

**NOVEL COMPOSITIONS OF ADENO-ASSOCIATED VIRUSES ENGINEERED
FOR ENHANCED TISSUE TRANSDUCTION AND SPECIFICITY**

CROSS-REFERENCE TO RELATED APPLICATIONS

- 5 [0001] This application claims the benefit of priority of Singapore application No. 10202300637W, filed 9 March 2023, the contents of it being hereby incorporated by reference in its entirety for all purposes.

TECHNICAL FIELD

- 10 [0002] The invention is in the field of biotechnology. In particular, the invention relates to production of engineered adeno-associated viruses. More specifically, the invention provides the use of engineered adeno-associated viruses for enhanced tissue transduction and specificity and compositions thereof.

BACKGROUND OF THE INVENTION

- 15 [0003] Adeno-associated virus (AAV) vector-based therapeutics are rapidly advancing to the clinic. Systemic vector infusion represents the ideal delivery route in many gene therapy applications, especially when local administration is not feasible. Currently, most AAV capsids are based on naturally occurring serotypes, which are sequestered in the liver and have reduced
20 therapeutic efficacy in organs such as in the central nervous system (CNS) or in skeletal muscles. Consequently, higher vector doses are required, resulting in off-target toxicities. Thus, there is a need for AAV capsids with organ-specific tropism at low vector doses.

SUMMARY

- 25 [0004] In one aspect, provided herein is a modified adeno-associated virus serotype DJ (AAV-DJ), comprising a nucleotide sequence encoding a 7-mer peptide inserted between the 1767th and 1768th nucleotides of SEQ ID NO: 399, wherein the modified AAV-DJ has a range of at least 50% to 60%, 60% to 65%, 65% to 70%, 70% to 75%, 75% to 80%, 80% to 85%, 85% to 90%, 90% to 95%, or 95% to 99% sequence identity with the sequence of SEQ ID NO: 399
30 outside the nucleotide sequence encoding the 7-mer peptide.
- [0005] In another aspect, provided herein is a modified adeno-associated virus serotype 2 (AAV2), comprising a nucleotide sequence encoding a 7-mer peptide inserted between the 1764th and 1765th nucleotides of SEQ ID NO: 401, wherein the modified AAV2 has a range of at least 50% to 60%, 60% to 65%, 65% to 70%, 70% to 75%, 75% to 80%, 80% to 85%,

85% to 90%, 90% to 95%, or 95% to 99% sequence identity with the sequence of SEQ ID NO: 401 outside the nucleotide sequence encoding the 7-mer peptide.

5 [0006] In another aspect, provided herein is a modified adeno-associated virus serotype 5 (AAV5), comprising a nucleotide sequence encoding a 7-mer peptide inserted between the 1722th and 1723th nucleotides of SEQ ID NO: 402, wherein the modified AAV5 has a range of at least 50% to 60%, 60% to 65%, 65% to 70%, 70% to 75%, 75% to 80%, 80% to 85%, 85% to 90%, 90% to 95%, or 95% to 99% sequence identity with the sequence of SEQ ID NO: 402 outside the nucleotide sequence encoding 7-mer peptide.

10 [0007] In another aspect, provided herein is a modified adeno-associated virus serotype 6 (AAV6), comprising a nucleotide sequence encoding a 7-mer peptide inserted between the 1770th and 1771th nucleotides of SEQ ID NO: 403, wherein the modified AAV6 has a range of at least 50% to 60%, 60% to 65%, 65% to 70%, 70% to 75%, 75% to 80%, 80% to 85%, 85% to 90%, 90% to 95%, or 95% to 99% sequence identity with the sequence of SEQ ID NO: 403 outside the nucleotide sequence encoding 7-mer peptide.

15 [0008] In another aspect, provided herein is a modified adeno-associated virus serotype 6 (AAV6), comprising a nucleotide sequence encoding a 7-mer peptide inserted between the 1764th and 1765th nucleotides of SEQ ID NO: 403, wherein the modified AAV6 has a range of at least 50% to 60%, 60% to 65%, 65% to 70%, 70% to 75%, 75% to 80%, 80% to 85%, 85% to 90%, 90% to 95%, or 95% to 99% sequence identity with the sequence of SEQ ID NO: 20 403 outside the nucleotide sequence encoding the 7-mer peptide.

[0009] In yet another aspect, provided herein is a modified adeno-associated virus serotype 9 (AAV9), comprising a nucleotide sequence encoding a 7-mer peptide inserted between the 1764th and 1765th nucleotides of SEQ ID NO: 404, wherein the modified AAV9 has a range of at least 50% to 60%, 60% to 65%, 65% to 70%, 70% to 75%, 75% to 80%, 80% to 85%, 25 85% to 90%, 90% to 95%, or 95% to 99% sequence identity with the sequence of SEQ ID NO: 404 outside the nucleotide sequence encoding the 7-mer peptide.

[0010] In another aspect, provided herein is a composition comprising any modified AAV as described herein, and a pharmaceutically acceptable excipient.

30 [0011] In another aspect, provided herein is a nucleic acid encoding any modified AAV as described herein.

DEFINITIONS

[0012] As used herein, the term “AAV” or “adeno-associated virus” refers to a non-pathogenic, small viruses of the *Parvovirus* family which infect humans. The term “AAV” includes, but is

not limited to, naturally occurring and engineered AAV subtypes or serotypes, for example, AAV type 1 (AAV-1), AAV type 2 (AAV-2), AAV type 3 (AAV-3), AAV type 4 (AAV-4), AAV type 5 (AAV-5), AAV type 6 (AAV-6), AAV type 7 (AAV-7), AAV type 8 (AAV-8) and AAV-DJ.

5 [0013] As used herein, the term “capsid” refers to the protein shell of a virus particle. The capsid of a virus is composed of one or more capsid units or subunits. For example, the capsid of an AAV is composed of VP1, VP2 and/or VP3 subunits. The capsid of a virus may have several functional purposes. For example, the capsid of a virus may protect the viral genome from degradation, assist the virus in evading host immune response, and/or determine viral

10 tropism to different cell or tissue types.

[0014] As used herein, the term “identity” in the context of a polynucleotide or polypeptide sequence refers to the overall relatedness or homology 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). 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.

25 [0015] As used herein, the term “library” refers to a mixture of heterogeneous polypeptides or polynucleotides. A library is composed of members that have similar polypeptide or polynucleotide sequences. Sequence differences between library members are responsible for the diversity of the library. The library can take the form of a mixture of polypeptides or polynucleotides, or can be in the form of organisms or cells, for example yeast cells and the like, that are transformed with a library of polynucleotides.

30 [0016] As used herein, “modified virus” and “virus variant” are interchangeable terms referring to an engineered or recombinant virus comprising an alteration, that is, “modification”, in the sequence of a polypeptide or a polynucleotide encoding a polypeptide compared to that

of a reference sequence. The reference sequence may be a genomic sequence or a subsection thereof of a virus, or the amino acid sequence encoded by the genomic sequence or a subsection thereof of a virus. The reference sequence may be a sequence from a wild-type or native virus, or it may be the sequence from a different modified virus. A wild-type virus refers to a virus with phenotype or genotype that predominates in nature. “Modified AAV” or “variant AAV” refers to an AAV that has a change in its genomic sequence or a subsection thereof, or in the polypeptide encoded by its genomic sequence or a subsection thereof, compared to a reference AAV. The alteration or modification of a sequence may refer to an insertion, deletion, or substitution of one or more residues in the sequence. For example, a modified AAV may be an AAV that has one or more nucleotides inserted into its genomic sequence or a subsection thereof compared to a reference AAV or has one or more amino acids inserted into the polypeptide encoded by its genomic sequence or a subsection thereof.

[0017] As used herein, “peptide” refers to the condensation product of two or more amino acids, wherein the length of the polypeptide is less than or equal to 50 amino acids long, e.g., 5, 6, 7, 8, 9, 10, 11-15, 15-20, 20-25, 25-30, 30-35, 35-40, 40-45 or 45-50 amino acids long.

[0018] As used herein, “targeting” and “tropism” are interchangeable terms that refer to the ability of a virus to infect different cell types to produce a successful infection. A successful infection may be defined as when the virus gains entry to the host cell, when the virus has begun replication of its genome in the host cell, when intact progeny virus is detectable within the host cell, when the virus progeny exits the host cell, or any combination thereof. In one example, a virus with tropism to the CNS or a CNS-targeting virus indicates that the virus is capable of infecting cells that are from or derived from the CNS and/or that the virus is capable of infecting cells that are from or derived from the CNS at a higher specificity than other cell types. In another example, a virus with tropism to the muscle or a muscle-targeting virus refers to a virus that is capable of successfully infecting cells that are from or derived from skeletal muscle and/or that the virus is capable of infecting cells that are from or derived from muscle at a higher specificity than other cell types. Conversely, a virus that does not have tropism or has reduced tropism to a cell type would not be capable or have a reduced capability of infecting said cell type. For example, a virus with reduced liver tropism or that is liver de-targeting indicates that the virus is less capable or unable to successfully infect cells that are from or derived from the liver. It would be understood by those skilled in the art that “tropism” may also mean “specificity to”. For example, virus tropism to the CNS means that a virus has specificity for the CNS. Therefore, as used herein, the terms “tropism” and “specificity” are interchangeable and mean the ability of a virus to successfully infect a selected cell type.

Further, a virus may also be defined as “specific targeting” or having “specific tropism”, to indicate that it is specific for a selected tissue type. For example, a virus with specific tropism to the brain is one that specifically infects the brain.

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BRIEF DESCRIPTION OF THE DRAWINGS

[0019] The invention will be better understood with reference to the detailed description when considered in conjunction with the non-limiting examples and the accompanying drawings, in which:

10 [0020] **Figure 1** shows a schematic map of the construction of the AAV-DJ library. The top diagram shows the AAV-DJ library plasmid, where the grey lines represent the insertion site of the peptide library (between N589 and R590), and the bottom diagram shows the full-length Rep2 plasmid. Abbreviations: ITR, inverted terminal repeat.

15 [0021] **Figure 2** shows the next-gen sequencing (NGS)-driven evolution of the AAV-DJ peptide library. C57BL/6 mice (n=5) were injected intravenously with 2.5×10^9 vg/mouse of AAV-DJ peptide library. 28 days later, organs were collected, mRNA were enriched and capsid DNA variants were amplified and analyzed by NGS. Figures 2A, 2B and 2C show distribution of the length of the inserted sequences in the AAV-DJ capsid DNA sequenced from the liver, brain, and muscle respectively. The X-axis represents the length of the nucleotide sequence inserted, and the Y-axis represents the probability density of each length of nucleotide sequences.

20 [0022] **Figure 3** shows a table of values of the fold-change difference detected by NGS of selected AAV-DJ variants normalized to wild-type AAV-DJ, leading to identification of AAV-DJ variants with enhanced brain, muscle transduction efficiency with complete liver de-targeting at low vector doses. The labels on the left denote the AAV-DJ variants, corresponding to the peptides listed in Table 3. The values in the table represent the fold-change of each variant in the liver, brain, and muscle, compared to wild-type AAV-DJ. The scale bar on the right represents the fold-change of the modified AAV genome sequenced from the respective organ versus the wild-type. Lighter shades denote higher fold-change, darker shades denote lower fold-change, with black denoting no change (baseline). Low or absence of a fold-change increase in an organ indicates a decrease or absence of infectivity or tropism in the organ, and high or presence of a fold-change increase in an organ indicates an increase or presence of infectivity or tropism in the organ.

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DETAILED DESCRIPTION OF THE INVENTION

[0023] The present disclosure provides for modified AAVs with altered tropism to various cell types, tissue types and/or organs compared to a reference AAV.

5 [0024] The reference AAV may be a wild-type AAV or unmodified AAV, and it may be of the same or different serotype as the modified AAV.

[0025] A modified virus or virus variant may be modified so that its tropism or targeting to one or more selected cell types, tissues and/or organs is altered. For example, a wild-type virus may be modified to possess enhanced tropism, reduced tropism, or no change in tropism towards one or more selected organs, tissues and/or cell types. In some examples, the reduction in
10 tropism is to the extent that tropism is abolished, that is, the virus is no longer capable of infecting the one or more selected organs, tissues and/or cell types. The organ may be any organ from a human or an animal. For example, the organ may be the CNS, ear, eye, heart, intestine, kidney, joint/synovium, lung, liver, pancreas, or skeletal muscle. The tissues may be primary or clinical isolates from an organ, or it may be a cultured tissue originating from an organ. The
15 cells may be primary or clinical isolates from an organ or tissue, or it may be a cultured cells originating from an organ or tissue.

[0026] An AAV with altered tropism may be obtained for example by introducing one or more mutations into the viral genome or sections thereof, or within a specific gene. For example, an AAV may be modified by introducing mutations into one or more genes encoding the capsid
20 protein. Mutations may be introduced by any method known by those skilled in the art, for example, site-directed mutagenesis or site-saturation mutagenesis, and may include insertion or deletion of nucleotides (frame-shift mutations), replacement/substitution of nucleotides, or combinations thereof. For example, site-saturation mutagenesis may be used to substitute a selected site in a polypeptide with all possible amino acids through the use of degenerate
25 codons in the nucleotide sequence encoding the polypeptide. In an example, the degenerate codon is NNK, where K stands for keto nucleotides such as guanine and thymine; and N is for any nucleotide. It would be understood by those skilled in the art that a modification of the polynucleotide sequence encoding a gene may result in the modification of the polypeptide encoded by the polynucleotide sequence. It would also be understood that mutations in the
30 context of the present invention may refer to mutations of a viral polynucleotide and/or viral polypeptide sequence.

[0027] In one example, a wild-type or reference AAV is modified by insertion of a polynucleotide sequence encoding a peptide to a desired site in the nucleotide sequence of the reference or wild-type AAV. The reference or wild-type AAV may include but is not limited to

the serotypes AAV-2, AAV-5, AAV-6, AAV-9, and AAV-DJ (Table 4). It would be understood by those skilled in the art that the resulting AAV, that is, “modified AAV”, will have a nucleotide sequence identical to that of the reference or wild-type AAV (i.e., the unmodified AAV) apart from, that is, “outside”, the nucleotide sequence encoding the inserted peptide.

5 [0028] The desired site at which the polynucleotide sequence is inserted may be located within a coding or non-coding region of the viral genome. In one example, the wild-type or reference AAV may be modified by insertion of one or more amino acids or a peptide into a polypeptide sequence that encodes for a protein or proteins forming the capsid or part of the virus.

10 [0029] The peptide that is inserted to alter tropism of a wild-type or reference virus may vary in length. For example, peptides may be 5-15 amino acids in length. As non-limiting examples, the peptide may be 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 amino acids in length. For example, the inserted peptide may be a 5-mer, 6-mer, 7-mer, 8-mer, 9-mer or 10-mer peptide. In one example, the peptide is a 7-mer peptide. The amino acid sequence of the 7-mer peptide may comprise any permutation of 7 amino acids. In some examples, the amino acids are the 20 standard amino acids. Therefore, provided herein are modified AAVs comprising a 7-mer peptide sequence, wherein the peptide sequence is any permutation of the 20 standard amino acids. It would be understood by those skilled in the art which amino acids are the 20 standard amino acids.

20 [0030] It would be understood by those skilled in the art that certain methods of modifying a polypeptide sequence, for example, site saturation mutagenesis, allows for the screening of every of the 20 standard amino acids for a selected site in a polypeptide sequence. Therefore, the peptides listed in the present disclosure are non-limiting examples of 7-mer peptides with the property of conferring altered tropism to an AAV when inserted to the viral capsid.

25 [0031] Provided herein are modified AAVs comprising a nucleotide sequence encoding a 7-mer peptide inserted between two nucleotides of a reference or wild-type AAV capsid gene. The two nucleotides may be within the sequence of a VP1, VP2 and/or VP3 gene. In one example, the two nucleotides are within the sequence of a VP3 gene. It would be understood by those skilled in the art that the VP1 gene encodes for the full-length capsid, while VP2 and VP3 genes encode for subunits of the capsid. Those skilled in the art will also recognize that the nucleotide sequences of the VP2 and VP3 genes are subsumed within the VP1 nucleotide sequence.

30 [0032] In one aspect, provided herein is a modified adeno-associated virus serotype DJ (AAV-DJ), comprising a nucleotide sequence encoding a 7-mer peptide inserted between the 1767th and 1768th nucleotides of SEQ ID NO: 399, wherein the modified AAV-DJ has a range of at

least 50% to 60%, 60% to 65%, 65% to 70%, 70% to 75%, 75% to 80%, 80% to 85%, 85% to 90%, 90% to 95%, or 95% to 99% sequence identity with the sequence of SEQ ID NO: 399 outside the nucleotide sequence encoding the 7-mer peptide.

5 [0033] In another aspect, provided herein is a modified adeno-associated virus serotype 2 (AAV2), comprising a nucleotide sequence encoding a 7-mer peptide inserted between the 1764th and 1765th nucleotides of SEQ ID NO: 401, wherein the modified AAV2 has a range of at least 50% to 60%, 60% to 65%, 65% to 70%, 70% to 75%, 75% to 80%, 80% to 85%, 85% to 90%, 90% to 95%, or 95% to 99% sequence identity with the sequence of SEQ ID NO: 401 outside the nucleotide sequence encoding the 7-mer peptide.

10 [0034] In another aspect, provided herein is a modified adeno-associated virus serotype 5 (AAV5), comprising a nucleotide sequence encoding a 7-mer peptide inserted between the 1722th and 1723th nucleotides of SEQ ID NO: 402, wherein the modified AAV5 has a range of at least 50% to 60%, 60% to 65%, 65% to 70%, 70% to 75%, 75% to 80%, 80% to 85%, 85% to 90%, 90% to 95%, or 95% to 99% sequence identity with the sequence of SEQ ID NO: 402 outside the nucleotide sequence encoding 7-mer peptide.

15 [0035] In another aspect, provided herein is a modified adeno-associated virus serotype 6 (AAV6), comprising a nucleotide sequence encoding a 7-mer peptide inserted between the 1770th and 1771th nucleotides of SEQ ID NO: 403, wherein the modified AAV6 has a range of at least 50% to 60%, 60% to 65%, 65% to 70%, 70% to 75%, 75% to 80%, 80% to 85%, 85% to 90%, 90% to 95%, or 95% to 99% sequence identity with the sequence of SEQ ID NO: 403 outside the nucleotide sequence encoding 7-mer peptide.

20 [0036] In another aspect, provided herein is a modified adeno-associated virus serotype 6 (AAV6), comprising a nucleotide sequence encoding a 7-mer peptide inserted between the 1764th and 1765th nucleotides of SEQ ID NO: 403, wherein the modified AAV6 has a range of at least 50% to 60%, 60% to 65%, 65% to 70%, 70% to 75%, 75% to 80%, 80% to 85%, 85% to 90%, 90% to 95%, or 95% to 99% sequence identity with the sequence of SEQ ID NO: 403 outside the nucleotide sequence encoding the 7-mer peptide.

25 [0037] In another aspect, provided herein is a modified adeno-associated virus serotype 9 (AAV9), comprising a nucleotide sequence encoding a 7-mer peptide inserted between the 1764th and 1765th nucleotides of SEQ ID NO: 404, wherein the modified AAV9 has a range of at least 50% to 60%, 60% to 65%, 65% to 70%, 70% to 75%, 75% to 80%, 80% to 85%, 85% to 90%, 90% to 95%, or 95% to 99% sequence identity with the sequence of SEQ ID NO: 404 outside the nucleotide sequence encoding the 7-mer peptide.

[0038] It would generally be understood that there may be some variation in the sequence identity of a virus, for example a modified virus, compared to a reference virus, for example a wild-type virus. For example, a virus may have at least 50% to 60%, 60% to 65%, 65% to 70%, 70% to 75%, 75% to 80%, 80% to 85%, 85% to 90%, 90% to 95%, or 95% to 99% sequence identity to a reference virus. The comparison may be between the AAV of the same or different serotypes. For example, an AAV-DJ may have at least 50% sequence identity with a reference AAV-2, AAV-5, AAV-6, AAV-9, or AAV-DJ virus. In one example, an AAV-DJ has at least 57% sequence identity with a reference AAV-5.

[0039] In one example, provided herein is a modified AAV-DJ as described herein, wherein the modified AAV-DJ has at least 57% sequence identity with the sequence of SEQ ID NO: 399 outside the 7-mer peptide sequence.

[0040] In another example, provided herein is a modified AAV2 as described herein, wherein the modified AAV2 has at least 57% sequence identity with the sequence of SEQ ID NO: 401 outside the 7-mer peptide sequence.

[0041] In another example, provided herein is a modified AAV5 as described herein, wherein the modified AAV5 has at least 57% sequence identity with the sequence of SEQ ID NO: 402 outside the 7-mer peptide sequence.

[0042] In another example, provided herein is a modified AAV6 comprising a sequence corresponding to a 7-mer peptide inserted between the 1770th and 1771th nucleotides of SEQ ID NO: 403, wherein the modified AAV6 has at least 57% sequence identity with the sequence of SEQ ID NO: 403 outside the 7-mer peptide sequence.

