonstrate that following two maturation approaches, matured TTM-001 and TTM-002 capsid variants (AAV9 capsid variants) with loop IV modifications were generated with significantly enhanced CNS tropism over wild-type AAV9 controls in both NHPs and mice, while also exhibiting de-targeting in peripheral tissues (e.g., the liver and DRG). These resulting matured variants therefore demonstrated cross-species CNS tropism in both NHPs and mice. Matured TTM-001 and TTM-002 capsid variants with liver-specific tropism were also generated with at least 10 times the expression compared to wild-type AAV9 in the liver of NHPs. Several matured variants were also generated with increased expression in the heart and skeletal muscle (e.g., quadriceps) relative to wild-type AAV9 in NHPs.

Example 5. Evaluation of TTM-001 and TTM-002 AAV capsid variants in Diverse Primate Species

[0520] This Example evaluates the tropism and cross-species compatibility of the TTM-001 (SEQ ID NO: 981 (amino acid) and 983 (DNA), comprising SEQ ID NO: 941) and TTM-002 (SEQ ID NO: 982 (amino acid) and 984 (DNA), comprising SEQ ID NO: 2) capsid variants in two diverse primate species, marmosets (*Callithrix jacchus*) and African green monkeys (*Chlorocebus sabaeus*), as compared to their tropism in cynomolgus macaques (*Macaca fascicularis*) provided in Example 1. The cross-species compatibility and tropism of an AAV9 capsid variant comprising the amino acid sequence of SPHKYG (SEQ ID NO: 966) was also investigated in this example. The amino acid and DNA sequences of TTM-001 and TTM-002 are provided, e.g., in Tables 4 and 5, respectively.

[0521] To investigate tropism in African green monkeys, AAV particles comprising the TTM-001 capsid variant, the TTM-002 capsid variant, an AAV9 capsid variant comprising SEQ ID NO: 966, or an AAV9 control under the control of a synapsin promoter, were intravenously injected into NHPs (n=2, 3-12 years of age) at a dose of 2E13 vg/kg. After 14-days in life, the brains and tissues (liver, DRG, quadriceps, and heart) of the NHPs were collected and RNA was extracted. Following RNA recovery and RT-PCR amplification, a systematic NGS enrichment analysis was performed to calculate the fold enrichment ratio relative to the AAV9 wild-type control.

[0522] To investigate tropism in marmoset monkeys, AAV particles comprising the TTM-001 capsid variant, the TTM-002 capsid variant, an AAV9 capsid variant comprising SEQ ID NO: 966, or an AAV9 control, were intravenously injected into NHPs (n=2, >10 months of age) at a dose of 2E13 vg/kg (8.75E12 vg/mL). After 28-days in life, the brains and tissues (liver quadriceps, and heart) of the NHPs were collected and RNA was extracted. Following RNA recovery and RT-PCR

amplification, a systematic NGS enrichment analysis was performed to calculate the fold enrichment ratio relative to the AAV9 wild-type control.

[0523] As provided in **Table 20** (African green monkeys) and **Table 21** (marmosets), both the TTM-001 and TTM-002 capsid variants demonstrated increased CNS tropism in diverse primate species. The TTM-001 capsid variant demonstrated a 73.6-fold increase in expression relative to AAV9 in the brain of cynomolgus macaques (**Table 9**, Example 1), a 43.5-fold increase in expression relative to AAV9 in the brain of African green monkeys, and a 703.3-fold increase in expression relative to AAV9 in the brain of marmosets. The TTM-002 capsid variant demonstrated a 62.6-fold increase in expression relative to AAV9 in the brain of cynomolgus macaques (**Table 9**), a 13.8-fold increase in expression relative to AAV9 in the brain of African green monkeys, and a 366.6-fold increase in expression relative to AAV9 in the brain of marmosets. Both TTM-001 and TTM-002 led to a significant increase in expression relative to AAV9 in the heart of both African green monkeys and marmosets (**Table 20** and **Table 21**). The AAV9 capsid variant comprising SEQ ID NO: 966 also demonstrated an increase in expression relative to AAV9 in the brain and heart of both African green monkeys and marmosets. Furthermore, TTM-001, TTM-002, and the AAV9 capsid variant comprising SEQ ID NO: 966, also all led to increased expression in the brain of both BALB/c and C57Bl/6 mice (**Table 11**, Example 1), demonstrating an average fold change in expression relative to AAV9 across both species of mice of 63.1, 66.8, and 126.97, respectively.

Table 20. NGS-fold enrichment of TTM-001 (comprises SEQ ID NO: 941), TTM-002 (comprises SEQ ID NO: 2), and an AAV9 capsid variant comprising SEQ ID NO: 966 in African green monkeys

Sequence	SEQ ID NO:	Fold Enrichment relative to AAV9					
		Brain	DRG	Heart	Liver DNA	Liver RNA	Muscle
SPHska	941	43.525	1.010	184.789	0.242	1.547	1.715
HDSPHK	2	13.779	0.678	35.991	0.084	0.087	0.144
SPHKYG	966	9.805	0.071	44.865	0.085	0.136	0.234

Table 21. NGS-fold enrichment of TTM-001 (comprises SEQ ID NO: 941), TTM-002 (comprises SEQ ID NO: 2), and an AAV9 capsid variant comprising SEQ ID NO: 966 in marmosets

Sequence	SEQ ID NO:	Fold Enrichment relative to AAV9				
		Brain	Heart	Liver DNA	Liver RNA	Muscle
SPHska	941	703.610	48.979	0.268	0.779	0.425
HDSPHK	2	366.625	18.572	0.075	0.276	0.229
SPHKYG	966	150.209	17.232	0.045	0.014	0.146

[0524] Taken together, these data demonstrate that the AAV9 capsid variants of TTM-001 and TTM-002 demonstrated increased CNS tropism relative to the AAV9 control in the CNS across three diverse primate species and two species of mice, providing evidence of strong cross-species capacity. The AAV9 capsid variant comprising the amino acid sequence of SEQ ID NO: 966 also demonstrated strong CNS expression relative to the AAV9 control in two species of NHPs and two species of mice, also showing strong cross-species capacity.

Example 6. Advanced maturation of TTM-002 capsid variant in mice

[0525] This Example describes additional maturation of the TTM-002 (SEQ ID NO: 982 (amino acid) and 984 (DNA), comprising SEQ ID NO: 2) capsid variant in mice. In order to mature the TTM-002 capsid variant, sets of three contiguous amino acids were randomized across the mutagenesis region in TTM-002 sequence, which spanned from position 450 to position 466, numbered according to SEQ ID NO: 982. Unlike the maturation performed in Example 3, where the SPH motif that was observed in the AAV capsid variants that demonstrated the greatest fold-enrichment in the NHP brain relative wild-type AAV9 was not disrupted, in the maturation approach used in this Example, the SPH motif was not held constant to further explore the role of this motif in the capsid variant. The matured TTM-002 capsid variants that resulted from the maturation approach were pooled together for subsequent testing and characterization in mice.

[0526] The library of matured AAV capsid variants generated from the TTM-002 matured AAV capsid variant were intravenously injected into the tail vein of three CD-1 Outbred mice (Charles River; 6-8 weeks of age) at a dose of 1.0×10^{12} VG/dose. After about 28 days in life, the brains of the mice were isolated, and RNA was extracted. Following RNA recovery and RT-PCR amplification, a systematic NGS enrichment analysis was performed to calculate the fold enrichment ratio relative to the corresponding TTM-002 non-matured control, and the peptides comprised within the variants were identified. Variants were filtered by those with a raw virus count in the sample above 10 and a coefficient of variance (CV) that was greater than 1 (identifies the peptides/variants reliably detected in the majority of the samples isolated from the three mice).

[0527] Following the advanced maturation screen and filtering of the variants, 1302 variants demonstrated an increase in expression relative to the non-matured TTM-002 capsid variant in the brain of the outbred mice. Of the 1302 variants with improved tropism relative to the non-matured TTM-002, 1283 comprised the SPH motif in the same position as the non-matured TTM-002 capsid variant (e.g., immediately subsequent to position 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138 or 982). Mutations in the region of the SPH motif present in the non-matured TTM-002 capsid variant only consistently appear in those variants with a fold change of 0.2 or 0.1 or lower relative to the non-matured TTM-002 control in the brain of the mice. This indicates that the SPH motif may be important to the increased brain tropism that observed for the TTM-002 capsid variant. In instances when the SPH motif was disrupted, the fold change of the matured variants of TTM-002 decreased considerably in relation to the non-matured TTM-002 variant which comprised the SPH motif.

Example 7. Tropism of TTM-002 AAV capsid variant

[0528] This Example further investigates the tropism and CNS cells transduced by the TTM-002 capsid variant (SEQ ID NO: 982 (amino acid) and 984 (DNA), comprising SEQ ID NO: 2), as

outlined in Table 3 above. The amino acid and DNA sequences of TTM-002 are provided, e.g., in Tables 4 and 5, respectively.

[0529] AAV particles were generated with the TTM-002 capsid variant encapsulating a GFP transgene (AAV_TTM-002.GFP) or a payload driven by a heterologous CBA constitutive promoter (AAV_TTM-002.Payload).

[0530] Two tandem single cell RNA sequencing runs (scRNA-Seq) of mouse cells derived from the midbrain area were performed. In the first run, cells were pooled from two mice at day 28 post treatment with AAV_TTM-002.Payload particles. In the second run we treated with AAV_TTM-002.GFP particles, in the same manner but without xenografts. Orthotopic xenografts of MDA-MB-361-Luc#1 high passage cells grown as tumorspheres (in tumorsphere media; Sigma # C-28070) were injected (250,000 cells/2 μ L/mouse) intracranially into 2-month old female SCID CB17 (Mutation: Icr-Prkdcscid/IcrIcoCr1) congenic immunodeficient mice (Charles River Laboratories). The injections were 2.5mm (lateral), -1mm (posterior) with respect to bregma, lowered -3mm ventral and raised +.5 mm dorsal to a final -2.5mm ventral position. Two days later, dilutions of the AAV_TTM-002.Payload particles (run 1), or in the case without xenografts, dilutions of AAV_TTM-002.GFP particles (run 2) were prepared. IV injections of 100 μ L (2.5e11 VG/animal) of the AAV_TTM-002.payload particles or AAV_TTM-002.GFP particles were administered through the tail veins of mice (n=5 mice per groups). At 7 days post-injection, mice from run 1 were imaged in an AmiHTX (Spectral Imager) for bioluminescence of the human tumor cells due to expression of luciferase in response to intraperitoneal luciferin injections.

