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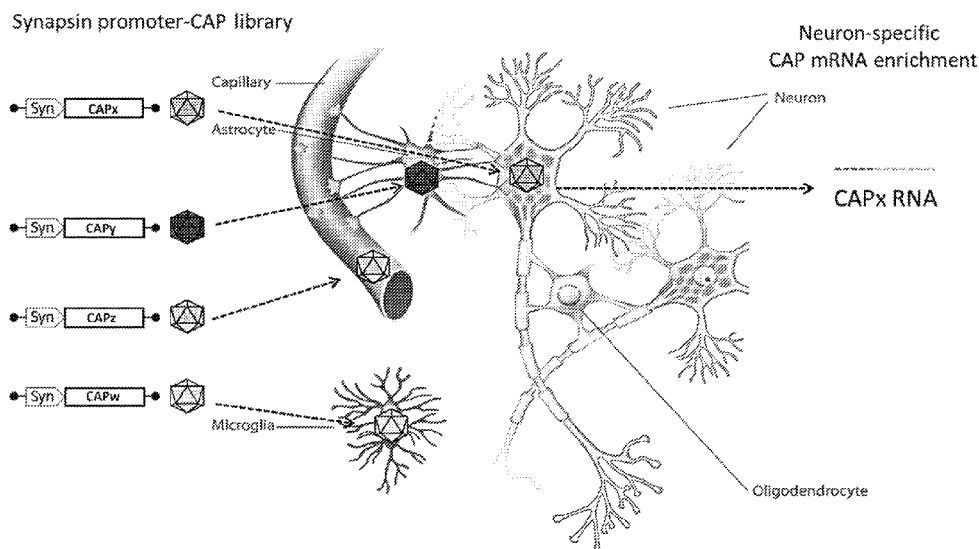
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FIG. 11



(57) Abstract: The disclosure relates to compositions, methods, and processes for the preparation, use, and/or formulation of adeno-associated virus capsid proteins, wherein the capsid proteins comprise targeting peptide inserts for enhanced tropism to a target tissue.

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REDIRECTION OF TROPISM OF AAV CAPSIDS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of: U.S. Provisional Patent Application No. 62/740,310, filed October 02, 2018, entitled AAV CAPSID LIBRARIES AND TISSUE TARGETING PEPTIDE INSERTS; U.S. Provisional Patent Application No. 62/839,883, filed April 29, 2019 entitled REDIRECTION OF TROPISM OF AAV CAPSIDS; the contents of which are each incorporated herein by reference in their entirety.

REFERENCE TO THE SEQUENCE LISTING

[0002] The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled 20571060PCTSL.txt, created on October 02, 2019, which is 428,491 bytes in size. The information in the electronic format of the sequence listing is incorporated herein by reference in its entirety.

FIELD OF THE DISCLOSURE

[0003] The disclosure relates to compositions, methods, and processes for the preparation, use, and/or formulation of adeno-associated virus capsid proteins, wherein the capsid proteins comprise targeting peptide inserts for enhanced tropism to a target tissue.

BACKGROUND

[0004] Gene delivery to the adult central nervous system (CNS) remains a major challenge in gene therapy, and engineered AAV capsids with improved brain tropism represent an attractive solution.

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

[0006] In order to perform directed evolution of AAV capsids, the sequence encoding the viral capsid is itself flanked by inverted terminal repeats (ITR) so it can be packaged into its

own capsid shell. Following infection of cultured cells or animals by the mixed population of capsids, the DNA encoding capsids variants that have successfully homed into the tissue of interest is recovered by PCR for further rounds of selection. In this approach, all viral DNA species present in a given tissue are recovered, with no discrimination for specific cell types or for vectors able to perform complete transduction (cell surface binding, endocytosis, trafficking, nuclear import, uncoating, second-strand synthesis, transcription). For example, in the case of highly complex tissues containing multiple cell types, such as the central nervous system (CNS), it would be highly preferable to apply a more stringent selective pressure aimed at recovering capsid variants capable of transducing neuron and/or astrocyte rather than microglia or blood vessel endothelial cells.

[0007] Attempts at improving the CNS tropism of AAV capsids upon systemic administration have been met with limited success.

[0008] Two previous approaches have been used to address this issue. The first strategy used co-infection of cultured cells (Grimm et al., 2008) or *in situ* animal tissue (Lisowski et al., 2014) with adenovirus, in order to trigger exponential replication of infectious AAV DNA. Another successful approach involved the use of cell-specific CRE transgenic mice (Deverman et al., 2016) allowing viral DNA recombination specifically in astrocytes, followed by recovery of CRE-recombined capsid variants. Both approaches proved successful, allowing the isolation of several capsid variants with enhanced transduction of target cell populations.

[0009] This finding suggested that cell type-specific library selection could improve the outcome of directed evolution. However, the transgenic CRE system used by Deverman et al. is not tractable in other animal species and AAV variants selected by directed evolution in mouse tissue do not show similar properties in large animals. Therefore, it would be necessary to perform the entire directed evolution process directly in non-human primates to increase the probability of translatability in human subjects. None of the previously described transduction-specific approaches are amenable to large animal studies because: 1) many tissues of interest (e.g. CNS) are not readily accessible to adenovirus co-infection, 2) the specific Ad tropism itself would bias the library distribution, and 3) large animals are typically not amenable to transgenesis and cannot be genetically engineered to express CRE recombinase in defined cell types.

[0010] To address this problem, we have developed a broadly-applicable functional AAV capsid library screening platform for cell type-specific biopanning in non-transgenic animals. In the TRACER (Tropism Redirection of AAV by Cell type-specific Expression of RNA)

platform system, the capsid gene is placed under the control of a cell type-specific promoter to drive capsid mRNA expression in the absence of helper virus co-infection. This RNA-driven screen increases the selective pressure in favor of capsid variants which transduce a specific cell type.

[0011] The TRACER platform allows generation of AAV capsid libraries whereby specific recovery and subcloning of capsid mRNA expressed in transduced cells is achieved with no need for transgenic animals or helper virus co-infection. Since mRNA transcription is a hallmark of full transduction, these methods will allow identification of fully infectious AAV capsid mutants. In addition to its higher stringency, this method allows identification of capsids with high tropism for particular cell types using libraries designed to express CAP mRNA under the control of any cell-specific promoter such as, but not limited to, synapsin-1 promoter (neurons), GFAP promoter (astrocytes), TBG promoter (liver), CAMK promoter (skeletal muscle), MYH6 promoter (cardiomyocytes).

SUMMARY OF THE DISCLOSURE

[0012] The present disclosure provides compositions and methods for the engineering and/or redirecting the tropism of AAV capsids. Also provided herein are peptides which may be inserted into AAV capsid sequences to increase the tropism of the capsid for a particular tissue. In one aspect, the peptides may be used to target the capsids to brain or regions of the brain or the spinal cord.

[0013] The present disclosure presents methods for generating one or more variant AAV capsid polypeptides. In certain embodiments, the variant AAV capsid polypeptides exhibit at least one of improved transduction or increased cell or tissue specificity, relative to a parental AAV capsid polypeptide. In certain embodiments, the method includes: (a) generating a library of variant AAV capsid polypeptides, wherein said library includes (i) a plurality of capsid polypeptides having a region of randomized sequence of 2, 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids, or (ii) a plurality of capsid polypeptides from more than one parental AAV capsid polypeptide; (b) generating an AAV vector library by cloning the capsid polypeptides of libraries (a)(i) or (a)(ii) into AAV vectors, wherein the AAV vectors include a first promoter and a second promoter, wherein said second promoter drives capsid mRNA expression in the absence of helper virus co-infection.

[0014] In certain embodiments, the first promoter is AAV2 P40. In certain embodiments, the second promoter is a ubiquitous promoter. In certain embodiments, the first promoter is AAV2 P40 and the second promoter is a ubiquitous promoter.

[0015] In certain embodiments, the first promoter is AAV2 P40. In certain embodiments, the second promoter is a cell-type-specific promoter. In certain embodiments, the first promoter is AAV2 P40 and the second promoter is a cell-type-specific promoter.

[0016] In certain embodiments, the promoter is selected from any promoter listed in Table 3. In certain embodiments, the ubiquitous or cell-specific promoter allows the expression of RNA encoding the capsid polypeptides.

[0017] In certain embodiments, the method includes recovery of the RNA encoding the capsid polypeptides. In certain embodiments, the method includes determining the sequence of the capsid polypeptides. In certain embodiments, the capsid polypeptides recovered exhibit increased target cell transduction or target cell specificity (tropism) as compared to a parental capsid polypeptide.

[0018] In certain embodiments, the target cell is a neuronal cell, a neural stem cell, an astrocyte, an oligodendrocyte, a microglia cell, a retinal cell, a tumor cell, a hematopoietic stem cell, an insulin producing beta cell, a lung epithelium cell, an endothelial cell, a liver cell, a skeletal muscle cell, a muscle stem cell, a muscle satellite cell, or a cardiac muscle cell.

[0019] In certain embodiments, the AAV vectors comprise a first promoter and a second promoter, wherein the second promoter is located the downstream of the capsid gene and drives its anti-sense RNA expression in the absence of helper virus co-infection.

[0020] In certain embodiments, the first promoter is AAV2 P40 and the second promoter is a ubiquitous promoter. In certain embodiments, the first promoter is AAV2 P40 and the second promoter is a cell-specific promoter. In certain embodiments, the ubiquitous or cell-specific promoter allows the expression of gene encoding the capsid polypeptide of variant AAV in an anti-sense direction, resulting in the anti-sense RNA. In certain embodiments, the method included the recovery of the anti-sense RNA that can be converted to RNA encoding the variant AAV capsid polypeptide that is used to determine the sequence of the variant AAV capsid polypeptides.

[0021] In certain embodiments, the variant AAV capsid polypeptide exhibits increased target cell transduction or target cell specificity (tropism) as compared to a parental capsid polypeptide.

The present invention as claimed herein is described in the following items 1 to 33:

1. A method for generating an adeno-associated virus (AAV) vector library encoding variant AAV capsid polypeptides, the method comprising:

(a) providing first nucleic acids comprising a P40 promoter and a cell-type specific promoter, wherein the cell-type specific promoter drives capsid mRNA expression in the absence of helper virus co-infection; and second nucleic acids encoding:

a plurality of the variant AAV capsid polypeptides having a region of randomized sequence of 2, 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids; and

(b) cloning the first nucleic acids and the second nucleic acids under conditions suitable to generate the AAV vector library.

2. The method of claim 1, wherein the cell-type specific promoter is a blood cell specific promoter, an eye specific promoter, a heart specific promoter, a muscle specific promoter, a kidney specific promoter, a lung specific promoter, a pancreas specific promoter, or a vasculature specific promoter, a neuron specific promoter or an astrocyte-specific promoter.

3. The method of item 1 or 2, wherein the cell-type specific promoter is a promoter selected from B29 promoter, Immunoglobulin heavy chain promoter, CD45 promoter, Mouse INF- β promoter, CD45 SV40 / CD45 promoter, WASP promoter, CD43 promoter, CD43 SV40 / CD43 promoter, CD68 promoter, GPIIb promoter, CD14 promoter, CD2 promoter, Osteocalcin, Bone sialoprotein, OG-2 promoter, GFAP promoter, Vga, Vglut2, NSE / RU5' promoter, SYN1 promoter, Neurofilament light chain, VGF, Nestin, Chx10, PrP, Dkk3, Math5, Ptf1a, Pcp2, Nefh, gamma-synuclein gene (SNCG), Grik4, Pdgfra, Chat, Thy1.2, hVmd2, Thy1, Modified α A-crystallin, hRgp, mMo, Opn4, RLBP1, Glast, Foxg1, hVmd2, Trp1, Six3, cx36, Grm6 - SV40 eukaryotic promoter, hVmd2, Dct, Rpc65, mRho, Irbp, hRho, Pcp2, Rhodopsin, mSo, MLC2v promoter, α MHC promoter, rat troponin T (Tnnt2), Tie2, Tcf21, ECAD, NKCC2, KSPC, NPHS1, SGLT2, SV40 / bAlb promoter, SV40 / hAlb promoter, Hepatitis B virus core promoter, Alpha fetoprotein, Surfactant protein B promoter, Surfactant protein C promoter, Desmin, Mb promoter, Myosin, Dystrophin, dMCK and tMCK, Elastase-1 promoter, PDX1 promoter, Insulin promoter, Slco1c1, tie, cadherin, ICAM-2, claudin 1, Cldn5, Flt-1 promoter, and Endoglin promoter.

4. The method of any one of items 1-3, wherein the cell-type specific promoter is a GFAP promoter.

6. The method of any one of items 1-5, wherein:

(i) the P40 promoter and/or the cell-type specific promoter are located upstream of a transgene encoding the variant AAV capsid polypeptide.

7. The method of any one of items 1-5, wherein the P40 promoter is located upstream of a transgene encoding the variant AAV capsid polypeptide and the cell-type specific promoter is located downstream of a transgene encoding the variant AAV capsid polypeptide.

8. The method of any one of items 1-7, wherein the region of randomized sequence comprises a peptide insert of 4, 5, 6, 7, 8, or 9 consecutive amino acids.

9. The method of any one of items 1-8, wherein the region of randomized sequence of 2, 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids is present in a hypervariable region of the parental AAV capsid polypeptide.

10. The method of any one of items 1-9, wherein the region of randomized sequence of 2, 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids is present in loop IV, loop VIII, or both loop IV and loop VIII of the parental AAV capsid polypeptide.

11. The method of any one of items 8-10, wherein the insert is present

(i) immediately subsequent to a position selected from 452-458 of the parental sequence; and/or

(ii) immediately subsequent to a position selected from 586-592 of the parental sequence.

12. The method of any one of items 1-11, wherein the parental AAV capsid polypeptide comprises an AAV9 capsid polypeptide or an AAV5 capsid polypeptide.

13. The method of any one of items 1-12, further comprising (c) generating a plurality of AAV particles comprising the AAV vector library.

14. The method of any one of items 1-13, further comprising (d) administering the AAV particles to an animal.

15. The method of item 14, wherein:

(i) the animal is a mouse or a non-human primate (NHP) and/or (ii) the particles are administered intravenously.

16. The method of any one of items 1-15, further comprising (e) collection and/or isolation of a target cell or tissue from the animal.

17. The method of item 16, wherein the target cell or tissue is collected four weeks post-administration of the particles.

18. The method of any one of items 1-17, further comprising (f) recovery of RNA and/or antisense RNA encoding the variant AAV capsid polypeptides from the target cell or tissue.

19. The method of item 18, wherein the RNA encoding the variant AAV capsid polypeptides is enriched and/or reverse transcribed to cDNA.

20. The method of item 19, wherein the cDNA is amplified.

21. The method of any one of items 1-20, further comprising (g) determination of the sequence of the variant AAV capsid polypeptides.

22. The method of any one of items 1-20, further comprising (h) measuring the amount of the amount of DNA encoding the variant AAV capsid polypeptides and/or the amount of RNA encoding the variant AAV capsid polypeptides in a target cell, or tissue.

23. The method of any one of items 1-22, wherein the method further comprises repeating comprises repeating steps (a)-(h).

24. The method of any one of items 16-23, wherein the target cell is a neuronal cell, a neural stem cell, an astrocyte, an oligodendrocyte, a microglia cell, a retinal cell, a tumor cell, a hematopoietic stem cell, an insulin producing beta cell, a lung epithelium cell, an endothelial cell, a liver cell, a skeletal muscle cell, a muscle stem cell, a muscle satellite cell, and/or a cardiac muscle cell.

25. The method of any one of items 16-24, wherein the target tissue is a CNS tissue, a PNS tissue, and/or a peripheral tissue.
26. The method of item 25, wherein the CNS tissue is a brain tissue, a spinal cord tissue, and/or a dorsal root ganglion tissue.
27. The method of item 26, wherein the brain tissue is a cortex tissue, a frontal cortex tissue, a parietal cortex tissue, a occipital cortex tissue, a temporal cortex tissue, a thalamus tissue, a hypothalamus tissue, a striatum tissue, a putamen tissue, a caudate nucleus tissue, a hippocampus tissue, a entorhinal cortex tissue, a basal ganglia tissue, and/or a deep cerebellar nuclei tissue.
28. The method of item 25, wherein the peripheral tissue is a muscle tissue, a liver tissue, a heart tissue, a gastrocnemius muscle tissue, a soleus muscle tissue, a pancreas tissue, a kidney tissue, a spleen tissue, a lung tissue, an adrenal glands tissue, a stomach tissue, a sciatic nerve tissue, a saphenous nerve tissue, a thyroid gland tissue, an eye tissue, a pituitary gland tissue, a skeletal muscle tissue, a colon tissue, a duodenum tissue, an ileum tissue, a jejunum tissue, a skin tissue of the leg, a superior cervical ganglia tissue, a urinary bladder tissue, an ovary tissue, a uterus tissue, a prostate gland tissue, and/or a testes tissue.
29. The method of any one of items 16 or 8-28, wherein the vectors of the AAV vector library comprise in order:
- (i) a first inverted terminal repeat region (ITR);
 - (ii) a cell-type specific promoter;
 - (iii) a P40 promoter
 - (iv) a transgene encoding the variant AAV capsid polypeptide comprising the region of randomized sequence of 2, 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids;
 - (v) a poly-A sequence region; and
 - (vi) a second ITR.
30. An AAV vector library made by the method of any one of items 1-29.
31. An adeno-associated virus (AAV) vector library comprising:

- (a) first nucleic acids comprising a P40 promoter, and a cell-type specific promoter which drives capsid mRNA expression in the absence of helper virus co-infection; and
- (b) second nucleic acids encoding:
 - a plurality of variant AAV capsid polypeptides having a region of randomized sequence of 2, 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids.

32. A method for generating a plurality of variant adeno-associated virus (AAV) capsid polypeptides, the method comprising:

- (a) providing a plurality of AAV particles comprising an AAV vector library, wherein the AAV vector library comprises nucleic acids comprising a P40 promoter and a cell-type specific promoter which drives capsid mRNA expression in the absence of helper virus co-infection; and wherein the nucleic acids encode a plurality of the variant AAV capsid polypeptides having a region of randomized sequence of 2, 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids;

- (b) administering the AAV particles to an animal wherein the particles are administered intravenously;

- (c) recovery of RNA and/or antisense RNA encoding the variant AAV capsid polypeptides from the target cell or tissue;

- (d) determination of the sequence of the variant AAV capsid polypeptides; and

- (e) measuring the amount of DNA encoding the variant AAV capsid polypeptides or the amount of RNA encoding the variant AAV capsid polypeptides, in a target cell or tissue; and

wherein the method occurs in the absence of a helper virus

thereby generating the plurality of variant AAV capsid polypeptides.

33. The method of item 32, wherein the cell-type specific promoter is a synapsin promoter or a GFAP promoter.

BRIEF DESCRIPTION OF THE DRAWINGS

[0022] The foregoing and other objects, features, and advantages will be apparent from the following description of particular embodiments of the disclosure, as illustrated in the accompanying drawings. The drawings are not necessarily to scale, emphasis instead being placed upon illustrating the principles of various embodiments of the disclosure.

[0023] FIG. 1A and FIG. 1B are maps of wild-type AAV capsid gene transcription and CMV-CAP vectors. FIG. 1A shows transcription of VP1, VP2 and VP3 AAV transcripts from wildtype AAV genome. Transcription start sites of each viral promoter are indicated. SD, splice donor, SA, splice acceptor. Sequence of start codons for each reading frame is indicated. Translation of AAP and VP3 is performed by leaky scanning of the major mRNA. FIG. 1B shows the structure of the CMV-p40 dual promoter vectors used to determine the minimal regulatory sequences necessary for efficient virus production. The pREP2 Δ CAP vector shown at the bottom is obtained by deletion of most CAP reading frame and is used to provide the REP protein in trans.

[0024] FIG. 2A and FIG. 2B are histogram representations of the data and show the effect of CMV promoter position on virus yield and CAP mRNA splicing. FIG. 2A shows average yield of AAV9 produced in HEK-293T cells using the constructs described in FIG. 1, co-transfected with an Ad Helper vector. Wild-type AAV9 plasmid (pAV9) is used as a positive control. Y-axis values indicate AAV DNA copies per μ l from each 15-cm plate ($\sim$ 1000ul total, left panel) or the percentage of wtAAV9 (right panel). FIG. 2B shows evidence for expression of CAP transcripts in transfected cells. mRNA from transfected 293T cells was subjected to RT-PCR using primers specific for the major spliced CAP transcript. Note the lack of p40-driven transcription in the absence of Ad Helper vector (lane 2).

[0025] FIG. 3A, FIG. 3B and FIG. 3C show the effect of REP helper plasmid optimization on virus yield. FIG. 3A shows the design of improved pREP helper vectors. The MscI fragment deletion removes the C-terminal part of VP proteins, which is necessary for capsid formation. Asterisks represent early stop codons introduced to disrupt the coding potential of VP1, VP2 and VP3 reading frames. FIG. 3B shows the yield of Synapsin-p40-CAP9 AAV produced with various REP plasmid architectures. Values on the Y-axis represent the percentage of VG relative to wild-type AAV9. FIG. 3C shows the quantification of recombination and/or illegitimate packaging of full-length REP from the pREP plasmids. Virus stocks produced were subjected to qPCR using Taqman probes located in the N-terminal part of REP absent from the ITR-containing vectors.

[0026] FIG. 4A, FIG. 4B, FIG. 4C and FIG. 4D describe the *in vivo* analysis of the second-generation vectors. FIG. 4A shows the design of Pro9 vectors. Architecture of all three vectors is based on the BstEII construct. AAV9 capsid RNA is placed under control of P40 and CMV, hSyn1 or GFAP promoters, respectively. FIG. 4B shows the silver stain of SDS-PAGE gel obtained by running 1e10 VG of each vector, after double iodixanol purification. FIG. 4C shows the biodistribution of viral DNA in mouse brain (cortex), liver

and heart following tail-vein injection of 1×10^{12} VG per mouse. AAV9 VP3 DNA is quantified by Taqman PCR and normalized to mouse transferrin receptor gene. FIG. 4D shows the capsid RNA recovery from mouse tissues. Total RNA was reverse transcribed and Taqman PCR was performed with capsid-specific Taqman primers and probe. Values represent VP3 cDNA copies normalized to TBP housekeeping gene.

[0027] FIG. 5A, FIG. 5B, FIG. 5C, FIG. 5D and FIG. 5E describes *in vitro* analysis of intronic second generation vectors. FIG. 5A shows the design of intronic Pro9 vectors harboring a hybrid CMV/Globin intron. AAV9 capsid RNA is placed under control of P40 and CBA, hSyn1 or GFAP promoters in a tandem configuration (top) or in an inverted configuration (bottom). In the inverted promoter vectors, an extra SV40 polyadenylation site (orange) is added at the 3' extremity to allow polyadenylation of antisense CAP9 transcripts. FIG. 5B shows the AAV9 CAP cDNA amplification. All vectors depicted were produced using triple transfection with pHelper and pREP-3stops and resulting viruses were used to infect HEK-293T cells at a MOI of 1×10^4 VG per cell. RNA was extracted 48 hours post-infection and subjected to RT-PCR with primers amplifying full capsid (top) or a C-terminal fragment (bottom). FIG. 5C shows the AAV9 VP3 cDNA from cells infected with intronless or intronic viruses with tandem promoters in forward orientation was quantified by Taqman PCR and normalized to GAPDH housekeeping gene. Values indicate the ratio of VP3 to GAPDH cDNA. FIG. 5D shows the mapping of capsid RNA recovery from cells infected with tandem or inverted constructs. Total RNA was reverse transcribed and PCR was performed with primers flanking the entire capsid gene. White arrowheads represent VP3 size variants resulting from aberrant splicing of antisense CAP mRNA. FIG. 5E shows the analysis of Globin intron splicing. CAG9 plasmid (left) or cDNA from HEK-293T cells transduced by CAG9 virus was submitted to PCR with forward primers located before (Glo ex1) or within (GloSpliceF4 (SEQ ID NO: 26) and GloSpliceF6 (SEQ ID NO: 13)) the Globin exon-exon junction. Primers spanning junction between exon 1 (no underline) and exon 2 (underline) are described at the bottom.

[0028] FIG. 6 provides *in vitro* evidence that the presence of the P40 promoter downstream of Synapsin or GfabclD promoters does not relieve the repression of either promoter in HEK-293T cells.

[0029] FIG. 7 illustrates the basic tenets of the TRACER platform.

[0030] FIG. 8 illustrates features of the TRACER platform including the use of a tissue specific promoter and RNA recovery.

[0031] FIG. 9 provides one embodiment of the TRACER production architecture.

- [0032] FIG. 10 provides a comparison between traditional vDNA recovery and 2nd generation vRNA recovery.
- [0033] FIG. 11 provides an overview of the use of cell-specific RNA expression for targeted evolution.
- [0034] FIG. 12A and FIG. 12B provide diagrams representing capsid gene transcription of natural AAV (FIG. 12A) and TRACER libraries (FIG. 12B).
- [0035] FIG. 13 is a diagram of the AAV6, AAV5 and AAV-DJ capsid peptide display libraries used for in vivo evolution (SEQ ID NOS 27-32, respectively, in order of appearance).
- [0036] FIG. 14 is a diagram of the AAV9 capsid peptide display libraries used for in vivo evolution (SEQ ID NOS 33-42, respectively, in order of appearance).
- [0037] FIG. 15A and FIG. 15B present the method used for library construction. FIG. 15A shows the sequence of the insertion site used to introduce random libraries (SEQ ID NOS 43-46, respectively, in order of appearance). FIG. 15B provides a description of the assembly procedure.
- [0038] FIG. 16 provides an exemplary diagram of cloning-free rolling circle procedure used for library amplification (SEQ ID NO 47; NNK₇).
- [0039] FIG. 17 provides the sequence of the codon-mutant AAV9 library shuttle designed to minimize wild-type contamination (SEQ ID NOS 33-34 and 48-52, respectively, in order of appearance).
- [0040] FIG. 18 provides a description of AAV9 peptide libraries biopanning.
- [0041] FIG. 19 illustrates the recovery process from an initial pool with recovery at 50%.
- [0042] FIG. 20 provides an example of the cDNA recovery and amplification from GFAP-driven libraries (B group and F group).
- [0043] FIG. 21A, FIG. 21B and FIG. 21C show the progression of AAV9 peptide library diversity throughout the biopanning process. FIG. 21A describes RNA library evolution. FIG. 21B and FIG. 21C show the amino acid distribution of NNK machine mix preparations for P0 and P1 virus.
- [0044] FIG. 22 provides neuron (SYN)-AAV9 Peptide Libraries Composition at P2.
- [0045] FIG. 23 provides astrocyte (GFAP)-AAV9 Peptide Libraries Composition at P2.
- [0046] FIG. 24 provides an estimation of brain/liver specificity in GFAP-AAV9 peptide library candidates.
- [0047] FIG. 25 provides an estimation of brain/liver specificity in GFAP-AAV9 peptide library candidates.

- [0048] FIG. 26 provide an example subpopulation selection of variants.
- [0049] FIG. 27 provides an exemplary design of a library generation and cloning procedure.
- [0050] FIG. 28 provides the NNK/NNM codon distribution (covariance of codon mutants) of AAV produced with a synthetic library of 666 sequence variants (GFAP promoter).
- [0051] FIG. 29 provides the NNK/NNM codon distribution (covariance of codon mutants) of AAV produced with a synthetic library of 666 sequence variants (SYN9 promoter).
- [0052] FIG. 30 provides the data from the tissue recovery, one-month post injection, from brain and a liver punch.
- [0053] FIG. 31A, FIG. 31B, FIG. 31C and FIG. 31D provide results of control capsids from the Syn-driven synthetic library NGS analysis. FIG. 31A shows the enrichment analysis of internal AAV9, PHP.B and PHP.eB controls (SEQ ID NOS 53-58 and 53-58, respectively, in order of appearance). FIG. 31B, FIG. 31C and FIG. 31D show the NNK/NNM codon distribution in mRNA from mouse brain tissue.
- [0054] FIG. 32A and FIG. 32B provide the results of the neuron synthetic library NGS analysis (SEQ ID NOS 59-60, 59-61, 61-63, 62, 64, 64, 63, 65-67, 67, 65, 68, 66, 69, 70-71, and 70-74, respectively, in order of appearance).
- [0055] FIG. 33 provides the results of the astrocyte synthetic library NGS analysis (SEQ ID NOS 53-58, 53-58, and 53-58, respectively, in order of appearance).
- [0056] FIG. 34A and FIG. 34B provide astrocyte synthetic library codon mutants covariance.
- [0057] FIG. 35 provides the results of the astrocyte synthetic library NGS analysis (SEQ ID NOS 75, 75-78, 76-77, 79-83, 65, 78, 84, 80, 85, 70, 86, 82, 81, 79, 87, 65, 85, 84, 70, 86, 88-90, 87, 91, 83, 88, 63, 89-90, 92-93, 91, 94-97, 93, 95, 98, 98, 97, 63, 92, 94, 99-101, 75, 75-78, 76-77, 79-83, 65, 78, 84, 80, 85, 70, 86, 82, 81, 79, 87, 65, 85, 84, 70, 86, 88-90, 87, 91, 83, 88, 63, 89-90, 92-93, 91, 94-97, 93, 95, 98, 98, 97, 63, 92, 94, 99-102, 99, 103, 103-104, 96, 105-106, 101, 100, 102, 107, 104-105, 108-113, 106, 60, 66, 114-117, 109, 113, 72, 108, 110, 67, 118-119, 116, 120, 120, 107, 112, 121-123, 66, 124-125, 115, 118, 126, 121, 127-128, 60, 129, 119, 130-132, 72, 133, 123, 125, 69, 134-139, 62, 124, 67, 111, 114, 126, 140-141, 122, 142, 128-129, 143, 138, 144, 134, 62, 136, 145, 141, 146-153, 127, 154, 69, 144, 155, 71, 156, 133, 132, 137, 147, 157-158, 135, 159, 140, 117, 160, 139, 161-162, 130, 163, 143, 164, 152, 151, 165-167, 155, 168, 71, 169, and 146, respectively, in order of appearance).
- [0058] FIG. 36 provides the GFAP synthetic library NGS analysis.

[0059] FIG. 37A and FIG. 37B provides the top 38 variants from the synthetic library screen. FIG. 37A shows the phylogenetic analysis of 9-mer peptide sequences, and also shows the sequence of the peptide variants (SEQ ID NOS 67, 59, 64, 61, 77, 84, 96, 60, 80, 82, 66, 62, 83, 85, 106, 131, 94, 90, 76, 68-69, 79, 75, 81, 88, 139, 78, 155, 102, 63, 140, 87, 70, 105, 120, 89, 65, and 109, respectively, in order of appearance). Highlighted sequences represent the peptides that were selected for individual transduction assay. FIG. 37B shows the graphic representation of the neuron and astrocyte tropism of each peptide, both axis indicate the inverted rank in Synapsin and GFAP screen.

[0060] FIG. 38 provides the top consensus sequences as compared to PHP.N and PHP.B (SEQ ID NOS 168 and 71, respectively, in order of appearance).

[0061] FIG. 39 is a diagram of the Gibson assembly library cloning procedure.

[0062] FIG. 40 provides an example of TRIM/NNK peptide prevalence (SEQ ID NOS 170-171, respectively, in order of appearance).

[0063] FIG. 41 provides peptide diversity statistics from a study using the Illumina adapter having 42 million bacterial transformants, 81 million sequence reads and 12 million sequence variants (SEQ ID NOS 172-173, 48-49, and 174-175, respectively, in order of appearance).

[0064] FIG. 42 provides an exemplary diagram of cloning-free DNA amplification by rolling circle amplification.

[0065] FIG. 43 provides a diagram of protelomerase monomer processing (SEQ ID NOS 176-178, respectively, in order of appearance).

[0066] FIG. 44 provides a diagram comparing the traditional and cloning-free methods.

[0067] FIG. 45A and FIG. 45C provide the full ranking of Syn-driven (FIG. 45A) and GFAP-driven (FIG. 45B) 333 variants in the brain, spinal cord, liver and heart tissues. Capsid variants are ranked by their average brain RNA enrichment score (average of NNK and NNM codons). The rank of internal control capsids PHP.B, PHP.eB and AAV9 is indicated (FIG. 45A and FIG. 45B). A comparison of combined Syn-driven results and GFAP-driven results is provided (FIG. 45C). Only 4 animals were represented for the GFAP-driven libraries because 2/6 mice showed a very different ranking profile and were considered as outliers.

[0068] FIG. 46A and FIG. 46B provide the comparison of results of the neuron and astrocyte synthetic library NGS analysis. FIG 46A shows the ranking of capsids using SYN or GFAP promoters; FIG. 46B shows the scatter plot showing the correlation of Syn- versus GFAP-driven libraries.

[0069] FIG. 47 illustrates one embodiment of a multi-species (e.g., rodent) study followed by next generation sequencing (NGS).

[0070] FIG. 48A, FIG. 48B and FIG. 48C provide results from a multi-strain/species comparison of 333 capsid variants. FIG. 48A shows the ranking of 333 capsids by brain RNA enrichment score in C57BL/6 mice, BALB/C mice and rats. Capsids are ranked according to Syn-driven brain enrichment score in C57BL/6 mice. FIG. 48B shows the scatter plots showing the correlation between C57BL/6 and BALB/C enrichment scores from Syn- and GFAP-driven pools. FIG. 48C shows the Venn diagram showing the intersection and consensus sequence of capsids with a brain enrichment score >10-fold higher than AAV9 (either Syn- or GFAP-driven) in C57BL/6 and BALB/C strains. In rats, no capsid showed an enrichment score >10-fold versus AAV9.

[0071] FIG. 49A, FIG. 49B, FIG. 49C and FIG. 49D provide transduction (RNA) and biodistribution (DNA) analysis of 10 capsid variants indicated in FIG. 49A (SEQ ID NOS 179-188, respectively, in order of appearance). Individual capsids were used to package self-complementary CBA-EGFP genomes (FIG. 49B) and injected intravenously to C57BL/6 mice. FIG. 49C shows the RNA expression in brain and spinal cord samples. FIG. 49D shows the DNA distribution in brain and spinal cord samples.

[0072] FIG. 50A, FIG. 50B and FIG. 50C provide the results of testing of individual capsids and their mRNA expression in brain, spinal cord and liver. EGFP mRNA expression results are shown for the brain (FIG. 50A), the spinal cord (FIG. 50B) and the liver (FIG. 50C).

[0073] FIG. 51 provides results for NGS screening using neuronal NeuN marker (FIG. 51) for both GFAP screening and SYN screening.

[0074] FIG. 52 provides the results of testing of individual capsids in whole brain.

[0075] FIG. 53 provides the results of testing of additional individual capsids in whole brain.

[0076] FIG. 54 provides the results of testing of individual capsids in cerebellum.

[0077] FIG. 55 provides the results of testing of individual capsids in cortex.

[0078] FIG. 56 provides the results of testing of individual capsids in hippocampus.

[0079] FIG. 57A and FIG. 57B provide transduction data of 10 capsid variants in mouse liver (FIG. 57B), analyzed by EGFP RNA expression and whole tissue fluorescence (FIG. 57A).

[0080] FIG. 58A and FIG. 58B provide results for comparison studies on the efficacy of the 333 capsid variants to transduce CNS for C57BL/6 mice BMVEC (FIG. 58A) and Human BMVEC (FIG. 58B).

[0081] FIG. 59A, FIG. 59B and FIG. 59C provide diagrams of external barcoding for NGS analysis and recovery of full-length capsid variants. A general barcode pair is shown (FIG. 59C). Full ITR-to-ITR constructs are shown with the barcode pair 5' of the CAP sequence (FIG. 59A) and 3' of the CAP sequence (FIG. 59B).

[0082] FIG. 60A, FIG. 60B and FIG. 60C provide detailed analysis of virus production and RNA splicing with several configurations of intronic barcoded platforms. A general ITR-to-ITR construct is shown in FIG. 60A (SEQ ID NOS 189-193, respectively, in order of appearance), with intronic barcode yields (FIG. 60B) and gel columns showing AAV intron splicing and Globin intron splicing results (FIG. 60C).

DETAILED DESCRIPTION OF THE DISCLOSURE

[0083] The details of one or more embodiments of the disclosure are set forth in the accompanying description below. Although any materials and methods similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, the preferred materials and methods are now described. Other features, objects and advantages of the disclosure will be apparent from the description. In the description, the singular forms also include the plural unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. In the case of conflict, the present description will control.

[0084] According to the present disclosure, AAV particles with enhanced tropism for a target tissue (e.g., CNS) are provided, as well as associated processes for their targeting, preparation, formulation and use. Targeting peptides and nucleic acid sequences encoding the targeting peptides are provided. These targeting peptides may be inserted into an AAV capsid protein sequence to alter tropism to a particular cell-type, tissue, organ or organism, *in vivo*, *ex vivo* or *in vitro*.

[0085] As used herein, an “AAV particle” or “AAV vector” comprises a capsid protein and a viral genome, wherein the viral genome comprises at least one payload region and at least one inverted terminal repeat (ITR). The AAV particle and/or its component capsid and viral genome may be engineered to alter tropism to a particular cell-type, tissue, organ or organism.

[0086] As used herein, “viral genome” or “vector genome” refers to the nucleic acid sequence(s) encapsulated in an AAV particle. A viral genome comprises a nucleic acid sequence with at least one payload region encoding a payload and at least one ITR.

[0087] As used herein, a “payload region” is any nucleic acid molecule which encodes one or more “payloads” of the disclosure. As non-limiting examples, a payload region may be a nucleic acid sequence encoding a payload comprising an RNAi agent or a polypeptide.

[0088] As used herein, a “targeting peptide” refers to a peptide of 3-20 amino acids in length. These targeting peptides may be inserted into, or attached to, a parent amino acid sequence to alter the characteristics (e.g., tropism) of the parent protein. As a non-limiting example, the targeting peptide can be inserted into an AAV capsid sequence for enhanced targeting to a desired cell-type, tissue, organ or organism.

[0089] The AAV particles and payloads of the disclosure may be delivered to one or more target cells, tissues, organs, or organisms. In a preferred embodiment, the AAV particles of the disclosure demonstrate enhanced tropism for a target cell type, tissue or organ. As a non-limiting example, the AAV particle may have enhanced tropism for cells and tissues of the central or peripheral nervous systems (CNS and PNS, respectively). The AAV particles of the disclosure may, in addition, or alternatively, have decreased tropism for an undesired target cell-type, tissue or organ.

[0090] Adeno-associated viruses (AAV) are small non-enveloped icosahedral capsid viruses of the Parvoviridae family characterized by a single stranded DNA viral genome. Parvoviridae family viruses consist of two subfamilies: Parvovirinae, which infect vertebrates, and Densovirinae, which infect invertebrates. The Parvoviridae family comprises the Dependovirus genus which includes AAV, capable of replication in vertebrate hosts including, but not limited to, human, primate, bovine, canine, equine, and ovine species.

[0091] The parvoviruses and other members of the Parvoviridae family are generally described in Kenneth I. Berns, “Parvoviridae: The Viruses and Their Replication,” Chapter 69 in *FIELDS VIROLOGY* (3d Ed. 1996), the contents of which are incorporated by reference in their entirety.

[0092] AAV have proven to be useful as a biological tool due to their relatively simple structure, their ability to infect a wide range of cells (including quiescent and dividing cells) without integration into the host genome and without replicating, and their relatively benign immunogenic profile. The genome of the virus may be manipulated to contain a minimum of components for the assembly of a functional recombinant virus, or viral particle, which is

loaded with or engineered to target a particular tissue and express or deliver a desired payload.

[0093] The wild-type AAV vector genome is a linear, single-stranded DNA (ssDNA) molecule approximately 5,000 nucleotides (nt) in length. Inverted terminal repeats (ITRs) traditionally cap the viral genome at both the 5' and the 3' end, providing origins of replication for the viral genome. While not wishing to be bound by theory, an AAV viral genome typically comprises two ITR sequences. These ITRs have a characteristic T-shaped hairpin structure defined by a self-complementary region (145nt in wild-type AAV) at the 5' and 3' ends of the ssDNA which form an energetically stable double stranded region. The double stranded hairpin structures comprise multiple functions including, but not limited to, acting as an origin for DNA replication by functioning as primers for the endogenous DNA polymerase complex of the host viral replication cell.

[0094] The wild-type AAV viral genome further comprises nucleotide sequences for two open reading frames, one for the four non-structural Rep proteins (Rep78, Rep68, Rep52, Rep40, encoded by Rep genes) and one for the three capsid, or structural, proteins (VP1, VP2, VP3, encoded by capsid genes or Cap genes). The Rep proteins are important for replication and packaging, while the capsid proteins are assembled to create the protein shell of the AAV, or AAV capsid. Alternative splicing and alternate initiation codons and promoters result in the generation of four different Rep proteins from a single open reading frame and the generation of three capsid proteins from a single open reading frame. Though it varies by AAV serotype, as a non-limiting example, for AAV9/hu.14 (SEQ ID NO: 123 of US 7,906,111, the contents of which are herein incorporated by reference in their entirety) VP1 refers to amino acids 1-736, VP2 refers to amino acids 138-736, and VP3 refers to amino acids 203-736. In other words, VP1 is the full-length capsid sequence, while VP2 and VP3 are shorter components of the whole. As a result, changes in the sequence in the VP3 region, are also changes to VP1 and VP2, however, the percent difference as compared to the parent sequence will be greatest for VP3 since it is the shortest sequence of the three. Though described here in relation to the amino acid sequence, the nucleic acid sequence encoding these proteins can be similarly described. Together, the three capsid proteins assemble to create the AAV capsid protein. While not wishing to be bound by theory, the AAV capsid protein typically comprises a molar ratio of 1:1:10 of VP1:VP2:VP3. As used herein, an "AAV serotype" is defined primarily by the AAV capsid. In some instances, the ITRs are also specifically described by the AAV serotype (e.g., AAV2/9).

[0095] AAV vectors of the present disclosure may be produced recombinantly and may be based on adeno-associated virus (AAV) parent or reference sequences. As used herein, a “vector” is any molecule or moiety which transports, transduces, or otherwise acts as a carrier of a heterologous molecule such as the nucleic acids described herein.

[0096] In addition to single stranded AAV viral genomes (e.g., ssAAVs), the present disclosure also provides for self-complementary AAV (scAAVs) viral genomes. scAAV vector genomes contain DNA strands which anneal together to form double stranded DNA. By skipping second strand synthesis, scAAVs allow for rapid expression in the transduced cell.

[0097] In one embodiment, the AAV particle of the present disclosure is an scAAV.

[0098] In one embodiment, the AAV particle of the present disclosure is an ssAAV.

[0099] Methods for producing and/or modifying AAV particles are disclosed in the art such as pseudotyped AAV vectors (PCT Patent Publication Nos. WO200028004; WO200123001; WO2004112727; WO2005005610; and WO2005072364, the content of each of which is incorporated herein by reference in its entirety).

[0100] In one embodiment, the AAV particles of the disclosure comprising a capsid with an inserted targeting peptide and a viral genome, may have enhanced tropism for a cell-type or tissue of the human CNS.

AAV Capsids

[0101] AAV particles of the present disclosure may comprise or be derived from any natural or recombinant AAV serotype. AAV serotypes may differ in characteristics such as, but not limited to, packaging, tropism, transduction and immunogenic profiles. While not wishing to be bound by theory, the AAV capsid protein is often considered to be the driver of AAV particle tropism to a particular tissue.

[0102] In one embodiment, an AAV particle may have a capsid protein and ITR sequences derived from the same parent serotype (e.g., AAV2 capsid and AAV2 ITRs). In another embodiment, the AAV particle may be a pseudo-typed AAV particle, wherein the capsid protein and ITR sequences are derived from different parent serotypes (e.g., AAV9 capsid and AAV2 ITRs; AAV2/9).

[0103] The AAV particles of the present disclosure may comprise an AAV capsid protein with a targeting peptide inserted into the parent sequence. The parent capsid or serotype may comprise or be derived from any natural or recombinant AAV serotype. As used herein, a “parent” sequence is a nucleotide or amino acid sequence into which a targeting sequence is

inserted (i.e., nucleotide insertion into nucleic acid sequence or amino acid sequence insertion into amino acid sequence).

[0104] In a preferred embodiment, the parent AAV capsid nucleotide sequence is as set forth in SEQ ID NO: 1.

[0105] In another embodiment, the parent AAV capsid nucleotide sequence is a K449R variant of SEQ ID NO: 1, wherein the codon encoding a lysine (e.g., AAA or AAG) at position 449 in the amino acid sequence (nucleotides 1345-1347) is exchanged for one encoding an arginine (CGT, CGC, CGA, CGG, AGA, AGG). The K449R variant has the same function as wild-type AAV9.

[0106] In one embodiment, the parent AAV capsid amino acid sequence is as set forth in SEQ ID NO: 2.

[0107] In another embodiment, the parent AAV capsid amino acid sequence is as set forth in SEQ ID NO: 3.

[0108] In one embodiment the parent AAV capsid sequence is any of those shown in Table 1.

Table 1. AAV Capsid Sequences

Serotype	SEQ ID NO	Reference Information
AAV9/hu.14 (nt)	1	US7906111 SEQ ID NO: 3; WO2015038958 SEQ ID NO: 11
AAV9/hu.14 (aa)	2	US7906111 SEQ ID NO: 123; WO2015038958 SEQ ID NO: 2
AAV9/hu.14 K449R (aa)	3	WO2017100671 SEQ ID NO: 45

[0109] Each of the patents, applications and or publications listed in Table 1 are hereby incorporated by reference in their entirety.

[0110] The parent AAV serotype and associated capsid sequence may be any of those known in the art. Non-limiting examples of such AAV serotypes include, AAV9, AAV9 K449R (or K449R AAV9), AAV1, AAVrh10, AAV-DJ, AAV-DJ8, AAV5, AAVPHP.B (PHP.B), AAVPHP.A (PHP.A), AAVG2B-26, AAVG2B-13, AAVTH1.1-32, AAVTH1.1-35, AAVPHP.B2 (PHP.B2), AAVPHP.B3 (PHP.B3), AAVPHP.N/PHP.B-DGT, AAVPHP.B-EST, AAVPHP.B-GGT, AAVPHP.B-ATP, AAVPHP.B-ATT-T, AAVPHP.B-DGT-T, AAVPHP.B-GGT-T, AAVPHP.B-SGS, AAVPHP.B-AQP, AAVPHP.B-QQP, AAVPHP.B-SNP(3), AAVPHP.B-SNP, AAVPHP.B-QGT, AAVPHP.B-NQT, AAVPHP.B-EGS, AAVPHP.B-SGN, AAVPHP.B-EGT, AAVPHP.B-DST, AAVPHP.B-DST, AAVPHP.B-STP, AAVPHP.B-PQP, AAVPHP.B-SQP, AAVPHP.B-QLP, AAVPHP.B-TMP, AAVPHP.B-TTP, AAVPHP.S/G2A12, AAVG2A15/G2A3 (G2A3), AAVG2B4

(G2B4), AAVG2B5 (G2B5), PHP.S, AAV2, AAV2G9, AAV3, AAV3a, AAV3b, AAV3-3, AAV4, AAV4-4, AAV6, AAV6.1, AAV6.2, AAV6.1.2, AAV7, AAV7.2, AAV8, AAV9.11, AAV9.13, AAV9.16, AAV9.24, AAV9.45, AAV9.47, AAV9.61, AAV9.68, AAV9.84, AAV9.9, AAV10, AAV11, AAV12, AAV16.3, AAV24.1, AAV27.3, AAV42.12, AAV42-1b, AAV42-2, AAV42-3a, AAV42-3b, AAV42-4, AAV42-5a, AAV42-5b, AAV42-6b, AAV42-8, AAV42-10, AAV42-11, AAV42-12, AAV42-13, AAV42-15, AAV42-aa, AAV43-1, AAV43-12, AAV43-20, AAV43-21, AAV43-23, AAV43-25, AAV43-5, AAV44.1, AAV44.2, AAV44.5, AAV223.1, AAV223.2, AAV223.4, AAV223.5, AAV223.6, AAV223.7, AAV1-7/rh.48, AAV1-8/rh.49, AAV2-15/rh.62, AAV2-3/rh.61, AAV2-4/rh.50, AAV2-5/rh.51, AAV3.1/hu.6, AAV3.1/hu.9, AAV3-9/rh.52, AAV3-11/rh.53, AAV4-8/r11.64, AAV4-9/rh.54, AAV4-19/rh.55, AAV5-3/rh.57, AAV5-22/rh.58, AAV7.3/hu.7, AAV16.8/hu.10, AAV16.12/hu.11, AAV29.3/bb.1, AAV29.5/bb.2, AAV106.1/hu.37, AAV114.3/hu.40, AAV127.2/hu.41, AAV127.5/hu.42, AAV128.3/hu.44, AAV130.4/hu.48, AAV145.1/hu.53, AAV145.5/hu.54, AAV145.6/hu.55, AAV161.10/hu.60, AAV161.6/hu.61, AAV33.12/hu.17, AAV33.4/hu.15, AAV33.8/hu.16, AAV52/hu.19, AAV52.1/hu.20, AAV58.2/hu.25, AAVA3.3, AAVA3.4, AAVA3.5, AAVA3.7, AAVC1, AAVC2, AAVC5, AAVF3, AAVF5, AAVH2, AAVrh.72, AAVhu.8, AAVrh.68, AAVrh.70, AAVpi.1, AAVpi.3, AAVpi.2, AAVrh.60, AAVrh.44, AAVrh.65, AAVrh.55, AAVrh.47, AAVrh.69, AAVrh.45, AAVrh.59, AAVhu.12, AAVH6, AAVH-1/hu.1, AAVH-5/hu.3, AAVLG-10/rh.40, AAVLG-4/rh.38, AAVLG-9/hu.39, AAVN721-8/rh.43, AAVCh.5, AAVCh.5R1, AAVcy.2, AAVcy.3, AAVcy.4, AAVcy.5, AAVCy.5R1, AAVCy.5R2, AAVCy.5R3, AAVCy.5R4, AAVcy.6, AAVhu.1, AAVhu.2, AAVhu.3, AAVhu.4, AAVhu.5, AAVhu.6, AAVhu.7, AAVhu.9, AAVhu.10, AAVhu.11, AAVhu.13, AAVhu.15, AAVhu.16, AAVhu.17, AAVhu.18, AAVhu.20, AAVhu.21, AAVhu.22, AAVhu.23.2, AAVhu.24, AAVhu.25, AAVhu.27, AAVhu.28, AAVhu.29, AAVhu.29R, AAVhu.31, AAVhu.32, AAVhu.34, AAVhu.35, AAVhu.37, AAVhu.39, AAVhu.40, AAVhu.41, AAVhu.42, AAVhu.43, AAVhu.44, AAVhu.44R1, AAVhu.44R2, AAVhu.44R3, AAVhu.45, AAVhu.46, AAVhu.47, AAVhu.48, AAVhu.48R1, AAVhu.48R2, AAVhu.48R3, AAVhu.49, AAVhu.51, AAVhu.52, AAVhu.54, AAVhu.55, AAVhu.56, AAVhu.57, AAVhu.58, AAVhu.60, AAVhu.61, AAVhu.63, AAVhu.64, AAVhu.66, AAVhu.67, AAVhu.14/9, AAVhu.t 19, AAVrh.2, AAVrh.2R, AAVrh.8, AAVrh.8R, AAVrh.10, AAVrh.12, AAVrh.13, AAVrh.13R, AAVrh.14, AAVrh.17, AAVrh.18, AAVrh.19, AAVrh.20, AAVrh.21, AAVrh.22, AAVrh.23, AAVrh.24, AAVrh.25, AAVrh.31, AAVrh.32, AAVrh.33, AAVrh.34, AAVrh.35, AAVrh.36, AAVrh.37, AAVrh.37R2,

AAVrh.38, AAVrh.39, AAVrh.40, AAVrh.46, AAVrh.48, AAVrh.48.1, AAVrh.48.1.2, AAVrh.48.2, AAVrh.49, AAVrh.51, AAVrh.52, AAVrh.53, AAVrh.54, AAVrh.56, AAVrh.57, AAVrh.58, AAVrh.61, AAVrh.64, AAVrh.64R1, AAVrh.64R2, AAVrh.67, AAVrh.73, AAVrh.74, AAVrh8R, AAVrh8R A586R mutant, AAVrh8R R533A mutant, AAV, BAAV, caprine AAV, bovine AAV, AAVhE1.1, AAVhEr1.5, AAVhEr1.14, AAVhEr1.8, AAVhEr1.16, AAVhEr1.18, AAVhEr1.35, AAVhEr1.7, AAVhEr1.36, AAVhEr2.29, AAVhEr2.4, AAVhEr2.16, AAVhEr2.30, AAVhEr2.31, AAVhEr2.36, AAVhEr1.23, AAVhEr3.1, AAV2.5T, AAV-PAEC, AAV-LK01, AAV-LK02, AAV-LK03, AAV-LK04, AAV-LK05, AAV-LK06, AAV-LK07, AAV-LK08, AAV-LK09, AAV-LK10, AAV-LK11, AAV-LK12, AAV-LK13, AAV-LK14, AAV-LK15, AAV-LK16, AAV-LK17, AAV-LK18, AAV-LK19, AAV-PAEC2, AAV-PAEC4, AAV-PAEC6, AAV-PAEC7, AAV-PAEC8, AAV-PAEC11, AAV-PAEC12, AAV-2-pre-miRNA-101, AAV-8h, AAV-8b, AAV-h, AAV-b, AAV SM 10-2, AAV Shuffle 100-1, AAV Shuffle 100-3, AAV Shuffle 100-7, AAV Shuffle 10-2, AAV Shuffle 10-6, AAV Shuffle 10-8, AAV Shuffle 100-2, AAV SM 10-1, AAV SM 10-8, AAV SM 100-3, AAV SM 100-10, BNP61 AAV, BNP62 AAV, BNP63 AAV, AAVrh.50, AAVrh.43, AAVrh.62, AAVrh.48, AAVhu.19, AAVhu.11, AAVhu.53, AAV4-8/rh.64, AAVLG-9/hu.39, AAV54.5/hu.23, AAV54.2/hu.22, AAV54.7/hu.24, AAV54.1/hu.21, AAV54.4R/hu.27, AAV46.2/hu.28, AAV46.6/hu.29, AAV128.1/hu.43, true type AAV (ttAAV), UPENN AAV 10, Japanese AAV 10 serotypes, AAV CBr-7.1, AAV CBr-7.10, AAV CBr-7.2, AAV CBr-7.3, AAV CBr-7.4, AAV CBr-7.5, AAV CBr-7.7, AAV CBr-7.8, AAV CBr-B7.3, AAV CBr-B7.4, AAV CBr-E1, AAV CBr-E2, AAV CBr-E3, AAV CBr-E4, AAV CBr-E5, AAV CBr-e5, AAV CBr-E6, AAV CBr-E7, AAV CBr-E8, AAV CHt-1, AAV CHt-2, AAV CHt-3, AAV CHt-6.1, AAV CHt-6.10, AAV CHt-6.5, AAV CHt-6.6, AAV CHt-6.7, AAV CHt-6.8, AAV CHt-P1, AAV CHt-P2, AAV CHt-P5, AAV CHt-P6, AAV CHt-P8, AAV CHt-P9, AAV CKd-1, AAV CKd-10, AAV CKd-2, AAV CKd-3, AAV CKd-4, AAV CKd-6, AAV CKd-7, AAV CKd-8, AAV CKd-B1, AAV CKd-B2, AAV CKd-B3, AAV CKd-B4, AAV CKd-B5, AAV CKd-B6, AAV CKd-B7, AAV CKd-B8, AAV CKd-H1, AAV CKd-H2, AAV CKd-H3, AAV CKd-H4, AAV CKd-H5, AAV CKd-H6, AAV CKd-N3, AAV CKd-N4, AAV CKd-N9, AAV CLg-F1, AAV CLg-F2, AAV CLg-F3, AAV CLg-F4, AAV CLg-F5, AAV CLg-F6, AAV CLg-F7, AAV CLg-F8, AAV CLv-1, AAV CLv1-1, AAV CLv1-10, AAV CLv1-2, AAV CLv-12, AAV CLv1-3, AAV CLv-13, AAV CLv1-4, AAV CLv1-7, AAV CLv1-8, AAV CLv1-9, AAV CLv-2, AAV CLv-3, AAV CLv-4, AAV CLv-6, AAV CLv-8, AAV CLv-D1, AAV CLv-D2, AAV CLv-D3, AAV CLv-D4, AAV CLv-D5, AAV CLv-D6, AAV CLv-D7, AAV CLv-D8,

AAV CL_v-E1, AAV CL_v-K1, AAV CL_v-K3, AAV CL_v-K6, AAV CL_v-L4, AAV CL_v-L5, AAV CL_v-L6, AAV CL_v-M1, AAV CL_v-M11, AAV CL_v-M2, AAV CL_v-M5, AAV CL_v-M6, AAV CL_v-M7, AAV CL_v-M8, AAV CL_v-M9, AAV CL_v-R1, AAV CL_v-R2, AAV CL_v-R3, AAV CL_v-R4, AAV CL_v-R5, AAV CL_v-R6, AAV CL_v-R7, AAV CL_v-R8, AAV CL_v-R9, AAV CSp-1, AAV CSp-10, AAV CSp-11, AAV CSp-2, AAV CSp-3, AAV CSp-4, AAV CSp-6, AAV CSp-7, AAV CSp-8, AAV CSp-8.10, AAV CSp-8.2, AAV CSp-8.4, AAV CSp-8.5, AAV CSp-8.6, AAV CSp-8.7, AAV CSp-8.8, AAV CSp-8.9, AAV CSp-9, AAV.hu.48R3, AAV.VR-355, AAV3B, AAV4, AAV5, AAVF1/HSC1, AAVF11/HSC11, AAVF12/HSC12, AAVF13/HSC13, AAVF14/HSC14, AAVF15/HSC15, AAVF16/HSC16, AAVF17/HSC17, AAVF2/HSC2, AAVF3/HSC3, AAVF4/HSC4, AAVF5/HSC5, AAVF6/HSC6, AAVF7/HSC7, AAVF8/HSC8, and/or AAVF9/HSC9 and variants thereof.

[0111] In some embodiments, the serotype may be AAVDJ or a variant thereof, such as AAVDJ8 (or AAV-DJ8), as described by Grimm et al. (Journal of Virology 82(12): 5887-5911 (2008), US Publication US20140359799 and US Patent No. 7,588,772, each of which is herein incorporated by reference in its entirety). The amino acid sequence of AAVDJ8 may comprise two or more mutations in order to remove the heparin binding domain (HBD). As a non-limiting example, the AAV-DJ sequence is as described by SEQ ID NO: 1 in U.S. Patent No. 7,588,772, the contents of which are herein incorporated by reference in their entirety, and the AAVDJ8 sequence may comprise two mutations: (1) R587Q where arginine (R; Arg) at amino acid 587 is changed to glutamine (Q; Gln) and (2) R590T where arginine (R; Arg) at amino acid 590 is changed to threonine (T; Thr). As another non-limiting example, the AAVDJ8 sequence may comprise three mutations: (1) K406R where lysine (K; Lys) at amino acid 406 is changed to arginine (R; Arg), (2) R587Q where arginine (R; Arg) at amino acid 587 is changed to glutamine (Q; Gln) and (3) R590T where arginine (R; Arg) at amino acid 590 is changed to threonine (T; Thr).

[0112] In one embodiment, the parent AAV capsid sequence comprises an AAV9 sequence.

[0113] In one embodiment, the parent AAV capsid sequence comprises an K449R AAV9 sequence.

[0114] In one embodiment, the parent AAV capsid sequence comprises an AAVDJ sequence.

[0115] In one embodiment, the parent AAV capsid sequence comprises an AAVDJ8 sequence.

[0116] In one embodiment, the parent AAV capsid sequence comprises an AAVrh10 sequence.

[0117] In one embodiment, the parent AAV capsid sequence comprises an AAV1 sequence.

[0118] In one embodiment, the parent AAV capsid sequence comprises an AAV5 sequence.

[0119] While not wishing to be bound by theory, it is understood that a parent AAV capsid sequence comprises a VP1 region. In one embodiment, a parent AAV capsid sequence comprises a VP1, VP2 and/or VP3 region, or any combination thereof. A parent VP1 sequence may be considered synonymous with a parent AAV capsid sequence.

[0120] The present disclosure refers to structural capsid proteins (including VP1, VP2 and VP3) which are encoded by capsid (Cap) genes. These capsid proteins form an outer protein structural shell (i.e. capsid) of a viral vector such as AAV. VP capsid proteins synthesized from Cap polynucleotides generally include a methionine as the first amino acid in the peptide sequence (Met1), which is associated with the start codon (AUG or ATG) in the corresponding Cap nucleotide sequence. However, it is common for a first-methionine (Met1) residue or generally any first amino acid (AA1) to be cleaved off after or during polypeptide synthesis by protein processing enzymes such as Met-aminopeptidases. This “Met/AA-clipping” process often correlates with a corresponding acetylation of the second amino acid in the polypeptide sequence (e.g., alanine, valine, serine, threonine, etc.). Met-clipping commonly occurs with VP1 and VP3 capsid proteins but can also occur with VP2 capsid proteins.

[0121] Where the Met/AA-clipping is incomplete, a mixture of one or more (one, two or three) VP capsid proteins comprising the viral capsid may be produced, some of which may include a Met1/AA1 amino acid (Met+/AA+) and some of which may lack a Met1/AA1 amino acid as a result of Met/AA-clipping (Met-/AA-). For further discussion regarding Met/AA-clipping in capsid proteins, see Jin, et al. Direct Liquid Chromatography/Mass Spectrometry Analysis for Complete Characterization of Recombinant Adeno-Associated Virus Capsid Proteins. *Hum Gene Ther Methods*. 2017 Oct. 28(5):255-267; Hwang, et al. N-Terminal Acetylation of Cellular Proteins Creates Specific Degradation Signals. *Science*. 2010 February 19. 327(5968): 973–977; the contents of which are each incorporated herein by reference in its entirety.

[0122] According to the present disclosure, references to capsid proteins is not limited to either clipped (Met-/AA-) or unclipped (Met+/AA+) and may, in context, refer to

independent capsid proteins, viral capsids comprised of a mixture of capsid proteins, and/or polynucleotide sequences (or fragments thereof) which encode, describe, produce or result in capsid proteins of the present disclosure. A direct reference to a “capsid protein” or “capsid polypeptide” (such as VP1, VP2 or VP3) may also comprise VP capsid proteins which include a Met1/AA1 amino acid (Met+/AA+) as well as corresponding VP capsid proteins which lack the Met1/AA1 amino acid as a result of Met/AA-clipping (Met-/AA-).

[0123] Further according to the present disclosure, a reference to a specific SEQ ID NO: (whether a protein or nucleic acid) which comprises or encodes, respectively, one or more capsid proteins which include a Met1/AA1 amino acid (Met+/AA+) should be understood to teach the VP capsid proteins which lack the Met1/AA1 amino acid as upon review of the sequence, it is readily apparent any sequence which merely lacks the first listed amino acid (whether or not Met1/AA1).

[0124] As a non-limiting example, reference to a VP1 polypeptide sequence which is 736 amino acids in length and which includes a “Met1” amino acid (Met+) encoded by the AUG/ATG start codon may also be understood to teach a VP1 polypeptide sequence which is 735 amino acids in length and which does not include the “Met1” amino acid (Met-) of the 736 amino acid Met+ sequence. As a second non-limiting example, reference to a VP1 polypeptide sequence which is 736 amino acids in length and which includes an “AA1” amino acid (AA1+) encoded by any NNN initiator codon may also be understood to teach a VP1 polypeptide sequence which is 735 amino acids in length and which does not include the “AA1” amino acid (AA1-) of the 736 amino acid AA1+ sequence.

[0125] References to viral capsids formed from VP capsid proteins (such as reference to specific AAV capsid serotypes), can incorporate VP capsid proteins which include a Met1/AA1 amino acid (Met+/AA1+), corresponding VP capsid proteins which lack the Met1/AA1 amino acid as a result of Met/AA1-clipping (Met-/AA1-), and combinations thereof (Met+/AA1+ and Met-/AA1-).

[0126] As a non-limiting example, an AAV capsid serotype can include VP1 (Met+/AA1+), VP1 (Met-/AA1-), or a combination of VP1 (Met+/AA1+) and VP1 (Met-/AA1-). An AAV capsid serotype can also include VP3 (Met+/AA1+), VP3 (Met-/AA1-), or a combination of VP3 (Met+/AA1+) and VP3 (Met-/AA1-); and can also include similar optional combinations of VP2 (Met+/AA1) and VP2 (Met-/AA1-).

[0127] In one embodiment, the parent AAV capsid sequence may comprise an amino acid sequence with 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%,

79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to any of the those described above.

[0128] In one embodiment, the parent AAV capsid sequence may be encoded by a nucleotide sequence with 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to any of those described above.

[0129] In one embodiment, the parent sequence is not an AAV capsid sequence and is instead a different vector (e.g., lentivirus, plasmid, etc.). In another embodiment, the parent sequence is a delivery vehicle (e.g., a nanoparticle) and the targeting peptide is attached thereto.

Targeting peptides

[0130] Disclosed herein are targeting peptides and associated AAV particles comprising a capsid protein with one or more targeting peptide inserts, for enhanced or improved transduction of a target tissue (e.g., cells of the CNS or PNS).

[0131] In one embodiment, the targeting peptide may direct an AAV particle to a cell or tissue of the CNS. The cell of the CNS may be, but is not limited to, neurons (e.g., excitatory, inhibitory, motor, sensory, autonomic, sympathetic, parasympathetic, Purkinje, Betz, etc.), glial cells (e.g., microglia, astrocytes, oligodendrocytes) and/or supporting cells of the brain such as immune cells (e.g., T cells). The tissue of the CNS may be, but is not limited to, the cortex (e.g., frontal, parietal, occipital, temporal), thalamus, hypothalamus, striatum, putamen, caudate nucleus, hippocampus, entorhinal cortex, basal ganglia, or deep cerebellar nuclei.

[0132] In one embodiment, the targeting peptide may direct an AAV particle to a cell or tissue of the PNS. The cell or tissue of the PNS may be, but is not limited to, a dorsal root ganglion (DRG).

[0133] The targeting peptide may direct an AAV particle to the CNS (e.g., the cortex) after intravenous administration.

[0134] The targeting peptide may direct an AAV particle to the PNS (e.g., DRG) after intravenous administration.

[0135] A targeting peptide may vary in length. In one embodiment, the targeting peptide is 3-20 amino acids in length. As non-limiting examples, the targeting peptide may be 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or 3-5, 3-8, 3-10, 3-12, 3-15, 3-18, 3-20, 5-10, 5-15, 5-20, 10-12, 10-15, 10-20, 12-20, or 15-20 amino acids in length.

[0136] Targeting peptides of the present disclosure may be identified and/or designed by any method known in the art. As a non-limiting example, the CREATE system as described in Deverman et al., (Nature Biotechnology 34(2):204-209 (2016)), Chan et al., (Nature Neuroscience 20(8):1172-1179 (2017)), and in International Patent Application Publication Nos. WO2015038958 and WO2017100671, the contents of each of which are herein incorporated by reference in their entirety, may be used as a means of identifying targeting peptides, in either mice or other research animals, such as, but not limited to, non-human primates.

[0137] Targeting peptides and associated AAV particles may be identified from libraries of AAV capsids comprised of targeting peptide variants. In one embodiment, the targeting peptides may be 7 amino acid sequences (7-mers). In another embodiment, the targeting peptides may be 9 amino acid sequences (9-mers). The targeting peptides may also differ in their method of creation or design, with non-limiting examples including, random peptide selection, site saturation mutagenesis, and/or optimization of a particular region of the peptide (e.g., flanking regions or central core).

[0138] In one embodiment, a targeting peptide library comprises targeting peptides of 7 amino acids (7-mer) in length randomly generated by PCR.

[0139] In one embodiment, a targeting peptide library comprises targeting peptides with 3 mutated amino acids. In one embodiment, these 3 mutated amino acids are consecutive amino acids. In another embodiment, these 3 mutated amino acids are not consecutive amino acids. In one embodiment, the parent targeting peptide is a 7-mer. In another embodiment, the parent peptide is a 9-mer.

[0140] In one embodiment, a targeting peptide library comprises 7-mer targeting peptides, wherein the amino acids of the targeting peptide and/or the flanking sequences are evolved through site saturation mutagenesis of 3 consecutive amino acids. In one embodiment, NNK (N = any base; K = G or T) codons are used to generate the site saturated mutation sequences.

[0141] AAV particles comprising capsid proteins with targeting peptide inserts are generated and viral genomes encoding a reporter (e.g., GFP) encapsulated within. These AAV particles (or AAV capsid library) are then administered to a transgenic mouse by intravenous delivery to the tail vein. Administration of these capsid libraries to cre-expressing mice results in expression of the reporter payload in the target tissue, due to the expression of Cre.

[0142] AAV particles and/or viral genomes may be recovered from the target tissue for identification of targeting peptides and associated AAV particles that are enriched, indicating

enhanced transduction of target tissue. Standard methods in the art, such as, but not limited to next generation sequencing (NGS), viral genome quantification, biochemical assays, immunohistochemistry and/or imaging of target tissue samples may be used to determine enrichment.

[0143] A target tissue may be any cell, tissue or organ of a subject. As non-limiting examples, samples may be collected from brain, spinal cord, dorsal root ganglia and associated roots, liver, heart, gastrocnemius muscle, soleus muscle, pancreas, kidney, spleen, lung, adrenal glands, stomach, sciatic nerve, saphenous nerve, thyroid gland, eyes (with or without optic nerve), pituitary gland, skeletal muscle (rectus femoris), colon, duodenum, ileum, jejunum, skin of the leg, superior cervical ganglia, urinary bladder, ovaries, uterus, prostate gland, testes, and/or any sites identified as having a lesion, or being of interest.

Targeting peptide sequences

[0144] In one embodiment the targeting peptide may comprise a sequence as set forth in Table 2. In Table 2, “_1” refers to NNM codons where A or C is in the third position and “_2” refers to NNK codons where G or T is in the third position. Additionally, the NNM codons cannot cover the entire repertoire of amino acids since Met or Trp can only be encoded by codons ATG and TGG, respectively. Therefore, some "NNM" sequences also contain some codons ending in G.

Table 2. Peptides

Peptide Sequence_ID	SEQ ID NO:	Peptide Sequence_ID	SEQ ID NO:
AQAGAGSER_1	194	DGTGQVTGW_1	68
AQAGAGSER_2	194	DGTGQVTGW_2	68
AQDQNPGRW_1	195	DGTGRLTGW_1	159
AQDQNPGRW_2	195	DGTGRLTGW_2	159
AQELTRPFL_1	144	DGTGRTVGW_1	117
AQELTRPFL_2	144	DGTGRTVGW_2	117
AQEVPGYRW_1	196	DGTGSGMMT_1	306
AQEVPGYRW_2	196	DGTGSGMMT_2	306
AQFPTNYDS_1	66	DGTGSISGW_1	307
AQFPTNYDS_2	66	DGTGSISGW_2	307
AQFVVQQY_1	95	DGTGSLAGW_1	308
AQFVVQQY_2	95	DGTGSLAGW_2	308
AQGASPGRW_1	149	DGTGSLNGW_1	309
AQGASPGRW_2	149	DGTGSLNGW_2	309
AQGENPGRW_1	96	DGTGSLQGW_1	310
AQGENPGRW_2	96	DGTGSLQGW_2	310
AQGGNPGRW_1	91	DGTGSLSGW_1	311
AQGGNPGRW_2	91	DGTGSLSGW_2	311
AQGGSTGSN_1	197	DGTGSLVGW_1	312
AQGGSTGSN_2	197	DGTGSLVGW_2	312
AQGPTRPFL_1	125	DGTGSTHGW_1	119
AQGPTRPFL_2	125	DGTGSTHGW_2	119
AQGRDGWAA_1	198	DGTGSTKGW_1	313
AQGRDGWAA_2	198	DGTGSTKGW_2	313

AQGRMTDSQ_1	199	DGTGSTMGW_1	314
AQGRMTDSQ_2	199	DGTGSTMGW_2	314
AQGSVDVGRW_1	128	DGTGSTQGW_1	315
AQGSVDVGRW_2	128	DGTGSTQGW_2	315
AQGSNPGRW_1	103	DGTGSTSGW_1	316
AQGSNPGRW_2	103	DGTGSTSGW_2	316
AQGSNSPQV_1	200	DGTGSTTGW_1	134
AQGSNSPQV_2	200	DGTGSTTGW_2	134
AQGSWNPPA_1	80	DGTGSVMGW_1	317
AQGSWNPPA_2	80	DGTGSVMGW_2	317
AQGTWNPPA_1	82	DGTGSVTGW_1	318
AQGTWNPPA_2	82	DGTGSVTGW_2	318
AQGVFIPPK_1	201	DGTGTLAGW_1	319
AQGVFIPPK_2	201	DGTGTLAGW_2	319
AQHVNASQS_1	202	DGTGTLHGW_1	320
AQHVNASQS_2	202	DGTGTLHGW_2	320
AQIKAGWAQ_1	203	DGTGTLKGW_1	321
AQIKAGWAQ_2	203	DGTGTLKGW_2	321
AQIMSGYAQ_1	204	DGTGTLSGW_1	322
AQIMSGYAQ_2	204	DGTGTLSGW_2	322
AQKSVGSVY_1	205	DGTGTTLGW_1	323
AQKSVGSVY_2	205	DGTGTTLGW_2	323
AQLEHGFAQ_1	206	DGTGTTMGW_1	324
AQLEHGFAQ_2	206	DGTGTTMGW_2	324
AQLGGVLSA_1	207	DGTGTTTGW_1	130
AQLGGVLSA_2	207	DGTGTTTGW_2	130
AQLGLSQGR_1	208	DGTGTTVGW_1	74
AQLGLSQGR_2	208	DGTGTTVGW_2	74
AQLGYGFAQ_1	209	DGTGTTYGW_1	325
AQLGYGFAQ_2	209	DGTGTTYGW_2	325
AQLKYGLAQ_1	115	DGTGTVHGW_1	326
AQLKYGLAQ_2	115	DGTGTVHGW_2	326
AQLRIGFAQ_1	210	DGTGTVQGW_1	327
AQLRIGFAQ_2	210	DGTGTVQGW_2	327
AQLRMGYSQ_1	211	DGTGTVSGW_1	328
AQLRMGYSQ_2	211	DGTGTVSGW_2	328
AQLRQGYAQ_1	212	DGTGTVTGW_1	329
AQLRQGYAQ_2	212	DGTGTVTGW_2	329
AQLRVGFAQ_1	123	DGTHARLSS_1	330
AQLRVGFAQ_2	123	DGTHARLSS_2	330
AQLSCRSQM_1	213	DGTHAYMAS_1	153
AQLSCRSQM_2	213	DGTHAYMAS_2	153
AQLTYSQSL_1	214	DGTHFAPPR_1	112
AQLTYSQSL_2	214	DGTHFAPPR_2	112
AQLYKGYSQ_1	215	DGTHIHLSS_1	162
AQLYKGYSQ_2	215	DGTHIHLSS_2	162
AQMPQRPFL_1	216	DGTHIRALS_1	331
AQMPQRPFL_2	216	DGTHIRALS_2	331
AQNGNPGRW_1	84	DGTHIRLAS_1	332
AQNGNPGRW_2	84	DGTHIRLAS_2	332
AQPEGSARW_1	60	DGTHLQPFR_1	333
AQPEGSARW_2	60	DGTHLQPFR_2	333
AQPLAVYGA_1	217	DGTHSFYDA_1	334
AQPLAVYGA_2	217	DGTHSFYDA_2	334
AQPQSSSMS_1	218	DGTHSTTGW_1	145
AQPQSSSMS_2	218	DGTHSTTGW_2	145
AQPSVGGYW_1	219	DGTHTRTGW_1	90
AQPSVGGYW_2	219	DGTHTRTGW_2	90

AQQAQVQSW_1	220	DGTHVRALS_1	335
AQQAQVQSW_2	220	DGTHVRALS_2	335
AQQRSLASG_1	221	DGTHVYMAS_1	336
AQQRSLASG_2	221	DGTHVYMAS_2	336
AQQVMNSQG_1	222	DGTHVYMSS_1	337
AQQVMNSQG_2	222	DGTHVYMSS_2	337
AQRGVGLSQ_1	223	DGTIALPFK_1	338
AQRGVGLSQ_2	223	DGTIALPFK_2	338
AQRHDAEGS_1	224	DGTIALPFR_1	339
AQRHDAEGS_2	224	DGTIALPFR_2	339
AQRKGEPHY_1	225	DGTIATRYV_1	340
AQRKGEPHY_2	225	DGTIATRYV_2	340
AQRYTGDSS_1	138	DGTIERPFR_1	87
AQRYTGDSS_2	138	DGTIERPFR_2	87
AQSAMAAKG_1	226	DGTIGYAYV_1	341
AQSAMAAKG_2	226	DGTIGYAYV_2	341
AQSGGLTGS_1	227	DGTIQAPFK_1	342
AQSGGLTGS_2	227	DGTIQAPFK_2	342
AQSGGVGVQV_1	228	DGTIRLPFK_1	343
AQSGGVGVQV_2	228	DGTIRLPFK_2	343
AQSLATPFR_1	169	DGTISKEVG_1	344
AQSLATPFR_2	169	DGTISKEVG_2	344
AQSMSRPFL_1	229	DGTISQPFK_1	105
AQSMSRPFL_2	229	DGTISQPFK_2	105
AQSOLRPFL_1	230	DGTKIQLSS_1	146
AQSOLRPFL_2	230	DGTKIQLSS_2	146
AQSVAKPFL_1	231	DGTKIRLSS_1	111
AQSVAKPFL_2	231	DGTKIRLSS_2	111
AQSVSQPFR_1	232	DGTKLMLSS_1	157
AQSVSQPFR_2	232	DGTKLMLSS_2	157
AQSVVRPFL_1	233	DGTKLRLSS_1	118
AQSVVRPFL_2	233	DGTKLRLSS_2	118
AQTALSSST_1	234	DGTKMVLQL_1	142
AQTALSSST_2	234	DGTKMVLQL_2	142
AQTEMGGRC_1	235	DGTKSLVQL_1	345
AQTEMGGRC_2	235	DGTKSLVQL_2	345
AQTGFAPPR_1	161	DGTKVLVQL_1	122
AQTGFAPPR_2	161	DGTKVLVQL_2	122
AQTIRGYSS_1	236	DGTLAAPFK_1	120
AQTIRGYSS_2	236	DGTLAAPFK_2	120
AQTISNYHT_1	237	DGTLAVNFK_1	346
AQTISNYHT_2	237	DGTLAVNFK_2	346
AQTLARPFV_1	98	DGTLAVPFK_1	71
AQTLARPFV_2	98	DGTLAVPFK_2	71
AQTLAVPFK_1	168	DGTLAYPFK_1	347
AQTLAVPFK_2	168	DGTLAYPFK_2	347
AQTPDRPWL_1	238	DGTLERPFR_1	156
AQTPDRPWL_2	238	DGTLERPFR_2	156
AQTRAGYAQ_1	126	DGTLEVHFK_1	348
AQTRAGYAQ_2	126	DGTLEVHFK_2	348
AQTRAGYSQ_1	141	DGTLLRLSS_1	121
AQTRAGYSQ_2	141	DGTLLRLSS_2	121
AQTREYLLG_1	93	DGTLNNPFR_1	109
AQTREYLLG_2	93	DGTLNNPFR_2	109
AQTSAPFL_1	163	DGTLQQPFR_1	89
AQTSAPFL_2	163	DGTLQQPFR_2	89
AQTSARPFL_1	100	DGTLSPQFR_1	65
AQTSARPFL_2	100	DGTLSPQFR_2	65

AQTTDRPFL_1	85	DGTL SRLW_1	349
AQTTDRPFL_2	85	DGTL SRLW_2	349
AQTTEKPWL_1	83	DGTL SSPFR_1	350
AQTTEKPWL_2	83	DGTL SSPFR_2	350
AQTVARPFY_1	239	DGTL TVPFR_1	351
AQTVARPFY_2	239	DGTL TVPFR_2	351
AQTVATPFR_1	240	DGTL VAPFR_1	352
AQTVATPFR_2	240	DGTL VAPFR_2	352
AQTVTQLFK_1	241	DGTM DPKFR_1	70
AQTVTQLFK_2	241	DGTM DPKFR_2	70
AQVHVGSVY_1	165	DGTM DRPFK_1	102
AQVHVGSVY_2	165	DGTM DRPFK_2	102
AQVLAGYNM_1	242	DGTM LRLSS_1	148
AQVLAGYNM_2	242	DGTM LRLSS_2	148
AQVSEARVR_1	243	DGTM QLTGW_1	353
AQVSEARVR_2	243	DGTM QLTGW_2	353
AQVVVGYSQ_1	244	DGTM NGLKGW_1	76
AQVVVGYSQ_2	244	DGTM NGLKGW_2	76
AQWAAGYNV_1	245	DGTM NSISGW_1	354
AQWAAGYNV_2	245	DGTM NSISGW_2	354
AQWELSGY_1	246	DGTM NSLSGW_1	355
AQWELSGY_2	246	DGTM NSLSGW_2	355
AQWEVKGGY_1	247	DGTM NSTTGW_1	143
AQWEVKGGY_2	247	DGTM NSTTGW_2	143
AQWEVKRGY_1	248	DGTM SVTGW_1	356
AQWEVKRGY_2	248	DGTM SVTGW_2	356
AQWEVQSGF_1	249	DGTM NTINGW_1	124
AQWEVQSGF_2	249	DGTM NTINGW_2	124
AQWEVRGGY_1	250	DGTM NLGGW_1	357
AQWEVRGGY_2	250	DGTM NLGGW_2	357
AQWEVTSGW_1	251	DGTM NTHGW_1	113
AQWEVTSGW_2	251	DGTM NTHGW_2	113
AQWGAPSHG_1	252	DGTM NYRLSS_1	358
AQWGAPSHG_2	252	DGTM NYRLSS_2	358
AQWMELGSS_1	253	DGTM QALSGW_1	359
AQWMELGSS_2	253	DGTM QALSGW_2	359
AQWMFGGSG_1	254	DGTM QFRLSS_1	129
AQWMFGGSG_2	254	DGTM QFRLSS_2	129
AQWMLGGAQ_1	255	DGTM QFSPPR_1	108
AQWMLGGAQ_2	255	DGTM QFSPPR_2	108
AQWPTAYDA_1	256	DGTM QGLKGW_1	158
AQWPTAYDA_2	256	DGTM QGLKGW_2	158
AQWPTS YDA_1	62	DGTM QTTSGW_1	360
AQWPTS YDA_2	62	DGTM QTTSGW_2	360
AQWQVQTGF_1	257	DGTM RALTGW_1	361
AQWQVQTGF_2	257	DGTM RALTGW_2	361
AQWSTEGGY_1	258	DGTM RFSLSS_1	362
AQWSTEGGY_2	258	DGTM RFSLSS_2	362
AQWTAAGGY_1	259	DGTM RGLSGW_1	363
AQWTAAGGY_2	259	DGTM RGLSGW_2	363
AQWTESGY_1	260	DGTM RIGLSS_1	364
AQWTESGY_2	260	DGTM RIGLSS_2	364
AQWVYGSSH_1	261	DGTM RLHLAS_1	365
AQWVYGSSH_2	261	DGTM RLHLAS_2	365
AQYLAGYTV_1	262	DGTM RLHLSS_1	366
AQYLAGYTV_2	262	DGTM RLHLSS_2	366
AQYLKGYSV_1	152	DGTM RLLSS_1	367
AQYLKGYSV_2	152	DGTM RLLSS_2	367

AQYLSGYNT_1	263	DGTRLMLSS_1	368
AQYLSGYNT_2	263	DGTRLMLSS_2	368
DGAAATTGW_1	264	DGTRLNLSS_1	369
DGAAATTGW_2	264	DGTRLNLSS_2	369
DGAGGTSW_1	151	DGTRMNVQL_1	370
DGAGGTSW_2	151	DGTRMNVQL_2	370
DGAGTTSW_1	265	DGTRNMYEG_1	135
DGAGTTSW_2	265	DGTRNMYEG_2	135
DGAHGLSGW_1	266	DGTRSITGW_1	371
DGAHGLSGW_2	266	DGTRSITGW_2	371
DGAHVGLSS_1	267	DGTRSLHGW_1	372
DGAHVGLSS_2	267	DGTRSLHGW_2	372
DGARTVLQL_1	268	DGTRSTTGW_1	373
DGARTVLQL_2	268	DGTRSTTGW_2	373
DGEYQKPFR_1	269	DGTRTTTGW_1	106
DGEYQKPFR_2	269	DGTRTTTGW_2	106
DGGGTTTGW_1	270	DGTRTVTGW_1	374
DGGGTTTGW_2	270	DGTRTVTGW_2	374
DGHATSMGW_1	271	DGTRTVVQL_1	375
DGHATSMGW_2	271	DGTRTVVQL_2	375
DGKGSTQGW_1	272	DGTRVHLSS_1	376
DGKGSTQGW_2	272	DGTRVHLSS_2	376
DGKQYQLSS_1	92	DGTSFPYAR_1	86
DGKQYQLSS_2	92	DGTSFPYAR_2	86
DGNGGLKGW_1	167	DGTSFTPPK_1	81
DGNGGLKGW_2	167	DGTSFTPPK_2	81
DGQGGLSGW_1	273	DGTSFTPPR_1	88
DGQGGLSGW_2	273	DGTSFTPPR_2	88
DGQHFAPPR_1	110	DGTSGLHGW_1	377
DGQHFAPPR_2	110	DGTSGLHGW_2	377
DGRATKTLY_1	274	DGTSGLKGW_1	101
DGRATKTLY_2	274	DGTSGLKGW_2	101
DGRNALTGW_1	275	DGTSIHLSS_1	378
DGRNALTGW_2	275	DGTSIHLSS_2	378
DGRRQVIQL_1	276	DGTSIMLSS_1	379
DGRRQVIQL_2	276	DGTSIMLSS_2	379
DGRVYGLSS_1	277	DGTSRLSS_1	166
DGRVYGLSS_2	277	DGTSRLSS_2	166
DGSGRTTGW_1	147	DGTSNYGAR_1	380
DGSGRTTGW_2	147	DGTSNYGAR_2	380
DGSGTTRGW_1	114	DGTSSYYDA_1	381
DGSGTTRGW_2	114	DGTSSYYDA_2	381
DGSGTVSGW_1	278	DGTSSYYDS_1	59
DGSGTVSGW_2	278	DGTSSYYDS_2	59
DGSPEKPFR_1	160	DGTSTISGW_1	382
DGSPEKPFR_2	160	DGTSTISGW_2	382
DGSQSTTGW_1	136	DGTSTITGW_1	383
DGSQSTTGW_2	136	DGTSTITGW_2	383
DGSSFYPPK_1	127	DGTSTLHGW_1	384
DGSSFYPPK_2	127	DGTSTLHGW_2	384
DGSSSYDA_1	64	DGTSTLRGW_1	385
DGSSSYDA_2	64	DGTSTLRGW_2	385
DGSTERPFR_1	99	DGTSTLSGW_1	386
DGSTERPFR_2	99	DGTSTLSGW_2	386
DGTAARLSS_1	132	DGTSYVPPK_1	97
DGTAARLSS_2	132	DGTSYVPPK_2	97
DGTADKPFR_1	63	DGTSYVPPR_1	78
DGTADKPFR_2	63	DGTSYVPPR_2	78

DGTADRPFR_1	155	DGTTATYYK_1	387
DGTADRPFR_2	155	DGTTATYYK_2	387
DGTAERPFR_1	140	DGTTFTPPR_1	79
DGTAERPFR_2	140	DGTTFTPPR_2	79
DGTAIHLSS_1	67	DGTTLAPFR_1	388
DGTAIHLSS_2	67	DGTTLAPFR_2	388
DGTAIYLSS_1	279	DGTTLVPPR_1	116
DGTAIYLSS_2	279	DGTTLVPPR_2	116
DGTALMLSS_1	280	DGTTSKTLW_1	389
DGTALMLSS_2	280	DGTTSKTLW_2	389
DGTASISGW_1	281	DGTTSRTLW_1	390
DGTASISGW_2	281	DGTTSRTLW_2	390
DGTASTSGW_1	282	DGTTTSLY_1	391
DGTASTSGW_2	282	DGTTTSLY_2	391
DGTASVTGW_1	283	DGTTTTTGW_1	392
DGTASVTGW_2	283	DGTTTTTGW_2	392
DGTASYYS_1	61	DGTTYGAR_1	77
DGTASYYS_2	61	DGTTYGAR_2	77
DGTATMGW_1	284	DGTTWTPPR_1	139
DGTATMGW_2	284	DGTTWTPPR_2	139
DGTATTTGW_1	285	DGTTYMLSS_1	393
DGTATTTGW_2	285	DGTTYMLSS_2	393
DGTAYRLSS_1	286	DGTTYVPPR_1	75
DGTAYRLSS_2	286	DGTTYVPPR_2	75
DGTDKMWSI_1	287	DGTVANPFR_1	394
DGTDKMWSI_2	287	DGTVANPFR_2	394
DGTGGIKGW_1	131	DGTVDRPFK_1	395
DGTGGIKGW_2	131	DGTVDRPFK_2	395
DGTGGIMGW_1	288	DGTVIHLSS_1	73
DGTGGIMGW_2	288	DGTVIHLSS_2	73
DGTGGISGW_1	289	DGTVILLSS_1	396
DGTGGISGW_2	289	DGTVILLSS_2	396
DGTGGLAGW_1	290	DGTVIMLSS_1	397
DGTGGLAGW_2	290	DGTVIMLSS_2	397
DGTGGLHGW_1	291	DGTVLHLSS_1	398
DGTGGLHGW_2	291	DGTVLHLSS_2	398
DGTGGLQGW_1	292	DGTVLMLSS_1	399
DGTGGLQGW_2	292	DGTVLMLSS_2	399
DGTGGLRGW_1	154	DGTVLVPFR_1	150
DGTGGLRGW_2	154	DGTVLVPFR_2	150
DGTGGLSGW_1	293	DGTVPYLAS_1	400
DGTGGLSGW_2	293	DGTVPYLAS_2	400
DGTGGLTGW_1	294	DGTVPYLSS_1	401
DGTGGLTGW_2	294	DGTVPYLSS_2	401
DGTGGTKGW_1	107	DGTVRVPFR_1	164
DGTGGTKGW_2	107	DGTVRVPFR_2	164
DGTGGTSGW_1	295	DGTVSMPEK_1	402
DGTGGTSGW_2	295	DGTVSMPEK_2	402
DGTGGVHGW_1	296	DGTVSNPFR_1	403
DGTGGVHGW_2	296	DGTVSNPFR_2	403
DGTGGVMGW_1	297	DGTVSTRWV_1	404
DGTGGVMGW_2	297	DGTVSTRWV_2	404
DGTGGVSGW_1	298	DGTVTTTGW_1	405
DGTGGVSGW_2	298	DGTVTTTGW_2	405
DGTGGVTGW_1	299	DGTVTVTGW_1	406
DGTGGVTGW_2	299	DGTVTVTGW_2	406
DGTGGVYGW_1	300	DGTVWVPPR_1	407
DGTGGVYGW_2	300	DGTVWVPPR_2	407

DGTGNLQGW_1	301	DGTVYRLSS_1	408
DGTGNLQGW_2	301	DGTVYRLSS_2	408
DGTGNLRGW_1	133	DGTYARLSS_1	409
DGTGNLRGW_2	133	DGTYARLSS_2	409
DGTGNLSGW_1	302	DGTYGKWLW_1	410
DGTGNLSGW_2	302	DGTYGKWLW_2	410
DGTGNTHGW_1	72	DGTYIHLSS_1	411
DGTGNTHGW_2	72	DGTYIHLSS_2	411
DGTGNTRGW_1	94	DGTYSTSGW_1	412
DGTGNTRGW_2	94	DGTYSTSGW_2	412
DGTGNTSGW_1	137	DGVHPGLSS_1	104
DGTGNTSGW_2	137	DGVHPGLSS_2	104
DGTGNVSGW_1	303	DGVVALLAS_1	413
DGTGNVSGW_2	303	DGVVALLAS_2	413
DGTGNVTGW_1	69	DGYVGVGSL_1	414
DGTGNVTGW_2	69	DGYVGVGSL_2	414
DGTGQLVGW_1	304	control (wtAAV9 - NNM)	
DGTGQLVGW_2	304	control (wtAAV9 - NNK)	
DGTGQTIGW_1	305		
DGTGQTIGW_2	305		

[0145] In one embodiment, the targeting peptide may comprise an amino acid sequence with 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to any of the sequences shown in Table 2.

[0146] In one embodiment, a targeting peptide may comprise 4 or more contiguous amino acids of any of the targeting peptides disclosed herein. In one embodiment the targeting peptide may comprise 4 contiguous amino acids of any of the sequences as set forth in Table 2. In one embodiment the targeting peptide may comprise 5 contiguous amino acids of any of the sequences as set forth in Table 2. In one embodiment the targeting peptide may comprise 6 contiguous amino acids of any of the sequences as set forth in Table 2.

[0147] In one embodiment, the AAV particle of the disclosure comprises an AAV capsid with a targeting peptide insert, wherein the targeting peptide has an amino acid sequence as set forth in any of Table 2.

[0148] In one embodiment, the AAV particle of the disclosure comprises an AAV capsid with a targeting peptide insert, wherein the targeting peptide has an amino acid sequence comprising at least 4 contiguous amino acids of any of the sequences as set forth in any of Table 2.

[0149] In one embodiment, the AAV particle of the disclosure comprises an AAV capsid with a targeting peptide insert, wherein the targeting peptide has an amino acid sequence substantially comprising any of the sequences as set forth in any of Table 2.

[0150] In one embodiment, the AAV particle of the disclosure comprises an AAV capsid polynucleotide with a targeting nucleic acid insert, wherein the targeting nucleic acid insert has a nucleotide sequence substantially comprising any of those set forth as Table 2.

[0151] The AAV particle of the disclosure comprising a targeting nucleic acid insert, may have a polynucleotide sequence with 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more, identity to the parent capsid sequence.

[0152] The AAV particle of the disclosure comprising a targeting peptide insert, may have an amino acid sequence with 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more, identity to the parent capsid sequence.

[0153] In any of the DNA and RNA 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; U for Uracil; W for weak bases such as adenine or thymine; S for strong nucleotides such as cytosine and guanine; M for amino nucleotides such as adenine and cytosine; K for keto nucleotides such as guanine and thymine; R for purines adenine and guanine; Y for pyrimidine cytosine and thymine; B for any base that is not A (e.g., cytosine, guanine, and thymine); D for any base that is not C (e.g., adenine, guanine, and thymine); H for any base that is not G (e.g., adenine, cytosine, and thymine); V for any base that is not T (e.g., adenine, cytosine, and guanine); N for any nucleotide (which is not a gap); and Z is for zero.

[0154] 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; T (Thr) for Threonine; B (Asx) for Aspartic acid or Asparagine; J

(Xle) for Leucine or Isoleucine; O (Pyl) for Pyrrolysine; U (Sec) for Selenocysteine; X (Xaa) for any amino acid; and Z (Glx) for Glutamine or Glutamic acid.

Use of targeting peptides in AAV particles

[0155] Targeting peptides may be stand-alone peptides or may be inserted into or conjugated to a parent sequence. In one embodiment, the targeting peptides are inserted into the capsid protein of an AAV particle.

[0156] One or more targeting peptides may be inserted into a parent AAV capsid sequence to generate the AAV particles of the disclosure.

[0157] Targeting peptides may be inserted into a parent AAV capsid sequence in any location that results in fully functional AAV particles. The targeting peptide may be inserted in VP1, VP2 and/or VP3. Numbering of the amino acid residues differs across AAV serotypes, and so the exact amino acid position of the targeting peptide insertion may not be critical. As used herein, amino acid positions of the parent AAV capsid sequence are described using AAV9 (SEQ ID NO: 2) as reference.

[0158] In one embodiment, the targeting peptides are inserted in a hypervariable region of the AAV capsid sequence. Non-limiting examples of such hypervariable regions include Loop IV and Loop VIII of the parent AAV capsid. While not wishing to be bound by theory, these surface exposed loops are unstructured and poorly conserved, making them ideal regions for insertion of targeting peptides.

[0159] In one embodiment, the targeting peptide is inserted into Loop IV. In another embodiment, the targeting peptide is used to replace a portion, or all of Loop IV. As a non-limiting example, addition of the targeting peptide to the parent AAV capsid sequence may result in the replacement or mutation of at least one amino acid of the parent AAV capsid.

[0160] In one embodiment, the targeting peptide is inserted into Loop VIII. In another embodiment, the targeting peptide is used to replace a portion, or all of Loop VIII. As a non-limiting example, addition of the targeting peptide to the parent AAV capsid sequence may result in the replacement or mutation of at least one amino acid of the parent AAV capsid.

[0161] In one embodiment, more than one targeting peptide is inserted into a parent AAV capsid sequence. As a non-limiting example, targeting peptides may be inserted at both Loop IV and Loop VIII in the same parent AAV capsid sequence.

[0162] Targeting peptides may be inserted at any amino acid position of the parent AAV capsid sequence, such as, but not limited to, between amino acids at positions 586-592, 588-589, 586-589, 452-458, 262-269, 464-473, 491-495, 546-557 and/or 659-668.

[0163] In a preferred embodiment, the targeting peptides are inserted into a parent AAV capsid sequence between amino acids at positions 588 and 589 (Loop VIII). In one embodiment, the parent AAV capsid is AAV9 (SEQ ID NO: 2). In a second embodiment, the parent AAV capsid is K449R AAV9 (SEQ ID NO: 3).

[0164] The targeting peptides described herein may increase the transduction of the AAV particles of the disclosure to a target tissue as compared to the parent AAV particle lacking a targeting peptide insert. In one embodiment, the targeting peptide increases the transduction of an AAV particle to a target tissue by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 125%, 150%, 200%, 300%, 400%, 500%, or more as compared to a parent AAV particle lacking a targeting peptide insert.

[0165] In one embodiment, the targeting peptide increases the transduction of an AAV particle to a cell or tissue of the CNS by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 125%, 150%, 200%, 300%, 400%, 500%, or more as compared to a parent AAV particle lacking a targeting peptide insert.

[0166] In one embodiment, the targeting peptide increases the transduction of an AAV particle to a cell or tissue of the PNS by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 125%, 150%, 200%, 300%, 400%, 500%, or more as compared to a parent AAV particle lacking a targeting peptide insert.

[0167] In one embodiment, the targeting peptide increases the transduction of an AAV particle to a cell or tissue of the DRG by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 125%, 150%, 200%, 300%, 400%, 500%, or more as compared to a parent AAV particle lacking a targeting peptide insert.

AAV Production

[0168] Viral production disclosed herein describes processes and methods for producing AAV particles (with enhanced, improved and/or increased tropism for a target tissue) that may be used to contact a target cell to deliver a payload.

[0169] The present disclosure provides methods for the generation of AAV particles comprising targeting peptides. In one embodiment, the AAV particles are prepared by viral genome replication in a viral replication cell. Any method known in the art may be used for the preparation of AAV particles. In one embodiment, AAV particles are produced in

mammalian cells (e.g., HEK293). In another embodiment, AAV particles are produced in insect cells (e.g., Sf9)

[0170] Methods of making AAV particles are well known in the art and are described in e.g., U.S. Patent Nos. US6204059, US5756283, US6258595, US6261551, US6270996, US6281010, US6365394, US6475769, US6482634, US6485966, US6943019, US6953690, US7022519, US7238526, US7291498 and US7491508, US5064764, US6194191, US6566118, US8137948; or International Publication Nos. WO1996039530, WO1998010088, WO1999014354, WO1999015685, WO1999047691, WO2000055342, WO2000075353 and WO2001023597; Methods In Molecular Biology, ed. Richard, Humana Press, NJ (1995); O'Reilly et al., *Baculovirus Expression Vectors, A Laboratory Manual*, Oxford Univ. Press (1994); Samulski et al., *J. Vir.* 63:3822-8 (1989); Kajigaya et al., *Proc. Nat'l. Acad. Sci. USA* 88: 4646-50 (1991); Ruffing et al., *J. Vir.* 66:6922-30 (1992); Kimbauer et al., *Vir.*, 219:37-44 (1996); Zhao et al., *Vir.* 272:382-93 (2000); the contents of each of which are herein incorporated by reference in their entirety. In one embodiment, the AAV particles are made using the methods described in International Patent Publication WO2015191508, the contents of which are herein incorporated by reference in their entirety.