[0043] In yet another example, provided herein is a modified AAV6 comprising a sequence corresponding to a 7-mer peptide inserted between the 1764th and 1765th nucleotides of SEQ ID NO: 403, wherein the modified AAV6 has at least 57% sequence identity with the sequence of SEQ ID NO: 403 outside the 7-mer peptide sequence.

[0044] In yet another example, provided herein is a modified AAV9 as described herein, wherein the modified AAV9 has at least 57% sequence identity with the sequence of SEQ ID NO: 404 outside the 7-mer peptide sequence.

[0045] In one example, the inserted peptides of the present invention may comprise a sequence as set forth in Table 1 and confers enhanced liver, brain, and muscle tropism to a modified AAV compared to a reference or wild-type AAV. In another example, the targeting peptide may comprise a sequence as set forth in Table 2 and confers enhanced brain and muscle tropism with reduced liver tropism to a modified AAV compared to a wild-type AAV. In yet another example, the targeting peptide may comprise a sequence as set forth in Table 3 and confers

enhanced brain and muscle tropism with liver de-targeting to a modified AAV compared to a wild-type AAV.

[0046] The modified virus or virus variant of the present invention may have increased or decreased specificity to one or more selected cell types compared to a reference virus. The increase or decrease in specificity may refer to the increased ability of the virus to bind to and/or infect said cell type. The increase or decrease in specificity of a virus to a cell type may be compared to that of a reference cell type may be measured by quantitative methods known to those skilled in the art. The degree of enhancement or reduction in tropism of a modified AAV relative to a reference AAV, such as a wild-type AAV, may be calculated by comparing the infectivity of the variant relative to the infectivity of the reference virus in a selected tissue sample. Those skilled in the art will be aware of the methods of measuring infectivity of viruses. For example, infectivity of a virus may be measured by plaque assay, enzyme-linked immunosorbent assay (ELSA), transduction assay using reporter genes, polymerase chain reaction (PCR), high-throughput sequencing or any combination thereof. In one example, the infectivity or tropism of an AAV is assessed by next-generation sequencing (NGS).

[0047] The comparing of the infectivity or tropism of an AAV variant relative to the infectivity of a reference or original AAV, wherein infectivity is measured by NGS, may be done by dividing the number of reads of the AAV variant in a selected tissue sample, for example the brain, muscle, or liver, by the number of reads of the reference or original virus in the tissue sample to obtain the degree fold-change in infectivity or tropism of the AAV variant relative to the reference or original virus. When the AAV variant has fold-change of > 1 relative to the reference or original AAV in a tissue type, it has increased or improved tropism for that tissue type compared to the reference or original virus. When the AAV variant has fold-change of < 1 relative to the reference or original AAV in a tissue type, it has decreased or reduced tropism for that tissue type compared to the reference or original virus. When the AAV variant has fold-change = 1 relative to the reference or original AAV in a tissue type, it has same or similar tropism for that tissue type compared to the reference or original virus. When the AAV variant has fold-change = 0 relative to the reference or original AAV in a tissue type, it is not detectable in that tissue type or de-targeting towards that tissue type compared to the reference or original virus.

Table 1: AAV-DJ variants with enhanced brain, muscle, and liver tropism

Variant	7-mer sequence	SEQ ID NO:	Variant	7-mer sequence	SEQ ID NO:
Peptide #1	VAHCREV	SEQ ID NO: 1	Peptide #171	SIILHPE	SEQ ID NO: 171

Peptide #2	DRMAWYN	SEQ ID NO: 2	Peptide #172	RTSTDHV	SEQ ID NO: 172
Peptide #3	CCLEWII	SEQ ID NO: 3	Peptide #173	WFSTQCS	SEQ ID NO: 173
Peptide #4	GFDFRVD	SEQ ID NO: 4	Peptide #174	MNCWEVG	SEQ ID NO: 174
Peptide #5	SFHHWMG	SEQ ID NO: 5	Peptide #175	GYEFGST	SEQ ID NO: 175
Peptide #6	ICLSYKF	SEQ ID NO: 6	Peptide #176	FDYVLHK	SEQ ID NO: 176
Peptide #7	LNLVGVF	SEQ ID NO: 7	Peptide #177	SDTYLGR	SEQ ID NO: 177
Peptide #8	DNYVLTS	SEQ ID NO: 8	Peptide #178	LYTNELD	SEQ ID NO: 178
Peptide #9	NNVLLLR	SEQ ID NO: 9	Peptide #179	IIQRYLL	SEQ ID NO: 179
Peptide #10	RDWFYNA	SEQ ID NO: 10	Peptide #180	ARVGSMG	SEQ ID NO: 180
Peptide #11	FPSNHKI	SEQ ID NO: 11	Peptide #181	ACVSSRT	SEQ ID NO: 181
Peptide #12	YRILGVR	SEQ ID NO: 12	Peptide #182	YDRRSHQ	SEQ ID NO: 182
Peptide #13	SRSRVSC	SEQ ID NO: 13	Peptide #183	VMELYA	SEQ ID NO: 183
Peptide #14	VIVEREL	SEQ ID NO: 14	Peptide #184	NSFFMLF	SEQ ID NO: 184
Peptide #15	FMTYPLY	SEQ ID NO: 15	Peptide #185	VRTIFLV	SEQ ID NO: 185
Peptide #16	TRVGGSE	SEQ ID NO: 16	Peptide #186	KLCLVYV	SEQ ID NO: 186
Peptide #17	RFTVRSM	SEQ ID NO: 17	Peptide #187	CNCLWDC	SEQ ID NO: 187
Peptide #18	HCCFFYGS	SEQ ID NO: 18	Peptide #188	IGFTGEH	SEQ ID NO: 188
Peptide #19	VSKMQYA	SEQ ID NO: 19	Peptide #189	HMVTASG	SEQ ID NO: 189
Peptide #20	RRSRYHR	SEQ ID NO: 20	Peptide #190	LIGPGYS	SEQ ID NO: 190
Peptide #21	LSRGFLW	SEQ ID NO: 21	Peptide #191	MATSRTI	SEQ ID NO: 191
Peptide #22	LYNLWQF	SEQ ID NO: 22	Peptide #192	EAVLTCV	SEQ ID NO: 192
Peptide #23	YVCMDHL	SEQ ID NO: 23	Peptide #193	DLWSWFM	SEQ ID NO: 193
Peptide #24	IVNLYGN	SEQ ID NO: 24	Peptide #194	VYGPWIE	SEQ ID NO: 194
Peptide #25	DLSLTCS	SEQ ID NO: 25	Peptide #195	GAFKHLM	SEQ ID NO: 195
Peptide #26	ENYHMVS	SEQ ID NO: 26	Peptide #196	TMYRQQC	SEQ ID NO: 196
Peptide #27	VSKFDDV	SEQ ID NO: 27	Peptide #197	ALFCYIL	SEQ ID NO: 197
Peptide #28	VYVVIVD	SEQ ID NO: 28	Peptide #198	VFPLPWV	SEQ ID NO: 198

Peptide #29	VIDIDNG	SEQ ID NO: 29	Peptide #199	DFSVMMH	SEQ ID NO: 199
Peptide #30	PFSSYLE	SEQ ID NO: 30	Peptide #200	QVGDLRE	SEQ ID NO: 200
Peptide #31	SLRIQGS	SEQ ID NO: 31	Peptide #201	KIYTVFD	SEQ ID NO: 201
Peptide #32	LSLGFQF	SEQ ID NO: 32	Peptide #202	TMVIRGI	SEQ ID NO: 202
Peptide #33	TVIVLIK	SEQ ID NO: 33	Peptide #203	GTATYNC	SEQ ID NO: 203
Peptide #34	VSDLVVK	SEQ ID NO: 34	Peptide #204	IAFDGTT	SEQ ID NO: 204
Peptide #35	IFHIGAY	SEQ ID NO: 35	Peptide #205	TMKRGTV	SEQ ID NO: 205
Peptide #36	CYNAVGF	SEQ ID NO: 36	Peptide #206	KLYIEGI	SEQ ID NO: 206
Peptide #37	INCLHVD	SEQ ID NO: 37	Peptide #207	VSLVGHA	SEQ ID NO: 207
Peptide #38	SFLMWKC	SEQ ID NO: 38	Peptide #208	ATTRLPY	SEQ ID NO: 208
Peptide #39	AGSRSEV	SEQ ID NO: 39	Peptide #209	DSTLYLL	SEQ ID NO: 209
Peptide #40	NIYVLKS	SEQ ID NO: 40	Peptide #210	FARWILC	SEQ ID NO: 210
Peptide #41	VFSVMMH	SEQ ID NO: 41	Peptide #211	IVLVLR	SEQ ID NO: 211
Peptide #42	FLREECG	SEQ ID NO: 42	Peptide #212	FIFPVNF	SEQ ID NO: 212
Peptide #43	SIRYVR	SEQ ID NO: 43	Peptide #213	VMYGWDS	SEQ ID NO: 213
Peptide #44	ASYDYDR	SEQ ID NO: 44	Peptide #214	TTCKTLA	SEQ ID NO: 214
Peptide #45	IGRWTVG	SEQ ID NO: 45	Peptide #215	SSYPYMS	SEQ ID NO: 215
Peptide #46	SLPGLVD	SEQ ID NO: 46	Peptide #216	PRDFTWV	SEQ ID NO: 216
Peptide #47	MVVWVTD	SEQ ID NO: 47	Peptide #217	NACFVLG	SEQ ID NO: 217
Peptide #48	ILVCLVL	SEQ ID NO: 48	Peptide #218	LYGYRLE	SEQ ID NO: 218
Peptide #49	KLFFCYM	SEQ ID NO: 49	Peptide #219	NRVCVYP	SEQ ID NO: 219
Peptide #50	TLYAGLS	SEQ ID NO: 50	Peptide #220	ISLLFIH	SEQ ID NO: 220
Peptide #51	NSYRFVR	SEQ ID NO: 51	Peptide #221	PVERVNLL	SEQ ID NO: 221
Peptide #52	SSKYTLP	SEQ ID NO: 52	Peptide #222	LTFAEAT	SEQ ID NO: 222
Peptide #53	WIIFQRV	SEQ ID NO: 53	Peptide #223	VSTLYLL	SEQ ID NO: 223
Peptide #54	TDLSLAS	SEQ ID NO: 54	Peptide #224	GYCMYCD	SEQ ID NO: 224
Peptide #55	LVALCDC	SEQ ID NO: 55	Peptide #225	LTGGFRL	SEQ ID NO: 225

Peptide #56	FWMYDPR	SEQ ID NO: 56	Peptide #226	MPNSSTC	SEQ ID NO: 226
Peptide #57	SLIRAHW	SEQ ID NO: 57	Peptide #227	TLLIGLL	SEQ ID NO: 227
Peptide #58	LNCLVNH	SEQ ID NO: 58	Peptide #228	TRVRNVY	SEQ ID NO: 228
Peptide #59	QICCYIF	SEQ ID NO: 59	Peptide #229	CPPGLVD	SEQ ID NO: 229
Peptide #60	VRFRSAG	SEQ ID NO: 60	Peptide #230	ASSYPSL	SEQ ID NO: 230
Peptide #61	NLKFTVR	SEQ ID NO: 61	Peptide #231	PSDCSIL	SEQ ID NO: 231
Peptide #62	LITTLRM	SEQ ID NO: 62	Peptide #232	YWEVHWL	SEQ ID NO: 232
Peptide #63	LYNTSWW	SEQ ID NO: 63	Peptide #233	FWKGLAY	SEQ ID NO: 233
Peptide #64	KCMLRQR	SEQ ID NO: 64	Peptide #234	VLWSWFM	SEQ ID NO: 234
Peptide #65	RRRGVGL	SEQ ID NO: 65	Peptide #235	LINLKRE	SEQ ID NO: 235
Peptide #66	WIIFQRM	SEQ ID NO: 66	Peptide #236	DSYVLTS	SEQ ID NO: 236
Peptide #67	LVRTRTI	SEQ ID NO: 67	Peptide #237	SAMWVIP	SEQ ID NO: 237
Peptide #68	NFLNGVN	SEQ ID NO: 68	Peptide #238	ESFTLYQ	SEQ ID NO: 238
Peptide #69	MAVVCAV	SEQ ID NO: 69	Peptide #239	SIFSKKY	SEQ ID NO: 239
Peptide #70	FDSVKTL	SEQ ID NO: 70	Peptide #240	LILYISP	SEQ ID NO: 240
Peptide #71	GVKVRAV	SEQ ID NO: 71	Peptide #241	ILLKRGQ	SEQ ID NO: 241
Peptide #72	SLKIQGS	SEQ ID NO: 72	Peptide #242	EVVCGRL	SEQ ID NO: 242
Peptide #73	DTATVDS	SEQ ID NO: 73	Peptide #243	YRLFLRL	SEQ ID NO: 243
Peptide #74	YRGKHGN	SEQ ID NO: 74	Peptide #244	YTARGLK	SEQ ID NO: 244
Peptide #75	FYFNMI	SEQ ID NO: 75	Peptide #245	FGFCGWR	SEQ ID NO: 245
Peptide #76	LSCCSDR	SEQ ID NO: 76	Peptide #246	SPPGLVD	SEQ ID NO: 246
Peptide #77	ARVGNMG	SEQ ID NO: 77	Peptide #247	GPKGLPD	SEQ ID NO: 247
Peptide #78	LSSLFWL	SEQ ID NO: 78	Peptide #248	ESSCTST	SEQ ID NO: 248
Peptide #79	IMRYLTY	SEQ ID NO: 79	Peptide #249	ILNAAGA	SEQ ID NO: 249
Peptide #80	WGMGHAN	SEQ ID NO: 80	Peptide #250	GWSYWIQ	SEQ ID NO: 250
Peptide #81	KLMDGNN	SEQ ID NO: 81	Peptide #251	VFMAETI	SEQ ID NO: 251
Peptide #82	ATIYNSY	SEQ ID NO: 82	Peptide #252	WMSRMAI	SEQ ID NO: 252

Peptide #83	ETLGNI	SEQ ID NO: 83	Peptide #253	SIFTKRY	SEQ ID NO: 253
Peptide #84	HIMDLSS	SEQ ID NO: 84	Peptide #254	WHLLCLD	SEQ ID NO: 254
Peptide #85	CIVFQIL	SEQ ID NO: 85	Peptide #255	NHVYPYC	SEQ ID NO: 255
Peptide #86	TSTTPSK	SEQ ID NO: 86	Peptide #256	DRCYRGA	SEQ ID NO: 256
Peptide #87	LYEHNMD	SEQ ID NO: 87	Peptide #257	TFGFSGG	SEQ ID NO: 257
Peptide #88	ATYYNHV	SEQ ID NO: 88	Peptide #258	HCISLRL	SEQ ID NO: 258
Peptide #89	KVTRTVS	SEQ ID NO: 89	Peptide #259	SIIVMRV	SEQ ID NO: 259
Peptide #90	VVVSFMW	SEQ ID NO: 90	Peptide #260	LFSVNMV	SEQ ID NO: 260
Peptide #91	DLIIWIA	SEQ ID NO: 91	Peptide #261	RCFGCLC	SEQ ID NO: 261
Peptide #92	LVNICAG	SEQ ID NO: 92	Peptide #262	PFLVELS	SEQ ID NO: 262
Peptide #93	KLMDSSN	SEQ ID NO: 93	Peptide #263	FGISVYR	SEQ ID NO: 263
Peptide #94	VSMQGEL	SEQ ID NO: 94	Peptide #264	FKSQLNC	SEQ ID NO: 264
Peptide #95	MLTSLLR	SEQ ID NO: 95	Peptide #265	RKVFIDS	SEQ ID NO: 265
Peptide #96	KLMDSNN	SEQ ID NO: 96	Peptide #266	SCNYTTV	SEQ ID NO: 266
Peptide #97	TFVCGQA	SEQ ID NO: 97	Peptide #267	CSLLTRH	SEQ ID NO: 267
Peptide #98	YFGKISI	SEQ ID NO: 98	Peptide #268	HTVGLMG	SEQ ID NO: 268
Peptide #99	LDNLHSV	SEQ ID NO: 99	Peptide #269	EPVLSRN	SEQ ID NO: 269
Peptide #100	NMCTIHS	SEQ ID NO: 100	Peptide #270	DIMWITC	SEQ ID NO: 270
Peptide #101	WTGVSP	SEQ ID NO: 101	Peptide #271	THRSYLM	SEQ ID NO: 271
Peptide #102	ATTRLPF	SEQ ID NO: 102	Peptide #272	PVERVSLL	SEQ ID NO: 272
Peptide #103	SYGHRLL	SEQ ID NO: 103	Peptide #273	YWYHKKL	SEQ ID NO: 273
Peptide #104	NSFITSI	SEQ ID NO: 104	Peptide #274	PFCMSRF	SEQ ID NO: 274
Peptide #105	SNCIVSL	SEQ ID NO: 105	Peptide #275	HINFRGT	SEQ ID NO: 275
Peptide #106	EECTLTI	SEQ ID NO: 106	Peptide #276	SNLLGI	SEQ ID NO: 276
Peptide #107	CVSEPKG	SEQ ID NO: 107	Peptide #277	CFNMLIN	SEQ ID NO: 277
Peptide #108	SKSRVSC	SEQ ID NO: 108	Peptide #278	YDKRSHQ	SEQ ID NO: 278
Peptide #109	NFSLHY	SEQ ID NO: 109	Peptide #279	DSLVGHA	SEQ ID NO: 279

Peptide #110	VLYTFIC	SEQ ID NO: 110	Peptide #280	VFYLVYW	SEQ ID NO: 280
Peptide #111	FFIVDSC	SEQ ID NO: 111	Peptide #281	DLQSNVN	SEQ ID NO: 281
Peptide #112	TSTTPGK	SEQ ID NO: 112	Peptide #282	SFSCLYH	SEQ ID NO: 282
Peptide #113	TDSKWSL	SEQ ID NO: 113	Peptide #283	YELGSIG	SEQ ID NO: 283
Peptide #114	SSWYAPS	SEQ ID NO: 114	Peptide #284	VASNALS	SEQ ID NO: 284
Peptide #115	DNQICRR	SEQ ID NO: 115	Peptide #285	CLEMCIL	SEQ ID NO: 285
Peptide #116	ATCTVSF	SEQ ID NO: 116	Peptide #286	GEGRSRM	SEQ ID NO: 286
Peptide #117	RVSYWFL	SEQ ID NO: 117	Peptide #287	LDRDVDR	SEQ ID NO: 287
Peptide #118	FKGLVSV	SEQ ID NO: 118	Peptide #288	YGGFFGI	SEQ ID NO: 288
Peptide #119	FIVWYMK	SEQ ID NO: 119	Peptide #289	NMTNTWP	SEQ ID NO: 289
Peptide #120	DSMQGEL	SEQ ID NO: 120	Peptide #290	SCSYTTV	SEQ ID NO: 290
Peptide #121	FIECLLL	SEQ ID NO: 121	Peptide #291	EAYLYQE	SEQ ID NO: 291
Peptide #122	TSTTPSR	SEQ ID NO: 122	Peptide #292	VSICDLV	SEQ ID NO: 292
Peptide #123	DTATIDS	SEQ ID NO: 123	Peptide #293	NCIFLCK	SEQ ID NO: 293
Peptide #124	PNSYLNS	SEQ ID NO: 124	Peptide #294	MATSRAI	SEQ ID NO: 294
Peptide #125	SCQLLLL	SEQ ID NO: 125	Peptide #295	CITLHCA	SEQ ID NO: 295
Peptide #126	IAGSETM	SEQ ID NO: 126	Peptide #296	GVMRPQY	SEQ ID NO: 296
Peptide #127	CLIWFVI	SEQ ID NO: 127	Peptide #297	ALVCMLF	SEQ ID NO: 297
Peptide #128	GTVYRES	SEQ ID NO: 128	Peptide #298	SRQYLKR	SEQ ID NO: 298
Peptide #129	CFLLTRH	SEQ ID NO: 129	Peptide #299	VYDCMNS	SEQ ID NO: 299
Peptide #130	MFCQSLT	SEQ ID NO: 130	Peptide #300	ILHRRGQ	SEQ ID NO: 300
Peptide #131	RVKWRFG	SEQ ID NO: 131	Peptide #301	EQMNFLR	SEQ ID NO: 301
Peptide #132	LEIRIND	SEQ ID NO: 132	Peptide #302	SLPFPPI	SEQ ID NO: 302
Peptide #133	STFLHDQ	SEQ ID NO: 133	Peptide #303	MGCRGPL	SEQ ID NO: 303
Peptide #134	CYCDLLT	SEQ ID NO: 134	Peptide #304	NEMTSFS	SEQ ID NO: 304
Peptide #135	TCQFRGV	SEQ ID NO: 135	Peptide #305	ELCLWET	SEQ ID NO: 305
Peptide #136	IVDCLCR	SEQ ID NO: 136	Peptide #306	KRQVLMT	SEQ ID NO: 306