[0531] At 28 days post-injection with the AAV_TTM-002.payload particles or AAV_TTM-002.GFP particles, two mice from each run were necropsied, brain samples were isolated, and the midbrain was dissected and isolated. The midbrain samples were then exposed to a cold protease inhibitor (Creative Biomart #NATE-0633) and were dissociated at 6 degrees centigrade. For the samples collected from the mice of run 1 (AAV_TTM-002.Payload particles), myelin depletion was performed (Miltenyi, #130-096-731), cells were filtered through a 40 μ M mesh to filter out neurons and loaded on a 10X chromium G chip. scRNA-Seq was performed (10X Genomics) and samples were sequenced on a NextGen500 Sequencing machine (Illumina). For the samples collected from run 2 (AAV_TTM-002.GFP particles and no xenografts), the cells were not myelin depleted or filtered through 40 μ M mesh to include neurons. The cells isolated after run 2 were FACS sorted for GFP+/7AAD- (live GFP+ cells). The resultant cells were loaded on a 10X chromium G chip and the scRNA-Seq was run and processed (10X Genomics).

[0532] For run 1, the scRNA-Seq data was filtered to include cells with only greater than 1000 genes per cell and less than 5000, and less than 20 percent mitochondrial gene expression. For run 2, the scRNA-Seq data was filtered to include cells with only greater than 200 genes per cell and less than 5000, and less than 20 percent mitochondrial gene expression. The data were normalized, scaled,

and integrated into one combined dataset. Clusters were generated with a resolution of 0.3 and each cluster identity was determined using a panel of cell type specific genes (e.g., as described in Brown *et al.*, 2021. “Deep Parallel Characterization of AAV Tropism and AAV-Mediated Transcriptional Changes via Single-Cell RNA Sequencing”. *Front. Immunol.* 12:730825; the contents of which are hereby incorporated by reference in its entirety). The percentage of GFP sorted cells per cluster was calculated as was the percentage of payload expressing genes per cluster as parallel measures of TTM-002 transduction.

[0533] For payload expressing cells, endothelial cells had the highest proportion of payload positive cells, followed by astrocytes (**Table 22**). For GFP+ sorted cells, endothelial cells had the highest proportion of GFP positive cells, and astrocytes were the third highest cell type when sorting by proportion of cells expressing GFP (**Table 22**). These data indicate TTM-002 transduction exhibits an endothelial and astrocytic tropism. Furthermore, the astrocytic cluster had the second highest level of expression of Olig2 (oligodendrocytes demonstrated the greatest Olig2 expression). IHC staining was performed on brain samples isolated from AAV_TTM-002.GFP infected mice and demonstrated that GFP co-localized with some but not all Olig2+ cells. No co-staining was observed with myelin basic protein (MBP), a marker of oligodendrocytes. Co-staining with GFP was also not observed in NeuN positive cells (neurons), GFAP positive cells (astrocytes), and Iba1 positive cells (microglia). GFP staining was observed throughout the sagittal section of the mouse brain, which was demonstrative of increased staining in the midbrain. The GFP expressing cells observed did not have a bipolar morphology like oligodendrocyte progenitor (OPC) cells and therefore, together with the scRNA-Seq data, these results indicated that at day 28 post AAV treatment, Olig2+ astrocytes in the midbrain are being transduced by AAV particles comprising a TTM-002 capsid, in a cell type specific tropism.

Table 22. Quantification of payload positive cells and GFP positive cells

Cluster Identity	% Payload Cells/Cluster	Cluster Identity	% GFP Cells/Cluster
Endothelial-2	6.58	Endothelial-2	6.58
Astrocyte	4.50	Endothelial-1	3.45
Pericytes	4.23	Vascular and leptomeningeal Cells (VLM)	2.38
Mature Oligos	3.85	Astrocyte	2.37
Endothelial-1	3.09	Vascular smooth muscle cells (VSC)	1.03
Committed Oligos	1.90	Pericytes	0.77
Vascular smooth muscle cells (VSC)	1.72	Microglia	0.00
Microglia	0.40	Committed Oligos	0.00
Macrophages	0.00	Macrophages	0.00
Vascular and leptomeningeal cells (VLM)	0.00	Oligodendrocytes	0.00
Oligodendrocytes	0.00	Committed Oligos-2	0.00
Committed Oligos-2	0.00	Mature Oligos	0.00

Example 8. Individual Capsid Characterization of TTM-002 in NHPs

[0534] This example describes the transduction level, tropism, ability to cross the blood brain barrier, and overall spatial distribution in the central nervous system (CNS) and peripheral tissues of the AAV capsid variant TTM-002 (SEQ ID NO: 982 (amino acid) and 984 (DNA), comprising SEQ ID NO: 2), relative to AAV9 following intravenous administration in African green monkeys (*Chlorocebus sabaeus*).

[0535] AAV particles were generated with the TTM-002 capsid variant or the AAV9 capsid control which comprised a self-complementary viral genome encoding an histone H2b protein with an HA tag driven by a ubiquitous CBA promoter. The AAV particles comprising the TTM-002 capsid variant or the AAV9 capsid control were administered to the NHPs (n=2) intravenously at a dose of 1e12 VG/kg or 1e13 VG/kg. The in-life period was 28 days and then various CNS and peripheral tissues were collected for measuring transgene mRNA (expression) by RT-qPCR and viral DNA (biodistribution) by ddPCR.

[0536] As shown in **Table 23**, the TTM-002 capsid variant resulted in increased brain biodistribution in all brain regions investigated as compared to AAV9 at both doses tested. The TTM-002 capsid variant also led to increased transgene expression in the brain relative to AAV9 at both doses tested (**Table 24**). In the spinal cord, the TTM-002 capsid variant distributed to the cervical spinal cord and the spinal cord ventral horn at a higher level relative to AAV9 (**Table 23**) and it mediated higher transgene expression than AAV9 in both the full spinal cord and the ventral horn (**Table 24**). The TTM-002 capsid variant exhibited lower biodistribution (**Table 23**) and transgene expression (**Table 24**) in the DRG relative to AAV9, indicating that TTM-002 capsid variant was detargeted in the DRG relative to AAV9. Similar expression and distribution were observed by immunohistochemistry performed on these CNS tissues.

[0537] Distribution and transgene expression was also measured in the peripheral tissues of the liver, heart, and quadriceps. In the liver, TTM-002 capsid variant exhibited lower biodistribution (**Table 23**) and transgene expression (**Table 24**) relative to AAV9, indicating that TTM-002 capsid variant was detargeted in the liver relative to AAV9. In the heart, the TTM-002 capsid variant exhibited comparable levels of biodistribution relative to AAV9 (**Table 23**), but increased transgene expression relative to AAV9 (**Table 24**). In the quadriceps, TTM-002 capsid variant exhibited lower biodistribution (**Table 23**) and lower transgene expression (**Table 24**), relative to AAV9. Similar expression and distribution were observed by immunohistochemistry performed on these peripheral tissues.

Table 23: Quantification of viral genome copies per diploid genome (biodistribution) by ddPCR following intravenous administration of AAV particles comprising a TTM-002 capsid

Tissue	1e12 VG/kg			1e13 VG/kg		
	AAV9 (VG copies/ diploid genome)	TTM-002 (VG copies/ diploid genome)	TTM-002 relative to AAV9	AAV9 (VG copies/ diploid genome)	TTM-002 (VG copies/ diploid genome)	TTM-002 relative to AAV9
Putamen	0.03	0.37	12.3	0.26	2.4	9.2
Caudate	0.02	0.58	29	0.14	2.1	14.7
Thalamus	0.06	0.21	3.5	0.25	1.0	4
Hippocampus	0.03	0.29	9.7	0.16	1.56	9.8
Substantia Nigra	0.05	0.34	6.8	0.37	1.38	3.7
Motor Cortex	0.03	0.56	19	0.27	2.4	8.9
Frontal Cortex	0.04	0.67	17	0.20	3.6	18
Temporal Cortex	0.03	0.31	10	0.11	2.67	24
Cerebral Cortex	0.008	0.08	10	0.03	0.16	5.3
Dentate Nucleus	0.06	0.10	1.7	0.32	3.21	10
Cervical Spinal Cord	0.03	0.12	4	0.19	0.91	4.8
Thoracic Spinal Cord	0.04	0.03	0.75	0.36	0.38	1.1
Lumbar Spinal Cord	0.04	0.03	0.75	0.29	0.37	1.3
C5 Ventral Horn	0.04	0.25	6.3	0.29	2.2	7.6
L5 Ventral Horn	0.06	0.28	4.7	0.31	1.9	6.1
Cervical DRG	0.07	0.01	-7	0.81	0.36	-2.3
Thoracic DRG	0.06	0.01	-6	1.31	0.43	-3
Lumbar DRG	0.07	0.01	-7	1.31	0.57	-2.3
Liver	9.5	1.2	-7.9	127	7.7	-16.5
Heart	0.6	0.7	1.2	5.4	5.4	1
Quadriceps	0.2	0.06	-3.3	1.7	0.6	-2.8

Table 24: Quantification of transgene mRNA by RT-qPCR following intravenous administration of AAV particles comprising a TTM-002 capsid

Tissue	1e12 VG/kg			1e13 VG/kg		
	AAV9 (transgene mRNA fold over housekeeping gene) ($2^{-\Delta\Delta CT}$)	TTM-002 (transgene mRNA fold over housekeeping gene) ($2^{-\Delta\Delta CT}$)	TTM-002 relative to AAV9	AAV9 (transgene mRNA fold over housekeeping gene) ($2^{-\Delta\Delta CT}$)	TTM-002 (transgene mRNA fold over housekeeping gene) ($2^{-\Delta\Delta CT}$)	TTM- 002 relative to AAV9
Putamen	0.02	0.3	15	0.09	4.22	47
Caudate	0.02	0.8	40	0.11	4.29	39
Thalamus	0.04	0.4	10	0.4	5.8	14.5
Hippocampus	0.02	0.4	20	0.1	4.3	43
Substantia Nigra	0.1	1.2	12	0.3	11.6	39
Motor Cortex	0.08	5.00	63	0.36	21.8	61
Frontal Cortex	0.04	3.1	78	0.3	27.7	92

Temporal Cortex	0.02	0.8	40	0.1	26.9	27
Cerebral Cortex	0.04	1.1	28	0.2	17.4	87
Dentate Nucleus	0.3	0.9	3	1.8	42.0	23
Cervical Spinal Cord	0.2	2.0	10	0.8	20.2	25
Thoracic Spinal Cord	0.13	0.25	1.9	0.7	4.8	6.9
Lumbar Spinal Cord	0.4	0.5	1.3	2.2	9.2	4.2
C5 Ventral Horn	0.2	1.4	7	1.7	33	19
L5 Ventral Horn	1.1	3.4	3.1	12.4	102	8.2
Cervical DRG	3.6	1.2	-3	63.1	15.9	-4
Thoracic DRG	1.8	1.3	-1.4	43.9	15.7	-2.8
Lumbar DRG	1.9	1.0	-1.9	34.9	27.6	-1.3
Liver	0.88	0.25	-3.5	2.2	0.97	-2.3
Heart	8.7	42	4.8	110	363	3.3
Quadriceps	9.7	1.1	-8.3	59	21	-2.8

[0538] Taken together, these data demonstrate that TTM-002 is an enhanced CNS tropic capsid in NHPs (African green monkeys) that can infect non-neuronal cells. TTM-002 was also detargeted in the DRG and liver relative to AAV9, but showed increased transgene expression in the heart relative to AAV9. Additionally, the TTM-002 capsid variant was able to successfully penetrate the blood brain barrier following intravenous injection.