Therapeutic Applications

[0171] The present disclosure provides a method for treating a disease, disorder and/or condition in a mammalian subject, including a human subject, comprising administering to the subject an AAV particle described herein where the AAV particle comprises the novel capsids ("TRACER AAV particles") defined by the present disclosure or administering to the subject any of the described compositions, including pharmaceutical compositions, described herein.

[0172] In one embodiment, the TRACER AAV particles of the present disclosure are administered to a subject prophylactically, to prevent on-set of disease. In another embodiment, the TRACER AAV particles of the present disclosure are administered to treat (lessen the effects of) a disease or symptoms thereof. In yet another embodiment, the TRACER AAV particles of the present disclosure are administered to cure (eliminate) a disease. In another embodiment, the TRACER AAV particles of the present disclosure are administered to prevent or slow progression of disease. In yet another embodiment, the TRACER AAV particles of the present disclosure are used to reverse the deleterious effects of a disease. Disease status and/or progression may be determined or monitored by standard methods known in the art.

[0173] In some embodiments, the TRACER AAV particles of the disclosure are useful in the field of medicine for the treatment, prophylaxis, palliation or amelioration of neurological diseases and/or disorders.

[0174] In some embodiments, the TRACER AAV particles of the disclosure are useful in the field of medicine for the treatment, prophylaxis, palliation or amelioration of tauopathy.

[0175] In some embodiments, the TRACER AAV particles of the disclosure are useful in the field of medicine for the treatment, prophylaxis, palliation or amelioration of Alzheimer's Disease.

[0176] In some embodiments, the TRACER AAV particles of the disclosure are useful in the field of medicine for the treatment, prophylaxis, palliation or amelioration of Friedreich's ataxia, or any disease stemming from a loss or partial loss of frataxin protein.

[0177] In some embodiments, the TRACER AAV particles of the disclosure are useful in the field of medicine for the treatment, prophylaxis, palliation or amelioration of Parkinson's Disease.

[0178] In some embodiments, the TRACER AAV particles of the disclosure are useful in the field of medicine for the treatment, prophylaxis, palliation or amelioration of Amyotrophic lateral sclerosis.

[0179] In some embodiments, the TRACER AAV particles of the disclosure are useful in the field of medicine for the treatment, prophylaxis, palliation or amelioration of Huntington's Disease.

[0180] In some embodiments, the TRACER AAV particles of the disclosure are useful in the field of medicine for the treatment, prophylaxis, palliation or amelioration of chronic or neuropathic pain.

[0181] In some embodiments, the TRACER AAV particles of the disclosure are useful in the field of medicine for treatment, prophylaxis, palliation or amelioration of a disease associated with the central nervous system.

[0182] In some embodiments, the TRACER AAV particles of the disclosure are useful in the field of medicine for treatment, prophylaxis, palliation or amelioration of a disease associated with the peripheral nervous system.

[0183] In one embodiment, the TRACER AAV particles of the present disclosure are administered to a subject having at least one of the diseases or symptoms described herein.

[0184] As used herein, any disease associated with the central or peripheral nervous system and components thereof (e.g., neurons) may be considered a "neurological disease".

[0185] Any neurological disease may be treated with the TRACER AAV particles of the disclosure, or pharmaceutical compositions thereof, including but not limited to, Absence of the Septum Pellucidum, Acid Lipase Disease, Acid Maltase Deficiency, Acquired Epileptiform Aphasia, Acute Disseminated Encephalomyelitis, Attention Deficit-Hyperactivity Disorder (ADHD), Adie's Pupil, Adie's Syndrome, Adrenoleukodystrophy, Agenesis of the Corpus Callosum, Agnosia, Aicardi Syndrome, Aicardi-Goutieres Syndrome Disorder, AIDS - Neurological Complications, Alexander Disease, Alpers' Disease, Alternating Hemiplegia, Alzheimer's Disease, Amyotrophic Lateral Sclerosis (ALS), Anencephaly, Aneurysm, Angelman Syndrome, Angiomatosis, Anoxia, Antiphospholipid Syndrome, Aphasia, Apraxia, Arachnoid Cysts, Arachnoiditis, Arnold-Chiari Malformation, Arteriovenous Malformation, Asperger Syndrome, Ataxia, Ataxia Telangiectasia, Ataxias and Cerebellar or Spinocerebellar Degeneration, Atrial Fibrillation and Stroke, Attention Deficit-Hyperactivity Disorder, Autism Spectrum Disorder, Autonomic Dysfunction, Back Pain, Barth Syndrome, Batten Disease, Becker's Myotonia, Bechet's Disease, Bell's Palsy, Benign Essential Blepharospasm, Benign Focal Amyotrophy, Benign Intracranial Hypertension, Bernhardt-Roth Syndrome, Binswanger's Disease, Blepharospasm, Bloch-Sulzberger Syndrome, Brachial Plexus Birth Injuries, Brachial Plexus Injuries, Bradbury-Eggleston Syndrome, Brain and Spinal Tumors, Brain Aneurysm, Brain Injury, Brown-Sequard Syndrome, Bulbar palsy, Bulbospinal Muscular Atrophy, Cerebral Autosomal Dominant Arteriopathy with Sub-cortical Infarcts and Leukoencephalopathy (CADASIL), Canavan Disease, Carpal Tunnel Syndrome, Causalgia, Cavemomas, Cavernous Angioma, Cavernous Malformation, Central Cervical Cord Syndrome, Central Cord Syndrome, Central Pain Syndrome, Central Pontine Myelinolysis, Cephalic Disorders, Ceramidase Deficiency, Cerebellar Degeneration, Cerebellar Hypoplasia, Cerebral Aneurysms, Cerebral Arteriosclerosis, Cerebral Atrophy, Cerebral Beriberi, Cerebral Cavernous Malformation, Cerebral Gigantism, Cerebral Hypoxia, Cerebral Palsy, Cerebro-Oculo-Facio-Skeletal Syndrome (COFS), Charcot-Marie-Tooth Disease, Chiari Malformation, Cholesterol Ester Storage Disease, Chorea, Choreoacanthocytosis, Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), Chronic Orthostatic Intolerance, Chronic Pain, Cockayne Syndrome Type II, Coffin Lowry Syndrome, Colpocephaly, Coma, Complex Regional Pain Syndrome, Concentric sclerosis (Baló's sclerosis), Congenital Facial Diplegia, Congenital Myasthenia, Congenital Myopathy, Congenital Vascular Cavernous Malformations, Corticobasal Degeneration, Cranial Arteritis, Craniosynostosis, Cree encephalitis, Creutzfeldt-Jakob Disease, Chronic progressive external opthalmoplegia, Cumulative Trauma Disorders,

Cushing's Syndrome, Cytomegalic Inclusion Body Disease, Cytomegalovirus Infection, Dancing Eyes-Dancing Feet Syndrome, Dandy-Walker Syndrome, Dawson Disease, De Morsier's Syndrome, Dejerine-Klumpke Palsy, Dementia, Dementia -Multi-Infarct, Dementia - Semantic, Dementia -Subcortical, Dementia With Lewy Bodies, Demyelination diseases, Dentate Cerebellar Ataxia, Dentatorubral Atrophy, Dermatomyositis, Developmental Dyspraxia, Devic's Syndrome, Diabetic Neuropathy, Diffuse Sclerosis, Distal hereditary motor neuronopathies, Dravet Syndrome, Dysautonomia, Dysgraphia, Dyslexia, Dysphagia, Dyspraxia, Dyssynergia Cerebellaris Myoclonica, Dyssynergia Cerebellaris Progressiva, Dystonias, Early Infantile Epileptic Encephalopathy, Empty Sella Syndrome, Encephalitis, Encephalitis Lethargica, Encephaloceles, Encephalomyelitis, Encephalopathy, Encephalopathy (familial infantile), Encephalotrigeminal Angiomatosis, Epilepsy, Epileptic Hemiplegia, Episodic ataxia, Erb's Palsy, Erb-Duchenne and Dejerine-Klumpke Palsies, Essential Tremor, Extrapontine Myelinolysis, Faber's disease, Fabry Disease, Fahr's Syndrome, Fainting, Familial Dysautonomia, Familial Hemangioma, Familial Idiopathic Basal Ganglia Calcification, Familial Periodic Paralysis, Familial Spastic Paralysis, Farber's Disease, Febrile Seizures, Fibromuscular Dysplasia, Fisher Syndrome, Floppy Infant Syndrome, Foot Drop, Friedreich's Ataxia, Frontotemporal Dementia, Gaucher Disease, Generalized Gangliosidoses (GM1, GM2), Gerstmann's Syndrome, Gerstmann-Straussler-Scheinker Disease, Giant Axonal Neuropathy, Giant Cell Arteritis, Giant Cell Inclusion Disease, Globoid Cell Leukodystrophy, Glossopharyngeal Neuralgia, Glycogen Storage Disease, Guillain-Barré Syndrome, Hallervorden-Spatz Disease, Head Injury, Headache, Hemicrania Continua, Hemifacial Spasm, Hemiplegia Alterans, Hereditary Neuropathies, Hereditary Spastic Paraplegia, Heredopathia Atactica Polyneuritiformis, Herpes Zoster, Herpes Zoster Oticus, Hirayama Syndrome, Holmes-Adie syndrome, Holoprosencephaly, HTLV-1 Associated Myelopathy, Hughes Syndrome, Huntington's Disease, Hurler syndrome, Hydranencephaly, Hydrocephalus, Hydrocephalus - Normal Pressure, Hydromyelia, Hypercortisolism, Hypersomnia, Hypertonia, Hypotonia, Hypoxia, Immune-Mediated Encephalomyelitis, Inclusion Body Myositis, Incontinentia Pigmenti, Infantile Hypotonia, Infantile Neuroaxonal Dystrophy, Infantile Phytanic Acid Storage Disease, Infantile Refsum Disease, Infantile Spasms, Inflammatory Myopathies, Iniencephaly, Intestinal Lipodystrophy, Intracranial Cysts, Intracranial Hypertension, Isaacs' Syndrome, Joubert Syndrome, Kearns-Sayre Syndrome, Kennedy's Disease, Kinsbourne syndrome, Kleine-Levin Syndrome, Klippel-Feil Syndrome, Klippel-Trenaunay Syndrome (KTS), Klüver-Bucy Syndrome, Korsakoff's Amnesic Syndrome, Krabbe Disease, Kugelberg-

Welder Disease, Kuru, Lambert-Eaton Myasthenic Syndrome, Landau-Kleffner Syndrome, Lateral Femoral Cutaneous Nerve Entrapment, Lateral Medullary Syndrome, Learning Disabilities, Leigh's Disease, Lennox-Gastaut Syndrome, Lesch-Nyhan Syndrome, Leukodystrophy, Levine-Critchley Syndrome, Lewy Body Dementia, Lichtheim's disease, Lipid Storage Diseases, Lipoid Proteinosis, Lissencephaly, Locked-In Syndrome, Lou Gehrig's Disease, Lupus - Neurological Sequelae, Lyme Disease - Neurological Complications, Lysosomal storage disorders, Machado-Joseph Disease, Macrencephaly, Megalencephaly, Melkersson-Rosenthal Syndrome, Meningitis, Meningitis and Encephalitis, Menkes Disease, Meralgia Paresthetica, Metachromatic Leukodystrophy, Microcephaly, Migraine, Miller Fisher Syndrome, Mini Stroke, Mitochondrial Myopathy, Mitochondrial DNA depletion syndromes, Moebius Syndrome, Monomelic Amyotrophy, Morvan Syndrome, Motor Neuron Diseases, Moyamoya Disease, Mucopolysaccharidoses, Mucopolysaccharidoses, Multi-Infarct Dementia, Multifocal Motor Neuropathy, Multiple Sclerosis, Multiple System Atrophy, Multiple System Atrophy with Orthostatic Hypotension, Muscular Dystrophy, Myasthenia - Congenital, Myasthenia Gravis, Myelinoclastic Diffuse Sclerosis, Myelitis, Myoclonic Encephalopathy of Infants, Myoclonus, Myoclonus epilepsy, Myopathy, Myopathy- Congenital, Myopathy -Thyrotoxic, Myotonia, Myotonia Congenita, Narcolepsy, NARP (neuropathy, ataxia and retinitis pigmentosa), Neuroacanthocytosis, Neurodegeneration with Brain Iron Accumulation, Neurodegenerative disease, Neurofibromatosis, Neuroleptic Malignant Syndrome, Neurological Complications of AIDS, Neurological Complications of Lyme Disease, Neurological Consequences of Cytomegalovirus Infection, Neurological Manifestations of Pompe Disease, Neurological Sequelae Of Lupus, Neuromyelitis Optica, Neuromyotonia, Neuronal Ceroid Lipofuscinosis, Neuronal Migration Disorders, Neuropathic pain, Neuropathy- Hereditary, Neuropathy, Neurosarcoidosis, Neurosyphilis, Neurotoxicity, Nevus Cavemosus, Niemann-Pick Disease, O'Sullivan-McLeod Syndrome, Occipital Neuralgia, Ohtahara Syndrome, Olivopontocerebellar Atrophy, Opsoclonus Myoclonus, Orthostatic Hypotension, Overuse Syndrome, Pain -Chronic, Pantothenate Kinase-Associated Neurodegeneration, Paraneoplastic Syndromes, Paresthesia, Parkinson's Disease, Paroxysmal Choreoathetosis, Paroxysmal Hemicrania, Parry-Romberg, Pelizaeus-Merzbacher Disease, Pena Shokeir II Syndrome, Perineural Cysts, Peroneal muscular atrophy, Periodic Paralysis, Peripheral Neuropathy, Periventricular Leukomalacia, Persistent Vegetative State, Pervasive Developmental Disorders, Phytanic Acid Storage Disease, Pick's Disease, Pinched Nerve, Piriformis Syndrome, Pituitary Tumors, Polymyositis, Pompe Disease, Porencephaly, Post-

Polio Syndrome, Postherpetic Neuralgia, Postinfectious Encephalomyelitis, Postural Hypotension, Postural Orthostatic Tachycardia Syndrome, Postural Tachycardia Syndrome, Primary Dentatum Atrophy, Primary Lateral Sclerosis, Primary Progressive Aphasia, Prion Diseases, Progressive bulbar palsy, Progressive Hemifacial Atrophy, Progressive Locomotor Ataxia, Progressive Multifocal Leukoencephalopathy, Progressive Muscular Atrophy, Progressive Sclerosing Poliodystrophy, Progressive Supranuclear Palsy, Prosopagnosia, Pseudobulbar palsy, Pseudo-Torch syndrome, Pseudotoxoplasmosis syndrome, Pseudotumor Cerebri, Psychogenic Movement, Ramsay Hunt Syndrome I, Ramsay Hunt Syndrome II, Rasmussen's Encephalitis, Reflex Sympathetic Dystrophy Syndrome, Refsum Disease, Refsum Disease - Infantile, Repetitive Motion Disorders, Repetitive Stress Injuries, Restless Legs Syndrome, Retrovirus-Associated Myelopathy, Rett Syndrome, Reye's Syndrome, Rheumatic Encephalitis, Riley-Day Syndrome, Sacral Nerve Root Cysts, Saint Vitus Dance, Salivary Gland Disease, Sandhoff Disease, Schilder's Disease, Schizencephaly, Seitelberger Disease, Seizure Disorder, Semantic Dementia, Septo-Optic Dysplasia, Severe Myoclonic Epilepsy of Infancy (SMEI), Shaken Baby Syndrome, Shingles, Shy-Drager Syndrome, Sjögren's Syndrome, Sleep Apnea, Sleeping Sickness, Sotos Syndrome, Spasticity, Spina Bifida, Spinal Cord Infarction, Spinal Cord Injury, Spinal Cord Tumors, Spinal Muscular Atrophy, Spinocerebellar Ataxia, Spinocerebellar Atrophy, Spinocerebellar Degeneration, Sporadic ataxia, Steele-Richardson-Olszewski Syndrome, Stiff-Person Syndrome, Striatonigral Degeneration, Stroke, Sturge-Weber Syndrome, Subacute Sclerosing Panencephalitis, Subcortical Arteriosclerotic Encephalopathy, Short-lasting, Unilateral, Neuralgiform (SUNCT) Headache, Swallowing Disorders, Sydenham Chorea, Syncope, Syphilitic Spinal Sclerosis, Syringohydromyelia, Syringomyelia, Systemic Lupus Erythematosus, Tabes Dorsalis, Tardive Dyskinesia, Tarlov Cysts, Tay-Sachs Disease, Temporal Arteritis, Tethered Spinal Cord Syndrome, Thomsen's Myotonia, Thoracic Outlet Syndrome, Thyrotoxic Myopathy, Tic Douloureux, Todd's Paralysis, Tourette Syndrome, Transient Ischemic Attack, Transmissible Spongiform Encephalopathies, Transverse Myelitis, Traumatic Brain Injury, Tremor, Trigeminal Neuralgia, Tropical Spastic Paraparesis, Troyer Syndrome, Tuberous Sclerosis, Vascular Erectile Tumor, Vasculitis Syndromes of the Central and Peripheral Nervous Systems, Vitamin B12 deficiency, Von Economo's Disease, Von Hippel-Lindau Disease (VHL), Von Recklinghausen's Disease, Wallenberg's Syndrome, Werdnig-Hoffman Disease, Wernicke-Korsakoff Syndrome, West Syndrome, Whiplash, Whipple's Disease, Williams Syndrome, Wilson Disease, Wolman's Disease, X-Linked Spinal and Bulbar Muscular Atrophy.

Methods of Treatment of Neurological Disease*TRACER AAV particles Encoding protein payloads*

[0186] Provided in the present disclosure are methods for introducing the TRACER AAV particles of the present disclosure into cells, the method comprising introducing into said cells any of the vectors in an amount sufficient for an increase in the production of target mRNA and protein to occur. In some aspects, the cells may be neurons such as but not limited to, motor, hippocampal, entorhinal, thalamic, cortical, sensory, sympathetic, or parasympathetic neurons, and glial cells such as astrocytes, microglia, and/or oligodendrocytes.

[0187] Disclosed in the present disclosure are methods for treating neurological disease associated with insufficient function/presence of a target protein (e.g., ApoE, FXN) in a subject in need of treatment. The method optionally comprises administering to the subject a therapeutically effective amount of a composition comprising TRACER AAV particles of the present disclosure. As a non-limiting example, the TRACER AAV particles can increase target gene expression, increase target protein production, and thus reduce one or more symptoms of neurological disease in the subject such that the subject is therapeutically treated.

[0188] In one embodiment, the composition comprising the TRACER AAV particles of the present disclosure is administered to the central nervous system of the subject via systemic administration. In one embodiment, the systemic administration is intravenous injection.

[0189] In some embodiments, the composition comprising the TRACER AAV particles of the present disclosure is administered to the central nervous system of the subject. In other embodiments, the composition comprising the TRACER AAV particles of the present disclosure is administered to a CNS tissue of a subject (e.g., putamen, thalamus or cortex of the subject).

[0190] In one embodiment, the composition comprising the TRACER AAV particles of the present disclosure is administered to the central nervous system of the subject via intraparenchymal injection. Non-limiting examples of intraparenchymal injections include intraputamenal, intracortical, intrathalamic, intrastriatal, intrahippocampal or into the entorhinal cortex.

[0191] In one embodiment, the composition comprising the TRACER AAV particles of the present disclosure is administered to the central nervous system of the subject via intraparenchymal injection and intravenous injection.

[0192] In one embodiment, the TRACER AAV particles of the present disclosure may be delivered into specific types of targeted cells, including, but not limited to, thalamic, hippocampal, entorhinal, cortical, motor, sensory, excitatory, inhibitory, sympathetic, or parasympathetic neurons; glial cells including oligodendrocytes, astrocytes and microglia; and/or other cells surrounding neurons such as T cells.

[0193] In one embodiment, the TRACER AAV particles of the present disclosure may be delivered to neurons in the putamen, thalamus and/or cortex.

[0194] In some embodiments, the TRACER AAV particles of the present disclosure may be used as a therapy for neurological disease.

[0195] In some embodiments, the TRACER AAV particles of the present disclosure may be used as a therapy for tauopathies.

[0196] In some embodiments, the TRACER AAV particles of the present disclosure may be used as a therapy for Alzheimer's Disease.

[0197] In some embodiments, the TRACER AAV particles of the present disclosure may be used as a therapy for Amyotrophic Lateral Sclerosis.

[0198] In some embodiments, the TRACER AAV particles of the present disclosure may be used as a therapy for Huntington's Disease.

[0199] In some embodiments, the TRACER AAV particles of the present disclosure may be used as a therapy for Parkinson's Disease.

[0200] In some embodiments, the TRACER AAV particles of the present disclosure may be used as a therapy for Friedreich's Ataxia.

[0201] In some embodiments, the TRACER AAV particles of the present disclosure may be used as a therapy for chronic or neuropathic pain.

[0202] In one embodiment, administration of the TRACER AAV particles described herein to a subject may increase target protein levels in a subject. The target protein levels may be increased by about 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95% and 100%, or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% or 95-100% in a subject such as, but not limited to, the CNS, a region of the CNS, or a specific cell of the CNS of a subject. As a non-limiting example, the TRACER AAV particles may increase the protein levels of a target protein by at least 50%. As a non-limiting example, the TRACER AAV particles may

increase the proteins levels of a target protein by at least 40%. As a non-limiting example, a subject may have an increase of 10% of target protein. As a non-limiting example, the TRACER AAV particles may increase the protein levels of a target protein by fold increases over baseline. In one embodiment, TRACER AAV particles lead to 5-6 times higher levels of a target protein.

[0203] In one embodiment, administration of the TRACER AAV particles described herein to a subject may increase the expression of a target protein in a subject. The expression of the target protein may be increased by about 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95% and 100%, or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% or 95-100% in a subject such as, but not limited to, the CNS, a region of the CNS, or a specific cell of the CNS of a subject. As a non-limiting example, the TRACER AAV particles may increase the expression of a target protein by at least 50%. As a non-limiting example, the TRACER AAV particles may increase the expression of a target protein by at least 40%.

[0204] In one embodiment, intravenous administration of the TRACER AAV particles described herein to a subject may increase the CNS expression of a target protein in a subject. The expression of the target protein may be increased by about 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95% and 100%, or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% or 95-100% in a subject such as, but not limited to, the CNS, a region of the CNS, or a specific cell of the CNS of a subject. As a non-limiting example, the TRACER AAV particles may increase the expression of a target protein in the CNS by at least 50%. As a non-limiting example, the TRACER AAV particles may increase the expression of a target protein in the CNS by at least 40%.

[0205] In some embodiments, the TRACER AAV particles of the present disclosure may be used to increase target protein expression in astrocytes in order to treat a neurological disease. Target protein in astrocytes may be increased by 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more than

95%, 5-15%, 5-20%, 5-25%, 5-30%, 5-35%, 5-40%, 5-45%, 5-50%, 5-55%, 5-60%, 5-65%, 5-70%, 5-75%, 5-80%, 5-85%, 5-90%, 5-95%, 10-20%, 10-25%, 10-30%, 10-35%, 10-40%, 10-45%, 10-50%, 10-55%, 10-60%, 10-65%, 10-70%, 10-75%, 10-80%, 10-85%, 10-90%, 10-95%, 15-25%, 15-30%, 15-35%, 15-40%, 15-45%, 15-50%, 15-55%, 15-60%, 15-65%, 15-70%, 15-75%, 15-80%, 15-85%, 15-90%, 15-95%, 20-30%, 20-35%, 20-40%, 20-45%, 20-50%, 20-55%, 20-60%, 20-65%, 20-70%, 20-75%, 20-80%, 20-85%, 20-90%, 20-95%, 25-35%, 25-40%, 25-45%, 25-50%, 25-55%, 25-60%, 25-65%, 25-70%, 25-75%, 25-80%, 25-85%, 25-90%, 25-95%, 30-40%, 30-45%, 30-50%, 30-55%, 30-60%, 30-65%, 30-70%, 30-75%, 30-80%, 30-85%, 30-90%, 30-95%, 35-45%, 35-50%, 35-55%, 35-60%, 35-65%, 35-70%, 35-75%, 35-80%, 35-85%, 35-90%, 35-95%, 40-50%, 40-55%, 40-60%, 40-65%, 40-70%, 40-75%, 40-80%, 40-85%, 40-90%, 40-95%, 45-55%, 45-60%, 45-65%, 45-70%, 45-75%, 45-80%, 45-85%, 45-90%, 45-95%, 50-60%, 50-65%, 50-70%, 50-75%, 50-80%, 50-85%, 50-90%, 50-95%, 55-65%, 55-70%, 55-75%, 55-80%, 55-85%, 55-90%, 55-95%, 60-70%, 60-75%, 60-80%, 60-85%, 60-90%, 60-95%, 65-75%, 65-80%, 65-85%, 65-90%, 65-95%, 70-80%, 70-85%, 70-90%, 70-95%, 75-85%, 75-90%, 75-95%, 80-90%, 80-95%, or 90-95%.

[0206] In some embodiments, the TRACER AAV particles may be used to increase target protein in microglia. The increase of target protein in microglia may be, independently, increased by 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more than 95%, 5-15%, 5-20%, 5-25%, 5-30%, 5-35%, 5-40%, 5-45%, 5-50%, 5-55%, 5-60%, 5-65%, 5-70%, 5-75%, 5-80%, 5-85%, 5-90%, 5-95%, 10-20%, 10-25%, 10-30%, 10-35%, 10-40%, 10-45%, 10-50%, 10-55%, 10-60%, 10-65%, 10-70%, 10-75%, 10-80%, 10-85%, 10-90%, 10-95%, 15-25%, 15-30%, 15-35%, 15-40%, 15-45%, 15-50%, 15-55%, 15-60%, 15-65%, 15-70%, 15-75%, 15-80%, 15-85%, 15-90%, 15-95%, 20-30%, 20-35%, 20-40%, 20-45%, 20-50%, 20-55%, 20-60%, 20-65%, 20-70%, 20-75%, 20-80%, 20-85%, 20-90%, 20-95%, 25-35%, 25-40%, 25-45%, 25-50%, 25-55%, 25-60%, 25-65%, 25-70%, 25-75%, 25-80%, 25-85%, 25-90%, 25-95%, 30-40%, 30-45%, 30-50%, 30-55%, 30-60%, 30-65%, 30-70%, 30-75%, 30-80%, 30-85%, 30-90%, 30-95%, 35-45%, 35-50%, 35-55%, 35-60%, 35-65%, 35-70%, 35-75%, 35-80%, 35-85%, 35-90%, 35-95%, 40-50%, 40-55%, 40-60%, 40-65%, 40-70%, 40-75%, 40-80%, 40-85%, 40-90%, 40-95%, 45-55%, 45-60%, 45-65%, 45-70%, 45-75%, 45-80%, 45-85%, 45-90%, 45-95%, 50-60%, 50-65%, 50-70%, 50-75%, 50-80%, 50-85%, 50-90%, 50-95%, 55-65%, 55-70%, 55-75%, 55-80%, 55-85%, 55-90%, 55-95%, 60-70%, 60-75%, 60-80%, 60-85%, 60-90%,

60-95%, 65-75%, 65-80%, 65-85%, 65-90%, 65-95%, 70-80%, 70-85%, 70-90%, 70-95%, 75-85%, 75-90%, 75-95%, 80-90%, 80-95%, or 90-95%.

[0207] In some embodiments, the TRACER AAV particles may be used to increase target protein in cortical neurons. The increase of target protein in the cortical neurons may be, independently, increased by 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more than 95%, 5-15%, 5-20%, 5-25%, 5-30%, 5-35%, 5-40%, 5-45%, 5-50%, 5-55%, 5-60%, 5-65%, 5-70%, 5-75%, 5-80%, 5-85%, 5-90%, 5-95%, 10-20%, 10-25%, 10-30%, 10-35%, 10-40%, 10-45%, 10-50%, 10-55%, 10-60%, 10-65%, 10-70%, 10-75%, 10-80%, 10-85%, 10-90%, 10-95%, 15-25%, 15-30%, 15-35%, 15-40%, 15-45%, 15-50%, 15-55%, 15-60%, 15-65%, 15-70%, 15-75%, 15-80%, 15-85%, 15-90%, 15-95%, 20-30%, 20-35%, 20-40%, 20-45%, 20-50%, 20-55%, 20-60%, 20-65%, 20-70%, 20-75%, 20-80%, 20-85%, 20-90%, 20-95%, 25-35%, 25-40%, 25-45%, 25-50%, 25-55%, 25-60%, 25-65%, 25-70%, 25-75%, 25-80%, 25-85%, 25-90%, 25-95%, 30-40%, 30-45%, 30-50%, 30-55%, 30-60%, 30-65%, 30-70%, 30-75%, 30-80%, 30-85%, 30-90%, 30-95%, 35-45%, 35-50%, 35-55%, 35-60%, 35-65%, 35-70%, 35-75%, 35-80%, 35-85%, 35-90%, 35-95%, 40-50%, 40-55%, 40-60%, 40-65%, 40-70%, 40-75%, 40-80%, 40-85%, 40-90%, 40-95%, 45-55%, 45-60%, 45-65%, 45-70%, 45-75%, 45-80%, 45-85%, 45-90%, 45-95%, 50-60%, 50-65%, 50-70%, 50-75%, 50-80%, 50-85%, 50-90%, 50-95%, 55-65%, 55-70%, 55-75%, 55-80%, 55-85%, 55-90%, 55-95%, 60-70%, 60-75%, 60-80%, 60-85%, 60-90%, 60-95%, 65-75%, 65-80%, 65-85%, 65-90%, 65-95%, 70-80%, 70-85%, 70-90%, 70-95%, 75-85%, 75-90%, 75-95%, 80-90%, 80-95%, or 90-95%.

[0208] In some embodiments, the TRACER AAV particles may be used to increase target protein in hippocampal neurons. The increase of target protein in the hippocampal neurons may be, independently, increased by 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more than 95%, 5-15%, 5-20%, 5-25%, 5-30%, 5-35%, 5-40%, 5-45%, 5-50%, 5-55%, 5-60%, 5-65%, 5-70%, 5-75%, 5-80%, 5-85%, 5-90%, 5-95%, 10-20%, 10-25%, 10-30%, 10-35%, 10-40%, 10-45%, 10-50%, 10-55%, 10-60%, 10-65%, 10-70%, 10-75%, 10-80%, 10-85%, 10-90%, 10-95%, 15-25%, 15-30%, 15-35%, 15-40%, 15-45%, 15-50%, 15-55%, 15-60%, 15-65%, 15-70%, 15-75%, 15-80%, 15-85%, 15-90%, 15-95%, 20-30%, 20-35%, 20-40%, 20-45%, 20-50%, 20-55%, 20-60%, 20-65%, 20-70%, 20-75%, 20-80%, 20-85%, 20-90%, 20-95%, 25-35%, 25-40%, 25-45%, 25-50%, 25-55%, 25-60%, 25-65%, 25-70%, 25-75%, 25-80%, 25-85%, 25-90%, 25-95%, 30-40%, 30-45%, 30-50%, 30-55%, 30-60%, 30-65%, 30-70%, 30-75%, 30-80%, 30-85%, 30-90%, 30-95%, 35-45%, 35-50%, 35-55%, 35-60%, 35-65%, 35-70%, 35-75%, 35-

80%, 35-85%, 35-90%, 35-95%, 40-50%, 40-55%, 40-60%, 40-65%, 40-70%, 40-75%, 40-80%, 40-85%, 40-90%, 40-95%, 45-55%, 45-60%, 45-65%, 45-70%, 45-75%, 45-80%, 45-85%, 45-90%, 45-95%, 50-60%, 50-65%, 50-70%, 50-75%, 50-80%, 50-85%, 50-90%, 50-95%, 55-65%, 55-70%, 55-75%, 55-80%, 55-85%, 55-90%, 55-95%, 60-70%, 60-75%, 60-80%, 60-85%, 60-90%, 60-95%, 65-75%, 65-80%, 65-85%, 65-90%, 65-95%, 70-80%, 70-85%, 70-90%, 70-95%, 75-85%, 75-90%, 75-95%, 80-90%, 80-95%, or 90-95%.

[0209] In some embodiments, the TRACER AAV particles may be used to increase target protein in DRG and/or sympathetic neurons. The increase of target protein in the DRG and/or sympathetic neurons may be, independently, increased by 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more than 95%, 5-15%, 5-20%, 5-25%, 5-30%, 5-35%, 5-40%, 5-45%, 5-50%, 5-55%, 5-60%, 5-65%, 5-70%, 5-75%, 5-80%, 5-85%, 5-90%, 5-95%, 10-20%, 10-25%, 10-30%, 10-35%, 10-40%, 10-45%, 10-50%, 10-55%, 10-60%, 10-65%, 10-70%, 10-75%, 10-80%, 10-85%, 10-90%, 10-95%, 15-25%, 15-30%, 15-35%, 15-40%, 15-45%, 15-50%, 15-55%, 15-60%, 15-65%, 15-70%, 15-75%, 15-80%, 15-85%, 15-90%, 15-95%, 20-30%, 20-35%, 20-40%, 20-45%, 20-50%, 20-55%, 20-60%, 20-65%, 20-70%, 20-75%, 20-80%, 20-85%, 20-90%, 20-95%, 25-35%, 25-40%, 25-45%, 25-50%, 25-55%, 25-60%, 25-65%, 25-70%, 25-75%, 25-80%, 25-85%, 25-90%, 25-95%, 30-40%, 30-45%, 30-50%, 30-55%, 30-60%, 30-65%, 30-70%, 30-75%, 30-80%, 30-85%, 30-90%, 30-95%, 35-45%, 35-50%, 35-55%, 35-60%, 35-65%, 35-70%, 35-75%, 35-80%, 35-85%, 35-90%, 35-95%, 40-50%, 40-55%, 40-60%, 40-65%, 40-70%, 40-75%, 40-80%, 40-85%, 40-90%, 40-95%, 45-55%, 45-60%, 45-65%, 45-70%, 45-75%, 45-80%, 45-85%, 45-90%, 45-95%, 50-60%, 50-65%, 50-70%, 50-75%, 50-80%, 50-85%, 50-90%, 50-95%, 55-65%, 55-70%, 55-75%, 55-80%, 55-85%, 55-90%, 55-95%, 60-70%, 60-75%, 60-80%, 60-85%, 60-90%, 60-95%, 65-75%, 65-80%, 65-85%, 65-90%, 65-95%, 70-80%, 70-85%, 70-90%, 70-95%, 75-85%, 75-90%, 75-95%, 80-90%, 80-95%, or 90-95%.

[0210] In some embodiments, the TRACER AAV particles of the present disclosure may be used to increase target protein in sensory neurons in order to treat neurological disease. Target protein in sensory neurons may be increased by 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more than 95%, 5-15%, 5-20%, 5-25%, 5-30%, 5-35%, 5-40%, 5-45%, 5-50%, 5-55%, 5-60%, 5-65%, 5-70%, 5-75%, 5-80%, 5-85%, 5-90%, 5-95%, 10-20%, 10-25%, 10-30%, 10-35%, 10-40%, 10-45%, 10-50%, 10-55%, 10-60%, 10-65%, 10-70%, 10-75%, 10-80%, 10-85%, 10-90%, 10-95%, 15-25%, 15-30%, 15-35%, 15-40%, 15-45%, 15-50%, 15-55%, 15-60%, 15-65%,

15-70%, 15-75%, 15-80%, 15-85%, 15-90%, 15-95%, 20-30%, 20-35%, 20-40%, 20-45%, 20-50%, 20-55%, 20-60%, 20-65%, 20-70%, 20-75%, 20-80%, 20-85%, 20-90%, 20-95%, 25-35%, 25-40%, 25-45%, 25-50%, 25-55%, 25-60%, 25-65%, 25-70%, 25-75%, 25-80%, 25-85%, 25-90%, 25-95%, 30-40%, 30-45%, 30-50%, 30-55%, 30-60%, 30-65%, 30-70%, 30-75%, 30-80%, 30-85%, 30-90%, 30-95%, 35-45%, 35-50%, 35-55%, 35-60%, 35-65%, 35-70%, 35-75%, 35-80%, 35-85%, 35-90%, 35-95%, 40-50%, 40-55%, 40-60%, 40-65%, 40-70%, 40-75%, 40-80%, 40-85%, 40-90%, 40-95%, 45-55%, 45-60%, 45-65%, 45-70%, 45-75%, 45-80%, 45-85%, 45-90%, 45-95%, 50-60%, 50-65%, 50-70%, 50-75%, 50-80%, 50-85%, 50-90%, 50-95%, 55-65%, 55-70%, 55-75%, 55-80%, 55-85%, 55-90%, 55-95%, 60-70%, 60-75%, 60-80%, 60-85%, 60-90%, 60-95%, 65-75%, 65-80%, 65-85%, 65-90%, 65-95%, 70-80%, 70-85%, 70-90%, 70-95%, 75-85%, 75-90%, 75-95%, 80-90%, 80-95%, or 90-95%.

[0211] In some embodiments, the TRACER AAV particles of the present disclosure may be used to increase target protein and reduce symptoms of neurological disease in a subject. The increase of target protein and/or the reduction of symptoms of neurological disease may be, independently, altered (increased for the production of target protein and reduced for the symptoms of neurological disease) by 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more than 95%, 5-15%, 5-20%, 5-25%, 5-30%, 5-35%, 5-40%, 5-45%, 5-50%, 5-55%, 5-60%, 5-65%, 5-70%, 5-75%, 5-80%, 5-85%, 5-90%, 5-95%, 10-20%, 10-25%, 10-30%, 10-35%, 10-40%, 10-45%, 10-50%, 10-55%, 10-60%, 10-65%, 10-70%, 10-75%, 10-80%, 10-85%, 10-90%, 10-95%, 15-25%, 15-30%, 15-35%, 15-40%, 15-45%, 15-50%, 15-55%, 15-60%, 15-65%, 15-70%, 15-75%, 15-80%, 15-85%, 15-90%, 15-95%, 20-30%, 20-35%, 20-40%, 20-45%, 20-50%, 20-55%, 20-60%, 20-65%, 20-70%, 20-75%, 20-80%, 20-85%, 20-90%, 20-95%, 25-35%, 25-40%, 25-45%, 25-50%, 25-55%, 25-60%, 25-65%, 25-70%, 25-75%, 25-80%, 25-85%, 25-90%, 25-95%, 30-40%, 30-45%, 30-50%, 30-55%, 30-60%, 30-65%, 30-70%, 30-75%, 30-80%, 30-85%, 30-90%, 30-95%, 35-45%, 35-50%, 35-55%, 35-60%, 35-65%, 35-70%, 35-75%, 35-80%, 35-85%, 35-90%, 35-95%, 40-50%, 40-55%, 40-60%, 40-65%, 40-70%, 40-75%, 40-80%, 40-85%, 40-90%, 40-95%, 45-55%, 45-60%, 45-65%, 45-70%, 45-75%, 45-80%, 45-85%, 45-90%, 45-95%, 50-60%, 50-65%, 50-70%, 50-75%, 50-80%, 50-85%, 50-90%, 50-95%, 55-65%, 55-70%, 55-75%, 55-80%, 55-85%, 55-90%, 55-95%, 60-70%, 60-75%, 60-80%, 60-85%, 60-90%, 60-95%, 65-75%, 65-80%, 65-85%, 65-90%, 65-95%, 70-80%, 70-85%, 70-90%, 70-95%, 75-85%, 75-90%, 75-95%, 80-90%, 80-95%, or 90-95%.

[0212] In one embodiment, the TRACER AAV particles of the present disclosure may be used to reduce the decline of functional capacity and activities of daily living as measured by a standard evaluation system such as, but not limited to, the total functional capacity (TFC) scale.

[0213] In one embodiment, the TRACER AAV particles of the present disclosure may be used to improve performance on any assessment used to measure symptoms of neurological disease. Such assessments include, but are not limited to ADAS-cog (Alzheimer Disease Assessment Scale – cognitive), MMSE (Mini-Mental State Examination), GDS (Geriatric Depression Scale), FAQ (Functional Activities Questionnaire), ADL (Activities of Daily Living), GPCOG (General Practitioner Assessment of Cognition), Mini-Cog, AMTS (Abbreviated Mental Test Score), Clock-drawing test, 6-CIT (6-item Cognitive Impairment Test), TYM (Test Your Memory), MoCa (Montreal Cognitive Assessment), ACE-R (Addenbrookes Cognitive Assessment), MIS (Memory Impairment Screen), BADLS (Bristol Activities of Daily Living Scale), Barthel Index, Functional Independence Measure, Instrumental Activities of Daily Living, IQCODE (Informant Questionnaire on Cognitive Decline in the Elderly), Neuropsychiatric Inventory, The Cohen-Mansfield Agitation Inventory, BEHAVE-AD, EuroQol, Short Form-36 and/or MBR Caregiver Strain Instrument, or any of the other tests as described in Sheehan B (Ther Adv Neurol Disord. 5(6):349-358 (2012)), the contents of which are herein incorporated by reference in their entirety.

[0214] In some embodiments, the present composition is administered as a solo therapeutic or as combination therapeutic for the treatment of neurological disease.

[0215] The TRACER AAV particles encoding the target protein may be used in combination with one or more other therapeutic agents. By “in combination with,” it is not intended to imply that the agents must be administered at the same time and/or formulated for delivery together, although these methods of delivery are within the scope of the present disclosure. Compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. In general, each agent will be administered at a dose and/or on a time schedule determined for that agent.

[0216] Therapeutic agents that may be used in combination with the TRACER AAV particles of the present disclosure can be small molecule compounds which are antioxidants, anti-inflammatory agents, anti-apoptosis agents, calcium regulators, antiglutamatergic agents, structural protein inhibitors, compounds involved in muscle function, and compounds involved in metal ion regulation. As a non-limiting example, the combination therapy may be in combination with one or more neuroprotective agents such as small molecule compounds,

growth factors and hormones which have been tested for their neuroprotective effect on motor neuron degeneration.

[0217] Compounds tested for treating neurological disease which may be used in combination with the TRACER AAV particles described herein include, but are not limited to, cholinesterase inhibitors (donepezil, rivastigmine, galantamine), NMDA receptor antagonists such as memantine, anti-psychotics, anti-depressants, anti-convulsants (e.g., sodium valproate and levetiracetam for myoclonus), secretase inhibitors, amyloid aggregation inhibitors, copper or zinc modulators, BACE inhibitors, inhibitors of tau aggregation, such as Methylene blue, phenothiazines, anthraquinones, n-phenylamines or rhodamines, microtubule stabilizers such as NAP, taxol or paclitaxel, kinase or phosphatase inhibitors such as those targeting GSK3 β (lithium) or PP2A, immunization with A β peptides or tau phospho-epitopes, anti-tau or anti-amyloid antibodies, dopamine-depleting agents (e.g., tetrabenazine for chorea), benzodiazepines (e.g., clonazepam for myoclonus, chorea, dystonia, rigidity, and/or spasticity), , amino acid precursors of dopamine (e.g., levodopa for rigidity), skeletal muscle relaxants (e.g., baclofen, tizanidine for rigidity and/or spasticity), inhibitors for acetylcholine release at the neuromuscular junction to cause muscle paralysis (e.g., botulinum toxin for bruxism and/or dystonia), atypical neuroleptics (e.g., olanzapine and quetiapine for psychosis and/or irritability, risperidone, sulpiride and haloperidol for psychosis, chorea and/or irritability, clozapine for treatment-resistant psychosis, aripiprazole for psychosis with prominent negative symptoms), selective serotonin reuptake inhibitors (SSRIs) (e.g., citalopram, fluoxetine, paroxetine, sertraline, mirtazapine, venlafaxine for depression, anxiety, obsessive compulsive behavior and/or irritability), hypnotics (e.g., xopiclone and/or zolpidem for altered sleep-wake cycle), anticonvulsants (e.g., sodium valproate and carbamazepine for mania or hypomania) and mood stabilizers (e.g., lithium for mania or hypomania).

[0218] Neurotrophic factors may be used in combination therapy with the TRACER AAV particles of the present disclosure for treating neurological disease. Generally, a neurotrophic factor is defined as a substance that promotes survival, growth, differentiation, proliferation and/or maturation of a neuron, or stimulates increased activity of a neuron. In some embodiments, the present methods further comprise delivery of one or more trophic factors into the subject in need of treatment. Trophic factors may include, but are not limited to, IGF-I, GDNF, BDNF, CTNF, VEGF, Colivelin, Xaliproden, Thyrotrophin-releasing hormone and ADNF, and variants thereof.

[0219] In one aspect, the TRACER AAV particle described herein may be co-administered with TRACER AAV particles expressing neurotrophic factors such as AAV-IGF-I (See e.g., Vincent et al., *Neuromolecular medicine*, 2004, 6, 79-85; the contents of which are incorporated herein by reference in their entirety) and AAV-GDNF (See e.g., Wang et al., *J Neurosci.*, 2002, 22, 6920-6928; the contents of which are incorporated herein by reference in their entirety).

[0220] In one embodiment, administration of the TRACER AAV particles to a subject will increase the expression of a target protein in a subject and the increase of the expression of the target protein will reduce the effects and/or symptoms of neurological disease in a subject.

[0221] As a non-limiting example, the target protein may be an antibody, or fragment thereof.

TRACER AAV particles Comprising RNAi agents or Modulatory Polynucleotides

[0222] Provided in the present disclosure are methods for introducing the TRACER AAV particles of the disclosure, comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules into cells, the method comprising introducing into said cells any of the vectors in an amount sufficient for degradation of a target mRNA to occur, thereby activating target-specific RNAi in the cells. In some aspects, the cells may be neurons such as but not limited to, motor, hippocampal, entorhinal, thalamic, cortical, sensory, sympathetic, or parasympathetic neurons, and glial cells such as astrocytes, microglia, and/or oligodendrocytes.

[0223] Disclosed in the present disclosure are methods for treating neurological diseases associated with dysfunction of a target protein in a subject in need of treatment. The method optionally comprises administering to the subject a therapeutically effective amount of a composition comprising TRACER AAV particles comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules. As a non-limiting example, the siRNA molecules can silence target gene expression, inhibit target protein production, and reduce one or more symptoms of neurological disease in the subject such that the subject is therapeutically treated.

[0224] In some embodiments, the composition comprising the TRACER AAV particles of the present disclosure comprising a viral genome encoding one or more siRNA molecules comprise an AAV capsid that allows for enhanced transduction of CNS and/or PNS cells after intravenous administration.

[0225] In some embodiments, the composition comprising the TRACER AAV particles of the present disclosure with a viral genome encoding at least one siRNA molecule is administered to the central nervous system of the subject. In other embodiments, the composition comprising the TRACER AAV particles of the present disclosure is administered to a tissue of a subject (e.g., putamen, thalamus or cortex of the subject).

[0226] In one embodiment, the composition comprising the TRACER AAV particles of the disclosure, comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules is administered to the central nervous system of the subject via systemic administration. In one embodiment, the systemic administration is intravenous injection.

[0227] In one embodiment, the composition comprising the TRACER AAV particles of the disclosure comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules is administered to the central nervous system of the subject via intraparenchymal injection. Non-limiting examples of intraparenchymal injections include intraputamenal, intracortical, intrathalamic, intrastriatal, intrahippocampal or into the entorhinal cortex.

[0228] In one embodiment, the composition comprising the TRACER AAV particles comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules is administered to the central nervous system of the subject via intraparenchymal injection and intravenous injection.

[0229] In one embodiment, the TRACER AAV particles comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules may be delivered into specific types or targeted cells, including, but not limited to, thalamic, hippocampal, entorhinal, cortical, motor, sensory, excitatory, inhibitory, sympathetic, or parasympathetic neurons; glial cells including oligodendrocytes, astrocytes and microglia; and/or other cells surrounding neurons such as T cells.

[0230] In one embodiment, the TRACER AAV particles comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules may be delivered to neurons in the putamen, thalamus, and/or cortex.

[0231] In one embodiment, the TRACER AAV particles comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules may be used as a therapy for neurological disease.

[0232] In one embodiment, the TRACER AAV particles comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules may be used as a therapy for tauopathies.

[0233] In one embodiment, the TRACER AAV particles comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules may be used as a therapy for Alzheimer's Disease.

[0234] In one embodiment, the TRACER AAV particles comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules may be used as a therapy for Amyotrophic Lateral Sclerosis.

[0235] In one embodiment, the TRACER AAV particles comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules may be used as a therapy for Huntington's Disease.

[0236] In one embodiment, the TRACER AAV particles comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules may be used as a therapy for Parkinson's Disease.

[0237] In one embodiment, the TRACER AAV particles comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules may be used as a therapy for Friedreich's Ataxia.

[0238] In one embodiment, the administration of TRACER AAV particles comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules to a subject may lower target protein levels in a subject. The target protein levels may be lowered by about 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95% and 100%, or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% or 95-100% in a subject such as, but not limited to, the CNS, a region of the CNS, or a specific cell of the CNS of a subject. As a non-limiting example, the TRACER AAV particles may lower the protein levels of a target protein by at least 50%. As a non-limiting example, the TRACER AAV particles may lower the proteins levels of a target protein by at least 40%.

[0239] In one embodiment, the administration of TRACER AAV particles comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules to a subject may lower the expression of a target protein in a subject. The expression of a target protein may be lowered by about 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95% and 100%, or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%,

40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% or 95-100% in a subject such as, but not limited to, the CNS, a region of the CNS, or a specific cell of the CNS of a subject. As a non-limiting example, the TRACER AAV particles may lower the expression of a target protein by at least 50%. As a non-limiting example, the TRACER AAV particles may lower the expression of a target protein by at least 40%.

[0240] In one embodiment, the administration of TRACER AAV particles comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules to a subject may lower the expression of a target protein in the CNS of a subject. The expression of a target protein may be lowered by about 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95% and 100%, or at least 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% or 95-100% in a subject such as, but not limited to, the CNS, a region of the CNS, or a specific cell of the CNS of a subject. As a non-limiting example, the TRACER AAV particles may lower the expression of a target protein by at least 50%. As a non-limiting example, the TRACER AAV particles may lower the expression of a target protein by at least 40%.

[0241] In one embodiment, the TRACER AAV particles comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules may be used to suppress a target protein in astrocytes in order to treat neurological disease. Target protein in astrocytes may be suppressed by 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more than 95%, 5-15%, 5-20%, 5-25%, 5-30%, 5-35%, 5-40%, 5-45%, 5-50%, 5-55%, 5-60%, 5-65%, 5-70%, 5-75%, 5-80%, 5-85%, 5-90%, 5-95%, 10-20%, 10-25%, 10-30%, 10-35%, 10-40%, 10-45%, 10-50%, 10-55%, 10-60%, 10-65%, 10-70%, 10-75%, 10-80%, 10-85%, 10-90%, 10-95%, 15-25%, 15-30%, 15-35%, 15-40%, 15-45%, 15-50%, 15-55%, 15-60%, 15-65%, 15-70%, 15-75%, 15-80%, 15-85%, 15-90%, 15-95%, 20-30%, 20-35%, 20-40%, 20-45%, 20-50%, 20-55%, 20-60%, 20-65%, 20-70%, 20-75%, 20-80%, 20-85%, 20-90%, 20-95%, 25-35%, 25-40%, 25-45%, 25-50%, 25-55%, 25-60%, 25-65%, 25-70%, 25-75%, 25-80%, 25-85%, 25-90%, 25-95%, 30-40%, 30-45%, 30-50%, 30-55%, 30-60%, 30-65%, 30-70%, 30-75%, 30-80%, 30-85%, 30-90%, 30-95%, 35-45%, 35-50%, 35-55%, 35-60%, 35-65%, 35-70%, 35-75%, 35-80%, 35-85%, 35-

90%, 35-95%, 40-50%, 40-55%, 40-60%, 40-65%, 40-70%, 40-75%, 40-80%, 40-85%, 40-90%, 40-95%, 45-55%, 45-60%, 45-65%, 45-70%, 45-75%, 45-80%, 45-85%, 45-90%, 45-95%, 50-60%, 50-65%, 50-70%, 50-75%, 50-80%, 50-85%, 50-90%, 50-95%, 55-65%, 55-70%, 55-75%, 55-80%, 55-85%, 55-90%, 55-95%, 60-70%, 60-75%, 60-80%, 60-85%, 60-90%, 60-95%, 65-75%, 65-80%, 65-85%, 65-90%, 65-95%, 70-80%, 70-85%, 70-90%, 70-95%, 75-85%, 75-90%, 75-95%, 80-90%, 80-95%, or 90-95%. Target protein in astrocytes may be reduced may be 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more than 95%, 5-15%, 5-20%, 5-25%, 5-30%, 5-35%, 5-40%, 5-45%, 5-50%, 5-55%, 5-60%, 5-65%, 5-70%, 5-75%, 5-80%, 5-85%, 5-90%, 5-95%, 10-20%, 10-25%, 10-30%, 10-35%, 10-40%, 10-45%, 10-50%, 10-55%, 10-60%, 10-65%, 10-70%, 10-75%, 10-80%, 10-85%, 10-90%, 10-95%, 15-25%, 15-30%, 15-35%, 15-40%, 15-45%, 15-50%, 15-55%, 15-60%, 15-65%, 15-70%, 15-75%, 15-80%, 15-85%, 15-90%, 15-95%, 20-30%, 20-35%, 20-40%, 20-45%, 20-50%, 20-55%, 20-60%, 20-65%, 20-70%, 20-75%, 20-80%, 20-85%, 20-90%, 20-95%, 25-35%, 25-40%, 25-45%, 25-50%, 25-55%, 25-60%, 25-65%, 25-70%, 25-75%, 25-80%, 25-85%, 25-90%, 25-95%, 30-40%, 30-45%, 30-50%, 30-55%, 30-60%, 30-65%, 30-70%, 30-75%, 30-80%, 30-85%, 30-90%, 30-95%, 35-45%, 35-50%, 35-55%, 35-60%, 35-65%, 35-70%, 35-75%, 35-80%, 35-85%, 35-90%, 35-95%, 40-50%, 40-55%, 40-60%, 40-65%, 40-70%, 40-75%, 40-80%, 40-85%, 40-90%, 40-95%, 45-55%, 45-60%, 45-65%, 45-70%, 45-75%, 45-80%, 45-85%, 45-90%, 45-95%, 50-60%, 50-65%, 50-70%, 50-75%, 50-80%, 50-85%, 50-90%, 50-95%, 55-65%, 55-70%, 55-75%, 55-80%, 55-85%, 55-90%, 55-95%, 60-70%, 60-75%, 60-80%, 60-85%, 60-90%, 60-95%, 65-75%, 65-80%, 65-85%, 65-90%, 65-95%, 70-80%, 70-85%, 70-90%, 70-95%, 75-85%, 75-90%, 75-95%, 80-90%, 80-95%, or 90-95%.

[0242] In one embodiment, the TRACER AAV particles comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules may be used to suppress a target protein in microglia. The suppression of the target protein in microglia may be, independently, suppressed by 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more than 95%, 5-15%, 5-20%, 5-25%, 5-30%, 5-35%, 5-40%, 5-45%, 5-50%, 5-55%, 5-60%, 5-65%, 5-70%, 5-75%, 5-80%, 5-85%, 5-90%, 5-95%, 10-20%, 10-25%, 10-30%, 10-35%, 10-40%, 10-45%, 10-50%, 10-55%, 10-60%, 10-65%, 10-70%, 10-75%, 10-80%, 10-85%, 10-90%, 10-95%, 15-25%, 15-30%, 15-35%, 15-40%, 15-45%, 15-50%, 15-55%, 15-60%, 15-65%, 15-70%, 15-75%, 15-80%, 15-85%, 15-90%, 15-95%, 20-30%, 20-35%, 20-40%, 20-45%, 20-50%, 20-55%, 20-60%, 20-65%, 20-70%, 20-75%, 20-80%, 20-85%, 20-90%, 20-95%, 25-35%, 25-40%, 25-45%, 25-

50%, 25-55%, 25-60%, 25-65%, 25-70%, 25-75%, 25-80%, 25-85%, 25-90%, 25-95%, 30-40%, 30-45%, 30-50%, 30-55%, 30-60%, 30-65%, 30-70%, 30-75%, 30-80%, 30-85%, 30-90%, 30-95%, 35-45%, 35-50%, 35-55%, 35-60%, 35-65%, 35-70%, 35-75%, 35-80%, 35-85%, 35-90%, 35-95%, 40-50%, 40-55%, 40-60%, 40-65%, 40-70%, 40-75%, 40-80%, 40-85%, 40-90%, 40-95%, 45-55%, 45-60%, 45-65%, 45-70%, 45-75%, 45-80%, 45-85%, 45-90%, 45-95%, 50-60%, 50-65%, 50-70%, 50-75%, 50-80%, 50-85%, 50-90%, 50-95%, 55-65%, 55-70%, 55-75%, 55-80%, 55-85%, 55-90%, 55-95%, 60-70%, 60-75%, 60-80%, 60-85%, 60-90%, 60-95%, 65-75%, 65-80%, 65-85%, 65-90%, 65-95%, 70-80%, 70-85%, 70-90%, 70-95%, 75-85%, 75-90%, 75-95%, 80-90%, 80-95%, or 90-95%. The reduction may be 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more than 95%, 5-15%, 5-20%, 5-25%, 5-30%, 5-35%, 5-40%, 5-45%, 5-50%, 5-55%, 5-60%, 5-65%, 5-70%, 5-75%, 5-80%, 5-85%, 5-90%, 5-95%, 10-20%, 10-25%, 10-30%, 10-35%, 10-40%, 10-45%, 10-50%, 10-55%, 10-60%, 10-65%, 10-70%, 10-75%, 10-80%, 10-85%, 10-90%, 10-95%, 15-25%, 15-30%, 15-35%, 15-40%, 15-45%, 15-50%, 15-55%, 15-60%, 15-65%, 15-70%, 15-75%, 15-80%, 15-85%, 15-90%, 15-95%, 20-30%, 20-35%, 20-40%, 20-45%, 20-50%, 20-55%, 20-60%, 20-65%, 20-70%, 20-75%, 20-80%, 20-85%, 20-90%, 20-95%, 25-35%, 25-40%, 25-45%, 25-50%, 25-55%, 25-60%, 25-65%, 25-70%, 25-75%, 25-80%, 25-85%, 25-90%, 25-95%, 30-40%, 30-45%, 30-50%, 30-55%, 30-60%, 30-65%, 30-70%, 30-75%, 30-80%, 30-85%, 30-90%, 30-95%, 35-45%, 35-50%, 35-55%, 35-60%, 35-65%, 35-70%, 35-75%, 35-80%, 35-85%, 35-90%, 35-95%, 40-50%, 40-55%, 40-60%, 40-65%, 40-70%, 40-75%, 40-80%, 40-85%, 40-90%, 40-95%, 45-55%, 45-60%, 45-65%, 45-70%, 45-75%, 45-80%, 45-85%, 45-90%, 45-95%, 50-60%, 50-65%, 50-70%, 50-75%, 50-80%, 50-85%, 50-90%, 50-95%, 55-65%, 55-70%, 55-75%, 55-80%, 55-85%, 55-90%, 55-95%, 60-70%, 60-75%, 60-80%, 60-85%, 60-90%, 60-95%, 65-75%, 65-80%, 65-85%, 65-90%, 65-95%, 70-80%, 70-85%, 70-90%, 70-95%, 75-85%, 75-90%, 75-95%, 80-90%, 80-95%, or 90-95%.

[0243] In one embodiment, the TRACER AAV particles comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules may be used to suppress target protein in cortical neurons. The suppression of a target protein in cortical neurons may be, independently, suppressed by 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more than 95%, 5-15%, 5-20%, 5-25%, 5-30%, 5-35%, 5-40%, 5-45%, 5-50%, 5-55%, 5-60%, 5-65%, 5-70%, 5-75%, 5-80%, 5-85%, 5-90%, 5-95%, 10-20%, 10-25%, 10-30%, 10-35%, 10-40%, 10-45%, 10-50%, 10-55%, 10-60%, 10-65%, 10-70%, 10-75%, 10-80%, 10-85%, 10-90%, 10-95%, 15-25%, 15-

30%, 15-35%, 15-40%, 15-45%, 15-50%, 15-55%, 15-60%, 15-65%, 15-70%, 15-75%, 15-80%, 15-85%, 15-90%, 15-95%, 20-30%, 20-35%, 20-40%, 20-45%, 20-50%, 20-55%, 20-60%, 20-65%, 20-70%, 20-75%, 20-80%, 20-85%, 20-90%, 20-95%, 25-35%, 25-40%, 25-45%, 25-50%, 25-55%, 25-60%, 25-65%, 25-70%, 25-75%, 25-80%, 25-85%, 25-90%, 25-95%, 30-40%, 30-45%, 30-50%, 30-55%, 30-60%, 30-65%, 30-70%, 30-75%, 30-80%, 30-85%, 30-90%, 30-95%, 35-45%, 35-50%, 35-55%, 35-60%, 35-65%, 35-70%, 35-75%, 35-80%, 35-85%, 35-90%, 35-95%, 40-50%, 40-55%, 40-60%, 40-65%, 40-70%, 40-75%, 40-80%, 40-85%, 40-90%, 40-95%, 45-55%, 45-60%, 45-65%, 45-70%, 45-75%, 45-80%, 45-85%, 45-90%, 45-95%, 50-60%, 50-65%, 50-70%, 50-75%, 50-80%, 50-85%, 50-90%, 50-95%, 55-65%, 55-70%, 55-75%, 55-80%, 55-85%, 55-90%, 55-95%, 60-70%, 60-75%, 60-80%, 60-85%, 60-90%, 60-95%, 65-75%, 65-80%, 65-85%, 65-90%, 65-95%, 70-80%, 70-85%, 70-90%, 70-95%, 75-85%, 75-90%, 75-95%, 80-90%, 80-95%, or 90-95%. The reduction may be 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more than 95%, 5-15%, 5-20%, 5-25%, 5-30%, 5-35%, 5-40%, 5-45%, 5-50%, 5-55%, 5-60%, 5-65%, 5-70%, 5-75%, 5-80%, 5-85%, 5-90%, 5-95%, 10-20%, 10-25%, 10-30%, 10-35%, 10-40%, 10-45%, 10-50%, 10-55%, 10-60%, 10-65%, 10-70%, 10-75%, 10-80%, 10-85%, 10-90%, 10-95%, 15-25%, 15-30%, 15-35%, 15-40%, 15-45%, 15-50%, 15-55%, 15-60%, 15-65%, 15-70%, 15-75%, 15-80%, 15-85%, 15-90%, 15-95%, 20-30%, 20-35%, 20-40%, 20-45%, 20-50%, 20-55%, 20-60%, 20-65%, 20-70%, 20-75%, 20-80%, 20-85%, 20-90%, 20-95%, 25-35%, 25-40%, 25-45%, 25-50%, 25-55%, 25-60%, 25-65%, 25-70%, 25-75%, 25-80%, 25-85%, 25-90%, 25-95%, 30-40%, 30-45%, 30-50%, 30-55%, 30-60%, 30-65%, 30-70%, 30-75%, 30-80%, 30-85%, 30-90%, 30-95%, 35-45%, 35-50%, 35-55%, 35-60%, 35-65%, 35-70%, 35-75%, 35-80%, 35-85%, 35-90%, 35-95%, 40-50%, 40-55%, 40-60%, 40-65%, 40-70%, 40-75%, 40-80%, 40-85%, 40-90%, 40-95%, 45-55%, 45-60%, 45-65%, 45-70%, 45-75%, 45-80%, 45-85%, 45-90%, 45-95%, 50-60%, 50-65%, 50-70%, 50-75%, 50-80%, 50-85%, 50-90%, 50-95%, 55-65%, 55-70%, 55-75%, 55-80%, 55-85%, 55-90%, 55-95%, 60-70%, 60-75%, 60-80%, 60-85%, 60-90%, 60-95%, 65-75%, 65-80%, 65-85%, 65-90%, 65-95%, 70-80%, 70-85%, 70-90%, 70-95%, 75-85%, 75-90%, 75-95%, 80-90%, 80-95%, or 90-95%.

[0244] In one embodiment, the TRACER AAV particles comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules may be used to suppress a target protein in hippocampal neurons. The suppression of a target protein in the hippocampal neurons may be, independently, suppressed by 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more than 95%, 5-15%, 5-

20%, 5-25%, 5-30%, 5-35%, 5-40%, 5-45%, 5-50%, 5-55%, 5-60%, 5-65%, 5-70%, 5-75%, 5-80%, 5-85%, 5-90%, 5-95%, 10-20%, 10-25%, 10-30%, 10-35%, 10-40%, 10-45%, 10-50%, 10-55%, 10-60%, 10-65%, 10-70%, 10-75%, 10-80%, 10-85%, 10-90%, 10-95%, 15-25%, 15-30%, 15-35%, 15-40%, 15-45%, 15-50%, 15-55%, 15-60%, 15-65%, 15-70%, 15-75%, 15-80%, 15-85%, 15-90%, 15-95%, 20-30%, 20-35%, 20-40%, 20-45%, 20-50%, 20-55%, 20-60%, 20-65%, 20-70%, 20-75%, 20-80%, 20-85%, 20-90%, 20-95%, 25-35%, 25-40%, 25-45%, 25-50%, 25-55%, 25-60%, 25-65%, 25-70%, 25-75%, 25-80%, 25-85%, 25-90%, 25-95%, 30-40%, 30-45%, 30-50%, 30-55%, 30-60%, 30-65%, 30-70%, 30-75%, 30-80%, 30-85%, 30-90%, 30-95%, 35-45%, 35-50%, 35-55%, 35-60%, 35-65%, 35-70%, 35-75%, 35-80%, 35-85%, 35-90%, 35-95%, 40-50%, 40-55%, 40-60%, 40-65%, 40-70%, 40-75%, 40-80%, 40-85%, 40-90%, 40-95%, 45-55%, 45-60%, 45-65%, 45-70%, 45-75%, 45-80%, 45-85%, 45-90%, 45-95%, 50-60%, 50-65%, 50-70%, 50-75%, 50-80%, 50-85%, 50-90%, 50-95%, 55-65%, 55-70%, 55-75%, 55-80%, 55-85%, 55-90%, 55-95%, 60-70%, 60-75%, 60-80%, 60-85%, 60-90%, 60-95%, 65-75%, 65-80%, 65-85%, 65-90%, 65-95%, 70-80%, 70-85%, 70-90%, 70-95%, 75-85%, 75-90%, 75-95%, 80-90%, 80-95%, or 90-95%.

The reduction may be 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more than 95%, 5-15%, 5-20%, 5-25%, 5-30%, 5-35%, 5-40%, 5-45%, 5-50%, 5-55%, 5-60%, 5-65%, 5-70%, 5-75%, 5-80%, 5-85%, 5-90%, 5-95%, 10-20%, 10-25%, 10-30%, 10-35%, 10-40%, 10-45%, 10-50%, 10-55%, 10-60%, 10-65%, 10-70%, 10-75%, 10-80%, 10-85%, 10-90%, 10-95%, 15-25%, 15-30%, 15-35%, 15-40%, 15-45%, 15-50%, 15-55%, 15-60%, 15-65%, 15-70%, 15-75%, 15-80%, 15-85%, 15-90%, 15-95%, 20-30%, 20-35%, 20-40%, 20-45%, 20-50%, 20-55%, 20-60%, 20-65%, 20-70%, 20-75%, 20-80%, 20-85%, 20-90%, 20-95%, 25-35%, 25-40%, 25-45%, 25-50%, 25-55%, 25-60%, 25-65%, 25-70%, 25-75%, 25-80%, 25-85%, 25-90%, 25-95%, 30-40%, 30-45%, 30-50%, 30-55%, 30-60%, 30-65%, 30-70%, 30-75%, 30-80%, 30-85%, 30-90%, 30-95%, 35-45%, 35-50%, 35-55%, 35-60%, 35-65%, 35-70%, 35-75%, 35-80%, 35-85%, 35-90%, 35-95%, 40-50%, 40-55%, 40-60%, 40-65%, 40-70%, 40-75%, 40-80%, 40-85%, 40-90%, 40-95%, 45-55%, 45-60%, 45-65%, 45-70%, 45-75%, 45-80%, 45-85%, 45-90%, 45-95%, 50-60%, 50-65%, 50-70%, 50-75%, 50-80%, 50-85%, 50-90%, 50-95%, 55-65%, 55-70%, 55-75%, 55-80%, 55-85%, 55-90%, 55-95%, 60-70%, 60-75%, 60-80%, 60-85%, 60-90%, 60-95%, 65-75%, 65-80%, 65-85%, 65-90%, 65-95%, 70-80%, 70-85%, 70-90%, 70-95%, 75-85%, 75-90%, 75-95%, 80-90%, 80-95%, or 90-95%.

[0245] In one embodiment, the TRACER AAV particles comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules may be used to suppress a

target protein in DRG and/or sympathetic neurons. The suppression of a target protein in the DRG and/or sympathetic neurons may be, independently, suppressed by 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more than 95%, 5-15%, 5-20%, 5-25%, 5-30%, 5-35%, 5-40%, 5-45%, 5-50%, 5-55%, 5-60%, 5-65%, 5-70%, 5-75%, 5-80%, 5-85%, 5-90%, 5-95%, 10-20%, 10-25%, 10-30%, 10-35%, 10-40%, 10-45%, 10-50%, 10-55%, 10-60%, 10-65%, 10-70%, 10-75%, 10-80%, 10-85%, 10-90%, 10-95%, 15-25%, 15-30%, 15-35%, 15-40%, 15-45%, 15-50%, 15-55%, 15-60%, 15-65%, 15-70%, 15-75%, 15-80%, 15-85%, 15-90%, 15-95%, 20-30%, 20-35%, 20-40%, 20-45%, 20-50%, 20-55%, 20-60%, 20-65%, 20-70%, 20-75%, 20-80%, 20-85%, 20-90%, 20-95%, 25-35%, 25-40%, 25-45%, 25-50%, 25-55%, 25-60%, 25-65%, 25-70%, 25-75%, 25-80%, 25-85%, 25-90%, 25-95%, 30-40%, 30-45%, 30-50%, 30-55%, 30-60%, 30-65%, 30-70%, 30-75%, 30-80%, 30-85%, 30-90%, 30-95%, 35-45%, 35-50%, 35-55%, 35-60%, 35-65%, 35-70%, 35-75%, 35-80%, 35-85%, 35-90%, 35-95%, 40-50%, 40-55%, 40-60%, 40-65%, 40-70%, 40-75%, 40-80%, 40-85%, 40-90%, 40-95%, 45-55%, 45-60%, 45-65%, 45-70%, 45-75%, 45-80%, 45-85%, 45-90%, 45-95%, 50-60%, 50-65%, 50-70%, 50-75%, 50-80%, 50-85%, 50-90%, 50-95%, 55-65%, 55-70%, 55-75%, 55-80%, 55-85%, 55-90%, 55-95%, 60-70%, 60-75%, 60-80%, 60-85%, 60-90%, 60-95%, 65-75%, 65-80%, 65-85%, 65-90%, 65-95%, 70-80%, 70-85%, 70-90%, 70-95%, 75-85%, 75-90%, 75-95%, 80-90%, 80-95%, or 90-95%. The reduction may be 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more than 95%, 5-15%, 5-20%, 5-25%, 5-30%, 5-35%, 5-40%, 5-45%, 5-50%, 5-55%, 5-60%, 5-65%, 5-70%, 5-75%, 5-80%, 5-85%, 5-90%, 5-95%, 10-20%, 10-25%, 10-30%, 10-35%, 10-40%, 10-45%, 10-50%, 10-55%, 10-60%, 10-65%, 10-70%, 10-75%, 10-80%, 10-85%, 10-90%, 10-95%, 15-25%, 15-30%, 15-35%, 15-40%, 15-45%, 15-50%, 15-55%, 15-60%, 15-65%, 15-70%, 15-75%, 15-80%, 15-85%, 15-90%, 15-95%, 20-30%, 20-35%, 20-40%, 20-45%, 20-50%, 20-55%, 20-60%, 20-65%, 20-70%, 20-75%, 20-80%, 20-85%, 20-90%, 20-95%, 25-35%, 25-40%, 25-45%, 25-50%, 25-55%, 25-60%, 25-65%, 25-70%, 25-75%, 25-80%, 25-85%, 25-90%, 25-95%, 30-40%, 30-45%, 30-50%, 30-55%, 30-60%, 30-65%, 30-70%, 30-75%, 30-80%, 30-85%, 30-90%, 30-95%, 35-45%, 35-50%, 35-55%, 35-60%, 35-65%, 35-70%, 35-75%, 35-80%, 35-85%, 35-90%, 35-95%, 40-50%, 40-55%, 40-60%, 40-65%, 40-70%, 40-75%, 40-80%, 40-85%, 40-90%, 40-95%, 45-55%, 45-60%, 45-65%, 45-70%, 45-75%, 45-80%, 45-85%, 45-90%, 45-95%, 50-60%, 50-65%, 50-70%, 50-75%, 50-80%, 50-85%, 50-90%, 50-95%, 55-65%, 55-70%, 55-75%, 55-80%, 55-85%, 55-90%, 55-95%, 60-70%,

60-75%, 60-80%, 60-85%, 60-90%, 60-95%, 65-75%, 65-80%, 65-85%, 65-90%, 65-95%, 70-80%, 70-85%, 70-90%, 70-95%, 75-85%, 75-90%, 75-95%, 80-90%, 80-95%, or 90-95%.

[0246] In one embodiment, the TRACER AAV particles comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules may be used to suppress a target protein in sensory neurons in order to treat neurological disease. Target protein in sensory neurons may be suppressed by 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more than 95%, 5-15%, 5-20%, 5-25%, 5-30%, 5-35%, 5-40%, 5-45%, 5-50%, 5-55%, 5-60%, 5-65%, 5-70%, 5-75%, 5-80%, 5-85%, 5-90%, 5-95%, 10-20%, 10-25%, 10-30%, 10-35%, 10-40%, 10-45%, 10-50%, 10-55%, 10-60%, 10-65%, 10-70%, 10-75%, 10-80%, 10-85%, 10-90%, 10-95%, 15-25%, 15-30%, 15-35%, 15-40%, 15-45%, 15-50%, 15-55%, 15-60%, 15-65%, 15-70%, 15-75%, 15-80%, 15-85%, 15-90%, 15-95%, 20-30%, 20-35%, 20-40%, 20-45%, 20-50%, 20-55%, 20-60%, 20-65%, 20-70%, 20-75%, 20-80%, 20-85%, 20-90%, 20-95%, 25-35%, 25-40%, 25-45%, 25-50%, 25-55%, 25-60%, 25-65%, 25-70%, 25-75%, 25-80%, 25-85%, 25-90%, 25-95%, 30-40%, 30-45%, 30-50%, 30-55%, 30-60%, 30-65%, 30-70%, 30-75%, 30-80%, 30-85%, 30-90%, 30-95%, 35-45%, 35-50%, 35-55%, 35-60%, 35-65%, 35-70%, 35-75%, 35-80%, 35-85%, 35-90%, 35-95%, 40-50%, 40-55%, 40-60%, 40-65%, 40-70%, 40-75%, 40-80%, 40-85%, 40-90%, 40-95%, 45-55%, 45-60%, 45-65%, 45-70%, 45-75%, 45-80%, 45-85%, 45-90%, 45-95%, 50-60%, 50-65%, 50-70%, 50-75%, 50-80%, 50-85%, 50-90%, 50-95%, 55-65%, 55-70%, 55-75%, 55-80%, 55-85%, 55-90%, 55-95%, 60-70%, 60-75%, 60-80%, 60-85%, 60-90%, 60-95%, 65-75%, 65-80%, 65-85%, 65-90%, 65-95%, 70-80%, 70-85%, 70-90%, 70-95%, 75-85%, 75-90%, 75-95%, 80-90%, 80-95%, or 90-95%. Target protein in the sensory neurons may be reduced may be 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more than 95%, 5-15%, 5-20%, 5-25%, 5-30%, 5-35%, 5-40%, 5-45%, 5-50%, 5-55%, 5-60%, 5-65%, 5-70%, 5-75%, 5-80%, 5-85%, 5-90%, 5-95%, 10-20%, 10-25%, 10-30%, 10-35%, 10-40%, 10-45%, 10-50%, 10-55%, 10-60%, 10-65%, 10-70%, 10-75%, 10-80%, 10-85%, 10-90%, 10-95%, 15-25%, 15-30%, 15-35%, 15-40%, 15-45%, 15-50%, 15-55%, 15-60%, 15-65%, 15-70%, 15-75%, 15-80%, 15-85%, 15-90%, 15-95%, 20-30%, 20-35%, 20-40%, 20-45%, 20-50%, 20-55%, 20-60%, 20-65%, 20-70%, 20-75%, 20-80%, 20-85%, 20-90%, 20-95%, 25-35%, 25-40%, 25-45%, 25-50%, 25-55%, 25-60%, 25-65%, 25-70%, 25-75%, 25-80%, 25-85%, 25-90%, 25-95%, 30-40%, 30-45%, 30-50%, 30-55%, 30-60%, 30-65%, 30-70%, 30-75%, 30-80%, 30-85%, 30-90%, 30-95%, 35-45%, 35-50%, 35-55%, 35-60%, 35-65%, 35-70%, 35-75%, 35-80%, 35-85%, 35-90%, 35-95%, 40-50%, 40-55%, 40-60%, 40-65%,

40-70%, 40-75%, 40-80%, 40-85%, 40-90%, 40-95%, 45-55%, 45-60%, 45-65%, 45-70%, 45-75%, 45-80%, 45-85%, 45-90%, 45-95%, 50-60%, 50-65%, 50-70%, 50-75%, 50-80%, 50-85%, 50-90%, 50-95%, 55-65%, 55-70%, 55-75%, 55-80%, 55-85%, 55-90%, 55-95%, 60-70%, 60-75%, 60-80%, 60-85%, 60-90%, 60-95%, 65-75%, 65-80%, 65-85%, 65-90%, 65-95%, 70-80%, 70-85%, 70-90%, 70-95%, 75-85%, 75-90%, 75-95%, 80-90%, 80-95%, or 90-95%.

[0247] In one embodiment, the TRACER AAV particles comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules may be used to suppress a target protein and reduce symptoms of neurological disease in a subject. The suppression of target protein and/or the reduction of symptoms of neurological disease may be, independently, reduced or suppressed by 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more than 95%, 5-15%, 5-20%, 5-25%, 5-30%, 5-35%, 5-40%, 5-45%, 5-50%, 5-55%, 5-60%, 5-65%, 5-70%, 5-75%, 5-80%, 5-85%, 5-90%, 5-95%, 10-20%, 10-25%, 10-30%, 10-35%, 10-40%, 10-45%, 10-50%, 10-55%, 10-60%, 10-65%, 10-70%, 10-75%, 10-80%, 10-85%, 10-90%, 10-95%, 15-25%, 15-30%, 15-35%, 15-40%, 15-45%, 15-50%, 15-55%, 15-60%, 15-65%, 15-70%, 15-75%, 15-80%, 15-85%, 15-90%, 15-95%, 20-30%, 20-35%, 20-40%, 20-45%, 20-50%, 20-55%, 20-60%, 20-65%, 20-70%, 20-75%, 20-80%, 20-85%, 20-90%, 20-95%, 25-35%, 25-40%, 25-45%, 25-50%, 25-55%, 25-60%, 25-65%, 25-70%, 25-75%, 25-80%, 25-85%, 25-90%, 25-95%, 30-40%, 30-45%, 30-50%, 30-55%, 30-60%, 30-65%, 30-70%, 30-75%, 30-80%, 30-85%, 30-90%, 30-95%, 35-45%, 35-50%, 35-55%, 35-60%, 35-65%, 35-70%, 35-75%, 35-80%, 35-85%, 35-90%, 35-95%, 40-50%, 40-55%, 40-60%, 40-65%, 40-70%, 40-75%, 40-80%, 40-85%, 40-90%, 40-95%, 45-55%, 45-60%, 45-65%, 45-70%, 45-75%, 45-80%, 45-85%, 45-90%, 45-95%, 50-60%, 50-65%, 50-70%, 50-75%, 50-80%, 50-85%, 50-90%, 50-95%, 55-65%, 55-70%, 55-75%, 55-80%, 55-85%, 55-90%, 55-95%, 60-70%, 60-75%, 60-80%, 60-85%, 60-90%, 60-95%, 65-75%, 65-80%, 65-85%, 65-90%, 65-95%, 70-80%, 70-85%, 70-90%, 70-95%, 75-85%, 75-90%, 75-95%, 80-90%, 80-95%, or 90-95%.

[0248] In one embodiment, the TRACER AAV particles comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules may be used to reduce the decline of functional capacity and activities of daily living as measured by a standard evaluation system such as, but not limited to, the total functional capacity (TFC) scale.

[0249] In some embodiments, the present composition is administered as a solo therapeutic or as combination therapeutic for the treatment of neurological disease.

[0250] The TRACER AAV particles comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules may be used in combination with one or more other therapeutic agents. By “in combination with,” it is not intended to imply that the agents must be administered at the same time and/or formulated for delivery together, although these methods of delivery are within the scope of the present disclosure. Compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. In general, each agent will be administered at a dose and/or on a time schedule determined for that agent.

[0251] Therapeutic agents that may be used in combination with the TRACER AAV particles comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules can be small molecule compounds which are antioxidants, anti-inflammatory agents, anti-apoptosis agents, calcium regulators, ant glutamatergic agents, structural protein inhibitors, compounds involved in muscle function, and compounds involved in metal ion regulation.

[0252] Compounds tested for treating neurological disease which may be used in combination with the TRACER AAV particles comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules include, but are not limited to, cholinesterase inhibitors (donepezil, rivastigmine, galantamine), NMDA receptor antagonists such as memantine, anti-psychotics, anti-depressants, anti-convulsants (e.g., sodium valproate and levetiracetam for myoclonus), secretase inhibitors, amyloid aggregation inhibitors, copper or zinc modulators, BACE inhibitors, inhibitors of tau aggregation, such as Methylene blue, phenothiazines, anthraquinones, n-phenylamines or rhodamines, microtubule stabilizers such as NAP, taxol or paclitaxel, kinase or phosphatase inhibitors such as those targeting GSK3 β (lithium) or PP2A, immunization with A β peptides or tau phospho-epitopes, anti-tau or anti-amyloid antibodies, dopamine-depleting agents (e.g., tetrabenazine for chorea), benzodiazepines (e.g., clonazepam for myoclonus, chorea, dystonia, rigidity, and/or spasticity), , amino acid precursors of dopamine (e.g., levodopa for rigidity), skeletal muscle relaxants (e.g., baclofen, tizanidine for rigidity and/or spasticity), inhibitors for acetylcholine release at the neuromuscular junction to cause muscle paralysis (e.g., botulinum toxin for bruxism and/or dystonia), atypical neuroleptics (e.g., olanzapine and quetiapine for psychosis and/or irritability, risperidone, sulpiride and haloperidol for psychosis, chorea and/or irritability, clozapine for treatment-resistant psychosis, aripiprazole for psychosis with prominent negative symptoms), selective serotonin reuptake inhibitors (SSRIs) (e.g., citalopram, fluoxetine, paroxetine, sertraline, mirtazapine, venlafaxine for depression,

anxiety, obsessive compulsive behavior and/or irritability), hypnotics (e.g., xopiclone and/or zolpidem for altered sleep-wake cycle), anticonvulsants (e.g., sodium valproate and carbamazepine for mania or hypomania) and mood stabilizers (e.g., lithium for mania or hypomania).

[0253] Neurotrophic factors may be used in combination therapy with the TRACER AAV particles comprising a viral genome with a nucleic acid sequence encoding one or more siRNA molecules for treating neurological disease. Generally, a neurotrophic factor is defined as a substance that promotes survival, growth, differentiation, proliferation and/or maturation of a neuron, or stimulates increased activity of a neuron. In some embodiments, the present methods further comprise delivery of one or more trophic factors into the subject in need of treatment. Trophic factors may include, but are not limited to, IGF-I, GDNF, BDNF, CTNF, VEGF, Colivelin, Xaliproden, Thyrotrophin-releasing hormone and ADNF, and variants thereof.

[0254] In one aspect, the TRACER AAV particle encoding the nucleic acid sequence for the at least one siRNA duplex targeting the gene of interest may be co-administered with TRACER AAV particles expressing neurotrophic factors such as AAV-IGF-I (See e.g., Vincent et al., *Neuromolecular medicine*, 2004, 6, 79-85; the content of which is incorporated herein by reference in its entirety) and AAV-GDNF (See e.g., Wang et al., *J Neurosci.*, 2002, 22, 6920-6928; the contents of which are incorporated herein by reference in their entirety).

[0255] In one embodiment, administration of the TRACER AAV particles to a subject will reduce the expression of a target protein in a subject and the reduction of expression of the target protein will reduce the effects and/or symptoms of neurological disease in a subject.

DEFINITIONS

[0256] *Adeno-associated virus*: As used herein, the term “adeno-associated virus” or “AAV” refers to members of the dependovirus genus comprising any particle, sequence, gene, protein, or component derived therefrom.

[0257] *AAV Particle*: As used herein, an “AAV particle” is a virus which comprises a capsid and a viral genome with at least one payload region and at least one ITR. As used herein “AAV particles of the disclosure” are AAV particles comprising a parent capsid sequence with at least one targeting peptide insert. AAV particles of the present disclosure may be produced recombinantly and may be based on adeno-associated virus (AAV) parent or reference sequences. AAV particle may be derived from any serotype, described herein or known in the art, including combinations of serotypes (i.e., “pseudotyped” AAV) or from

various genomes (e.g., single stranded or self-complementary). In addition, the AAV particle may be replication defective and/or targeted. In one embodiment, the AAV particle may have a targeting peptide inserted into the capsid to enhance tropism for a desired target tissue. It is to be understood that reference to the AAV particles of the disclosure also includes pharmaceutical compositions thereof, even if not explicitly recited.

[0258] *Administering*: As used herein, the term "administering" refers to providing a pharmaceutical agent or composition to a subject.

[0259] *Amelioration*: As used herein, the term "amelioration" or "ameliorating" refers to a lessening of severity of at least one indicator of a condition or disease. For example, in the context of neurodegeneration disorder, amelioration includes the reduction of neuron loss.

[0260] *Animal*: As used herein, the term "animal" refers to any member of the animal kingdom. In some embodiments, "animal" refers to humans at any stage of development. In some embodiments, "animal" refers to non-human animals at any stage of development. In certain embodiments, the non-human animal is a mammal (e.g., a rodent, a mouse, a rat, a rabbit, a monkey, a dog, a cat, a sheep, cattle, a primate, or a pig). In some embodiments, animals include, but are not limited to, mammals, birds, reptiles, amphibians, fish, and worms. In some embodiments, the animal is a transgenic animal, genetically engineered animal, or a clone.

[0261] *Antisense strand*: As used herein, the term "the antisense strand" or "the first strand" or "the guide strand" of a siRNA molecule refers to a strand that is substantially complementary to a section of about 10-50 nucleotides, e.g., about 15-30, 16-25, 18-23 or 19-22 nucleotides of the mRNA of a gene targeted for silencing. The antisense strand or first strand has sequence sufficiently complementary to the desired target mRNA sequence to direct target-specific silencing, e.g., complementarity sufficient to trigger the destruction of the desired target mRNA by the RNAi machinery or process.

[0262] *Approximately*: As used herein, the term "approximately" or "about," as applied to one or more values of interest, refers to a value that is similar to a stated reference value. In certain embodiments, the term "approximately" or "about" refers to a range of values that fall within 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less in either direction (greater than or less than) of the stated reference value unless otherwise stated or otherwise evident from the context (except where such number would exceed 100% of a possible value).

[0263] *Capsid*: As used herein, the term "capsid" refers to the protein shell of a virus particle.

[0264] *Complementary and substantially complementary:* As used herein, the term “complementary” refers to the ability of polynucleotides to form base pairs with one another. Base pairs are typically formed by hydrogen bonds between nucleotide units in antiparallel polynucleotide strands. Complementary polynucleotide strands can form base pairs in the Watson-Crick manner (e.g., A to T, A to U, C to G), or in any other manner that allows for the formation of duplexes. As persons skilled in the art are aware, when using RNA as opposed to DNA, uracil rather than thymine is the base that is considered to be complementary to adenine. However, when a U is denoted in the context of the present disclosure, the ability to substitute a T is implied, unless otherwise stated. Perfect complementarity or 100% complementarity refers to the situation in which each nucleotide unit of one polynucleotide strand can form a hydrogen bond with a nucleotide unit of a second polynucleotide strand. Less than perfect complementarity refers to the situation in which some, but not all, nucleotide units of two strands can form hydrogen bond with each other. For example, for two 20-mers, if only two base pairs on each strand can form a hydrogen bond with each other, the polynucleotide strands exhibit 10% complementarity. In the same example, if 18 base pairs on each strand can form hydrogen bonds with each other, the polynucleotide strands exhibit 90% complementarity. As used herein, the term “substantially complementary” means that the siRNA has a sequence (e.g., in the antisense strand) which is sufficient to bind the desired target mRNA, and to trigger the RNA silencing of the target mRNA.

[0265] *Control Elements:* As used herein, “control elements”, “regulatory control elements” or “regulatory sequences” refers to promoter regions, polyadenylation signals, transcription termination sequences, upstream regulatory domains, origins of replication, internal ribosome entry sites (“IRES”), enhancers, and the like, which provide for the replication, transcription and translation of a coding sequence in a recipient cell. Not all of these control elements need always be present as long as the selected coding sequence is capable of being replicated, transcribed and/or translated in an appropriate host cell.

[0266] *Delivery:* As used herein, “delivery” refers to the act or manner of delivering an AAV particle, a compound, substance, entity, moiety, cargo or payload.

[0267] *Element:* As used herein, the term “element” refers to a distinct portion of an entity. In some embodiments, an element may be a polynucleotide sequence with a specific purpose, incorporated into a longer polynucleotide sequence.

[0268] *Encapsulate:* As used herein, the term “encapsulate” means to enclose, surround or encase. As an example, a capsid protein often encapsulates a viral genome.

[0269] *Engineered*: As used herein, embodiments of the disclosure are “engineered” when they are designed to have a feature or property, whether structural or chemical, that varies from a starting point, wild type or native molecule.

[0270] *Effective Amount*: As used herein, the term “effective amount” of an agent is that amount sufficient to effect beneficial or desired results, for example, clinical results, and, as such, an “effective amount” depends upon the context in which it is being applied. For example, in the context of administering an agent that treats cancer, an effective amount of an agent is, for example, an amount sufficient to achieve treatment, as defined herein, of cancer, as compared to the response obtained without administration of the agent.

[0271] *Expression*: As used herein, “expression” of a nucleic acid sequence refers to one or more of the following events: (1) production of an RNA template from a DNA sequence (*e.g.*, by transcription); (2) processing of an RNA transcript (*e.g.*, by splicing, editing, 5' cap formation, and/or 3' end processing); (3) translation of an RNA into a polypeptide or protein; and (4) post-translational modification of a polypeptide or protein.

[0272] *Feature*: As used herein, a “feature” refers to a characteristic, a property, or a distinctive element.

[0273] *Formulation*: As used herein, a “formulation” includes at least one AAV particle (active ingredient) and an excipient, and/or an inactive ingredient.

[0274] *Fragment*: A “fragment,” as used herein, refers to a portion. For example, an antibody fragment may comprise a CDR, or a heavy chain variable region, or a scFv, etc.

[0275] *Functional*: As used herein, a “functional” biological molecule is a biological molecule in a form in which it exhibits a property and/or activity by which it is characterized.

[0276] *Gene expression*: The term “gene expression” refers to the process by which a nucleic acid sequence undergoes successful transcription and in most instances translation to produce a protein or peptide. For clarity, when reference is made to measurement of “gene expression”, this should be understood to mean that measurements may be of the nucleic acid product of transcription, *e.g.*, RNA or mRNA or of the amino acid product of translation, *e.g.*, polypeptides or peptides. Methods of measuring the amount or levels of RNA, mRNA, polypeptides and peptides are well known in the art.

[0277] *Homology*: As used herein, the term “homology” refers to the overall relatedness between polymeric molecules, *e.g.* between polynucleotide molecules (*e.g.* DNA molecules and/or RNA molecules) and/or between polypeptide molecules. In some embodiments, polymeric molecules are considered to be “homologous” to one another if their sequences are at least 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%,

95%, or 99% identical or similar. The term “homologous” necessarily refers to a comparison between at least two sequences (polynucleotide or polypeptide sequences). In accordance with the disclosure, two polynucleotide sequences are considered to be homologous if the polypeptides they encode are at least about 50%, 60%, 70%, 80%, 90%, 95%, or even 99% for at least one stretch of at least about 20 amino acids. In some embodiments, homologous polynucleotide sequences are characterized by the ability to encode a stretch of at least 4–5 uniquely specified amino acids. For polynucleotide sequences less than 60 nucleotides in length, homology is determined by the ability to encode a stretch of at least 4–5 uniquely specified amino acids. In accordance with the disclosure, two protein sequences are considered to be homologous if the proteins are at least about 50%, 60%, 70%, 80%, or 90% identical for at least one stretch of at least about 20 amino acids.

[0278] *Identity:* As used herein, the term “identity” refers to the overall relatedness between polymeric molecules, *e.g.*, between polynucleotide molecules (*e.g.* DNA molecules and/or RNA molecules) and/or between polypeptide molecules. Calculation of the percent identity of two polynucleotide sequences, for example, can be performed by aligning the two sequences for optimal comparison purposes (*e.g.*, gaps can be introduced in one or both of a first and a second nucleic acid sequences for optimal alignment and non-identical sequences can be disregarded for comparison purposes). In certain embodiments, the length of a sequence aligned for comparison purposes is at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or 100% of the length of the reference sequence. The nucleotides at corresponding nucleotide positions are then compared. When a position in the first sequence is occupied by the same nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which needs to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. For example, the percent identity between two nucleotide sequences can be determined using methods such as those described in Computational Molecular Biology, Lesk, A. M., ed., Oxford University Press, New York, 1988; Biocomputing: Informatics and Genome Projects, Smith, D. W., ed., Academic Press, New York, 1993; Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press, 1987; Computer Analysis of Sequence Data, Part I, Griffin, A. M., and Griffin, H. G., eds., Humana Press, New Jersey, 1994; and Sequence Analysis Primer, Gribskov, M. and

Devereux, J., eds., M Stockton Press, New York, 1991; the contents of each of which are incorporated herein by reference in their entirety. For example, the percent identity between two nucleotide sequences can be determined using the algorithm of Meyers and Miller (CABIOS, 1989, 4:11-17), which has been incorporated into the ALIGN program (version 2.0) using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. The percent identity between two nucleotide sequences can, alternatively, be determined using the GAP program in the GCG software package using an NWSgapdna.CMP matrix. Methods commonly employed to determine percent identity between sequences include, but are not limited to those disclosed in Carillo, H., and Lipman, D., SIAM J Applied Math., 48:1073 (1988); incorporated herein by reference. Techniques for determining identity are codified in publicly available computer programs. Exemplary computer software to determine homology between two sequences include, but are not limited to, GCG program package, Devereux, J., *et al.*, *Nucleic Acids Research*, 12(1), 387 (1984)), BLASTP, BLASTN, and FASTA Altschul, S. F. *et al.*, *J. Molec. Biol.*, 215, 403 (1990)).

[0279] *Inhibit expression of a gene:* As used herein, the phrase “inhibit expression of a gene” means to cause a reduction in the amount of an expression product of the gene. The expression product can be an RNA transcribed from the gene (*e.g.*, an mRNA) or a polypeptide translated from an mRNA transcribed from the gene. Typically, a reduction in the level of an mRNA results in a reduction in the level of a polypeptide translated therefrom. The level of expression may be determined using standard techniques for measuring mRNA or protein.

[0280] *Insert:* As used herein the term “insert” may refer to the addition of a targeting peptide sequence to a parent AAV capsid sequence. An “insertion” may result in the replacement of one or more amino acids of the parent AAV capsid sequence. Alternatively, an insertion may result in no changes to the parent AAV capsid sequence beyond the addition of the targeting peptide sequence.

[0281] *Inverted terminal repeat:* As used herein, the term “inverted terminal repeat” or “ITR” refers to a cis-regulatory element for the packaging of polynucleotide sequences into viral capsids.

[0282] *Library:* As used herein, the term “library” refers to a diverse collection of linear polypeptides, polynucleotides, viral particles, or viral vectors. As examples, a library may be a DNA library or an AAV capsid library.

[0283] *Neurological disease*: As used herein, a “neurological disease” is any disease associated with the central or peripheral nervous system and components thereof (e.g., neurons).

[0284] *Naturally Occurring*: As used herein, “naturally occurring” or “wild-type” means existing in nature without artificial aid, or involvement of the hand of man.

[0285] *Open reading frame*: As used herein, “open reading frame” or “ORF” refers to a sequence which does not contain a stop codon in a given reading frame.

[0286] *Parent sequence*: As used herein, a “parent sequence” is a nucleic acid or amino acid sequence from which a variant is derived. In one embodiment, a parent sequence is a sequence into which a heterologous sequence is inserted. In other words, a parent sequence may be considered an acceptor or recipient sequence. In one embodiment, a parent sequence is an AAV capsid sequence into which a targeting sequence is inserted.

[0287] *Particle*: As used herein, a “particle” is a virus comprised of at least two components, a protein capsid and a polynucleotide sequence enclosed within the capsid.

[0288] *Patient*: As used herein, “patient” refers to a subject who may seek or be in need of treatment, requires treatment, is receiving treatment, will receive treatment, or a subject who is under care by a trained professional for a particular disease or condition.

[0289] *Payload region*: As used herein, a “payload region” is any nucleic acid sequence (e.g., within the viral genome) which encodes one or more “payloads” of the disclosure. As non-limiting examples, a payload region may be a nucleic acid sequence within the viral genome of an AAV particle, which encodes a payload, wherein the payload is an RNAi agent or a polypeptide. Payloads of the present disclosure may be, but are not limited to, peptides, polypeptides, proteins, antibodies, RNAi agents, etc.

[0290] *Peptide*: As used herein, “peptide” is less than or equal to 50 amino acids long, e.g., about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 amino acids long.

[0291] *Pharmaceutically acceptable*: The phrase “pharmaceutically acceptable” is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0292] *Preventing*: As used herein, the term “preventing” or “prevention” refers to partially or completely delaying onset of an infection, disease, disorder and/or condition; partially or completely delaying onset of one or more symptoms, features, or clinical manifestations of a particular infection, disease, disorder, and/or condition; partially or

completely delaying onset of one or more symptoms, features, or manifestations of a particular infection, disease, disorder, and/or condition; partially or completely delaying progression from an infection, a particular disease, disorder and/or condition; and/or decreasing the risk of developing pathology associated with the infection, the disease, disorder, and/or condition.

[0293] *Prophylactic*: As used herein, “prophylactic” refers to a therapeutic or course of action used to prevent the spread of disease.

[0294] *Prophylaxis*: As used herein, a “prophylaxis” refers to a measure taken to maintain health and prevent the spread of disease.

[0295] *Region*: As used herein, the term “region” refers to a zone or general area. In some embodiments, when referring to a protein or protein module, a region may comprise a linear sequence of amino acids along the protein or protein module or may comprise a three-dimensional area, an epitope and/or a cluster of epitopes. In some embodiments, regions comprise terminal regions. As used herein, the term “terminal region” refers to regions located at the ends or termini of a given agent. When referring to proteins, terminal regions may comprise N- and/or C-termini.

[0296] In some embodiments, when referring to a polynucleotide, a region may comprise a linear sequence of nucleic acids along the polynucleotide or may comprise a three-dimensional area, secondary structure, or tertiary structure. In some embodiments, regions comprise terminal regions. As used herein, the term “terminal region” refers to regions located at the ends or termini of a given agent. When referring to polynucleotides, terminal regions may comprise 5’ and/or 3’ termini.

