COMPOSITIONS AND METHODS FOR REGULATING MAPT

RELATED APPLICATIONS

[0001] The application claims priority to U.S. Provisional Application No. 63/477,736 filed on December 29, 2022; the entire contents of which are hereby incorporated by reference in their entirety.

SEQUENCE LISTING

[0002] The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing file, entitled V2071-3010PCT_SL.xml, was created on December 13, 2023 and is 2,478,152 bytes in size. The information in electronic format of the Sequence Listing is incorporated herein by reference in its entirety.

FIELD OF THE DISCLOSURE

[0003] The present disclosure relates generally to compositions and methods for vectorized delivery of an agent, e.g., an RNA agent, that that inhibits a mutant, variant, or wild type human microtubule-associated protein tau (MAPT) gene, mRNA, and/or protein.

BACKGROUND

[0004] Tauopathies, which may also be referred to herein as tau-associated diseases, are a heterogeneous group of neurodegenerative diseases characterized by the dysfunction and/or aggregation of the microtubule-associated protein tau (MAPT) which may also be referred to as Tau herein, which is encoded by the MAPT gene. Tau is normally a very soluble protein known to associate with microtubules based on the extent of its phosphorylation. In tauopathies, tau becomes hyperphosphorylated, misfolds and aggregates as neurofibrillary tangles (NFT) of paired helical filaments (PHF), twisted ribbons or straight filaments. These NFT are largely considered indicative of impending neuronal cell degeneration which can contribute to widespread neuronal cell loss, leading to a variety of behavioral and cognitive deficits, and can also be fatal. Currently, very limited treatment options are available for tauopathies, often with only symptomatic relief and supportive therapies available. As such, there is a medical need for improved compositions and methods of prevention, treatment, and diagnosis for diseases associated with aberrant tau expression, including tauopathies and related neurodegenerative disorders.

SUMMARY

[0005] The present disclosure provides AAV particles encoding an agent for targeting MAPT, e.g., an RNA agent to modulate, e.g., inhibit, MAPT gene expression and/or MAPT protein production and methods of use thereof. In some embodiments, the agent for targeting MAPT, e.g., a MAPT gene, mRNA, or protein (e.g., a tau protein) is an RNA agent for targeting MAPT, e.g., a siRNA duplex for targeting MAPT. In some embodiments, the agent for targeting MAPT comprises a modulatory polynucleotide encoding a siRNA duplex for targeting MAPT. Methods for treating diseases associated MAPT expression, e.g., aberrant

expression, such as tauopathies, including but not limited to Alzheimer's disease (AD), frontotemporal dementia (FTD), and/or Dravet syndrome (DS) in a subject in need thereof.

[0006] Accordingly, in one aspect, the present disclosure provides a short interfering ribonucleic acid (siRNA) for inhibiting expression of microtubule-associated protein tau (MAPT) which comprises a sense strand sequence and an antisense strand sequence, wherein the antisense sequence is complementary to at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides comprising 0, 1, 2, or 3 mismatches of a MAPT sequence comprising the nucleotide sequence of SEQ ID NO: 5024 or a nucleotide sequence provided in Table 3 or 19. In some embodiments, the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from any one of the antisense strand sequences provided in Tables 3 4, 5, 9A, or 9B; and the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from any one of the sense strand sequences provided in Tables 3 4, 5, 9A, or 9B, wherein the sense strand sequence and the antisense strand sequence comprise a region of complementarity of at least 15 nucleotides. In some embodiments, the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, 21 contiguous nucleotides from any one of the antisense strand sequences provided in Tables 3 4, 5, 9A, or 9B; and the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, 21 contiguous nucleotides from any one of the sense strand sequences provided in Tables 3 4, 5, 9A, or 9B, wherein the sense strand sequence and the antisense strand sequence comprise a region of complementarity of at least 15 nucleotides. In some embodiments, the antisense strand sequence comprises nucleotide sequence of any one of the antisense strand sequences provided in Tables 3 4, 5, 9A, or 9B; and the sense strand sequence comprises the nucleotide sequence of any one of the sense strand sequences provided in Tables 3 4, 5, 9A, or 9B, wherein the sense strand sequence and the antisense strand sequence comprise a region of complementarity of at least 15 nucleotides.

[0007] In yet another aspect, the present disclosure provides a short interfering ribonucleic acid (siRNA) for inhibiting expression of microtubule-associated protein tau (MAPT) which comprises a sense strand sequence and an antisense strand sequence, wherein: (i) the antisense strand sequence comprises at least 20 or 21 contiguous nucleotides of any one of SEQ ID NOs: 4908, 4920, 4924, 5057, 4916, 4912, 5080, 5104, or 5128; and (ii) the sense strand sequence comprises at least 20 or 21 contiguous nucleotides of any one of SEQ ID NOs: 4906, 4926, 4946, 4966, 4986, 5006, 4918, 4938, 4958, 4978, 4998, 4922, 4942, 4962, 4982, 5002, 5022, 5054, 5060, 5064, 5066, 5070, 5074, 4914, 4934, 4954, 4974, 4994, 5014, 4910, 4930, 4950, 4970, 4990, 5010, 5077, 5084, 5088, 5092, 5096, 5098, 5101, 5108, 5112, 5116, 5120, 5122, 5125, 5132, 5136, 5140, 5144, or 5146; wherein the sense strand sequence and the antisense strand sequence comprise a region of complementarity of at least 15 nucleotides.

[0008] In yet another aspect, the present disclosure provides an adeno-associated virus (AAV) viral genome comprising a nucleotide sequence positioned between two inverted terminal repeats (ITRs), wherein

the nucleotide sequence encodes an siRNA for inhibiting MAPT, wherein the siRNA comprises a sense strand sequence and an antisense strand sequence, wherein: (i) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides of any one of SEQ ID NOs: 4908, 4920, 4924, 5057, 4916, 4912, 5080, 5104, or 5128; and (ii) the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides of any one of SEQ ID NOs: 4906, 4926, 4946, 4966, 4986, 5006, 4918, 4938, 4958, 4978, 4998, 4922, 4942, 4962, 4982, 5002, 5022, 5054, 5060, 5064, 5066, 5070, 5074, 4914, 4934, 4954, 4974, 4994, 5014, 4910, 4930, 4950, 4970, 4990, 5010, 5077, 5084, 5088, 5092, 5096, 5098, 5101, 5108, 5112, 5116, 5120, 5122, 5125, 5132, 5136, 5140, 5144, or 5146; wherein the sense strand sequence and the antisense strand sequence comprise a region of complementarity of at least 15 nucleotides.

[0009] In another aspect, the present disclosure provides a modulatory polynucleotide encoding an siRNA for targeting MAPT described herein. In some embodiments, the modulatory polynucleotide further comprises a 5' flanking region, a loop region, and/or a 3' flanking region.

[0010] In another aspect, the present disclosure provides an AAV particle comprising a promoter operably linked a nucleic acid encoding a modulatory polynucleotide comprising an siRNA for targeting MAPT described herein.

[0011] In another aspect, the present disclosure provides a method of making an AAV particle comprising an AAV capsid protein, e.g., an AAV capsid variant, encoding an siRNA for targeting MAPT described herein. In some embodiments, the method comprises providing a host cell comprising a viral genome encoding an siRNA described herein and incubating the host cell under conditions suitable to enclose the viral genome in the AAV capsid protein, e.g., an AAV capsid variant, thereby making the AAV particle.

[0012] In yet another aspect, the present disclosure provides a method of delivering an siRNA for inhibiting MAPT to a cell. In some embodiments, the method comprises administering an effective amount of an siRNA or an AAV particle encoding an siRNA described herein.

[0013] In yet another aspect, the present disclosure provides, a method of treating a subject having or diagnosed with having a genetic disorder e.g., a monogenic disorder or a polygenic disorder. The method comprising administering an effective amount of an siRNA or an AAV particle encoding an siRNA described herein.

[0014] In yet another aspect, the present disclosure provides, a method of treating a subject having or diagnosed with having a neurological disorder e.g., a neurodegenerative disorder. The method comprising administering an effective amount of an siRNA or an AAV particle encoding an siRNA described herein.

[0015] In yet another aspect, the present disclosure provides, a method of treating a subject having or diagnosed with having a disorder associated with tau expression, e.g., aberrant tau expression. The method comprising administering an effective amount of an siRNA or an AAV particle encoding an siRNA described herein.

[0016] In yet another aspect, the present disclosure provides, a method of treating a subject having or diagnosed with a tauopathy. The method comprising administering an effective amount of an siRNA or an AAV particle encoding an siRNA described herein.

[0017] In some embodiments, the genetic disorder, neurological disorder (e.g., neurodegenerative disorder), disorder associated with tau expression (e.g., aberrant tau expression), and/or tauopathy is Alzheimer's disease, Frontotemporal dementia (FTD), frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), frontotemporal lobar degeneration (FTLD), Dravet syndrome, neurodegenerative disease, traumatic brain injury (TBI), chronic traumatic encephalopathy (CTE), progressive supranuclear palsy (PSP), Down's syndrome, Pick's disease, corticobasal degeneration (CBD), corticobasal syndrome, amyotrophic lateral sclerosis (ALS), Prion diseases, CJD, Multiple system atrophy, mild cognitive impairment, Tangle-only dementia, or Progressive subcortical gliosis.

Enumerated Embodiments

1. A short interfering ribonucleic acid (siRNA) for inhibiting expression of microtubule-associated protein tau (MAPT) which comprises a sense strand sequence and an antisense strand sequence, wherein the antisense sequence is complementary to at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides comprising 0, 1, 2, or 3 mismatches of a MAPT sequence comprising the nucleotide sequence of SEQ ID NO: 5024 or a nucleotide sequence provided in Table 3 or 19.

2. The siRNA of embodiment 1, wherein the antisense strand is complementary to at least 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides with 0, 1, 2, or 3 mismatches to an exon of a MAPT sequence, wherein the exon comprises nucleotides 1277 to 1332 of SEQ ID NO: 5024, nucleotides 1712-1977 of SEQ ID NO: 5024, or nucleotides 2266-6644 of SEQ ID NO: 5024.

3. The siRNA of embodiment 1 or 2, wherein the antisense strand is complementary to at least 15, 16, 17, or 18, contiguous nucleotides with 0, 1, 2, or 3 mismatches to nucleotides 1300-1317, 1305-1322, 1860-1877, 2279-2297, 2286-2303, 2402-2419, 2581-2958, 2584-2601, 2633-2650, or 2634-2653 of SEQ ID NO: 5024.

4. The siRNA of any one of embodiments 1-3, wherein the sense strand comprises:

(i) at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides comprising 0, 1, 2, or 3 mismatches of a MAPT sequence comprising the nucleotide sequence of SEQ ID NO: 5024 or a nucleotide sequence provided in Table 3 or 19;

(ii) at least 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides with 0, 1, 2, or 3 mismatches to an exon of a MAPT sequence, wherein the exon comprises nucleotides 1277 to 1332 of SEQ ID NO: 5024, nucleotides 1712-1977 of SEQ ID NO: 5024, or nucleotides 2266-6644 of SEQ ID NO: 5024; or

(iii) at least 15, 16, 17, or 18, contiguous nucleotides with 0, 1, 2, or 3 mismatches to nucleotides 1300-1317, 1305-1322, 1860-1877, 2279-2297, 2286-2303, 2402-2419, 2581-2958, 2584-2601, 2633-2650, or 2634-2653 of SEQ ID NO: 5024.

5. The siRNA of any one of embodiments 1-4, wherein the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from any one of the antisense strand sequences provided in Tables 3 4, 5, 9A, or 9B.

6. The siRNA of any one of embodiments 1-5, wherein the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from any one of the sense strand sequences provided in Table 4, 5, 9A, or 9B.

7. The siRNA of any one of embodiments 1-6, wherein the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from any one of the antisense strand sequences provided in Tables 3 4, 5, 9A, or 9B; and the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from any one of the sense strand sequences provided in Tables 3 4, 5, 9A, or 9B, wherein the sense strand sequence and the antisense strand sequence comprise a region of complementarity of at least 15 nucleotides.

8. The siRNA of embodiment 7, wherein the region of complementarity is 15-30, 19-21, or 25-30 nucleotides in length, e.g., 17, 18, 20, 21, 22, 25, or 30 nucleotides in length.

9. The siRNA of any one of embodiments 1-8, wherein:

(i) the antisense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4700 and the sense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4502-4505;

(ii) the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4920 and the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing

by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4918, 4938, 4958, 4978, or 4998;

(iii) the antisense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4697 and the sense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4495-4499;

(iv) the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4908 and the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4906, 4926, 4946, 4966, 4986, or 5006;

(v) the antisense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4690 and the sense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4480-4484;

(vi) the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4924 and the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4922, 4942, 4962, 4982, 5002, or 5022;

(vii) the antisense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4694 and the sense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4492;

(viii) the antisense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4691 and the sense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4485-4489;

(ix) the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4916 and the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4914, 4934, 4954, 4974, 4994, or 5014;

(x) the antisense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4701 and the sense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4506-4510;

(xi) the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4912 and the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4910, 4930, 4950, 4970, 4990, or 5010;

(xii) the antisense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4687 and the sense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4477;

(xiii) the antisense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4712 and the sense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4521;

(xiv) the antisense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4696 and the sense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4494; or

(xv) the antisense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4718 and the sense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4527.

10. The siRNA of any one of claims 1-9, wherein:

(i) the antisense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4700 and the sense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4502-4505;

(ii) the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4920 and the sense strand sequence comprises

at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing from the nucleotide sequence of any one of SEQ ID NOs: 4918, 4938, 4958, 4978, or 4998;

(iii) the antisense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4697 and the sense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4495-4499;

(iv) the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4908 and the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4906, 4926, 4946, 4966, 4986, or 5006;

(v) the antisense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4690 and the sense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4480-4484;

(vi) the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4924 and the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4922, 4942, 4962, 4982, 5002, or 5022;

(vii) the antisense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4694 and the sense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4492;

(viii) the antisense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4691 and the sense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4485-4489;

(ix) the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4916 and the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4914, 4934, 4954, 4974, 4994, or 5014;

(x) the antisense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4701 and the sense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4506-4510;

(xi) the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4912 and the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4910, 4930, 4950, 4970, 4990, or 5010;

(xii) the antisense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4687 and the sense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4477;

(xiii) the antisense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4712 and the sense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4521;

(xiv) the antisense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4696 and the sense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4494; or

(xv) the antisense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4718 and the sense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4527.

11. A short interfering ribonucleic acid (siRNA) for inhibiting expression of microtubule-associated protein tau (MAPT) which comprises a sense strand sequence and an antisense strand sequence, wherein:

(i) the antisense strand sequence comprises at least 20 or 21 contiguous nucleotides of any one of SEQ ID NOs: 4908, 4920, 4924, 5057, 4916, 4912, 5080, 5104, or 5128; and

(ii) the sense strand sequence comprises at least 20 or 21 contiguous nucleotides of any one of SEQ ID NOs: 4906, 4926, 4946, 4966, 4986, 5006, 4918, 4938, 4958, 4978, 4998, 4922, 4942, 4962, 4982, 5002, 5022, 5054, 5060, 5064, 5066, 5070, 5074, 4914, 4934, 4954, 4974, 4994, 5014, 4910, 4930, 4950, 4970, 4990, 5010, 5077, 5084, 5088, 5092, 5096, 5098, 5101, 5108, 5112, 5116, 5120, 5122, 5125, 5132, 5136, 5140, 5144, or 5146;

wherein the sense strand sequence and the antisense strand sequence comprise a region of complementarity of at least 15 nucleotides.

12. An adeno-associated virus (AAV) viral genome comprising a nucleotide sequence positioned between two inverted terminal repeats (ITRs), wherein the nucleotide sequence encodes an siRNA for inhibiting MAPT, wherein the siRNA comprises a sense strand sequence and an antisense strand sequence, wherein:

(i) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides of any one of SEQ ID NOs: 4908, 4920, 4924, 5057, 4916, 4912, 5080, 5104, or 5128; and

(ii) the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides of any one of SEQ ID NOs: 4906, 4926, 4946, 4966, 4986, 5006, 4918, 4938, 4958, 4978, 4998, 4922, 4942, 4962, 4982, 5002, 5022, 5054, 5060, 5064, 5066, 5070, 5074, 4914, 4934, 4954, 4974, 4994, 5014, 4910, 4930, 4950, 4970, 4990, 5010, 5077, 5084, 5088, 5092, 5096, 5098, 5101, 5108, 5112, 5116, 5120, 5122, 5125, 5132, 5136, 5140, 5144, or 5146;

wherein the sense strand sequence and the antisense strand sequence comprise a region of complementarity of at least 15 nucleotides.

13. The siRNA of any one of embodiments 8-11 or the AAV viral genome of embodiment 12, wherein the region of complementarity comprises at least 18, 19, or 20 nucleotides.

14. The siRNA of any one of embodiments 1-10 or the AAV viral genome of embodiment 12 or 13, wherein the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides of any one of SEQ ID NOs: 4908, 4920, 4924, or 4912.

15. The siRNA of any one of embodiments 1-10 or the AAV viral genome of any one of embodiments 12-14, wherein the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides of any one of SEQ ID NOs: 4906, 4926, 4946, 4966, 4986, 5006, 4918, 4938, 4958, 4978, 4998, 4922, 4942, 4962, 4982, 5002, 5022, 4910, 4930, 4950, 4970, 4990, or 5010.

16. The siRNA of any one of embodiments 1-10 or the AAV viral genome of any one of embodiments 12-15, wherein:

(i) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4908 and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4906, 4926, 4946, 4966, 4986, or 5006;

(ii) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4920 and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4918, 4938, 4958, 4978, or 4998;

(iii) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4924 and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4922, 4942, 4962, 4982, 5002, or 5022;

(iv) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4912 and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4910, 4930, 4950, 4970, 4990, or 5010;

(v) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4916 and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4914, 4934, 4954, 4974, 4994, or 5014;

(vi) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5104; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 5101, 5108, 5112, 5116, 5120, or 5122;

(vii) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5128; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 5125, 5132, 5136, 5140, 5144, or 5146;

(viii) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5080; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 5077, 5084, 5088, 5092, 5096, or 5098; or

(ix) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5057; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 5054, 5060, 5064, 5066, 5070, or 5074.

17. The siRNA of any one of embodiments 1-10 or the AAV viral genome of any one of embodiments 12-16, wherein the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4908 and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4906.

18. The siRNA of any one of embodiments 1-10 or the AAV viral genome of any one of embodiments 12-16, wherein the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4920 and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4918.

19. The siRNA of any one of embodiments 1-10 or the AAV viral genome of any one of embodiments 12-16, wherein the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4924 and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4922.

20. The siRNA of any one of embodiments 1-10 or the AAV viral genome of any one of embodiments 12-16, wherein the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4908 and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4966.

21. The siRNA of any one of embodiments 1-10 or the AAV viral genome of any one of embodiments 12-16, wherein the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4912 and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4970.

22. The siRNA of any one of embodiments 1-10 or the AAV viral genome of any one of embodiments 12-16, wherein the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4920 and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4978.

23. The siRNA of any one of embodiments 1-10 or the AAV viral genome of any one of embodiments 12-16, wherein the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4924 and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4982.

24. The siRNA of any one of embodiments 1-10 or the AAV viral genome of any one of embodiments 12-16, wherein:

(i) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4912; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4910;

(ii) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4916; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4914;

(iii) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5057; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5054;

(iv) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4908; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4926;

(v) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4912; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4930;

(vi) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4916; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4934;

(vii) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4920; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4938;

(viii) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4924; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4942;

(ix) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5057; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5060;

(x) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4908; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4946;

(xi) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4912; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4950;

(xii) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4916; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4954;

(xiii) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4920; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4958;

(xiv) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4924; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4962;

(xv) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5057; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5064;

(xvi) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4916; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4974;

(xvii) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5057; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5066;

(xviii) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4908; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4986;

(xix) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4912; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4990;

(xx) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4916; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4994;

(xxi) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4920; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4998;

(xxii) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4924; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5002;

(xxiii) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5057; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5070;

(xxiv) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4908; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5006;

(xxv) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4912; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5010;

(xxvi) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4916; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5014;

(xxvii) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4920; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4958;

(xxviii) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4924; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5022;

(xxvii) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5057; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5074;

(xxix) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5080; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5077;

(xxx) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5080; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5084;

(xxxi) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5080; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5088;

(xxxii) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5080; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5092;

(xxxiii) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5080; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5096;

(xxxiv) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5080; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5098;

(xxxv) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5104; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5101;

(xxxvi) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5104; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5108;

(xxxvii) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5104; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5112;

(xxxviii) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5104; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5116;

(xxxix) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5104; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5120;

(xl) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5104; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5122;

(xli) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5128; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5125;

(xlii) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5128; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5132;

(xliii) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5128; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5136;

(xliv) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5128; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5140;

(xlv) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5128; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5144; or

(xlvi) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5128; and the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5146.

25. The siRNA of any one of embodiments 1-11 or 13 or the AAV viral genome of any one of embodiments 12-24, wherein the antisense strand sequence comprises at least 20 contiguous nucleotides of any one of SEQ ID NOs: 4908, 4920, 4924, or 4912.

26. The siRNA of any one of embodiments 1-11, 13, or 25 or the AAV viral genome of any one of embodiments 12-25, wherein the sense strand sequence comprises at least 20 contiguous nucleotides of any one of SEQ ID NOs: 4906, 4926, 4946, 4966, 4986, 5006, 4918, 4938, 4958, 4978, 4998, 4922, 4942, 4962, 4982, 5002, 5022, 4910, 4930, 4950, 4970, 4990, or 5010.

27. The siRNA of any one of embodiments 1-11, 13, 25, or 26 or the AAV viral genome of any one of embodiments 12-26, wherein:

(i) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4908 and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4906, 4926, 4946, 4966, 4986, or 5006;

(ii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4920 and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4918, 4938, 4958, 4978, or 4998;

(iii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4924 and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4922, 4942, 4962, 4982, 5002, or 5022;

(iv) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4912 and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4910, 4930, 4950, 4970, 4990, or 5010;

(v) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4916 and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4914, 4934, 4954, 4974, 4994, or 5014;

(vi) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5104; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 5101, 5108, 5112, 5116, 5120, or 5122;

(vii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5128; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 5125, 5132, 5136, 5140, 5144, or 5146;

(viii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5080; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 5077, 5084, 5088, 5092, 5096, or 5098; or

(ix) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5057; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 5054, 5060, 5064, 5066, 5070, or 5074.

28. The siRNA of any one of embodiments 1-11, 13, or 25-27 or the AAV viral genome of any one of embodiments 11-17 or 25-27, wherein the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4908 and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4906.

29. The siRNA of any one of embodiments 1-11, 13, or 25-27 or the AAV viral genome of any one of embodiments 11-16, 18, or 25-27, wherein the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4920 and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4918.

30. The siRNA of any one of embodiments 1-11, 13, or 25-27 or the AAV viral genome of any one of embodiments 11-16, 19, or 25-27, wherein the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4924 and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4922.

31. The siRNA of any one of embodiments 1-11, 13, or 25-27 or the AAV viral genome of any one of embodiments 11-16, 20, or 25-27, wherein the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4908 and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4966.

32. The siRNA of any one of embodiments 1-11, 13, or 25-27 or the AAV viral genome of any one of embodiments 11-16, 21, or 25-27, wherein the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4912 and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4970.

33. The siRNA of any one of embodiments 1-11, 13, or 25-27 or the AAV viral genome of any one of embodiments 11-16, 22, or 25-27, wherein the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4920 and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4978.

34. The siRNA of any one of embodiments 1-11, 13, or 25-27 or the AAV viral genome of any one of embodiments 11-16, 23, or 25-27, wherein the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4924 and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4982.

35. The siRNA of any one of embodiments 1-11, 13, or 25-27 or the AAV viral genome of any one of embodiments 11-16 or 24-27, wherein:

(i) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4912; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4910;

(ii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4916; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4914;

(iii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5057; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5054;

(iv) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4908; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4926;

(v) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4912; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4930;

(vi) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4916; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4934;

(vii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4920; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4938;

(viii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4924; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4942;

(ix) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5057; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5060;

(x) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4908; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4946;

(xi) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4912; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4950;

(xii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4916; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4954;

(xiii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4920; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4958;

(xiv) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4924; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4962;

(xv) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5057; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5064;

(xvi) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4916; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4974;

(xvii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5057; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5066;

(xviii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4908; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4986;

(xix) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4912; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4990;

(xx) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4916; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4994;

(xxi) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4920; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4998;

(xxii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4924; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5002;

(xxiii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5057; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5070;

(xxiv) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4908; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5006;

(xxv) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4912; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5010;

(xxvi) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4916; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5014;

(xxvii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4920; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4958;

(xxviii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4924; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5022;

(xxvii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5057; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5074;

(xxix) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5080; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5077;

(xxx) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5080; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5084;

(xxxi) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5080; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5088;

(xxxii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5080; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5092;

(xxxiii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5080; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5096;

(xxxiv) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5080; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5098;

(xxxv) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5104; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5101;

(xxxvi) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5104; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5108;

(xxxvii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5104; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5112;

(xxxviii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5104; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5116;

(xxxix) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5104; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5120;

(xl) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5104; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5122;

(xli) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5128; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5125;

(xlii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5128; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5132;

(xliii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5128; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5136;

(xliv) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5128; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5140;

(xlv) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5128; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5144; or

(xlvi) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5128; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5146.

36. The siRNA of any one of embodiments 1-11, 13, or 25-35 or the AAV viral genome of any one of embodiments 12-35, wherein the antisense strand sequence comprises the nucleotide sequence of any one of SEQ ID NOs: 4908, 4920, 4924, or 4912.

37. The siRNA of any one of embodiments 1-11, 13, or 25-36 or the AAV viral genome of any one of embodiments 12-36, wherein the sense strand sequence comprises at the nucleotide sequence of any one of SEQ ID NOs: 4906, 4926, 4946, 4966, 4986, 5006, 4918, 4938, 4958, 4978, 4998, 4922, 4942, 4962, 4982, 5002, 5022, 4910, 4930, 4950, 4970, 4990, or 5010.

38. The siRNA of any one of embodiments 1-11, 13, or 25-37 or the AAV viral genome of any one of embodiments 12-37, wherein:

(i) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4908 and the sense strand sequence comprises the nucleotide sequence of any one of SEQ ID NOs: 4906, 4926, 4946, 4966, 4986, or 5006;

(ii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4920 and the sense strand sequence comprises the nucleotide sequence of any one of SEQ ID NOs: 4918, 4938, 4958, 4978, or 4998;

(iii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4924 and the sense strand sequence comprises the nucleotide sequence of any one of SEQ ID NOs: 4922, 4942, 4962, 4982, 5002, or 5022;

(iv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4912 and the sense strand sequence comprises the nucleotide sequence of any one of SEQ ID NOs: 4910, 4930, 4950, 4970, 4990, or 5010;

(v) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4916 and the sense strand sequence comprises the nucleotide sequence of any one of SEQ ID NOs: 4914, 4934, 4954, 4974, 4994, or 5014;

(vi) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5104; and the sense strand sequence comprises the nucleotide sequence of any one of SEQ ID NOs: 5101, 5108, 5112, 5116, 5120, or 5122;

(vii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5128; and the sense strand sequence comprises the nucleotide sequence of any one of SEQ ID NOs: 5125, 5132, 5136, 5140, 5144, or 5146;

(viii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5080; and the sense strand sequence comprises the nucleotide sequence of any one of SEQ ID NOs: 5077, 5084, 5088, 5092, 5096, or 5098; or

(ix) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5057; and the sense strand sequence comprises the nucleotide sequence of any one of SEQ ID NOs: 5054, 5060, 5064, 5066, 5070, or 5074.

39. The siRNA of any one of embodiments 1-11, 13, 25-28, or 36-39 or the AAV viral genome of any one of embodiments 11-17, 25-28, or 36-39, wherein the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4908 and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4906.

40. The siRNA of any one of embodiments 1-11, 13, 25-27, 29, or 36-39 or the AAV viral genome of any one of embodiments 11-16, 18, 25-27, 29, or 36-39, wherein the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4920 and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4918.

41. The siRNA of any one of embodiments 1-11, 13, 25-27, 30, or 36-39 or the AAV viral genome of any one of embodiments 11-16, 19, 25-27, 30, or 36-39, wherein the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4924 and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4922.

42. The siRNA of any one of embodiments 1-11, 13, 25-27, 31, or 36-39 or the AAV viral genome of any one of embodiments 11-16, 19, 25-27, 31, or 36-39, wherein the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4908 and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4966.

43. The siRNA of any one of embodiments 1-11, 13, 25-27, 32, or 36-39 or the AAV viral genome of any one of embodiments 11-16, 19, 25-27, 62, or 36-39, wherein the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4912 and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4970.

44. The siRNA of any one of embodiments 1-11, 13, 25-27, 33, or 36-39 or the AAV viral genome of any one of embodiments 11-16, 19, 25-27, 33, or 36-39, wherein the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4920 and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4978.

45. The siRNA of any one of embodiments 1-11, 13, 25-27, 34, or 36-39 or the AAV viral genome of any one of embodiments 11-16, 19, 25-27, 34, or 36-39, wherein the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4924 and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4982.

46. The siRNA of any one of embodiments 1-11, 13, 25-27, 35, or 36-39 or the AAV viral genome of any one of embodiments 11-16, 19, 25-27, 35, or 36-39, wherein:

(i) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4912; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4910;

(ii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4916; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4914;

(iii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5057; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5054;

(iv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4908; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4926;

(v) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4912; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4930;

(vi) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4916; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4934;

(vii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4920; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4938;

(viii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4924; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4942;

(ix) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5057; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5060;

(x) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4908; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4946;

(xi) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4912; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4950;

(xii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4916; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4954;

(xiii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4920; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4958;

(xiv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4924; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4962;

(xv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5057; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5064;

(xvi) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4916; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4974;

(xvii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5057; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5066;

(xviii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4908; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4986;

(xix) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4912; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4990;

(xx) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4916; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4994;

(xxi) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4920; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4998;

(xxii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4924; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5002;

(xxiii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5057; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5070;

(xxiv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4908; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5006;

(xxv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4912; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5010;

(xxvi) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4916; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5014;

(xxvii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4920; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4958;

(xxviii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4924; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5022;

(xxvii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5057; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5074;

(xxix) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5080; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5077;

(xxx) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5080; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5084;

(xxxi) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5080; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5088;

(xxxii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5080; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5092;

(xxxiii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5080; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5096;

(xxxiv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5080; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5098;

(xxxv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5104; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5101;

(xxxvi) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5104; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5108;

(xxxvii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5104; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5112;

(xxxviii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5104; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5116;

(xxxix) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5104; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5120;

(xl) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5104; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5122;

(xli) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5128; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5125;

(xlii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5128; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5132;

(xliii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5128; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5136;

(xlv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5128; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5140;

(xliv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5128; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5144; or

(xlvi) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5128; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5146.

47. The siRNA of any one of embodiments 1-11 or 13-46 or the AAV viral genome of any one of embodiments 12-46, wherein:

(i) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4700 and the sense strand sequence comprises the nucleotide sequence of any one of SEQ ID NOs: 4502-4505;

(ii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4920 and the sense strand sequence comprises the nucleotide sequence of any one of SEQ ID NOs: 4918, 4938, 4958, 4978, or 4998;

(iii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4697 and the sense strand sequence comprises the nucleotide sequence of any one of SEQ ID NOs: 4495-4499;

(iv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4908 and the sense strand sequence comprises the nucleotide sequence of any one of SEQ ID NOs: 4906, 4926, 4946, 4966, 4986, or 5006;

(v) the antisense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4690 and the sense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4480-4484;

(vi) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4924 and the sense strand sequence comprises the nucleotide sequence of any one of SEQ ID NOs: 4922, 4942, 4962, 4982, 5002, or 5022;

(vii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4694 and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4492;

(viii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4691 and the sense strand sequence comprises the nucleotide sequence of any one of SEQ ID NOs: 4485-4489;

(ix) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4916 and the sense strand sequence comprises the nucleotide sequence of any one of SEQ ID NOs: 4914, 4934, 4954, 4974, 4994, or 5014;

(x) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4701 and the sense strand sequence comprises the nucleotide sequence of any one of SEQ ID NOs: 4506-4510;

(xi) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4912 and the sense strand sequence comprises the nucleotide sequence of any one of SEQ ID NOs: 4910, 4930, 4950, 4970, 4990, or 5010;

(xii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4687 and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4477;

(xiii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4712 and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4521;

(xiv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4696 and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4494; or

(xv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4718 and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4527.

48. The siRNA of any one of embodiments 1-11 or 13-47 or the AAV viral genome of any one of embodiments 12-47, wherein

(i) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4420 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4434;

(ii) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4905 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4907;

(iii) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4421 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4435;

(iv) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4909 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4911;

(v) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4422 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4436;

(vi) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4913 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4915;

(vii) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4423 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4437;

(viii) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4917 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4919;

(ix) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4424 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4438;

(x) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4921 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4923;

(xi) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4410 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4434;

(xii) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4925 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4907;

(xiii) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4411 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4435;

(xiv) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4929 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4911;

(xv) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4412 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4436;

(xvi) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4933 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4915;

(xvii) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4413 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4437;

(xviii) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4937 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4419;

(xix) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4414 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4438;

(xx) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4941 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4923;

(xxi) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4415 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4434;

(xxii) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4945 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4907;

(xxiii) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4416 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4435;

(xxiv) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4949 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4911;

(xxv) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4417 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4436;

(xxvi) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4953 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4915;

(xxvii) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4418 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4437;

(xxviii) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4957 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4919;

(xxix) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4419 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4438;

(xxx) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4961 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4923;

(xxxi) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4420 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4434;

(xxxii) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4965 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4907;

(xxxii) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4421 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4435;

(xxxiii) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4969 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4911;

(xxxiv) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4422 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4436;

(xxxv) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4973 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4915;

(xxxvi) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4423 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4437;

(xxxvii) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4977 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4919;

(xxxviii) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4424 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4438;

(xxxix) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4981 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4923;

(xl) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4425 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4434;

(xli) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4985 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4907;

(xlii) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4426 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4435;

(xliii) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4989 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4911;

(xliv) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4427 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4436;

(xlv) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4993 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4915;

(xlvi) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4428 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4437;

(xlvii) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4997 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4919;

(xlviii) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4429 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4438;

(xlix) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5001 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4923;

(l) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4430 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4434;

(li) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5005 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4907;

(lii) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4431 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4435;

(liii) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5009 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4911;

(liv) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4432 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4436;

(lv) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5013 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4915;

(lvi) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4433 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4438;

(lvii) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5021 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4923;

(lviii) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5053 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 5056;

(lix) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5059 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 5056;

(lx) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5063 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 5056;

(lxi) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5065 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 5056;

(lxii) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5069 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 5056;

(lxiii) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5073 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 5056;

(lxiv) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5076 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 5079;

(lxv) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5083 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 5079;

(lxvi) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5087 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 5079;

(lxvii) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5091 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 5079;

(lxviii) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5095 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 5079;

(lxix) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5097 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 5079;

(lxx) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5100 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 5103;

(lxxi) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5107 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 5103;

(lxxii) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5111 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 5103;

(lxxiii) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5115 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 5103;

(lxxiv) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5119 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 5103;

(lxxv) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5121 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 5103;

(lxxvi) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5124 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 5127;

(lxxvii) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5131 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 5127;

(lxxviii) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5135 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 5127;

(lxxix) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5139 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 5127;

(lxxx) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5143 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 5127; or

(lxxxi) the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5145 and the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 5127.

49. The siRNA of any one of embodiments 1-11, 13, 25-28, 36-39, 47, or 48, or the AAV viral genome of any one of embodiments 11-17, 25-28, 36-39, or 47, or 48, wherein the nucleotide sequence encoding the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4907 and the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4905.

50. The siRNA of any one of embodiments 1-11, 13, 25-27, 29, 36-39, 47, or 48 or the AAV viral genome of any one of embodiments 11-16, 18, 25-27, 29, 36-39, 47, or 48, wherein the nucleotide sequence encoding the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4919 and the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4917.

51. The siRNA of any one of embodiments 1-11, 13, 25-27, 30, 36-39, 47, or 48 or the AAV viral genome of any one of embodiments 11-16, 19, 25-27, 30, 36-39, 47, or 48, wherein the nucleotide sequence encoding the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4923 and the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4921.

52. The siRNA of any one of embodiments 1-11, 13, 25-27, 31, 36-39, 47, or 48 or the AAV viral genome of any one of embodiments 11-16, 19, 25-27, 31, 36-39, 47, or 48, wherein the nucleotide sequence encoding the

antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4907 and the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4965.

53. The siRNA of any one of embodiments 1-11, 13, 25-27, 32, 36-39, 47, or 48 or the AAV viral genome of any one of embodiments 11-16, 19, 25-27, 62, 36-39, 47, or 48, wherein the nucleotide sequence encoding the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4911 and the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4969.

54. The siRNA of any one of embodiments 1-11, 13, 25-27, 33, 36-39, 47, or 48 or the AAV viral genome of any one of embodiments 11-16, 19, 25-27, 33, 36-39, 47, or 48, wherein the nucleotide sequence encoding the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4919 and the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4977.

55. The siRNA of any one of embodiments 1-11, 13, 25-27, 34, 36-39, 47, or 48 or the AAV viral genome of any one of embodiments 11-16, 19, 25-27, 34, 36-39, 47, or 48, wherein the nucleotide sequence encoding the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4923 and the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4981.

56. The siRNA of any one of embodiments 1-11 or 13-55, or the AAV viral genome of any one of embodiments 12-55, wherein the sense strand sequence, the antisense strand sequence, or both the sense strand sequence and the antisense strand sequence comprise at least 15-30, 19-21, or 25-30 nucleotides in length, e.g., 17, 18, 20, 21, 22, 25, or 30 nucleotides in length.

57. The siRNA of any one of embodiments 1-11 or 13-56 or the AAV viral genome of any one of embodiments 12-56, wherein the sense strand sequence, the antisense strand sequence, or both the sense strand sequence and the antisense strand sequence comprise an overhang, e.g., an overhang at the 5' end of the sense strand sequence and/or at the 3' end of the antisense strand sequence, of 1 or 2 nucleotides.

58. The siRNA of any one of embodiments 1-11 or 13-57 or the AAV viral genome of any one of embodiments 12-57, wherein:

(i) the sense strand and the antisense strand comprise one mismatch; and/or

(ii) the antisense strand and the target sequence comprise one mismatch.

59. A modulatory polynucleotide comprising the siRNA of any one of embodiments 1-12 or 13-58.

60. The AAV viral genome of any one of embodiments 13-58, wherein the nucleotide sequence further encodes a modulatory polynucleotide comprising the sense strand sequence and the antisense strand sequence.

61. The modulatory polynucleotide of embodiment 59, or the AAV viral genome of embodiment 60, wherein the modulatory polynucleotide further comprises one, two, three or all of:

(i) a 5' flanking region;

(ii) a loop region; and

(iii) a 3' flanking region.

62. The modulatory polynucleotide of embodiment 61, or the AAV viral genome of embodiment 61, wherein:

(i) the 5' flanking region comprises the nucleotide sequence of any one of SEQ ID NOs: 4878-4886; a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical thereto; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of any of SEQ ID NOs: 4878-4886; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of any of SEQ ID NOs: 4878-4886;

(ii) the loop region comprises the nucleotide sequence of any of SEQ ID NOs: 4887-4896; a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical thereto; a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of any of SEQ ID NOs: 4887-4896; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of any of SEQ ID NOs: 4887-4896; and/or

(iii) the 3' flanking region comprises the nucleotide sequence of any one of SEQ ID NOs: 4897-4904; a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical thereto; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of any of SEQ ID NOs: 4897-4904; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of any of SEQ ID NOs: 4897-4904.

63. The modulatory polynucleotide of embodiment 61 or 62 or the AAV viral genome of embodiment 61 or 62, wherein:

(i) the nucleotide sequence encoding the 5' flanking region comprises the nucleotide sequence of any of SEQ ID NOs: 4353-4361, a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical thereto; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of any of SEQ ID NOs: 4353-4361; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of any of SEQ ID NOs: 4353-4361;

(ii) the nucleotide sequence encoding the loop region comprises the nucleotide sequence of any of SEQ ID NOs: 4362-4371; a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical thereto; a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of any of SEQ ID NOs: 4362-4371; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of any of SEQ ID NOs: 4362-4371; and/or

(iii) the nucleotide sequence encoding the 3' flanking region comprises the nucleotide sequence of any of SEQ ID NOs: 4372-4379; a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical thereto; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of any of SEQ ID NOs: 4372-4379; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of any of SEQ ID NOs: 4372-4379.

64. The modulatory polynucleotide of any one of embodiments 59 or 61-63 or the AAV viral genome of any one of embodiments 60-63, wherein the modulatory polynucleotide comprises:

(i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4879, a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4879, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4879; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4879;

(ii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4887, a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4887, a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4887; or a nucleotide sequence comprising one, two,

three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4887; and

(iii) a 3' flanking region of SEQ ID NO: 4898, a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4898, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4898, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4898.

65. The modulatory polynucleotide of any one of embodiments 59 or 61-63 or the AAV viral genome of any one of embodiments 60-63, wherein the modulatory polynucleotide comprises:

(i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4879, a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4879, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4879; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4879;

(ii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4888, a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4888, a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4888; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4888; and

(iii) a 3' flanking region of SEQ ID NO: 4898, a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4898, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4898, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4898.

66. The modulatory polynucleotide of any one of embodiments 59 or 61-63 or the AAV viral genome of any one of embodiments 60-63, wherein the modulatory polynucleotide comprises:

(i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4879, a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4879, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different

nucleotides relative to the nucleotide sequence of SEQ ID NO: 4879; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4879;

(ii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4887, a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4887, a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4887; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4887; and

(iii) a 3' flanking region of SEQ ID NO: 4899, a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4899, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4899, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4899.

67. The modulatory polynucleotide of any one of embodiments 59 or 61-63 or the AAV viral genome of any one of embodiments 60-63, wherein the modulatory polynucleotide comprises:

(i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4880, a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4880, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4880; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4880;

(ii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4891, a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4891, a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4891; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4891; and

(iii) a 3' flanking region of SEQ ID NO: 4900, a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4900, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4900, or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to SEQ ID NO: 4900.

68. The modulatory polynucleotide of any one of embodiments 59 or 61-67 or the AAV viral genome of any one of embodiments 62-67, wherein the modulatory polynucleotide comprises in 5' to 3' order:

(i) the 5' flanking region, sense strand sequence, loop region, antisense strand sequence, and 3' flanking region; or

(ii) the 5' flanking region, antisense strand sequence, loop region, sense strand sequence, and 3' flanking region.

69. The modulatory polynucleotide of any one of embodiments 59, 61-63, 67, 68 or the AAV viral genome of any one of embodiments 60-63, 67, 68, where the modulatory polynucleotide comprises:

(i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4880; a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4880; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4880; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4880;

(ii) the sense strand sequence of SEQ ID NO: 4906;

(iii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4891; a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4891; a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4891; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4891;

(iv) the antisense strand sequence of SEQ ID NO: 4908; and

(v) a 3' flanking region comprising the nucleotide sequence of SEQ ID NO: 4900; a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4900; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4900; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to SEQ ID NO: 4900.

70. The modulatory polynucleotide of any one of embodiments 59, 61-63, or 67-69, or the AAV viral genome of any one of embodiments 60-63 or 67-69, where the nucleotide sequence encoding the modulatory polynucleotide comprises:

(i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4355; a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4355; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different

nucleotides relative to the nucleotide sequence of SEQ ID NO: 4355; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4355;

(ii) the sense strand sequence of SEQ ID NO: 4905;

(iii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4366; a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4366; a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4366; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4366;

(iv) the antisense strand sequence of SEQ ID NO: 4907; and

(v) a 3' flanking region comprising the nucleotide sequence of SEQ ID NO: 4375; a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4375; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4375; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to SEQ ID NO: 4375.

71. The modulatory polynucleotide of any one of embodiments 59, 61-63, 67, or 68 or the AAV viral genome of any one of embodiments 60-63, 67, or 68, where the modulatory polynucleotide comprises:

(i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4880; a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4880; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4880; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4880;

(ii) the sense strand sequence of SEQ ID NO: 4918;

(iii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4891; a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4891; a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4891; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4891;

(iv) the antisense strand sequence of SEQ ID NO: 4920; and

(v) a 3' flanking region comprising the nucleotide sequence of SEQ ID NO: 4900; a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4900; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different

nucleotides relative to the nucleotide sequence of SEQ ID NO: 4900; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to SEQ ID NO: 4900.

72. The modulatory polynucleotide of any one of embodiments 59, 61-63, 67, 68, or 71 or the AAV viral genome of any one of embodiments 60-63, 67, 68 or 71, where the nucleotide sequence encoding the modulatory polynucleotide comprises:

(i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4355; a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4355; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4355; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4355;

(ii) the sense strand sequence of SEQ ID NO: 4917;

(iii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4366; a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4366; a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4366; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4366;

(iv) the antisense strand sequence of SEQ ID NO: 4919; and

(v) a 3' flanking region comprising the nucleotide sequence of SEQ ID NO: 4375; a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4375; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4375; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to SEQ ID NO: 4375.

73. The modulatory polynucleotide of any one of embodiments 59, 61-63, 67, or 68 or the AAV viral genome of any one of embodiments 60-63, 67, or 68, where the modulatory polynucleotide comprises:

(i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4880; a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4880; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4880; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4880;

(ii) the sense strand sequence of SEQ ID NO: 4922;

(iii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4891; a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4891; a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4891; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4891;

(iv) the antisense strand sequence of SEQ ID NO: 4924; and

(v) a 3' flanking region comprising the nucleotide sequence of SEQ ID NO: 4900; a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4900; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4900; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to SEQ ID NO: 4900.

74. The modulatory polynucleotide of any one of embodiments 59, 61-63, 67, 68, or 73 or the AAV viral genome of any one of embodiments 60-63, 67, 68, or 73, where the nucleotide sequence encoding the modulatory polynucleotide comprises:

(i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4355; a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4355; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4355; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4355;

(ii) the sense strand sequence of SEQ ID NO: 4921;

(iii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4366; a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4366; a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4366; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4366;

(iv) the antisense strand sequence of SEQ ID NO: 4923; and

(v) a 3' flanking region comprising the nucleotide sequence of SEQ ID NO: 4375; a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4375; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4375; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to SEQ ID NO: 4375.

75. The modulatory polynucleotide of any one of embodiments 59, 60-63, 65, or 68 or the AAV viral genome of any one of embodiments 60-63, 65, or 68, wherein the modulatory polynucleotide comprises:

(i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4879, a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4879, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4879; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4879;

(ii) the sense strand sequence of SEQ ID NO: 4966;

(iii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4888, a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4888, a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4888; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4888;

(iv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4908; and

(v) a 3' flanking region of SEQ ID NO: 4898, a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4898, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4898, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4898.

76. The modulatory polynucleotide of any one of embodiments 59, 61-63, 65, 68, or 76 or the AAV viral genome of any one of embodiments 60-63, 65, 68, or 76, wherein the nucleotide sequence encoding the modulatory polynucleotide comprises:

(i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4354, a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4354, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4354; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4354;

(ii) the sense strand sequence of SEQ ID NO: 4965;

(iii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4363, a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4363,

a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4363; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4363;

(iv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4907; and

(v) a 3' flanking region of SEQ ID NO: 4373, a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4373, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4373, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4373.

77. The modulatory polynucleotide of any one of embodiments 59, 61-63, 65, or 68 or the AAV viral genome of any one of embodiments 60-63, 65, or 68, wherein the modulatory polynucleotide comprises:

(i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4879, a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4879, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4879; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4879;

(ii) the sense strand sequence of SEQ ID NO: 4970;

(iii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4888, a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4888, a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4888; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4888;

(iv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4912; and

(v) a 3' flanking region of SEQ ID NO: 4898, a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4898, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4898, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4898.

78. The modulatory polynucleotide of any one of embodiments 59, 61-63, 65, 68, or 77 or the AAV viral genome of any one of embodiments 60-63, 65, 68, or 77, wherein the nucleotide sequence encoding the modulatory polynucleotide comprises:

(i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4354, a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4354, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4354; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4354;

(ii) the sense strand sequence of SEQ ID NO: 4969;

(iii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4363, a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4363, a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4363; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4363;

(iv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4911; and

(v) a 3' flanking region of SEQ ID NO: 4373, a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4373, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4373, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4373.

79. The modulatory polynucleotide of any one of embodiments 59, 61-63, 65, or 68 or the AAV viral genome of any one of embodiments 60-63, 65, or 68, wherein the modulatory polynucleotide comprises:

(i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4879, a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4879, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4879; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4879;

(ii) the sense strand sequence of SEQ ID NO: 4978;

(iii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4888, a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4888,

a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4888; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4888;

(iv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4920; and

(v) a 3' flanking region of SEQ ID NO: 4898, a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4898, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4898, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4898.

80. The modulatory polynucleotide of any one of embodiments 59, 61-63, 65, 68, or 79 or the AAV viral genome of any one of embodiments 60-63, 65, 68, or 79, wherein the nucleotide sequence encoding the modulatory polynucleotide comprises:

(i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4354, a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4354, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4354; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4354;

(ii) the sense strand sequence of SEQ ID NO: 4977;

(iii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4363, a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4363, a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4363; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4363;

(iv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4919; and

(v) a 3' flanking region of SEQ ID NO: 4373, a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4373, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4373, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4373.

81. The modulatory polynucleotide of any one of embodiments 59, 61-63, 65, or 68 or the AAV viral genome of any one of embodiments 60-63, 65, or 68, wherein the modulatory polynucleotide comprises:

(i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4879, a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4879, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4879; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4879;

(ii) the sense strand sequence of SEQ ID NO: 4982;

(iii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4888, a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4888, a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4888; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4888;

(iv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4924; and

(v) a 3' flanking region of SEQ ID NO: 4898, a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4898, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4898, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4898.

82. The modulatory polynucleotide of any one of embodiments 59, 61-63, 65, 68, or 81 or the AAV viral genome of any one of embodiments 60-63, 65, 68, or 81, wherein the nucleotide sequence encoding the modulatory polynucleotide comprises:

(i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4354, a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4354, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4354; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4354;

(ii) the sense strand sequence of SEQ ID NO: 4981;

(iii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4363, a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4363,

a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4363; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4363;

(iv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4923; and

(v) a 3` flanking region of SEQ ID NO: 4373, a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4373, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4373, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4373.

83. The modulatory polynucleotide of any one of embodiments 59 or 61-82 or the AAV viral genome of any one of embodiments 62-82, wherein the nucleotide sequence encoding the modulatory polynucleotide comprises the nucleotide sequence of the nucleotide sequence of any one of SEQ ID NOs: 4380-4409 or 5027-5050, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto.

84. The modulatory polynucleotide of any one of embodiments 59, 61-63, 67-70, or 83, or the AAV viral genome of any one of embodiments 60-63, 67-70, or 83, wherein the nucleotide sequence encoding the modulatory polynucleotide comprises the nucleotide sequence of the nucleotide sequence of SEQ ID NO: 4405, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto.

85. The modulatory polynucleotide of any one of embodiments 59, 61-63, 67, 68, 71, 72, or 83, or the AAV viral genome of any one of embodiments 60-63, 67, 68, 71, 72, or 83, wherein the nucleotide sequence encoding the modulatory polynucleotide comprises the nucleotide sequence of SEQ ID NO: 4408, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto.