Peptide #137	GMLCKTS	SEQ ID NO: 137	Peptide #307	DYGPWIE	SEQ ID NO: 307
Peptide #138	LLDDHVW	SEQ ID NO: 138	Peptide #308	FYDKSDG	SEQ ID NO: 308
Peptide #139	DSKFDDV	SEQ ID NO: 139	Peptide #309	IPCFQVS	SEQ ID NO: 309
Peptide #140	YVVRSL	SEQ ID NO: 140	Peptide #310	GSSACTS	SEQ ID NO: 310
Peptide #141	SYIQVSW	SEQ ID NO: 141	Peptide #311	YALYFRS	SEQ ID NO: 311
Peptide #142	CKLFDLD	SEQ ID NO: 142	Peptide #312	FMYVSKI	SEQ ID NO: 312
Peptide #143	GYREGFS	SEQ ID NO: 143	Peptide #313	YFPGRCT	SEQ ID NO: 313
Peptide #144	SPNLIMG	SEQ ID NO: 144	Peptide #314	CVRWGCI	SEQ ID NO: 314
Peptide #145	GRFWNVE	SEQ ID NO: 145	Peptide #315	RKRGVGL	SEQ ID NO: 315
Peptide #146	QECRLC	SEQ ID NO: 146	Peptide #316	RAKDAWV	SEQ ID NO: 316
Peptide #147	SFLGGA	SEQ ID NO: 147	Peptide #317	SIIVMGV	SEQ ID NO: 317
Peptide #148	MWLYWRR	SEQ ID NO: 148	Peptide #318	PLRSLCF	SEQ ID NO: 318
Peptide #149	SFVAFGY	SEQ ID NO: 149	Peptide #319	MLIVILV	SEQ ID NO: 319
Peptide #150	YLYYLS	SEQ ID NO: 150	Peptide #320	SYILISY	SEQ ID NO: 320
Peptide #151	VTAWFGF	SEQ ID NO: 151	Peptide #321	SMLLCYL	SEQ ID NO: 321
Peptide #152	RFWTWSN	SEQ ID NO: 152	Peptide #322	WKHHYFF	SEQ ID NO: 322
Peptide #153	MLFSILF	SEQ ID NO: 153	Peptide #323	YRDLIYK	SEQ ID NO: 323
Peptide #154	FTFWHRL	SEQ ID NO: 154	Peptide #324	CYRFQEV	SEQ ID NO: 324
Peptide #155	SIFTKKY	SEQ ID NO: 155	Peptide #325	WVLRTSR	SEQ ID NO: 325
Peptide #156	VRSQDVF	SEQ ID NO: 156	Peptide #326	RRVFIDS	SEQ ID NO: 326
Peptide #157	MPNSSRC	SEQ ID NO: 157	Peptide #327	KIRVRIN	SEQ ID NO: 327
Peptide #158	ILHKRGQ	SEQ ID NO: 158	Peptide #328	WYKFRPL	SEQ ID NO: 328
Peptide #159	LVQRGPV	SEQ ID NO: 159	Peptide #329	SVVVGLC	SEQ ID NO: 329
Peptide #160	NPSAWL	SEQ ID NO: 160	Peptide #330	HFTSLFA	SEQ ID NO: 330
Peptide #161	VIMKIAG	SEQ ID NO: 161	Peptide #331	KESVWEL	SEQ ID NO: 331
Peptide #162	LDDNVLD	SEQ ID NO: 162	Peptide #332	ESYHMVS	SEQ ID NO: 332
Peptide #163	CVYFLSP	SEQ ID NO: 163	Peptide #333	CLFSHDC	SEQ ID NO: 333

Peptide #164	RLSLGPC	SEQ ID NO: 164	Peptide #334	RSVGGIC	SEQ ID NO: 334
Peptide #165	PFSDGWC	SEQ ID NO: 165	Peptide #335	SFCQCLF	SEQ ID NO: 335
Peptide #166	DFSVESD	SEQ ID NO: 166	Peptide #336	MGCELRR	SEQ ID NO: 336
Peptide #167	ELYFMFV	SEQ ID NO: 167	Peptide #337	CDAFYVE	SEQ ID NO: 337
Peptide #168	LASCSGE	SEQ ID NO: 168	Peptide #338	TFWSRFT	SEQ ID NO: 338
Peptide #169	SSGHLKF	SEQ ID NO: 169	Peptide #339	SNERATN	SEQ ID NO: 339
Peptide #170	ISCCWDI	SEQ ID NO: 170			

Table 2: AAV-DJ Variants with Enhanced Brain and Muscle Tropism and Reduced Liver Tropism

Variant	7-mer sequence	SEQ ID NO:	Variant	7-mer sequence	SEQ ID NO:
Peptide #340	GYLDLSD	SEQ ID NO: 340	Peptide #386	TIWKTLI	SEQ ID NO: 345
Peptide #341	HEKGLYM	SEQ ID NO: 341	Peptide #387	SSGGGVC	SEQ ID NO: 344
Peptide #342	WVFLVDS	SEQ ID NO: 342	Peptide #388	NVCSGLV	SEQ ID NO: 350
Peptide #343	TSMTLNR	SEQ ID NO: 343	Peptide #389	GLHYHHS	SEQ ID NO: 359
Peptide #344	SSGGGVC	SEQ ID NO: 344	Peptide #390	SFQCLAA	SEQ ID NO: 362
Peptide #345	TIWKTLI	SEQ ID NO: 345	Peptide #391	SSEVNCS	SEQ ID NO: 364
Peptide #346	YRVFVVV	SEQ ID NO: 346	Peptide #392	SYMINFE	SEQ ID NO: 369
Peptide #347	LVNCTWN	SEQ ID NO: 347	Peptide #393	FYYKATW	SEQ ID NO: 373
Peptide #348	LRCRWFR	SEQ ID NO: 348	Peptide #394	GYLDLSD	SEQ ID NO: 340
Peptide #349	LERGDTV	SEQ ID NO: 349	Peptide #395	HEKGLYM	SEQ ID NO: 341
Peptide #350	NVCSGLV	SEQ ID NO: 350	Peptide #396	YRVFVVV	SEQ ID NO: 346
Peptide #351	DCDGLLM	SEQ ID NO: 351	Peptide #397	LRCRWFR	SEQ ID NO: 348
Peptide #352	QLVLLKL	SEQ ID NO: 352	Peptide #398	DCDGLLM	SEQ ID NO: 351
Peptide #353	SLFVKFQ	SEQ ID NO: 353	Peptide #399	SLFVKFQ	SEQ ID NO: 353
Peptide #354	DRVMISV	SEQ ID NO: 354	Peptide #400	LVIRPSN	SEQ ID NO: 357
Peptide #355	FYCLDFH	SEQ ID NO: 355	Peptide #401	DRVMISV	SEQ ID NO: 354

Peptide #356	LICMLYQ	SEQ ID NO: 356	Peptide #402	YSMCRAY	SEQ ID NO: 372
Peptide #357	LVIRPSN	SEQ ID NO: 357	Peptide #403	SRQYLKR	SEQ ID NO: 298
Peptide #358	CCMWWLC	SEQ ID NO: 358	Peptide #404	VYDCMNS	SEQ ID NO: 299
Peptide #359	GLHYHHS	SEQ ID NO: 359	Peptide #405	ILHRRGQ	SEQ ID NO: 300
Peptide #360	LVLYYGI	SEQ ID NO: 360	Peptide #406	DSMQGEL	SEQ ID NO: 120
Peptide #361	IKGLIEL	SEQ ID NO: 361	Peptide #407	EQMNFLR	SEQ ID NO: 301
Peptide #362	SFQCLAA	SEQ ID NO: 362	Peptide #408	FIECLLL	SEQ ID NO: 121
Peptide #363	CWNLLGC	SEQ ID NO: 363	Peptide #409	SLPFPAL	SEQ ID NO: 302
Peptide #364	SSEVNCS	SEQ ID NO: 364	Peptide #410	MGCRGPL	SEQ ID NO: 303
Peptide #365	FFRCPLG	SEQ ID NO: 365	Peptide #411	TSTTPSR	SEQ ID NO: 122
Peptide #366	VTPNQTY	SEQ ID NO: 366	Peptide #412	NEMTSFS	SEQ ID NO: 304
Peptide #367	SNCYRSK	SEQ ID NO: 367	Peptide #413	PNSYLNS	SEQ ID NO: 124
Peptide #368	ANYDYDR	SEQ ID NO: 368	Peptide #414	SCQLLLL	SEQ ID NO: 125
Peptide #369	SYMINFE	SEQ ID NO: 369	Peptide #415	CLWFWVI	SEQ ID NO: 127
Peptide #370	MCYQGPK	SEQ ID NO: 370	Peptide #416	KRQVLMT	SEQ ID NO: 306
Peptide #371	RNKFVLF	SEQ ID NO: 371	Peptide #417	DYGPWIE	SEQ ID NO: 307
Peptide #372	YSMCRAY	SEQ ID NO: 372	Peptide #418	CFLLTRH	SEQ ID NO: 129
Peptide #373	FYYKATW	SEQ ID NO: 373	Peptide #419	MFCQSLT	SEQ ID NO: 130
Peptide #374	DIKSTFF	SEQ ID NO: 374	Peptide #420	IPCFQVS	SEQ ID NO: 309
Peptide #375	FYCLDFH	SEQ ID NO: 355	Peptide #421	RVKWRFG	SEQ ID NO: 131
Peptide #376	LERGDTV	SEQ ID NO: 349	Peptide #422	STFLHDQ	SEQ ID NO: 133
Peptide #377	CCMWWLC	SEQ ID NO: 358	Peptide #423	IVDCLCR	SEQ ID NO: 136
Peptide #378	LVLYYGI	SEQ ID NO: 360	Peptide #424	LVNCTWN	SEQ ID NO: 347
Peptide #379	IKGLIEL	SEQ ID NO: 361	Peptide #425	CWNLLGC	SEQ ID NO: 363
Peptide #380	SNCYRSK	SEQ ID NO: 367	Peptide #426	FFRCPLG	SEQ ID NO: 365
Peptide #381	QLVLLKL	SEQ ID NO: 352	Peptide #427	VTPNQTY	SEQ ID NO: 366
Peptide #382	LICMLYQ	SEQ ID NO: 356	Peptide #428	ANYDYDR	SEQ ID NO: 368

Peptide #383	DIKSTFF	SEQ ID NO: 374	Peptide #429	MCYQGPK	SEQ ID NO: 370
Peptide #384	WVFLVDS	SEQ ID NO: 342	Peptide #430	RNKFVLF	SEQ ID NO: 371
Peptide #385	TSMTLNR	SEQ ID NO: 343			

Table 3: AAV-DJ Variants with Superior Brain and Muscle Tropism and Liver De-targeting

Variant	7-mer sequence	SEQ ID NO:	Variant	7-mer sequence	SEQ ID NO:
Peptide #431	RGMYWLR	SEQ ID NO: 375	Peptide #443	VLYILVH	SEQ ID NO: 387
Peptide #432	WLTWLLG	SEQ ID NO: 376	Peptide #444	FEHSGAV	SEQ ID NO: 388
Peptide #433	NNHGFSI	SEQ ID NO: 377	Peptide #445	YYARREG	SEQ ID NO: 389
Peptide #434	LSRSKGY	SEQ ID NO: 378	Peptide #446	RHSWLFD	SEQ ID NO: 390
Peptide #435	MIHASDD	SEQ ID NO: 379	Peptide #447	YIWRQLI	SEQ ID NO: 391
Peptide #436	SYRAKRG	SEQ ID NO: 380	Peptide #448	ALRAKEC	SEQ ID NO: 392
Peptide #437	RFMCKVG	SEQ ID NO: 381	Peptide #449	MMWVGFS	SEQ ID NO: 393
Peptide #438	LLTMHRR	SEQ ID NO: 382	Peptide #450	GLRERFG	SEQ ID NO: 394
Peptide #439	LDWVLIP	SEQ ID NO: 383	Peptide #451	SFFGETS	SEQ ID NO: 395
Peptide #440	QLLVPLG	SEQ ID NO: 384	Peptide #452	SDMDHWW	SEQ ID NO: 396
Peptide #441	CQLLGRE	SEQ ID NO: 385	Peptide #453	GVCSCSG	SEQ ID NO: 397
Peptide #442	MFARTAL	SEQ ID NO: 386	Peptide #454	CQVMTVW	SEQ ID NO: 398

- 5 **[0048]** In one example, the modified AAV comprises a 7-mer peptide sequence selected from the sequences set forth in Table 1, and the insertion increases brain, muscle, and liver tropism compared to a wild-type AAV without a 7-mer peptide sequence insertion.
- [0049]** In another example, the modified AAV comprises a 7-mer peptide sequence selected from the sequences set forth in Table 2, and the insertion increases brain, and muscle tropism, and decreases liver tropism compared to a wild-type AAV without a 7-mer peptide sequence insertion.
- 10 **[0050]** In yet another example, the modified AAV comprises a 7-mer peptide sequence selected from the sequences set forth in Table 3, and wherein the insertion increases brain, and muscle tropism, and is liver de-targeting.

[0051] In yet another example, the modified AAV comprises a 7-mer peptide sequence selected from the group consisting of SEQ ID NOs: 22, 24, 32, 85, 106, 198, 216, 232, 251, 293, 312, 320, 321, 224, 346 or 376.

Table 4: AAV nucleotide sequences

AAV type	Nucleotide sequences of the capsid	SEQ ID NO:
Wild-type AAV-DJ VP1 sequence	ATGGCTGCCGATGGTTATCTTCCAGATTGGCTCG AGGACACTCTCTCTGAAGGAATAAGACAGTGGT GGAAGCTCAAACCTGGCCCACCACCACCAAAG CCCGCAGAGCGGCATAAGGACGACAGCAGGGG TCTTGTGCTTCCTGGGTACAAGTACCTCGGACCC TTCAACGGACTCGACAAGGGAGAGCCGGTCAA CGAGGCAGACGCCGCGGCCCTCGAGCACGACA AAGCCTACGACCGGCAGCTCGACAGCGGAGAC AACCCGTACCTCAAGTACAACCACGCCGACGCC GAGTTCAGGAGCGGCTCAAAGAAGATACGTCT TTTGGGGGCAACCTCGGGCGAGCAGTCTTCCAG GCCAAAAAGAGGCTTCTTGAACCTCTTGGTCTG GTTGAGGAAGCGGCTAAGACGGCTCCTGGAAA GAAGAGGCCTGTAGAGCACTCTCCTGTGGAGCC AGACTCCTCCTCGGGAACCGGAAAGGCGGGCC AGCAGCCTGCAAGAAAAAGATTGAATTTGGTC AGACTGGAGACGCAGACTCAGTCCCAGACCCT CAACCAATCGGAGAACCTCCCGCAGCCCCCTCA GGTGTGGGATCTCTTACAATGGCTGCAGGCGGT GGCGCACC AATGGCAGACAATAACGAGGGCGC CGACGGAGTGGGTAATTCCTCGGGAATTTGGCA TTGCGATTCCACATGGATGGGCGACAGAGTCAT CACCACCAGCACCCGAACCTGGGCCCTGCCCCAC CTACAACAACCACCTCTACAAGCAAATCTCCAA CAGCACATCTGGAGGATCTTCAAATGACAACGC CTACTTCGGCTACAGCACCCCTGGGGGTATTTT GACTTTAACAGATTCCACTGCCACTTTTCACCAC GTGACTGGCAGCGACTCATCAACAACAACCTGGG GATTCCGGCCCAAGAGACTCAGCTTCAAGCTCT TCAACATCCAGGTCAAGGAGGTCACGCAGAATG AAGGCACCAAGACCATCGCCAATAACCTCACCA GCACCATCCAGGTGTTTACGGA CT CGGAGTACC AGCTGCCGTACGTTCTCGGCTCTGCCACCAGG GCTGCCTGCCTCCGTTCCCGGCGGACGTGTTCA TGATTCCCCAGTACGGCTACCTAACACTCAACA ACGGTAGTCAGGCCGTGGGACGCTCCTCCTTCT ACTGCCTGGAATACTTTCTTCGCGATGCTGAG AACCGGCAACAACCTCCAGTTTACTTACACCTT CGAGGACGTGCCTTTCCACAGCAGCTACGCCCCA CAGCCAGAGCTTGGACCGGCTGATGAATCCTCT GATTGACCAGTACCTGTACTACTTGTCTCGGACT CAAACAACAGGAGGCACGACAAATACGCAGAC	SEQ ID NO: 399

	TCTGGGCTTCAGCCAAGGTGGGCCTAATACAAT GGCCAATCAGGCAAAGAAGTGGCTGCCAGGAC CCTGTTACCGCCAGCAGCGAGTATCAAAGACAT CTGCGGATAACAACAACAGTGAATACTCGTGGA CTGGAGCTACCAAGTACCACCTCAATGGCAGAG ACTCTCTGGTGAATCCGGGCCCCGGCCATGGCAA GCCACAAGGACGATGAAGAAAAGTTTTTCCTC AGAGCGGGGTTCTCATCTTTGGGAAGCAAGGCT CAGAGAAAACAAATGTGGACATTGAAAAGGTC ATGATTACAGACGAAGAGGAAATCAGGACAACC AATCCCGTGGCTACGGAGCAGTATGGTTCTGTAtc tACCAACCTCCAGAGAGGCAACAGACAAGCAGC TACCGCAGATGTCAACACACAAGGCGTTCTTCC AGGCATGGTCTGGCAGGACAGAGATGTGTACCT TCAGGGGCCCCATCTGGGCAAAGATTCCACACAC GGACGGACATTTTCACCCCTCTCCCCTCATGGGT GGATTGCGACTTAAACACCCTCCGCCTCAGATC CTGATCAAGAACACGCCTGTACCTGCGGATCCT CCGACCACCTTCAACCAGTCAAAGCTGAACTCT TTCATCACCCAGTATTCTACTGGCCAAGTCAGCG TGGAGATCGAGTGGGAGCTGCAGAAGGAAAAC AGCAAGCGCTGGAACCCCGAGATCCAGTACACC TCCAATACTACAAATCTACAAGTGTGGACTTTG CTGTTAATACAGAAGGCGTGTACTCTGAACCCC GCCCCATTGGCACCCGTTACCTCACCCGTAATCT GTAA	
AAV-DJ VP1 sequence (with library insertion site)	ATGGCTGCCGATGGTTATCTTCCAGATTGGCTCG AGGACACTCTCTCTGAAGGAATAAGACAGTGGT GGAAGCTCAAACCTGGCCCACCACCACCAAAG CCCGCAGAGCGGCATAAGGACGACAGCAGGGG TCTTGTGCTTCCTGGGTACAAGTACCTCGGACCC TTCAACGGACTCGACAAGGGAGAGCCGGTCAA CGAGGCAGACGCCGCGGCCCTCGAGCACGACA AAGCCTACGACCGGCAGCTCGACAGCGGAGAC AACCCGTACCTCAAGTACAACCACGCCGACGCC GAGTTCCAGGAGCGGCTCAAAGAAGATACGTCT TTTGGGGGCAACCTCGGGCGAGCAGTCTTCCAG GCCAAAAAGAGGCTTCTTGAACCTCTTGGTCTG GTTGAGGAAGCGGCTAAGACGGCTCCTGGAAA GAAGAGGCCTGTAGAGCACTCTCCTGTGGAGCC AGACTCCTCCTCGGGAACCGGAAAGGCGGGCC AGCAGCCTGCAAGAAAAAGATTGAATTTTGGTC AGACTGGAGACGCAGACTCAGTCCCAGACCCT CAACCAATCGGAGAACCTCCCGCAGCCCCCTCA GGTGTGGGATCTCTTACAATGGCTGCAGGCGGT GGCGCACCAATGGCAGACAATAACGAGGGCGC CGACGGAGTGGGTAATTCCTCGGGAATTTGGCA TTGCGATTCCACATGGATGGGCGACAGAGTCAT CACCACCAGCACCCGAACCTGGGCCCTGCCAC CTACAACAACCACCTCTACAAGCAAATCTCCAA	SEQ ID NO: 400

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Wild-type AAV-DJ VP3 sequence	ATGGCAGACAATAACGAGGGCGCCGACGGAGT GGGTAATTCCTCGGGAAATTGGCATTGCGATTCC ACATGGATGGGCGACAGAGTCATCACCAACCAGC ACCCGAACCTGGGGCCCTGCCACCTACAACAAC CACCTCTACAAGCAAATCTCCAACAGCACATCT GGAGGATCTTCAAATGACAACGCCTACTTCGGC TACAGCACCCCTGGGGGTATTTTGACTTTAACA GATTCCACTGCCACTTTTCACCACGTGACTGGC	SEQ ID NO: 406