[0297] *RNA or RNA molecule*: As used herein, the term “RNA” or “RNA molecule” or “ribonucleic acid molecule” refers to a polymer of ribonucleotides; the term “DNA” or “DNA molecule” or “deoxyribonucleic acid molecule” refers to a polymer of deoxyribonucleotides. DNA and RNA can be synthesized naturally, e.g., by DNA replication and transcription of DNA, respectively; or be chemically synthesized. DNA and RNA can be single-stranded (i.e., ssRNA or ssDNA, respectively) or multi-stranded (e.g., double stranded, i.e., dsRNA and dsDNA, respectively). The term “mRNA” or “messenger RNA”, as used herein, refers to a single stranded RNA that encodes the amino acid sequence of one or more polypeptide chains.

[0298] *RNA interfering or RNAi*: As used herein, the term “RNA interfering” or “RNAi” refers to a sequence specific regulatory mechanism mediated by RNA molecules which results in the inhibition or interfering or “silencing” of the expression of a corresponding

protein-coding gene. RNAi has been observed in many types of organisms, including plants, animals and fungi. RNAi occurs in cells naturally to remove foreign RNAs (e.g., viral RNAs). Natural RNAi proceeds via fragments cleaved from free dsRNA which direct the degradative mechanism to other similar RNA sequences. RNAi is controlled by the RNA-induced silencing complex (RISC) and is initiated by short/small dsRNA molecules in cell cytoplasm, where they interact with the catalytic RISC component argonaute. The dsRNA molecules can be introduced into cells exogenously. Exogenous dsRNA initiates RNAi by activating the ribonuclease protein Dicer, which binds and cleaves dsRNAs to produce double-stranded fragments of 21-25 base pairs with a few unpaired overhang bases on each end. These short double stranded fragments are called small interfering RNAs (siRNAs).

[0299] *RNAi agent*: As used herein, the term “RNAi agent” refers to an RNA molecule, or its derivative, that can induce inhibition, interfering, or “silencing” of the expression of a target gene and/or its protein product. An RNAi agent may knock-out (virtually eliminate or eliminate) expression, or knock-down (lessen or decrease) expression. The RNAi agent may be, but is not limited to, dsRNA, siRNA, shRNA, pre-miRNA, pri-miRNA, miRNA, stRNA, lncRNA, piRNA, or snoRNA.

[0300] *Sample*: As used herein, the term “sample” or “biological sample” refers to a subset of its tissues, cells or component parts (e.g. body fluids, including but not limited to blood, serum, mucus, lymphatic fluid, synovial fluid, cerebrospinal fluid, saliva, amniotic fluid, amniotic cord blood, urine, vaginal fluid and semen). A sample further may include a homogenate, lysate or extract prepared from a whole organism or a subset of its tissues, cells or component parts, or a fraction or portion thereof, including but not limited to, for example, plasma, serum, spinal fluid, lymph fluid, the external sections of the skin, respiratory, intestinal, and genitourinary tracts, tears, saliva, milk, blood cells, tumors, organs. A sample further refers to a medium, such as a nutrient broth or gel, which may contain cellular components, such as proteins or nucleic acid molecule.

[0301] *Self-complementary viral particle*: As used herein, a “self-complementary viral particle” is a particle comprised of at least two components, a protein capsid and a self-complementary viral genome enclosed within the capsid.

[0302] *Sense Strand*: As used herein, the term “the sense strand” or “the second strand” or “the passenger strand” of a siRNA molecule refers to a strand that is complementary to the antisense strand or first strand. The antisense and sense strands of a siRNA molecule are hybridized to form a duplex structure. As used herein, a “siRNA duplex” includes a siRNA strand having sufficient complementarity to a section of about 10-50 nucleotides of the

mRNA of the gene targeted for silencing and a siRNA strand having sufficient complementarity to form a duplex with the other siRNA strand.

[0303] *Similarity:* As used herein, the term “similarity” refers to the overall relatedness between polymeric molecules, *e.g.* between polynucleotide molecules (*e.g.* DNA molecules and/or RNA molecules) and/or between polypeptide molecules. Calculation of percent similarity of polymeric molecules to one another can be performed in the same manner as a calculation of percent identity, except that calculation of percent similarity takes into account conservative substitutions as is understood in the art.

[0304] *Short interfering RNA or siRNA:* As used herein, the terms “short interfering RNA,” “small interfering RNA” or “siRNA” refer to an RNA molecule (or RNA analog) comprising between about 5-60 nucleotides (or nucleotide analogs) which is capable of directing or mediating RNAi. Preferably, a siRNA molecule comprises between about 15-30 nucleotides or nucleotide analogs, such as between about 16-25 nucleotides (or nucleotide analogs), between about 18-23 nucleotides (or nucleotide analogs), between about 19-22 nucleotides (or nucleotide analogs) (*e.g.*, 19, 20, 21 or 22 nucleotides or nucleotide analogs), between about 19-25 nucleotides (or nucleotide analogs), and between about 19-24 nucleotides (or nucleotide analogs). The term “short” siRNA refers to a siRNA comprising 5-23 nucleotides, preferably 21 nucleotides (or nucleotide analogs), for example, 19, 20, 21 or 22 nucleotides. The term “long” siRNA refers to a siRNA comprising 24-60 nucleotides, preferably about 24-25 nucleotides, for example, 23, 24, 25 or 26 nucleotides. Short siRNAs may, in some instances, include fewer than 19 nucleotides, *e.g.*, 16, 17 or 18 nucleotides, or as few as 5 nucleotides, provided that the shorter siRNA retains the ability to mediate RNAi. Likewise, long siRNAs may, in some instances, include more than 26 nucleotides, *e.g.*, 27, 28, 29, 30, 35, 40, 45, 50, 55, or even 60 nucleotides, provided that the longer siRNA retains the ability to mediate RNAi or translational repression absent further processing, *e.g.*, enzymatic processing, to a short siRNA. siRNAs can be single stranded RNA molecules (ss-siRNAs) or double stranded RNA molecules (ds-siRNAs) comprising a sense strand and an antisense strand which hybridized to form a duplex structure called an siRNA duplex.

[0305] *Subject:* As used herein, the term “subject” or “patient” refers to any organism to which a composition in accordance with the disclosure may be administered, *e.g.*, for experimental, diagnostic, prophylactic, and/or therapeutic purposes. Typical subjects include animals (*e.g.*, mammals such as mice, rats, rabbits, non-human primates, and humans) and/or plants.

[0306] *Substantially*: As used herein, the term “substantially” refers to the qualitative condition of exhibiting total or near-total extent or degree of a characteristic or property of interest. One of ordinary skill in the biological arts will understand that biological and chemical phenomena rarely, if ever, go to completion and/or proceed to completeness or achieve or avoid an absolute result. The term “substantially” is therefore used herein to capture the potential lack of completeness inherent in many biological and chemical phenomena.

[0307] *Targeting peptide*: As used herein, a “targeting peptide” refers to a peptide of 3-20 amino acids in length. These targeting peptides may be inserted into, or attached to, a parent amino acid sequence to alter the characteristics (e.g., tropism) of the parent protein. As a non-limiting example, the targeting peptide can be inserted into an AAV capsid sequence for enhanced targeting to a desired cell-type, tissue, organ or organism. It is to be understood that a targeting peptide is encoded by a targeting polynucleotide which may similarly be inserted into a parent polynucleotide sequence. Therefore, a “targeting sequence” refers to a peptide or polynucleotide sequence for insertion into an appropriate parent sequence (amino acid or polynucleotide, respectively).

[0308] *Target Cells*: As used herein, “target cells” or “target tissue” refers to any one or more cells of interest. The cells may be found *in vitro*, *in vivo*, *in situ* or in the tissue or organ of an organism. The organism may be an animal, preferably a mammal, more preferably a human and most preferably a patient.

[0309] *Therapeutic Agent*: The term “therapeutic agent” refers to any agent that, when administered to a subject, has a therapeutic, diagnostic, and/or prophylactic effect and/or elicits a desired biological and/or pharmacological effect.

[0310] *Therapeutically effective amount*: As used herein, the term “therapeutically effective amount” means an amount of an agent to be delivered (e.g., nucleic acid, drug, therapeutic agent, diagnostic agent, prophylactic agent, *etc.*) that is sufficient, when administered to a subject suffering from or susceptible to an infection, disease, disorder, and/or condition, to treat, improve symptoms of, diagnose, prevent, and/or delay the onset of the infection, disease, disorder, and/or condition. In some embodiments, a therapeutically effective amount is provided in a single dose.

[0311] *Therapeutically effective outcome*: As used herein, the term “therapeutically effective outcome” means an outcome that is sufficient in a subject suffering from or susceptible to an infection, disease, disorder, and/or condition, to treat, improve symptoms of, diagnose, prevent, and/or delay the onset of the infection, disease, disorder, and/or condition.

[0312] *Treating*: As used herein, the term “treating” refers to partially or completely alleviating, ameliorating, improving, relieving, delaying onset of, inhibiting progression of, reducing severity of, and/or reducing incidence of one or more symptoms or features of a particular infection, disease, disorder, and/or condition. For example, “treating” cancer may refer to inhibiting survival, growth, and/or spread of a tumor. Treatment may be administered to a subject who does not exhibit signs of a disease, disorder, and/or condition and/or to a subject who exhibits only early signs of a disease, disorder, and/or condition for the purpose of decreasing the risk of developing pathology associated with the disease, disorder, and/or condition.

[0313] *Vector*: As used herein, the term “vector” refers to any molecule or moiety which transports, transduces or otherwise acts as a carrier of a heterologous molecule. In some embodiments, vectors may be plasmids. In some embodiments, vectors may be viruses. An AAV particle is an example of a vector. Vectors of the present disclosure may be produced recombinantly and may be based on and/or may comprise adeno-associated virus (AAV) parent or reference sequences. The heterologous molecule may be a polynucleotide and/or a polypeptide.

[0314] *Viral Genome*: As used herein, the terms “viral genome” or “vector genome” refer to the nucleic acid sequence(s) encapsulated in an AAV particle. A viral genome comprises a nucleic acid sequence with at least one payload region encoding a payload and at least one ITR.

Equivalents and Scope

[0315] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments in accordance with the disclosure described herein. The scope of the present disclosure is not intended to be limited to the above Description, but rather is as set forth in the appended claims.

[0316] In the claims, articles such as “a,” “an,” and “the” may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include “or” between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The disclosure includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The disclosure includes embodiments in which more than one, or the entire group members are present in, employed in, or otherwise relevant to a given product or process.

[0317] It is also noted that the term “comprising” is intended to be open and permits but does not require the inclusion of additional elements or steps. When the term “comprising” is used herein, the term “consisting of” is thus also encompassed and disclosed.

[0318] Where ranges are given, endpoints are included. Furthermore, it is to be understood that unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or subrange within the stated ranges in different embodiments of the disclosure, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[0319] In addition, it is to be understood that any particular embodiment of the present disclosure that falls within the prior art may be explicitly excluded from any one or more of the claims. Since such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the compositions of the disclosure (e.g., any antibiotic, therapeutic or active ingredient; any method of production; any method of use; etc.) can be excluded from any one or more claims, for any reason, whether or not related to the existence of prior art.

[0320] It is to be understood that the words which have been used are words of description rather than limitation, and that changes may be made within the purview of the appended claims without departing from the true scope and spirit of the disclosure in its broader aspects.

[0321] While the present disclosure has been described at some length and with some particularity with respect to the several described embodiments, it is not intended that it should be limited to any such particulars or embodiments or any particular embodiment, but it is to be construed with references to the appended claims so as to provide the broadest possible interpretation of such claims in view of the prior art and, therefore, to effectively encompass the intended scope of the disclosure.

[0322] The present disclosure is further illustrated by the following non-limiting examples.

EXAMPLES

Example 1. TRACER proof of concept: promoter selection

[0323] Proof-of-concept experiments were conducted by placing the genes encoding an AAV9 peptide display capsid library under the control of either the neuron-specific synapsin promoter (SYN) or the astrocyte-specific GFAP promoter. Following intravenous

administration to C57BL/6 mice, RNA was recovered from brain tissue and used for further library evolution. Next-generation sequencing (NGS) showed sequence convergence between animals after only two rounds of selection. Interestingly, several variants highly similar to the PHP.eB capsid were recovered, suggesting that our method allowed a rapid selection of high-performance capsids. A subset of capsids having peptide sequences with high CNS enrichment was selected for further study. It is understood that any promoter may be selected depending on the desired tropism. Examples of such promoters are found in Table 3.

Table 3 Promoters, tissue and cell type

Promoter name	Tissue	Cell type
B29 promoter	Blood	B cells
Immunoglobulin heavy chain promoter	Blood	B cells
CD45 promoter	Blood	Hematopoietic
Mouse INF- β promoter	Blood	Hematopoietic
CD45 SV40 / CD45 promoter	Blood	Hematopoietic
WASP promoter	Blood	Hematopoietic
CD43 promoter	Blood	Leuko & Platelets
CD43 SV40 / CD43 promoter	Blood	Leuko & Platelets
CD68 promoter	Blood	Macrophages
GPIIb promoter	Blood	Megakaryocyte
CD14 promoter	Blood	Monocytes
CD2 promoter	Blood	T cells
Osteocalcin	Bone	Osteoblasts
Bone sialoprotein	Bone	Osteoblasts
OG-2 promoter	Bone	Osteoblasts, odontoblasts
GFAP promoter	Brain	Astrocytes
Vga	Brain	GABAergic neurons
Vglut2	Brain	glutamatergic neurons
NSE / RU5' promoter	Brain	Neurons
SYN1 promoter	Brain	Neurons
Neurofilament light chain	Brain	Neurons
VGF	Brain	Neurons
Nestin	Brain	NSC
Chx10	Eye	All retinal neurons
PrP	Eye	All retinal neurons
Dkk3	Eye	All retinal neurons
Math5	Eye	Amacrine and horizontal cells
Ptf1a	Eye	Amacrine and horizontal cells
Pcp2	Eye	Bipolar cells
Nefh	Eye	Ganglion cells
gamma-synuclein gene (SNCG)	Eye	ganglion cells
Grik4	Eye	GC

Pdgfra	Eye	GC and ONL Müller cells
Chat	Eye	GC/Amacrine cells
Thy 1.2	Eye	GC/neural retina
hVmd2	Eye	INL Müller cells
Thy 1	Eye	INL Müller cells
Modified α A-crystallin	Eye	Lens/neural retina
hRgp	Eye	M- and S-cone
mMo	Eye	M-cone
Opn4	Eye	Melanopsin-expressing GC
RLBP1	Eye	Müller cells
Glast	Eye	Müller cells
Foxg1	Eye	Müller cells
hVmd2	Eye	Müller cells/optic nerve/INL
Trp1	Eye	Neural retina
Six3	Eye	Neural retina
cx36	Eye	Neurons
Grm6 - SV40 eukaryotic promoter	Eye	ON bipolar
hVmd2	Eye	Optic nerve
Dct	Eye	Pigmented cells
Rpc65	Eye	Retinal pigment epithelium
mRho	Eye	Rod
Irbp	Eye	Rod
hRho	Eye	Rod
Pcp2	Eye	Rod bipolar cells
Rhodopsin	Eye	Rod Photoreceptors
mSo	Eye	S-cone
MLC2v promoter	Heart	Cardiomyocyte
α MHC promoter	Heart	Cardiomyocyte
rat troponin T (Tnnt2)	Heart	Cardiomyocyte
Tie2	Heart	Endothelial
Tcf21	Heart	Fibroblasts
ECAD	Kidney	Collecting duct
NKCC2	Kidney	Loop of Henle
KSPC	Kidney	Nephron
NPHS1	Kidney	Podocyte
SGLT2	Kidney	Proximal tubular cells
SV40 / bAlb promoter	Liver	hepatocytes
SV40 / hAlb promoter	Liver	hepatocytes
Hepatitis B virus core promoter	Liver	hepatocytes
Alpha fetoprotein	Liver	hepatocytes
Surfactant protein B promoter	Lung	AT II cells and Clara cells
Surfactant protein C promoter	Lung	AT II cells and Clara cells
Desmin	Muscle	Muscle stem cells + Myocytes

Mb promoter	Muscle	Myocyte
Myosin	Muscle	Myocyte
Dystrophin	Muscle	Myocyte
dMCK and tMCK	Muscle	Myocytes
Elastase-1 promoter	Pancreas	Acinar cells
PDX1 promoter	Pancreas	Beta cells
Insulin promoter	Pancreas	langherans
Slco1c1	Vasculature	BBB Endothelial
tie	Vasculature	Endothelial
cadherin	Vasculature	Endothelial
ICAM-2	Vasculature	Endothelial
claudin 1	Vasculature	Endothelial
Cldn5	Vasculature	Endothelial
Flt-1 promoter	Vasculature	Endothelial
Endoglin promoter	Vasculature	Endothelial

[0324] Capsid pools were injected to three rodent species, followed by RNA enrichment analysis for characterization of transduction efficiency in neurons or astrocytes and cross-species performance. Top-ranking capsids were then individually tested and several variants showed CNS transduction similar to or higher than the PHP.eB benchmark. These results suggest that the TRACER platform allows rapid *in vivo* evolution of AAV capsids in non-transgenic animals with a high degree of tropism improvement. The following examples illustrate the findings in more detail.

Example 2. Generation of an AAV vectors capable of capsid mRNA expression in the absence of helper virus

[0325] In order to perform cell type- and transduction-restricted *in vivo* evolution of AAV capsid libraries, a capsid library system was engineered in which the capsid mutant gene can be transcribed in the absence of a helper virus, in a specific cell type. In the wild-type AAV virus, the mRNA encoding the capsid proteins VP1, VP2 and VP3, as well as the AAP accessory protein, are expressed by the P40 promoter located in the 3' region of the REP gene (FIG. 1A), that is only active in the presence of the REP protein as well as the helper virus functions (Berns et al., 1996). In order to allow expression of the capsid mRNA in animal tissue or in cultured cells, another promoter must be inserted upstream or downstream of the CAP gene. Because of the limited packaging capacity of the AAV capsid, a portion of the REP gene must be deleted to accommodate the extra promoter insertion, and the REP gene has to be provided in *trans* by another plasmid to allow virus production. The minimal viral sequence required for high titer AAV production was determined by introducing a CMV

promoter at various locations upstream of the CAP gene of AAV9 (FIG. 1B). The REP protein was provided in trans by the pREP2 plasmid obtained by deleting the CAP gene from a REP2-CAP2 packaging vector using EcoNI and ClaI (SEQ. ID NO:4). For small-scale virus production test, HEK-293T cells grown in DMEM supplemented with 5% FBS and 1X pen/strep were plated in 15-cm dishes and co-transfected with 15ug of pHelper (pFdelta6) plasmid, 10ug pREP2 plasmid and 1ug ITR-CMV-CAP plasmid using calcium phosphate transfection. After 72 hours, cells were harvested by scraping, pelleted by a brief centrifugation and suspended in 1ml of a buffer containing 10mM Tris and 2mM MgCl₂. Cells were lysed by addition of triton X-100 to 0.1% final concentration and treated with 50U of benzonase for 1 hour. Virus from the supernatants was precipitated with 8% polyethylene glycol and 0.5M NaCl, suspended in 1ml of 10mM TRIS-2mM MgCl₂ and combined with the cell lysate. The pooled virus was adjusted to 0.5M NaCl, cleared by centrifugation for 15 minutes at 4,000xg and fractionated on a step iodixanol gradient of 15%, 25%, 40% and 60% for 3 hours at 40,000rpm (Zolotukhin et al., 1999). The 40% fraction containing the purified AAV particles was harvested and viral titers were measured by real-time PCR using a Taqman primer/probe mix specific for the 3'-end of REP, shared by all the constructs. Virus yields were significantly lower than the fully wild-type ITR-REP2-CAP9-ITR used as a reference (1.7% to 8.8%), but the CMV-BstEII construct allowed the highest yields of all three CMV constructs. See FIG. 2. The CMV-HindIII construct, in which most of the P40 promoter sequence is deleted, generated the lowest yield (1.7% of wtAAV9), indicating that even the potent CMV promoter cannot replace the P40 promoter without a severe drop in virus yields. Following these observations, the BstEII architecture (SEQ. ID NO:5), which preserves the minimal P40 sequence and the CAP mRNA splice donor, was used in all further experiments.

[0326] The REP-expressing plasmid was then improved by preserving the AAP reading frame together with a large portion of the capsid gene from the REP2-CAP9 helper vector, which may contain sequences necessary for the regulation of CAP transcription and/or splicing. In order to eliminate the capsid coding potential of the vector, a C-terminus fragment of the capsid gene was deleted by a triple cut with the MscI restriction enzyme followed by self-ligation, in order to obtain the pREP-AAP plasmid (FIG. 3A, SEQ. ID NO:6).

[0327] An iteration of this construct was engineered by introducing premature stop codons immediately after the start codons of VP1, VP2 and VP3, without perturbing the amino acid sequence of the colinear AAP reading frame (FIG. 3A). This construct was named pREP-

3stop (SEQ. ID NO:7). A neuron-specific syn-CAP9 vector (SEQ. ID NO:8) was derived from the CMV9-BstEII plasmid by swapping the CMV promoter with the neuron-specific human synapsin 1 promoter.

[0328] Production efficiency of this Syn-CAP9 was tested as described previously using pREP, pREP-AAP or pREP-3stop plasmid to supply REP in trans. As shown in FIG. 3B, the REP plasmids harboring a longer capsid sequence as well as AAP increased virus yields by approximately 3-fold compared to the pREP plasmid. Virus titers obtained with the pREP-AAP or pREP-3stop vectors reached ~30% of wild-type AAV9. An important concern with plasmids harboring long homologous regions is the potential for unwanted recombination with the ITR-CAP vector, that would reconstitute a wild-type ITR-REP-CAP vector and contaminate combinatorial libraries.

[0329] To evaluate the risk of wild-type virus reconstitution, the viral preparations obtained in FIG. 3B were subjected to real-time PCR with a Taqman probe located in the N terminus of REP. The percentage of capsids containing a detectable full-length REP was less than 0.03% of wild-type virus (FIG. 3C), which was even lower than the routinely detected 0.1% illegitimate REP-CAP packaging occurring in most recombinant AAV preparations obtained from 293T cell transfection (FIG. 3C, our unpublished observations). Because the premature stop codons of the pREP-3stop vector offer an extra layer of safety against potential reconstitution of wild-type capsids and prevents the translation of truncated capsid proteins, the 3stop plasmid was used for all subsequent studies.

[0330] Following this, the feasibility of RNA-driven biopanning in C57BL/6 mice using AAV9-packaged vectors where the AAV9 capsid gene is driven by the CMV promoter, the Synapsin promoter or the astrocyte-specific GFabc1D promoter (SEQ. ID NO:9), thereafter referred to as GFAP promoter (Brenner et al., 2008) was tested (FIG. 4A). The three vectors were produced in HEK-293T cells as previously described and analyzed by PAGE-silver stain. As shown in FIG. 4B, all vectors showed a normal ratio of VP1, VP2 and VP3 capsid proteins, indicating that the particular promoter architecture does not disrupt the balance of capsid protein expression. Six-week old male C57BL/6 mice were injected intravenously with 1×10^{12} VG per mouse and sacrificed after 28 days. DNA biodistribution and capsid mRNA expression were tested in the brain, liver and heart tissues.

[0331] Total DNA was extracted from brain, liver and heart tissues using Qiagen DNeasy Blood and Tissue columns, and viral DNA was quantified by real-time PCR using a Taqman probe located in the VP3 N-terminal region. DNA abundance was normalized using a pre-designed probe detecting the single-copy transferrin receptor gene (Life Technologies ref.

4458366). Viral DNA was highly abundant in the liver and to a lower extent in the heart. The DNA distribution did not show any noticeable difference between the three vectors (FIG. 4C). RNA was extracted with Qiagen RNeasy plus universal kit following manufacturer's instructions, then treated with ezDNAse (Qiagen) to remove residual DNA, and reverse transcribed with Superscript IV (Life technologies).

[0332] RNA expression was evaluated using the same VP3 probe used to quantify viral DNA and normalized using TBP as a reference RNA (Life technologies Mm01277042_m1). In the brain, the GFAP promoter allowed the strongest expression level, and the Synapsin promoter allowed a comparable expression as the potent CMV promoter. In the liver, all promoters resulted in a similar expression level, which could be the result of a leaky expression at very high copy number (FIG. 4D). In the heart, the cell type specificity of the Syn and GFAP promoters was evident, since they allowed only ~3 and 10% of CMV expression, respectively despite of a similar DNA biodistribution.

[0333] Overall the experiment showed that mRNA from transduction-competent capsids could be recovered from various animal organs, including weakly transduced tissues such as the brain.

Example 3. AAV vector configuration

[0334] Various vector configurations were explored toward increasing RNA expression to maximize library recovery. The CMV promoter was replaced by a hybrid CMV enhancer/Chicken beta-actin promoter sequence (Niwa et al., 1991) and a potent cytomegalovirus-beta-globin hybrid intron derived from the AAV-MCS cloning vector (Stratagene) was inserted between the promoter sequence and the capsid gene, as introns have been shown to increase mRNA processing and stability (Powell et al., 2015). This resulted in the constructs CAG9 (SEQ. ID NO:10), SYNG9 (SEQ. ID NO:11) and GFAPG (SEQ. ID NO:12).

[0335] An inverted vector configuration was also tested where the helper-independent promoter was placed downstream of the capsid gene in reverse orientation, in order to avoid potential interference with the P40 promoter (FIG. 5A). This configuration allows the expression of an antisense capsid transcript in animal tissue. Because most polyadenylation signals (AATAAA) are orientation-dependent, it was hypothesized that the natural AAV capsid polyA would not prematurely terminate transcription when placed in reverse orientation. All constructs were co-transfected with pHelper and pREP-3stop plasmids to generate AAV9-packaged virions that were used to transduce HEK-293T cells at a MOI of

1e4 VG per cell. RNA was extracted 48 hours post-transfection and reverse transcribed using the Quantitect kit (Qiagen).

[0336] PCR was performed with primers allowing amplification of the full-length capsid or a partial sequence localized close to the C-terminus (FIG. 5B). Overall, the presence of an intron had little influence on the expression from low-activity promoters Syn and GFAP, which indicates that mRNA splicing did not alleviate promoter repression in nonpermissive cells. The combination of the CMV enhancer with a Chicken beta-actin promoter and the hybrid intron allowed a significantly higher (> 10-fold) mRNA expression compared to CMV promoter alone (FIG. 5B, C).

[0337] When comparing endpoint PCR amplification between forward and inverted intronic vectors, a discrepancy was obvious between full-length and partial capsid amplicons (FIG. 5B, right-hand lanes), which led us to question the integrity of capsid RNA. When cDNA from inverted iCAG9 genome was amplified using primers flanking the full-length capsid, multiple low-molecular weight bands were detected, whereas the forward orientation vector allowed amplification of a single product with the expected length (FIG. 5D). Sanger sequencing of low-molecular weight amplicons showed that each band corresponded to an illegitimate splicing product from the antisense capsid RNA.

[0338] In light of these results, the forward tandem promoter architecture for subsequent experiments.

[0339] Splice-specific PCR amplification was tested to avoid amplification of residual DNA present in RNA preparations. Two candidate PCR primers overlapping the CMV/Globin exon-exon junction were designed and tested them for amplification of cDNA (spliced) or plasmid DNA (still containing the intron sequence). As shown in FIG. 5E, the GloSpliceF6 primer (SEQ. ID NO:13) allowed a fully specific amplification from cDNA without producing a detectable amplicon from the plasmid DNA sequence. This primer was used in subsequent assays to ascertain the absence of amplification from contaminating DNA.

[0340] Tandem constructs were then tested for potential interference of the P40 promoter with the cell-specific promoter placed upstream. For this, two series of AAV genomes were tested for transgene mRNA expression in HEK-293T cells. A series of transgenes where the GFP gene was placed immediately downstream of the CAG, SYNG or GFAPG promoter without P40 sequence were tested, and compared to the library constructs where AAV9 capsid was placed downstream of the P40 promoter (FIG. 6A). All genomes were packaged into the AAV9 capsid and used to infect HEK-293T at a MOI of 1e4 VG per cell. RNA was extracted 48 hours post-infection and transgene RNA was quantified by using a Taqman

primer/probe mix specific for the spliced globin exon-exon junction. As shown in FIG. 6B, the expression from the CAG promoter was similar between the GFP and the P40-CAP9 constructs (2-fold lower in p40-CAP9, within the error margin of AAV titration). Expression from the synapsin promoter was drastically lower with both constructs and even lower for GFAP-driven mRNA (FIG. 6B). This was expected since HEK-293T cells are not permissive to Synapsin or GFAP promoter expression. Overall, this experiment confirmed that the presence of the P40 sequence did not alter the cell type specificity of synapsin or GFAP promoters.

[0341] This novel platform was termed TRACER (Tropism Redirection of AAV by Cell type-specific Expression of RNA). The TRACER platform solves the problems of standard methods including transduction and cell-type restrictions. (FIG. 7). Use of the TRACER system is well suited to capsid discovery where targeting peptide libraries are utilized. Screening of such a library may be conducted as outlined in FIG. 8.

[0342] While several variations of the AAV vectors which encode the capsids as payloads are taught herein, one canonical design is shown in FIG. 9B and in FIG. 12A and FIG. 12B.

[0343] Further advantages of the TRACER platform relate to the nature of the virus pool and the recovery of RNA only from fully transduced cells (FIG. 10). Consequently, capsid discovery can be accelerated in a manner that results in cell and/or tissue specific tropism (FIG. 11).

Example 4. Generation of peptide display libraries and cloning-free amplification

[0344] Several peptide display capsid libraries were generated by insertion of seven contiguous randomized amino acids into the surface-exposed hypervariable loop VIII region of AAV5, AAV6, or AAV-DJ8 capsids (FIG. 13 and FIG. 39) as well as AAV9 (FIG. 14). For AAV9 libraries, two extra libraries by modifying residues at positions -2, -1 and +1 of the insertion to match the flanking sequence of the highly neurotrophic PHP.eB vector (Chan et al., 2018). In order to facilitate the insertion of various loops and to prevent contamination by wild-type capsids, defective shuttle vectors were generated in which the C-terminal region of the capsid gene comprised between the loop VIII and the stop codon was deleted and replaced by a unique BsrGI restriction site (FIG. 15A, B). Degenerate primers containing randomized NNK (K=T or G) sequences able to encode all amino acids were synthesized by IDT and used to amplify the missing capsid fragment using gBlock (IDT) double-stranded linear DNA as templates (SEQ. ID NO 14, 15, 16, 17). Linear PCR templates were preferred to plasmids in order to completely prevent the possibility of plasmid carryover in the PCR reaction. Amplicons containing the random library sequence (500 ng) were inserted in the

shuttle plasmid linearized by BsrGI (2ug) using 100ul of NEBuilder HiFi DNA assembly master mix (NEB) during 30 minutes at 50°C. Unassembled linear templates were eliminated by addition of 5ul of T5 exonuclease to the reaction and digestion for 30 minutes at 37°C. The entire reaction was purified with DNA Clean and Concentrator-5 and quantified with a nanodrop to estimate the efficiency of assembly. This method routinely allows the recovery of 0.5-1ug assembled material.

[0345] gBlock templates were engineered by introducing silent mutations to remove unique restriction sites, to allow selective elimination of wild-type virus contaminants from the libraries by restriction enzyme treatment. As an example, AAV9 gBlock was engineered to remove BamHI and AfeI sites present in the parental sequence (SEQ. ID NO 17).

Example 5. Cloning free amplification

[0346] Transformation of assembled library DNA into competent bacteria represents a major bottleneck in library diversity, since even highly competent strains rarely exceed 1e7-1e8 colonies per transformation. By comparison, 100 nanograms of a 6-kilobase plasmid contain 1.5e10 DNA molecules. Therefore, bacterial transformation arbitrarily eliminates more than 99% of DNA species in a given pool. A cloning-free method was therefore created that allows >100-fold amplification of Gibson-assembled DNA while bypassing the bacterial transformation bottleneck (FIG. 16). A protocol based on rolling-circle amplification was optimized, which allows unbiased exponential amplification of circular DNA templates with an extremely low error rate (Hutchinson et al., 2005). One issue with rolling circle amplification is that it produces very large (~70 kilobases on average) heavily branched concatemers that have to be cleaved into monomers for efficient cell transfection. This process can be accomplished by several methods, for example by using restriction enzymes to generate open-ended linear templates (Hutchinson et al., 2005, Huovinen, 2012), or CRE-Lox recombination to generates self-ligated circular templates (Huovinen et al., 2011). However, open-ended DNA is sensitive to degradation by cytoplasmic exonucleases, and the CRE recombination method showed relatively low efficiency (our unpublished observations). Therefore, an alternative monomer resolution method was chosen based on the use of TelN protelomerase (Rybchin et al., 1999), an enzyme that catalyzes the formation of closed-ended linear “dogbone” DNA monomers that are highly suitable for mammalian cell transfection (Heinrich et al., 2002).

[0347] To that end, the protelomerase recognition sequence
TATCAGCACACAATTGCCCATTATACGC*GCGTATAATGGACTATTGTGTGCTGA
TA (SEQ ID NO: 176) was introduced outside both ITRs in all the BsrGI shuttle vectors used

for capsid library insertion (the asterisk depicts the position where the two complementary strands get covalently linked to each other), in order to obtain the following plasmids: TelN-Syn9-BsrGI (SEQ ID NO 18), TelN-GFAP9-BsrGI (SEQ ID NO 19), TelN-Syn5-BsrGI (SEQ ID NO 20), TelN-GFAP5-BsrGI (SEQ ID NO 21), TelN-Syn6-BsrGI (SEQ ID NO 22), TelN-GFAP6-BsrGI (SEQ ID NO 23), TelN-SynDJ8-BsrGI (SEQ ID NO 24), TelN-GFAPDJ8-BsrGI (SEQ ID NO 25). Several methods for rolling circle amplification were tested, and the best results (high yield and low non-specific amplification) were obtained with the TruePrime technology (Expedeon), which relies on primerless amplification (Picher et al., 2016).

[0348] Briefly, the entire column-purified assembly reaction was used in a 900- μ l TruePrime reaction following the manufacturer's instructions and incubated overnight at 30°C. The following day, the rolling circle reaction product was incubated 10 minutes at 65°C to inactivate the enzymes and was diluted 5-fold in 1X thermoPol buffer with 50 μ l protelomerase (NEB) in a 4.5-ml reaction. After 1 hour at 30°C, the reaction was heat-treated for 10 minutes at 70°C to inactivate the protelomerase, and a 4.5- μ l aliquot was run on an agarose gel. The entire reaction was then purified on multiple (10-12) Qiagen QiaPrep 2.0 columns following manufacturer's instructions. The typical yield obtained with this method was 160-180 μ g DNA, which indicates >100-fold amplification of the starting material (typically 0.5-1 μ g) and provides enough DNA for transfection of 200 cell culture dishes (FIG. 16).

[0349] The composition of all libraries was tested by next-gen sequencing with an Illumina NextSeq sequencing platform to estimate the number of variants and the eventual contamination by wild-type viruses. Amplicons were generated by PCR with Q5 polymerase (NEB) using primers containing Illumina TruSeq adapters and index barcodes. Amplicons were obtained by low-cycle PCR amplification (15 cycles), ran on 3% agarose gels and purified using Zymo gel extraction reagents. Libraries were quantified using a nanodrop, pooled into equimolar mixes and re-quantified with a KAPA library quantification kit following manufacturer's instruction. Libraries were mixed with 20-40% of PhiX control library to increase sequence diversity.

[0350] All DNA libraries generated by rolling circle showed a high sequence diversity (typically >1e8 unique variants, beyond the limits of NextSeq sequencing). By comparison, plasmid libraries generated by bacterial transformation rarely exceeded 1-2e7 variants.

Example 6. Prevention and/or reduction of contamination

[0351] In another embodiment, a primer/vector system aimed at completely preventing contamination of AAV9 libraries by wild-type virus possibly recovered from environmental contamination or from naturally infected primate animal tissues was created. This was achieved by introducing a maximum number of silent mutations in the sequences surrounding the library insertion site, as well as the sequence immediately before the CAP stop codon, used for PCR amplification (FIG. 17). These libraries showed an extremely low number of wild-type AAV9 detection by NGS (<2 AAV9 reads per 5e7 total reads), suggesting that the alteration of codons surrounding the library amplification and cloning sites is a very efficient way to preserve libraries from environmental or experimental contaminations.

[0352] Libraries were produced as described previously by calcium phosphate transfection of HEK-293T cells, dual iodixanol gradient fractionation and membrane ultrafiltration using 100,000 Da MWCO Amicon-15 membranes (Millipore), quantified by real-time PCR and an aliquot was used for NGS amplicon generation and NextSeq sequencing. The diversity of viral libraries was significantly lower than that of DNA libraries (typically ~1-2e7 unique variants) and showed a very strong counter-selection of variants containing stop codons (from 20% in DNA libraries to ~1% in virus libraries), evincing a very high rate of cis-packaging, as observed in previous studies (Nonnenmacher et al., 2014).

Example 7. *In vivo* selection of AAV9 libraries for mouse brain transduction

[0353] An RNA-driven library selection for increased brain transduction in a murine model was then developed. AAV9 libraries generated as described above were intravenously injected to male C57BL/6 mice at a dose 2e12 VG per mouse. Two groups of mice were injected with a single SYN-driven or GFAP-driven libraries derived from wild-type AAV9 flanking sequences, and two other groups received pooled libraries containing wild-type and PHP.eB-derived flanking sequences (FIG. 18). After one month, RNA was extracted from 200mg of brain tissue corresponding to a whole hemisphere using RNeasy Universal Plus procedure (Qiagen). In order to minimize the possibility of RNA under sampling, the entire RNA preparation (~200ug) was subjected to mRNA enrichment using Oligotex beads (Qiagen) as recommended by the manufacturer. The entire preparation of enriched mRNA (~5ug, equivalent to 2% of total RNA) was then reverse transcribed in a 40-ul Superscript IV reaction (Life Technologies) using a library-specific primer with the following sequence: 5'-GAAACGAATTAAACGGTTTATTGATTAACAATCGATTA-3' (SEQ ID NO: 415) (CAP stop codon is underlined) (FIG. 19). The entire pool of cDNA was then amplified 30 cycles with 55°C annealing temperature and 2 minutes elongation in a 500-ul PCR reaction

assembled with Q5 master mix, GloSpliceF6 forward primer and a CAP9-specific reverse primer: 5'-CGGTTTATTGATTAACAATCGATTACAGATTACGAGTCAGGTATC-3' (SEQ ID NO: 416) (CAP stop codon is underlined). This method allowed recovery of abundant amplicons from all brain samples (FIG. 20).

[0354] Full-length capsid amplicons were then used as templates for NGS library generation, as well as cloning into a P1 DNA library for the next round of biopanning, using the exact same assembly and cloning-free procedure. NGS analysis performed on PCR amplicons indicated that the library diversity dropped ~25-fold (from $1e7$ to $4e5$) after the first round of biopanning for both Syn-driven and GFAP-driven libraries (FIG. 21). The number of 1st pass variants (P1) recovered was too high to show any significant sequence convergence at this point, and there was very little overlap between the composition of pools recovered from individual animals. Therefore, a second round of selection was performed. After the second biopanning (P2), the total number of unique variants further dropped by 4-5-fold, down to $<1e5$ peptides. Importantly, some libraries recovered after the first round of biopanning showed significant counts of wild-type AAV9 and AAV-PHP.eB sequences, presumably from environmental contamination. These later became useful benchmarks in the second round of enrichment.

[0355] Following RNA recovery and PCR amplification, a systematic enrichment analysis by NGS was performed by calculating the ratio of P2/P1 reads and comparing it to AAV9 or PHP.eB P2/P1 ratio. As shown in FIG. 22, Table 4, FIG. 23 and Table 5, several capsids showed a higher enrichment ratio than the benchmark PHP.eB in both Syn-driven and GFAP-driven libraries, and sequence convergence was obvious, as represented by consensus sequence generation.

Table 4. Capsid analysis results

Rank (enrichment factor)	Ranking (count)	Peptide	SEQ ID NO	Average of brain	p1 AEvirus_S11	Brain/virus stock
1	136	DGTLAVHFK	417	2546.3	6	254.6
2	153	DGTFVVPFK	418	2321.7	6	232.2
3	155	EGTLAVPFK	419	2351.0	7	201.5
4	147	DGTMAVPFK	420	2547.0	8	191.0
5	32	DGTGGTKGW	107	11116.0	35	190.6
6	3	AQWPTSUDA	62	119359.7	512	139.9
7	99	DGTLAVTFK	421	3779.7	19	119.4
8	176	DGTLAVPIK	422	1882.0	13	86.9
9	36	AQTTEKPWL	83	10192.0	76	80.5

10	165	DGTAIHLSS	67	2885.0	23	75.3
11	13	DGTLSQPFR	65	42145.7	344	73.5
12	2	DGTLAAPFK	120	157129.3	1,300	72.5
13	8	AQPEGSARW	60	70884.0	594	71.6
14	48	AQWPTAYDA	256	5934.0	53	67.2
15	198	DGTLQQPFR	89	2793.3	25	67.0
16	104	DGTLAVNFK	346	3511.0	32	65.8
17	31	DGTGNLSGW	302	14521.3	133	65.5
18	158	DGTLEVTFK	423	2337.7	22	63.8
19	51	DGTMDKPFR	70	23962.3	234	61.4
20	80	DGTGQVTGW	68	6242.7	62	60.4
21	42	AQFPTNYDS	66	8640.0	86	60.3
22	127	ERTLAVPFK	424	2873.3	31	55.6
23	1	DGTLAVPFK	71	9885065.7	110,785	53.5
24	61	DGTGTTMGW	324	6753.0	76	53.3
25	69	DGSQSTTGW	136	7227.7	82	52.9
26	186	DGTVSNPFR	403	2074.3	24	51.9
27	160	DGTLEVHFK	348	2245.0	26	51.8
28	29	DGTISQPFK	105	20505.7	243	50.6
29	102	AQGSWNPPA	80	3746.0	45	49.9
30	59	DGTHSTTGW	145	7499.0	91	49.4
31	23	DGTGSTTGW	134	21582.0	272	47.6
32	142	DGTGTTTGW	130	3077.3	39	47.3
33	74	DGTVTTTGW	405	5088.7	66	46.3
34	35	DGTTYVPPR	75	9614.7	126	45.8
35	40	DGTMDRPFK	102	7868.3	104	45.4
36	4	DGTGTTLGW	323	88397.3	1,169	45.4
37	156	DGTALMLSS	280	2444.0	34	43.1
38	116	DGTNTTHGW	113	3065.0	43	42.8
39	98	SGSLAVPFK	425	4107.3	58	42.5
40	38	DGTATTTGW	285	10529.7	150	42.1
41	11	DGTSYVPPR	78	36293.3	526	41.4
42	89	DGTGNTHGW	72	3399.3	50	40.8
43	129	DGTASVTGW	283	4824.3	71	40.8
44	12	AQWELSNGY	246	40837.0	611	40.1
45	115	DGTGNTSGW	137	3405.0	51	40.1
46	67	DGKGSTQGW	272	5818.0	88	39.7
47	137	DGTVIMLSS	397	3781.0	58	39.1
48	119	DGTGGVMGW	297	2302.3	36	38.4
49	58	DGGGTTTGW	270	11174.3	175	38.3
50	71	DGTSIHLSS	378	5703.7	90	38.0

Table 5. Capsid analysis results

Rank (enrichment factor)	Ranking (count)	Peptide	SEQ ID NO	Average of brain	p1 AEvirus_S11	Brain/virus stock
1	106	DGTGGTKGW	107	3620.7	0	NA

2	264	GGTRNTAPM	426	831.0	0	NA
3	295	AQGRMTDSQ	199	716.0	0	NA
4	677	DGNSYVPPR	427	474.3	0	NA
5	700	AQAGVSGQR	428	456.0	0	NA
6	731	AQAGNSNAV	429	844.0	0	NA
7	181	DGTGGLTGW	294	4044.3	4	606.7
8	558	AQWVYGQTV	430	977.7	1	586.6
9	123	DGTSFSPPK	431	4227.3	10	253.6
10	35	DGTIERPFR	87	29872.0	92	194.8
11	105	DGTTLVPPR	116	5597.3	19	176.8
12	18	DGTADKPFR	63	103305.3	363	170.8
13	22	DGTASYYS	61	61841.3	233	159.2
14	26	AQTTDRPFL	85	38893.7	147	158.7
15	8	DGTQFSPPR	108	206660.7	801	154.8
16	169	DGTTTYGAR	77	4237.3	17	149.6
17	11	AQFVVGQY	95	152965.0	625	146.8
18	61	DGTSYVPPR	78	13968.0	58	144.5
19	16	DGTAERPFR	140	134132.7	565	142.4
20	21	AQGENPGRW	96	68919.7	292	141.6
21	157	DGTSFTPPR	88	3210.0	14	137.6
22	73	AQTLARPFV	98	5947.7	26	137.3
23	9	DGTTWTPPR	139	184936.7	825	134.5
24	721	DGTATTMGW	284	5562.3	25	133.5
25	129	AQGTWNPPA	82	12379.3	57	130.3
26	215	DGTRLMLSS	368	2505.0	12	125.3
27	60	AQPLAVYGA	217	13419.3	66	122.0
28	909	AQGLDLGRW	432	405.0	2	121.5
29	53	DGTSFTPPK	81	13673.3	68	120.6
30	412	AQVMMSGVQ	433	583.0	3	116.6
31	390	AQKSVGSVY	205	4415.7	23	115.2
32	70	AQTREYLLG	93	5752.7	30	115.1
33	43	DGTNGLKGW	76	15068.7	79	114.4
34	93	AQYLAGYTV	262	6223.3	33	113.2
35	54	AQTGFAPPR	161	14611.3	78	112.4
36	115	DGTLNNPFR	109	4719.7	26	108.9
37	968	DGNGGLKGW	167	3199.0	18	106.6
38	120	AQSVAKPFL	231	6929.7	39	106.6
39	544	DGTHGLRGW	434	528.0	3	105.6
40	159	AQSVVRPFL	233	2457.3	14	105.3
41	65	DGTRNMYEG	135	21086.3	124	102.0
42	556	AQRWAADSS	435	500.7	3	100.1
43	30	AQGPTRPFL	125	46225.3	279	99.4
44	64	DGTVPYLSS	401	22384.3	137	98.0
45	870	AQTGASGAT	436	473.7	3	94.7
46	341	AQLVAGYSQ	437	1240.0	8	93.0
47	375	AQSGGVQV	228	768.3	5	92.2
48	145	AQSLARLFP	438	4435.3	29	91.8

49	1	DGTLAVPFK	71	1445517.0	9453	91.7
50	124	DGTGNVTGW	69	5424.3	36	90.4

[0356] Importantly, there was also a strong sequence convergence between different animals, suggesting an efficient selection after only two passages. FIG. 24 and FIG. 25 provide an estimation of brain/liver specificity in GFAP-AAV9 peptide library candidates.

Example 8. Multiplexing selections

[0357] For the final multiplex *in vivo* screen by individual variant pooling in equimolar library, a subpopulation of variants with promising properties (such as, but not limited to, enrichment factor, liver detargeting, high counts in more than one mouse, etc.) may be selected as shown in FIG. 26 and then an equimolar pool of primers encoding all the 7-mers (microchip solid-phase synthesis, up to 3,800 primers per chip) can be synthesized. The limited diversity library may be produced including internal controls such as, but not limited to, PHP.N, PHP.B, wild-type AAV9 (wtAAV9) and/or any other serotype including those taught herein. The mice are injected and then the RNA enrichment is compared to internal controls in a similar manner to a barcoding study, which is known in the art and described herein.

Example 9. Codon optimization

[0358] Codon variants may be used to improve data strength when using synthesized libraries. A listing of NNK codons, NNM codons and the most favorable NNM codons in mammals for various amino acids is provided in Table 6. In Table 6, * means that no NNM codon was available and ** means “avoid homopolymeric stretches if possible.”

Table 6. Codon Variants

Amino acid	NNK codon	NNM codons	Most favorable NNM codon in mammals
F	TTT	TTC	TTC
L	TTG, CTT, CTG	TTA, CTC, CTA	CTC
S	TCT, TCG, AGT	TCC, TCA, AGC	AGC
Y	TAT	TAC	TAC
C	TGT	TGC	TGC
W	TGG		TGG*
P	CCT, CCG	CCC, CCA	CCA**
H	CAT	CAC	CAC
Q	CAG	CAA	CAA
R	CGT, CGG, AGG	CGC, CGA, AGA	AGA
I	ATT	ATC, ATA	ATC
M	ATG		ATT*
T	ACT, ACG	ACC, ACA	ACC
N	AAT	AAC	AAC

K	AAG	AAA	AAA
V	GTT, GTG	GTC, GTA	GTC
A	GCT, GCG	GCC, GCA	GCC
D	GAT	GAC	GAC
E	GAG	GAA	GAA
G	GGT, GGG	GGC, GGA	GGC
stop	TAG	TAC, TAA	n/a
*no NNM codon available			
**avoid homopolymeric stretches if possible			

[0359] In order to have a balanced library it is recommended to establish a list of potential candidates. Then, using Table 6, a pooled primer library containing every peptide variant with encoded by NNK codons (original from library) and non-NNK codons (maximum variation). If similar behavior is seen between the two variants of the same peptide, this would strengthen the analysis of that peptide. Additionally, it is recommended to choose the most favorable NNM codons (M= A or C).

Example 10. Library generation

[0360] The top-ranking 330 peptide variants from SYN-driven and GFAP-driven libraries that showed enhanced performance relative to the parental AAV9 were selected. *A de novo* library by pooled primer synthesis of all 330 peptide sequences plus AAV9, AAV-PHP.B and AAV-PHP.eB controls was generated (Table 7). In order to exclude potential artifacts due to the DNA sequence and to increase the robustness of the assay, each peptide variant was encoded by two different DNA sequences, one where all amino acids were encoded by NNK codons (identical to the original library) and another one where NNM codons were used whenever possible (M=C or A, Table 6).

Table 7. Peptide variants selected after 2 rounds of RNA-driven mouse brain biopanning

Peptide Sequence	SEQ ID NO:	Nucleotide sequence (NNK codons)	SEQ ID NO:	Nucleotide sequence (NNM codons)	SEQ ID NO:
AQ (AAV9)		CAGAGTGCTCAG GCACAG	439	CAGAGTGCCCAA GCACAG	772
AQAGAGSER	194	CAGAGTGCCCAA GCGGGTGCAGGG TCGGAGCGGGCA CAG	440	CAGAGTGCACAA GCAGGAGCAGGA AGCGAAAGAGCA CAG	773
AQDQNPGRW	195	CAGAGTGCCCAA GATCAGAATCCG GGGCGTTGGGCA CAG	441	CAGAGTGCACAA GACCAAAACCCA GGAAGATGGGCA CAG	774

AQELTRPFL	144	CAGAGTGCCCAA GAGTTGACGCGT CCGTTTTTGGCAC AG	442	CAGAGTGCACAA GAACTCACAAGA CCATTCCTCGCAC AG	775
AQEVPGYRW	196	CAGAGTGCCCAA GAGGTGCCTGGG TATAGGTGGGCA CAG	443	CAGAGTGCACAA GAAGTCCCAGGA TACAGATGGGCA CAG	776
AQFPTNYDS	66	CAGAGTGCCCAA TTTCCTACGAATT ATGATTCTGCACA G	444	CAGAGTGCACAA TTCCCAACAAACT ACGACAGCGCAC AG	777
AQFVVGQQY	95	CAGAGTGCCCAA TTTGTGGTTGGTC AGCAGTATGCAC AG	445	CAGAGTGCACAA TTCGTCGTCGGAC AACAATACGCAC AG	778
AQGASPGRW	149	CAGAGTGCCCAA GGGGCTAGTCCG GGGCGGTGGGCA CAG	446	CAGAGTGCACAA GGAGCAAGCCCA GGAAGATGGGCA CAG	779
AQGENPGRW	96	CAGAGTGCCCAA GGGGAGAATCCG GGTAGGTGGGCA CAG	447	CAGAGTGCACAA GGAGAAAACCCA GGAAGATGGGCA CAG	780
AQGGNPGRW	91	CAGAGTGCCCAA GGGGGGAATCCG GGTCGGTGGGCA CAG	448	CAGAGTGCACAA GGAGGAAAACCCA GGAAGATGGGCA CAG	781
AQGGSTGSN	197	CAGAGTGCCCAA GGTGGTTCTACG GGGTCGAATGCA CAG	449	CAGAGTGCACAA GGAGGAAGCACA GGAAGCAACGCA CAG	782
AQGPTRPFL	125	CAGAGTGCCCAA GGGCCGACTAGG CCGTTTTTGGCAC AG	450	CAGAGTGCACAA GGACCAACAAGA CCATTCCTCGCAC AG	783
AQGRDGWAA	198	CAGAGTGCCCAA GGTCGGGATGGT TGGGCGGCGGCA CAG	451	CAGAGTGCACAA GGAAGAGACGGA TGGGCAGCAGCA CAG	784
AQGRMTDSQ	199	CAGAGTGCCCAA GGTCGTATGACT GATTTCGAGGCA CAG	452	CAGAGTGCACAA GGAAGAATGACA GACAGCCAAGCA CAG	785
AQGS DVGRW	128	CAGAGTGCCCAA GGTAGTGATGTG GGGCGGTGGGCA CAG	453	CAGAGTGCACAA GGAAGCGACGTC GGAAGATGGGCA CAG	786
AQGSNPGRW	103	CAGAGTGCCCAA GGTAGTAATCCG GGGAGGTGGGCA CAG	454	CAGAGTGCACAA GGAAGCAACCCA GGAAGATGGGCA CAG	787
AQGSNSPQV	200	CAGAGTGCCCAA GGGTCTAATTCGC CTCAGGTGGCAC AG	455	CAGAGTGCACAA GGAAGCAACAGC CCACAAGTCGCA CAG	788
AQGSWNPPA	80	CAGAGTGCCCAA GGTTCGTGGAAT CCGCCGGCGGCA CAG	456	CAGAGTGCACAA GGAAGCTGGAAC CCACCAGCAGCA CAG	789

AQGTWNPPA	82	CAGAGTGCCCAA GGTACTTGGAAT CCGCCGGCTGCA CAG	457	CAGAGTGCACAA GGAACATGGAAC CCACCAGCAGCA CAG	790
AQGVFIPPK	201	CAGAGTGCCCAA GGTGTITTTTATTC CGCCGAAGGCAC AG	458	CAGAGTGCACAA GGAGTCTTCATCC CACCAAAAGCAC AG	791
AQHVNASQS	202	CAGAGTGCCCAA CATGTGAATGCTT CTCAGTCTGCACA G	459	CAGAGTGCACAA CACGTCAACGCA AGCCAAAGCGCA CAG	792
AQIKAGWAQ	203	CAGAGTGCCCAA ATTAAGGCGGGG TGGGCGCAGGCA CAG	460	CAGAGTGCACAA ATCAAAGCAGGA TGGGCACAAGCA CAG	793
AQIMSGYAQ	204	CAGAGTGCCCAA ATTATGAGTGGG TATGCTCAGGCA CAG	461	CAGAGTGCACAA ATCATGAGCGGA TACGCACAAGCA CAG	794
AQKSVGSVY	205	CAGAGTGCCCAA AAGAGTGTGGGT AGTGTTTATGCAC AG	462	CAGAGTGCACAA AAAAGCGTCGGA AGCGTCTACGCA CAG	795
AQLEHGFAQ	206	CAGAGTGCCCAA CTTGAGCATGGG TTTGCTCAGGCAC AG	463	CAGAGTGCACAA CTCGAACACGGA TTCGCACAAGCA CAG	796
AQLGGVLSA	207	CAGAGTGCCCAA CTGGGTGGGGTG TTGAGTGCTGCAC AG	464	CAGAGTGCACAA CTCGGAGGAGTC CTCAGCGCAGCA CAG	797
AQLGLSQGR	208	CAGAGTGCCCAA CTGGGGCTTTCGC AGGGGCGGGCAC AG	465	CAGAGTGCACAA CTCGGACTCAGC CAAGGAAGAGCA CAG	798
AQLGYGFAQ	209	CAGAGTGCCCAA TTGGGGTATGGG TTTGCTCAGGCAC AG	466	CAGAGTGCACAA CTCGGATACGGA TTCGCACAAGCA CAG	799
AQLKYGLAQ	115	CAGAGTGCCCAA TTGAAGTATGGTC TTGCGCAGGCAC AG	467	CAGAGTGCACAA CTCAAATACGGA CTCGCACAAGCA CAG	800
AQLRIGFAQ	210	CAGAGTGCCCAA CTTCGGATTGGTT TTGCTCAGGCAC AG	468	CAGAGTGCACAA CTCAGAATCGGA TTCGCACAAGCA CAG	801
AQLRMGYSQ	211	CAGAGTGCCCAA TTGCGTATGGGTT ATAGTCAGGCAC AG	469	CAGAGTGCACAA CTCAGAATGGGA TACAGCCAAGCA CAG	802
AQLRQGYAQ	212	CAGAGTGCCCAA CTGAGGCAGGGG TATGCTCAGGCA CAG	470	CAGAGTGCACAA CTCAGACAAGGA TACGCACAAGCA CAG	803
AQLRVGFAQ	123	CAGAGTGCCCAA TTGCGTGTTGGTT TTGCGCAGGCAC AG	471	CAGAGTGCACAA CTCAGAGTCGGA TTCGCACAAGCA CAG	804

AQLSCRSQM	213	CAGAGTGCCCAA CTGTCTGTGTCGGA GTCAGATGGCAC AG	472	CAGAGTGCACAA CTCAGCTGCAGA AGCCAAATGGCA CAG	805
AQLTYSQSL	214	CAGAGTGCCCAA TTGACGTATAGTC AGTCGCTGGCAC AG	473	CAGAGTGCACAA CTCACATACAGC CAAAGCCTCGCA CAG	806
AQLYKGYSQ	215	CAGAGTGCCCAA CTGTATAAGGGTT ATAGTCAGGCAC AG	474	CAGAGTGCACAA CTCTACAAAGGA TACAGCCAAGCA CAG	807
AQMPQRPFL	216	CAGAGTGCCCAA ATGCCTCAGCGG CCGTTTTTGGCAC AG	475	CAGAGTGCACAA ATGCCACAAAGA CCATTCTCGCAC AG	808
AQNGNPGRW	84	CAGAGTGCCCAA AATGGTAATCCG GGGCGGTGGGCA CAG	476	CAGAGTGCACAA AACGGAAACCCA GGAAGATGGGCA CAG	809
AQPEGSARW	60	CAGAGTGCCCAA CCTGAGGGTAGT GCGAGGTGGGCA CAG	477	CAGAGTGCACAA CCAGAAGGAAGC GCAAGATGGGCA CAG	810
AQPLAVYGA	217	CAGAGTGCCCAA CCGTTGGCTGTTT ATGGGGCGGCAC AG	478	CAGAGTGCACAA CCACTCGCAGTCT ACGGAGCAGCAC AG	811
AQPQSSMS	218	CAGAGTGCCCAA CCGAGTCGTCGT CGATGAGTGCAC AG	479	CAGAGTGCACAA CCACAAAGCAGC AGCATGAGCGCA CAG	812
AQPSVGGYW	219	CAGAGTGCCCAA CCGAGTGTGGGT GGGTATTGGGCA CAG	480	CAGAGTGCACAA CCAAGCGTCGGA GGATACTGGGCA CAG	813
AQQAVGQSW	220	CAGAGTGCCCAA CAGGCTGTGGGT CAGTCTTGGGCA CAG	481	CAGAGTGCACAA CAAGCAGTCGGA CAAAGCTGGGCA CAG	814
AQQRSLASG	221	CAGAGTGCCCAA CAGCGTTCGCTG GCTTCGGGTGCA CAG	482	CAGAGTGCACAA CAAAGAAGCCTC GCAAGCGGAGCA CAG	815
AQQVMNSQG	222	CAGAGTGCCCAA CAGGTGATGAAT AGTCAGGGGGCA CAG	483	CAGAGTGCACAA CAAGTCATGAAC AGCCAAGGAGCA CAG	816
AQRGVGLSQ	223	CAGAGTGCCCAA CGTGGGGTTGGG TTGAGTCAGGCA CAG	484	CAGAGTGCACAA AGAGGAGTCGGA CTCAGCCAAGCA CAG	817
AQRHDAEGS	224	CAGAGTGCCCAA AGGCATGATGCG GAGGGTAGTGCA CAG	485	CAGAGTGCACAA AGACACGACGCA GAAGGAAGCGCA CAG	818
AQRKGEPHY	225	CAGAGTGCCCAA CGTAAGGGGGAG CCTCATTATGCAC AG	486	CAGAGTGCACAA AGAAAAGGAGAA CCACACTACGCA CAG	819

AQRYTGDSS	138	CAGAGTGCCCAA AGGTATACGGGG GATTCTAGTGCAC AG	487	CAGAGTGCACAA AGATACACAGGA GACAGCAGCGCA CAG	820
AQSAMAAKG	226	CAGAGTGCCCAA TCGGCGATGGCT GCGAAGGGTGCA CAG	488	CAGAGTGCACAA AGCGCAATGGCA GCAAAAGGAGCA CAG	821
AQSGGLTGS	227	CAGAGTGCCCAA TCTGGGGGTCTTA CGGGGAGTGCAC AG	489	CAGAGTGCACAA AGCGGAGGACTC ACAGGAAGCGCA CAG	822
AQSGGVGVQV	228	CAGAGTGCCCAA TCGGGTGGGGTG GGGCAGGTGGCA CAG	490	CAGAGTGCACAA AGCGGAGGAGTC GGACAAGTCGCA CAG	823
AQSLATPFR	169	CAGAGTGCCCAA TCTCTGGCGACGC CTTTTCGTGCACA G	491	CAGAGTGCACAA AGCCTCGCAACA CCATTCAGAGCA CAG	824
AQMSRPFL	229	CAGAGTGCCCAA AGTATGTCGCGTC CGTTTCTGGCACA G	492	CAGAGTGCACAA AGCATGAGCAGA CCATTCTCGCAC AG	825
AQSQLRPFL	230	CAGAGTGCCCAA AGTCAGCTTAGG CCGTTTCTTGAC AG	493	CAGAGTGCACAA AGCCAACTCAGA CCATTCTCGCAC AG	826
AQSVAKPFL	231	CAGAGTGCCCAA TCTGTGGCTAAGC CTTTTTTGGCACA G	494	CAGAGTGCACAA AGCGTCGCAAAA CCATTCTCGCAC AG	827
AQSVSQPFR	232	CAGAGTGCCCAA TCGGTTTCGCAGC CGTTTAGGGCAC AG	495	CAGAGTGCACAA AGCGTCAGCCAA CCATTCAGAGCA CAG	828
AQSVVRPFL	233	CAGAGTGCCCAA TCTGTGGTGCGTC CTTTTCTGGCACA G	496	CAGAGTGCACAA AGCGTCGTCAGA CCATTCTCGCAC AG	829
AQTALSSST	234	CAGAGTGCCCAA ACTGCGCTTTCGT CGTCGACGGCAC AG	497	CAGAGTGCACAA ACAGCACTCAGC AGCAGCACAGCA CAG	830
AQTEMGGRC	235	CAGAGTGCCCAA ACGGAGATGGGT GGGAGGTGTGCA CAG	498	CAGAGTGCACAA ACAGAAATGGGA GGAAGATGCGCA CAG	831
AQTGFAPPR	161	CAGAGTGCCCAA ACGGGGTTTGCTC CGCCGCGTGCAC AG	499	CAGAGTGCACAA ACAGGATTGCA CCACCAAGAGCA CAG	832
AQTIRGYSS	236	CAGAGTGCCCAA ACGATTCGGGGG TATTCGTCTGCAC AG	500	CAGAGTGCACAA ACAATCAGAGGA TACAGCAGCGCA CAG	833
AQTISNYHT	237	CAGAGTGCCCAA ACTATTTCTAATT ATCATACGGCAC AG	501	CAGAGTGCACAA ACAATCAGCAAC TACCACACAGCA CAG	834

AQTLARPFV	98	CAGAGTGCCCAA ACTTTGGCGCGTC CGTTTGTGGCACA G	502	CAGAGTGCACAA ACACTCGCAAGA CCATTCTGTCGCAC AG	835
AQTLAVPFK (PHP.B)	168	CAGAGTGCCCAA ACTTTGGCGGTGC CTTTTAAGGCACA G	503	CAGAGTGCACAA ACACTCGCAGTC CCATTCAAAGCA CAG	836
AQTPDRPWL	238	CAGAGTGCCCAA ACTCCTGATCGTC CTTGGTTGGCACA G	504	CAGAGTGCACAA ACACCAGACAGA CCATGGCTCGCA CAG	837
AQTRAGYAQ	126	CAGAGTGCCCAA ACTCGGGCTGGG TATGCTCAGGCA CAG	505	CAGAGTGCACAA ACAAGAGCAGGA TACGCACAAGCA CAG	838
AQTRAGYSQ	141	CAGAGTGCCCAA ACTAGGGCGGGG TATTCTCAGGCAC AG	506	CAGAGTGCACAA ACAAGAGCAGGA TACAGCCAAGCA CAG	839
AQTREYLLG	93	CAGAGTGCCCAA ACGCGTGAGTAT CTGCTGGGGGCA CAG	507	CAGAGTGCACAA ACAAGAGAATAC CTCCTCGGAGCA CAG	840
AQTSAPFL	163	CAGAGTGCCCAA ACTTCTGCGAAG CCGTTTCTTGAC AG	508	CAGAGTGCACAA ACAAGCGCAAAA CCATTCTCGCAC AG	841
AQTSARPFL	100	CAGAGTGCCCAA ACTTCTGCTAGGC CTTTTCTGGCACA G	509	CAGAGTGCACAA ACAAGCGCAAGA CCATTCTCGCAC AG	842
AQTTDRPFL	85	CAGAGTGCCCAA ACTACTGATAGG CCTTTTTTGGCAC AG	510	CAGAGTGCACAA ACAACAGACAGA CCATTCTCGCAC AG	843
AQTTEKPWL	83	CAGAGTGCCCAA ACGACTGAGAAG CCGTGGCTGGCA CAG	511	CAGAGTGCACAA ACAACAGAAAAA CCATGGCTCGCA CAG	844
AQTVARPFY	239	CAGAGTGCCCAA ACGGTTGCGCGG CCTTTTATGCAC AG	512	CAGAGTGCACAA ACAGTCGCAAGA CCATTCTACGCAC AG	845
AQTVATPFR	240	CAGAGTGCCCAA ACTGTTGCTACGC CGTTTAGGGCAC AG	513	CAGAGTGCACAA ACAGTCGCAACA CCATTCTAGAGCA CAG	846
AQTVTQLFK	241	CAGAGTGCCCAA ACGGTGACGCAG TTGTTTAAGGCAC AG	514	CAGAGTGCACAA ACAGTCACACAA CTCTCAAAGCAC AG	847
AQVHVGSVY	165	CAGAGTGCCCAA GTTTCATGTTGGGA GTGTTTATGCACA G	515	CAGAGTGCACAA GTCCACGTCGGA AGCGTCTACGCA CAG	848
AQVLAGYNM	242	CAGAGTGCCCAA GTTCTTGCTGGGT ATAATATGGCAC AG	516	CAGAGTGCACAA GTCCTCGCAGGA TACAACATGGCA CAG	849

AQVSEARVR	243	CAGAGTGCCCAA GTTTCTGAGGCG AGGGTTAGGGCA CAG	517	CAGAGTGCACAA GTCAGCGAAGCA AGAGTCAGAGCA CAG	850
AQVVVGYSQ	244	CAGAGTGCCCAA GTTGTGGTGGGTT ATAGTCAGGCAC AG	518	CAGAGTGCACAA GTCGTCGTCGGAT ACAGCCAAGCAC AG	851
AQWAAGYNV	245	CAGAGTGCCCAA TGGGCTGCTGGG TATAATGTGGCA CAG	519	CAGAGTGCACAA TGGGCAGCAGGA TACAACGTCGCA CAG	852
AQWELSNGY	246	CAGAGTGCCCAA TGGGAGCTGAGT AATGGGTATGCA CAG	520	CAGAGTGCACAA TGGGAACTCAGC AACGGATACGCA CAG	853
AQWEVKGGY	247	CAGAGTGCCCAA TGGGAGGTGAAG GGGGGTTATGCA CAG	521	CAGAGTGCACAA TGGGAAGTCAAA GGAGGATACGCA CAG	854
AQWEVKRGY	248	CAGAGTGCCCAA TGGGAGGTGAAG CGGGGGTATGCA CAG	522	CAGAGTGCACAA TGGGAAGTCAAA AGAGGATACGCA CAG	855
AQWEVQSGF	249	CAGAGTGCCCAA TGGGAGGTTTCTAG TCTGGGTTTGCAC AG	523	CAGAGTGCACAA TGGGAAGTCCAA AGCGGATTCGCA CAG	856
AQWEVRGGY	250	CAGAGTGCCCAA TGGGAGGTTCTGT GGTGGTTATGCA CAG	524	CAGAGTGCACAA TGGGAAGTCAGA GGAGGATACGCA CAG	857
AQWEVTSGW	251	CAGAGTGCCCAA TGGGAGGTGACG AGTGGTTGGGCA CAG	525	CAGAGTGCACAA TGGGAAGTCACA AGCGGATGGGCA CAG	858
AQWGAPSHG	252	CAGAGTGCCCAA TGGGGGGCGCCG AGTCATGGGGCA CAG	526	CAGAGTGCACAA TGGGGAGCACCA AGCCACGGAGCA CAG	859
AQWMELGSS	253	CAGAGTGCCCAA TGGATGGAGCTT GGTAGTTCGGCA CAG	527	CAGAGTGCACAA TGGATGGAACTC GGAAGCAGCGCA CAG	860
AQWMFGGSG	254	CAGAGTGCCCAA TGGATGTTTGGG GGTAGTGGGGCA CAG	528	CAGAGTGCACAA TGGATGTTTCGGA GGAAGCGGAGCA CAG	861
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AQWPTAYDA	256	CAGAGTGCCCAA TGGCCGACTGCTT ATGATGCGGCAC AG	530	CAGAGTGCACAA TGGCCAACAGCA TACGACGCAGCA CAG	863
AQWPTS YDA	62	CAGAGTGCCCAA TGGCCTACGAGTT ATGATGCTGCAC AG	531	CAGAGTGCACAA TGGCCAACAAGC TACGACGCAGCA CAG	864

AQWQVQTGF	257	CAGAGTGCCCAA TGGCAGGTTTCAG ACGGGGTTTGCA CAG	532	CAGAGTGCACAA TGGCAAGTCCAA ACAGGATTCGCA CAG	865
AQWSTEGGY	258	CAGAGTGCCCAA TGGTCGACTGAG GGTGGGTATGCA CAG	533	CAGAGTGCACAA TGGAGCACAGAA GGAGGATACGCA CAG	866
AQWTAAGGY	259	CAGAGTGCCCAA TGGACTGCTGCG GGTGGTTATGCA CAG	534	CAGAGTGCACAA TGGACAGCAGCA GGAGGATACGCA CAG	867
AQWTTESGY	260	CAGAGTGCCCAA TGGACGACGGAG TCGGGTATGCAC AG	535	CAGAGTGCACAA TGGACAACAGAA AGCGGATACGCA CAG	868
AQWVYGSSH	261	CAGAGTGCCCAA TGGGTTTATGGG AGTTCGCATGCA CAG	536	CAGAGTGCACAA TGGGTCTACGGA AGCAGCCACGCA CAG	869
AQYLAGYTV	262	CAGAGTGCCCAA TATTTGGCGGGGT ATACGGTGGCAC AG	537	CAGAGTGCACAA TACCTCGCAGGA TACACAGTCGCA CAG	870
AQYLKGYSV	152	CAGAGTGCCCAA TATCTGAAGGGG TATTCTGTGGCAC AG	538	CAGAGTGCACAA TACCTCAAAGGA TACAGCGTCGCA CAG	871
AQYLSGYNT	263	CAGAGTGCCCAA TATTTGTGGGTT ATAATACGGCAC AG	539	CAGAGTGCACAA TACCTCAGCGGA TACAACACAGCA CAG	872
DGAAATTGW	264	CAGAGTGATGGC GCTGCGGCGACT ACTGGGTGGGCA CAG	540	CAGAGTGACGGA GCAGCAGCAACA ACAGGATGGGCA CAG	873
DGAGGTSGW	151	CAGAGTGATGGC GCGGGTGGGACG AGTGGTTGGGCA CAG	541	CAGAGTGACGGA GCAGGAGGAACA AGCGGATGGGCA CAG	874
DGAGTTSW	265	CAGAGTGATGGC GCGGGTACTACTT CGGGTTGGGCAC AG	542	CAGAGTGACGGA GCAGGAACAACA AGCGGATGGGCA CAG	875
DGAHGLSGW	266	CAGAGTGATGGC GCTCATGGGCTGT CGGGGTGGGCAC AG	543	CAGAGTGACGGA GCACACGGACTC AGCGGATGGGCA CAG	876
DGAHVGLSS	267	CAGAGTGATGGC GCTCATGTTGGGC TGTCGTCGGCAC AG	544	CAGAGTGACGGA GCACACGTCGGA CTCAGCAGCGCA CAG	877
DGARTVLQL	268	CAGAGTGATGGC GCTCGGACGGTG CTTCAGTTGGCAC AG	545	CAGAGTGACGGA GCAAGAACAGTC CTCCAACCTCGCAC AG	878
DGEYQKPFR	269	CAGAGTGATGGC GAGTATCAGAAG CCGTTTAGGGCA CAG	546	CAGAGTGACGGA GAATACCAAAAA CCATTCAGAGCA CAG	879

DGGGTTTGW	270	CAGAGTGATGGC GGTGGGACTACG ACGGGGTGGGCA CAG	547	CAGAGTGACGGA GGAGGAACAACA ACAGGATGGGCA CAG	880
DGHATSMGW	271	CAGAGTGATGGC CATGCGACGAGT ATGGGTGGGCA CAG	548	CAGAGTGACGGA CACGCAACAAGC ATGGGATGGGCA CAG	881
DGKGSTQGW	272	CAGAGTGATGGC AAGGGTTCGACG CAGGGGTGGGCA CAG	549	CAGAGTGACGGA AAAGGAAGCACA CAAGGATGGGCA CAG	882
DGKQYQLSS	92	CAGAGTGATGGC AAGCAGTATCAG CTGTCTTCGGCAC AG	550	CAGAGTGACGGA AAACAATACCAA CTCAGCAGCGCA CAG	883
DGNGGLKGW	167	CAGAGTGATGGC AATGGTGGGTTG AAGGGGTGGGCA CAG	551	CAGAGTGACGGA AACGGAGGACTC AAAGGATGGGCA CAG	884
DGQGGLSGW	273	CAGAGTGATGGC CAGGGGGGTTTG TCTGGGTGGGCA CAG	552	CAGAGTGACGGA CAAGGAGGACTC AGCGGATGGGCA CAG	885
DGQHFAPPR	110	CAGAGTGATGGC CAGCATTTTGCTC CGCCGCGGGCAC AG	553	CAGAGTGACGGA CAACACTTCGCA CCACCAAGAGCA CAG	886
DGRATKTLY	274	CAGAGTGATGGC CGTGCGACTAAG ACGCTTTATGCAC AG	554	CAGAGTGACGGA AGAGCAACAAAA ACACTCTACGCA CAG	887
DGRNALTGW	275	CAGAGTGATGGC CGTAATGCGTTG ACGGGGTGGGCA CAG	555	CAGAGTGACGGA AGAAACGCACTC ACAGGATGGGCA CAG	888
DGRRQVIQL	276	CAGAGTGATGGC AGGAGGCAGGTG ATTCAGCTGGCA CAG	556	CAGAGTGACGGA AGAAGACAAGTC ATCCAACCTCGCA CAG	889
DGRVYGLSS	277	CAGAGTGATGGC AGGGTTTATGGTC TTTCGTCCGCACA G	557	CAGAGTGACGGA AGAGTCTACGGA CTCAGCAGCGCA CAG	890
DGSGRTTGW	147	CAGAGTGATGGC AGTGGGCGTACG ACGGGTGGGCA CAG	558	CAGAGTGACGGA AGCGGAAGAACA ACAGGATGGGCA CAG	891
DSGTTRGW	114	CAGAGTGATGGC TCTGGTACGACG CGGGGTGGGCA CAG	559	CAGAGTGACGGA AGCGGAACAACA AGAGGATGGGCA CAG	892
DSGTVSGW	278	CAGAGTGATGGC TCGGGTACGGTT AGTGGGTGGGCA CAG	560	CAGAGTGACGGA AGCGGAACAGTC AGCGGATGGGCA CAG	893
DGSPEKPFR	160	CAGAGTGATGGC AGTCCGGAGAAG CCGTTTCGGGCAC AG	561	CAGAGTGACGGA AGCCCAGAAAAA CCATTCAGAGCA CAG	894

DGSQSTTGW	136	CAGAGTGATGGC AGTCAGTCTACTA CGGGGTGGGCAC AG	562	CAGAGTGACGGA AGCCAAAGCACA ACAGGATGGGCA CAG	895
DGSSFYPPK	127	CAGAGTGATGGC AGTAGTTTTTATC CTCCTAAGGCAC AG	563	CAGAGTGACGGA AGCAGCTTCTACC CACCAAAGGCAC AG	896
DGSSSYDA	64	CAGAGTGATGGC AGTAGTTCTTATT ATGATGCGGCAC AG	564	CAGAGTGACGGA AGCAGCAGCTAC TACGACGCAGCA CAG	897
DGSTERPFR	99	CAGAGTGATGGC TCTACGGAGAGG CCGTTTAGGGCA CAG	565	CAGAGTGACGGA AGCACAGAAAGA CCATTCAGAGCA CAG	898
DGTAARLSS	132	CAGAGTGATGGC ACCGCGGCTCGG CTGTCGTCGGCAC AG	566	CAGAGTGACGGA ACAGCAGCAAGA CTCAGCAGCGCA CAG	899
DGTADKPFR	63	CAGAGTGATGGC ACCGCTGATAAG CCGTTTCGGGCAC AG	567	CAGAGTGACGGA ACAGCAGACAAA CCATTCAGAGCA CAG	900
DGTADRPFR	155	CAGAGTGATGGC ACGGCGGATCGT CCTTTTCGGGCAC AG	568	CAGAGTGACGGA ACAGCAGACAGA CCATTCAGAGCA CAG	901
DGTAERPFR	140	CAGAGTGATGGC ACCGCGGAGAGG CCTTTTAGGGCAC AG	569	CAGAGTGACGGA ACAGCAGAAAGA CCATTCAGAGCA CAG	902
DGTAIHLSS	67	CAGAGTGATGGC ACCGCGATTCATC TTTCGTCTGCACA G	570	CAGAGTGACGGA ACAGCAATCCAC CTCAGCAGCGCA CAG	903
DGTAIYLSS	279	CAGAGTGATGGC ACCGCGATTTATC TGTCTTCTGCACA G	571	CAGAGTGACGGA ACAGCAATCTAC CTCAGCAGCGCA CAG	904
DGTALMLSS	280	CAGAGTGATGGC ACCGCTCTTATGT TGTCGTCTGCACA G	572	CAGAGTGACGGA ACAGCAATCTATG CTCAGCAGCGCA CAG	905
DGTASISGW	281	CAGAGTGATGGC ACCGCGAGTATT AGTGTTGGGCA CAG	573	CAGAGTGACGGA ACAGCAAGCATC AGCGGATGGGCA CAG	906
DGTASTSGW	282	CAGAGTGATGGC ACCGCGTCGACG AGTGGTGGGCA CAG	574	CAGAGTGACGGA ACAGCAAGCACA AGCGGATGGGCA CAG	907
DGTASVTGW	283	CAGAGTGATGGC ACCGCGTCGGTG ACGGGTGGGCA CAG	575	CAGAGTGACGGA ACAGCAAGCGTC ACAGGATGGGCA CAG	908
DGTASYIDS	61	CAGAGTGATGGC ACCGCGAGTTATT ATGATTCTGCACA G	576	CAGAGTGACGGA ACAGCAAGCTAC TACGACAGCGCA CAG	909

DGTATTMGW	284	CAGAGTGATGGC ACCGCGACGACG ATGGGGTGGGCA CAG	577	CAGAGTGACGGA ACAGCAACAACA ATGGGATGGGCA CAG	910
DGTATTTGW	285	CAGAGTGATGGC ACCGCGACGACG ACGGGTGGGCA CAG	578	CAGAGTGACGGA ACAGCAACAACA ACAGGATGGGCA CAG	911
DGTAYRLSS	286	CAGAGTGATGGC ACCGCGTATCGTT TGTCGTCTGCACA G	579	CAGAGTGACGGA ACAGCATAACAGA CTCAGCAGCGCA CAG	912
DGTDKMWSI	287	CAGAGTGATGGC ACCGATAAGATG TGGAGTATTGCA CAG	580	CAGAGTGACGGA ACAGACAAAATG TGGAGCATCGCA CAG	913
DGTGGIKGW	131	CAGAGTGATGGC ACCGGTGGTATT AAGGGTGGGCA CAG	581	CAGAGTGACGGA ACAGGAGGAATC AAAGGATGGGCA CAG	914
DGTGGIMGW	288	CAGAGTGATGGC ACCGGGGGGATT ATGGGTGGGCA CAG	582	CAGAGTGACGGA ACAGGAGGAATC ATGGGATGGGCA CAG	915
DGTGGISGW	289	CAGAGTGATGGC ACCGGTGGGATT TCGGGTGGGCA CAG	583	CAGAGTGACGGA ACAGGAGGAATC AGCGGATGGGCA CAG	916
DGTGGLAGW	290	CAGAGTGATGGC ACCGGGGGTCTT GCTGGTTGGGCA CAG	584	CAGAGTGACGGA ACAGGAGGACTC GCAGGATGGGCA CAG	917
DGTGGLHGW	291	CAGAGTGATGGC ACCGGGGGGTTG CATGGTTGGGCA CAG	585	CAGAGTGACGGA ACAGGAGGACTC CACGGATGGGCA CAG	918
DGTGGLQGW	292	CAGAGTGATGGC ACCGGGGGTTTG CAGGGTTGGGCA CAG	586	CAGAGTGACGGA ACAGGAGGACTC CAAGGATGGGCA CAG	919
DGTGGLRGW	154	CAGAGTGATGGC ACCGGGGGTTTG CGTGGTTGGGCA CAG	587	CAGAGTGACGGA ACAGGAGGACTC AGAGGATGGGCA CAG	920
DGTGGLSGW	293	CAGAGTGATGGC ACCGGTGGGTTG TCGGGTGGGCA CAG	588	CAGAGTGACGGA ACAGGAGGACTC AGCGGATGGGCA CAG	921
DGTGGLTGW	294	CAGAGTGATGGC ACCGGGGGGTTG ACGGTTGGGCA CAG	589	CAGAGTGACGGA ACAGGAGGACTC ACAGGATGGGCA CAG	922
DGTGGTKGW	107	CAGAGTGATGGC ACCGGTGGGACT AAGGGTGGGCA CAG	590	CAGAGTGACGGA ACAGGAGGAACA AAAGGATGGGCA CAG	923
DGTGGTSGW	295	CAGAGTGATGGC ACCGGGGGGACG AGTGGTTGGGCA CAG	591	CAGAGTGACGGA ACAGGAGGAACA AGCGGATGGGCA CAG	924

DGTGGVHGW	296	CAGAGTGATGGC ACCGGTGGGGTG CATGGTTGGGCA CAG	592	CAGAGTGACGGA ACAGGAGGAGTC CACGGATGGGCA CAG	925
DGTGGVMGW	297	CAGAGTGATGGC ACCGGTGGTGT ATGGGGTGGGCA CAG	593	CAGAGTGACGGA ACAGGAGGAGTC ATGGGATGGGCA CAG	926
DGTGGVSGW	298	CAGAGTGATGGC ACCGGGGGGGTG TCTGGTTGGGCAC AG	594	CAGAGTGACGGA ACAGGAGGAGTC AGCGGATGGGCA CAG	927
DGTGGVTGW	299	CAGAGTGATGGC ACCGGTGGTGTG ACGGGGTGGGCA CAG	595	CAGAGTGACGGA ACAGGAGGAGTC ACAGGATGGGCA CAG	928
DGTGGVYGW	300	CAGAGTGATGGC ACCGGTGGTGTG TATGGGTGGGCA CAG	596	CAGAGTGACGGA ACAGGAGGAGTC TACGGATGGGCA CAG	929
DGTGNLQGW	301	CAGAGTGATGGC ACCGGTAATTTGC AGGGTTGGGCAC AG	597	CAGAGTGACGGA ACAGGAAACCTC CAAGGATGGGCA CAG	930
DGTGNLRGW	133	CAGAGTGATGGC ACCGGGAATCTT AGGGGGTGGGCA CAG	598	CAGAGTGACGGA ACAGGAAACCTC AGAGGATGGGCA CAG	931
DGTGNLSGW	302	CAGAGTGATGGC ACCGGGAATTTG AGTGGGTGGGCA CAG	599	CAGAGTGACGGA ACAGGAAACCTC AGCGGATGGGCA CAG	932
DGTGNTHGW	72	CAGAGTGATGGC ACCGGGAATACT CATGGGTGGGCA CAG	600	CAGAGTGACGGA ACAGGAAACACA CACGGATGGGCA CAG	933
DGTGNTRGW	94	CAGAGTGATGGC ACCGGGAATACT CGGGGGTGGGCA CAG	601	CAGAGTGACGGA ACAGGAAACACA AGAGGATGGGCA CAG	934
DGTGNTSGW	137	CAGAGTGATGGC ACCGGTAATACT AGTGGTTGGGCA CAG	602	CAGAGTGACGGA ACAGGAAACACA AGCGGATGGGCA CAG	935
DGTGNVSGW	303	CAGAGTGATGGC ACCGGGAATGTG TCGGGGTGGGCA CAG	603	CAGAGTGACGGA ACAGGAAACGTC AGCGGATGGGCA CAG	936
DGTGNVTGW	69	CAGAGTGATGGC ACCGGTAATGTG ACGGGGTGGGCA CAG	604	CAGAGTGACGGA ACAGGAAACGTC ACAGGATGGGCA CAG	937
DGTGQLVGW	304	CAGAGTGATGGC ACCGGGCAGCTT GTGGGTGGGCA CAG	605	CAGAGTGACGGA ACAGGACAACTC GTCGGATGGGCA CAG	938
DGTGQTIGW	305	CAGAGTGATGGC ACCGGTCAGACG ATTGGTTGGGCA CAG	606	CAGAGTGACGGA ACAGGACAAACA ATCGGATGGGCA CAG	939

DGTGQVTGW	68	CAGAGTGATGGC ACCGGGCAGGTG ACTGGGTGGGCA CAG	607	CAGAGTGACGGA ACAGGACAAGTC ACAGGATGGGCA CAG	940
DGTGRLTGW	159	CAGAGTGATGGC ACCGGTCGGTTG ACGGGTGGGCA CAG	608	CAGAGTGACGGA ACAGGAAGACTC ACAGGATGGGCA CAG	941
DGTGRTVGW	117	CAGAGTGATGGC ACCGGTCGGACT GTTGGGTGGGCA CAG	609	CAGAGTGACGGA ACAGGAAGAACA GTCGGATGGGCA CAG	942
DGTGSGMMT	306	CAGAGTGATGGC ACCGGTTCCGGT ATGATGACGGCA CAG	610	CAGAGTGACGGA ACAGGAAGCGGA ATGATGACAGCA CAG	943
DGTGSISGW	307	CAGAGTGATGGC ACCGGGTCGATT AGTGGGTGGGCA CAG	611	CAGAGTGACGGA ACAGGAAGCATC AGCGGATGGGCA CAG	944
DGTGSLAGW	308	CAGAGTGATGGC ACCGGTTCTTTGG CGGGTGGGCAC AG	612	CAGAGTGACGGA ACAGGAAGCCTC GCAGGATGGGCA CAG	945
DGTGSLNGW	309	CAGAGTGATGGC ACCGGGTCTTTGA ATGGGTGGGCAC AG	613	CAGAGTGACGGA ACAGGAAGCCTC AACGGATGGGCA CAG	946
DGTGSLQGW	310	CAGAGTGATGGC ACCGGGTCGCTG CAGGGTTGGGCA CAG	614	CAGAGTGACGGA ACAGGAAGCCTC CAAGGATGGGCA CAG	947
DGTGSLSGW	311	CAGAGTGATGGC ACCGGGAGTCTG TCGGGTGGGCA CAG	615	CAGAGTGACGGA ACAGGAAGCCTC AGCGGATGGGCA CAG	948
DGTGSLVGW	312	CAGAGTGATGGC ACCGGGTCGTTG GTGGGTGGGCA CAG	616	CAGAGTGACGGA ACAGGAAGCCTC GTCGGATGGGCA CAG	949
DGTGSTHGW	119	CAGAGTGATGGC ACCGGGAGTACG CATGGGTGGGCA CAG	617	CAGAGTGACGGA ACAGGAAGCACA CACGGATGGGCA CAG	950
DGTGSTKGW	313	CAGAGTGATGGC ACCGGGAGTACT AAGGGTGGGCA CAG	618	CAGAGTGACGGA ACAGGAAGCACA AAAGGATGGGCA CAG	951
DGTGSTMGW	314	CAGAGTGATGGC ACCGGTTCTACTA TGGGTGGGCAC AG	619	CAGAGTGACGGA ACAGGAAGCACA ATGGGATGGGCA CAG	952
DGTGSTQGW	315	CAGAGTGATGGC ACCGGTAGTACG CAGGGTTGGGCA CAG	620	CAGAGTGACGGA ACAGGAAGCACA CAAGGATGGGCA CAG	953
DGTGSTSGW	316	CAGAGTGATGGC ACCGGGAGTACT TCGGGTGGGCA CAG	621	CAGAGTGACGGA ACAGGAAGCACA AGCGGATGGGCA CAG	954

DGTGSTTGW	134	CAGAGTGATGGC ACCGGGAGTACG ACGGGGTGGGCA CAG	622	CAGAGTGACGGA ACAGGAAGCACA ACAGGATGGGCA CAG	955
DGTGSVMGW	317	CAGAGTGATGGC ACCGGTTTCGGTTA TGGGGTGGGCAC AG	623	CAGAGTGACGGA ACAGGAAGCGTC ATGGGATGGGCA CAG	956
DGTGSVTGW	318	CAGAGTGATGGC ACCGGGTCTGTG ACTGGGTGGGCA CAG	624	CAGAGTGACGGA ACAGGAAGCGTC ACAGGATGGGCA CAG	957
DGTGTLAGW	319	CAGAGTGATGGC ACCGGGACGCTT GCGGGTGGGCA CAG	625	CAGAGTGACGGA ACAGGAACACTC GCAGGATGGGCA CAG	958
DGTGTLHGW	320	CAGAGTGATGGC ACCGGTACTTTGC ATGGTTGGGCAC AG	626	CAGAGTGACGGA ACAGGAACACTC CACGGATGGGCA CAG	959
DGTGTLKGW	321	CAGAGTGATGGC ACCGGTACTCTTA AGGGTTGGGCAC AG	627	CAGAGTGACGGA ACAGGAACACTC AAAGGATGGGCA CAG	960
DGTGTLSGW	322	CAGAGTGATGGC ACCGGGACTCTG TCGGGTGGGCA CAG	628	CAGAGTGACGGA ACAGGAACACTC AGCGGATGGGCA CAG	961
DGTGTTLGW	323	CAGAGTGATGGC ACCGGGACTACG CTGGGGTGGGCA CAG	629	CAGAGTGACGGA ACAGGAACAACA CTCGGATGGGCA CAG	962
DGTGTTMGW	324	CAGAGTGATGGC ACCGGGACTACT ATGGGTGGGCA CAG	630	CAGAGTGACGGA ACAGGAACAACA ATGGGATGGGCA CAG	963
DGTGTTTGW	130	CAGAGTGATGGC ACCGGGACTACT ACGGGGTGGGCA CAG	631	CAGAGTGACGGA ACAGGAACAACA ACAGGATGGGCA CAG	964
DGTGTTVGW	74	CAGAGTGATGGC ACCGGTACTACG GTGGGGTGGGCA CAG	632	CAGAGTGACGGA ACAGGAACAACA GTCGGATGGGCA CAG	965
DGTGTTYGW	325	CAGAGTGATGGC ACCGGGACGACG TATGGTTGGGCA CAG	633	CAGAGTGACGGA ACAGGAACAACA TACGGATGGGCA CAG	966
DGTGTVHGW	326	CAGAGTGATGGC ACCGGTACGGTT CATGGTTGGGCA CAG	634	CAGAGTGACGGA ACAGGAACAGTC CACGGATGGGCA CAG	967
DGTGTVQGW	327	CAGAGTGATGGC ACCGGGACTGTG CAGGGGTGGGCA CAG	635	CAGAGTGACGGA ACAGGAACAGTC CAAGGATGGGCA CAG	968
DGTGTVSGW	328	CAGAGTGATGGC ACCGGTACTGTTT CTGGTTGGGCAC AG	636	CAGAGTGACGGA ACAGGAACAGTC AGCGGATGGGCA CAG	969

DGTGTVTGW	329	CAGAGTGATGGC ACCGGTACTGTTA CTGGGTGGGCAC AG	637	CAGAGTGACGGA ACAGGAACAGTC ACAGGATGGGCA CAG	970
DGTHARLSS	330	CAGAGTGATGGC ACCCATGCGAGG TTGTCTTCGGCAC AG	638	CAGAGTGACGGA ACACACGCAAGA CTCAGCAGCGCA CAG	971
DGTHAYMAS	153	CAGAGTGATGGC ACCCATGCTTATA TGGCGTCTGCAC AG	639	CAGAGTGACGGA ACACACGCATAC ATGGCAAGCGCA CAG	972
DGTHFAPPR	112	CAGAGTGATGGC ACCCATTTTGGCG CGCCGCGTGCAC AG	640	CAGAGTGACGGA ACACACTTCGCA CCACCAAGAGCA CAG	973
DGTHIHLSS	162	CAGAGTGATGGC ACCCATATTTCATC TGAGTAGTGCAC AG	641	CAGAGTGACGGA ACACACATCCAC CTCAGCAGCGCA CAG	974
DGTHIRALS	331	CAGAGTGATGGC ACCCATATTAGG GCTCTGAGTGCA CAG	642	CAGAGTGACGGA ACACACATCAGA GCACTCAGCGCA CAG	975
DGTHIRLAS	332	CAGAGTGATGGC ACCCATATTTCGTT TGGCGAGTGCAC AG	643	CAGAGTGACGGA ACACACATCAGA CTCGCAAGCGCA CAG	976
DGTHLQFPR	333	CAGAGTGATGGC ACCCATCTGCAG CCGTTTAGGGCA CAG	644	CAGAGTGACGGA ACACACCTCCAA CCATTCAGAGCA CAG	977
DGTHSFYDA	334	CAGAGTGATGGC ACCCATAGTTTTT ATGATGCGGCAC AG	645	CAGAGTGACGGA ACACACAGCTTCT ACGACGAGCAC AG	978
DGTHSTTGW	145	CAGAGTGATGGC ACCCATTCTACTA CGGGTTGGGCAC AG	646	CAGAGTGACGGA ACACACAGCACA ACAGGATGGGCA CAG	979
DGTHTRTGW	90	CAGAGTGATGGC ACCCATACGCGG ACGGGTTGGGCA CAG	647	CAGAGTGACGGA ACACACACAAGA ACAGGATGGGCA CAG	980
DGTHVRALS	335	CAGAGTGATGGC ACCCATGTTAGG GCGTTGTCGGCA CAG	648	CAGAGTGACGGA ACACACGTCAGA GCACTCAGCGCA CAG	981
DGTHVYMAS	336	CAGAGTGATGGC ACCCATGTTTATA TGGCTAGTGCAC AG	649	CAGAGTGACGGA ACACACGTCTAC ATGGCAAGCGCA CAG	982
DGTHVYMSS	337	CAGAGTGATGGC ACCCATGTGTATA TGTCTAGTGCACA G	650	CAGAGTGACGGA ACACACGTCTAC ATGAGCAGCGCA CAG	983
DGTIALPFK	338	CAGAGTGATGGC ACCATGCGCTTC CGTTTAAGGCAC AG	651	CAGAGTGACGGA ACAATCGCACTC CCATTCAAAGCA CAG	984

DGTIALPFR	339	CAGAGTGATGGC ACCATTGCTTTGC CGTTTAGGGCAC AG	652	CAGAGTGACGGA ACAATCGCACTC CCATTCAGAGCA CAG	985
DGTIATRYV	340	CAGAGTGATGGC ACCATTGCGACG CGGTATGTGGCA CAG	653	CAGAGTGACGGA ACAATCGCAACA AGATACGTCGCA CAG	986
DGTIERPFR	87	CAGAGTGATGGC ACCATTGAGCGG CCTTTTCGTGCAC AG	654	CAGAGTGACGGA ACAATCGAAAGA CCATTCAGAGCA CAG	987
DGTIGYAYV	341	CAGAGTGATGGC ACCATTGTTATG CGTATGTTGCACA G	655	CAGAGTGACGGA ACAATCGGATAC GCATACGTCGCA CAG	988
DGTIQAPFK	342	CAGAGTGATGGC ACCATTCAGGCTC CGTTTAAGGCAC AG	656	CAGAGTGACGGA ACAATCCAAGCA CCATTCAAAGCA CAG	989
DGTIRLPFK	343	CAGAGTGATGGC ACCATTCGTCTTC CTTTTAAGGCACA G	657	CAGAGTGACGGA ACAATCAGACTC CCATTCAAAGCA CAG	990
DGTISKEVG	344	CAGAGTGATGGC ACCATTTCTAAGG AGGTGGGGGCAC AG	658	CAGAGTGACGGA ACAATCAGCAAA GAAGTCGGAGCA CAG	991
DGTISQPFK	105	CAGAGTGATGGC ACCATTTTCGCAGC CTTTTAAGGCACA G	659	CAGAGTGACGGA ACAATCAGCCAA CCATTCAAAGCA CAG	992
DGTKIQLSS	146	CAGAGTGATGGC ACCAAGATTCAG CTGTCTAGTGCAC AG	660	CAGAGTGACGGA ACAAAAATCCAA CTCAGCAGCGCA CAG	993
DGTKIRLSS	111	CAGAGTGATGGC ACCAAGATTCGG TTGTCGTCTGCAC AG	661	CAGAGTGACGGA ACAAAAATCAGA CTCAGCAGCGCA CAG	994
DGTKLMLSS	157	CAGAGTGATGGC ACCAAGCTGATG TTGAGTAGTGCA CAG	662	CAGAGTGACGGA ACAAAATCATG CTCAGCAGCGCA CAG	995
DGTKLRLSS	118	CAGAGTGATGGC ACCAAGTTGAGG CTTAGTTCTGCAC AG	663	CAGAGTGACGGA ACAAAATCAGA CTCAGCAGCGCA CAG	996
DGTKMVLQL	142	CAGAGTGATGGC ACCAAGATGGTG TTGCAGCTGGCA CAG	664	CAGAGTGACGGA ACAAAAATGGTC CTCCAATCGCAC AG	997
DGTKSLVQL	345	CAGAGTGATGGC ACCAAGAGTCTT GTGCAGCTTGCA CAG	665	CAGAGTGACGGA ACAAAAGCCTC GTCCAATCGCA CAG	998
DGTKVLVQL	122	CAGAGTGATGGC ACCAAGGTGCTG GTGCAGTTGGCA CAG	666	CAGAGTGACGGA ACAAAAGTCCTC GTCCAATCGCA CAG	999