86. The modulatory polynucleotide of any one of embodiments 59, 61-63, 67, 68, 73, 74, or 83, or the AAV viral genome of any one of embodiments 60-63, 67, 68, 73, 74, or 83, wherein the nucleotide sequence encoding the modulatory polynucleotide comprises the nucleotide sequence of SEQ ID NO: 4409, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto.

87. The modulatory polynucleotide of any one of embodiments 59, 61-63, 65, 68, 75, 76, or 83, or the AAV viral genome of any one of embodiments 60-63, 65, 68, 75, 76, or 83, wherein the nucleotide sequence encoding the modulatory polynucleotide comprises the nucleotide sequence of SEQ ID NO: 4390, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto.

88. The modulatory polynucleotide of any one of embodiments 59, 61-63, 65, 68, 77, 78, or 83, or the AAV viral genome of any one of embodiments 60-63, 65, 68, 77, 78, or 83, wherein the nucleotide sequence encoding the modulatory polynucleotide comprises the nucleotide sequence of SEQ ID NO: 4391, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto.

89. The modulatory polynucleotide of any one of embodiments 59, 61-63, 65, 68, 79, 80, or 83, or the AAV viral genome of any one of embodiments 60-63, 65, 68, 79, 80, or 83, wherein the nucleotide sequence encoding the modulatory polynucleotide comprises the nucleotide sequence of SEQ ID NO: 4393, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto.

90. The modulatory polynucleotide of any one of embodiments 59, 61-63, 65, 68, 81, 82, or 83, or the AAV viral genome of any one of embodiments 60-63, 65, 68, 81, 82, or 83, wherein the nucleotide sequence encoding the modulatory polynucleotide comprises the nucleotide sequence of SEQ ID NO: 4394, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto.

91. An adeno-associated virus (AAV) viral genome comprising a promoter operably linked to a nucleic acid encoding the modulatory polynucleotide of any one of embodiments 59-90 or the siRNA of any one of embodiments 1-11 or 13-58.

92. The AAV viral genome of any one of embodiments 12-58 or 60-90, wherein the AAV viral genome further comprises a promoter operably linked to the nucleotide sequence encoding the sense strand sequence and the antisense strand sequence or the modulatory polynucleotide.

93. The AAV viral genome of embodiment 92, wherein the promoter is a ubiquitous promoter.

94. The AAV viral genome of embodiment 92, wherein the promoter is a cell or tissue specific promoter.

95. The AAV viral genome of any one of embodiments 92-94, wherein the promoter is chosen from human elongation factor 1α-subunit (EF1α), cytomegalovirus (CMV) immediate-early enhancer and/or promoter, chicken β-actin (CBA) and its derivative CAG, β glucuronidase (GUSB), or ubiquitin C (UBC), neuron-specific enolase (NSE), platelet-derived growth factor (PDGF), platelet-derived growth factor B-chain (PDGF-β), intercellular adhesion molecule 2 (ICAM-2), synapsin (Syn), methyl-CpG binding protein 2 (MeCP2), Ca2+/calmodulin-dependent protein kinase II (CaMKII), metabotropic glutamate receptor 2 (mGluR2), neurofilament light chain (NFL) or neurofilament heavy chain (NFH), β-globin minigene nβ2, preproenkephalin (PPE), enkephalin (Enk) and excitatory amino acid transporter 2 (EAAT2), glial fibrillary acidic protein (GFAP), myelin basic protein (MBP), a cardiovascular promoter (e.g., αMHC, cTnT, and CMV-MLC2k), a liver promoter (e.g., hAAT, TBG), a skeletal muscle promoter (e.g., desmin, MCK, C512) or a functional fragment, e.g., a truncation, or a functional variant thereof.

96. The AAV viral genome of any one of embodiments 92-95, wherein the promoter comprises a CBA promoter or a variant thereof.

97. The AAV viral genome of any one of embodiments 92-95, wherein the promoter comprises the nucleotide sequence of any one of the nucleotide sequences provided in Table 2; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to any one of the nucleotide sequences provided in Table 2; or a nucleotide sequence with at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity to any one of the nucleotide sequences provided in Table 2.

98. The AAV viral genome of any one of embodiments 92-97, wherein the promoter comprises the nucleotide sequence of SEQ ID NO: 5199; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5199; or a nucleotide sequence with at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO: 5199.

99. The AAV viral genome of any one of embodiments 92-97, wherein the AAV viral genome further comprises a polyA signal sequence.

100. The AAV viral genome of embodiment 99, wherein the polyA signal sequence comprises the nucleotide sequence of SEQ ID NO: 4476; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4476; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4476.

101. The AAV viral genome of any one of embodiments 26-32, wherein the AAV viral genome further comprises an inverted terminal repeat (ITR) sequence.

102. The AAV viral genome of embodiment 101, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 5197, 5200, 4469, or 4470; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5197, 5200, 4469, or 4470; or a nucleotide sequence with at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO: 5197, 5200, 4469, or 4470.

103. The AAV viral genome of any one of embodiments 12-58 or 60-102, wherein the AAV viral genome comprises an ITR sequence positioned 5' relative to the nucleic acid encoding the modulatory polynucleotide or siRNA.

104. The AAV viral genome of embodiment 103, wherein the ITR positioned 5' relative to the nucleic acid encoding the modulator polynucleotide or siRNA comprises the nucleotide sequence of SEQ ID NO: 5197 or 4469; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5197 or 4469; or a nucleotide sequence with at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO: 5197 or 4469.

105. The AAV viral genome of any one of embodiments 12-58 or 60-104, wherein the AAV viral genome comprises an ITR sequence positioned 3' relative to the nucleic acid encoding the modulatory polynucleotide or siRNA.

106. The AAV viral genome of embodiment 103, wherein the ITR positioned 3' relative to the nucleic acid encoding the modulator polynucleotide or siRNA comprises the nucleotide sequence of SEQ ID NO: 5200 or 4470; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5200 or 4470; or a

nucleotide sequence with at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO: 5200 or 4470.

107. The AAV viral genome particle of any one of embodiments 12-58 or 60-106, wherein the AAV viral genome comprises an ITR sequence positioned 5' relative to the nucleic acid encoding the modulatory polynucleotide or siRNA and an ITR sequence positioned 3' relative to the nucleic acid encoding the modulatory polynucleotide or siRNA.

108. The AAV viral genome of any one of embodiments 105-107, wherein:

(i) the ITR positioned 5' relative to the nucleic acid encoding the modulatory polynucleotide or siRNA comprises the nucleotide sequence of SEQ ID NO: 5197; a nucleotide sequence at least 80%, 85%, 90%, 92% 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5197; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5197; and

(ii) the ITR positioned 3' relative to the nucleic acid encoding the modulatory polynucleotide or siRNA comprises the nucleotide sequence of SEQ ID NO: 5200; a nucleotide sequence at least 80%, 85%, 90%, 92% 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5200; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5200.

109. The AAV viral genome of any one of embodiments 105-107, wherein:

(i) the ITR positioned 5' relative to the nucleic acid encoding the modulatory polynucleotide or siRNA comprises the nucleotide sequence of SEQ ID NO: 4469; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4469; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4469; and

(ii) the ITR positioned 3' relative to the nucleic acid encoding the modulatory polynucleotide or siRNA comprises the nucleotide sequence of SEQ ID NO: 4470; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4470; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4470.

110. The AAV viral genome of any one of embodiments 12-58 or 60-109, wherein the AAV viral genome further comprises an enhancer, a Kozak sequence, an intron region, and/or an exon region.

111. The AAV viral genome of embodiment 110, wherein the enhancer comprises:

(i) a CMVie enhancer or variant thereof; or

(ii) the nucleotide sequence of SEQ ID NO: 4471 or 4472; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4471 or 4472; or a nucleotide sequence with at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO: 4471 or 4472.

112. The AAV viral genome of embodiment 110 or 111, wherein the enhancer comprises the nucleotide sequence of SEQ ID NO: 4471; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4471; or a nucleotide sequence with at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO: 4471.

113. The AAV viral genome of any one of embodiments 12-58 or 60-112, which comprises a CMVie enhancer or variant thereof; and a CBA promoter or variant thereof; optionally wherein the CMVie enhancer or variant thereof is present 5' relative to the CBA promoter or variant thereof.

114. The AAV viral genome of any one of embodiments 110-113, wherein the enhancer and promoter comprise the nucleotide sequence of SEQ ID NO: 4473 or 4474; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4473 or 4474; or a nucleotide sequence with at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO: 4473 or 4474.

115. The AAV viral genome of any one of embodiments 110-114, wherein the intron comprises:

(i) a human beta globin intron (hBG intron) or variant thereof; or

(ii) the nucleotide sequence of SEQ ID NO: 4475; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4475; or a nucleotide sequence with at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO: 4475.

116. The AAV viral genome of any one of embodiments 12-58 or 60-115, wherein the AAV viral genome further comprises a nucleotide sequence encoding a miR binding site, e.g., a miR binding site that modulates, e.g., reduces expression of the payload encoded by the viral genome in a cell or tissue where the corresponding miRNA is expressed.

117. The AAV viral genome of embodiment 116, wherein the encoded miR binding site modulates, e.g., reduces expression of the encoded payload in a cell or tissue of the DRG, liver, heart, hematopoietic lineage, or a combination thereof.

118. The AAV viral genome of any one of embodiments 12-58 or 60-117, wherein the AAV viral genome comprises at least 1-5 copies of the encoded miR binding site, e.g., at least 1, 2, 3, 4, or 5 copies, optionally wherein the at least 1-5 copies are continuous (e.g., not separated by a spacer) or the at least 1-5 copies are separated by a spacer.

119. The AAV viral genome of any one of embodiments 12-58 or 60-118, wherein the AAV viral genome is self-complementary.

120. The AAV viral genome of any one of embodiments 12-58 or 60-118, wherein the AAV viral genome is single stranded.

121. The AAV viral genome of any one of embodiments 12-58 or 60-120, wherein the AAV viral genome further comprises a nucleotide sequence encoding a Rep protein, e.g., a non-structural protein, wherein the Rep protein comprises a Rep78 protein, a Rep68, Rep52 protein, and/or a Rep40 protein (e.g., a Rep78 and a Rep52 protein).

122. The AAV viral genome of any one of embodiments 12-58 or 60-121, wherein the AAV viral genome comprises in 5' to 3' order:

(i) an ITR;

(ii) an enhancer (e.g., a CMVie enhancer or variant thereof);

(iii) a promoter (e.g., a CBA promoter or variant thereof);

(iv) an intron (e.g., an hBG intron or variant thereof);

(v) a nucleic acid sequence encoding a modulatory polynucleotide (e.g. the modulatory polynucleotide of any one of embodiments 59-90);

(vi) a polyA signal sequence; and

(vii) an ITR.

123. The AAV viral genome of any one of embodiments 12-58 or 60-122, wherein the AAV viral genome comprises in 5' to 3' order:

(i) an ITR, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 5197; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5197; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5197;

(ii) an enhancer, wherein the enhancer comprises the nucleotide sequence of SEQ ID NO: 4471; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4471; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4471;

(iii) a promoter, wherein the promoter comprises the nucleotide sequence of SEQ ID NO: 5199; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5199; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5199;

(iv) an intron, wherein the intro comprises the nucleotide sequence of SEQ ID NO: 4475; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4475; or a nucleotide sequence at least 80%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4475;

(v) a nucleotide sequence encoding a modulatory polynucleotide, wherein the nucleotide sequence comprises any one of SEQ ID NOs: 4380-4409 or 5027-5050, or nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto;

(vi) a polyA signal sequence, wherein the polyA signal sequence comprises the nucleotide sequence of SEQ ID NO: 4476; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4476; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4476; and

(vii) an ITR, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 5200; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5200; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5200.

124. The AAV viral genome of any one of embodiments 12-58 or 60-122, wherein the AAV viral genome comprises in 5' to 3' order:

(i) an ITR, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 5197; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5197; or a

nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5197;

(ii) an enhancer, wherein the enhancer comprises the nucleotide sequence of SEQ ID NO: 4471; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4471; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4471;

(iii) a promoter, wherein the promoter comprises the nucleotide sequence of SEQ ID NO: 5199; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5199; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5199;

(iv) an intron, wherein the intro comprises the nucleotide sequence of SEQ ID NO: 4475; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4475; or a nucleotide sequence at least 80%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4475;

(v) a nucleotide sequence encoding a modulatory polynucleotide, wherein the nucleotide sequence comprises any one of SEQ ID NOs: 4405, 4408, 4409, 4390, 4391, 4393, or 4394, or nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto;

(vi) a polyA signal sequence, wherein the polyA signal sequence comprises the nucleotide sequence of SEQ ID NO: 4476; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4476; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4476; and

(vii) an ITR, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 5200; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5200; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5200.

125. The AAV viral genome of any one of embodiments 12-58 or 60-122, wherein the AAV viral genome comprises in 5' to 3' order:

(i) an ITR, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 5197; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5197; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5197;

(ii) an enhancer, wherein the enhancer comprises the nucleotide sequence of SEQ ID NO: 4471; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4471; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4471;

(iii) a promoter, wherein the promoter comprises the nucleotide sequence of SEQ ID NO: 5199; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5199; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5199;

(iv) an intron, wherein the intro comprises the nucleotide sequence of SEQ ID NO: 4475; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4475; or a nucleotide sequence at least 80%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4475;

(v) a nucleotide sequence encoding a modulatory polynucleotide, wherein the nucleotide sequence comprises SEQ ID NO: 4405, or nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto;

(vi) a polyA signal sequence, wherein the polyA signal sequence comprises the nucleotide sequence of SEQ ID NO: 4476; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4476; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4476; and

(vii) an ITR, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 5200; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5200; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5200.

126. The AAV viral genome of any one of embodiments 12-58 or 60-122, wherein the AAV viral genome comprises in 5' to 3' order:

(i) an ITR, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 5197; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5197; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5197;

(ii) an enhancer, wherein the enhancer comprises the nucleotide sequence of SEQ ID NO: 4471; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten

modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4471; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4471;

(iii) a promoter, wherein the promoter comprises the nucleotide sequence of SEQ ID NO: 5199; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5199; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5199;

(iv) an intron, wherein the intro comprises the nucleotide sequence of SEQ ID NO: 4475; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4475; or a nucleotide sequence at least 80%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4475;

(v) a nucleotide sequence encoding a modulatory polynucleotide, wherein the nucleotide sequence comprises SEQ ID NO: 4408, or nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto;

(vi) a polyA signal sequence, wherein the polyA signal sequence comprises the nucleotide sequence of SEQ ID NO: 4476; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4476; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4476; and

(vii) an ITR, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 5200; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5200; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5200.

127. The AAV viral genome of any one of embodiments 12-58 or 60-122, wherein the AAV viral genome comprises in 5' to 3' order:

(i) an ITR, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 5197; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5197; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5197;

(ii) an enhancer, wherein the enhancer comprises the nucleotide sequence of SEQ ID NO: 4471; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4471; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4471;

(iii) a promoter, wherein the promoter comprises the nucleotide sequence of SEQ ID NO: 5199; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5199; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5199;

(iv) an intron, wherein the intro comprises the nucleotide sequence of SEQ ID NO: 4475; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4475; or a nucleotide sequence at least 80%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4475;

(v) a nucleotide sequence encoding a modulatory polynucleotide, wherein the nucleotide sequence comprises SEQ ID NO: 4409, or nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto;

(vi) a polyA signal sequence, wherein the polyA signal sequence comprises the nucleotide sequence of SEQ ID NO: 4476; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4476; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4476; and

(vii) an ITR, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 5200; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5200; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5200.

128. The AAV viral genome of any one of embodiments 12-58 or 60-122, wherein the AAV viral genome comprises in 5' to 3' order:

(i) an ITR, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 5197; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5197; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5197;

(ii) an enhancer, wherein the enhancer comprises the nucleotide sequence of SEQ ID NO: 4471; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4471; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4471;

(iii) a promoter, wherein the promoter comprises the nucleotide sequence of SEQ ID NO: 5199; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten

modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5199; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5199;

(iv) an intron, wherein the intro comprises the nucleotide sequence of SEQ ID NO: 4475; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4475; or a nucleotide sequence at least 80%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4475;

(v) a nucleotide sequence encoding a modulatory polynucleotide, wherein the nucleotide sequence comprises SEQ ID NO: 4390, or nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto;

(vi) a polyA signal sequence, wherein the polyA signal sequence comprises the nucleotide sequence of SEQ ID NO: 4476; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4476; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4476; and

(vii) an ITR, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 5200; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5200; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5200.

129. The AAV viral genome of any one of embodiments 12-58 or 60-122, wherein the AAV viral genome comprises in 5' to 3' order:

(i) an ITR, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 5197; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5197; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5197;

(ii) an enhancer, wherein the enhancer comprises the nucleotide sequence of SEQ ID NO: 4471; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4471; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4471;

(iii) a promoter, wherein the promoter comprises the nucleotide sequence of SEQ ID NO: 5199; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5199; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5199;

(iv) an intron, wherein the intro comprises the nucleotide sequence of SEQ ID NO: 4475; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4475; or a nucleotide sequence at least 80%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4475;

(v) a nucleotide sequence encoding a modulatory polynucleotide, wherein the nucleotide sequence comprises SEQ ID NO: 4391, or nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto;

(vi) a polyA signal sequence, wherein the polyA signal sequence comprises the nucleotide sequence of SEQ ID NO: 4476; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4476; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4476; and

(vii) an ITR, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 5200; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5200; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5200.

130. The AAV viral genome of any one of embodiments 12-58 or 60-122, wherein the AAV viral genome comprises in 5' to 3' order:

(i) an ITR, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 5197; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5197; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5197;

(ii) an enhancer, wherein the enhancer comprises the nucleotide sequence of SEQ ID NO: 4471; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4471; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4471;

(iii) a promoter, wherein the promoter comprises the nucleotide sequence of SEQ ID NO: 5199; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5199; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5199;

(iv) an intron, wherein the intro comprises the nucleotide sequence of SEQ ID NO: 4475; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g.,

substitutions, insertions, or deletions, relative to SEQ ID NO: 4475; or a nucleotide sequence at least 80%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4475;

(v) a nucleotide sequence encoding a modulatory polynucleotide, wherein the nucleotide sequence comprises SEQ ID NO: 4393, or nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto;

(vi) a polyA signal sequence, wherein the polyA signal sequence comprises the nucleotide sequence of SEQ ID NO: 4476; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4476; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4476; and

(vii) an ITR, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 5200; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5200; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5200.

131. The AAV viral genome of any one of embodiments 12-58 or 60-122, wherein the AAV viral genome comprises in 5' to 3' order:

(i) an ITR, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 5197; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5197; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5197;

(ii) an enhancer, wherein the enhancer comprises the nucleotide sequence of SEQ ID NO: 4471; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4471; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4471;

(iii) a promoter, wherein the promoter comprises the nucleotide sequence of SEQ ID NO: 5199; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5199; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5199;

(iv) an intron, wherein the intro comprises the nucleotide sequence of SEQ ID NO: 4475; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4475; or a nucleotide sequence at least 80%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4475;

(v) a nucleotide sequence encoding a modulatory polynucleotide, wherein the nucleotide sequence comprises SEQ ID NO: 4394, or nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto;

(vi) a polyA signal sequence, wherein the polyA signal sequence comprises the nucleotide sequence of SEQ ID NO: 4476; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4476; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4476; and

(vii) an ITR, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 5200; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5200; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5200.

132. The AAV viral genome of any one of embodiments 12-58 or 60-122, wherein the AAV viral genome comprises in 5' to 3' order:

(i) an ITR, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 4469; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4469; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4469;

(ii) an enhancer, wherein the enhancer comprises the nucleotide sequence of SEQ ID NO: 4472; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4472; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4472;

(iii) a promoter, wherein the promoter comprises the nucleotide sequence of SEQ ID NO: 5199; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5199; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5199;

(iv) an intron, wherein the intro comprises the nucleotide sequence of SEQ ID NO: 4475; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4475; or a nucleotide sequence at least 80%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4475;

(v) a nucleotide sequence encoding a modulatory polynucleotide, wherein the nucleotide sequence comprises any one of SEQ ID NOs: 4380-4409 or 5027-5050, or nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto;

(vi) a polyA signal sequence, wherein the polyA signal sequence comprises the nucleotide sequence of SEQ ID NO: 4476; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4476; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4476; and

(vii) an ITR, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 4470; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4470; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4470.

133. The AAV viral genome of any one of embodiments 12-58 or 60-132, which comprises the nucleotide sequence of any one of SEQ ID NOs: 4439-4468 or 5149-5196, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to any one of SEQ ID NOs: 4439-4468 or 5149-5196.

134. The AAV viral genome of any one of embodiments 12-58, 60-96, 98-108, or 110-133, which comprises the nucleotide sequence of any one of SEQ ID NOs: 5149-5196, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to any one of SEQ ID NOs: 5149-5196.

135. The AAV viral genome of any one of embodiments 12-58, 60-96, 98-108, 110-133, or 134, which comprises the nucleotide sequence of any one of SEQ ID NOs: 5173, 5195, 5196, 5182, 5183, 5184, or 5185, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to any one of SEQ ID NOs: 5173, 5195, 5196, 5182, 5183, 5184, or 5185.

136. The AAV viral genome of any one of embodiments 12-58, 60-96, 98-108, 110-125, or 133-135, which comprises the nucleotide sequence of SEQ ID NO: 5173, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5173.

137. The AAV viral genome of any one of embodiments 12-58, 60-96, 98-108, 110-124, 126, or 133-135, which comprises the nucleotide sequence of SEQ ID NO: 5195, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5195.

138. The AAV viral genome of any one of embodiments 12-58, 60-96, 98-108, 110-124, 127, or 133-135, which comprises the nucleotide sequence of SEQ ID NO: 5196, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5196.

139. The AAV viral genome of any one of embodiments 12-58, 60-96, 98-108, 110-124, 128, or 133-135, which comprises the nucleotide sequence of SEQ ID NO: 5182, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5182.

140. The AAV viral genome of any one of embodiments 12-58, 60-96, 98-108, 110-124, 129, or 133-135, which comprises the nucleotide sequence of SEQ ID NO: 5183, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5183.

141. The AAV viral genome of any one of embodiments 12-58, 60-96, 98-108, 110-124, 130, or 133-135, which comprises the nucleotide sequence of SEQ ID NO: 5184, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5184.

142. The AAV viral genome of any one of embodiments 12-58, 60-96, 98-108, 110-124, 131, or 133-135, which comprises the nucleotide sequence of SEQ ID NO: 5185, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5185.

143. The AAV viral genome of any one of embodiments 12-58, 60-96, 98-107, 109-122, or 133, which comprises the nucleotide sequence of any one of SEQ ID NOs: 4439-4468, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to any one of SEQ ID NOs: 4439-4468.

144. An AAV particle comprising the AAV viral genome of any one of embodiments 12-58 or 60-143, an AAV viral genome encoding the modulatory polynucleotide of any one of embodiments 59-90, or an AAV viral genome encoding the siRNA of any one of embodiments 11 or 13-58, and an AAV capsid protein.

145. The AAV particle of embodiment 48, wherein the AAV capsid protein comprises an AAV5 capsid protein, an AAV9 capsid protein, VOY101 capsid protein, a PHPeB capsid protein, a PHP.B capsid protein, a PHP.N capsid protein, an AAV1 capsid protein, a VOY9P39 capsid protein, an AAV2 capsid protein, an AAVrh10 capsid protein, or a variant thereof (e.g., an AAV9 capsid protein or a variant thereof or an AAV5 capsid protein or variant thereof).

146. The AAV particle of embodiment 144 or 145, wherein the AAV capsid protein comprises an AAV9 capsid or variant thereof.

147. The AAV particle of embodiment 144 or 145, wherein the AAV capsid protein comprises an AAV5 capsid or variant thereof.

148. The AAV particle of any one of embodiments 144-147, wherein:

(i) the AAV capsid protein comprises an amino acid sequence provided in Table 1 or an amino acid sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% identical thereto; or

(ii) the nucleotide sequence encoding the AAV capsid protein comprises any one of the nucleotide sequences in Table 1, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% identical thereto.

149. A vector comprising the AAV viral genome of any one of embodiments 12-58 or 60-143, a nucleotide sequence encoding the modulatory polynucleotide of any one of embodiments 59-90, or a nucleotide sequence encoding the siRNA of any one of embodiments 11 or 13-58.

150. A cell comprising the AAV particle of any one of embodiments 144-148, the AAV viral genome of any one of embodiments 12-58 or 60-143, the modulatory polynucleotide of any one of embodiments 59-90, or the siRNA of any one of embodiments 11 or 13-58.

151. The cell of embodiment 150, wherein the cell is a mammalian cell or an insect cell.

152. The cell of embodiment 150 or 151, wherein the cell is a cell of a brain region or a spinal cord region (e.g., a CNS cell).

153. The cell of any one of embodiments 150-152, wherein the cell is a cell of the cortex, hippocampus, thalamus, or brainstem.

154. The cell of any one of embodiments 150-153, wherein the cell is a neuron, a glial cell, or an oligodendrocyte.

155. A method of making an AAV particle, comprising:

(i) providing a host cell comprising the AAV viral genome of any one of embodiments 12-58 or 60-143, an AAV viral genome encoding the modulatory polynucleotide of any one of embodiments 59-90, or a viral genome encoding the siRNA of any one of embodiments 11 or 13-58;

(ii) incubating the host cell under conditions suitable to enclose the AAV viral genome in an AAV capsid protein;

thereby making the AAV particle.

156. The method of embodiment 155, further comprising, prior to step (i), introducing a first nucleic acid molecule comprising the viral genome into the host cell.

157. The method of embodiment 155 or 156, wherein the host cell comprises a second nucleic acid encoding the AAV capsid protein.

158. The method of embodiment 157, wherein the second nucleic acid molecule is introduced into the host cell prior to, concurrently with, or after the first nucleic acid molecule.

159. A pharmaceutical composition comprising the AAV particle of any one of embodiments 144-148, an AAV particle comprising the AAV viral genome of any one of embodiments 12-58 or 60-143, the modulatory polynucleotide of any one of embodiments 59-90, or the siRNA of any one of embodiments 11 or 13-58, and a pharmaceutically acceptable excipient.

160. A method of delivering an siRNA for inhibiting MAPT expression (e.g., MAPT gene, mRNA, or protein expression) to a cell, comprising administering an effective amount of the pharmaceutical composition of embodiment 159, the AAV particle of any one of embodiments 144-159, an AAV particle comprising the AAV viral genome of any one of embodiments 12-58 or 60-143, the modulatory polynucleotide of any one of embodiments 59-90, or the siRNA of any one of embodiments 11 or 13-58, thereby delivering the siRNA for inhibiting MAPT expression to the cell.

161. The method of embodiment 160, wherein the cell is a cell of a brain region or a spinal cord region.

162. The method of embodiment 160 or 161, wherein the cell is a cell of the cortex, hippocampus, thalamus, or brainstem.

163. The method of any one of embodiments 160-162, wherein the cell is a neuron, an astrocyte, a glial cell, or an oligodendrocyte.

164. The method of any one of embodiments 160-163, wherein delivery decreases (e.g., inhibits) MAPT mRNA levels, e.g., by at least 40%, 44%, 45%, 50%, 55%, 60%, 64%, 65%, 70%, 75%, 76%, 79%, 80%, 84%, 85%, 87%, or 90%, e.g., in a cell of a brain region (e.g., cortex, hippocampus, or brain stem), e.g., as compared to a reference level (e.g., the mRNA levels in a cell that has not been delivered or prior to delivering the AAV particle, modulatory polynucleotide, siRNA, or pharmaceutical composition), e.g., when measured by an assay (e.g., an assay as described in Example 6).

165. The method of any one of embodiments 160-164, wherein delivery decreases (e.g., inhibits) MAPT protein levels, e.g., by at least 15%, 17%, 20%, 25%, 30%, 35%, 37%, 40%, 44%, 45%, 46%, 50%, 53%, 55%, 60%, 63%, 64%, 65%, 70%, 72%, 74%, or 75%, e.g., in a cell of a brain region (e.g., cortex, hippocampus, thalamus, or brain stem), e.g., as compared to a reference level (e.g., the protein levels in a cells that has not been delivered or prior to delivering the AAV particle, modulatory polynucleotide, siRNA, or pharmaceutical composition), e.g., when measured by an assay (e.g., an assay as described in Example 6).

166. The method of any one of embodiments 160-165, wherein the cell is in a subject.

167. The method of embodiment 166, wherein the subject has or has been diagnosed with having a genetic disorder (e.g., a monogenic disorder or a polygenic disorder).

168. The method of embodiment 166 or 167, wherein the subject has or has been diagnosed with having a neurological disorder (e.g., a neurodegenerative disorder).

169. The method of any one of embodiments 166-168, wherein the subject has or has been diagnosed with having a disorder associated with tau expression, e.g., aberrant tau expression.

170. The method of any one of embodiments 166-169, wherein the subject has or has been diagnosed with having a tauopathy.

171. A method of treating a subject having or diagnosed with having a genetic disorder, e.g., a monogenic disorder or a polygenic disorder, comprising administering to the subject an effective amount of the pharmaceutical composition of embodiment 159, the AAV particle of any one of embodiments 144-159, an

AAV particle comprising the AAV viral genome of any one of embodiments 12-58 or 60-143, the modulatory polynucleotide of any one of embodiments 59-90, or the siRNA of any one of embodiments 11 or 13-58, thereby treating the subject having or diagnosed with having the genetic disorder, e.g., the monogenic disorder or the polygenic disorder.

172. A method of treating a subject having or diagnosed with having a neurological disorder (e.g., a neurodegenerative disorder), comprising administering to the subject an effective amount of the pharmaceutical composition of embodiment 159, the AAV particle of any one of embodiments 144-159, an AAV particle comprising the AAV viral genome of any one of embodiments 12-58 or 60-143, the modulatory polynucleotide of any one of embodiments 59-90, or the siRNA of any one of embodiments 11 or 13-58, thereby treating the subject having or diagnosed with having the neurological disorder (e.g., the neurodegenerative disorder).

173. A method of treating a subject having or diagnosed with having a disorder associated with tau expression, e.g., aberrant tau expression, comprising administering to the subject an effective amount of the pharmaceutical composition of embodiment 159, the AAV particle of any one of embodiments 144-159, an AAV particle comprising the AAV viral genome of any one of embodiments 12-58 or 60-143, the modulatory polynucleotide of any one of embodiments 59-90, or the siRNA of any one of embodiments 11 or 13-58, thereby treating the subject having or diagnosed with having the disorder associate with tau expression, e.g., aberrant tau expression.

174. A method of treating a subject having or diagnosed with having a tauopathy, comprising administering to the subject an effective amount of the pharmaceutical composition of embodiment 159, the AAV particle of any one of embodiments 144-159, an AAV particle comprising the AAV viral genome of any one of embodiments 12-58 or 60-143, the modulatory polynucleotide of any one of embodiments 59-90, or the siRNA of any one of embodiments 11 or 13-58, thereby treating the subject having or diagnosed with having the tauopathy.

175. The method of any one of embodiments 167-174, wherein the genetic disorder, neurological disorder (e.g., neurodegenerative disorder), disorder associated with tau expression (e.g., aberrant tau expression), and/or tauopathy is Alzheimer's disease (AD), Frontotemporal dementia (FTD), frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), frontotemporal lobar degeneration (FTLD), Dravet syndrome (DS), neurodegenerative disease, traumatic brain injury (TBI), chronic traumatic encephalopathy (CTE), progressive supranuclear palsy (PSP), Down's syndrome, Pick's disease, corticobasal degeneration

(CBD), corticobasal syndrome, amyotrophic lateral sclerosis (ALS), Prion diseases, CJD, Multiple system atrophy, mild cognitive impairment, Tangle-only dementia, or Progressive subcortical gliosis.

176. The method of any one of embodiments 171-175, wherein treating comprises prevention of progression of the genetic disorder, neurological disorder (e.g., neurodegenerative disorder), disorder associated with tau expression (e.g., aberrant tau expression), and/or tauopathy in the subject.

177. The method of any one of embodiments 171-176, further comprising performing a blood test, an imaging test (e.g., a PET scan or a PET scan in combination with biomarker, e.g., serum biomarker staining), a CNS biopsy sample, or an aqueous cerebral spinal fluid biopsy, optionally wherein the blood test, imaging test, biopsy sample, or aqueous cerebral spinal fluid biopsy is performed prior to, during, or after treatment with the AAV particle, modulatory polynucleotide, siRNA, or pharmaceutical composition.

178. The method of any one of embodiments 160-177, wherein administration decreases, e.g., reduces or inhibits, expression of a MAPT gene, mRNA, and/or protein.

179. The method of embodiments 178, wherein the MAPT gene, mRNA, and/or protein is a wild-type MAPT gene, mRNA, or protein.

180. The method of embodiment 178 or 179, wherein the MAPT gene, mRNA, and/or protein is a mutated MAPT gene, mRNA, or protein (e.g., comprises at least 1 mutation).

181. The method of any one of embodiments 171-180, wherein administration of the AAV particle, modulatory polynucleotide, siRNA, or pharmaceutical composition results in a reduction and/or prevention of tau pathology, e.g., a decrease in a biomarker of tau pathology (e.g., ^{18}F-flortaucipir, plasma ptau 181, or ^{18}F-PM-PBB3), e.g., as measured by a PET scan or PET scan in combination with Braak neuropathological staging and/or serum biomarker staining, e.g., as compared to a reference (e.g., a subject that as not received the AAV particle, modulatory polynucleotide, siRNA, or pharmaceutical composition).

182. The method of any one of embodiments 171-181, wherein the administration decreases MAPT mRNA levels in the subject, e.g., by at least 40%, 44%, 45%, 50%, 55%, 60%, 64%, 65%, 70%, 75%, 76%, 79%, 80%, 84%, 85%, 87%, or 90%, e.g., in a cell of a brain region (e.g., cortex, hippocampus, or brain stem), e.g., as compared to a reference level (e.g., the mRNA levels in a subject that has not received or prior to receiving

the AAV particle, modulatory polynucleotide, siRNA, or pharmaceutical composition), e.g., when measured by an assay (e.g., an assay as described in Example 6).

183. The method of any one of embodiments 171-182, wherein the administration decreases MAPT protein levels in the subject, e.g., by at least 15%, 17%, 20%, 25%, 30%, 35%, 37%, 40%, 44%, 45%, 46%, 50%, 53%, 55%, 60%, 63%, 64%, 65%, 70%, 72%, 74%, or 75%, e.g., in a cell of a brain region (e.g., cortex, hippocampus, thalamus, or brain stem), e.g., as compared to a reference level (e.g., the protein levels in a subject that has not received or prior to receiving the AAV particle, modulatory polynucleotide, siRNA, or pharmaceutical composition), e.g., when measured by an assay (e.g., an assay as described in Example 6).

184. The method of any one of embodiments 166-183, wherein the subject is a human.

185. The method of any one of embodiments 166-184, wherein the pharmaceutical composition, AAV particle, modulatory polynucleotide, or siRNA are administered to the subject intravenously, intramuscularly, via intraparenchymal administration, intracerebroventricularly, via intra-cisterna magna (ICM) injection, intrathecally, via focused ultrasound (FUS), *e.g.*, coupled with the intravenous administration of microbubbles (FUS-MB), or MRI-guided FUS coupled with intravenous administration.

186. The method of any one of embodiments 166-185, wherein the pharmaceutical composition, AAV particle, modulatory polynucleotide, or siRNA are administered to the subject intravenously.

187. The method of any one of embodiments 166-186, wherein the pharmaceutical composition, AAV particle, modulatory polynucleotide, or siRNA are administered to the subject via intra-cisterna magna injection (ICM).

188. The method of any one of embodiments 166-187, wherein the pharmaceutical composition, AAV particle, modulatory polynucleotide, or siRNA are administered to the subject intrathecally.

189. The pharmaceutical composition of embodiment 159, the AAV particle of any one of embodiments 144-159, an AAV particle comprising the AAV viral genome of any one of embodiments 12-58 or 60-143, the modulatory polynucleotide of any one of embodiments 59-90, or the siRNA of any one of embodiments 11 or 13-58 for use in a method of delivering an siRNA for inhibiting MAPT expression to a cell.

190. The pharmaceutical composition of embodiment 159, the AAV particle of any one of embodiments 144-159, an AAV particle comprising the AAV viral genome of any one of embodiments 12-58 or 60-143, the

modulatory polynucleotide of any one of embodiments 59-90, or the siRNA of any one of embodiments 11 or 13-58, for use in the manufacture of a medicament.

191. The pharmaceutical composition of embodiment 159, the AAV particle of any one of embodiments 144-159, an AAV particle comprising the AAV viral genome of any one of embodiments 12-58 or 60-143, the modulatory polynucleotide of any one of embodiments 59-90, or the siRNA of any one of embodiments 11 or 13-58, for use in the treatment of a genetic disorder, neurological disorder (e.g., neurodegenerative disorder), disorder associated with tau expression (e.g., aberrant tau expression), and/or tauopathy.

192. Use of the pharmaceutical composition of embodiment 159, the AAV particle of any one of embodiments 144-159, an AAV particle comprising the AAV viral genome of any one of embodiments 12-58 or 60-143, the modulatory polynucleotide of any one of embodiments 59-90, or the siRNA of any one of embodiments 11 or 13-58, in the manufacture of a medicament for delivering an siRNA for inhibiting MAPT expression to a cell.

193. Use of the pharmaceutical composition of embodiment 159, the AAV particle of any one of embodiments 144-159, an AAV particle comprising the AAV viral genome of any one of embodiments 12-58 or 60-143, the modulatory polynucleotide of any one of embodiments 59-90, or the siRNA of any one of embodiments 11 or 13-58, in the manufacture of a medicament.

194. Use of the pharmaceutical composition of embodiment 159, the AAV particle of any one of embodiments 144-159, an AAV particle comprising the AAV viral genome of any one of embodiments 12-58 or 60-143, the modulatory polynucleotide of any one of embodiments 59-90, or the siRNA of any one of embodiments 11 or 13-58, in the manufacture of a medicament for treating a genetic disorder, neurological disorder (e.g., neurodegenerative disorder), disorder associated with tau expression (e.g., aberrant tau expression), and/or tauopathy.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018] **FIG. 1** is a graph depicting the relative R/F activity as % over non-target control (NTC) on the Y-axis post-transfection with the modulatory polynucleotide constructs targeting MAPT indicated on the X-axis (from left to right: VOYTaumiR-102-530 (SEQ ID NO: 4380), VOYTaumiR-102-556 (SEQ ID NO: 4381), VOYTaumiR-102-579 (SEQ ID NO: 4383), VOYTaumiR-102-586 (SEQ ID NO: 4384), VOYTaumiR-104-530 (SEQ ID NO: 4385), VOYTaumiR-104-556 (SEQ ID NO: 4386), VOYTaumiR-104-579 (SEQ ID NO: 4388), VOYTaumiR-104-586 (SEQ ID NO: 4389), VOYTaumiR-109-530 (SEQ ID NO: 4390), VOYTaumiR-109-556 (SEQ ID NO: 4391), VOYTaumiR-109-579 (SEQ ID NO: 4393), VOYTaumiR-109-

586 (SEQ ID NO: 4394), VOYTaumiR-114-530 (SEQ ID NO: 4395), VOYTaumiR-114-556 (SEQ ID NO: 4396), VOYTaumiR-114-579 (SEQ ID NO: 4398), VOYTaumiR-114-586 (SEQ ID NO: 4399), VOYTaumiR-116-530 (SEQ ID NO: 4400), VOYTaumiR-116-556 (SEQ ID NO: 4401), VOYTaumiR-116-579 (SEQ ID NO: 4403), VOYTaumiR-116-586 (SEQ ID NO: 4404), VOYTaumiR-127-530 (SEQ ID NO: 4405), VOYTaumiR-127-556 (SEQ ID NO: 4406), VOYTaumiR-127-579 (SEQ ID NO: 4408), and VOYTaumiR-127-586 (SEQ ID NO: 4409)).

[0019] **FIG. 2** is a graph showing the fold-change in MAPT mRNA remaining for each vectorized modulatory polynucleotide relative to the non-target control (fold change relative to NTC) on the Y-axis post-transfection with the modulatory polynucleotide constructs targeting MAPT indicated on the X-axis (from left to right: mock, non-target control (NTC), VOYTaumiR-127-530 (SEQ ID NO: 4405), VOYTaumiR-127-556 (SEQ ID NO: 4406), VOYTaumiR-127-579 (SEQ ID NO: 4408), VOYTaumiR-127-586 (SEQ ID NO: 4409), VOYTaumiR-116-530 (SEQ ID NO: 4400), VOYTaumiR-116-556 (SEQ ID NO: 4401), VOYTaumiR-116-579 (SEQ ID NO: 4403), VOYTaumiR-116-586 (SEQ ID NO: 4404), VOYTaumiR-114-530 (SEQ ID NO: 4395), VOYTaumiR-114-556 (SEQ ID NO: 4396), VOYTaumiR-114-579 (SEQ ID NO: 4398), VOYTaumiR-114-586 (SEQ ID NO: 4399), VOYTaumiR-109-530 (SEQ ID NO: 4390), VOYTaumiR-109-556 (SEQ ID NO: 4391), VOYTaumiR-109-579 (SEQ ID NO: 4393), VOYTaumiR-109-586 (SEQ ID NO: 4394), VOYTaumiR-104-530 (SEQ ID NO: 4385), VOYTaumiR-104-556 (SEQ ID NO: 4386), VOYTaumiR-104-579 (SEQ ID NO: 4388), VOYTaumiR-104-586 (SEQ ID NO: 4389), VOYTaumiR-102-530 (SEQ ID NO: 4380), VOYTaumiR-102-556 (SEQ ID NO: 4381), VOYTaumiR-102-579 (SEQ ID NO: 4383), and VOYTaumiR-102-586 (SEQ ID NO: 4384)).

[0020] **FIG. 3** is a graph showing the fold-change in MAPT mRNA remaining for each vectorized modulatory polynucleotide relative to the non-target control (fold change relative to NTC) on the Y-axis post-transfection with increasing concentrations (0.05 μg, 0.16 μg, 0.50 μg, or 1.50 μg per well) of the modulatory polynucleotides on the X-axis (from left to right: mock, non-target control (NTC), VOYTaumiR-127-530 (SEQ ID NO: 4405), VOYTaumiR-127-556 (SEQ ID NO: 4406), VOYTaumiR-127-579 (SEQ ID NO: 4408), VOYTaumiR-127-586 (SEQ ID NO: 4409), VOYTaumiR-109-530 (SEQ ID NO: 4390), VOYTaumiR-109-556 (SEQ ID NO: 4391), VOYTaumiR-109-579 (SEQ ID NO: 4393), VOYTaumiR-109-586 (SEQ ID NO: 4394), VOYTaumiR-116-579 (SEQ ID NO: 4403), VOYTaumiR-104-556 (SEQ ID NO: 4386), and VOYTaumiR-104-586 (SEQ ID NO: 4389)).

[0021] **FIG. 4** is a graph depicting the fold-change in MAPT mRNA remaining for each vectorized modulatory polynucleotide relative to the non-target control (fold change relative to NTC) on the Y-axis post-transfection with the indicated concentrations (0.5 μg or 1.0 μg) of the modulatory polynucleotides on the X-axis (from left to right: mock, GFP, NTC, MAPT antisense oligonucleotide (ASO) positive control, VOYTaumiR-127-530 (SEQ ID NO: 4405), VOYTaumiR-109-530 (SEQ ID NO: 4390), VOYTaumiR-102-

582 (SEQ ID NO: 5027), VOYTaumiR-104-582 (SEQ ID NO: 5031), VOYTaumiR-109-582 (SEQ ID NO: 5035), VOYTaumiR-114-582 (SEQ ID NO: 5039), VOYTaumiR-127-582 (SEQ ID NO: 5047), VOYTaumiR-102-587 (SEQ ID NO: 5028), VOYTaumiR-109-587 (SEQ ID NO: 5036), VOYTaumiR-114-587 (SEQ ID NO: 5040), VOYTaumiR-104-552 (SEQ ID NO: 5033), VOYTaumiR-104-549 (SEQ ID NO: 5034), and VOYTaumiR-116-549 (SEQ ID NO: 5046).

[0022] **FIGs. 5A-5E** are a series of graphs depicting the vector genome copies per diploid cells in the cortex (**FIG. 5A**), hippocampus (**FIG. 5B**), brainstem (**FIG. 5C**), thalamus (**FIG. 5D**), or liver (**FIG. 5E**) of mice following intravenous injection of the vehicle control or AAV particles comprising the VOY9P39 capsid encoding the VOYTaumiR-127-530 modulatory polynucleotide (VOY9P39_127-530) at a dose of 3e12 vg/kg, 1e13 vg/kg, or 3e13 vg/kg. Statistical significance was evaluated with a one-way ANOVA with Tukey's multiple comparisons post-hoc test: *, **, ***, and **** indicate $p < 0.05$, 0.005, 0.0005 and 0.0001, respectively. Data are shown as the group mean ± SEM. The numbers above the bars indicate the group mean in vg/dg (biodistribution).

[0023] **FIGs. 6A-6D** are a series of graphs depicting the fold-change in MAPT mRNA levels remaining post-treatment in each treatment group relative to the vehicle on the Y-axis, in the cortex (**FIG. 6A**), hippocampus (**FIG. 6B**), thalamus (**FIG. 6C**), or brainstem (**FIG. 6D**) of mice following intravenous injection of AAV particles comprising the payload and capsid combinations indicated on the X-axis, which are from left to right: vehicle control, VOY9P39 capsid and mCherry reporter control at 3e13 vg/kg, VOY9P39 capsid and non-target control (NTC) at 3e13 vg/kg, VOY9P39 capsid and VOYTaumiR-127-530 modulatory polynucleotide (127-530) at 3e12 vg/kg, VOY9P39 capsid and VOYTaumiR-127-530 modulatory polynucleotide (127-530) at 1e13 vg/kg, VOY9P39 capsid and VOYTaumiR-127-530 modulatory polynucleotide (127-530) at 3e13 vg/kg, VOY101 capsid and mCherry reporter control at 3e13 vg/kg, and VOY101 capsid and VOYTaumiR-127-530 modulatory polynucleotide (127-530) at 3e13 vg/kg. Statistical significance was evaluated with a one-way ANOVA with Tukey's multiple comparison with p-value as shown on the graphs.

[0024] **FIGs. 7A-7D** are a series of graphs depicting the MAPT protein levels remaining post-treatment in each treatment group relative to the vehicle in the cortex (**FIG. 7A**), hippocampus (**FIG. 7B**), thalamus (**FIG. 7C**), or brainstem (**FIG. 7D**) of mice following intravenous injection of the vehicle control (vehicle); or AAV particles comprising the VOY9P39 capsid encoding VOYTaumiR-127-530 modulatory polynucleotide (127-530) administered at a dose of 3e12 vg/kg, 1e13 vg/kg, or 3e13 vg/kg. The percentages above the bars represent the percent knockdown of tau protein following treatment. Statistical significance was evaluated with a one-way ANOVA with Tukey's multiple comparison.

[0025] **FIGs. 8A-8D** are a series of graphs depicting the MAPT mRNA levels remaining post-treatment in each treatment group relative to the vehicle in the cortex (**FIG. 8A**), hippocampus (**FIG. 8B**), thalamus

(FIG. 8C), or brainstem **(FIG. 8D)** of mice following intravenous injection of the vehicle control (vehicle); AAV particles comprising the VOY9P39 capsid encoding the non-target control (NTC) at dose of 1e13 vg/kg (C9P39-NTC_1E13); AAV particles comprising the VOY9P39 capsid encoding the VOYTaumiR-127-530 modulatory polynucleotide at a dose of 1e12 vg/kg (C9P39-127.530_1E12) or 1e13 vg/kg (C9P39-127.530_1E13); or AAV particles comprising the VOY9P39 capsid encoding the VOYTaumiR-127-579 modulatory polynucleotide at a dose of 1e13 vg/kg (C9P39-127.579_1E13). Statistical significance was evaluated with a one-way ANOVA with Tukey's multiple comparison with p-value as shown on the graphs.

DETAILED DESCRIPTION

[0026] Described herein, inter alia, are compositions comprising isolated, e.g., recombinant, viral particles, e.g., AAV particles, for delivery, e.g., vectorized delivery, of an RNA agent for targeting MAPT (e.g., a siRNA duplex for targeting MAPT) and methods of making and using the same. In some embodiments, the RNA agent for targeting MAPT is siRNA duplex that modulates, e.g., inhibits MAPT expression, e.g., a siRNA duplex for targeting MAPT as described herein. Generally, the recombinant AAV particles will include a viral genome comprising a nucleotide sequence, e.g., encoding a transgene encoding an RNA agent for targeting MAPT (e.g., a siRNA duplex for targeting MAPT) and an AAV capsid protein, e.g., an AAV capsid variant described herein.

[0027] Mutations in the MAPT gene were identified in the autosomal dominantly inherited tauopathy frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), which demonstrates that mutations in the MAPT gene and/or tau protein could lead to neurodegenerative changes in the brain. Mutant tau is considered more amyloidogenic than wild-type tau, meaning it is more likely to become hyperphosphorylated and to aggregate as NFT (Hutton, M. et al., 1998, Nature 393(6686):702-5), and these NFT can be composed of pathological forms of tau including, but not limited to, hyperphosphorylated, misfolded and aggregated tau species, each of which has yielded a set of avidly pursued targets. Hyperphosphorylation of tau depresses its binding to microtubules and microtubule assembly/stability activity. Further, hyperphosphorylation of tau renders it prone to misfolding and aggregation. Without wishing to be bound by theory, it is believed in some embodiments that administration of an siRNA targeting MAPT (e.g., a mutated MAPT gene or a wild-type MAPT gene), e.g., a siRNA for targeting MAPT described herein, and vectorized forms thereof, can reduce tau, e.g., pathological tau, protein expression, aggregation, hyperphosphorylation, and/or misfolding, thereby modulating, e.g., reducing or slowing, pathology associated with aberrant tau expression and/or tauopathies (e.g., Alzheimer's disease (AD), frontotemporal dementia (FTD), and/or Dravet syndrome (DS)).

[0028] Without wishing to be bound by theory, it is believed in some embodiments, that the use of an AAV particle or plurality of AAV particles for the vectorized delivery of an RNA agent for targeting MAPT (e.g., a siRNA duplex for targeting MAPT) described herein would lead to increased exposure in the central

nervous system (CNS), and robust expression of the RNA agent targeting MAPT in the subject, e.g., a subject having or diagnosed with having a disease associated with expression of tau or a neurological disorder described herein (e.g., a tauopathy).

I. COMPOSITIONS

[0029] According to the present disclosure, compositions for delivering a functional RNA agent for targeting MAPT by adeno-associated virus particles (AAVs), e.g., an AAV particle comprising an AAV capsid polypeptide are provided. In some embodiments, an AAV particle, e.g., an AAV particle comprising a an AAV capsid polypeptide, as described herein, or plurality of particles, may be provided, e.g., delivered, via any of several routes of administration (e.g., via intravenous administration), to a cell, tissue, organ, or organism, *in vivo*, *ex vivo*, or *in vitro*

Adeno-associated viruses (AAVs) and AAV particles

[0030] Described herein, inter alia, are compositions comprising isolated, e.g., recombinant, viral particles, e.g., AAV particles, for delivery, e.g., vectorized delivery, of a polynucleotide, e.g., a MAPT targeting siRNA, and methods of making and using the same.