We claim:

1. An AAV capsid variant, comprising an amino acid sequence having the following formula:

[N1]-[N2]-[N3], wherein:

(i) [N1] comprises X1, X2, and X3, wherein at least one of X1, X2, or X3 is G;

(ii) [N2] comprises the amino acid sequence of SPH;

(ii) [N3] comprises X4, X5, and X6, wherein at least one of X4, X5, or X6 is a basic amino acid, e.g., a K or R;

wherein [N1]-[N2]-[N3] is present from N-terminus to C-terminus, immediately subsequent to position 452, numbered according to any one of SEQ ID NO: 982, 981, or 138; and

wherein the AAV capsid variant comprises:

(a) an amino acid sequence at least 95% identical to the amino acid sequence of positions 203-742, e.g., a VP3, of any one of SEQ ID NO: 982 or 981;

(b) an amino acid sequence at least 95% identical to the amino acid sequence of positions 203-736, e.g., a VP3, of SEQ ID NO: 138.

2. The AAV capsid variant of claim 1, wherein:

(a) position X4 of [N3] is: K, S, A, V, T, G, F, W, V, N, or R;

(b) position X5 of [N3] is: S, K, T, F, I, L, Y, H, M, or R; and/or

(c) position X6 of [N3] is: G, A, R, M, I, N, T, Y, D, P, V, L, E, W, N, Q, K, or S;

optionally wherein the AAV capsid variant comprises an amino acid modification, e.g., a conservative substitution, of any of the aforesaid amino acids in (a)-(c).

3. The AAV capsid variant of claim 1 or 2, wherein [N3] comprises KSG, SKA, ARM, VKS, ASR, VKI, KKN, VRM, RKA, KTS, KFG, KIG, KLK, KTT, KTY, KYG, SKD, SKP, TRG, VRG, KRG, GAR, KSA, KSR, SKL, SRA, SKR, SLR, SRG, SSR, FLR, SKW, SKS, WKA, VRR, SKV, SKT, SKG, GKA, TKA, NKA, SKL, SKN, AKA, KTG, KSL, KSE, KSV, KSW, KSN, KHG, KSQ, KSK, KLW, WKG, KMG, KMA, or RSG

optionally, wherein the AAV capsid variant comprises an amino acid modification, e.g., a conservative substitution, of any of the aforesaid amino acid sequences.

4. The AAV capsid variant of any one of claims 1-3, wherein [N2]-[N3] comprises:

(i) SPHKSG (SEQ ID NO: 946), SPHKA (SEQ ID NO: 941), SPHARM (SEQ ID NO: 947), SPHVKS (SEQ ID NO: 948), SPHASR (SEQ ID NO: 949), SPHVKI (SEQ ID NO: 950), SPHKKN (SEQ ID NO: 954), SPHVRM (SEQ ID NO: 955), SPHRKA (SEQ ID NO: 956), SPHKFG (SEQ ID NO: 957), SPHKIG (SEQ ID NO: 958), SPHKLK (SEQ ID NO: 959), SPHKTS (SEQ ID NO: 963), SPHKTT (SEQ ID NO: 964), SPHKTY (SEQ ID NO: 965), SPHKYG (SEQ ID NO: 966), SPHAKD (SEQ ID NO: 967), SPHAKP (SEQ ID NO: 968), SPHTRG (SEQ ID NO: 972), SPHVRG (SEQ ID

NO: 973), SPHKRG (SEQ ID NO: 974), SPHGAR (SEQ ID NO: 975), SPHKSA (SEQ ID NO: 977), SPHKSR (SEQ ID NO: 951), SPHSL (SEQ ID NO: 960), SPHSRA (SEQ ID NO: 969), SPHSCR (SEQ ID NO: 978), SPHSLR (SEQ ID NO: 952), SPHSRG (SEQ ID NO: 961), SPHSSR (SEQ ID NO: 970), SPHFLR (SEQ ID NO: 979), SPHSKW (SEQ ID NO: 953), SPHSKS (SEQ ID NO: 962), SPHWKA (SEQ ID NO: 971), SPHVR (SEQ ID NO: 980), SPHKT (SEQ ID NO: 4731), SPHSG (SEQ ID NO: 4732), SPHGKA (SEQ ID NO: 4733), SPHNKA (SEQ ID NO: 4734), SPHSKN (SEQ ID NO: 4735), SPHAKA (SEQ ID NO: 4736), SPHSKV (SEQ ID NO: 4737), SPHKTG (SEQ ID NO: 4738), SPHTKA (SEQ ID NO: 4739), SPHKSL (SEQ ID NO: 4740), SPHKSE (SEQ ID NO: 4741), SPHKSV (SEQ ID NO: 4742), SPHKSW (SEQ ID NO: 4743), SPHKSN (SEQ ID NO: 4744), SPKHHG (SEQ ID NO: 4745), SPKHSQ (SEQ ID NO: 4746), SPKHSK (SEQ ID NO: 4747), SPKHLW (SEQ ID NO: 4748), SPHWKG (SEQ ID NO: 4749), SPKHM (SEQ ID NO: 4750), SPKMA (SEQ ID NO: 4751), or SPHRS (SEQ ID NO: 976):

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, or 5 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

5. The AAV capsid variant of any one of claims 1-4, wherein:

(a) position X1 of [N1] is: G, V, R, D, E, M, T, I, S, A, N, L, K, H, P, W, or C;

(b) position X2 of [N1] is: H, S, V, L, N, D, R, P, G, T, I, A, E, Y, M, or Q; and/or

(c) position X3 of [N1] is: D, G, C, L, E, Y, H, V, A, N, P, or S;

optionally wherein the AAV capsid variant comprises an amino acid modification, e.g., a conservative substitution, of any of the aforesaid amino acids in (a)-(c).

6. The AAV capsid variant of any one of claims 1-5, wherein [N1] comprises GHD, GSG, GQD, VSG, CSG, GRG, CSH, GQS, GSH, RVG, GSC, GLL, GDD, GHE, GNY, MSG, RNG, TSG, ISG, GPG, ESG, SSG, GNG, ASG, NSG, LSG, GGG, KSG, HSG, GTG, PSG, GSV, RSG, GIG, WSG, DSG, IDG, GLG, DAG, DGG, MEG, ENG, GSA, KNG, KEG, AIG, GYD, GHG, GRD, GND, GPD, GMG, GOV, GHN, GHP, or GHS

optionally, wherein the AAV capsid variant comprises an amino acid modification, e.g., a conservative substitution, of any of the aforesaid amino acid sequences.

7. The AAV capsid variant of any one of claims 1-6, wherein [N1]-[N2] comprises:

(i) GHDSPH (SEQ ID NO: 4784), GSGSPH (SEQ ID NO: 4695), GQDSPH (SEQ ID NO: 4785), VSGSPH (SEQ ID NO: 4786), CSGSPH (SEQ ID NO: 4787), GRGSPH (SEQ ID NO: 4788), CSHSPH (SEQ ID NO: 4789), GQSSPH (SEQ ID NO: 4790), GSHSPH (SEQ ID NO: 4791), GDDSPH (SEQ ID NO: 4792), GHESPH (SEQ ID NO: 4793), GNYSPH (SEQ ID NO: 4794), RVGSPH (SEQ ID NO: 4795), GSCSPH (SEQ ID NO: 4796), GLLSPH (SEQ ID NO: 4797), MSGSPH (SEQ ID NO: 4798), RNGSPH (SEQ ID NO: 4799), TSGSPH (SEQ ID NO: 4800), ISGSPH (SEQ ID NO: 4801), GPGSPH (SEQ ID NO: 4802), ESGSPH (SEQ ID NO: 4803), SSGSPH (SEQ ID NO: 4804), GNGSPH (SEQ ID NO: 4805), ASGSPH (SEQ ID NO: 4806), NSGSPH (SEQ ID NO: 4807), LSGSPH (SEQ ID NO: 4808), GGGSPH (SEQ ID NO: 4809), KSGSPH (SEQ ID NO: 4810), HSGSPH (SEQ ID NO: 4811), GTGSPH (SEQ ID NO: 4812), PSGSPH (SEQ ID NO: 4813), GSVSPH (SEQ ID NO: 4814), RSGSPH (SEQ ID NO: 4815), GIGSPH (SEQ ID NO: 4816), WSGSPH (SEQ ID NO: 4817), DSGSPH (SEQ ID NO: 4818), IDGSPH (SEQ ID NO: 4819), GLGSPH (SEQ ID NO: 4820), DAGSPH (SEQ ID NO: 4821), DGGSPH (SEQ ID NO: 4822), MEGSPH (SEQ ID NO: 4823), ENGSPH (SEQ ID NO: 4824), GSASPH (SEQ ID NO: 4825), KNGSPH (SEQ ID NO: 4826), KEGSPH (SEQ ID NO: 4827), AIGSPH (SEQ ID NO: 4828), GYDSPH (SEQ ID NO: 4829), GHGSPH (SEQ ID NO: 4830), GRDSPH (SEQ ID NO: 4831), GNDSPH (SEQ ID NO: 4832), GPDSPH (SEQ ID NO: 4833), GMGSPH (SEQ ID NO: 4834), GQVSPH (SEQ ID NO: 4835), GHNSPH (SEQ ID NO: 4836), GHPSPH (SEQ ID NO: 4837), or GHSSPH (SEQ ID NO: 4838);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, or 5 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

8. The AAV capsid variant of any one of claims 1-7, wherein [N1]-[N2]-[N3] comprises:

(i) GHDSPHKSG (SEQ ID NO: 4698), GSGSPHKA (SEQ ID NO: 4697), GSGSPHARM (SEQ ID NO: 4906), GSGSPHVKS (SEQ ID NO: 4907), GQDSPHKSG (SEQ ID NO: 4908), GSGSPHASR (SEQ ID NO: 4909), GSGSPHVKI (SEQ ID NO: 4910), GSGSPHKKN (SEQ ID NO: 4911), GSGSPHVRM (SEQ ID NO: 4912), VSGSPHKA (SEQ ID NO: 4913), CSGSPHKA (SEQ ID NO: 4914), GSGSPHRKA (SEQ ID NO: 4915), CSGSPHKTS (SEQ ID NO: 4916), CSHSPHKSG (SEQ ID NO: 4917), GQSSPHRSG (SEQ ID NO: 4918), GRGSPHASR (SEQ ID NO: 4919), GRGSPHKA (SEQ ID NO: 4920), GSGSPHKFG (SEQ ID NO: 4921), GSGSPHKIG (SEQ ID NO: 4922), GSGSPHKLK (SEQ ID NO: 4923), GSGSPHKTS (SEQ ID NO: 4924), GSGSPHKTT (SEQ ID NO: 4925), GSGSPHKTY (SEQ ID NO: 4926), GSGSPHKYG (SEQ ID