DGTLAAPFK	120	CAGAGTGATGGC ACCTTGGCTGCTC CTTTTAAGGCACA G	667	CAGAGTGACGGA ACACTCGCAGCA CCATTCAAAGCA CAG	1000
DGTLAVNFK	346	CAGAGTGATGGG ACTTTGGCGGTG AATTTTAAGGCA CAG	668	CAGAGTGACGGA ACACTCGCAGTC AACTTCAAAGCA CAG	1001
DGTLAVPFK (PHP.eB)	71	CAGAGTGATGGG ACTTTGGCGGTGC CTTTTAAGGCACA G	669	CAGAGTGACGGA ACACTCGCAGTC CCATTCAAAGCA CAG	1002
DGTLAYPFK	347	CAGAGTGATGGC ACCCTTGCGTATC CTTTTAAGGCACA G	670	CAGAGTGACGGA ACACTCGCATAC CCATTCAAAGCA CAG	1003
DGTLERPFR	156	CAGAGTGATGGC ACCCTGGAGAGG CCGTTTCGGGCAC AG	671	CAGAGTGACGGA ACACTCGAAAGA CCATTCAGAGCA CAG	1004
DGTLVHFK	348	CAGAGTGATGGG ACTTTGGAGGTG CATTTTAAGGCAC AG	672	CAGAGTGACGGA ACACTCGAAGTC CACTTCAAAGCA CAG	1005
DGTLRLSS	121	CAGAGTGATGGC ACCTTGCTGAGG CTGAGTAGTGCA CAG	673	CAGAGTGACGGA ACACTCCTCAGA CTCAGCAGCGCA CAG	1006
DGTLNNPFR	109	CAGAGTGATGGC ACCTTGAATAATC CGTTTAGGGCAC AG	674	CAGAGTGACGGA ACACTCAACAAC CCATTCAGAGCA CAG	1007
DGTLQQPFR	89	CAGAGTGATGGC ACCTTGCAGCAG CCGTTTCGGGCAC AG	675	CAGAGTGACGGA ACACTCCAACAA CCATTCAGAGCA CAG	1008
DGTLSPFR	65	CAGAGTGATGGC ACCCTGTCTCAGC CTTTTAGGGCAC G	676	CAGAGTGACGGA ACACTCAGCCAA CCATTCAGAGCA CAG	1009
DGTLSTRWL	349	CAGAGTGATGGC ACCTTGTCGCGTA CGCTTTGGGCAC AG	677	CAGAGTGACGGA ACACTCAGCAGA ACACTCTGGGCA CAG	1010
DGTLSSPFR	350	CAGAGTGATGGC ACCCTGTCTAGTC CGTTTAGGGCAC AG	678	CAGAGTGACGGA ACACTCAGCAGC CCATTCAGAGCA CAG	1011
DGTLTVPFR	351	CAGAGTGATGGC ACCTTGACGGTTC CTTTTCGGGCACA G	679	CAGAGTGACGGA ACACTCACAGTC CCATTCAGAGCA CAG	1012
DGTLVAPFR	352	CAGAGTGATGGC ACCCTTGTTGCGC CGTTTAGGGCAC AG	680	CAGAGTGACGGA ACACTCGTCGCA CCATTCAGAGCA CAG	1013
DGTMCKPFR	70	CAGAGTGATGGC ACGATGGATAAG CCTTTTAGGGCAC AG	681	CAGAGTGACGGA ACAATGGACAAA CCATTCAGAGCA CAG	1014

DGTMDRPFK	102	CAGAGTGATGGC ACCATGGATAGG CCGTTTAAGGCA CAG	682	CAGAGTGACGGA ACAATGGACAGA CCATTCAAAGCA CAG	1015
DGTMLRLSS	148	CAGAGTGATGGC ACCATGTTGCGTC TTAGTTCGGCACA G	683	CAGAGTGACGGA ACAATGCTCAGA CTCAGCAGCGCA CAG	1016
DGTMQLTGW	353	CAGAGTGATGGC ACCATGCAGCTT ACGGGGTGGGCA CAG	684	CAGAGTGACGGA ACAATGCAACTC ACAGGATGGGCA CAG	1017
DGTNGLKGW	76	CAGAGTGATGGC ACCAATGGTCTG AAGGGGTGGGCA CAG	685	CAGAGTGACGGA ACAAACGGACTC AAAGGATGGGCA CAG	1018
DGTNSISGW	354	CAGAGTGATGGC ACCAATAGTATT AGTGGGTGGGCA CAG	686	CAGAGTGACGGA ACAAACAGCATC AGCGGATGGGCA CAG	1019
DGTNSLSGW	355	CAGAGTGATGGC ACCAATTCTCTGT CGGGTTGGGCAC AG	687	CAGAGTGACGGA ACAAACAGCCTC AGCGGATGGGCA CAG	1020
DGTNSTTGW	143	CAGAGTGATGGC ACCAATTCTACG ACGGGTGGGCA CAG	688	CAGAGTGACGGA ACAAACAGCACA ACAGGATGGGCA CAG	1021
DGTNSVTGW	356	CAGAGTGATGGC ACCAATAGTGTT ACGGGTGGGCA CAG	689	CAGAGTGACGGA ACAAACAGCGTC ACAGGATGGGCA CAG	1022
DGTNTINGW	124	CAGAGTGATGGC ACCAATACTATTA ATGGGTGGGCAC AG	690	CAGAGTGACGGA ACAAACACAATC AACGGATGGGCA CAG	1023
DGTNTLGGW	357	CAGAGTGATGGC ACCAATACGTTG GGGGGTGGGCA CAG	691	CAGAGTGACGGA ACAAACACACTC GGAGGATGGGCA CAG	1024
DGTNTTHGW	113	CAGAGTGATGGC ACCAATACTACTC ATGGGTGGGCAC AG	692	CAGAGTGACGGA ACAAACACAACA CACGGATGGGCA CAG	1025
DGTNYRLSS	358	CAGAGTGATGGC ACCAATTATAGG CTGTCGAGTGCA CAG	693	CAGAGTGACGGA ACAAACTACAGA CTCAGCAGCGCA CAG	1026
DGTQALSGW	359	CAGAGTGATGGC ACCCAGGCGCTG TCGGGGTGGGCA CAG	694	CAGAGTGACGGA ACACAAGCACTC AGCGGATGGGCA CAG	1027
DGTQFRLSS	129	CAGAGTGATGGC ACCCAGTTTAGGT TGTCTTCGGCACA G	695	CAGAGTGACGGA ACACAATTCAGA CTCAGCAGCGCA CAG	1028
DGTQFSPPR	108	CAGAGTGATGGC ACCCAGTTTAGTC CTCCGCGTGCAC AG	696	CAGAGTGACGGA ACACAATTCAGC CCACCAAGAGCA CAG	1029

DGTQGLKGW	158	CAGAGTGATGGC ACCCAGGGGCTG AAGGGGTGGGCA CAG	697	CAGAGTGACGGA ACACAAGGACTC AAAGGATGGGCA CAG	1030
DGTQTTSGW	360	CAGAGTGATGGC ACCCAGACTACG AGTGGGTGGGCA CAG	698	CAGAGTGACGGA ACACAAACAACA AGCGGATGGGCA CAG	1031
DGTRALTGW	361	CAGAGTGATGGC ACCAGGGCTCTT ACGGGTGGGCA CAG	699	CAGAGTGACGGA ACAAGAGCACTC ACAGGATGGGCA CAG	1032
DGTRFSLSS	362	CAGAGTGATGGC ACCCGGTTTTTCGC TTTCGAGTGCACA G	700	CAGAGTGACGGA ACAAGATTCAGC CTCAGCAGCGCA CAG	1033
DGTRGLSGW	363	CAGAGTGATGGC ACCAGGGGGTTG TCGGGTGGGCA CAG	701	CAGAGTGACGGA ACAAGAGGACTC AGCGGATGGGCA CAG	1034
DGTRIGLSS	364	CAGAGTGATGGC ACCAGGATTGGG CTGAGTAGTGCA CAG	702	CAGAGTGACGGA ACAAGAATCGGA CTCAGCAGCGCA CAG	1035
DGTRLHLAS	365	CAGAGTGATGGC ACCAGGCTTCATC TGGCGAGTGCAC AG	703	CAGAGTGACGGA ACAAGACTCCAC CTCGCAAGCGCA CAG	1036
DGTRLHLSS	366	CAGAGTGATGGC ACCAGGCTTCATC TGTCGTCGGCAC AG	704	CAGAGTGACGGA ACAAGACTCCAC CTCAGCAGCGCA CAG	1037
DGTRLLLSS	367	CAGAGTGATGGC ACCCGTTTGCTGC TGTCGAGTGCAC AG	705	CAGAGTGACGGA ACAAGACTCCTC CTCAGCAGCGCA CAG	1038
DGTRLMLSS	368	CAGAGTGATGGC ACCCGTTTGATGC TTTCTAGTGCACA G	706	CAGAGTGACGGA ACAAGACTCATG CTCAGCAGCGCA CAG	1039
DGTRLNLSS	369	CAGAGTGATGGC ACCCGTTTGAATC TTAGTTCGGCAC G	707	CAGAGTGACGGA ACAAGACTCAAC CTCAGCAGCGCA CAG	1040
DGTRMVVQL	370	CAGAGTGATGGC ACCCGGATGGTT GTTTCAGCTGCAC AG	708	CAGAGTGACGGA ACAAGAATGGTC GTCCAACCTCGCA CAG	1041
DGTRNMYEG	135	CAGAGTGATGGC ACCCGTAATATGT ATGAGGGGGCAC AG	709	CAGAGTGACGGA ACAAGAAACATG TACGAAGGAGCA CAG	1042
DGTRSITGW	371	CAGAGTGATGGC ACCAGGAGTATT ACGGGTGGGCA CAG	710	CAGAGTGACGGA ACAAGAAGCATC ACAGGATGGGCA CAG	1043
DGTRSLHWG	372	CAGAGTGATGGC ACCAGGAGTTTG CATGGGTGGGCA CAG	711	CAGAGTGACGGA ACAAGAAGCCTC CACGGATGGGCA CAG	1044

DGTRSTTGW	373	CAGAGTGATGGC ACCCGGAGTACT ACGGGTGGGCA CAG	712	CAGAGTGACGGA ACAAGAAGCACA ACAGGATGGGCA CAG	1045
DGTRTTTGW	106	CAGAGTGATGGC ACCCGTACTACG ACGGGTGGGCA CAG	713	CAGAGTGACGGA ACAAGAACAACA ACAGGATGGGCA CAG	1046
DGTRIVTGW	374	CAGAGTGATGGC ACCCGGACGGTG ACTGGTGGGCA CAG	714	CAGAGTGACGGA ACAAGAACAGTC ACAGGATGGGCA CAG	1047
DGTRTVVQL	375	CAGAGTGATGGC ACCCGTACTGTG GTGCAGTTGGCA CAG	715	CAGAGTGACGGA ACAAGAACAGTC GTCCAACCTCGCA CAG	1048
DGTRVHLSS	376	CAGAGTGATGGC ACCCGGGTGCAT CTTTCTAGTCAC AG	716	CAGAGTGACGGA ACAAGAGTCCAC CTCAGCAGCGCA CAG	1049
DGTSFPYAR	86	CAGAGTGATGGC ACCTCGTTTCCGT ATGCTCGGGCAC AG	717	CAGAGTGACGGA ACAAGCTTCCCAT ACGCAAGAGCAC AG	1050
DGTSFTPPK	81	CAGAGTGATGGC ACCTCGTTTACGC CGCCTAAGGCAC AG	718	CAGAGTGACGGA ACAAGCTTCACA CCACCAAAAGCA CAG	1051
DGTSFTPPR	88	CAGAGTGATGGC ACCTCGTTTACTC CGCCGCGGGCAC AG	719	CAGAGTGACGGA ACAAGCTTCACA CCACCAAGAGCA CAG	1052
DGTSGLHGW	377	CAGAGTGATGGC ACCTCTGGGTTGC ATGGGTGGGCAC AG	720	CAGAGTGACGGA ACAAGCGGACTC CACGGATGGGCA CAG	1053
DGTSGLKGW	101	CAGAGTGATGGC ACCAGTGGGCTT AAGGGTGGGCA CAG	721	CAGAGTGACGGA ACAAGCGGACTC AAAGGATGGGCA CAG	1054
DGTSIHLSS	378	CAGAGTGATGGC ACCTCGATTATT TGAGTAGTCAC AG	722	CAGAGTGACGGA ACAAGCATCCAC CTCAGCAGCGCA CAG	1055
DGTSIMLSS	379	CAGAGTGATGGC ACCTCGATTATGT TGAGTTCTGCACA G	723	CAGAGTGACGGA ACAAGCATCATG CTCAGCAGCGCA CAG	1056
DGTSRLRSS	166	CAGAGTGATGGC ACCTCTTTGCGGC TTTCTTCTGCACA G	724	CAGAGTGACGGA ACAAGCCTCAGA CTCAGCAGCGCA CAG	1057
DGTSNYGAR	380	CAGAGTGATGGC ACCTCTAATTATG GGGCGCGGGCAC AG	725	CAGAGTGACGGA ACAAGCAACTAC GGAGCAAGAGCA CAG	1058
DGTSSYYDA	381	CAGAGTGATGGC ACCAGTTCGTATT ATGATGCGGCAC AG	726	CAGAGTGACGGA ACAAGCAGCTAC TACGACGAGCA CAG	1059

DGTSSYYDS	59	CAGAGTGATGGC ACCTCGAGTTATT ATGATTCTGCACA G	727	CAGAGTGACGGA ACAAGCAGCTAC TACGACAGCGCA CAG	1060
DGTSTISGW	382	CAGAGTGATGGC ACCTCTACGATTT CTGGTTGGGCAC AG	728	CAGAGTGACGGA ACAAGCACAATC AGCGGATGGGCA CAG	1061
DGTSTITGW	383	CAGAGTGATGGC ACCAGTACTATTA CGGGTTGGGCAC AG	729	CAGAGTGACGGA ACAAGCACAATC ACAGGATGGGCA CAG	1062
DGTSTLHGW	384	CAGAGTGATGGC ACCTCGACGTTGC ATGGGTGGGCAC AG	730	CAGAGTGACGGA ACAAGCACACTC CACGGATGGGCA CAG	1063
DGTSTLRGW	385	CAGAGTGATGGC ACCTCTACTCTGC GTGGGTGGGCAC AG	731	CAGAGTGACGGA ACAAGCACACTC AGAGGATGGGCA CAG	1064
DGTSTLSGW	386	CAGAGTGATGGC ACCTCGACGCTGT CGGGGTGGGCAC AG	732	CAGAGTGACGGA ACAAGCACACTC AGCGGATGGGCA CAG	1065
DGTSYVPPK	97	CAGAGTGATGGC ACCTCTTATGTGC CGCCGAAGGCAC AG	733	CAGAGTGACGGA ACAAGCTACGTC CCACCAAAAGCA CAG	1066
DGTSYVPPR	78	CAGAGTGATGGC ACCAGTTATGTGC CGCCTCGGGCAC AG	734	CAGAGTGACGGA ACAAGCTACGTC CCACCAAGAGCA CAG	1067
DGTTATYYK	387	CAGAGTGATGGC ACCACGGCGACT TATTATAAGGCA CAG	735	CAGAGTGACGGA ACAACAGCAACA TACTACAAAGCA CAG	1068
DGTTFTPPR	79	CAGAGTGATGGC ACCACTTTTACTC CTCCTCGGGCAC AG	736	CAGAGTGACGGA ACAACATTCA CCACCAAGAGCA CAG	1069
DGTTLAPFR	388	CAGAGTGATGGC ACCACTCTGGCTC CTTTTAGGGCACA G	737	CAGAGTGACGGA ACAACACTCGCA CCATTCAAGAGCA CAG	1070
DGTTLVPPR	116	CAGAGTGATGGC ACCACTTTGGTTC CGCCGCGTGCAC AG	738	CAGAGTGACGGA ACAACACTCGTC CCACCAAGAGCA CAG	1071
DGTTSKTLW	389	CAGAGTGATGGC ACCACGAGTAAG ACGCTTTGGGCA CAG	739	CAGAGTGACGGA ACAACAAGCAAA ACACTCTGGGCA CAG	1072
DGTTSRTLW	390	CAGAGTGATGGC ACCACTTCTAGG ACTTTGTGGGCAC AG	740	CAGAGTGACGGA ACAACAAGCAGA ACACTCTGGGCA CAG	1073
DGTTTRSLY	391	CAGAGTGATGGC ACCACGACTCGT AGTTTGTATGCAC AG	741	CAGAGTGACGGA ACAACAACAAGA AGCCTCTACGCA CAG	1074

DGTTTTTGW	392	CAGAGTGATGGC ACCACTACGACT ACGGGTGGGCA CAG	742	CAGAGTGACGGA ACAACAACAACA ACAGGATGGGCA CAG	1075
DGTTYGAR	77	CAGAGTGATGGC ACCACTACGTAT GGGGCTCGTGCA CAG	743	CAGAGTGACGGA ACAACAACATAC GGAGCAAGAGCA CAG	1076
DGTTWTPPR	139	CAGAGTGATGGC ACCACTTGGACG CCGCCGCGTGCA CAG	744	CAGAGTGACGGA ACAACATGGACA CCACCAAGAGCA CAG	1077
DGTTYMLSS	393	CAGAGTGATGGC ACCACGTATATG CTTAGTAGTGAC AG	745	CAGAGTGACGGA ACAACATACATG CTCAGCAGCGCA CAG	1078
DGTTYVPPR	75	CAGAGTGATGGC ACCACGTATGTTT CTCCGCGGGCAC AG	746	CAGAGTGACGGA ACAACATACGTC CCACCAAGAGCA CAG	1079
DGTVANPFR	394	CAGAGTGATGGC ACCGTGGCGAAT CCTTTTCGGGCAC AG	747	CAGAGTGACGGA ACAGTCGCAAAAC CCATTTCAGAGCA CAG	1080
DGTVDRPFK	395	CAGAGTGATGGC ACCGTGGATCGG CCTTTTAAGGCAC AG	748	CAGAGTGACGGA ACAGTCGACAGA CCATTCAAAGCA CAG	1081
DGTVIHLSS	73	CAGAGTGATGGC ACCGTTATTTCATC TGAGTAGTGAC AG	749	CAGAGTGACGGA ACAGTCATCCAC CTCAGCAGCGCA CAG	1082
DGTVILLSS	396	CAGAGTGATGGC ACCGTTATTCTGT TGTCGAGTGAC AG	750	CAGAGTGACGGA ACAGTCATCCTCC TCAGCAGCGCAC AG	1083
DGTVIMLSS	397	CAGAGTGATGGC ACCGTGATTATGC TGTCGAGTGAC AG	751	CAGAGTGACGGA ACAGTCATCATG CTCAGCAGCGCA CAG	1084
DGTVLHLSS	398	CAGAGTGATGGC ACCGTGCTTCATT TGTCGTCTGCACA G	752	CAGAGTGACGGA ACAGTCCTCCACC TCAGCAGCGCAC AG	1085
DGTVLMLSS	399	CAGAGTGATGGC ACCGTTTTGATGC TGAGTAGTGAC AG	753	CAGAGTGACGGA ACAGTCCTCATGC TCAGCAGCGCAC AG	1086
DGTVLVPFR	150	CAGAGTGATGGC ACCGTGTTGGTGC CGTTTAGGGCAC AG	754	CAGAGTGACGGA ACAGTCCTCGTCC CATTTCAGAGCAC AG	1087
DGTVPYLAS	400	CAGAGTGATGGC ACCGTTCCGTATC TTGCTTCTGCACA G	755	CAGAGTGACGGA ACAGTCCCATAC CTCGCAAGCGCA CAG	1088
DGTVPYLSS	401	CAGAGTGATGGC ACCGTGCCGTATT TGTCTTCGGCACA G	756	CAGAGTGACGGA ACAGTCCCATAC CTCAGCAGCGCA CAG	1089

DGTVRVPFR	164	CAGAGTGATGGC ACCGTTCGTGTGC CGTTTAGGGCAC AG	757	CAGAGTGACGGA ACAGTCAGAGTC CCATTCAGAGCA CAG	1090
DGTVSMPFK	402	CAGAGTGATGGC ACCGTGTCGATG CCGTTTAAGGCA CAG	758	CAGAGTGACGGA ACAGTCAGCATG CCATTCAAAGCA CAG	1091
DGTVSNPFR	403	CAGAGTGATGGC ACCGTGCTAATC CGTTTAGGGCAC AG	759	CAGAGTGACGGA ACAGTCAGCAAC CCATTCAGAGCA CAG	1092
DGTVSTRWV	404	CAGAGTGATGGC ACCGTTTCTACGC GTTGGGTGGCAC AG	760	CAGAGTGACGGA ACAGTCAGCACA AGATGGGTTCGCA CAG	1093
DGTVTTTGW	405	CAGAGTGATGGC ACCGTGACGACG ACTGGGTGGGCA CAG	761	CAGAGTGACGGA ACAGTCACAACA ACAGGATGGGCA CAG	1094
DGTVTVTGW	406	CAGAGTGATGGC ACCGTGACGGTT ACGGGGTGGGCA CAG	762	CAGAGTGACGGA ACAGTCACAGTC ACAGGATGGGCA CAG	1095
DGTVWVPPR	407	CAGAGTGATGGC ACCGTTTGGGTGC CTCCTAGGGCAC AG	763	CAGAGTGACGGA ACAGTCTGGGTC CCACCAAGAGCA CAG	1096
DGTVYRLSS	408	CAGAGTGATGGC ACCGTTTATAGGT TGTCGAGTGCAC AG	764	CAGAGTGACGGA ACAGTCTACAGA CTCAGCAGCGCA CAG	1097
DGTYARLSS	409	CAGAGTGATGGC ACCTATGCGCGTT TGTCTTCTGCACA G	765	CAGAGTGACGGA ACATACGCAAGA CTCAGCAGCGCA CAG	1098
DGTYGNKLW	410	CAGAGTGATGGC ACCTATGGTAAT AAGTTGTGGGCA CAG	766	CAGAGTGACGGA ACATACGGAAAC AAACTCTGGGCA CAG	1099
DGTYIHLSS	411	CAGAGTGATGGC ACCTATATTCATC TGTCTTCGGCACA G	767	CAGAGTGACGGA ACATACATCCAC CTCAGCAGCGCA CAG	1100
DGTYSTSGW	412	CAGAGTGATGGC ACCTATTCGACG AGTGGGTGGGCA CAG	768	CAGAGTGACGGA ACATACAGCACA AGCGGATGGGCA CAG	1101
DGVHPGLSS	104	CAGAGTGATGGC GTGCATCCTGGG CTTTCGAGTGCAC AG	769	CAGAGTGACGGA GTCCACCCAGGA CTCAGCAGCGCA CAG	1102
DGVVALLAS	413	CAGAGTGATGGC GTGGTTGCGTTGC TTGCTAGTGCACA G	770	CAGAGTGACGGA GTCGTCGCACTCC TCGCAAGCGCAC AG	1103
DGYVGVSGL	414	CAGAGTGATGGC TATGTGGGTGTTG GTAGTTTGGCAC AG	771	CAGAGTGACGGA TACGTCGGAGTC GGAAGCCTCGCA CAG	1104

[0361] Primer pools were produced by Twist biosciences using solid-phase synthesis and were used to generate a balanced library of 666 nucleotide variants by PCR amplification of CAP C-terminus and Gibson assembly as described in FIG. 27. 666 primers were provided a 1 fmole each, resulting in 0.6 pmole (regular PCR requires ~25 pmole of primer). Primerless amplification on capsid gBlock template was performed over 10 cycles. Forward and reverse primers were added, followed by an additional 10, 15 or 20 PCR cycles. Constructs were then cloned into AAV9 backbone plasmids by Gibson/RCA (like regular libraries).

[0362] NGS analysis of SYN- and GFAP-driven AAV libraries produced with the pooled DNA showed a good correlation between the codon variants of each peptide, suggesting that the DNA sequence itself had little influence on virus production (FIG. 28 and FIG. 29). The pooled synthetic library was injected intravenously to C57BL/6 mice (5e11 VG per mouse, N=9), BALB/C mice (5e11 VG per mouse, N=6) and to rats (5e12 VG per rat, N=6), and after one month in-life RNA was extracted from the brain and spinal cord, and DNA was extracted from liver and heart tissue samples for biodistribution analysis (FIG. 30). Because the Synapsin and GFAP promoters are not fully active in non-CNS tissue, DNA was analyzed instead of RNA in peripheral organs. The initial focus was on the C57BL/6 mouse analysis because this is the mouse strain in which library evolution was performed.

[0363] The enrichment score of each capsid was determined by NGS analysis and defined as the ratio of reads per million (RPM) in the target tissue versus RPM in the inoculum. An example of analysis performed on the control capsids is shown in FIG. 31A. As expected from the published data, the PHP.B and PHP.eB (aka, PHP.N) capsids allowed significantly higher RNA expression in neurons compared to the AAV9 parental capsid (8-fold and 25-fold, respectively). There was a very high correlation between the codon variants of each peptide species in each animal ($r=0.92$, 0.93 and 0.95), confirming the robustness of the NGS assay (FIG. 31B – FIG. 31D).

[0364] An example of enrichment analysis is presented in FIG. 32A – FIG. 36. The 333 capsid variants are ranked by average brain enrichment score from all animals, and the individual enrichment values are indicated by a color scale. As indicated by the position of the reference capsids, a group of novel variants showed a higher enrichment score than the PHP.eB benchmark capsid in both neurons (Syn-driven) and astrocytes (GFAP-driven). Interestingly, many variants showed a different enrichment score in neurons vs. astrocytes, as indicated by the medium level of correlation between Syn- and GFAP-driven RNA. This

suggests that certain capsids display an enhanced tropism for neurons, and others for astrocytes (FIG. 33).

[0365] A group of 38 capsids showed potentially interesting properties based on their tropism for neurons, astrocytes or both (Table 8A and Table 8B) (FIG. 38) and showed a strong consensus peptide sequence similarity, different between neuron- and astrocyte-targeting variants (FIG. 45A–FIG. 45C and FIG. 46A–FIG. 46B).

Table 8A TOP 38 candidates from C57BL/6 screen #1 (N=3)

Groups	variant	peptide	SEQ ID NO:	SYN ranking	GFAP ranking
A	9p32	DGTAIHLSS	67	15, 16	113, 133
	9p35	DGTSSYYDS	59	1, 3	565, 581
B	9p36	DGSSSYDA	64	10, 11	591, 594
	9p37	DGTASYYS	61	5, 6	553, 560
C	9p26	DGTTTYGAR	77	225, 262	49, 56
D	9p2	AQNGNPGRW	84	156, 160	38, 44
	9p13	AQGENPGRW	96	77, 87	7, 13
	9p30	AQPEGSARW	60	2, 4	154, 160
E	9p1	AQGSWNPPA	80	348, 361	8, 15
	9p14	AQGTWNPPA	82	448, 467	14, 17
F	9p29	AQFPTNYDS	66	14, 19	490, 537
	9p31	AQWPTSUDA	62	7, 9	290, 304
G	9p3	AQTTEKPWL	83	53, 72	35, 70
	9p15	AQTDRPFL	85	206, 219	26, 43
H	9p10	DGTRTTTGW	106	161, 220	10, 22
	9p18	DGTGGIKGW	131	346, 388	41, 68
	9p19	DGTGNTRGW	94	322, 340	45, 54
	9p20	DGTHTRTGW	90	380, 427	31, 39
	9p23	DGTNGLKGW	76	132, 153	5, 16
	9p33	DGTGQVTGW	68	18, 33	172, 213
I	9p38	DGTGNVTGW	69	20, 31	117, 137
	9p11	DGTTFTPPR	79	183, 199	11, 19
	9p12	DGTTYVPPR	75	146, 154	4, 9
	9p24	DGTSFTPPK	81	210, 243	29, 40
	9p25	DGTSFTPPR	88	250, 273	28, 37
	9p27	DGTTWTTPR	139	567, 570	46, 59
J	9p28	DGTSYVPPR	78	162, 179	20, 25
	9p4	DGTADRPFR	155	109, 118	48, 57
	9p9	DGTMDRPFR	102	102, 113	23, 34
	9p16	DGTADKPFR	63	8, 12	1, 6
	9p17	DGTAERPFR	140	106, 138	42, 50
	9p21	DGTIERPFR	87	186, 235	21, 33
K	9p34	DGTMDKPFR	70	21, 23	107, 112
	9p5	DGTISQPFK	105	184, 193	12, 18
	9p6	DGTLAAPFK	120	110, 112	27, 30
	9p7	DGTLQQPFR	89	46, 57	32, 47
	9p8	DGTLSPQFR	65	13, 17	2, 3
Ref.	9p22	DGTLNNPFR	109	30, 41	24, 36
	PHPN	DGTLAVPFK	71	22, 24	51, 60
	PHPB	AQTLAVPFK	168	253, 261	61, 62
	wtAAV9	AQ		630, 631	611, 620

Table 8B. Variant 9mer and encoding sequences

variant	9mer peptide	SEQ ID NO:	NNK nucleotide sequences	SEQ ID NO:	NNM nucleotide sequences	SEQ ID NO:
9p1	AQGSWNPPA	80	GCCCAAGGTT CGTGAATCC GCCGGCG	1105	GCACAAGGAAG CTGGAACCCACC AGCA	1143
9p2	AQNGNPGRW	84	GCCCCAAATG GTAATCCGGG GCGGTGG	1106	GCACAAAACGG AAACCCAGGAA GATGG	1144
9p3	AQTTEKPWL	83	GCCCCAACGA CTGAGAAGCC GTGGCTG	1107	GCACAAACAAC AGAAAAACCAT GGCTC	1145
9p4	DGTADRPFR	155	GATGGCACGG CGGATCGTCCT TTTCGG	1108	GACGGAACAGC AGACAGACCATT CAGA	1146
9p5	DGTISQPFK	105	GATGGCACCA TTTCGCAGCCT TTTAAG	1109	GACGGAACAAT CAGCCAACCATT CAAA	1147
9p6	DGTLAAPFK	120	GATGGCACCTT GGCTGCTCCTT TTAAG	1110	GACGGAACACTC GCAGCACCATT AAA	1148
9p7	DGTLQQPFR	89	GATGGCACCTT GCAGCAGCCG TTTCGG	1111	GACGGAACACTC CAACAACCATT AGA	1149
9p8	DGTLSPFR	65	GATGGCACCC TGTCTCAGCCT TTTAGG	1112	GACGGAACACTC AGCCAACCATT AGA	1150
9p9	DGTMDRPFK	102	GATGGCACCA TGGATAGGCC GTTTAAG	1113	GACGGAACAAT GGACAGACCATT CAAA	1151
9p10	DGTRTTGW	106	GATGGCACCC GTACTACGAC GGGTTGG	1114	GACGGAACAAG AACAACAACAG GATGG	1152
9p11	DGTTFTPPR	79	GATGGCACCA CTTTTACTCCT CCTCGG	1115	GACGGAACAAC ATTCACACCACC AAGA	1153
9p12	DGTTYVPPR	75	GATGGCACCA CGTATGTTCT CCGCGG	1116	GACGGAACAAC ATACGTCCCACC AAGA	1154
9p13	AQGENPGRW	96	GCCCAAGGGG AGAATCCGGG TAGGTGG	1117	GCACAAGGAGA AAACCCAGGAA GATGG	1155
9p14	AQGTWNPPA	82	GCCCAAGGTA CTTGAATCCG CCGGCT	1118	GCACAAGGAAC ATGGAACCCACC AGCA	1156
9p15	AQTDRPFL	85	GCCCCAACTA CTGATAGGCCT TTTTTG	1119	GCACAAACAAC AGACAGACCATT CCTC	1157
9p16	DGTADKPFR	63	GATGGCACCG CTGATAAGCC GTTTCGG	1120	GACGGAACAGC AGACAAACCATT CAGA	1158
9p17	DGTAERPFR	140	GATGGCACCG CGGAGAGGCC TTTTAGG	1121	GACGGAACAGC AGAAAGACCATT CAGA	1159

9p18	DGTGGIKGW	131	GATGGCACCG GTGGTATTAA GGGGTGG	1122	GACGGAACAGG AGGAATCAAAG GATGG	1160
9p19	DGTGNTRGW	94	GATGGCACCG GGAATACTCG GGGGTGG	1123	GACGGAACAGG AAACACAAGAG GATGG	1161
9p20	DGTHTRTGW	90	GATGGCACCC ATACGCGGAC GGGTTGG	1124	GACGGAACACA CACAAGAACAG GATGG	1162
9p21	DGTIERPFR	87	GATGGCACCA TTGAGCGGCCT TTTCGT	1125	GACGGAACAAT CGAAAGACCATT CAGA	1163
9p22	DGTLNPNFR	109	GATGGCACCTT GAATAATCCG TTTAGG	1126	GACGGAACACTC AACAACCCATT AGA	1164
9p23	DGTNGLKGW	76	GATGGCACCA ATGGTCTGAA GGGGTGG	1127	GACGGAACAAA CGGACTCAAAG GATGG	1165
9p24	DGTSFTPPK	81	GATGGCACCT CGTTTACGCCG CCTAAG	1128	GACGGAACAAG CTTCACACCACC AAAA	1166
9p25	DGTSFTPPR	88	GATGGCACCT CGTTTACTCCG CCGCGG	1129	GACGGAACAAG CTTCACACCACC AAGA	1167
9p26	DGTTYGAR	77	GATGGCACCA CTACGTATGG GGCTCGT	1130	GACGGAACAAC AACATACGGAG CAAGA	1168
9p27	DGTTWTPPR	139	GATGGCACCA CTTGGACGCC GCCGCGT	1131	GACGGAACAAC ATGGACACCACC AAGA	1169
9p28	DGTSYVPPR	78	GATGGCACCA GTTATGTTCT CCGAGG	1132	GACGGAACAAG CTACGTCCACC AAGA	1170
9p29	AQFPTNYDS	66	GCCCAATTTCC TACGAATTATG ATTCT	1133	GCACAATTCCCA ACAACTACGAC AGC	1171
9p30	AQPEGSARW	60	GCCCAACCTG AGGGTAGTGC GAGGTGG	1134	GCACAACCAGA AGGAAGCGCAA GATGG	1172
9p31	AQWPTSYDA	62	GCCCAATGGC CTACGAGTTAT GATGCT	1135	GCACAATGGCCA ACAAGCTACGAC GCA	1173
9p32	DGTAIHLSS	67	GATGGCACCG CGATTCATCTT TCGTCT	1136	GACGGAACAGC AATCCACCTCAG CAGC	1174
9p33	DGTGQVTGW	68	GATGGCACCG GGCAGGTGAC TGGGTGG	1137	GACGGAACAGG ACAAGTCACAG GATGG	1175
9p34	DGTMDKPFR	70	GATGGCACGA TGGATAAGCC TTTTAGG	1138	GACGGAACAAT GGACAAACCATT CAGA	1176
9p35	DGTSSYYDS	59	GATGGCACCT CGAGTTATTAT GATTCT	1139	GACGGAACAAG CAGCTACTACGA CAGC	1177

9p36	DGSSSYDA	64	GATGGCAGTA GTTCTTATTAT GATGCG	1140	GACGGAAGCAG CAGCTACTACGA CGCA	1178
9p37	DGTASYYS	61	GATGGCACCG CGAGTTATTAT GATTCT	1141	GACGGAACAGC AAGCTACTACGA CAGC	1179
9p38	DGTGNVTGW	69	GATGGCACCG GTAATGTGAC GGGGTGG	1142	GACGGAACAGG AAACGTCACAG GATGG	1180
AAV9	AQ		AGTGCTCAGG CACAGGCGCA GACC	54	AGTGCCCAAGCA CAGGCGCAGAC C	53
PHPN	DGTLAVPFK	71	GATGGGACTTT GGCGGTGCCTT TTAAG	56	GACGGAACACTC GCAGTCCCATT AAA	55
PHPB	AQTLAVPFK	168	GCCCAAACCTT GGCGGTGCCTT TTAAG	58	GCACAAACACTC GCAGTCCCATT AAA	57

Example 11. Phylogenetic grouping

[0366] Phylogenetic grouping of peptide sequences showed an evident correlation between sequence homology clusters and capsid phenotypes (Figure 37). For example, 9-mer variants with the sequence DGTxxxPFK/R (SEQ ID NO: 1181) presented a similar behavior as PHP.eB capsid (high transduction of both neurons and astrocytes), whereas variants harboring the sequence DGTxxxYDS/A (SEQ ID NO: 1182) showed a preference for neuron transduction. By contrast, peptides with the consensus DGTxxxxGW (SEQ ID NO: 1183) or CGTxxxPPR/K (SEQ ID NO: 1184) presented a higher tropism for astrocytes.

Example 12. Capsid testing

[0367] Capsid variants representative of distinct sequence clusters (highlighted in FIG. 37B) were chosen for individual transduction analysis in C57BL/6 mice. Each capsid was produced as a recombinant AAV packaging a self-complementary EGFP transgene driven by the ubiquitous promoter (FIG. 49A, B). Mouse groups (N=3) were injected intravenously with 6e10 VG and transduction efficiency was assessed after 1 month by quantifying EGFP mRNA in the brain, spinal cord, and liver tissue. EGFP mRNA expression was normalized using mouse TBP as a housekeeping gene, and DNA biodistribution was normalized to the single-copy mouse TfR gene (FIG. 50A – FIG. 50C). Reverse transcription was performed with the Quantitect kit and included a DNA removal treatment. All capsid variants showed a significant improvement in brain and spinal cord mRNA expression by comparison to the parent AAV9 capsid, and 3 out of 7 variants (9P16, 9P31 and 9P35) showed similar or higher transduction than the PHP.eB benchmark capsid (FIG. 49C, Table 10). The viral DNA biodistribution showed a very strong tropism of 9P31 and 9P35 for the brain and spinal cord,

but all the variants showed a 40- to 260-fold increase of biodistribution compared to AAV9 (FIG. 49D, Table 10).

[0368] Expected cellular tropism was tested using an NGS screen by labeling the neuronal NeuN marker (FIG. 51). Within the cortex, the top capsids in the GFAP screen showed mostly GFP expression in NeuN-negative cells with glial morphology. Conversely, top capsids in the SYN screen showed a very high transduction of NeuN-positive cells, and the dual-specificity capsids 9P08 and 9P16 - ranking high in both assays - showed mixed cell preference with multiple NeuN+ cells and glial cells.

[0369] Cellular tropism was also tested using mouse brain microvascular EC (mBMVEC) binding relative to AAV9. Results are shown in Table 9.

Table 9. mBMVEC binding results

PEPTIDE	SEQUENCE	SEQUENCE ID	BINDING TO mBMVEC (fold over AAV9)
AAV9	AQ		1
PHP.eB	DGTLAVPFK	71	153
9P03	AQTTEKPWL	83	170
9P08	DGTLSQPFR	65	349
9P09	DGTMDRPFK	102	222
9P13	AQGENPGRW	96	2.5
9P16	DGTADKPFR	63	176
9P31	AQWPTSYDA	62	2
9P32	DGTAIHLSS	67	16
9P33	DGTGQVTGW	68	5
9P36	DGSSSYDA	64	0
9P39	DGTGSTTGW	134	2

[0370] Fluorescent EGFP expression in tissues of whole brain, cerebellum, cortex, and hippocampus revealed transduction patterns across a spectrum and demonstrate the identification of tissue-specific capsids (FIG. 52 – FIG. 56).

[0371] The liver transduction, measured by mRNA expression and by whole tissue GFP expression, showed that several variants outperformed AAV9, which was unexpected in light of the NGS results. Some variants, such as 9P08 or 9P23, showed a relative liver detargeting by comparison with AAV9 (FIG. 57A – FIG. 57B).

Table 10. Brain and Spinal cord tropism

BRAIN EGFP mRNA*							
CAPSID	EGFP/TBP m1	EGFP/TBP m2	EGFP/TBP m3	group mean	group SD	Mean Fold over AAV9	Fold SDEV
AAV9	0.11	0.1	0.15	0.12	0.03	1	0.21
PHPN	2.94	4.44	3.42	3.6	0.77	30	6.38
9P08	2.46	3.47	2.73	2.89	0.53	24	4.38
9P12	3.07	2.27	2.98	2.77	0.44	23	3.65
9P16	4.31	4.75	5.28	4.78	0.49	39	4.06
9P23	3.28	2.37	2.79	2.81	0.46	23	3.79
9P30	1.06	1.7	1.32	1.36	0.32	11	2.66
9P31	4.87	5.53	4.2	4.87	0.66	40	5.54
9P35	3.9	3.24	3.45	3.53	0.33	29	2.78
PHPB***	2.68	2.68	2.68	2.68	0	22	0
ctrl	0	0	0	0	0	0	0
SPINAL CORD EGFP mRNA*							
CAPSID	EGFP/TBP m1	EGFP/TBP m2	EGFP/TBP m3	group mean	group SD	Mean Fold over AAV9	Fold SD
AAV9	0.84	0.29	0.3	0.48	0.31	1	0.66
PHPN	3.36	5.8	5.4	4.86	1.31	10.22	2.75
9P08	4.3	5.62	4.65	4.86	0.68	10.22	1.43
9P12	6.09	5.94	5.78	5.94	0.16	12.49	0.33
9P16	4.42	5.31	5.37	5.04	0.53	10.6	1.12
9P23	5.41	5.95	5.04	5.47	0.46	11.5	0.96
9P30	1.53	1.83	2.11	1.82	0.29	3.84	0.61
9P31	6.92	7.06	6.94	6.98	0.08	14.68	0.16
9P35	4.68	4.81	4.79	4.76	0.07	10.02	0.15
PHPB	3.84	3.84	3.84	3.84	0	8.09	0
ctrl	0	0	0	0	0	0	0
BRAIN EGFP DNA** (VG/Cell)							
CAPSID	EGFP/TERT m1	EGFP/TERT m2	EGFP/TERT m3	Group mean	Group SD	Mean Fold over AAV9	Fold SDEV
AAV9	0.03	0.04	0.01	0.03	0.01	1	0
PHPN	2.07	2.79	1.94	2.27	0.46	87	18
P08	1.25	1.62	5.47	2.78	2.34	107	90
P12	1.43	0.94	1.41	1.26	0.27	48	10
P16	4.13	1.15	3.56	2.95	1.58	113	60
P23	1.34	2.68	1.87	1.96	0.68	75	26
P30	0.59	1.42	1.21	1.08	0.43	41	17
P31	6.47	5.6	8.81	6.96	1.66	267	64
P35	4.62	5.55	2.52	4.23	1.55	162	59
PHPB	1.5	1.5	1.5	1.5	0	58	0
ctrl	0	0	0	0	0	0	0
SPINAL CORD EGFP DNA** (VG/Cell)							
CAPSID	EGFP/TERT m 1	EGFP/TERT m 2	EGFP/TERT m 3	Group AVG	Group SD	Mean Fold over AAV9	Fold SDEV
AAV9	0.03	0.04	0.04	0.03	0.007	1	0.2
PHPN	1.75	2.96	3.14	2.62	0.752	75	21.7
P08	3.81	3.47	3.66	3.65	0.174	105	5
P12	1.62	3.31	2.87	2.6	0.873	75	25.2
P16	3.3	3.34	2.96	3.2	0.211	92	6.1
P23	2.63	2.47	3.1	2.73	0.322	79	9.3
P30	0.8	1.8	1.43	1.34	0.507	39	14.6
P31	9.88	6.19	5.47	7.18	2.366	207	68.2
P35	2.95	3.92	2.41	3.1	0.765	89	22
PHPB	1.34	1.34	1.34	1.34	0	39	0
ctrl	0	0	0	0	0	0	0

*EGFP mRNA expression was normalized to TBP as a housekeeping marker

**GFP DNA was normalized to single-copy TfR DNA

***N=1

Example 13. Multi-rodent testing (cross species)

[0372] The efficacy of the 333 capsid variants to transduce CNS was tested in other rodent strains or species (FIG. 47). Side-by-side comparison of neuron and astrocyte transduction in C57BL/6 mice, BALB/C mice and rats showed major differences in the enrichment scores of multiple variants between the two mouse strains, and even more pronounced differences between mice and rats (FIG. 48A – FIG. 48C). Strikingly, the most efficient capsid for rat brain transduction was the parental AAV9, which suggests that directed evolution “bottlenecks” capsid variants that are highly performant in one given species, as opposed to the versatility of wild-type AAV capsids.

[0373] Correlation analysis showed that some capsids shared high CNS transduction between C57BL/6 and BALB/C mice, whereas others were restricted to only one strain (FIG. 48B).

[0374] Interestingly, the PHP.B and PHP.eB capsid showed poor brain transduction in BALB/C mice, in line with a recent publication (Hordeaux et al., 2018). When focusing on the capsids that showed >10-fold increase in brain transduction, 62 variants were improved only in C57BL/6 mice, 28 variants were improved only in BALB/C mice and 30 variants showed improved brain transduction in both strains (Table 11). Consensus sequence analysis showed a “C57BL/6 signature” closely resembling the PHP.eB peptide (DGTxxxPFR (SEQ ID NO: 1185)) whereas the BALB/C signature showed a different consensus (DGTxxxxGW (SEQ ID NO: 1183)), suggesting the use of a different cellular receptor (FIG. 48C).

Table 11. TOP 30 candidates from C57BL/6 and BALB/C mouse screen

SYNAPSIN PROMOTER					
C57BL/6				BALB/C	
REPLICATE 1 (N=3)		REPLICATE 2 (N=6)		REPLICATE 1 (N=6)	
9-mer peptide insert	Brain Enrichment Factor (fold over AAV9)	9-mer peptide insert	Brain Enrichment Factor (fold over AAV9)	9-mer peptide insert	Brain Enrichment Factor (fold over AAV9)
DGTSSYYDS (SEQ ID NO: 59)	36.40	AQWPTSYDA (SEQ ID NO: 62)	39.97	DGTGSTTGW (SEQ ID NO: 134)	57.05
AQPEGSARW (SEQ ID NO: 60)	35.95	AQPEGSARW (SEQ ID NO: 60)	31.83	DGTGQVTGW (SEQ ID NO: 68)	49.87
DGTASYYS (SEQ ID NO: 61)	32.34	DGTGQVTGW (SEQ ID NO: 68)	20.35	DGTGSTHGW (SEQ ID NO: 119)	43.08
AQWPTSYDA (SEQ ID NO: 62)	30.81	DGTAIHLSS (SEQ ID NO: 67)	19.55	DGTGSTQGW (SEQ ID NO: 315)	38.31

DGTADKPFR (SEQ ID NO: 63)	29.30	DGTMDRPFK (SEQ ID NO: 102)	19.48	DGTGTTTGW (SEQ ID NO: 130)	37.29
DGSSSYDA (SEQ ID NO: 64)	28.05	DGTGSTTGW (SEQ ID NO: 134)	19.20	AQWAAAGYN V (SEQ ID NO: 245)	34.57
DGTLSQPFR (SEQ ID NO: 65)	26.73	DGSSSYDA (SEQ ID NO: 64)	18.08	DGTGGTKGW (SEQ ID NO: 107)	33.59
DGTAIHLSS (SEQ ID NO: 67)	26.23	DGTSSYDA (SEQ ID NO: 381)	17.93	DGTGSTKGW (SEQ ID NO: 313)	29.64
AQFPTNYDS (SEQ ID NO: 66)	26.07	DGSQSTTGW (SEQ ID NO: 136)	17.59	DGSQSTTGW (SEQ ID NO: 136)	25.19
DGTMDKPFR (SEQ ID NO: 70)	25.05	DGTGSTQGW (SEQ ID NO: 315)	17.24	AQWEVKGGY (SEQ ID NO: 247)	23.44
DGTLAVPFK (SEQ ID NO: 71)	24.62	DGTGTTTGW (SEQ ID NO: 130)	17.00	DGTAIHLSS (SEQ ID NO: 67)	22.81
DGTGNVTG W (SEQ ID NO: 69)	24.05	DGTLAVPFK (SEQ ID NO: 71)	16.84	DGGGTTTGW (SEQ ID NO: 270)	22.62
DGTGQVTG W (SEQ ID NO: 68)	23.83	DGTASYDS (SEQ ID NO: 61)	16.68	DGTGGLTGW (SEQ ID NO: 294)	22.42
DGTHIHLSS (SEQ ID NO: 162)	22.93	DGTMDKPFR (SEQ ID NO: 70)	16.68	DGTNTINGW (SEQ ID NO: 124)	20.76
DGTGNTHG W (SEQ ID NO: 72)	22.63	DGTVANPFR (SEQ ID NO: 394)	16.32	DGAGGTSGW (SEQ ID NO: 151)	19.55
DGTVIHLSS (SEQ ID NO: 73)	22.62	DGTNNPFR (SEQ ID NO: 109)	16.24	DGTNTTHGW (SEQ ID NO: 113)	18.99
DGTNNPFR (SEQ ID NO: 109)	22.33	DGTLAAPFK (SEQ ID NO: 120)	15.96	DGTGTVQGW (SEQ ID NO: 327)	18.84
DGTGNTSGW (SEQ ID NO: 137)	22.10	DGTLSQPFR (SEQ ID NO: 65)	15.43	DGTGQTIGW (SEQ ID NO: 305)	18.55
DGTGTTVGW (SEQ ID NO: 74)	21.72	DGTHIHLSS (SEQ ID NO: 162)	15.11	AQWELSNGY (SEQ ID NO: 246)	18.13
DGTSSYDA (SEQ ID NO: 381)	20.94	AQTTEKPWL (SEQ ID NO: 83)	15.00	DGTGSLNGW (SEQ ID NO: 309)	17.93
DGAGTTSGW (SEQ ID NO: 265)	20.42	DGTGNVTG W (SEQ ID NO: 69)	14.90	DGTGTTLGW (SEQ ID NO: 323)	17.48
DGGGTTTGW (SEQ ID NO: 270)	20.27	DGTGGVTG W (SEQ ID NO: 299)	14.89	AQPEGSARW (SEQ ID NO: 60)	17.11
DGTLQQPFR (SEQ ID NO: 89)	19.88	DGTSSYDS (SEQ ID NO: 59)	14.80	DGTGSTMGW (SEQ ID NO: 314)	16.91
DGTGQTIGW (SEQ ID NO: 305)	19.52	DGTGNTSGW (SEQ ID NO: 137)	14.48	DGTGNTHGW (SEQ ID NO: 72)	16.47

DGTVTTTGW (SEQ ID NO: 405)	19.49	AQWPTAYDA (SEQ ID NO: 256)	14.48	DGSGTTTRGW (SEQ ID NO: 114)	15.83
DGTSIHLSS (SEQ ID NO: 378)	19.45	AQGENPGRW (SEQ ID NO: 96)	14.41	DGTNSTTGW (SEQ ID NO: 143)	15.48
DGTGSTTGW (SEQ ID NO: 134)	19.45	DGTADKPFR (SEQ ID NO: 63)	14.32	DGRNALTGW (SEQ ID NO: 275)	15.13
DGTGGVTGW (SEQ ID NO: 299)	19.44	DGTGQTIGW (SEQ ID NO: 305)	14.27	DGAAATTGW (SEQ ID NO: 264)	15.02
DGTVANPFR (SEQ ID NO: 394)	19.42	DGTISQPFK (SEQ ID NO: 105)	13.84	DGTATTMGW (SEQ ID NO: 284)	14.54
DGTGTTTGW (SEQ ID NO: 130)	19.16	DGTKLMLSS (SEQ ID NO: 157)	13.71	AQRYTGDSS (SEQ ID NO: 138)	14.35
DGAGGTSGW (SEQ ID NO: 151)	18.99	AOTLAVPEK (SEQ ID NO: 168)	13.69	DGAGTTSGW (SEQ ID NO: 265)	14.29
GFAP PROMOTER					
C57BL/6			BALB/C		
REPLICATE 1 (N=2)		REPLICATE 2 (N=6)		REPLICATE 1 (N=6)	
9-mer peptide insert	Brain Enrichment Factor (fold over AAV9)	9-mer peptide insert	Brain Enrichment Factor (fold over AAV9)	9-mer peptide insert	Brain Enrichment Factor (fold over AAV9)
DGTADKPFR (SEQ ID NO: 63)	37.60	DGTMDRPFK (SEQ ID NO: 102)	24.89	DGTGSTTGW (SEQ ID NO: 134)	21.03
DGTLSQPFK (SEQ ID NO: 65)	35.97	DGTAERPFR (SEQ ID NO: 140)	24.66	DGTGQVTGW (SEQ ID NO: 68)	19.24
DGTTYVPPR (SEQ ID NO: 75)	33.09	DGTADKPFR (SEQ ID NO: 63)	23.03	DGTGTTTGW (SEQ ID NO: 130)	15.56
DGTNGLKG W (SEQ ID NO: 76)	32.14	DGTLNPPFR (SEQ ID NO: 109)	22.91	DGTGSTHGW (SEQ ID NO: 119)	14.45
AQGENPGRW (SEQ ID NO: 96)	31.99	DGTLSQPFK (SEQ ID NO: 65)	21.60	DGTAIHLSS (SEQ ID NO: 67)	11.74
AQGSWNPPA (SEQ ID NO: 80)	30.78	DGTMDKPFR (SEQ ID NO: 70)	20.52	DGTGSTQGW (SEQ ID NO: 315)	11.40
AQGTWNPPA (SEQ ID NO: 82)	29.19	DGTISQPFK (SEQ ID NO: 105)	20.47	DGTGGLTGW (SEQ ID NO: 294)	8.87
DGTISQPFK (SEQ ID NO: 105)	29.01	AQGENPGRW (SEQ ID NO: 96)	20.09	AQNGNPGRW (SEQ ID NO: 84)	8.82
DGTTFTPPR (SEQ ID NO: 79)	28.94	AQTTEKPWL (SEQ ID NO: 83)	18.04	DGTGGIKGW (SEQ ID NO: 131)	8.62
DGTRTTTGW (SEQ ID NO: 106)	28.59	DGTVANPFR (SEQ ID NO: 394)	16.87	DGRNALTGW (SEQ ID NO: 275)	8.39

DGTSYVPPR (SEQ ID NO: 78)	26.17	DGTTYVPPR (SEQ ID NO: 75)	16.31	DGTGSTKGW (SEQ ID NO: 313)	8.38
DGTIERPFR (SEQ ID NO: 87)	25.37	AQTDRPFL (SEQ ID NO: 85)	16.27	AQRYTGDSS (SEQ ID NO: 138)	8.13
DGTMDRPFK (SEQ ID NO: 102)	24.85	DGTTTYGAR (SEQ ID NO: 77)	15.62	DGTGGTKGW (SEQ ID NO: 107)	8.06
DGTLAAPFK (SEQ ID NO: 120)	24.67	DGTADRPFR (SEQ ID NO: 155)	15.60	DGTATTTGW (SEQ ID NO: 285)	8.04
DGTLNNPFR (SEQ ID NO: 109)	24.62	DGTIERPFR (SEQ ID NO: 87)	15.11	DGTMVLQL (SEQ ID NO: 142)	7.87
DGTSFTPPR (SEQ ID NO: 88)	24.14	AQGSWNPPA (SEQ ID NO: 80)	15.11	DGTGSLNGW (SEQ ID NO: 309)	7.71
AQTDRPFL (SEQ ID NO: 85)	23.85	AQGTWNPPA (SEQ ID NO: 82)	15.03	DGTNTINGW (SEQ ID NO: 124)	7.59
DGTSFTPPK (SEQ ID NO: 81)	23.75	DGSTERPFR (SEQ ID NO: 99)	15.01	AQWELSNGY (SEQ ID NO: 246)	7.57
DGTHTRTGW (SEQ ID NO: 90)	23.54	AQSVAKPFL (SEQ ID NO: 231)	14.90	DGTNGLKGW (SEQ ID NO: 76)	7.50
DGTLQQPFR (SEQ ID NO: 89)	22.94	DGTVDRPFK (SEQ ID NO: 395)	14.74	DGTNTTHGW (SEQ ID NO: 113)	7.25
AQNGNPGR W (SEQ ID NO: 84)	22.80	DGTTFTPPR (SEQ ID NO: 79)	14.56	DGTRMVVQL (SEQ ID NO: 370)	7.25
DGTAERPFR (SEQ ID NO: 140)	21.65	AQTLARPFV (SEQ ID NO: 98)	14.51	DGTNSTTGW (SEQ ID NO: 143)	6.41
DGTGNTRGW (SEQ ID NO: 94)	21.12	DGTGGTKG W (SEQ ID NO: 107)	14.13	DGSQSTTGW (SEQ ID NO: 136)	6.29
AQTEKPWL (SEQ ID NO: 83)	20.58	AQGPTRPFL (SEQ ID NO: 125)	13.47	AQPEGSARW (SEQ ID NO: 60)	6.23
DGTADRPFR (SEQ ID NO: 155)	20.49	DGTRTTTGW (SEQ ID NO: 106)	13.39	DGTGQTIGW (SEQ ID NO: 305)	6.16
DGTTWTPPR (SEQ ID NO: 139)	20.44	AQNGNPGR W (SEQ ID NO: 84)	13.09	DGTGGVTGW (SEQ ID NO: 299)	6.07
DGTTTYGAR (SEQ ID NO: 77)	20.43	DGTVSNPFR (SEQ ID NO: 403)	12.77	DGTVTTTGW (SEQ ID NO: 405)	6.04
DGTGGIKGW (SEQ ID NO: 131)	20.20	AQGGNPGR W (SEQ ID NO: 91)	12.21	DGKGSTQGW (SEQ ID NO: 272)	5.97
DGTLAVPFK (SEQ ID NO: 71)	19.43	AQWPTSODA (SEQ ID NO: 62)	11.93	AQGENPGRW (SEQ ID NO: 96)	5.88
DGKQYQLSS (SEQ ID NO: 92)	18.74	DGTLQQPFR (SEQ ID NO: 89)	11.92	DGNGGLKGW (SEQ ID NO: 167)	5.82

DGSPEKPFR (SEQ ID NO: 160)	18.73	DGTNGLKG W (SEQ ID NO: 76)	11.53	DGTGTVHGW (SEQ ID NO: 326)	5.82

[0375] The efficacy of the 333 capsid variants to transduce CNS was also compared for C57BL/6 mice BMVEC and Human BMVEC (FIG. 58A and FIG. 58B).

Example 14. Engineering of a NGS-driven selection system for full-length capsid variants

[0376] A barcode system was engineered to allow enrichment studies with full capsid length modifications. While the TRACER platform described here was initially developed for the use of peptide display libraries, where the randomized peptide sequence itself can be used for Illumina NGS analysis due to its short size, the Illumina sequencing technology does not typically allow sequencing of more than 300 contiguous bases, and therefore our platform cannot be used for NGS analysis of full-length capsid variants, such as those generated by DNA shuffling technology or error-prone PCR.

[0377] An alternative RNA-driven platform for full-length capsid libraries in which a unique molecular identified (UMI) is placed outside the capsid gene and can be used for NGS enrichment analysis was designed (FIG. 59A – FIG. 59C). Once the variants with desired properties are identified by UMI enrichment analysis from animal tissue, the UMI sequence must allow highly specific recovery of the full-length capsid from the starting material with a minimal error rate. The system should have one or more of the following properties to be effective: 1) the UMI should be transcribed under control of a cell type-specific promoter, 2) the UMI should not interfere with capsid expression or splicing during virus production, 3) the UMI should be short enough for Illumina NGS sequencing (typically less than 60nt for standard single-end 75nt sequencing), and 4) the UMI should allow sequence-specific recovery of full-length capsids of interest from the starting DNA/virus library with a minimal error rate.

[0378] To address these properties: 1) the UMI was placed in the transcribed region of capsid library (i.e., anywhere between the transcription start site and the polyadenylation signal), 2) the UMI was placed either in various locations of the AAV intron (which mostly unspliced in the absence of helper functions) or between the capsid stop codon and the polyadenylation signal, 3) the UMI cassette was composed of two randomized 21-nt sequences separated by a 15-nt spacer, for a total length of 57nt, which allows 18 extra nucleotides for primer annealing, and 4) the UMI randomized sequences were formed of NSW triplets (N=A, T, G, C; S=G, C; W=A, T) to prevent large variations in annealing

temperature with amplification primers, avoid homopolymeric stretches and prevent the formation of a premature polyA signal (AATAAA).

[0379] Importantly, the UMI cassette contained two random sequences in tandem. The first sequence (outermost) is used to design a matching capsid recovery primer, and the second sequence (innermost) to confirm the identity of the capsid amplicon after cloning. This method should allow to eliminate all clones containing non-specific amplification products. In an alternative embodiment, the innermost sequence can also be used to design a nested PCR primer in order to increase the specificity of amplification (FIG. 59A – FIG. 59C).

[0380] Several insertion sites of the tandem barcode to test the impact on virus viability and titers were explored. A series of constructs were engineered with the barcode inserted in the AAV intron of the CAG9 plasmid (FIG. 60A). Since AAV intron is spliced during virus production, the presence of the barcode should have only a minimal impact on the yields. Conversely, the AAV splicing is very ineffective in the absence of helper functions (Mouw et al., 2000), therefore the barcode sequence will be preserved in the RNA recovered from animal tissue. All intronic barcode constructs were tested for their ability to produce high titer AAV progeny by cotransfecting them with pHelper and pREP3stop plasmids. All constructs allowed high titer AAV production going from 50% to 80% of non-barcoded CAG9 virus (FIG. 60B).

[0381] RNA splicing analysis from transfected cells showed that the rate of AAV intron splicing was slightly different between constructs and was more efficient when the intronic barcode was inserted after a conserved intervening sequence downstream of the splice donor (FIG. 58C, upper panel).

[0382] Globin intron splicing was 100% effective in all tested conditions (FIG. 60C, lower panel). As expected, AAV intron splicing was almost undetectable in the absence of helper functions.

[0383] An alternative platform was tested where the tandem barcode was placed between the capsid stop codon and the polyadenylation signal (FIG. 59B). Titers produced by the 3'-barcoded constructs were identical to the non-barcoded CAG9 construct.

[0384] Overall, external barcoding of full-length capsid allows highly efficient AAV production, and the novel tandem barcode platform allows NGS-driven sequence-specific recovery from library preparations with high confidence.

Table 12 Sequences

DESCRIPTION SEQ ID NO:	NUCLEIC ACID SEQUENCE
PREP2 SEQ ID NO: 4	CGCAGGGTCTCCATTTTGAAGCGGGAGGTTTGAACGCGCAGCCGCCATGCCGGGGTTTTA CGAGATTGTGATTAAGGTCCCCAGCGACCTTGACGAGCATCTGCCCGGCATTTCTGACAG CTTTGTGAACTGGGTGGCCGAGAAGGAATGGGAGTTGCCGCCAGATTCTGACATGGATCT GAATCTGATTGAGCAGGCACCCCTGACCGTGGCCGAGAAGCTGCAGCGCGACTTTCTGAC GGAATGGCGCCGTGTGAGTAAGGCCCCGGAGGCTCTTTCTTTGTGCAATTTGAGAAGGG AGAGAGCTACTTCCACATGCACGTGCTCGTGGAACCACCGGGGTGAAATCCATGGTTTT GGGACGTTTTCTGAGTCAGATTGCGGAAAAACTGATTTCAGAGAATTTACCGCGGGATCGA GCCGACTTTGCCAAACTGGTTCGCGGTCAAAAAGACCAGAAATGGCGCCGGAGGCGGGA ACAAGGTGGTGGATGAGTGCTACATCCCCAATTACTTGCTCCCCAAAACCCAGCCTGAGC TCCAGTGGGCGTGGACTAATATGGAACAGTATTAAAGCGCCTGTTGAATCTCACGGAGC GTAAACGGTTGGTGGCGCAGCATCTGACGCACGTGTCGACAGCGCAGGAGCAGAACAAA GAGAATCAGAATCCCAATTCTGATGCGCCGGTGATCAGATCAAAAACTTCAGCCAGGTAC ATGGAGCTGGTGGGTGGCTCGTGGAACAAGGGGATTACCTCGGAGAAGCAGTGGATCCA GGAGGACCAGGCCTCATACATCTCCTTCAATGCGGCCTCCAACCTCGCGGTCCCAATCAA GGCTGCCTTGGACAATGCGGGAAAGATTATGAGCCTGACTAAAACCGCCCCCGACTACCT GGTGGGCCAGCAGCCCGTGGAGGACATTTCCAGCAATCGGATTTATAAAATTTTGAAGT AAACGGGTACGATCCCCAATATGCGGCTTCCGTCTTTCTGGGATGGGCCACGAAAAAGTT CGGCAAGAGGAACACCATCTGGCTGTTTGGGCCTGCAACTACCGGGAAGACCAACATCG CGGAGGCCATAGCCACACTGTGCCCTTCTACGGGTGCGTAAACTGGACCAATGAGAACT TTCCCTTCAACGACTGTGTGACAAGATGGTGATCTGGTGGGAGGAGGGGAAGATGACC GCCAAGGTCTGGAGTCGGCCAAAGCCATTCTCGGAGGAAGCAAGGTGCGCGTGGACCA GAAATGCAAGTCTCGGCCAGATAGACCCGACTCCCGTGATCGTCACCTCCAACACCAA CATGTGCGCCGTGATTGACGGGAACCTCAACGACCTTCGAACACCAGCAGCCGTTGCAAGA CCGGATGTTCAAATTTGAACTACCCGCGCTCTGGATCATGACTTTGGGAAGGTCACCAA GCAGGAAGTCAAAGACTTTTTCCGGTGGGCAAAGGATCACGTGGTTGAGGTGGAGCATG AATTCTACGTCAAAAAGGGTGGAGCCAAGAAAAAGACCCGCCCCAGTGACGCAGATATA AGTGAGCCCAAACGGGTGCGCGAGTCAGTTGCGCAGCCATCGACGTACAGACGCGGAAGC TTCGATCAACTACGCAGACAGGTACCAAAAACAAATGTTCTCGTCACGTGGGCATGAATCT GATGCTGTTCCCTGCAGACAATGCGAGAGAATGAATCAGAATTCAAATATCTGCTTCAC TCACGGACAGAAAGACTGTTTAGAGTGCTTTCCCGTGTCAGAATCTCAACCCGTTTCTGTC GTCAAAAAGGCGTATCAGAACTGTGCTACATTATCATATCATATGAGGAAAGGTGCCAGAC GCTTGCACTGCCTGCGATCTGGTCAATGTGGATTTGGATGACTGCATCTTTGAACAATAA ATGATTTAAATCAGGTATGGCTGCCGATGGTTATCTTCCAGATTGGCTCGAGGACACTCTC TCTGAAGGAATAAGACAGTGGTGGAAGCTCAAACCTGGCCACCACCAACAAAGCCCGC AGAGCGGCATAAGGACGACAGCAGGGTCTTGTGCTTCCTGGGTACAAGTACCTCGGAC CCTTCAACGGACTCGACAAGGGAGAGCCGGTCAACGAGGCAGACGCCGCGGCCCTCGAG CACGACAAAGCCTACGACCGGCAGCTCGACAGCGGAGACAACCCGTACCTCAAGTACAA CCACGCCGACGCGGAGTTTCAGGAGCGCCTTAAAGAAGATACGTCTTTTGGGGGCAACCT CGGACGAGCAGTCTTCAGGCGAAAAAGAGGGTCTTGAACCTCTGGGCCTGGTCCACCA TACCTTCGATTATCCGATTTGCTTGTTAATCAATAAACCGTTTAATTCGTTTCAGTTGAACT TTGGTCTCTGCGTATTTCTTTCTATCTAGTTTCCATGCTCTAGAGCGGCCCGCCACCGCGGT GGAGCTCCAGCTTTTGT

CMV9-BSTEII SEQ ID NO: 5	TTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCC CGACGCCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGT GGCCAACTCCATCACTAGGGGTTCTTGGAGGGGTGGAGTCGTGACGATATCGTTTAAACC GCGTCGTTACATAACTTACGGTAAATGGCCCCGCTGGCTGACCGCCCAACGACCCCCGCC CATTGACGTCAATAATGACGTATGTTCCCATAGTAACGCCAATAGGGGACTTTCCATTGAC GTCAATGGGTGGAGTATTTACGGTAAACTGCCCCTTGGCAGTACATCAAGTGTATCATA TGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAATGGCCCCGCTGGCATTATGCCC AGTACATGACCTTATGGGACTTTCTACTTGGCAGTACATCTACGTATTAGTCATCGCTAT TACCATGGTGATGCGGTTTTTGGCAGTACATCAATGGGCGTGGATAGCGGTTTGACTCACG GGGATTTCCAAGTCTCCACCCCATTTGACGTCAATGGGAGTTTGTGTTTGGCACCAAAATCA ACGGGACTTTCCAAAATGTCGTAACAACCTCCGCCCCATTGACGCAAATGGGCGGTAGGCG TGTACGGTGGGAGGTCTATATAAGCAGAGCTCGGGAGCGGTCAACCAAGCAGGAAGTCAA AGACTTTTTCCGGTGGGCAAAGGATCACGTGGTTGAGGTGGAGCATGAATTTACGTCAA AAAGGGTGGAGCCAAGAAAAAGACCCGCCCCAGTGACGCAGATATAAGTGAGCCCAAAAC GGGTGCAGGAGTCAAGTGGCAGCCATCGACGTGACGCGGGAAGCTTCGATCAACTAC GCGGACAGGTACCAAAACAAATGTTCTCGTCACGTGGGCATGAATCTGATGCTGTTTCCC TGCAGACAATGCGAGAGACTGAATCAGAATTCAAATATCTGCTTCACTCACGGTGTCAAA GACTGTTTAGAGTGCTTTCCCGTGTGAGAATCTCAACCCGTTTCTGTGTCGCAAAAGGCGT ATCAGAAACTGTGCTACATTACATCATCATGGGAAAGGTGCCAGCGCTTGCACTGCTT GCGACCTGGTCAATGTGGACTTGGATGACTGTGTTTCTGAACAATAAATGACTTAAACCA GGTATGGCTGCCGATGGTTATCTTCCAGATTGGCTCGAGGACAACCTTAGTGAAGGAATT CGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCCTCAACCCAAGGCAAATCAACAACATCA AGACAACGCTCGAGGTCTGTGCTTCCGGGTTACAAATACCTTGGACCCGGCAACGACT CGACAAGGGGGAGCGGTCAACGCAGCAGACGCGCGGCCCTCGAGCACGACAAGGCCT ACGACCAGCAGCTCAAGGCCGAGACAACCCGTACCTCAAGTACAACCACGCCGACGCC GAGTTCAGGAGCGGCTCAAAGAAGATACGTCTTTGGGGGCAACCTCGGGCGAGCAGT CTTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCTGGTTGAGGAAGCGGCTAAGAC GGCTCCTGGAAAGAAGAGGGCTGTAGAGCAGTCTCCTCAGGAACCGGACTCCTCCGCGG GTATTGGCAAATCGGGTGACAGCCCGCTAAAAAGAGACTCAATTTCCGTCAGACTGGCG ACACAGAGTCAGTCCAGACCCTCAACCAATCGGAGAACCTCCCGCAGCCCCCTCAGGTG TGGGATCTCTACAATGGCTTCAGGTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTG CCGATGGAGTGGGTAGTTCCTCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACA GAGTCATCACCAACAGCACCCGAACCTGGGCCCTGCCCACCTACAACAATCACTCTACA AGCAAATCTCCAACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACA GCACCCCTGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTACCACGTGACTG GCAGCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCTT CAACATTCAAGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATGCCAATAACC TTACCAGCACGGTCCAGGTCTTACGGACTCAGACTATCAGTCCCGTACGTGCTCGGGT CGGCTCACGAGGGCTGCCTCCCGCGTTCACAGCGGACGTTTTTCATGATTCTCAGTACG GGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTGCTTCGTCTTTTACTGCCTGG AATATTTCCCGTCGCAAAATGCTAAGAACGGGTAAACAACCTTCCAGTTCAGCTACGAGTTT AGAACGTACCTTTCCATAGCAGTACGCTACAGCCAAAGCCTGGACCGTCACTTGAATC CACTCATCGACCAATACTTGTACTATCTCTCAAAGACTATTAACGGTCTGGACAGAATC AACAAACGCTAAAATTCAGTGTGGCCGGACCCAGCAACATGGCTGTCCAGGGAAGAAAC TACATACCTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAAACAAC AACAGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTTGA TGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTCCTTTGT CTGGATCTTTAATTTTTTGGCAAAACAAGGAACTGGAAGAGACAACGTGGATGCGGACAAA GTCATGATAACCAACGAAGAAGAAATTAATACTACTAACCCGTAGCAACGGAGTCCCTA TGGACAAGTGGCCACAAACACAGAGTGGCCAAGCACAGGCGCAGACCGGCTGGGTTT AAAACCAAGGAATACTTCCGGGTATGGTTTGGCAGGACAGAGATGTGTACCTGCAAGGA CCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTTTACCCCTTCTCCGCTGATGGGA GGGTTTGGGAATGAAGCACCCGCCTCTCAGATCCTCATCAAAAACACACCTGTACCTGCG GATCCTCCAACGGCCTTCAACAAGGACAAGCTGAACTCTTTCATCACCCAGTATTCTACT GGCCAAGTCAGCGTGGAGATCGAGTGGGAGCTGCAGAAGGAAAACAGCAAGCGCTGGA ACCCGGAGATCCAGTACACTTCCAATTACAAGTCTAATAATGTTGAATTTGCTGTTAA TACTGAAGGTGTATATAGTGAACCCCGCCCCATTGGCACCAAGATACCTGACTCGTAATCT GTAATCGATTGTTAATCAATAAACCGTTTAATTCGTTTCAGTTGAACCTTTGGTCTCTGCGT ATTTCTTTCTTATCTAGTTTCCATGGCTACGTAGATAAGTAGCATGGCGGGTTAATCATT ACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCA CTGAGGCCGGGCGACCAAAGTCCGCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTG AGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAA

PREP-AAP SEQ ID NO: 6	GTCGACGGTATCGGGGGAGCTCGCAGGGTCTCCATTTTGAAGCGGGAGGTTTGAACGCGC AGCCGCCATGCCGGGGTTTACGAGATTGTGATTAAGGTCCCCAGCGACCTTGACGAGCA TCTGCCCGGCATTTCTGACAGCTTTGTGAAGTGGTGGCCGAGAAGGAATGGGAGTTGCC GCCAGATTCTGACATGGATCTGAATCTGATTGAGCAGGCACCCCTGACCGTGGCCGAGAA GCTGCAGCGCGACTTTCTGACGGAATGGCGCCGTGTGAGTAAGGCCCCGGAGGCTCTTTT CTTTGTGCAATTTGAGAAGGGAGAGAGCTACTTCCACATGCACGTGCTCGTGAAACCAC CGGGGTGAAATCCATGGTTTTGGGACGTTTCCTGAGTCAGATTCCGCAAAAAGTATTCA GAGAATTTACCGCGGGATCGAGCCGACTTTGCCAACTGGTTCGCGGTACAAAAGACCAG AAATGGCGCCGGAGGCGGGAACAAGGTGGTGGATGAGTGCTACATCCCAATTACTTGC TCCCCAAAACCCAGCCTGAGCTCAGTGGGCGTGGACTAATATGGAACAGTATTTAAGCG CCTGTTTGAATCTCACGGAGCGTAAACGGTTGGTGGCGCAGCATCTGACGCACGTGTGCG AGACGCAGGAGCAGAACAAAGAGAATCAGAATCCCAATTCTGATGCGCCGGTGATCAGA TCAAAAACCTTCAGCCAGGTACATGGAGCTGGTGGGTGGCTCGTGGAACAAGGGGATTAC CTCGGAGAAGCAGTGGATCCAGGAGGACCAGGCCTCATACATCTCCTCAATCGCGCCTC CAACTCGCGGTCCCAAATCAAGGCTGCCTTGGACAATGCGGGAAGATTATGAGCCTGAC TAAAACCGCCCCGACTACCTGGTGGGCCAGCAGCCCGTGGAGGACATTTCCAGCAATCG GATTTATAAAATTTTGAAGTAAACGGGTACGATCCCCAATATGCGGCTTCCGCTTTCTG GGATGGGCCACGAAAAGTTTCGGCAAGAGGAACACCATCTGGCTGTTTGGGCTGCAAC TACCGGGAAGACCAACATCGCGGAGGCCATAGCCACACTGTGCCCTTACCGGTGCGT AAAGTGGACCAATGAGAACTTTCCCTTCAACGACTGTGTGACAAGATGGTGATCTGGTG GGAGGAGGGGAAGATGACCGCCAAGGTCTGGAGTGGGCCAAAGCCATTCTCGGAGGAA GCAAGGTGCGCGTGGACCAGAAATGCAAGTCTCGGCCAGATAGACCCGACTCCCGTG ATCGTCACTCCAACACCAACATGTGCGCCGTGATTGACGGGAACCTAACGACCTTCGAA CACCAGCAGCCGTTGCAAGACCGGATGTTCAAATTTGAAGTCAACCGCCGTCTGGATCAT GACTTTGGGAAGGTCACCAAGCAGGAAGTCAAAGACTTTTTCCGGTGGGCAAAGGATCA CGTGGTTGAGGTGGAGCATGAATTCTACGTCAAAAAGGTTGGAGCCAAGAAAAGACCCG CCCCCAGTGACGCAGATATAAGTGAGCCCAAACGGGTGCGCGAGTCAGTTGCGCAGCCA TCGACGTGACAGCGGGAAGCTTCGATCAACTACGCGGACAGGTACCAAAAACAAATGTTCT CGTCACGTGGGCATGAATCTGATGCTGTTTCCCTGCAGACAATGCGAGAGACTGAATCAG AATTCAAATATCTGCTTCACTACGGTGTCAAAGACTGTTTAGAGTGCTTTCCCGTGTGAG AATCTCAACCCGTTTCTGTGCTCAAAAAGGCGTATCAGAACTGTGCTACATTATCACA TCATGGGAAAGGTGCCAGACGCTTGCAGTGTGCGACCTGGTCAATGTGGACTTGGATG ACTGTGTTTCTGAACAATAAATGACTTAAACCAAGGTATGGCTGCCGATGGTATCTTCCA GATTGGCTCGAGGACAACCTTAGTGAAGGAATTCGCGAGTGGTGGGCTTTGAAACCTGGA GCCCCTCAACCCAAGGCAAAATCAACAACATCAAGACAACGCTCGAGGTCTTGTGCTCCG GGTTACAAATACCTTGACCCGGCAACGGACTCGACAAGGGGGAGCCGGTCAACGCAGC AGACGCGGCGCCCTCGAGCAGGACAAGGCCTACGACCAGCAGCTCAAGGCCGAGACA ACCCGTACCTCAAGTACAACCAACGCGGACGCGGAGTTCCAGGAGCGGCTCAAAGAAGAT ACGTCTTTTGGGGCAACCTCGGGCGAGCAGTCTTCCAGGCCAAAAGAGGCTTCTTGAA CCTCTTGGTCTGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGA GCAGTCTCCTCAGGAACCGGACTCCTCCGCGGTATTGGCAAATCGGGTGACAGCCCGC TAAAAAGAGACTCAATTTGGTCAAGTGGCGACACAGAGTCACTCCGACCCCTCAACCT AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAGGTGG TGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCTCTCGGGAA ATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAGCACCCGAACCT GGGCCCTGCCACCTACAACAATCACCTCTACAAGCAAATCTCCAACAGCACATCTGGAG GATCTTCAAATGACAACGCTACTTCGGCTACAGCACCCCTGGGGGTATTTTGACTTCA ACAGATTCCACTGCCACTTCTACCCACGTGACTGGCAGCGACTCATCAACAACAAGTGGG GATTCCGGCCTAAGCGACTCAACTTCAAGCTCTTCAACATTCAGGTCAAAGAGGTTACGG ACAACAATGGAGTCAAGACCATCGCCAATAACCTTACCAGCACGGTCCAGGTCTTACGG ACTCAGACTATCAGTCTCCGTACGTGCTCGGGTCCGCTCACGAGGGCTGCCTCCCGCCGT TCCCAGCGGACGTTTTTCATGATTCTCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCC AGGCCGTGGGTCTTCGTCCTTTTACTGCCTGGAATATTTCCCGTCGCAAAATGCTAAGAAC GGGTAACAACCTTCCAGTTCAGTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGC TCACAGCCAAAGCCTGGACCGACTAATGAATCCACTCATCGACCAATACTTGTACTATCT CTCAAAGACTATTAACGGTTCTGGACAGAATCAACAAACGCTAAATTCAGTGTGGCCGG ACCAGCAACATGGCTGTCCAGGGAAGAACTACATACCTGGACCCAGTACCGACAAC AACGTGTCTCAACCACTGTGACTCAAAACAACAACAGCGAATTTGCTTGGCTGGAGCTT CTTCTTGGGCTCTCAATGGACGTAATAGCTTGATGAATCCTGGACCTGCTATGGCCAAGTC AGCGTGGAGATCGAGTGGGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGA TCCAGTCACTTCCAACATAATTACAAGTCTAATAATGTTGAATTTGCTGTTAATGAAGG TGTATATAGTGAACCCCGCCCCATTGGCACCAAGATACCTGACTCGTAATCTGTAATTGCTT GTTAATCAATAAACCGTTTAATTCGTTTCAAGTTGAAGTTTGGTCTC

PREP3STOP SEQ ID NO: 7	GTCGACGGTATCGGGGGAGCTCGCAGGGTCTCCATTTTGAAGCGGGAGGTTTGAACGCGC AGCCGCCATGCCGGGGTTTACGAGATTGTGATTAAGGTCCCCAGCGACCTTGACGAGCA TCTGCCCGGCATTTCTGACAGCTTTGTGAAGTGGGTGGCCGAGAAGGAATGGGAGTTGCC GCCAGATTCTGACATGGATCTGAATCTGATTGAGCAGGCACCCCTGACCGTGGCCGAGAA GCTGCAGCGCGACTTTCTGACGGAATGGCGCCGTGTGAGTAAGGCCCCCGAGGCTCTTTT CTTTGTGCAATTTGAGAAGGGAGAGAGCTACTTCCACATGCACGTGCTCGTGAAACCAC CGGGGTGAAATCCATGGTTTGGGACGTTTCCTGAGTCAGATTCCGCAAAAACCTGATTCA GAGAATTTACCGCGGGATCGAGCCGACTTTGCCAACTGGTTCGCGGTCACAAGACCAG AAATGGCGCCGGAGGCGGGAACAAGGTGGTGGATGAGTGCTACATCCCAATTACTTGC TCCCCAAAACCCAGCCTGAGCTCAGTGGGCGTGGACTAATATGGAACAGTATTTAAGCG CCTGTTTGAATCTCACGGAGCGTAAACGGTTGGTGGCGCAGCATCTGACGCACGTGTGCG AGACGCAGGAGCAGAACAAAGAGAATCAGAATCCCAATTCTGATGCGCCGGTGATCAGA TCAAAAACCTTCAGCCAGGTACATGGAGCTGGTGGGTGGCTCGTGGACAAGGGGATTAC CTCGGAGAAGCAGTGGATCCAGGAGGACCAGGCCTCATACATCTCCTTCAATCGCGCTC CAACTCGCGGTCCCAAATCAAGGCTGCCTTGGACAATGCGGGAAGATTATGAGCCTGAC TAAAACCGCCCCGACTACCTGGTGGGCCAGCAGCCGTGGAGGACATTTCCAGCAATCG GATTTATAAAATTTTGAAGTAAACGGGTACGATCCCCAATATGCGGCTTCCGCTTTCTG GGATGGGCCACGAAAAAGTTCGGCAAGAGGAACACCATCTGGCTGTTTGGGCCTGCAAC TACCGGGAAGACCAACATCGCGGAGGCCATAGCCACACTGTGCCCTTACCGGTGCGT AAAGTGGACCAATGAGAACTTTCCCTTCAACGACTGTGTGACAAGATGGTGATCTGGTG GGAGGAGGGGAAGATGACCGCCAAGGTCTGGAGTGGGCCAAAGCCATTCTCGGAGGAA GCAAGGTGCGCGTGGACCAGAAATGCAAGTCTCGGCCAGATAGACCCGACTCCCGTG ATCGTCACTCCACACCAACATGTGCGCCGTGATTGACGGGAACCTAACGACCTTCGAA CACCAGCAGCCGTTGCAAGACCGGATGTTCAAATTTGAAGTCAACCGCCGTCTGGATCAT GACTTTGGGAAGGTCACCAAGCAGGAAGTCAAAGACTTTTCCGGTGGGCAAAGGATCA CGTGGTTGAGGTGGAGCATGAATTCTACGTCAAAAAGGTTGGAGCCAAGAAAAGACCCG CCCCCAGTGACGCAGATATAAGTGAGCCCAAACGGGTGCGCGAGTCAGTTGCGCAGCCA TCGACGTGACAGCGGGAAGCTTCGATCAACTACGCGGACAGGTACCAAAAACAAATGTTCT CGTCACGTGGGCATGAATCTGATGCTGTTTCCCTGCAGACAATGCGAGAGACTGAATCAG AATTCAAATATCTGCTTCACTACGGTGTCAAAGACTGTTTAGAGTGCTTTCCCGTGTGAG AATCTCAACCCGTTTCTGTGCTCAAAAAGGCGTATCAGAACTGTGCTACATTCATACA TCATGGGAAAGGTGCCAGACGCTTGCAGTGTGCGACCTGGTCAATGTGGACTTGGATG ACTGTGTTTCTGAACAATAAATGACTTAAACCAAGGTATGGCTGCCGATGGTTAGCTTCCA GATTGGCTCGAGGACAACCTTAGTGAAGGAATTCGCGAGTGGTGGGCTTTGAAACCTGGA GCCCCTCAACCAAGGCAAAATCAACAACATCAAGACAACGCTCGAGGTCTTGTGCTTCCG GGTTACAAATACCTTGACCCGGCAACGGACTCGACAAGGGGGAGCCGGTCAACGCAGC AGACGCGGCGCCCTCGAGCAGCAGCAAGGCCTACGACCAGCAGCTCAAGGCCGAGACA ACCCGTACCTCAAGTACAACCAACGCGGACGCGGAGTTCCAGGAGCGGCTCAAGAAGAT ACGTCTTTTGGGGCAACCTCGGGCGAGCAGTCTTCCAGGCCAAAAGAGGCTTCTTGAA CCTCTTGGTCTGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAGTAGAGGCCGTGTAGAG CAGTCTCCTCAGGAACCGGACTCCTCCGCGGTATTGGCAAATCGGGTGACAGCCCGCT AAAAAGAGACTCAATTTCCGTGACAGTGGCGACACAGAGTCACTGCTCAACCCCTCAAC AATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAGGTGG TGGCGCACCAGTGGCAGACAATAACTAAGGTGCCGATGGAGTGGGTAGTTCTCTCGGGAA ATTGGCATTGCGATTCCCAATGGCTGGGGGACAGATCATCACCACCAGCACCCGAACCT GGGCCCTGCCACCTACAACAATCACCTCTACAAGCAAATCTCCAACAGCACATCTGGAG GATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCTGGGGGTATTTTGACTTCA ACAGATTCCACTGCCACTTCTACACCGTGAAGTGGCAGCGACTCATCAACAACAAGTGGG GATTCCGGCCTAAGCGACTCAACTTCAAGCTCTTCAACATTCAGGTCAAAGAGGTTACGG ACAACAATGGAGTCAAGACCATCGCCAATAACCTTACCAGCACGGTCCAGGTCTTACGG ACTCAGACTATCAGTCTCCGTACGTGCTCGGGTCCGCTCACGAGGGCTGCCTCCCGCCGT TCCAGCGGACGTTTTCATGATTCTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCC AGGCCGTGGGTCTTCGTCCTTTTACTGCCTGGAATATTTCCCGTCGCAAAATGCTAAGAAC GGGTAACAACCTTCCAGTTCAGTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGC TCACAGCCAAAGCCTGGACCGACTAATGAATCCACTCATCGACCAATACTTGTACTATCT CTCAAAGACTATTAACGGTTCTGGACAGAATCAACAAACGCTAAATTCAGTGTGGCCGG ACCAGCAACATGGCTGTCCAGGGAAGAACTACATACCTGGACCCAGTACCGACAAC AACGTGTCTCAACCACTGTGACTCAAAACAACAACAGCGAATTTGCTTGGCTGGAGCTT CTTCTTGGGCTCTCAATGGACGTAATAGCTTGATGAATCCTGACCTGCTATGGCCAAGTC AGCGTGGAGATCGAGTGGGAGCTGCAGAAGGAAAAACAGCAAGCGCTGGAACCCGGAGA TCCAGTCACTTCCAACATAAAGTCTAATAATGTTGAATTTGCTGTTAATGTAAGG TGTATATAGTGAACCCCGCCCCATTGGCACCAAGATACCTGACTCGTAATCTGTAATTGCTT GTTAATCAATAAACCGTTTAATTCGTTTCAAGTTGAAGTTTGGTCTC

SYN-CAP9 SEQ ID NO: 8	TTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCC CGACGCCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGT GGCCAACTCCATCACTAGGGGTTCTTGGAGGGGTGGAGTCGTGACGATATCTAGTATCTG CAGAGGGCCCTGCGTATGAGTGCAAGTGGGTTTTAGGACCAGGATGAGGCGGGGTGGGG GTGCTACCTGACGACCGACCCCGACCACTGGACAAGCACCCAACCCCATTTCCCCAAA TTGCGCATCCCCATCAGAGAGGGGGAGGGGAAACAGGATGCGGCGAGGCGCGTGCACA CTGCCAGCTTCAGCACCGCGGACAGTGCCTTCGCCCCCGCTGGCGGCGCGGCCACCGC CGCCTCAGCACTGAAGGCGCGCTGACGTCACTCGCCGGTCCCCCGCAAACCTCCCTTCCC GGCCACCTTGCTCGCGTCCGCGCCGCGCCGCGCCAGCCGACCGCACACGCGAGGCG CGAGATAGGGGGGCACGGGCGCGACCATCTGCGCTGCGGCGCCGCGCACTCAGCGCTGC CTCAGTCTGCGGTGGGCAGCGGAGGAGTCGTGTCGTGCTGAGAGCGCAGCTGTGCTCCT GGGCACCGCGCAGTCCGCCCCCGCGGCTCCTGGCCAGACCACCCCTAGGACCCCTGCC CAAGTCGCAGCCGGTACCAAGCAGGAAGTCAAAGACTTTTTCCGGTGGGCAAAGGATC ACGTGGTTGAGGTGGAGCATGAATTCTACGTCAAAAAGGGTGGAGCCAAAGAAAAGACC GCCCCAGTGACGCAGATATAAGTGAGCCCAAACGGGTGCGCGAGTCAGTTGCGCAGCC ATCGACGTCAGACGCGGAAGCTTCGATCAACTACGCGGACAGGTACCAAAACAAATGTT CTCGTCACGTGGGCATGAATCTGATGCTGTTTCCCTGCAGACAATGCGAGAGACTGAATC AGAATTCAAATATCTGCTTCACTCACGGTGTCAAAGACTGTTAGAGTGCTTTCCCGTGTC AGAATCTCAACCCGTTTCTGTCTCAAAAAGCGGTATCAGAAACTGTGCTACATTCATCA CATCATGGGAAAGGTGCCAGACGCTTGCCTGCTTGCACCTGGTCAATGTGGACTTGGA TGACTGTGTTTCTGAACAATAAATGACTTAAACAGGTATGGCTGCCGATGGTTATCTTCC AGATTGGCTCGAGGACAACCTTAGTGAAGGAATTCGCGAGTGGTGGGCTTTGAAACCTGG AGCCCTCAACCCAAGGCAAATCAACAACATCAAGACAACGCTCGAGGCTTCAAGCTTCC GGGTTACAAATACCTTGACCCGGCAACGGACTCGACAAGGGGGAGCCGGTCAACGCAG CAGACGCGGCGGCCCTCGAGCACGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGAC AACCCGTACCTCAAGTACAACACGCGGACGCGGAGTTCAGGAGCGGCTCAAAGAAGA TACGTCTTTTGGGGCAACCTCGGGCGAGCAGTCTTCCAGGCCAAAAGAGGCTTCTTGA ACCTCTTGCTGCTGGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAAGAGAGCCCTGTAG AGCAGTCTCCTCAGGAACCGGACTCCTCCGCGGTATTGGCAAATCGGGTGCACAGCCCG CTAAAAGAGACTCAATTCGGTCAGACTGGCGACACAGAGTCAGTCCCAGACCCTCAAC CAATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAAATGGCTTCAGGTG GTGGCGCACCAAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCCTCGGGA AATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACACCAGCACCCGAACC TGGGCCCTGCCACCTACAACAATCACCTCTACAAGCAAATCTCCAACAGCACATCTGGA GGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCTGGGGGTATTTTGACTTC AACAGATTCCACTGCCACTTCTACACCGTGACTGGCAGCGACTCATCAACAACAACCTGG GGATTCCGGCCTAAGCGACTCAACTTCAAGCTCTTCAACATTCAGGTCAAAGAGGTTACG GACAACAATGGAGTCAAGACCATCGCCAATAACCTTACCAGCACGGTCAAGGTTTCAAG GACTCAGACTATCAGCTCCCGTACGTGCTCGGGTGGCTCACGAGGGCTGCTCCCGCG TTCCAGCGGACGTTTTATGATTCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCC AGGCCGTGGGTCTTCGTCCTTTTACTGCCTGGAATATTTCCCGTCGAAATGCTAAGAAC GGGTAAACAATTCCAGTTACGTACGAGTTTGAGAACGTACCTTTCCATAGTACCGC TCACAGCCAAAGCCTGGACCGACTAATGAATCCACTCATCGACCAATACTTGTACTATCT CTCAAAGACTATTAACGTTCTGGACAGAATCAACAAACGCTAAAATTCAGTGTGGCCGG ACCCAGCAACATGGCTGTCCAGGGAAGAACTACATACCTGGACCCAGCTACCGACAAC AACGTGTCTCAACCACTGTGACTCAAAACAACAACAGCGAATTTGCTTGGCCTGGAGCTT CTTCTTGGGCTCTCAATGGACGTAATAGCTTGATGAATCCTGGACCTGCTATGGCCAGCC ACAAAGAAGGAGAGGACCGTTTCTTCTTTGTCTGGATCTTTAATTTTTTGGCAAAACAAG GAAGTGAAGAGACAACGTGGATGCGGACAAAGTCATGATAACCAACGAAGAAGAAAT AAAATACTAACCCTGTAGCAACCGGAGTCTATGGACAAGTGGCCACAAACCACAGAG TGCCCAAGCACAGGCGCAGACCGGCTGGGTTCAAACCAAGGAATACTTCCGGGTATGG TTTGGCAGGACAGAGATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGG ACGGCAACTTTACCCCTTCTCCGCTGATGGGAGGGTTTGAATGAAGCACCCGCTCCTC AGATCCTCATAAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACA AGCTGAACTCTTTCATACCCAGTATTCTACTGGCCAAAGTCAGCGTGGAGATCGAGTGGG AGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCAACTAT TACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATAGTGAACCCGCG CCCATTGGCACCAGATACCTGACTCGTAATCTGTAATCGATTGTTAATCAATAAACCGTTT AATTCGTTTCAGTTGAACTTTGGTCTCTGCGTATTTCTTTCTATCTAGTTTCCATGGCTAC GTAGATAAGTAGCATGGCGGGTTAATCATTAACATAAGGAACCCCTAGTGATGGAGTTG GCACTCCCTCTCTGCGCGCTCGCTCACTGAGGCCGGGCGACCAAGGTGCGCCGA CGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGC CAA

GFAP-CAP9 SEQ ID NO: 9	TTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCC CGACGCCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGT GGCCAACTCCATCACTAGGGGTTCTTGGAGGGGTGGAGTCGTGACGATATCGATCTAACA TATCTTGGTGTGGAGTAGCGGACGCTGTATGACAGAGGCTCGGGGGCCTGAGCTGGCTC TGTGAGCTGGGGAGGAGGCAGACAGCCAGGCCCTTGTCTGCAAGCAGACCTGGCAGCATT GGGCTGGCCGCCCCCAGGGCCTCTCTTCATGCCCAGTGAATGACTACCTTGGCACAG ACACAATGTTTCGGGTGGGCACAGTGCCTGCTTCCCGCCGCACCCAGCCCCCTCAAAT GCCTTCCGAGAAGCCCATTTAGCAGGGGGCTTGCATTGCACCCAGCCTGACAGCCTGGC ATCTTGGGATAAAAAGCAGCACAGCCCCCTAGGGGGCTGCCCTTGCTGTGTGGCGCCACCGG CGGTGGAGAACAAGGCTCTATTACGCTGTGCCAGGAAAGGGGATCAGGGGATGCCCA GGCATGGACAGTGGGTGGCAGGGGGGAGAGGAGGGCTGTCTGCTTCCAGAAGTCCAA GGACACAAATGGGTGAGGGGAGAGCTCTCCCATAGCTGGGTGCGGGCCCAACCCACC CCCTCAGGCTATGCCAGGGGGTGTGGCAGGGGCACCCGGGCATCGCCAGTCTAGCCCCAC TCTTTCATAAAGCCCTCGCATCCAGGAGCGAGCAGAGCCAGAGCAGGTTGGAGAGGAG ACGCATCACCTCCGCTGCTCGCGGGGATCCTCTAGGGTCACCAAGCAGGAAGTCAAAGAC TTTTCCGGTGGGCAAAGGATCACGTGGTTGAGGTGGAGCATGAATTCTACGTCAAAAAG GGTGGAGCCAAGAAAAGACCCGCCCCAGTGACGCAGATATAAGTGAGCCCAAACGGGT GCGCGAGTCAGTTGCGCAGCCATCGACGTCAGACGCGGAAGCTTCGATCAACTACGCGG ACAGGTACCAAAACAAATGTTCTCGTCACGTGGGCATGAATCTGATGCTGTTCCCTGCA GACAATGCGAGAGACTGAATCAGAATTCAAATATCTGCTTCACTACGGTGTCAAAGACT GTTTAGAGTGCTTTCCCGTGTGAGAATCTCAACCCGTTTCTGTGTCGTAAGGCGTATCA GAAACTGTGCTACATTCATCATCATGCGGAAAGGTGCCAGACGCTTGCATTGCTTGGCA CCTGGTCAATGTGACTTGGATGACTGTGTTTCTGAACAATAAATGAAACACGAGT TGGCTGCCGATGGTTATCTTCCAGATTGGCTCGAGGACAACCTTAGTGAAGGAATTCGCG AGTGGTGGGCTTTGAAACCTGGAGCCCCCTCAACCAAGGCAAATCAACAACATCAAGAC AACGCTCGAGGTCTTGTGCTTCCGGGTACAAATACCTTGGACCCGGCAACGGACTCGAC AAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCAGACAAGGCCTACGA CCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACAACCAACGCGCAGCCGAGT TCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGCAACCTCGGGCGAGCAGTCTTCC AGGCCAAAAGAGGCTTCTTGAACCTCTTGGTCTGGTTGAGGAAGCGGCTAAGACGGCTC CTGGAAAAGAAGAGGCCTGTAGAGCAGTCTCCTCAGGAACCCGACTCCTCCGCGGGTATTG GCAAATCGGGTGCACAGCCCGCTAAAAAGAGACTCAATTCGGTCAGACTGGCGACACA GAGTCAGTCCCAGACCCTCAACCAATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGA TCTCTTACAATGGCTTCAGGTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGAT GGAGTGGGTAGTTCCTCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTC ATCACCACCAGCACCCGAACCTGGGCCCTGCCACCTACAACAATCACCTCTACAAGCAA ATCTCCAACAGCAGATCTGGAGGATCTTCAAATGACAACGCTACTCTCGGCTACAGCACC CCTGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTACCACGTGACTGCGCAGC GACTCATCAACAACAACCTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCTTACA TTCAGGTCAAAGAGGTACCGGACAACAATGGAGTCAAGACCATCGCCAATAACCTTACC AGCAGGTTCCAGGTCTTACGGACTCAGACTATCAGTCCCGTACGTGCTCGGGTGGGT CACGAGGGCTGCCTCCCGCGTTCAGCGGACGTTTTCATGATTCCTCAGTACGGGTATC TGACGCTTAATGATGGAAGCCAGGCCGTGGGTGCTTCGTCTTTTACTGCCTGGAATATTT CCCGTCGCAATGCTAAGAACGGGTAAACAACCTCCAGTTCAGCTACGAGTTTGAGAACGT ACCTTTCCATAGCAGTACGCTCACAGCCAAAGCCTGGACCGACTAATGAATCCACTCAT CGACCAATACTTGTACTATCTCTCAAAGACTATTAACGGTTCTGGACAGAATCAACAAAC GTAAAATTAGTGTGGCCGGACCCAGCAACATGGCTGTCCAGGGAAGAAAACATACATAC CTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAACAGC GAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTTGATGAATC CTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTCTTTGTCTGGAT CTTTAAATTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGATGCGGACAAAGTCATG ATAACCAACGAAGAAGAAATTAATACTACTAACCCTAGCAACGGAGTCCCTATGGACA AGTGGCCACAACACCAGAGTGCCCAAGCACAGGCGCAGACCGGCTGGGTTCAAACACC AAGGAATACTTCCGGGTATGGTTTGGCAGGACAGAGATGTGTACCTGCAAGGACCCATT GGGCAAAATTCCTCACACGGACGGCAACTTTCACCTTCTCCGCTGATGGGAGGGTTTG GAATGAAGCACCCGCCTCTCAGATCCTCATCAAAAACACACCTGTACCTGCGGATCCTC CAACGGCCTTCAACAAGGACAAGCTGAACTCTTTCATCACCCAGTATTCTACTGGCCAAG TCAGCGTGGAGATCGAGTGGGAGCTGCAGAAGGAAAAACAGCAAGCGCTGGAACCCGGA GATCCAGTACACTTCCAATATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAA GGTGTATATAGTGAACCCCGCCCCATTGGCACCAGATACCTGACTCGTAATCTGTAATCG ATTGTTAATCAATAAACCGTTTAAATTCGTTTCACTTGAACCTTGGTCTTTCGCTATCTT CTTATCTAGTTTCCATGGCTACGTAGATAAGTAGCATGGCGGGTTAATCATTAACCTACAA GGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGC CGGGCGACCAAAGGTCGCCCGACGCCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGC GAGCGCGCAGAGAGGGAGTGGCCAA