[0031] In some embodiments, an adeno-associated virus (AAV) comprises a small non-enveloped icosahedral capsid virus of the Parvoviridae family and is characterized by a single stranded DNA viral genome. 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. In some embodiments, AAV is capable of replication in vertebrate hosts including, but not limited to, human, primate, bovine, canine, equine, and ovine species

[0032] In some embodiments, an AAV particle is used as a biological tool due to a relatively simple structure, their ability to infect a wide range of cells (including quiescent and dividing cells) without integration into the host genome and without replicating, and their relatively benign immunogenic profile. The genome of the virus may be manipulated to contain a minimum of components for the assembly of a functional recombinant virus, or viral particle, which is loaded with or engineered to target a particular tissue and express or deliver a desired payload, e.g., a polynucleotide encoding a siRNA for targeting MAPT.

[0033] In some embodiments, the AAV particle is a naturally occurring (e.g., wild-type) AAV or a recombinant AAV. In some embodiments, the wild-type AAV viral genome is a linear, single-stranded DNA (ssDNA) molecule approximately 5,000 nucleotides (nt) in length. In some embodiments, inverted terminal repeats (ITRs) cap the viral genome at both the 5' and the 3' end, providing origins of replication for the viral genome. In some embodiments, an AAV viral genome typically comprises two ITR sequences. These ITRs have a characteristic T-shaped hairpin structure defined by a self-complementary region (145nt in wild-type

AAV) at the 5' and 3' ends of the ssDNA which form an energetically stable double stranded region. The double stranded hairpin structures comprise multiple functions including, but not limited to, acting as an origin for DNA replication by functioning as primers for the endogenous DNA polymerase complex of the host viral replication cell.

[0034] In some embodiments, the AAV particle, e.g., an AAV particle (e.g., ssAAVs) described herein comprises a viral genome that is self-complementary (scAAV). In some embodiments, the ssAAV comprises nucleic acid molecules, e.g., DNA strands, that anneal together to form double stranded DNA. In some embodiments, a scAAV allows for rapid expression in a transduced cell as it bypasses second strand synthesis.

[0035] In some embodiments, the wild-type AAV viral genome further comprises nucleotide sequences for two open reading frames, one for the four non-structural Rep proteins (Rep78, Rep68, Rep52, Rep40, encoded by Rep genes) and one for the three capsid, or structural, proteins (VP1, VP2, VP3, encoded by capsid genes or Cap genes). The Rep proteins are used for replication and packaging, while the capsid proteins are assembled to create the protein shell of the AAV, or AAV capsid polypeptide, e.g., an AAV capsid variant. Alternative splicing and alternate initiation codons and promoters result in the generation of four different Rep proteins from a single open reading frame and the generation of three capsid proteins from a single open reading frame. Though it varies by AAV serotype, as a non-limiting example, for AAV9 (SEQ ID NO: 138) 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. In some embodiments, a viral genome of a wild-type, e.g., naturally occurring, AAV can be modified to replace the rep/cap sequences with a nucleic acid comprising a transgene encoding a payload, e.g., an antibody molecule, wherein the genetic element comprises at least one ITR region. In some embodiments, the viral genome of a recombinant AAV comprises two ITR regions, e.g., a 5'ITR or a 3'ITR. In some embodiments, the rep/cap sequences can be provided *in trans* during production to generate AAV particles. In some embodiments, the viral genome of an AAV is comprised in an AAV vector, which further encodes a capsid protein e.g., a structural protein, wherein the capsid protein comprises a VP1 polypeptide, a VP2 polypeptide, and/or a VP3 polypeptide; and/or a Rep protein, e.g., a non-structural protein, wherein the Rep protein comprises a Rep78 protein, a Rep68, Rep52 protein, and/or a Rep40 protein.

[0036] In some embodiments, AAV particles of the present disclosure are recombinant AAV particles which are replication defective and lacking the nucleotide sequences encoding functional Rep and Cap proteins. In some embodiments, these defective AAV particles may lack most or all parental coding sequences and carry only one or two AAV ITR sequences and the nucleic acid of interest for delivery to a cell, a tissue, an organ, or an organism.

[0037] Methods for producing and/or modifying AAV particles are disclosed in the art such as pseudotyped AAV particles (PCT Patent Publication Nos. WO200028004; WO200123001; WO2004112727; WO2005005610; and WO2005072364, the content of each of which is incorporated herein by reference in its entirety).

[0038] As described herein, the AAV particles of the disclosure comprising an AAV capsid polypeptide, and a viral genome are capable of providing, e.g., delivering, a transgene to a cell, e.g., mammalian cell ad/or a subject. In some embodiments, the recombinant AAV particles of the present disclosure are capable of vectorized delivery of a siRNA (e.g., an siRNA for targeting MAPT).

AAV Capsids and Variants thereof

[0039] In some embodiments, an AAV particle, e.g., an AAV particle for the vectorized delivery of an siRNA described herein (e.g., an siRNA for targeting MAPT), may comprise an AAV capsid polypeptide, e.g., an AAV capsid variant.

[0040] In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, allows for blood brain barrier penetration following intravenous administration. In some embodiments, the AAV capsid, e.g., AAV capsid variant, allows for blood brain barrier penetration following focused ultrasound (FUS), e.g., coupled with the intravenous administration of microbubbles (FUS-MB), or MRI-guided FUS coupled with intravenous administration. In some embodiments the AAV capsid, e.g., AAV capsid variant allows for increased distribution to a brain region. In some embodiments, the brain region comprises a frontal cortex, sensory cortex, motor cortex, caudate, dentate nucleus, cerebellar cortex, cerebral cortex, brain stem, hippocampus, thalamus, putamen, or a combination thereof. In some embodiments, the AAV capsid, e.g., AAV capsid variant allows for preferential transduction in a brain region relative to the transduction in the dorsal root ganglia (DRG).

[0041] In some embodiments the AAV capsid polypeptide, e.g., AAV capsid variant allows for increased distribution to a spinal cord region. In some embodiments, the spinal region comprises a cervical spinal cord region, thoracic spinal cord region, and/or lumbar spinal cord region.

[0042] In some embodiments, the AAV capsid polypeptide, e.g., an AAV capsid variant comprises a VOY101 capsid polypeptide, a PHPeB capsid polypeptide, an AAVPHP.B (PHP.B) capsid polypeptide, a AAVPHP.N (PHP.N) capsid polypeptide, an AAV1 capsid polypeptide, an AAV2 capsid polypeptide, an AAV5 capsid polypeptide, an AAV9 capsid polypeptide, an AAV9 K449R capsid polypeptide, an AAVrh10

capsid polypeptide, or a functional variant thereof. In some embodiments, the AAV capsid polypeptide, e.g., AAV capsid variant, comprises an amino acid sequence of any of the AAV capsid polypeptides in Table 1, or an amino acid sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto. In some embodiments, the nucleotide sequence encoding the AAV capsid polypeptide comprises any one of the nucleotide sequences in Table 1, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto.

Table 1: Exemplary full length capsid sequences

Description	SEQ ID NO:	Sequence Information
VOY101	1	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPGNGL DKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGGNLGRAV FQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAKKRLNFGQTG DTESVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSSSGNWHCDSQWLG DRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWGYFDFNRFHCHFSP RDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIANNLTSTVQVFTDSDYQLPY VLGSAHEGCLPPFPADVFMIPQYGYLTLNDGSQAVGRSSFYCLEYFPSQMLRTGNNFQF SYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLSKTINGSGQNQQTLKFSVAGPSNMA VQGRNYIPGPSYRQQRVSTTVTQNNNSEFAWPGASSWALNGRNSLMNPGPAMASHKEGE DRFFPLSGSLIFGKQGTGRDNVDADKVMITNEEEIKTTNPVATESYGQVATNHQSDGTL AVPFKAQAQTGWVQNQGILPGMVWQDRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKH PPPQILIKNTPVPADPPTAFNKDKLNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQY TSNYYKSNNVEFAVNTEGVYSEPRPIGTRYLTRNL
AAV9/hu.14 K449R	11	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPGNGL DKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGGNLGRAV FQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAKKRLNFGQTG DTESVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSSSGNWHCDSQWLG DRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWGYFDFNRFHCHFSP RDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIANNLTSTVQVFTDSDYQLPY VLGSAHEGCLPPFPADVFMIPQYGYLTLNDGSQAVGRSSFYCLEYFPSQMLRTGNNFQF SYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLSRTINGSGQNQQTLKFSVAGPSNMA VQGRNYIPGPSYRQQRVSTTVTQNNNSEFAWPGASSWALNGRNSLMNPGPAMASHKEGE DRFFPLSGSLIFGKQGTGRDNVDADKVMITNEEEIKTTNPVATESYGQVATNHQSAQAQ AQTGWVQNQGILPGMVWQDRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPPQILI KNTPVPADPPTAFNKDKLNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYYKS NNVEFAVNTEGVYSEPRPIGTRYLTRNL
AAV9/hu.14 WT (amino acid)	138	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPGNGL DKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGGNLGRAV FQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAKKRLNFGQTG DTESVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSSSGNWHCDSQWLG DRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWGYFDFNRFHCHFSP RDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIANNLTSTVQVFTDSDYQLPY VLGSAHEGCLPPFPADVFMIPQYGYLTLNDGSQAVGRSSFYCLEYFPSQMLRTGNNFQF SYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLSKTINGSGQNQQTLKFSVAGPSNMA VQGRNYIPGPSYRQQRVSTTVTQNNNSEFAWPGASSWALNGRNSLMNPGPAMASHKEGE DRFFPLSGSLIFGKQGTGRDNVDADKVMITNEEEIKTTNPVATESYGQVATNHQSAQAQ AQTGWVQNQGILPGMVWQDRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPPQILI KNTPVPADPPTAFNKDKLNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYYKS NNVEFAVNTEGVYSEPRPIGTRYLTRNL

AAV9/hu.14 WT (DNA)	137	ATGGCTGCCGATGGTTATCTTCCAGATTGGCTCGAGGACAACCTTAGTGAAGGAATTCG CGAGTGGTGGGCTTTGAAACCTGGAGCCCCTCAACCCAAGGCAAATCAACAACATCAAG ACAACGCTCGAGGTCTTGTGCTTCCGGGTTACAAATACCTTGGACCCGGCAACGGACTC GACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCACGACAAGGCCTA CGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACAACCACGCCGACGCCG AGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGCAACCTCGGGCGAGCAGTC TTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCTGGTTGAGGAAGCGGCTAAGAC GGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTCCTCAGGAACCGGACTCCTCCGCGG GTATTGGCAAATCGGGTGCACAGCCCGCTAAAAAGAGACTCAATTTCGGTCAGACTGGC GACACAGAGTCAGTCCCAGACCCTCAACCAATCGGAGAACCTCCCGCAGCCCCCTCAGG TGTGGGATCTCTTACAATGGCTTCAGGTGGTGGCGCACCAGTGGCAGACAATAACGAAG GTGCCGATGGAGTGGGTAGTTCCTCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGG GACAGAGTCATCACCACCAGCACCCGAACCTGGGCCCTGCCCACCTACAACAATCACCT CTACAAGCAAATCTCCAACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCG GCTACAGCACCCCCTGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCA CGTGACTGGCAGCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTT CAAGCTCTTCAACATTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCG CCAATAACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTATCAGCTCCCGTAC GTGCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCCCAGCGGACGTTTTCATGAT TCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCGTTCGTCCT TTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTTCCAGTTC AGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCCAAAGCCTGGA CCGACTAATGAATCCACTCATCGACCAATACTTGTACTATCTCTCAAAGACTATTAACG GTTCTGGACAGAATCAACAAACGCTAAAATTCAGTGTGGCCGGACCCAGCAACATGGCT GTCCAGGGAAGAAACTACATACCTGGACCCAGCTACCGACAACAACGTGTCTCAACCAC TGTGACTCAAAACAACAACAGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCA ATGGACGTAATAGCTTGATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAG GACCGTTTCTTTCCTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAACTGGAAGAGA CAACGTGGATGCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAAACTACTAACC CGGTAGCAACGGAGTCCTATGGACAAGTGGCCACAAACCACCAGAGTGCCCAAGCACAG GCGCAGACCGGCTGGGTTCAAAACCAAGGAATACTTCCGGGTATGGTTTGGCAGGACAG AGATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCTCACACGGACGGCAACTTTC ACCCTTCTCCGCTGATGGGAGGGTTTGGAATGAAGCACCCGCCTCCTCAGATCCTCATC AAAAACACACCTGTACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAGCTGAACTC TTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAGTGGGAGCTGCAGA AGGAAAACAGCAAGCGCTGGAACCCGGAGATCCAGTACACTTCCAACTATTACAAGTCT AATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATATAGTGAACCCCGCCCCATTGG CACCAGATACCTGACTCGTAATCTGTAA
PHP.eB (amino acid)	3	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPGNGL DKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGGNLGRAV FQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAKKRLNFGQTG DTESVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSSSGNWHCDSQWLG DRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWGYFDFNRFHCHFSP RDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIANNLTSTVQVFTDSDYQLPY VLGSAHEGCLPPFPADVFMIPQYGYLTLNDGSQAVGRSSFYCLEYFPSQMLRTGNNFQF SYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLSRTINGSGQNQQTLKFSVAGPSNMA VQGRNYIPGPSYRQQRVSTTVTQNNNSEFAWPGASSWALNGRNSLMNPGPAMASHKEGE DRFFPLSGSLIFGKQGTGRDNVDADKVMITNEEEIKTTNPVATESYGQVATNHQSDGTL AVPFKAQAQTGWVQNQGILPGMVWQDRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKH PPPQILIKNTPVPADPPTAFNKDKLNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQY TSNYYKSNNVEFAVNTEGVYSEPRPIGTRYLTRNL
PHP.B (amino acid)	12	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPGNGL DKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGGNLGRAV FQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAKKRLNFGQTG DTESVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSSSGNWHCDSQWLG DRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWGYFDFNRFHCHFSP RDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIANNLTSTVQVFTDSDYQLPY

		VLGSAHEGCLPPFPADVFMIPQYGYLTLNDGSQAVGRSSFYCLEYFPSQMLRTGNNFQF SYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLSRTINGSGQNQQTLKFSVAGPSNMA VQGRNYIPGPSYRQQRVSTTVTQNNNSEFAWPGASSWALNGRNSLMNPGPAMASHKEGE DRFFPLSGSLIFGKQGTGRDNVDADKVMITNEEEIKTTNPVATESYGQVATNHQSAQTL AVPFKAQAQTGWVQNQGILPGMVWQDRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKH PPPQILIKNTPVPADPPTAFNKDKLNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQY TSNYYKSNNVEFAVNTEGVYSEPRPIGTRYLTRNL
PHP.N (amino acid)	13	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPGNGL DKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGGNLGRAV FQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAKKRLNFGQTG DTESVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSSSGNWHCDSQWLG DRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWGYFDFNRFHCHFSP RDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIANNLTSTVQVFTDSDYQLPY VLGSAHEGCLPPFPADVFMIPQYGYLTLNDGSQAVGRSSFYCLEYFPSQMLRTGNNFQF SYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLSRTINGSGQNQQTLKFSVAGPSNMA VQGRNYIPGPSYRQQRVSTTVTQNNNSEFAWPGASSWALNGRNSLMNPGPAMASHKEGE DRFFPLSGSLIFGKQGTGRDNVDADKVMITNEEEIKTTNPVATESYGQVATNHQSAQTL AVPFSNPAQTGWVQNQGILPGMVWQDRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKH PPPQILIKNTPVPADPPTAFNKDKLNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQY TSNYYKSNNVEFAVNTEGVYSEPRPIGTRYLTRNL
AAVrh10 (amino acid)	14	MAADGYLPDWLEDNLSEGIREWWDLKPGAPKPKANQQKQDDGRGLVLPGYKYLGPFNGL DKGEPVNAADAAALEHDKAYDQQLKAGDNPYLRYNHADAEFQERLQEDTSFGGNLGRAV FQAKKRVLEPLGLVEEGAKTAPGKKRPVEPSPQRSPDSSTGIGKKGQQPAKKRLNFGQT GDSESVPDPQPIGEPPAGPSGLGSGTMAAGGGAPMADNNEGADGVGSSSGNWHCDSTWL GDRVITTSTRTWALPTYNNHLYKQISNGTSGGSTNDNTYFGYSTPWGYFDFNRFHCHFS PRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTQNEGTKTIANNLTSTIQVFTDSEYQLP YVLGSAHQGCLPPFPADVFMIPQYGYLTLNNGSQAVGRSSFYCLEYFPSQMLRTGNNFE FSYQFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLSRTQSTGGTAGTQQLLFSQAGPNN MSAQAKNWLPGPCYRQQRVSTTLSQNNNSNFAWTGATKYHLNGRDSLVNPGVAMATHKD DEERFFPSSGVLMFGKQGAGKDNVDYSSVMLTSEEEIKTTNPVATEQYGVVADNLQQQN AAPIVGAVNSQGALPGMVWQNRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGLKHPPPQI LIKNTPVPADPPTTFSQAKLASFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYY KSTNVDFAVNTDGTYSEPRPIGTRYLTRNL
AAVrh10 (DNA)	15	ATGGCTGCCGATGGTTATCTTCCAGATTGGCTCGAGGACAACCTCTCTGAGGGCATTCG CGAGTGGTGGGACTTGAAACCTGGAGCCCCGAAACCCAAAGCCAACCAGCAAAAGCAGG ACGACGGCCGGGGTCTGGTGCTTCCTGGCTACAAGTACCTCGGACCCTTCAACGGACTC GACAAGGGGGAGCCCGTCAACGCGGCGGACGCAGCGGCCCTCGAGCACGACAAGGCCTA CGACCAGCAGCTCAAAGCGGGTGACAATCCGTACCTGCGGTATAACCACGCCGACGCCG AGTTTCAGGAGCGTCTGCAAGAAGATACGTCTTTTGGGGGCAACCTCGGGCGAGCAGTC TTCCAGGCCAAGAAGCGGGTTCTCGAACCTCTCGGTCTGGTTGAGGAAGGCGCTAAGAC GGCTCCTGGAAAGAAGAGACCGGTAGAGCCATCACCCCAGCGTTCTCCAGACTCCTCTA CGGGCATCGGCAAGAAAGGCCAGCAGCCCGCGAAAAAGAGACTCAACTTTGGGCAGACT GGCGACTCAGAGTCAGTGCCCGACCCTCAACCAATCGGAGAACCCCCCGCAGGCCCCTC TGGTCTGGGATCTGGTACAATGGCTGCAGGCGGTGGCGCTCCAATGGCAGACAATAACG AAGGCGCCGACGGAGTGGGTAGTTCCTCAGGAAATTGGCATTGCGATTCCACATGGCTG GGCGACAGAGTCATCACCACCAGCACCCGAACCTGGGCCCTCCCCACCTACAACAACCA CCTCTACAAGCAAATCTCCAACGGGACTTCGGGAGGAAGCACCAACGACAACACCTACT TCGGCTACAGCACCCCCTGGGGGTATTTTGACTTTAACAGATTCCACTGCCACTTCTCA CCACGTGACTGGCAGCGACTCATCAACAACAACTGGGGATTCCGGCCCAAGAGACTCAA CTTCAAGCTCTTCAACATCCAGGTCAAGGAGGTCACGCAGAATGAAGGCACCAAGACCA TCGCCAATAACCTTACCAGCACGATTCAGGTCTTTACGGACTCGGAATACCAGCTCCCG TACGTCCTCGGCTCTGCGCACCAGGGCTGCCTGCCTCCGTTCCCGGCGGACGTCTTCAT GATTCCTCAGTACGGGTACCTGACTCTGAACAATGGCAGTCAGGCCGTGGGCCGTTCCT CCTTCTACTGCCTGGAGTACTTTCCTTCTCAAATGCTGAGAACGGGCAACAACTTTGAG TTCAGCTACCAGTTTGAGGACGTGCCTTTTCACAGCAGCTACGCGCACAGCCAAAGCCT GGACCGGCTGATGAACCCCCTCATCGACCAGTACCTGTACTACCTGTCTCGGACTCAGT CCACGGGAGGTACCGCAGGAACTCAGCAGTTGCTATTTTCTCAGGCCGGGCCTAATAAC

		ATGTCGGCTCAGGCCAAAAACTGGCTACCCGGGCCCTGCTACCGGCAGCAACGCGTCTC CACGACACTGTCGCAAAATAACAACAGCAACTTTGCCTGGACCGGTGCCACCAAGTATC ATCTGAATGGCAGAGACTCTCTGGTAAATCCCGGTGTCGCTATGGCAACCCACAAGGAC GACGAAGAGCGATTTTTTCCGTCCAGCGGAGTCTTAATGTTTGGGAAACAGGGAGCTGG AAAAGACAACGTGGACTATAGCAGCGTTATGCTAACCAGTGAGGAAGAAATTAAAACCA CCAACCCAGTGGCCACAGAACAGTACGGCGTGGTGGCCGATAACCTGCAACAGCAAAAC GCCGCTCCTATTGTAGGGGCCGTCAACAGTCAAGGAGCCTTACCTGGCATGGTCTGGCA GAACCGGGACGTGTACCTGCAGGGTCCTATCTGGGCCAAGATTCCTCACACGGACGGAA ACTTTCATCCCTCGCCGCTGATGGGAGGCTTTGGACTGAAACACCCGCCTCCTCAGATC CTGATTAAGAATACACCTGTTCCCGCGGATCCTCCAACTACCTTCAGTCAAGCTAAGCT GGCGTCGTTCATCACGCAGTACAGCACCGGACAGGTCAGCGTGGAAATTGAATGGGAGC TGCAGAAAGAAAACAGCAAACGCTGGAACCCAGAGATTCAATACACTTCCAACTACTAC AAATCTACAAATGTGGACTTTGCTGTTAACACAGATGGCACTTATTCTGAGCCTCGCCC CATCGGCACCCGTTACCTCACCCGTAATCTGTAA
AAV2 (amino acid)	16	MAADGYLPDWLEDTLSEGIRQWWKLKPGPPPPKPAERHKDDSRGLVLPGYKYLGPFNGL DKGEPVNEADAAALEHDKAYDRQLDSGDNPYLKYNHADAEFQERLKEDTSFGGNLGRAV FQAKKRVLEPLGLVEEPVKTAPGKKRPVEHSPVEPDSSSGTGKAGQQPARKRLNFGQTG DADSVPDPQPLGQPPAAPSGLGTNTMATGSGAPMADNNEGADGVGNSSGNWHCDSTWMG DRVITTSTRTWALPTYNNHLYKQISSQSGASNDNHYFGYSTPWGYFDFNRFHCHFSPRD WQRLINNNWGFRPKRLNFKLFNIQVKEVTQNDGTTTIANNLTSTVQVFTDSEYQLPYVL GSAHQGCLPPFPADVFMVPQYGYLTLNNGSQAVGRSSFYCLEYFPSQMLRTGNNFTFSY TFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLSRTNTPSGTTTQSRLQFSQAGASDIRD QSRNWLPGPCYRQQRVSKTSADNNNSEYSWTGATKYHLNGRDSLVNPGPAMASHKDDEE KFFPQSGVLIFGKQGSEKTNVDIEKVMITDEEEIRTTNPVATEQYGSVSTNLQRGNRQA ATADVNTQGVLPGMVWQDRDVYLQGPIWAKIPHTDGHFHPSPLMGGFGLKHPPPQILIK NTPVPANPSTTFSAAKFASFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYNKSV NVDFTVDTNGVYSEPRPIGTRYLTRNL
AAV2 (DNA)	17	ATGGCTGCCGATGGTTATCTTCCAGATTGGCTCGAGGACACTCTCTCTGAAGGAATAAG ACAGTGGTGGAAGCTCAAACCTGGCCCACCACCACCAAAGCCCGCAGAGCGGCATAAGG ACGACAGCAGGGGTCTTGTGCTTCCTGGGTACAAGTACCTCGGACCCTTCAACGGACTC GACAAGGGAGAGCCGGTCAACGAGGCAGACGCCGCGGCCCTCGAGCACGACAAAGCCTA CGACCGGCAGCTCGACAGCGGAGACAACCCGTACCTCAAGTACAACCACGCCGACGCGG AGTTTCAGGAGCGCCTTAAAGAAGATACGTCTTTTGGGGGCAACCTCGGACGAGCAGTC TTCCAGGCGAAAAAGAGGGTTCTTGAACCTCTGGGCCTGGTTGAGGAACCTGTTAAGAC GGCTCCGGGAAAAAAGAGGCCGGTAGAGCACTCTCCTGTGGAGCCAGACTCCTCCTCGG GAACCGGAAAGGCGGGCCAGCAGCCTGCAAGAAAAAGATTGAATTTTGGTCAGACTGGA GACGCAGACTCAGTACCTGACCCCCAGCCTCTCGGACAGCCACCAGCAGCCCCCTCTGG TCTGGGAACTAATACGATGGCTACAGGCAGTGGCGCACCAATGGCAGACAATAACGAGG GCGCCGACGGAGTGGGTAATTCCTCGGGAAATTGGCATTGCGATTCCACATGGATGGGC GACAGAGTCATCACCACCAGCACCCGAACCTGGGCCCTGCCCACCTACAACAACCACCT CTACAAACAAATTTCCAGCCAATCAGGAGCCTCGAACGACAATCACTACTTTGGCTACA GCACCCCTTGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTTTCACCACGTGAC TGGCAAAGACTCATCAACAACAACTGGGGATTCCGACCCAAGAGACTCAACTTCAAGCT CTTTAACATTCAAGTCAAAGAGGTCACGCAGAATGACGGTACGACGACGATTGCCAATA ACCTTACCAGCACGGTTCAGGTGTTTACTGACTCGGAGTACCAGCTCCCGTACGTCCTC GGCTCGGCGCATCAAGGATGCCTCCCGCCGTTCCCAGCAGACGTCTTCATGGTGCCACA GTATGGATACCTCACCCTGAACAACGGGAGTCAGGCAGTAGGACGCTCTTCATTTTACT GCCTGGAGTACTTTCCTTCTCAGATGCTGCGTACCGGAAACAACTTTACCTTCAGCTAC ACTTTTGAGGACGTTCCTTTCCACAGCAGCTACGCTCACAGCCAGAGTCTGGACCGTCT CATGAATCCTCTCATCGACCAGTACCTGTATTACTTGAGCAGAACAAACACTCCAAGTG GAACCACCACGCAGTCAAGGCTTCAGTTTTCTCAGGCCGGAGCGAGTGACATTCGGGAC CAGTCTAGGAACTGGCTTCCTGGACCCTGTTACCGCCAGCAGCGAGTATCAAAGACATC TGCGGATAACAACAACAGTGAATACTCGTGGACTGGAGCTACCAAGTACCACCTCAATG GCAGAGACTCTCTGGTGAATCCGGGCCCGGCCATGGCAAGCCACAAGGACGATGAAGAA AAGTTTTTTCCTCAGAGCGGGGTTCTCATCTTTGGGAAGCAAGGCTCAGAGAAAACAAA TGTGGACATTGAAAAGGTCATGATTACAGACGAAGAGGAAATCAGGACAACCAATCCCG TGGCTACGGAGCAGTATGGTTCTGTATCTACCAACCTCCAGAGAGGCAACAGACAAGCA

		GCTACCGCAGATGTCAACACACAAGGCGTTCTTCCAGGCATGGTCTGGCAGGACAGAGA TGTGTACCTTCAGGGGCCCATCTGGGCAAAGATTCCACACACGGACGGACATTTTCACC CCTCTCCCCTCATGGGTGGATTCGGACTTAAACACCCTCCTCCACAGATTCTCATCAAG AACACCCCGGTACCTGCGAATCCTTCGACCACCTTCAGTGCGGCAAAGTTTGCTTCCTT CATCACACAGTACTCCACGGGACAGGTCAGCGTGGAGATCGAGTGGGAGCTGCAGAAGG AAAACAGCAAACGCTGGAATCCCGAAATTCAGTACACTTCCAACTACAACAAGTCTGTT AATGTGGACTTTACTGTGGACACTAATGGCGTGTATTCAGAGCCTCGCCCCATTGGCAC CAGATACCTGACTCGTAATCTGTAA
AAV1 (amino acid)	18	MAADGYLPDWLEDNLSEGIREWWDLKPGAPKPKANQQKQDDGRGLVLPGYKYLGPFNGL DKGEPVNAADAAALEHDKAYDQQLKAGDNPYLRYNHADAEFQERLQEDTSFGGNLGRAV FQAKKRVLEPLGLVEEGAKTAPGKKRPVEQSPQEPDSSSGIGKTGQQPAKKRLNFGQTG DSESVPDPQPLGEPPATPAAVGPTTMASGGGAPMADNNEGADGVGNASGNWHCDSTWLG DRVITTSTRTWALPTYNNHLYKQISSASTGASNDNHYFGYSTPWGYFDFNRFHCHFSPR DWQRLINNNWGFRPKRLNFKLFNIQVKEVTTNDGVTTIANNLTSTVQVFSDSEYQLPYV LGSAHQGCLPPFPADVFMIPQYGYLTLNNGSQAVGRSSFYCLEYFPSQMLRTGNNFTFS YTFEEVPFHSSYAHSQSLDRLMNPLIDQYLYYLNRTQNQSGSAQNKDLLFSRGSPAGMS VQPKNWLPGPCYRQQRVSKTKTDNNNSNFTWTGASKYNLNGRESIINPGTAMASHKDDE DKFFPMSGVMIFGKESAGASNTALDNVMITDEEEIKATNPVATERFGTVAVNFQSSSTD PATGDVHAMGALPGMVWQDRDVYLQGPIWAKIPHTDGHFHPSPLMGGFGLKNPPPQILI KNTPVPANPPAEFSATKFASFITQYSTGQVSVEIEWELQKENSKRWNPEVQYTSNYAKS ANVDFTVDNNGLYTEPRPIGTRYLTRPL
AAV1 (DNA)	19	atggctgccgatggttatcttccagattggctcgaggacaacctctctgagggcattcg cgagtggtgggacttgaaacctggagccccgaagcccaaagccaaccagcaaaagcagg acgacggccggggtctggtgcttcctggctacaagtacctcggacccttcaacggactc gacaagggggagcccgtcaacgcggcggacgcagcggccctcgagcacgacaaggccta cgaccagcagctcaaagcgggtgacaatccgtacctgcggtataaccacgccgacgccg agtttcaggagcgtctgcaagaagatacgtcttttgggggcaacctcgggcgagcagtc ttccaggccaagaagcgggttctcgaacctctcggtctggttgaggaaggcgctaagac ggctcctggaaagaaacgtccggtagagcagtcgccacaagagccagactcctcctcgg gcatcggcaagacaggccagcagcccgctaaaaagagactcaattttggtcagactggc gactcagagtcagtccccgatccacaacctctcggagaacctccagcaacccccgctgc tgtgggacctactacaatggcttcaggcggtggcgcaccaatggcagacaataacgaag gcgccgacggagtgggtaatgcctcaggaaattggcattgcgattccacatggctgggc gacagagtcatcaccaccagcacccgcacctgggccttgcccacctacaataaccacct ctacaagcaaatctccagtgcttcaacgggggccagcaacgacaaccactacttcggct acagcacccctgggggtattttgatttcaacagattccactgccacttttcaccacgt gactggcagcgactcatcaacaacaattggggattccggcccaagagactcaacttcaa actcttcaacatccaagtcaaggaggtcacgacgaatgatggcgtcacaaccatcgcta ataaccttaccagcacggttcaagtcttctcggactcggagtaccagcttccgtacgtc ctcggctctgcgcaccagggctgcctccctccgttcccggcggacgtgttcatgattcc gcaatacggctacctgacgctcaacaatggcagccaagccgtgggacgttcatccttttt actgcctggaatatttcccttctcagatgctgagaacgggcaacaactttaccttcagc tacacctttgaggaagtgcctttccacagcagctacgcgcacagccagagcctggaccg gctgatgaatcctctcatcgaccaatacctgtattacctgaacagaactcaaaatcagt ccggaagtgcccaaaacaaggacttgctgtttagccgtgggtctccagctggcatgtct gttcagcccaaaaactggctacctggaccctgttatcggcagcagcgcgtttctaaaac aaaaacagacaacaacaacagcaattttacctggactggtgcttcaaaatataacctca atgggcgtgaatccatcatcaaccctggcactgctatggcctcacacaaagacgacgaa gacaagttctttcccatgagcggtgtcatgatttttggaaaagagagcgccggagcttc aaacactgcattggacaatgtcatgattacagacgaagaggaaattaaagccactaacc ctgtggccaccgaaagatttgggaccgtggcagtcaatttccagagcagcagcacagac cctgcgaccggagatgtgcatgctatgggagcattacctggcatggtgtggcaagatag agacgtgtacctgcagggtcccatttgggccaaaattcctcacacagatggacactttc acccgtctcctcttatgggcggctttggactcaagaacccgcctcctcagatcctcatc aaaaacacgcctgttcctgcgaatcctccggcggagttttcagctacaaagtttgcttc attcatcacccaatactccacaggacaagtgagtgtggaaattgaatgggagctgcaga aagaaaacagcaagcgctggaatcccgaagtgcagtacacatccaattatgcaaaatct

		gccaacgttgattttactgtggacaacaatggactttatactgagcctcgccccattgg cacccgttaccttacccgtcccctgtaa
AAV5 (amino acid)	20	MSFVDHPPDWLEEVGEGLREFLGLEAGPPKPKPNQQHQDQARGLVLPGYNYLGPGNGLD RGEPVNRADEVAREHDISYNEQLEAGDNPYLKYNHADAEFQEKLADDTSFGGNLGKAVF QAKKRVLEPFGLVEEGAKTAPTGKRIDDHFPKRKKARTEEDSKPSTSSDAEAGPSGSQQ LQIPAQPASSLGADTMSAGGGGPLGDNNQGADGVGNASGDWHCDSTWMGDRVVTKSTRT WVLPSYNNHQYREIKSGSVDGSNANAYFGYSTPWGYFDFNRFHSHWSPRDWQRLINNYW GFRPRSLRVKIFNIQVKEVTVQDSTTTIANNLTSTVQVFTDDDYQLPYVVGNGTEGCLP AFPPQVFTLPQYGYATLNRDNTENPTERSSFFCLEYFPSKMLRTGNNFEFTYNFEEVPF HSSFAPSQNLFKLANPLVDQYLYRFVSTNNTGGVQFNKNLAGRYANTYKNWFPGPMGRT QGWNLGSGVNRASVSAFATTNRMELEGASYQVPPQPNGMTNNLQGSNTYALENTMIFNS QPANPGTTATYLEGNMLITSESETQPVNRVAYNVGGQMATNNQSSTTAPATGTYNLQEI VPGSVWMERDVYLQGPIWAKIPETGAHFHPSPAMGGFGLKHPPPMMLIKNTPVPGNITS FSDVPVSSFITQYSTGQVTVEMEWELKKENSKRWNPEIQYTNNYNDPQFVDFAPDSTGE YRTTRPIGTRYLTRPL
AAV5 (DNA)	21	atgtcttttgttgatcaccctccagattggttggaagaagttggtgaaggtcttcgcga gtttttgggccttgaagcgggcccaccgaaaccaaaacccaatcagcagcatcaagatc aagcccgtggtcttgtgctgcctggttataactatctcggacccggaaacggtctcgat cgaggagagcctgtcaacagggcagacgaggtcgcgcgagagcacgacatctcgtacaa cgagcagcttgaggcgggagacaacccctacctcaagtacaaccacgcggacgccgagt ttcaggagaagctcgccgacgacacatccttcgggggaaacctcggaaaggcagtcttt caggccaagaaaagggttctcgaacctttggcctggttgaagagggtgctaagacggc ccctaccggaaagcggatagacgaccactttccaaaaagaaagaaggcccggaccgaag aggactccaagccttccacctcgtcagacgccgaagctggacccagcggatcccagcag ctgcaaatcccagcccaaccagcctcaagtttgggagctgatacaatgtctgcgggagg tggcggcccattgggcgacaataaccaaggtgccgatggagtgggcaatgcctcgggag attggcattgcgattccacgtggatgggggacagagtcgtcaccaagtccacccgaacc tgggtgctgcccagctacaacaaccaccagtaccgagagatcaaaagcggctccgtcga cggaagcaacgccaacgcctactttggatacagcacccctgggggtactttgacttta accgcttccacagccactggagcccccgagactggcaaagactcatcaacaactactgg ggcttcagaccccggtccctcagagtcaaaatcttcaacattcaagtcaaagaggtcac ggtgcaggactccaccaccaccatcgccaacaacctcacctccaccgtccaagtgttta cggacgacgactaccagctgccctacgtcgtcggcaacgggaccgagggatgcctgccg gccttccctccgcaggtctttacgctgccgcagtacggttacgcgacgctgaaccgcga caacacagaaaatcccaccgagaggagcagcttcttctgcctagagtactttcccagca agatgctgagaacgggcaacaactttgagtttacctacaactttgaggaggtgcccttc cactccagcttcgctcccagtcagaacctcttcaagctggccaacccgctggtggacca gtacttgtaccgcttcgtgagcacaaataactggcggagtccagttcaacaagaacc tggccgggagatacgccaacacctacaaaaactggttcccggggcccatgggccgaacc cagggctggaacctgggctccggggtcaaccgcgccagtgtcagcgccttcgccacgac caataggatggagctcgagggcgcgagttaccaggtgcccccgcagccgaacggcatga ccaacaacctccagggcagcaacacctatgccctggagaacactatgatcttcaacagc cagccggcgaacccgggcaccaccgccacgtacctcgagggcaacatgctcatcaccag cgagagcgagacgcagccggtgaaccgcgtggcgtacaacgtcggcgggcagatggcca ccaacaaccagagctccaccactgccccgcgaccggcacgtacaacctccaggaaatc gtgcccggcagcgtgtggatggagagggacgtgtacctccaaggacccatctgggccaa gatcccagagacgggggcgcactttcacccctctccggccatgggcggattcggactca aacacccaccgcccatgatgctcatcaagaacacgcctgtgcccggaaatatcaccagc ttctcggacgtgcccgtcagcagcttcatcacccagtacagcaccgggcaggtcaccgt ggagatggagtgggagctcaagaaggaaaactccaagaggtggaacccagagatccagt acacaaacaactacaacgacccccagtttgtggactttgccccggacagcaccgggggaa tacagaaccaccagacctatcggaacccgataccttacccgaccccctttaa
TTD-001 9mer peptide underlined, starts at position 587	3636	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPGNGL DKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGGNLGRAV FQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAKKRLNFGQTG DTESVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSSSGNWHCDSQWLG DRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWGYFDFNRFHCHFSP

(immediately subsequent to position 586); 743 aa		RDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIANNLTSTVQVFTDSDYQLPY VLGSAHEGCLPPFPADVFMIPQYGYLTLNDGSQAVGRSSFYCLEYFPSQMLRTGNNFQF SYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLSKTINGSGQNQQTLKFSVAGPSNMA VQGRNYIPGPSYRQQRVSTTVTQNNNSEFAWPGASSWALNGRNSLMNPGPAMASHKEGE DRFFPLSGSLIFGKQGTGRDNVDADKVMITNEEEIKTTNPVATESYGQVATNHQS**PLNG** **AVHLY**AQAQTGWVQNQGILPGMVWQDRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKH PPPQILIKNTPVPADPPTAFNKDKLNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQY TSNYYKSNNVEFAVNTEGVYSEPRPIGTRYLTRNL
TTD-001 9mer peptide underlined	3623	ATGGCTGCCGATGGTTATCTTCCAGATTGGCTCGAGGACAACCTTAGTGAAGGAATTCG CGAGTGGTGGGCTTTGAAACCTGGAGCCCCTCAACCCAAGGCAAATCAACAACATCAAG ACAACGCTCGAGGTCTTGTGCTTCCGGGTTACAAATACCTTGGACCCGGCAACGGACTC GACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCACGACAAGGCCTA CGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACAACCACGCCGACGCCG AGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGCAACCTCGGGCGAGCAGTC TTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCTGGTTGAGGAAGCGGCTAAGAC GGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTCCTCAGGAACCGGACTCCTCCGCGG GTATTGGCAAATCGGGTGCACAGCCCGCTAAAAAGAGACTCAATTTCGGTCAGACTGGC GACACAGAGTCAGTCCCAGACCCTCAACCAATCGGAGAACCTCCCGCAGCCCCCTCAGG TGTGGGATCTCTTACAATGGCTTCAGGTGGTGGCGCACCAGTGGCAGACAATAACGAAG GTGCCGATGGAGTGGGTAGTTCCTCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGG GACAGAGTCATCACCACCAGCACCCGAACCTGGGCCCTGCCCACCTACAACAATCACCT CTACAAGCAAATCTCCAACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCG GCTACAGCACCCCCTGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCA CGTGACTGGCAGCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTT CAAGCTCTTCAACATTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCG CCAATAACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTATCAGCTCCCGTAC GTGCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCCCAGCGGACGTTTTCATGAT TCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCGTTCGTCCT TTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTTCCAGTTC AGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCCAAAGCCTGGA CCGACTAATGAATCCACTCATCGACCAATACTTGTACTATCTCTCAAAGACTATTAACG GTTCTGGACAGAATCAACAAACGCTAAAATTCAGTGTGGCCGGACCCAGCAACATGGCT GTCCAGGGAAGAAACTACATACCTGGACCCAGCTACCGACAACAACGTGTCTCAACCAC TGTGACTCAAAACAACAACAGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCA ATGGACGTAATAGCTTGATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAG GACCGTTTCTTTCCTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAACTGGAAGAGA CAACGTGGATGCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAAACTACTAACC CGGTAGCAACGGAGTCCTATGGACAAGTGGCCACAAACCACCAGAGT**CCGCTTAATGGT** **GCCGTCCATCTTTAT**GCTCAGGCGCAGACCGGCTGGGTTCAAAACCAAGGAATACTTCC GGGTATGGTTTGGCAGGACAGAGATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTC CTCACACGGACGGCAACTTTCACCCTTCTCCGCTGATGGGAGGGTTTGGAATGAAGCAC CCGCCTCCTCAGATCCTCATCAAAAACACACCTGTACCTGCCGATCCTCCAACGGCCTT CAACAAGGACAAGCTGAACTCTTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGG AGATCGAGTGGGAGCTGCAGAAGGAAAACAGCAAGCGGTGGAACCCGGAGATCCAGTAC ACTTCCAACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATA TAGTGAACCCCGCCCCATTGGCACCAGATACCTGACTCGTAATCTGTAA
VOY9P39 (amino acid)	5147	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPGNGL DKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGGNLGRAV FQAKKRLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAKKRLNFGQTG DTESVPDPQPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSSSGNWHCDSQWLG DRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWGYFDFNRFHCHFSP RDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIANNLTSTVQVFTDSDYQLPY VLGSAHEGCLPPFPADVFMIPQYGYLTLNDGSQAVGRSSFYCLEYFPSQMLRTGNNFQF SYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLSKTINGSGQNQQTLKFSVAGPSNMA VQGRNYIPGPSYRQQRVSTTVTQNNNSEFAWPGASSWALNGRNSLMNPGPAMASHKEGE DRFFPLSGSLIFGKQGTGRDNVDADKVMITNEEEIKTTNPVATESYGQVATNHQSDGTG STTGWAQAQTGWVQNQGILPGMVWQDRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKH

		PPPQILIKNTPVPADPPTAFNKDKLNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQY TSNYYKSNNVEFAVNTEGVYSEPRPIGTRYLTRNL
VOY9P39 (DNA)	5148	ATGGCTGCCGATGGTTATCTTCCAGATTGGCTCGAGGACAACCTTAGTGAAGGAATTCG CGAGTGGTGGGCTTTGAAACCTGGAGCCCCTCAACCCAAGGCAAATCAACAACATCAAG ACAACGCTCGAGGTCTTGTGCTTCCGGGTTACAAATACCTTGGACCCGGCAACGGACTC GACAAGGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCACGACAAGGCCTA CGACCAGCAGCTCAAGGCCGGAGACAACCCGTACCTCAAGTACAACCACGCCGACGCCG AGTTCCAGGAGCGGCTCAAAGAAGATACGTCTTTTGGGGGCAACCTCGGGCGAGCAGTC TTCCAGGCCAAAAAGAGGCTTCTTGAACCTCTTGGTCTGGTTGAGGAAGCGGCTAAGAC GGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTCCTCAGGAACCGGACTCCTCCGCGG GTATTGGCAAATCGGGTGCACAGCCCGCTAAAAAGAGACTCAATTTCGGTCAGACTGGC GACACAGAGTCAGTCCCAGACCCTCAACCAATCGGAGAACCTCCCGCAGCCCCCTCAGG TGTGGGATCTCTTACAATGGCTTCAGGTGGTGGCGCACCAGTGGCAGACAATAACGAAG GTGCCGATGGAGTGGGTAGTTCCTCGGGAAATTGGCATTGCGATTCCCAATGGCTGGGG GACAGAGTCATCACCACCAGCACCCGAACCTGGGCCCTGCCCACCTACAACAATCACCT CTACAAGCAAATCTCCAACAGCACATCTGGAGGATCTTCAAATGACAACGCCTACTTCG GCTACAGCACCCCCTGGGGGTATTTTGACTTCAACAGATTCCACTGCCACTTCTCACCA CGTGACTGGCAGCGACTCATCAACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTT CAAGCTCTTCAACATTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACCATCG CCAATAACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAGACTATCAGCTCCCGTAC GTGCTCGGGTCGGCTCACGAGGGCTGCCTCCCGCCGTTCCCAGCGGACGTTTTCATGAT TCCTCAGTACGGGTATCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCGTTCGTCCT TTTACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACAACTTCCAGTTC AGCTACGAGTTTGAGAACGTACCTTTCCATAGCAGCTACGCTCACAGCCAAAGCCTGGA CCGACTAATGAATCCACTCATCGACCAATACTTGTACTATCTCTCAAAGACTATTAACG GTTCTGGACAGAATCAACAAACGCTAAAATTCAGTGTGGCCGGACCCAGCAACATGGCT GTCCAGGGAAGAAACTACATACCTGGACCCAGCTACCGACAACAACGTGTCTCAACCAC TGTGACTCAAAACAACAACAGCGAATTTGCTTGGCCTGGAGCTTCTTCTTGGGCTCTCA ATGGACGTAATAGCTTGATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAG GACCGTTTCTTTCCTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAACTGGAAGAGA CAACGTGGATGCGGACAAAGTCATGATAACCAACGAAGAAGAAATTAAAACTACTAACC CGGTAGCAACGGAGTCCTATGGACAAGTGGCCACAAACCACCAGAGTGACGGAACAGGA AGCACAACAGGATGGGCACAGGCGCAGACCGGCTGGGTTCAAAACCAAGGAATACTTCC GGGTATGGTTTGGCAGGACAGAGATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTC CTCACACGGACGGCAACTTTCACCCTTCTCCGCTGATGGGAGGGTTTGGAATGAAGCAC CCGCCTCCTCAGATCCTCATCAAAAACACACCTGTACCTGCCGATCCTCCAACGGCCTT CAACAAGGACAAGCTGAACTCTTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGG AGATCGAGTGGGAGCTGCAGAAGGAAAACAGCAAGCGGTGGAACCCGGAGATCCAGTAC ACTTCCAACTATTACAAGTCTAATAATGTTGAATTTGCTGTTAATACTGAAGGTGTATA TAGTGAACCCCGCCCCATTGGCACCAGATACCTGACTCGTAATCTGTAA

[0043] In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises the amino acid sequence of any of SEQ ID NOs: 1, 3, 11, 138, 12, 13, 14, 16, 18, 20, 5147, 3636, or an amino acid sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto. In some embodiments the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises an amino acid sequence comprising at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but no more than 30, 20, or 10 modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the amino acid sequence of any of SEQ ID NOs: 1, 3, 11, 138, 12, 13, 14, 16, 18, 20, or 3636. In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises an amino acid sequence encoded by the nucleotide sequence of any of SEQ ID NOs: 137, 15, 17, 19, 21, 3623, or a nucleotide

sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto.

[0044] In some embodiments, the nucleotide sequence encoding the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises the nucleotide sequence of any of SEQ ID NOs: 137, 15, 17, 19, 21, 5148, or 3623, or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto. In some embodiments, the nucleotide sequence encoding the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises a nucleotide sequence comprising at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but no more than 30, 20, or 10 modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the nucleotide sequence of any of SEQ ID NOs: 137, 15, 17, 19, 21, or 3623.

[0045] In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises the amino acid sequence of SEQ ID NO: 138 or an amino acid sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto. In some embodiments the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises an amino acid sequence comprising at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), but no more than 30, 20, or 10 modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of SEQ ID NO: 138. In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 137 or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto. In some embodiments, the nucleotide sequence encoding the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises the nucleotide sequence of SEQ ID NO: 137 or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto. In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises substitution at position K449, e.g., a K449R substitution, numbered according to SEQ ID NO: 138.

[0046] In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises the amino acid sequence of SEQ ID NO: 11 or an amino acid sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto. In some embodiments the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises an amino acid sequence comprising at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), but no more than 30, 20, or 10 modifications, e.g., substitutions (conservative substitutions), relative to the amino acid sequence of SEQ ID NO: 11, optionally wherein position 449 is not R.

[0047] In some embodiments, the capsid polypeptide, comprises the amino acid sequence of SEQ ID NO: 1 or an amino acid sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto. In some embodiments the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises an amino acid sequence comprising at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), but no more than 30, 20, or 10 modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of SEQ ID NO: 1.

[0048] In some embodiments, the capsid polypeptide, comprises the amino acid sequence of SEQ ID NO: 3 or an amino acid sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto. In some embodiments the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises an amino acid sequence comprising at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), but no more than 30, 20, or 10 modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of SEQ ID NO: 3.

[0049] In some embodiments, the capsid polypeptide, comprises the amino acid sequence of SEQ ID NO: 5147 or an amino acid sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto. In some embodiments the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises an amino acid sequence comprising at least one, two, or three modifications, e.g., substitutions (e.g., conservative substitutions), but no more than 30, 20, or 10 modifications, e.g., substitutions (e.g., conservative substitutions), relative to the amino acid sequence of SEQ ID NO: 5147.

[0050] In some embodiments, an AAV capsid variant disclosed herein comprises a modification in loop VIII of AAV9, e.g., at positions between 580-599, e.g., at positions 587, 588, 589, and/or 590, numbered relative to SEQ ID NO: 5, 8, 138 or 3636-3647. In some embodiments, loop (e.g., loop VIII) is used interchangeably herein with the term variable region (e.g., variable region VIII), or VR (e.g., VR-VIII). In some embodiments loop VIII comprises positions 580-599 (e.g., amino acids VATNHQSAQAQAQTGWVQNQ (SEQ ID NO: 1195)), numbered according to SEQ ID NO: 138. In some embodiments, loop VIII comprises positions 582-593 (e.g., amino acids TNHQSAQAQAQT (SEQ ID NO: 1196)), numbered according to SEQ ID NO: 138. In some embodiments loop VIII comprises positions 587-593 (e.g., amino acids AQAQAQT (SEQ ID NO: 1197)), numbered according to SEQ ID NO: 138. In some embodiments loop VIII comprises positions 587-590 (e.g., amino acids AQAQ (SEQ ID NO: 5026)), numbered according to SEQ ID NO: 138. In some embodiments, loop VIII or variable region VIII (VR-VIII) is as described in DiMattia et al. "Structural Insights into the Unique Properties of the Adeno-Associated Virus Serotype 9," *Journal of Virology*, 12(86):6947-6958 (the contents of which are hereby incorporated by

reference in their entirety), e.g., comprising positions 581-593 (e.g., ATNHQSAQAQAQT (SEQ ID NO: 1198)), numbered according to SEQ ID NO: 138.