	AGCGACTCATCAACAACAACTGGGGATTCCGGC CCAAGAGACTCAGCTTCAAGCTCTTCAACATCC AGGTCAAGGAGGTACGCAGAATGAAGGCACC AAGACCATCGCCAATAACCTCACCAGCACCATC CAGGTGTTTACGGACTCGGAGTACCAGCTGCCG TACGTTCTCGGCTCTGCCCACCAGGGCTGCCTG CCTCCGTTCCCGGCGGACGTGTTTCATGATCCCC AGTACGGCTACCTAACACTCAACAACGGTAGTC AGGCCGTGGGACGCTCCTCCTTCTACTGCCTGG AATACTTTCCTTCGCAGATGCTGAGAACCGGCA ACAACCTCCAGTTTACTTACACCTTCGAGGACG TGCCTTTCCACAGCAGCTACGCCCACAGCCAGA GCTTGGACCGGCTGATGAATCCTCTGATTGACC AGTACCTGTACTACTTGTCTCGGACTCAAACAA CAGGAGGCACGACAAATACGCAGACTCTGGGCT TCAGCCAAGGTGGGCCTAATACAATGGCCAATC AGGCAAAGAACTGGCTGCCAGGACCCTGTTACC GCCAGCAGCGAGTATCAAAGACATCTGCGGATA ACAACAACAGTGAATACTCGTGGACTGGAGCTA CCAAGTACCACCTCAATGGCAGAGACTCTCTGG TGAATCCGGGCCCCGCCATGGCAAGCCACAAGG ACGATGAAGAAAAGTTTTTTCCTCAGAGCGGGG TTCTCATCTTTGGGAAGCAAGGCTCAGAGAAAA CAAATGTGGACATTGAAAAGGTCATGATTACAG ACGAAGAGGAAATCAGGACAACCAATCCCGTG GCTACGGAGCAGTATGGTTCTGTAtctACCAACCT CCAGAGAGGCAACAGACAAGCAGCTACCGCAG ATGTCAACACACAAGGCGTTCTTCCAGGCATGG TCTGGCAGGACAGAGATGTGTACCTTCAGGGGC CCATCTGGGCAAAGATTCCACACACGGACGGAC ATTTTACCCCTCTCCCCTCATGGGTGGATTTCGG ACTTAAACACCCTCCGCCTCAGATCCTGATCAA GAACACGCCTGTACCTGCGGATCCTCCGACCAC CTTCAACCAGTCAAAGCTGAACTCTTTCATCAC CCAGTATTCTACTGGCCAAGTCAGCGTGGAGAT CGAGTGGGAGCTGCAGAAGGAAAACAGCAAGC GCTGGAACCCCGAGATCCAGTACACCTCCAAC ACTACAAATCTACAAGTGTGGACTTTGCTGTAA TACAGAAGGCGTGTACTCTGAACCCCGCCCCAT TGGCACCCGTTACCTCACCCGTAATCTGTAA	
Wild-type AAV-2 VP2 sequence	acggctccgggaaaaaagaggccggtagagcactctcctgtggagccagac tcctcctcgggaaccggaaggcgggcccagcagcctgcaagaaaaagattg aatTTTgtcagactggagacgcagactcagtacctgacccccagcctctcgg acagccaccagcagccccctctgtctgggaactaatacgtggctacaggc agtggcgaccaatggcagacaataacgaggcgccgacggagtgggtaat tcctcgggaaattggcattgcatccacatggatggcgacagagtcacac caccagcaccggaacctgggacctgcccacctaacaacacacctctacaaa caaattccagccaatcaggagcctcgaacgacaatcactactttggctacagc acccttgggggtattttgactcaacagattccactgccactttccaccagtga ctggcaagactcatcaacaacaactggggattccgaccaagagactcaac	SEQ ID NO: 407

	ttcaagctctttaacattcaagtc aaagaggtcacgcagaatgacggtagcacg acgattgccaataaccttaccagcacgggtcaggtgtttactgactcggagtac cagctcccgtagctcctcggctcggcgcatcaaggatgcctcccgccgtccc agcagacgtctcatggtgccacagtatggatacctcacctgaacaacggga gtcaggcagtaggacgctcttctttactgcctggagtacttcttctcagatg ctgctgaccggaaacaactttacctcagctacacttttgaggacgttcttcca cagcagctacgctcacagccagagtctggaccgtctcatgaatcctctcatcg accagtacctgtattacttgagcagaacaaacactccaagtggaaaccaccag cagtaagggttcagtttctcagcgccggagcgagtgacattcgggaccagtct aggaaactggcttctggaccctgttaccgccagcagcgagtaicaaagacatc tgccgataacaacaacagtgaatactcgtggactggagctaccaagtaccacc tcaatggcagagactctctggtgaatccggggcccgccatggcaagccaca ggacgatgaagaaaagttttctcagagcgggttctcatcttgggaagca aggctcagagaaaacaatgtggacattgaaaaggctcatgattacagacgaa gaggaaatcaggacaaccaatcccggtgctacggagcagtatggttctgtatc taccaacctccagagaggcaacagacaagcagctaccgcagatgtcaacac acaaggcgttcttcaggcatggtctggcaggacagagatgtgtaccttcagg ggcccatctgggcaaagattccacacacggacggacatttcacccctctccc ctcatgggtggttcggacttaaacacctctccacagattctcatcaagaac accccggtacctgcgaatccttcgaccacctcagtcggcgaagtgttctctct tcatcacacagtactccacgggacaggtcagcgtggagatcgagtgggagct gcagaaggaacagcaaacgtggaatccgaaattcagtaacttccaac tacaacaagtctgtaattgtggactttactgtggacactaatggcgtgtattcaga gcctcgcctcatggcaccagatactgactcgtaatctgtaa	
Wild-type AAV-2 VP3 sequence	atggcagacaataacgaggcgccgacggagtggtgaattcctcgggaaatt ggcattgcgattccacatggatggcgacagagtcacaccaccagcaccgg aacctggggccctgccacctacaacaaccctctacaacaaatttcagcc aatcaggagcctcgaacgacaatcactcttggctacagcacccttggggg tattttgacttcaacagattccactgccactttaccacgtgactggcaagact catcaacaacaactggggttcgacccaagagactcaactcaagctcttaa cattcaagtcaaaagggtcacgcagaatgacggtagcacgacgattgccaat aaccttaccagcacgggtcaggtgttactgactcggagtaccagctccgtac gtcctcggctcggcgcatcaaggatgcctcccgcttccagcagacgtctt catggtgccacagtatggatacctcacctgaacaacgggagtcaggcagta ggacgctcttcttactgcctggagtacttcttctcagatgctgctgaccgg aaacaactttacctcagctacacttttgaggacgttcttccacagcagctacg ctcacagccagagtctggaccgtctcatgaatcctctcagcaccagtaacctgt attacttgagcagaacaacactccaagtggaaaccaccagcagtcagggtt cagtttctcaggccggagcgagtgacattcgggaccagtctaggaactggct tcctggaccctgttaccgccagcagcgagtataaagacatctgcggataaca acaacagtgaatactcgtggactggagctaccaagtaccacctcaatggcaga gactctctggtgaatccggggcccgccatggcaagccacaaggacgatgaa gaaaagtgttctcagagcgggttctcatcttgggaagcaaggctcagag aaaacaaatgtggacattgaaaaggctcatgattacagacgaagaggaaatca ggacaaccaatccgtggctacggagcagtatggttctgtatctaccaacctcc agagaggcaacagacaagcagctaccgcagatgtcaacacacaaggcgttc ttccaggcatggtctggcaggacagagatgttacctcaggggcccatctgg gcaaagattccacacacggacggacatttccacctctccctcatgggtgg attcggacttaaacacctctccacagattctcatcaagaacaccccggtacc tgcgaatccttcgaccacctcagtcggcgaagtgttcttctcatcacacag	SEQ ID NO: 408

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Wild-type AAV-5 VP2 sequence	acgGCCCCTACCGGAAAGCGGATAGACGACCACT TTCCAAAAGAAAGAAGGCTCGGACCGAAGAG GACTCCAAGCCTTCCACCTCGTCAGACGCCGAA GCTGGACCCAGCGGATCCCAGCAGCTGCAAATC CCAGCCCAACCAGCCTCAAGTTTGGGAGCTGAT ACAATGTCTGCGGGAGGTGGCGGCCCATTTGGGC GACAATAACCAAGGTGCCGATGGAGTGGGCAAT GCCTCGGGAGATTGGCATTGCGATTCCACGTGG ATGGGGGACAGAGTCGTCACCAAGTCCACCCG AACCTGGGTGCTGCCAGCTACAACAACCA GTACCGAGAGATCAAAAGCGGCTCCGTCGACGG AAGCAACGCCAACGCCTACTTTGGATACAGCAC CCCCTGGGGGTACTTTGACTTTAACCGCTTCCAC AGCCACTGGAGCCCCGAGACTGGCAAAGACT CATCAACAATACTGGGGCTTCAGACCCCGGTC CCTCAGAGTCAAAATCTTCAACATTCAAGTCAA AGAGGTCACGGTGCAGGACTCCACCACCACCAT CGCCAACAACCTCACCTCCACCGTCCAAGTGTT TACGGACGACGACTACCAGCTGCCCTACGTCGT CGGCAACGGGACCGAGGGATGCCTGCCGGCCTT CCCTCCGCAGGTCTTTACGCTGCCGCAGTACGG TTACGCGACGCTGAACCGCGACAACACAGAAA ATCCCACCGAGAGGAGCAGCTTCTTCTGCCTAG AGTACTTTCCAGCAAGATGCTGAGAACGGGCA ACAACTTTGAGTTTACCTACAACTTTGAGGAGG TGCCCTTCCACTCCAGCTTCGCTCCAGTCAGA ACCTGTTCAAGCTGGCCAACCCGCTGGTGGACC AGTACTTGTACCGCTTCGTGAGCACAAATAACA CTGGCGGAGTCCAGTTCAACAAGAACCTGGCC GGGAGATACGCCAACACCTACAAAACTGGTTC CCGGGGCCCATGGGCCGAACCCAGGGCTGGAA CCTGGGCTCCGGGGTCAACCGCGCCAGTGTCAG CGCCTTCGCCACGACCAATAGGATGGAGCTCGA GGGCGCGAGTTACCAGGTGCCCCCGCAGCCGA ACGGCATGACCAACAACCTCCAGGGCAGCAAC ACCTATGCCCTGGAGAACACTATGATCTTCAACA GCCAGCCGGCGAACCCGGGCACCACCGCCACG TACCTCGAGGGCAACATGCTCATCACCAGCGAG AGCGAGACGCAGCCGGTGAACCGCGTGGCGTA CAACGTCGGCGGGCAGATGGCCACCAACAACC AGAGCTCCACCACTGCCCCCGCAGCGGCACGT ACAACCTCCAGGAAATCGTGCCCGGCAGCGTGT GGATGGAGAGGGACGTGTACCTCCAAGGACCC ATCTGGGCCAAGATCCCAGAGACGGGGGCGCA CTTTCACCCCTCTCCGGCCATGGGCGGATTTCGG ACTCAAACACCCACCGCCCATGATGCTCATCAA	SEQ ID NO: 409

	GAACACGCCTGTGCCCCGAAATATCACCAGCTT CTCGGACGTGCCCCGTCAGCAGCTTCATCACCCA GTACAGCACCGGGCAGGTACCGTGAGATGG AGTGGGAGCTCAAGAAGGAAAACCTCCAAGAGG TGGAACCCAGAGATCCAGTACACAAACAACTAC AACGACCCCCAGTTTGTGGACTTTGCCCCGGAC AGCACCGGGGAATACAGAACCACCAGACCTATC GGAACCCGATACCTTACCCGACCCCTTTAA	
Wild-type AAV-5 VP3 sequence	TTGGGCGACAATAACCAAGGTGCCGATGGAGTG GGCAATGCCTCGGGAGATTGGCATTGCGATTCC ACGTGGATGGGGGACAGAGTCGTCACCAAGTC CACCCGAACCTGGGTGCTGCCAGCTACAACAA CCACCAGTACCGAGAGATCAAAAGCGGCTCCGT CGACGGAAGCAACGCCAACGCCTACTTTGGATA CAGCACCCCCCTGGGGGTACTTTGACTTTAACCG CTTCCACAGCCACTGGAGCCCCCGAGACTGGCA AAGACTCATCAACAATACTAGGGGCTTCAGACC CCGGTCCCTCAGAGTCAAAATCTTCAACATTCA AGTCAAAAGAGGTCACGGTGCAGGACTCCACCA CCACCATCGCCAACAACCTCACCTCCACCGTCC AAGTGTTTACGGACGACGACTACCAGCTGCCCT ACGTCGTCGGCAACGGGACCGAGGGATGCCTG CCGGCCTTCCCTCCGCAGGTCTTACGCTGCCGC AGTACGGTTACGCGACGCTGAACCGCGACAACA CAGAAAATCCCACCGAGAGGAGCAGCTTCTTCT GCCTAGAGTACTTTCCCAGCAAGATGCTGAGAA CGGGCAACAACCTTTGAGTTTACCTACAACCTTG AGGAGGTGCCCTTCCACTCCAGCTTCGCTCCCA GTCAGAACCTGTTCAAGCTGGCCAACCCGCTGG TGGACCAGTACTTGTACCGCTTCGTGAGCACAA ATAACACTGGCGGAGTCCAGTTCAACAAGAACC TGGCCGGGAGATACGCCAACACCTACAAAAACT GGTTCCCGGGGCCCATGGGCCGAACCCAGGGCT GGAACCTGGGCTCCGGGGTCAACCGCGCCAGT GTCAGCGCCTTCGCCACGACCAATAGGATGGAG CTCGAGGGCGCGAGTTACCAGGTGCCCCCGCAG CCGAACGGCATGACCAACAACCTCCAGGGCAG CAACACCTATGCCCTGGAGAACAATACTATGATCTT AACAGCCAGCCGGCGAACCCGGGCACCACCGC CACGTACCTCGAGGGCAACATGCTCATCACCA CGAGAGCGAGACGCAGCCGGTGAACCGCGTGG CGTACAACGTCGGCGGGCAGATGGCCACCAACA ACCAGAGCTCCACCACTGCCCCCGCGACCGGCA CGTACAACCTCCAGGAAATCGTGCCCGGCAGCG TGTGGATGGAGAGGGACGTGTACCTCCAAGGAC CCATCTGGGCCAAGATCCCAGAGACGGGGGCGC ACTTTCACCCCTCTCCGGCCATGGGCGGATTCTG GACTCAAACACCCACCGCCCATGATGCTCATCA AGAACACGCCTGTGCCCCGAAATATCACCAGCT TCTCGGACGTGCCCCGTCAGCAGCTTCATCACCC	SEQ ID NO: 410

	AGTACAGCACCGGGCAGGTCACCGTGGAGATG GAGTGGGAGCTCAAGAAGGAAAACCTCCAAGAG GTGGAACCCAGAGATCCAGTACACAAACAATA CAACGACCCCCAGTTTGTGGACTTTGCCCCGA CAGCACCGGGGAATACAGAACCACCAGACCTAT CGGAACCCGATACCTTACCCGACCCCTTTAA	
Wild-type AAV-6 VP2 sequence	acggctcctggaagaacgtccggtagagcagtcgccacaagagccagac tctcctcgggcattggcaagacaggccagcagcccgtaaaaagagactca attttggtcagactggcgactcagagtcagtcacccgaccacaacctctcgga gaacctccagcaacccccgctgctgtgggacactactacaatggcttcaggcg gtggcgaccaatggcagacaatacgaaggcgccgacggagtggttaatg cctcaggaaattggcattgcgattccacatggctggcgacagagtcacacc accagcaccgaacatgggcttggccacctataacaaccacctctacaagc aatctccagtgttcaacggggccagcaacgacaaccactacttcggctac agcaccctcgggggtattttgatttcaacagattccactgccatttctaccac gtgactggcagcgactcatcaacaacattggggattccggcccaagagact caacttcaagctctcaacatccaagtcaaggaggtcacgacgaatgatggcg tcacgaccatcgctaataacctaccagcacgggtcaagtcttctcgactcgg agtaccagtggcgtagctcctcggctctgcgcaccagggtcgctcctcctcg ttcccgcgagcgtgttcatgattccgcagtcaggtacctaacgctcaacaat ggcagccaggcagtgggacggtcatccttttactgcctggaatatttccatcg cagatgctgagaacgggcaataactttaccttcagctacaccttcgaggacgtg cctttccacagcagctacgcgcacagccagagcctggaccggctgatgaatc ctctcatcgaccagtacgtgtattacctaacaagaactcagaatcagtcggaa gtgccccaaaaaggacttgcgtgttagccgggggtctccagctggcagtcct gttcagccccaaaaactggctacctggaccctgttacggcgacgagcggttct aaaaaaaaacagacaacaacacagcaactttacctggactgggtgttcaaa atataaccttaattggcggtgaatctataatcaacctggcactgctatggcctca cacaagacgacaagacaagttcttcccatgagcgggtgtcatgattttgga aaggagagcgccggagcttcaaacatgcattggacaatgtcatgatcacag acgaagaggaaatcaaagccactaacccgtggccaccgaaagatttggga ctgtggcagtcattctccagagcagcagcacagacctgcgacggagatgt gcatgttatgggagccttacctggaatggtgtggcaagacagagacgtatacc tgcagggtcctatttgggcaaaattcctcacacggtggacactttaccctgt ctcctctcatggcggttggacttaagcaccgcctcctcagatcctcatcaa aaacacgcctgttctcgcgaatcctcggcagagttttcggtacaaagtgtgt tcattcatcaccagatttccacaggacaagtgagcgtggagattgaaatggga gctgcagaaaagaaacagcaaacgtggaatcccgaaatgcagtatacatct aactatgcaaaatctgccaacgttgatttactgtggacaacaatggactttatac tgagcctcgccccattggcaccctgttacctacccgtccctgttaa	SEQ ID NO: 411
Wild-type AAV-6 VP3 sequence	atggcagacaataacgaaggcgccgacggagtggtgtaatgcctcaggaaatt ggcattgagattccacatggctggcgacagagtcacaccaccagcaccgg aacatgggccttggccacctataacaaccacctctacaagcaaatctccagtgc ttcaacggggggccagcaacgacaaccactacttcggctacagcacccttg gggtattttgatttcaacagattccactgccatttctaccacgtgactggcagcg actcatcaacaacaattggggattccggcccaagagactcaacttcaagctctt caacatccaagtcaaggaggtcacgacgaatgatggcgtcacgaccatcgct aataacctaccagcacgggtcaagtcttctcgactcggagtaccagtggccg tacgtcctcggctctgcgcaccagggtgcctcctcctccgtccggcgagcgt gttcatgattccgagtcagtgtaacctaacgctcaacaatggcagccaggcag	SEQ ID NO: 412

	tgggacgggtcatccttttactgcctgggaatatttcccacgcagatgctgagaac gggcaataactttaccttcagctacaccttcgaggacgtgcccttccacagcag ctacgcgcacagccagagcctggaccggctgatgaatcctctcatcgaccag tacctgtattacctgaacagaactcagaatcagtcgggaagtgcacacacaa ggacttgctgttttagccgggggtctccagctggcatgtctgttcagccacaaa ctggctacctggaccctgttaccggcagcagcgcttctaaaaacaaaacag acaacaacaacagcaactttacctggactgggtcttcaaaatataaccttaagg gctggaatctataatcaaccctggcactgctatggcctcacacaaagacgaca aagacaagttcttcccatgagcgggtgcatgatttttgaaaggagagcgccg gagcttcaaacactgcattggacaatgtcatgacacagcgaagaggaaatc aaagccactaaccctggccaccgaaagatttgggactgtggcagtcaatct ccagagcagcagcagacacctgacggagatgtcatgttatgggagc cttacctggaatgggtggcaagacagagacgtatactgcagggtcctatttg ggccaaaattcctcacaggatggacacttaccctctcctcatggcgcg ctttggactaagcaccgcctcctcagatcctcatcaaaaacacgcctgtcct gcgaatcctccggcagagtttccgctacaaagtgtcttcattcatcccagt attccacagagacaagtgcgtggagattgaatgggagctgcagaaagaaaa cagcaaacgctggaatcccgaagtgcagtatacatctaactatgcaaatctgc caacgttgaatttactgtggacaacaatggactttatactgagcctcgccctatt ggcaccctgttacctaccctgccctgttaa	
Wild-type AAV-9 VP2 sequence	acggctcctggaaagaagagcctgtagagcagtcctcaggaaacgggact cctccgcgggtattggcaaatcgggtgcacagcccgtaaaaagagactcaa tttcggtcagactggcgacacagagtcagtcacagacctcaaccaatcgga gaacctcccgcagccccctcaggtgtgggatctcttacaatggcttcaggtgt ggcgaccagtggcagataataacgaagtgcggatggagtggttagttcct cgggaaattggcattgcgattccaatggctggggacagagtcaccac cagcaccggaacctgggcccctgccacctacaacaatcacctctacaagcaa atctcaacagcacatctggaggtatcttcaaatgacaacgcctacttcggctac agcaccctcgggggtatttgcattcaacagattccactgccacttctaccac gtgactggcagcagactcatcaacaacaactggggattcggcctaagcgact caacttcaagctcttcaacattcaggtcaagaggttacggacaacaatggagt caagaccatcgcaataaccttaccagcacggtcagggtcttcacggactcag actatcagctcccgtacgtgctcgggtcggctcacgagggctgcctcccgcc gttcccagcggacgttttcatgattcctcagtcagggtatctgacgttaatgatg gaagccaggccgtgggtcgttcgtcttttactgcctgggaatatttccgtcgca aatgctaagaacgggtaacaacttccagttcagctacgagtttgagaacgtacc tttccatagcagctacgtctcacagccaagcctggaccgactaatgaatccact catcgaccaatactgtactatctctcaagactattaacgggtcttgacagaatc aacaacgcataaaatcagtggtggccggaccagcaacatggctgtccaggg aagaactacatacctggaccagctaccgacaacaacgtgtctcaaccactg tgactcaaaacaacaacagcgaatttcttggcctggagcttcttcttgggtct caatggacgtaatagcttgatgaatcctggacctgctatggccagccacaaag aaggagaggaccgtttcttcttctgtctggtatcttatttttgcaacaaggaa ctggaagagacaacgtggatgcggacaagtcataaacaacgaagaag aaattaaaactactaaccggtagcaacggagtcctatggacaagtggccaca aaccaccagagtgcccaagcacaggcgcagaccggctgggttcaaaaccaa ggaatacttccgggtatggtttggcaggacagagatgtgtacctgcaaggacc catttggccaaaattcctcacaggacggcaacttccaccttctccgtgatg ggagggttggaaatgaagcaccgcctcctcagatcctcatcaaaaacacacc tgtacctgcggtatctccaacggccttcaacaaggacaagctgaactttcat	SEQ ID NO: 413