CAG-CAP9 SEQ ID NO: 10	TTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCC CGACGCCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGT GGCCAACTCCATCACTAGGGGTTCTTGGAGGGGTGGAGTCGTGACGATATCCATGCGTCG ACATAACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGGGTCATT AGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCCCTGG CTGACCGCCCAACGACCCCCGCCATTGACGTCAATAATGACGTATGTTCCCATAGTAAC GCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAACTGCCCACTT GGCAGTACATCAAGTGATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAA ATGGCCCCCTGGCATTATGCCAGTACATGACCTTATGGGACTTCTACTTGGCAGTAC ATCTACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCAT CTCCCCCCCCCTCCCCACCCCCAATTTGTATTATTTATTTTAAATTATTTGTGCAGCGA TGGGGGCGGGGGGGGGGGGGCGCGGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCG GGGGCGAGGCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCC TTTTATGGCGAGGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGG GAGCAAGCTTCGTTTAGTGAACCGTCAGATCGCTGGAGACGCCATCCACGTGTTTTGA CCTCCATAGAAGACACCGGACCGATCCAGCCTCCGCGGATTGCAATCCCGGCCGGGAA CGGTGCATTGGAACGCGGATTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTC TATAGGCCACAAAAATGCTTTCTTTTAAATATACTTTTTTGTATCTTATTTCTAAT ACTTTCCCTAATCTCTTTCTTTCAGGGCAATAATGATACAATGTATCATGCTCTTTGCGAC CATTCTAAAGAATAACAGTGATAATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATAT AAATATTTCTGCATATAAATTGTAACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTA CAATCCAGCTACCATTTCTGCTTTTATTTATGGTTGGGATAAGGCTGGATTATTTCTGAGTC CAAGCTAGGCCCTTTGCTAATCATGTTTCATACCTCTTATCTTCCCTCAGCTCTGGG CAACGTGCTGGTCTGTGTGCTGGCCCATCACTTTGGCAAAGAATTGGGATTGCAACCGGT CACCAAGCAGGAAGTCAAAGACTTTTTCCGGTGGGCAAAGGATCACGTGGTTGAGGTGG AGCATGAATTCTACGTCAAAAAGGGTGGAGCCAAGAAAAGACCCGCCCCAGTGACGCA GATATAAGTGAGCCCAAACGGGTGCGCGAGTCAGTTGCGCAGCCATCCAGCTCAGACGC GGAAGCTTCGATCAACTACGCGGACAGGTACCAAAACAAATGTTCTCGTACGTGGGCAT GAATCTGATGCTGTTTCCCTGCAGACAATGCGAGAGACTGAATCAGAATTCAAAATATCTG CTTCACTACGGTGTCAAAGACTGTTTAGAGTGCTTTCCCGTGTGAGAATCTCAACCCGTT TCTGTCTGCAAAAAGGCGTATCAGAACTGTGTACATTATCATCATGGAAGAGGTG CCAGACGCTTGCACTGCTTGCAGCTGGTCAATGTGGACTTGGATGACTGTGTTTCTGAAC AATAAATGACTTAAACCAGGTATGGCTGCCGATGGTTATCTTCCAGATTGGCTCGAGGAC AACCTTAGTGAAGGAATTCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCCTCAACCCAAG GCAAAATCAACAACATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTTACAAATACCTT GGACCCGGCAACGGAATCGACAAGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCT CGAGCAGACAAGGCCTACGACAGCTCAAGGCCGAGACAACCCGTAACCTCAAGT ACAACACGCGGACGCGGAGTTCCAGGAGCGGCTCAAAGAAGATACGCTTTTGGGGGC AACCTCGGGCGAGCAGTCTTCCAGGCCAAAAGAGGCTTCTTGAACCTCTTGGTCTGGTT GAGGAAGCGGCTAAGACGGCTCCTGGAAAAGAGAGGCTGTAGAGCAGTCTCTCAGGA ACCGGACTCTCCGCGGGTATTGGCAAATCGGGTGACAGCCCGCTAAAAAGAGACTCA ATTTCCGTACAGCTGGCGACACAGAGTCACTCCAGACCTCAACCAATCCGAGGACCTC CCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAGGTGGTGGCGCACCAGTGG CAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCTCGGGAATTTGGCATTGCGATT CCCAATGGCTGGGGGACAGAGTCATCACACCAGCACCAGAACCTGGGGCCTGCCACCT ACAACAATCACCTCTACAAGCAAATCTCCAACAGCACATCTGGAGGATCTTCAAAATGACA ACGCCTACTTCGGCTACAGCACCCCTGGGGGTATTTTGACTTCAACAGATCTTCACTGCCA CTTCTCACACGTGACTGGCAGCGACTCATCAACAACAACCTGGGGATTCCGGCCTAAGCG ACTCAACTTCAAGTCTTCAACATTCAAGGTCAAAGAGGTTACGGACAACAATGGAGTCAA GACCATCGCCAATAACCTTACCAGCACGGTCCAGGTCTTACGGACTCAGACTATCAGCT CCCGTACGTGCTCGGGTGGGCTACGAGGGCTGCTCCCGCGTTCAGCGGACGTTTTT CATGATTCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCTGTTT GTCCTTTTACTGCCTGGAATATTTCCCGTCGCAATGCTAAGAACGGGTAACAACCTCCA GTTCAGCTACGAGTTTGAGAACGTACCTTCCATAGCAGCTACGCTCACAGCCAAAGCCT GGACCGACTAATGAATCCACTCATCGACCAATACTTGTACTATCTCTCAAAGACTATTAA CGGTTCTGGACAGAATCAACAAACGCTAAAATTCAGTGTGGCCGACCCAGCAACATGG CTGTCCAGGGAAGAACTACATACCTGGACCCAGCTACCGACAACAACGTGTCTCAACCA CTGTGACTCAAAACAACAACAGCGAATTTGCTTGGCCTGGAGCTTCTTCTGGGCTCTCA ATGGACGTAATAGCTTGATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAG GACCGTTTTCTTCTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAACTGGAAGAGACA ACGTGGATGCGGACAAAAGTCATGATAACCAACGAAGAAGAAATTAACACTACTAACCCG GTAGCAACGGAGTCTATGGACAAGTGGCCACAAACCACAGAGTGGCCAAGCACAGGC GCAGACCGGCTGGGTTCAAACCAAGGAATACTTCCGGGTATGGTTTGGCAGGACAGAG ATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTTTCACC CTTCTCCGCTGATGGGAGGGTTTGAATGAAGCACCCGCTCTCAGATCCTCATCAAAA ACACACCTGTACCTGCGGATCTTCAACGGCTTCAACAAGGACAAGTGAACCTTTCA TCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTGGGAGCTGCAGAAGGAA

	AACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCAACATTACAAGTCTAATAAT GTTGAATTTGCTGTTAATACTGAAGGTGTATATAGTGAACCCCGCCCCATTGGCACCAGA TACCTGACTCGTAATCTGTAATCGATTGTTAATCAATAAACCGTTTAATTCGTTTCAGTTG AACTTTGGTCTCTGCGTATTTCTTTCTTATCTAGTTTCCATGGCTACGTAGATAAGTAGCAT GGCGGGTTAATCATTAATACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTG CGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCCGACGCCCGGGCTTTGCC CGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAA

SYNG-CAP9 SEQ ID NO: 11	TTGGCCACTCCCTCTCTGCGCGCTCGCTCGTCACTGAGGCCGGGCGACCAAAGGTCGCC CGACGCCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGT GGCCAACTCCATCACTAGGGGTTCTTGGAGGGGTGGAGTCGTGACGATATCCATGCGTCG ACATAACGCGTGATCTAACATATCCTGGTGTGGAGTAGCGGACGCTGCTATGACAGAGGC TCGGGGGCTGAGCTGGCTCTGTGAGCTGGGGAGGAGGCAGACAGCCAGGCCTTGTCTG CAAGCAGACCTGGCAGCATTGGGCTGGCCGCCCCCAGGGCCTCTCTTCATGCCCAGTG AATGACTCACCTTGGCACAGACACAATGTTCTGGGTGGGCACAGTGCCTGCTTCCCGCCG CACCCAGCCCCCTCAAATGCCTTCCGAGAAGCCATTGAGCAGGGGGCTTGCAATTGCA CCCCAGCCTGACAGCCTGGCATCTTGGGATAAAAGCAGCACAGCCCCCTAGGGGTGCC TTGCTGTGTGGCGCCACCGGCGGTGGAGAACAAGGCTCTATTAGCCTGTGCCAGGAAA GGGGATCAGGGGATGCCAGGCATGGACAGTGGGTGGCAGGGGGGAGAGGAGGGCTG TCTGCTTCCCAGAAGTCCAAGGACACAAATGGGTGAGGGGAGAGCTCTCCCCATAGCTGG GCTGCGGGCCCAACCCACCCCTCAGGCTATGCCAGGGGGTGTGCCAGGGGCACCCGGG CATCGCCAGTCTAGCCCACTCCTTCATAAAGCCCTCGCATCCCAGGAGCGAGCAGAGCCA GAGCAGGTTGGAGAGGAGACGCATCACCTCCGCTGCTCGCGGGGATCCTCTAGAAGCTTC GTTTAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTGGACCTCCATAGAA GACACCGGGACCGATCCAGCCTCCGCGGATTGCAATCCCGGCCGGGAACGGTGCATTGG AACGCGGATTTCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGCCCCAC AAAAAATGCTTTCTTTTAAATATACTTTTGTGTTATCTTATTCTAATCTTCCCTAAT CTCTTTCTTTAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTTCTAAAGAA TAACAGTGATAATTTCTGGGTAAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCA TATAAATTGTAAGTGTAGTAAGAGTTTCATATTGCTAATAGCAGCTACAATCCAGTAC CATTTGCTTTTATTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGTCCGCC TTTTGCTAATCATGTTTACCTCTTATCTTCTCCACAGCTCCTGGGCAACGTGCTGGTC TGTGTGCTGGCCATCACTTTGGCAAAGAATTGGGATTGCAACCGGTGCGCACCGGTAC CAAGCAGGAAGTCAAAGACTTTTCCGGTGGGCAAAGGATCACGTGGTTGAGGTGGAGC ATGAATTCTACGTCAAAAAGGGTGGAGCCAAGAAAAGACCCGCCCCCAGTGACGCAGAT ATAAGTGAGCCCAAACGGGTGCGCGAGTCAGTTGCGCAGCCATCGACGTCAGACGCGGA AGCTTCGATCAACTACGCGGACAGGTACCAAAACAAATGTTCTCGTCACGTGGGCATGAA TCTGATGCTGTTTCCCTGCAGACAATGCGAGAGACTGAATCAGAATTCAAATATCTGCTT CACTCACGGTGTCAAAGACTGTTTAGAGTGCTTTCCCGTGTGAGAATCTCAACCCGTTCT GTCGTCAAAAAGGCGTATCAGAACTGTGCTACATTCATCACATCATGGGAAAGGTGCCA GACGCTTGCACTGCTTGCGACCTGGTCAATGTGGACTTGGATGACTGTGTTTCTGAACAAT AAATGACTTAAACCAGGTATGGCTGCCGATGGTTATCTTCCAGATTGGCTCGAGGACAAC CTTAGTGAAGGAATTCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCCTCAACCAAGGCA AATCAACAACATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGGTACAAATACCTTGGA CCCGCAACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGCCCTCGA GCACGACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACTCAATGATACA ACCACGCCGACGCCGAGTTCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGCAAC CTCGGGCGAGCAGTCTCCAGGCCAAAAGAGGCTTCTTGAACCTCTTGGTCTGGTTGAG GAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTCCTCAGGAACC GGACTCCTCCGCGGTATTGGCAAATCGGGTGCACAGCCCGCTAAAAGAGACTAATTT CGGTACAGACTGGCGACACAGAGTCAGTCCCAGACCCTCAACCAATCGGAGAACCCTCCCG CAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAGGTGGTGGCGCACCACTGGCAG ACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCTCGGGAAATTGGCATTGCGATTCCC AATGGCTGGGGGACAGAGTCATCAACACCAGCACCCGAACCTGGGCCCCTGCCACCTAC AACAATCACCTCTACAAGCAAAATCTCCAACAGCACATCTGGAGGATCTTCAAATGACAAC GCCTACTTCGGCTACAGCACCCCTGGGGGTATTTTGAATTCACAGATTCCACTGCCACT TCTCACCACGTGACTGGCAGCGACTCATCAACAACAACCTGGGGATTCCGGCTAAGCGAC TCAACTTCAAGCTCTTCAACATTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGA CCATCGCCAATAACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTATCAGTCC CGTACGTGCTCGGGTCCGGCTCACGAGGGCTGCCTCCCGCCGTTCCAGCGGACGTTTTCA TGATTCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTGCTTCGT CCTTTTACTGCTGGAATATTTCCCGTCGCAAAATGCTAAGAACGGGTAAACAACCTTCCAGT CAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCCAAAGCCTGGA CCGACTAATGAATCCACTCATCGACCAATACTTGTACTATCTCTCAAAGACTATTAACGGT TCTGGACAGAATCAACAAACGCTAAAATTCAGTGTGGCCGGACCCAGCAACATGGCTGTC CAGGGAAGAACTACATACCTGGACCCAGCTACCGACAACAACGTGTCTCAACCACTGT GACTCAAAACAACAACAGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGG ACGTAATAGCTTGATGAATCCTGGACCTGCTATGGCCAGCCACAAGAAGGAGAGGACC GTTTCTTCTTTTGTGGATCTTTAATTTTTGGCAAACAAGGAATGGAAGAGACACGCT GGATGCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAATACTACTAACCCGGTAG CAACGGAGTCTTATGGACAAGTGGCCACAACACCAGAGTGCCCAAGCACAGGCGCAG ACCGGCTGGGTTCAAACCAAGGAATACTTCCGGGTATGGTTTGGCAGGACAGAGATGT GTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCACTTTCAACCTTC TCCGCTGATGGGAGGGTTTGAATGAAGCACCCGCTCCTCAGATCCTCAAAAACAC ACCTGTACCTGCGGATCCTCCAACGGCTTCAACAAGGACAAGCTGAACCTTTTCATCAC

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GFAPG-CAP9 SEQ ID NO: 12	TTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCC CGACGCCCCGGGCTTTGCCCGGGCGGCCTCAGTGACGAGCGAGCGCGCAGAGAGGGAGT GGCCAACTCCATCACTAGGGGTTCTTGGAGGGGTGGAGTCGTGACGATATCCATGCGTCG ACATAACGCGTTAGTATCTGACAGAGGCCCTGCGTATGAGTGCAAGTGGGTTTATAGGACC AGGATGAGGCGGGGTGGGGGTGCGTACCTGACGACCGACCCCGACCCACTGGACAAGCA CCCCAACCCCATTCCCCAAATTGCGCATCCCCTATCAGAGAGGGGGAGGGGAAACAGGA TGCGGCGAGGCGCGTGCCTACTGCCAGCTTCAGCACCGCGGACAGTGCCTTCGCCCCCGC CTGGCGGCGCGCGCCACCGCCGCTCAGCACTGAAGGCGCGCTGACGTCACTCGCCGGTC CCCCGCAAACTCCCTTCCCGGCCACCTTGGTCGCGTCCGCGCCGCGCCGCGCCGAGCCG GACCGCACCGCGAGGCGCGAGATAGGGGGGACGCGCGGACCATCTGCGCTGCGGC GCCGGCGACTCAGCGTGCCTCAGTCTGCGGTGGGCGAGCGGAGGAGTCGTGTCTGCTGCTG AGAGCGCAGCTGTGCTCTGGGACCGCGCAGTCCGCCCCCGCGGCTCCTGGCCAGACCA CCCCTAGGACCCCTGCCCAAGTCGACGCCAAGCTTCGTTTATGTAACCGTCAGATCGC CTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACACCGGGACCGATCCAGCCT CCGCGGATTGCAATCCCGGCCGGAACGGTGCATTGGAACGCGGATTCCCCGTGCCAAG AGTGACGTAAGTACCGCTATAGAGTCTATAGGCCCAAAAAATGCTTTCTTTCTTTAAT ATACTTTTTTGTATTCTTATTTCTAATACTTTCCCTAATCTCTTTCTTTTCAGGGCAATAATG ATACAATGTATCATGCCTCTTTGCACCATTTCTAAAGAATAACAGTGATAATTTCTGGGTTA AGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTAAGTATGTAAG AGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTTCTGCTTTTATTTTATGGTT GGGATAAGGCTGGATTATTTCTGAGTCCAAGCTAGGCCCTTTTGTAATCATGTTTCATACCT CTTATCTTCTCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCATCACTTTG GCAAGAATTGGGATTGCAACCGGTGCGCACCGGTACCAAGCAGAGGTCACAGACTTT TTTCCGGTGGGCAAAAGGATCACGTGGTTGAGGTGGAGCATGAATTCTACGTCAAAAAAGG GTGGAGCCAAGAAAAGACCCGCCCCCAGTGACGCAGATATAAGTGAGCCAAACGGGTG CGCGAGTCAGTTGCGCAGCCATCGACGTCAGACGCGGAAGCTTCGATCAACTACGCGGA CAGGTACCAAAACAAATGTTCTCGTCACGTGGGCATGAATCTGATGCTGTTTCCCTGCAG ACAATGCGAGAGACTGAATCAGAATTCAAATATCTGCTTCACTCAGGTGTCAAAGACTG TTTAGAGTGCTTTCCCGTGTGAGAATCTCAACCCGTTTCTGTCTGCAAAAAAGCGGTATCAG AACTGTGCTACATTCATCACATCATGGGAAAGGTGCCAGACGCTTGCACTGCTTGCAGC CTGGTCAATGTGGACTTGGATGACTGTGTTTCTGAACAATAAATGACTTAAACCAGGTAT GGCTGCCGATGGTTATCTTCCAGATTGGCTCGAGGACAACCTTAGTGAAAGGAATTCGCGA GTGGTGGGCTTTGAAACCTGGAGCCCCCTCAACCCAAAGGCAAAATCAACAACATCAAGACA ACGCTCGAGGTCTTGTGCTTCCGGGTACAAATACCTTGGACCCGGCAACGGAAGTTCGACA AGGGGGAGCCGGTCAACGCAGCAGACGCGCGGCCCTCGAGCACGACAAGGCCTACGAC CAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACAACACGCGGACGCGGAGTT CCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGCAACCTCGGGCGAGCAGTCTTCCA GGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCTGGTTGAGGAAGCGGCTAAGACGGCTCC TGGAAGAAGAGGCTGTAGAGCAGTCTCTCAGGAACCGGACTCCTCCGCGGGTATTG GCAAAATCGGGTGCACAGCCCGCTAAAAAGAGACTCAATTTCCGGTCAGACTGGCGACACA GAGTCAGTCCCAGACCCTCAACCAATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGA TGTCTTACAATGGCTTCAGGTGGTGGCGCACCAAGTGGCAGACAATAACGAAGTCCGAT GGAGTGGGTAGTTCCTCGGGAATTTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTC ATCACCACCAGCACCCGAACCTGGGCCCTGCCACCTACAACAATCACCTCTACAAGCAA ATCTCCAACAGCATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACC CCCTGGGGGTATTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCAGC GACTCATCAACAACAACCTGGGGATTCCGGCCCTAAGCGACTCAACTTCTTCAACA TTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAATAACCTTACC AGCACGGTCCAGGTCTTACGGACTCAGACTATCAGCTCCCGTACGTGCTCGGGTGGGCT CACGAGGGCTGCCTCCCGCGGTTCCAGCGGACGTTTTTCATGATTCTCAGTACGGGTATC TGACGCTTAATGATGGAAGCCAGGCCGTGGGTGCTTCGTCTTTTACTGCCTGGAATATTT CCCGTCGCAAAATGCTAAGAACGGGTAAACAACCTTCCAGTTTACGTACGAGTTTGAGAACGT ACCTTTCCATAGCAGCTACGCTCACAGCCAAAGCCTGGACCGACTAATGAATCCACTCAT CGACCAATACTTGTACTATCTCTCAAAGACTATTAACGGTTCTGGACAGAATCAACAAAC GCTAAATTCAGTGTGGCCGGACCCAGCAACATGGCTGTCCAGGGAAGAACTACATAC CTGGACCCAGTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAACAGC GAATTTGCTTGGCCTGGAGCTTCTTGGGCTCTCAATGGACGTAATAGCTTGATGAATC CTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTCTTTGTCTGGAT CTTTAATTTTGGCAAACAAGGAACTGGAAGAGACAACGTGGATGCGGACAAAGTCATG ATAACCAACGAAGAAGAAATTTAACTACTAACCCTGGTAGCAACGGAGTCTTATGGACA AGTGGCCACAACCAACAGAGTGCCCCAAGCACAGGCGCAGACCGGTGGGTTCAAAGACC AAGGAATACTTCCGGGTATGGTTTGGCAGGACAGAGATGTGTACCTGCAAGGACCCATTT GGGCCAAAATTCCTCACACGGACGGCAACTTTACCCCTTCTCCGCTGATGGGAGGGTTT GAATGAAGCACCCGCTCCTCAGATCCTCATCAAAAAACACCTGTACCTGCGGATCCTC CAACGGCCTTCAACAAGGACAAGCTGAACTTTTATCACCAGTATTCTACTGGCCAAAG TCAGCGTGGAGATCGAGTGGGAGCTGCAGAAGGAAACAGCAAGCGCTGGAACCCGGA GATCCAGTACACTTCAACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAA

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GLOSPLICEF6 SEQ ID NO: 13	GTGCCAAGAGTGACCTCCTG
CAP5L8 GBLOCK SEQ ID NO: 14	ACTGCCCCCGCGACCGGCACGTACAACCTCCAGGAAATCGTGCCCGGCAGCGTGTGGATG GAGAGGGACGTGTACCTCCAAGGACCCATCTGGGCCAAGATCCCAGAGACGGGGGCGCA CTTTCACCCCTCTCCGGCTATGGGCGGATTTCGGACTCAAACACCCACCGCCCATGATGCTC ATCAAGAACACGCCTGTGCCCCGAAATATCACCAGCTTCTCGGACGTGCCGCTCAGCAGC TTCATCACCCAGTACAGCACCGGGCAGGTCACCGTGGAGATGGAGTGGGAGCTCAAGAA GGAAAACTCCAAGAGGTGGAACCCAGAGATCCAGTACACAAACAACCTACACGACCCCC AGTTTGTGGACTTTGCCCGGACAGCACCGGGGAATACAGAACCACAGACCTATCGGA ACCCGATACCTTACCCGACCCCTTTAA
CAP6L8 GBLOCK SEQ ID NO: 15	ACCGGAGATGTGCATGTTATGGGAGCCTTACCTGGAATGGTGTGGCAAGACAGGGACGT CTACCTGCAGGGTCCTATTTGGGCCAAAATTCCTCACACGGATGGACACTTTCACCCATCT CCTCTCATGGGCGGCTTTGGACTTAAGCACCCCGCCTCCTCAGATCCTCATCAAAAACACG CCTGTTCTGCGAATCCTCCGGCAGAGTTTTTCGGCTACAAAGTTTGCTTCATTTCATCACC AGTATTCCACAGGACAAGTGAGCGTGGAGATTGAATGGGAGCTGCAGAAAGAAAACAGC AAACGCTGGAATCCCGAAGTGCAATATACATCTAACTATGCAAAATCTGCCAACGTTGAT TTCCTGTGGACAACAATGGACTTTATACTGAGCCTCGCCCCATTGGCACCCGTTACCTCA CCCGTCCCTGTAATCGAT
CAPDJ8L8 GBLOCK SEQ ID NO: 16	ACACAAGCAGCTACCGCAGATGTCAACACACAAGGCGTTCTTCCAGGCATGGTCTGGCAG GACAGAGATGTGTACCTTCAGGGGCCCATCTGGGCCAAAGATTCCACACACGGACGGACA TTTTACCCCTCTCCCTCATGGGTGGATTTCGGACTTAAACACCCCTCCGCCTCAGATCCTG ATCAAGAACACGCCTGTACCTGCGGACCCTCCGACCACCTTCAACCAGTCAAAGCTGAAC TCTTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTGGGAGCTGCAG AAGGAAAACAGCAAGCGCTGGAACCCCGAGATCCAGTACACCTCCAACCTACTACAAATC TACAAGTGTGGACTTTGCTGTTAATACAGAAGGCGTGTACTCTGAACCCCGCCCCATTGG CACCCGTTACCTCACCCGTAATCTGTAA
CAP9L8M GBLOCK SEQ ID NO: 17	GCACAGGCGCAGACCGGCTGGGTTCAAAAACCAAGGAATACTTCCGGGTATGGTTTGGCA GGACAGAGATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCTCACACGGACGGCA ACTTTCACCCCTTCTCCGCTGATGGGAGGGTTTGAATGAAGCACCCGCCTCCTCAGATCCT CATCAAAAACACACCTGTACCTGCCGATCCTCCAACGGCCTTCAACAAGGACAAGCTGAA CTCTTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTGGGAGCTGCA GAAGGAAAACAGCAAGCGGTGGAACCCCGAGATCCAGTACACTTCCAACCTATTACAAGT CTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGTGAACCCCGCCCCATTGG CACCAGATACCTGACTCGTAATCTGTAA

TELN-SYNG9- BSRGI SEQ ID NO: 18	TATCAGCACACAATAGTCCATTATACGCGCGTATAATGGGCAATTGTGTGCTGATACAGC TGGCACGACAGGTTTCCCGACTGGAAGCGGGCAGTGAGCGCAACGCAATTAATGTGAG TTAGCTCACTCATTAGGCACCCAGGCTTTACACTTTATGCTTCCGGCTCGTATGTTGTGT GGAATTGTGAGCGGATAACAATTTACACAGGAAACAGCTATGACCATGATTACGCCAG ATTTAATTAAGGCCTTAATTAGGCTAGCTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTC ACTGAGGCCGGGCGACCAAAGGTCGCCCCGACGCCCCGGGCTTTGCCCGGGCGGCCTCAGT GAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCTGGAGGG GTGGAGTCGTGACGATATCCATGCGTCGACATAACGCGTTAGTATCTGCAGAGGGCCCTG CGTATGAGTGCAAGTGGGTTTTAGGACCAGGATGAGGCGGGGTGGGGGTGCCTACCTGA CGACCGACCCCGACCCACTGGACAAGCACCCAACCCCAATTCCCAAAATTGCGCATCCCC TATCAGAGAGGGGGAGGGGAAACAGGATGCGGCGAGGCGCGTGCGCACTGCCAGTTCA GCACCGCGGACAGTGCTTCCGCCCCGCTGGCGGCGCGCGCCACCGCCGCTCAGCACT GAAGGCGCGCTGACGTCACTCGCCGGTCCCCGCAAACTCCCTTCCCGGCCACCTTGGT CGCGTCCGCGCCGCGCGGCCAGCCGACCGCACACCGGAGGCGGAGATAGGGGG GCACGGGCGCGACCATCTGCGCTGCGGCGCCGGCGACTCAGCGCTGCCTCAGTCTGCGGT GGGCAGCGGAGGAGTCGTGTCTGCTGAGAGCGCAGCTGTGCTCCTGGGCACCGCGCA GTCCGCCCCCGCGGCTCCTGGCCAGACCACCCCTAGGACCCCTGCCCAAGTCGCAGCC AAGTTTCGTTTAGTGAACCGTCAGATCGCTGGAGACGCCATCCACGCTGTTTTGACCTCC ATAGAAGACACCGGGACCGATCCAGCCTCCGCGGATTGGAATCCCGCCGGGAACGCTG CATTGGAACGCGGATTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAG GCCCCAAAAAATGCTTCTTCTTTAATATACTTTTTGTTTATCTTATTTCTAATACTTTC CCTAATCTCTTCTTTCAGGGCAATAATGATACAATGTATCATGCCTCTTTCACCACTTCT AAAGAATAACAGTGATAATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATAT TTCTGCATATAAATTGTAAGTGTGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCC AGCTACCATTTCTGCTTTTATTTATGGTTGGGATAAGGCTGGATTATTTCTGAGTCCAAGCT AGGCCCTTTTGTCAATCATGTTACATCTTATCTTCTCCACAGCTCCTGGGCAACGT GCTGGTCTGTGTGCTGGCCATCACTTTGGCAAAGAATTGGGATTGCAACCGGTGCGCAC CGGTCACCAAGCAGGAAGTCAAAGACTTTTTCCGGTGGGCAAGGATCACGTGGTTGAG GTGGAGCATGAATTCTACGTCAAAAAGGGTGGAGCCAAGAAAAGACCCGCCCCCAGTGA CGCAGATATAAGTGAGCCAAACGGGTGCGCGAGTCAGTTGCGCAGCCATCGACGTCAG ACGCGGAAGCTTCGATCAACTACGCGGACAGGTACCAAAACAAATGTTCTCGTCACGTGG GCATGAATCTGATGCTGTTTCCCTGCAGACAATGCGAGAGACTGAATCAGAATTCAAATA TCTGCTTCACTACGGTGTCAAAGACTGTTTAGAGTGCTTTCCCGTGTCAAGATCTCAACC CGTTTTCTGTCGTCAAAAAGGCGTATCAGAACTGTGCTACATTCATCATCATGCGGAAA GGTGCCAGACGCTTGCCTGCTTGGCAGCTGGTCAATGTGGACTTGGATGACTGTGTTTCT GAACAATAAATGACTTAAACAGGTATGGCTGCCGATGGTTATCTTCCAGATTGGCTCGA GGACAACCTTAGTGAAGGAATTGCGGAGTGGTGGGCTTTGAAACCTGGAGCCCCCTCAACC CAAGGCAAAATCAACAACATCAAGACAACGCTCGAGGTCTTGTGCTTCCGGTTCAAAATA CCTTGGACCCGCAACGGACTCGACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGG CCCTCGAGCAGCACAAGGCTACGACCAGCAGCTCAAGGCCGAGACAACCCGTACCTC AAGTACAACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATACGCTCTTTTGG GGCAACCTCGGGCGAGCAGTCTTCCAGGCCAAAAAGAGGCTTCTGAACTCTTGGTCT GGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTCCTC AGGAACCGGACTCCTCCGCGGTATTGGCAAATCGGGTGACAGCCCCGCTAAAAAGAGA CTCAATTTCCGCTCAGACTGGCGACACAGAGTCACTCCAGACCCCTCAACCAATCGGAGAA CCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTTCAGGTGGTGGCGCACC TTGGCAGACAATAACGAAGGTGCGGATGGAGTGGGTAGTTCTCGGGAATGCGCATTTG CGATTCCCAATGGCTGGGGGACAGAGTCATCACCACCAGCACCCGAACCTGGGCCCTGCC CACCTACAACAATCACTCTACAAGCAAATCTCCAACAGCACATCTGGAGGATCTTCAAA TGACAACGCCTACTTCGGCTACAGCACCCCTGGGGGTATTTTGACTTCAACAGATTCCA CTGCCACTTCTCACCACGTGACTGGCAGCGACTCATCAACAACAACCTGGGGATTCCGGCC TAAGCGACTCAACTTCAAGCTCTTCAACATTCAGGTCAAAGAGGTTACGGGACAACAATGG AGTCAAGACCATCGCCAATAACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTA TCAGTCCCGTACGTGCTCGGGTCCGCTCACGAGGGCTGCCTCCCGCGGTTCCAGCGGA CGTTTTCATGATTCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGG TCGTTCTGCTCTTTACTGCCTGGAATATTTCCGTCGCAATGCTAAGAACGGGTAACAAC TTCCAGTTCAGTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCCAA AGCCTGGACCGACTAATGAATCCACTCATCGACCAATACTTGTACTATCTCTCAAAGACT ATTAACGGTTCTGGACAGAATCAACAACGCTAAAAATTCAGTGTGGCCGACCCAGCAA CATGGCTGTCCAGGGAAGAACTACATACCTGGACCCAGCTACCGACAACAACGTTGTCTC AACCTGTGACTCAAAAACAACAACAGCGAATTTGCTTGGCTGGAGTCTTCTTGGGC TCTCAATGGACGTAATAGCTTGATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGG AGAGGACCGTTTCTTCTTTGTCTGGATCTTTAATTTTGGCAAACAAGGAAGTGAAGA GACAACGTGGATGCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAATACTACTAA CCCGGTAGCAACGGAGTCCTATGGACAAGTGGCCACAAACCACAGAGTGATACATCGAT TGTTAATCAATAAACCGTTTAATTCTTTCAGTTGAACTTTGGTCTCTGCGTATTTCTTCT TATCTAGTTTCCATGGCTACGTAGATAAGTAGCATGGCGGGTTAATCATTAATACTACAAGG

	AACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCG GGCGACCAAAGGTCGCCCCACGCCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGA GCGCGCAGAGAGGGAGTGGCCAAGCATGCAATTAAGTGGCCGTCGTTTTACAACGTCGTG ACTGGGAAAACCTGGCGTTACCCAACTTAATCGCCTTGCAGCACATCCCCCTTTCGCCA GCTGTATCAGCACACAATTGCCATTATACGCGCGTATAATGGACTATTGTGTGCTGATA

TELN- GFAPG9- BSRGI SEQ ID NO: 19	TATCAGCACACAATAGTCCATTATACGCGCGTATAATGGGCAATTGTGTGCTGATACAGC TGGCACGACAGGTTTCCCCGACTGGAAGCGGGCAGTGAGCGCAACGCAATTAATGTGAG TTAGCTCACTCATTAGGCACCCAGGCTTTACACTTTATGCTTCCGGCTCGTATGTTGTGT GGAATTGTGAGCGGATAACAATTTACACAGGAAACAGCTATGACCATGATTACGCCAG ATTTAATTAAGGCCTTAATTAGGCTAGCTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTC ACTGAGGCCGGGCGACCAAAGGTGCCCCGACGCCCCGGGCTTTGCCCGGGCGGCCTCAGT GAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCTGGAGGG GTGGAGTCGTGACGATATCCATGCGTCGACATAACGCGTGATCTAACATATCCTGGTGTG GAGTAGCGGACGCTGCTATGACAGAGGCTCGGGGGCTGAGCTGGCTCTGTGAGCTGGG GAGGAGGCAGACAGCCAGGCCTTGTCTGCAAGCAGACCTGGCAGCATTGGGCTGGCCGC CCCCAGGGCTCTCTTTCATGCCCAGTGAATGACTCACCTTGGCACAGACACAATGTTT GGGGTGGGCACAGTGCCTGCTTCCCGCCGACCCCCAGCCCCCTCAAATGCCTTCCGAGA AGCCCCATTGAGCAGGGGGCTTGCAATGACCCCCAGCCTGACAGCCTGGCATCTTGGGATA AAAGCAGCACAGCCCCCTAGGGGCTGCCCTTGTGTGTGGCGCCACCGCGGTGGAGAA CAAGGCTCTATTACGCTGTGCCAGGAAAGGGGATCAGGGGATGCCAGGCATGGACA GTGGGTGGCAGGGGGGGAGAGGAGGGCTGTCTGCTTCCAGAAAGTCCAAGGACACAAAT GGGTGAGGGGAGAGCTCTCCCCATAGCTGGGCTGCGGCCAACCCACCCCCCTCAGGCTA TGCCAGGGGTGTTGCCAGGGGCACCCGGGCATCGCCAGTCTAGCCCACTCCTTCATAAA GCCCTCGCATCCAGGAGCGAGCAGAGCCAGAGCAGGTTGGAGAGAGACGCATCACCT CCGCTGCTCGCGGGATCCTCTAGAAGCTTCGTTTAGTGAACCGTCAGATCGCCTGGAGA CGCCATCCACGCTGTTTTGACCTCCATAGAAGACACCGGGACCGATCCAGCCTCCGCGGA TTCGAATCCCGCGCGGGAACGGTGCAATGGAACGCGGATTCCCCGTGCCAAGAGTGACGT AAGTACCGCTATAGAGTCTATAGGCCACAAAAAATGCTTTCTTTTAAATATACTTTT TTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTTTTACGGGCAATAATGATAAAT GTATCATGCCTCTTTGCACCATTTCTAAAGAATAACAGTGATAATTTCTGGGTTAAGGCAAT AGCAATATTTCTGCATATAAATATTTCTGCATATAAATTTGTAAGTATGTAAGAGGTTTCA TATTGCTAATAGCAGCTACAATCCAGCTACCATTTCTGCTTTTATTTTATGGTTGGGATAAG GCTGGATTATTTCTGAGTCCAAGCTAGGCCCTTTTGTCTAATCATGTTTATACCTCTTATCTTC CTCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCATCACTTTGGCAAAGAA TTGGGATTGCAACCGTTCGCCACCGGTCACCAAGCAGGAAGTCAAAGACTTTTTCCGGTG GGCAAAGGATCACGTGGTTGAGGTGGAGCATGAATTTACGTCAAAAAGGGTGGAGCCA AGAAAAGACCCGCCCCAGTGACGCAGATATAAGTGAGCCAAACGGGTGCGCGAGTCA GTTGCGCAGCCATCGACGTGACAGCGGGAAGCTTCGATCAACTACGCGGACAGGTACCA AAACAAATGTTCTCGTCACGTGGGCATGAATCTGATGCTGTTTCCCTGCAGACAATGCCA GAGACTGAATCAGAATTCAAATATCTGCTTCACTCACGGTGTCAAAGACTGTTTAGAGTG CTTTCCCGTGTGAGAATCTCAACCCGTTTCTGTGCTCAAAAAGGCGTATCAGAACTGTGC TACATTCATCATCATGGAAGGTGCCAGACGCTTGCAGTCTTGCAGCTTGGCAGCTGGTCAAT GTGGATTGGATGACTGTGTTTCTGAACAATAAATGACTTAAACCGGATGATGGTGGCGA TGGTTATCTTCCAGATTGGCTCGAGGACAACCTTAGTGAAGGAATTCGCGAGTGGTGGGC TTTGAAACCTGGAGCCCTCAACCCAAGGCAAAATCAACAACATCAAGACAACGCTCGAG GTCTTGTGCTTCCGGGTTACAAATACCTTGGACCCGGCAACGGACTCGACAAGGGGGAGC CGGTCAACGCAGCAGACGCGCGGCCCTCGAGCAGACAAGGCCTCAGACCAAGCTC AAGGCCGAGACAACCCGTACCTCAAGTACAACCACGCGGACGCGGAGTTCCAGGAGCG GCTCAAAGAAGATACGTCTTTTGGGGCAACCTCGGGCGAGCAGTCTTCCAGGCCAAAA AGAGGCTTCTTGAACCTCTTGGTCTGGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGA AGAGGCTGTAGAGCAGTCTCCTCAGGAACCGGACTCCTCCGCGGGTATTGGCAAACTCGG GTGCACAGCCCGCTAAAAAGAGACTCAATTTTCGTGACAGTGGCGACACAGTCAGT CCAGACCCTCAACCAATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACA ATGGCTTCAGGTGGTGGCGCACCAGTGGCAGACAATAACGAAGGTGCCGATGGAGTGGG TAGTTCCTCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACAC CAGCACCCGAACCTGGGCCCTGCCCACCTACAACAATCACCTCTACAAGCAAATCTCCAA CAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCGGCTACAGCACCCCCCTGGGG GTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCACGTGACTGGCAGCGACTCATC AACAACAATGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCTTCAACATTCAGGTC AAAGAGGTTACGGACAACAATGGAGTCAAGACCATCGCCAATAACCTTACCAGCACGGT CCAGGTCTTACGGACTCAGACTATCAGTCCCGTACGTGCTCGGTTCGGCTCAGAGGG CTGCCTCCCGCGTTCAGCGGACGTTTTCATGATTCTCAGTACGGGTATCTGACGCTT AATGATGGAAGCCAGGCCGTGGGTCGTTCTGCTCTTTTACTGCCTGGAATATTTCCCGTCGC AAATGCTAAGAACGGGTAAACAACTTCCAGTTCAGTACGAGTTTGAGAACGTACCTTTCC ATAGCAGCTACGCTCAGCCAAAGCCTGGACCGACTAATGAATCCCACTATCGACCAAT ACTTGTACTATCTCTCAAAGACTATTAACGGTTCTGGACAGAAATCAACAACGCTAAAT TCAGTGTGGCCGGACCCAGCAACATGGCTGTCCAGGGAGAAACTACATACCTGGACCC AGCTACCGACAACAACGTGTCTCAACCACTGTGACTCAAAACAACAACAGCGAATTTGCT TGGCCTGGAGCTTCTTCTGGGCTCTCAATGGACGTAATAGCTTGATGAATCCTGGACCTG CTATGGCCAGCCACAAAGAAGGAGAGGACCGTTTCTTTCTTTGTCTGGATCTTTAATTTT TGGCAACAAGGAAGTGAAGAGACAACGTGGATGCGGACAAAGTCAAGTCAACGACG AAGAAGAAATTAATACTACTAACCCGGTAGCAACGGAGTCTTATGGACAAGTGGCCACA

	AACCACCAGAGTGTACATCGATTGTTAATCAATAAACCGTTTAATTTCGTTTCAGTTGAACT TTGGTCTCTGCGTATTTCTTTCTTATCTAGTTTCCATGGCTACGTAGATAAGTAGCATGGC GGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGC GCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCACGCCCCGGGCTTTGCCCGG GCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAAGCATGCAATTAACTG GCCGTCGTTTTACAACGTCGTGACTGGGAAAAACCCTGGCGTTACCCAACCTAATCGCCTT GCAGCACATCCCCCTTTCCGCGAGCTGTATCAGCACACAATTGCCATTATACGCGCGTAT AATGGACTATTGTGTGCTGATA

TELN-SYNG5- BSRGI SEQ ID NO: 20	TATCAGCACACAATAGTCCATTATACGCGCGTATAATGGGCAATTGTGTGCTGATACAGC TGGCAGCAGAGGTTTCCCCGACTGGAAGCGGGCAGTGAGCGCAACGCAATTAATGTGAG TTAGCTCACTCATTAGGCACCCAGGCTTTACACTTTATGCTTCCGGCTCGTATGTTGTGT GGAATTGTGAGCGGATAACAATTTACACAGGAAACAGCTATGACCATGATTACGCCAG ATTTAATTAAGGCCTTAATTAGGCTAGCTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTC ACTGAGGCCGGGCGACCAAAGGTGCCCCGACGCCCCGGGCTTTGCCCGGGCGGCCTCAGT GAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCCTGGAGGG GTGGAGTCGTGACGATATCCATGCGTCGACATAACGCGTTAGTATCTGCAGAGGGCCCTG CGTATGAGTGCAAGTGGGTTTTAGGACCAGGATGAGGCGGGGTGGGGGTGCCTACCTGA CGACCGACCCCGACCCACTGGACAAGCACCAACCCCAATTCCTCAAATTTGCGCATCCCC TATCAGAGAGGGGGAGGGGAAACAGGATGCGGCGAGGCGCGTGCGCACTGCCAGTTCA GCACCGCGGACAGTGCCCTTCGCCCCCGCTGGCGGCGCGCGCCACCGCCGCTCAGCACT GAAGGCGCGCTGACGTCACTCGCCGGTCCCCGCAAACTCCCTTCCCGGCCACCTTGGT CGCGTCCGCGCCGCGCGGCCGACCGGACCGCACACGCGAGGCGCGGATAGAGGGG GCACGGGCGCGACCATCTGCGCTGCGGCGCGCGGCGACTCAGCGCTGCCTCAGTCTGCGGT GGGCAGCGGAGGAGTCGTGTCTGCTGAGAGCGCAGCTGTGCTCCTGGGCACCGCGCA GTCCGCCCCCGCGGCTCCTGGCCAGACCACCCCTAGGACCCCTGCCCCAAGTCGCAGCC AAGCTTCGTTTAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTC ATAGAAGACACCGGGACCGATCCAGCCTCCGCGGATTGGAATCCCGCGCGGAACCGTG CATTGGAACGCGGATTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAG GCCCCAAAAAATGCTTCTTCTTTAATATACTTTTTGTTTATCTTATTTCTAATACTTTC CCTAATCTCTTCTTTCAGGGCAATAATGATACAATGTATCATGCCTCTTTCACCACTTCT AAAGAATAACAGTGATAATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATAT TTCTGCATATAAATTGTAAGTGTGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCC AGCTACCATTTCTGCTTTTATTTATGGTTGGGATAAGGCTGGATTATTTCTGAGTCCAAGCT AGGCCCTTTTGTCTAATCATGTTACATCTTATCTTCTCCACAGCTCCTGGGCAACGT GCTGGTCTGTGTGCTGGCCATCACTTTGGCAAAGAATTGGGATTGCAACCGGTGCGCCAG CGGTACACAAGCAGGAAGTCAAAGACTTTTTCCGGTGGGCAAAGGATCACGTGGTTGAGG TGGAGCATGAATTTCTACGTCAAAAAGGGTGGAGCCAAGAAAAGACCCGCCCCCAGTGAC GCAGATATAAGTGAGCCCAAACGGGTGCGCGAGTCAGTTGCGCAGCCATCGACGTCAGA CGCGGAAGCTTCGATCAACTACGCGGACAGGTACCAAAACAAATGTTCTCGTCACGTGGG CATGAATCTGATGCTGTTTCCCTGCAGACAATGCGAGAGAATGAATCAGAATTCAAATAT CTGCTTCACTCACGGACAGAAAAGACTGTTTAGAGTGCTTTCCCGTGTGCAGAATCTCAACC CGTTTTCTGCTGTCAAAAAGGCGTATCAGAAACTGTGCTACATTCATCATATCATGGGAAA GGTGCCAGACGCTTGCCTGCGATCTGGTCAATGTGGATTGGATGACTGCATCTTT GAACAATAAATGATTTAAATCAGGTATGTCTTTTGTGATCACCTCCAGATTGGTTGGAA GAAATTGGTGAAGTCTTCGCGAGTTTTTGGGCTTGAAGCGGGCCACCGAAACCAAAA CCAAATCAGCAGCATCAAGATCAAGCCCGTGGTCTTGTGCTGCTGCTTATAACTATCTC GGACCCGGAACGGTCTCGATCGAGGAGAGCCTGTCAACAGGGCAGACGAGGTGCGCGG AGAGCACGACATCTCGTACAACGAGCAGCTTGAGGCGGGAGACAACCCCTACCTCAAGT ACAACCGCGGACGCCGAGTTTCAGGAGAAGCTCGCCGACGACATCTTCGGGGGA AACCTCGGAAAGGCACTTTTCAGGCCAAGAAAAGGGTTCTGAACTTTTGGCCTGGTT GAAGAGGGTGCTAAGACGGCCCTACCGGAAAGCGGATAGACGACCACTTTCCAAAAAG AAAGAAGGCCCGGACCGAAGAGGACTCCAAGCCTTCCACCTCGTCAGACGCCGAAGCTG GACCCAGCGGATCCCAGCAGCTGCAAATCCAGGCCAACACGCTCAAGTTTGGGAGCTG ATACAATGTCTGCGGGAGGTGGCGGCCCATTTGGGCGACAATAACCAAGGTGCCGATGGA GTGGGCAATGCCTCGGGAGATTGGCATTGCGATTCCACGTGGATGGGGGACAGATGCTC ACCAAGTCCACCCGAACCTGGGTGCTGCCCAGCTACAACAACACACAGTACCGAGAGAT CAAAAGCGGCTCCGTGACGGAAGCAACGCCAACGCCTACTTTGGATACAGCACCCCTG GGGGTACTTTGACTTTAACCGCTTCCACAGCCACTGGAGCCCCGAGACTGGCAAAGACT CATCAACAATACTGGGGCTTCAGACCCCGTCCCTCAGAGTCAAAATCTTCAACATTCA AGTGCCCTTCCACTCCAGCTTCGCTCCAGTCAGAACCTCTTCAAGCTGGCCAACCCGCT CGTCCAAGTGTTTACGGACGACGACTACCAGCTGCCCTACGTGCTCGGCAACGGGACCGA GGGATGCTGCGCGCTTCCCTCCGCAAGTCTTTACGCTGCGCAGTACGGTTACGCGAC GCTGAACCGCGACAACACAGAAAATCCACCGAGAGGAGCAGCTTCTTCTGCCTAGAGT ACTTTCCAGCAAGATGCTGAGAACGGGCAACAACCTTTGAGTTTACCTACAACCTTTGAGG AGGTGCCCTTCCACTCCAGCTTCGCTCCAGTCAGAACCTCTTCAAGCTGGCCAACCCGCT GGTGGACCACTTGTACCGCTTTCGTGAGCACAATAACACTGGCGGAGTCCAGTTCAA CAAGAACCTGGCCGGGAGATACGCCAACACCTACAAAAACTGGTTCCCGGGGCCCATGG GCCGAACCCAGGGCTGGAACCTGGGCTCCGGGGTCAACCGCGCCAGTGTCTCAGCGCCTTCG CCACGACCAATAGGATGGAGCTCGAGGGCGCGAGTTACAGGTGCCCCGCGACCGAAC GGCATGACCAACAACCTCCAGGGCAGCAACACCTATGCCCTGGAGAACAATATGATCTTC AACAGCCAGCCGGCGAACCCGGGCACCAACCGCCACGTACCTCAGGGGCAACATGCTCAT CACCAGCGAGAGCGAGACGCGAGCCGGTGAACCGCGTGGCGTACAACGTCGGCGGGCAGA TGGCCACCAACAACAGAGCTCTGTACATCGATTGTTAATCAATAAACCGTTTAATTCGTT TCAGTTGAACCTTGGTCTGCGTATTTCTTCTTATCTAGTTTCCATGGCTACGTAGATAA GTAGCATGGCGGGTTAATCATTAATACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCC

	CTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCCGACGCCCGGG CTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAAGCATG CAATTAAGTGGCCGTCGTTTTACAACGTCGTGACTGGGAAAACCCTGGCGTTACCCAAGT TAATCGCCTTGCAGCACATCCCCCTTTCGCCAGCTGTATCAGCACACAATTGCCCATATA CGCGCGTATAATGGACTATTGTGTGCTGATA

TELN- GFAPG5- BSRGI SEQ ID NO: 21	TATCAGCACACAATAGTCCATTATACGCGCGTATAATGGGCAATTGTGTGCTGATACAGC TGGCACGACAGGTTTCCCCACTGGAAGCGGGCAGTGAGCGCAACGCAATTAATGTGAG TTAGCTCACTCATTAGGCACCCAGGCTTTACACTTTATGCTTCCGGCTCGTATGTTGTGT GGAATTGTGAGCGGATAACAATTTACACAGGAAACAGCTATGACCATGATTACGCCAG ATTTAATTAAGGCCTTAATTAGGCTAGCTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTC ACTGAGGCCGGGCGACCAAAGGTGCGCCGACGCCCCGGGCTTTGCCCGGGCGGCCTCAGT GAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCTGGAGGG GTGGAGTCGTGACGATATCCATGCGTCGACATAACGCGTGATCTAACATATCCTGGTGTG GAGTAGCGGACGCTGCTATGACAGAGGCTCGGGGGCTGAGCTGGCTCTGTGAGCTGGG GAGGAGGCAGACAGCCAGGCCTTGTCTGCAAGCAGACCTGGCAGCATTGGGCTGGCCGC CCCCAGGGCTCTCTTCATGCCCAGTGAATGACTCACCTTGGCAGACACAAATGTTT GGGGTGGGCACAGTGCCTGCTTCCCGCCGACCCCCAGCCCCCTCAAATGCCTTCCGAGA AGCCCATTGAGCAGGGGGCTTGCAATGACCCCCAGCCTGACAGCCTGGCATCTTGGGATA AAAGCAGCACAGCCCCCTAGGGGCTGCCCTTGTGTGTGGCGCCACCGGCGGTGGAGAA CAAGGCTCTATTACGCTGTGCCAGGAAAGGGGATCAGGGGATGCCAGGCATGGACA GTGGGTGGCAGGGGGGAGAGGAGGGCTGTCTGCTTCCAGAAAGTCCAAGGACACAAAT GGGTGAGGGGAGAGCTCTCCCCATAGCTGGGCTGCGGCCAACCCACCCCTCAGGCTA TGCCAGGGGTGTTGCCAGGGGCACCCGGGCATCGCCAGTCTAGCCCACTCCTTCATAAA GCCCTCGCATCCCAGGAGCGAGCAGAGCCAGAGCAGGTTGGAGAGGACGCATCACCT CCGCTGCTCGCGGGATCCTCTAGAAGCTTCGTTTAGTGAACCGTCAGATCGCTGGAGA CGCCATCCACGCTGTTTTGACCTCCATAGAAGACACCGGGACCGATCCAGCCTCCGCGGA TTCGAATCCCGCGCGGAACGGTGCAATTGGAACGCGGATTCCCCGTGCCAAGAGTGACGT AAGTACCGCTATAGAGTCTATAGGCCACAAAAAATGCTTTCTTTTAAATATACTTTT TTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTTTTACGGGCAATAATGATAAAT GTATCATGCCTCTTTGCACCATTTCTAAAGAATAACAGTGATAATTTCTGGGTTAAGGCAAT AGCAATATTTCTGCATATAAATATTTCTGCATATAAATTTGTAAGTATGTAAGAGGTTTCA TATTGCTAATAGCAGCTACAATCCAGCTACCATTTCTGCTTTTATTTTATGGTTGGGATAAG GCTGGATTATTTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATGTTTATACCTCTTATCTTC CTCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCATCACTTTGGCAAAGAA TTGGGATTGCAACCGTCGCCACCGGTCACCAAGCAGGAAGTCAAAGACTTTTTCCGGTG GGCAAAGGATCACGTGGTTGAGGTGGAGCATGAATTTACGTCAAAAAGGGTGGAGCCA AGAAAAGACCCGCCCCAGTGACGCAGATATAAGTGAGCCAAACGGGTGCGCGAGTCA GTTGCGCAGCCATCGACGTGACAGCGGAAGCTTCGATCAACTACGCGGACAGGTACCA AAACAAATGTTCTCGTCACGTGGGCATGAATCTGATGCTGTTTCCCTGCAGACAATGCCA GAGAATGAATCAGAATTCAAATATCTGCTTCACTACGGACAGAAAGACTGTTTAGAGTG CTTTCCCGTGTCAGAATCTCAACCCGTTTCTGTCTGCTCAAAAAGGCGTATCAGAACTGTGC TACATTCATCATATCATGGGAAAGGTGCCAGACGCTTGCACTGCCTGCGATCTGGTCAAT GTGGATTTGGATGACTGCATCTTTGAACAATAAATGATTTAAATCAGGTATGTCTTTTGT GATCACCTCCAGATTGGTTGGAAGAAGTTGGTGAAGGTCTTCGCGAGTTTTTGGGCCCTT GAAGCGGGGCCACCGAAACCAAAACCAATCAGCAGCATCAAGATCAAGCCCGTGGTCT TGTGCTGCCTGGTTATAACTATCTCGGACCCGGAACGGTCTCGATCGAGGAGAGCCTGT CAACAGGGCAGACGAGGTGCGCGGAGAGCACGACATCTCGTACAAACGAGCATCTGAGG CGGGAGACAACCCCTACCTCAAGTACAACCACGCGGACGCGGAGTTTCAGGAGAAGCTC GCCGACGACACATCTTCGGGGGAAACCTCGGAAAGGCAGTCTTCAGGCCAAGAAAAG GGTTCTCGAACCTTTTGGCCTGGTTGAAGAGGGTGCTAAGACGGCCCCTACCGGAAAGCG GATAGACGACCACTTTCCAAAAAGAAAGAGGCCCGGACCGAAGAGGACTCCAAGCCTT CCACCTCGTCAGACGCGGAAGCTGGACCCAGCGGATCCCAGCAGCTGCAAAATCCAGCCC AACCAGCCTCAAGTTTGGGAGCTGATACAATGTCTGCGGGAGGTGGCGGCCATTGGGCG ACAATAACCAAGGTGCCGATGGAGTGGGCAATGCCTCGGGAGATTGGCATTGCGATTCC ACGTGGATGGGGGACAGAGTCGTACCAAGTCCACCCGAACCTGGGTGCTGCCAGCTA CAACAACCAACAGTACCGAGAGATCAAAAGCGGCTCCGTCGACGGAAGCAACGCCAACG CCTACTTTGGATACAGCACCCCTGGGGTACTTTGACTTTAACCGCTTCCACAGCCACTG GAGCCCCGAGACTGGCAAAGACTCATCAACAATACTGGGGCTTCAGACCCCGGTCCCT CAGAGTCAAAATCTTCAACATTCAAGTCAAAGAGGTACGGTGACGAGTCCACCAACAC CATCGCCAACAACCTCACCTCCACCGTCCAAGTGTTTACGGACGACGACTACCAAGCTGCC CTACGTCGTGCGCAACGGGACCGAGGGATGCCTGCCGGCTTCCCTCCGACAGTCTTTAC GCTGCCGAGTACGGTTACGCGACGCTGAACCGCGACAACACAGAAAATCCACCGAGA GGAGCAGCTTCTTCTGCTAGAGTACTTTCCAGCAAGATGCTGAGAACGGGCAACAAT TTGAGTTTACCTACAACCTTTGAGGAGGTGCCCTTCCACTCCAGCTTCGCTCCAGTCAGAA CTCTTTCAAGCTGGCAACCCGCTGGTGGACAGTACTTGTACCGCTTCTGTGAGCAAAA TAACACTGGCGGAGTCAAGTTCAACAAGAACCTGGCCGGGAGATACGCCAACACATA AAAAGTGGTTCCCGGGGCCATGGGCCGAACCCAGGGCTGGAACTGGGCTCCGGGGTGC AACCGCGCCAGTGTACGCGCTTTCGCCACGACCAATAGGATGGAGCTCGAGGGCGCGAG TTACCAGGTGCCCCCGAGCCGAACGGCATGACCAACAACCTCCAGGGCAGCAACACCT ATGCCCTGGAGAACACTATGATCTTCAACAGCCAGCCGGCGAACCAGGGCACCCGCC ACGTACCTCGAGGGCAACATGCTCATCACAGCGAGAGCGAGACGCGGCTGTAACCG CGTGGCGTACAACGTCGGCGGGCAGATGGCCACCAACAACAGAGCTCTGTACATCGATT

	GTTAATCAATAAACCGTTTAATTCGTTTCAGTTGAACTTTGGTCTCTGCGTATTTCTTTCTT ATCTAGTTTCCATGGCTACGTAGATAAGTAGCATGGCGGGTTAATCATTAACTACAAGGA ACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGG GCGACCAAAGGTCGCCCACGCCCCGGGCTTTGCCCGGGCGCCTCAGTGAGCGAGCGAG CGCGCAGAGAGGGAGTGGCCAAGCATGCAATTAAGTGGCCGTCGTTTTACAACGTCGTGA CTGGGAAAACCTGGCGTTACCCAACCTAATCGCCTTGCAGCACATCCCCCTTTCGCCAG CTGTATCAGCACACAATTGCCATTATACGCGGTATAATGGACTATTGTGTGCTGATA

TELN-SYNG6- BSRGI SEQ ID NO: 22	TATCAGCACACAATAGTCCATTATACGCGCGTATAATGGGCAATTGTGTGCTGATACAGC TGGCACGACAGGTTTCCCGACTGGAAGCGGGCAGTGAGCGCAACGCAATTAATGTGAG Ttagctactcattagggacccccaggctttacactttatgcttccggctcgtatgttgtgt GGAATTGTGAGCGGATAACAATTTACACAGGAAACAGCTATGACCATTATACGCCAG ATTTAATTAAGGCCTTAATTAGGCTAGCTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTC ACTGAGGCCGGGGCACCAGGTCGCCCCGACGCCCCGGGCTTTGCCCGGGCGGCCTCAGT GAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCTGGAGGG GTGGAGTCGTGACGATATCCATGCGTCGACATAACGCGTTAGTATCTGCAGAGGGCCCTG CGTATGAGTGCAAGTGGGTTTTAGGACCAGGATGAGGCGGGGTGGGGGTGCTACCTGA CGACCGACCCCGACCCACTGGACAAGCACCAACCCCAATTCCCAAAATTGCGCATCCCC TATCAGAGAGGGGGAGGGGAAACAGGATGCGGCGAGGCGCGTGCGCACTGCCAGTTCA GCACCGCGGACAGTGCCCTTCGCCCCCGCTGGCGGCGCGCGCCACCGCCGCTCAGCACT GAAGGCGCGCTGACGTCACTCGCCGGTCCCCGCAAACTCCCTTCCCGGCCACCTTGGT CGCGTCCGCGCCCGCGGCCAGCCGACCGCACACCGGAGGCGGAGATAGGGGG GCACGGGCGCGACCATCTGCGCTGCGGCGCCGGCGACTCAGCGCTGCCTCAGTCTGCGGT GGGCAGCGGAGGAGTCGTGTCTGCTGAGAGCGCAGCTGTGCTCCTGGGCACCGCGCA GTCCGCCCCCGCGGCTCCTGGCCAGACCACCCCTAGGACCCCTGCCCAAGTCGCAGCC AAGCTTCGTTTGTGTAACCGTCAGATCGCTGGAGACGCCATCCACGCTGTTTGTACCTC ATAGAAGACACCGGGACCGATCCAGCCTCCGCGGATTGCAATCCCGCCGGGAACGCTG CATTGGAACGCGGATTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAG GCCCCAAAAAATGCTTCTTCTTTAATATACTTTTTGTATTCTTATTTCTAATACTTTC CCTAATCTCTTCTTTCAGGGCAATAATGATACAATGTATCATGCCTCTTTCACCAATTCT AAAGAATAACAGTGATAATTCTGGGTTAAGGCAATAGCAATATTTCTGCAATAAATAT TTCTGCATATAAATTGTAAGTGTGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCC AGCTACCATTCTGCTTTTATTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCT AGGCCCTTTTGTAAATCATGTTACATCTTATCTTCTCCACAGCTCCTGGGCAACGT GCTGGTCTGTGTGCTGGCCATCACTTTGGCAAAGAATTGGGATTGCAACCGGTGCGCCAC CGGTACAAGCAGGAAGTCAAAGACTTTTTCCGCTGGGCAAAAGGATCACGTGGTTGAGG TGGAGCATGAATTCTACGTCAAAAAGGGTGGAGCCAAGAAAAGACCCGCCCCCAGTGAC GCAGATATAAGTGAGCCAAACGGGTGCGCGAGTCAGTTGCGCAGCCATCGACGTCAGA CGCGGAAGCTTCGATCAACTACGCGGACAGGTACCAAAACAAATGTTCTCGTCACGTGGG CATGAATCTGATGCTGTTTCCCTGCAGACAATGCGAGAGAATGAATCAGAATTCAAATAT CTGCTTCACTCACGGACAGAAAGACTGTTTAGAGTGCTTTCCCGTGTCAGAATCTCAACC CGTTTTCTGCTCAAAAAGGCGTATCAGAAACTGTGCTACATTATCATATCATGGGAAA GGTGCCAGACGCTTGCCTGCGATCTGGTCAATGTGGATTGGATGACTGCATCTTT GAACAATAAATGATTTAAATCAGGTATGGCTGCCGATGGTTATCTTCCAGATTGGCTCGA GGACAACCTCTCTGAGGGCATTGCGGAGTGGTGGGACTTGAAACCTGGAGCCCCGAAAC CCAAAGCCAACAGCAAAAGCAGGACGACGCGCGGGGTCTGGTGCTTCTGGCTACAAG TACCTCGGACCTTCAACGGACTCGACAAGGGGGAGCCCGTCAACGCGGCGGATGCAGC GGCCCTCGAGCAGCAAGGCTACGACCAGCAGCTCAAAGCGGGTGACAATCCGTACC TGCGGTATAACCACGCCGACGCCGAGTTTCAGGAGCGTCTGCAAGAAGATACGCTTTTTG GGGCAACCTCGGGCGAGCAGTCTTCCAGGCCAAGAAGAGGGTTCTGCAACTCTTTGGTC TGGTTGAGGAAGGTGCTAAGACGGCTCCTGGAAAGAAACGTCGCGTAGAGCAGTCGCCA CAAGAGCCAGACTCCTCCTCGGGCATTGGCAAGACAGGCCAGCAGCCGCTAAAAAGAG ACTCAATTTTGGTCAAGTGGCGACTCAGAGTCAGTCCCCGACCCACAACCTCTCGGAGA ACCTCCAGCAACCCCGCTGCTGTGGGACCTACTACAATGGCTTCAGGCGGTGGCGCACC AATGGCAGACAATAACGAAGGCGCGACGAGTGGGTAATGCCTCAGGAATTTGGCAATT GCGATTCCACATGGCTGGGCGACAGAGTCATCACCACCAGCACCCGAACATGGGCCTTGC CCACCTATAACAACCACTCTACAAGCAAATCTCCAGTGCTTCAACGGGGGCCAGCAACG ACAACCACTACTTCGGCTACAGCACCCCTGGGGGTATTTTGATTTCACAGATTCCACTG CCATTTCTACACAGTGAAGTGGCAGCGACTCATCAACAACAATTGGGGATTCCGGCCCCAA GAGACTCAACTTCAAGCTCTTCAACATCCAAGTCAAGGAGGTCACGACGAATGATGGCGT CACGACCATCGCTAATAACCTTACCAGCACGGTTCAAGTCTTCTCGGACTCGGAGTACCA GTTGCCGTACGCTCCTCGGCTCTGCGCACCAGGGCTGCCTCCCTCCGTTCCCGCGGACGCTG TTCATGATTCCGAGTACGGCTACCTAACGCTCAACAATGGCAGCCAGGCAAGTGGGACGG TCATCTTTTACTGCCTGGAATATTTCCATCGCAGATGCTGAGAACGGCAATAACTTAA CCTTCAGCTACACCTTCGAGGACGTGCCTTTCCACAGCAGCTACGCGCACAGCAAGGCC TGGACCGGCTGATGAATCCTCTCATCGACCAGTACCTGTATTACCTGAACAGAACTCAGA ATCAGTCCGGAAGTGCCCAAAACAAGGACTTGCTGTTAGCCGGGGGTCTCCAGCTGGCA TGCTGTTCAGCCCCAAAACCTGGCTACCTGGACCCTGTTACCGGCAGCAGCGCGTTTCTA AAACAAAAACAGACAACAACAACAGCAACTTTACCTGGAGTGGTGTCTTCAAAATAAAC CTTAATGGGCGTGAATCTATAATCAACCCTGGCACTGCTATGGCCTCACACAAAGACGAC AAAGACAAGTTCTTTCCATGAGCGGTGTATGATTTTGGAAAAGGAGAGCGCCGAGCT TCAAACACTGCATTGGACAATGTCATGATCAGACGAAGAGGAAATCAAAGCCACTAA CCCCGTGGCCACCGAAAGATTTGGGACTGTGGCAGTCAATCTCCAGAGTGTACATCGATT GTTAATCAATAAACCGTTTAATTCTGTTTCAAGTGAACCTTTGGTCTCTCGCTTCTTCTT ATCTAGTTTCCATGGCTACGTAGATAAGTAGCATGGCGGGTTAATCATTAACATAAGGA

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TELN- GFAPG6- BSRGI SEQ ID NO: 23	TATCAGCACACAATAGTCCATTATACGCGCGTATAATGGGCAATTGTGTGCTGATACAGC TGGCAGCAGAGGTTTCCCGACTGGAAGCGGGCAGTGAGCGCAACGCAATTAATGTGAG TTAGCTCACTCATTAGGCACCCAGGCTTTACACTTTATGCTTCCGGCTCGTATGTTGTGT GGAATTGTGAGCGGATAACAATTTACACAGGAAACAGCTATGACCATGATTACGCCAG ATTTAATTAAGGCCTTAATTAGGCTAGCTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTC ACTGAGGCCGGGCGACCAAAGGTGCGCCGACGCGGGGCTTTGCCCGGGCGGCCTCAGT GAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCCTGGAGGG GTGGAGTCGTGACGATATCCATGCGTCGACATAACGCGTGATCTAACATATCCTGGTGTG GAGTAGCGGACGCTGCTATGACAGAGGCTCGGGGGCTGAGCTGGCTCTGTGAGCTGGG GAGGAGGCAGACAGCCAGGCCTTGTCTGCAAGCAGACCTGGCAGCATTGGGCTGGCCGC CCCCAGGGCTCCTCTTCATGCCCAGTGAATGACTCACCTTGGCAGACACAAATGTTT GGGGTGGGCACAGTGCCTGCTTCCCGCCGACCCAGCCCCCTCAAATGCCTTCCGAGA AGCCCATTGAGCAGGGGGCTTGCAATGACCCAGCCTGACAGCCTGGCATCTTGGGATA AAAGCAGCACAGCCCCCTAGGGGCTGCCCTTGTGTGTGGCGCCACCGGCGGTGGAGAA CAAGGCTCTATTACGCTGTGCCAGGAAAGGGGATCAGGGGATGCCAGGCATGGACA GTGGGTGGCAGGGGGGAGAGGAGGGCTGTCTGCTTCCAGAAAGTCCAAGGACACAAAT GGGTGAGGGGAGAGCTCTCCCATAGCTGGGCTGCGGCCAACCCACCCCTCAGGCTA TGCCAGGGGTGTTGCCAGGGGCACCCGGGCATCGCCAGTCTAGCCCACTCCTTCATAAA GCCCTCGCATCCAGGAGCGAGCAGAGCCAGAGCAGGTTGGAGAGAGCAGCATCACT CCGCTGCTCGCGGGATCCTCTAGAAGCTTCGTTTAGTGAACCGTCAGATCGCTGGAGA CGCCATCCACGCTGTTTTGACCTCCATAGAAGACACCGGGACCGATCCAGCTCCGCGGA TTCGAATCCCGCGCGGAACGGTGCAATTGGAACGCGGATTCCCGTGCCAAGAGTGACGT AAGTACCGCTATAGAGTCTATAGGCCACAAAAAATGCTTTCTTTTAAATACTTTT TTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTTTTACGGGCAATAATGATAAAT GTATCATGCCTCTTTGCACCATTTCTAAAGAATAACAGTGATAATTTCTGGGTAAAGCAAT AGCAATATTTCTGCATATAAATATTTCTGCATATAAATGTAACTGATGTAAGAGGTTTCA TATTGCTAATAGCAGCTACAATCCAGCTACCATTTCTGCTTTTATTTTATGGTTGGGATAAG GCTGGATTATTTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATGTTTCATACCTCTTATCTTC CTCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCATCACTTTGGCAAAGAA TTGGGATTGCAACCGTTCGCCACCGGTCACCAAGCAGGAAGTCAAAGACTTTTTCCGGTG GGCAAAGGATCACGTGGTTGAGGTGGAGCATGAATTTACGTCAAAAAGGGTGGAGCCA AGAAAAGACCCGCCCCAGTGACGCAGATATAAGTGAGCCAAACGGGTGCGCGAGTCA GTTGCGCAGCCATCGACGTGACAGCGGGAAGCTTCGATCAACTACGCGGACAGGTACCA AAACAAATGTTCTCGTCACGTGGGCATGAATCTGATGCTGTTTCCCTGCAGACAATGCCA GAGAATGAATCAGAATTCAAATATCTGCTTCACTCACGGACAGAAAGACTGTTTAGAGTG CTTTCCCGTGTCAGAATCTCAACCCGTTTCTGTCTGTCAAAAAGGCGTATCAGAACTGTGC TACATTCATCATATCATGGGAAAGGTGCCAGACGCTTGCACTGCCTGCGATCTGGTCAAT GTGGATTTGGATGACTGCATCTTTGAACAATAAATGATTTAAATCAGGTATGGCTGCCGA TGGTTATCTTCCAGATTGGCTCGAGGACAACCTCTCTGAGGGCATTGCGGAGTGGTGGGA CTTGAAACCTGGAGCCCCGAAACCCAAAGCCAACAGCAAAAGCAGGACGACGGCCGGG GTCTGGTGCTTCTGGCTACAAGTACCTCGGACCCTTCAACGGACTCGACAAGGGGGAGC CCGTCAACGCGGCGGATGACGCGGCCCTCGAGCAGCACAAGGCTTACAGCAACGCTC AAAGCGGGTGACAATCCGTACCTGCGGTATAACCACGCCGACGCCGAGTTTCAGGAGCG TCTGCAAGAAGATACGTCTTTTGGGGGCAACCTCGGGCGAGCAGTCTTCCAGGCCAAGAA GAGGGTTCTCGAACCTTTTGGTCTGCTTGAGGAAGGTGCTAAGACGGCTCCTGGAAAGAA ACGTCCGGTAGAGCAGTCGCCACAAGAGCCAGACTCCTCCTCGGGCATTGGCAAGACAG GCCAGCAGCCGCTAAAAAGAGACTCAATTTTGGTCAGACTGGCAGTCAAGTCACTGTC CCGACCCACAACCTCTCGGAGAACCTCCAGCAACCCCGCTGCTGTGGGACCTACTACAA TGGCTTCAGGCGGTGGCGCACCAATGGCAGACAATAACGAAGGCGCCGACGGAGTGGGT AATGCCTCAGGAAATTGGCATTGCGATTCCACATGGCTGGGCGACAGAGTCAACACC AGCACCCGAACATGGGCCTTGCCACCTATAACAACCACTCTACAAGCAATCTCCAGT GCTTCAACGGGGGCCAGCAACGACAACCACTACTTCGGCTACAGCACCCCTGGGGGTAT TTTGATTTCAACAGATTCCACTGCCATTTCTCACCACGTGACTGGCAGCGACTCATCAACA ACAATTGGGGATTCCGGCCCAAGAGACTCAACTTCAAGCTCTTCAACATCCAAGTCAAGG AGGTACAGACGAATGATGGCGTCACGACCATCGCTAATAACCTTACCAGCACGGTTCAAG TCTTCTCGGACTCGGAGTACCAGTTGCCGTACGTCCTCGGCTCTGCGCACCAGGGCTGCCT CCCTCCGTTCCCGGCGGACGTGTTTCATGATTCCGCAGTACGGCTACCTAACGCTCAACAA TGGCAGCCAGGCAGTGGGACGGTCATCTTTTACTGCCTGGAATATTTCCCATCGCAGAT GCTGAGAACGGGCAATAACTTTACCTTACGCTACACCTTCGAGGACGTGCCTTTCCACAG CAGTACGCGCACAGCCAGAGCCTGGACCGGCTGATGAATCCTCTCATCGACCAGTACCT GTATTACCTGAACAGAACTCAGAATCAGTCCGGAAGTGCCCAAAAACAAGGACTTGTGTT TAGCCGGGGGTCTCCAGCTGGCATGTCTGTTTACGCCAAAAAACTGGCTACCTGGACCCTG TTACCGGCAGCAGCGCTTTCTAAAACAAAAACAGACAACAACAACAGCAACTTTACCT GGACTGGTGCTTCAAAATATAACCTTAATGGGCGTGAATCTATAATCAACCTGGCACTG CTATGGCCTCACACAAAGACGACAAAGACAAGTTCTTTCCCATGAGCGGTGTCATGATTT TTGAAAGGAGAGCGCGGAGCTTCAAAACACTGCATTGGACAATGTCATGATCACAGAC GAAGAGGAAATCAAAGCCACTAACCCCGTGGCCACCGAAAGATTGGGACTGTGGCAGT

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TELN- SYNGDJ8- BSRGI SEQ ID NO: 24	TATCAGCACACAATAGTCCATTATACGCGCGTATAATGGGCAATTGTGTGCTGATACAGC TGGCACGACAGGTTTCCCGACTGGAAGCGGGCAGTGAGCGCAACGCAATTAATGTGAG TTAGCTCACTCATTAGGCACCCAGGCTTTACACTTTATGCTTCCGGCTCGTATGTTGTGT GGAATTGTGAGCGGATAACAATTTACACAGGAAACAGCTATGACCATGATTACGCCAG ATTTAATTAAGGCCTTAATTAGGCTAGCTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTC ACTGAGGCCGGGCGACCAAAGGTGCGCCGACGCCCCGGGCTTTGCCCGGGCGGCCTCAGT GAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCCTGGAGGG GTGGAGTCGTGACGATATCCATGCGTCGACATAACGCGTTAGTATCTGCAGAGGGCCCTG CGTATGAGTGCAAGTGGGTTTTAGGACCAGGATGAGGCGGGGTGGGGGTGCTTACCTGA CGACCGACCCCGACCCACTGGACAAGCACCAACCCCAATTCCCAAAATTGCGCATCCCC TATCAGAGAGGGGGAGGGGAAACAGGATGCGGCGAGGCGCGTGCGCACTGCCAGTTCA GCACCGCGGACAGTGCTTCGCCCCCGCTGGCGGCGCGCGCCACCGCCGCTCAGCACT GAAGGCGCGCTGACGTCACTCGCCGGTCCCCGCAAACTCCCTTCCCGGCCACCTTGGT CGCGTCCGCGCGCGCGCCGCGCCAGCCGACCGCACACGCGAGGCGGAGATAGGGGG GCACGGGCGCGACCATCTGCGCTGCGGCGCGCGGCGACTCAGCGCTGCCTCAGTCTGCGGT GGGCAGCGGAGGAGTCGTGTCTGCTGAGAGCGCAGCTGTGCTCCTGGGCACCGCGCA GTCCGCCCCCGCGGCTCCTGGCCAGACCACCCCTAGGACCCCTGCCCAAGTCGCAGCC AAGTTTCGTTTAGTGAACCGTCAGATCGCTGGAGACGCCATCCACGCTGTTTGGACCTC ATAGAAGACACCGGGACCGATCCAGCCTCCGCGGATTGCAATCCCGCCGGGAACCGTG CATTGGAACGCGGATTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAG GCCCCAAAAAATGCTTCTTCTTTAATATACTTTTTGTTTATCTTATTTCTAATACTTTC CCTAATCTCTTCTTTCAGGGCAATAATGATACAATGTATCATGCCTCTTTCACCAATTCT AAGAATAACAGTGATAATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATAT TTCTGCATATAAATTGTAAGTGTGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCC AGCTACCATTTCTGCTTTTATTTTATGGTTGGGATAAGGCTGGATTATTTCTGAGTCCAAGCT AGGCCCTTTTGTCTAATCATGTTTCATACCTCTTATCTTCTCCACAGCTCCTGGGCAACGT GCTGGTCTGTGTCTGGCCATCACTTTGGCAAAGAATTGGGATTGCAACCGGTGCGCCAG CGGTACAAGCAGGAAGTCAAAGACTTTTTCCGGTGGGCAAAAGGATCACGTGGTTGAGG TGGAGCATGAATTCTACGTCAAAAAGGGTGGAGCCAAGAAAAGACCCGCCCCCAGTGAC GCAGATATAAGTGAGCCAAACGGGTGCGCGAGTCAAGTTGCGCAGCCATCGACGTCAGA CGCGGAAGCTTCGATCAACTACGCGGACAGGTACCAAAACAAATGTTCTCGTCACGTGGG CATGAATCTGATGCTGTTTCCCTGCAGACAATGCGAGAGAATGAATCAGAATTCAAATAT CTGCTTCACTCACGGACAGAAAGACTGTTTAGAGTGCTTTCCCGTGTCAAGATCTCAACC CGTTTTCTGCTCAAAAAGGCGTATCAGAAACTGTGCTACATTCATCATATCATGGGAAA GGTGCCAGACGCTTGCCTGCGATCTGGTCAATGTGGATTGGATGACTGCATCTTT GAACAATAAATGATTTAAATCAGGTATGGCTGCCGATGGTTATCTTCCAGATTGGCTCGA GGACACTCTCTGAAGGAATAAGACAGTGGTGGAAGCTCAAACCTGGGCCACCAAC CAAGCCGCGAGAGCGGCATAAGGACGACAGCAGGGGTCTTGCTTCTGGGTACAAG TACCTCGGACCCCTCAACGGACTCGACAAGGAGAGCCGGTCAACGAGGCAGACGCCGC GGCCCTCGAGCAGACAAAGCCTACGACCGGCAGCTCGACAGCGGAGACAACCCGTACC TCAAGTACAACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAGAAGATAAGTCTTTTG GGGCAACCTCGGGCGAGCAGTCTTCCAGGCCAAAAGAGGCTTTGTAACCTCTTGGTC TGGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAGAAGAGGCCTGTAGAGCACTCTCCT GTGGAGCCAGACTCCTCCTCGGGAACCGGAAAGGCGGGCCAGCAGCTGCAAGAAAAAG ATTGAATTTTGGTCAAGTGGAGACGCAAGTCAAGTCCCAGACCTCAACCAATCGGAGA ACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTACAATGGCTGCAGGCGGTGGCGCACC AATGGCAGACAATAACGAGGGCGCGGACCGAGTGGGTAATTCCTCGGGAATTCGCAATT GCGATTCCACATGGATGGGCGACAGAGTCATCACCACCAGCACCCGAACCTGGGCCCTGC CCACCTACAACAACCACTCTACAAGCAAATCTCCAACAGCACATCTGGAGGATCTTCAA ATGACAACGCCTACTTCGGCTACAGCACCCCTGGGGGTATTTTGACTTTAACAGATTCC ACTGCCACTTTTCACCACGTGACTGGCAGCGACTCATCAACAACAACCTGGGGATTCCGGC CCAAGAGACTCAGCTTCAAGCTCTTCAACATCCAGGTCAAGGAGGTCACGCAAGATGAA GGCACCAAGACCATCGCCAATAACCTCACCAGCACCATCCAGGTGTTTACGGACTCGGAG TACCAGCTGCCGTACGTTCTCGGCTCTGCCACCAGGGCTGCCTGCCTCCGTTCCCGGCGG ACGTGTTTCATGATTCCCCAGTACGGCTACCTAACACTCAACAACGGTAGTCAGGCCGTGG GACGCTCCTCCTTCTACTGCCTGGAATACTTTCTTGCAGATGCTGAGAACCAGGCAACA ACTTCCAGTTTACTTACACCTTCGAGGACGTGCCTTTCCACAGCAGCTACGCCACAGCCA GAGCTTGGACCGGCTGATGAATCCTCTGATTGACCAGTACCTGTACTACTTGTCTCGGACT CAAACAACAGGAGGCACGACAAATACGCAAGTCTGGGCTTACGCCAAGGTGGGCCTAA TACAATGGCCAATCAGGCAAGAAGTGGCTGCCAGGACCTGTTACCGCCAGCAGCGAG TATCAAAGACATCTGCGGATAACAACAACAGTGAATACTCGTGAGGCTGAGCTGAGCTA TACCACCTCAATGGCAGAGACTCTCTGGTGAATCCGGGCCCGGCCATGGCAAGCCACAAG GACGATGAAGAAAAGTTTTTCTCAGAGCGGGGTCTCATCTTTGGGAAGCAAGGCTCA GAGAAAACAAATGTGGACATTGAAAAGGTCATGATTACAGACGAAGAGGAAATCAGGAC AACCAATCCCGTGGCTACGGAGCAGTATGGTTCTGTATCTACCAACCTCCAGCAAGGTGT ACATCGATTGTTAATCAATAAACCGTTTAATTCGTTTCAAGTTGAACCTTGGTCTCTGCGTA TTTCTTCTTATCTAGTTTCCATGGCTACGTAGATAAGTAGCATGGCGGGTTAATCATTA

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TELN-GFAPG-DJ8-BSRGI SEQ ID NO: 25	TATCAGCACACAATAGTCCATTATACGCGCGTATAATGGGCAATTGTGTGCTGATACAGC TGGCAGCAGACAGGTTTCCCGACTGGAAGCGGGCAGTGAGCGCAACGCAATTAATGTGAG TTAGCTCACTCATTAGGCACCCAGGCTTTACACTTTATGCTTCCGGCTCGTATGTTGTGT GGAATTGTGAGCGGATAACAATTTACACAGGAAACAGCTATGACCATGATTACGCCAG ATTTAATTAAGGCCTTAATTAGGCTAGCTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTC ACTGAGGCCGGGCGACCAAAGGTCGCCCCAGCGCCGGGCTTTGCCCGGGCGGCCTCAGT GAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCTGGAGGG GTGGAGTCGTGACGATATCCATGCGTCGACATAACGCGTGATCTAACATATCCTGGTGTG GAGTAGCGGACGCTGCTATGACAGAGGCTCGGGGGCTGAGCTGGCTCTGTGAGCTGGG GAGGAGGCAGACAGCCAGGCCTTGTCTGCAAGCAGACCTGGCAGCATTGGGCTGGCCGC CCCCAGGGCTCTCTTCATGCCCAGTGAATGACTCACCTTGGCAGACACAAATGTTT GGGGTGGGCACAGTGCCTGCTTCCCGCCGACCCCCAGCCCCCTCAAATGCCTTCCGAGA AGCCCATTGAGCAGGGGGCTTGCAATGACCCCCAGCCTGACAGCCTGGCATCTTGGGATA AAGCAGCACAGCCCCCTAGGGGCTGCCCTTGTGTGTGGCGCCACCGCGGTGGAGAA CAAGGCTCTATTACGCTGTGCCAGGAAAGGGGATCAGGGGATGCCAGGCATGGACA GTGGGTGGCAGGGGGGAGAGGAGGGCTGTCTGCTTCCAGAAAGTCCAAGGACACAAAT GGGTGAGGGGAGAGCTCTCCCCATAGCTGGGCTGCGGCCAACCCACCCCTCAGGCTA TGCCAGGGGTGTTGCCAGGGGCACCCGGGCATCGCCAGTCTAGCCCACTCCTTCATAAA GCCCTCGCATCCAGGAGCGAGCAGAGCCAGAGCAGGTTGGAGAGGAGCGCATCACCT CCGCTGCTCGCGGGATCCTCTAGAAGCTTCGTTTAGTGAACCGTCAGATCGCTGGAGA CGCCATCCACGCTGTTTTGACCTCCATAGAAGACACCGGGACCGATCCAGCCTCCGCGGA TTCGAATCCCGCGCGGAACGGTGCAATTGGAACGCGGATTCCCCGTGCCAAGAGTGACGT AAGTACCGCTATAGAGTCTATAGGCCACAAAAAATGCTTTCTTTTAAATATCTTTT TTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTTTTACGGGCAATAATGATAAAT GTATCATGCCTCTTTGCACCATTTCTAAAGAATAACAGTGATAATTTCTGGGTTAAGGCAAT AGCAATATTTCTGCATATAAATATTTCTGCATATAAATTTGTAAGTATGTAAGAGGTTTCA TATTGCTAATAGCAGCTACAATCCAGCTACCATTTCTGCTTTTATTTTATGGTTGGGATAAG GCTGGATTATTTCTGAGTCCAAGCTAGGCCCTTTTGTCTAATCATGTTTCATACCTCTTATCTTC CTCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCATCACTTTGGCAAAGAA TTGGGATTGCAACCGTTCGCCACCGGTCACCAAGCAGGAAGTCAAAGACTTTTTCCGGTG GGCAAAGGATCACGTGGTTGAGGTGGAGCATGAATTTACGTCAAAAAGGGTGGAGCCA AGAAAAGACCCGCCCCAGTGACGCAGATATAAGTGAGCCAAACGGGTGCGCGAGTCA GTTGCGCAGCCATCGACGTGACGCGGGAAGCTTCGATCAACTACGCGGACAGGTACCA AAACAAATGTTCTCGTCACGTGGGCATGAATCTGATGCTGTTTCCCTGCAGACAATGCCA GAGAATGAATCAGAATTCAAATATCTGCTTCACTCACGGACAGAAAGACTGTTTAGAGTG CTTTCCCGTGTGAGAATCTCAACCCGTTTCTGTCTGCTCAAAAAGGCGTATCAGAACTGTGC TACATTCATCATATCATGGGAAAGGTGCCAGACGCTTGCACTGCCTGCATCTGGTCAAT GTGGATTTGGATGACTGCATCTTTGAACAATAAATGATTTAAATCAGGTATGGCTGCCGA TGGTTATCTTCCAGATTGGCTCGAGGACACTCTCTCTGAAGGAATAAGACAGTGGTGGAA GCTCAAACCTGGCCACCACCACCAAAGCCCGCAGAGCGGCATAAGGACGACAGCAGGG GTCTTGTGCTTCTGGGTACAAGTACCTCGGACCCTTCAACGGACTCGACAAGGGAGAGC CGGTCAACGAGGCAGACGCGCGGCCCTCGAGCAGCAGACAAAGCCTACGACCGGCACGCTC GACAGCGGAGACAACCCGTACCTCAAGTACAACCACGCGCAGCGCGAGTTCCAGGAGCG GCTCAAAGAAGATACGTCTTTTGGGGCAACCTCGGGCGAGCAGTCTTCCAGGCCAAAA AGAGGCTTCTTGAACTCTTGGTCTGGTTGAGGAAGCGGCTAAGACGGCTCCTGGAAAGA AGAGGCTGTAGAGCACTCTCTGTGGAGCCAGACTCCTCCTCGGGAACCGGAAAGGCG GGCCAGCAGCCTGCAAGAAAAAGATTGAATTTTGGTCAGACTGGAGCAGCAGACTCAGT CCCAGACCCTCAACCAATCGGAGAACCTCCCGCAGCCCCCTCAGGTGTGGGATCTCTTAC AATGGCTGCAGGCGGTGGCGACCAATGGCAGACAATAACGAGGGCGCGCAGCGAGTGG GTAATTCCTCGGGAATTTGGCATTGCGATTCCACATGGATGGGCGACAGAGTCATCACCA CCAGCACCCGAACCTGGGCCCTGCCACCTACAACAACCACTCTACAAGCAAAATCTCCA ACAGCACATCTGGAGGATCTTCAAATGACAACGCTACTTCGGCTACAGCACCCCTGGG GGTATTTTGACTTTAACAGATTCCACTGCCACTTTTACCACGTGACTGGCAGCGACTCAT CAACAACAACCTGGGGATTCCGGCCCAAGAGACTCAGTTCAAGCTCTTCAACATCCAGGT CAAGGAGGTACGCAGAAATGAAGGCACCAAGACCATCGCCAATAACCTCACCAGCACCA TCCAGGTGTTACGGACTCGGAGTACCAGTGCCTGACGTTCTCGGCTGCCCCACCAGG GCTGCCTGCCCTCCGTTCCCGGCGGACGTGTTTCATGATTCCCCAGTACGGTACCTAACACT CAACAACGGTAGTCAGGCCGTGGGACGCTCCTCCTTCTACTGCCTGGAATACTTTCTCTCG CAGATGCTGAGAACCAGCAACAACCTTCCAGTTTACTTACACCTTCGAGGACGTGCCTTTC CACAGCAGCTACGCCACAGCCAGAGCTTGGACCGGCTGATGAATCCTCTGATTGACCAG TACCTGTACTACTTGTCTCGGACTCAACAACAGGAGGCACGACAAATACGACAGCTCTG GGCTTCAGCCAAGGTGGGCTAATAACAATGGCCAAATCAGGCAAGAACTGGCTGCCAGG ACCCTGTTACCGCCAGCAGCGAGTATCAAAGACATCTGCGGATAACAACAACAGTGAAT ACTCGTGGACTGGAGTACCAAGTACCACCTCAATGGCAGAGACTCTCTGGTGAATCCGG GCCCGCCATGGCAAGCCACAAGGACGATGAAGAAAAGTTTTTCTCAGAGCGGGGT CTCATCTTTGGGAAGCAAGGCTCAGAGAAAACAATGTGGACATTGAAAAGTTCATGAT TACAGACGAAGAGGAAATCAGGACAACCAATCCCGTGGCTACGGAGCAGTATGGTTCTG

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In the claims which follow and in the preceding description of the invention, except where the context requires otherwise due to express language or necessary implication, the word “comprise” or variations such as “comprises” or “comprising” is used in an inclusive sense, i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

It is to be understood that, if any prior art publication is referred to herein, such reference does not constitute an admission that the publication forms a part of the common general knowledge in the art, in Australia or any other country.

CLAIMS

1. A method for generating an adeno-associated virus (AAV) vector library encoding variant AAV capsid polypeptides, the method comprising:

(a) providing first nucleic acids comprising a P40 promoter and a cell-type specific promoter, wherein the cell-type specific promoter drives capsid mRNA expression in the absence of helper virus co-infection; and second nucleic acids encoding: a plurality of the variant AAV capsid polypeptides having a region of randomized sequence of 2, 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids; and

(b) cloning the first nucleic acids and the second nucleic acids under conditions suitable to generate the AAV vector library.

2. The method of claim 1, wherein the cell-type specific promoter is a blood cell specific promoter, an eye specific promoter, a heart specific promoter, a muscle specific promoter, a kidney specific promoter, a lung specific promoter, a pancreas specific promoter, or a vasculature specific promoter, a neuron specific promoter or an astrocyte-specific promoter.

3. The method of claim 1 or 2, wherein the cell-type specific promoter is a promoter selected from B29 promoter, Immunoglobulin heavy chain promoter, CD45 promoter, Mouse INF- β promoter, CD45 SV40 / CD45 promoter, WASP promoter, CD43 promoter, CD43 SV40 / CD43 promoter, CD68 promoter, GPIIb promoter, CD14 promoter, CD2 promoter, Osteocalcin, Bone sialoprotein, OG-2 promoter, GFAP promoter, Vga, Vglut2, NSE / RU5' promoter, SYN1 promoter, Neurofilament light chain, VGF, Nestin, Chx10, PrP, Dkk3, Math5, Ptf1a, Pcp2, Nefh, gamma-synuclein gene (SNCG), Grik4, Pdgfra, Chat, Thy1.2, hVmd2, Thy1, Modified α A-crystallin, hRgp, mMo, Opn4, RLBP1, Glast, Foxg1, hVmd2, Trp1, Six3, cx36, Grm6 - SV40 eukaryotic promoter, hVmd2, Dct, Rpc65, mRho, Irbp, hRho, Pcp2, Rhodopsin, mSo, MLC2v promoter, α MHC promoter, rat troponin T (Tnnt2), Tie2, Tcf21, ECAD, NKCC2, KSPC, NPHS1, SGLT2, SV40 / bAlb promoter, SV40 / hAlb promoter, Hepatitis B virus core promoter, Alpha fetoprotein, Surfactant protein B promoter, Surfactant protein C promoter, Desmin, Mb promoter, Myosin, Dystrophin, dMCK and tMCK, Elastase-1 promoter, PDX1 promoter, Insulin promoter, Slco1c1, tie, cadherin, ICAM-2, claudin 1, Cldn5, Flt-1 promoter, and Endoglin promoter.

4. The method of any one of claims 1-3, wherein the cell-type specific promoter is a synapsin promoter.
5. The method of any one of claims 1-3, wherein the cell-type specific promoter is a GFAP promoter.
6. The method of any one of claims 1-5, wherein the P40 promoter and the cell-type specific promoter are located upstream of a transgene encoding the variant AAV capsid polypeptide.
7. The method of any one of claims 1-5, wherein the P40 promoter is located upstream of a transgene encoding the variant AAV capsid polypeptide and the cell-type specific promoter is located downstream of a transgene encoding the variant AAV capsid polypeptide.
8. The method of any one of claims 1-7, wherein the region of randomized sequence comprises a peptide insert of 4, 5, 6, 7, 8, or 9 consecutive amino acids.
9. The method of any one of claims 1-8, wherein the region of randomized sequence of 2, 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids is present in a hypervariable region of the parental AAV capsid polypeptide.
10. The method of any one of claims 1-9, wherein the region of randomized sequence of 2, 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids is present in loop IV, loop VIII, or both loop IV and loop VIII of the parental AAV capsid polypeptide.
11. The method of any one of claims 8-10, wherein the insert is present
 - (i) immediately subsequent to a position selected from 452-458 of the parental sequence; and/or
 - (ii) immediately subsequent to a position selected from 586-592 of the parental sequence.
12. The method of any one of claims 1-11, wherein the parental AAV capsid polypeptide comprises an AAV9 capsid polypeptide or an AAV5 capsid polypeptide.

13. The method of any one of claims 1-12, further comprising (c) generating a plurality of AAV particles comprising the AAV vector library.
14. The method of any one of claims 1-13, further comprising (d) administering the AAV particles to an animal.
15. The method of claim 14, wherein:
 - (i) the animal is a mouse or a non-human primate (NHP); and/or
 - (ii) the particles are administered intravenously.
16. The method of any one of claims 1-15, further comprising (e) collection and/or isolation of a target cell or tissue from the animal.
17. The method of claim 16, wherein the target cell or tissue is collected four weeks post-administration of the particles.
18. The method of any one of claims 1-17, further comprising (f) recovery of RNA and/or antisense RNA encoding the variant AAV capsid polypeptides from the target cell or tissue.
19. The method of claim 18, wherein the RNA encoding the variant AAV capsid polypeptides is enriched and/or reverse transcribed to cDNA.
20. The method of claim 19 wherein the cDNA is amplified.
21. The method of any one of claims 1-20, further comprising (g) determination of the sequence of the variant AAV capsid polypeptides.
22. The method of any one of claims 1-20, further comprising (h) measuring the amount of the amount of DNA encoding the variant AAV capsid polypeptides and/or the amount of RNA encoding the variant AAV capsid polypeptides in a target cell, or tissue.
23. The method of any one of claims 1-22, wherein the method further comprises repeating steps (a)-(h).

24. The method of any one of claims 16-23, wherein the target cell is a neuronal cell, a neural stem cell, an astrocyte, an oligodendrocyte, a microglia cell, a retinal cell, a tumor cell, a hematopoietic stem cell, an insulin producing beta cell, a lung epithelium cell, an endothelial cell, a liver cell, a skeletal muscle cell, a muscle stem cell, a muscle satellite cell, and/or a cardiac muscle cell.

25. The method of any one of claims 16-24, wherein the target tissue is a CNS tissue, a PNS tissue, and/or a peripheral tissue.

26. The method of claim 25, wherein the CNS tissue is a brain tissue, a spinal cord tissue, and/or a dorsal root ganglion tissue.

27. The method of claim 26, wherein the brain tissue is a cortex tissue, a frontal cortex tissue, a parietal cortex tissue, a occipital cortex tissue, a temporal cortex tissue, a thalamus tissue, a hypothalamus tissue, a striatum tissue, a putamen tissue, a caudate nucleus tissue, a hippocampus tissue, a entorhinal cortex tissue, a basal ganglia tissue, and/or a deep cerebellar nuclei tissue.

28. The method of claim 25, wherein the peripheral tissue is a muscle tissue, a liver tissue, a heart tissue, a gastrocnemius muscle tissue, a soleus muscle tissue, a pancreas tissue, a kidney tissue, a spleen tissue, a lung tissue, an adrenal glands tissue, a stomach tissue, a sciatic nerve tissue, a saphenous nerve tissue, a thyroid gland tissue, an eye tissue, a pituitary gland tissue, a skeletal muscle tissue, a colon tissue, a duodenum tissue, an ileum tissue, a jejunum tissue, a skin tissue of the leg, a superior cervical ganglia tissue, a urinary bladder tissue, an ovary tissue, a uterus tissue, a prostate gland tissue, and/or a testes tissue.