[0051] In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises a peptide comprising the amino acid sequence of TLAVPFK (SEQ ID NO: 1262). In some embodiments, the peptide is present immediately subsequent to position 588, relative to a reference sequence numbered according to SEQ ID NO: 138. In some embodiments, the capsid polypeptide comprises the amino acid substitutions of A587D and Q588G, numbered according to SEQ ID NO: 138.

[0052] In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises the amino acid substitution of K449R, numbered according to SEQ ID NO: 138; and a peptide comprising the amino acid sequence of TLAVPFK (SEQ ID NO: 1262), wherein the peptide is present immediately subsequent to position 588, relative to a reference sequence numbered according to SEQ ID NO: 138.

[0053] In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises the amino acid substitution of K449R, numbered according to SEQ ID NO: 138; an peptide comprising the amino acid sequence of TLAVPFK (SEQ ID NO: 1262), wherein the insert is present immediately subsequent to position 588, relative to a reference sequence numbered according to SEQ ID NO: 138; and the amino acid substitutions of A587D and Q588G, numbered according to SEQ ID NO: 138.

[0054] In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises a peptide comprising the amino acid sequence of TLAVPFK (SEQ ID NO: 1262), wherein the insert is present immediately subsequent to position 588, relative to a reference sequence numbered according to SEQ ID NO: 138; and the amino acid substitutions of A587D and Q588G, numbered according to SEQ ID NO: 138.

[0055] In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises at least 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648). In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648), an amino acid sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648), or an amino acid sequence comprising at least one, two, or three but no more than four different amino acids relative to the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648), optionally wherein position 7 is H. In some embodiments, the amino acid sequence is present in loop VIII. In some embodiments, the amino acid sequence is present immediately subsequent to position 586, relative to a reference sequence numbered according to the amino acid sequence of SEQ ID NO: 138. In some embodiments, the amino acid sequence replaces positions replaces positions 587 and 588 (e.g., A587 and Q 588), numbered according to SEQ ID NO: 138. In some embodiments, the amino acid sequence is present at immediately subsequent to position 586 and replaces positions 587 and 588 (e.g., A587 and Q 588), numbered according to SEQ ID NO: 138.

[0056] In some embodiments, the 3 consecutive amino acids comprise PLN. In some embodiments, the 4 consecutive amino acids comprise PLNG (SEQ ID NO: 3678). In some embodiments, the 5 consecutive amino acids comprise PLNGA (SEQ ID NO: 3679). In some embodiments, the 6 consecutive amino acids comprise PLNGAV (SEQ ID NO: 3680). In some embodiments, the 7 consecutive amino acids comprise PLNGAVH (SEQ ID NO: 3681). In some embodiments, the 8 consecutive amino acids comprise PLNGAVHL (SEQ ID NO: 3682). In some embodiments, the 9 consecutive amino acids comprise PLNGAVHLY (SEQ ID NO: 3648).

[0057] In some embodiments, the four consecutive amino acids comprise NGAV (SEQ ID NO: 3683). In some embodiments, the four consecutive amino acids comprise GAVH (SEQ ID NO: 3684). In some embodiments, the five consecutive amino acids comprise NGAVH (SEQ ID NO: 3685). In some embodiments, the five consecutive amino acids comprise GAVHL (SEQ ID NO: 3686). In some embodiments, the five consecutive amino acids comprise AVHLY (SEQ ID NO: 3687). In some embodiments, the six consecutive amino acids comprise NGAVHL (SEQ ID NO: 3688). In some embodiments, the seven consecutive amino acids comprise NGAVHLY (SEQ ID NO: 3689).

[0058] In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant (e.g., an AAV capsid variant described herein), comprises an amino acid sequence encoded by the nucleotide sequence of CCGCTTAATGGTGCCGTCCATCTTTAT (SEQ ID NO: 3660), or a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto. In some embodiments, the AAV capsid, e.g., an AAV capsid variant described herein, comprises an amino acid sequence encoded by a nucleotide sequence comprising at least one, two, three, four, five, six, or seven modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, but no more than ten modifications, e.g., substitutions (e.g., conservative substitutions), insertions, or deletions, relative to the nucleotide sequence of CCGCTTAATGGTGCCGTCCATCTTTAT (SEQ ID NO: 3660). In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant (e.g., an AAV capsid variant described herein), comprises an amino acid sequence encoded by a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of CCGCTTAATGGTGCCGTCCATCTTTAT (SEQ ID NO: 3660).

[0059] In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises the amino acid P at position 587, the amino acid L at position 588, and the amino acid sequence NGAVHLY (SEQ ID NO: 3689), which is present immediately subsequent to position 588, corresponding to or numbered according to SEQ ID NO: 3636.

[0060] In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, e.g., an AAV capsid variant described herein, comprises the amino acid sequence of SEQ ID NO: 3636, or an amino acid sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto. In

some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, e.g., an AAV capsid variant described herein, comprises the amino acid sequence of SEQ ID NO: 3636, or an amino acid sequence at least 95% identical thereto. In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, e.g., an AAV capsid variant described herein, comprises the amino acid sequence of SEQ ID NO: 3636, or an amino acid sequence at least 99% identical thereto.

[0061] In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, e.g., an AAV capsid variant described herein, comprises an amino acid sequence comprising at least one, two, or three modifications, substitutions (e.g., conservative substitutions), insertions, or deletions, but not more than 30, 20 or 10 modifications, substitutions (e.g., conservative substitutions), insertions, or deletions relative to the amino acid sequence of SEQ ID NO: 3636. In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, e.g., an AAV capsid variant described herein, comprises an amino acid sequence having at least one, two, or three but no more than 30, 20, or 10 different amino acids relative to the amino acid sequence of SEQ ID NO: 3636.

[0062] In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises the amino acid sequence corresponding to positions 138-743, e.g., a VP2, of SEQ ID NO: 3636, or a sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto. In some embodiments, the AAV capsid variant comprises the amino acid sequence corresponding to positions 203-743, e.g., a VP3, of SEQ ID NO: 3636, or a sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto. In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises the amino acid sequence corresponding to positions 138-736, e.g., a VP2, of SEQ ID NO: 138, or a sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto. In some embodiments, the AAV capsid variant comprises the amino acid sequence corresponding to positions 203-736, e.g., a VP3, of SEQ ID NO: 138, or a sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto. In some embodiments, the amino acid sequence is present immediately subsequent to position 586, numbered according to any one of SEQ ID NO: 138 or 3636, optionally wherein the amino acid replaces positions 587 and 588 (e.g., A587 and Q588), numbered according to SEQ ID NO: 138. In some embodiments, the amino acid sequence corresponds to positions 587-595 of SEQ ID NO: 3636.

[0063] In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises one or two, but no more than three different amino acids (e.g., substitutions, e.g., conservative substitutions) relative to the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648), wherein the AAV capsid variant comprises (a) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 138 or 3636; (b) a VP2 protein comprising the amino acid sequence of positions 138-736 of SEQ ID NO: 138 or positions 138-743 of SEQ ID NO: 5, 8, or 3636; (c) a VP3 protein comprising the amino acid sequence of positions 203-736 of

SEQ ID NO: 138 or positions 203-743 of SEQ ID NO: 5, 8, or 3636; or (d) an amino acid sequence with at least 90% (e.g., at least about 95, 96, 97, 98, or 99%) sequence identity to any of the amino acid sequences in (a)-(c). In some embodiments, the amino acid sequence is present immediately subsequent to position 586, numbered according to any one of SEQ ID NO: 138 or 3636, optionally wherein the amino acid replaces positions 587 and 588 (e.g., A587 and Q588), numbered according to SEQ ID NO: 138. In some embodiments, the amino acid sequence corresponds to positions 587-595 of SEQ ID NO: 3636.

[0064] In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises one or two, but no more than three different amino acids (e.g., substitutions, e.g., conservative substitutions) relative to the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648), wherein the AAV capsid variant comprises the amino acid sequence of any one of SEQ ID NOs: 5, 8, 138, or 3636 or an amino acid sequence with at least 90% (e.g., at least about 95, 96, 97, 98, or 99%) sequence identity to SEQ ID NO: 3636. In some embodiments, the amino acid sequence is present immediately subsequent to position 586, numbered according to any one of SEQ ID NO: 138 or 3636, optionally wherein the amino acid replaces positions 587 and 588 (e.g., A587 and Q588), numbered according to SEQ ID NO: 138. In some embodiments, the amino acid sequence corresponds to positions 587-595 of SEQ ID NO: 3636.

[0065] In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises an amino acid sequence comprising at least 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648), wherein: (i) the 5 consecutive amino acids comprise PLNGA (SEQ ID NO: 3679); (ii) the 6 consecutive amino acids comprise PLNGAV (SEQ ID NO: 3680); (iii) the 7 consecutive amino acids comprise PLNGAVH (SEQ ID NO: 3681); (iv) the 8 consecutive amino acids comprise PLNGAVHL (SEQ ID NO: 3682); or (v) the 9 consecutive amino acids comprise PLNGAVHLY (SEQ ID NO: 3648), wherein the AAV capsid variant comprises: (a) a VP1 protein comprising the amino acid sequence of SEQ ID NO: 138 or SEQ ID NO: 3636; (b) a VP2 protein comprising the amino acid sequence of positions 138-736 of SEQ ID NO: 138 or positions 138-743 of SEQ ID NO: 3636; (c) a VP3 protein comprising the amino acid sequence of positions 203-736 of SEQ ID NO: 138 or positions 203-743 of SEQ ID NO: 3636; or (d) an amino acid sequence with at least 90% (e.g., at least about 95, 96, 97, 98, or 99%) sequence identity to any of the amino acid sequences in (a)-(c). In some embodiments, the amino acid sequence is present immediately subsequent to position 586, numbered according to any one of SEQ ID NO: 138 or 3636, optionally wherein the amino acid replaces positions 587 and 588 (e.g., A587 and Q588), numbered according to SEQ ID NO: 138. In some embodiments, the amino acid sequence corresponds to positions 587-595 of SEQ ID NO: 3636.

[0066] In some embodiments, the AAV capsid polypeptide, e.g., the AAV capsid variant, comprises an amino acid sequence comprising at least 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of PLNGAVHLY (SEQ ID NO: 3648), wherein: (i) the 5 consecutive amino acids comprise

PLNGA (SEQ ID NO: 3679); (ii) the 6 consecutive amino acids comprise PLNGAV (SEQ ID NO: 3680); (iii) the 7 consecutive amino acids comprise PLNGAVH (SEQ ID NO: 3681); (iv) the 8 consecutive amino acids comprise PLNGAVHL (SEQ ID NO: 3682); or (v) the 9 consecutive amino acids comprise PLNGAVHLY (SEQ ID NO: 3648), wherein the AAV capsid variant comprises the amino acid sequence of any one of SEQ ID NOs: 5, 8, or 3636 or an amino acid sequence with at least 90% (e.g., at least about 95, 96, 97, 98, or 99%) sequence identity to any one of SEQ ID NO: 3636. In some embodiments, the amino acid sequence is present immediately subsequent to position 586, numbered according to any one of SEQ ID NO: 138 or 3636, optionally wherein the amino acid replaces positions 587 and 588 (e.g., A587 and Q588), numbered according to SEQ ID NO: 138. In some embodiments, the amino acid sequence corresponds to positions 587-595 of SEQ ID NO: 3636.

[0067] In some embodiments, the nucleotide sequence encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein comprises the nucleotide sequence of SEQ ID NO: 3623, or a nucleotide sequence with at least 80% (e.g., at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto. In some embodiments, nucleotide sequence encoding the AAV capsid variant comprises a nucleotide sequence comprising at least one, two or three modifications, e.g., substitutions, insertions, or deletions, but not more than 30, 20 or 10 modifications, e.g., substitutions, insertions, or deletions, relative to the nucleotide sequence of SEQ ID NO: 3623. In some embodiments, the nucleotide sequence encoding the AAV capsid variant comprises a nucleotide sequence comprising at least one, two or three, but not more than 30, 20 or 10 different nucleotides, relative to the nucleotide sequence of SEQ ID NO: 3623. In some embodiments, the nucleic acid sequence encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein is codon optimized.

[0068] In some embodiments, an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein has an increased tropism for a CNS cell or tissue, e.g., a brain cell, brain tissue, spinal cord cell, or spinal cord tissue, relative to the tropism of a reference sequence comprising the amino acid sequence of SEQ ID NO: 138.

[0069] In some embodiments, an AAV capsid polypeptide, e.g., an AAV capsid variant, of the present disclosure has decreased tropism for the liver. In some embodiments, an AAV capsid variant comprises a modification, e.g., substitution (e.g., conservative substitution), insertion, or deletion, that results in reduced tropism (e.g., de-targeting) and/or activity in the liver. In some embodiments, the reduced tropism in the liver is compared to an otherwise similar capsid that does not comprise the modification, e.g., a wild-type capsid polypeptide. In some embodiments, an AAV capsid variant described comprises a modification, e.g., substitution (e.g., conservative substitution), insertion, or deletion, that results in one or more of the following properties: (1) reduced tropism in the liver; (2) de-targeted expression in the liver; (3) reduced activity in the liver; and/or (4) reduced binding to galactose. In some embodiments, the reduction in any one, or all of

properties (1)-(3) is compared to an otherwise similar AAV capsid variant that does not comprise the modification. Exemplary modifications are provided in WO 2018/119330; Pulicherla et al. (2011) *Mol. Ther.* 19(6): 1070-1078; Adachi et al. (2014) *Nature Communications* 5(3075), DOI: 10.1038/ncomms4075; and Bell et al. (2012) *J. Virol.* 86(13): 7326-33; the contents of which are hereby incorporated by reference in their entirety. In some embodiments, the AAV capsid variant comprises a modification e.g., substitution (e.g., conservative substitution), insertion, or deletion, at position N470 (e.g., N470A), D271 (e.g., D271A), N272 (e.g., N272A), Y446 (e.g., Y446A), N498 (e.g., N498Y or N498I), W503 (e.g., W503R or W503A), L620 (e.g., L620F), or a combination thereof, relative to a reference sequence numbered according to SEQ ID NO: 138. In some embodiments, the AAV capsid variant comprises one, two, three, four, five or all of an amino acid other than N at position 470 (e.g., A), an amino acid other than D at position 271 (e.g., A), an amino acid other than N at position 272 (e.g., A), an amino acid other than Y at position 446 (e.g., A), and amino acid other than N at position 498 (e.g., Y or I), and amino acid other than W at position 503 (e.g., R or A), and amino acid other than L at position 620 (e.g., F), relative to a reference sequence numbered according to SEQ ID NO: 138. In some embodiments, the AAV capsid variant comprises a modification e.g., substitution (e.g., conservative substitution), insertion, or deletion, at position N470 (e.g., N470A), D271 (e.g., D271A), N272 (e.g., N272A), Y446 (e.g., Y446A), and W503 (e.g., W503R or W03A), relative to a reference sequence numbered according to SEQ ID NO: 138. In some embodiments, the AAV capsid variant comprises a modification e.g., substitution (e.g., conservative substitution), insertion, or deletion, at N498 (e.g., N498Y) and L620 (e.g., L620F).

[0070] In some embodiments, an AAV capsid variant comprised herein comprises a modification as described in Adachi et al. (2014) *Nature Communications* 5(3075), DOI: 10.1038/ncomms4075, the contents of which are hereby incorporated by reference in its entirety. Exemplary modifications that alter or do not alter tissue transduction in at least the brain, liver, heart, lung, and/or kidney can be found in Supplementary Data 2 showing the AAV Barcode-Seq data obtained with AAV9-AA-VBCLib of Adachi et al. (*supra*), the contents of which are hereby incorporated by reference in its entirety.

[0071] In some embodiments, an, AAV capsid polypeptide, e.g., an AAV capsid variant, of the present disclosure is isolated, e.g., recombinant. In some embodiments, a polynucleotide encoding an AAV capsid polypeptide, e.g., an AAV capsid variant, of the present disclosure is isolated, e.g., recombinant.

[0072] 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.

[0073] 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.

[0074] 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 VP2) may also comprise VP capsid proteins which include a Met1/AA1 amino acid (Met+/AA+) as well as corresponding VP capsid proteins which lack the Met1/AA1 amino acid as a result of Met/AA-clipping (Met-/AA-).

[0075] 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).

[0076] 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.

[0077] 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-).

[0078] 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-).

[0079] Also provided herein are polynucleotide sequences encoding any of the AAV capsid variants described above and AAV particles, vectors, and cells comprising the same

Viral Genome

[0080] In some aspects, an AAV particle of the present disclosure, e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant described herein, comprises a viral genome which encodes a an agent for targeting MAPT, e.g., a siRNA duplex for targeting MAPT or a modulatory polynucleotide encoding a siRNA duplex for targeting MAPT.

[0081] In some embodiments, an AAV particle as described herein comprising an AAV capsid polypeptide, e.g., AAV capsid variant, described herein, may be used for the delivery of a viral genome to a tissue (e.g., CNS, DRG, and/or muscle). In some embodiments, an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant, described herein can be used for delivery of a viral genome to a tissue or cell, e.g., CNS, DRG, or muscle cell or tissue. In some embodiments, an AAV particle of the present disclosure is a recombinant AAV particle. In some embodiments, an AAV particle of the present disclosure is an isolated AAV particle.

[0082] In some embodiments, the AAV particles described herein are used to deliver the agent to target MAPT (e.g., a MAPT targeting siRNA duplex or a modulatory polynucleotide encoding a siRNA duplex to cells of the CNS, after intravenous delivery.

[0083] In some embodiments, a viral genome of an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant, as described herein, comprises a nucleic acid comprising a transgene encoding the agent to target MAPT (e.g., a MAPT targeting siRNA duplex or a modulatory polynucleotide encoding a siRNA duplex (e.g., a siRNA duplex for targeting MAPT)). In some embodiments, the viral genome comprises an inverted terminal repeat (ITR) sequence. In some embodiments, the viral genome comprises two ITR sequences, e.g., one at the 5' end of the viral genome (e.g., 5' relative to the encoded payload) and one at the 3' end of the viral genome (e.g., 3' relative to the encoded payload). In some embodiments, a viral genome of the AAV particles described herein (e.g., comprising an AAV capsid variant described herein) may comprise a regulatory element (e.g., promoter), untranslated regions (UTR), a miR binding site a polyadenylation sequence (polyA), a filler or stuffer sequence, an intron, and/or a linker sequence, e.g., for enhancing transgene expression.

[0084] In some embodiments, the viral genome components are selected and/or engineered for expression of an agent for targeting MAPT (e.g., a MAPT targeting siRNA duplex or a modulatory polynucleotide encoding a siRNA duplex (e.g., a siRNA duplex for targeting MAPT)) in a target tissue (e.g., a CNS tissue, e.g., a brain tissue or a spinal cord tissue), or a target cell (e.g., a cell of the CNS, e.g., a brain cell or a spinal cord cell).

Viral Genome Component: Inverted Terminal Repeats (ITRs)

[0085] In some embodiments, the viral genome comprises an ITR and a transgene encoding a payload. In some embodiment, the viral genome has two ITRs. In some embodiments, the two ITRs flank the nucleotide sequence encoding the payload at the 5' and 3' ends. In some embodiments, the ITRs function as origins of replication comprising recognition sites for replication. In some embodiments, the ITRs comprise sequence regions which can be complementary and symmetrically arranged. In some embodiments, the ITRs incorporated into viral genomes as described herein may be comprised of naturally occurring polynucleotide sequences or recombinantly derived polynucleotide sequences.

[0086] In some embodiments, the ITR may be of the same serotype as the capsid polypeptide, e.g., capsid variant, selected from any of the known serotypes, or a variant thereof. In some embodiments, the ITR may be of a different serotype than the capsid. In one embodiment, the viral genome comprises two ITR sequence regions, wherein the ITRs are of the same serotype as one another. In another embodiment, the viral genome comprises two ITR sequence regions, wherein the ITRs are of different serotypes. Non-limiting examples include zero, one or both of the ITRs having the same serotype as the capsid. In one embodiment both ITRs of the viral genome of the AAV particle are AAV2 ITRs.

[0087] In some embodiments, the ITR comprises the nucleotide sequence of SEQ ID NO: 5197, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto. In some embodiments, the ITR comprises the nucleotide sequence of SEQ ID NO: 5200, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto. In some embodiments, an AAV viral genome comprises an ITR comprising the nucleotide sequence of SEQ ID NO: 5197, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto, and an ITR comprising the nucleotide sequence of SEQ ID NO: 5200, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto.

[0088] In some embodiments, the ITR comprises the nucleotide sequence of SEQ ID NO: 4469, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto. In some embodiments, the ITR comprises the nucleotide sequence of SEQ ID NO: 4470, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto. In some embodiments, an AAV viral genome comprises an ITR comprising the nucleotide sequence

of SEQ ID NO: 4469, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto, and an ITR comprising the nucleotide sequence of SEQ ID NO: 4470, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto.

Viral Genome Component: Promoters

[0089] In some embodiments, the viral genome comprises at least one element to enhance the payload target specificity and expression (See e.g., Powell et al. Viral Expression Cassette Elements to Enhance Transgene Target Specificity and Expression in Gene Therapy, 2015; the contents of which are herein incorporated by reference in their entirety). Non-limiting examples of elements to enhance payload target specificity and expression include promoters, endogenous miRNAs, post-transcriptional regulatory elements (PREs), polyadenylation (PolyA) signal sequences and upstream enhancers (USEs), CMV enhancers and introns.

[0090] In some embodiments, an AAV particle comprising an AAV capsid variant described herein comprises a viral genome comprising a nucleic acid comprising a transgene encoding a payload, wherein the transgene is operably linked to a promoter. In some embodiments, the promoter is a species-specific promoter, an inducible promoter, a tissue-specific promoter, or a cell cycle-specific promoter (e.g., a promoter as described in Parr et al., *Nat. Med.*3:1145-9 (1997); the contents of which are herein incorporated by reference in their entirety).

[0091] In some embodiments, the promoter may be naturally occurring or non-naturally occurring. Non-limiting examples of promoters include those derived from viruses, plants, mammals, or humans. In some embodiments, the promoters may be those derived from human cells or systems. In some embodiments, the promoter may be truncated or mutated, e.g., a promoter variant.

[0092] In some embodiments, the promoter is a ubiquitous promoter, e.g., capable of expression in multiple tissues. In some embodiments the promoter is a human elongation factor 1α-subunit (EF1α) promoter, the cytomegalovirus (CMV) immediate-early enhancer and/or promoter, the chicken β-actin (CBA) promoter and its derivative CAG, β glucuronidase (GUSB) promoter, or ubiquitin C (UBC) promoter. In some embodiments, the promoter is a cell or tissue specific promoter, e.g., capable of expression in tissues or cells of the central or peripheral nervous systems, targeted regions within (e.g., frontal cortex), and/or sub-sets of cells therein (e.g., excitatory neurons). In some embodiments, the promoter is a cell-type specific promoters capable of expression of a payload in excitatory neurons (e.g., glutamatergic), inhibitory neurons (e.g., GABA-ergic), neurons of the sympathetic or parasympathetic nervous system, sensory neurons, neurons of the dorsal root ganglia, motor neurons, or supportive cells of the nervous systems such as microglia, glial cells, astrocytes, oligodendrocytes, and/or Schwann cells.

[0093] In some embodiments, the promoter is a liver specific promoter (e.g., hAAT, TBG), skeletal muscle specific promoter (e.g., desmin, MCK, C512), B cell promoter, monocyte promoter, leukocyte promoter, macrophage promoter, pancreatic acinar cell promoter, endothelial cell promoter, lung tissue promoter, and/or cardiac or cardiovascular promoter (e.g., αMHC, cTnT, and CMV-MLC2k).

[0094] In some embodiments, the promoter is a tissue-specific promoter for payload expression in a tissue or cell of the central nervous system. In some embodiments, the promoter is a synapsin (Syn) promoter, glutamate vesicular transporter (VGLUT) promoter, vesicular GABA transporter (VGAT) promoter, parvalbumin (PV) promoter, sodium channel Na_V 1.8 promoter, tyrosine hydroxylase (TH) promoter, choline acetyltransferase (ChaT) promoter, methyl-CpG binding protein 2 (MeCP2) promoter, Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) promoter, metabotropic glutamate receptor 2 (mGluR2) promoter, neurofilament light chain (NFL) or heavy chain (NFH) promoter, neuron-specific enolase (NSE) promoter, β-globin minigene nβ2 promoter, preproenkephalin (PPE) promoter, enkephalin (Enk) promoter, and excitatory amino acid transporter 2 (EAAT2) promoter, or a fragment thereof. In some embodiments, the promoter is a cell-type specific promoter capable of expression in an astrocyte, e.g., a glial fibrillary acidic protein (GFAP) promoter and a EAAT2 promoter, or a fragment thereof. In some embodiments, the promoter is a cell-type specific promoter capable of expression in an oligodendrocyte, e.g., a myelin basic protein (MBP) promoter or a fragment thereof.

[0095] In some embodiments, the promoter is a GFAP promoter. In some embodiments, the promoter is a synapsin (syn or syn1) promoter, or a fragment thereof.

[0096] In some embodiments, the promoter comprises a CBA promoter or a variant thereof, e.g., a functional variant thereof. In some embodiments, the promoter comprises the nucleotide sequence of SEQ ID NO: 5199, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto.

[0097] In some embodiments, the AAV viral genome comprises an enhancer. In some embodiments, the enhancer comprises a CMVie enhancer, or a variant thereof. In some embodiments, the enhancer comprises the nucleotide sequence of SEQ ID NO: 4471, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto. In some embodiments, the enhancer comprises the nucleotide sequence of SEQ ID NO: 4472, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto.

[0098] In some embodiments, the AAV viral genome comprises an enhancer and a promoter. In some embodiments, the enhancer comprises a CMVie enhancer and the promoter comprises a CBA promoter. In some embodiments, the enhancer and the promoter comprise the nucleotide sequence of SEQ ID NO: 4474, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto.

[0099] In some embodiments, the promoter comprises an insulin promoter or a fragment thereof.

[0100] In some embodiments, the viral genome comprises a ubiquitous promoter. Non-limiting examples of ubiquitous promoters include CMV, CBA (including derivatives CAG, CB6, CBh, *etc.*), EF-1α, PGK, UBC, GUSB (hGBp), and UCOE (promoter of HNRPA2B1-CBX3). In some embodiments, the viral genome comprises an EF-1α promoter or EF-1α promoter variant, e.g., as provided in Table 2. In some embodiments, the EF-1α promoter comprises the nucleotide sequence of any one of SEQ ID NOs: 1874-1889 or any of the sequences provided in Table 40, a nucleotide sequence comprising at least one, two, or three but no more than four modifications, e.g., substitutions, relative to the nucleotide sequence of SEQ ID NOs: 1874-1889 or any of the sequences provided in Table 40, or a nucleotide sequence with at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, or 99%) sequence identity to any one of SEQ ID NOs: 1874-1889 or any of the sequences provided in Table 2.

Table 2. Exemplary Promoter Variants

Description	Sequences	SEQ ID NO:
EF1a Promoter (intron underlined)	CGTGAGGCTCCGGTGCCCGTCAGTGGGCAGAGCGCACATCGCCCACAGTCCCCG AGAAGTTGGGGGGAGGGGTCGGCAATTGAACCGGTGCCTAGAGAAGGTGGCGCG GGGTAAACTGGGAAAGTGATGTCGTGTACTGGCTCCGCCTTTTTCCCGAGGGTG GGGGAGAACCGTATATAAGTGCAGTAGTCGCCGTGAACGTTCTTTTTCGCAACG GGTTTGCCGCCAGAACACAGGTAAGTGCCGTGTGTGGTTCCCGCGGGCCTGGCC TCTTTACGGGTTATGGCCCTTGCGTGCCTTGAATTACTTCCACCTGGCTGCAGT ACGTGATTCTTGATCCCGAGCTTCGGGTTGGAAGTGGGTGGGAGAGTTCGAGGC CTTGCGCTTAAGGAGCCCCTTCGCCTCGTGCTTGAGTTGAGGCCTGGCCTGGGC GCTGGGGCCGCCGCGTGCGAATCTGGTGGCACCTTCGCGCCTGTCTCGCTGCTT TCGATAAGTCTCTAGCCATTTAAAATTTTTGATGACCTGCTGCGACGCTTTTTTT TCTGGCAAGATAGTCTTGTAAATGCGGGCCAAGATCTGCACACTGGTATTTCGG TTTTTGGGGCCGCGGGCGGCGACGGGGCCCGTGCGTCCCAGCGCACATGTTCGG CGAGGCGGGGCCTGCGAGCGCGGCCACCGAGAATCGGACGGGGGTAGTCTCAAG CTGGCCGGCCTGCTCTGGTGCCTGGCCTCGCGCCGCCGTGTATCGCCCCGCCCT GGGCGGCAAGGCTGGCCCGGTCGGCACCAGTTGCGTGAGCGGAAAGATGGCCGC TTCCCGGCCCTGCTGCAGGGAGCTCAAAATGGAGGACGCGGCGCTCGGGAGAGC GGGCGGGTGAGTCACCCACACAAAGGAAAAGGGCCTTTCCGTCCTCAGCCGTCG CTTCATGTGACTCCACGGAGTACCGGGCGCCGTCCAGGCACCTCGATTAGTTCT CGAGCTTTTGGAGTACGTCGTCTTTAGGTTGGGGGGAGGGGTTTTATGCGATGG AGTTTCCCCACACTGAGTGGGTGGAGACTGAAGTTAGGCCAGCTTGGCACTTGA TGTAATTCTCCTTGGAATTTGCCCTTTTTGAGTTTGGATCTTGGTTCATTCTCA AGCCTCAGACAGTGGTTCAAAGTTTTTTTCTTCCATTTCAGGTGTCGTGA	1874
miniEF1a	GCCCGTCAGTGGGCAGAGCGCACATCGCCCACAGTCCCCGAGAAGTTGGGGGGA GGGGTCGGCAATTGAACCGGTGCCTAGAGAAGGTGGCGCGGGGTAAACTGGGAA AGTGATGTCGTGTACTGGCTCCGCCTTTTTCCCGAGGGTGGGGGAGAACCGTAT ATAAGTGCAGTAGTCGCCGTGAACGTTCTTTTTCGCAACGGGTTTGCCGCCAGA ACACGCGTAAG	1875
Promoter Variant 1	GCATG	
Promoter Variant 2	GGTGGAGAAGAGCATG	1876
Promoter Variant 3	GTCATCACTGAGGTGGAGAAGAGCATG	1877

Promoter Variant 4	CGTGAG	
Promoter Variant 5	GT	
Promoter Variant 6	GCTCCGGT	
Promoter Variant 19	GCCCGTCAGTGGGCAGAGCGCACATCGCCCACAGTCCCCGAGAAGTTGGGGGGA GGGGTCGGCAATTGAACCGGTGCCTAGAGAAGGTGGCGCGGGGTAAACTGGGAA AGTGATGTCGTGTACTGGCTCCGCCTTTTTCCCGAGGGTGGGGGAGAACCGTAT ATAAGTGCAGTAGTCGCCGTGAACGTTCTTTTTCGCAACGGGTTTGCCGCCAGA ACACAG	1878
Promoter Variant 20	GCCCGTCAGTGGGCAGAGCGCACATCGCCCACAGTCCCCGAGAAGTTGGGGGGA GGGGTCGGCAATTGAACCGGTGCCTAGAGAAGGTGGCGCGGGGTAAACTGGGAA AGTGATGTCGTGTACTGGCTCCGCCTTTTTCCCGAGGGTGGGGGAGAACCGTAT ATAAGTGCAGTAGTCGCCGTGAACGTTCTTTTTCGCAACGGGTTTGCCGCCAGA ACACGC	1879
Promoter Variant 7	GTAAG	
Promoter Variant 8	GTGCCCGTCAGTGGGCAGAGCGCACATCGCCCACAGTCCCCGAGAAGTTGGGGG GAGGGGTCGGCAATTGAACCGGTGCCTAGAGAAGGTGGCGCGGGGTAAACTGGG AAAGTGATGTCGTGTACTGGCTCCGCCTTTTTCCCGAGGGTGGGGGAGAACCGT ATATAAGTGCAGTAGTCGCCGTGAACGTTCTTTTTCGCAACGGGTTTGCCGCCA GAACACGCGTAAG	1880
Promoter Variant 9	GCTCCGGTGCCCGTCAGTGGGCAGAGCGCACATCGCCCACAGTCCCCGAGAAGT TGGGGGGAGGGGTCGGCAATTGAACCGGTGCCTAGAGAAGGTGGCGCGGGGTAA ACTGGGAAAGTGATGTCGTGTACTGGCTCCGCCTTTTTCCCGAGGGTGGGGGAG AACCGTATATAAGTGCAGTAGTCGCCGTGAACGTTCTTTTTCGCAACGGGTTTG CCGCCAGAACACGCGTAAG	1881
Promoter Variant 10	CGTGAGGCTCCGGTGCCCGTCAGTGGGCAGAGCGCACATCGCCCACAGTCCCCG AGAAGTTGGGGGGAGGGGTCGGCAATTGAACCGGTGCCTAGAGAAGGTGGCGCG GGGTAAACTGGGAAAGTGATGTCGTGTACTGGCTCCGCCTTTTTCCCGAGGGTG GGGGAGAACCGTATATAAGTGCAGTAGTCGCCGTGAACGTTCTTTTTCGCAACG GGTTTGCCGCCAGAACACGCGTAAG	1882
Promoter Variant 11	CGTGAGGCTCCGGTGCCCGTCAGTGGGCAGAGCGCACATCGCCCACAGTCCCCG AGAAGTTGGGGGGAGGGGTCGGCAATTGAACCGGTGCCTAGAGAAGGTGGCGCG GGGTAAACTGGGAAAGTGATGTCGTGTACTGGCTCCGCCTTTTTCCCGAGGGTG GGGGAGAACCGTATATAAGTGCAGTAGTCGCCGTGAACGTTCTTTTTCGCAACG GGTTTGCCGCCAGAACACAG	1883
Promoter Variant 12	GCATGCGTGAGGCTCCGGTGCCCGTCAGTGGGCAGAGCGCACATCGCCCACAGT CCCCGAGAAGTTGGGGGGAGGGGTCGGCAATTGAACCGGTGCCTAGAGAAGGTG GCGCGGGGTAAACTGGGAAAGTGATGTCGTGTACTGGCTCCGCCTTTTTCCCGA GGGTGGGGGAGAACCGTATATAAGTGCAGTAGTCGCCGTGAACGTTCTTTTTCG CAACGGGTTTGCCGCCAGAACACGCGTAAG	1884
Promoter Variant 13	GCATGCGTGAGGCTCCGGTGCCCGTCAGTGGGCAGAGCGCACATCGCCCACAGT CCCCGAGAAGTTGGGGGGAGGGGTCGGCAATTGAACCGGTGCCTAGAGAAGGTG GCGCGGGGTAAACTGGGAAAGTGATGTCGTGTACTGGCTCCGCCTTTTTCCCGA GGGTGGGGGAGAACCGTATATAAGTGCAGTAGTCGCCGTGAACGTTCTTTTTCG CAACGGGTTTGCCGCCAGAACACAG	1885
Promoter Variant 14	GGTGGAGAAGAGCATGCGTGAGGCTCCGGTGCCCGTCAGTGGGCAGAGCGCACA TCGCCCACAGTCCCCGAGAAGTTGGGGGGAGGGGTCGGCAATTGAACCGGTGCC TAGAGAAGGTGGCGCGGGGTAAACTGGGAAAGTGATGTCGTGTACTGGCTCCGC CTTTTTCCCGAGGGTGGGGGAGAACCGTATATAAGTGCAGTAGTCGCCGTGAAC GTTCTTTTTCGCAACGGGTTTGCCGCCAGAACACGCGTAAG	1886
Promoter Variant 15	GGTGGAGAAGAGCATGCGTGAGGCTCCGGTGCCCGTCAGTGGGCAGAGCGCACA TCGCCCACAGTCCCCGAGAAGTTGGGGGGAGGGGTCGGCAATTGAACCGGTGCC TAGAGAAGGTGGCGCGGGGTAAACTGGGAAAGTGATGTCGTGTACTGGCTCCGC	1887

	CTTTTTCCCGAGGGTGGGGGAGAACCGTATATAAGTGCAGTAGTCGCCGTGAAC GTTCTTTTTCGCAACGGGTTTGCCGCCAGAACACAG	
Promoter Variant 16	GTCATCACTGAGGTGGAGAAGAGCATGCGTGAGGCTCCGGTGCCCGTCAGTGGG CAGAGCGCACATCGCCCACAGTCCCCGAGAAGTTGGGGGGAGGGGTCGGCAATT GAACCGGTGCCTAGAGAAGGTGGCGCGGGGTAAACTGGGAAAGTGATGTCGTGT ACTGGCTCCGCCTTTTTCCCGAGGGTGGGGGAGAACCGTATATAAGTGCAGTAG TCGCCGTGAACGTTCTTTTTCGCAACGGGTTTGCCGCCAGAACACGCGTAAG	1888
Promoter Variant 18	GTCATCACTGAGGTGGAGAAGAGCATGCGTGAGGCTCCGGTGCCCGTCAGTGGG CAGAGCGCACATCGCCCACAGTCCCCGAGAAGTTGGGGGGAGGGGTCGGCAATT GAACCGGTGCCTAGAGAAGGTGGCGCGGGGTAAACTGGGAAAGTGATGTCGTGT ACTGGCTCCGCCTTTTTCCCGAGGGTGGGGGAGAACCGTATATAAGTGCAGTAG TCGCCGTGAACGTTCTTTTTCGCAACGGGTTTGCCGCCAGAACACAG	1889

Viral Genome Component: Introns

[0101] In some embodiments, the viral genome comprises an element to enhance the payload target specificity and expression (See e.g., Powell et al. *Viral Expression Cassette Elements to Enhance Transgene Target Specificity and Expression in Gene Therapy*, Discov. Med, 2015, 19(102): 49-57; the contents of which are herein incorporated by reference in their entirety), such as an intron. Non-limiting examples of introns include, MVM (67-97 bps), F.IX truncated intron 1 (300 bps), β-globin SD/immunoglobulin heavy chain splice acceptor (250 bps), adenovirus splice donor/immunoglobin splice acceptor (500 bps), SV40 late splice donor/splice acceptor (19S/16S) (180 bps) and hybrid adenovirus splice donor/IgG splice acceptor (230 bps). In some embodiments, the intron comprises a human beta-globin intron or a variant thereof.

[0102] In some embodiments, the intron comprises the nucleotide sequence of SEQ ID NO: 4475, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto.

Viral Genome Component: Untranslated Regions (UTRs)

[0103] In some embodiments, a wild type untranslated region (UTR) of a gene is transcribed but not translated. Generally, the 5' UTR starts at the transcription start site and ends at the start codon and the 3' UTR starts immediately following the stop codon and continues until the termination signal for transcription.

[0104] Features typically found in abundantly expressed genes of specific target organs may be engineered into UTRs to enhance the stability and protein production. As a non-limiting example, a 5' UTR from mRNA normally expressed in the liver (*e.g.*, albumin, serum amyloid A, Apolipoprotein A/B/E, transferrin, alpha fetoprotein, erythropoietin, or Factor VIII) may be used in the viral genomes of the AAV particles of the disclosure to enhance expression in hepatic cell lines or liver.

[0105] In some embodiments, the viral genome encoding a transgene described herein (e.g., a transgene encoding a GBA protein) comprises a Kozak sequence. While not wishing to be bound by theory, wild-type 5′ untranslated regions (UTRs) include features that play roles in translation initiation. Kozak sequences, which are commonly known to be involved in the process by which the ribosome initiates translation of many genes, are usually included in 5' UTRs. Kozak sequences have the consensus CCR(A/G)CCAUGG, where R

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

[0106] In some embodiments, the 5'UTR in the viral genome includes a Kozak sequence.

[0107] In some embodiments, the 5'UTR in the viral genome does not include a Kozak sequence.

[0108] While not wishing to be bound by theory, wild-type 3′ UTRs are known to have stretches of adenosines and uridines embedded therein. These AU rich signatures are particularly prevalent in genes with high rates of turnover. Based on their sequence features and functional properties, the AU rich elements (AREs) can be separated into three classes (Chen et al, 1995, the contents of which are herein incorporated by reference in their entirety): Class I AREs, such as, but not limited to, c-Myc and MyoD, contain several dispersed copies of an AUUUA motif within U-rich regions. Class II AREs, such as, but not limited to, GM-CSF and TNF-a, possess two or more overlapping UUAUUUA(U/A)(U/A) nonamers. Class III ARES, such as, but not limited to, c-Jun and Myogenin, are less well defined. These U rich regions do not contain an AUUUA motif. Most proteins binding to the AREs are known to destabilize the messenger, whereas members of the ELAV family, most notably HuR, have been documented to increase the stability of mRNA. HuR binds to AREs of all the three classes. Engineering the HuR specific binding sites into the 3′ UTR of nucleic acid molecules will lead to HuR binding and thus, stabilization of the message *in vivo*.

[0109] Introduction, removal or modification of 3′ UTR AU rich elements (AREs) can be used to modulate the stability of polynucleotides. When engineering specific polynucleotides, *e.g.*, payload regions of viral genomes, one or more copies of an ARE can be introduced to make polynucleotides less stable and thereby curtail translation and decrease production of the resultant protein. Likewise, AREs can be identified and removed or mutated to increase the intracellular stability and thus increase translation and production of the resultant protein.

[0110] In some embodiments, the 3' UTR of the viral genome may include an oligo(dT) sequence for templated addition of a poly-A tail.

[0111] Any UTR from any gene known in the art may be incorporated into the viral genome of the AAV particle. These UTRs, or portions thereof, may be placed in the same orientation as in the gene from which they were selected or they may be altered in orientation or location. In some embodiments, the UTR used in the viral genome of the AAV particle may be inverted, shortened, lengthened, or made with one or more other 5′ UTRs or 3′ UTRs known in the art. As used herein, the term "altered," as it relates to a UTR, means that the UTR has been changed in some way in relation to a reference sequence. For example, a 3′ or 5′ UTR may be altered relative to a wild type or native UTR by the change in orientation or location as taught above or may be altered by the inclusion of additional nucleotides, deletion of nucleotides, swapping or transposition of nucleotides.

[0112] In some embodiments, the viral genome of the AAV particle comprises at least one artificial UTR,

which is not a variant of a wild type UTR.

[0113] In some embodiments, the viral genome of the AAV particle comprises UTRs which have been selected from a family of transcripts whose proteins share a common function, structure, feature, or property.

Viral Genome Component: miR Binding Site

[0114] Tissue- or cell-specific expression of the AAV viral particles of the invention can be enhanced by introducing tissue- or cell-specific regulatory sequences, *e.g.*, promoters, enhancers, microRNA binding sites, *e.g.*, a detargeting site. Without wishing to be bound by theory, it is believed that an encoded miR binding site can modulate, *e.g.*, prevent, suppress, or otherwise inhibit, the expression of a gene of interest on the viral genome of the invention, based on the expression of the corresponding endogenous microRNA (miRNA) or a corresponding controlled exogenous miRNA in a tissue or cell, *e.g.*, a non-targeting cell or tissue. In some embodiments, a miR binding site modulates, *e.g.*, reduces, expression of the payload encoded by a viral genome of an AAV particle described herein in a cell or tissue where the corresponding mRNA is expressed. In some embodiments, the miR binding site modulates, e.g., reduces, expression of the encoded GBA protein in a cell or tissue of the DRG, liver, hematopoietic lineage, or a combination thereof.

[0115] In some embodiments, the viral genome of an AAV particle described herein comprises a nucleotide sequence encoding a microRNA binding site, *e.g.*, a detargeting site. In some embodiments, the viral genome of an AAV particle described herein comprises a nucleotide sequence encoding a miR binding site, a microRNA binding site series (miR BSs), or a reverse complement thereof.

[0116] In some embodiments, the nucleotide sequence encoding the miR binding site series or the miR binding site is located in the 3'-UTR region of the viral genome (*e.g.*, 3' relative to the nucleic acid sequence encoding a payload), *e.g.*, before the polyA sequence, 5'-UTR region of the viral genome (*e.g.*, 5' relative to the nucleic acid sequence encoding a payload), or both.

[0117] In some embodiments, the encoded miR binding site series comprise at least 1-5 copies, *e.g.*, at least 1-3, 2-4, 3-5, 1, 2, 3, 4, 5 or more copies of a miR binding site (miR BS). In some embodiments, the encoded miR binding site series comprises 4 copies of a miR binding site. In some embodiments, all copies are identical, *e.g.*, comprise the same miR binding site. In some embodiments, the miR binding sites within the encoded miR binding site series are continuous and not separated by a spacer. In some embodiments, the miR binding sites within an encoded miR binding site series are separated by a spacer, *e.g.*, a non-coding sequence. In some embodiments, the spacer is about 1 to 6 nucleotides or about 5 to 10 nucleotides, *e.g.*, about 7-8 nucleotides, nucleotides in length. In some embodiments, the spacer is about 8 nucleotides in length. In some embodiments, the spacer sequence comprises one or more of (i) GGAT; (ii) CACGTG; (iii) GCATGC, or a repeat of one or more of (i)-(iii). In some embodiments, the spacer comprises the nucleotide sequence of GATAGTTA, or a nucleotide sequence having at least one, two, or three modifications, but no more than four modifications of GATAGTTA.

[0118] In some embodiments, the encoded miR binding site series comprise at least 1-5 copies, *e.g.*, at least 1-3, 2-4, 3-5, 1, 2, 3, 4, 5 or more copies of a miR binding site (miR BS). In some embodiments, at least 1, 2, 3, 4, 5, or all of the copies are different, *e.g.*, comprise a different miR binding site. In some embodiments, the miR binding sites within the encoded miR binding site series are continuous and not separated by a spacer. In some embodiments, the miR binding sites within an encoded miR binding site series are separated by a spacer, *e.g.*, a non-coding sequence. In some embodiments, the spacer is about 1 to 6 nucleotides or about 5 to 10 nucleotides, *e.g.*, about 7-8 nucleotides or about 8 nucleotides, in length. In some embodiments, the spacer sequence comprises one or more of (i) GGAT; (ii) CACGTG; (iii) GCATGC, or a repeat of one or more of (i)-(iii). In some embodiments, the spacer comprises the nucleotide sequence of GATAGTTA, or a nucleotide sequence having at least one, two, or three modifications, but no more than four modifications of GATAGTTA.

[0119] In some embodiments, the encoded miR binding site is substantially identical (*e.g.*, at least 70%, 75%, 80%, 85%, 90%, 95%, 99% or 100% identical), to the miR in the host cell. In some embodiments, the encoded miR binding site comprises at least 1, 2, 3, 4, or 5 mismatches or no more than 6, 7, 8, 9, or 10 mismatches to a miR in the host cell. In some embodiments, the mismatched nucleotides are contiguous. In some embodiments, the mismatched nucleotides are non-contiguous. In some embodiments, the mismatched nucleotides occur outside the seed region-binding sequence of the miR binding site, such as at one or both ends of the miR binding site. In some embodiments, the encoded miR binding site is 100% identical to the miR in the host cell.

[0120] In some embodiments, the nucleotide sequence encoding the miR binding site is substantially complimentary (*e.g.*, at least 70%, 75%, 80%, 85%, 90%, 95%, 99% or 100% complementary), to the miR in the host cell. In some embodiments, the sequence complementary to the nucleotide sequence encoding the miR binding site comprises at least 1, 2, 3, 4, or 5 mismatches or no more than 6, 7, 8, 9, or 10 mismatches relative to the corresponding miR in the host cell. In some embodiments, the mismatched nucleotides are contiguous. In some embodiments, the mismatched nucleotides are non-contiguous. In some embodiments, the mismatched nucleotides occur outside the seed region-binding sequence of the miR binding site, such as at one or both ends of the miR binding site. In some embodiments, the encoded miR binding site is 100% complementary to the miR in the host cell.

[0121] In some embodiments, the encoded miR binding site or the encoded miR binding site series is about 10 to about 125 nucleotides in length, *e.g.*, about 10 to 50 nucleotides, 10 to 100 nucleotides, 50 to 100 nucleotides, 50 to 125 nucleotides, or 100 to 125 nucleotides in length. In some embodiments, an encoded miR binding site or the encoded miR binding site series is about 7 to about 28 nucleotides in length, *e.g.*, about 8-28 nucleotides, 7-28 nucleotides, 8-18 nucleotides, 12-28 nucleotides, 20-26 nucleotides, 22 nucleotides, 24 nucleotides, or 26 nucleotides in length, and optionally comprises at least one consecutive

region (*e.g.*, 7 or 8 nucleotides) complementary (e.g., full complementary or partially complementary) to the seed sequence of a miRNA (*e.g.*, a miR122, a miR142, a miR-1, a miR183).

[0122] In some embodiments, the encoded miR binding site is complementary (e.g., fully complementary or partially complementary) to a miR expressed in liver or hepatocytes, such as miR122. In some embodiments, the encoded miR binding site or encoded miR binding site series comprises a miR122 binding site sequence. In some embodiments, the encoded miR122 binding site comprises the nucleotide sequence of ACAAACACCATTGTCACACTCCA (SEQ ID NO: 1865), or a nucleotide sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, at least 95%, at least 99%, or 100% sequence identity, or having at least one, two, three, four, five, six, or seven modifications but no more than ten modifications to SEQ ID NO: 1865, *e.g.*, wherein the modification can result in a mismatch between the encoded miR binding site and the corresponding miRNA. In some embodiments, the viral genome comprises at least 3, 4, or 5 copies of the encoded miR122 binding site, *e.g.*, an encoded miR122 binding site series, optionally wherein the encoded miR122 binding site series comprises the nucleotide sequence of: ACAAACACCATTGTCACACTCCACACAAACACCATTGTCACACTCCACACAAACACCATTGTCACACTCCA (SEQ ID NO: 1866), or a nucleotide sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, at least 95%, at least 99%, or 100% sequence identity, or having at least one, two, three, four, five, six, or seven modifications but no more than ten modifications to SEQ ID NO: 1866, *e.g.*, wherein the modification can result in a mismatch between the encoded miR binding site and the corresponding miRNA. In some embodiments, at least two of the encoded miR122 binding sites are connected directly, *e.g.*, without a spacer. In other embodiments, at least two of the encoded miR122 binding sites are separated by a spacer, *e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides in length, which is located between two or more consecutive encoded miR122 binding site sequences. In embodiments, the spacer is about 1 to 6 nucleotides or about 5 to 10 nucleotides, *e.g.*, about 7-8 nucleotides or about 8 nucleotides, in length. In some embodiments, the spacer sequence comprises one or more of (i) GGAT; (ii) CACGTG; (iii) GCATGC, or a repeat of one or more of (i)-(iii). In some embodiments, the spacer comprises the nucleotide sequence of GATAGTTA, or a nucleotide sequence having at least one, two, or three modifications, but no more than four modifications of GATAGTTA.