NO: 4927), GSGSPHSDK (SEQ ID NO: 4928), GSGSPHSPK (SEQ ID NO: 4929), GSGSPHTRG (SEQ ID NO: 4930), GSGSPHVRG (SEQ ID NO: 4931), GSHSPHKRG (SEQ ID NO: 4932), GSHSPHKSG (SEQ ID NO: 4933), VSGSPHASR (SEQ ID NO: 4934), VSGSPHGAR (SEQ ID NO: 4935), VSGSPHKFG (SEQ ID NO: 4936), GHDSPHKRG (SEQ ID NO: 4937), GDDSPHKSG (SEQ ID NO: 4938), GHESPHKSA (SEQ ID NO: 4939), GHDSPHKSA (SEQ ID NO: 4940), GNYSPHKIG (SEQ ID NO: 4941), GHDSPHKSR (SEQ ID NO: 4942), GSGSPHSL (SEQ ID NO: 4943), GSGSPHSRA (SEQ ID NO: 4944), GSGSPHSPK (SEQ ID NO: 4945), GSGSPHSLR (SEQ ID NO: 4946), GSGSPHSRG (SEQ ID NO: 4947), GSGSPHSSR (SEQ ID NO: 4948), RVGSPHKA (SEQ ID NO: 4949), GSCSPHKA (SEQ ID NO: 4950), GSGSPHFLR (SEQ ID NO: 4951), GSGSPHSPK (SEQ ID NO: 4952), GSGSPHSPK (SEQ ID NO: 4953), GLLSPHWKA (SEQ ID NO: 4954), GSGSPHVRR (SEQ ID NO: 4955), GSGSPHSPK (SEQ ID NO: 4956), MSGSPHKA (SEQ ID NO: 4957), RNGSPHKA (SEQ ID NO: 4958), TSGSPHKA (SEQ ID NO: 4959), ISGSPHKA (SEQ ID NO: 4960), GPGSPHKA (SEQ ID NO: 4961), GSGSPHSPK (SEQ ID NO: 4962), ESGSPHKA (SEQ ID NO: 4963), SSGSPHKA (SEQ ID NO: 4964), NGSPHKA (SEQ ID NO: 4965), ASGSPHKA (SEQ ID NO: 4966), NSGSPHKA (SEQ ID NO: 4967), LSGSPHKA (SEQ ID NO: 4968), GGGSPHKA (SEQ ID NO: 4969), KSGSPHKA (SEQ ID NO: 4970), GGGSPHSPK (SEQ ID NO: 4971), GSGSPHSPK (SEQ ID NO: 4972), HSGSPHKA (SEQ ID NO: 4973), GTGSPHKA (SEQ ID NO: 4974), PSGSPHKA (SEQ ID NO: 4975), GSVSPHGKA (SEQ ID NO: 4976), RSGSPHKA (SEQ ID NO: 4977), GSGSPHTKA (SEQ ID NO: 4978), GIGSPHKA (SEQ ID NO: 4979), WSGSPHKA (SEQ ID NO: 4980), DSGSPHKA (SEQ ID NO: 4981), IDGSPHKA (SEQ ID NO: 4982), GSGSPHNKA (SEQ ID NO: 4983), GLGSPHSPK (SEQ ID NO: 4984), DAGSPHKA (SEQ ID NO: 4985), DGGSPHKA (SEQ ID NO: 4986), MEGSPHKA (SEQ ID NO: 4987), ENGSPHKA (SEQ ID NO: 4988), GSASPHKA (SEQ ID NO: 4989), NGSPHSPK (SEQ ID NO: 4990), KNGSPHKA (SEQ ID NO: 4991), KEGSPHKA (SEQ ID NO: 4992), AIGSPHKA (SEQ ID NO: 4993), GSGSPHSPK (SEQ ID NO: 4994), GSGSPHAKA (SEQ ID NO: 4995), GHDSPHKIG (SEQ ID NO: 4996), GYDSPHKSG (SEQ ID NO: 4997), GHESPHKSG (SEQ ID NO: 4998), GHDSPHKGT (SEQ ID NO: 4999), GRGSPHKRG (SEQ ID NO: 5000), GQDSPHKSG (SEQ ID NO: 4908), GHDSPHKSL (SEQ ID NO: 5001), GHGSPHKA (SEQ ID NO: 5002), GHDSPHKSE (SEQ ID NO: 5003), VSGSPHKA (SEQ ID NO: 4913), GRDSPHKSG (SEQ ID NO: 5004), GNDSPHSPK (SEQ ID NO: 5005), GQDSPHKIG (SEQ ID NO: 5006), GHDSPHKSV (SEQ ID NO: 5007), GPDSPHKIG (SEQ ID NO: 5008), GPDSPHKSG (SEQ ID NO: 5009), GHDSPHKSW (SEQ ID NO: 5010), GHDSPHKSN (SEQ ID NO: 5011), GMGSPHSPK (SEQ ID NO: 5012), GHDSPHKHG (SEQ ID NO: 5013), GQVSPHKSG (SEQ ID NO: 5014), GDDSPHSPK (SEQ ID NO: 5015), GHNSPHKSG (SEQ ID NO: 5016), NGSPHSPK (SEQ ID NO: 5017), GHDSPHKYG (SEQ ID NO: 5018), GHDSPHKSPK (SEQ ID NO: 5019), GNDSPHKIG (SEQ ID NO: 5020), GHDSPHKSK (SEQ ID NO: 5021), GHDSPHKLW (SEQ ID NO: 5022), GHSPHSPK (SEQ ID NO: 5023),

GHDSPHKMG (SEQ ID NO: 5024), GHDSPHKMA (SEQ ID NO: 5025), or GHSSPHRSG (SEQ ID NO: 5026);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, 5, 6, 7, or 8 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

9. The AAV capsid variant of any one of claims 1-8, wherein:

(a) [N1]-[N2]-[N3] comprises GHDSPHKSG (SEQ ID NO: 4698); or

(b) [N1]-[N2]-[N3] comprises GSGSPHKA (SEQ ID NO: 4697).

10. The AAV capsid variant of any one of claims 1-9, which further comprises [N4], wherein [N4] comprises

(i) QNQQ (SEQ ID NO: 5028), WNQQ (SEQ ID NO: 5029), QYYV (SEQ ID NO: 5030), RRQQ (SEQ ID NO: 5031), GCGQ (SEQ ID NO: 5032), LRQQ (SEQ ID NO: 5033), RNQQ (SEQ ID NO: 5034), VNQQ (SEQ ID NO: 5035), FRLQ (SEQ ID NO: 5036), FNQQ (SEQ ID NO: 5037), LLQQ (SEQ ID NO: 5038), SNQQ (SEQ ID NO: 5039), RLQQ (SEQ ID NO: 5040), LNQQ (SEQ ID NO: 5041), QRKL (SEQ ID NO: 5042), LRRQ (SEQ ID NO: 5043), QRLR (SEQ ID NO: 5044), QRRL (SEQ ID NO: 5045), RRLQ (SEQ ID NO: 5046), RLRQ (SEQ ID NO: 5047), SKRQ (SEQ ID NO: 5048), QLYR (SEQ ID NO: 5049), QLTV (SEQ ID NO: 5050), QNKQ (SEQ ID NO: 5051), KNQQ (SEQ ID NO: 5052), QKQQ (SEQ ID NO: 5053), QTQQ (SEQ ID NO: 5054), QNHQ (SEQ ID NO: 5055), QHQQ (SEQ ID NO: 5056), QNQH (SEQ ID NO: 5057), QHRQ (SEQ ID NO: 5058), LTQQ (SEQ ID NO: 5059), QNQW (SEQ ID NO: 5060), QNTH (SEQ ID NO: 5061), RRRQ (SEQ ID NO: 5062), QYQQ (SEQ ID NO: 5063), QNDQ (SEQ ID NO: 5064), QNRH (SEQ ID NO: 5065), RDQQ (SEQ ID NO: 5066), PNLQ (SEQ ID NO: 5067), HVRQ (SEQ ID NO: 5068), PNQH (SEQ ID NO: 5069), HNQQ (SEQ ID NO: 5070), QSQQ (SEQ ID NO: 5071), QPAK (SEQ ID NO: 5072), QNLA (SEQ ID NO: 5073), QNQL (SEQ ID NO: 5074), QGQQ (SEQ ID NO: 5075), LNRQ (SEQ ID NO: 5076), QNPP (SEQ ID NO: 5077), QNLQ (SEQ ID NO: 5078), QDQE (SEQ ID NO: 5079), QDQQ (SEQ ID NO: 5080), HWQQ (SEQ ID NO: 5081), PNQQ (SEQ ID NO: 5082), PEQQ (SEQ ID NO: 5083), QRTM (SEQ ID NO: 5084), LHQH (SEQ ID NO: 5085), QHRI (SEQ ID NO: 5086), QYIH (SEQ ID NO: 5087), QKFE (SEQ ID NO: 5088), QFPS (SEQ ID NO: 5089), QNPL (SEQ ID NO: 5090), QAIK (SEQ ID NO: 5091), QNRQ (SEQ ID NO: 5092), QYQH (SEQ ID NO: 5093), QNPQ (SEQ ID NO: 5094), QHQL (SEQ ID NO: 5095), QSPP (SEQ ID NO: 5096), QAKL (SEQ ID NO: 5097), KSQQ (SEQ ID NO: 5098), QDRP (SEQ ID NO: 5099), QNLG (SEQ ID NO: 5100),