29. The method of any one of claims 1-6 or 8-28, wherein the vectors of the AAV vector library comprise in order:

- (i) a first inverted terminal repeat region (ITR);
- (ii) a cell-type specific promoter;
- (iii) a P40 promoter
- (iv) a transgene encoding the variant AAV capsid polypeptide comprising the region of randomized sequence of 2, 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids;
- (v) a poly-A sequence region; and

(vi) a second ITR.

30. An adeno-associated virus (AAV) vector library made by the method of any one of claims 1-29.

31. An adeno-associated virus (AAV) vector library comprising:

(a) first nucleic acids comprising a P40 promoter, and a cell-type specific promoter which drives capsid mRNA expression in the absence of helper virus co-infection; and

(b) second nucleic acids encoding a plurality of variant AAV capsid polypeptides having a region of randomized sequence of 2, 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids.

32. A method for generating a plurality of variant adeno-associated virus (AAV) capsid polypeptides, the method comprising:

(a) providing a plurality of AAV particles comprising an AAV vector library, wherein the AAV vector library comprises nucleic acids comprising a P40 promoter and a cell-type specific promoter which drives capsid mRNA expression in the absence of helper virus co-infection; and wherein the nucleic acids encode a plurality of the variant AAV capsid polypeptides having a region of randomized sequence of 2, 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids;

(b) administering the AAV particles to an animal, wherein the particles are administered intravenously;

(c) recovery of RNA and/or antisense RNA encoding the variant AAV capsid polypeptides from the target cell or tissue;

(d) determination of the sequence of the variant AAV capsid polypeptides; and

(e) measuring the amount of DNA encoding the variant AAV capsid polypeptides or the amount of RNA encoding the variant AAV capsid polypeptides, in a target cell or tissue; and

wherein the method occurs in the absence of a helper virus;

thereby generating the plurality of variant AAV capsid polypeptides.

33. The method of claim 32, wherein the cell-type specific promoter is a synapsin promoter or a GFAP promoter.

FIG. 1A

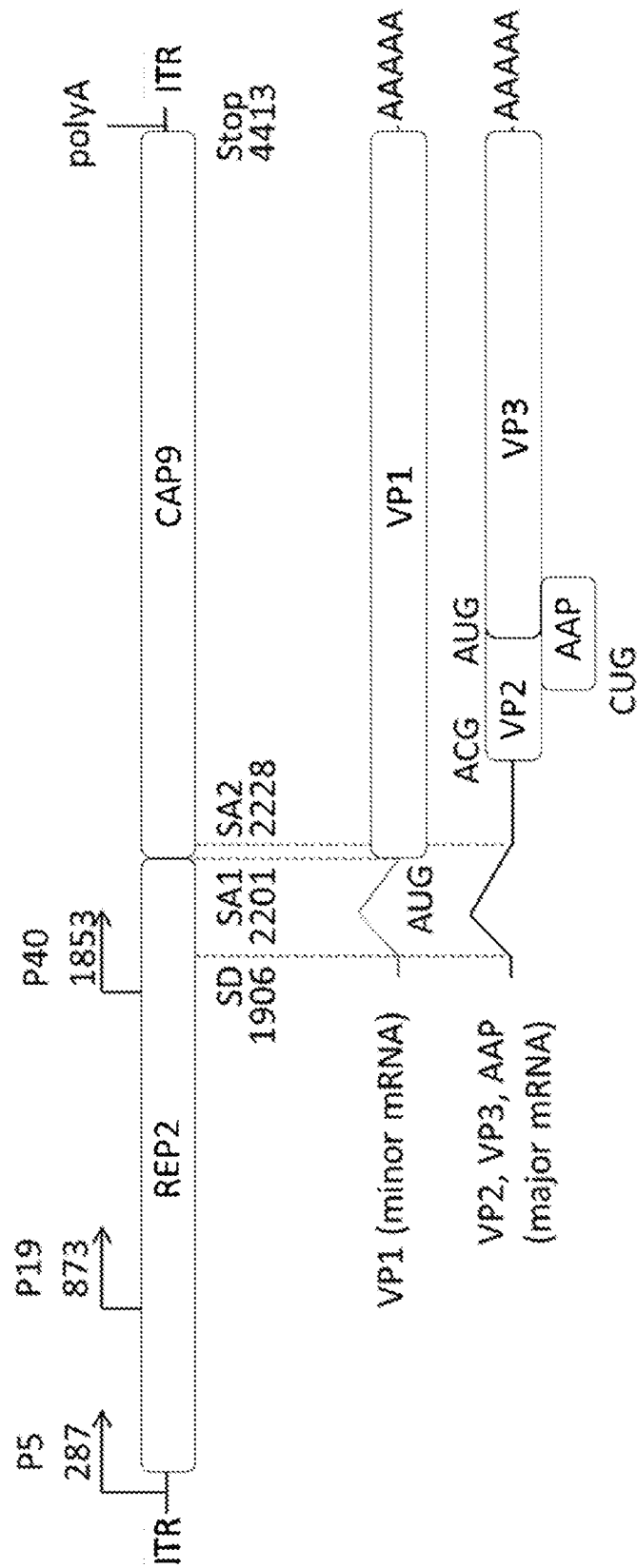
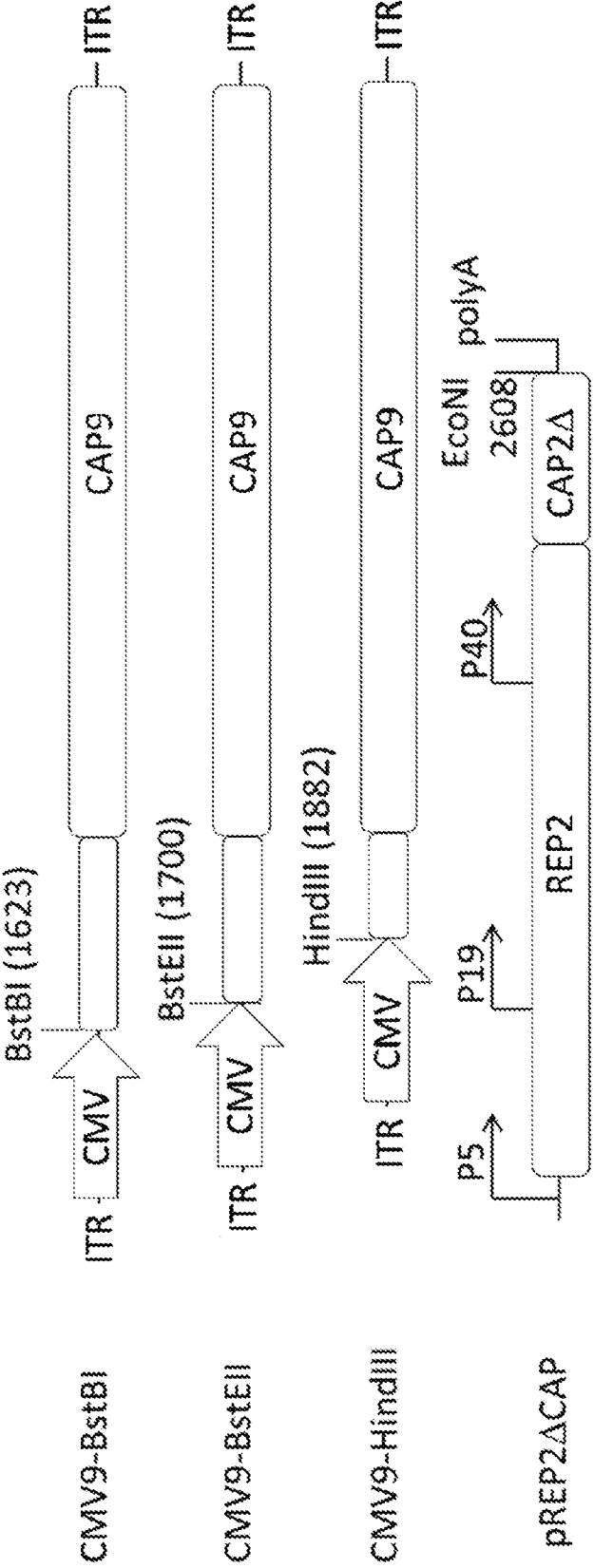


FIG. 1B



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FIG. 2A

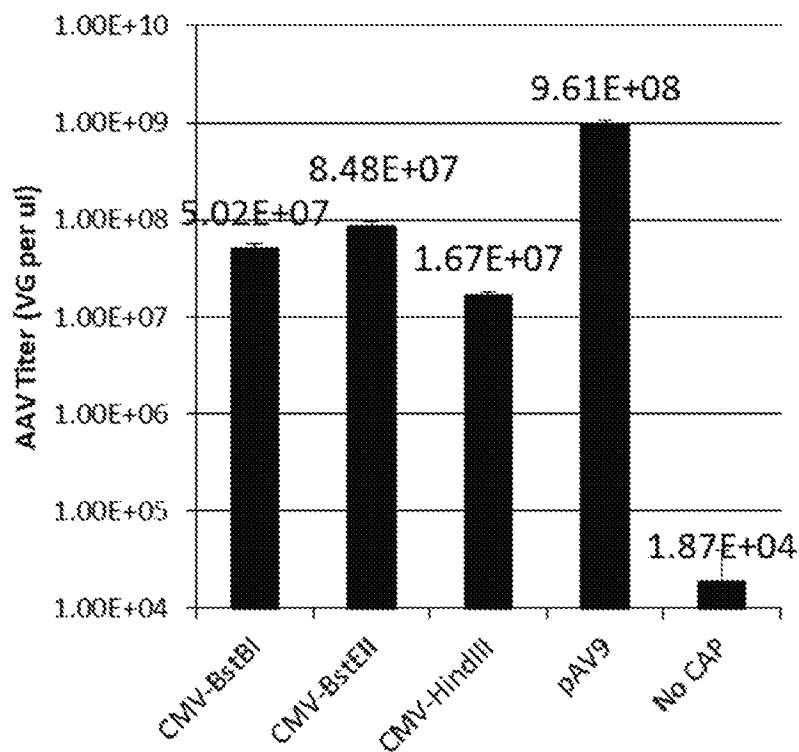


FIG. 2B

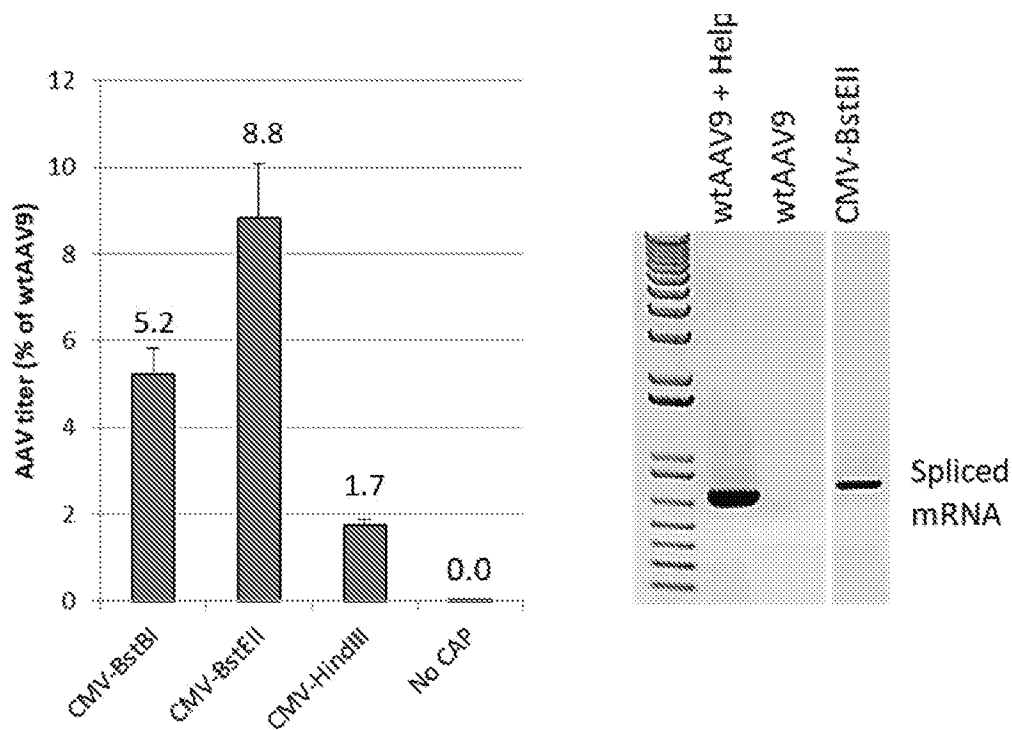
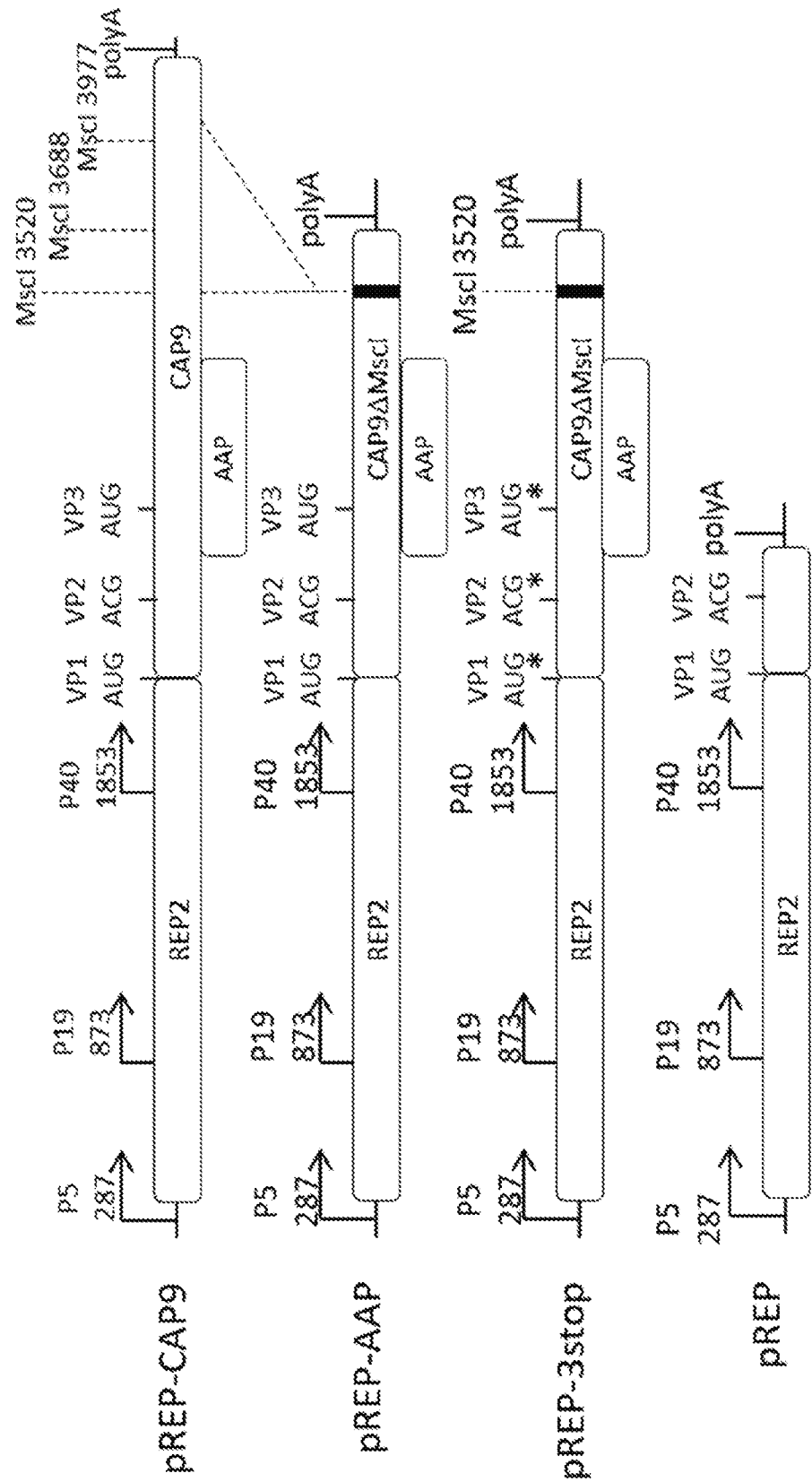


FIG. 3A



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FIG. 3B

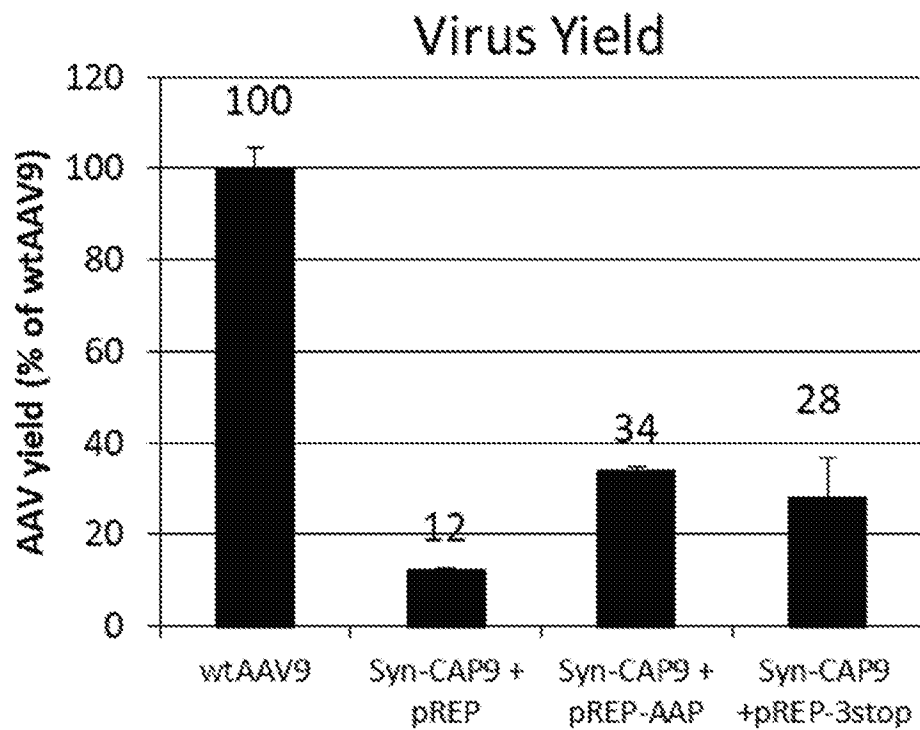
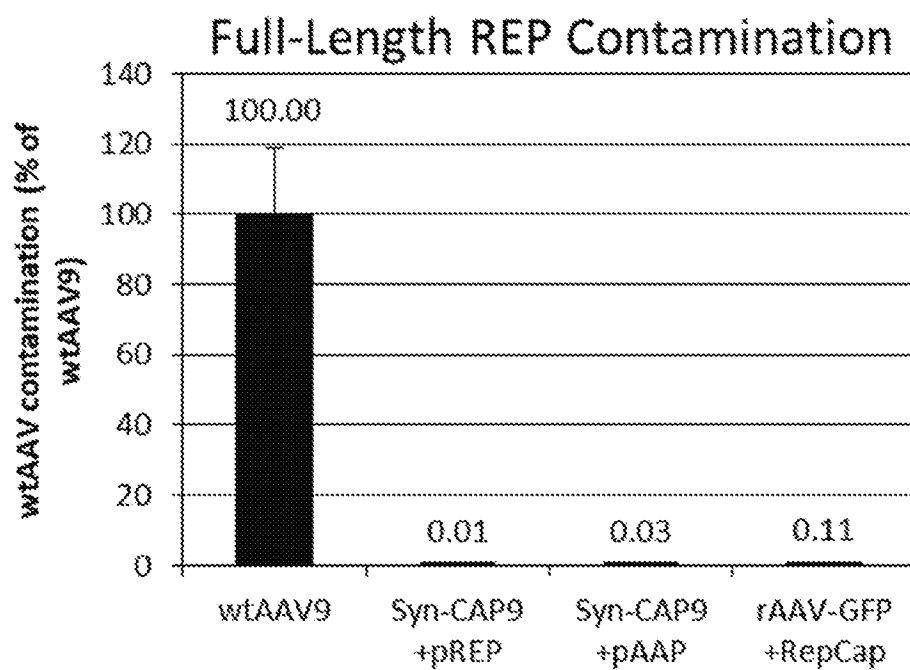


FIG. 3C



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FIG. 4A

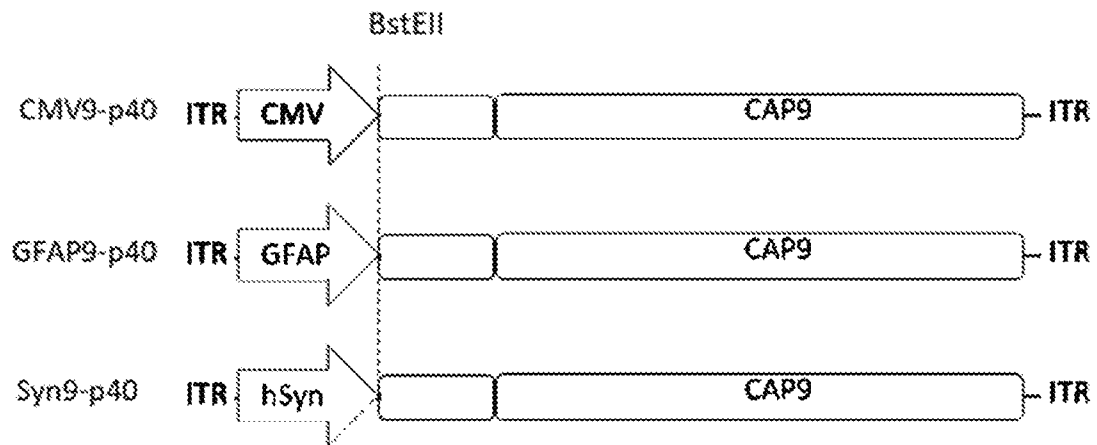


FIG. 4B

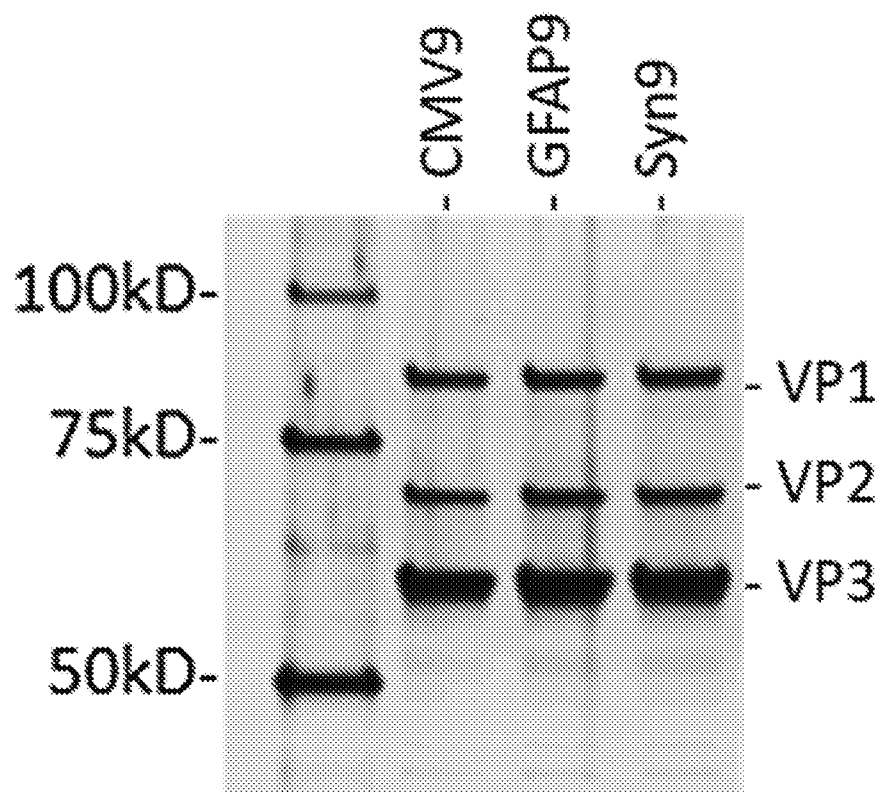


FIG. 4C

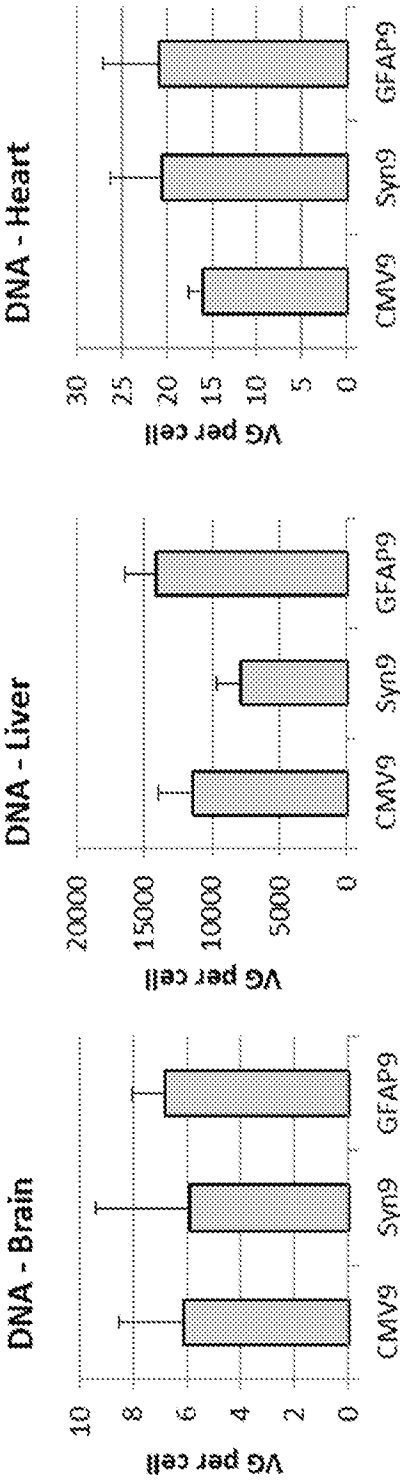


FIG. 4D

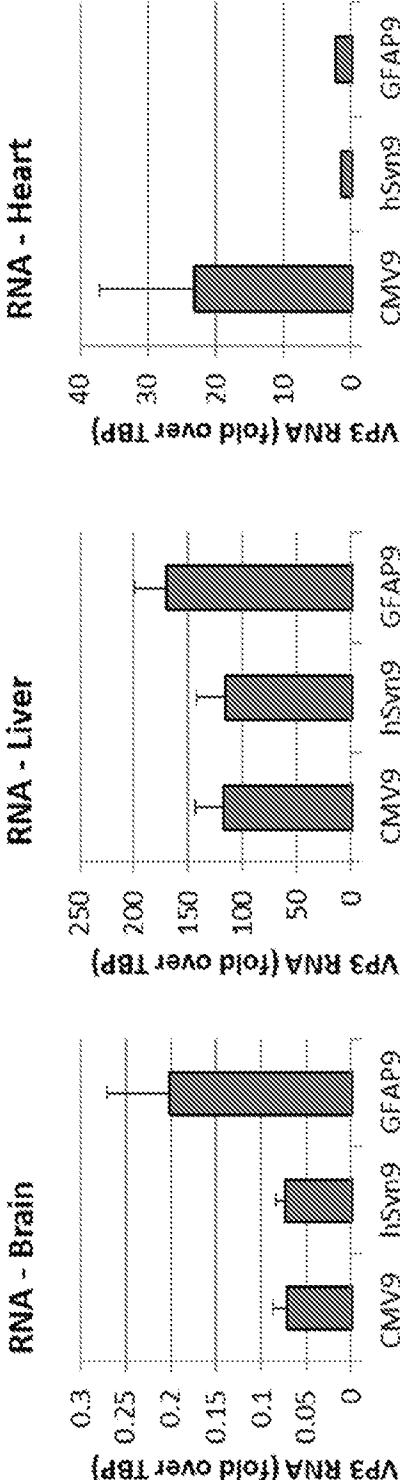


FIG. 5A

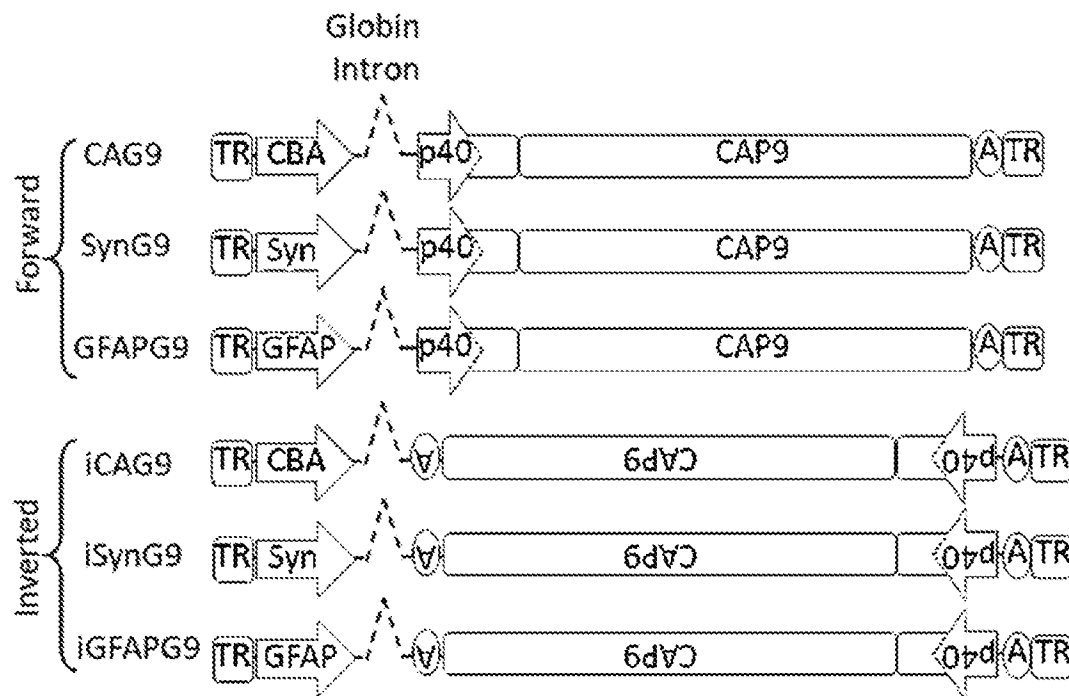


FIG. 5B

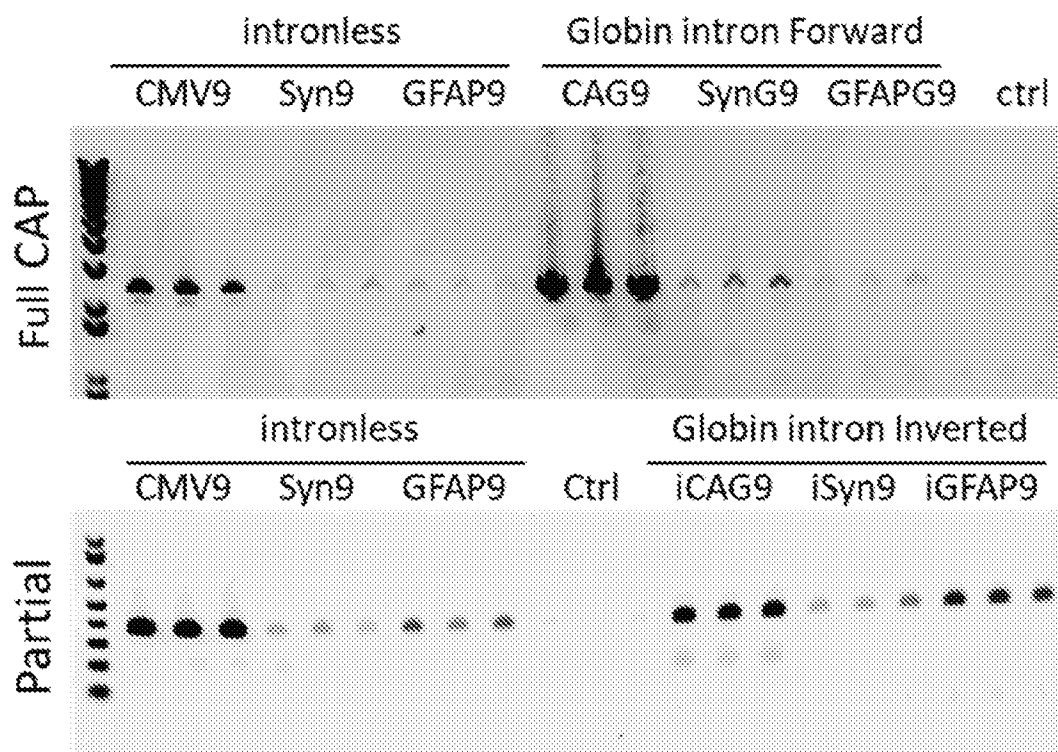


FIG. 5C

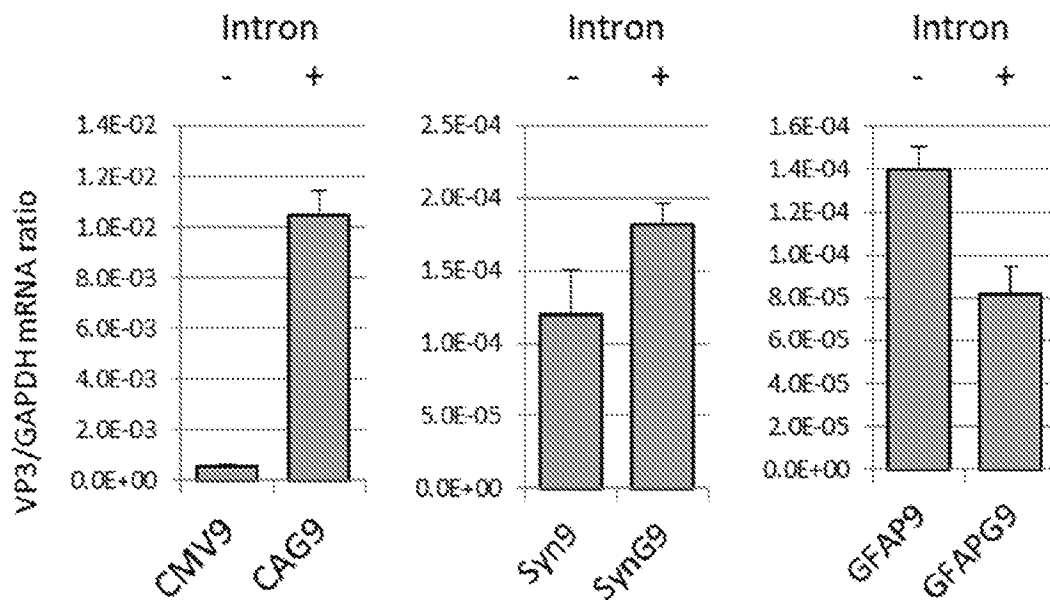


FIG. 5D

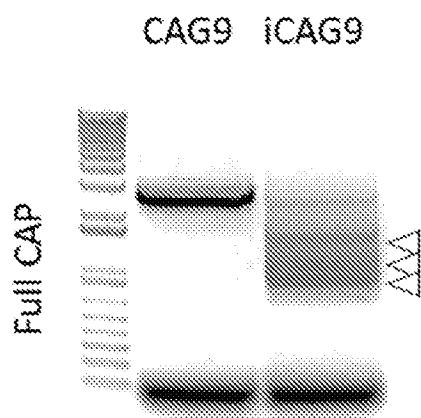


FIG. 5E

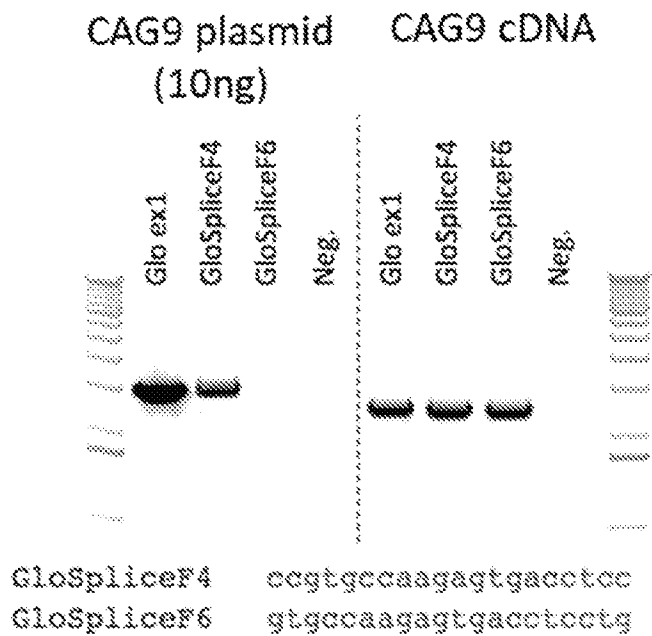


FIG. 6

Promoter Activity in TRACER Vectors

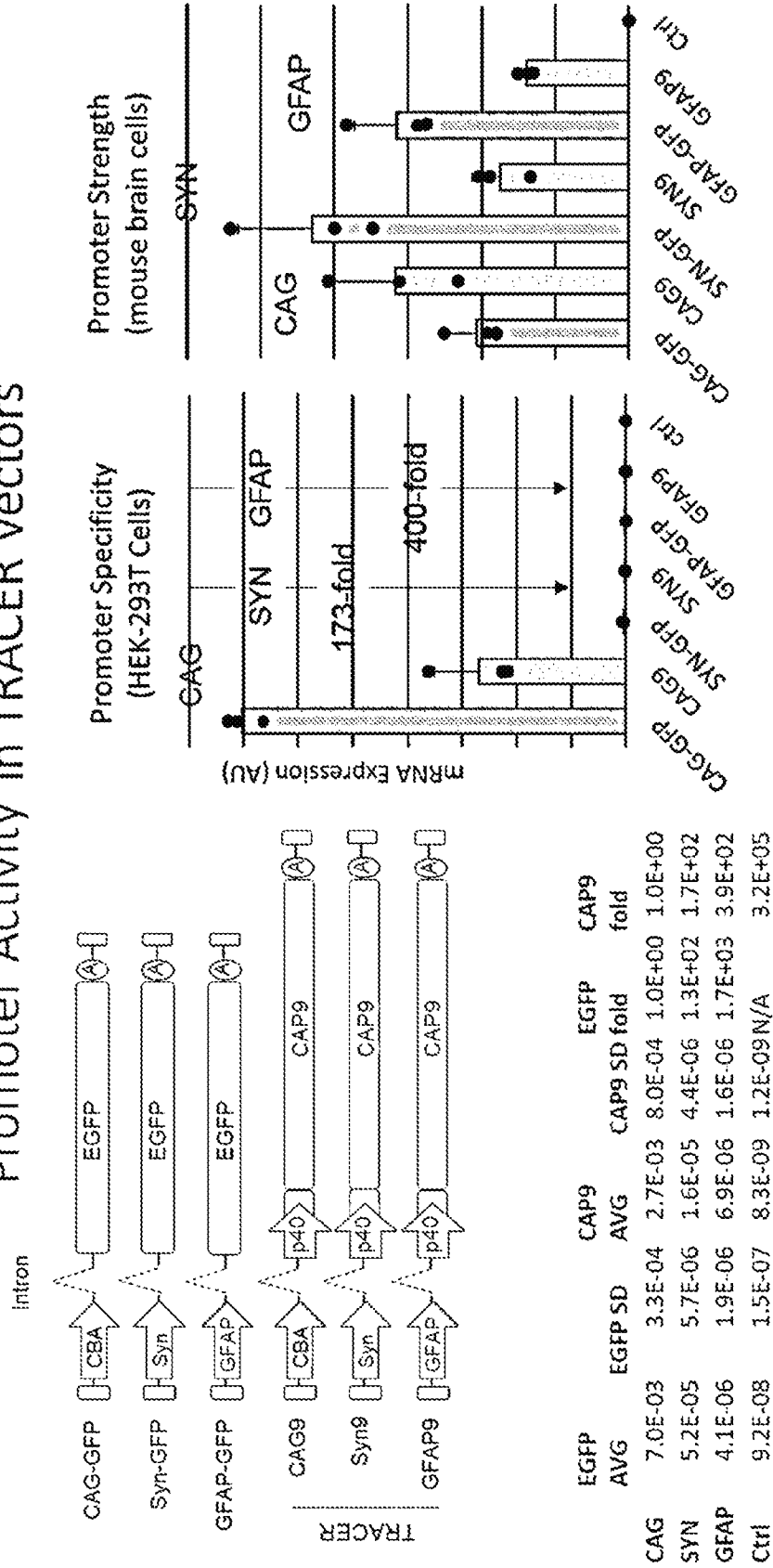
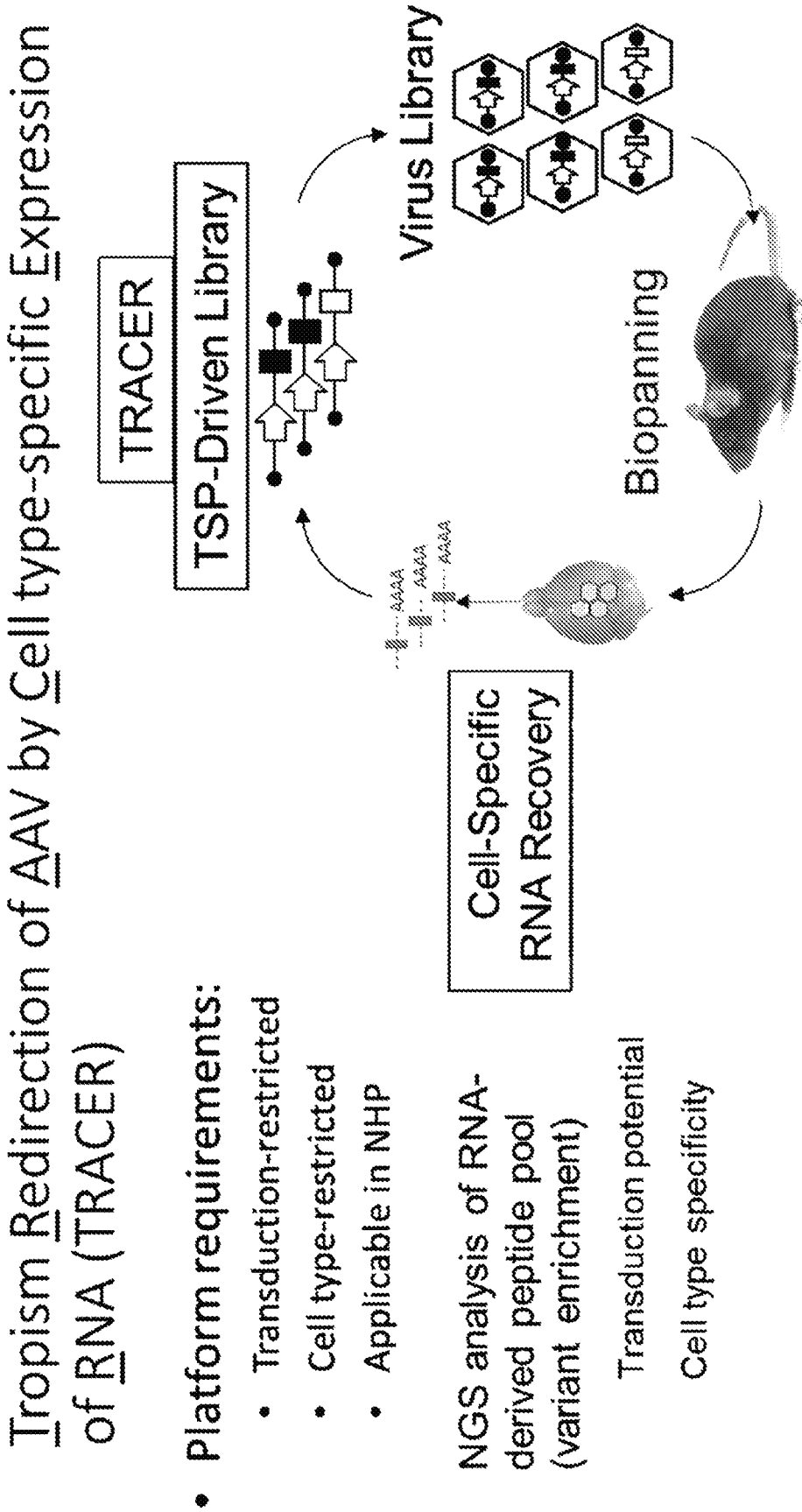


FIG. 7



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FIG. 8

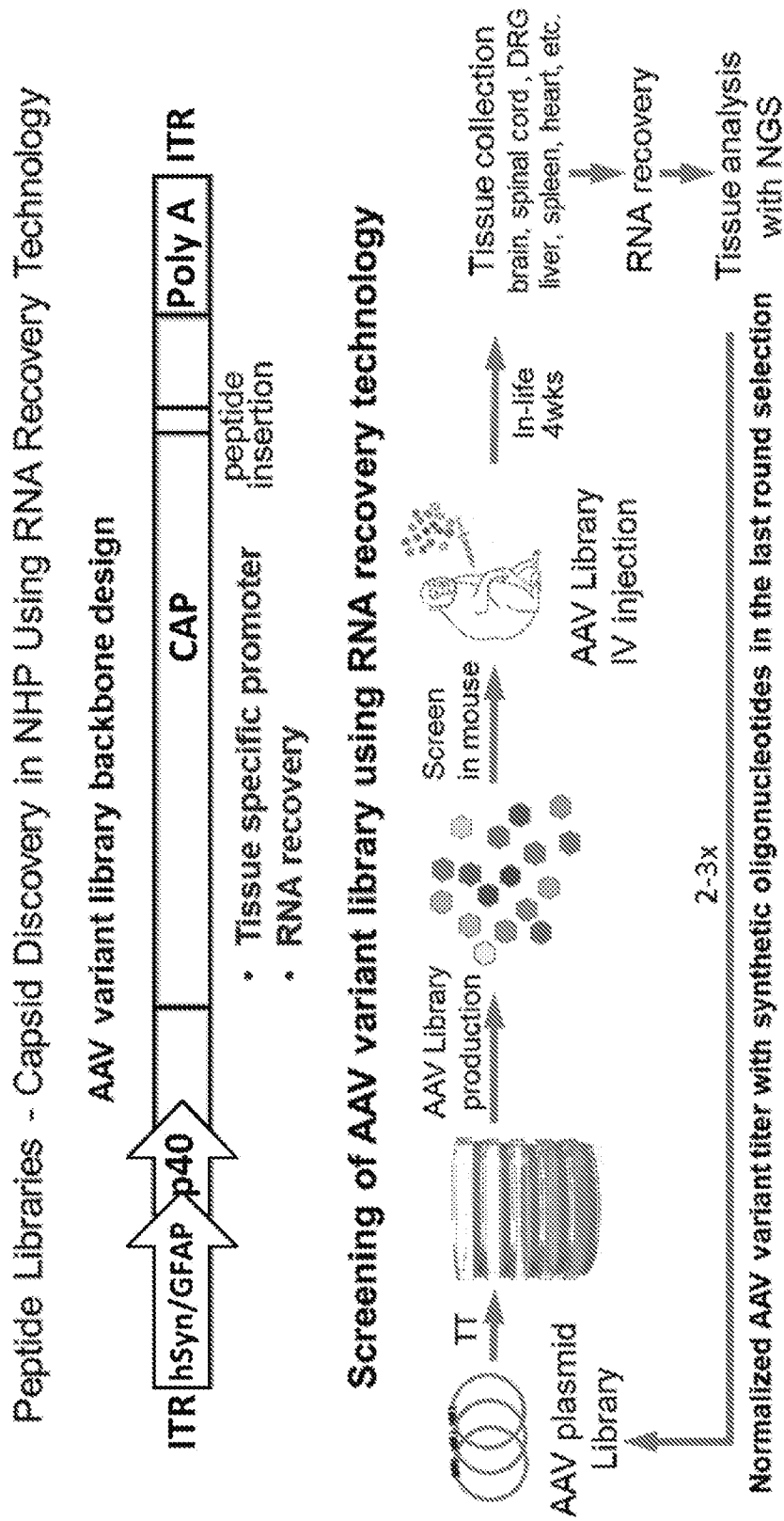


FIG. 9

TRACER Architecture

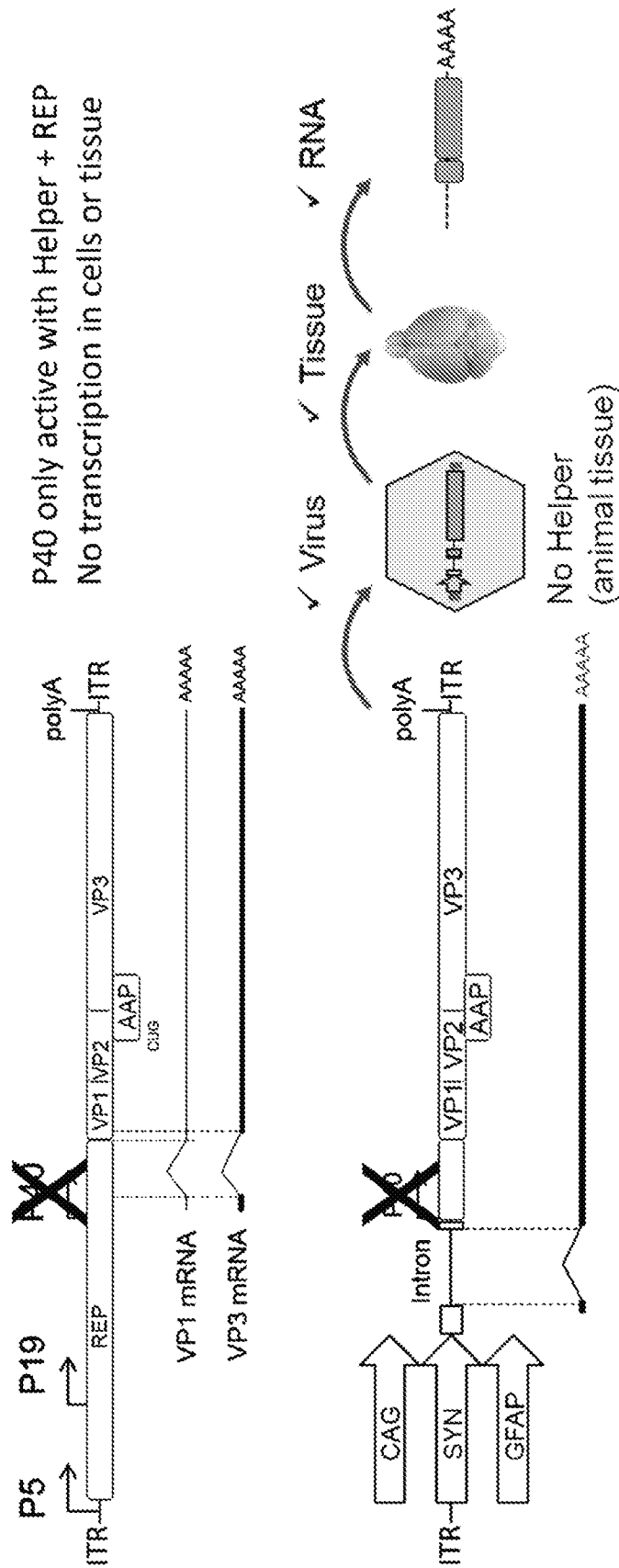


FIG. 10

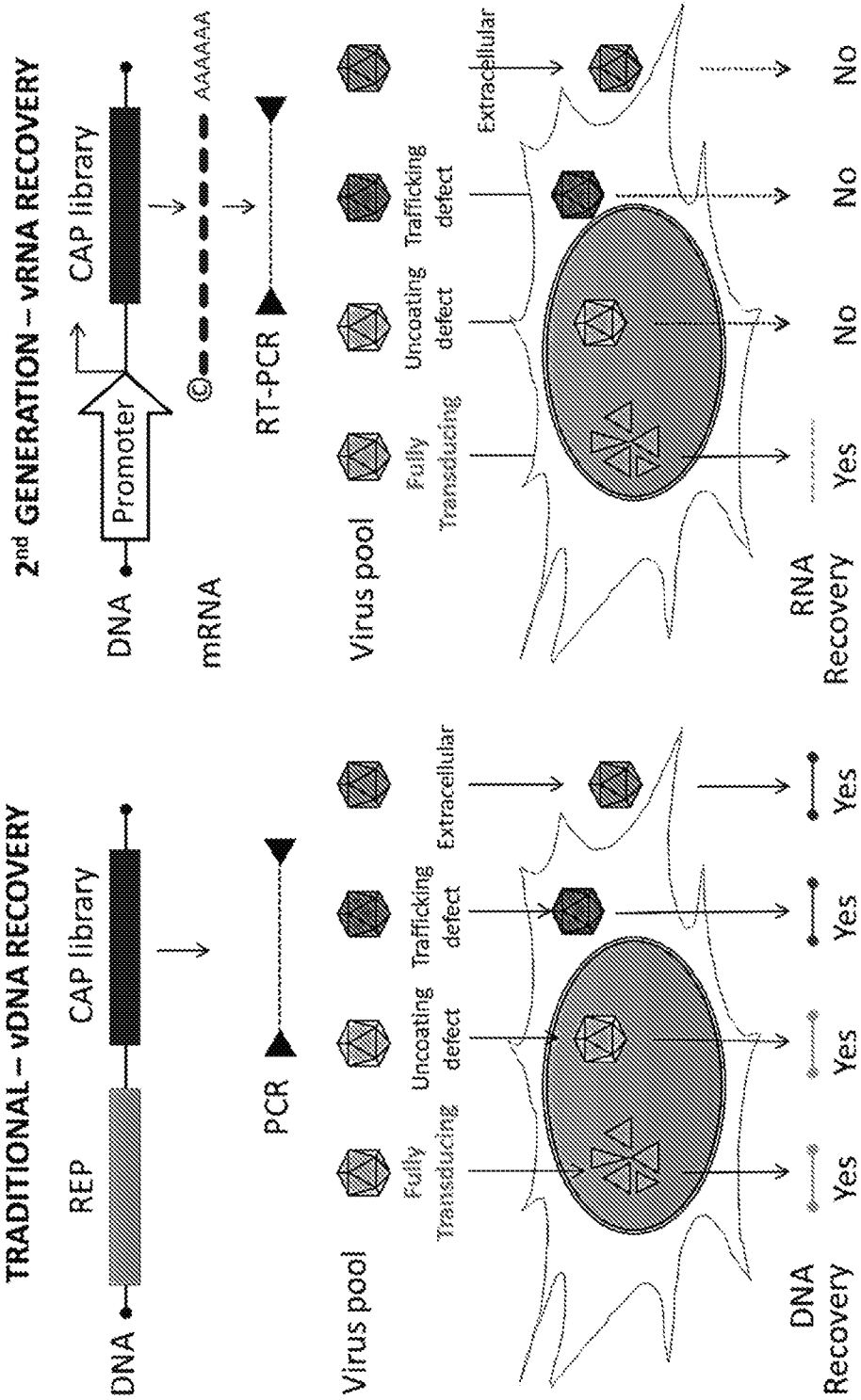


FIG. 11

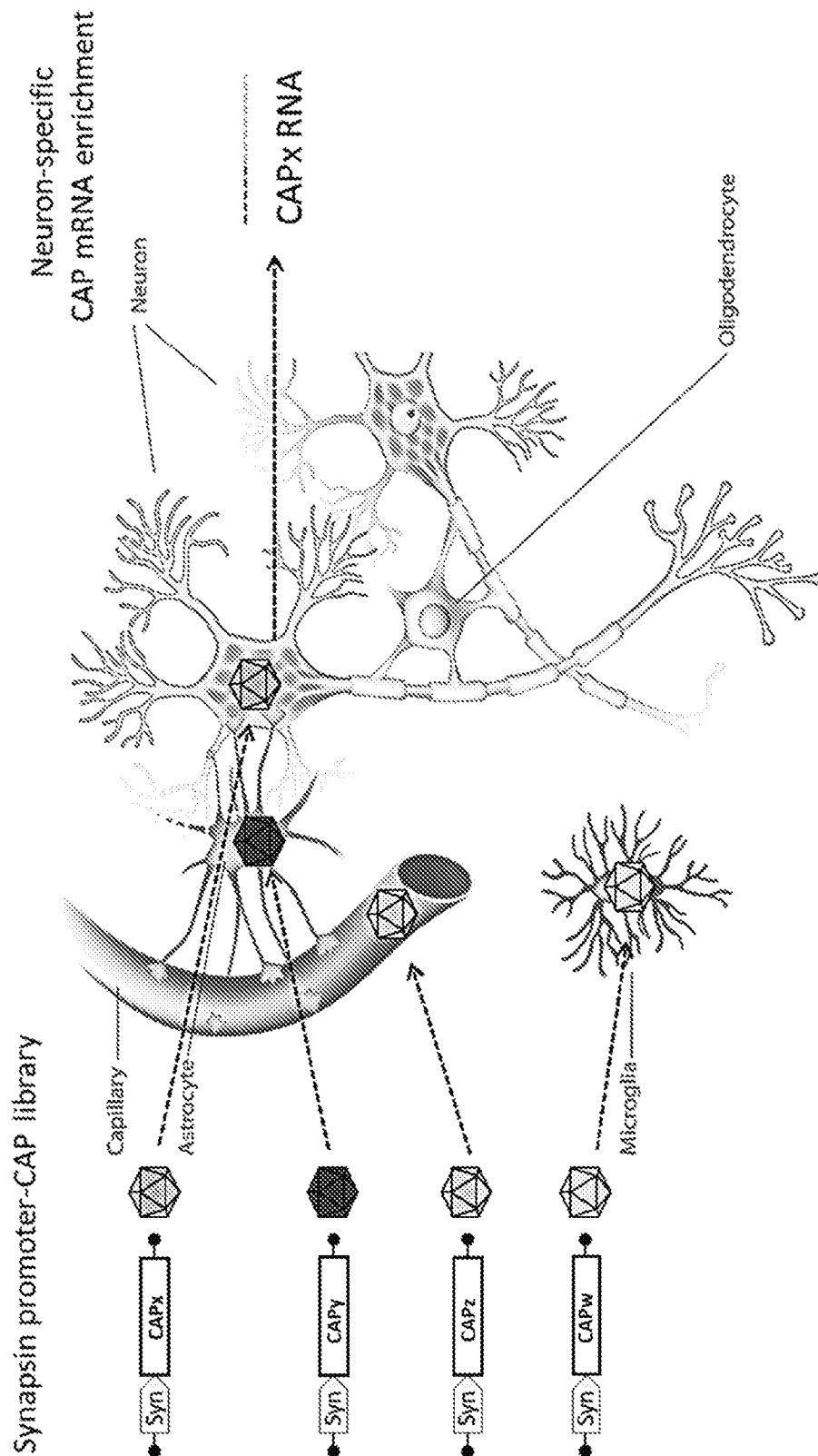


FIG. 12A

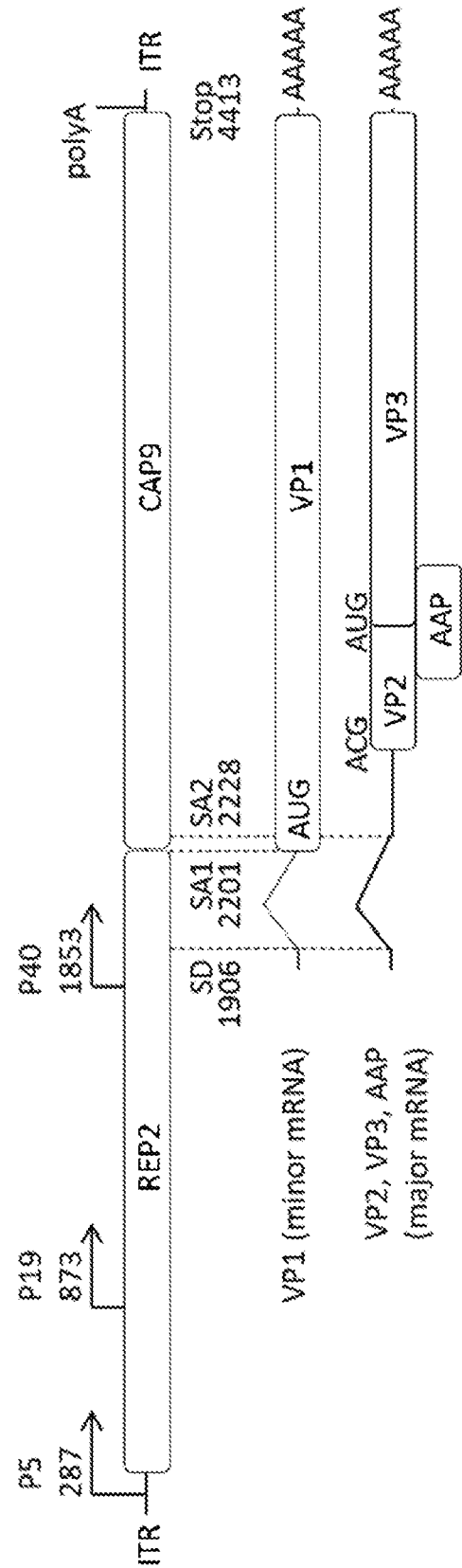


FIG. 12B

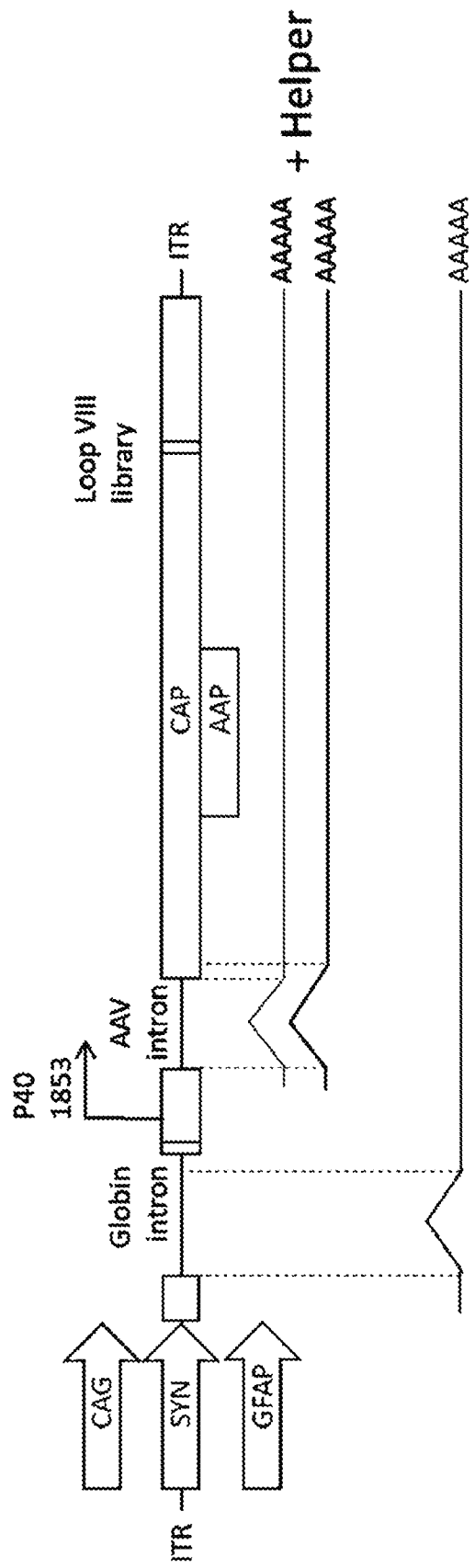


FIG. 15A

		<u>BsrGI</u>		<u>polyA</u>
AAV5	:	GCCACCAACAACCAGAGCTCT/	GTAC/	Atcgattggttaatcaataaaa
AAV6	:	GTGGCAGTCAATCTCCAGAGT/	GTAC/	Atcgattggttaatcaataaaa
AAV-DJ8	:	TCTACCAACCTCCAGCAAGGT/	GTAC/	Atcgattggttaatcaataaaa
AAV9	:	GTGGCCACAACCACCAGAGT/	GTAC/	Atcgattggttaatcaataaaa

FIG. 15B

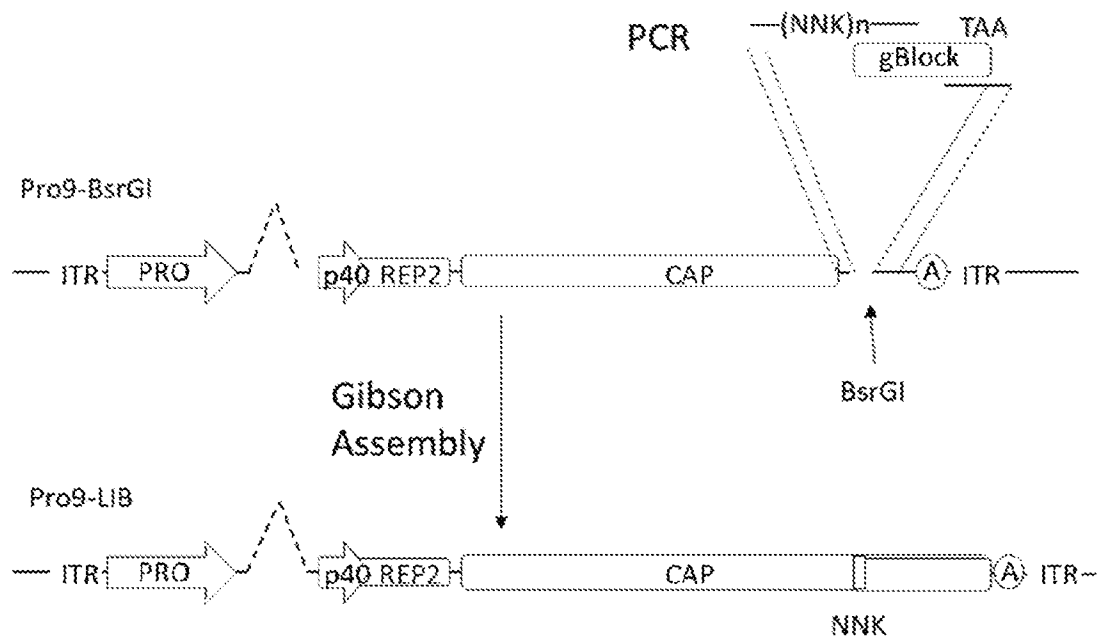


FIG. 16

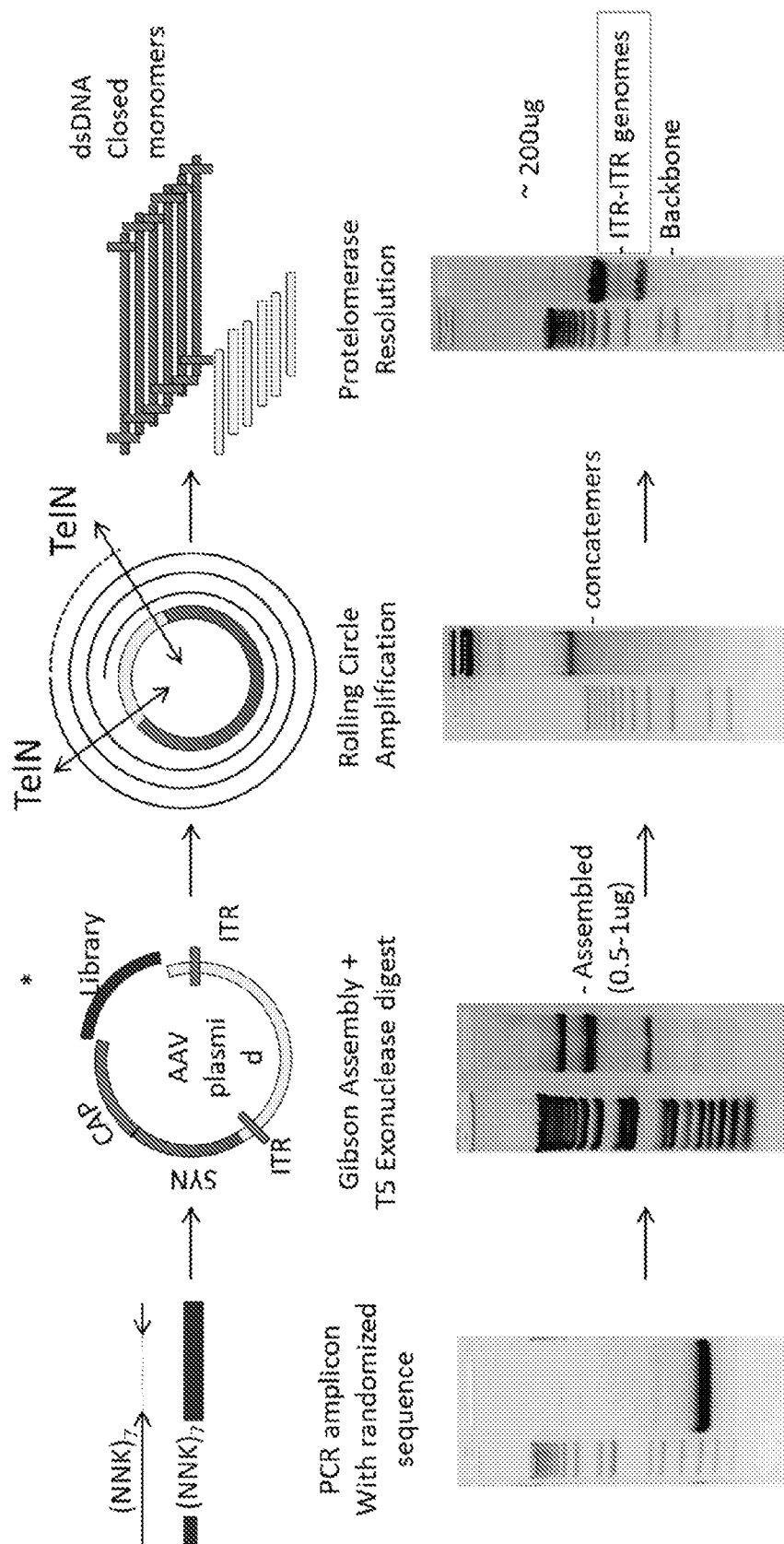
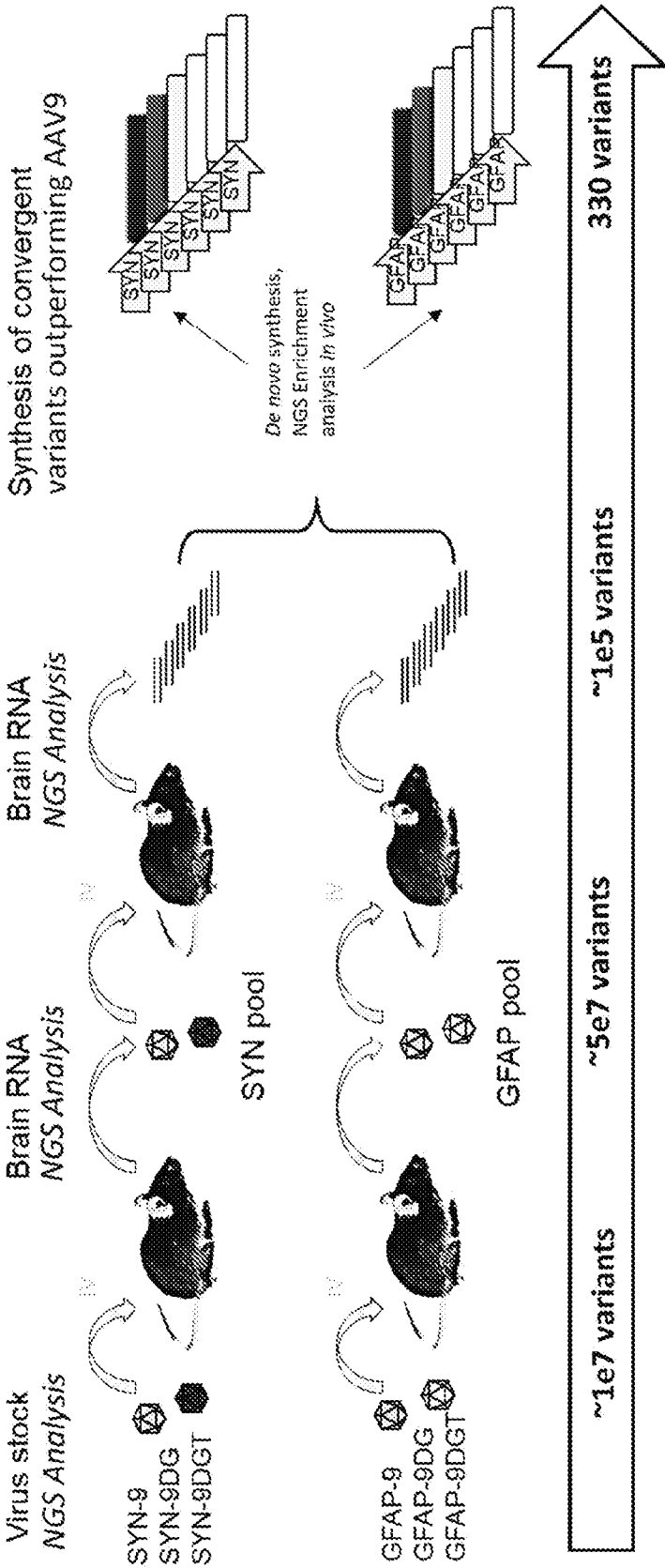
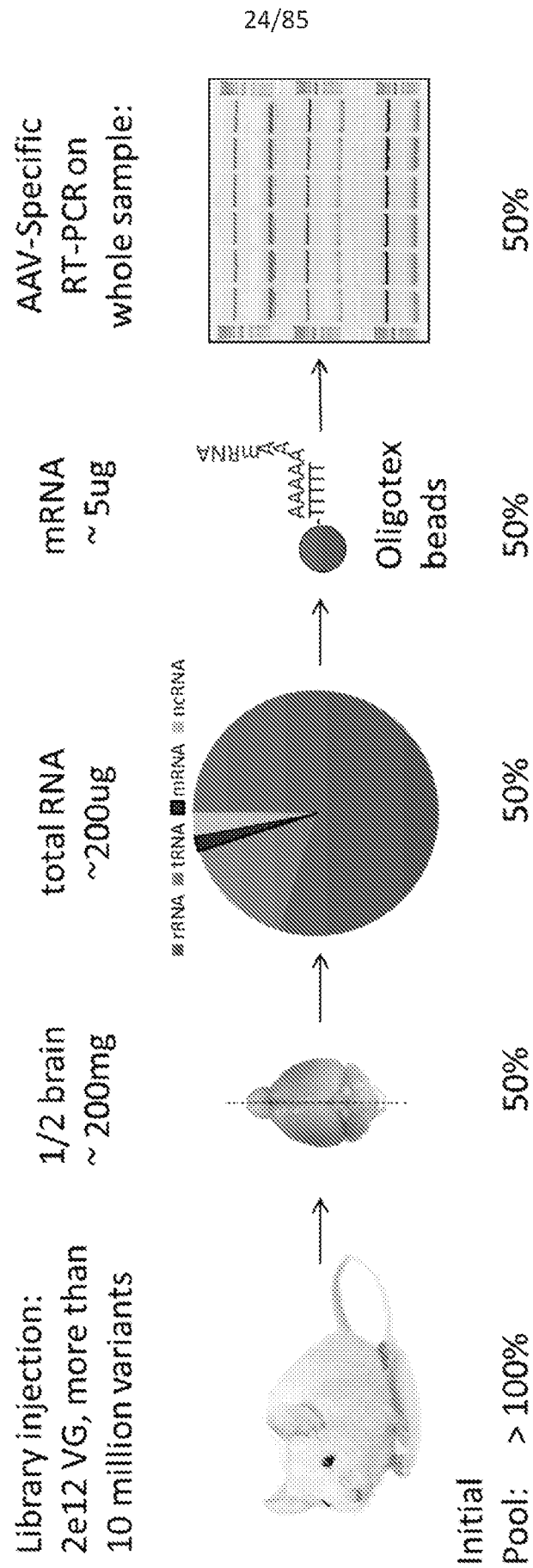


FIG. 18

TRACER Library Biopanning



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FIG. 20

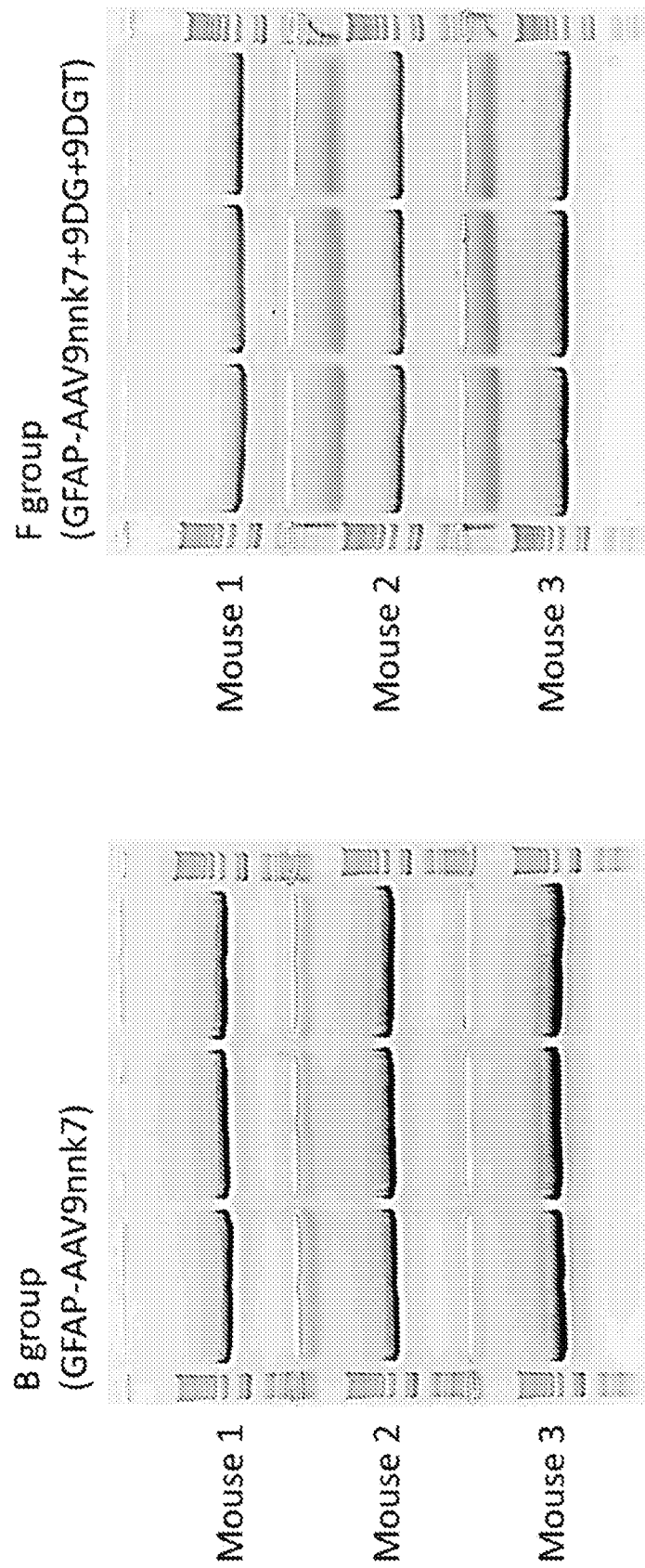


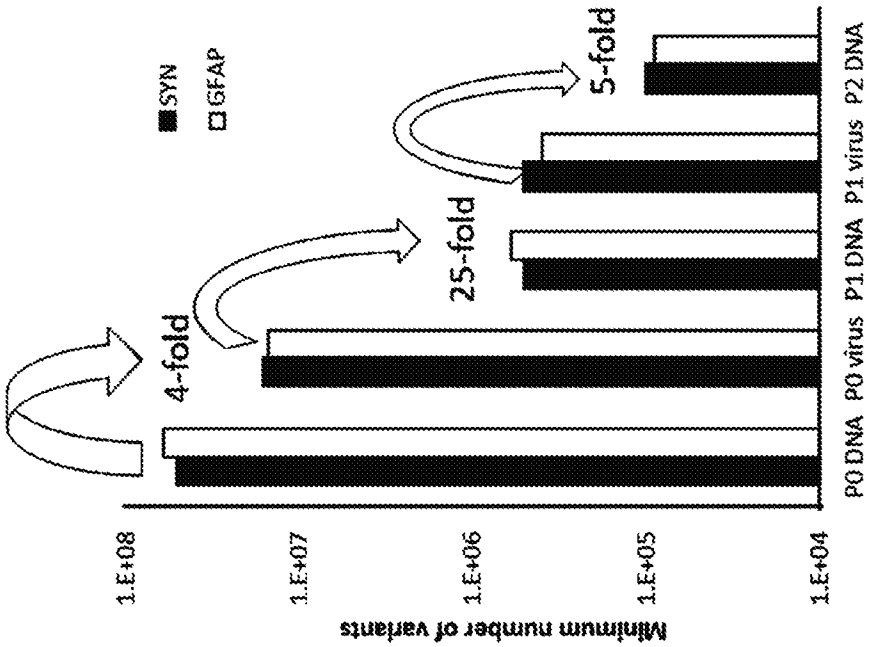
FIG. 21C

NNK machine mix: P1 virus											
0.01	0.02	0.02	0.01	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
0.02	0.01	0	0	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.03
0.07	0.09	0.09	0.09	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.12
0.27	0.06	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.05
0.08	0.11	0.11	0.12	0.11	0.11	0.11	0.11	0.11	0.11	0.11	0.09
0.06	0.08	0.07	0.08	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.15
0.03	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.03
0.03	0.03	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04
0.02	0.04	0.05	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.02
0.02	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.04
0.05	0.08	0.05	0.05	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06
0.02	0.02	0.06	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.05
0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
0.12	0.15	0.16	0.17	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.1
0.01	0.02	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
0.03	0.05	0.06	0.06	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.04
0.03	0.04	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.03
0	0	0	0	0	0	0	0	0	0	0	0
0.08	0.08	0.1	0.08	0.09	0.09	0.09	0.09	0.09	0.09	0.09	0.08
0	0	0	0	0	0	0	0	0	0	0	0

FIG. 21B

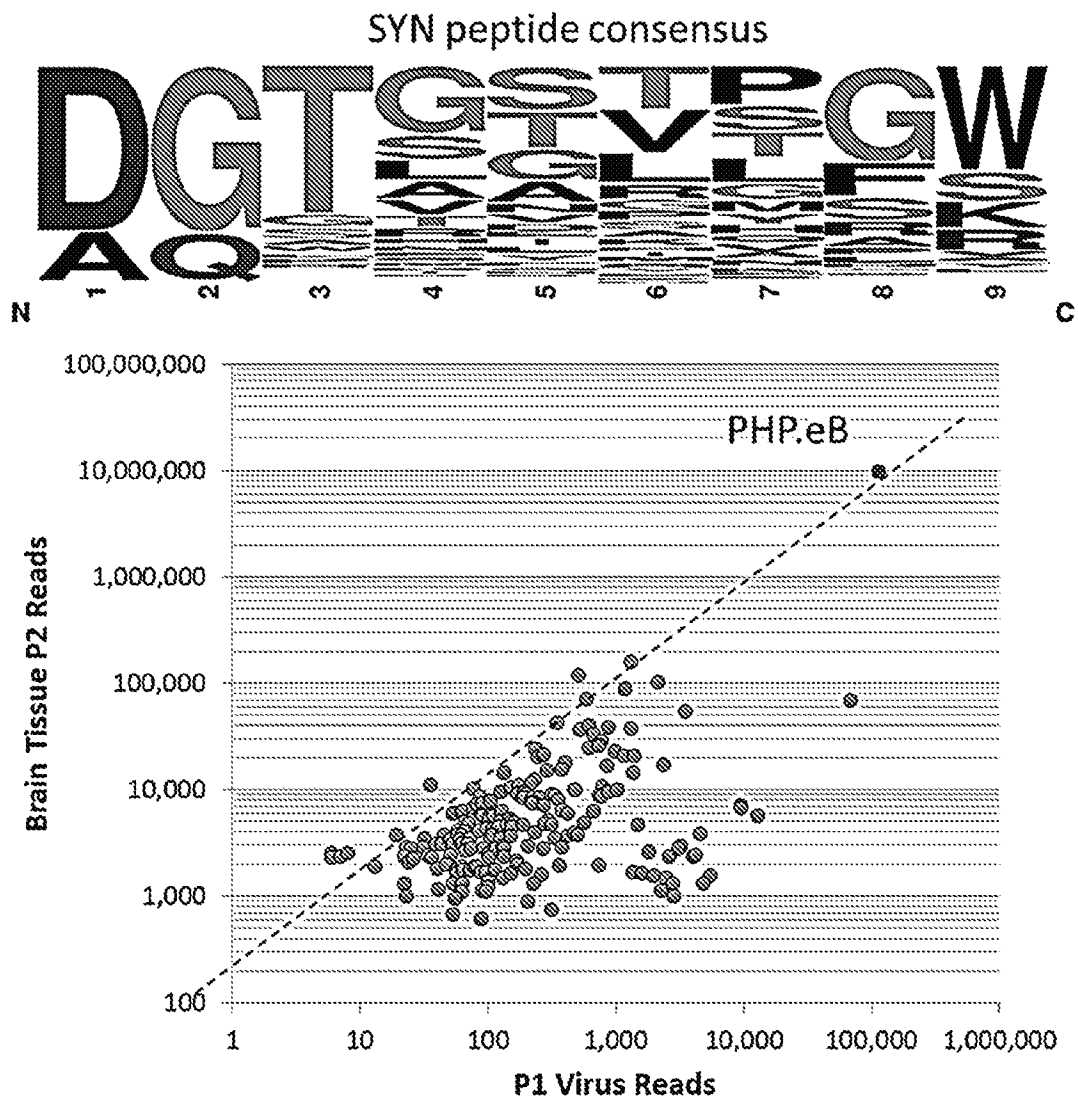
NNK machine mix: P0 virus											
0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
0.04	0.02	0.03	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.04
0.08	0.09	0.08	0.09	0.07	0.07	0.09	0.09	0.09	0.09	0.09	0.1
0.05	0.05	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.05
0.1	0.09	0.11	0.1	0.11	0.11	0.09	0.09	0.09	0.09	0.09	0.08
0.11	0.11	0.09	0.11	0.11	0.1	0.09	0.09	0.09	0.09	0.09	0.11
0.03	0.03	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.03
0.04	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.02
0.03	0.03	0.03	0.03	0.02	0.02	0.03	0.03	0.03	0.03	0.03	0.04
0.06	0.07	0.07	0.07	0.06	0.06	0.07	0.07	0.07	0.07	0.07	0.08
0.09	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
0.02	0.02	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.02
0.14	0.14	0.13	0.13	0.13	0.15	0.14	0.14	0.14	0.14	0.14	0.15
0.02	0.02	0.02	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
0.04	0.04	0.05	0.05	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06
0.03	0.03	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.03
0.01	0	0	0	0	0	0	0	0	0	0	0
0.08	0.08	0.08	0.08	0.08	0.08	0.09	0.09	0.09	0.09	0.09	0.08
0	0	0	0	0	0	0	0	0	0	0	0

FIG. 21A



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FIG. 22



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FIG. 23

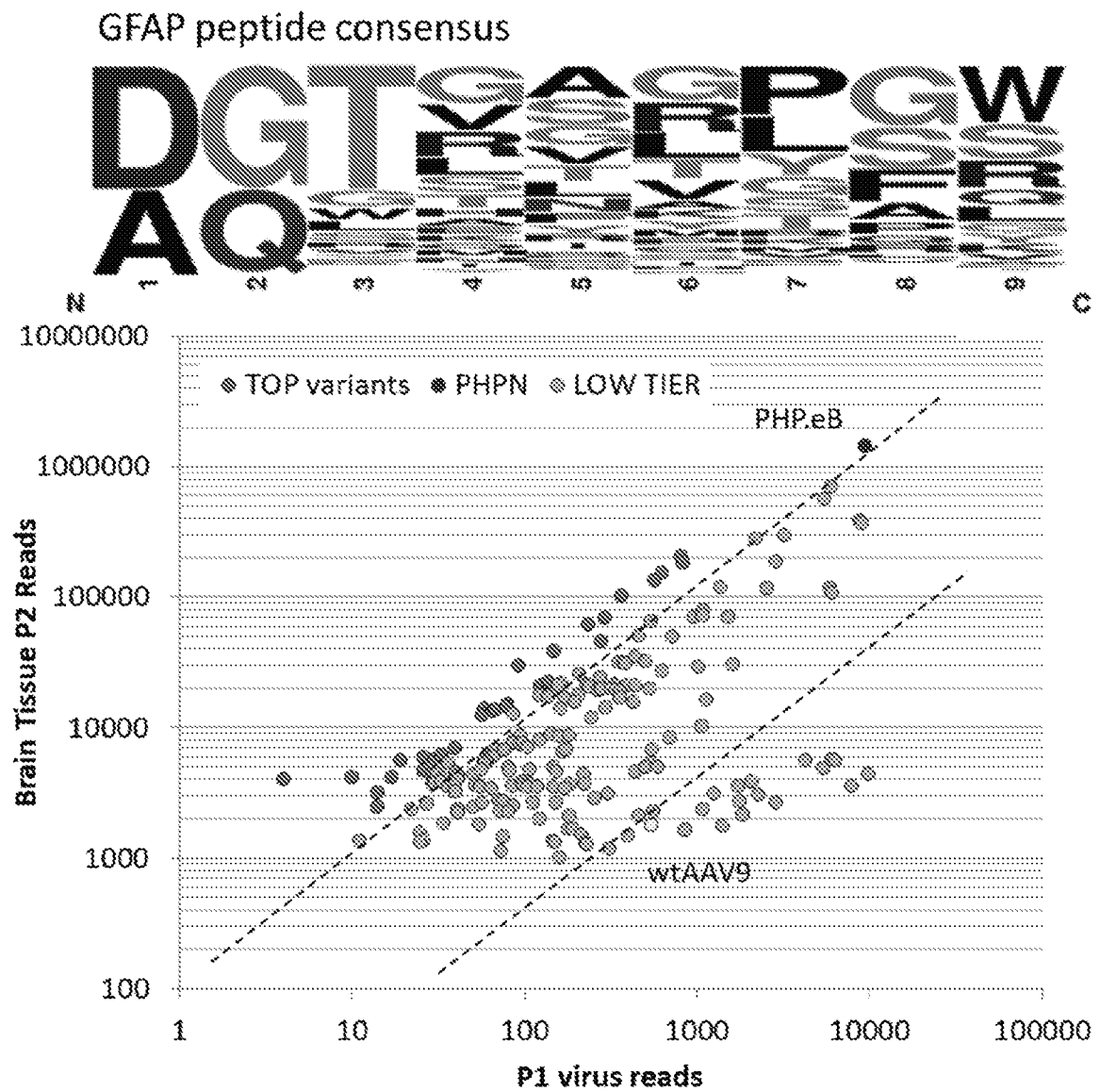


FIG. 24

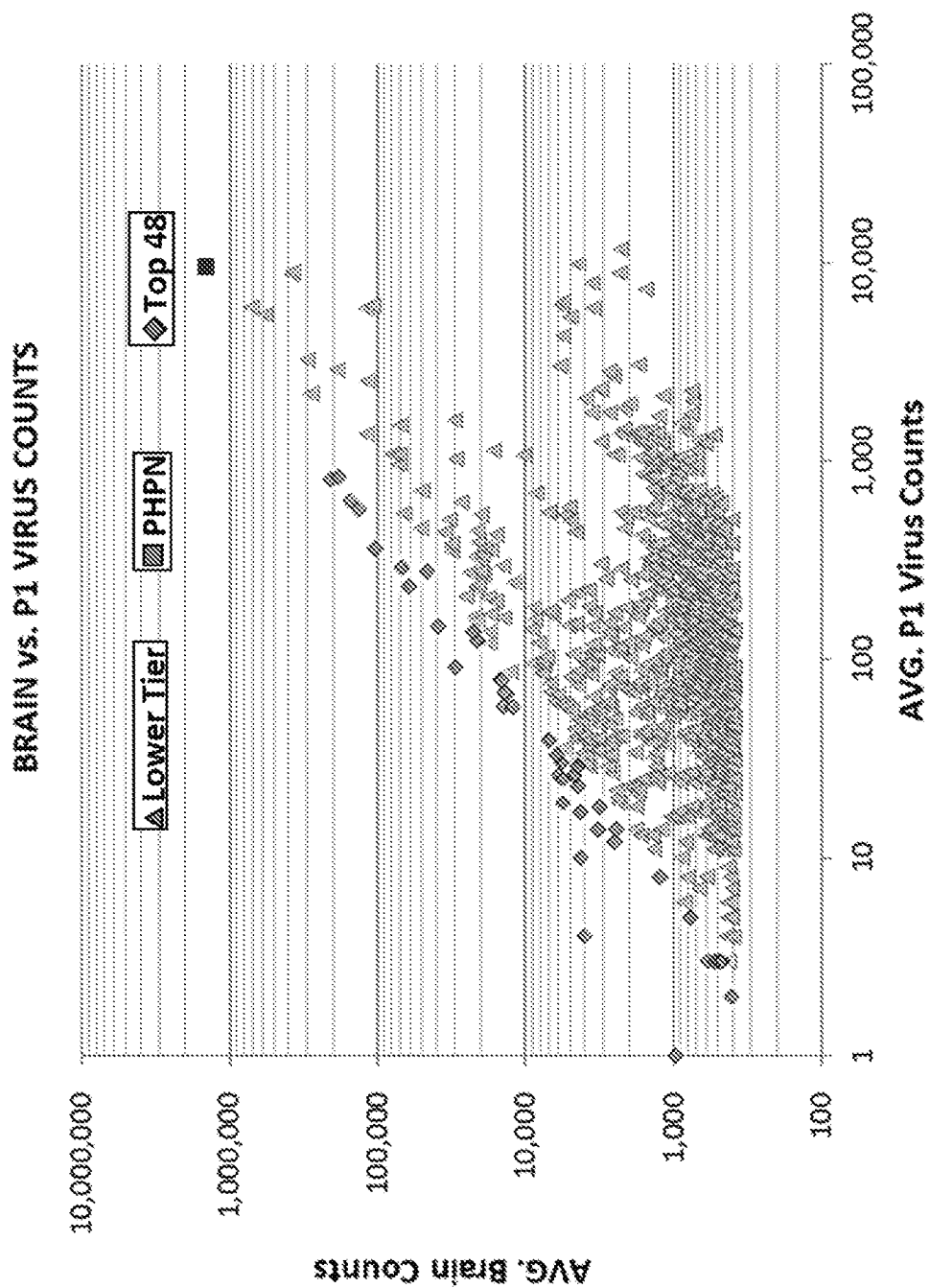
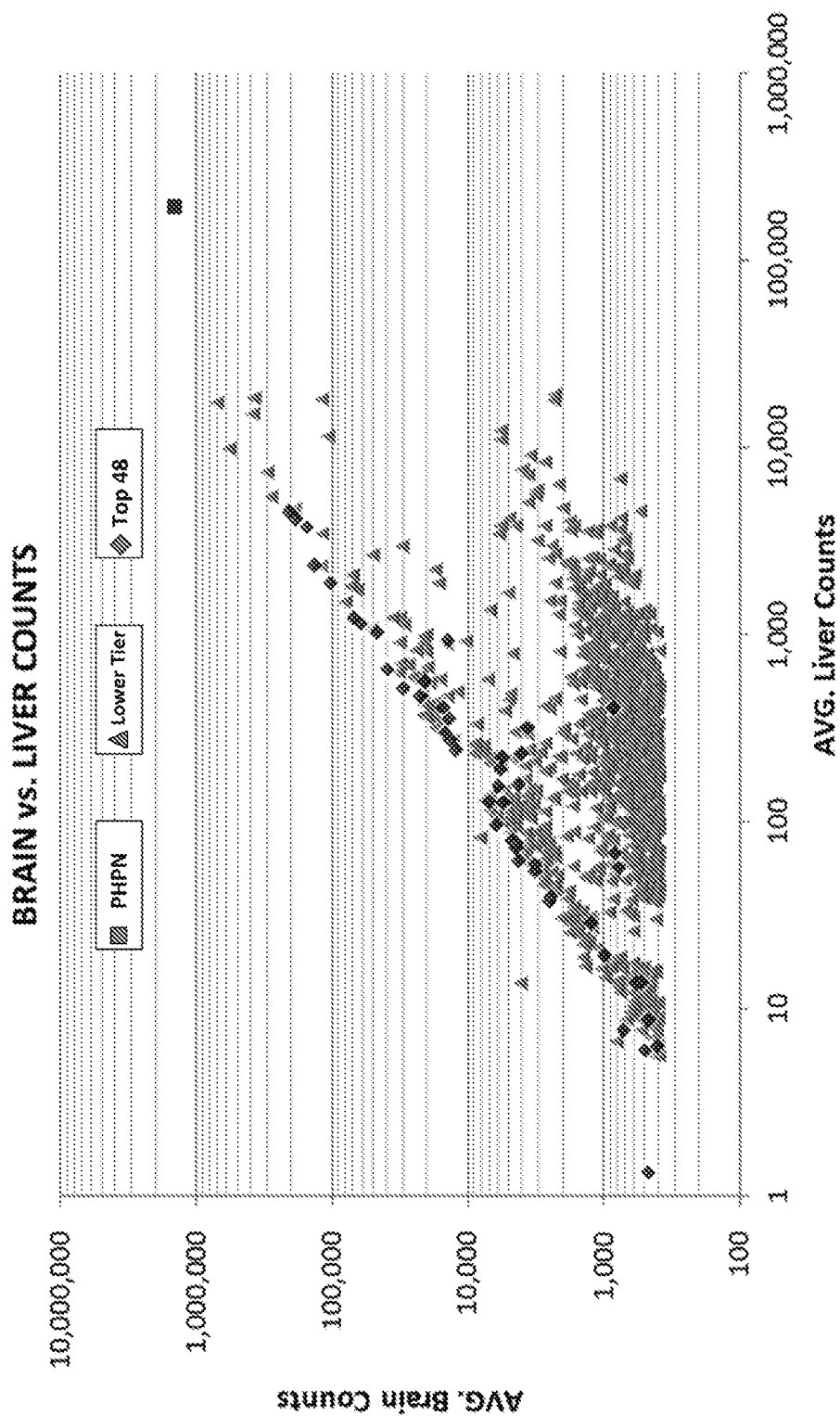