[0123] In some embodiments, the encoded miR binding site is complementary (e.g., fully or partially complementary) to a miR expressed in the heart. In embodiments, the encoded miR binding site or encoded miR binding site series comprises a miR-1 binding site. In some embodiments, the encoded miR-1 binding site comprises the nucleotide sequence of ATACATACTTCTTTACATTCCA (SEQ ID NO: 5025), a nucleotide sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, at least 95%, at least 99%, or 100% sequence identity, or having at least one, two, three, four, five, six, or seven modifications but no more than ten modifications to SEQ ID NO: 5025, e.g., wherein the modification can result in a mismatch

between the encoded miR binding site and the corresponding miRNA. In some embodiments, the viral genome comprises at least 2, 3, 4, or 5 copies of the encoded miR-1 binding site, e.g., an encoded miR-1 binding site series. In some embodiments, the at least 2, 3, 4, or 5 copies (e.g., 2 or 3 copies) of the encoded miR-1 binding site are continuous (e.g., not separated by a spacer) or separated by a spacer. In some embodiments, the spacer is about 1 to 6 nucleotides or about 5 to 10 nucleotides, e.g., about 7-8 nucleotides or about 8 nucleotides, in length. In some embodiments, the spacer sequence comprises one or more of (i) GGAT; (ii) CACGTG; (iii) GCATGC, or a repeat of one or more of (i)-(iii). In some embodiments, the spacer comprises the nucleotide sequence of GATAGTTA, or a nucleotide sequence having at least one, two, or three modifications, but no more than four modifications of GATAGTTA.

[0124] In some embodiments, the encoded miR binding site is complementary (e.g., fully complementary or partially complementary) to a miR expressed in hematopoietic lineage, including immune cells (*e.g.*, antigen presenting cells or APC, including dendritic cells (DCs), macrophages, and B-lymphocytes). In some embodiments, the encoded miR binding site is complementary (e.g., fully complementary or partially complementary) to a miR expressed in hematopoietic lineage comprises a nucleotide sequence disclosed, *e.g.*, in US 2018/0066279, the contents of which are incorporated by reference herein in its entirety.

[0125] In some embodiments, the encoded miR binding site or encoded miR binding site series comprises a miR-142-3p binding site sequence. In some embodiments, the encoded miR-142-3p binding site comprises the nucleotide sequence of TCCATAAAGTAGGAAACACTACA (SEQ ID NO: 1869), a nucleotide sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, at least 95%, at least 99%, or 100% sequence identity, or having at least one, two, three, four, five, six, or seven modifications but no more than ten modifications to SEQ ID NO: 1842, *e.g.*, wherein the modification can result in a mismatch between the encoded miR binding site and the corresponding miRNA. In some embodiments, the viral genome comprises at least 3, 4, or 5 copies of an encoded miR-142-3p binding site, *e.g.*, an encoded miR-142-3p binding site series. In some embodiments, the at least 3, 4, or 5 copies (*e.g.*, 4 copies) of the encoded miR-142-3p binding site are continuous (e.g., not separated by a spacer) or separated by a spacer. In some embodiments, the spacer is about 1 to 6 nucleotides or about 5 to 10 nucleotides, *e.g.*, about 7-8 nucleotides or about 8 nucleotides, in length. In some embodiments, the spacer sequence comprises one or more of (i) GGAT; (ii) CACGTG; (iii) GCATGC, or a repeat of one or more of (i)-(iii). In some embodiments, the spacer comprises the nucleotide sequence of GATAGTTA, or a nucleotide sequence having at least one, two, or three modifications, but no more than four modifications of GATAGTTA.

[0126] In some embodiments, the encoded miR binding site is complementary (e.g., fully complementary or partially complementary) to a miR expressed in a DRG (dorsal root ganglion) neuron, *e.g.*, a miR183, a miR182, and/or miR96 binding site. In some embodiments, the encoded miR binding site is complementary (e.g., fully complementary or partially complementary) to a miR expressed in expressed in a DRG neuron. In

some embodiments, the encoded miR binding site comprises a nucleotide sequence disclosed, *e.g.*, in WO2020/132455, the contents of which are incorporated by reference herein in its entirety.

[0127] In some embodiments, the encoded miR binding site or encoded miR binding site series comprises a miR183 binding site sequence. In some embodiments, the encoded miR183 binding site comprises the nucleotide sequence of AGTGAATTCTACCAGTGCCATA (SEQ ID NO: 1847), or a nucleotide sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, at least 95%, at least 99%, or 100% sequence identity, or having at least one, two, three, four, five, six, or seven modifications but no more than ten modifications to SEQ ID NO: 1847, *e.g.*, wherein the modification can result in a mismatch between the encoded miR binding site and the corresponding miRNA. In some embodiments, the sequence complementary (e.g., fully complementary or partially complementary) to the seed sequence corresponds to the double underlined of the encoded miR-183 binding site sequence. In some embodiments, the viral genome comprises at least comprises at least 3, 4, or 5 copies (e.g., 4 copies) of the encoded miR183 binding site, *e.g.* an encoded miR183 binding site. In some embodiments, the viral genome comprises at least comprises 4 copies of the encoded miR183 binding site, *e.g.* an encoded miR183 binding site comprising 4 copies of a miR183 binding site. In some embodiments, the at least 3, 4, or 5 copies (e.g., 4 copies) of the encoded miR183 binding site are continuous (e.g., not separated by a spacer) or separated by a spacer. In some embodiments, the spacer is about 1 to 6 nucleotides or about 5 to 10 nucleotides, *e.g.*, about 7-8 nucleotides or about 8 nucleotides, in length. In some embodiments, the spacer comprises the nucleotide sequence of GATAGTTA, or a nucleotide sequence having at least one, two, or three modifications, but no more than four modifications of GATAGTTA. In some embodiments, the encoded miR183 binding site series comprises the nucleotide sequence of SEQ ID NO: 1849, or a nucleotide sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, at least 95%, at least 99%, or 100% sequence identity, or having at least one, two, three, four, five, six, or seven modifications but no more than ten modifications to SEQ ID NO: 1849.

[0128] In some embodiments, the encoded miR binding site or encoded miR binding site series comprises a miR182 binding site sequence. In some embodiments, the encoded miR182 binding site comprises, the nucleotide sequence of AGTGTGAGTTCTACCATTGCCAAA (SEQ ID NO: 1867), a nucleotide sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, at least 95%, at least 99%, or 100% sequence identity, or having at least one, two, three, four, five, six, or seven modifications but no more than ten modifications to SEQ ID NO: 1867, *e.g.*, wherein the modification can result in a mismatch between the encoded miR binding site and the corresponding miRNA. In some embodiments, the viral genome comprises at least 3, 4, or 5 copies of the encoded miR182 binding site, *e.g.*, an encoded miR182 binding site series. In some embodiments, the at least 3, 4, or 5 copies (*e.g.*, 4 copies) of the encoded miR182 binding site are continuous (e.g., not separated by a spacer) or separated by a spacer. In some embodiments, the spacer is

about 1 to 6 nucleotides or about 5 to 10 nucleotides, *e.g.*, about 7-8 nucleotides or about 8 nucleotides, in length. In some embodiments, the spacer comprises the nucleotide sequence of GATAGTTA, or a nucleotide sequence having at least one, two, or three modifications, but no more than four modifications of GATAGTTA.

[0129] In some embodiments, the encoded miR binding site or encoded miR binding site series comprises a miR96 binding site sequence. In some embodiments, the encoded miR96 binding site comprises the nucleotide sequence of AGCAAAAATGTGCTAGTGCCAAA (SEQ ID NO: 1868), a sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, at least 95%, at least 99%, or 100% sequence identity, or having at least one, two, three, four, five, six, or seven modifications but no more than ten modifications to SEQ ID NO: 1868, *e.g.*, wherein the modification can result in a mismatch between the encoded miR binding site and the corresponding miRNA. In some embodiments, the viral genome comprises at least 3, 4, or 5 copies of the encoded miR96 binding site, *e.g.*, an encoded miR96 binding site series. In some embodiments, the at least 3, 4, or 5 copies (*e.g.*, 4 copies) of the encoded miR96 binding site are continuous (e.g., not separated by a spacer) or separated by a spacer. In some embodiments, the spacer is about 1 to 6 nucleotides or about 5 to 10 nucleotides, *e.g.*, about 7-8 nucleotides or about 8 nucleotides, in length. In some embodiments, the spacer comprises the nucleotide sequence of GATAGTTA, or a nucleotide sequence having at least one, two, or three modifications, but no more than four modifications of GATAGTTA.

[0130] In some embodiments, the encoded miR binding site series comprises a miR122 binding site, a miR142 binding site, a miR183 binding site, a miR182 binding site, a miR 96 binding site, or a combination thereof. In some embodiments, the encoded miR binding site series comprises at least 3, 4, or 5 copies of a miR122 binding site, a miR-1, a miR142 binding site, a miR183 binding site, a miR182 binding site, a miR 96 binding site, or a combination thereof. In some embodiments, at least two of the encoded miR binding sites are connected directly, *e.g.*, without a spacer. In other embodiments, at least two of the encoded miR binding sites are separated by a spacer, *e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides in length, which is located between two or more consecutive encoded miR binding site sequences. In embodiments, the spacer is at least about 5 to 10 nucleotides, *e.g.*, about 7-8 nucleotides or about 8 nucleotides, in length. In some embodiments, the spacer sequence comprises one or more of (i) GGAT; (ii) CACGTG; (iii) GCATGC, or a repeat of one or more of (i)-(iii). In some embodiments, the spacer comprises the nucleotide sequence of GATAGTTA, or a nucleotide sequence having at least one, two, or three modifications, but no more than four modifications of GATAGTTA.

[0131] In some embodiments, an encoded miR binding site series comprises at least 3-5 copies (*e.g.*, 4 copies) of a combination of at least two, three, four, five, or all of a miR122 binding site, a miR-1 a miR142 binding site, a miR183 binding site, a miR182 binding site, a miR96 binding site, wherein each of the miR binding sites within the series are continuous (e.g., not separated by a spacer) or separated by a spacer. In

some embodiments, the spacer is about 1 to 6 nucleotides or about 5 to 10 nucleotides, *e.g.*, about 7-8 nucleotides or about 8 nucleotides, in length. In some embodiments, the spacer sequence comprises one or more of (i) GGAT; (ii) CACGTG; (iii) GCATGC, or a repeat of one or more of (i)-(iii). In some embodiments, the spacer comprises the nucleotide sequence of GATAGTTA, or a nucleotide sequence having at least one, two, or three modifications, but no more than four modifications of GATAGTTA.

Viral Genome Component: Filler Sequence

[0132] In some embodiments, the viral genome of an AAV particle described herein comprises an element to improve packaging efficiency and expression, such as a filler or stuffer sequence. Non-limiting examples of filler or stuffer sequences include albumin and/or alpha-1 antitrypsin. Any known viral, mammalian, or plant sequence may be manipulated for use as a filler sequence. In some embodiments, the filler sequence may be from about 100-3500 nucleotides in length. The stuffer sequence may have a length of about 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, 2000, 2100, 2200, 2300, 2400, 2500, 2600, 2700, 2800, 2900, or 3000 nucleotides.

Viral Genome Component: Polyadenylation Sequence

[0133] The viral genome comprises a polyadenylation (polyA) sequence. In some embodiments, the viral genome of the AAV particle (e.g., an AAV particle comprising an AAV capsid variant, described herein) comprises a polyadenylation sequence between the 3' end of the nucleotide sequence encoding the payload and the 5' end of the 3'ITR. In some embodiments, the polyA sequence comprises the nucleotide sequence of SEQ ID NO: 4476, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto.

Payloads

[0134] In some embodiments, an AAV particle, e.g., an AAV particle for the vectorized delivery of a siRNA, e.g., a MAPT targeting siRNA described herein, comprises a payload. In some embodiments, an AAV particle, e.g., an AAV particle for the vectorized delivery of a siRNA described herein (e.g., a MAPT targeting siRNA), comprises a viral genome encoding a payload. In some embodiments, the viral genome comprises a promoter operably linked to a nucleic acid comprising a transgene encoding a payload. In some embodiments, the payload comprises a siRNA or a modulatory polynucleotide comprising or encoding an siRNA duplex.

[0135] In some aspects, the present disclosure relates to a composition containing or comprising a nucleic acid sequence encoding a MAPT targeting siRNA or functional fragment or variants thereof and methods of administering the composition *in vitro* or *in vivo* in a subject, e.g., a humans and/or an animal model of disease, e.g., a disease related to expression of MAPT.

[0136] AAV particles of the present disclosure may comprise a nucleic acid sequence encoding at least one payload. As used herein, payload or payload region refers to one or more polynucleotides or

polynucleotide regions encoded by or within a viral genome or an expression product of such polynucleotide or polynucleotide region, *e.g.*, a transgene encoding a siRNA duplex, a modulatory polynucleotide, or a gene editing system for inhibiting expression of MAPT, or fragment or variant thereof. The payload may comprise any nucleic acid known in the art that is useful for the expression (by supplementation of the MAPT siRNA or gene replacement using a modulatory nucleic acid) of the MAPT targeting siRNA in a target cell transduced or contacted with the AAV particle carrying the payload.

MAPT

[0137] AAV particle viral genomes of the present disclosure may comprise a payload region, which when expressed, results in the silencing, suppression, and/or reduction of the MAPT gene expression, corresponding transcript expression, and/or protein production.

[0138] The present disclosure provides small interfering RNA (siRNA) duplexes (and modulatory polynucleotides comprising or encoding them) that target MAPT transcript to modulate, e.g., inhibit or silence MAPT gene expression, mRNA production, and/or protein production. In some embodiments, the MAPT gene is a wild type gene. In some embodiments, the MAPT gene comprises at least one, e.g., one or more mutations, e.g., a mutated MAPT gene. In some embodiments, the MAPT gene to be targeted by a siRNA duplex as described herein comprises a mutation that results in the production of a tau protein comprising one, two, or all of a mutation at position 272, 301, and/or 406, e.g., G272V, P301L, and/or R406W.

[0139] In some embodiments, the MAPT gene to be targeted by a siRNA described herein is provided in Table 3. In some embodiments, a siRNA for targeting MAPT described herein targets a MAPT gene comprising a nucleotide sequence provided in Table 3 or a fragment or variant thereof (e.g., the nucleotide sequence of any one of SEQ ID NOs: 3944-3951 or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, or 99% identical thereto). In some embodiments, the siRNA for targeting MAPT as described herein modulates the level of a protein comprising the amino acid sequence of any one of SEQ ID Nos. 3936-3943, or a fragment or variant thereof (e.g., an amino acid sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, or 99% identical to SEQ ID NOs: 3936-3943).

Table 3. Exemplary MAPT Sequences

ID	Sequence	Type	SEQ ID NO	ID	Sequence	Type	SEQ ID NO
MAPT SEQ-001	NP_058519.3	PRT	3936	MAPT SEQ-009	NM_016835.4	DNA	3944
MAPT SEQ-002	NP_005901.2	PRT	3937	MAPT SEQ-010	NM_005910.5	DNA	3945
MAPT SEQ-003	NP_058518.1	PRT	3938	MAPT SEQ-011	NM_016834.4	DNA	3946
MAPT SEQ-004	NP_058525.1	PRT	3939	MAPT SEQ-012	NM_016841.4	DNA	3947
MAPT SEQ-005	NP_001116539.1	PRT	3940	MAPT SEQ-013	NM_001123067.3	DNA	3948
MAPT SEQ-006	NP_001116538.2	PRT	3941	MAPT SEQ-014	NM_001123066.3	DNA	3949
MAPT SEQ-007	NP_001190180.1	PRT	3942	MAPT SEQ-015	NM_001203251.1	DNA	3950
MAPT SEQ-008	NP_001190181.1	PRT	3943	MAPT SEQ-016	NM_001203252.1	DNA	3951

MAPT SEQ-017	NM_001123066.4	DNA	5024				

Modulatory Polynucleotides

[0140] In some embodiments, modulatory polynucleotides, e.g., RNA or DNA molecules, may be used to treat a neurodegenerative disease, e.g., a tauopathy, e.g., Alzheimer's disease (AD) and frontotemporal dementia (FTD). In some embodiments, the tauopathy may be a neurodegenerative disease. In some embodiments, the tauopathy may be a non-neurodegenerative disease without neurodegeneration. In some embodiments, the tauopathy is a familial tauopathy (e.g., genetic) or a sporadic tauopathy (e.g., idiopathic). In some embodiments, a modulatory polynucleotide described herein, e.g., an RNA or DNA molecule, is used to treat epilepsy or Dravet syndrome (DS).

[0141] In some embodiments, the modulatory polynucleotides may comprise a nucleic acid sequence encoding a siRNA molecule. In some embodiments, the modulatory polynucleotides may comprise a nucleic acid sequence encoding at least 1, 2, 3, 4, 5, 6, 7, 8, or 9 siRNA molecules. In some embodiments the modulatory polynucleotide comprises a siRNA molecule, e.g., an siRNA molecule described herein.

siRNA Molecules for Targeting MAPT

[0142] The present disclosure relates to RNA interference (RNAi) agents, e.g., a siRNA, that modulate (e.g., inhibit) expression of MAPT. In some embodiments, an siRNA molecule described herein modulates, reduces and/or silences, e.g., inhibits a MAPT gene, mRNA, and or protein expression. In some embodiments,, a siRNA molecule described herein modulates, reduces, and/or silences, e.g., inhibits, MAPT transcript expression, gene expression and/or protein production in cortical neurons, thereby ameliorating symptoms of Alzheimer's disease (AD) and/or frontotemporal dementia (FTD). In some embodiments, a siRNA molecule described herein modulates, reduces, and/or silences, e.g., inhibits, MAPT transcript expression, gene expression and/or protein production in interneurons and/or hippocampal neurons, thereby ameliorating symptoms of Dravet syndrome (DS). In some embodiments, the hippocampal neuron is a dentate gyrus granule cell neuron.

[0143] RNAi (also known as post-transcriptional gene silencing (PTGS), quelling, or co-suppression) is a post-transcriptional gene silencing process in which RNA molecules, in a sequence-specific manner, inhibit gene expression, typically by causing the destruction of specific mRNA molecules. The active components of RNAi are short/small double stranded RNAs (dsRNAs), called small interfering RNAs (siRNAs), that typically contain 15-30 nucleotides (e.g., 19 to 25, 19 to 24 or 19-21 nucleotides) and 2 nucleotide 3' overhangs, and that match the nucleic acid sequence of the target gene. These short RNA species may be naturally produced *in vivo* by Dicer-mediated cleavage of larger dsRNAs and they are functional in mammalian cells.

[0144] Naturally expressed small RNA molecules, named microRNAs (miRNAs), elicit gene silencing by regulating the expression of mRNAs. The miRNAs-containing RNA Induced Silencing Complex (RISC)

targets mRNAs presenting a perfect sequence complementarity with nucleotides 2-7 in the 5' region of the miRNA which is called the seed region, and other base pairs with its 3' region. miRNA-mediated downregulation of gene expression may be caused by cleavage of the target mRNAs, translational inhibition of the target mRNAs, or mRNA decay. miRNA targeting sequences are usually located in the 3'-UTR of the target mRNAs. A single miRNA may target more than 100 transcripts from various genes, and one mRNA may be targeted by different miRNAs.

[0145] siRNA duplexes or dsRNA targeting a specific mRNA may be designed and synthesized in vitro and introduced into cells for activating RNAi processes (e.g., as described in Elbashir SM et al., Nature, 2001, 411, 494-498, the contents of which are hereby incorporated by reference in their entirety).

[0146] In vitro synthetized siRNA molecules may be introduced into cells to activate RNAi. An exogenous siRNA duplex, when it is introduced into cells, similar to the endogenous dsRNAs, can be assembled to form the RNA Induced Silencing Complex (RISC), a multiunit complex that interacts with RNA sequences that are complementary to one of the two strands of the siRNA duplex (i.e., the antisense strand). During the process, the sense strand (or passenger strand) of the siRNA is lost from the complex, while the antisense strand (or guide strand) of the siRNA is matched with its complementary RNA. In particular, the targets of siRNA containing RISC complexes are mRNAs presenting a perfect sequence complementarity. Then, siRNA mediated gene silencing occurs by cleaving, releasing and degrading the target.

[0147] The siRNA duplex comprised of a sense strand homologous to the target RNA transcript and an antisense strand that is complementary to the target RNA transcript offers much more advantage in terms of efficiency for target RNA destruction compared to the use of the single strand (ss)-siRNAs (e.g., antisense strand RNA or antisense oligonucleotides). In many cases, it requires higher concentration of the ss-siRNA to achieve the effective gene silencing potency of the corresponding duplex.

[0148] While not wishing to be bound by theory, a vector genome may encode a pri-miRNA or pre-miRNA, which when expressed in the target cells is processed via the cell's endogenous pathway to a miRNA duplex. Once the miRNA duplex unwinds, the guide strand may bind to its complementary mRNA substrate and recruit the RNA-induced silencing complex, which leads to the cleavage of the substrate mRNA. Hence, delivery of an AAV particle comprising a vector genome encoding an RNAi precursor (pre- or pri-miR), enters the processing pathway at a different step than would occur with direct administration of an shRNA or siRNA, for example.

[0149] Any of the foregoing molecules may be encoded by an AAV vector or vector genome.

[0150] In some embodiments, a nucleic acid sequence encoding such siRNA molecules, or a single strand of the siRNA molecules, is inserted into the vector genome of an AAV particle and introduced into cells, specifically neurons, including interneurons, and/or other surrounding cells in the central nervous system.

[0151] According to the present disclosure, siRNA molecules (e.g., siRNA duplexes or encoded dsRNA) that target the MAPT transcript may be designed which can modulate, e.g., suppress, inhibit, or silence MAPT gene expression, mRNA expression and/or protein expression. In some embodiments, the siRNA molecule is able to modulate, e.g., inhibit, expression of a wild type MAPT gene, mRNA, and/or protein. In some embodiments, the siRNA molecule is able to modulate, e.g., inhibit, expression of a MAPT gene, mRNA, and/or protein comprising at least one mutation, e.g., a mutated MAPT gene, mRNA, and/or protein. In some embodiments, the mutation is a mutation associate with a tauopathy, e.g., frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17). In some embodiments, the MAPT is a human MAPT. In some embodiments, the MAPT sequence, e.g., the MAPT sequence targeted by an siRNA described herein, comprises the nucleotide sequence of NM_001123066.4, which comprises the nucleotide sequence of:

GCAGTCACCGCCACCCACCAGCTCCGGCACCAACAGCAGCGCCGCTGCCACCGCCCACCTTCTGCCGCCGCCACCACAGC
CACCTTCTCCTCCTCCGCTGTCCTCTCCCGTCCTCGCCTCTGTCGACTATCAGGTGAACTTTGAACCAGGATGGCTGAGC
CCCGCCAGGAGTTCGAAGTGATGGAAGATCACGCTGGGACGTACGGGTTGGGGGACAGGAAAGATCAGGGGGGCTACACC
ATGCACCAAGACCAAGAGGGTGACACGGACGCTGGCCTGAAAGAATCTCCCCTGCAGACCCCCACTGAGGACGGATCTGA
GGAACCGGGCTCTGAAACCTCTGATGCTAAGAGCACTCCAACAGCGGAAGATGTGACAGCACCCTTAGTGGATGAGGGAG
CTCCCGGCAAGCAGGCTGCCGCGCAGCCCCACACGGAGATCCCAGAAGGAACCACAGCTGAAGAAGCAGGCATTGGAGAC
ACCCCCAGCCTGGAAGACGAAGCTGCTGGTCACGTGACCCAAGAGCCTGAAAGTGGTAAGGTGGTCCAGGAAGGCTTCCT
CCGAGAGCCAGGCCCCCCAGGTCTGAGCCACCAGCTCATGTCCGGCATGCCTGGGGCTCCCCTCCTGCCTGAGGGCCCCA
GAGAGGCCACACGCCAACCTTCGGGGACAGGACCTGAGGACACAGAGGGCGGCCGCCACGCCCCTGAGCTGCTCAAGCAC
CAGCTTCTAGGAGACCTGCACCAGGAGGGGCCGCCGCTGAAGGGGGCAGGGGGCAAAGAGAGGCCGGGGAGCAAGGAGGA
GGTGGATGAAGACCGCGACGTCGATGAGTCCTCCCCCCAAGACTCCCCTCCCTCCAAGGCCTCCCCAGCCCAAGATGGGC
GGCCTCCCCAGACAGCCGCCAGAGAAGCCACCAGCATCCCAGGCTTCCCAGCGGAGGGTGCCATCCCCCTCCCTGTGGAT
TTCCTCTCCAAAGTTTCCACAGAGATCCCAGCCTCAGAGCCCGACGGGCCCAGTGTAGGGCGGGCCAAAGGGCAGGATGC
CCCCCTGGAGTTCACGTTTCACGTGGAAATCACACCCAACGTGCAGAAGGAGCAGGCGCACTCGGAGGAGCATTTGGGAA
GGGCTGCATTTCCAGGGGCCCCTGGAGAGGGGCCAGAGGCCCGGGGCCCCTCTTTGGGAGAGGACACAAAAGAGGCTGAC
CTTCCAGAGCCCTCTGAAAAGCAGCCTGCTGCTGCTCCGCGGGGGAAGCCCGTCAGCCGGGTCCCTCAACTCAAAGCTCG
CATGGTCAGTAAAAGCAAAGACGGGACTGGAAGCGATGACAAAAAAGCCAAGACATCCACACGTTCCTCTGCTAAAACCT
TGAAAAATAGGCCTTGCCTTAGCCCCAAACACCCCACTCCTGGTAGCTCAGACCCTCTGATCCAACCCTCCAGCCCTGCT
GTGTGCCCAGAGCCACCTTCCTCTCCTAAATACGTCTCTTCTGTCACTTCCCGAACTGGCAGTTCTGGAGCAAAGGAGAT
GAAACTCAAGGGGGCTGATGGTAAAACGAAGATCGCCACACCGCGGGGAGCAGCCCCTCCAGGCCAGAAGGGCCAGGCCA
ACGCCACCAGGATTCCAGCAAAAACCCCGCCCGCTCCAAAGACACCACCCAGCTCTGCGACTAAGCAAGTCCAGAGAAGA
CCACCCCCTGCAGGGCCCAGATCTGAGAGAGGTGAACCTCCAAAATCAGGGGATCGCAGCGGCTACAGCAGCCCCGGCTC
CCCAGGCACTCCCGGCAGCCGCTCCCGCACCCCGTCCCTTCCAACCCCACCCACCCGGGAGCCCAAGAAGGTGGCAGTGG
TCCGTACTCCACCCAAGTCGCCGTCTTCCGCCAAGAGCCGCCTGCAGACAGCCCCCGTGCCCATGCCAGACCTGAAGAAT
GTCAAGTCCAAGATCGGCTCCACTGAGAACCTGAAGCACCAGCCGGGAGGCGGGAAGGTGCAGATAATTAATAAGAAGCT
GGATCTTAGCAACGTCCAGTCCAAGTGTGGCTCAAAGGATAATATCAAACACGTCCCGGGAGGCGGCAGTGTGCAAATAG
TCTACAAACCAGTTGACCTGAGCAAGGTGACCTCCAAGTGTGGCTCATTAGGCAACATCCATCATAAACCAGGAGGTGGC
CAGGTGGAAGTAAAATCTGAGAAGCTTGACTTCAAGGACAGAGTCCAGTCGAAGATTGGGTCCCTGGACAATATCACCCA
CGTCCCTGGCGGAGGAAATAAAAAGATTGAAACCCACAAGCTGACCTTCCGCGAGAACGCCAAAGCCAAGACAGACCACG
GGGCGGAGATCGTGTACAAGTCGCCAGTGGTGTCTGGGGACACGTCTCCACGGCATCTCAGCAATGTCTCCTCCACCGGC
AGCATCGACATGGTAGACTCGCCCCAGCTCGCCACGCTAGCTGACGAGGTGTCTGCCTCCCTGGCCAAGCAGGGTTTGTG
ATCAGGCCCCTGGGGCGGTCAATAATTGTGGAGAGGAGAGAATGAGAGAGTGTGGAAAAAAAAAAGAATAATGACCCGGCC
CCCGCCCTCTGCCCCCAGCTGCTCCTCGCAGTTCGGTTAATTGGTTAATCACTTAACCTGCTTTTGTCACTCGGCTTTGG
CTCGGGACTTCAAAATCAGTGATGGGAGTAAGAGCAAATTTCATCTTTCCAAATTGATGGGTGGGCTAGTAATAAAATAT
TTAAAAAAAAACATTCAAAAACATGGCCACATCCAACATTTCCTCAGGCAATTCCTTTTGATTCTTTTTTCTTCCCCCTC
CATGTAGAAGAGGGAGAAGGAGAGGCTCTGAAAGCTGCTTCTGGGGGATTTCAAGGGACTGGGGGTGCCAACCACCTCTG
GCCCTGTTGTGGGGGTGTCACAGAGGCAGTGGCAGCAACAAAGGATTTGAAACTTGGTGTGTTCGTGGAGCCACAGGCAG
ACGATGTCAACCTTGTGTGAGTGTGACGGGGGTTGGGGTGGGGCGGGAGGCCACGGGGGAGGCCGAGGCAGGGGCTGGGC
AGAGGGGAGAGGAAGCACAAGAAGTGGGAGTGGGAGAGGAAGCCACGTGCTGGAGAGTAGACATCCCCCTCCTTGCCGCT
GGGAGAGCCAAGGCCTATGCCACCTGCAGCGTCTGAGCGGCCGCCTGTCCTTGGTGGCCGGGGGTGGGGGCCTGCTGTGG

GTCAGTGTGCCACCCTCTGCAGGGCAGCCTGTGGGAGAAGGGACAGCGGGTAAAAAGAGAAGGCAAGCTGGCAGGAGGGT
GGCACTTCGTGGATGACCTCCTTAGAAAAGACTGACCTTGATGTCTTGAGAGCGCTGGCCTCTTCCTCCCTCCCTGCAGG
GTAGGGGGCCTGAGTTGAGGGGCTTCCCTCTGCTCCACAGAAACCCTGTTTTATTGAGTTCTGAAGGTTGGAACTGCTGC
CATGATTTTGGCCACTTTGCAGACCTGGGACTTTAGGGCTAACCAGTTCTCTTTGTAAGGACTTGTGCCTCTTGGGAGAC
GTCCACCCGTTTCCAAGCCTGGGCCACTGGCATCTCTGGAGTGTGTGGGGGTCTGGGAGGCAGGTCCCGAGCCCCCTGTC
CTTCCCACGGCCACTGCAGTCACCCCGTCTGCGCCGCTGTGCTGTTGTCTGCCGTGAGAGCCCAATCACTGCCTATACCC
CTCATCACACGTCACAATGTCCCGAATTCCCAGCCTCACCACCCCTTCTCAGTAATGACCCTGGTTGGTTGCAGGAGGTA
CCTACTCCATACTGAGGGTGAAATTAAGGGAAGGCAAAGTCCAGGCACAAGAGTGGGACCCCAGCCTCTCACTCTCAGTT
CCACTCATCCAACTGGGACCCTCACCACGAATCTCATGATCTGATTCGGTTCCCTGTCTCCTCCTCCCGTCACAGATGTG
AGCCAGGGCACTGCTCAGCTGTGACCCTAGGTGTTTCTGCCTTGTTGACATGGAGAGAGCCCTTTCCCCTGAGAAGGCCT
GGCCCCTTCCTGTGCTGAGCCCACAGCAGCAGGCTGGGTGTCTTGGTTGTCAGTGGTGGCACCAGGATGGAAGGGCAAGG
CACCCAGGGCAGGCCCACAGTCCCGCTGTCCCCCACTTGCACCCTAGCTTGTAGCTGCCAACCTCCCAGACAGCCCAGCC
CGCTGCTCAGCTCCACATGCATAGTATCAGCCCTCCACACCCGACAAAGGGGAACACACCCCCTTGGAAATGGTTCTTTT
CCCCCAGTCCCAGCTGGAAGCCATGCTGTCTGTTCTGCTGGAGCAGCTGAACATATACATAGATGTTGCCCTGCCCTCCC
CATCTGCACCCTGTTGAGTTGTAGTTGGATTTGTCTGTTTATGCTTGGATTCACCAGAGTGACTATGATAGTGAAAAGAA
AAAAAAAAAAAAAAAAAGGACGCATGTATCTTGAAATGCTTGTAAAGAGGTTTCTAACCCACCCTCACGAGGTGTCTCTCA
CCCCCACACTGGGACTCGTGTGGCCTGTGTGGTGCCACCCTGCTGGGGCCTCCCAAGTTTTGAAAGGCTTTCCTCAGCAC
CTGGGACCCAACAGAGACCAGCTTCTAGCAGCTAAGGAGGCCGTTCAGCTGTGACGAAGGCCTGAAGCACAGGATTAGGA
CTGAAGCGATGATGTCCCCTTCCCTACTTCCCCTTGGGGCTCCCTGTGTCAGGGCACAGACTAGGTCTTGTGGCTGGTCT
GGCTTGCGGCGCGAGGATGGTTCTCTCTGGTCATAGCCCGAAGTCTCATGGCAGTCCCAAAGGAGGCTTACAACTCCTGC
ATCACAAGAAAAAGGAAGCCACTGCCAGCTGGGGGGATCTGCAGCTCCCAGAAGCTCCGTGAGCCTCAGCCACCCCTCAG
ACTGGGTTCCTCTCCAAGCTCGCCCTCTGGAGGGGCAGCGCAGCCTCCCACCAAGGGCCCTGCGACCACAGCAGGGATTG
GGATGAATTGCCTGTCCTGGATCTGCTCTAGAGGCCCAAGCTGCCTGCCTGAGGAAGGATGACTTGACAAGTCAGGAGAC
ACTGTTCCCAAAGCCTTGACCAGAGCACCTCAGCCCGCTGACCTTGCACAAACTCCATCTGCTGCCATGAGAAAAGGGAA
GCCGCCTTTGCAAAACATTGCTGCCTAAAGAAACTCAGCAGCCTCAGGCCCAATTCTGCCACTTCTGGTTTGGGTACAGT
TAAAGGCAACCCTGAGGGACTTGGCAGTAGAAATCCAGGGCCTCCCCTGGGGCTGGCAGCTTCGTGTGCAGCTAGAGCTT
TACCTGAAAGGAAGTCTCTGGGCCCAGAACTCTCCACCAAGAGCCTCCCTGCCGTTCGCTGAGTCCCAGCAATTCTCCTA
AGTTGAAGGGATCTGAGAAGGAGAAGGAAATGTGGGGTAGATTTGGTGGTGGTTAGAGATATGCCCCCCTCATTACTGCC
AACAGTTTCGGCTGCATTTCTTCACGCACCTCGGTTCCTCTTCCTGAAGTTCTTGTGCCCTGCTCTTCAGCACCATGGGC
CTTCTTATACGGAAGGCTCTGGGATCTCCCCCTTGTGGGGCAGGCTCTTGGGGCCAGCCTAAGATCATGGTTTAGGGTGA
TCAGTGCTGGCAGATAAATTGAAAAGGCACGCTGGCTTGTGATCTTAAATGAGGACAATCCCCCCAGGGCTGGGCACTCC
TCCCCTCCCCTCACTTCTCCCACCTGCAGAGCCAGTGTCCTTGGGTGGGCTAGATAGGATATACTGTATGCCGGCTCCTT
CAAGCTGCTGACTCACTTTATCAATAGTTCCATTTAAATTGACTTCAGTGGTGAGACTGTATCCTGTTTGCTATTGCTTG
TTGTGCTATGGGGGGAGGGGGGAGGAATGTGTAAGATAGTTAACATGGGCAAAGGGAGATCTTGGGGTGCAGCACTTAAA
CTGCCTCGTAACCCTTTTCATGATTTCAACCACATTTGCTAGAGGGAGGGAGCAGCCACGGAGTTAGAGGCCCTTGGGGT
TTCTCTTTTCCACTGACAGGCTTTCCCAGGCAGCTGGCTAGTTCATTCCCTCCCCAGCCAGGTGCAGGCGTAGGAATATG
GACATCTGGTTGCTTTGGCCTGCTGCCCTCTTTCAGGGGTCCTAAGCCCACAATCATGCCTCCCTAAGACCTTGGCATCC
TTCCCTCTAAGCCGTTGGCACCTCTGTGCCACCTCTCACACTGGCTCCAGACACACAGCCTGTGCTTTTGGAGCTGAGAT
CACTCGCTTCACCCTCCTCATCTTTGTTCTCCAAGTAAAGCCACGAGGTCGGGGCGAGGGCAGAGGTGATCACCTGCGTG
TCCCATCTACAGACCTGCAGCTTCATAAAACTTCTGATTTCTCTTCAGCTTTGAAAAGGGTTACCCTGGGCACTGGCCTA
GAGCCTCACCTCCTAATAGACTTAGCCCCATGAGTTTGCCATGTTGAGCAGGACTATTTCTGGCACTTGCAAGTCCCATG
ATTTCTTCGGTAATTCTGAGGGTGGGGGGAGGGACATGAAATCATCTTAGCTTAGCTTTCTGTCTGTGAATGTCTATATA
GTGTATTGTGTGTTTTAACAAATGATTTACACTGACTGTTGCTGTAAAAGTGAATTTGGAAATAAAGTTATTACTCTGAT
TAAA (SEQ ID NO: 5024).

[0152] In some embodiments, an siRNA molecule of the present disclosure comprises a sense strand and a complementary antisense strand in which both strands are hybridized together to form a duplex structure. The antisense strand may have sufficient complementarity to the MAPT transcript sequence to direct target-specific RNAi to the target mRNA, e.g., the siRNA molecule has a sequence sufficient to trigger the destruction of the target transcript by the RNAi machinery or process.

[0153] In some embodiments, an siRNA molecule of the present disclosure comprises a sense strand and a corresponding antisense strand. In some embodiments, the antisense strand is complementary, e.g., substantially complementary or fully complementary to at least a portion of a MAPT gene, e.g., a MAPT gene

as described in Table 3 or 19, or a variant thereof (e.g., a human MAPT). In some embodiments, the antisense strand is complementary, e.g., partially complementary or fully complementary, to a region of the MAPT transcript, e.g., a region between nucleotide 1 and 6850 on the MAPT transcript sequence, e.g., as described in Table 19. As a non-limiting example, the region of complementary comprises nucleotides 1-50, 50-100, 100-150, 150-200, 200-250, 250-300, 300-350, 350-400, 400-450, 450-500, 500-550, 550-600, 600-650, 650-700, 700-750, 750-800, 800-850, 850-900, 900-950, 950-1000, 1000-1050, 1050-1100, 1100-1150, 1150-1200, 1200-1250, 1250-1300, 1300-1350, 1350-1400, 1400-1450, 1450-1500, 1500-1550, 1550-1600, 1600-1650, 1650-1700, 1700-1750, 1750-1800, 1800-1850, 1850-1900, 1900-1950, 1950-2000, 2000-2050, 2050-2100, 2100-2150, 2150-2200, 2200-2250, 2250-2300, 2300-2350, 2350-2400, 2400-2450, 2450-2500, 2500-2550, 2550-2600, 2600-2650, 2650-2700, 2700-2750, 2750-2800, 2800-2850, 2850-2900, 2900-2950, 2950-3000, 3000-3050, 3050-3100, 3100-3150, 3150-3200, 3200-3250, 3250-3300, 3300-3350, 3350-3400, 3400-3450, 3450-3500, 3500-3550, 3550-3600, 3600-3650, 3650-3700, 3700-3750, 3750-3800, 3800-3850, 3850-3900, 3900-3950, 3950-4000, 4000-4050, 4050-4100, 4100-4150, 4150-4200, 4200-4250, 4250-4300, 4300-4350, 4350-4400, 4400-4450, 4450-4500, 4500-4550, 4550-4600, 4600-4650, 4650-4700, 4700-4750, 4750-4800, 4800-4850, 4850-4900, 4900-4950, 4950-5000, 5000-5050, 5050-5100, 5100-5150, 5150-5200, 5200-5250, 5250-5300, 5300-5350, 5350-5400, 5400-5450, 5450-5500, 5500-5550, 5550-5600, 5600-5650, 5650-5700, 5700-5750, 5750-5800, 5800-5850, 5850-5900, 5900-5950, 5950-6000, 6000-6050, 6050-6100, 6100-6150, 6150-6200, 6200-6250, 6250-6300, 6300-6350, 6350-6400, 6400-6450, 6450-6500, 6500-6550, 6550-6600, 6600-6650, 6650-6700, 6700-6750, 6750-6800, or 6800-6850 of the MAPT transcript sequence, e.g., as described in Table 3 or 19, e.g., SEQ ID NO: 5024.

[0154] In some embodiments, the antisense strand sequence comprises a region of complementarity to the target sequence (e.g., a MAPT target), which is 15-30, 19-21, or 25-30 nucleotides in length, e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length. In some embodiments, the antisense strand sequence is fully complementary to the target sequence (e.g., 100% complementary). In some embodiments, the antisense strand sequence is substantially complementary to the target sequence. In some embodiments, the antisense strand sequence comprises a region of complementarity to a portion of a the target sequence (e.g., a MAPT sequence provided in Table 3 or 19 or a variant thereof), e.g., a portion of at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides that comprises one, two, or three mismatches relative to the target sequence. In some embodiments, the antisense strand sequence is complementary to at least 15, 16, 17, or 18, contiguous nucleotides with 0, 1, 2, or 3 mismatches to nucleotides 1300-1317, 1305-1322, 1860-1877, 2279-2297, 2286-2303, 2402-2419, 2581-2958, 2584-2601, 2633-2650, or 2634-2653 of SEQ ID NO: 5024. In some embodiments, the antisense strand sequence is complementary to at least 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides with 0, 1, 2, or 3 mismatches to a portion of the target sequence present in an exon (e.g., an exon comprising nucleotides 1277 to 1332 of SEQ ID NO: 5024, an exon comprising nucleotides

1712-1977 of SEQ ID NO: 5024, or an exon comprising nucleotides 2266-6644 of SEQ ID NO: 5024) of a coding sequence of a MAPT mRNA, e.g., a MAPT sequence of SEQ ID NO: 5024, e.g., a coding sequence comprising nucleotides 151 to 2481 of SEQ ID NO: 5024.

[0155] In some embodiments, the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides with 0, 1, 2, or 3 mismatches of the corresponding portion of a MAPT sequence, e.g., a MAPT sequence provided in Table 3 or 19, or a variant thereof. In some embodiments, the sense strand sequence or a portion thereof corresponds to positions 1300-1317, 1305-1322, 1860-1877, 2279-2297, 2286-2303, 2402-2419, 2581-2958, 2584-2601, 2633-2650, or 2634-2653 of SEQ ID NO: 5024. In some embodiments, the sense strand sequence comprises a nucleotide sequence comprising at least 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides with 0, 1, 2, or 3 mismatches of the corresponding portion of an exon (e.g., an exon comprising nucleotides 1277 to 1332 of SEQ ID NO: 5024, an exon comprising nucleotides 1712-1977 of SEQ ID NO: 5024, or an exon comprising nucleotides 2266-6644 of SEQ ID NO: 5024) of a coding sequence of a MAPT mRNA, e.g., a MAPT sequence of SEQ ID NO: 5024, e.g., a coding sequence comprising nucleotides 151 to 2481 of SEQ ID NO: 5024. In some embodiments, the sense strand sequence comprises at least 15, 16, 17, or 18 contiguous nucleotides with 0, 1, 2, or 3 mismatches from nucleotides 1300-1317, 1305-1322, 1860-1877, 2279-2297, 2286-2303, 2402-2419, 2581-2958, 2584-2601, 2633-2650, or 2634-2653 of SEQ ID NO: 5024.

[0156] In some embodiments, the sense strand sequence and the antisense strand sequence of an siRNA described herein comprise a region of complementarity, which is 15-30, 19-21, or 25-30 nucleotides in length, e.g., 17, 18, 20, 21, 22, 25, or 30 nucleotides in length. In some embodiments, the sense strand, antisense strand, or both comprise at least 15-30, 19-21, or 25-30 nucleotides in length, e.g., 17, 18, 20, 21, 22, 25, or 30 nucleotides in length. In some embodiments, the sense strand, antisense strand, or both the sense strand comprise one or two nucleotide overhangs, e.g., at the 5' end of the sense strand and the 3' end of the antisense strand or at the 5' end of the antisense strand and the 3' end of the sense strand. In some embodiments, the sense strand and the antisense strand comprise one mismatch. In some embodiments, the antisense strand sequence comprises one mismatch with the target sequence.

[0157] In some embodiments, the siRNA molecules of the present disclosure can be synthetic RNA duplexes comprising about 19 nucleotides to about 25 nucleotides, and two overhanging nucleotides at the 3'-end. In some aspects, the siRNA molecules may be unmodified RNA molecules. In other aspects, the siRNA molecules may contain at least one modified nucleotide, such as base, sugar or backbone modifications. In some embodiments, the overhanging nucleotides at the 3'-end of each of the sense and the antisense strand is a dTdT overhang. In some embodiments, the sense strand, antisense strand, or both the sense strand and the antisense strand does not comprise a dTdT overhang.

[0158] In some embodiments, the siRNA molecule comprises an antisense (e.g., guide) strand sequence. In some embodiments, the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from any one of the antisense strand sequences provided in Tables 4, 5, 9A, or 9B. In some embodiments, the antisense sequence comprises the nucleotide sequence of any one of the antisense strand sequences provided in Tables 4, 5, 9A, or 9B, or a nucleotide sequence 70%, 80%, 85%, 90%, 95% identical thereto. In some embodiments, the antisense strand sequence comprises at least 15, 16, 17, 18, 19, or more than 19 consecutive nucleotides of a nucleotide sequence of any one of the antisense strand sequences provided in Tables 4, 5, 9A, or 9B. In some embodiments, the antisense sequence comprises nucleotides 1 to 19, 1 to 18, 1 to 17, 1 to 16, 2 to 19, or 2 to 18, 2 to 17 of any one of the antisense strand sequences provided in Tables 4, 5, 9A, or 9B. In some embodiments, the antisense sequence may comprise a dTdT overhang, e.g., at the 3' end of the antisense strand sequence. In some embodiments, the antisense sequence does not comprise a dTdT overhang, e.g., does not comprise a dTdT overhang at the 3' end of the sequence. In some embodiments, the antisense strand sequence is a DNA sequence (e.g., comprises T in place of U in any one of the sequences provided in Tables 4 and 5). In some embodiments, the antisense strand sequence is an RNA sequence (e.g., comprises U in place of T in any one of the sequences provided in Table 9A or 9B).

[0159] In some embodiments, the siRNA molecule comprises a sense (e.g., passenger) strand sequence. In some embodiments, the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from any one of the sense strand sequences provided in Tables 4, 5, 9A, or 9B. In some embodiments, the sense sequence comprises the nucleotide sequence of any one of the sense strand sequences provided in Tables 4, 5, 9A, or 9B, or a nucleotide sequence 70%, 80%, 85%, 90%, 95% identical thereto. In some embodiments, the sense strand sequence comprises at least 15, 16, 17, 18, 19, or more than 19 consecutive nucleotides of a nucleotide sequence of any one of the sense strand sequences provided in Tables 4, 5, 9A, or 9B. In some embodiments, the sense sequence comprises nucleotides 1 to 19, 1 to 18, 1 to 17, 1 to 162 to 19, or 2 to 18, 2 to 17 of any one of the sense strand sequences provided in Tables 4, 5, 9A, or 9B. In some embodiments, the sense sequence may comprise a dTdT overhang, e.g. at the 3' end of the sense strand sequence. In some embodiments, the sense sequence does not comprise a dTdT overhang, e.g., does not comprise the dTdT overhang at the 3' end of the sequence. In some embodiments, the sense strand sequence is a DNA sequence (e.g., comprises T in place of U in any one of the sequences provided in Tables 4 and 5). In some embodiments, the sense strand sequence is an RNA sequence (e.g., comprises U in place of T in any one of the sequences provided in Table 9A or 9B).

[0160] In some embodiments, the siRNA comprises an antisense strand sequence comprising a nucleotide sequence comprising at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by no more than 3, 2, 1, or 0 nucleotides from the antisense strand sequences provided in Tables 4, 5, 9A, or 9B; and a sense

strand sequence comprising a nucleotide sequence comprising at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by no more than 3, 2, 1, or 0 nucleotides from the sense strand sequences provided in Tables 4, 5, 9A, or 9B, optionally wherein the sense strand sequence and the antisense strand sequence comprise a region of complementarity of at least 15 nucleotides. In some embodiments, the siRNA molecules of the present disclosure may comprise a siRNA duplex as described in Table 4, 5 9A, or 9B, or a variant, e.g., functional variant, thereof.

[0161] In some embodiments, the dTdT nucleotides of the sense strand and/or the antisense strand of the siRNA provided in Table 4 or herein may be replaced with any two nucleotides (e.g., UU, UC, AA, AG, AC, etc.). Alternatively, the dTdT nucleotides of the sense strand and/or the antisense strand of Table 4 or provided herein may be replaced with a single nucleotide (e.g., U, A, C, or G).