QAFH (SEQ ID NO: 5101), QNAQ (SEQ ID NO: 5102), HNQL (SEQ ID NO: 5103), QKLN (SEQ ID NO: 5104), QNVQ (SEQ ID NO: 5105), QAAQ (SEQ ID NO: 5106), QTPP (SEQ ID NO: 5107), QPPA (SEQ ID NO: 5108), QERP (SEQ ID NO: 5109), QDLQ (SEQ ID NO: 5110), QAMH (SEQ ID NO: 5111), QHPS (SEQ ID NO: 5112), PGLQ (SEQ ID NO: 5113), QGIR (SEQ ID NO: 5114), QAPA (SEQ ID NO: 5115), QIPP (SEQ ID NO: 5116), QTQL (SEQ ID NO: 5117), QAPS (SEQ ID NO: 5118), QNTY (SEQ ID NO: 5119), QDKQ (SEQ ID NO: 5120), QNHL (SEQ ID NO: 5121), QIGM (SEQ ID NO: 5122), LNKQ (SEQ ID NO: 5123), PNQL (SEQ ID NO: 5124), QLQQ (SEQ ID NO: 5125), QRMS (SEQ ID NO: 5126), QGIL (SEQ ID NO: 5127), QDRQ (SEQ ID NO: 5128), RDWQ (SEQ ID NO: 5129), QERS (SEQ ID NO: 5130), QNYQ (SEQ ID NO: 5131), QRTC (SEQ ID NO: 5132), QIGH (SEQ ID NO: 5133), QGAI (SEQ ID NO: 5134), QVPP (SEQ ID NO: 5135), QVQQ (SEQ ID NO: 5136), LMRQ (SEQ ID NO: 5137), QYSV (SEQ ID NO: 5138), QAIT (SEQ ID NO: 5139), QKTL (SEQ ID NO: 5140), QLHH (SEQ ID NO: 5141), QNII (SEQ ID NO: 5142), QGHH (SEQ ID NO: 5143), QSKV (SEQ ID NO: 5144), QLPS (SEQ ID NO: 5145), IGKQ (SEQ ID NO: 5146), QAIH (SEQ ID NO: 5147), QHGL (SEQ ID NO: 5148), QFMC (SEQ ID NO: 5149), QNQM (SEQ ID NO: 5150), QHLQ (SEQ ID NO: 5151), QPAR (SEQ ID NO: 5152), QSLQ (SEQ ID NO: 5153), QSQL (SEQ ID NO: 5154), HSQQ (SEQ ID NO: 5155), QMPS (SEQ ID NO: 5156), QGSL (SEQ ID NO: 5157), QVPA (SEQ ID NO: 5158), HYQQ (SEQ ID NO: 5159), QVPS (SEQ ID NO: 5160), RGEQ (SEQ ID NO: 5161), PGQQ (SEQ ID NO: 5162), LEQQ (SEQ ID NO: 5163), QNQS (SEQ ID NO: 5164), QKVI (SEQ ID NO: 5165), QNND (SEQ ID NO: 5166), QSVH (SEQ ID NO: 5167), QPLG (SEQ ID NO: 5168), HNQE (SEQ ID NO: 5169), QIQQ (SEQ ID NO: 5170), QVRN (SEQ ID NO: 5171), PSNQ (SEQ ID NO: 5172), QVGH (SEQ ID NO: 5173), QRDI (SEQ ID NO: 5174), QMPN (SEQ ID NO: 5175), RGLQ (SEQ ID NO: 5176), PSLQ (SEQ ID NO: 5177), QRDQ (SEQ ID NO: 5178), QAKG (SEQ ID NO: 5179), QSAH (SEQ ID NO: 5180), QSTM (SEQ ID NO: 5181), QREM (SEQ ID NO: 5182), QYRA (SEQ ID NO: 5183), QRQQ (SEQ ID NO: 5184), QWQQ (SEQ ID NO: 5185), QRMN (SEQ ID NO: 5186), GDSQ (SEQ ID NO: 5187), QKIS (SEQ ID NO: 5188), PSMQ (SEQ ID NO: 5189), SPRQ (SEQ ID NO: 5190), MEQQ (SEQ ID NO: 5191), QYQN (SEQ ID NO: 5192), QIRQ (SEQ ID NO: 5193), QSVQ (SEQ ID NO: 5194), RSQQ (SEQ ID NO: 5195), QNKL (SEQ ID NO: 5196), QIQH (SEQ ID NO: 5197), PRQQ (SEQ ID NO: 5198), HTQQ (SEQ ID NO: 5199), QRQH (SEQ ID NO: 5200), RNQE (SEQ ID NO: 5201), QSKQ (SEQ ID NO: 5202), QNQP (SEQ ID NO: 5203), QSPQ (SEQ ID NO: 5204), QTRQ (SEQ ID NO: 5205), QNLH (SEQ ID NO: 5206), QNQE (SEQ ID NO: 5207), LNQP (SEQ ID NO: 5208), QNQD (SEQ ID NO: 5209), QNLL (SEQ ID NO: 5210), QLVI (SEQ ID NO: 5211), RTQE (SEQ ID NO: 5212), QTHQ (SEQ ID NO: 5213), QDQH (SEQ ID NO: 5214), QSQH (SEQ ID NO: 5215), VRQQ (SEQ ID NO: 5216), AWQQ (SEQ ID NO: 5217), QSVP (SEQ ID NO: 5218), QNIQ (SEQ ID NO: 5219), LDQQ (SEQ ID NO: 5220), PDQQ (SEQ ID NO: 5221), ESQQ (SEQ ID NO: 5222), QRQL (SEQ ID NO: 5223), QIIV (SEQ ID NO: 5224), QKQS (SEQ ID NO: 5225), QSHQ (SEQ ID NO: 5226), QFVV (SEQ ID NO: 5227), QSQP (SEQ ID NO: 5228), QNEQ (SEQ ID NO: 5229), INQQ (SEQ ID

NO: 5230), RNRQ (SEQ ID NO: 5231), RDQK (SEQ ID NO: 5232), QWKR (SEQ ID NO: 5233), ENRQ (SEQ ID NO: 5234), QTQP (SEQ ID NO: 5235), QKQL (SEQ ID NO: 5236), RNQL (SEQ ID NO: 5237), ISIQ (SEQ ID NO: 5238), QTVC (SEQ ID NO: 5239), QQIM (SEQ ID NO: 5240), LNHQ (SEQ ID NO: 5241), QNQA (SEQ ID NO: 5242), QMIH (SEQ ID NO: 5243), RNHQ (SEQ ID NO: 5244), or QKMN (SEQ ID NO: 5245);

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, or 3 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one or two modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one or two different amino acids, relative to any one of the amino acid sequences in (i).

11. The AAV capsid variant of any one of claims 1-10, which further comprises [N0], wherein [N0] comprises:

(i) TIN, SMN, TIM, YLS, GLS, MPE, MEG, MEY, AEW, CEW, ANN, IPE, ADM, IEY, ADY, IET, MEW, CEY, RIN, MEL, LEY, ADW, IEI, DIM, FEQ, MEF, CDQ, LPE, IEN, MES, AEI, VEY, IIN, TSN, IEV, MEM, AEW, MDA, VEW, AEQ, LEW, MEL, MET, MEA, IES, MEV, CEI, ATN, MDG, QEV, ADQ, NMN, IEM, ISN, TGN, QQQ, HDW, IEG, TII, TFP, TEK, EIN, TVN, TFN, SIN, TER, TSY, ELH, AIN, SVN, TDN, TFH, TVH, TEN, TSS, TID, TCN, NIN, TEH, AEM, AIK, TDK, TFK, SDQ, TEL, NTN, TET, SIK, TEL, TEA, TAN, TIY, TFS, TES, TTN, TED, TNN, EVH, TIS, TVR, TDR, TIK, NHI, TIP, ESD, TDL, TVP, TVI, AEH, NCL, TVK, NAD, TIT, NCV, TIR, NAL, VIN, TIQ, TEF, TRE, QGE, SEK, NVN, GGE, EFV, SDK, TEQ, EVQ, TEY, NCW, TDV, SDI, NSI, NSL, EVV, TEP, SEL, TWQ, TEV, AVN, GVL, TLN, TEG, TRD, NAI, AEN, AET, ETA, NNL;

(ii) any dipeptide of any one of the amino acid sequences in (i); or

(iii) an amino acid sequence comprising one or two modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one or two different amino acids, relative to any one of the amino acid sequences in (i).

12. The AAV capsid variant of claim 10 or 11, wherein [N0]-[N1]-[N2]-[N3]-[N4] comprises:

(i) the amino acid sequence of any one of SEQ ID NOs: 2243, 2242, 2242-2886;

(ii) an amino acid sequence comprising any portion of an amino acid sequence in (i), e.g., any 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 amino acids, e.g., consecutive amino acids, thereof;

(iii) an amino acid sequence comprising one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to any of the amino acid sequences in (i); or

(iv) an amino acid sequence comprising one, two, or three but no more than four different amino acids, relative to any one of the amino acid sequences in (i).

13. The AAV capsid variant of claims 11 or 12, which comprises from N-terminus to C-terminus [N0]-[N1]-[N2]-[N3]-[N4], wherein:

(i) [N0] is present immediately subsequent to position 449 and replaces positions 450-452 (e.g., T450, I451, and N452), numbered according to the amino acid sequence of any one of SEQ ID NOs: 982, 981, or 138;

(ii) [N1] is present immediately subsequent to position 452 and replaces positions 453-455, numbered according to the amino acid sequence of SEQ ID NO: 138;

(iii) [N2] is present immediately subsequent to position 455, numbered according to the amino acid sequence of SEQ ID NO: 138;

(iv) [N3] is present immediately subsequent to [N2]; and/or

(v) [N4] is present immediately subsequent to position 455 and replaces positions 456-459 (e.g., Q456, N457, Q458, and Q459), numbered according to the amino acid sequence of SEQ ID NO: 138.

14. The AAV capsid variant of any one of claims 11-13, wherein

(i) [N2]-[N3]-[N4] corresponds to positions 456-465 of SEQ ID NO: 982 or 981;

(ii) [N1]-[N2]-[N3] corresponds to positions 453-461 of SEQ ID NO: 982 or 981; and/or

(iii) [N0]-[N1]-[N2]-[N3]-[N4] corresponds to positions 450-465 of SEQ ID NO: 982 or 981.

15. An AAV capsid variant comprising an amino acid sequence having the following formula: [N1]-[N2]-[N3] (SEQ ID NO: 6408), wherein:

(i) [N1] comprises positions X1, X2, and X3, wherein position X2 is an amino acid other than S and position X3 is an amino acid other than G;

(ii) [N2] comprises the amino acid sequence SPH; and

(iii) [N3] comprises positions X4, X5, and X6, wherein position X4 is K;

wherein [N1]-[N2]-[N3] is present from N-terminus to C-terminus, immediately subsequent to position 452, numbered according to any one of SEQ ID NO: 982; and

wherein the AAV capsid variant comprises:

(a) an amino acid sequence at least 95% identical to the amino acid sequence of positions 203-742, e.g., a VP3, of SEQ ID NO: 982;

(b) an amino acid sequence at least 95% identical to the amino acid sequence of positions 203-736, e.g., a VP3, of SEQ ID NO: 138.

16. An AAV capsid variant comprising an amino acid sequence having the following formula: [N1]-[N2]-[N3] (SEQ ID NO: 6407), wherein:

(i) [N1] comprises positions X1, X2, and X3, wherein position X2 is S and position X3 is G;

(ii) [N2] comprises the amino acid sequence SPH; and

(iii) [N3] comprises positions X4, X5, and X6, wherein position X5 is K;

wherein [N1]-[N2]-[N3] is present from N-terminus to C-terminus, immediately subsequent to position 452, numbered according to any one of SEQ ID NO: 981; and

wherein the AAV capsid variant comprises:

(a) an amino acid sequence at least 95% identical to the amino acid sequence of positions 203-742, e.g., a VP3, of SEQ ID NO: 981;

(b) an amino acid sequence at least 95% identical to the amino acid sequence of positions 203-736, e.g., a VP3, of SEQ ID NO: 138.