FIG. 25



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FIG. 26

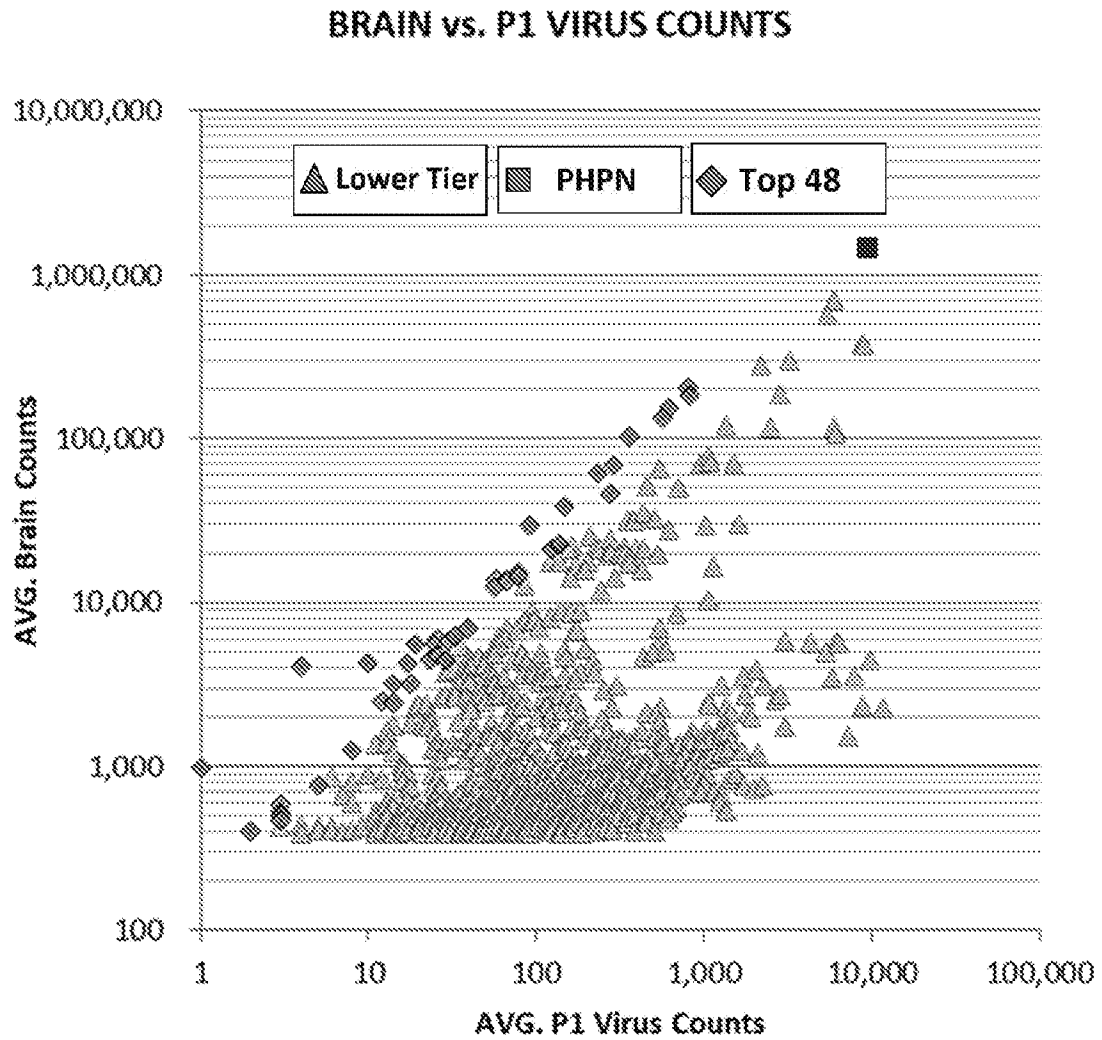
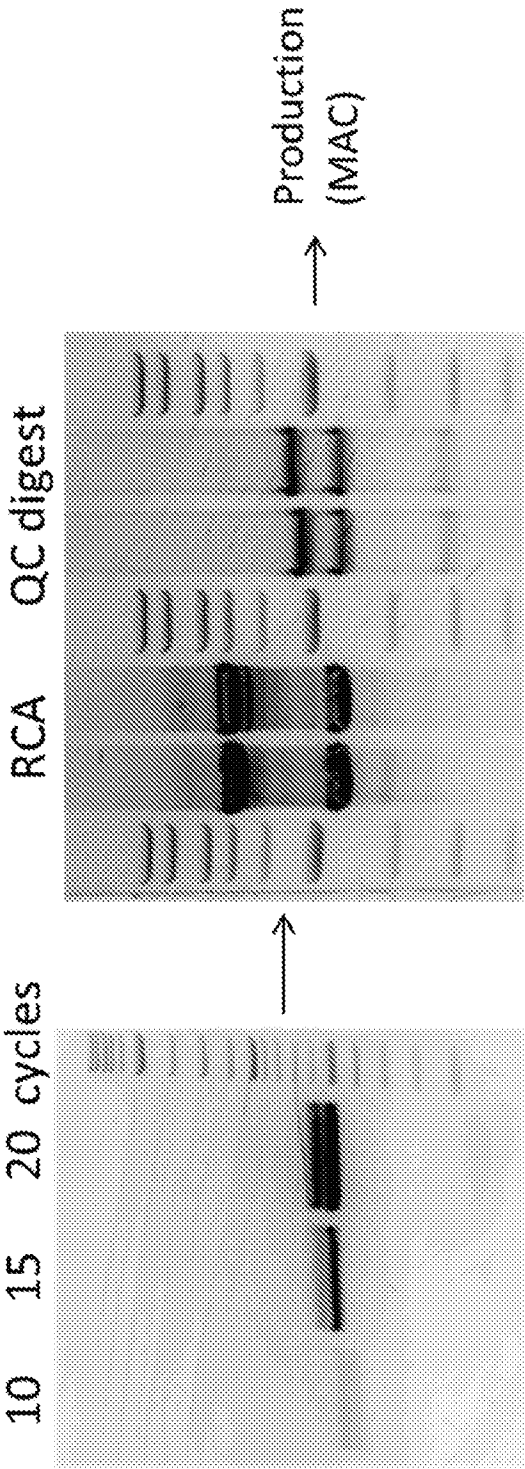


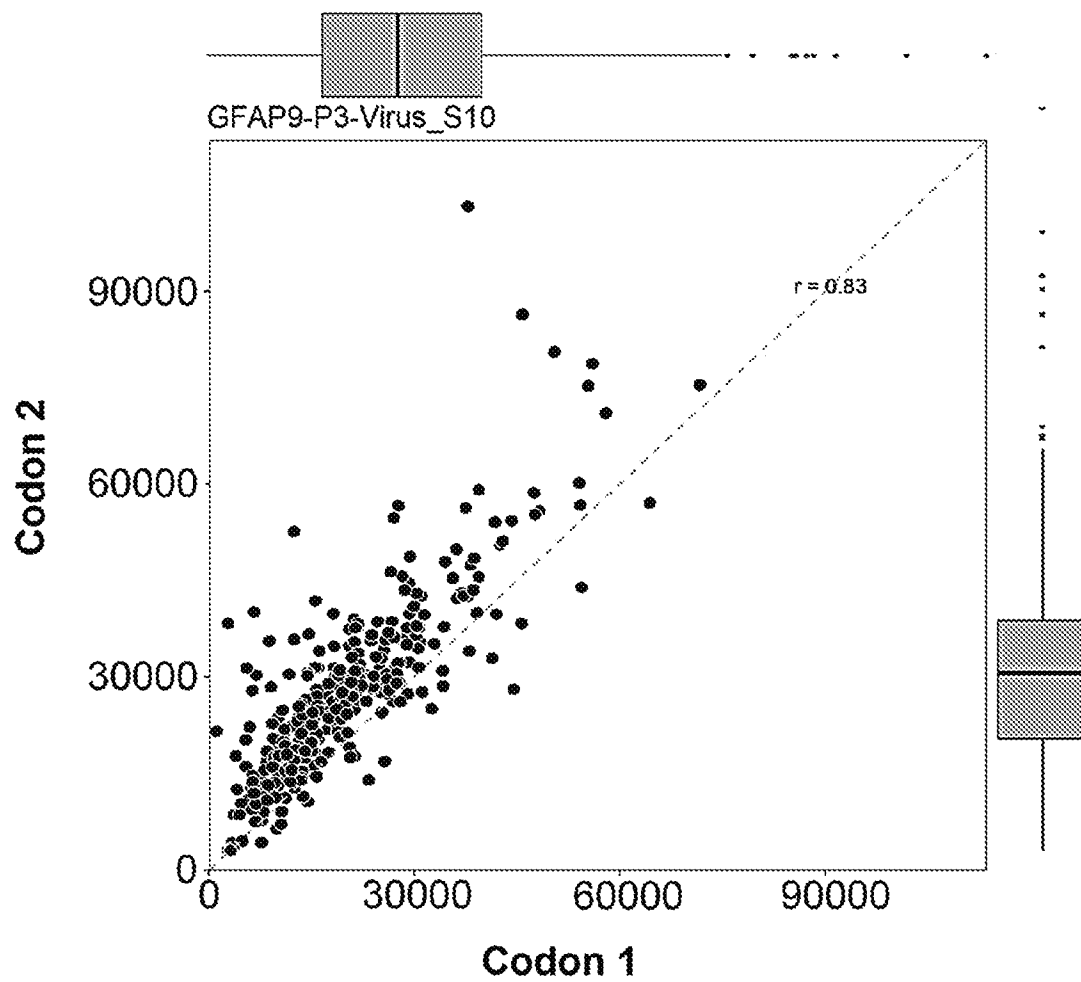
FIG. 27



Study VEO-142-2017-Ms							
Peptide Libraries	Titer (VG/ml)	Endotoxin	Mouse group	Number of animals	route	volume/ mouse (ul)	VG/mouse
NEUR-P3-300	4.45E+13*	<0.5	SYN9P3	3	IV	50	2.00E+12
ASTR-P3-300	4.85E+13*	<0.5	GFAP9P3	3	IV	50	2.00E+12

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FIG. 28



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FIG. 29

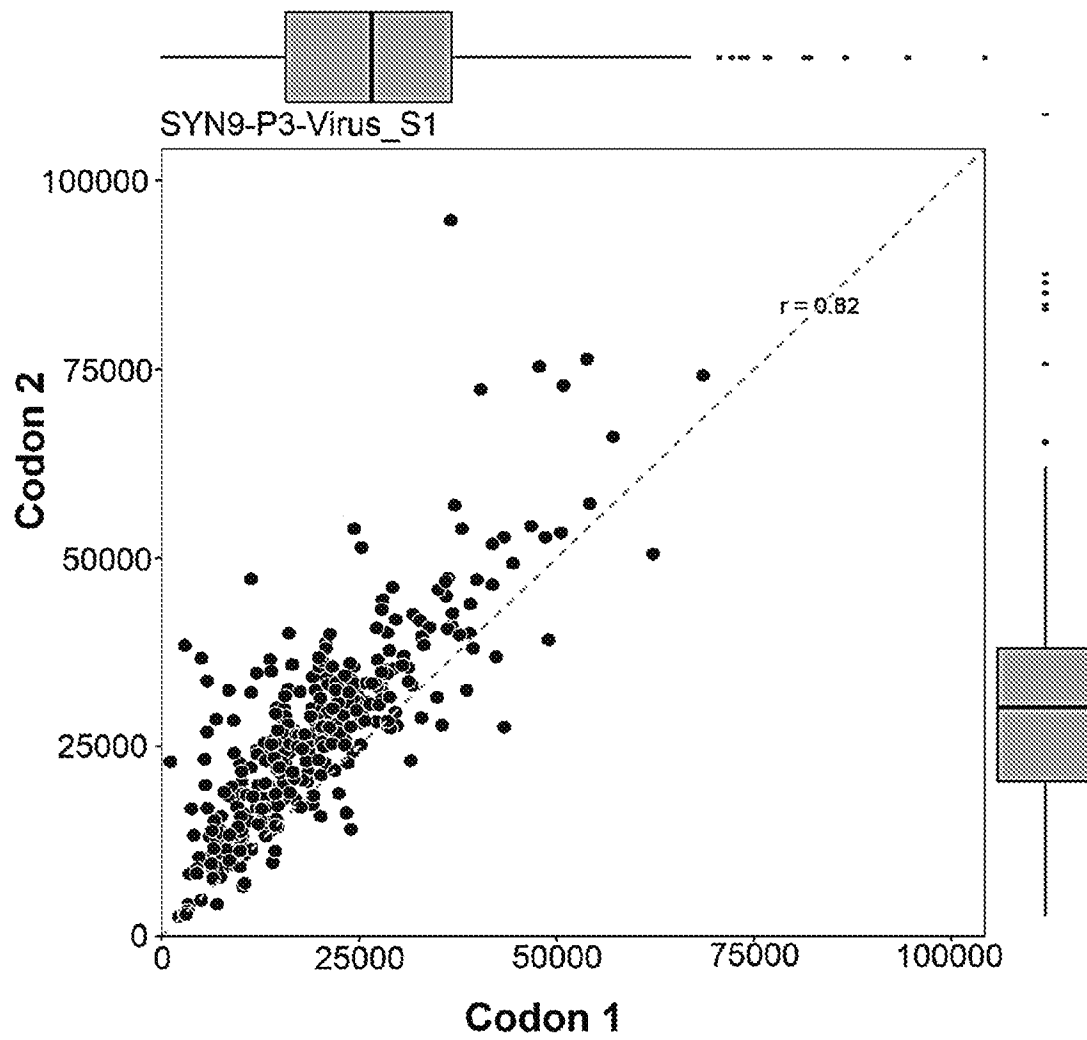
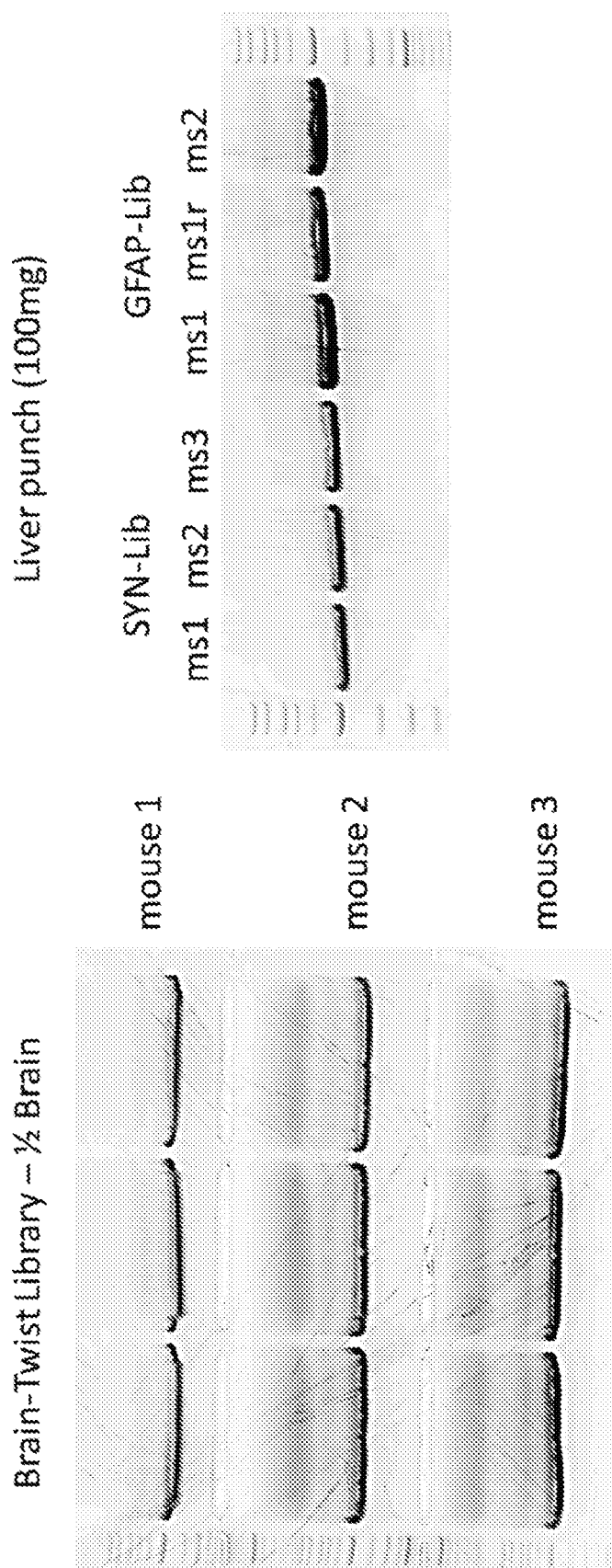


FIG. 30

Synthesis Library Tissue Recovery (one month post-injection)



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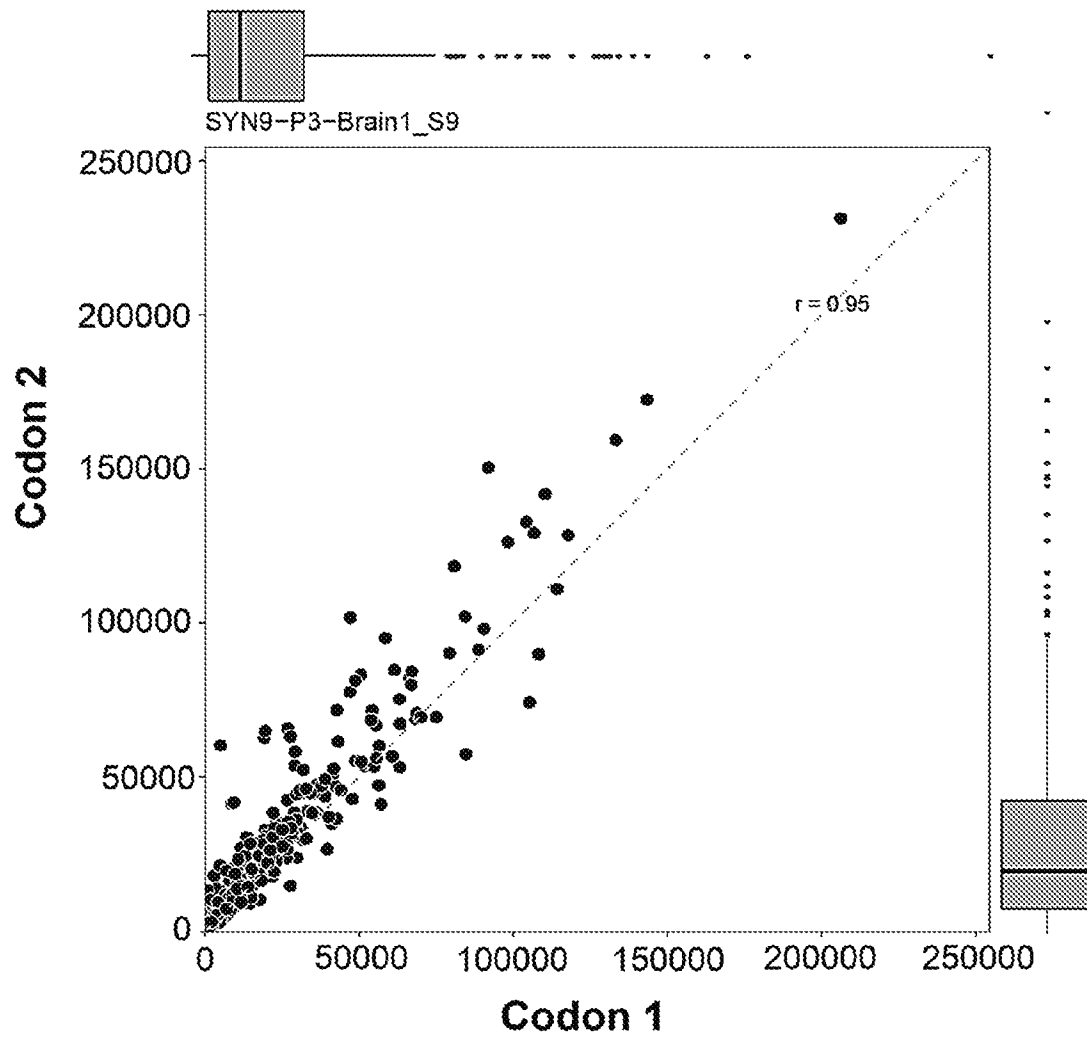
FIG. 31A

NEU-LIB		Brain1	Brain2	Brain3	mean of brain
wtAAV9 - NNM codon	AGTGCCCAAGCACAGGGCGCAGACC	14,012	9,198	9,473	10894.3
wtAAV9 - NNK codon	AGTGCTCAGGCACAGGGCGCAGACC	10,407	8,116	7,768	8763.7
PHP.N - NNM codon	GACGGAACACTGCGAGTCCCATTCAAA	58,553	203,200	95,929	119227.3
PHP.N - NNK codon	GATGGGACTTTGGCGGTGCTTTTAAG	4,827	13,936	7,507	8756.7
PHP.B - NNM codon	GCACAAACACTGCGAGTCCCATTCAAA	15,971	6,970	32,396	18445.7
PHP.B - NNK codon	GCCCAAACTTTGGCGGTGCTTTTAAG	8,002	2,259	14,051	8104.0

NEU-LIB		Virus Stock	Brain/Virus	Brain/Virus (depth adjusted)	Brain/Virus average of two codons	Brain/virus vs. wtAAV9
wtAAV9 - NNM codon	AGTGCCCAAGCACAGGGCGCAGACC	86423	0.1	0.11		
wtAAV9 - NNK codon	AGTGCTCAGGCACAGGGCGCAGACC	67395	0.1	0.12	0.116	
PHP.N - NNM codon	GACGGAACACTGCGAGTCCCATTCAAA	36898	3.2	2.9		
PHP.N - NNK codon	GATGGGACTTTGGCGGTGCTTTTAAG	2802	3.1	2.8	2.889	24.8
PHP.B - NNM codon	GCACAAACACTGCGAGTCCCATTCAAA	17813	1.0	0.9		
PHP.B - NNK codon	GCCCAAACTTTGGCGGTGCTTTTAAG	8206	1.0	0.9	0.920	7.9

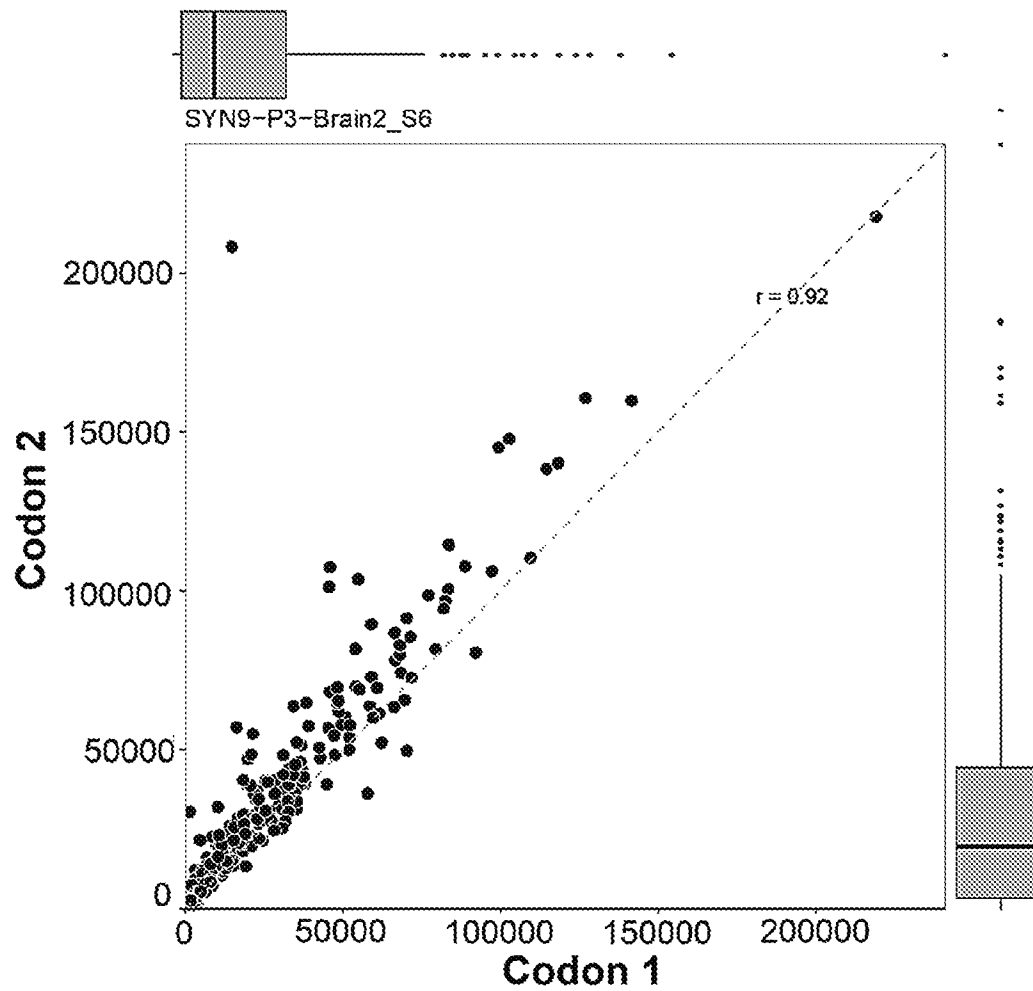
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FIG. 31B



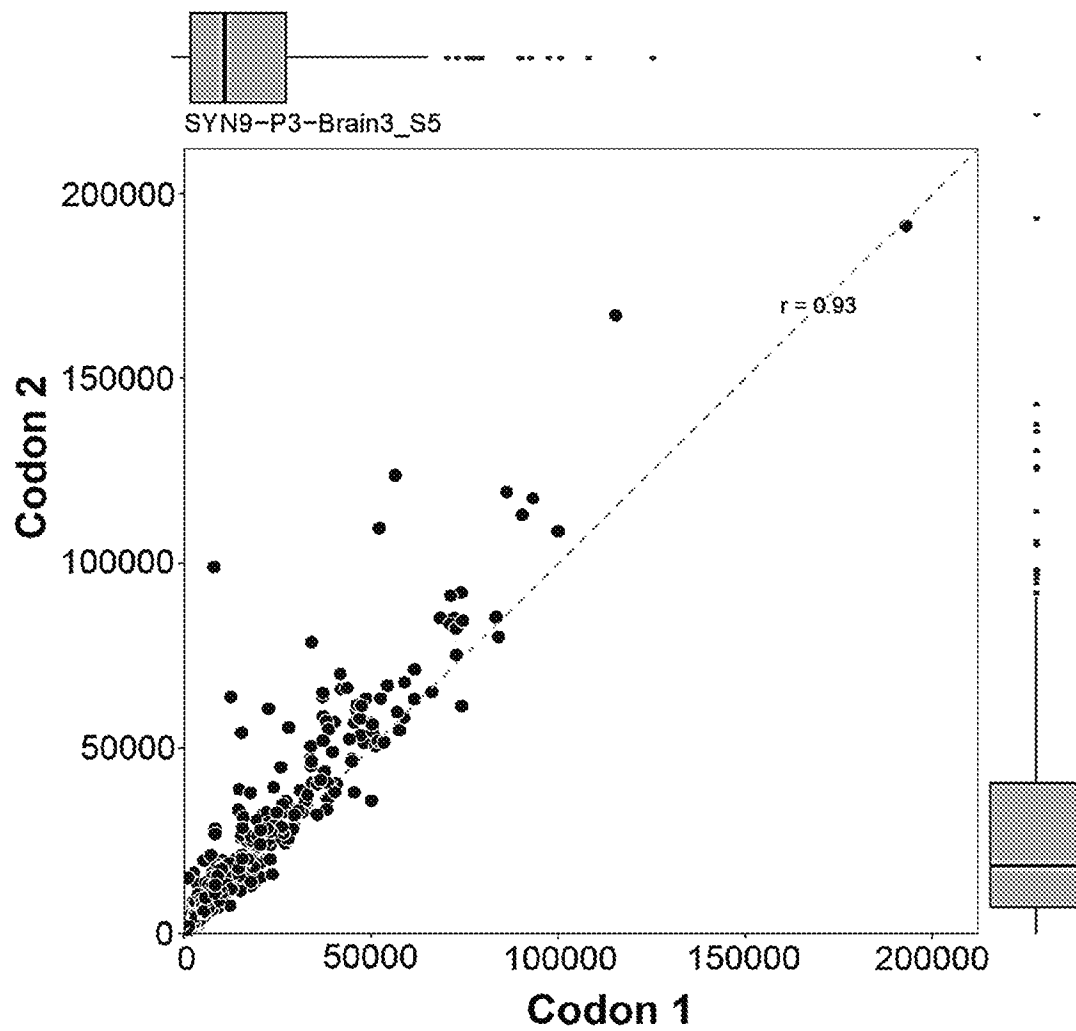
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FIG. 31C



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FIG. 31D



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FIG. 32A

Neuron synthesis library-NGS-P3

pepSeq	Brain1	Brain2	Brain3	mean of brain	virus stock	Brain/ Virus	Br1/vi rus	Br2/vir us	Br3/vi rus
DGTSSYYDS_1	61531	48295	24838	44888	9427	4.76	6.53	5.12	2.63
AQPEGSARW_1	106764	59048	72175	79329	16862	4.70	6.33	3.50	4.28
DGTSSYYDS_2	84784	69506	32611	62300	13416	4.64	6.32	5.18	2.43
AQPEGSARW_2	129187	72820	85144	95717	21279	4.50	6.07	3.42	4.00
DGTASYIDS_1	90508	82418	24663	65863	15547	4.24	5.82	5.30	1.59
DGTASYIDS_2	98081	96707	30517	75102	18088	4.15	5.42	5.35	1.69
AQWPTSYDA_1	206147	5013	61696	90952	22049	4.12	9.35	0.23	2.80
DGTADKPFER_1	114140	219057	192943	175380	44512	3.94	2.56	4.92	4.33
AQWPTSYDA_2	231396	5433	71311	102713	26944	3.81	8.59	0.20	2.65
DGSSSYIDA_2	62708	56941	26771	48807	13289	3.67	4.72	4.28	2.01
DGSSSYIDA_1	19195	16367	8397	14653	4105	3.57	4.68	3.99	2.05
DGTADKPFER_2	111033	217899	191385	173439	49321	3.52	2.25	4.42	3.88
DGTLSQPFER_1	23175	99366	115373	79305	23204	3.42	1.00	4.28	4.97
AQFPTNYDS_2	141935	3078	47247	64087	18860	3.40	7.53	0.16	2.51
DGTAIHLSS_2	150492	89416	65976	101961	30112	3.39	5.00	2.97	2.19
DGTAIHLSS_1	91896	59070	42010	64325	19081	3.37	4.82	3.10	2.20
DGTLSQPFER_2	30944	145129	167147	114407	34444	3.32	0.90	4.21	4.85
DGTGQVTGW_1	104223	66451	46346	72340	21828	3.31	4.77	3.04	2.12
AQFPTNYDS_1	110378	2154	33870	48801	14732	3.31	7.49	0.15	2.30
DGTGNVTGW_1	98253	66566	50174	71664	21878	3.28	4.49	3.04	2.29
DGTMDKPFER_1	31800	126945	90386	83044	25950	3.20	1.23	4.89	3.48
DGTLAVPEFK_2	60273	208417	99023	122571	38435	3.19	1.57	5.42	2.58
DGTMDKPFER_2	44872	160645	113192	106236	33416	3.18	1.34	4.81	3.39
DGTLAVPEFK_1	5079	14812	8024	9305	2983	3.12	1.70	4.97	2.69
DGTGNTHGW_1	133298	88815	71161	97758	31834	3.07	4.19	2.79	2.24
DGTVIHLSS_2	118419	57659	37350	71143	23256	3.06	5.09	2.48	1.61
DGTGTTVGW_1	84623	70422	50121	68389	22452	3.05	3.77	3.14	2.23

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FIG. 32B

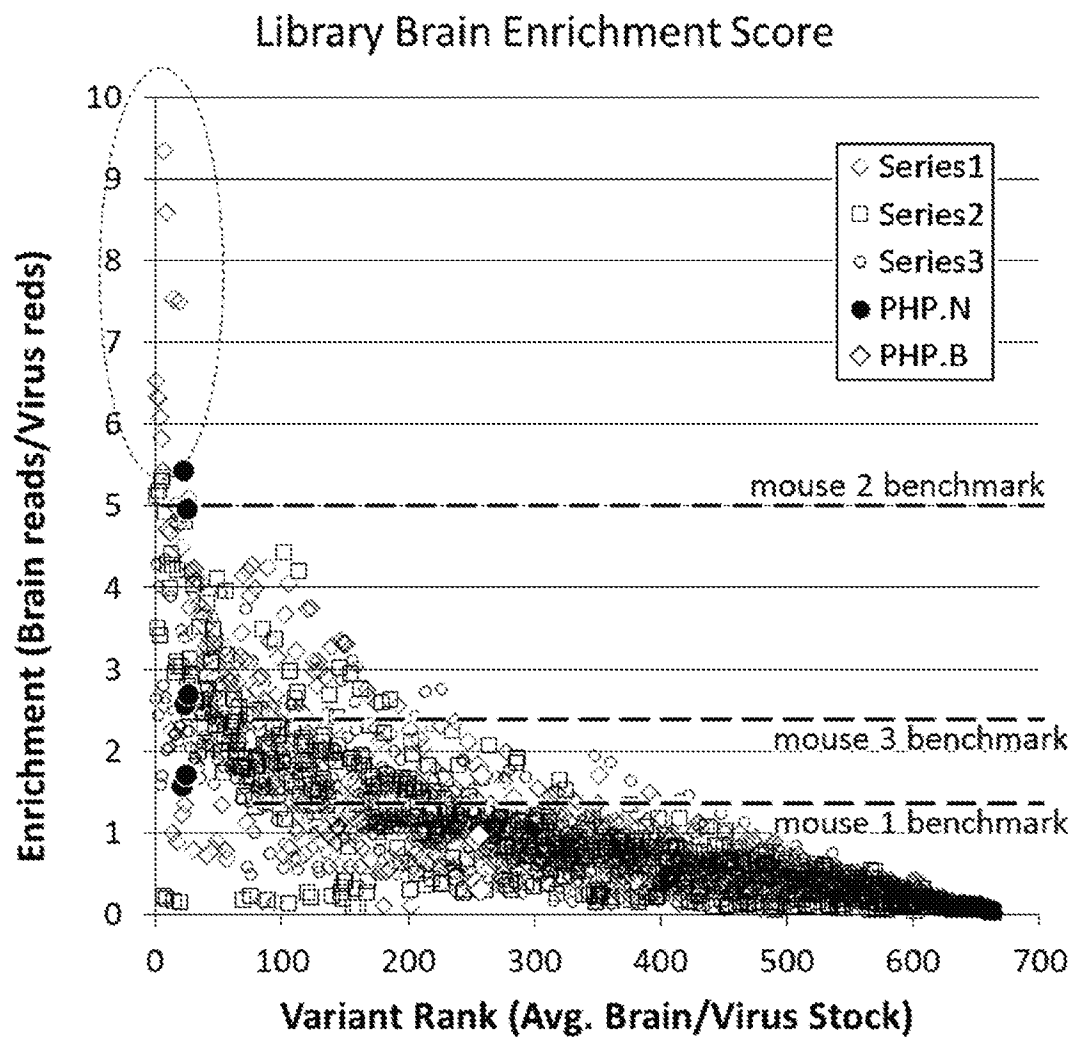


FIG. 33

Astrocyte synthesis library-P3

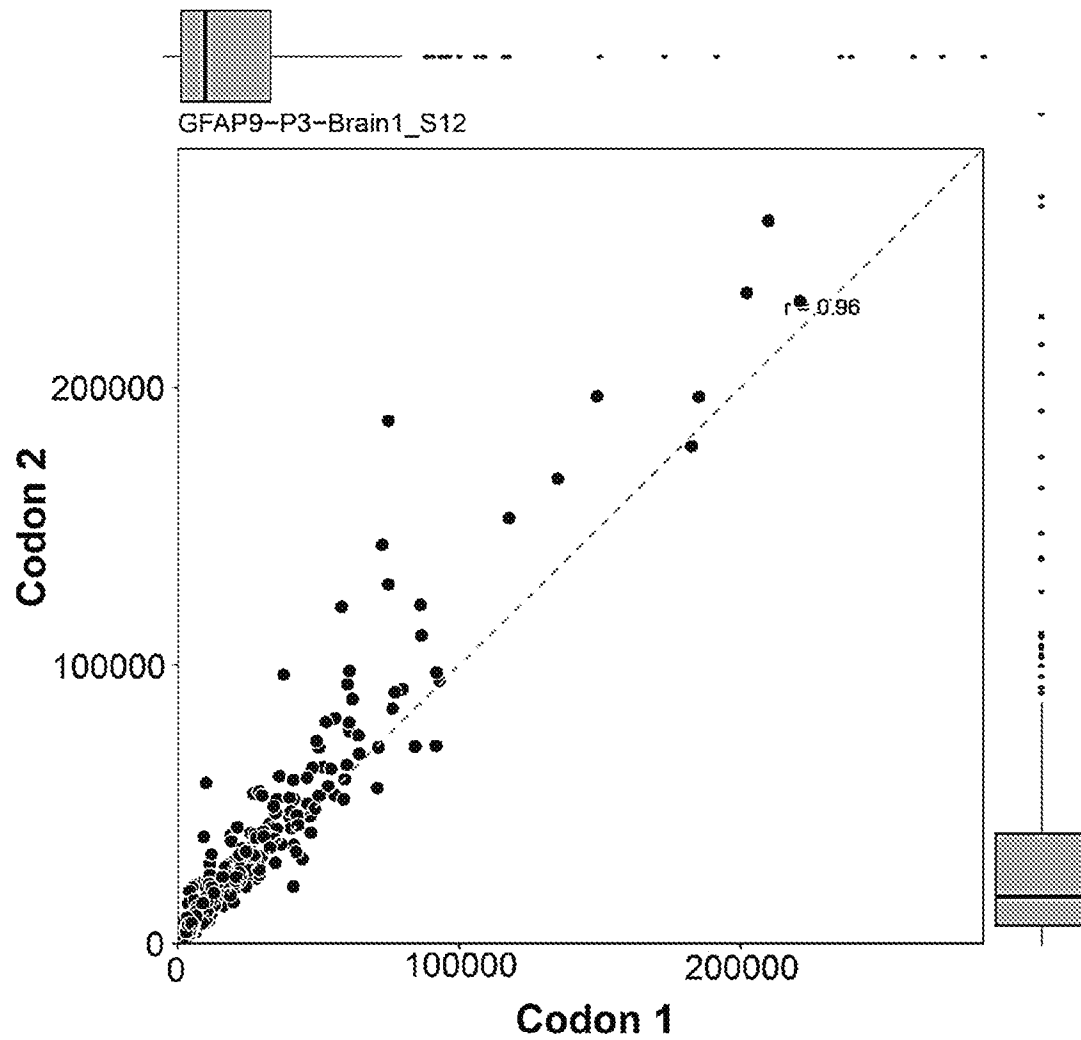
GFAP-LIB		Brain1	Brain2	Liver1	Liver2	mean of brain	mean of liver	Virus Stock	Brain/Virus	Brain/liver
wtAAV9 - NNM codon	AGTGGCCCAAGGCACAGGCGCAGACC	12,798	9,282	530,908	637,731	11,040	584,320	83,439	0.132	0.019
wtAAV9 - NNK codon	AGTGGCCCAAGGCACAGGCGCAGACC	11,667	8,447	389,373	452,574	10,042	420,974	66,967	0.150	0.024
PHP N - NNM codon	GACGGACACTGCGCAGTCCCATTCAAA	6,756	90,000	5,078	12,075	48,378	8,577	36,976	1.308	5.641
PHP N - NNK codon	GATGGACTTTGGCGGTGCTTTTAAAG	457	5,815	207	778	3,136	493	2,593	1.209	6.368
PHP B - NNM codon	GCACAAACACTGCGCAGTCCCATTCAAA	3,701	43,200	4,331	23,858	23,451	14,095	19,812	1.184	1.664
PHP B - NNK codon	GCCAAACTTTGGCGGTGCTTTTAAAG	1,452	19,963	1,264	11,801	10,708	6,533	8,982	1.192	1.639

AST mouse 1		Brain mouse 1	Liver mouse 1	virus stock	Brain/virus mouse 1	Brain/liver mouse 1	Liver/virus mouse 1	Brain vs. AAV9	Liver vs. AAV9
wtAAV9 - NNM codon	AGTGGCCCAAGGCACAGGCGCAGACC	12,798	530,908	83,439	0.15	0.02	6.36	1.00	1.00
wtAAV9 - NNK codon	AGTGGCCCAAGGCACAGGCGCAGACC	11,667	389,373	66,967	0.17	0.03	5.81	1.00	1.00
PHP N - NNM codon	GACGGACACTGCGCAGTCCCATTCAAA	6,756	5,078	36,976	0.18	1.33	0.14	1.59	0.02
PHP N - NNK codon	GATGGACTTTGGCGGTGCTTTTAAAG	457	207	2,593	0.18	2.21	0.08	1.53	0.01
PHP B - NNM codon	GCACAAACACTGCGCAGTCCCATTCAAA	3,701	4,331	19,812	0.19	0.85	0.22	1.62	0.03
PHP B - NNK codon	GCCAAACTTTGGCGGTGCTTTTAAAG	1,452	1,264	8,982	0.16	1.15	0.14	1.41	0.02

GFAP mouse 2		Brain mouse 2	Liver mouse 2	virus stock	Brain/virus mouse 2	Brain/liver mouse 2	Liver/virus mouse 2	Brain vs. AAV9	Liver vs. AAV9
wtAAV9 - NNM codon	AGTGGCCCAAGGCACAGGCGCAGACC	9,282	637,731	83,439	0.11	0.01	7.64	1.00	1.00
wtAAV9 - NNK codon	AGTGGCCCAAGGCACAGGCGCAGACC	8,447	452,574	66,967	0.13	0.02	6.76	1.00	1.00
PHP N - NNM codon	GACGGACACTGCGCAGTCCCATTCAAA	90,000	12,075	36,976	2.43	7.45	0.33	21.17	0.05
PHP N - NNK codon	GATGGACTTTGGCGGTGCTTTTAAAG	5,815	778	2,593	2.24	7.47	0.30	19.50	0.04
PHP B - NNM codon	GCACAAACACTGCGCAGTCCCATTCAAA	43,200	23,858	19,812	2.18	1.81	1.20	18.96	0.17
PHP B - NNK codon	GCCAAACTTTGGCGGTGCTTTTAAAG	19,963	11,801	8,982	2.22	1.69	1.31	19.33	0.19

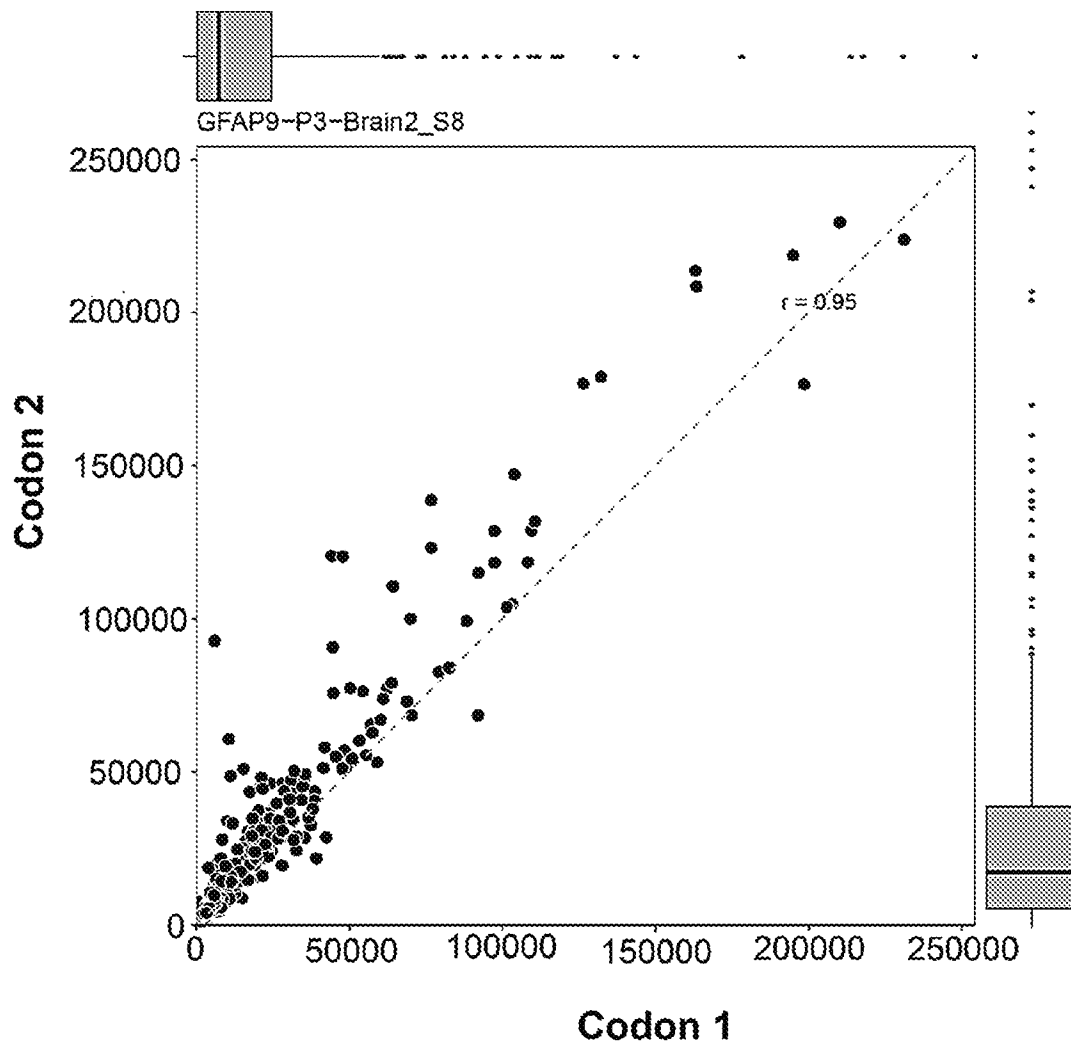
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FIG. 34A

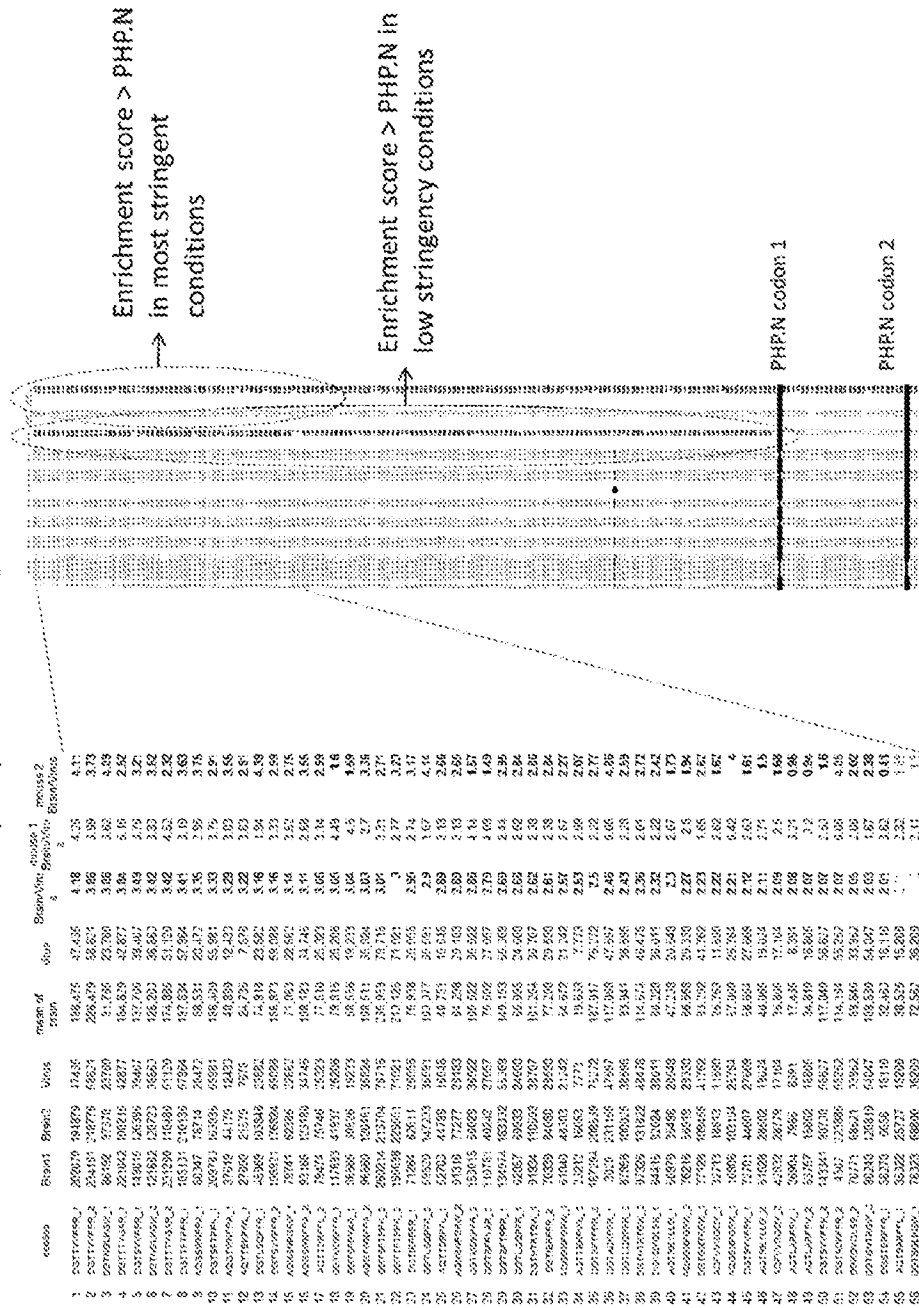


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FIG. 34B



Astrocyte synthesis library-P3 Enrichment



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FIG. 37A

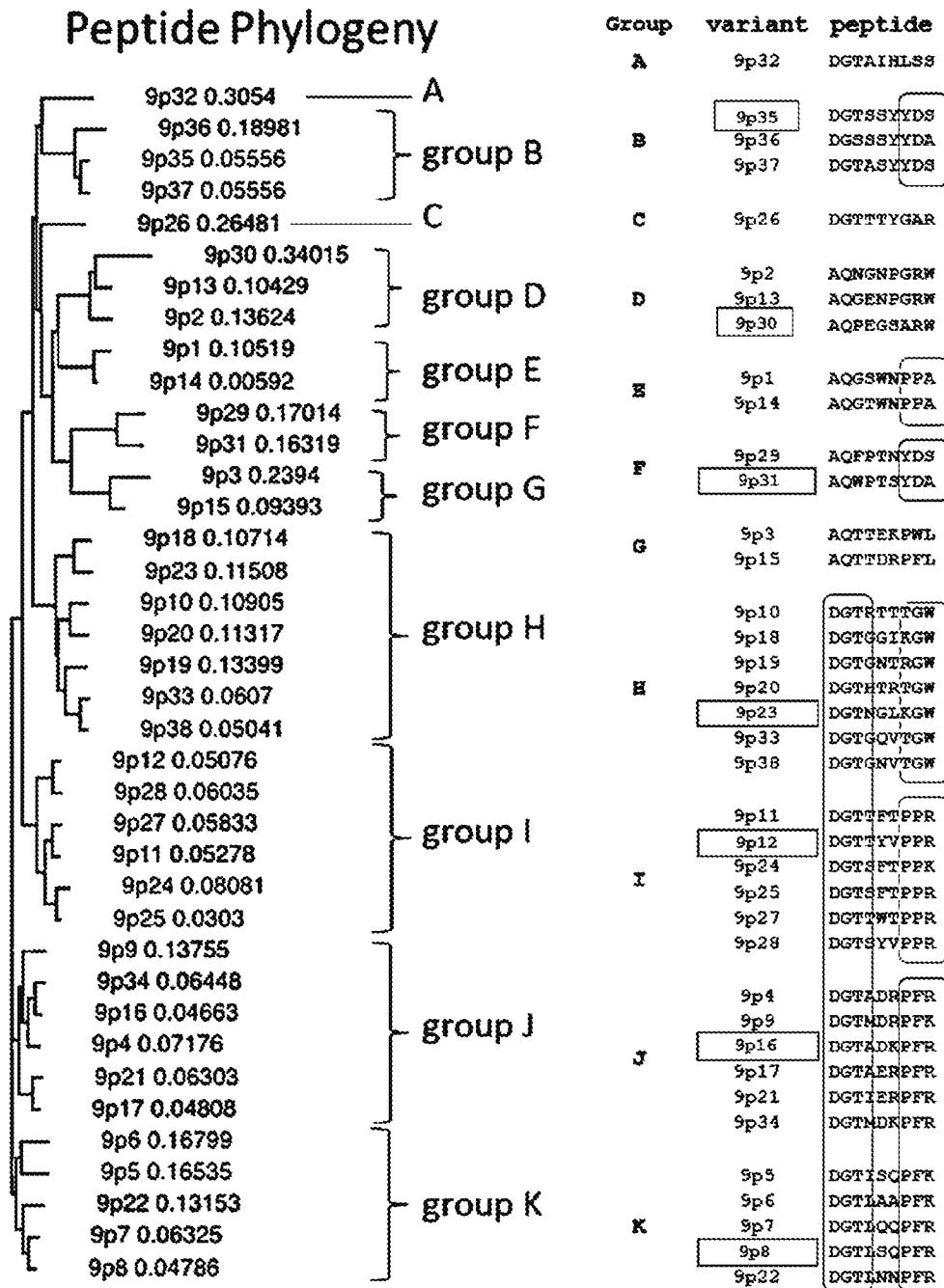
Top Variants from
P3 enrichment

FIG. 37B

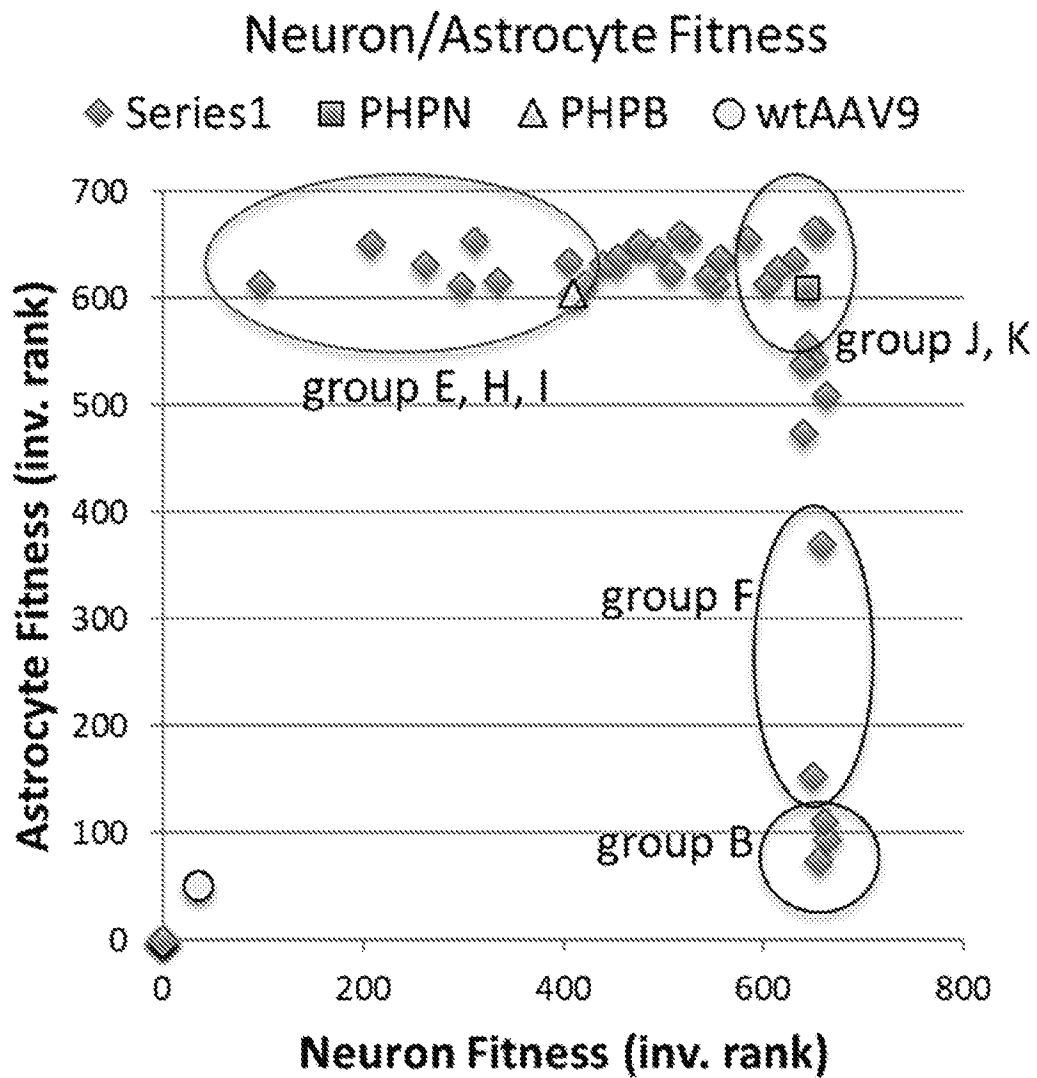


FIG. 38

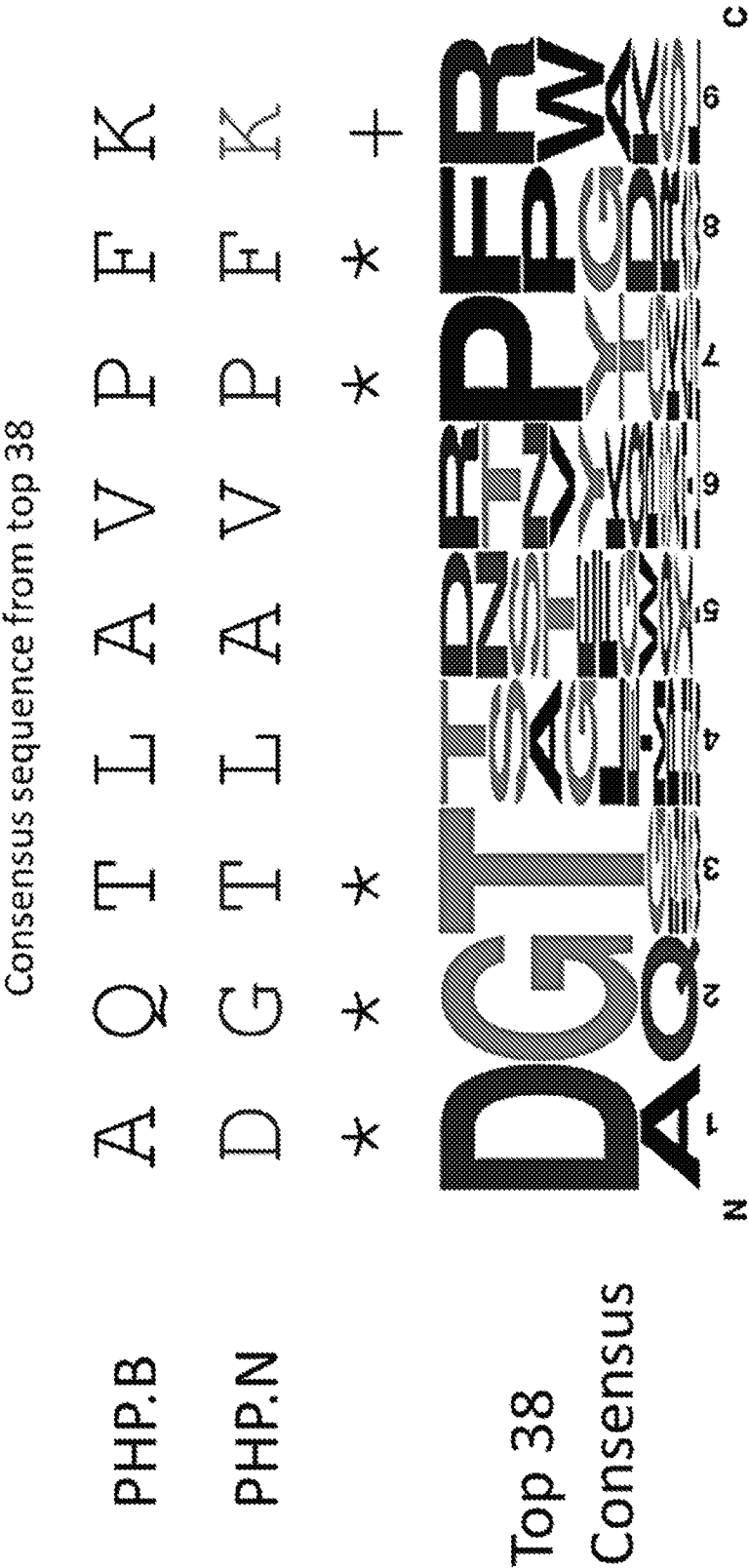


FIG. 39

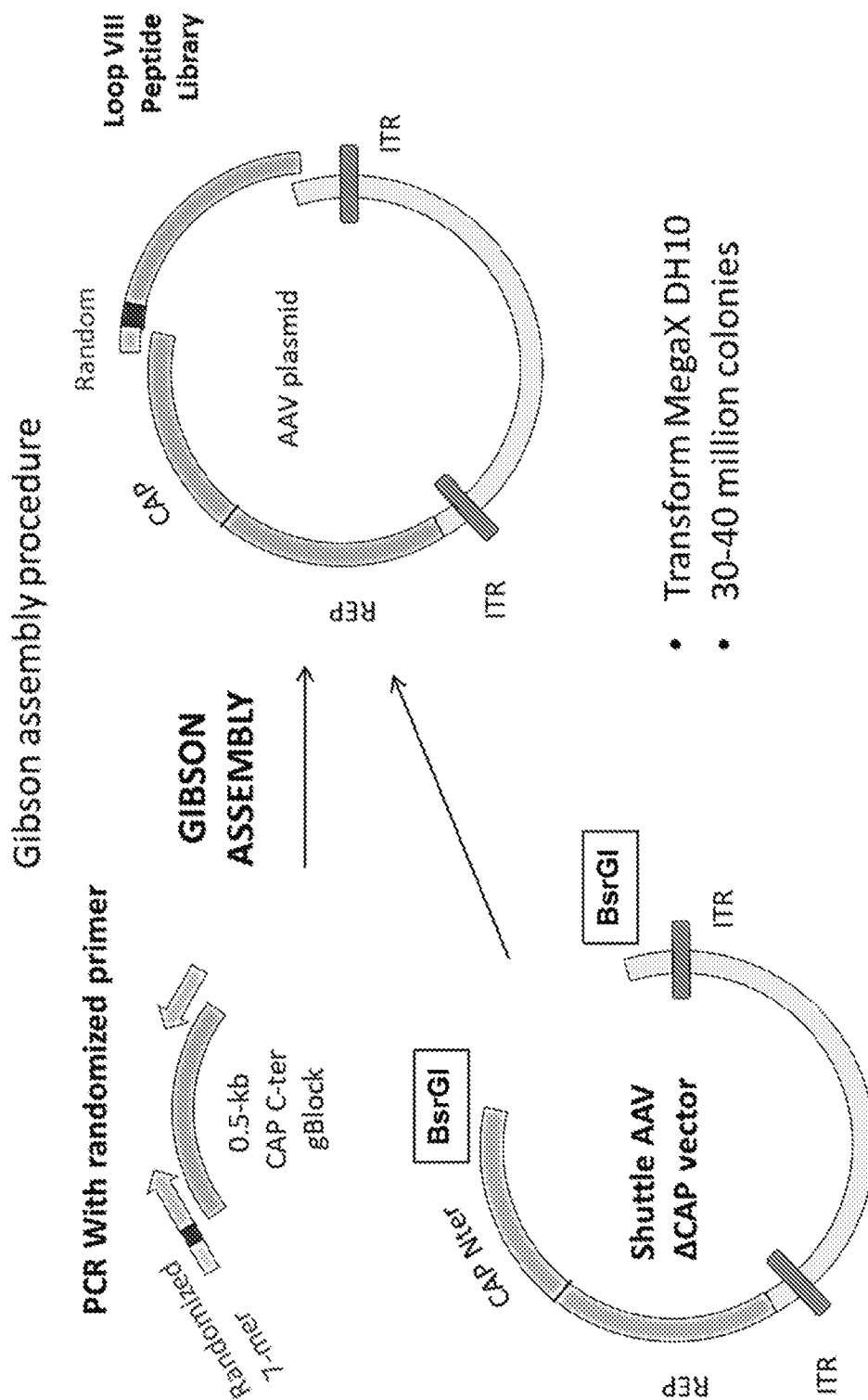


FIG. 40

TRIM/NNK Peptide Cloning

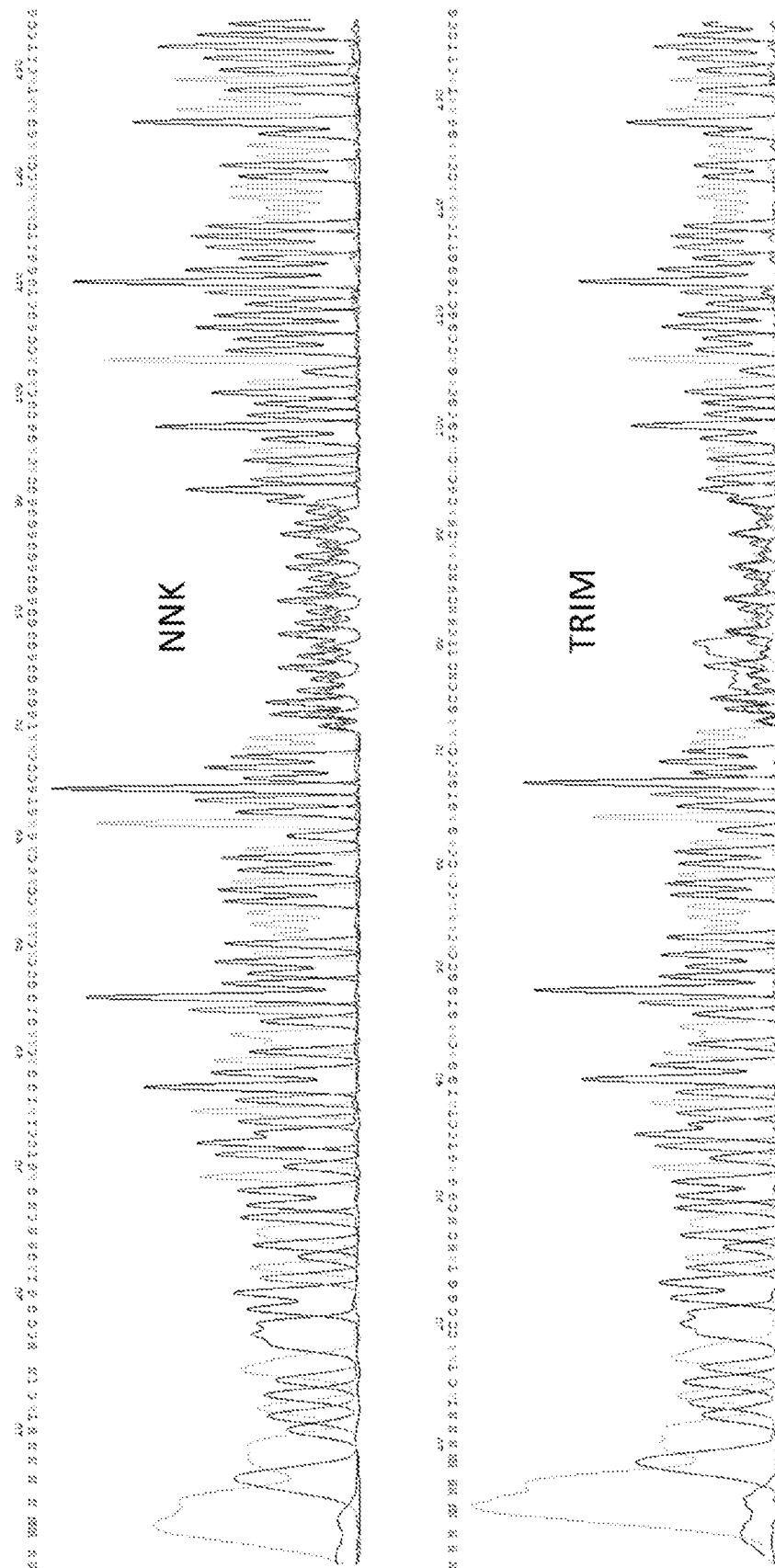


FIG. 42

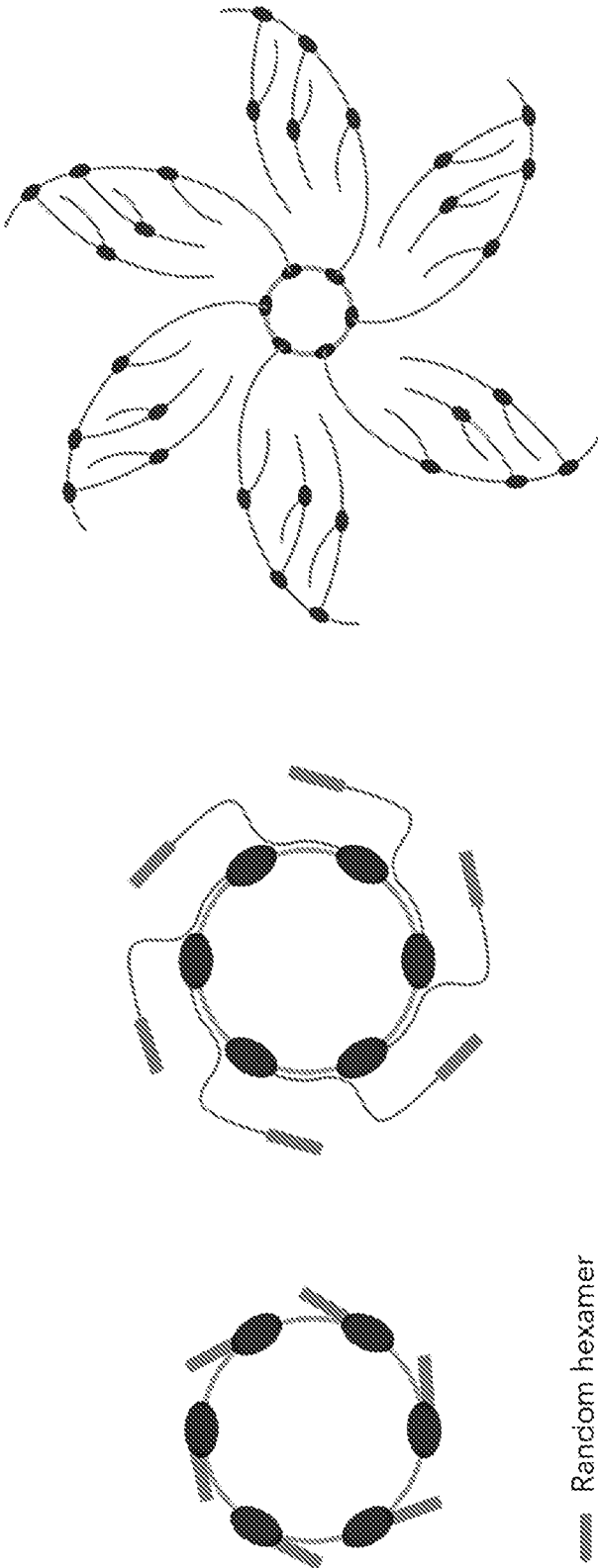


FIG. 43

Protelomerase monomer processing

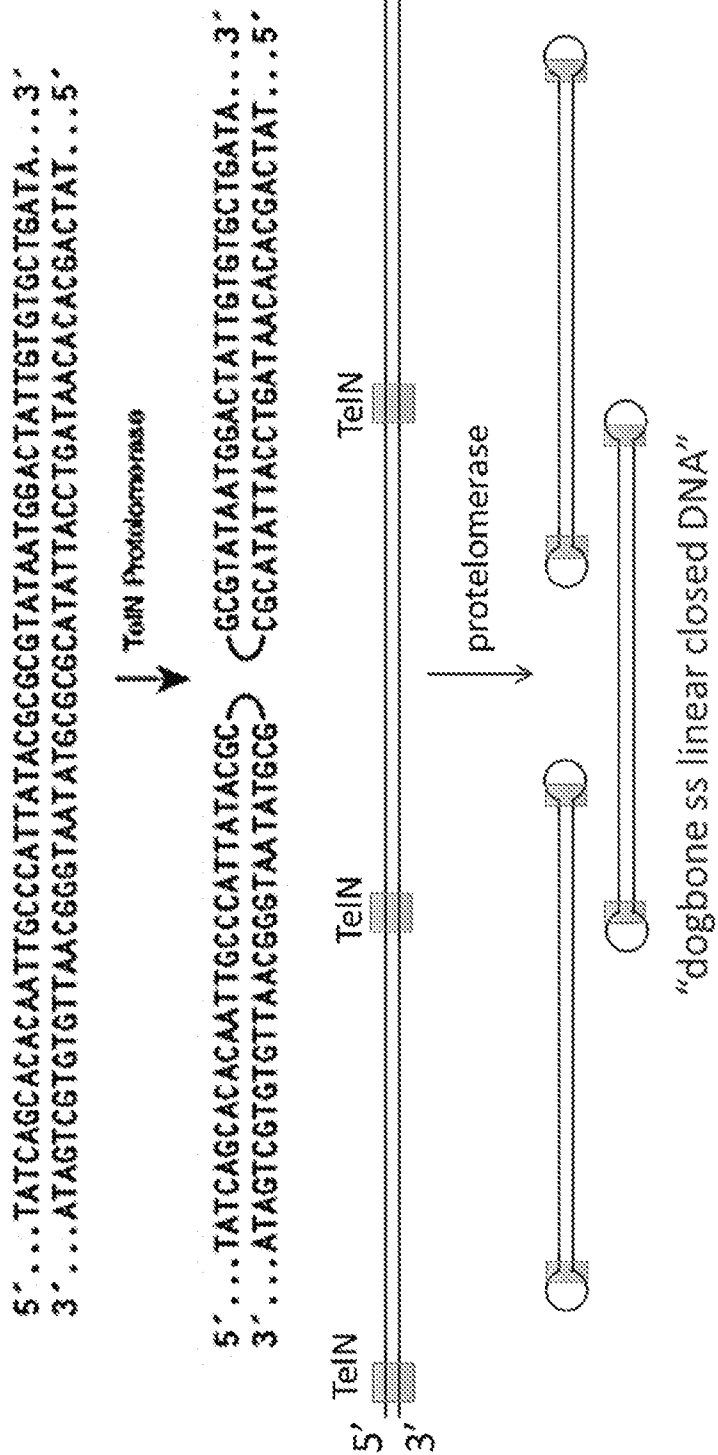


FIG. 44

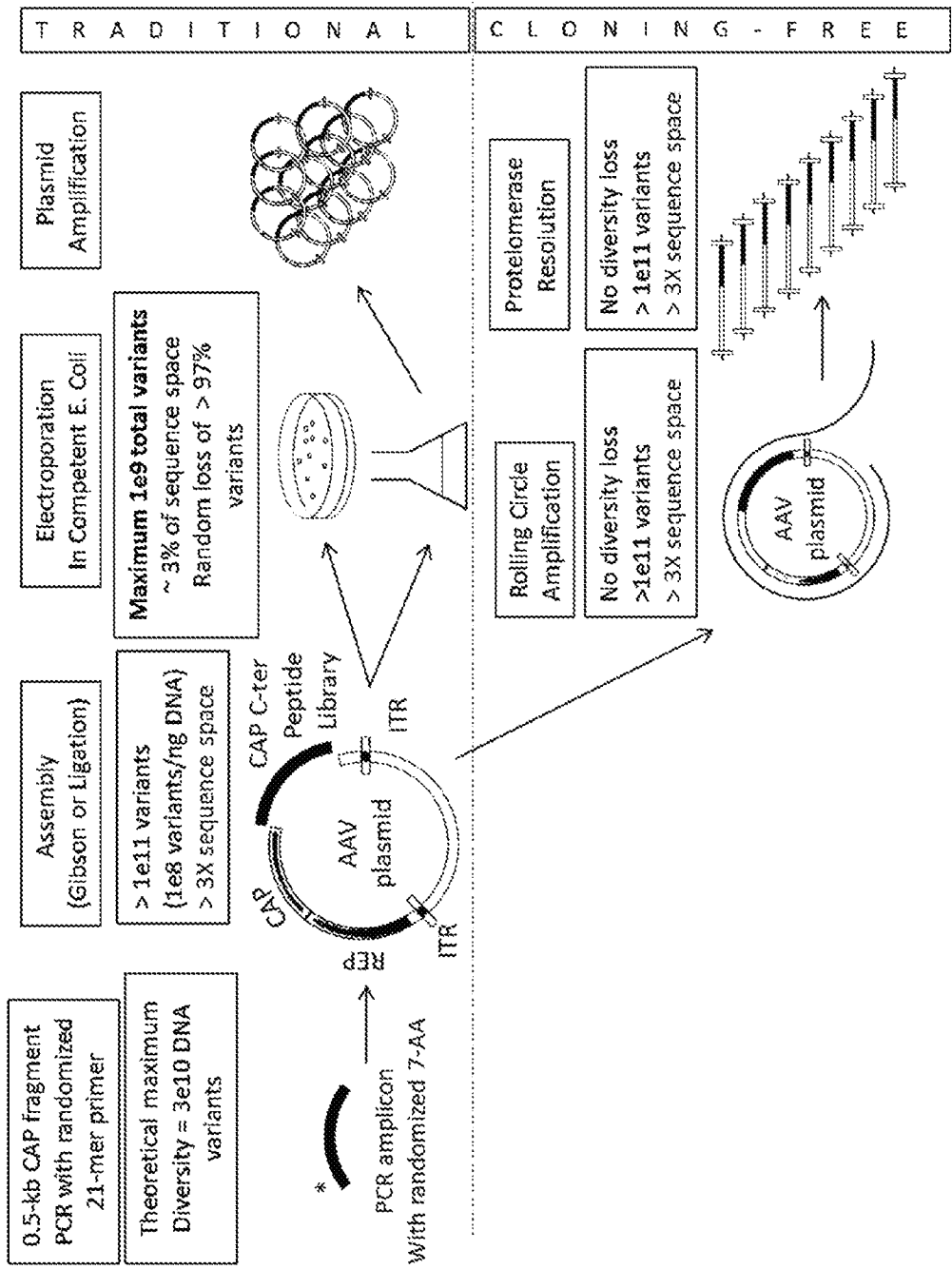
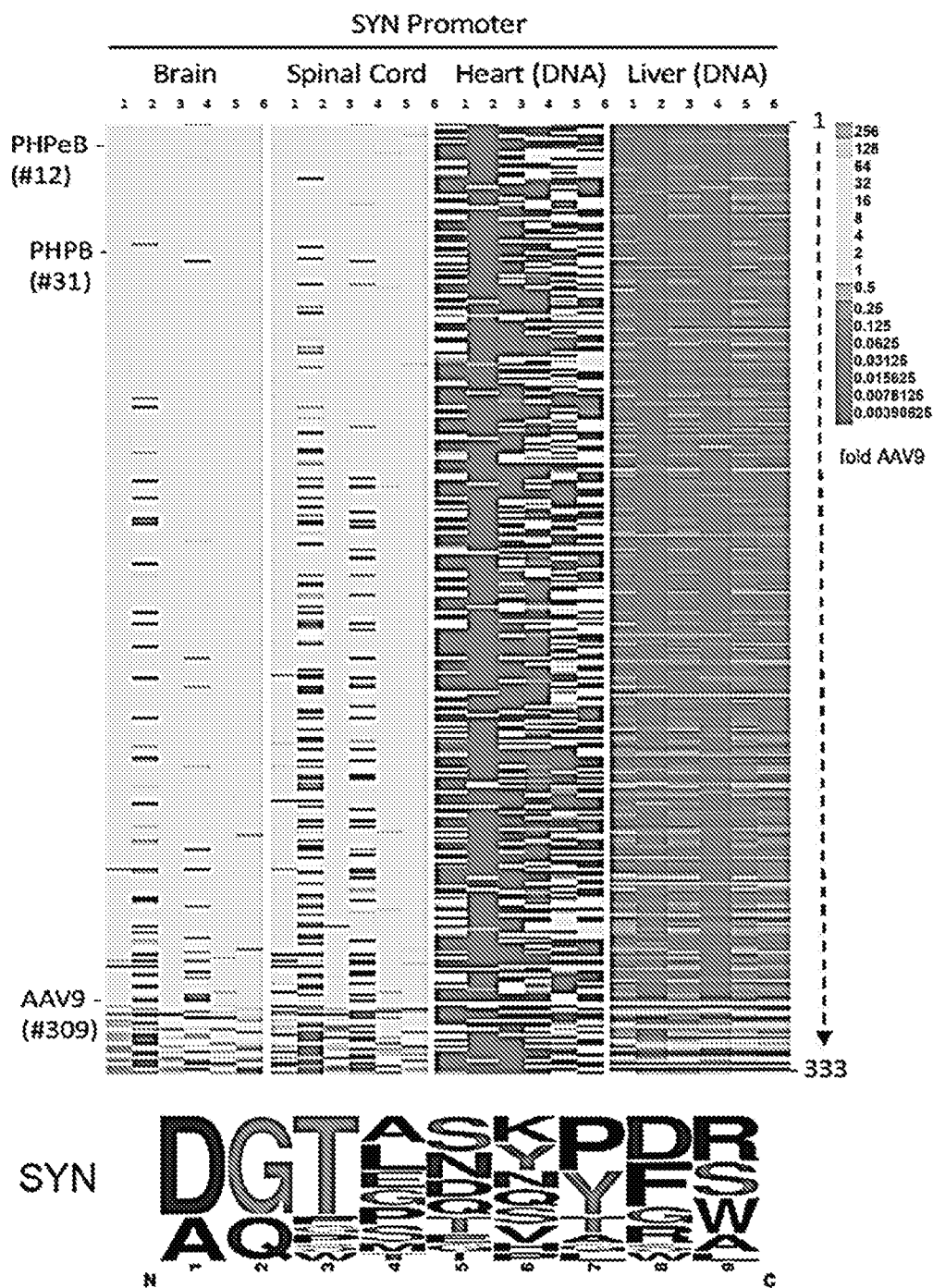
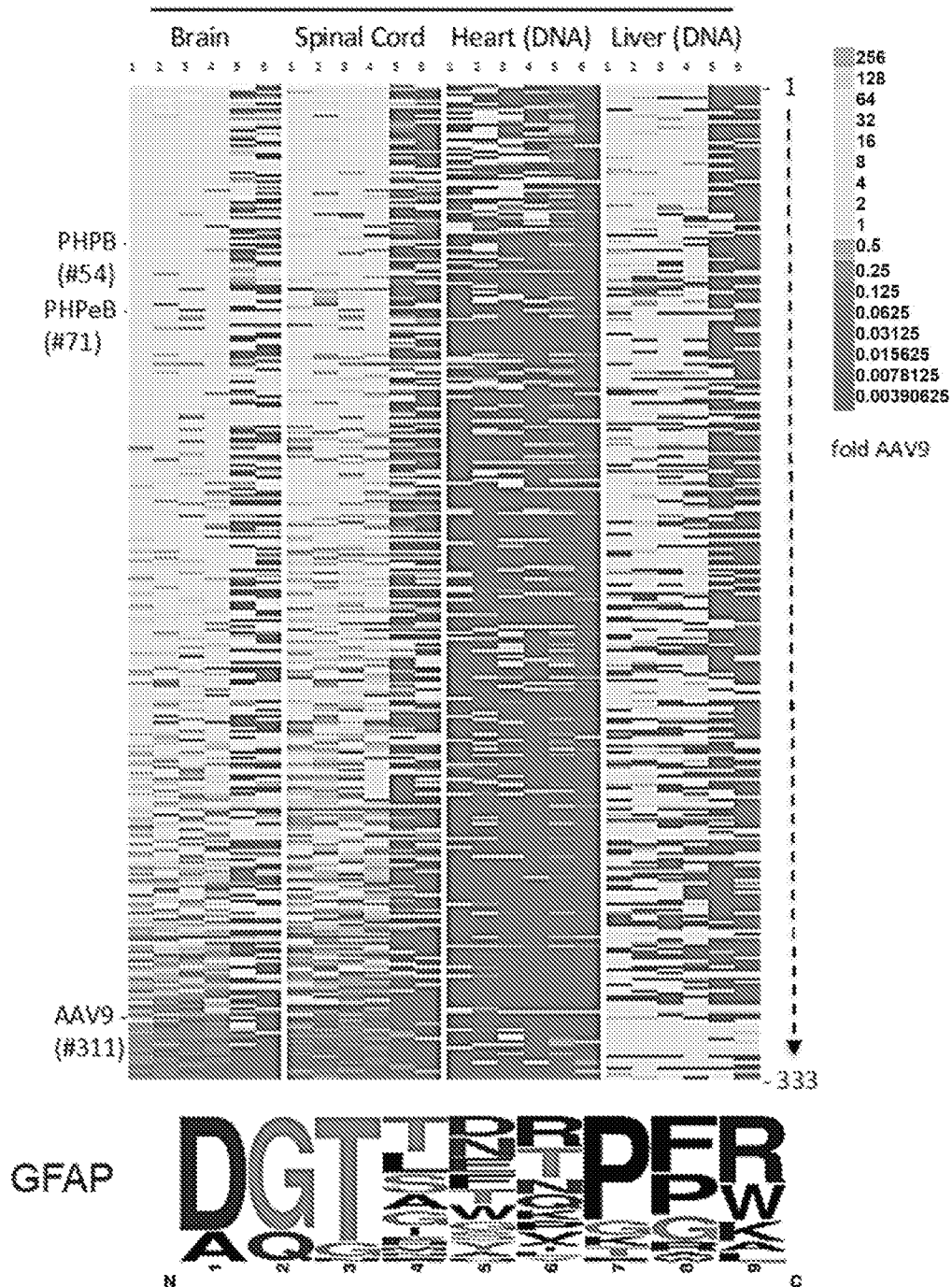


FIG. 45A

Peptide Enrichment Analysis – C57BL/6

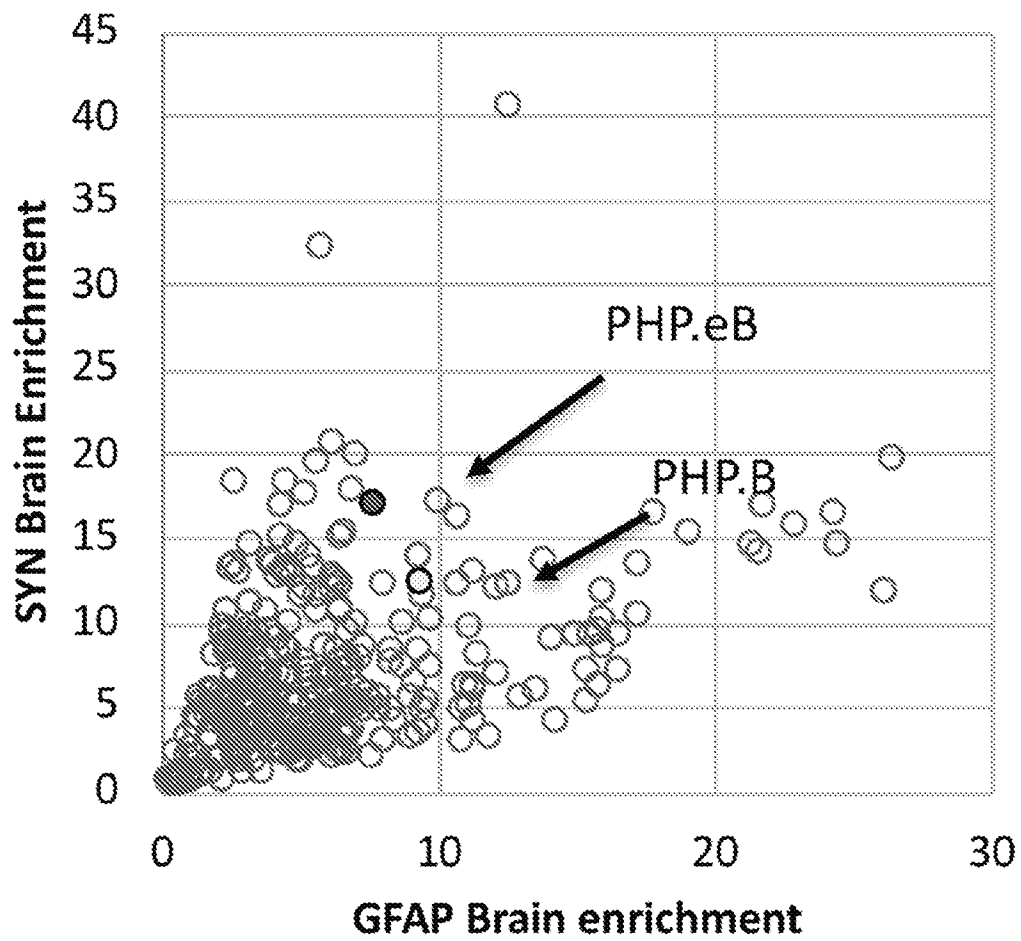


GFAP Promoter

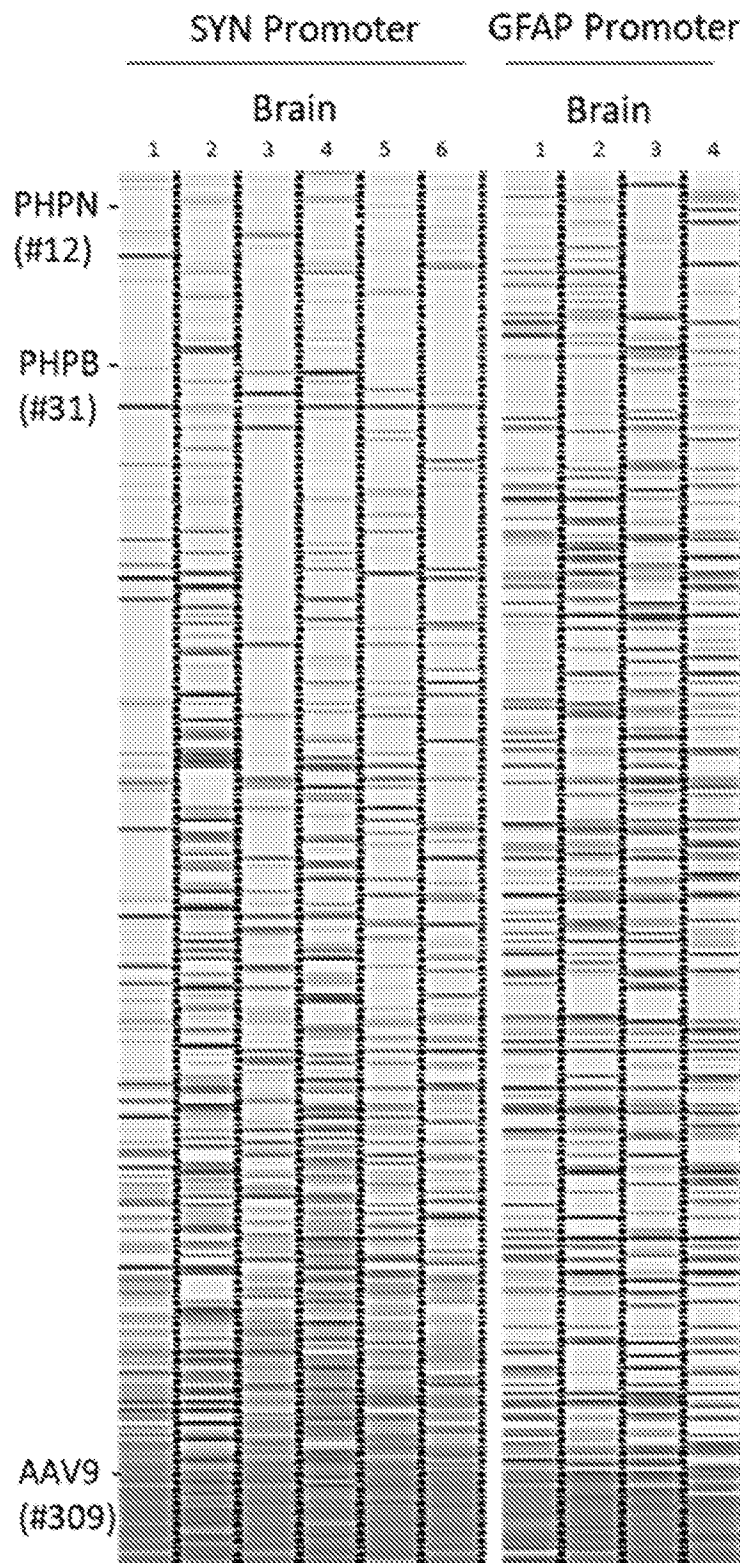


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FIG. 45C



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FIG. 46A

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FIG. 46B

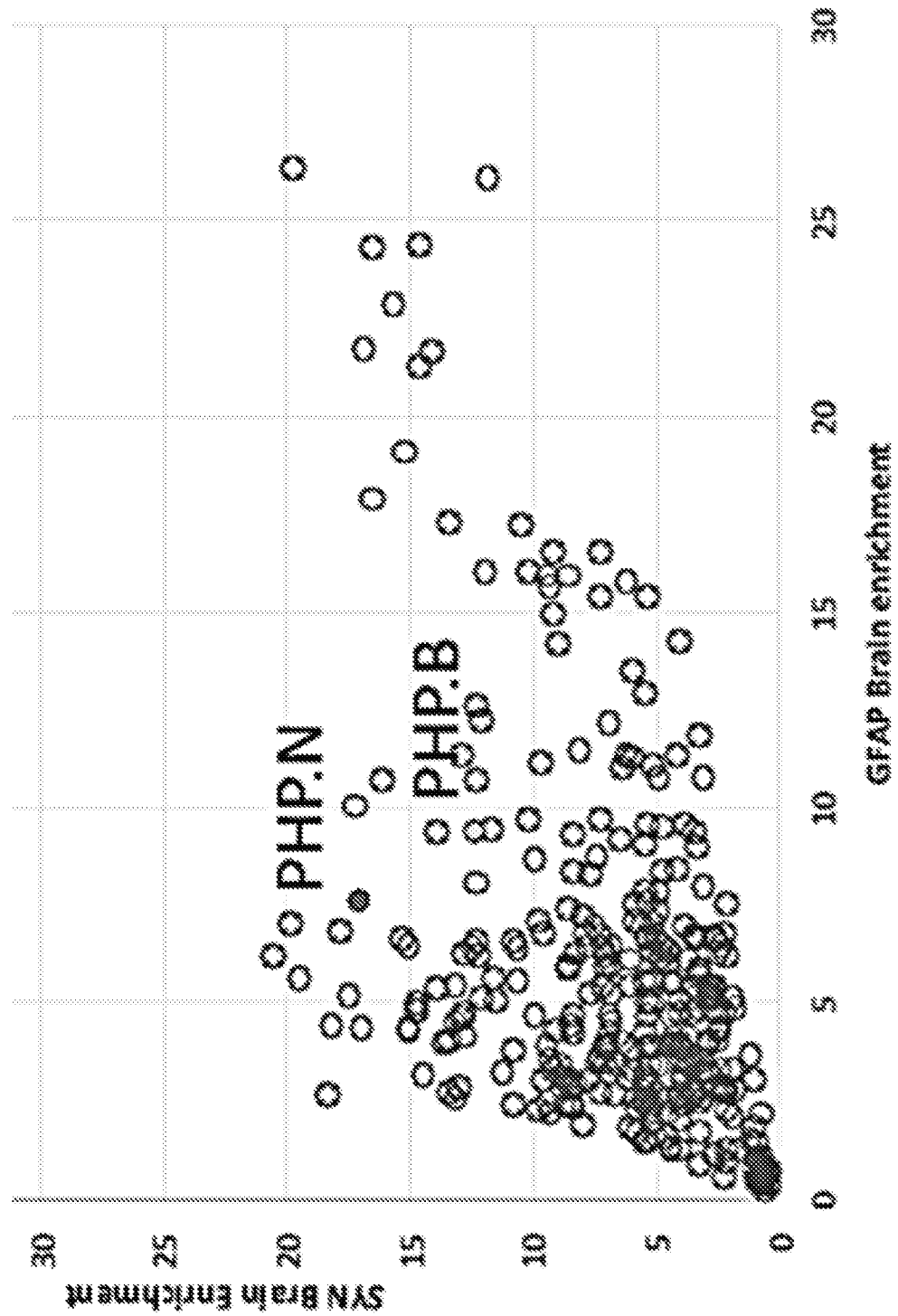
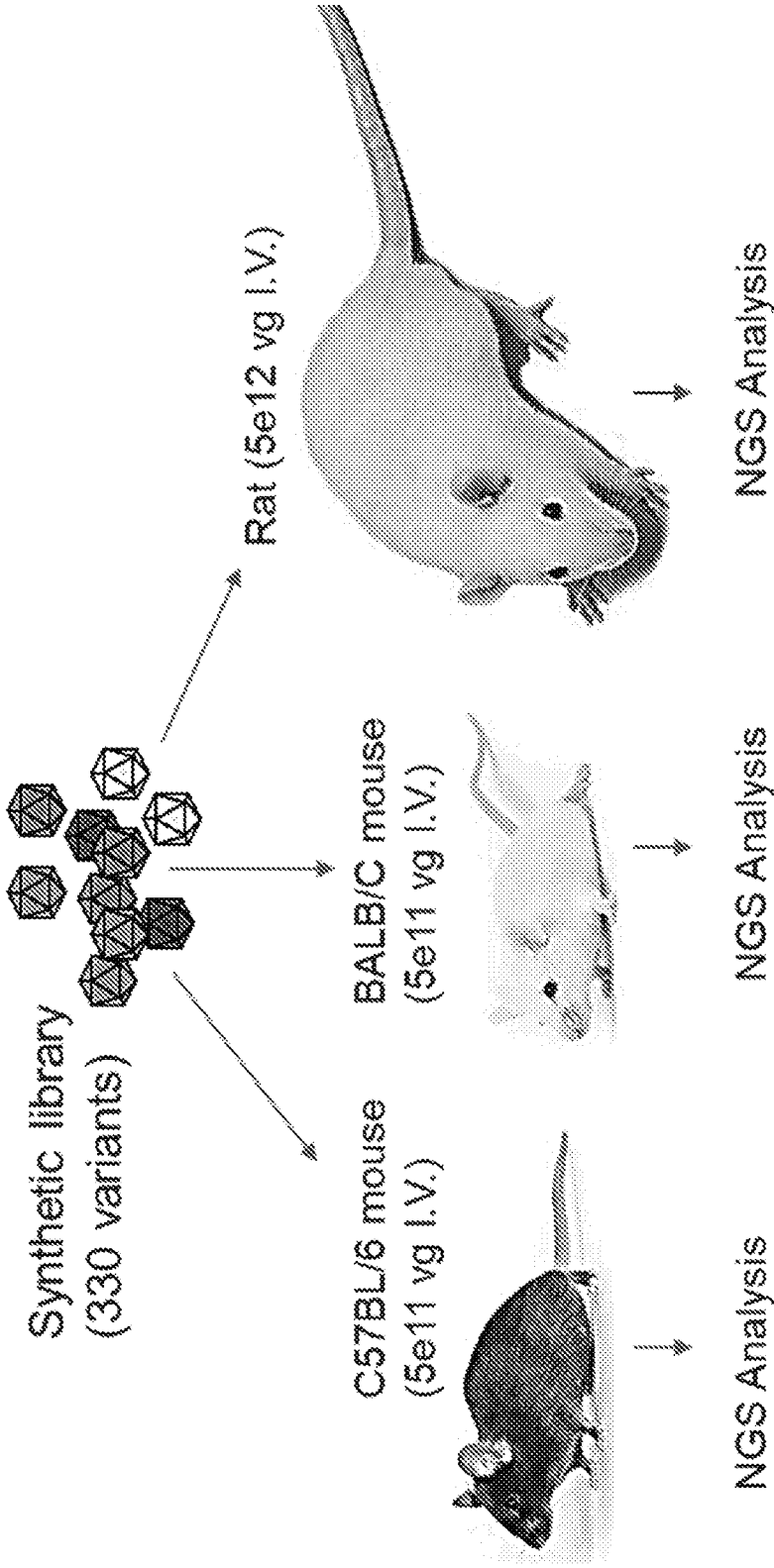
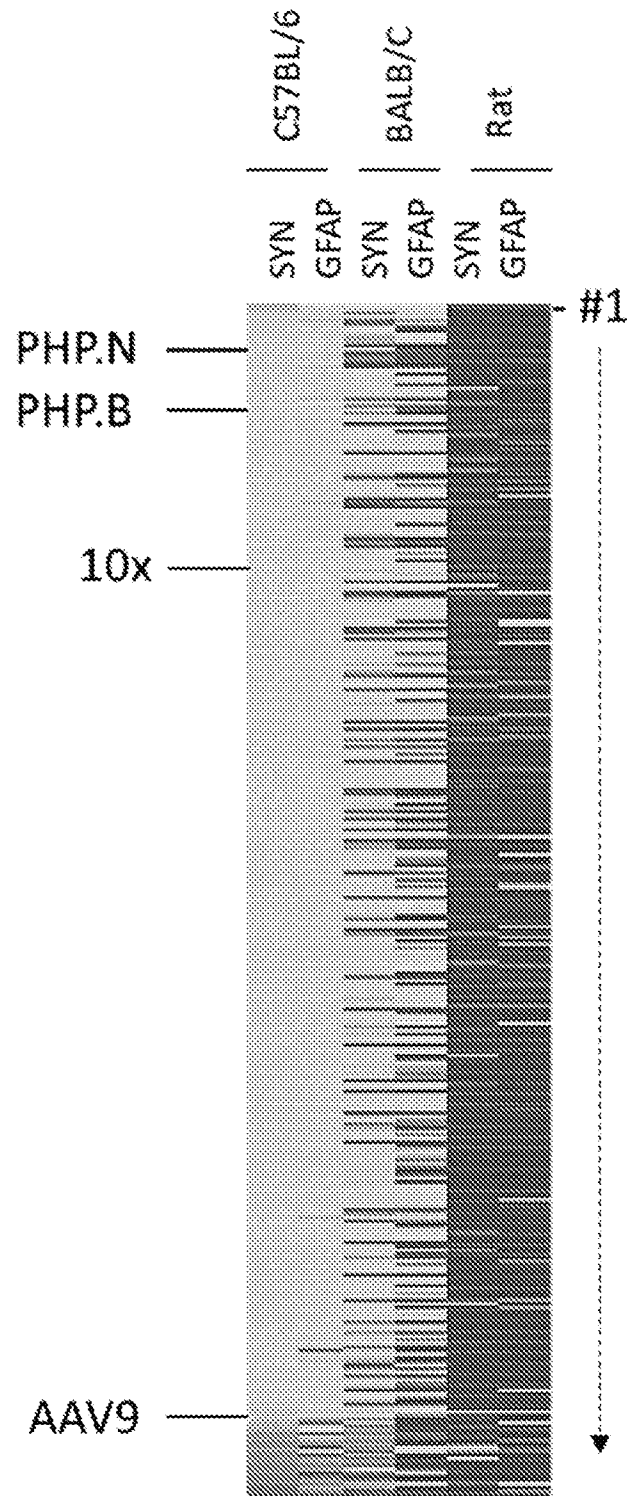