Table 4. Exemplary Sense and Antisense Strand Sequences of MAPT dsRNA

siRNA Duplex ID	SS ID	Sense Strand Sequence (5'-3')	SS SEQ ID NO	AS ID	Antisense Strand Sequence (5'-3')	AS SEQ ID NO
D-001	SS-001	GCUUUGGCUCGG GACUUCCdTdT	4143	AS-001	UGAAGUCCCGAGCC AAAGCdTdT	3952
D-002	SS-002	CGACAUGGUAG ACUCGCCCdTdT	4144	AS-002	UGGCGAGUCUACCA UGUCGdTdT	3953
D-003	SS-003	CUCCUCGCAGUU CGGUUACdTdT	4145	AS-003	UUAACCGAACUGCG AGGAGdTdT	3954
D-004	SS-004	GGCUUUGGCUCG GGACUUCdTdT	4146	AS-004	UAAGUCCCGAGCCA AAGCCdTdT	3955
D-005	SS-005	GGCUUUGGCUCG GGACUUAdTdT	4147	AS-004	UAAGUCCCGAGCCA AAGCCdTdT	3955
D-006	SS-006	GGCUUUGGCUCG GGACUUUdTdT	4148	AS-004	UAAGUCCCGAGCCA AAGCCdTdT	3955
D-007	SS-007	GGCUUUGGCACG GGACUUCdTdT	4149	AS-004	UAAGUCCCGAGCCA AAGCCdTdT	3955
D-008	SS-008	GGCUUUGGCUCG GGACUUGdTdT	4150	AS-004	UAAGUCCCGAGCCA AAGCCdTdT	3955
D-009	SS-009	GCAUCGACAUGG UAGACUCdTdT	4151	AS-005	UAGUCUACCAUGUC GAUGCdTdT	3956
D-010	SS-010	GCAUCGACAUGG UAGACUAdTdT	4152	AS-005	UAGUCUACCAUGUC GAUGCdTdT	3956
D-011	SS-011	GCAUCGACAUGG UAGACUUdTdT	4153	AS-005	UAGUCUACCAUGUC GAUGCdTdT	3956
D-012	SS-012	GCAUCGACAAGG UAGACUCdTdT	4154	AS-005	UAGUCUACCAUGUC GAUGCdTdT	3956
D-013	SS-013	GCAUCGACAUGG UAGACUGdTdT	4155	AS-005	UAGUCUACCAUGUC GAUGCdTdT	3956
D-014	SS-014	UGCUCCUCGCAG UUCGGUCdTdT	4156	AS-006	UACCGAACUGCGAG GAGCAdTdT	3957
D-015	SS-015	CACCCAAGUCGC CGUCUUCdTdT	4157	AS-007	UAAGACGGCGACUU GGGUGdTdT	3958
D-016	SS-016	CCUCGCAGUUCG GUUAAUCdTdT	4158	AS-008	UAUUAACCGAACUG CGAGGdTdT	3959

D-017	SS-017	UCCUCGCAGUUC GGUUAACdTdT	4159	AS-009	UUUAACCGAACUGC GAGGAdTdT	3960
D-018	SS-018	AGCUGACCUUCC GCGAGACdTdT	4160	AS-010	UUCUCGCGGAAGGU CAGCUdTdT	3961
D-019	SS-019	GACUGGAAGCG AUGACAACdTdT	4161	AS-011	UUUGUCAUCGCUUC CAGUCdTdT	3962
D-020	SS-020	GACUGGAAGCG AUGACAAAdTdT	4162	AS-011	UUUGUCAUCGCUUC CAGUCdTdT	3962
D-021	SS-021	GACUGGAAGCG AUGACAAUdTdT	4163	AS-011	UUUGUCAUCGCUUC CAGUCdTdT	3962
D-022	SS-022	GACUGGAAGGG AUGACAACdTdT	4164	AS-011	UUUGUCAUCGCUUC CAGUCdTdT	3962
D-023	SS-023	GACUGGAAGCG AUGACAAGdTdT	4165	AS-011	UUUGUCAUCGCUUC CAGUCdTdT	3962
D-024	SS-024	AGCUCGCAUGGU CAGUAACdTdT	4166	AS-012	UUUACUGACCAUGC GAGCUdTdT	3963
D-025	SS-025	AGUCUACAAACC AGUUGACdTdT	4167	AS-013	UUCAACUGGUUUGU AGACUdTdT	3964
D-026	SS-026	GCUCCUCGCAGU UCGGUUCdTdT	4168	AS-014	UAACCGAACUGCGA GGAGCdTdT	3965
D-027	SS-027	GCUCCUCGCAGU UCGGUUGdTdT	4169	AS-014	UAACCGAACUGCGA GGAGCdTdT	3965
D-028	SS-028	GCUCCUCGCAGU UCGGUUUdTdT	4170	AS-014	UAACCGAACUGCGA GGAGCdTdT	3965
D-029	SS-029	GCUCCUCGCUGU UCGGUUCdTdT	4171	AS-014	UAACCGAACUGCGA GGAGCdTdT	3965
D-030	SS-030	CUUCCGCGAGAA CGCCAACdTdT	4172	AS-015	UUUGGCGUUCUCGC GGAAGdTdT	3966
D-031	SS-031	CUUCCGCGAGAA CGCCAAAdTdT	4173	AS-015	UUUGGCGUUCUCGC GGAAGdTdT	3966
D-032	SS-032	CUUCCGCGAGAA CGCCAAUdTdT	4174	AS-015	UUUGGCGUUCUCGC GGAAGdTdT	3966
D-033	SS-033	CUUCCGCGACAA CGCCAACdTdT	4175	AS-015	UUUGGCGUUCUCGC GGAAGdTdT	3966
D-034	SS-034	CUUCCGCGAGAA CGCCAAGdTdT	4176	AS-015	UUUGGCGUUCUCGC GGAAGdTdT	3966
D-035	SS-035	AAAUCAGUGAU GGGAGUACdTdT	4177	AS-016	UUACUCCCAUCACU GAUUUdTdT	3967
D-036	SS-036	GUCGCCGUCUUC CGCCAACdTdT	4178	AS-017	UUUGGCGGAAGACG GCGACdTdT	3968
D-037	SS-037	AUGGUAAAACG AAGAUCGCdTdT	4179	AS-018	UCGAUCUUCGUUUU ACCAUdTdT	3969
D-038	SS-038	ACGAAGAUCGCC ACACCGCdTdT	4180	AS-019	UCGGUGUGGCGAUC UUCGUdTdT	3970
D-039	SS-039	CGCAGUUCGGUU AAUUGGCdTdT	4181	AS-020	UCCAAUUAACCGAA CUGCGdTdT	3971
D-040	SS-040	GUACUCCACCCA AGUCGCCdTdT	4182	AS-021	UGCGACUUGGGUGG AGUACdTdT	3972
D-041	SS-041	CUCGGCUUUGGC UCGGGACdTdT	4183	AS-022	UUCCCGAGCCAAAG CCGAGdTdT	3973
D-042	SS-042	GCCCCUGGGGCG GUCAAUCdTdT	4184	AS-023	UAUUGACCGCCCCA GGGGCdTdT	3974
D-043	SS-043	CUCGCAGUUCGG UUAAUUCdTdT	4185	AS-024	UAAUUAACCGAACU GCGAGdTdT	3975

D-044	SS-044	UCGCCGUCUUCC GCCAAGCdTdT	4186	AS-025	UCUUGGCGGAAGAC GGCGAdTdT	3976
D-045	SS-045	GACGGGACUGG AAGCGAUCdTdT	4187	AS-026	UAUCGCUUCCAGUC CCGUCdTdT	3977
D-046	SS-046	UGGUAAAACGA AGAUCGCCdTdT	4188	AS-027	UGCGAUCUUCGUUU UACCAdTdT	3978
D-047	SS-047	GUAAAACGAAG AUCGCCACdTdT	4189	AS-028	UUGGCGAUCUUCGU UUUACdTdT	3979
D-048	SS-048	ACAAUAUCACCC ACGUCCCdTdT	4190	AS-029	UGGACGUGGGUGAU AUUGUdTdT	3980
D-049	SS-049	CCUUCCGCGAGA ACGCCACdTdT	4191	AS-030	UUGGCGUUCUCGCG GAAGGdTdT	3981
D-050	SS-050	GGGGGCUGAUG GUAAAACCdTdT	4192	AS-031	UGUUUUACCAUCAG CCCCCdTdT	3982
D-051	SS-051	GCCGUCUUCCGC CAAGAGCdTdT	4193	AS-032	UCUCUUGGCGGAAG ACGGCdTdT	3983
D-052	SS-052	CACCGGCAGCAU CGACAUCdTdT	4194	AS-033	UAUGUCGAUGCUGC CGGUGdTdT	3984
D-053	SS-053	GUAAAAGCAAA GACGGGACdTdT	4195	AS-034	UUCCCGUCUUUGCU UUUACdTdT	3985
D-054	SS-054	AGGUUUCUAACC CACCCUCdTdT	4196	AS-035	UAGGGUGGGUUAGA AACCUdTdT	3986
D-055	SS-055	UUCCGCGAGAAC GCCAAACdTdT	4197	AS-036	UUUUGGCGUUCUCG CGGAAdTdT	3987
D-056	SS-056	GACCUUCCGCGA GAACGCCdTdT	4198	AS-037	UGCGUUCUCGCGGA AGGUCdTdT	3988
D-057	SS-057	CGCCACGCUAGC UGACGACdTdT	4199	AS-038	UUCGUCAGCUAGCG UGGCGdTdT	3989
D-058	SS-058	ACCUGCGUGUCC CAUCUACdTdT	4200	AS-039	UUAGAUGGGACACG CAGGUdTdT	3990
D-059	SS-059	CCCCAGCUCGCC ACGCUACdTdT	4201	AS-040	UUAGCGUGGCGAGC UGGGGdTdT	3991
D-060	SS-060	GCCGUUCAGCUG UGACGACdTdT	4202	AS-041	UUCGUCACAGCUGA ACGGCdTdT	3992
D-061	SS-061	GCUGAUGGUAA AACGAAGCdTdT	4203	AS-042	UCUUCGUUUUACCA UCAGCdTdT	3993
D-062	SS-062	ACGAGGUGUCUC UCACCCCdTdT	4204	AS-043	UGGGUGAGAGACAC CUCGUdTdT	3994
D-063	SS-063	GGGCCAGCCUAA GAUCAUCdTdT	4205	AS-044	UAUGAUCUUAGGCU GGCCCdTdT	3995
D-064	SS-064	UCUAACCCACCC UCACGACdTdT	4206	AS-045	UUCGUGAGGGUGGG UUAGAdTdT	3996
D-065	SS-065	UAAAGAGGUUU CUAACCCCdTdT	4207	AS-046	UGGGUUAGAAACCU CUUUAdTdT	3997
D-066	SS-066	CUCACCUCCUAA UAGACUCdTdT	4208	AS-047	UAGUCUAUUAGGAG GUGAGdTdT	3998
D-067	SS-067	GGAUAUACUGU AUGCCGGCdTdT	4209	AS-048	UCCGGCAUACAGUA UAUCCdTdT	3999
D-068	SS-068	CACCCUCACGAG GUGUCUCdTdT	4210	AS-049	UAGACACCUCGUGA GGGUGdTdT	4000
D-069	SS-069	CACGCUAGCUGA CGAGGUCdTdT	4211	AS-050	UACCUCGUCAGCUA GCGUGdTdT	4001
D-070	SS-070	UCCCAUGAUUUC UUCGGUCdTdT	4212	AS-051	UACCGAAGAAAUCA UGGGAdTdT	4002

D-071	SS-071	UUGAGUUGUAG UUGGAUUCdTdT	4213	AS-052	UAAUCCAACUACAA CUCAAdTdT	4003
D-072	SS-072	CUGCGUGUCCCA UCUACACdTdT	4214	AS-053	UUGUAGAUGGGACA CGCAGdTdT	4004
D-073	SS-073	GUUGAGUUGUA GUUGGAUCdTdT	4215	AS-054	UAUCCAACUACAAC UCAACdTdT	4005
D-074	SS-074	GGUGGUGGUUA GAGAUAUCdTdT	4216	AS-055	UAUAUCUCUAACCA CCACCdTdT	4006
D-075	SS-075	GGGCUAGAUAG GAUAUACCdTdT	4217	AS-056	UGUAUAUCCUAUCU AGCCCdTdT	4007
D-076	SS-076	AGGAUUCCAGCA AAAACCCdTdT	4218	AS-057	UGGUUUUUGCUGGA AUCCUdTdT	4008
D-077	SS-077	GGCCCCUGGGGC GGUCAACdTdT	4219	AS-058	UUUGACCGCCCCAG GGGCCdTdT	4009
D-078	SS-078	GAUUAGGACUG AAGCGAUCdTdT	4220	AS-059	UAUCGCUUCAGUCC UAAUCdTdT	4010
D-079	SS-079	CUCCCAAGUUUU GAAAGGCdTdT	4221	AS-060	UCCUUUCAAAACUU GGGAGdTdT	4011
D-080	SS-080	GCUGGUCUGGCU UGCGGCCdTdT	4222	AS-061	UGCCGCAAGCCAGA CCAGCdTdT	4012
D-081	SS-081	GUUCCACUCAUC CAACUGCdTdT	4223	AS-062	UCAGUUGGAUGAGU GGAACdTdT	4013
D-082	SS-082	CACCUCCUAAUA GACUUACdTdT	4224	AS-063	UUAAGUCUAUUAGG AGGUGdTdT	4014
D-083	SS-083	UUCUAACCCACC CUCACGCdTdT	4225	AS-064	UCGUGAGGGUGGGU UAGAAdTdT	4015
D-084	SS-084	AAGCCCACAAUC AUGCCUCdTdT	4226	AS-065	UAGGCAUGAUUGUG GGCUUdTdT	4016
D-085	SS-085	ACCUUCCGCGAG AACGCCCdTdT	4227	AS-066	UGGCGUUCUCGCGG AAGGUdTdT	4017
D-086	SS-086	GCUGGUCACGUG ACCCAACdTdT	4228	AS-067	UUUGGGUCACGUGA CCAGCdTdT	4018
D-087	SS-087	UAACCCACCCUC ACGAGGCdTdT	4229	AS-068	UCCUCGUGAGGGUG GGUUAdTdT	4019
D-088	SS-088	CUUACAACUCCU GCAUCACdTdT	4230	AS-069	UUGAUGCAGGAGUU GUAAGdTdT	4020
D-089	SS-089	UGGGACUUUAG GGCUAACCdTdT	4231	AS-070	UGUUAGCCCUAAAG UCCCAdTdT	4021
D-090	SS-090	GCCACAGGCAGA CGAUGUCdTdT	4232	AS-071	UACAUCGUCUGCCU GUGGCdTdT	4022
D-091	SS-091	GCCUCUUGGGAG ACGUCCCdTdT	4233	AS-072	UGGACGUCUCCCAA GAGGCdTdT	4023
D-092	SS-092	GAGAUAUGCCCC CCUCAUCdTdT	4234	AS-073	UAUGAGGGGGGCAU AUCUCdTdT	4024
D-093	SS-093	UCCCAAGUUUUG AAAGGCCdTdT	4235	AS-074	UGCCUUUCAAAACU UGGGAdTdT	4025
D-094	SS-094	AGUUAUUACUC UGAUUAACdTdT	4236	AS-075	UUUAAUCAGAGUAA UAACUdTdT	4026
D-095	SS-095	UAUGCCCCCCUC AUUACUCdTdT	4237	AS-076	UAGUAAUGAGGGGG GCAUAdTdT	4027
D-096	SS-096	CAAAAUCAGGG GAUCGCACdTdT	4238	AS-077	UUGCGAUCCCCUGA UUUUGdTdT	4028
D-097	SS-097	CAGACCACGGGG CGGAGACdTdT	4239	AS-078	UUCUCCGCCCCGUG GUCUGdTdT	4029

D-098	SS-098	CUUGGGUGGGC UAGAUAGCdTdT	4240	AS-079	UCUAUCUAGCCCAC CCAAGdTdT	4030
D-099	SS-099	CUCGCCACGCUA GCUGACCdTdT	4241	AS-080	UGUCAGCUAGCGUG GCGAGdTdT	4031
D-100	SS-100	UGUUGAGUUGU AGUUGGACdTdT	4242	AS-081	UUCCAACUACAACU CAACAdTdT	4032
D-101	SS-101	UAUACAUAGAU GUUGCCCCdTdT	4243	AS-082	UGGGCAACAUCUAU GUAUAdTdT	4033
D-102	SS-102	AACCCACCCUCA CGAGGUCdTdT	4244	AS-083	UACCUCGUGAGGGU GGGUUdTdT	4034
D-103	SS-103	GUUGAGCAGGA CUAUUUCCdTdT	4245	AS-084	UGAAAUAGUCCUGC UCAACdTdT	4035
D-104	SS-104	CCACGCUAGCUG ACGAGGCdTdT	4246	AS-085	UCCUCGUCAGCUAG CGUGGdTdT	4036
D-105	SS-105	CUCCUAAUAGAC UUAGCCCdTdT	4247	AS-086	UGGCUAAGUCUAUU AGGAGdTdT	4037
D-106	SS-106	GAUUUCUUCGG UAAUUCUCdTdT	4248	AS-087	UAGAAUUACCGAAG AAAUCdTdT	4038
D-107	SS-107	GUCCCAAAGGAG GCUUACCdTdT	4249	AS-088	UGUAAGCCUCCUUU GGGACdTdT	4039
D-108	SS-108	GGUGGUUAGAG AUAUGCCCdTdT	4250	AS-089	UGGCAUAUCUCUAA CCACCdTdT	4040
D-109	SS-109	GGCUAGAUAGG AUAUACUCdTdT	4251	AS-090	UAGUAUAUCCUAUC UAGCCdTdT	4041
D-110	SS-110	AUUCACCAGAGU GACUAUCdTdT	4252	AS-091	UAUAGUCACUCUGG UGAAUdTdT	4042
D-111	SS-111	GAUAUACUGUA UGCCGGCCdTdT	4253	AS-092	UGCCGGCAUACAGU AUAUCdTdT	4043
D-112	SS-112	GACCACAGCAGG GAUUGGCdTdT	4254	AS-093	UCCAAUCCCUGCUG UGGUCdTdT	4044
D-113	SS-113	GAGCCACAGGCA GACGAUCdTdT	4255	AS-094	UAUCGUCUGCCUGU GGCUCdTdT	4045
D-114	SS-114	CUAGCUGACGAG GUGUCUCdTdT	4256	AS-095	UAGACACCUCGUCA GCUAGdTdT	4046
D-115	SS-115	AAGGGGGCUGA UGGUAAACdTdT	4257	AS-096	UUUUACCAUCAGCC CCCUUdTdT	4047
D-116	SS-116	AUCAGGGGAUC GCAGCGGCdTdT	4258	AS-097	UCCGCUGCGAUCCC CUGAUdTdT	4048
D-117	SS-117	CCCAGCUCGCCA CGCUAGCdTdT	4259	AS-098	UCUAGCGUGGCGAG CUGGGdTdT	4049
D-118	SS-118	CGUUCAGCUGUG ACGAAGCdTdT	4260	AS-099	UCUUCGUCACAGCU GAACGdTdT	4050
D-119	SS-119	CACUUGCAAGUC CCAUGACdTdT	4261	AS-100	UUCAUGGGACUUGC AAGUGdTdT	4051
D-120	SS-120	UGGGCUAGAUA GGAUAUACdTdT	4262	AS-101	UUAUAUCCUAUCUA GCCCAdTdT	4052
D-121	SS-121	UUUAUGCUUGG AUUCACCCdTdT	4263	AS-102	UGGUGAAUCCAAGC AUAAAdTdT	4053
D-122	SS-122	CCAAAAUCAGGG GAUCGCCdTdT	4264	AS-103	UGCGAUCCCCUGAU UUUGGdTdT	4054
D-123	SS-123	CCGUUCAGCUGU GACGAACdTdT	4265	AS-104	UUUCGUCACAGCUG AACGGdTdT	4055
D-124	SS-124	GGCCACAUCCAA CAUUUCCdTdT	4266	AS-105	UGAAAUGUUGGAUG UGGCCdTdT	4056

D-125	SS-125	UUUAUCAAUAG UUCCAUUCdTdT	4267	AS-106	UAAUGGAACUAUUG AUAAAdTdT	4057
D-126	SS-126	GGCGGAGAUCG UGUACAACdTdT	4268	AS-107	UUUGUACACGAUCU CCGCCdTdT	4058
D-127	SS-127	UCGCCACGCUAG CUGACGCdTdT	4269	AS-108	UCGUCAGCUAGCGU GGCGAdTdT	4059
D-128	SS-128	GUCUGGCUUGCG GCGCGACdTdT	4270	AS-109	UUCGCGCCGCAAGC CAGACdTdT	4060
D-129	SS-129	ACCUCCUAAUAG ACUUAGCdTdT	4271	AS-110	UCUAAGUCUAUUAG GAGGUdTdT	4061
D-130	SS-130	UGUCCCAUCUAC AGACCUCdTdT	4272	AS-111	UAGGUCUGUAGAUG GGACAdTdT	4062
D-131	SS-131	CGGUAAUUCUG AGGGUGGCdTdT	4273	AS-112	UCCACCCUCAGAAU UACCGdTdT	4063
D-132	SS-132	UUUCUUCGGUA AUUCUGACdTdT	4274	AS-113	UUCAGAAUUACCGA AGAAAdTdT	4064
D-133	SS-133	GCACCCUGUUGA GUUGUACdTdT	4275	AS-114	UUACAACUCAACAG GGUGCdTdT	4065
D-134	SS-134	AUAUACUGUAU GCCGGCUCdTdT	4276	AS-115	UAGCCGGCAUACAG UAUAUdTdT	4066
D-135	SS-135	ACUUCUGGUUU GGGUACACdTdT	4277	AS-116	UUGUACCCAAACCA GAAGUdTdT	4067
D-136	SS-136	GAAGCACAGGA UUAGGACCdTdT	4278	AS-117	UGUCCUAAUCCUGU GCUUCdTdT	4068
D-137	SS-137	CUUUCAGGGGUC CUAAGCCdTdT	4279	AS-118	UGCUUAGGACCCCU GAAAGdTdT	4069
D-138	SS-138	GAUAUGCCCCCC UCAUUACdTdT	4280	AS-119	UUAAUGAGGGGGGC AUAUCdTdT	4070
D-139	SS-139	CUAAGGAGGCCG UUCAGCCdTdT	4281	AS-120	UGCUGAACGGCCUC CUUAGdTdT	4071
D-140	SS-140	GGAACACACCCC CUUGGACdTdT	4282	AS-121	UUCCAAGGGGGUGU GUUCCdTdT	4072
D-141	SS-141	CCUAAGCCCACA AUCAUGCdTdT	4283	AS-122	UCAUGAUUGUGGGC UUAGGdTdT	4073
D-142	SS-142	CUGGGGCCUCCC AAGUUUCdTdT	4284	AS-123	UAAACUUGGGAGGC CCCAGdTdT	4074
D-143	SS-143	UGUCCCCCACUU GCACCCCdTdT	4285	AS-124	UGGGUGCAAGUGGG GGACAdTdT	4075
D-144	SS-144	AAGUUAUUACU CUGAUUACdTdT	4286	AS-125	UUAAUCAGAGUAAU AACUUdTdT	4076
D-145	SS-145	AAUAGACUUAG CCCCAUGCdTdT	4287	AS-126	UCAUGGGGCUAAGU CUAUUdTdT	4077
D-146	SS-146	CAGUAAUGACCC UGGUUGCdTdT	4288	AS-127	UCAACCAGGGUCAU UACUGdTdT	4078
D-147	SS-147	GGAGGAAUGUG UAAGAUACdTdT	4289	AS-128	UUAUCUUACACAUU CCUCCdTdT	4079
D-148	SS-148	CAAUCAUGCCUC CCUAAGCdTdT	4290	AS-129	UCUUAGGGAGGCAU GAUUGdTdT	4080
D-149	SS-149	UCCACUCAUCCA ACUGGGCdTdT	4291	AS-130	UCCCAGUUGGAUGA GUGGAdTdT	4081
D-150	SS-150	AGGUGCAGGCG UAGGAAUCdTdT	4292	AS-131	UAUUCCUACGCCUG CACCUdTdT	4082
D-151	SS-151	GAUAGGAUAUA CUGUAUGCdTdT	4293	AS-132	UCAUACAGUAUAUC CUAUCdTdT	4083

D-152	SS-152	UCCUAAGCCCAC AAUCAUCdTdT	4294	AS-133	UAUGAUUGUGGGCU UAGGAdTdT	4084
D-153	SS-153	GGCCGUUCAGCU GUGACGCdTdT	4295	AS-134	UCGUCACAGCUGAA CGGCCdTdT	4085
D-154	SS-154	UGGCCACAUCCA ACAUUUCdTdT	4296	AS-135	UAAAUGUUGGAUGU GGCCAdTdT	4086
D-155	SS-155	AGCAGGACUAU UUCUGGCCdTdT	4297	AS-136	UGCCAGAAAUAGUC CUGCUdTdT	4087
D-156	SS-156	AUAUGGACAUC UGGUUGCCdTdT	4298	AS-137	UGCAACCAGAUGUC CAUAUdTdT	4088
D-157	SS-157	ACUUGCACCCUA GCUUGUCdTdT	4299	AS-138	UACAAGCUAGGGUG CAAGUdTdT	4089
D-158	SS-158	GUAAAGAGGUU UCUAACCCdTdT	4300	AS-139	UGGUUAGAAACCUC UUUACdTdT	4090
D-159	SS-159	GACUCACUUUAU CAAUAGCdTdT	4301	AS-140	UCUAUUGAUAAAGU GAGUCdTdT	4091
D-160	SS-160	AGCUGCUGACUC ACUUUACdTdT	4302	AS-141	UUAAAGUGAGUCAG CAGCUdTdT	4092
D-161	SS-161	AAGGGUUACCCU GGGCACCdTdT	4303	AS-142	UGUGCCCAGGGUAA CCCUUdTdT	4093
D-162	SS-162	UGUAAAGAGGU UUCUAACCdTdT	4304	AS-143	UGUUAGAAACCUCU UUACAdTdT	4094
D-163	SS-163	UGGCUUGCGGCG CGAGGACdTdT	4305	AS-144	UUCCUCGCGCCGCA AGCCAdTdT	4095
D-164	SS-164	GCCACGCUAGCU GACGAGCdTdT	4306	AS-145	UCUCGUCAGCUAGC GUGGCdTdT	4096
D-165	SS-165	CCCAAAGGAGGC UUACAACdTdT	4307	AS-146	UUUGUAAGCCUCCU UUGGGdTdT	4097
D-166	SS-166	UGUUGUGCUAU GGGGGGACdTdT	4308	AS-147	UUCCCCCCAUAGCA CAACAdTdT	4098
D-167	SS-167	GGGAACACACCC CCUUGGCdTdT	4309	AS-148	UCCAAGGGGGUGUG UUCCCdTdT	4099
D-168	SS-168	UUCCAAAUUGA UGGGUGGCdTdT	4310	AS-149	UCCACCCAUCAAUU UGGAAdTdT	4100
D-169	SS-169	ACCGGCAGCAUC GACAUGCdTdT	4311	AS-150	UCAUGUCGAUGCUG CCGGUdTdT	4101
D-170	SS-170	CUGGCUUGCGGC GCGAGGCdTdT	4312	AS-151	UCCUCGCGCCGCAA GCCAGdTdT	4102
D-171	SS-171	GUGUAAGAUAG UUAACAUCdTdT	4313	AS-152	UAUGUUAACUAUCU UACACdTdT	4103
D-172	SS-172	AGGAUUAGGAC UGAAGCGCdTdT	4314	AS-153	UCGCUUCAGUCCUA AUCCUdTdT	4104
D-173	SS-173	AAUGUGUAAGA UAGUUAACdTdT	4315	AS-154	UUUAACUAUCUUAC ACAUUdTdT	4105
D-174	SS-174	GGCCAGCCUAAG AUCAUGCdTdT	4316	AS-155	UCAUGAUCUUAGGC UGGCCdTdT	4106
D-175	SS-175	AGUUCCAUUUA AAUUGACCdTdT	4317	AS-156	UGUCAAUUUAAAUG GAACUdTdT	4107
D-176	SS-176	UCCAUUUAAAU UGACUUCCdTdT	4318	AS-157	UGAAGUCAAUUUAA AUGGAdTdT	4108
D-177	SS-177	CCCACCCUCACG AGGUGUCdTdT	4319	AS-158	UACACCUCGUGAGG GUGGGdTdT	4109
D-178	SS-178	CAUCUUAGCUUA GCUUUCCdTdT	4320	AS-159	UGAAAGCUAAGCUA AGAUGdTdT	4110

D-179	SS-179	ACUUAGCCCCAU GAGUUUCdTdT	4321	AS-160	UAAACUCAUGGGGC UAAGUdTdT	4111
D-180	SS-180	UCAUGGUUUAG GGUGAUCCdTdT	4322	AS-161	UGAUCACCCUAAAC CAUGAdTdT	4112
D-181	SS-181	GCCUGAAGCACA GGAUUACdTdT	4323	AS-162	UUAAUCCUGUGCUU CAGGCdTdT	4113
D-182	SS-182	CAUACUGAGGG UGAAAUUCdTdT	4324	AS-163	UAAUUUCACCCUCA GUAUGdTdT	4114
D-183	SS-183	AAGAUCAUGGU UUAGGGUCdTdT	4325	AS-164	UACCCUAAACCAUG AUCUUdTdT	4115
D-184	SS-184	GGGAUCUCCCCC UUGUGGCdTdT	4326	AS-165	UCCACAAGGGGGAG AUCCCdTdT	4116
D-185	SS-185	GAGGAAUGUGU AAGAUAGCdTdT	4327	AS-166	UCUAUCUUACACAU UCCUCdTdT	4117
D-186	SS-186	AUCAUGGUUUA GGGUGAUCdTdT	4328	AS-167	UAUCACCCUAAACC AUGAUdTdT	4118
D-187	SS-187	CAGCAUCGACAU GGUAGACdTdT	4329	AS-168	UUCUACCAUGUCGA UGCUGdTdT	4119
D-188	SS-188	GGUGCAGGCGU AGGAAUACdTdT	4330	AS-169	UUAUUCCUACGCCU GCACCdTdT	4120
D-189	SS-189	AGGAAUGUGUA AGAUAGUCdTdT	4331	AS-170	UACUAUCUUACACA UUCCUdTdT	4121
D-190	SS-190	CAUGGUUUAGG GUGAUCACdTdT	4332	AS-171	UUGAUCACCCUAAA CCAUGdTdT	4122
D-191	SS-191	UCCACCCAAGUC GCCGUCCdTdT	4333	AS-172	UGACGGCGACUUGG GUGGAdTdT	4123
D-192	SS-192	UCAGUAAUGACC CUGGUUCdTdT	4334	AS-173	UAACCAGGGUCAUU ACUGAdTdT	4124
D-193	SS-193	CUGGGACUUUA GGGCUAACdTdT	4335	AS-174	UUUAGCCCUAAAGU CCCAGdTdT	4125
D-194	SS-194	CAGGCGUAGGA AUAUGGACdTdT	4336	AS-175	UUCCAUAUUCCUAC GCCUGdTdT	4126
D-195	SS-195	GCAGGCGUAGG AAUAUGGCdTdT	4337	AS-176	UCCAUAUUCCUACG CCUGCdTdT	4127
D-196	SS-196	AGCCACGAGGUC GGGGCGCdTdT	4338	AS-177	UCGCCCCGACCUCG UGGCUdTdT	4128
D-197	SS-197	AAUCAUGCCUCC CUAAGACdTdT	4339	AS-178	UUCUUAGGGAGGCA UGAUUdTdT	4129
D-198	SS-198	UAAGCCGUUGGC ACCUCUCdTdT	4340	AS-179	UAGAGGUGCCAACG GCUUAdTdT	4130
D-199	SS-199	AUCGACAUGGU AGACUCGCdTdT	4341	AS-180	UCGAGUCUACCAUG UCGAUdTdT	4131
D-200	SS-200	UCUUCGGUAAU UCUGAGGCdTdT	4342	AS-181	UCCUCAGAAUUACC GAAGAdTdT	4132
D-201	SS-201	AAGUCGCCAGUG GUGUCUCdTdT	4343	AS-182	UAGACACCACUGGC GACUUdTdT	4133
D-202	SS-202	AUAAAUUGAAA AGGCACGCdTdT	4344	AS-183	UCGUGCCUUUUCAA UUUAUdTdT	4134
D-203	SS-203	GUUAGAGGCCCU UGGGGUCdTdT	4345	AS-184	UACCCCAAGGGCCU CUAACdTdT	4135
D-204	SS-204	AAUCAGGGGAU CGCAGCGCdTdT	4346	AS-185	UCGCUGCGAUCCCC UGAUUdTdT	4136
D-205	SS-205	UAAGAUAGUUA ACAUGGGCdTdT	4347	AS-186	UCCCAUGUUAACUA UCUUAdTdT	4137

D-206	SS-206	UGUAAGAUAGU UAACAUGCdTdT	4348	AS-187	UCAUGUUAACUAUC UUACAdTdT	4138
D-207	SS-207	CGGCCGCCUGUC CUUGGUCdTdT	4349	AS-188	UACCAAGGACAGGC GGCCGdTdT	4139
D-208	SS-208	UUAGAGGCCCUU GGGGUUCdTdT	4350	AS-189	UAACCCCAAGGGCC UCUAAdTdT	4140
D-209	SS-209	GGGAUCGCAGCG GCUACACdTdT	4351	AS-190	UUGUAGCCGCUGCG AUCCCdTdT	4141
D-210	SS-210	CACGAGGUCGGG GCGAGGCdTdT	4352	AS-191	UCCUCGCCCCGACC UCGUGdTdT	4142

Table 5: Exemplary sense and antisense strand sequence for targeting MAPT

siRNA Duplex ID	SS ID	Sense Strand Sequence (5'-3')	SS SEQ ID NO	AS ID	Antisense Strand Sequence (5'-3')	AS SEQ ID NO
D-001	SS-001	GCUUUGGCUCGG GACUUCC	4477	AS-001	UGAAGUCCCGAGCC AAAGC	4687
D-002	SS-002	CGACAUGGUAG ACUCGCCC	4478	AS-002	UGGCGAGUCUACCA UGUCG	4688
D-003	SS-003	CUCCUCGCAGUU CGGUUAC	4479	AS-003	UUAACCGAACUGCG AGGAG	4689
D-004	SS-004	GGCUUUGGCUCG GGACUUC	4480	AS-004	UAAGUCCCGAGCCA AAGCC	4690
D-005	SS-005	GGCUUUGGCUCG GGACUUA	4481	AS-004	UAAGUCCCGAGCCA AAGCC	4690
D-006	SS-006	GGCUUUGGCUCG GGACUUU	4482	AS-004	UAAGUCCCGAGCCA AAGCC	4690
D-007	SS-007	GGCUUUGGCACG GGACUUC	4483	AS-004	UAAGUCCCGAGCCA AAGCC	4690
D-008	SS-008	GGCUUUGGCUCG GGACUUG	4484	AS-004	UAAGUCCCGAGCCA AAGCC	4690
D-009	SS-009	GCAUCGACAUGG UAGACUC	4485	AS-005	UAGUCUACCAUGUC GAUGC	4691
D-010	SS-010	GCAUCGACAUGG UAGACUA	4486	AS-005	UAGUCUACCAUGUC GAUGC	4691
D-011	SS-011	GCAUCGACAUGG UAGACUU	4487	AS-005	UAGUCUACCAUGUC GAUGC	4691
D-012	SS-012	GCAUCGACAAGG UAGACUC	4488	AS-005	UAGUCUACCAUGUC GAUGC	4691
D-013	SS-013	GCAUCGACAUGG UAGACUG	4489	AS-005	UAGUCUACCAUGUC GAUGC	4691
D-014	SS-014	UGCUCCUCGCAG UUCGGUC	4490	AS-006	UACCGAACUGCGAG GAGCA	4692
D-015	SS-015	CACCCAAGUCGC CGUCUUC	4491	AS-007	UAAGACGGCGACUU GGGUG	4693
D-016	SS-016	CCUCGCAGUUCG GUUAAUC	4492	AS-008	UAUUAACCGAACUG CGAGG	4694
D-017	SS-017	UCCUCGCAGUUC GGUUAAC	4493	AS-009	UUUAACCGAACUGC GAGGA	4695
D-018	SS-018	AGCUGACCUUCC GCGAGAC	4494	AS-010	UUCUCGCGGAAGGU CAGCU	4696
D-019	SS-019	GACUGGAAGCG AUGACAAC	4495	AS-011	UUUGUCAUCGCUUC CAGUC	4697

D-020	SS-020	GACUGGAAGCG AUGACAAA	4496	AS-011	UUUGUCAUCGCUUC CAGUC	4697
D-021	SS-021	GACUGGAAGCG AUGACAAU	4497	AS-011	UUUGUCAUCGCUUC CAGUC	4697
D-022	SS-022	GACUGGAAGGG AUGACAAC	4498	AS-011	UUUGUCAUCGCUUC CAGUC	4697
D-023	SS-023	GACUGGAAGCG AUGACAAG	4499	AS-011	UUUGUCAUCGCUUC CAGUC	4697
D-024	SS-024	AGCUCGCAUGGU CAGUAAC	4500	AS-012	UUUACUGACCAUGC GAGCU	4698
D-025	SS-025	AGUCUACAAACC AGUUGAC	4501	AS-013	UUCAACUGGUUUGU AGACU	4699
D-026	SS-026	GCUCCUCGCAGU UCGGUUC	4502	AS-014	UAACCGAACUGCGA GGAGC	4700
D-027	SS-027	GCUCCUCGCAGU UCGGUUG	4503	AS-014	UAACCGAACUGCGA GGAGC	4700
D-028	SS-028	GCUCCUCGCAGU UCGGUUU	4504	AS-014	UAACCGAACUGCGA GGAGC	4700
D-029	SS-029	GCUCCUCGCUGU UCGGUUC	4505	AS-014	UAACCGAACUGCGA GGAGC	4700
D-030	SS-030	CUUCCGCGAGAA CGCCAAC	4506	AS-015	UUUGGCGUUCUCGC GGAAG	4701
D-031	SS-031	CUUCCGCGAGAA CGCCAAA	4507	AS-015	UUUGGCGUUCUCGC GGAAG	4701
D-032	SS-032	CUUCCGCGAGAA CGCCAAU	4508	AS-015	UUUGGCGUUCUCGC GGAAG	4701
D-033	SS-033	CUUCCGCGACAA CGCCAAC	4509	AS-015	UUUGGCGUUCUCGC GGAAG	4701
D-034	SS-034	CUUCCGCGAGAA CGCCAAG	4510	AS-015	UUUGGCGUUCUCGC GGAAG	4701
D-035	SS-035	AAAUCAGUGAU GGGAGUAC	4511	AS-016	UUACUCCCAUCACU GAUUU	4702
D-036	SS-036	GUCGCCGUCUUC CGCCAAC	4512	AS-017	UUUGGCGGAAGACG GCGAC	4703
D-037	SS-037	AUGGUAAAACG AAGAUCGC	4513	AS-018	UCGAUCUUCGUUUU ACCAU	4704
D-038	SS-038	ACGAAGAUCGCC ACACCGC	4514	AS-019	UCGGUGUGGCGAUC UUCGU	4705
D-039	SS-039	CGCAGUUCGGUU AAUUGGC	4515	AS-020	UCCAAUUAACCGAA CUGCG	4706
D-040	SS-040	GUACUCCACCCA AGUCGCC	4516	AS-021	UGCGACUUGGGUGG AGUAC	4707
D-041	SS-041	CUCGGCUUUGGC UCGGGAC	4517	AS-022	UUCCCGAGCCAAAG CCGAG	4708
D-042	SS-042	GCCCCUGGGGCG GUCAAUC	4518	AS-023	UAUUGACCGCCCCA GGGGC	4709
D-043	SS-043	CUCGCAGUUCGG UUAAUUC	4519	AS-024	UAAUUAACCGAACU GCGAG	4710
D-044	SS-044	UCGCCGUCUUCC GCCAAGC	4520	AS-025	UCUUGGCGGAAGAC GGCGA	4711
D-045	SS-045	GACGGGACUGG AAGCGAUC	4521	AS-026	UAUCGCUUCCAGUC CCGUC	4712
D-046	SS-046	UGGUAAAACGA AGAUCGCC	4522	AS-027	UGCGAUCUUCGUUU UACCA	4713

D-047	SS-047	GUAAAACGAAG AUCGCCAC	4523	AS-028	UUGGCGAUCUUCGU UUUAC	4714
D-048	SS-048	ACAAUAUCACCC ACGUCCC	4524	AS-029	UGGACGUGGGUGAU AUUGU	4715
D-049	SS-049	CCUUCCGCGAGA ACGCCAC	4525	AS-030	UUGGCGUUCUCGCG GAAGG	4716
D-050	SS-050	GGGGGCUGAUG GUAAAACC	4526	AS-031	UGUUUUACCAUCAG CCCCC	4717
D-051	SS-051	GCCGUCUUCCGC CAAGAGC	4527	AS-032	UCUCUUGGCGGAAG ACGGC	4718
D-052	SS-052	CACCGGCAGCAU CGACAUC	4528	AS-033	UAUGUCGAUGCUGC CGGUG	4719
D-053	SS-053	GUAAAAGCAAA GACGGGAC	4529	AS-034	UUCCCGUCUUUGCU UUUAC	4720
D-054	SS-054	AGGUUUCUAACC CACCCUC	4530	AS-035	UAGGGUGGGUUAGA AACCU	4721
D-055	SS-055	UUCCGCGAGAAC GCCAAAC	4531	AS-036	UUUUGGCGUUCUCG CGGAA	4722
D-056	SS-056	GACCUUCCGCGA GAACGCC	4532	AS-037	UGCGUUCUCGCGGA AGGUC	4723
D-057	SS-057	CGCCACGCUAGC UGACGAC	4533	AS-038	UUCGUCAGCUAGCG UGGCG	4724
D-058	SS-058	ACCUGCGUGUCC CAUCUAC	4534	AS-039	UUAGAUGGGACACG CAGGU	4725
D-059	SS-059	CCCCAGCUCGCC ACGCUAC	4535	AS-040	UUAGCGUGGCGAGC UGGGG	4726
D-060	SS-060	GCCGUUCAGCUG UGACGAC	4536	AS-041	UUCGUCACAGCUGA ACGGC	4727
D-061	SS-061	GCUGAUGGUAA AACGAAGC	4537	AS-042	UCUUCGUUUUACCA UCAGC	4728
D-062	SS-062	ACGAGGUGUCUC UCACCCC	4538	AS-043	UGGGUGAGAGACAC CUCGU	4729
D-063	SS-063	GGGCCAGCCUAA GAUCAUC	4539	AS-044	UAUGAUCUUAGGCU GGCCC	4730
D-064	SS-064	UCUAACCCACCC UCACGAC	4540	AS-045	UUCGUGAGGGUGGG UUAGA	4731
D-065	SS-065	UAAAGAGGUUU CUAACCCC	4541	AS-046	UGGGUUAGAAACCU CUUUA	4732
D-066	SS-066	CUCACCUCCUAA UAGACUC	4542	AS-047	UAGUCUAUUAGGAG GUGAG	4733
D-067	SS-067	GGAUAUACUGU AUGCCGGC	4543	AS-048	UCCGGCAUACAGUA UAUCC	4734
D-068	SS-068	CACCCUCACGAG GUGUCUC	4544	AS-049	UAGACACCUCGUGA GGGUG	4735
D-069	SS-069	CACGCUAGCUGA CGAGGUC	4545	AS-050	UACCUCGUCAGCUA GCGUG	4736
D-070	SS-070	UCCCAUGAUUUC UUCGGUC	4546	AS-051	UACCGAAGAAAUCA UGGGA	4737
D-071	SS-071	UUGAGUUGUAG UUGGAUUC	4547	AS-052	UAAUCCAACUACAA CUCAA	4738
D-072	SS-072	CUGCGUGUCCCA UCUACAC	4548	AS-053	UUGUAGAUGGGACA CGCAG	4739
D-073	SS-073	GUUGAGUUGUA GUUGGAUC	4549	AS-054	UAUCCAACUACAAC UCAAC	4740

D-074	SS-074	GGUGGUGGUUAGAGAUAUC	4550	AS-055	UAUAUCUCUAACCACCACC	4741
D-075	SS-075	GGGCUAGAUAGGAUAUACC	4551	AS-056	UGUAUAUCCUAUCUAGCCC	4742
D-076	SS-076	AGGAUUCCAGCAAAAACCC	4552	AS-057	UGGUUUUUGCUGGAAUCCU	4743
D-077	SS-077	GGCCCCUGGGGCGGUCAAC	4553	AS-058	UUUGACCGCCCCAGGGGCC	4744
D-078	SS-078	GAUUAGGACUGAAGCGAUC	4554	AS-059	UAUCGCUUCAGUCCUAAUC	4745
D-079	SS-079	CUCCCAAGUUUUGAAAGGC	4555	AS-060	UCCUUUCAAAACUUGGGAG	4746
D-080	SS-080	GCUGGUCUGGCUUGCGGCC	4556	AS-061	UGCCGCAAGCCAGACCAGC	4747
D-081	SS-081	GUUCCACUCAUCCAACUGC	4557	AS-062	UCAGUUGGAUGAGUGGAAC	4748
D-082	SS-082	CACCUCCUAAUAGACUUAC	4558	AS-063	UUAAGUCUAUUAGGAGGUG	4749
D-083	SS-083	UUCUAACCCACCCUCACGC	4559	AS-064	UCGUGAGGGUGGGUUAGAA	4750
D-084	SS-084	AAGCCCACAAUCAUGCCUC	4560	AS-065	UAGGCAUGAUUGUGGGCUU	4751
D-085	SS-085	ACCUUCCGCGAGAACGCCC	4561	AS-066	UGGCGUUCUCGCGGAAGGU	4752
D-086	SS-086	GCUGGUCACGUGACCCAAC	4562	AS-067	UUUGGGUCACGUGACCAGC	4753
D-087	SS-087	UAACCCACCCUCACGAGGC	4563	AS-068	UCCUCGUGAGGGUGGGUUA	4754
D-088	SS-088	CUUACAACUCCUGCAUCAC	4564	AS-069	UUGAUGCAGGAGUUGUAAG	4755
D-089	SS-089	UGGGACUUUAGGGCUAACC	4565	AS-070	UGUUAGCCCUAAAGUCCCA	4756
D-090	SS-090	GCCACAGGCAGACGAUGUC	4566	AS-071	UACAUCGUCUGCCUGUGGC	4757
D-091	SS-091	GCCUCUUGGGAGACGUCCC	4567	AS-072	UGGACGUCUCCCAAGAGGC	4758
D-092	SS-092	GAGAUAUGCCCCCCUCAUC	4568	AS-073	UAUGAGGGGGGCAUAUCUC	4759
D-093	SS-093	UCCCAAGUUUUGAAAGGCC	4569	AS-074	UGCCUUUCAAAACUUGGGA	4760
D-094	SS-094	AGUUAUUACUCUGAUUAAC	4570	AS-075	UUUAAUCAGAGUAAUAACU	4761
D-095	SS-095	UAUGCCCCCCUCAUUACUC	4571	AS-076	UAGUAAUGAGGGGGGCAUA	4762
D-096	SS-096	CAAAAUCAGGGGAUCGCAC	4572	AS-077	UUGCGAUCCCCUGAUUUUG	4763
D-097	SS-097	CAGACCACGGGGCGGAGAC	4573	AS-078	UUCUCCGCCCCGUGGUCUG	4764
D-098	SS-098	CUUGGGUGGGCUAGAUAGC	4574	AS-079	UCUAUCUAGCCCACCCAAG	4765
D-099	SS-099	CUCGCCACGCUAGCUGACC	4575	AS-080	UGUCAGCUAGCGUGGCGAG	4766
D-100	SS-100	UGUUGAGUUGUAGUUGGAC	4576	AS-081	UUCCAACUACAACUCAACA	4767

D-101	SS-101	UAUACAUAGAUGUUGCCCC	4577	AS-082	UGGGCAACAUCUAUGUAUA	4768
D-102	SS-102	AACCCACCCUCACGAGGUC	4578	AS-083	UACCUCGUGAGGGUGGGUU	4769
D-103	SS-103	GUUGAGCAGGACUAUUUCC	4579	AS-084	UGAAAUAGUCCUGCUCAAC	4770
D-104	SS-104	CCACGCUAGCUGACGAGGC	4580	AS-085	UCCUCGUCAGCUAGCGUGG	4771
D-105	SS-105	CUCCUAAUAGACUUAGCCC	4581	AS-086	UGGCUAAGUCUAUUAGGAG	4772
D-106	SS-106	GAUUUCUUCGGUAAUUCUC	4582	AS-087	UAGAAUUACCGAAGAAAUC	4773
D-107	SS-107	GUCCCAAAGGAGGCUUACC	4583	AS-088	UGUAAGCCUCCUUUGGGAC	4774
D-108	SS-108	GGUGGUUAGAGAUAUGCCC	4584	AS-089	UGGCAUAUCUCUAACCACC	4775
D-109	SS-109	GGCUAGAUAGGAUAUACUC	4585	AS-090	UAGUAUAUCCUAUCUAGCC	4776
D-110	SS-110	AUUCACCAGAGUGACUAUC	4586	AS-091	UAUAGUCACUCUGGUGAAU	4777
D-111	SS-111	GAUAUACUGUAUGCCGGCC	4587	AS-092	UGCCGGCAUACAGUAUAUC	4778
D-112	SS-112	GACCACAGCAGGGAUUGGC	4588	AS-093	UCCAAUCCCUGCUGUGGUC	4779
D-113	SS-113	GAGCCACAGGCAGACGAUC	4589	AS-094	UAUCGUCUGCCUGUGGCUC	4780
D-114	SS-114	CUAGCUGACGAGGUGUCUC	4590	AS-095	UAGACACCUCGUCAGCUAG	4781
D-115	SS-115	AAGGGGGCUGAUGGUAAAC	4591	AS-096	UUUUACCAUCAGCCCCCUU	4782
D-116	SS-116	AUCAGGGGAUCGCAGCGGC	4592	AS-097	UCCGCUGCGAUCCCCUGAU	4783
D-117	SS-117	CCCAGCUCGCCACGCUAGC	4593	AS-098	UCUAGCGUGGCGAGCUGGG	4784
D-118	SS-118	CGUUCAGCUGUGACGAAGC	4594	AS-099	UCUUCGUCACAGCUGAACG	4785
D-119	SS-119	CACUUGCAAGUCCCAUGAC	4595	AS-100	UUCAUGGGACUUGCAAGUG	4786
D-120	SS-120	UGGGCUAGAUAGGAUAUAC	4596	AS-101	UUAUAUCCUAUCUAGCCCA	4787
D-121	SS-121	UUUAUGCUUGGAUUCACCC	4597	AS-102	UGGUGAAUCCAAGCAUAAA	4788
D-122	SS-122	CCAAAAUCAGGGGAUCGCC	4598	AS-103	UGCGAUCCCCUGAUUUUGG	4789
D-123	SS-123	CCGUUCAGCUGUGACGAAC	4599	AS-104	UUUCGUCACAGCUGAACGG	4790
D-124	SS-124	GGCCACAUCCAACAUUUCC	4600	AS-105	UGAAAUGUUGGAUGUGGCC	4791
D-125	SS-125	UUUAUCAAUAGUUCCAUUC	4601	AS-106	UAAUGGAACUAUUGAUAAA	4792
D-126	SS-126	GGCGGAGAUCGUGUACAAC	4602	AS-107	UUUGUACACGAUCUCCGCC	4793
D-127	SS-127	UCGCCACGCUAGCUGACGC	4603	AS-108	UCGUCAGCUAGCGUGGCGA	4794