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Wild-type AAV-9 VP3 sequence	gtggcagataataacgaaggtgccgatggagtggttagttcctcgggaaattg gcattgcatcccaatggctggggacagagtcaccaccagcaccgga acctgggcccctgcccactacaacaatcacctctacaagcaaatctccaacag cacatctggaggatcttcaaatgacaacgcctacttcggctacagcaccctctg ggggtattttgacttcaacagattccactgccacttctcaccacgtgactggcag cgactcatcaacaacaactggggattccggcctaagcgactcaactcaagct cttcaacattcaggtcaagaggttacggacaacaatggagtaagaccatcg ccaataacctaccagcacgggtccaggtcttcacggactcagactatcagctcc cgtacgtgctcgggtcggctcacgagggtgctcccgccgttccagcggga cgttttcatgattcctcagtcagggtatctgacgcttaatgatgaagccaggcc gtgggtcgttctccttttactgcctggaatatttccgctcgcaaatgctaagaac gggtaacaacttccagttcagctacaggtttgagaacgtacctttccatagcag ctacgtcagcagccaagcctggaccgactaatgaatccactcatcgaccaat actgtactatctcctaagactattaacgggtctggacagaatcaacaacgct aaaattcagtggtggccggaccagcaacatggctgtccagggaagaaactac atacctggaccagctaccgacaacaacgtgtctcaaccactgtgactcaaaa caacaacagcgaatttgcctggcctggagcttcttctgggctcctaatggacgt aatagcttgatgaatcctggacctgctatggccagccacaaagaaggagagg accgtttcttcttctgtctggatcttatttttggcaacaaggaaactggaagag acaacgtggatgcggacaagtcataatacaacgaagaagaattaaac tactaaccggtagcaacggagtcctatggacaagtggccacaaccaccag agtggccaagcacaggcgacagaccggctgggtcaaaaccaagggaatacttc cgggtatggttggcaggacagagatgtgtacctgcaaggaccatttgggcc aaaattcctcacacggacggcaactttacccttctccgctgatgggagggttt ggaatgaagcaccgcctcctcagatcctcatcaaaaacacacctgtacctgc ggatcctccaacggccttcaacaaggacaagctgaacttttcatcaccagta tttactggccaagtcagcgtggagatcgagtgaggagctcagaaggaaaac agcaagcgtggaaacccggagatccagtacactccaactattacaagtcta aatgttgaafttgcgttaatactgaaggtgtatatagtgaacccgccccattgg caccagatacctgactcgtaatctg	SEQ ID NO: 414

[0052] In any of the DNA sequences referenced and/or described herein, the single letter symbol has the following description: A for adenine; C for cytosine; G for guanine; T for thymine; K for keto nucleotides such as guanine and thymine; and N is for any nucleotide (which is not a gap). The use of the NNK codon in site-saturation mutagenesis allows for coverage of codons for all 20 standard amino acids, including degenerate codons. “Degenerate codons” refers to codons differing in one or two nucleotides but coding for the same amino acid. For example, the amino acid Alanine may be encoded by the codons GCT, GCC, GCA or GCG and the amino acid Leucine may be encoded by the codons CTT, CTC, CTA, CTG, TTA and TTG.

[0053] In any of the amino acid sequences referenced and/or described herein, the single letter symbol has the following description: G (Gly) for Glycine; A (Ala) for Alanine; L (Leu) for Leucine; M (Met) for Methionine; F (Phe) for Phenylalanine; W (Trp) for Tryptophan; K (Lys) for Lysine; Q (Gln) for Glutamine; E (Glu) for Glutamic Acid; S (Ser) for Serine; P (Pro) for Proline; V (Val) for Valine; I (Ile) for Isoleucine; C (Cys) for Cysteine; Y (Tyr) for Tyrosine; H (His) for Histidine; R (Arg) for Arginine; N (Asn) for Asparagine; D (Asp) for Aspartic Acid; and T (Thr) for Threonine.

[0054] The modified AAVs provided herein may possess advantageous characteristics when used for research and/or therapeutic applications as a result of their enhanced tropism to an organ, tissue and/or cell type. For example, modified AAVs with enhanced tropism may be used at lower vector doses resulting reduced off-target toxicities. Modified AAVs with enhanced tropism may also allow for the regulation of anti-capsid immune responses, and may be used for therapeutic purposes, such as CRISPR delivery and gene augmentation therapy. Such targeting may enhance the specificity of AAVs to the desired cell types and improve the overall therapeutic effect. In yet another example, in the case of liver targeting, liver sinusoidal endothelial cells (LSECs) and hepatocytes and other cell types in the liver could be targeted, whereas in the case of brain targeting, neurons and astrocytes and other cell types in the brain could be targeted. Additionally, the LSEC targeting can reduce the induction of the immune responses to AAV capsid. The modified AAVs provided herein may also possess advantageous characteristics when used for research and/or therapeutic applications as a result of their reduced tropism to an organ, tissue and/or cell type. For example, the modified AAVs with reduced tropism could be used in therapy at lower vector doses because they are not sequestered in the liver, leading to reduced off-target toxicities. AAV dosage in therapy may be represented as the amount of vector genomes or viral genomes administered to a subject. For example, the dose may be specified as the amount of vector genomes per body weight (vg/kg) or amount of vector genomes per volume (vg/ml or vg/L) or vector genomes per animal (vg/animal). The therapeutically effective vector dose may be a range. For example, the effective dose per animal may be as low as 1×10^9 to as high as 1×10^{17} vg, depending on the route and site of administration.

[0055] In one example, provided herein is the modified AAV as described herein, wherein the 7-mer peptide sequence is selected from the sequences set forth in Table 1 or Table 7, and wherein the insertion increases specificity to cells selected from the group consisting of: liver sinusoidal endothelial cells, or hepatocytes, compared to a wild-type AAV without a 7-mer peptide sequence insertion.

- [0056] In another example, provided herein is the modified AAV as described herein, wherein the 7-mer peptide sequence is selected from the sequences set forth in Table 1, Table 2 or Table 3, and wherein the insertion increases specificity to cells selected from the group consisting of: neurons, or astrocytes, compared to a wild-type AAV without a 7-mer peptide sequence insertion.
- [0057] In another example, provided herein is the modified AAV as described herein, wherein the 7-mer peptide sequence is selected from the sequences set forth in Table 7, and wherein the insertion increases production of antigen-specific regulatory T cells compared to a wild-type AAV without a 7-mer peptide sequence insertion.
- [0059] In some examples, insertion of the 7-mer peptide sequence may reduce the induction of immune responses to the modified AAV capsid compared to a wild-type AAV without a 7-mer peptide sequence insertion.
- [0060] In other examples, insertion of the 7-mer peptide sequence may regulate anti-capsid immune response compared to a wild-type AAV without a 7-mer peptide sequence insertion.
- [0058] In yet another example, provided herein is the modified AAV as described herein, wherein the 7-mer peptide sequence is selected from the sequences set forth in Table 1, Table 2 or Table 3, and wherein the insertion improves therapeutic effect compared to a wild-type AAV without a 7-mer peptide sequence insertion. In some examples, the improvement in therapeutic effect may be reduction of off-target effects or the reduction of vector dose required for therapy. Off-target effects refer to effects in organs or tissues other than in the intended organ or tissue when an AAV is used in therapy.
- [0059] In one aspect, there is provided herein a composition comprising one or more of the modified AAV described herein. In one example, the composition is a pharmaceutical composition comprising one or more of the modified AAV described herein and a pharmaceutically acceptable excipient.
- [0060] In another aspect, there is provided a nucleic acid encoding the modified AAV as described herein.
- [0061] The modified AAV described herein may be produced using several methods known in the art. For example, the modified AAV may be produced via the use of a virus packaging cell, such as the HEK-293T cell line. It would be understood by those skilled in the art that one or more nucleic acid molecules comprising a nucleic acid sequence encoding the virus would be introduced into the packaging cell, which would then produce intact, infectious virus particles.
- [0062] The invention illustratively described herein may suitably be practiced in the absence of any element or elements, limitation or limitations, not specifically disclosed herein. Thus,

for example, the terms “comprising”, “including”, “containing”, etc. shall be read expansively and without limitation. Additionally, the terms and expressions employed herein have been used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the inventions embodied therein herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention.

[0063] The invention has been described broadly and generically herein. Each of the narrower species and subgeneric groupings falling within the generic disclosure also form part of the invention. This includes the generic description of the invention with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

[0064] Other embodiments are within the following claims and non-limiting examples. In addition, where features or aspects of the invention are described in terms of Markush groups, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group.

EXPERIMENTAL SECTION

[0065] Non-limiting examples of the invention and comparative examples will be further described in greater detail by reference to specific Examples, which should not be construed as in any way limiting the scope of the invention.

[0066] **Example 1: Construction of the NNK-based 7-mer peptide insertion library and vector production.**

[0067] AAV-DJ-based capsid libraries were generated by the insertion of random 7-mer peptide between amino acids 589 and 590. In order to generate a transcription-competent library for mRNA-driven directed evolution, the capsid gene is placed under the control of a ubiquitous promoter (cytomegalovirus “CMV” promoter) in tandem with Rep2 P40 promoter (starting at nucleotide #1700). The P40 sequence is required for capsid mRNA expression and splicing during AAV production. The sequence is itself flanked by inverted terminal repeats (ITR) so each variant will encapsulate its own capsid sequence (Figure 1).

- [0068] For cloning of capsid libraries, a 453-bp gBlock fragment of the wtAAV-DJ capsid was synthesized and used as a template to introduce the random 7-mer peptide library and overhangs for subcloning. PCR was performed for 15 cycles using Neb Q5 polymerase. The CMV promoter was amplified by PCR to introduce the *SwaI* restriction site and overhangs.
- 5 The resulting amplicons were purified via gel-extraction. The remaining fragments were synthesized as gBlocks. The different fragments were then assembled by Gibson assembly following manufacturer's instructions into the recipient ITR plasmid previously digested with *SphI* and *MfeI*. The gBlocks were synthesized by IDT.
- [0069] The full-length and unmodified Rep2 (Rep2-ΔCap, Figure 1) was provided in *trans* by a separate plasmid during vector production. The VP1 (M1L), VP2 (T138A), and VP3 (M205L, M211L, and M235L) were silenced and the plasmid was assembled by Gibson assembly using pRep2-Cap-DJ_M1L as a template and gBlock containing the AAV-DJ fragment with VP2/VP3 start codon mutations.
- 10 [0070] The diversity of the plasmid library was determined by the number of clones growing from a representative aliquot of transformed chemically competent DH5α bacteria. Library plasmids were harvested and purified using a maxi prep plasmid purification kit.
- [0071] Virus production was performed by triple transfection in HEK293T cells using 15 μg of helper plasmid, 10 μg of Rep2-Δcap plasmid and 1 μg of library DNA plasmid per T175 flask. 24 hours later, the medium was changed to a fresh culture medium containing 2%FBS.
- 20 Three days after transfection, cells were collected and resuspended in lysis buffer (Tris HCl pH 7.5 + 2 mM MgCl₂ + 150 mM NaCl) and lysed by three cycles of freezing/thawing. The supernatant was collected and treated with 50 U/ml of benzonase and 1 U/ml of Rnase cocktail for 30 min at 37°C to remove unpackaged nucleic acids. After incubation, the lysate was loaded on top of a discontinuous density gradient (15%, 25%, 40%, and 60%) and ultracentrifuged at
- 25 54,000 rpm, at 18 °C, for 1.5 hr, on a Type 70 Ti rotor. The 40% fraction was extracted and dialyzed with 1x PBS (pH 7.2) with 0.001% pluronic acid, using Amicon® Ultra-15 (100 kDa MWCO) filters. Primers and probes localizing to within the AAV2 ITR were used for the quantification of the viral titer by digital droplet PCR (ddPCR).
- [0072] **Example 2: *in vivo* library screening in mice**
- 30 [0073] AAV-DJ libraries were injected into C57BL/6 mice (male, *N* = 5) at a vector dose of 2.5 x10⁹ vg/mouse into the lateral tail vein. Animals were euthanized 28 days later, and the organs were harvested and stored at -80°C. Total RNA was extracted from different organs using the Rneasy® Plus mini kit. The sample was then enriched for mRNA using Oligo(dT)25 magnetic beads, and cDNA synthesis was performed using SuperScript™ IV reverse

transcriptase following the manufacturer’s instructions. Capsid DNA variants were amplified from cDNA for the generation of NGS amplicons. The amplicons were quantified using a fluorometer, pooled at an equimolar ratio, and sequenced on an iSeq™ sequencer. Following *in vivo* selection, more than 10,000 unique capsid variants were identified, with some showing superior transduction efficiency in the liver, brain, and skeletal muscle (Figure 2, A-C). Moreover, potential variants with enhanced brain-tropic or myotropic with complete liver de-targeting were also identified (Figure 3).

[0074] The altered tropism of the AAV variants compared to that of the reference AAV, that is, a wild-type AAV, was assessed by calculating transduction fold-change of the variant relative to the wild-type virus for a selected tissue type. First, a normalization factor was calculated by factoring the wild-type count in the original virus pool (that is, the library) by the wild-type count in a selected tissue (Normalisation factor (NF)= AAV_WT count in original virus pool / AAV_WT count in tissue). Next, a normalized variant count for each variant was obtained by multiplying each variant count in the selected tissue by the normalization factor of that tissue (Normalised AAV variant count = count AAV variant in tissue x NF Tissue). Finally, the transduction fold change of each variant was calculated by factoring the normalized variant count by the wild-type count in the original virus pool (Transduction fold-change (FC) = Normalised AAV variant count /AAV wt count in original virus pool). The counts, normalized counts and transduction fold change in each selected tissue for each variant relative to wild-type AAV can be found in Tables 5 and 6. In said tables, a count of “-” indicates that the variant was not detected in that tissue sample. The amino acids “N” and “R” at the beginning and end of each sequence respectively denote N589 and R590 of the wild-type AAV-DJ capsid, between which the 7-mer peptide is inserted.

Table 5. Fold-change analysis of AAV variants in brain, muscle and liver

prod_variant	prod_count	brain_count	muscle_count	liver_count	Norm_brain_count	Norm_muscle_count	Norm_liver_count
NR (WT)	38245	178454	126872	549936	38245.00	38245.00	38245.00
NSLKIQGSR	58931	2123	3228	1122	454.99	973.07	78.03
NLINLKRER	41690	1758	1708	1051	376.76	514.87	73.09
NTRVGGSER	40865	2404	3280	1765	515.21	988.74	122.75
NSCNYTTVR	23081	2932	3249	1985	628.37	979.40	138.05
NKLMDSNNR	22891	2120	2899	2214	454.34	873.89	153.97
NTSTTPSKR	20250	1443	2016	1114	309.25	607.71	77.47
NSDTYLGRR	15440	887	1198	737	190.10	361.13	51.25
NILNAAGAR	14878	1009	1732	558	216.24	522.10	38.81
NIAGSETMR	14472	1393	1306	1115	298.54	393.69	77.54
NVTPNQTYR	14220	1407	2023	72	301.54	609.82	5.01

NCLFSDHCR	14155	2639	2910	1670	565.57	877.21	116.14
NLVGPGYVR	14126	1350	1961	959	289.32	591.13	66.69
NLYTNELDR	13941	2566	3074	1451	549.93	926.64	100.91
NFKSQLNCR	13317	1788	2401	1533	383.19	723.77	106.61
NLLDDHVWR	9483	969	1263	794	207.67	380.73	55.22
NGAFKHLMR	9437	814	1141	627	174.45	343.95	43.60
NGYREGFSR	8111	795	893	203	170.38	269.19	14.12
NVSKFDDVR	8033	1052	1071	282	225.46	322.85	19.61
NMAVVC AVR	7911	3632	5013	2243	778.38	1511.15	155.99
NMVVWVTDR	6432	3143	4167	1679	673.59	1256.12	116.77
NCYRFQEV R	6273	2357	3312	1530	505.14	998.39	106.40
NIKGLIELR	5518	477	651	164	102.23	196.24	11.41
NSIFTKKYR	5094	2863	3071	1549	613.58	925.74	107.72
NRKVFIDSR	5065	4112	4646	3363	881.25	1400.52	233.88
NLASCSEGR	4859	801	923	183	171.66	278.23	12.73
NATYYNHVR	4800	437	579	1052	93.65	174.54	73.16
NSVVVGLCR	4626	1030	1070	621	220.74	322.55	43.19
NCKLFDLDR	4526	2900	3873	2964	621.51	1167.50	206.13
NILHKGQR	4486	2517	3219	1371	539.43	970.35	95.35
NDTATIDSR	4350	4517	4993	2328	968.05	1505.12	161.90
NRSVGGICR	4179	351	655	338	75.22	197.45	23.51
NVFMELYAR	4166	164	130	281	35.15	39.19	19.54
NLDDNVLDR	4111	3022	3602	711	647.65	1085.81	49.45
NWIIQQRVR	4107	2871	3342	1628	615.29	1007.43	113.22
NRVSYWFLR	3980	2161	2947	817	463.13	888.36	56.82
NDCAVYGGR	3962	1341	1620	553	287.39	488.34	38.46
NSSYPYMSR	3959	2000	2377	990	428.63	716.54	68.85
NATIYNSYR	3936	2165	3011	2024	463.99	907.65	140.76
NVAHCREVR	3919	3232	3556	1876	692.66	1071.94	130.47
NDNYVLISR	3850	3583	3917	1466	767.88	1180.76	101.95
NYWYHKCLR	3790	2417	2931	2128	517.99	883.54	147.99
NHCFYGSR	3570	2560	2786	1960	548.64	839.83	136.31
NRFWTWSNR	3513	3982	5010	2037	853.39	1510.24	141.66
NIMRYLT YR	3507	2817	3683	1542	603.72	1110.22	107.24
NISCCWDIR	3385	2095	2443	1004	448.99	736.43	69.82
NGYEFSTR	3296	2272	2942	1102	486.92	886.85	76.64
NCYCDLLTR	3282	2737	3066	1109	586.57	924.23	77.12
NTFVCGQAR	3186	1916	2440	394	410.62	735.53	27.40
NVYGPWIER	3172	2993	3423	2378	641.44	1031.85	165.38
NSPPGLVDR	3144	3622	4361	1066	776.24	1314.60	74.13
NRFTVRSMR	3141	2169	2703	200	464.84	814.81	13.91
NVSLVG HAR	3059	2516	3100	1122	539.21	934.48	78.03
NCSLLTRHR	3052	2009	2460	750	430.55	741.56	52.16
NEAYLYQER	3051	2773	3752	1339	594.29	1131.02	93.12
NCLLQVPYR	3044	1261	1493	580	270.25	450.06	40.34