17. An AAV capsid variant comprising:

(a) the amino acid sequence of any of the sequences provided in Tables 1, 2A, 2B, 9-11, 13-19;

(b) an amino acid sequence comprising at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or 17 consecutive amino acids from any one of the sequences provided in Tables 1, 2A, 2B, 9-11, 13-19; or

(c) an amino acid sequence comprising at least one, two, or three but no more than four different amino acids, relative to any one of the sequences provided in Tables 1, 2A, 2B, 9-11, 13-19; or

(d) an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of any one of the sequences provided in Tables 1, 2A, 2B, 9-11, 13-19.

18. The AAV capsid variant of claim 17, comprising an amino acid sequence comprising at least 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 consecutive amino acids from any one of SEQ ID NOs: 2, 200, 201, 941, 943, 204, 208, 404, or 903-909.

19. The AAV capsid variant of claim 17 or 18, wherein:

(i) the 3 consecutive amino acids comprise HDS;

(ii) the 4 consecutive amino acids comprise HDSP (SEQ ID NO: 4702);

(iii) the 5 consecutive amino acids comprise HDSPH (SEQ ID NO: 4703); and/or

(iv) the 6 consecutive amino acids comprise HDSPHK (SEQ ID NO: 2);
optionally wherein the amino acid sequence of (i)-(iv) is present immediately subsequent to position 453, numbered according to SEQ ID NO: 982 or 138.

20. The AAV capsid variant of any one of claim 17 or 18, wherein:

(i) the 3 consecutive amino acids comprise SPH;
(ii) the 4 consecutive amino acids comprise SPHS (SEQ ID NO: 4700);
(iii) the 5 consecutive amino acids comprise SPHSK (SEQ ID NO: 4701); and/or
(iv) the 6 consecutive amino acids comprise SPHKA (SEQ ID NO: 941)
optionally wherein the amino acid sequence of (i)-(iv) is present immediately subsequent to position 455, numbered according to SEQ ID NO: 982 or 138.

21. The AAV capsid variant of any one of claims 17-19, which comprises:

(i) an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of HDSPHK (SEQ ID NO: 2); or
(ii) an amino acid sequence comprising at least one, two, or three but no more than four different amino acids relative to the amino acid sequence of HDSPHK (SEQ ID NO: 2).

22. The AAV capsid variant of any one of claims 17-19 or 21, wherein:

(i) the AAV capsid variant comprises an amino acid sequence encoded by: the nucleotide sequence of SEQ ID NO: 3; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequence of SEQ ID NO: 3; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 3; and/or
(ii) the nucleotide sequence encoding the capsid variant comprises the nucleotide sequence of SEQ ID NO: 3; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequence of SEQ ID NO: 3; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 3.

23. The AAV capsid variant of any one of claims 17, 18, or 20, which comprises:

(i) an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of SPHSKA (SEQ ID NO: 941); or

(ii) comprises an amino acid sequence comprising at least one, two, or three but no more than four different amino acids relative to the amino acid sequence of SPHSKA (SEQ ID NO: 941).

24. The AAV capsid variant of any one of claims 17, 18, 20, or 23, wherein:

(i) the AAV capsid variant comprises an amino acid sequence encoded by: the nucleotide sequence of SEQ ID NO: 942; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequence of SEQ ID NO: 942; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 942; and/or

(ii) the nucleotide sequence encoding the capsid variant comprises the nucleotide sequence of SEQ ID NO: 942; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequence of SEQ ID NO: 942; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 942.

25. The AAV capsid variant of any one of claims 17-24, wherein the amino acid sequence is present:

(i) in loop IV, optionally wherein loop IV comprises positions 449-460, numbered according to SEQ ID NO: 138;

(ii) immediately subsequent to position 448, 449, 450, 451, 452, 453, 454, or 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138;

(iii) immediately subsequent to position 453, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138 or 982; and/or

(iv) immediately subsequent to position 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138 or 981.

26. The AAV capsid variant of any one of claims 1-24, comprising:

(i) the amino acid sequence of HDSPHK (SEQ ID NO: 2), wherein the amino acid sequence is present immediately subsequent to position 453, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138 or 982; or

(ii) the amino acid sequence of SPHSKA (SEQ ID NO: 941), wherein the amino acid sequence is present immediately subsequent to position 455, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138 or 981.

27. The AAV capsid variant of any one of the preceding claims, wherein:

(i) the AAV capsid variant further comprises a modification, e.g., an insertion, substitution (e.g., conservative substitution), and/or deletion, in loop I, II, VI and/or VIII;

(ii) the AAV capsid variant further comprises a substitution at position K449, e.g., a K449R substitution, numbered according to SEQ ID NO: 138;

(iii) the AAV capsid variant comprises an amino acid sequence comprising at least one, two or three modifications, e.g., substitutions (e.g., conservative substitutions), but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of SEQ ID NO: 138;

(iv) the AAV capsid variant comprises an amino acid sequence comprising at least one, two or three, but no more than 30, 20 or 10 different amino acids relative to the amino acid sequence of SEQ ID NO: 138;

(v) the AAV capsid variant comprises the amino acid sequence of positions 138-742, e.g., a VP2, of SEQ ID NO: 138, or a sequence with at least 90%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto;

(vi) the AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 138, or an amino acid sequence with at least 90%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto;

(vii) the AAV capsid variant comprises an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 137, or a sequence with at least 90%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and/or

(viii) the nucleotide sequence encoding the capsid variant comprises the nucleotide sequence of SEQ ID NO: 137, or a sequence with at least 90%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.

28. The AAV capsid variant of any one of the preceding claims, which comprises:

(i) a VP1 protein, a VP2 protein, a VP3 protein, or a combination thereof;

(ii) the amino acid sequence corresponding to positions 138-742, e.g., a VP2, of SEQ ID NO: 981 or 982, or a sequence with at least 90%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto;

(iii) the amino acid sequence of any one of SEQ ID NO: 981 or 982 (e.g., a VP1), or an amino acid sequence with at least 90%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto;

(iv) an amino acid sequence comprising at least one, two or three modifications, e.g., substitutions (e.g., conservative substitutions), but not more than 30, 20 or 10 modifications, e.g.,

substitutions (e.g., conservative substitutions), relative to the amino acid sequence of SEQ ID NO: 981 or 982; and/or

(v) an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids, relative to the amino acid sequence of SEQ ID NO: 981 or 982.

29. The AAV capsid variant of any one of claims 1-15, 17-19, 21, 22, 25-28, wherein:

(i) the AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 982, or an amino acid sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto;

(ii) the AAV capsid variant comprises an amino acid sequence comprising at least one, two or three modifications, e.g., substitutions (e.g., conservative substitutions), but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of SEQ ID NO: 982;

(iii) the AAV capsid variant comprises an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids, relative to the amino acid sequence of SEQ ID NO: 982;

(iv) the AAV capsid variant comprises an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 984, or a nucleotide sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto;

(v) the nucleotide sequence encoding the AAV capsid variant comprises the nucleotide sequence of SEQ ID NO: 984, or a nucleotide sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto, optionally wherein the nucleotide sequence is codon optimized.

30. The AAV capsid variant of any one of claims 1-14, 16-18, 20, 23-28, wherein:

(i) the AAV capsid variant comprises the amino acid sequence of SEQ ID NO: 981, or an amino acid sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto;

(ii) the AAV capsid variant comprises an amino acid sequence comprising at least one, two or three modifications, e.g., substitutions (e.g., conservative substitutions), but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of SEQ ID NO: 981;

(iii) the AAV capsid variant comprises an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids, relative to the amino acid sequence of SEQ ID NO: 981;

(iv) the AAV capsid variant comprises an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 983, or a nucleotide sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto; and/or

(v) the nucleotide sequence encoding the AAV capsid variant comprises the nucleotide sequence of SEQ ID NO: 983, or a nucleotide sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto, optionally wherein the nucleotide sequence is codon optimized.

31. An AAV capsid variant comprising:

(i) the amino acid sequence of any one of claims 1-15, 17-19, 21, 22, 25-30, and further comprising an amino acid sequence at least 95% identical to SEQ ID NO: 982; or

(ii) the amino acid sequence of SEQ ID NO: 982;

optionally wherein the amino acid sequence is present immediately subsequent to position 453, numbered according to SEQ ID NO: 138 or 982.

32. An AAV capsid variant comprising:

(i) the amino acid sequence of any one of claims 1-14, 16-18, 20, 23-30, and further comprising an amino acid sequence at least 95% identical to SEQ ID NO: 981; or

(ii) the amino acid sequence of SEQ ID NO: 981;

optionally wherein the amino acid sequence is present immediately subsequent to position 455, numbered according to SEQ ID NO: 138 or 981.

33. An AAV capsid variant comprising the amino acid sequence of HDSPHK (SEQ ID NO: 2), wherein the amino acid sequence is present immediately subsequent to position 453, numbered according to the amino acid sequence of SEQ ID NO: 982.

34. The AAV capsid variant of claim 33, which further comprises:

(i) the amino acid sequence of positions 203-742, e.g., a VP3, of SEQ ID NO: 982;

(ii) the amino acid sequence of positions 138-742, e.g., a VP2, of SEQ ID NO: 982;

(iii) the amino acid sequence of SEQ ID NO: 982; or

(iv) an amino acid sequence at least 90%, 95%, 96%, 97%, 98%, or 99% identical to any of the amino acid sequences in (i)-(iii).

35. An AAV capsid variant comprising the amino acid sequence of SPHKA (SEQ ID NO: 941), wherein the amino acid sequence is present immediately subsequent to position 455, numbered according to the amino acid sequence of SEQ ID NO: 981.