D-128	SS-128	GUCUGGCUUGCG GCGCGAC	4604	AS-109	UUCGCGCCGCAAGC CAGAC	4795
D-129	SS-129	ACCUCCUAAUAG ACUUAGC	4605	AS-110	UCUAAGUCUAUUAG GAGGU	4796
D-130	SS-130	UGUCCCAUCUAC AGACCUC	4606	AS-111	UAGGUCUGUAGAUG GGACA	4797
D-131	SS-131	CGGUAAUUCUG AGGGUGGC	4607	AS-112	UCCACCCUCAGAAU UACCG	4798
D-132	SS-132	UUUCUUCGGUA AUUCUGAC	4608	AS-113	UUCAGAAUUACCGA AGAAA	4799
D-133	SS-133	GCACCCUGUUGA GUUGUAC	4609	AS-114	UUACAACUCAACAG GGUGC	4800
D-134	SS-134	AUAUACUGUAU GCCGGCUC	4610	AS-115	UAGCCGGCAUACAG UAUAU	4801
D-135	SS-135	ACUUCUGGUUU GGGUACAC	4611	AS-116	UUGUACCCAAACCA GAAGU	4802
D-136	SS-136	GAAGCACAGGA UUAGGACC	4612	AS-117	UGUCCUAAUCCUGU GCUUC	4803
D-137	SS-137	CUUUCAGGGGUC CUAAGCC	4613	AS-118	UGCUUAGGACCCCU GAAAG	4804
D-138	SS-138	GAUAUGCCCCCC UCAUUAC	4614	AS-119	UUAAUGAGGGGGGC AUAUC	4805
D-139	SS-139	CUAAGGAGGCCG UUCAGCC	4615	AS-120	UGCUGAACGGCCUC CUUAG	4806
D-140	SS-140	GGAACACACCCC CUUGGAC	4616	AS-121	UUCCAAGGGGGUGU GUUCC	4807
D-141	SS-141	CCUAAGCCCACA AUCAUGC	4617	AS-122	UCAUGAUUGUGGGC UUAGG	4808
D-142	SS-142	CUGGGGCCUCCC AAGUUUC	4618	AS-123	UAAACUUGGGAGGC CCCAG	4809
D-143	SS-143	UGUCCCCCACUU GCACCCC	4619	AS-124	UGGGUGCAAGUGGG GGACA	4810
D-144	SS-144	AAGUUAUUACU CUGAUUAC	4620	AS-125	UUAAUCAGAGUAAU AACUU	4811
D-145	SS-145	AAUAGACUUAG CCCCAUGC	4621	AS-126	UCAUGGGGCUAAGU CUAUU	4812
D-146	SS-146	CAGUAAUGACCC UGGUUGC	4622	AS-127	UCAACCAGGGUCAU UACUG	4813
D-147	SS-147	GGAGGAAUGUG UAAGAUAC	4623	AS-128	UUAUCUUACACAUU CCUCC	4814
D-148	SS-148	CAAUCAUGCCUC CCUAAGC	4624	AS-129	UCUUAGGGAGGCAU GAUUG	4815
D-149	SS-149	UCCACUCAUCCA ACUGGGC	4625	AS-130	UCCCAGUUGGAUGA GUGGA	4816
D-150	SS-150	AGGUGCAGGCG UAGGAAUC	4626	AS-131	UAUUCCUACGCCUG CACCU	4817
D-151	SS-151	GAUAGGAUAUA CUGUAUGC	4627	AS-132	UCAUACAGUAUAUC CUAUC	4818
D-152	SS-152	UCCUAAGCCCAC AAUCAUC	4628	AS-133	UAUGAUUGUGGGCU UAGGA	4819
D-153	SS-153	GGCCGUUCAGCU GUGACGC	4629	AS-134	UCGUCACAGCUGAA CGGCC	4820
D-154	SS-154	UGGCCACAUCCA ACAUUUC	4630	AS-135	UAAAUGUUGGAUGU GGCCA	4821

D-155	SS-155	AGCAGGACUAU UUCUGGCC	4631	AS-136	UGCCAGAAAUAGUC CUGCU	4822
D-156	SS-156	AUAUGGACAUC UGGUUGCC	4632	AS-137	UGCAACCAGAUGUC CAUAU	4823
D-157	SS-157	ACUUGCACCCUA GCUUGUC	4633	AS-138	UACAAGCUAGGGUG CAAGU	4824
D-158	SS-158	GUAAAGAGGUU UCUAACCC	4634	AS-139	UGGUUAGAAACCUC UUUAC	4825
D-159	SS-159	GACUCACUUUAU CAAUAGC	4635	AS-140	UCUAUUGAUAAAGU GAGUC	4826
D-160	SS-160	AGCUGCUGACUC ACUUUAC	4636	AS-141	UUAAAGUGAGUCAG CAGCU	4827
D-161	SS-161	AAGGGUUACCCU GGGCACC	4637	AS-142	UGUGCCCAGGGUAA CCCUU	4828
D-162	SS-162	UGUAAAGAGGU UUCUAACC	4638	AS-143	UGUUAGAAACCUCU UUACA	4829
D-163	SS-163	UGGCUUGCGGCG CGAGGAC	4639	AS-144	UUCCUCGCGCCGCA AGCCA	4830
D-164	SS-164	GCCACGCUAGCU GACGAGC	4640	AS-145	UCUCGUCAGCUAGC GUGGC	4831
D-165	SS-165	CCCAAAGGAGGC UUACAAC	4641	AS-146	UUUGUAAGCCUCCU UUGGG	4832
D-166	SS-166	UGUUGUGCUAU GGGGGGAC	4642	AS-147	UUCCCCCCAUAGCA CAACA	4833
D-167	SS-167	GGGAACACACCC CCUUGGC	4643	AS-148	UCCAAGGGGGUGUG UUCCC	4834
D-168	SS-168	UUCCAAAUUGA UGGGUGGC	4644	AS-149	UCCACCCAUCAAUU UGGAA	4835
D-169	SS-169	ACCGGCAGCAUC GACAUGC	4645	AS-150	UCAUGUCGAUGCUG CCGGU	4836
D-170	SS-170	CUGGCUUGCGGC GCGAGGC	4646	AS-151	UCCUCGCGCCGCAA GCCAG	4837
D-171	SS-171	GUGUAAGAUAG UUAACAUC	4647	AS-152	UAUGUUAACUAUCU UACAC	4838
D-172	SS-172	AGGAUUAGGAC UGAAGCGC	4648	AS-153	UCGCUUCAGUCCUA AUCCU	4839
D-173	SS-173	AAUGUGUAAGA UAGUUAAC	4649	AS-154	UUUAACUAUCUUAC ACAUU	4840
D-174	SS-174	GGCCAGCCUAAG AUCAUGC	4650	AS-155	UCAUGAUCUUAGGC UGGCC	4841
D-175	SS-175	AGUUCCAUUUA AAUUGACC	4651	AS-156	UGUCAAUUUAAAUG GAACU	4842
D-176	SS-176	UCCAUUUAAAU UGACUUCC	4652	AS-157	UGAAGUCAAUUUAA AUGGA	4843
D-177	SS-177	CCCACCCUCACG AGGUGUC	4653	AS-158	UACACCUCGUGAGG GUGGG	4844
D-178	SS-178	CAUCUUAGCUUA GCUUUCC	4654	AS-159	UGAAAGCUAAGCUA AGAUG	4845
D-179	SS-179	ACUUAGCCCCAU GAGUUUC	4655	AS-160	UAAACUCAUGGGGC UAAGU	4846
D-180	SS-180	UCAUGGUUUAG GGUGAUCC	4656	AS-161	UGAUCACCCUAAAC CAUGA	4847
D-181	SS-181	GCCUGAAGCACA GGAUUAC	4657	AS-162	UUAAUCCUGUGCUU CAGGC	4848

D-182	SS-182	CAUACUGAGGG UGAAAUUC	4658	AS-163	UAAUUUCACCCUCA GUAUG	4849
D-183	SS-183	AAGAUCAUGGU UUAGGGUC	4659	AS-164	UACCCUAAACCAUG AUCUU	4850
D-184	SS-184	GGGAUCUCCCCC UUGUGGC	4660	AS-165	UCCACAAGGGGGAG AUCCC	4851
D-185	SS-185	GAGGAAUGUGU AAGAUAGC	4661	AS-166	UCUAUCUUACACAU UCCUC	4852
D-186	SS-186	AUCAUGGUUUA GGGUGAUC	4662	AS-167	UAUCACCCUAAACC AUGAU	4853
D-187	SS-187	CAGCAUCGACAU GGUAGAC	4663	AS-168	UUCUACCAUGUCGA UGCUG	4854
D-188	SS-188	GGUGCAGGCGU AGGAAUAC	4664	AS-169	UUAUUCCUACGCCU GCACC	4855
D-189	SS-189	AGGAAUGUGUA AGAUAGUC	4665	AS-170	UACUAUCUUACACA UUCCU	4856
D-190	SS-190	CAUGGUUUAGG GUGAUCAC	4666	AS-171	UUGAUCACCCUAAA CCAUG	4857
D-191	SS-191	UCCACCCAAGUC GCCGUCC	4667	AS-172	UGACGGCGACUUGG GUGGA	4858
D-192	SS-192	UCAGUAAUGACC CUGGUUC	4668	AS-173	UAACCAGGGUCAUU ACUGA	4859
D-193	SS-193	CUGGGACUUUA GGGCUAAC	4669	AS-174	UUUAGCCCUAAAGU CCCAG	4860
D-194	SS-194	CAGGCGUAGGA AUAUGGAC	4670	AS-175	UUCCAUAUUCCUAC GCCUG	4861
D-195	SS-195	GCAGGCGUAGG AAUAUGGC	4671	AS-176	UCCAUAUUCCUACG CCUGC	4862
D-196	SS-196	AGCCACGAGGUC GGGGCGC	4672	AS-177	UCGCCCCGACCUCG UGGCU	4863
D-197	SS-197	AAUCAUGCCUCC CUAAGAC	4673	AS-178	UUCUUAGGGAGGCA UGAUU	4864
D-198	SS-198	UAAGCCGUUGGC ACCUCUC	4674	AS-179	UAGAGGUGCCAACG GCUUA	4865
D-199	SS-199	AUCGACAUGGU AGACUCGC	4675	AS-180	UCGAGUCUACCAUG UCGAU	4866
D-200	SS-200	UCUUCGGUAAU UCUGAGGC	4676	AS-181	UCCUCAGAAUUACC GAAGA	4867
D-201	SS-201	AAGUCGCCAGUG GUGUCUC	4677	AS-182	UAGACACCACUGGC GACUU	4868
D-202	SS-202	AUAAAUUGAAA AGGCACGC	4678	AS-183	UCGUGCCUUUUCAA UUUAU	4869
D-203	SS-203	GUUAGAGGCCCU UGGGGUC	4679	AS-184	UACCCCAAGGGCCU CUAAC	4870
D-204	SS-204	AAUCAGGGGAU CGCAGCGC	4680	AS-185	UCGCUGCGAUCCCC UGAUU	4871
D-205	SS-205	UAAGAUAGUUA ACAUGGGC	4681	AS-186	UCCCAUGUUAACUA UCUUA	4872
D-206	SS-206	UGUAAGAUAGU UAACAUGC	4682	AS-187	UCAUGUUAACUAUC UUACA	4873
D-207	SS-207	CGGCCGCCUGUC CUUGGUC	4683	AS-188	UACCAAGGACAGGC GGCCG	4874
D-208	SS-208	UUAGAGGCCCUU GGGGUUC	4684	AS-189	UAACCCCAAGGGCC UCUAA	4875

D-209	SS-209	GGGAUCGCAGCG GCUACAC	4685	AS-190	UUGUAGCCGCUGCG AUCCC	4876
D-210	SS-210	CACGAGGUCGGG GCGAGGC	4686	AS-191	UCCUCGCCCCGACC UCGUG	4877
D-211	SS-211	GACUGGAAGCG AUGACAAUCU	4906	AS-192	UUUGUCAUCGCUUC CAGUCUU	4908
D-212	SS-212	CUUCCGCGAGAA CGCCAAUCU	4910	AS-193	UUUGGCGUUCUCGC GGAAGUU	4912
D-213	SS-213	GCAUCGACAUGG UAGACUUCU	4914	AS-194	UAGUCUACCAUGUC GAUGCUU	4916
D-214	SS-214	GCUCCUCGCAGU UCGGUUUCU	4918	AS-195	UAACCGAACUGCGA GGAGCUU	4920
D-215	SS-215	GGCUUUGGCUCG GGACUUUCU	4922	AS-196	UAAGUCCCGAGCCA AAGCCUU	4924
D-216	SS-216	GACUGGAAGCG AUGACAACCC	4926	AS-192	UUUGUCAUCGCUUC CAGUCUU	4908
D-217	SS-217	CUUCCGCGAGAA CGCCAACCC	4930	AS-193	UUUGGCGUUCUCGC GGAAGUU	4912
D-218	SS-218	GCAUCGACAUGG UAGACUCCC	4934	AS-194	UAGUCUACCAUGUC GAUGCUU	4916
D-219	SS-219	GCUCCUCGCAGU UCGGUUCCC	4938	AS-195	UAACCGAACUGCGA GGAGCUU	4920
D-220	SS-220	GGCUUUGGCUCG GGACUUCCC	4942	AS-196	UAAGUCCCGAGCCA AAGCCUU	4924
D-221	SS-221	GACUGGAAGCG AUGACAAACC	4946	AS-192	UUUGUCAUCGCUUC CAGUCUU	4908
D-222	SS-222	CUUCCGCGAGAA CGCCAAACC	4950	AS-193	UUUGGCGUUCUCGC GGAAGUU	4912
D-223	SS-223	GCAUCGACAUGG UAGACUACC	4954	AS-194	UAGUCUACCAUGUC GAUGCUU	4916
D-224	SS-224	GCUCCUCGCAGU UCGGUUGCC	4958	AS-195	UAACCGAACUGCGA GGAGCUU	4920
D-225	SS-225	GGCUUUGGCUCG GGACUUACC	4962	AS-196	UAAGUCCCGAGCCA AAGCCUU	4924
D-226	SS-226	GACUGGAAGCG AUGACAAUCC	4966	AS-192	UUUGUCAUCGCUUC CAGUCUU	4908
D-227	SS-227	CUUCCGCGAGAA CGCCAAUCC	4970	AS-193	UUUGGCGUUCUCGC GGAAGUU	4912
D-228	SS-228	GCAUCGACAUGG UAGACUUCC	4974	AS-194	UAGUCUACCAUGUC GAUGCUU	4916
D-229	SS-229	GCUCCUCGCAGU UCGGUUUCC	4978	AS-195	UAACCGAACUGCGA GGAGCUU	4920
D-230	SS-230	GGCUUUGGCUCG GGACUUUCC	4982	AS-196	UAAGUCCCGAGCCA AAGCCUU	4924
D-231	SS-231	GACUGGAAGGG AUGACAACCC	4986	AS-192	UUUGUCAUCGCUUC CAGUCUU	4908
D-232	SS-232	CUUCCGCGACAA CGCCAACCC	4990	AS-193	UUUGGCGUUCUCGC GGAAGUU	4912
D-233	SS-233	GCAUCGACAAGG UAGACUCCC	4994	AS-194	UAGUCUACCAUGUC GAUGCUU	4916
D-234	SS-234	GCUCCUCGCUGU UCGGUUCCC	4998	AS-195	UAACCGAACUGCGA GGAGCUU	4920
D-235	SS-235	GGCUUUGGCACG GGACUUCCC	5002	AS-196	UAAGUCCCGAGCCA AAGCCUU	4924

D-236	SS-236	GACUGGAAGCG AUGACAAGCC	5006	AS-192	UUUGUCAUCGCUUC CAGUCUU	4908
D-237	SS-237	CUUCCGCGAGAA CGCCAAGCC	5010	AS-193	UUUGGCGUUCUCGC GGAAGUU	4912
D-238	SS-238	GCAUCGACAUGG UAGACUGCC	5014	AS-194	UAGUCUACCAUGUC GAUGCUU	4916
D-239	SS-239	GGCUUUGGCUCG GGACUUGCC	5022	AS-196	UAAGUCCCGAGCCA AAGCCUU	4924
D-240	SS-240	CCUCGCAGUUCG GUUAAUU	5052	AS-008	UAUUAACCGAACUG CGAGG	4694
D-241	SS-241	CCUCGCAGUUCG GUUAAUUCU	5054	AS-197	UAUUAACCGAACUG CGAGGUU	5057
D-242	SS-242	CCUCGCAGUUCG GUUAAUCCC	5060	AS-197	UAUUAACCGAACUG CGAGGUU	5057
D-243	SS-243	CCUCGCAGUUCG GUUAAUA	5062	AS-008	UAUUAACCGAACUG CGAGG	4694
D-244	SS-244	CCUCGCAGUUCG GUUAAUACC	5064	AS-197	UAUUAACCGAACUG CGAGGUU	5057
D-245	SS-245	CCUCGCAGUUCG GUUAAUUCC	5066	AS-197	UAUUAACCGAACUG CGAGGUU	5057
D-246	SS-246	CCUCGCAGUACG GUUAAUC	5068	AS-008	UAUUAACCGAACUG CGAGG	4694
D-247	SS-247	CCUCGCAGUACG GUUAAUCCC	5070	AS-197	UAUUAACCGAACUG CGAGGUU	5057
D-248	SS-248	CCUCGCAGUUCG GUUAAUG	5072	AS-008	UAUUAACCGAACUG CGAGG	4694
D-249	SS-249	CCUCGCAGUUCG GUUAAUGCC	5074	AS-197	UAUUAACCGAACUG CGAGGUU	5057
D-250	SS-250	GCUUUGGCUCGG GACUUCCCC	5077	AS-198	UGAAGUCCCGAGCC AAAGCUU	5080
D-251	SS-251	GCUUUGGCUCGG GACUUCA	5082	AS-001	UGAAGUCCCGAGCC AAAGC	4687
D-252	SS-252	GCUUUGGCUCGG GACUUCACC	5084	AS-198	UGAAGUCCCGAGCC AAAGCUU	5080
D-253	SS-253	GCUUUGGCUCGG GACUUCU	5086	AS-001	UGAAGUCCCGAGCC AAAGC	4687
D-254	SS-254	GCUUUGGCUCGG GACUUCUCC	5088	AS-198	UGAAGUCCCGAGCC AAAGCUU	5080
D-255	SS-255	GCUUUGGCUGG GGACUUCC	5090	AS-001	UGAAGUCCCGAGCC AAAGC	4687
D-256	SS-256	GCUUUGGCUGG GGACUUCCCC	5092	AS-198	UGAAGUCCCGAGCC AAAGCUU	5080
D-257	SS-257	GCUUUGGCUCGG GACUUCG	5094	AS-001	UGAAGUCCCGAGCC AAAGC	4687
D-258	SS-258	GCUUUGGCUCGG GACUUCGCC	5096	AS-198	UGAAGUCCCGAGCC AAAGCUU	5080
D-259	SS-259	GCUUUGGCUCGG GACUUCUCU	5098	AS-198	UGAAGUCCCGAGCC AAAGCUU	5080
D-260	SS-260	AGCUGACCUUCC GCGAGACCC	5101	AS-199	UUCUCGCGGAAGGU CAGCUUU	5104
D-261	SS-261	AGCUGACCUUCC GCGAGAA	5106	AS-010	UUCUCGCGGAAGGU CAGCU	4696
D-262	SS-262	AGCUGACCUUCC GCGAGAACC	5108	AS-199	UUCUCGCGGAAGGU CAGCUUU	5104

D-263	SS-263	AGCUGACCUUCC GCGAGAU	5110	AS-010	UUCUCGCGGAAGGU CAGCU	4696
D-264	SS-264	AGCUGACCUUCC GCGAGAUCC	5112	AS-199	UUCUCGCGGAAGGU CAGCUUU	5104
D-265	SS-265	AGCUGACCUACC GCGAGAC	5114	AS-010	UUCUCGCGGAAGGU CAGCU	4696
D-266	SS-266	AGCUGACCUACC GCGAGACCC	5116	AS-199	UUCUCGCGGAAGGU CAGCUUU	5104
D-267	SS-267	AGCUGACCUUCC GCGAGAG	5118	AS-010	UUCUCGCGGAAGGU CAGCU	4696
D-268	SS-268	AGCUGACCUUCC GCGAGAGCC	5120	AS-199	UUCUCGCGGAAGGU CAGCUUU	5104
D-269	SS-269	AGCUGACCUUCC GCGAGAUCU	5122	AS-199	UUCUCGCGGAAGGU CAGCUUU	5104
D-270	SS-270	GCCGUCUUCCGC CAAGAGCCC	5125	AS-200	UCUCUUGGCGGAAG ACGGCUU	5128
D-271	SS-271	GCCGUCUUCCGC CAAGAGA	5130	AS-032	UCUCUUGGCGGAAG ACGGC	4718
D-272	SS-272	GCCGUCUUCCGC CAAGAGACC	5132	AS-200	UCUCUUGGCGGAAG ACGGCUU	5128
D-273	SS-273	GCCGUCUUCCGC CAAGAGU	5134	AS-032	UCUCUUGGCGGAAG ACGGC	4718
D-274	SS-274	GCCGUCUUCCGC CAAGAGUCC	5136	AS-200	UCUCUUGGCGGAAG ACGGCUU	5128
D-275	SS-275	GCCGUCUUCGGC CAAGAGC	5138	AS-032	UCUCUUGGCGGAAG ACGGC	4718
D-276	SS-276	GCCGUCUUCGGC CAAGAGCCC	5140	AS-200	UCUCUUGGCGGAAG ACGGCUU	5128
D-277	SS-277	GCCGUCUUCCGC CAAGAGG	5142	AS-032	UCUCUUGGCGGAAG ACGGC	4718
D-278	SS-278	GCCGUCUUCCGC CAAGAGGCC	5144	AS-200	UCUCUUGGCGGAAG ACGGCUU	5128
D-279	SS-279	GCCGUCUUCCGC CAAGAGUCU	5146	AS-200	UCUCUUGGCGGAAG ACGGCUU	5128

[0162] In some embodiments, the siRNA for targeting MAPT comprises an antisense strand sequence comprising at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4700. In some embodiments, the siRNA comprises a sense strand sequence comprising at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4502-4505. In some embodiments, the antisense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4700 and the sense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4502-4505.

[0163] In some embodiments, the siRNA for targeting MAPT comprises an antisense strand sequence comprising at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4920. In some embodiments, the siRNA comprises a sense

strand sequence comprising at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4918, 4938, 4958, 4978, or 4998. In some embodiments, the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4920 and the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4918, 4938, 4958, 4978, or 4998.

[0164] In some embodiments, the siRNA for targeting MAPT comprises an antisense strand sequence comprising at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4920. In some embodiments, the antisense strand comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4920. In some embodiments, the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4920. In some embodiments, the siRNA comprises a sense strand sequence comprising at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4918. In some embodiments, the sense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4918. In some embodiments, the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4918. In some embodiments, the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4920 and the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4918. In some embodiments, the antisense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4920; and the sense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4918. In some embodiments, the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4920; and the sense strand comprises the nucleotide sequence of SEQ ID NO: 4918.

[0165] In some embodiments, the nucleotide sequence encoding the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4919. In some embodiments, the nucleotide sequence encoding the antisense strand comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4919. In some embodiments, the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4919. In some embodiments, the nucleotide sequence encoding the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4917. In some embodiments, the nucleotide sequence encoding the sense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4917. In some embodiments, the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence

of SEQ ID NO: 4917. In some embodiments, the nucleotide sequence encoding the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4919 and the nucleotide sequence encoding the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4917. In some embodiments, the nucleotide sequence encoding the antisense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4919; and the nucleotide sequence encoding the sense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4917. In some embodiments, the nucleotide sequence encoding the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4919; and the nucleotide sequence encoding the sense strand comprises the nucleotide sequence of SEQ ID NO: 4917.

[0166] In some embodiments, the siRNA for targeting MAPT comprises an antisense strand sequence comprising at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4920. In some embodiments, the antisense strand comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4920. In some embodiments, the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4920. In some embodiments, the siRNA comprises a sense strand sequence comprising at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4978. In some embodiments, the sense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4978. In some embodiments, the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4978. In some embodiments, the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4920; and the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4978. In some embodiments, the antisense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4920; and the sense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4978. In some embodiments, the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4920; and the sense strand comprises the nucleotide sequence of SEQ ID NO: 4978.

[0167] In some embodiments, the nucleotide sequence encoding the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4919. In some embodiments, the nucleotide sequence encoding the antisense strand comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4919. In some embodiments, the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4919. In some embodiments, the nucleotide sequence encoding the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides

from the nucleotide sequence of SEQ ID NO: 4977. In some embodiments, the nucleotide sequence encoding the sense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4977. In some embodiments, the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4977. In some embodiments, the nucleotide sequence encoding the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4919; and the nucleotide sequence encoding the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4977. In some embodiments, the nucleotide sequence encoding the antisense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4919; and the nucleotide sequence encoding the sense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4977. In some embodiments, the nucleotide sequence encoding the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4919; and the nucleotide sequence encoding the sense strand comprises the nucleotide sequence of SEQ ID NO: 4977.

[0168] In some embodiments, the siRNA for targeting MAPT comprises an antisense strand sequence comprising at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4697. In some embodiments, the siRNA comprises a sense strand sequence comprising at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4495-4499. In some embodiments, the antisense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4697 and the sense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4495-4499.

[0169] In some embodiments, the siRNA for targeting MAPT comprises an antisense strand sequence comprising at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4908. In some embodiments, the siRNA comprises a sense strand sequence comprising at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4906, 4926, 4946, 4966, 4986, or 5006. In some embodiments, the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4908 and the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4906, 4926, 4946, 4966, 4986, or 5006.

[0170] In some embodiments, the siRNA for targeting MAPT comprises an antisense strand sequence comprising at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides

from the nucleotide sequence of SEQ ID NO: 4908. In some embodiments, the antisense strand comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4908. In some embodiments, the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4908. In some embodiments, the siRNA comprises a sense strand sequence comprising at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4906. In some embodiments, the sense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4906. In some embodiments, the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4906. In some embodiments, the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4908; and the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4906. In some embodiments, the antisense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4908; and the sense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4906. In some embodiments, the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4908; and the sense strand comprises the nucleotide sequence of SEQ ID NO: 4906.

[0171] In some embodiments, the nucleotide sequence encoding the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4907. In some embodiments, the nucleotide sequence encoding the antisense strand comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4907. In some embodiments, the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4907. In some embodiments, the nucleotide sequence encoding the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4905. In some embodiments, the nucleotide sequence encoding the sense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4905. In some embodiments, the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4905. In some embodiments, the nucleotide sequence encoding the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4907; and the nucleotide sequence encoding the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4905. In some embodiments, the nucleotide sequence encoding the antisense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4907; and the nucleotide sequence encoding the sense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4905. In some embodiments, the nucleotide sequence encoding the

antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4907; and the nucleotide sequence encoding the sense strand comprises the nucleotide sequence of SEQ ID NO: 4905.

[0172] In some embodiments, the siRNA for targeting MAPT comprises an antisense strand sequence comprising at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4908. In some embodiments, the antisense strand comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4908. In some embodiments, the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4908. In some embodiments, the siRNA comprises a sense strand sequence comprising at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4966. In some embodiments, the sense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4966. In some embodiments, the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4966. In some embodiments, the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4908 and the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4966. In some embodiments, the antisense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4908; and the sense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4966. In some embodiments, the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4908; and the sense strand comprises the nucleotide sequence of SEQ ID NO: 4966.

[0173] In some embodiments, the nucleotide sequence encoding the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4907. In some embodiments, the nucleotide sequence encoding the antisense strand comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4907. In some embodiments, the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4907. In some embodiments, the nucleotide sequence encoding the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4965. In some embodiments, the nucleotide sequence encoding the sense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4965. In some embodiments, the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4965. In some embodiments, the nucleotide sequence encoding the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4907; and the nucleotide sequence encoding the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4965. In some embodiments, the nucleotide

sequence encoding the antisense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4907; and the nucleotide sequence encoding the sense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4965. In some embodiments, the nucleotide sequence encoding the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4907; and the nucleotide sequence encoding the sense strand comprises the nucleotide sequence of SEQ ID NO: 4965.

[0174] In some embodiments, the siRNA for targeting MAPT comprises an antisense strand sequence comprising at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4690. In some embodiments, the siRNA comprises a sense strand sequence comprising at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4480-4484. In some embodiments, the antisense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4690 and the sense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4480-4484.

[0175] In some embodiments, the siRNA for targeting MAPT comprises an antisense strand sequence comprising at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4924. In some embodiments, the siRNA comprises a sense strand sequence comprising at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4922, 4942, 4962, 4982, 5002, or 5022. In some embodiments, the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4924 and the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4922, 4942, 4962, 4982, 5002, or 5022.

[0176] In some embodiments, the siRNA for targeting MAPT comprises an antisense strand sequence comprising at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4924. In some embodiments, the antisense strand comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4924. In some embodiments, the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4924. In some embodiments, the siRNA comprises a sense strand sequence comprising at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4922. In some embodiments, the sense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4922. In some embodiments, the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4922. In some embodiments, the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by

3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4924; and the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4922. In some embodiments, the antisense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4924; and the sense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4922. In some embodiments, the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4924; and the sense strand comprises the nucleotide sequence of SEQ ID NO: 4922.

[0177] In some embodiments, the nucleotide sequence encoding the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4923. In some embodiments, the nucleotide sequence encoding the antisense strand comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4923. In some embodiments, the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4923. In some embodiments, the nucleotide sequence encoding the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4921. In some embodiments, the nucleotide sequence encoding the sense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4921. In some embodiments, the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4921. In some embodiments, the nucleotide sequence encoding the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4923; and the nucleotide sequence encoding the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4921. In some embodiments, the nucleotide sequence encoding the antisense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4923; and the nucleotide sequence encoding the sense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4921. In some embodiments, the nucleotide sequence encoding the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4923; and the nucleotide sequence encoding the sense strand comprises the nucleotide sequence of SEQ ID NO: 4921.

[0178] In some embodiments, the siRNA for targeting MAPT comprises an antisense strand sequence comprising at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4924. In some embodiments, the antisense strand comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4924. In some embodiments, the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4924. In some embodiments, the siRNA comprises a sense strand sequence comprising at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4982. In some embodiments, the sense strand

sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4982. In some embodiments, the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4982. In some embodiments, the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4924; and the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4982. In some embodiments, the antisense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4924; and the sense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4982. In some embodiments, the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4924; and the sense strand comprises the nucleotide sequence of SEQ ID NO: 4982.

[0179] In some embodiments, the nucleotide sequence encoding the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4923. In some embodiments, the nucleotide sequence encoding the antisense strand comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4923. In some embodiments, the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4923. In some embodiments, the nucleotide sequence encoding the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4981. In some embodiments, the nucleotide sequence encoding the sense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4981. In some embodiments, the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4981. In some embodiments, the nucleotide sequence encoding the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4923; and the nucleotide sequence encoding the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4981. In some embodiments, the nucleotide sequence encoding the antisense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4923; and the nucleotide sequence encoding the sense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4981. In some embodiments, the nucleotide sequence encoding the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4923; and the nucleotide sequence encoding the sense strand comprises the nucleotide sequence of SEQ ID NO: 4981.

[0180] In some embodiments, the siRNA for targeting MAPT comprises an antisense strand sequence comprising at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4694. In some embodiments, the siRNA comprises a sense strand sequence comprising at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides

from the nucleotide sequence of any one of SEQ ID NOs: 4492, 5052, 5062, 5068, or 5072. In some embodiments, the antisense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4694 and the sense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4492, 5052, 5062, 5068, or 5072.

[0181] In some embodiments, the siRNA for targeting MAPT comprises an antisense strand sequence comprising at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 5057. In some embodiments, the siRNA comprises a sense strand sequence comprising at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 5054, 5060, 5064, 5066, 5070, or 5074. In some embodiments, the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 5057; and the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 5054, 5060, 5064, 5066, 5070, or 5074.

[0182] In some embodiments, the siRNA for targeting MAPT comprises an antisense strand sequence comprising at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4691. In some embodiments, the siRNA comprises a sense strand sequence comprising at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4485-4489. In some embodiments, the antisense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4691 and the sense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4485-4489.

[0183] In some embodiments, the siRNA for targeting MAPT comprises an antisense strand sequence comprising at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4916. In some embodiments, the siRNA comprises a sense strand sequence comprising at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4914, 4934, 4954, 4974, 4994, or 5014. In some embodiments, the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4916 and the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4914, 4934, 4954, 4974, 4994, or 5014.

[0184] In some embodiments, the siRNA for targeting MAPT comprises an antisense strand sequence comprising at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4701. In some embodiments, the siRNA comprises a sense strand sequence comprising at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4506-4510. In some embodiments, the antisense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4701 and the sense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4506-4510.

[0185] In some embodiments, the siRNA for targeting MAPT comprises an antisense strand sequence comprising at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4912. In some embodiments, the siRNA comprises a sense strand sequence comprising at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4910, 4930, 4950, 4970, 4990, or 5010. In some embodiments, the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4912 and the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4910, 4930, 4950, 4970, 4990, or 5010.

[0186] In some embodiments, the siRNA for targeting MAPT comprises an antisense strand sequence comprising at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4912. In some embodiments, the antisense strand comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4912. In some embodiments, the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4912. In some embodiments, the siRNA comprises a sense strand sequence comprising at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4970. In some embodiments, the sense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4970. In some embodiments, the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4970. In some embodiments, the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4912; and the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4970. In some embodiments, the antisense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4912; and the sense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4970. In some embodiments, the antisense

strand sequence comprises the nucleotide sequence of SEQ ID NO: 4912; and the sense strand comprises the nucleotide sequence of SEQ ID NO: 4970.

[0187] In some embodiments, the nucleotide sequence encoding the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4911. In some embodiments, the nucleotide sequence encoding the antisense strand comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4911. In some embodiments, the nucleotide sequence encoding the antisense strand comprises the nucleotide sequence of SEQ ID NO: 4911. In some embodiments, the nucleotide sequence encoding the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4969. In some embodiments, the nucleotide sequence encoding the sense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4969. In some embodiments, the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4969. In some embodiments, the nucleotide sequence encoding the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4911; and the nucleotide sequence encoding the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4969. In some embodiments, the nucleotide sequence encoding the antisense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4911; and the nucleotide sequence encoding the sense strand sequence comprises at least 20 or 21 contiguous nucleotides of SEQ ID NO: 4969. In some embodiments, the nucleotide sequence encoding the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4911; and the nucleotide sequence encoding the sense strand comprises the nucleotide sequence of SEQ ID NO: 4969.

[0188] In some embodiments, the siRNA for targeting MAPT comprises an antisense strand sequence comprising at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4687. In some embodiments, the siRNA comprises a sense strand sequence comprising at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4477, 5082, 5086, 5090, 5094, or 5086. In some embodiments, the antisense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4687 and the sense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4477, 5082, 5086, 5090, 5094, or 5086.

[0189] In some embodiments, the siRNA for targeting MAPT comprises an antisense strand sequence comprising at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 5080. In some embodiments, the siRNA comprises a sense

strand sequence comprising at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 5077, 5084, 5088, 5092, 5096, or 5098. In some embodiments, the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 5080; and the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 5077, 5084, 5088, 5092, 5096, or 5098.

[0190] In some embodiments, the siRNA for targeting MAPT comprises an antisense strand sequence comprising at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4712. In some embodiments, the siRNA comprises a sense strand sequence comprising at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4521. In some embodiments, the antisense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4712 and the sense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4521.

[0191] In some embodiments, the siRNA for targeting MAPT comprises an antisense strand sequence comprising at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4696. In some embodiments, the siRNA comprises a sense strand sequence comprising at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4494, 5106, 5110, 5114, or 5118. In some embodiments, the antisense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4696 and the sense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4494, 5106, 5110, 5114, or 5118.

[0192] In some embodiments, the siRNA for targeting MAPT comprises an antisense strand sequence comprising at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 5104. In some embodiments, the siRNA comprises a sense strand sequence comprising at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 5101, 5108, 5112, 5116, 5120, or 5122. In some embodiments, the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 5104; and the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides

differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 5101, 5108, 5112, 5116, 5120, or 5122.

[0193] In some embodiments, the siRNA for targeting MAPT comprises an antisense strand sequence comprising at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4718. In some embodiments, the siRNA comprises a sense strand sequence comprising at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4527, 5130, 5134, 5138, or 5142. In some embodiments, the antisense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 4718 and the sense strand sequence comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4527, 5130, 5134, 5138, or 5142.

[0194] In some embodiments, the siRNA for targeting MAPT comprises an antisense strand sequence comprising at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 5128. In some embodiments, the siRNA comprises a sense strand sequence comprising at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 5125, 5132, 5136, 5140, 5144, or 5146. In some embodiments, the antisense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of SEQ ID NO: 5128; and the sense strand sequence comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides differing by 3, 2, 1, or 0 nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 5125, 5132, 5136, 5140, 5144, or 5146.

[0195] In some embodiments, the siRNA molecule is screened for the ability to inhibit tau (MAPT) expression in a cell. As a non-limiting example, the cell is a HEK293 cell. As another non-limiting example, the cell is a human tau transgenic primary neuron and/or astrocyte. As another non-limiting example, the cell is a frontotemporal lobar degeneration (FTLD) patient fibroblast. As a non-limiting example, other standard cell lines that may be used for initial screening are: naïve neuronal SK-N-AS cells, monkey cell lines (CYNOM-K1, FRhK-4, or LLC-MK2), primary neuron and astrocyte cultures from htau mice, frontotemporal lobar degeneration (FTLD)-tau patient induced pluripotent stem cells (iPSCs), FTLD-tau patient fibroblasts; nervous system cells derived from multiple affected or at-risk donors (with and without MAPT mutations), FTLD-tau patient lymphoblasts, and human neural stem cells bearing homozygous or heterozygous mutations in MAPT (e.g., P301L, R406W, V337M) that may be introduced using CRISPR-Cas9 gene editing technology. The screened siRNA duplex may be selected from any of the siRNA duplexes presented in Table 4 or 5 of the present disclosure.

[0196] In some embodiments, the siRNA molecules of the present disclosure can be encoded by a vector, e.g., plasmid vector, a viral genome (e.g., an AAV viral genome), or another nucleic acid expression vector for delivery to a cell. In some embodiments, a siRNA molecule is encoded by a viral genome of an AAV particle.

[0197] DNA expression plasmids can be used to stably express the siRNA duplexes or dsRNA of the present disclosure in cells and achieve long-term inhibition of the target gene expression. In one aspect, the sense and antisense strands of a siRNA duplex are typically linked by a short spacer sequence leading to the expression of a stem-loop structure termed short hairpin RNA (shRNA). The hairpin is recognized and cleaved by Dicer, thus generating mature siRNA molecules.

[0198] In some embodiments, the sense and antisense strands of a siRNA duplex may be linked by a short spacer sequence, which may optionally be linked to additional flanking sequence, leading to the expression of a flanking arm-stem-loop structure termed primary microRNA (pri-miRNA). The pri-miRNA may be recognized and cleaved by Drosha and Dicer, and thus generate mature siRNA molecules.

[0199] The expression of MAPT may be assessed based on the level of expression of MAPT mRNA or MAPT protein. In some embodiments, the expression of MAPT, e.g., MAPT mRNA, is inhibited by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%. In some embodiments, the siRNA duplexes or encoded dsRNA of the present disclosure suppress (or degrade) the target mRNA in a cell, e.g., a neuron (e.g., a cortical neuron) or a glial cell.

[0200] According to the present disclosure, the siRNA molecules are designed and tested for their ability to reduce MAPT transcript levels in cultured cells. Such siRNA molecules may form a duplex such as, but not limited to, any of the sequences listed in Tables 4, 5, 9A, or 9B.

[0201] In some embodiments, the siRNA molecules comprise a miRNA seed match for the target (e.g., MAPT transcript) located in the guide strand. In another embodiment, the siRNA molecules comprise a miRNA seed match for the target (e.g., MAPT transcript) located in the passenger strand. In yet another embodiment, the siRNA duplexes or encoded dsRNA targeting MAPT transcript do not comprise a seed match for the target (e.g., MAPT transcript) located in the guide or passenger strand. In some embodiments, the siRNA duplex is designed so there is no miRNA seed match for the sense or antisense sequence to non-MAPT sequences.

[0202] The present disclosure also provides a pharmaceutical composition comprising a siRNA duplex targeting a MAPT gene, mRNA, or protein, and a pharmaceutically acceptable carrier. In some aspects, the siRNA duplex is encoded by a viral genome and/or modulatory polynucleotide. In some embodiments, an

AAV particle comprises the viral genome and an AAV capsid protein, e.g., an AAV capsid variant described herein.

[0203] In some embodiments, the guide to passenger (G:P) (also referred to as the antisense to sense) strand ratio is 1:10, 1:9, 1:8, 1:7, 1:6, 1:5, 1:4, 1:3, 1:2, 1;1, 2:10, 2:9, 2:8, 2:7, 2:6, 2:5, 2:4, 2:3, 2:2, 2:1, 3:10, 3:9, 3:8, 3:7, 3:6, 3:5, 3:4, 3:3, 3:2, 3:1, 4:10, 4:9, 4:8, 4:7, 4:6, 4:5, 4:4, 4:3, 4:2, 4:1, 5:10, 5:9, 5:8, 5:7, 5:6, 5:5, 5:4, 5:3, 5:2, 5:1, 6:10, 6:9, 6:8, 6:7, 6:6, 6:5, 6:4, 6:3, 6:2, 6:1, 7:10, 7:9, 7:8, 7:7, 7:6, 7:5, 7:4, 7:3, 7:2, 7:1, 8:10, 8:9, 8:8, 8:7, 8:6, 8:5, 8:4, 8:3, 8:2, 8:1, 9:10, 9:9, 9:8, 9:7, 9:6, 9:5, 9:4, 9:3, 9:2, 9:1, 10:10, 10:9, 10:8, 10:7, 10:6, 10:5, 10:4, 10:3, 10:2, 10:1, 1:99, 5:95, 10:90, 15:85, 20:80, 25:75, 30:70, 35:65, 40:60, 45:55, 50:50, 55:45, 60:40, 65:35, 70:30, 75:25, 80:20, 85:15, 90:10, 95:5, or 99:1 *in vitro* or *in vivo*. In some embodiments, the guide to passenger ratio refers to the ratio of the guide strands to the passenger strands after the intracellular processing of the pri-microRNA. For example, a 80:20 guide-to-passenger ratio would have 8 guide strands to every 2 passenger strands processed from the precursor.

[0204] In some embodiments, the passenger to guide (P:G) (also referred to as the sense to antisense) strand ratio is 1:10, 1:9, 1:8, 1:7, 1:6, 1:5, 1:4, 1:3, 1:2, 1;1, 2:10, 2:9, 2:8, 2:7, 2:6, 2:5, 2:4, 2:3, 2:2, 2:1, 3:10, 3:9, 3:8, 3:7, 3:6, 3:5, 3:4, 3:3, 3:2, 3:1, 4:10, 4:9, 4:8, 4:7, 4:6, 4:5, 4:4, 4:3, 4:2, 4:1, 5:10, 5:9, 5:8, 5:7, 5:6, 5:5, 5:4, 5:3, 5:2, 5:1, 6:10, 6:9, 6:8, 6:7, 6:6, 6:5, 6:4, 6:3, 6:2, 6:1, 7:10, 7:9, 7:8, 7:7, 7:6, 7:5, 7:4, 7:3, 7:2, 7:1, 8:10, 8:9, 8:8, 8:7, 8:6, 8:5, 8:4, 8:3, 8:2, 8:1, 9:10, 9:9, 9:8, 9:7, 9:6, 9:5, 9:4, 9:3, 9:2, 9:1, 10:10, 10:9, 10:8, 10:7, 10:6, 10:5, 10:4, 10:3, 10:2, 10:1, 1:99, 5:95, 10:90, 15:85, 20:80, 25:75, 30:70, 35:65, 40:60, 45:55, 50:50, 55:45, 60:40, 65:35, 70:30, 75:25, 80:20, 85:15, 90:10, 95:5, or 99:1 *in vitro* or *in vivo*. In some embodiments, the passenger to guide ratio refers to the ratio of the passenger strands to the guide strands after the excision of the guide strand. For example, a 80:20 passenger to guide ratio would have 8 passenger strands to every 2 guide strands processed from the precursor.

Molecular Scaffold

[0205] In some embodiments, a viral genome described herein encodes a modulatory polynucleotide comprising a siRNA, e.g., an siRNA described herein for targeting MAPT. In some embodiments, a viral genome described herein comprises a modulatory polynucleotide encoding a siRNA, e.g., an siRNA described herein for targeting MAPT. In some embodiments, the modulatory polynucleotide comprises a molecular scaffold. In some embodiments, a molecular scaffold comprises a framework or starting molecule that forms the sequence or structural basis against which to design or make a subsequent molecule. In some embodiments, the modulatory polynucleotide comprises a 5' flanking region, a loop region, and a 3' flanking region. In some embodiments, the modulatory polynucleotide further comprises a passenger strand (e.g., a passenger strand or guide strand sequence of a siRNA for targeting MAPT described herein) and/or a guide strand (e.g., a guide strand or antisense strand sequence of a siRNA for targeting MAPT described herein). In some embodiments, the modulatory polynucleotide is an RNA molecule, e.g., an encoded modulatory

polynucleotide. In some embodiments, the modulatory polynucleotide is a DNA molecule, e.g., a DNA molecule encoding the RNA modulatory polynucleotide.

[0206] In some embodiments, the encoded modulatory polynucleotide comprises in 5' to 3' order: a 5' flanking region, a passenger strand (e.g., a passenger strand or guide strand sequence of a siRNA for targeting MAPT described herein), a loop region, a guide strand (e.g., a guide strand or antisense strand sequence of a siRNA for targeting MAPT described herein), and a 3' flanking region. In some embodiments, the encoded modulatory polynucleotide is an RNA molecule.

[0207] In some embodiments, the modulatory polynucleotide comprises in 5' to 3' order: a 5' flanking region, a guide strand (e.g., a guide strand or antisense strand sequence of a siRNA for targeting MAPT described herein), a loop region, a passenger strand (e.g., a passenger strand or sense strand sequence of a siRNA for targeting MAPT described herein), and a 3' flanking region. In some embodiments, the modulatory polynucleotide is a DNA molecule.

[0208] In some embodiments, the modulatory polynucleotide comprises a stem-loop structure. In some embodiments, the passenger strand and the guide strand are located, respectively, on a 5' arm and a 3' arm of a stem loop structure, wherein the passenger strand is located between the 5' flanking region and the loop region and the guide strand is located between the loop region and the 3' flanking region. In some embodiments, the guide strand and the passenger strand are located, respectively, on a 5' arm and a 3' arm of a stem loop structure, wherein the guide strand is located between the 5' flanking region and the loop region and the passenger strand is located between the loop region and the 3' flanking region.

[0209] In some embodiments the 5' and 3' flanking sequences comprise the same nucleotide sequence. In some embodiments the nucleotide sequence of the 5' flanking region differs by at least 2%, 3%, 4%, 5%, relative to the 3' flanking region, when aligned to each other. In some embodiments, the 5' flanking region and the 3' flanking region comprise different nucleotide sequences.

[0210] In some embodiments, the loop region comprises a nucleic acid sequence encoding at least one UGUG motif. In some embodiments, the nucleic acid sequence encoding the UGUG motif is located at the 5' terminus of the loop sequence.

[0211] In some embodiments, a molecular scaffold described herein comprises the nucleotide sequence of a 5' flanking region, a loop region and a 3' flanking region, provided in Tables 6-8, or a fragment thereof. In some embodiments, the 5' flanking region, loop region, and 3' flanking region comprises or is encoded by a nucleotide sequence provided in Tables 6-8, or a fragment thereof.

Table 6. Exemplary 5' Flanking Regions

Name	Sequence	SEQ ID NO
5F1 (DNA)	TTTATGCCTCATCCTCTGAGTGCTGAAGGCTTGCTGTAGGCTGTATGCTG	4353

5F1 (RNA)	UUUAUGCCUCAUCCUCUGAGUGCUGAAGGCUUGCUG UAGGCUGUAUGCUG	4878
5F2 (DNA)	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAAC ACCATGCGCTCTTCGGAA	4354
5F2 (RNA)	GUGCUGGGCGGGGGGCGGCGGGCCCUCCCGCAGAAC ACCAUGCGCUCUUCGGAA	4879
5F3 (DNA)	GAAGCAAAGAAGGGGCAGAGGGAGCCCGTGAGCTGA GTGGGCCAGGGACTGGGAGAAGGAGTGAGGAGGCAG GGCCGGCATGCCTCTGCTGCTGGCCAGA	4355
5F3 (RNA)	GAAGCAAAGAAGGGGCAGAGGGAGCCCGUGAGCUG AGUGGGCCAGGGACUGGGAGAAGGAGUGAGGAGGC AGGGCCGGCAUGCCUCUGCUGCUGGCCAGA	4880
5F4 (DNA)	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAAC ACCATGCGCTCTTCGGGA	4356
5F4 (RNA)	GUGCUGGGCGGGGGGCGGCGGGCCCUCCCGCAGAAC ACCAUGCGCUCUUCGGGA	4881
5F5 (DNA)	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAAC ACCATGCGCTCCACGGAA	4357
5F5 (RNA)	GUGCUGGGCGGGGGGCGGCGGGCCCUCCCGCAGAAC ACCAUGCGCUCCACGGAA	4882
5F6 (DNA)	GGGCCCTCCCGCAGAACACCATGCGCTCCACGGAA	4358
5F5 (RNA)	GGGCCCUCCCGCAGAACACCAUGCGCUCCACGGAA	4883
5F7 (DNA)	CTCCCGCAGAACACCATGCGCTCCACGGAA	4359
5F7 (RNA)	CUCCCGCAGAACACCAUGCGCUCCACGGAA	4884
5F8 (DNA)	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAAC ACCATGCGCTCCACGGAAG	4360
5F8 (RNA)	GUGCUGGGCGGGGGGCGGCGGGCCCUCCCGCAGAAC ACCAUGCGCUCCACGGAAG	4885
5F9 (DNA)	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAAC ACCATGCGCTCCTCGGAA	4361
5F9 (RNA)	GUGCUGGGCGGGGGGCGGCGGGCCCUCCCGCAGAAC ACCAUGCGCUCCUCGGAA	4886

Table 7. Exemplary Loop Regions

Name	Sequence	SEQ ID NO
L1 (DNA)	TGTGACCTGG	4362
L1 (RNA)	UGUGACCUGG	4887
L2 (DNA)	TGTGATTTGG	4363
L2 (RNA	UGUGAUUUGG	4888
L3 (DNA)	TATAATTTGG	4364
L3 (RNA)	UAUAAUUUGG	4889
L4 (DNA)	CCTGACCCAGT	4365
L4 (RNA)	CCUGACCCAGU	4890
L5 (DNA)	GTCTGCACCTGTCACTAG	4366
L5 (RNA)	GUCUGCACCUGUCACUAG	4891
L6 (DNA)	GTGACCCAAG	4367
L6 (RNA)	GUGACCCAAG	4892
L7 (DNA)	GTGGCCACTGAGAAG	4368
L7 (RNA)	GUGGCCACUGAGAAG	4893
L8 (DNA)	GTGACCCAAT	4369
L8 (RNA)	GUGACCCAAU	4894
L9 (DNA)	GTGACCCAAC	4370
L9 (RNA)	GUGACCCAAC	4895
L10 (DNA)	GTGGCCACTGAGAAA	4371

L10 (RNA)	GUGGCCACUGAGAAA	4896

Table 8. Exemplary 3' Flanking Regions

Name	Sequence	SEQ ID NO
3F1 (DNA)	AGTGTATGATGCCTGTTACTAGCATTCACATGGAACA AATTGCTGCCGTG	4372
3F1 (RNA)	AGUGUAUGAUGCCUGUUACUAGCAUUCACAUGGAA CAAAUUGCUGCCGUG	4897
3F2 (DNA)	CTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCG CCCCCTACCTCAGTGA	4373
3F2 (RNA)	CUGAGGAGCGCCUUGACAGCAGCCAUGGGAGGGCCG CCCCCUACCUCAGUGA	4898
3F3 (DNA)	CTGTGGAGCGCCTTGACAGCAGCCATGGGAGGGCCG CCCCCTACCTCAGTGA	4374
3F3 (RNA)	CUGUGGAGCGCCUUGACAGCAGCCAUGGGAGGGCCG CCCCCUACCUCAGUGA	4899
3F4 (DNA)	TGGCCGTGTAGTGCTACCCAGCGCTGGCTGCCTCCTC AGCATTGCAATTCCTCTCCCATCTGGGCACCAGTCAG CTACCCTGGTGGGAATCTGGGTAGCC	4375
3F4 (RNA)	UGGCCGUGUAGUGCUACCCAGCGCUGGCUGCCUCCU CAGCAUUGCAAUUCCUCUCCCAUCUGGGCACCAGUC AGCUACCCUGGUGGGAAUCUGGGUAGCC	4900
3F5 (DNA)	GGCCGTGTAGTGCTACCCAGCGCTGGCTGCCTCCTCA GCATTGCAATTCCTCTCCCATCTGGGCACCAGTCAGC TACCCTGGTGGGAATCTGGGTAGCC	4376
3F5 (RNA)	GGCCGUGUAGUGCUACCCAGCGCUGGCUGCCUCCUC AGCAUUGCAAUUCCUCUCCCAUCUGGGCACCAGUCA GCUACCCUGGUGGGAAUCUGGGUAGCC	4901
3F6 (DNA)	TCCTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGC CGCCCCCTACCTCAGTGA	4377
3F6 (RNA)	UCCUGAGGAGCGCCUUGACAGCAGCCAUGGGAGGGC CGCCCCCUACCUCAGUGA	4902
3F7 (DNA)	CTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCC	4378
3F7 (RNA)	CUGAGGAGCGCCUUGACAGCAGCCAUGGGAGGGCC	4903
3F8 (DNA)	CTGCGGAGCGCCTTGACAGCAGCCATGGGAGGGCCG CCCCCTACCTCAGTGA	4379
3F8 (RNA)	CUGCGGAGCGCCUUGACAGCAGCCAUGGGAGGGCCG CCCCCUACCUCAGUGA	4904

[0212] Any of the regions described in Table 6, Table 7, and Table 8 or a fragment of variant thereof may be used in the molecular scaffolds described herein, e.g., a molecular scaffold encoding or comprising a siRNA for targeting MAPT described herein.