NYVVRSLR	3037	2134	2401	966	457.34	723.77	67.18
NNSYRFVRR	3002	2153	2382	1577	461.42	718.04	109.67
NNIYVLKSR	2951	1901	1872	760	407.41	564.31	52.85
NYDKRSHQR	2917	2349	2693	1287	503.42	811.79	89.50
NLSSLFWLR	2870	1826	2546	1295	391.34	767.48	90.06
NKLFFCYMR	2816	1381	1455	1235	295.97	438.60	85.89
NNNVLLRR	2799	1963	2180	462	420.70	657.15	32.13
NEAVLTCVR	2774	2343	2249	787	502.14	677.95	54.73
NRKRGVGLR	2749	1521	1965	851	325.97	592.34	59.18
NKLYIEGIR	2731	1684	1771	1003	360.90	533.86	69.75
NSGLSTFYR	2666	1359	1501	806	291.25	452.47	56.05
NRCFGCLCR	2665	1679	2538	1394	359.83	765.07	96.94
NGTATYNCR	2650	2752	3881	1538	589.79	1169.91	106.96
NCNCLWDCR	2619	3006	3370	1128	644.22	1015.87	78.45
NYRGKHGNR	2618	1793	2218	928	384.26	668.61	64.54
NYLYYLSSR	2614	1233	1642	760	264.25	494.97	52.85
NRDWTYNAR	2596	1564	1910	686	335.19	575.76	47.71
NDFSVESDR	2595	1638	1635	543	351.04	492.86	37.76
NMCYQGPKR	2576	1212	1194	164	259.75	359.93	11.41
NLEIRINDR	2572	1893	2331	1095	405.69	702.67	76.15
NSFHHWMGR	2542	2139	2658	1844	458.42	801.24	128.24
NNVCSGLVR	2524	1517	1794	116	325.11	540.79	8.07
NLTGGFRLR	2477	889	1456	339	190.52	438.90	23.58
NIGFTGEHR	2460	257	349	344	55.08	105.20	23.92
NLDRDVDRR	2449	1455	2102	870	311.83	633.64	60.50
NPFSDGWCR	2440	1521	1773	1468	325.97	534.46	102.09
NVYVVIVDR	2430	1653	1903	1124	354.26	573.65	78.17
NVIDIDNGR	2410	1735	1986	1159	371.83	598.67	80.60
NVSMQGELR	2382	2912	3595	1603	624.08	1083.70	111.48
NNFSLHYR	2354	2335	2551	1563	500.42	768.99	108.70
NSVSMFWCR	2328	1301	1756	406	278.82	529.34	28.24
NLVALCDCR	2312	1927	2192	502	412.98	660.77	34.91
NMATSRITR	2311	2347	3009	1764	502.99	907.05	122.68
NDIMWITCR	2271	1709	1911	568	366.26	576.06	39.50
NATTRLPYR	2259	3383	3349	2839	725.02	1009.54	197.44
NVSTLYLLR	2257	1579	1769	542	338.40	533.26	37.69
NVIMKIAGR	2253	3090	3351	1325	662.23	1010.14	92.15
NMWLYWRRR	2202	1969	2628	1166	421.98	792.20	81.09
NNMCTIHSR	2191	1221	1527	797	261.68	460.31	55.43
NSSGHLKFR	2175	1221	1276	1026	261.68	384.64	71.35
NCITLHCAR	2156	1396	1747	622	299.18	526.63	43.26
NVRFRSAGR	2105	1538	2186	1472	329.61	658.96	102.37
NIAFDGTTR	2063	1888	2237	635	404.62	674.33	44.16
NCVYFLSPR	2062	1675	2018	1315	358.97	608.32	91.45
NCFNMLINR	2062	1256	1590	797	269.18	479.30	55.43

NSFLLGGAR	2055	1932	2268	257	414.05	683.68	17.87
NTRVRNVYR	2019	2562	2773	908	549.07	835.91	63.15
NLDNLHsvR	1976	1580	1637	1522	338.61	493.47	105.85
NKCMLRQRR	1965	1509	1853	1154	323.40	558.58	80.25
NSAMWVIPR	1961	1224	1111	760	262.32	334.91	52.85
NSCQLLLR	1958	1695	2086	548	363.26	628.82	38.11
NFDYVLHKR	1939	2328	2343	1645	498.92	706.29	114.40
NGSSACTSR	1928	3515	4999	1446	753.31	1506.93	100.56
NFWMYDPRR	1883	2290	2487	1379	490.78	749.70	95.90
NWYKFRPLR	1882	2232	3104	993	478.35	935.69	69.06
NFWKGLAYR	1875	677	897	815	145.09	270.40	56.68
NYELGSIGR	1857	940	1105	517	201.45	333.10	35.95
NVSICDLVR	1843	3102	4075	1751	664.80	1228.39	121.77
NYVCMDHLR	1842	1876	1838	516	402.05	554.06	35.88
NNEMTSFSR	1842	1444	1795	2	309.47	541.09	0.14
NCYNAVGFRR	1827	399	496	536	85.51	149.52	37.28
NMGCELRRR	1811	2861	3140	1006	613.15	946.54	69.96
NIVDCLCRR	1809	1080	1914	425	231.46	576.97	29.56
NSLCARRKR	1807	1332	1574	629	285.46	474.48	43.74
NVASNALSR	1779	1754	2261	448	375.90	681.57	31.16
NHFTSLFAR	1768	1749	2101	1152	374.83	633.34	80.12
NLTFAEATR	1742	1812	1861	188	388.34	560.99	13.07
NLSCCSDRR	1701	772	988	335	165.45	297.83	23.30
NTCQFRGVR	1694	2582	2597	711	553.36	782.85	49.45
NVMYGWDSR	1671	1774	2213	921	380.19	667.10	64.05
NTLLIGLLR	1652	937	1254	521	200.81	378.01	36.23
NIVLVLRFR	1643	995	1439	594	213.24	433.78	41.31
NDLIIWIAR	1614	3119	3623	2261	668.44	1092.14	157.24
NYFPGRCTR	1603	1489	2152	1350	319.11	648.71	93.89
NELCLWETR	1602	2355	3253	1244	504.71	980.60	86.51
NTRYAGLSR	1596	1206	1567	1227	258.46	472.37	85.33
NFKGLVSVR	1586	1150	1252	355	246.46	377.41	24.69
NMPNSSTCR	1571	924	1200	619	198.03	361.73	43.05
NFTFWHLR	1570	1415	1317	669	303.25	397.00	46.53
NNSFITSIR	1567	2341	2388	1590	501.71	719.85	110.58
NVIVERELR	1562	1101	1252	169	235.96	377.41	11.75
NTMYRQCCR	1524	398	531	480	85.30	160.07	33.38
NVTAWFGFR	1510	3893	4400	3079	834.32	1326.36	214.13
NSYGHRLLR	1509	2644	3387	783	566.64	1021.00	54.45
NQICCYIFR	1506	929	1096	439	199.10	330.38	30.53
NTFGFSGGR	1505	1598	1849	771	342.47	557.37	53.62
NCLEMCILR	1504	1620	1732	1176	347.19	522.10	81.78
NAGSRSEVR	1502	3023	3866	1187	647.87	1165.39	82.55
NALVCMLFR	1493	1143	1489	418	244.96	448.85	29.07
NWTGVSPER	1491	1385	1522	1807	296.82	458.80	125.67

NSNERATNR	1488	953	1206	190	204.24	363.54	13.21
NTDLSLASR	1475	1370	1765	718	293.61	532.05	49.93
NDRCYRGAR	1463	777	1153	615	166.52	347.57	42.77
NSNLLLGIR	1458	713	1127	594	152.81	339.73	41.31
NLVRTRTIR	1458	936	1123	183	200.60	338.52	12.73
NFPSNHKIR	1448	768	900	887	164.59	271.30	61.69
NRAKDAWVR	1440	1409	1956	820	301.97	589.63	57.03
NMLIVILVR	1439	784	714	646	168.02	215.23	44.93
NLYNTSWWR	1438	828	860	292	177.45	259.24	20.31
NFEHSGAVR	1412	347	283	-	74.37	85.31	0.00
NDRMAWYNR	1407	1588	1926	763	340.33	580.58	53.06
NPMRSYTLR	1388	1302	1631	1364	279.04	491.66	94.86
NFTVWYMKR	1382	1051	868	232	225.24	261.65	16.13
NGTVYRESR	1380	1654	2016	897	354.47	607.71	62.38
NNREAPPVR	1375	30	126	-	6.43	37.98	0.00
NVVVSFMWR	1355	1007	1438	198	215.81	433.48	13.77
NITQRTIWR	1350	1349	1566	468	289.11	472.06	32.55
NFDSVKTLR	1349	971	984	381	208.10	296.62	26.50
NTIWKTILR	1331	689	771	147	147.66	232.41	10.22
NLNLVGVFR	1326	558	846	316	119.59	255.02	21.98
NFYDKSDGR	1289	767	888	1095	164.38	267.68	76.15
NCCMWWLCR	1280	729	775	170	156.23	233.62	11.82
NLILYISPR	1268	1545	1538	1209	331.11	463.62	84.08
NRTSTDHVR	1267	1401	1636	505	300.25	493.16	35.12
NTHRSYLMR	1258	2735	3069	1271	586.15	925.14	88.39
NFYFNMIIR	1257	712	978	530	152.59	294.81	36.86
NKTVVDNTR	1248	1253	1474	1044	268.53	444.33	72.60
NISLLFIHR	1238	657	1138	578	140.80	343.05	40.20
NCCLEWIIR	1232	438	851	350	93.87	256.53	24.34
NESFTLYQR	1226	1014	1116	908	217.31	336.41	63.15
NCWNLLGCR	1223	665	689	156	142.52	207.70	10.85
NLITTLRMR	1218	1379	1983	714	295.54	597.77	49.65
NDCDGLLMR	1191	824	915	78	176.59	275.82	5.42
NVFPLPWVR	1185	844	1089	960	180.88	328.27	66.76
NKRQVLMTR	1173	1041	1007	384	223.10	303.56	26.71
NFGISVYRR	1145	670	758	299	143.59	228.50	20.79
NLVNICAGR	1140	1887	2464	380	404.41	742.76	26.43
NGRFWNVER	1126	1538	1695	639	329.61	510.95	44.44
NPFCMSRFR	1115	1228	1441	842	263.18	434.38	58.56
NWGMGHANR	1115	628	850	355	134.59	256.23	24.69
NSITGALPR	1079	1346	1493	498	288.47	450.06	34.63
NANYDYDRR	1074	416	564	27	89.15	170.02	1.88
NSFCQCLFR	1074	632	651	515	135.45	196.24	35.82
NGLHYHHSR	1074	541	617	166	115.94	185.99	11.54
NYALYFRSR	1072	753	893	658	161.38	269.19	45.76

NRFMCKVGR	1067	521	705	-	111.66	212.52	0.00
NALFCYLIR	1065	1002	1464	688	214.74	441.32	47.85
NSSGGGVCR	1065	631	748	152	135.23	225.48	10.57
NNFLNGVNR	1061	970	1172	644	207.88	353.29	44.79
NNCIFLCKR	1058	435	529	333	93.23	159.46	23.16
NVSKMQYAR	1057	774	724	524	165.88	218.25	36.44
NVFSVMMHR	1046	2147	2484	480	460.13	748.79	33.38
NDLQSNVNR	1030	717	1109	239	153.66	334.30	16.62
NPLRSLCFR	1023	685	826	923	146.80	248.99	64.19
NEECTLTIR	1015	2120	2443	2246	454.34	736.43	156.20
NFFIVDSCR	1013	825	855	824	176.81	257.74	57.30
NIPCFQVSR	999	923	1302	587	197.81	392.48	40.82
NGVMRPQYR	999	777	1154	179	166.52	347.87	12.45
NARVGNMGR	986	2341	2857	703	501.71	861.23	48.89
NIGRWTVGR	978	1978	2419	1031	423.91	729.20	71.70
NWMSRMAIR	977	1016	1225	696	217.74	369.27	48.40
NYRILGVRR	975	1657	1727	1140	355.12	520.60	79.28
NYTARGLKR	974	665	860	382	142.52	259.24	26.57
NSYRAKRGR	955	572	743	-	122.59	223.97	0.00
NFGFCGWRR	954	1820	1414	1668	390.05	426.24	116.00
NGWSYWIQR	951	648	910	364	138.87	274.32	25.31
NLYGYRLER	946	544	630	343	116.59	189.91	23.85
NPFLVELSR	923	960	1104	177	205.74	332.80	12.31
NLVQRGPVR	918	641	727	8	137.37	219.15	0.56
NSYIQVSWR	908	1410	1613	789	302.18	486.23	54.87
NSKSRVSCR	904	1543	1929	511	330.68	581.49	35.54
NASSYPSLR	903	622	897	357	133.30	270.40	24.83
NWFSTQCSR	866	1681	1936	379	360.26	583.60	26.36
NINCLHVDR	863	680	809	319	145.73	243.87	22.18
NMLTSLLR	851	536	601	514	114.87	181.17	35.75
NTTCKTLAR	848	769	1172	855	164.81	353.29	59.46
NSLFVKFQR	840	480	507	150	102.87	152.83	10.43
NELYFMFVR	839	600	646	352	128.59	194.73	24.48
NSLIRAHWR	836	393	479	246	84.22	144.39	17.11
NGEGRSRMR	822	992	1240	439	212.60	373.79	30.53
NRVKWRFRGR	813	1364	1378	549	292.32	415.39	38.18
NFMTYPLYR	807	1028	1192	762	220.31	359.32	52.99
NLSRGFLWR	804	711	775	706	152.38	233.62	49.10
NVRTIFLVR	800	1407	1521	1111	301.54	458.50	77.26
NGVKVRAVR	798	822	1163	791	176.17	350.58	55.01
NCLIWVIR	787	556	552	314	119.16	166.40	21.84
NGMLCKTSR	782	509	505	189	109.09	152.23	13.14
NSYMINFER	782	359	463	78	76.94	139.57	5.42
NQVGDLRER	772	660	830	364	141.45	250.20	25.31
NPSDCSILR	757	603	530	207	129.23	159.77	14.40

NCDAFYVER	757	422	681	373	90.44	205.28	25.94
NYSMCRAYR	741	479	433	150	102.66	130.53	10.43
NESSCTSTR	730	496	703	422	106.30	211.92	29.35
NGPKGLPDR	724	1427	1470	1049	305.82	443.12	72.95
NFYKATWR	723	191	318	142	40.93	95.86	9.88
NNLKFTVRR	711	731	656	725	156.66	197.75	50.42
NQLLVPLGR	697	460	619	-	98.58	186.59	0.00
NRNKFVLR	696	286	368	129	61.29	110.93	8.97
NWKHHYFR	695	2608	2435	2533	558.93	734.02	176.16
NRGMYWLR	695	899	1142	-	192.67	344.25	0.00
NSFVAFGYR	677	241	355	774	51.65	107.01	53.83
NWVFLVDSR	667	1121	1471	164	240.24	443.43	11.41
NLYEHNMDR	658	407	476	271	87.23	143.49	18.85
NRRSRYHRR	654	970	1577	691	207.88	475.38	48.06
NSFLMWKCR	653	751	763	404	160.95	230.00	28.10
NDIKSTFFR	652	75	148	139	16.07	44.61	9.67
NYDSMYTDR	650	1312	1661	483	281.18	500.70	33.59
NVFYLVYWR	639	1585	1862	353	339.69	561.29	24.55
NPRDFTWVR	638	3501	3337	1703	750.31	1005.92	118.43
NDLSLTCSR	637	491	407	343	105.23	122.69	23.85
NSNCIVSLR	632	944	993	1036	202.31	299.34	72.05
NKIRVRINR	626	988	1399	462	211.74	421.72	32.13
NVLWSWFMR	625	670	621	236	143.59	187.20	16.41
NCVSEPKGR	621	1687	2040	1389	361.55	614.95	96.60
NILVCLVLR	619	1898	1922	577	406.77	579.38	40.13
NTDSKWSLR	617	287	401	166	61.51	120.88	11.54
NTFWSRIFR	608	616	510	363	132.02	153.74	25.24
NHCISLRLR	608	348	333	336	74.58	100.38	23.37
NDLWCKRLR	604	1273	1919	735	272.82	578.47	51.12
NYRLFLRLR	603	811	875	498	173.81	263.76	34.63
NSIIVMRVR	599	900	1050	458	192.88	316.52	31.85
NHIMDLSSR	592	648	644	173	138.87	194.13	12.03
NFIFPVNFR	590	265	317	436	56.79	95.56	30.32
NLDWVLIPR	582	496	518	-	106.30	156.15	0.00
NLLTMHRRR	579	506	898	-	108.44	270.70	0.00
NRHSWLFDR	573	322	481	-	69.01	145.00	0.00
NRSETWFR	571	1266	1285	188	271.32	387.36	13.07
NVLYTFICR	571	138	381	426	29.58	114.85	29.63
NICLSYKFR	554	781	960	231	167.38	289.39	16.06
NLNCLVNHR	551	254	309	169	54.44	93.15	11.75
NYIWRQLIR	550	312	350	-	66.87	105.51	0.00
NNNHGFSIR	546	628	629	-	134.59	189.61	0.00
NNACFVLGR	542	694	916	1096	148.73	276.12	76.22
NWHLLCLDR	539	1489	1775	443	319.11	535.07	30.81
NQLVLLKLR	534	126	196	131	27.00	59.08	9.11

NHMTASGR	528	1060	1255	351	227.17	378.31	24.41
NACVSSRTR	524	690	1110	559	147.88	334.60	38.88
NSRQYLKRR	520	859	702	565	184.09	211.61	39.29
NNHVYPYCR	517	297	353	359	63.65	106.41	24.97
NVLYILVHR	509	372	359	-	79.72	108.22	0.00
NFIECLLLR	507	1904	2191	372	408.05	660.47	25.87
NGYCMYCDR	503	1506	1503	374	322.76	453.07	26.01
NCQVMTVWR	500	234	404	-	50.15	121.78	0.00
NLVLYYGIR	494	194	162	156	41.58	48.83	10.85
NSLPFPAIR	493	273	332	171	58.51	100.08	11.89
NSPNLMGR	490	430	351	2	92.15	105.81	0.14
NSYILISYR	489	3126	3035	2151	669.94	914.89	149.59
NSNCYRSKR	482	179	327	153	38.36	98.57	10.64
NHTVGLMGR	478	264	422	189	56.58	127.21	13.14
NSTFLHDQR	473	465	324	184	99.66	97.67	12.80
NNRVCVYPR	469	687	794	188	147.23	239.35	13.07
NWVLRTSRR	468	2128	2647	1338	456.06	797.93	93.05
NLVNCTWNR	468	324	512	143	69.44	154.34	9.94
NCQLLGRER	467	442	327	-	94.73	98.57	0.00
NIQRYLLR	465	529	806	535	113.37	242.97	37.21
NCVRWGCIR	464	1581	1962	808	338.83	591.44	56.19
NIVNLYGMR	447	153	321	519	32.79	96.76	36.09
NDNQICRRR	438	1121	1181	488	240.24	356.01	33.94
NLRCRWFR	436	439	380	127	94.08	114.55	8.83
NATCTVSFR	435	434	444	208	93.01	133.84	14.47
NSSEVNCSR	434	106	245	161	22.72	73.85	11.20
NRLSLGPCR	426	695	688	1238	148.95	207.39	86.10
NMFCQSLTR	416	849	630	398	181.95	189.91	27.68
NTVIVLIK	414	454	465	318	97.30	140.17	22.12
NTDKTCSVR	414	111	244	-	23.79	73.55	0.00
NFMYVSKIR	408	1131	1202	473	242.39	362.34	32.89
NYGGFFGIR	403	461	519	609	98.80	156.45	42.35
NLERGDTVR	401	539	777	159	115.51	234.22	11.06
NMNCWEVGR	399	377	561	359	80.80	169.11	24.97
NVRSQDVFR	398	52	307	189	11.14	92.54	13.14
NVYDCMNSR	394	579	858	614	124.09	258.64	42.70
NSFFGETSR	384	246	328	-	52.72	98.87	0.00
NSKSCVVS	383	164	220	-	35.15	66.32	0.00
NVSDLVVKR	372	462	619	189	99.01	186.59	13.14
NKLCLVYVR	370	297	544	206	63.65	163.99	14.33
NLVIRPSNR	361	257	334	135	55.08	100.68	9.39
NFQVLFGR	360	1334	1713	771	285.89	516.38	53.62
NHELRFVNR	358	144	202	-	30.86	60.89	0.00
NENYHMSR	358	739	1117	594	158.38	336.71	41.31
NIYFLSFTR	358	214	188	-	45.86	56.67	0.00