36. The AAV capsid variant of claim 35, which further comprises:
- (i) the amino acid sequence of positions 203-742, e.g., a VP3, of SEQ ID NO: 981;
 - (ii) the amino acid sequence of positions 138-742, e.g., a VP2, of SEQ ID NO: 981;
 - (iii) the amino acid sequence of SEQ ID NO: 981; or
 - (iv) an amino acid sequence at least 90%, 95%, 96%, 97%, 98%, or 99% identical to any of the amino acid sequences in (i)-(iii).
37. The AAV capsid variant of any one of claims 1-36, wherein the AAV capsid variant
- (i) has an increased tropism for a CNS cell or tissue, e.g., a brain cell, brain tissue, spinal cord cell, or spinal cord tissue, relative to the tropism of a reference sequence comprising the amino acid sequence of SEQ ID NO: 138
 - (ii) transduces a brain region, e.g., a midbrain region (e.g., the hippocampus, or thalamus) or the brain stem, optionally wherein the level of transduction is at least 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, or 65-fold greater as compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay, e.g., an immunohistochemistry assay or a qPCR assay, e.g., as described in Example 2;
 - (iii) transduces a brain region, e.g., a midbrain region (e.g., the hippocampus, or thalamus) or the brain stem, optionally wherein the level of transduction is at least 30, 35, 40, 45, 50, 55, 60, or 65-fold greater as compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay, e.g., an immunohistochemistry assay or a qPCR assay, e.g., as described in Example 2;
 - (iv) is enriched at least about 3, 4, 5, 6, 7, 8, 9, or 10-fold, in the brain compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay as described in Example 1;
 - (v) is enriched at least about 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80 or 85-fold, in the brain compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay as described in Example 1;
 - (vi) is enriched at least about 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100-fold, in the brain of at least two to three species, e.g., a non-human primate and rodent (e.g., *Macaca fascicularis*, *Chlorocebus sabaeus*, *Callithrix jacchus*, and/or mouse (e.g., BALB/c mice, C57Bl/6 mice, and/or CD-1 outbred mice), compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay as described in Example 1;
 - (vii) delivers an increased level of a payload to a brain region, optionally wherein the level of the payload is increased by at least 5, 10, 15, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, or 70-fold, as compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay, e.g., a qRT-PCR or a qPCR assay (e.g., as described in Example 2 or 8), optionally wherein the brain region is a midbrain region (e.g., the hippocampus or thalamus), frontal cortex, temporal cortex, motor cortex, cerebral cortex, caudate, putamen, dentate nucleus, substantia nigra, or the brainstem;

(viii) delivers an increased level of viral genomes to a brain region, optionally wherein the level of viral genomes is increased by at least 5, 10, 15, 17, 18, 19, 20, 25, 30, 35, 40, 45, or 50-fold, as compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay, e.g., a qRT-PCR or a qPCR assay (e.g., as described in Example 2 or 8), optionally wherein the brain region is a midbrain region (e.g., the hippocampus or thalamus), frontal cortex, temporal cortex, motor cortex, cerebral cortex, caudate, putamen, dentate nucleus, substantia nigra, or the brainstem;

(ix) is enriched at least about 5, 10, 15, 20, 25, 30, or 35-fold, in the spinal cord compared to a reference sequence of SEQ ID NO: 138, e.g., when measured by an assay as described in Example 1 or 8, optionally wherein the region of the spinal cord is a thoracic spinal cord region, cervical spinal cord region, C5 ventral horn region, lumbar spinal cord region, or L5 ventral horn region;

(x) shows preferential transduction in a brain region relative to the transduction in the dorsal root ganglia (DRG); and/or

(xi) is capable of transducing non-neuronal cells, e.g., glial cells (e.g., oligodendrocytes or astrocytes).

38. A polynucleotide encoding the AAV capsid variant of any one of claims 1-37.

39. The polynucleotide of claim 38, which comprises:

(i) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequences of SEQ ID NO: 942 or 3;

(ii) a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten different nucleotides, relative to the nucleotide sequences of SEQ ID NO: 942 or 3;

(iii) the nucleotide sequence of SEQ ID NOs: 942 or 3, or nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; and/or

(iv) the nucleotide sequence of SEQ ID NO: 983 or 984, or a nucleotide sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto,

optionally wherein the polynucleotide comprises a nucleotide sequence that is codon optimized.

40. A peptide comprising:

(a) the amino acid sequence of any of the sequences provided in Tables 1, 2A, 2B, 9-11, 13-19;

(b) an amino acid sequence comprising at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or 17 consecutive amino acids from any one of the sequences provided in Tables 1, 2A, 2B, 9-11, 13-19; or

(c) an amino acid sequence comprising at least one, two, or three but no more than four different amino acids, relative to any one of the sequences provided in Tables 1, 2A, 2B, 9-11, 13-19; or

(d) an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of any one of the sequences provided in Tables 1, 2A, 2B, 9-11, 13-19..

41. A peptide comprising:

(i) the amino acid sequence of HDSPHK (SEQ ID NO: 2); at least 3, 4, or 5 consecutive amino acids from the amino acid sequence of HDSPHK (SEQ ID NO: 2); at least one, two, or three, but no more than four different amino acids, relative to the amino acid sequence of HDSPHK (SEQ ID NO: 2); or at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of HDSPHK (SEQ ID NO: 2); or

(ii) the amino acid sequence of SPHSKA (SEQ ID NO: 941); at least 3, 4, or 5 consecutive amino acids from the amino acid sequence of SPHSKA (SEQ ID NO: 941); at least one, two, or three, but no more than four different amino acids relative to the amino acid sequence of SPHSKA (SEQ ID NO: 941); or at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of SPHSKA (SEQ ID NO: 941).

42. The peptide of claim 40 or 41, wherein at least 1-5, e.g., at least 1, 2, 3, 4, or 5, peptides are fused or coupled, e.g., conjugated, to an active agent, e.g., a therapeutic agent or a diagnostic agent, optionally wherein:

(i) the at least 1-5, e.g., at least 1, 2, 3, 4, or 5, peptides are present in tandem (e.g., connected directly or indirectly via a linker) or in a multimeric configuration;

(ii) the peptide comprises an amino acid sequence of at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 15, 20, 25, 30, or 35 amino acids in length;

(iii) the peptide is present N-terminal relative to the active agent;

(iv) the peptide is present C-terminal relative to the active agent;

(v) the active agent is or comprises a therapeutic agent chosen from a protein (e.g., an enzyme), an antibody molecule, a nucleic acid molecule (e.g., an RNAi agent), or a small molecule;

(vi) the active agent is or comprises a ribonucleic acid complex (e.g., a Cas9/gRNA complex), a plasmid, a closed-end DNA, a circ-RNA, or an mRNA;

(vii) the active agent is an RNAi agent (e.g., a dsRNA, a siRNA, a shRNA, a pre-miRNA, a pri-miRNA, a miRNA, a stRNA, a lncRNA, a piRNA, an antisense oligonucleotide agent (ASO), or a snoRNA, optionally wherein the RNAi agent is an siRNA or an ASO, which optionally comprises at least one modified nucleotide);

(viii) the active agent modulates, e.g., inhibits, decreases or increases, expression of, a CNS related gene, mRNA, and/or protein; and/or

(ix) the active agent is a diagnostic agent or comprises an imaging agent (e.g., a protein or small molecule compound coupled to a detectable moiety).

43. The peptide of claim 42, wherein:

(i) the peptide covalently linked, e.g., directly or indirectly via a linker, to the active agent;

(ii) the peptide is conjugated to the active agent via a linker, wherein the linker is a cleavable linker or a non-cleavable linker optionally wherein:

(a) the cleavable linker is a pH sensitive linker, wherein the pH sensitive linker comprises a hydrazine/hydrazone linker or a disulfide linker;

(b) the cleavable linker is an enzyme sensitive, wherein the enzyme sensitive linker comprises a peptide based linker, e.g., a peptide linker sensitive to a protease (e.g., a lysosomal protease); or a beta-glucuronide linker;

(c) the non-cleavable linker is a linker comprising a thioether group or a maleimidocaproyl group.

44. An AAV particle comprising the AAV capsid variant of any one of claims 1-37, an AAV capsid variant encoded by the polynucleotide of claim 38 or 39, or an AAV capsid variant comprising the peptide of claim 40 or 41.

45. The AAV particle of claim 44, which comprises a nucleotide sequence encoding a payload, optionally wherein the encoded payload comprises a therapeutic protein or functional variant thereof; an antibody or antibody fragment; an enzyme; a component of a gene editing system; an RNAi agent (e.g., a dsRNA, siRNA, shRNA, pre-miRNA, pri-miRNA, miRNA, stRNA, lncRNA, piRNA, or snoRNA); or a combination thereof.

46. The AAV particle of claim 45, wherein:

(i) the therapeutic protein or functional variant thereof, e.g., a recombinant protein, is associated with (e.g., aberrantly expressed in) a neurological or neurodegenerative disorder, a muscular or neuromuscular disorder, or a neuro-oncological disorder, optionally wherein the therapeutic protein or functional variant thereof is chosen from apolipoprotein E (APOE) (e.g., ApoE2, ApoE3 and/or ApoE4); human survival of motor neuron (SMN) 1 or SMN2;

glucocerebrosidase (GBA1); aromatic L-amino acid decarboxylase (AADC); aspartoacylase (ASPA); tripeptidyl peptidase I (CLN2); beta-galactosidase (GLB1); N-sulphoglucosamine sulphohydrolase (SGSH); N-acetyl-alpha-glucosaminidase (NAGLU); iduronate 2-sulfatase (IDS); intracellular cholesterol transporter (NPC1); gigaxonin (GAN); or a combination thereof;

(ii) the antibody or antibody binding fragment binds to

(a) a CNS related target, e.g. an antigen associated with a neurological or neurodegenerative disorder, e.g., β -amyloid, APOE, tau, SOD1, TDP-43, huntingtin (HTT), and/or synuclein;

(b) a muscular or neuromuscular related target, e.g., an antigen associated with a muscular or neuromuscular disorder; or

(c) a neuro-oncology related target, e.g., an antigen associated with a neuro-oncological disorder, e.g., HER2, or EGFR (e.g., EGFRvIII);

(iii) the enzyme comprises a meganuclease, a zinc finger nuclease, a TALEN, a recombinase, integrase, a base editor, a Cas9, or a fragment thereof;

(iv) the component of a gene editing system comprises one or more components of a CRISPR-Cas system, optionally wherein the one or more components of the CRISPR-Cas system comprises a Cas9, e.g., a Cas9 ortholog or a Cpf1, and a single guide RNA (sgRNA), wherein:

(a) the sgRNA is located upstream (5') of the cas9 enzyme; and/or

(b) the sgRNA is located downstream (3') of the cas9 enzyme; and/or

(v) the RNAi agent (e.g., a dsRNA, siRNA, shRNA, pre-miRNA, pri-miRNA, miRNA, stRNA, lncRNA, piRNA, or snoRNA), modulates, e.g., inhibits, expression of, a CNS related gene, mRNA, and/or protein, optionally wherein the CNS related gene is chosen from SOD1, MAPT, APOE, HTT, C9ORF72, TDP-43, APP, BACE, SNCA, ATXN1, ATXN3, ATXN7, SCN1A-SCN5A, SCN8A-SCN11A, or a combination thereof.