FIG. 47
Multi-Rodent Comparison



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FIG. 48A



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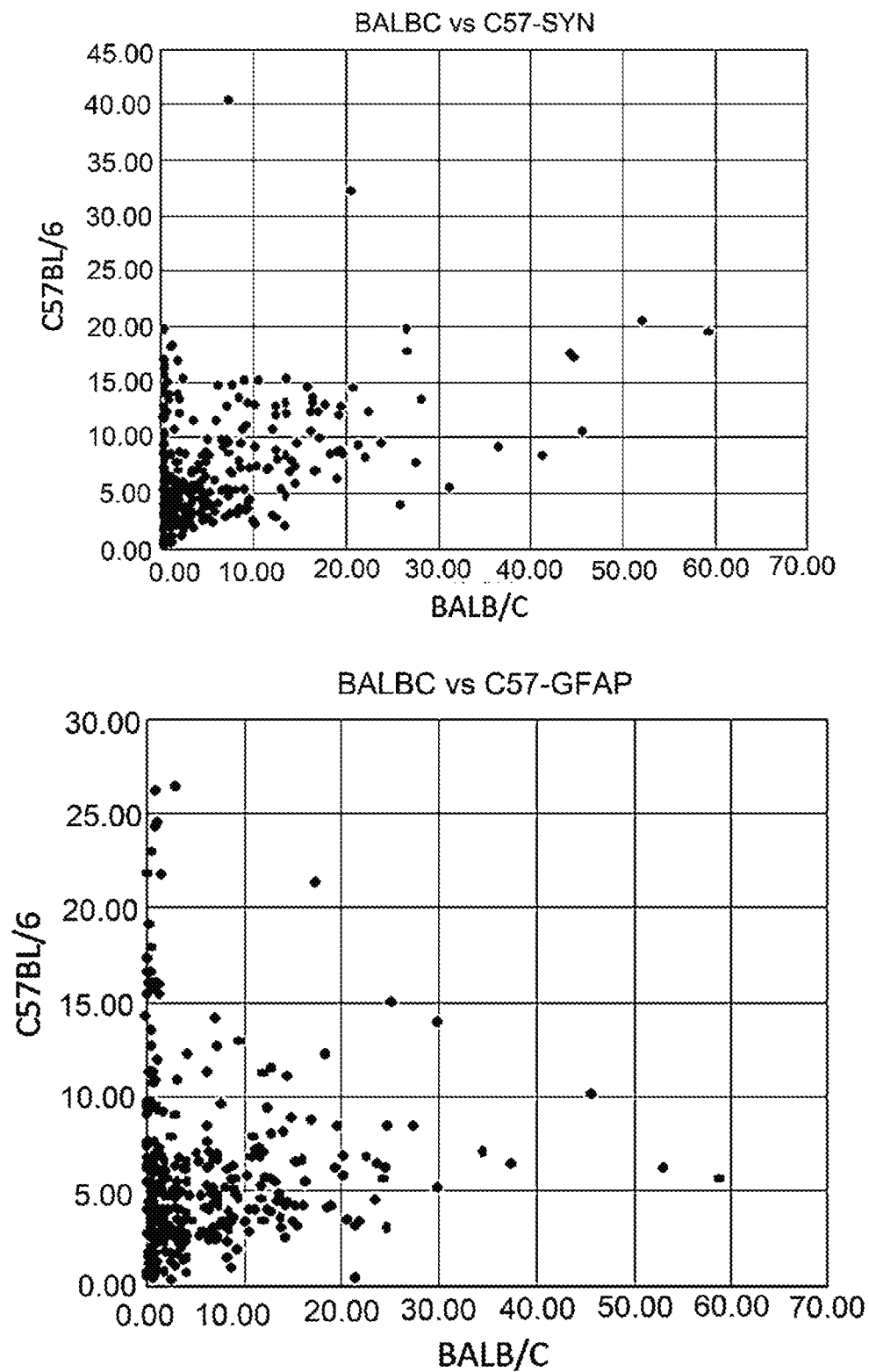
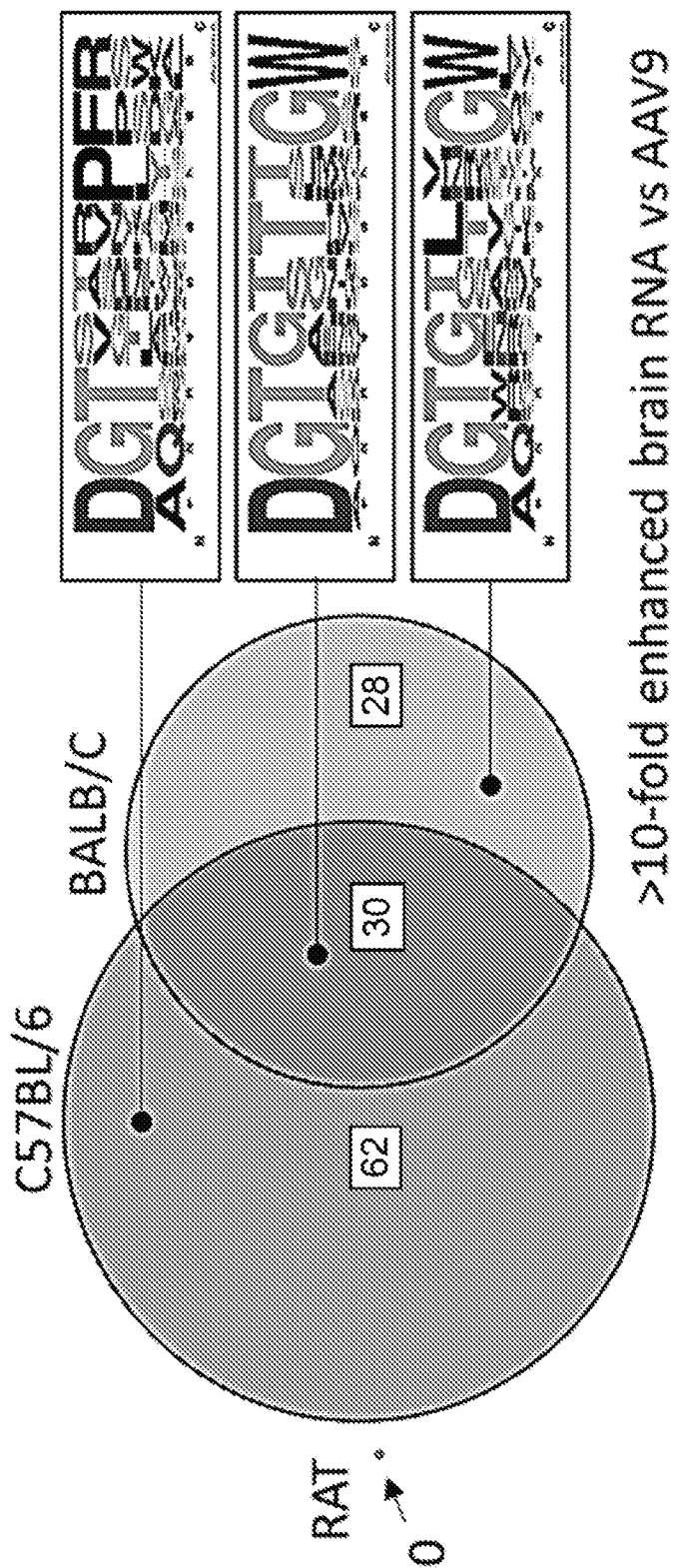
FIG. 48B

FIG. 48C

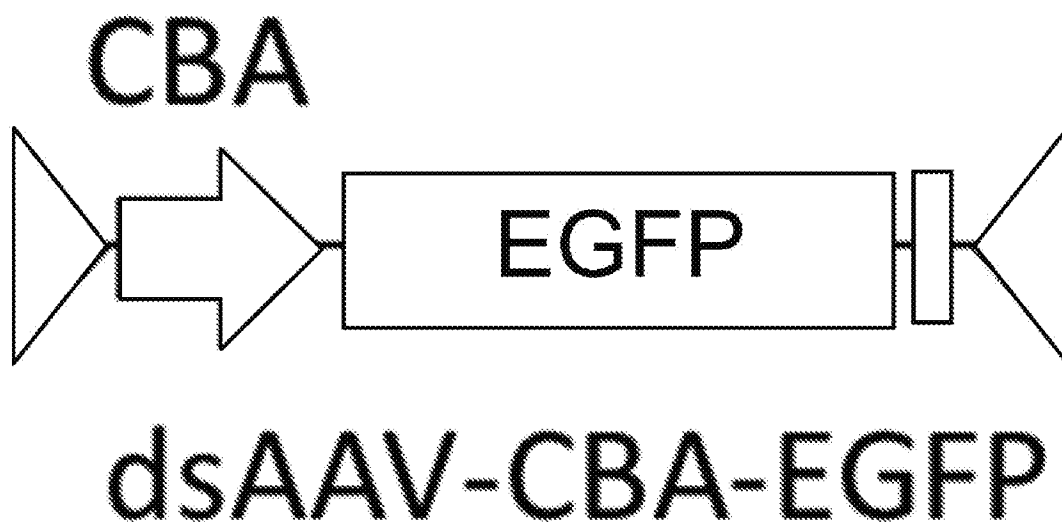


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FIG. 49A

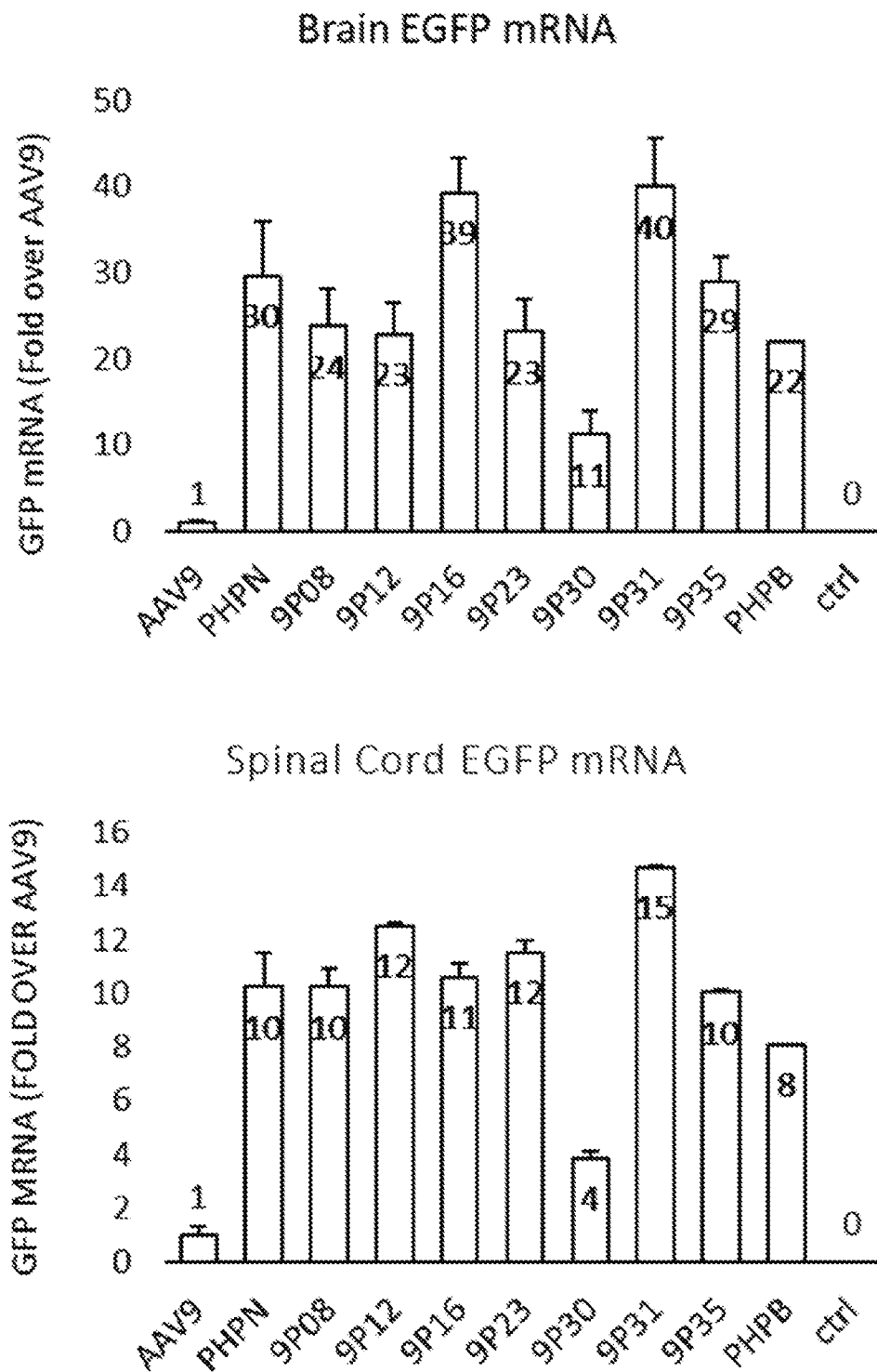
Variant	Translate
9p8	TNHQSDGTLSQPFRAQAQTG
9p12	TNHQSDGTTYVPPRAQAQTG
9p16	TNHQSDGTADKPFRAQAQTG
9p23	TNHQSDGTNGLKGWAQAQTG
9p30	TNHQSAQPEGSARWAQAQTG
9p31	TNHQSAQWPTS YDAAQAQTG
9p35	TNHQSDGTSSYYDSAQAQTG
PHPN	TNHQSDGTLAVPFKAQAQTG
PHPB	TNHQSAQTLAVPFKAQAQTG
AAV9	TNHQSAQ-----AQAQTG

FIG. 49B



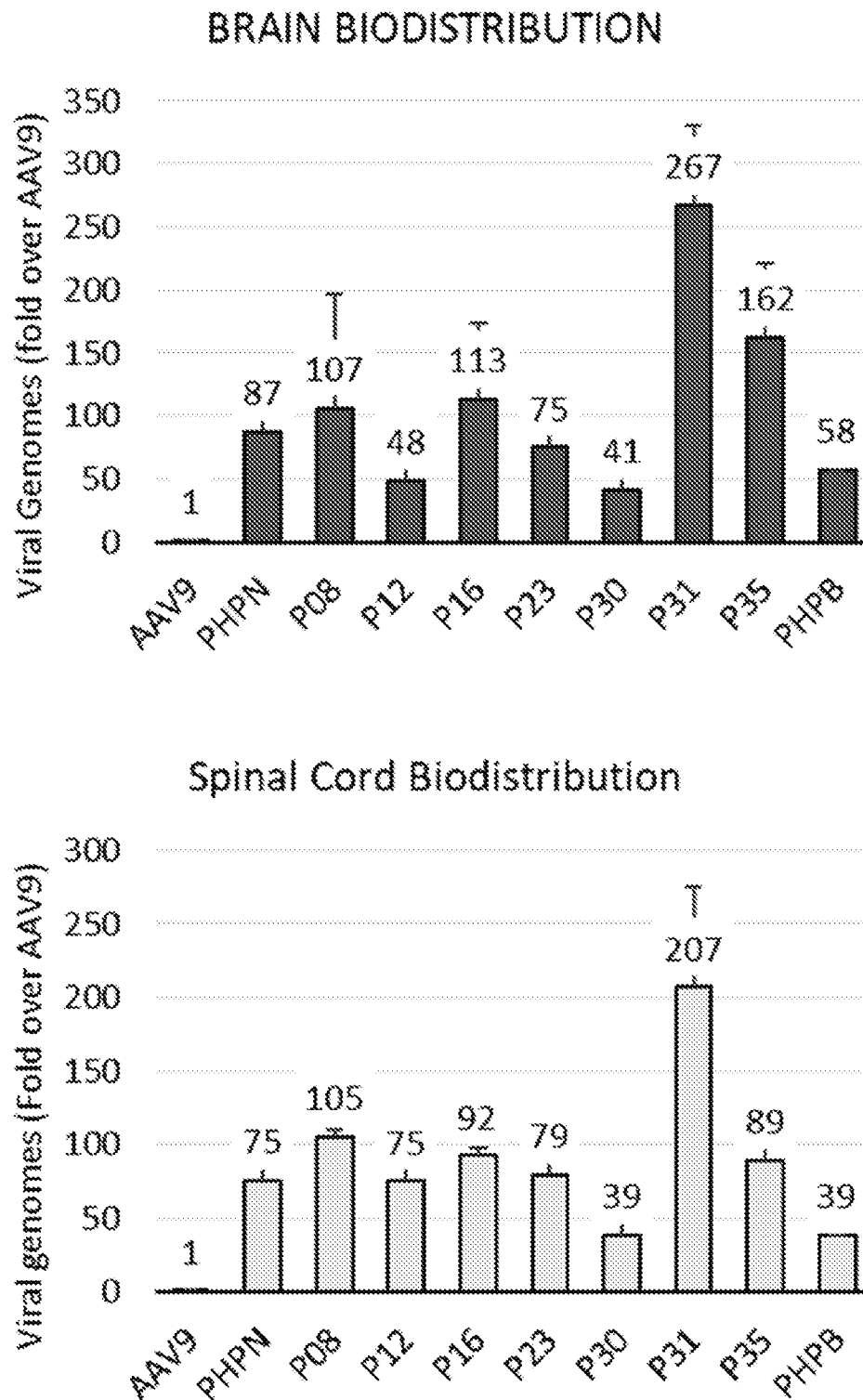
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FIG. 49C



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FIG. 49D

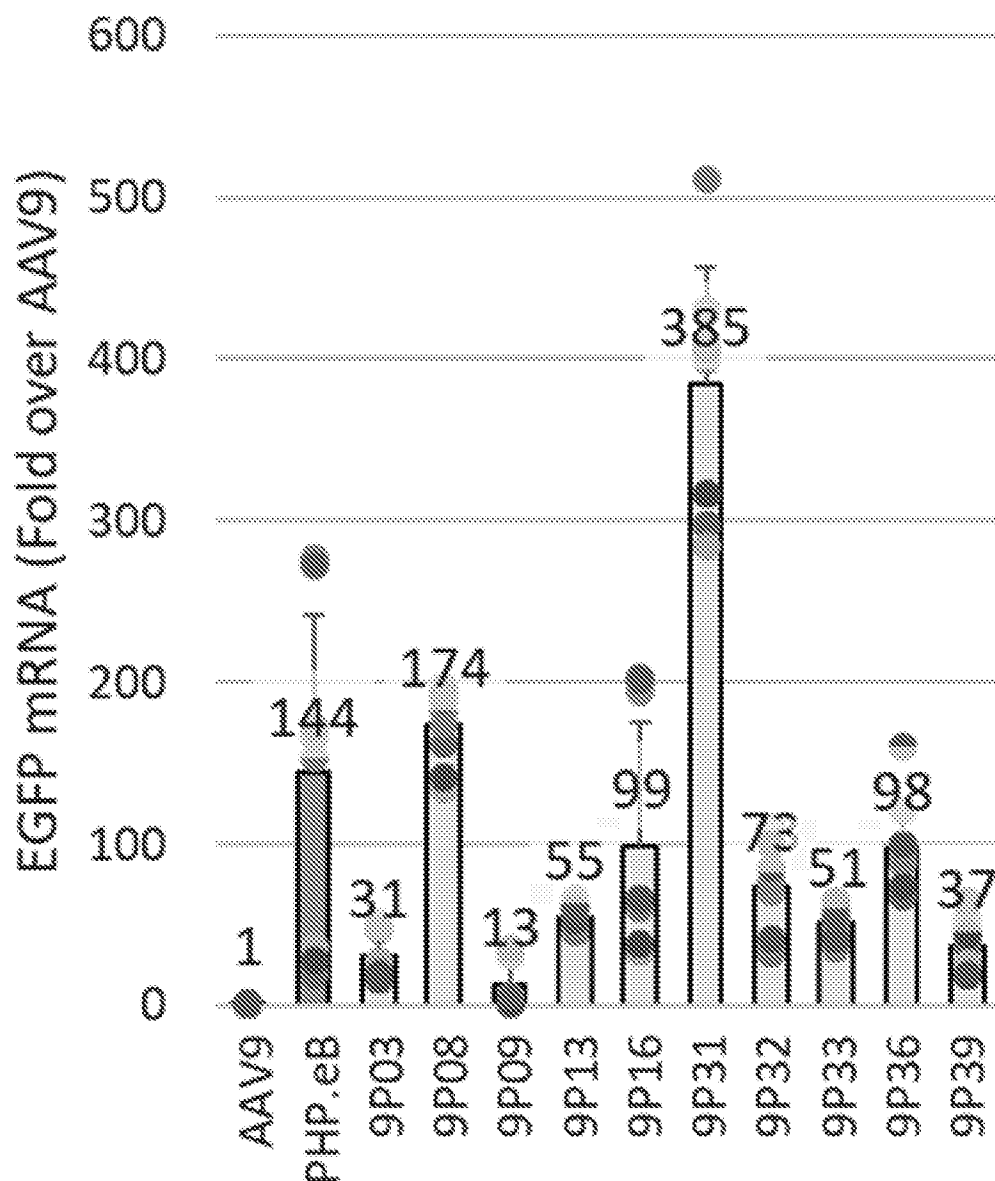


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FIG. 50A

Individual Capsid test
EGFP mRNA Expression

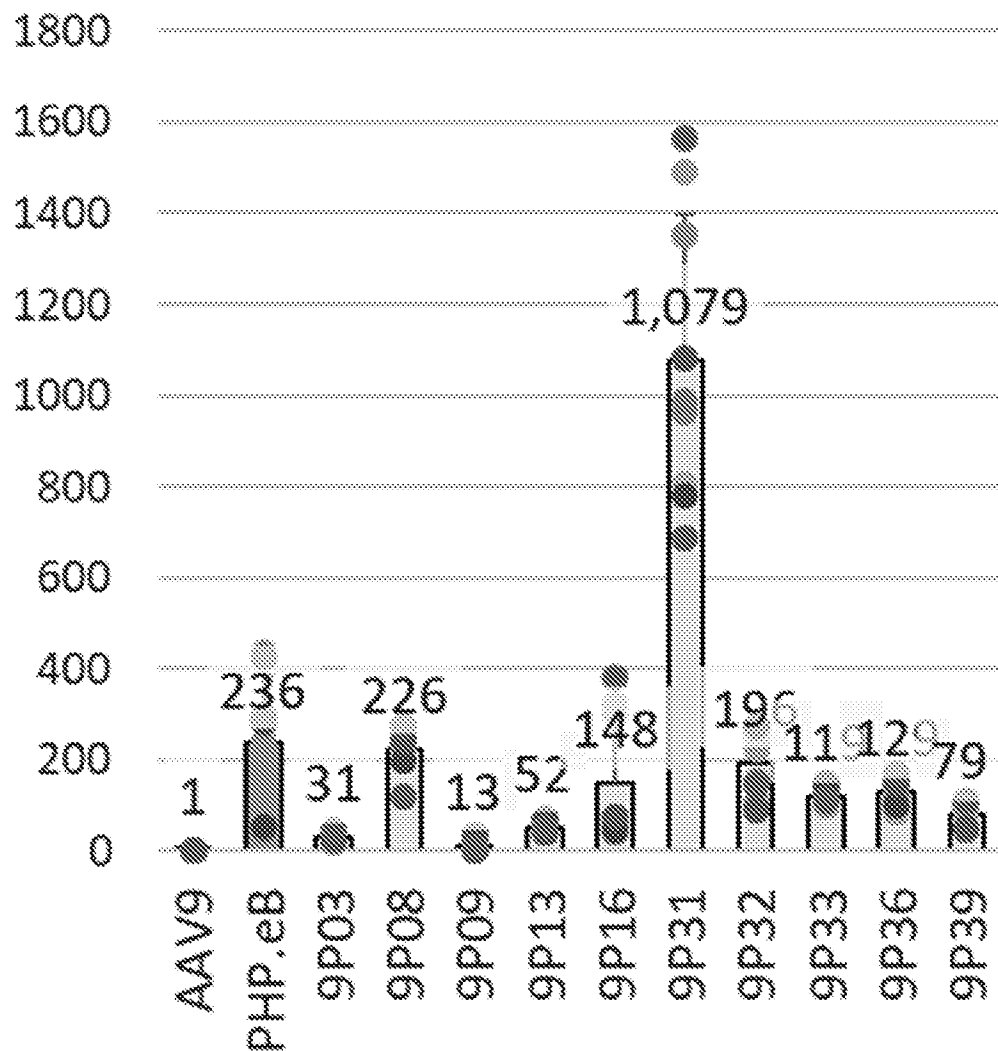
Brain



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FIG. 50B

Individual Capsid test
EGFP mRNA Expression
Spinal Cord



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FIG. 50C

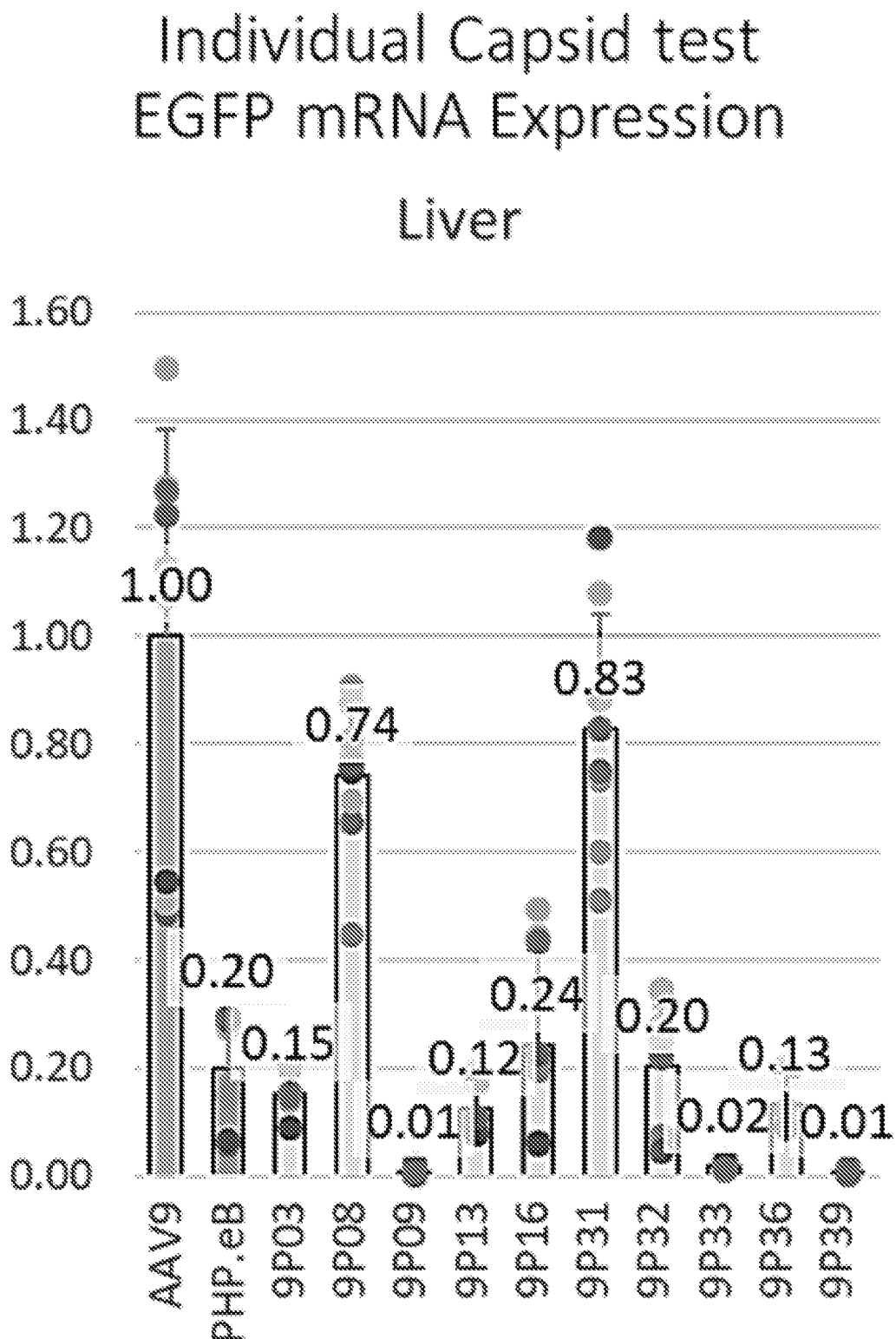


FIG. 51

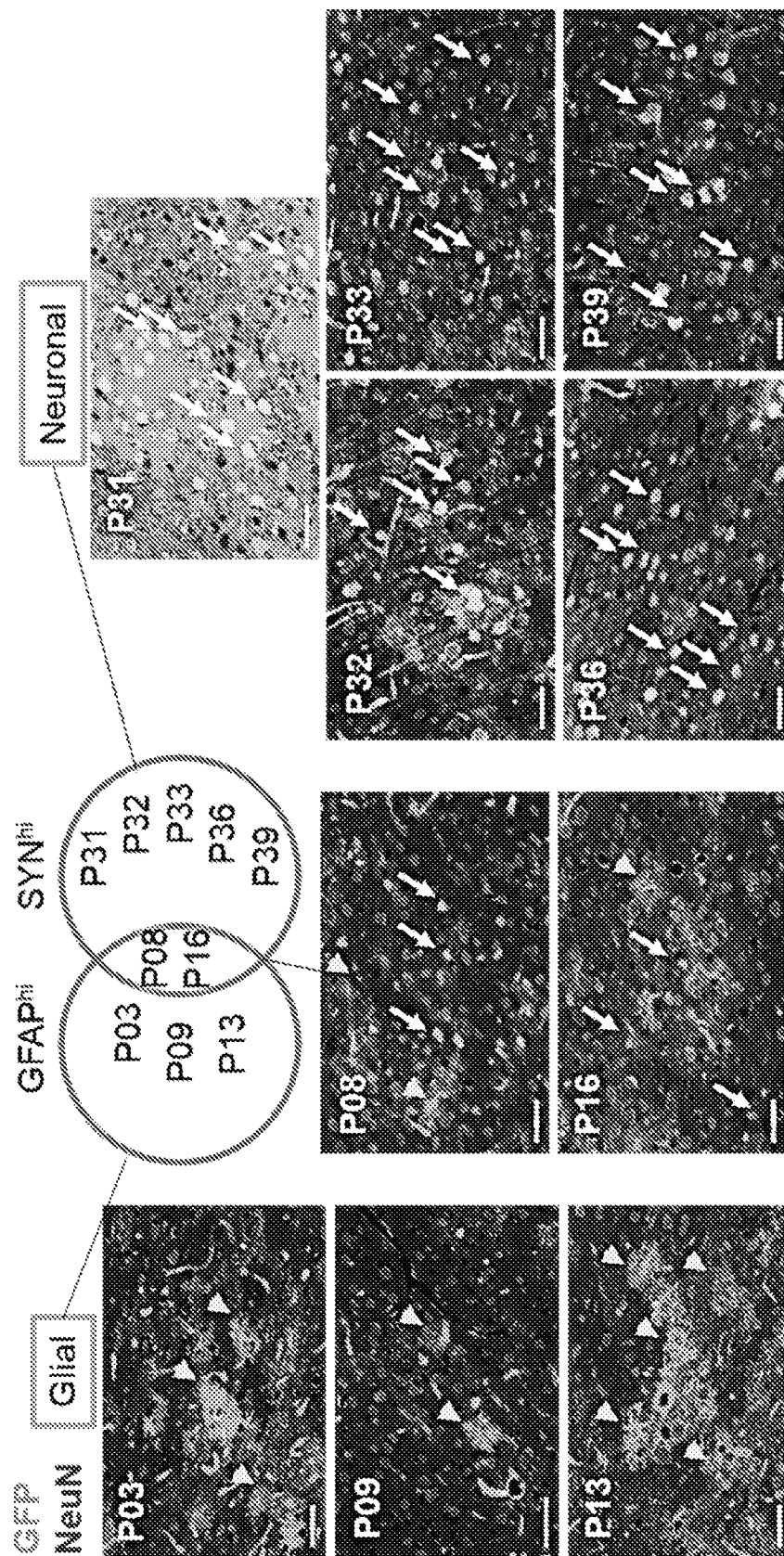


FIG. 52
Individual Capsid test – Whole Brain Transduction

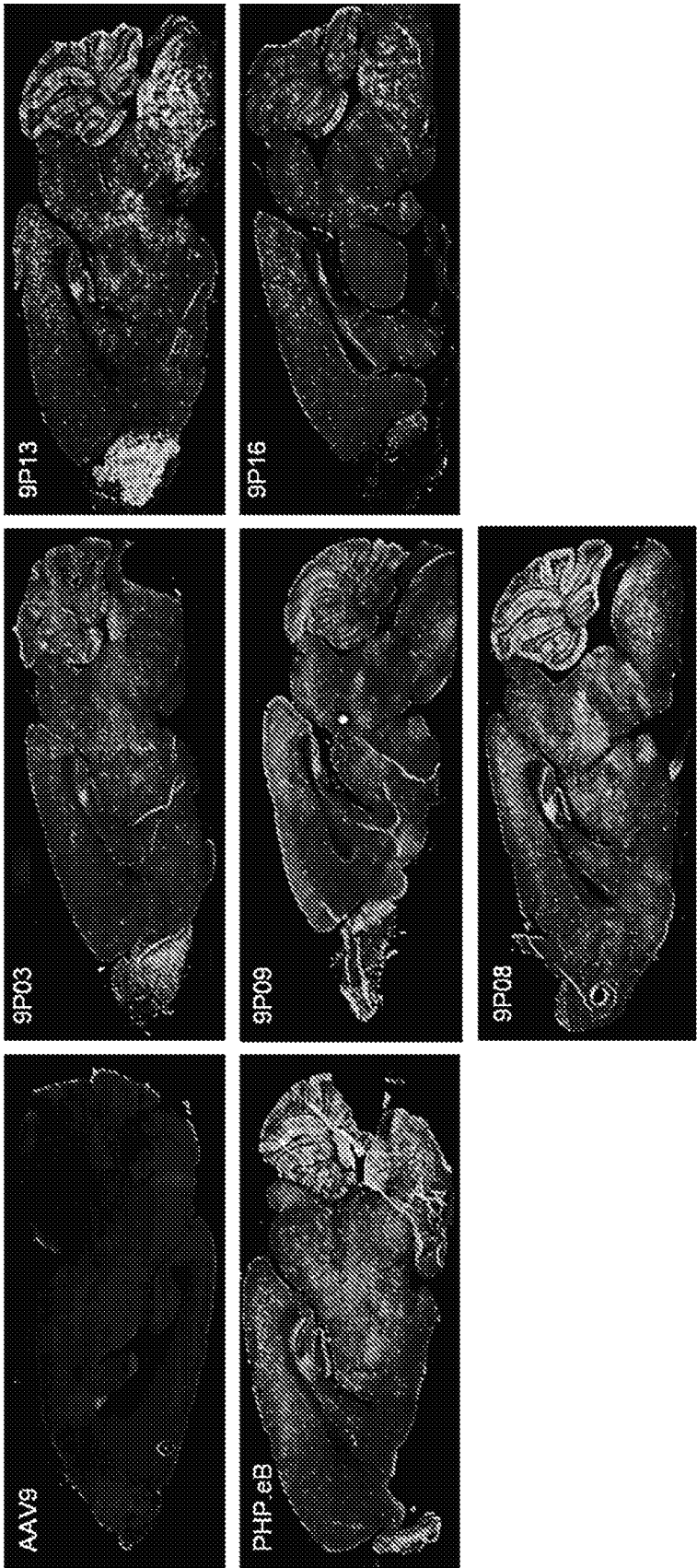
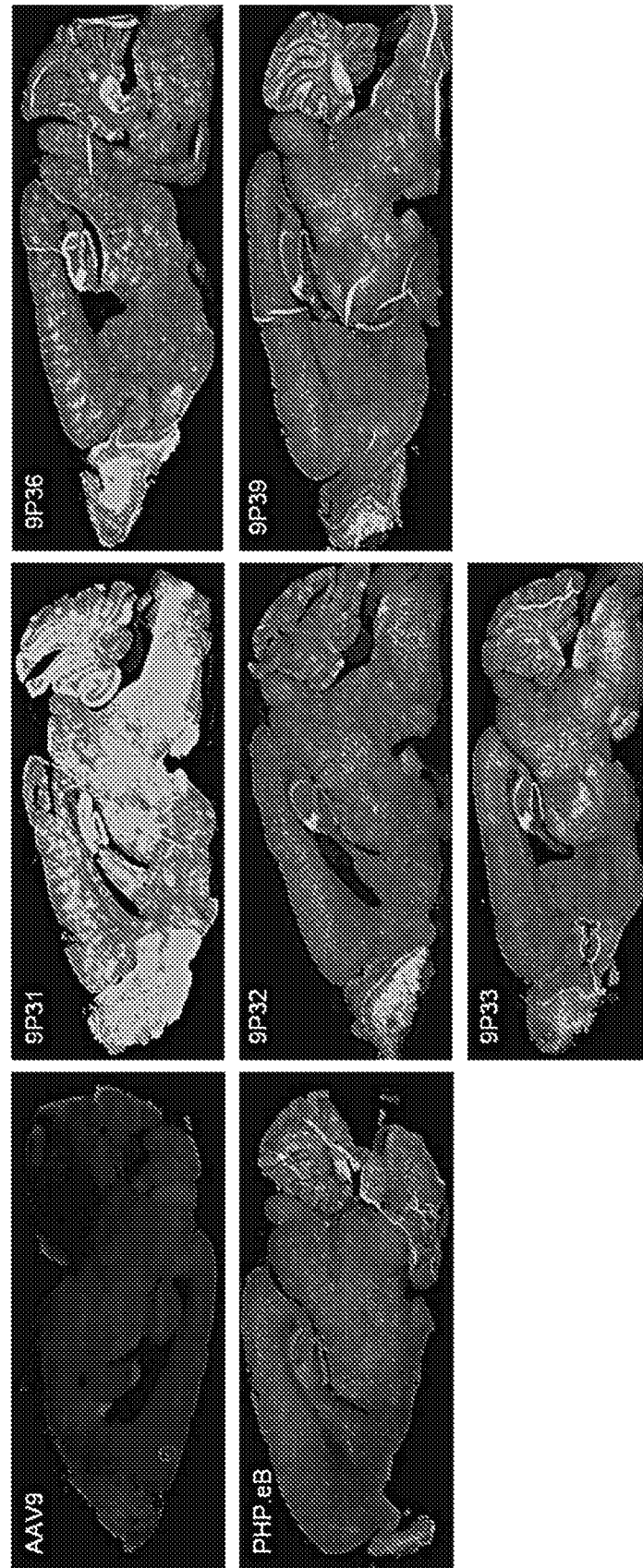


FIG. 53
Individual Capsid test – Whole Brain Transduction



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FIG. 54
Individual Capsid test – Cerebellum Transduction

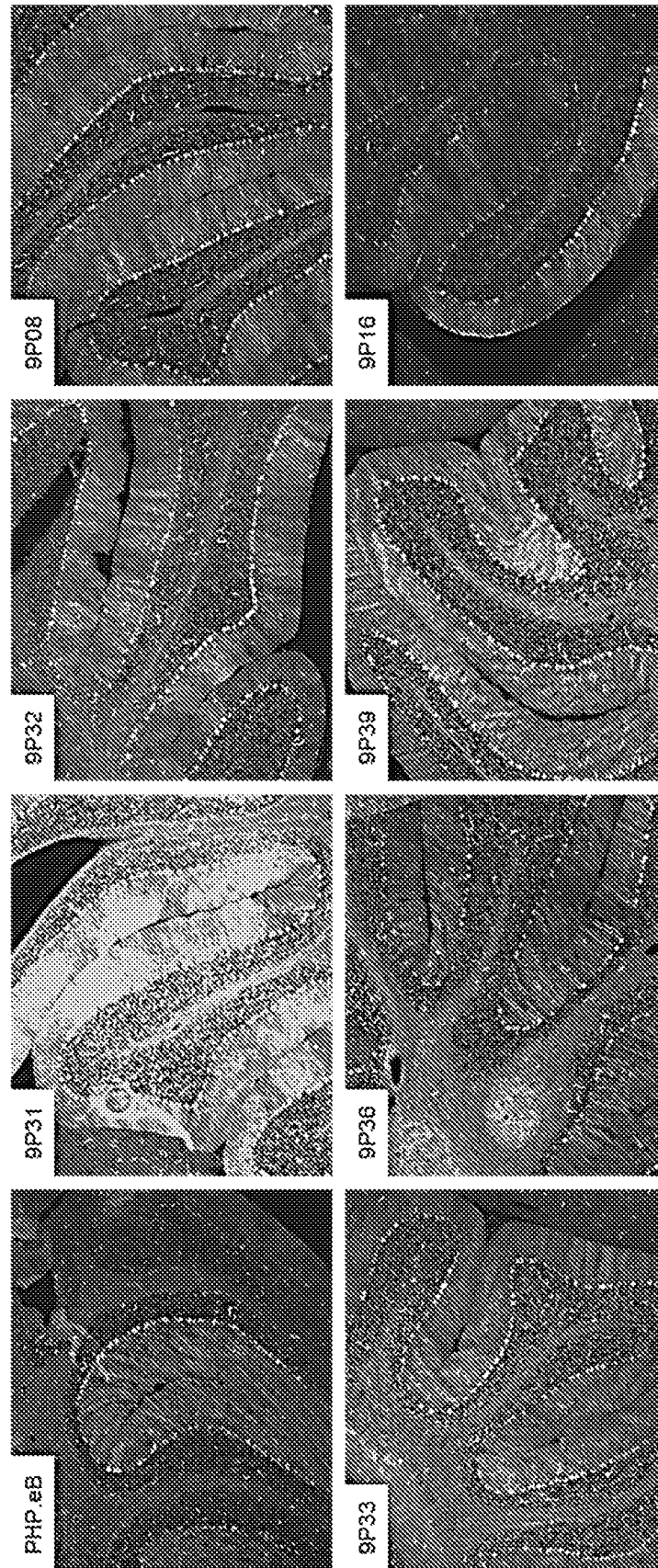


FIG. 55

Individual Capsid test — Cortex Transduction

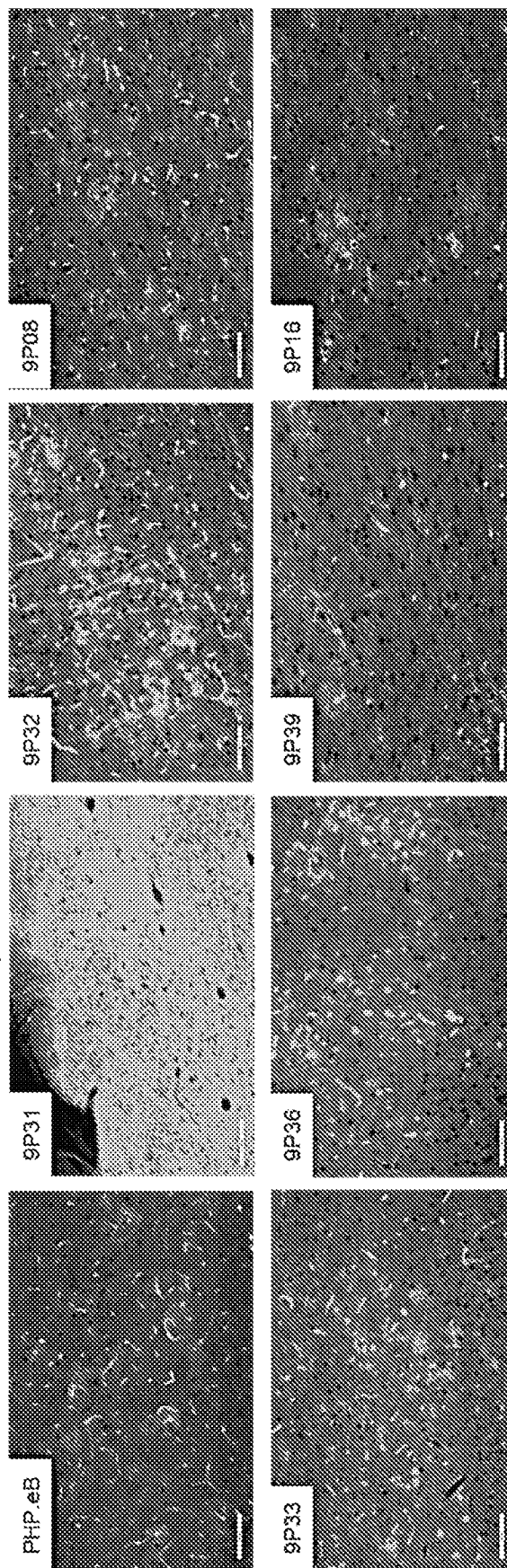
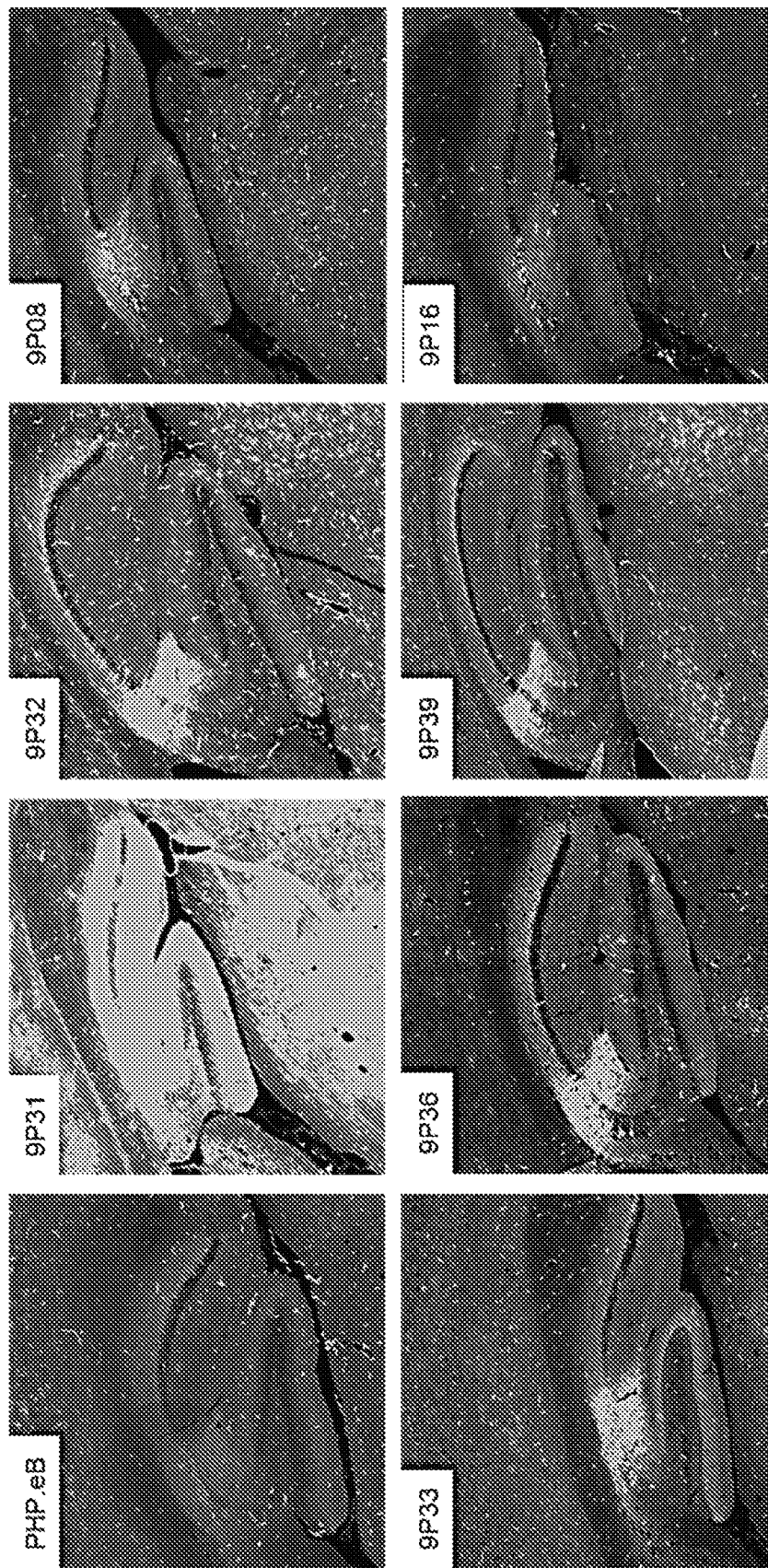


FIG. 56
Individual Capsid test – Hippocampus Transduction



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FIG. 57A

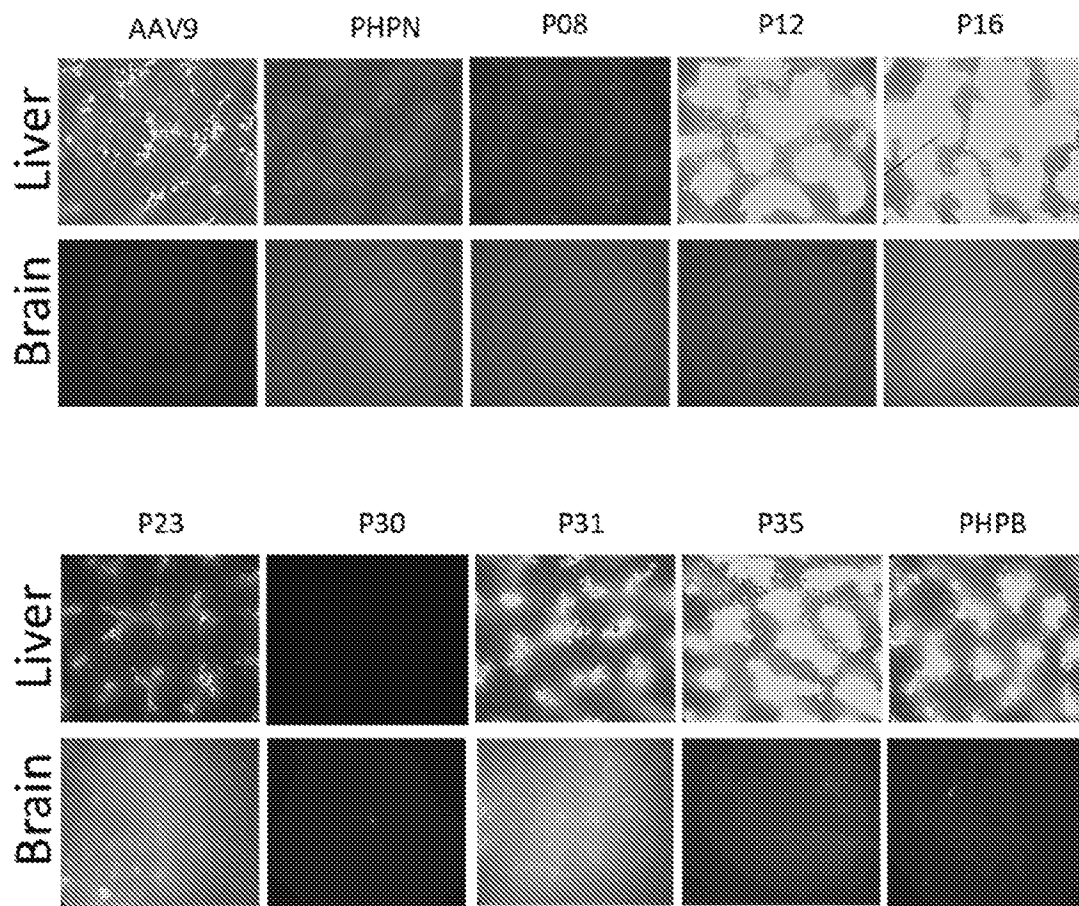


FIG. 57B
LIVER TRANSDUCTION (EGFP mRNA)

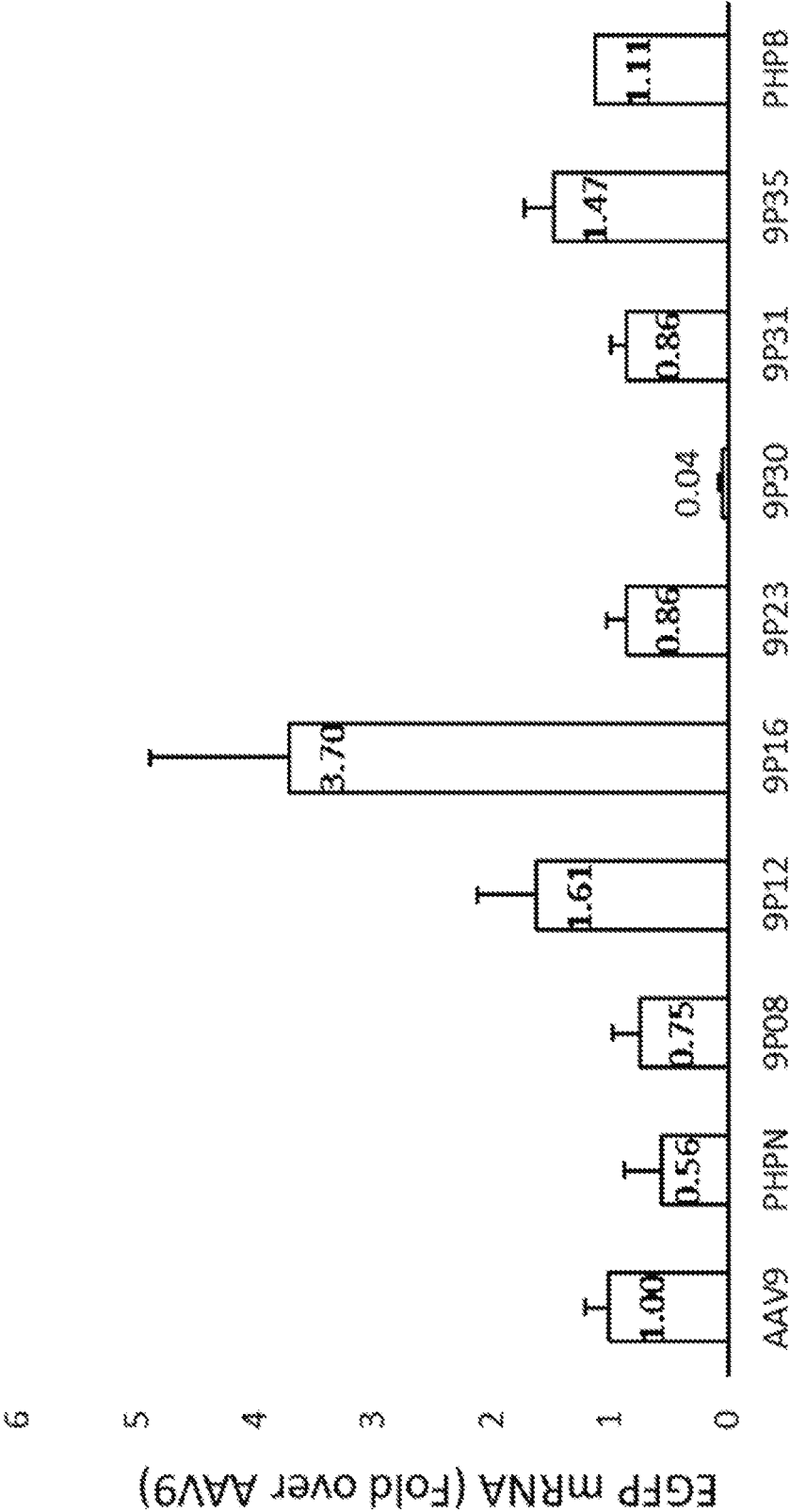


FIG. 58A

C57BL/6 BMVEC Binding

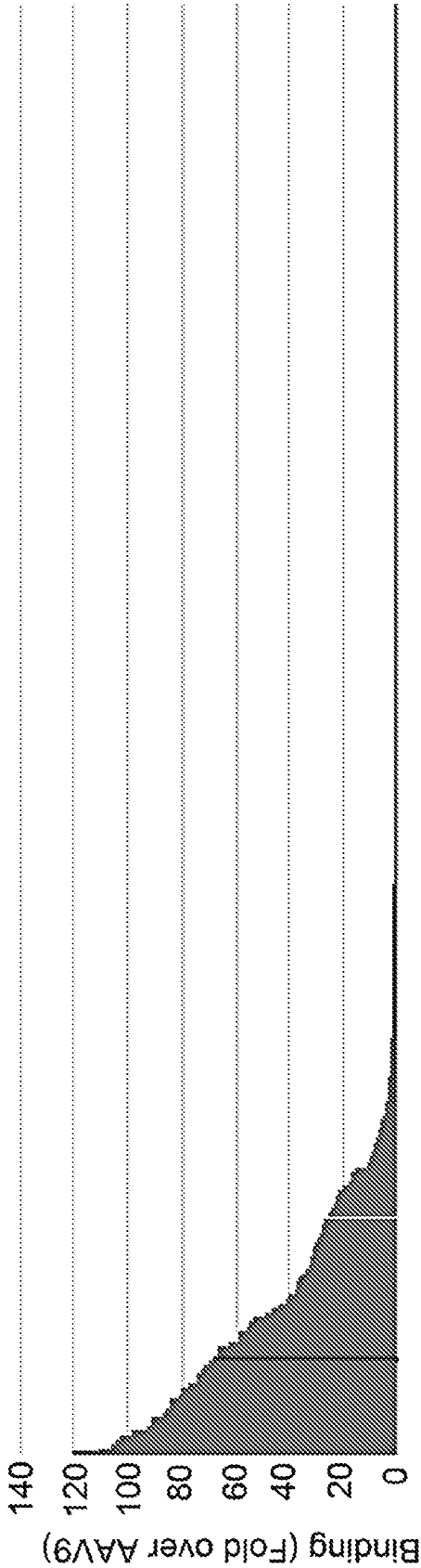


FIG. 58B

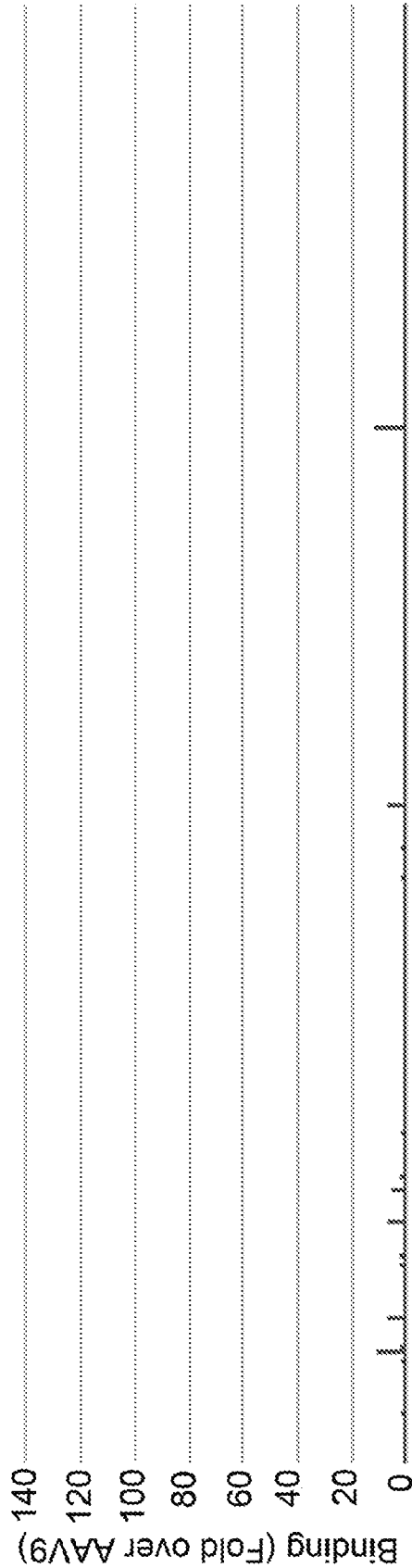


FIG. 59A

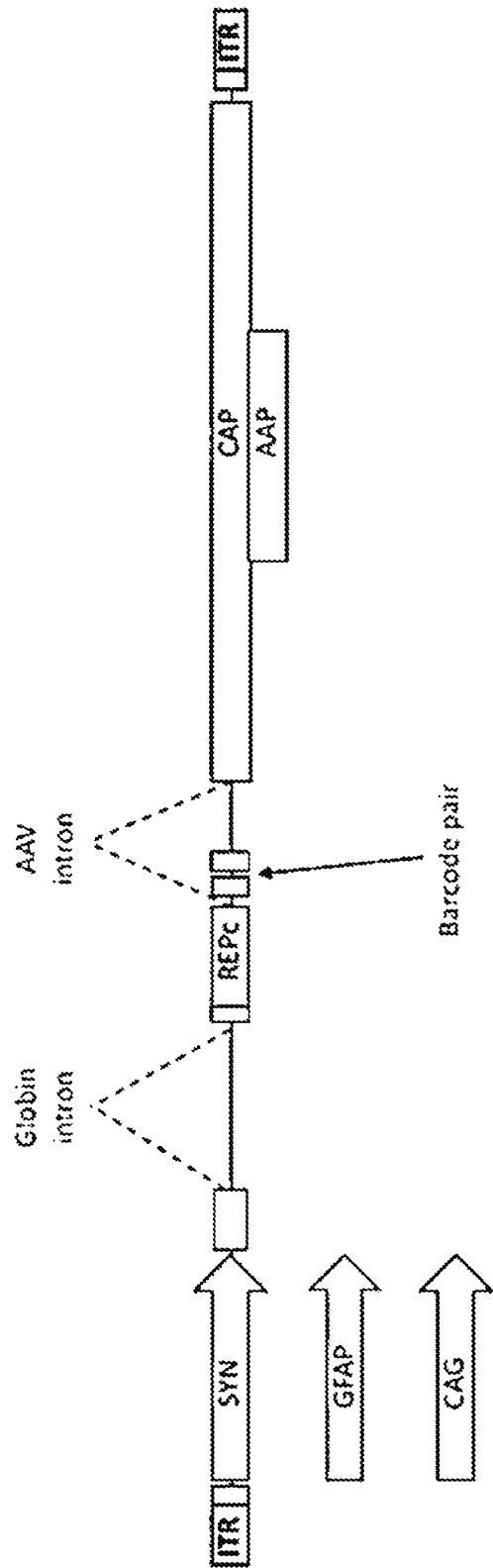


FIG. 59B

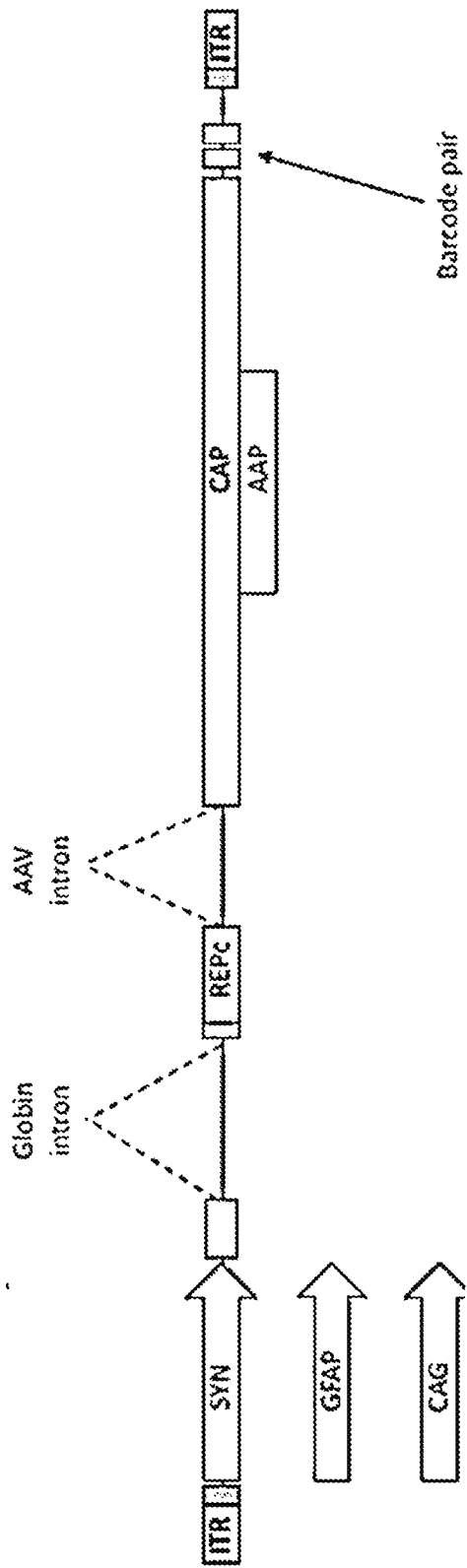
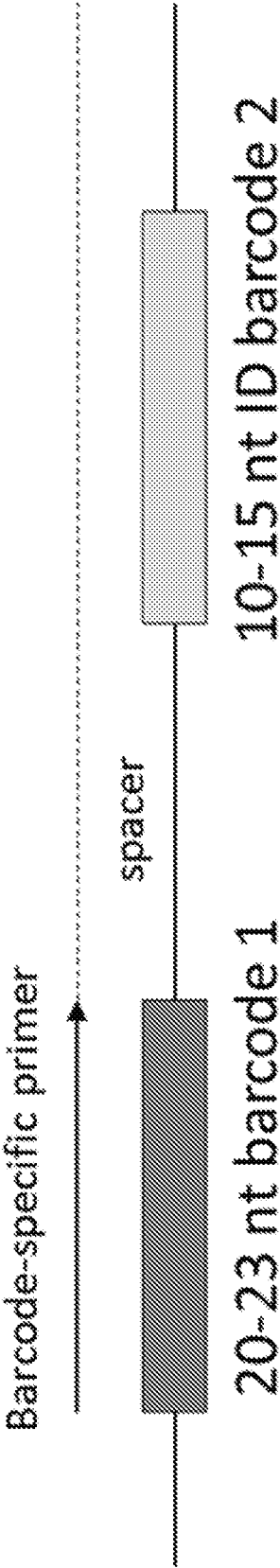


FIG. 59C



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FIG. 60B

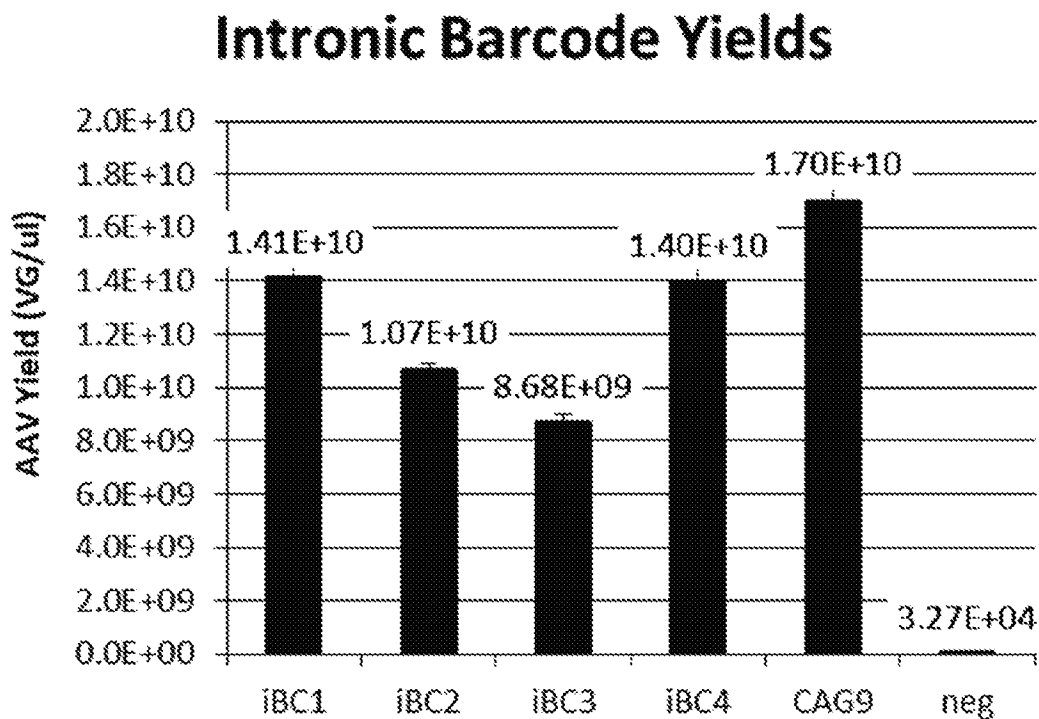
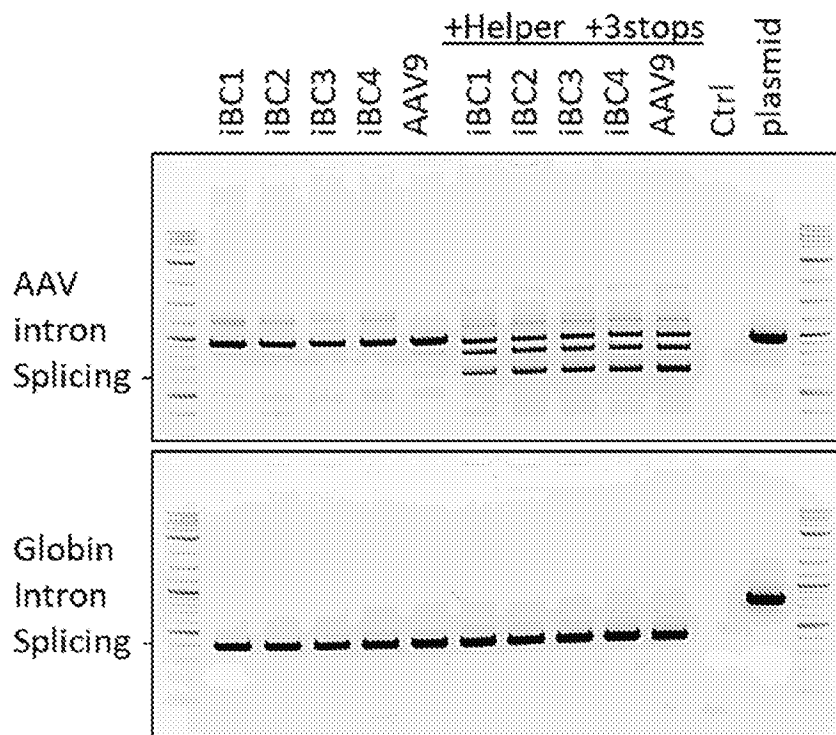


FIG. 60C



SEQUENCE LISTING

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<120> REDIRECTION OF TROPISM OF AAV CAPSIDS

<130> 2057.1060PCT

<140> PCT/US2019/XXXXXX

<141> 2019-10-02

<150> 62/839,883

<151> 2019-04-29

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<151> 2018-10-02

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capsid of hu.14/AAV9"

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Glu Gly Ile Arg Glu Trp Trp Ala Leu Lys Pro Gly Ala Pro Gln Pro
20 25 30

Lys Ala Asn Gln Gln His Gln Asp Asn Ala Arg Gly Leu Val Leu Pro
35 40 45

Gly Tyr Lys Tyr Leu Gly Pro Gly Asn Gly Leu Asp Lys Gly Glu Pro
50 55 60

Val Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
65 70 75 80

Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Lys Tyr Asn His Ala
85 90 95

Asp Ala Glu Phe Gln Glu Arg Leu Lys Glu Asp Thr Ser Phe Gly Gly
100 105 110

Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Leu Leu Glu Pro
115 120 125

Leu Gly Leu Val Glu Glu Ala Ala Lys Thr Ala Pro Gly Lys Lys Arg
130 135 140

Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ala Gly Ile Gly
145 150 155 160

Lys Ser Gly Ala Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr
165 170 175

Gly Asp Thr Glu Ser Val Pro Asp Pro Gln Pro Ile Gly Glu Pro Pro
180 185 190

Ala Ala Pro Ser Gly Val Gly Ser Leu Thr Met Ala Ser Gly Gly Gly
195 200 205

Ala Pro Val Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Ser Ser
210 215 220

Ser Gly Asn Trp His Cys Asp Ser Gln Trp Leu Gly Asp Arg Val Ile
225 230 235 240

Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu
245 250 255

Tyr Lys Gln Ile Ser Asn Ser Thr Ser Gly Gly Ser Ser Asn Asp Asn
260 265 270

Ala Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg
275 280 285

Phe His Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn
290 295 300

Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile
305 310 315 320

Gln Val Lys Glu Val Thr Asp Asn Asn Gly Val Lys Thr Ile Ala Asn
325 330 335

Asn Leu Thr Ser Thr Val Gln Val Phe Thr Asp Ser Asp Tyr Gln Leu
340 345 350

Pro Tyr Val Leu Gly Ser Ala His Glu Gly Cys Leu Pro Pro Phe Pro
355 360 365

Ala Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asp
370 375 380

Gly Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe
385 390 395 400

Pro Ser Gln Met Leu Arg Thr Gly Asn Asn Phe Gln Phe Ser Tyr Glu
405 410 415

Phe Glu Asn Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu
420 425 430

Asp Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Ser
435 440 445

Lys Thr Ile Asn Gly Ser Gly Gln Asn Gln Gln Thr Leu Lys Phe Ser
450 455 460

Val Ala Gly Pro Ser Asn Met Ala Val Gln Gly Arg Asn Tyr Ile Pro
465 470 475 480

Gly Pro Ser Tyr Arg Gln Gln Arg Val Ser Thr Thr Val Thr Gln Asn
485 490 495

Asn Asn Ser Glu Phe Ala Trp Pro Gly Ala Ser Ser Trp Ala Leu Asn
500 505 510

Gly Arg Asn Ser Leu Met Asn Pro Gly Pro Ala Met Ala Ser His Lys
515 520 525

Glu Gly Glu Asp Arg Phe Phe Pro Leu Ser Gly Ser Leu Ile Phe Gly
530 535 540

Lys Gln Gly Thr Gly Arg Asp Asn Val Asp Ala Asp Lys Val Met Ile
545 550 555 560

Thr Asn Glu Glu Glu Ile Lys Thr Thr Asn Pro Val Ala Thr Glu Ser
565 570 575

Tyr Gly Gln Val Ala Thr Asn His Gln Ser Ala Gln Ala Gln Ala Gln
580 585 590

Thr Gly Trp Val Gln Asn Gln Gly Ile Leu Pro Gly Met Val Trp Gln
595 600 605

Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His
610 615 620

Thr Asp Gly Asn Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Met
625 630 635 640

Lys His Pro Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala
645 650 655

Asp Pro Pro Thr Ala Phe Asn Lys Asp Lys Leu Asn Ser Phe Ile Thr
660 665 670

Gln Tyr Ser Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu Gln
675 680 685

Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu Ile Gln Tyr Thr Ser Asn
690 695 700

Tyr Tyr Lys Ser Asn Asn Val Glu Phe Ala Val Asn Thr Glu Gly Val
705 710 715 720

Tyr Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Asn Leu
725 730 735

<210> 3

<211> 736

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic
AAV9 Capsid Sequence"

<400> 3

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Glu Gly Ile Arg Glu Trp Trp Ala Leu Lys Pro Gly Ala Pro Gln Pro
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Lys Ala Asn Gln Gln His Gln Asp Asn Ala Arg Gly Leu Val Leu Pro
35 40 45

Gly Tyr Lys Tyr Leu Gly Pro Gly Asn Gly Leu Asp Lys Gly Glu Pro
50 55 60

Val Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
65 70 75 80

Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Lys Tyr Asn His Ala
85 90 95

Asp Ala Glu Phe Gln Glu Arg Leu Lys Glu Asp Thr Ser Phe Gly Gly
100 105 110

Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Leu Leu Glu Pro
115 120 125

Leu Gly Leu Val Glu Glu Ala Ala Lys Thr Ala Pro Gly Lys Lys Arg
130 135 140

Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ala Gly Ile Gly
145 150 155 160

Lys Ser Gly Ala Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr
165 170 175

Gly Asp Thr Glu Ser Val Pro Asp Pro Gln Pro Ile Gly Glu Pro Pro
180 185 190

Ala Ala Pro Ser Gly Val Gly Ser Leu Thr Met Ala Ser Gly Gly Gly
195 200 205

Ala Pro Val Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Ser Ser
210 215 220

Ser Gly Asn Trp His Cys Asp Ser Gln Trp Leu Gly Asp Arg Val Ile
225 230 235 240

Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu
245 250 255

Tyr Lys Gln Ile Ser Asn Ser Thr Ser Gly Gly Ser Ser Asn Asp Asn

260

265

270

Ala Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg
 275 280 285

Phe His Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn
 290 295 300

Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile
 305 310 315 320

Gln Val Lys Glu Val Thr Asp Asn Asn Gly Val Lys Thr Ile Ala Asn
 325 330 335

Asn Leu Thr Ser Thr Val Gln Val Phe Thr Asp Ser Asp Tyr Gln Leu
 340 345 350

Pro Tyr Val Leu Gly Ser Ala His Glu Gly Cys Leu Pro Pro Phe Pro
 355 360 365

Ala Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asp
 370 375 380

Gly Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe
 385 390 395 400

Pro Ser Gln Met Leu Arg Thr Gly Asn Asn Phe Gln Phe Ser Tyr Glu
 405 410 415

Phe Glu Asn Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu
 420 425 430

Asp Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Ser
 435 440 445

Arg Thr Ile Asn Gly Ser Gly Gln Asn Gln Gln Thr Leu Lys Phe Ser
 450 455 460

Val Ala Gly Pro Ser Asn Met Ala Val Gln Gly Arg Asn Tyr Ile Pro
 465 470 475 480

Gly Pro Ser Tyr Arg Gln Gln Arg Val Ser Thr Thr Val Thr Gln Asn
485 490 495

Asn Asn Ser Glu Phe Ala Trp Pro Gly Ala Ser Ser Trp Ala Leu Asn
500 505 510

Gly Arg Asn Ser Leu Met Asn Pro Gly Pro Ala Met Ala Ser His Lys
515 520 525

Glu Gly Glu Asp Arg Phe Phe Pro Leu Ser Gly Ser Leu Ile Phe Gly
530 535 540

Lys Gln Gly Thr Gly Arg Asp Asn Val Asp Ala Asp Lys Val Met Ile
545 550 555 560

Thr Asn Glu Glu Glu Ile Lys Thr Thr Asn Pro Val Ala Thr Glu Ser
565 570 575

Tyr Gly Gln Val Ala Thr Asn His Gln Ser Ala Gln Ala Gln Ala Gln
580 585 590

Thr Gly Trp Val Gln Asn Gln Gly Ile Leu Pro Gly Met Val Trp Gln
595 600 605

Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His
610 615 620

Thr Asp Gly Asn Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Met
625 630 635 640

Lys His Pro Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala
645 650 655

Asp Pro Pro Thr Ala Phe Asn Lys Asp Lys Leu Asn Ser Phe Ile Thr
660 665 670

Gln Tyr Ser Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu Gln
675 680 685

Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu Ile Gln Tyr Thr Ser Asn

690

695

700

Tyr Tyr Lys Ser Asn Asn Val Glu Phe Ala Val Asn Thr Glu Gly Val
 705 710 715 720

Tyr Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Asn Leu
 725 730 735

<210> 4

<211> 2470

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic
 polynucleotide"

<400> 4

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<211> 3681
<212> DNA
<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

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<210> 6

<211> 3755

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

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3755

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<211> 3755

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<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic
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<211> 3710

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

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<211> 3852

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

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<211> 4425

<212> DNA

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<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 10

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<211> 4480

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<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

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<212> DNA

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<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

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cctagtgatg gagttggcca ctccctctct gcgcgctcgc tcgctcactg aggccgggcg	4260
accaaaggtc gcccgacgcc cgggctttgc ccgggcggcc tcagtgagcg agcgagcgcg	4320
cagagaggga gtggccaa	4338

<210> 13

<211> 20

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 13

gtgccaagag tgacctcctg

20

<210> 14

<211> 444

<212> DNA

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 14
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gagagggacg tgtacctcca aggacccatc tgggccaaga tcccagagac gggggcgcac 120
tttcaccct ctccggctat gggcggattc ggactcaaac acccaccgcc catgatgctc 180
atcaagaaca cgcctgtgcc cggaaatatc accagcttct cggacgtgcc cgtcagcagc 240
ttcatcacc agtacgcac cgggcaggtc accgtggaga tggagtggga gctcaagaag 300
gaaaactcca agaggtggaa cccagagatc cagtacacaa acaactacaa cgacccccag 360
tttgtggact ttgccccgga cagcaccggg gaatacagaa ccaccagacc tatcggaacc 420
cgatacctta cccgaccct ttaa 444

<210> 15
<211> 440
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 15
accggagatg tgcatgttat gggagcctta cctggaatgg tgtggcaaga caggacgtc 60
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cctctcatgg gcggctttgg acttaagcac ccgcctcctc agatcctcat caaaaacacg 180
cctgttcctg cgaatcctcc ggcagagttt tcggctacaa agtttgcttc attcatcacc 240
cagtattcca caggacaagt gagcgtggag attgaatggg agctgcagaa agaaaacagc 300
aaacgctgga atcccgaagt gcaatatata tctaactatg caaaatctgc caacgttgat 360
ttcactgtgg acaacaatgg actttatact gagcctcgcc ccattggcac ccgttacctc 420
acccgtcccc tgtaatcgat 440

<210> 16
<211> 447
<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 16

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gacagagatg tgtaccttca ggggcccata tgggcaaaga ttccacacac ggacggacat	120
tttcaccctt ctcccctcat ggggtggattc ggacttaaac accctccgcc tcagatcctg	180
atcaagaaca cgcctgtacc tgcggaccct ccgaccacct tcaaccagtc aaagctgaac	240
tctttcatca cccagtattc tactggccaa gtcagcgtgg agatcgagtg ggagctgcag	300
aaggaaaaca gcaagcgctg gaaccccgag atccagtaca cttccaacta ctacaaatct	360
acaagtgtgg actttgctgt taatacagaa ggcgtgtact ctgaaccccg cccattggc	420
accggttacc tcacccgtaa tctgtaa	447

<210> 17

<211> 447

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 17

gcacaggcgc agaccggctg ggttcaaaac caaggaatac ttccgggtat ggtttggcag	60
gacagagatg tgtacctgca aggaccatt tgggcaaaaa ttctcacac ggacggcaac	120
tttcaccctt ctccgctgat gggagggttt ggaatgaagc acccgctcc tcagatcctc	180
atcaaaaaca cacctgtacc tgccgatact ccaacggcct tcaacaagga caagctgaac	240
tctttcatca cccagtattc tactggccaa gtcagcgtgg agatcgagtg ggagctgcag	300
aaggaaaaca gcaagcggctg gaacccggag atccagtaca cttccaacta ttacaagtct	360
aataatgttg aatttgctgt taatactgaa ggtgtatata gtgaaccccg cccattggc	420
accagatacc tgactcgtaa tctgtaa	447

<210> 18

<211> 4314
<212> DNA
<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 18

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gtataatggg caattgtgtg ctgatacagc	
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ggcagtgagc gcaacgcaat taatgtgagt	
tagctcactc attaggcacc ccaggcttta	180
cactttatgc ttccggctcg tatgttgtgt	
ggaattgtga gcggataaca atttcacaca	240
ggaaacagct atgaccatga ttacgccaga	
tttaattaag gccttaatta ggctagcttg	300
gccactccct ctctgcgcgc tcgctcgctc	
actgaggccg ggcgaccaa ggtcgcccga	360
cgcccgggct ttgcccgggc ggcctcagtg	
agcgagcgag cgcgagaga gggagtggcc	420
aactccatca ctaggggttc ctggaggggt	
ggagtctga cgatatccat gcgtcgacat	480
aacgcgttag tatctgcaga gggccctgcg	
tatgagtgca agtgggtttt aggaccagga	540
tgaggcgggg tgggggtgcc tacctgacga	
ccgaccccga cccactggac aagcacccaa	600
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cagagagggg gaggggaaac aggatgcggc	660
gaggcgcgtg cgactgcca gcttcagcac	
cgcgagcagt gccttcgccc ccgcctggcg	720
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gaccccctgc cccaagtcgc agccaagctt	
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aacgcggatt ccccgtgcca agagtgcgt	1200
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aaaaaatgct ttcttctttt aatatacttt	1260
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aatctctttc tttcagggca ataatactac	1320
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agaataacag tgataatttc tgggttaagg caatagcaat atttctgcat ataaatattt	1380
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aaaaccctgg cgttaccaa cttaatcgcc ttgcagcaca tccccctttc gccagctgta	4260
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<210> 19

<211> 4456

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 19

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tagctcactc attaggcacc ccaggcttta	180
cactttatgc ttccggctcg tatgttgtgt	
ggaattgtga gcggataaca atttcacaca	240
ggaaacagct atgaccatga ttacgccaga	
tttaattaag gccttaatta ggctagcttg	300
gccactccct ctctgcgcgc tcgctcgctc	
actgaggccg ggcgaccaa ggtcgcccga	360
cgcccgggct ttgcccgggc ggccctcagt	
agcgagcgag cgcgagaga gggagtggcc	420
aactccatca ctagggggtt ctggaggggt	
ggagtctgta cgatatccat gcgtcgacat	480
aacgcgtgat ctaacatatc ctggtgtgga	
gtagcggacg ctgctatgac agaggctcgg	540
gggcctgagc tggctctgtg agctggggag	
gaggcagaca gccaggcctt gtctgcaagc	600
agacctggca gcattgggct ggccgcccc	
cagggcctcc tcttcatgcc cagtgaatga	660
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cattgagcag ggggcttgca ttgcaccca	780
gcctgacagc ctggcatctt gggataaaag	
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ctctattcag cctgtgcccc ggaaagggga	900
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ggcagggggg gagaggaggg ctgtctgctt	960
cccagaagtc caaggacaca aatgggtgag	
gggagagctc tccccatagc tgggctgcgg	1020
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gggtgttgcc aggggcaccc gggcatcgcc	1080
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cgcggggatc ctctagaagc ttcgtttagt	1200
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ctattgtgtg ctgata	4456

<210> 20

<211> 4283

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 20

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<210> 21

<211> 4426

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 21

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<210> 22

<211> 4313

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 22

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<210> 23

<211> 4456

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

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<211> 4319

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<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

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<210> 25

<211> 4462

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 25

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<220>
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 <223> /note="Description of Artificial Sequence: Synthetic
 oligonucleotide"

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<210> 27
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<222> (1)..(51)

<220>

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<222> (16)..(17)

<223> a, c, t, g, unknown or other

<220>

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<222> (19)..(20)

<223> a, c, t, g, unknown or other

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<222> (22)..(23)

<223> a, c, t, g, unknown or other

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<222> (25)..(26)

<223> a, c, t, g, unknown or other

<220>

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<222> (28)..(29)

<223> a, c, t, g, unknown or other

<220>

<221> modified_base

<222> (31)..(32)

<223> a, c, t, g, unknown or other

<220>

<221> modified_base

<222> (34)..(35)

<223> a, c, t, g, unknown or other

<400> 27

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48

acc

Thr

51

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<220>

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<220>

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<222> (6)..(12)

<223> Any naturally occurring amino acid

<400> 28

Leu	Gln	Ser	Ser	Ser	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Thr	Asp	Pro	Ala
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Thr

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<211> 51

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Asn Gln Ser Ser Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Thr Ala Pro Ala
1 5 10 15

acc 51
Thr

<210> 30
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1 5 10 15

Thr

<210> 31
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<400> 32
Leu Gln Gln Gly Asn Xaa Xaa Xaa Xaa Xaa Xaa Xaa Thr Gln Ala Ala
1 5 10 15

Thr

<210> 33
<211> 30
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<222> (1)..(30)

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His Gln Ser Ala Gln Ala Gln Ala Gln Thr
1 5 10

<210> 34
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His Gln Ser Ala Gln Ala Gln Ala Gln Thr
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<210> 35

<211> 51

<212> DNA

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<220>

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<222> (1)..(51)

<400> 35

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His Gln Ser Asp Gly Thr Leu Ala Val Pro Phe Lys Ala Gln Ala Gln
1 5 10 15

acc

51

Thr

<210> 36

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<400> 36

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Thr

<210> 37

<211> 51

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<223> a, c, t, g, unknown or other

<400> 37
cac cag agt gcc caa nnk nnk nnk nnk nnk nnk gca cag gcg cag 48
His Gln Ser Ala Gln Xaa Xaa Xaa Xaa Xaa Xaa Xaa Ala Gln Ala Gln
1 5 10 15

acc 51

Thr

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1 5 10 15

Thr

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<400> 39
cac cag agt gat ggg nnk nnk nnk nnk nnk nnk gca cag gcg cag 48
His Gln Ser Asp Gly Xaa Xaa Xaa Xaa Xaa Xaa Xaa Ala Gln Ala Gln
1 5 10 15

acc 51
Thr

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1 5 10 15

Thr

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<400> 41
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1	5	10	15	
acc				51
Thr				

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1				5				10					15		

Thr

<210> 43
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<210> 44
<211> 45
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gtggcagtca atctccagag tgtacatcga ttgttaatca ataaa 45

<210> 45
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
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oligonucleotide"

<400> 45
tctaccaacc tccagcaagg tgtacatcga ttgttaatca ataaa 45

<210> 46
<211> 45
<212> DNA
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<210> 47
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21

<210> 48
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<223> a, c, t, g, unknown or other

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Gln Val Ala Thr Asn His Gln Ser Ala Gln Xaa Xaa Xaa Xaa Xaa Xaa
1 5 10 15

nnk gca cag gcg cag acc ggc tg 71
Xaa Ala Gln Ala Gln Thr Gly
20

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Xaa Ala Gln Ala Gln Thr Gly
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<210> 50

<211> 69

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 <223> a, c, t, g, unknown or other

<400> 50
 cag gtc gct acc aat cat caa tcc gca cag nnk nnk nnk nnk nnk nnk 48
 Gln Val Ala Thr Asn His Gln Ser Ala Gln Xaa Xaa Xaa Xaa Xaa Xaa
 1 5 10 15
 nnk gct caa gca caa aca gga 69
 Xaa Ala Gln Ala Gln Thr Gly
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<210> 51
 <211> 24
 <212> DNA
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<220>
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<400> 51
 caagtggcca caaaccacca gagt 24

<210> 52
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<400> 52
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<210> 53
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 agtgcccaag cacaggcgca gacc 24

<210> 54
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agtgctcagg cacaggcgca gacc

24

<210> 55
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27

<210> 56
<211> 27
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gatgggactt tggcggtgcc ttttaag

27

<210> 57
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<400> 57

gcacaaacac tcgcagtccc attcaaa

27

<210> 58

<211> 27

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27

<210> 59

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<212> PRT

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Asp Gly Thr Ser Ser Tyr Tyr Asp Ser
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<210> 60

<211> 9

<212> PRT

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<400> 60

Ala Gln Pro Glu Gly Ser Ala Arg Trp
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<210> 61

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<210> 62

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<400> 62

Ala Gln Trp Pro Thr Ser Tyr Asp Ala
1 5

<210> 63

<211> 9

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<400> 63

Asp Gly Thr Ala Asp Lys Pro Phe Arg
1 5

<210> 64

<211> 9

<212> PRT

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<400> 64

Asp Gly Ser Ser Ser Tyr Tyr Asp Ala
1 5

<210> 65

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<400> 65
Asp Gly Thr Leu Ser Gln Pro Phe Arg
1 5

<210> 66
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<400> 66
Ala Gln Phe Pro Thr Asn Tyr Asp Ser
1 5

<210> 67
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<400> 67
Asp Gly Thr Ala Ile His Leu Ser Ser
1 5

<210> 68
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Asp Gly Thr Gly Gln Val Thr Gly Trp
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<210> 69

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<210> 70

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<210> 71

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<400> 71

Asp Gly Thr Leu Ala Val Pro Phe Lys
1 5

<210> 72

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1 5

<210> 73
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<400> 73
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<210> 74
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<210> 75
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1 5

<210> 77
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<210> 78
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<400> 78
Asp Gly Thr Ser Tyr Val Pro Pro Arg
1 5

<210> 79
<211> 9
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<400> 79

Asp Gly Thr Thr Phe Thr Pro Pro Arg
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<210> 80

<211> 9

<212> PRT

<213> Artificial Sequence

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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 80

Ala Gln Gly Ser Trp Asn Pro Pro Ala
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<210> 81

<211> 9

<212> PRT

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<400> 81

Asp Gly Thr Ser Phe Thr Pro Pro Lys
1 5

<210> 82

<211> 9

<212> PRT

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<400> 82

Ala Gln Gly Thr Trp Asn Pro Pro Ala
1 5

<210> 83

<211> 9
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<400> 83
Ala Gln Thr Thr Glu Lys Pro Trp Leu
1 5

<210> 84
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<400> 84
Ala Gln Asn Gly Asn Pro Gly Arg Trp
1 5

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<400> 86
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<210> 87
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<400> 89
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<210> 90
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<400> 90
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<210> 91
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<400> 91
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<210> 92
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<400> 92
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1 5

<210> 93
<211> 9
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<210> 168
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Ala Gln Thr Leu Ala Val Pro Phe Lys
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<210> 169
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<223> a, c, t, g, unknown or other

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<210> 174

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<223> /note="Description of Artificial Sequence: Synthetic
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Ala Gln Thr Gly
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Ala Gln Thr Gly
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Ala Gln Thr Gly
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Ala Gln Thr Gly
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<400> 183
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Ala Gln Thr Gly
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<210> 184
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<400> 184
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Ala Gln Thr Gly
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<400> 185

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Ala Gln Thr Gly
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Ala Gln Thr Gly
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<400> 187
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1 5 10 15

Ala Gln Thr Gly
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<210> 188
<211> 13
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<400> 188

Thr Asn His Gln Ser Ala Gln Ala Gln Ala Gln Thr Gly

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<210> 189

<211> 133

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cgggtgtcaaa gac 133

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$\langle 211 \rangle$ 107

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<223> a, c, t, g, unknown or other

<400> 190

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ctnswnswns wnswnswgtt taaaccttca ctcacggtgt caaagac 107

<210> 191

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cgggtgtcaaaa gac 133

<210> 194
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<210> 195
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<400> 195
Ala Gln Asp Gln Asn Pro Gly Arg Trp

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<210> 196

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<400> 196

Ala Gln Glu Val Pro Gly Tyr Arg Trp

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<210> 198

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<400> 198

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<400> 211

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<210> 212

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<400> 212

Ala Gln Leu Arg Gln Gly Tyr Ala Gln
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<210> 213

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<223> /note="Description of Artificial Sequence: Synthetic peptide"

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<223> /note="Description of Artificial Sequence: Synthetic peptide"

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<223> /note="Description of Artificial Sequence: Synthetic peptide"

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Ala Gln Ser Met Ser Arg Pro Phe Leu
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<400> 231

Ala Gln Ser Val Ala Lys Pro Phe Leu

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<223> /note="Description of Artificial Sequence: Synthetic peptide"

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Ala Gln Ser Val Ser Gln Pro Phe Arg

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<400> 233

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<400> 237
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Ala Gln Trp Glu Leu Ser Asn Gly Tyr
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Ala Gln Trp Glu Val Gln Ser Gly Phe

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<400> 726
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39

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<210> 885
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<400> 885
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<400> 886
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<210> 898
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<210> 899
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<400> 911
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<400> 1077
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<400> 1078
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<400> 1079
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<210> 1080
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<400> 1080
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<210> 1084
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<210> 1090
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<400> 1090
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<210> 1091
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<210> 1094
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<210> 1097
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<210> 1098
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<210> 1101
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<210> 1102
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<210> 1103
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<400> 1103
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<210> 1104
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 <400> 1104
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 <210> 1105
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 <400> 1105
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 <210> 1106
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 <400> 1106
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 <210> 1107
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 <400> 1107
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<212> DNA
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 <400> 1108
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<210> 1109
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 <400> 1109
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<210> 1110
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 <400> 1110
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<210> 1111
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 <400> 1111
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<210> 1112
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<220>
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<210> 1118
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<400> 1122
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<220>
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<210> 1125
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<210> 1126
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<220>
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<400> 1126
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<210> 1128
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<210> 1132
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<400> 1132
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<400> 1133
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<210> 1134
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<220>
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<400> 1134
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<210> 1135
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<212> DNA
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<210> 1136
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<210> 1137
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 <400> 1137
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<400> 1147
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<210> 1154
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<210> 1155
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<210> 1156
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<400> 1156
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<400> 1158
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<400> 1159
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<400> 1160
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<400> 1161
 gacggaacag gaaacacaag aggatgg 27

<210> 1162
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<212> DNA
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 <400> 1162
 gacggaacac acacaagaac aggatgg 27

<210> 1163
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 <400> 1163
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<210> 1164
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 <400> 1164
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<210> 1165
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<210> 1167
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<210> 1168
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<210> 1169
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<400> 1169
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<210> 1170
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oligonucleotide"

<400> 1170
gacggaacaa gctacgtccc accaaga

27

<210> 1171
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oligonucleotide"

<400> 1171
gcacaattcc caacaaacta cgacagc

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<210> 1172
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<400> 1172
gcacaaccag aaggaagcgc aagatgg

27

<210> 1173
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<400> 1173
gcacaatggc caacaagcta cgacgca 27

<210> 1174
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<400> 1174
gacggaacag caatccacct cagcagc 27

<210> 1175
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<400> 1175
gacggaacag gacaagtcac aggatgg 27

<210> 1176
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<220>
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<400> 1176
gacggaacaa tggacaaacc attcaga 27

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<400> 1177
gacggaacaa gcagctacta cgacagc 27

<210> 1178
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<400> 1178
gacggaagca gcagctacta cgacgca 27

<210> 1179
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<400> 1179
gacggaacag caagctacta cgacagc 27

<210> 1180
<211> 27
<212> DNA
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<223> /note="Description of Artificial Sequence: Synthetic
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<400> 1180
gacggaacag gaaacgtcac aggatgg 27

<210> 1181
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<220>
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<222> (9)..(9)
<223> /replace="Arg"

<220>
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<223> /note="Variant residues given in the sequence have no preference with respect to those in the annotations for variant positions"

<400> 1181
Asp Gly Thr Xaa Xaa Xaa Pro Phe Lys
1 5

<210> 1182
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
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<222> (4)..(6)
<223> Any amino acid

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<222> (9)..(9)
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<220>
<221> SITE
<222> (1)..(9)
<223> /note="Variant residues given in the sequence have no preference with respect to those in the annotations for variant positions"

<400> 1182
Asp Gly Thr Xaa Xaa Xaa Tyr Asp Ser
1 5

<210> 1183
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<220>
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<222> (4)..(7)
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<400> 1183
Asp Gly Thr Xaa Xaa Xaa Xaa Gly Trp
1 5

<210> 1184
<211> 9
<212> PRT
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1 5