NEVCWCLLR	342	211	266	-	45.22	80.18	0.00
NETLGNHIR	336	96	229	211	20.57	69.03	14.67
NSILHPER	322	634	819	285	135.87	246.88	19.82
NIFHIGAYR	320	164	185	198	35.15	55.77	13.77
NYRDLIYKR	316	331	508	542	70.94	153.13	37.69
NYWEVHWLR	315	1751	2272	1051	375.26	684.88	73.09
NKESVWELR	304	595	680	2	127.52	204.98	0.14
NNMTNTWPR	296	68	178	203	14.57	53.66	14.12
NLYNLWQFR	295	2004	2078	742	429.48	626.40	51.60
NLSLGFQFR	295	1883	2116	605	403.55	637.86	42.07
NMIHASDDR	286	572	433	-	122.59	130.53	0.00
NEVVCGRLR	281	866	1054	545	185.59	317.72	37.90
NMFARTALR	278	417	228	-	89.37	68.73	0.00
NFARWILCR	278	1230	1781	1948	263.60	536.87	135.47
NPFSSYLER	277	98	101	328	21.00	30.45	22.81
NSSWYAPSR	275	1481	1612	508	317.40	485.93	35.33
NHSRGDGRR	274	160	147	-	34.29	44.31	0.00
NTMVIRGIR	273	474	817	430	101.58	246.28	29.90
NLIGPGYSR	266	1010	1439	302	216.46	433.78	21.00
NSSKYTLPR	260	265	341	213	56.79	102.79	14.81
NNSFFMLFR	257	797	1045	725	170.81	315.01	50.42
NSDMDHWWR	254	242	223	-	51.86	67.22	0.00
NGYLDLSDR	250	522	539	159	111.87	162.48	11.06
NEPVLNR	246	144	114	18	30.86	34.36	1.25
NEFTHQRT	243	82	274	-	17.57	82.60	0.00
NFVYSSRYR	242	107	115	-	22.93	34.67	0.00
NKVTRTVSR	233	203	212	205	43.51	63.91	14.26
NPNSYLSNR	229	260	432	182	55.72	130.22	12.66
NGLRERFGR	225	257	206	-	55.08	62.10	0.00
NHEKGLYMR	223	165	195	156	35.36	58.78	10.85
NDRVMISVR	218	264	265	151	56.58	79.88	10.50
NMLFSILFR	208	480	700	174	102.87	211.01	12.10
NECTWGRNR	205	228	216	-	48.86	65.11	0.00
NMGCRGPLR	204	416	445	180	89.15	134.14	12.52
NYARREGR	191	321	377	-	68.79	113.64	0.00
NRLVDIRTR	190	164	188	-	35.15	56.67	0.00
NSMLLCYLR	187	706	1041	402	151.30	313.80	27.96
NLSRSKGYR	183	628	558	-	134.59	168.21	0.00
NLVASMLVR	181	226	149	-	48.43	44.92	0.00
NPYCLDFHR	170	352	330	153	75.44	99.48	10.64
NHVWGVYNR	166	54	56	-	11.57	16.88	0.00
NTSMTLNR	164	425	537	146	91.08	161.88	10.15
NFSGDFNGR	163	147	124	-	31.50	37.38	0.00
NPCQDFNR	156	73	87	-	15.64	26.23	0.00
NVFMAETIR	152	1697	2017	646	363.69	608.02	44.93

NYLGYAWGR	152	14	26	-	3.00	7.84	0.00
NSFQCLAAR	146	212	240	141	45.43	72.35	9.81
NSYYFLAFR	144	36	116	-	7.72	34.97	0.00
NTMKRGTVR	140	112	136	2	24.00	41.00	0.14
NKIYTVFDR	136	464	397	392	99.44	119.67	27.26
NIWTVTGIR	129	166	170	-	35.58	51.25	0.00
NCVSIWRR	128	171	147	-	36.65	44.31	0.00
NEQMNFLRR	120	132	67	131	28.29	20.20	9.11
NALRAKECR	115	266	457	-	57.01	137.76	0.00
NWLTWLLGR	111	837	1177	-	179.38	354.80	0.00
NYSNCEQCR	110	66	125	-	14.14	37.68	0.00
NSCNYSTVR	110	5	13	10	1.07	3.92	0.70
NYRVFVVVR	109	947	1131	159	202.95	340.93	11.06
NCIVFQILR	108	2599	2703	1388	557.00	814.81	96.53
NLICMLYQR	103	120	151	169	25.72	45.52	11.75
NTWVGGSER	101	1	2	1	0.21	0.60	0.07
NHINFRGTR	101	179	145	226	38.36	43.71	15.72

Table 5 (continued). Fold-change analysis of AAV variants in brain, muscle and liver

prod_variant	Norm_liver_count	FC_Brain	FC_muscle	FC_liver
NR (WT)	38245.00	1.00	1.00	1.00
NSLKIQGSR	78.03	0.01	0.02	0.00
NLINLKRRR	73.09	0.01	0.01	0.00
NTRVGGSER	122.75	0.01	0.02	0.00
NSCNYTTVR	138.05	0.03	0.04	0.01
NKLMDNNR	153.97	0.02	0.04	0.01
NTSTTPSKR	77.47	0.02	0.03	0.00
NSDTYLGRR	51.25	0.01	0.02	0.00
NILNAAGAR	38.81	0.01	0.04	0.00
NIAGSETMR	77.54	0.02	0.03	0.01
NVTPNQTYR	5.01	0.02	0.04	0.00
NCLFSHDCR	116.14	0.04	0.06	0.01
NLVGPGYVR	66.69	0.02	0.04	0.00
NLYTNELDR	100.91	0.04	0.07	0.01
NFKSQLNCR	106.61	0.03	0.05	0.01
NLLDDHVWR	55.22	0.02	0.04	0.01
NGAFKHLMR	43.60	0.02	0.04	0.00
NGYREGFSR	14.12	0.02	0.03	0.00
NVSKFDDVR	19.61	0.03	0.04	0.00
NMAVVCAVR	155.99	0.10	0.19	0.02
NMVVWVTDR	116.77	0.10	0.20	0.02
NCYRFQEV	106.40	0.08	0.16	0.02
NIKGLIELR	11.41	0.02	0.04	0.00

NSIITKKYR	107.72	0.12	0.18	0.02
NRKVFIDSR	233.88	0.17	0.28	0.05
NLASCSGER	12.73	0.04	0.06	0.00
NATYYNHVR	73.16	0.02	0.04	0.02
NSVVVGLCR	43.19	0.05	0.07	0.01
NCKLFDLDR	206.13	0.14	0.26	0.05
NILHKRGQR	95.35	0.12	0.22	0.02
NDTATIDSR	161.90	0.22	0.35	0.04
NRSVGGICR	23.51	0.02	0.05	0.01
NVFMELYAR	19.54	0.01	0.01	0.00
NLDDNVLDR	49.45	0.16	0.26	0.01
NWIIQQRVR	113.22	0.15	0.25	0.03
NRVSYWFLR	56.82	0.12	0.22	0.01
NDCAVYGGR	38.46	0.07	0.12	0.01
NSSYPYMSR	68.85	0.11	0.18	0.02
NATTYSYR	140.76	0.12	0.23	0.04
NVAHCREVR	130.47	0.18	0.27	0.03
NDNYVLTSR	101.95	0.20	0.31	0.03
NYWYHKCLR	147.99	0.14	0.23	0.04
NHCFYGSR	136.31	0.15	0.24	0.04
NRFWTWSNR	141.66	0.24	0.43	0.04
NIMRYLTYR	107.24	0.17	0.32	0.03
NISCCWDIR	69.82	0.13	0.22	0.02
NGYFEGSTR	76.64	0.15	0.27	0.02
NCYCDLLTR	77.12	0.18	0.28	0.02
NTFVCGQAR	27.40	0.13	0.23	0.01
NVYGPWIER	165.38	0.20	0.33	0.05
NSPPGLVDR	74.13	0.25	0.42	0.02
NRFTVRSMR	13.91	0.15	0.26	0.00
NVSLVG HAR	78.03	0.18	0.31	0.03
NCSLLTRHR	52.16	0.14	0.24	0.02
NEAYLYQER	93.12	0.19	0.37	0.03
NCLLQVPYR	40.34	0.09	0.15	0.01
NYVVRSLR	67.18	0.15	0.24	0.02
NNSYRFVRR	109.67	0.15	0.24	0.04
NNIYVLKSR	52.85	0.14	0.19	0.02
NYDKRSHQR	89.50	0.17	0.28	0.03
NLSSLFWLR	90.06	0.14	0.27	0.03
NKLFFCYMR	85.89	0.11	0.16	0.03
NNNVLLRR	32.13	0.15	0.23	0.01
NEAVLTCVR	54.73	0.18	0.24	0.02
NRKRGVGLR	59.18	0.12	0.22	0.02
NKLYIEGIR	69.75	0.13	0.20	0.03
NSGLSTFYR	56.05	0.11	0.17	0.02
NRCFGCLCR	96.94	0.14	0.29	0.04

NGTATYNCR	106.96	0.22	0.44	0.04
NCNCLWDCR	78.45	0.25	0.39	0.03
NYRGKHGNR	64.54	0.15	0.26	0.02
NYLYYLSSR	52.85	0.10	0.19	0.02
NRDWFYNAR	47.71	0.13	0.22	0.02
NDFSVESDR	37.76	0.14	0.19	0.01
NMCYQGPKR	11.41	0.10	0.14	0.00
NLEIRINDR	76.15	0.16	0.27	0.03
NSFHHWMGR	128.24	0.18	0.32	0.05
NNVCSGLVR	8.07	0.13	0.21	0.00
NLTGGFRLR	23.58	0.08	0.18	0.01
NIGFTGEHR	23.92	0.02	0.04	0.01
NLDRDVDRR	60.50	0.13	0.26	0.02
NPFSDGWCR	102.09	0.13	0.22	0.04
NVYVVIVDR	78.17	0.15	0.24	0.03
NVIDIDNGR	80.60	0.15	0.25	0.03
NVSMQGELR	111.48	0.26	0.45	0.05
NNFSCLHYR	108.70	0.21	0.33	0.05
NSVSMFWCR	28.24	0.12	0.23	0.01
NLVALCDCR	34.91	0.18	0.29	0.02
NMATSRITR	122.68	0.22	0.39	0.05
NDIMWITCR	39.50	0.16	0.25	0.02
NATTRLPYR	197.44	0.32	0.45	0.09
NVSTLYLLR	37.69	0.15	0.24	0.02
NVIMKIAGR	92.15	0.29	0.45	0.04
NMWLYWRRR	81.09	0.19	0.36	0.04
NNMCTIHSR	55.43	0.12	0.21	0.03
NSSGHLKFR	71.35	0.12	0.18	0.03
NCITLHCAR	43.26	0.14	0.24	0.02
NVRFRSAGR	102.37	0.16	0.31	0.05
NIAFDGTTR	44.16	0.20	0.33	0.02
NCVYFLSPR	91.45	0.17	0.30	0.04
NCFNMLINR	55.43	0.13	0.23	0.03
NSFLGGAR	17.87	0.20	0.33	0.01
NTRVRNVYR	63.15	0.27	0.41	0.03
NLDNLHSVR	105.85	0.17	0.25	0.05
NKCMLRQRR	80.25	0.16	0.28	0.04
NSAMWVIPR	52.85	0.13	0.17	0.03
NSCQLLLR	38.11	0.19	0.32	0.02
NPDYVLHKR	114.40	0.26	0.36	0.06
NGSSACTSR	100.56	0.39	0.78	0.05
NFWMYDPRR	95.90	0.26	0.40	0.05
NWYKFRPLR	69.06	0.25	0.50	0.04
NFWKGLAYR	56.68	0.08	0.14	0.03
NYELGSIGR	35.95	0.11	0.18	0.02

NVSICDLVR	121.77	0.36	0.67	0.07
NYVCMDHLR	35.88	0.22	0.30	0.02
NNEMTSFSR	0.14	0.17	0.29	0.00
NCYNAVGFR	37.28	0.05	0.08	0.02
NMGCELRRR	69.96	0.34	0.52	0.04
NIVDCLCRR	29.56	0.13	0.32	0.02
NSLCARRKR	43.74	0.16	0.26	0.02
NVASNALSR	31.16	0.21	0.38	0.02
NHFTSLFAR	80.12	0.21	0.36	0.05
NLTFAEATR	13.07	0.22	0.32	0.01
NLSCCSDRR	23.30	0.10	0.18	0.01
NTCQFRGVR	49.45	0.33	0.46	0.03
NVMYGWDSR	64.05	0.23	0.40	0.04
NTLLIGLLR	36.23	0.12	0.23	0.02
NIVLVLRFR	41.31	0.13	0.26	0.03
NDLIWIAR	157.24	0.41	0.68	0.10
NYTPGRCTR	93.89	0.20	0.40	0.06
NELCLWETR	86.51	0.32	0.61	0.05
NTLYAGLSR	85.33	0.16	0.30	0.05
NFKGLVSVR	24.69	0.16	0.24	0.02
NMPNSSTCR	43.05	0.13	0.23	0.03
NFTFWHRLR	46.53	0.19	0.25	0.03
NNSFITSIR	110.58	0.32	0.46	0.07
NVIVERELR	11.75	0.15	0.24	0.01
NTMYRQQCR	33.38	0.06	0.11	0.02
NVTAWFGFR	214.13	0.55	0.88	0.14
NSYGHRLLR	54.45	0.38	0.68	0.04
NQICCYIFR	30.53	0.13	0.22	0.02
NTFGFSGGR	53.62	0.23	0.37	0.04
NCLEMCILR	81.78	0.23	0.35	0.05
NAGSRSEVR	82.55	0.43	0.78	0.05
NALVCMLFR	29.07	0.16	0.30	0.02
NWTGVSPER	125.67	0.20	0.31	0.08
NSNERATNR	13.21	0.14	0.24	0.01
NTDLSLASR	49.93	0.20	0.36	0.03
NDRCYRGAR	42.77	0.11	0.24	0.03
NSNLLGIR	41.31	0.10	0.23	0.03
NLVRTRTIR	12.73	0.14	0.23	0.01
NPPSNHKIR	61.69	0.11	0.19	0.04
NRAKDAWVR	57.03	0.21	0.41	0.04
NMLIVILVR	44.93	0.12	0.15	0.03
NLYNTSWWR	20.31	0.12	0.18	0.01
NFEHSGAVR	0.00	0.05	0.06	0.00
NDRMAWYNR	53.06	0.24	0.41	0.04
NPMRSYTLR	94.86	0.20	0.35	0.07

NIIVWYMKR	16.13	0.16	0.19	0.01
NGTVYRESR	62.38	0.26	0.44	0.05
NNREAPPVR	0.00	0.00	0.03	0.00
NVVVSFMWR	13.77	0.16	0.32	0.01
NFTQRTIWR	32.55	0.21	0.35	0.02
NFDSVKTLR	26.50	0.15	0.22	0.02
NTIWKTILR	10.22	0.11	0.17	0.01
NLNLVGVFR	21.98	0.09	0.19	0.02
NFYDKSDGR	76.15	0.13	0.21	0.06
NCCMWWLCR	11.82	0.12	0.18	0.01
NLILYISPR	84.08	0.26	0.37	0.07
NRTSTDHVR	35.12	0.24	0.39	0.03
NTHRSYLMR	88.39	0.47	0.74	0.07
NFYFNMIIR	36.86	0.12	0.23	0.03
NKTVVDNTR	72.60	0.22	0.36	0.06
NISLLFIHR	40.20	0.11	0.28	0.03
NCCLEWIIR	24.34	0.08	0.21	0.02
NESFTLYQR	63.15	0.18	0.27	0.05
NCWNLLGCR	10.85	0.12	0.17	0.01
NLITFLRMR	49.65	0.24	0.49	0.04
NDCDGLLMR	5.42	0.15	0.23	0.00
NVFPLPWVR	66.76	0.15	0.28	0.06
NKRQVLMTR	26.71	0.19	0.26	0.02
NFGISVYRR	20.79	0.13	0.20	0.02
NLVNICAGR	26.43	0.35	0.65	0.02
NGRFWNVER	44.44	0.29	0.45	0.04
NPFMSRFR	58.56	0.24	0.39	0.05
NWGMGHANR	24.69	0.12	0.23	0.02
NSITGALPR	34.63	0.27	0.42	0.03
NANYDYDRR	1.88	0.08	0.16	0.00
NSFCQCLFR	35.82	0.13	0.18	0.03
NGLHYHHSR	11.54	0.11	0.17	0.01
NYALYFRSR	45.76	0.15	0.25	0.04
NRFMCKVGR	0.00	0.10	0.20	0.00
NALFCYILR	47.85	0.20	0.41	0.04
NSSGGGVCR	10.57	0.13	0.21	0.01
NNFLNGVNR	44.79	0.20	0.33	0.04
NNCIFLCKR	23.16	0.09	0.15	0.02
NVSKMQYAR	36.44	0.16	0.21	0.03
NVFSVMMHR	33.38	0.44	0.72	0.03
NDLQSNVNR	16.62	0.15	0.32	0.02
NPLRSLCFR	64.19	0.14	0.24	0.06
NEECTLTIR	156.20	0.45	0.73	0.15
NFFIVDSCR	57.30	0.17	0.25	0.06
NIPCFQVSR	40.82	0.20	0.39	0.04

NGVMRPQYR	12.45	0.17	0.35	0.01
NARVGNMGR	48.89	0.51	0.87	0.05
NIGRWTVGR	71.70	0.43	0.75	0.07
NWMSRMAIR	48.40	0.22	0.38	0.05
NYRILGVRR	79.28	0.36	0.53	0.08
NYTARGLKR	26.57	0.15	0.27	0.03
NSYRAKRGR	0.00	0.13	0.23	0.00
NPGFCGWRR	116.00	0.41	0.45	0.12
NGWSYWIQR	25.31	0.15	0.29	0.03
NLYGYRLER	23.85	0.12	0.20	0.03
NPFLVELSR	12.31	0.22	0.36	0.01
NLVQRGPVR	0.56	0.15	0.24	0.00
NSYQVSWR	54.87	0.33	0.54	0.06
NSKSRVSCR	35.54	0.37	0.64	0.04
NASSYPSLR	24.83	0.15	0.30	0.03
NWFSTQCSR	26.36	0.42	0.67	0.03
NINCLHVDR	22.18	0.17	0.28	0.03
NMLTSLLR	35.75	0.13	0.21	0.04
NTTCKTLAR	59.46	0.19	0.42	0.07
NSLFVKFQR	10.43	0.12	0.18	0.01
NELYFMFVR	24.48	0.15	0.23	0.03
NSLIRAHWR	17.11	0.10	0.17	0.02
NGEGRSRMR	30.53	0.26	0.45	0.04
NRVKWRFGFR	38.18	0.36	0.51	0.05
NFMITYPLYR	52.99	0.27	0.45	0.07
NLSRGFLWR	49.10	0.19	0.29	0.06
NVRTIFLVR	77.26	0.38	0.57	0.10
NGVKVRAVR	55.01	0.22	0.44	0.07
NCLIWFVIR	21.84	0.15	0.21	0.03
NGMLCKTSR	13.14	0.14	0.19	0.02
NSYMINFER	5.42	0.10	0.18	0.01
NQVGDLRER	25.31	0.18	0.32	0.03
NPSDCSILR	14.40	0.17	0.21	0.02
NCDAFYVER	25.94	0.12	0.27	0.03
NYSMCRAYR	10.43	0.14	0.18	0.01
NESSCTSTR	29.35	0.15	0.29	0.04
NGPKGLPDR	72.95	0.42	0.61	0.10
NFYKATWR	9.88	0.06	0.13	0.01
NNLKFTVRR	50.42	0.22	0.28	0.07
NQLLVPLGR	0.00	0.14	0.27	0.00
NRNKFVLFR	8.97	0.09	0.16	0.01
NWKHHYFFR	176.16	0.80	1.06	0.25
NRGMYWLRR	0.00	0.28	0.50	0.00
NSFVAFGYR	53.83	0.08	0.16	0.08
NWVFLVDSR	11.41	0.36	0.66	0.02

NLYEHNMDR	18.85	0.13	0.22	0.03
NRRSRYHRR	48.06	0.32	0.73	0.07
NSFLMWKCR	28.10	0.25	0.35	0.04
NDIKSTFFR	9.67	0.02	0.07	0.01
NYDSMYTDR	33.59	0.43	0.77	0.05
NVFYLVYWR	24.55	0.53	0.88	0.04
NPRDFTWVR	118.43	1.18	1.58	0.19
NDLSLTCSR	23.85	0.17	0.19	0.04
NSNCIVSLR	72.05	0.32	0.47	0.11
NKIRVRINR	32.13	0.34	0.67	0.05
NVLWSWFMR	16.41	0.23	0.30	0.03
NCVSEPKGR	96.60	0.58	0.99	0.16
NILVCLVLR	40.13	0.66	0.94	0.06
NTDSKWSLR	11.54	0.10	0.20	0.02
NTFWSRFIR	25.24	0.22	0.25	0.04
NHCISLRLR	23.37	0.12	0.17	0.04
NDLWCKRLR	51.12	0.45	0.96	0.08
NYRFLRLR	34.63	0.29	0.44	0.06
NSIIVMRVR	31.85	0.32	0.53	0.05
NHIMDLSSR	12.03	0.23	0.33	0.02
NFIFPVNFR	30.32	0.10	0.16	0.05
NLDWVLIPR	0.00	0.18	0.27	0.00
NLLTMHRRR	0.00	0.19	0.47	0.00
NRHSWLFDR	0.00	0.12	0.25	0.00
NRSETWFGR	13.07	0.48	0.68	0.02
NVLYTFICR	29.63	0.05	0.20	0.05
NICLSYKFR	16.06	0.30	0.52	0.03
NLNCLVNHR	11.75	0.10	0.17	0.02
NYIWRQLIR	0.00	0.12	0.19	0.00
NNNHGFSIR	0.00	0.25	0.35	0.00
NNACFVLGR	76.22	0.27	0.51	0.14
NWHLLCLDR	30.81	0.59	0.99	0.06
NQLVLLKLR	9.11	0.05	0.11	0.02
NHMTASGR	24.41	0.43	0.72	0.05
NACVSSRTR	38.88	0.28	0.64	0.07
NSRQYLKRR	39.29	0.35	0.41	0.08
NNHVYPYCR	24.97	0.12	0.21	0.05
NVLYILVHR	0.00	0.16	0.21	0.00
NPIECLLLR	25.87	0.80	1.30	0.05
NGYCMYCDR	26.01	0.64	0.90	0.05
NCQVMTVWR	0.00	0.10	0.24	0.00
NLVLYYGIR	10.85	0.08	0.10	0.02
NSLPFPAIR	11.89	0.12	0.20	0.02
NSPNLIMGR	0.14	0.19	0.22	0.00
NSYILISYR	149.59	1.37	1.87	0.31