47. The AAV particle of any one of claims 44-46, which comprises a viral genome comprising a promoter operably linked to the nucleic acid sequence encoding the payload, optionally wherein:

(i) the promoter is chosen from human elongation factor 1 α -subunit (EF1 α), cytomegalovirus (CMV) immediate-early enhancer and/or promoter, chicken β -actin (CBA) and its derivative CAG, β glucuronidase (GUSB), or ubiquitin C (UBC), neuron-specific enolase (NSE), platelet-derived growth factor (PDGF), platelet-derived growth factor B-chain (PDGF- β), intercellular adhesion molecule 2 (ICAM-2), synapsin (Syn), methyl-CpG binding protein 2 (MeCP2), Ca²⁺/calmodulin-dependent protein kinase II (CaMKII), metabotropic glutamate receptor 2 (mGluR2), neurofilament light (NFL) or heavy (NFH), β -globin minigene n β 2, preproenkephalin (PPE), enkephalin (Enk) and excitatory amino acid transporter 2 (EAAT2), glial fibrillary acidic protein (GFAP), myelin basic protein (MBP), a cardiovascular promoter (e.g., α MHC, cTnT, and CMV-MLC2k), a liver promoter (e.g.,

hAAT, TBG), a skeletal muscle promoter (e.g., desmin, MCK, C512) or a fragment, e.g., a truncation, or a functional variant thereof;

(ii) the promoter is an EF-1a promoter variant, e.g., a truncated EF-1a promoter; or

(iii) the promoter comprises the nucleotide sequence of any one of SEQ ID NOs: 987, 988, 990, 991, 995, 996, 998-1007 or any one of the sequences provided in Table 8, a nucleotide sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequence of SEQ ID NOs: 987, 988, 990, 991, 995, 996, 998-1007 or any one of the sequences provided in Table 8, or a nucleotide sequence with at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, or 99%) sequence identity to any one of SEQ ID NOs: 987, 988, 990, 991, 995, 996, 998-1007 or any one of the sequences provided in Table 8.

48. The AAV particle of claim 45, wherein the viral genome further comprises:

(i) a polyA signal sequence;

(ii) an inverted terminal repeat (ITR) sequence, optionally wherein the ITR sequence is positioned 5' relative to the encoded payload and/or the ITR sequence is positioned 3' relative to the encoded payload;

(iii) an enhancer, a Kozak sequence, an intron region, and/or an exon region;

(iv) a nucleotide sequence encoding a miR binding site, e.g., a miR binding site that modulates, e.g., reduces, expression of the antibody molecule encoded by the viral genome in a cell or tissue where the corresponding miRNA is expressed, optionally wherein the encoded miR binding site modulates, e.g., reduces, expression of the encoded antibody molecule in a cell or tissue of the DRG, liver, heart, hematopoietic lineage, or a combination thereof; and/or

(v) a nucleotide sequence encoding a Rep protein, e.g., a non-structural protein, wherein the Rep protein comprises a Rep78 protein, a Rep68, Rep52 protein, and/or a Rep40 protein, optionally wherein the Rep78 protein, the Rep68 protein, the Rep52 protein, and/or the Rep40 protein are encoded by at least one Rep gene.

the viral genome further comprises a polyA signal sequence.

49. The AAV particle of claim 47 or 48, wherein the viral genome comprises:

(i) at least 1-5 copies of the encoded miR binding site, e.g., at least 1, 2, 3, 4, or 5 copies;

(ii) at least 3 copies of an encoded miR binding sites, optionally wherein:

(a) all three copies comprise the same miR binding site, or at least one, two, three, or all of the copies comprise a different miR binding site; and/or

(b) the 3 copies of the encoded miR binding sites are continuous (e.g., not separated by a spacer), or are separated by a spacer, optionally wherein the spacer comprises the nucleotide sequence of GATAGTTA, or a nucleotide sequence having at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), but no more than four

modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequence of GATAGTTA; or

(iii) at least 4 copies of an encoded miR binding site, optionally wherein

(a) all four copies comprise the same miR binding site, or at least one, two, three, or all of the copies comprise a different miR binding site; and/or

(b) the 4 copies of the encoded miR binding sites are continuous (e.g., not separated by a spacer), or are separated by a spacer, optionally wherein the spacer comprises the nucleotide sequence of GATAGTTA, or a nucleotide sequence having at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), relative to the nucleotide sequence of GATAGTTA.

50. The AAV particle of claim 48 or 49, wherein the encoded miR binding site comprises a miR122 binding site, a miR183 binding site, a miR-1 binding site, a miR-142-3p, or a combination thereof, optionally wherein:

(i) the encoded miR122 binding site comprises the nucleotide sequence of SEQ ID NO: 4673, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or a nucleotide sequence having at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to SEQ ID NO: 4673;

(ii) the encoded miR183 binding site comprises the nucleotide sequence of SEQ ID NO: 4676, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or a nucleotide sequence having at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to SEQ ID NO: 4676;

(iii) the encoded miR-1 binding site comprises the nucleotide sequence of SEQ ID NO: 4679, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or a nucleotide sequence having at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to SEQ ID NO: 4679; and/or

(iv) the encoded miR-142-3p binding site comprises the nucleotide sequence of SEQ ID NO: 4675, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or a nucleotide sequence having at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative

substitutions), but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), relative to SEQ ID NO: 4675.

51. The AAV particle of any one of claims 47-50, wherein the viral genome:

- (i) is single stranded;
- (ii) is self-complementary; and/or
- (ii) further comprises a nucleic acid encoding the AAV capsid variant of any one of claims 1-37.

52. The AAV capsid variant, polynucleotide, peptide, or AAV particle of any one of the preceding claims which is isolated, e.g., recombinant.

53. A vector comprising a polynucleotide encoding the AAV capsid variant of any one of claims 1-37 or 52, the polynucleotide of any one of claims 38, 39, or 52, or a polynucleotide encoding the peptide of any one of claims 40, 41, or 52.

54. A cell, e.g., a host cell, comprising the AAV capsid variant of any one of claims 1-37 or 52, the polynucleotide of any one of claim 38, 39, or 52, the peptide of any one of claims 40, 41, or 52, the AAV particle of any one of claims 44-52, or the vector of claim 53, optionally wherein:

- (i) the cell is a mammalian cell or an insect cell;
- (ii) the cell is a cell of a brain region or a spinal cord region, optionally a cell of the brain stem, hippocampus, or thalamus; and/or
- (iii) the cell is a neuron, a sensory neuron, a motor neuron, an astrocyte, a glial cell, oligodendrocyte, or a muscle cell (e.g., a cell of the heart, diaphragm, or quadriceps).

55. A method of making an AAV particle, comprising

- (i) providing a host cell comprising a viral genome; and
 - (ii) incubating the host cell under conditions suitable to enclose the viral genome in the AAV capsid variant of any one of claims 1-37 or 52, or an AAV capsid variant encoded by the polynucleotide of any one of claims 40, 41, or 52;
- thereby making the AAV particle.

56. A pharmaceutical composition comprising the AAV particle of any one of claims 44-52, an AAV particle comprising the AAV capsid variant of any one of claims 1-37 or 52, an AAV particle comprising the peptide of any one of claims 40, 41, or 52, and a pharmaceutically acceptable excipient.

57. A method of delivering a payload to a cell or tissue (e.g., a CNS cell or a CNS tissue), comprising administering an effective amount of the pharmaceutical composition of claim 56, the AAV particle of any one of claims 44-52, an AAV particle comprising the capsid variant of any one of claims 1-37 or 52, or an AAV particle comprising the peptide of any one of claims 40, 41, or 52.

58. The method of claim 57, wherein the cell is:

(i) a cell of a brain region or a spinal cord region, optionally a cell of the frontal cortex, sensory cortex, motor cortex, caudate, cerebellar cortex, cerebral cortex, brain stem, hippocampus, or thalamus;

(ii) a neuron, a sensory neuron, a motor neuron, an astrocyte, a glial cell, or an oligodendrocyte; and/or

(iii) within a subject, optionally wherein the subject has, has been diagnosed with having, or is at risk of having a neurological disorder, e.g., a neurodegenerative disorder, a neuro-oncological disorder, a muscular disorder, or a neuromuscular disorder.

59. A method of treating a subject having or diagnosed with having a neurological disorder, e.g., a neurodegenerative disorder, a neuro-oncological disorder, a muscular disorder, or a neuromuscular disorder, comprising administering to the subject an effective amount of the pharmaceutical composition of claim 56, the AAV particle of any one of claims 44-52, an AAV particle comprising the capsid variant of any one of claims 1-37 or 52, or an AAV particle comprising the peptide of any one of claims 40, 41, or 52.

60. The method of claim 58 or 59, wherein the neurological disorder, neurodegenerative disorder, muscular disorder, neuromuscular disorder, or neuro-oncological disorder is Huntington's Disease, Amyotrophic Lateral Sclerosis (ALS), Gaucher Disease, Dementia with Lewy Bodies, Parkinson's disease, Spinal Muscular Atrophy, Alzheimer's Disease, a leukodystrophy (e.g., Alexander disease, autosomal dominant leukodystrophy with autonomic diseases (ADLD), Canavan disease, cerebrotendinous xanthomatosis (CTX), metachromatic leukodystrophy (MLD), Pelizaeus-Merzbacher disease, or Refsum disease), or a cancer (e.g., a HER2/neu positive cancer or a glioblastoma).

61. The method of claim 59 or 60, where treating comprises prevention of progression of the disease or disorder in the subject, optionally wherein the subject is a human.

62. The method of any one of claims 58-61, wherein the AAV particle is administered to the subject:

(i) intravenously, via intra-cisterna magna injection (ICM), intracerebrally, intrathecally, intracerebroventricularly, via intraparenchymal administration, or intramuscularly;

(ii) via focused ultrasound (FUS), e.g., coupled with the intravenous administration of microbubbles (FUS-MB), or MRI-guided FUS coupled with intravenous administration; or

(iii) intravenously.

63. The pharmaceutical composition of claim 56, the AAV particle of any one of claims 44-52, an AAV particle comprising the capsid variant of any one of claims 1-37 or 52, or an AAV particle comprising the peptide of any one of claims 40, 41, or 52, for use in a method of delivering a payload to a cell or tissue.

64. The pharmaceutical composition of claim 56, the AAV particle of any one of claims 44-52, an AAV particle comprising the capsid variant of any one of claims 1-37 or 52, or an AAV particle comprising the peptide of any one of claims 40, 41, or 52, for use in a method of treating a neurological disorder, a neurodegenerative disorder, a muscular disorder, a neuromuscular disorder, or a neuro-oncological disorder.

65. The pharmaceutical composition of claim 56, the AAV particle of any one of claims 44-52, an AAV particle comprising the capsid variant of any one of claims 1-37 or 52, or an AAV particle comprising the peptide of any one of claims 40, 41, or 52, for use in the manufacture of a medicament.

66. Use of the pharmaceutical composition of claim 56, the AAV particle of any one of claims 44-52, an AAV particle comprising the capsid variant of any one of claims 1-37 or 52, or an AAV particle comprising the peptide of any one of claims 40, 41, or 52, in the manufacture of a medicament for treating a neurological disorder, a neurodegenerative disorder, a muscular disorder, a neuromuscular disorder, or a neuro-oncological disorder.

67. Use of the pharmaceutical composition of claim 56, the AAV particle of any one of claims 44-52, an AAV particle comprising the capsid variant of any one of claims 1-37 or 52, or an AAV particle comprising the peptide of any one of claims 40, 41, or 52, in the manufacture of a medicament.