NSNCYRSKR	10.64	0.08	0.20	0.02
NHTVGLMGR	13.14	0.12	0.27	0.03
NSTFLHDQR	12.80	0.21	0.21	0.03
NNRVCVYPR	13.07	0.31	0.51	0.03
NWVLRTSRR	93.05	0.97	1.70	0.20
NLVNCTWNR	9.94	0.15	0.33	0.02
NCQLLGRRR	0.00	0.20	0.21	0.00
NIIQRYLLR	37.21	0.24	0.52	0.08
NCVRWGCIR	56.19	0.73	1.27	0.12
NIVNLYGNR	36.09	0.07	0.22	0.08
NDNQICRRR	33.94	0.55	0.81	0.08
NLRCRWFR	8.83	0.22	0.26	0.02
NATCTVSFR	14.47	0.21	0.31	0.03
NSSEVNCSS	11.20	0.05	0.17	0.03
NRLSLGPCR	86.10	0.35	0.49	0.20
NMFCQSLTR	27.68	0.44	0.46	0.07
NTVIVLIKR	22.12	0.24	0.34	0.05
NTDKTCSVR	0.00	0.06	0.18	0.00
NFMYVSKIR	32.89	0.59	0.89	0.08
NYGGFFGIR	42.35	0.25	0.39	0.11
NLERGDTVR	11.06	0.29	0.58	0.03
NMNCWEVGR	24.97	0.20	0.42	0.06
NVRSQDVFR	13.14	0.03	0.23	0.03
NVYDCMNSR	42.70	0.31	0.66	0.11
NSFFGETSR	0.00	0.14	0.26	0.00
NSKSCVVS	0.00	0.09	0.17	0.00
NVSDLVVKR	13.14	0.27	0.50	0.04
NKLCLVYVR	14.33	0.17	0.44	0.04
NLVIRPSNR	9.39	0.15	0.28	0.03
NFQVLFGR	53.62	0.79	1.43	0.15
NHELRFVNR	0.00	0.09	0.17	0.00
NENYHMSVR	41.31	0.44	0.94	0.12
NIYFLSFTR	0.00	0.13	0.16	0.00
NEVCWCLLR	0.00	0.13	0.23	0.00
NETLGNHIR	14.67	0.06	0.21	0.04
NSIILHPR	19.82	0.42	0.77	0.06
NIFHIGAYR	13.77	0.11	0.17	0.04
NYRDLIYKR	37.69	0.22	0.48	0.12
NYWEVHWLR	73.09	1.19	2.17	0.23
NKESVWELR	0.14	0.42	0.67	0.00
NNMTNTWPR	14.12	0.05	0.18	0.05
NLYNLWQFR	51.60	1.46	2.12	0.17
NLSLGFQFR	42.07	1.37	2.16	0.14
NMIHASDDR	0.00	0.43	0.46	0.00
NEVVCGRLR	37.90	0.66	1.13	0.13

NMFARTALR	0.00	0.32	0.25	0.00
NFARWILCR	135.47	0.95	1.93	0.49
NPFSYLER	22.81	0.08	0.11	0.08
NSSWYAPSR	35.33	1.15	1.77	0.13
NHSRGDGRR	0.00	0.13	0.16	0.00
NTMVIRGIR	29.90	0.37	0.90	0.11
NLIGPGYSR	21.00	0.81	1.63	0.08
NSSKYTLPR	14.81	0.22	0.40	0.06
NNSFFMLFR	50.42	0.66	1.23	0.20
NSDMDHWWR	0.00	0.20	0.26	0.00
NGYLDLSDR	11.06	0.45	0.65	0.04
NEPVLNR	1.25	0.13	0.14	0.01
NEFTFQTR	0.00	0.07	0.34	0.00
NFVYSSRYR	0.00	0.09	0.14	0.00
NKVTRTVSR	14.26	0.19	0.27	0.06
NPNSYLSNR	12.66	0.24	0.57	0.06
NGLRERFGR	0.00	0.24	0.28	0.00
NHEKGLYMR	10.85	0.16	0.26	0.05
NDRVMISVR	10.50	0.26	0.37	0.05
NMLFSILFR	12.10	0.49	1.01	0.06
NECTWGRNR	0.00	0.24	0.32	0.00
NMGCRGPLR	12.52	0.44	0.66	0.06
NYARREGR	0.00	0.36	0.59	0.00
NRLVDIRTR	0.00	0.18	0.30	0.00
NSMLLCYLR	27.96	0.81	1.68	0.15
NLSRSKGYR	0.00	0.74	0.92	0.00
NLVASMLVR	0.00	0.27	0.25	0.00
NFYCLDFHR	10.64	0.44	0.59	0.06
NHVWGVYNR	0.00	0.07	0.10	0.00
NTSMTLNRR	10.15	0.56	0.99	0.06
NFSGDFNGR	0.00	0.19	0.23	0.00
NFCQDFNR	0.00	0.10	0.17	0.00
NVMAETIR	44.93	2.39	4.00	0.30
NYLGYAWGR	0.00	0.02	0.05	0.00
NSFQCLAAR	9.81	0.31	0.50	0.07
NSYYFLAFR	0.00	0.05	0.24	0.00
NTMKRGTVR	0.14	0.17	0.29	0.00
NKIYTVFDR	27.26	0.73	0.88	0.20
NIWTVTGIR	0.00	0.28	0.40	0.00
NCVSIWRR	0.00	0.29	0.35	0.00
NEQMNFLRR	9.11	0.24	0.17	0.08
NALRAKECR	0.00	0.50	1.20	0.00
NWLTWLLGR	0.00	1.62	3.20	0.00
NYSNCEQCR	0.00	0.13	0.34	0.00
NSCNYSTVR	0.70	0.01	0.04	0.01

NYRVFVVVR	11.06	1.86	3.13	0.10
NCIVFQILR	96.53	5.16	7.54	0.89
NLICMLYQR	11.75	0.25	0.44	0.11
NTWVGGSER	0.07	0.00	0.01	0.00
NHINFRGTR	15.72	0.38	0.43	0.16

Table 6. Fold-change analysis of AAV variants in LSECs

variant	P_count	LSEC_count	Normalised LSEC_count	FC_LSEC
NR (WT)	38245	37375	38245.00	1.00
NTRVGGSER	40865	1234	1262.72	0.03
NKLMDSNNR	22891	1208	1236.12	0.05
NTSTTPSKR	20250	1161	1188.03	0.06
NSDTYLGR	15440	1241	1269.89	0.08
NIAGSETMR	14472	2591	2651.31	0.18
NFKSQLNCR	13317	1189	1216.68	0.09
NGAFKHLMR	9437	1950	1995.39	0.21
NMVVWVTDR	6432	2608	2668.71	0.41
NPSMQY_VR	4539	3835	3924.27	0.86
NRSVGGICR	4179	1339	1370.17	0.33
NLDDNVLDR	4111	4767	4877.96	1.19
NRVSYWFLR	3980	1165	1192.12	0.30
NHCFFYGSR	3570	1042	1066.26	0.30
NIMRYLTYR	3507	1324	1354.82	0.39
NISCCWDIR	3385	1226	1254.54	0.37
NVYGPWIER	3172	1202	1229.98	0.39
NSPPGLVDR	3144	1239	1267.84	0.40
NRFTVRSMR	3141	1198	1225.89	0.39
NCSLLTRHR	3052	2549	2608.33	0.85
NCLLQVPYR	3044	2538	2597.08	0.85
NYVVRSLR	3037	2554	2613.45	0.86
NNIYVLKSR	2951	221	226.14	0.08
NYDKRSHQR	2917	2489	2546.94	0.87
NKLYIEGIR	2731	156	159.63	0.06
NRCFGCLCR	2665	2312	2365.82	0.89
NLEIRINDR	2572	1056	1080.58	0.42
NIGFTGEHR	2460	953	975.18	0.40
NNFSLHYR	2354	971	993.60	0.42
NSVSMFWCR	2328	3830	3919.15	1.68
NLVALCDCR	2312	1194	1221.79	0.53
NATTRLPYR	2259	1077	1102.07	0.49
NVIMKIAGR	2253	1831	1873.62	0.83
NSSGHLKFR	2175	2212	2263.49	1.04

NVRFRSAGR	2105	2396	2451.77	1.16
NSCQLLLR	1958	1248	1277.05	0.65
NFDYVLHKKR	1939	2124	2173.44	1.12
NYELGSIGR	1857	1003	1026.35	0.55
NVSICDLVR	1843	2460	2517.26	1.37
NYVCMDHLR	1842	1341	1372.22	0.74
NVASNALSR	1779	1123	1149.14	0.65
NHFTSLFAR	1768	1065	1089.79	0.62
NVMYGWDSR	1671	2492	2550.01	1.53
NDLIWIAR	1614	2160	2210.28	1.37
NELCLWETR	1602	2356	2410.84	1.50
NFTFWHRLR	1570	1126	1152.21	0.73
NNSFITSIR	1567	884	904.58	0.58
NVTAWFGFR	1510	1309	1339.47	0.89
NSYGHRLLR	1509	651	666.15	0.44
NSNERATNR	1488	2381	2436.42	1.64
NSNLLLGIR	1458	1269	1298.54	0.89
NDRMAWYNR	1407	1228	1256.58	0.89
NRTSTDHVR	1267	1965	2010.74	1.59
NVFPLPWVR	1185	2358	2412.89	2.04
NGRFWNVER	1126	1147	1173.70	1.04
NKVSVGL_R	1122	1315	1345.61	1.20
NSITGALPR	1079	1092	1117.42	1.04
NNCIFLCKR	1058	2184	2234.84	2.11
NVFSVMMHR	1046	1166	1193.14	1.14
NSHCFSC_R	1039	945	967.00	0.93
NEECTLTIR	1015	5035	5152.20	5.08
NWMSRMAIR	977	1310	1340.49	1.37
NRGMYWLRR	695	1183	1210.54	1.74
NWVFLVDSR	667	2445	2501.91	3.75
NRRSRYHRR	654	1262	1291.38	1.97
NPRDFTWVR	638	622	636.48	1.00
NKIRVRINR	626	1053	1077.51	1.72
NDLWCKRLR	604	1198	1225.89	2.03
NYRLFLRLR	603	935	956.76	1.59
NGYCMYCDR	503	1309	1339.47	2.66
NIQRYLLR	465	1315	1345.61	2.89
NCVRWGCIR	464	1360	1391.66	3.00
NIVNLYGNR	447	2387	2442.56	5.46
NFMYVSKIR	408	1217	1245.33	3.05
NMNCWEVGR	399	1116	1141.98	2.86
NFQVLFGR	360	1116	1141.98	3.17
NLYNLWQFR	295	1231	1259.65	4.27
NNSFFMLFR	257	1039	1063.19	4.14
NPNSYLNRSR	229	1002	1025.32	4.48

NHEKGLYMR	223	1204	1232.03	5.52
NMLFSILFR	208	1057	1081.60	5.20
NMGCRGPLR	204	2431	2487.59	12.19
NSMLLCYLR	187	1313	1343.56	7.18
NTSMTLNRR	164	577	590.43	3.60
NCIVFQILR	108	1203	1231.00	11.40

[0075] Example 3: selection of peptides conferring tropism to liver sinusoidal endothelial cells (LSECs)

[0076] Animals received injections of 2.5×10^9 vg/animal of AAV. One month after the injection of the AAV library, organs were harvested. Specifically, for this round of selection, after liver collection, a portion of the liver was sectioned off to prepare a cell suspension. From this suspension, CD146+ liver sinusoidal endothelial cells (LSECs) were isolated using fluorescence-activated cell sorting (FACS). This process led to the identification of AAV-DJ variants with improved tropism to LSECs (Table 7).

10 **Table 7. Peptides identified conferring tropism to liver sinusoidal endothelial cells (LSECs)**

Variant	7-mer sequence	FC_Brain	FC_muscle	FC_liver	FC_LSEC	SEQ ID NO:
Peptide #22	LYNLWQF	1.46	2.12	0.17	4.27	SEQ ID NO: 22
Peptide #24	IVNLYGN	0.07	0.22	0.08	5.48	SEQ ID NO: 24
Peptide #85	CIVFQIL	5.16	7.54	0.89	11.38	SEQ ID NO: 85
Peptide #106	EECTLTI	0.45	0.73	0.15	5.09	SEQ ID NO: 106
Peptide #198	VFPLPWV	0.15	0.28	0.06	2.04	SEQ ID NO: 198
Peptide #293	NCIFLCK	0.09	0.15	0.02	2.11	SEQ ID NO: 293
Peptide #312	FMYVSKI	0.59	0.89	0.08	3.01	SEQ ID NO: 312
Peptide #321	SMLLCYL	0.81	1.68	0.15	7.22	SEQ ID NO: 321
Peptide #224	GYCMYCD	0.64	0.9	0.05	2.68	SEQ ID NO: 224
Peptide #341	HEKGLYM	0.16	0.26	0.05	5.54	SEQ ID NO: 341
Peptide #342	WVFLVDS	0.36	0.66	0.02	3.74	SEQ ID NO: 342

[0077] Equivalents

[0078] The foregoing examples are presented for the purpose of illustrating the invention and should not be construed as imposing any limitation on the scope of the invention. It will readily

be apparent that numerous modifications and alterations may be made to the specific embodiments of the invention described above and illustrated in the examples without departing from the principles underlying the invention. All such modifications and alterations are intended to be embraced by this application.

CLAIMS

1. A modified adeno-associated virus serotype DJ (AAV-DJ), comprising a nucleotide sequence encoding a 7-mer peptide inserted between the 1767th and 1768th nucleotides of SEQ ID NO: 399, wherein the modified AAV-DJ has a range of at least 50% to 60%, 60% to 65%, 65% to 70%, 70% to 75%, 75% to 80%, 80% to 85%, 85% to 90%, 90% to 95%, or 95% to 99% sequence identity with the sequence of SEQ ID NO: 399 outside the nucleotide sequence encoding the 7-mer peptide.
2. A modified adeno-associated virus serotype 2 (AAV2), comprising a nucleotide sequence encoding a 7-mer peptide inserted between the 1764th and 1765th nucleotides of SEQ ID NO: 401, wherein the modified AAV2 has a range of at least 50% to 60%, 60% to 65%, 65% to 70%, 70% to 75%, 75% to 80%, 80% to 85%, 85% to 90%, 90% to 95%, or 95% to 99% sequence identity with the sequence of SEQ ID NO: 401 outside the nucleotide sequence encoding the 7-mer peptide.
3. A modified adeno-associated virus serotype 5 (AAV5), comprising a nucleotide sequence encoding a 7-mer peptide inserted between the 1722th and 1723th nucleotides of SEQ ID NO: 402, wherein the modified AAV5 has a range of at least 50% to 60%, 60% to 65%, 65% to 70%, 70% to 75%, 75% to 80%, 80% to 85%, 85% to 90%, 90% to 95%, or 95% to 99% sequence identity with the sequence of SEQ ID NO: 402 outside the nucleotide sequence encoding the 7-mer peptide.
4. A modified adeno-associated virus serotype 6 (AAV6), comprising a nucleotide sequence encoding a 7-mer peptide inserted between the 1770th and 1771th nucleotides of SEQ ID NO: 403, wherein the modified AAV6 has a range of at least 50% to 60%, 60% to 65%, 65% to 70%, 70% to 75%, 75% to 80%, 80% to 85%, 85% to 90%, 90% to 95%, or 95% to 99% sequence identity with the sequence of SEQ ID NO: 403 outside the nucleotide sequence encoding the 7-mer peptide.
5. A modified adeno-associated virus serotype 6 (AAV6), comprising a nucleotide sequence encoding a 7-mer peptide inserted between the 1764th and 1765th nucleotides of SEQ ID NO: 403, wherein the modified AAV6 has a range of at least 50% to 60%, 60% to 65%, 65% to 70%, 70% to 75%, 75% to 80%, 80% to 85%, 85% to 90%, 90% to 95%, or 95% to 99% sequence identity with the sequence of SEQ ID NO: 403 outside the nucleotide sequence encoding the 7-mer peptide.

to 99% sequence identity with the sequence of SEQ ID NO: 403 outside the nucleotide sequence encoding the 7-mer peptide.

- 5 6. A modified adeno-associated virus serotype 9 (AAV9), comprising a nucleotide sequence encoding a 7-mer peptide inserted between the 1764th and 1765th nucleotides of SEQ ID NO: 404, wherein the modified AAV9 has a range of at least 50% to 60%, 60% to 65%, 65% to 70%, 70% to 75%, 75% to 80%, 80% to 85%, 85% to 90%, 90% to 95%, or 95% to 99% sequence identity with the sequence of SEQ ID NO: 404 outside the nucleotide sequence encoding the 7-mer peptide.
10
7. The modified AAV-DJ of claim 1, wherein the modified AAV-DJ has at least 57% sequence identity with the sequence of SEQ ID NO: 399 outside the nucleotide sequence encoding the 7-mer peptide.
- 15 8. The modified AAV2 of claim 2, wherein the modified AAV2 has at least 57% sequence identity with the sequence of SEQ ID NO: 401 outside the nucleotide sequence encoding the 7-mer peptide.
- 20 9. The modified AAV5 of claim 3, wherein the modified AAV5 has at least 57% sequence identity with the sequence of SEQ ID NO: 402 outside the nucleotide sequence encoding the 7-mer peptide.
- 25 10. The modified AAV6 of claim 4, wherein the modified AAV6 has at least 57% sequence identity with the sequence of SEQ ID NO: 403 outside the nucleotide sequence encoding the 7-mer peptide.
- 30 11. The modified AAV6 of claim 5, wherein the modified AAV6 has at least 57% sequence identity with the sequence of SEQ ID NO: 403 outside the nucleotide sequence encoding the 7-mer peptide.
12. The modified AAV9 of claim 6, wherein the modified AAV9 has at least 57% sequence identity with the sequence of SEQ ID NO: 404 outside the nucleotide sequence encoding the 7-mer peptide.

13. The modified AAV of any one of claims 1-12, wherein the 7-mer peptide sequence is selected from the sequences set forth in Table 1, and wherein the insertion increases brain, muscle, and liver tropism compared to a wild-type AAV without a 7-mer peptide sequence insertion.
- 5
14. The modified AAV of any one of claims 1-12, wherein the 7-mer peptide sequence is selected from the sequences set forth in Table 2, and wherein the insertion increases brain, and muscle tropism, and decreases liver tropism compared to a wild-type AAV without a 7-mer peptide sequence insertion.
- 10
15. The modified AAV of any one of claims 1-12, wherein the 7-mer peptide sequence is selected from the sequences set forth in Table 3, and wherein the insertion increases brain, and muscle tropism, and is liver de-targeting.
- 15
16. The modified AAV-DJ of any one of claims 1-12, wherein the 7-mer peptide sequence is selected from the group consisting of SEQ ID NOs: 22, 24, 32, 85, 106, 198, 216, 232, 251, 293, 312, 320, 321, 224, 346 or 376.
- 20
17. The modified AAV of any one of claims 1-12, wherein the 7-mer peptide sequence is selected from the sequences set forth in Table 1 or Table 7, and wherein the insertion increases specificity to cells selected from the group consisting of: liver sinusoidal endothelial cells or hepatocytes, compared to a wild-type AAV without a 7-mer peptide sequence insertion.
- 25
18. The modified AAV of any one of claims 1-12, wherein the 7-mer peptide sequence is selected from the sequences set forth in Table 1, Table 2 or Table 3, and wherein the insertion increases specificity to cells selected from the group consisting of: neurons, or astrocytes, compared to a wild-type AAV without a 7-mer peptide sequence insertion.
- 30
19. The modified AAV of any one of claims 1-12, wherein the 7-mer peptide sequence is selected from the sequences set forth in Table 7, and wherein the insertion increases production of antigen-specific regulatory T cells compared to a wild-type AAV without a 7-mer peptide sequence insertion.

20. The modified AAV of any one of claims 1-12, wherein the 7-mer peptide sequence is selected from the sequences set forth in Table 1, Table 2, or Table 3, and wherein the insertion improves therapeutic effect compared to a wild-type AAV without a 7-mer peptide sequence insertion.
- 5
21. A composition comprising the modified AAV of any one of the preceding claims, and a pharmaceutically acceptable excipient.
22. A nucleic acid encoding the modified AAV of any one of the preceding claims.