[0213] In some embodiments, the modulatory polynucleotide comprises a 5' flanking region, fragment or variant thereof, e.g., as listed in Table 6 or as provided in WO2016077689, WO2017201248, WO2018204797, WO2017201258, WO2018204803, or WO2021016505, the contents of which are hereby incorporated by reference in their entirety.

[0214] In some embodiments, the encoded 5' flanking region comprises the nucleotide sequence of any one of SEQ ID NOs: 4878-4886; a nucleotide sequence substantially identical (e.g., having at least 70%,

75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) thereto; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of any of SEQ ID NOs: 4878-4886; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of any of SEQ ID NOs: 4878-4886.

[0215] In some embodiments, the nucleotide sequence encoding the 5' flanking region comprises the nucleotide sequence of any of SEQ ID NOs: 4353-4361, a nucleotide sequence, substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) thereto; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of any of SEQ ID NOs: 4353-4361; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of any of SEQ ID NOs: 4353-4361.

[0216] In some embodiments, the 5' flanking region comprises the nucleotide sequence of SEQ ID NO: 4354; a nucleotide sequence, substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4354; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4354; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4354. In some embodiments, the 5' flanking region comprises the nucleotide sequence of SEQ ID NO: 4355; a nucleotide sequence, substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4355; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4355; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4355.

[0217] In some embodiments, the encoded 5' flanking region comprises the nucleotide sequence of SEQ ID NO: 4879; a nucleotide sequence, substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4879; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4879; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4879. In some embodiments, the nucleotide sequence encoding the 5' flanking region comprises the nucleotide sequence of SEQ ID NO: 4354; a nucleotide sequence, substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4354; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide

sequence of SEQ ID NO: 4354; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4354.

[0218] In some embodiments, the encoded 5' flanking region comprises the nucleotide sequence of SEQ ID NO: 4880; a nucleotide sequence, substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4880; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4880; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4880. In some embodiments, the nucleotide sequence encoding the 5' flanking region comprises the nucleotide sequence of SEQ ID NO: 4355; a nucleotide sequence, substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4355; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4355; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4355.

[0219] In some embodiments, the modulatory polynucleotide comprises a loop region, fragment or variant thereof, e.g., as provided in Table 7 or as provided in WO2016077689, WO2017201248, WO2018204797, WO2017201258, WO2018204803, or WO2021016505, the contents of which are hereby incorporated by reference in their entirety.

[0220] In some embodiments, the encoded loop region comprises the nucleotide sequence of any of SEQ ID NOs: 4887-4896; a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) thereto; a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of any of SEQ ID NOs: 4887-4896; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of any of SEQ ID NOs: 4887-4896.

[0221] In some embodiments, the nucleotide sequence encoding the loop region comprises the nucleotide sequence of any of SEQ ID NOs: 4362-4371; a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) thereto; a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of any of SEQ ID NOs: 4362-4371; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of any of SEQ ID NOs: 4362-4371.

[0222] In some embodiments, the loop region comprises the nucleotide sequence of SEQ ID NO: 4362; a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4362; a nucleotide sequence comprising one, two, three, or four,

but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4362; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4362. In some embodiments, the loop region comprises the nucleotide sequence of SEQ ID NO: 4363; a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4363; a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4363; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4363. In some embodiments, the loop region comprises the nucleotide sequence of SEQ ID NO: 4366; a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4366; a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4366; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4366.

[0223] In some embodiments, the encoded loop region comprises the nucleotide sequence of SEQ ID NO: 4887; a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4887; a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4887; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4887. In some embodiments, the nucleotide sequence encoding the loop region comprises the nucleotide sequence of SEQ ID NO: 4362; a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4362; a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4362; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4362.

[0224] In some embodiments, the encoded loop region comprises the nucleotide sequence of SEQ ID NO: 4888; a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4888; a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4888; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4888. In some embodiments, the nucleotide sequence encoding the loop region comprises the nucleotide sequence of SEQ ID NO: 4363; a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence

identity) to SEQ ID NO: 4363; a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4363; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4363.

[0225] In some embodiments, the encoded loop region comprises the nucleotide sequence of SEQ ID NO: 4891; a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4891; a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4891; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4891. In some embodiments, the nucleotide sequence encoding the loop region comprises the nucleotide sequence of SEQ ID NO: 4366; a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4366; a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4366; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4366.

[0226] In some embodiments, the modulatory polynucleotide comprises a 3' flanking region, fragment or variant thereof, e.g., as listed in Table 8 or as provided in WO2016077689, WO2017201248, WO2018204797, WO2017201258, WO2018204803, or WO2021016505, the contents of which are hereby incorporated by reference in their entirety.

[0227] In some embodiments, the encoded 3' flanking region comprises the nucleotide sequence of any one of SEQ ID NOs: 4897-4904; a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) thereto; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of any of SEQ ID NOs: 4897-4904; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of any of SEQ ID NOs: 4897-4904.

[0228] In some embodiments, the nucleotide sequence encoding the 3' flanking region comprises the nucleotide sequence of any of SEQ ID NOs: 4372-4379; a nucleotide sequence, substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) thereto; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of any of SEQ ID NOs: 4372-4379; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of any of SEQ ID NOs: 4372-4379.

[0229] In some embodiments, the 3' flanking region comprises the nucleotide sequence of SEQ ID NO: 4373; a nucleotide sequence, substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4373; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4373; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4373. In some embodiments, the 3' flanking region comprises the nucleotide sequence of SEQ ID NO: 4374; a nucleotide sequence, substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4374; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4374; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4374. In some embodiments, the 3' flanking region comprises the nucleotide sequence of SEQ ID NO: 4375; a nucleotide sequence, substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4375; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4375; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4375.

[0230] In some embodiments, the encoded 3' flanking region comprises the nucleotide sequence of SEQ ID NO: 4898; a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4898; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4898; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4898. In some embodiments, the nucleotide sequence encoding the 3' flanking region comprises the nucleotide sequence of SEQ ID NO: 4373; a nucleotide sequence, substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4373; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4373; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4373.

[0231] In some embodiments, the encoded 3' flanking region comprises the nucleotide sequence of SEQ ID NO: 4899; a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4899; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide

sequence of SEQ ID NO: 4898; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4899. In some embodiments, the nucleotide sequence encoding the 3' flanking region comprises the nucleotide sequence of SEQ ID NO: 4374; a nucleotide sequence, substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4374; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4374; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4374.

[0232] me embodiments, the encoded 3' flanking region comprises the nucleotide sequence of SEQ ID NO: 4900; a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4900; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4898; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4900. In some embodiments, the nucleotide sequence encoding the 3' flanking region comprises the nucleotide sequence of SEQ ID NO: 4375; a nucleotide sequence, substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4375; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4375; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4375.

[0233] In some embodiments, the encoded modulatory polynucleotide comprises: (i) a 5' flanking region comprising the nucleotide sequence of any one of SEQ ID NOs: 4878-4886, a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) thereto, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of any one of SEQ ID NOs: 4878-4886; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of any one of SEQ ID NOs: 4878-4886; (ii) a loop region comprising the nucleotide sequence of any one of SEQ ID NOs: 4887-4896, a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) thereto, a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of any one of SEQ ID NOs: 4887-4896; or a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of any one of SEQ ID NOs: 4887-4896; and (iii) a 3' flanking region of any one of SEQ ID NOs: 4897-4904, a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%,

90%, 95% 96%, 97%, 98%, 99% sequence identity) thereto, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of any one of SEQ ID NOs: 4897-4904, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of any one of SEQ ID NOs: 4897-4904.

[0234] In some embodiments, the modulatory polynucleotide comprises: (i) a 5' flanking region comprising the nucleotide sequence of any one of SEQ ID NOs: 4353-4361, a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) thereto, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of any one of SEQ ID NOs: 4353-4361; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of any one of SEQ ID NOs: 4353-4361; (ii) a loop region comprising the nucleotide sequence of any one of SEQ ID NOs: 4362-4371, a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) thereto, a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of any one of SEQ ID NOs: 4362-4371; or a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of any one of SEQ ID NOs: 4362-4371; and (iii) a 3' flanking region of any one of SEQ ID NOs: 4372-4379, a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) thereto, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of any one of SEQ ID NOs: 4372-4379, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of any one of SEQ ID NOs: 4372-4379.

[0235] In some embodiments, the encoded modulatory polynucleotide comprises: (i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4879, a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4879, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4879; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4879; (ii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4887, a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4887, a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID

NO: 4887; or a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4887; and (iii) a 3' flanking region of SEQ ID NO: 4898, a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4898, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4898, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4898.

[0236] In some embodiments, the modulatory polynucleotide comprises: (i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4354, a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4354, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4354; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4354; (ii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4362, a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4362, a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4362; or a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4362; and (iii) a 3' flanking region of SEQ ID NO: 4373, a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4373, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4373, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4373.

[0237] In some embodiments, the encoded modulatory polynucleotide comprises: (i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4879, a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4879, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4879; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4879; (ii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4888, a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4888, a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID

NO: 4888; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4888; and (iii) a 3' flanking region of SEQ ID NO: 4898, a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4898, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4898, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4898.

[0238] In some embodiments, the modulatory polynucleotide comprises: (i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4354, a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4354, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4354; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4354; (ii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4363, a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4363, a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4363; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4363; and (iii) a 3' flanking region of SEQ ID NO: 4373, a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4373, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4373, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4373.

[0239] In some embodiments, the encoded modulatory polynucleotide comprises: (i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4879, a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4879, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4879; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4879; (ii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4887, a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4887, a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID

NO: 4887; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4887; and (iii) a 3' flanking region of SEQ ID NO: 4899, a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4899, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4899, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4899.

[0240] In some embodiments, the encoded modulatory polynucleotide comprises: (i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4354, a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4354, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4354; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4354; (ii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4362, a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4362, a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4362, or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4362; and (iii) a 3' flanking region of SEQ ID NO: 4374, a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4374, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4374, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4374.

[0241] In some embodiments, the encoded modulatory polynucleotide comprises: (i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4880, a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4880, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4880; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4880; (ii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4891, a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4891, a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID

NO: 4891; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4891; and (iii) a 3' flanking region of SEQ ID NO: 4900, a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4900, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4900, or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to SEQ ID NO: 4900.

[0242] In some embodiments, the encoded modulatory polynucleotide comprises: (i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4355, a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4355, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4355; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4355; (ii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4366, a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4366, a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4366; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4366; and (iii) a 3' flanking region of SEQ ID NO: 4375, a nucleotide sequence substantially identical (e.g., having at least 70%, 75%, 80%, 85%, 90%, 95% 96%, 97%, 98%, 99% sequence identity) to SEQ ID NO: 4375, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4375, or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to SEQ ID NO: 4375.

[0243] In some embodiments, a molecular scaffold may comprise one or more linkers known in the art. The linkers may separate regions or one molecular scaffold from another. As a non-limiting example, the molecular scaffold or modulatory polynucleotide may be polycistronic.

Modulatory Polynucleotide Comprising the Molecular Scaffold and siRNA Molecule

[0244] In some embodiments, the modulatory polynucleotide comprises 5' and 3' flanking regions, loop region, and nucleic acid sequences encoding the sense strand sequence and the antisense strand sequence as described in Table 9A and Table 9B.

[0245] In some embodiments, the modulatory polynucleotide comprises the nucleotide sequence of any one of SEQ ID NOs: 4380-4409 or 5027-5050, or nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 987%, or 99% identical thereto. In some embodiments, the modulatory polynucleotide

comprises a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of any one of SEQ ID NOs: 4380-4409 or 5027-5050. In some embodiments, the modulatory polynucleotide comprises a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of any one of SEQ ID NOs: 4380-4409 or 5027-5050.

[0246] In some embodiments, the modulatory polynucleotide comprises the nucleotide sequence of SEQ ID NO: 4405, or nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 987%, or 99% identical thereto. In some embodiments, the modulatory polynucleotide comprises a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4405. In some embodiments, the modulatory polynucleotide comprises a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4405.

[0247] In some embodiments, the modulatory polynucleotide comprises the nucleotide sequence of SEQ ID NO: 4408, or nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 987%, or 99% identical thereto. In some embodiments, the modulatory polynucleotide comprises a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4408. In some embodiments, the modulatory polynucleotide comprises a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4408. In some embodiments, the modulatory polynucleotide comprises the nucleotide sequence of SEQ ID NO: 4408.

[0248] In some embodiments, the modulatory polynucleotide comprises the nucleotide sequence of SEQ ID NO: 4409, or nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 987%, or 99% identical thereto. In some embodiments, the modulatory polynucleotide comprises a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4409. In some embodiments, the modulatory polynucleotide comprises a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4409. In some embodiments, the modulatory polynucleotide comprises the nucleotide sequence of SEQ ID NO: 4409.

[0249] In some embodiments, the modulatory polynucleotide comprises the nucleotide sequence of SEQ ID NO: 4390, or nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 987%, or 99% identical thereto. In some embodiments, the modulatory polynucleotide comprises a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4390. In some embodiments, the modulatory polynucleotide comprises a nucleotide sequence comprising at least one, two, three, four, five, six, or seven,

but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4390. In some embodiments, the modulatory polynucleotide comprises the nucleotide sequence of SEQ ID NO: 4390.

[0250] In some embodiments, the modulatory polynucleotide comprises the nucleotide sequence of SEQ ID NO: 4391, or nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 987%, or 99% identical thereto. In some embodiments, the modulatory polynucleotide comprises a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4391. In some embodiments, the modulatory polynucleotide comprises a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4391. In some embodiments, the modulatory polynucleotide comprises the nucleotide sequence of SEQ ID NO: 4391.

[0251] In some embodiments, the modulatory polynucleotide comprises the nucleotide sequence of SEQ ID NO: 4393, or nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 987%, or 99% identical thereto. In some embodiments, the modulatory polynucleotide comprises a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4393. In some embodiments, the modulatory polynucleotide comprises a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4393. In some embodiments, the modulatory polynucleotide comprises the nucleotide sequence of SEQ ID NO: 4393.

[0252] In some embodiments, the modulatory polynucleotide comprises the nucleotide sequence of SEQ ID NO: 4394, or nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 987%, or 99% identical thereto. In some embodiments, the modulatory polynucleotide comprises a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4394. In some embodiments, the modulatory polynucleotide comprises a nucleotide sequence comprising at least one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4394. In some embodiments, the modulatory polynucleotide comprises the nucleotide sequence of SEQ ID NO: 4394.

[0253] It is understood that in some embodiments, any of the sequences in Tables 3-8, 9A, and 9B, or herein, can comprise a U nucleotide (uridine) in place of any of or all T nucleotides (thymine) within the sequence (e.g., an RNA molecule). It is also understood that in some embodiments, that any sequence provided herein can comprise a T nucleotide (thymine) in place of any of or all U nucleotides (uracil) within the sequence (e.g., a DNA molecule).

Table 9A. Exemplary Modulatory Polynucleotide Sequence Region (5' to 3')

Modulatory Polynucleotide	5' Flanking to 3' Flanking SEQ ID NO	5' Flanking SEQ ID NO	Passenger SEQ ID NO	Loop SEQ ID NO	Guide SEQ ID NO	3' Flanking SEQ ID NO
VOYTaumiR-102-530	4380	4354	4410	4362	4434	4373
VOYTaumiR-102-556	4381	4354	4411	4362	4435	4373
VOYTaumiR-102-564	4382	4354	4412	4362	4436	4373
VOYTaumiR-102-579	4383	4354	4413	4362	4437	4373
VOYTaumiR-102-586	4384	4354	4414	4362	4438	4373
VOYTaumiR-102-582	5027	4354	5058	4362	5055	4373
VOYTaumiR-102-587	5028	4354	5075	4362	5078	4373
VOYTaumiR-102-552	5029	4354	5099	4362	5102	4373
VOYTaumiR-102-549	5030	4354	5123	4362	5126	4373
VOYTaumiR-104-530	4385	4354	4415	4362	4434	4373
VOYTaumiR-104-556	4386	4354	4416	4362	4435	4373
VOYTaumiR-104-564	4387	4354	4417	4362	4436	4373
VOYTaumiR-104-579	4388	4354	4418	4362	4437	4373
VOYTaumiR-104-586	4389	4354	4419	4362	4438	4373
VOYTaumiR-104-582	5031	4354	5061	4362	5055	4373
VOYTaumiR-104-587	5032	4354	5081	4362	5078	4373
VOYTaumiR-104-552	5033	4354	5105	4362	5102	4373
VOYTaumiR-104-549	5034	4354	5129	4362	5126	4373
VOYTaumiR-109-530	4390	4354	4420	4363	4434	4373
VOYTaumiR-109-556	4391	4354	4421	4363	4435	4373
VOYTaumiR-109-564	4392	4354	4422	4363	4436	4373
VOYTaumiR-109-579	4393	4354	4423	4363	4437	4373
VOYTaumiR-109-586	4394	4354	4424	4363	4438	4373
VOYTaumiR-109-582	5035	4354	5051	4363	5055	4373
VOYTaumiR-109-587	5036	4354	5085	4363	5078	4373
VOYTaumiR-109-552	5037	4354	5109	4363	5102	4373
VOYTaumiR-109-549	5038	4354	5133	4363	5126	4373
VOYTaumiR-114-530	4395	4354	4425	4362	4434	4374
VOYTaumiR-114-556	4396	4354	4426	4362	4435	4374
VOYTaumiR-114-564	4397	4354	4427	4362	4436	4374
VOYTaumiR-114-579	4398	4354	4428	4362	4437	4374
VOYTaumiR-114-586	4399	4354	4429	4362	4438	4374
VOYTaumiR-114-582	5039	4354	5067	4362	5055	4374
VOYTaumiR-114-587	5040	4354	5089	4362	5078	4374
VOYTaumiR-114-552	5041	4354	5113	4362	5102	4374
VOYTaumiR-114-549	5042	4354	5137	4362	5126	4374
VOYTaumiR-116-530	4400	4354	4430	4362	4434	4374
VOYTaumiR-116-556	4401	4354	4431	4362	4435	4374
VOYTaumiR-116-564	4402	4354	4432	4362	4436	4374
VOYTaumiR-116-579	4403	4354	4418	4362	4437	4374
VOYTaumiR-116-586	4404	4354	4433	4362	4438	4374
VOYTaumiR-116-582	5043	4354	5071	4362	5055	4374
VOYTaumiR-116-587	5044	4354	5093	4362	5078	4374
VOYTaumiR-116-552	5045	4354	5117	4362	5102	4374
VOYTaumiR-116-549	5046	4354	5141	4362	5126	4374
VOYTaumiR-127-530	4405	4355	4420	4366	4434	4375
VOYTaumiR-127-556	4406	4355	4421	4366	4435	4375
VOYTaumiR-127-564	4407	4355	4422	4366	4436	4375
VOYTaumiR-127-579	4408	4355	4423	4366	4437	4375

VOYTaumiR-127-586	4409	4355	4424	4366	4438	4375
VOYTaumiR-127-582	5047	4355	5051	4366	5055	4375
VOYTaumiR-127-587	5048	4355	5085	4366	5078	4375
VOYTaumiR-127-552	5049	4355	5109	4366	5102	4375
VOYTaumiR-127-549	5050	4355	5133	4366	5126	4375

Table 9B. Exemplary Modulatory Polynucleotides

Name	SEQ ID NO	Description	Sequence
VOYTaumiR-127-530	4405	5' flanking to 3' flanking	GAAGCAAAGAAGGGGCAGAGGGAGCCCGTGAGCTGAGTGGGCCAGG GACTGGGAGAAGGAGTGAGGAGGCAGGGCCGGCATGCCTCTGCTGC TGGCCAGAGACTGGAAGCGATGACAATCTGTCTGCACCTGTCACTA GTTTGTCATCGCTTCCAGTCTTTGGCCGTGTAGTGCTACCCAGCGC TGGCTGCCTCCTCAGCATTGCAATTCCTCTCCCATCTGGGCACCAG TCAGCTACCCTGGTGGGAATCTGGGTAGCC
	4355	5' flanking	GAAGCAAAGAAGGGGCAGAGGGAGCCCGTGAGCTGAGTGGGCCAGG GACTGGGAGAAGGAGTGAGGAGGCAGGGCCGGCATGCCTCTGCTGC TGGCCAGA
	4420	Passenger Strand (DNA)	GACTGGAAGCGATGACAAT
	4497	Passenger Strand (RNA)	GACUGGAAGCGAUGACAAU
	4905	Passenger Strand (DNA) v2	GACTGGAAGCGATGACAATCT
	4906	Passenger Strand (RNA) v2	GACUGGAAGCGAUGACAAUCU
	4366	Loop	GTCTGCACCTGTCACTAG
	4434	Guide Strand (DNA)	TTTGTCATCGCTTCCAGTC
	4697	Guide Strand (RNA)	UUUGUCAUCGCUUCCAGUC
	4907	Guide Strand (DNA) v2	TTTGTCATCGCTTCCAGTCTT
	4908	Guide Strand (RNA) v2	UUUGUCAUCGCUUCCAGUCUU
	4375	3' Flanking	TGGCCGTGTAGTGCTACCCAGCGCTGGCTGCCTCCTCAGCATTGCA ATTCCTCTCCCATCTGGGCACCAGTCAGCTACCCTGGTGGGAATCT GGGTAGCC
VOYTaumiR-127-556	4406	5' flanking to 3' flanking	GAAGCAAAGAAGGGGCAGAGGGAGCCCGTGAGCTGAGTGGGCCAGG GACTGGGAGAAGGAGTGAGGAGGCAGGGCCGGCATGCCTCTGCTGC TGGCCAGACTTCCGCGAGAACGCCAATCTGTCTGCACCTGTCACTA GTTTGGCGTTCTCGCGGAAGTTTGGCCGTGTAGTGCTACCCAGCGC TGGCTGCCTCCTCAGCATTGCAATTCCTCTCCCATCTGGGCACCAG TCAGCTACCCTGGTGGGAATCTGGGTAGCC
	4355	5' flanking	GAAGCAAAGAAGGGGCAGAGGGAGCCCGTGAGCTGAGTGGGCCAGG GACTGGGAGAAGGAGTGAGGAGGCAGGGCCGGCATGCCTCTGCTGC TGGCCAGA
	4421	Passenger Strand (DNA)	CTTCCGCGAGAACGCCAAT
	4508	Passenger Strand (RNA)	CUUCCGCGAGAACGCCAAU
	4909	Passenger Strand (DNA) v2	CTTCCGCGAGAACGCCAATCT
	4910	Passenger Strand (RNA) v2	CUUCCGCGAGAACGCCAAUCU

	4366	Loop	GTCTGCACCTGTCACTAG
	4435	Guide Strand (DNA)	TTTGGCGTTCTCGCGGAAG
	4701	Guide Strand (RNA)	UUUGGCGUUCUCGCGGAAG
	4911	Guide Strand (DNA) v2	TTTGGCGTTCTCGCGGAAGTT
	4912	Guide Strand (RNA) v2	UUUGGCGUUCUCGCGGAAGUU
	4375	3' Flanking	TGGCCGTGTAGTGCTACCCAGCGCTGGCTGCCTCCTCAGCATTGCA ATTCCTCTCCCATCTGGGCACCAGTCAGCTACCCTGGTGGGAATCT GGGTAGCC
VOYTaumiR-127-564	4407	5' flanking to 3' flanking	GAAGCAAAGAAGGGGCAGAGGGAGCCCGTGAGCTGAGTGGGCCAGG GACTGGGAGAAGGAGTGAGGAGGCAGGGCCGGCATGCCTCTGCTGC TGGCCAGAGCATCGACATGGTAGACTTCTGTCTGCACCTGTCACTA GTAGTCTACCATGTCGATGCTTTGGCCGTGTAGTGCTACCCAGCGC TGGCTGCCTCCTCAGCATTGCAATTCCTCTCCCATCTGGGCACCAG TCAGCTACCCTGGTGGGAATCTGGGTAGCC
	4355	5' flanking	GAAGCAAAGAAGGGGCAGAGGGAGCCCGTGAGCTGAGTGGGCCAGG GACTGGGAGAAGGAGTGAGGAGGCAGGGCCGGCATGCCTCTGCTGC TGGCCAGA
	4422	Passenger Strand (DNA)	GCATCGACATGGTAGACTT
	4487	Passenger Strand (RNA)	GCAUCGACAUGGUAGACUU
	4913	Passenger Strand (DNA) v2	GCATCGACATGGTAGACTTCT
	4914	Passenger Strand (RNA) v2	GCAUCGACAUGGUAGACUUCU
	4366	Loop	GTCTGCACCTGTCACTAG
	4436	Guide Strand (DNA)	TAGTCTACCATGTCGATGC
	4691	Guide Strand (RNA)	UAGUCUACCAUGUCGAUGC
	4915	Guide Strand (DNA) v2	TAGTCTACCATGTCGATGCTT
	4916	Guide Strand (RNA) v2	UAGUCUACCAUGUCGAUGCUU
	4375	3' Flanking	TGGCCGTGTAGTGCTACCCAGCGCTGGCTGCCTCCTCAGCATTGCA ATTCCTCTCCCATCTGGGCACCAGTCAGCTACCCTGGTGGGAATCT GGGTAGCC
VOYTaumiR-127-579	4408	5' flanking to 3' flanking	GAAGCAAAGAAGGGGCAGAGGGAGCCCGTGAGCTGAGTGGGCCAGG GACTGGGAGAAGGAGTGAGGAGGCAGGGCCGGCATGCCTCTGCTGC TGGCCAGAGCTCCTCGCAGTTCGGTTTCTGTCTGCACCTGTCACTA GTAACCGAACTGCGAGGAGCTTTGGCCGTGTAGTGCTACCCAGCGC TGGCTGCCTCCTCAGCATTGCAATTCCTCTCCCATCTGGGCACCAG TCAGCTACCCTGGTGGGAATCTGGGTAGCC
	4355	5' flanking	GAAGCAAAGAAGGGGCAGAGGGAGCCCGTGAGCTGAGTGGGCCAGG GACTGGGAGAAGGAGTGAGGAGGCAGGGCCGGCATGCCTCTGCTGC TGGCCAGA
	4423	Passenger Strand (DNA)	GCTCCTCGCAGTTCGGTTT
	4504	Passenger Strand (RNA)	GCUCCUCGCAGUUCGGUUU
	4917	Passenger Strand (DNA) v2	GCTCCTCGCAGTTCGGTTTCT

	4918	Passenger Strand (RNA) v2	GCUCCUCGCAGUUCGGUUUCU
	4366	Loop	GTCTGCACCTGTCACTAG
	4437	Guide Strand (DNA)	TAACCGAACTGCGAGGAGC
	4700	Guide Strand (RNA)	UAACCGAACUGCGAGGAGC
	4919	Guide Strand (DNA) v2	TAACCGAACTGCGAGGAGCTT
	4920	Guide Strand (RNA) v2	UAACCGAACUGCGAGGAGCUU
	4375	3' Flanking	TGGCCGTGTAGTGCTACCCAGCGCTGGCTGCCTCCTCAGCATTGCA ATTCCTCTCCCATCTGGGCACCAGTCAGCTACCCTGGTGGGAATCT GGGTAGCC
VOYTaumiR-127-586	4409	5' flanking to 3' flanking	GAAGCAAAGAAGGGGCAGAGGGAGCCCGTGAGCTGAGTGGGCCAGG GACTGGGAGAAGGAGTGAGGAGGCAGGGCCGGCATGCCTCTGCTGC TGGCCAGAGGCTTTGGCTCGGGACTTTCTGTCTGCACCTGTCACTA GTAAGTCCCGAGCCAAAGCCTTTGGCCGTGTAGTGCTACCCAGCGC TGGCTGCCTCCTCAGCATTGCAATTCCTCTCCCATCTGGGCACCAG TCAGCTACCCTGGTGGGAATCTGGGTAGCC
	4355	5' flanking	GAAGCAAAGAAGGGGCAGAGGGAGCCCGTGAGCTGAGTGGGCCAGG GACTGGGAGAAGGAGTGAGGAGGCAGGGCCGGCATGCCTCTGCTGC TGGCCAGA
	4424	Passenger Strand (DNA)	GGCTTTGGCTCGGGACTTT
	4482	Passenger Strand (RNA)	GGCUUUGGCUCGGGACUUU
	4921	Passenger Strand (DNA) v2	GGCTTTGGCTCGGGACTTTCT
	4922	Passenger Strand (RNA) v2	GGCUUUGGCUCGGGACUUUCU
	4366	Loop	GTCTGCACCTGTCACTAG
	4438	Guide Strand (DNA)	TAAGTCCCGAGCCAAAGCC
	4690	Guide Strand (RNA)	UAAGUCCCGAGCCAAAGCC
	4923	Guide Strand (DNA) v2	TAAGTCCCGAGCCAAAGCCTT
	4924	Guide Strand (RNA) v2	UAAGUCCCGAGCCAAAGCCUU
	4375	3' Flanking	TGGCCGTGTAGTGCTACCCAGCGCTGGCTGCCTCCTCAGCATTGCA ATTCCTCTCCCATCTGGGCACCAGTCAGCTACCCTGGTGGGAATCT GGGTAGCC
VOYTaumiR-127-582	5047	5' flanking to 3' flanking	GAAGCAAAGAAGGGGCAGAGGGAGCCCGTGAGCTGAGTGGGCCAGG GACTGGGAGAAGGAGTGAGGAGGCAGGGCCGGCATGCCTCTGCTGC TGGCCAGACCTCGCAGTTCGGTTAATTCTGTCTGCACCTGTCACTA GTATTAACCGAACTGCGAGGTTTGGCCGTGTAGTGCTACCCAGCGC TGGCTGCCTCCTCAGCATTGCAATTCCTCTCCCATCTGGGCACCAG TCAGCTACCCTGGTGGGAATCTGGGTAGCC
	4355	5' flanking	GAAGCAAAGAAGGGGCAGAGGGAGCCCGTGAGCTGAGTGGGCCAGG GACTGGGAGAAGGAGTGAGGAGGCAGGGCCGGCATGCCTCTGCTGC TGGCCAGA
	5051	Passenger Strand (DNA)	CCTCGCAGTTCGGTTAATT
	5052	Passenger Strand (RNA)	CCUCGCAGUUCGGUUAAUU

	5053	Passenger Strand (DNA) v2	CCTCGCAGTTCGGTTAATTCT
	5054	Passenger Strand (RNA) v2	CCUCGCAGUUCGGUUAAUUCU
	4366	Loop	GTCTGCACCTGTCACTAG
	5055	Guide Strand (DNA)	TATTAACCGAACTGCGAGG
	4694	Guide Strand (RNA)	UAUUAACCGAACUGCGAGG
	5056	Guide Strand (DNA) v2	TATTAACCGAACTGCGAGGTT
	5057	Guide Strand (RNA) v2	UAUUAACCGAACUGCGAGGUU
	4375	3' Flanking	TGGCCGTGTAGTGCTACCCAGCGCTGGCTGCCTCCTCAGCATTGCA ATTCCTCTCCCATCTGGGCACCAGTCAGCTACCCTGGTGGGAATCT GGGTAGCC
VOYTaumiR-102-530	4380	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAAGACTGGAAGCGATGACAACCCTGTGACCTGGTTTGTCA TCGCTTCCAGTCTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	4410	Passenger Strand (DNA)	GACTGGAAGCGATGACAAC
	4495	Passenger Strand (RNA)	GACUGGAAGCGAUGACAAC
	4925	Passenger Strand (DNA) v2	GACTGGAAGCGATGACAACCC
	4926	Passenger Strand (RNA) v2	GACUGGAAGCGAUGACAACCC
	4362	Loop	TGTGACCTGG
	4434	Guide Strand (DNA)	TTTGTCATCGCTTCCAGTC
	4697	Guide Strand (RNA)	UUUGUCAUCGCUUCCAGUC
	4907	Guide Strand (DNA) v2	TTTGTCATCGCTTCCAGTCTT
	4908	Guide Strand (RNA) v2	UUUGUCAUCGCUUCCAGUCUU
	4373	3' Flanking	CTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-102-556	4381	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAACTTCCGCGAGAACGCCAACCCTGTGACCTGGTTTGGCG TTCTCGCGGAAGTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	4411	Passenger Strand (DNA)	CTTCCGCGAGAACGCCAAC
	4506	Passenger Strand (RNA)	CUUCCGCGAGAACGCCAAC
	4929	Passenger Strand (DNA) v2	CTTCCGCGAGAACGCCAACCC
	4930	Passenger Strand (RNA) v2	CUUCCGCGAGAACGCCAACCC

	4362	Loop	TGTGACCTGG
	4435	Guide Strand (DNA)	TTTGGCGTTCTCGCGGAAG
	4701	Guide Strand (RNA)	UUUGGCGUUCUCGCGGAAG
	4911	Guide Strand (DNA) v2	TTTGGCGTTCTCGCGGAAGTT
	4912	Guide Strand (RNA) v2	UUUGGCGUUCUCGCGGAAGUU
	4373	3' Flanking	CTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-102-564	4382	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAAGCATCGACATGGTAGACTCCCTGTGACCTGGTAGTCTA CCATGTCGATGCTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	4412	Passenger Strand (DNA)	GCATCGACATGGTAGACTC
	4485	Passenger Strand (RNA)	GCAUCGACAUGGUAGACUC
	4933	Passenger Strand (DNA) v2	GCATCGACATGGTAGACTCCC
	4934	Passenger Strand (RNA) v2	GCAUCGACAUGGUAGACUCCC
	4362	Loop	TGTGACCTGG
	4436	Guide Strand (DNA)	TAGTCTACCATGTCGATGC
	4691	Guide Strand (RNA)	UAGUCUACCAUGUCGAUGC
	4915	Guide Strand (DNA) v2	TAGTCTACCATGTCGATGCTT
	4916	Guide Strand (RNA) v2	UAGUCUACCAUGUCGAUGCUU
	4373	3' Flanking	CTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-102-579	4383	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAAGCTCCTCGCAGTTCGGTTCCCTGTGACCTGGTAACCGA ACTGCGAGGAGCTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	4413	Passenger Strand (DNA)	GCTCCTCGCAGTTCGGTTC
	4502	Passenger Strand (RNA)	GCUCCUCGCAGUUCGGUUC
	4937	Passenger Strand (DNA) v2	GCTCCTCGCAGTTCGGTTCCC
	4938	Passenger Strand (RNA) v2	GCUCCUCGCAGUUCGGUUCCC
	4362	Loop	TGTGACCTGG
	4437	Guide Strand (DNA)	TAACCGAACTGCGAGGAGC
	4700	Guide Strand (RNA)	UAACCGAACUGCGAGGAGC

	4919	Guide Strand (DNA) v2	TAACCGAACTGCGAGGAGCTT
	4920	Guide Strand (RNA) v2	UAACCGAACUGCGAGGAGCUU
	4373	3' Flanking	CTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-102-586	4384	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAAGGCTTTGGCTCGGGACTTCCCTGTGACCTGGTAAGTCC CGAGCCAAAGCCTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	4414	Passenger Strand (DNA)	GGCTTTGGCTCGGGACTTC
	4480	Passenger Strand (RNA)	GGCUUUGGCUCGGGACUUC
	4941	Passenger Strand (DNA) v2	GGCTTTGGCTCGGGACTTCCC
	4942	Passenger Strand (RNA) v2	GGCUUUGGCUCGGGACUUCCC
	4362	Loop	TGTGACCTGG
	4438	Guide Strand (DNA)	TAAGTCCCGAGCCAAAGCC
	4690	Guide Strand (RNA)	UAAGUCCCGAGCCAAAGCC
	4923	Guide Strand (DNA) v2	TAAGTCCCGAGCCAAAGCCTT
	4924	Guide Strand (RNA) v2	UAAGUCCCGAGCCAAAGCCUU
	4373	3' Flanking	CTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-102-582	5027	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAACCTCGCAGTTCGGTTAATCCCTGTGACCTGGTATTAAC CGAACTGCGAGGTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	5058	Passenger Strand (DNA)	CCTCGCAGTTCGGTTAATC
	4492	Passenger Strand (RNA)	CCUCGCAGUUCGGUUAAUC
	5059	Passenger Strand (DNA) v2	CCTCGCAGTTCGGTTAATCCC
	5060	Passenger Strand (RNA) v2	CCUCGCAGUUCGGUUAAUCCC
	4362	Loop	TGTGACCTGG
	5055	Guide Strand (DNA)	TATTAACCGAACTGCGAGG
	4694	Guide Strand (RNA)	UAUUAACCGAACUGCGAGG
	5056	Guide Strand (DNA) v2	TATTAACCGAACTGCGAGGTT
	5057	Guide Strand (RNA) v2	UAUUAACCGAACUGCGAGGUU

	4373	3' Flanking	CTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-104-530	4385	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAAGACTGGAAGCGATGACAAACCTGTGACCTGGTTTGTCA TCGCTTCCAGTCTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	4415	Passenger Strand (DNA)	GACTGGAAGCGATGACAAA
	4496	Passenger Strand (RNA)	GACUGGAAGCGAUGACAAA
	4945	Passenger Strand (DNA) v2	GACTGGAAGCGATGACAAACC
	4946	Passenger Strand (RNA) v2	GACUGGAAGCGAUGACAAACC
	4362	Loop	TGTGACCTGG
	4434	Guide Strand (DNA)	TTTGTCATCGCTTCCAGTC
	4697	Guide Strand (RNA)	UUUGUCAUCGCUUCCAGUC
	4907	Guide Strand (DNA) v2	TTTGTCATCGCTTCCAGTCTT
	4908	Guide Strand (RNA) v2	UUUGUCAUCGCUUCCAGUCUU
	4373	3' Flanking	CTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-104-556	4386	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAACTTCCGCGAGAACGCCAAACCTGTGACCTGGTTTGGCG TTCTCGCGGAAGTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	4416	Passenger Strand (DNA)	CTTCCGCGAGAACGCCAAA
	4507	Passenger Strand (RNA)	CUUCCGCGAGAACGCCAAA
	4949	Passenger Strand (DNA) v2	CTTCCGCGAGAACGCCAAACC
	4950	Passenger Strand (RNA) v2	CUUCCGCGAGAACGCCAAACC
	4362	Loop	TGTGACCTGG
	4435	Guide Strand (DNA)	TTTGGCGTTCTCGCGGAAG
	4701	Guide Strand (RNA)	UUUGGCGUUCUCGCGGAAG
	4911	Guide Strand (DNA) v2	TTTGGCGTTCTCGCGGAAGTT
	4912	Guide Strand (RNA) v2	UUUGGCGUUCUCGCGGAAGUU
	4373	3' Flanking	CTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-104-564	4387	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAAGCATCGACATGGTAGACTACCTGTGACCTGGTAGTCTA CCATGTCGATGCTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA

	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	4417	Passenger Strand (DNA)	GCATCGACATGGTAGACTA
	4486	Passenger Strand (RNA)	GCAUCGACAUGGUAGACUA
	4953	Passenger Strand (DNA) v2	GCATCGACATGGTAGACTACC
	4954	Passenger Strand (RNA) v2	GCAUCGACAUGGUAGACUACC
	4362	Loop	TGTGACCTGG
	4436	Guide Strand (DNA)	TAGTCTACCATGTCGATGC
	4691	Guide Strand (RNA)	UAGUCUACCAUGUCGAUGC
	4915	Guide Strand (DNA) v2	TAGTCTACCATGTCGATGCTT
	4916	Guide Strand (RNA) v2	UAGUCUACCAUGUCGAUGCUU
	4373	3' Flanking	CTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-104-579	4388	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAAGCTCCTCGCAGTTCGGTTGCCTGTGACCTGGTAACCGA ACTGCGAGGAGCTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	4418	Passenger Strand (DNA)	GCTCCTCGCAGTTCGGTTG
	4503	Passenger Strand (RNA)	GCUCCUCGCAGUUCGGUUG
	4957	Passenger Strand (DNA) v2	GCTCCTCGCAGTTCGGTTGCC
	4958	Passenger Strand (RNA) v2	GCUCCUCGCAGUUCGGUUGCC
	4362	Loop	TGTGACCTGG
	4437	Guide Strand (DNA)	TAACCGAACTGCGAGGAGC
	4700	Guide Strand (RNA)	UAACCGAACUGCGAGGAGC
	4919	Guide Strand (DNA) v2	TAACCGAACTGCGAGGAGCTT
	4920	Guide Strand (RNA) v2	UAACCGAACUGCGAGGAGCUU
	4373	3' Flanking	CTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-104-586	4389	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAAGGCTTTGGCTCGGGACTTACCTGTGACCTGGTAAGTCC CGAGCCAAAGCCTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	4419	Passenger Strand (DNA)	GGCTTTGGCTCGGGACTTA

	4481	Passenger Strand (RNA)	GGCUUUGGCUCGGGACUUA
	4961	Passenger Strand (DNA) v2	GGCTTTGGCTCGGGACTTACC
	4962	Passenger Strand (RNA) v2	GGCUUUGGCUCGGGACUUACC
	4362	Loop	TGTGACCTGG
	4438	Guide Strand (DNA)	TAAGTCCCGAGCCAAAGCC
	4690	Guide Strand (RNA)	UAAGUCCCGAGCCAAAGCC
	4923	Guide Strand (DNA) v2	TAAGTCCCGAGCCAAAGCCTT
	4924	Guide Strand (RNA) v2	UAAGUCCCGAGCCAAAGCCUU
	4373	3' Flanking	CTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-104-582	5031	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAACCTCGCAGTTCGGTTAATACCTGTGACCTGGTATTAAC CGAACTGCGAGGTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	5061	Passenger Strand (DNA)	CCTCGCAGTTCGGTTAATA
	5062	Passenger Strand (RNA)	CCUCGCAGUUCGGUUAAUA
	5063	Passenger Strand (DNA) v2	CCTCGCAGTTCGGTTAATACC
	5064	Passenger Strand (RNA) v2	CCUCGCAGUUCGGUUAAUACC
	4362	Loop	TGTGACCTGG
	5055	Guide Strand (DNA)	TATTAACCGAACTGCGAGG
	4694	Guide Strand (RNA)	UAUUAACCGAACUGCGAGG
	5056	Guide Strand (DNA) v2	TATTAACCGAACTGCGAGGTT
	5057	Guide Strand (RNA) v2	UAUUAACCGAACUGCGAGGUU
	4373	3' Flanking	CTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-109-530	4390	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAAGACTGGAAGCGATGACAATCCTGTGATTTGGTTTGTCA TCGCTTCCAGTCTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	4420	Passenger Strand (DNA)	GACTGGAAGCGATGACAAT
	4497	Passenger Strand (RNA)	GACUGGAAGCGAUGACAAU
	4965	Passenger Strand (DNA) v2	GACTGGAAGCGATGACAATCC

	4966	Passenger Strand (RNA) v2	GACUGGAAGCGAUGACAAUCC
	4363	Loop	TGTGATTTGG
	4434	Guide Strand (DNA)	TTTGTCATCGCTTCCAGTC
	4697	Guide Strand (RNA)	UUUGUCAUCGCUUCCAGUC
	4907	Guide Strand (DNA) v2	TTTGTCATCGCTTCCAGTCTT
	4908	Guide Strand (RNA) v2	UUUGUCAUCGCUUCCAGUCUU
	4373	3' Flanking	CTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTCAGTGA
VOYTaumiR-109-556	4391	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCTCTTCGGAACTTCCGCGAGAACGCCAATCCTGTGATTTGGTTTGGCGTTCTCGCGGAAGTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCTCTTCGGAA
	4421	Passenger Strand (DNA)	CTTCCGCGAGAACGCCAAT
	4508	Passenger Strand (RNA)	CUUCCGCGAGAACGCCAAU
	4969	Passenger Strand (DNA) v2	CTTCCGCGAGAACGCCAATCC
	4970	Passenger Strand (RNA) v2	CUUCCGCGAGAACGCCAAUCC
	4363	Loop	TGTGATTTGG
	4435	Guide Strand (DNA)	TTTGGCGTTCTCGCGGAAG
	4701	Guide Strand (RNA)	UUUGGCGUUCUCGCGGAAG
	4911	Guide Strand (DNA) v2	TTTGGCGTTCTCGCGGAAGTT
	4912	Guide Strand (RNA) v2	UUUGGCGUUCUCGCGGAAGUU
	4373	3' Flanking	CTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTCAGTGA
VOYTaumiR-109-564	4392	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCTCTTCGGAAGCATCGACATGGTAGACTTCCTGTGATTTGGTAGTCTACCATGTCGATGCTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCTCTTCGGAA
	4422	Passenger Strand (DNA)	GCATCGACATGGTAGACTT
	4487	Passenger Strand (RNA)	GCAUCGACAUGGUAGACUU
	4973	Passenger Strand (DNA) v2	GCATCGACATGGTAGACTTCC
	4974	Passenger Strand (RNA) v2	GCAUCGACAUGGUAGACUUCC
	4363	Loop	TGTGATTTGG
	4436	Guide Strand (DNA)	TAGTCTACCATGTCGATGC

	4691	Guide Strand (RNA)	UAGUCUACCAUGUCGAUGC
	4915	Guide Strand (DNA) v2	TAGTCTACCATGTCGATGCTT
	4916	Guide Strand (RNA) v2	UAGUCUACCAUGUCGAUGCUU
	4373	3' Flanking	CTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-109-579	4393	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAAGCTCCTCGCAGTTCGGTTTCCTGTGATTTGGTAACCGA ACTGCGAGGAGCTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	4423	Passenger Strand (DNA)	GCTCCTCGCAGTTCGGTTT
	4504	Passenger Strand (RNA)	GCUCCUCGCAGUUCGGUUU
	4977	Passenger Strand (DNA) v2	GCTCCTCGCAGTTCGGTTTCC
	4978	Passenger Strand (RNA) v2	GCUCCUCGCAGUUCGGUUUCC
	4363	Loop	TGTGATTTGG
	4437	Guide Strand (DNA)	TAACCGAACTGCGAGGAGC
	4700	Guide Strand (RNA)	UAACCGAACUGCGAGGAGC
	4919	Guide Strand (DNA) v2	TAACCGAACTGCGAGGAGCTT
	4920	Guide Strand (RNA) v2	UAACCGAACUGCGAGGAGCUU
	4373	3' Flanking	CTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-109-586	4394	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAAGGCTTTGGCTCGGGACTTTCCTGTGATTTGGTAAGTCC CGAGCCAAAGCCTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	4424	Passenger Strand (DNA)	GGCTTTGGCTCGGGACTTT
	4482	Passenger Strand (RNA)	GGCUUUGGCUCGGGACUUU
	4981	Passenger Strand (DNA) v2	GGCTTTGGCTCGGGACTTTCC
	4982	Passenger Strand (RNA) v2	GGCUUUGGCUCGGGACUUUCC
	4363	Loop	TGTGATTTGG
	4438	Guide Strand (DNA)	TAAGTCCCGAGCCAAAGCC
	4690	Guide Strand (RNA)	UAAGUCCCGAGCCAAAGCC
	4923	Guide Strand (DNA) v2	TAAGTCCCGAGCCAAAGCCTT

	4924	Guide Strand (RNA) v2	UAAGUCCCGAGCCAAAGCCUU
	4373	3' Flanking	CTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-109-582	5035	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAACCTCGCAGTTCGGTTAATTCCTGTGATTTGGTATTAAC CGAACTGCGAGGTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	5051	Passenger Strand (DNA)	CCTCGCAGTTCGGTTAATT
	5052	Passenger Strand (RNA)	CCUCGCAGUUCGGUUAAUU
	5065	Passenger Strand (DNA) v2	CCTCGCAGTTCGGTTAATTCC
	5066	Passenger Strand (RNA) v2	CCUCGCAGUUCGGUUAAUUCC
	4363	Loop	TGTGATTTGG
	5055	Guide Strand (DNA)	TATTAACCGAACTGCGAGG
	4694	Guide Strand (RNA)	UAUUAACCGAACUGCGAGG
	5056	Guide Strand (DNA) v2	TATTAACCGAACTGCGAGGTT
	5057	Guide Strand (RNA) v2	UAUUAACCGAACUGCGAGGUU
	4373	3' Flanking	CTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-114-530	4395	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAAGACTGGAAGGGATGACAACCCTGTGACCTGGTTTGTCA TCGCTTCCAGTCTTCTGTGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	4425	Passenger Strand (DNA)	GACTGGAAGGGATGACAAC
	4498	Passenger Strand (RNA)	GACUGGAAGGGAUGACAAC
	4985	Passenger Strand (DNA) v2	GACTGGAAGGGATGACAACCC
	4986	Passenger Strand (RNA) v2	GACUGGAAGGGAUGACAACCC
	4362	Loop	TGTGACCTGG
	4434	Guide Strand (DNA)	TTTGTCATCGCTTCCAGTC
	4697	Guide Strand (RNA)	UUUGUCAUCGCUUCCAGUC
	4907	Guide Strand (DNA) v2	TTTGTCATCGCTTCCAGTCTT
	4908	Guide Strand (RNA) v2	UUUGUCAUCGCUUCCAGUCUU
	4374	3' Flanking	CTGTGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA

VOYTaumiR-114-556	4396	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAACTTCCGCGACAACGCCAACCCTGTGACCTGGTTTGGCG TTCTCGCGGAAGTTCTGTGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	4426	Passenger Strand (DNA)	CTTCCGCGACAACGCCAAC
	4509	Passenger Strand (RNA)	CUUCCGCGACAACGCCAAC
	4989	Passenger Strand (DNA) v2	CTTCCGCGACAACGCCAACCC
	4990	Passenger Strand (RNA) v2	CUUCCGCGACAACGCCAACCC
	4362	Loop	TGTGACCTGG
	4435	Guide Strand (DNA)	TTTGGCGTTCTCGCGGAAG
	4701	Guide Strand (RNA)	UUUGGCGUUCUCGCGGAAG
	4911	Guide Strand (DNA) v2	TTTGGCGTTCTCGCGGAAGTT
	4912	Guide Strand (RNA) v2	UUUGGCGUUCUCGCGGAAGUU
	4374	3' Flanking	CTGTGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-114-564	4397	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAAGCATCGACAAGGTAGACTCCCTGTGACCTGGTAGTCTA CCATGTCGATGCTTCTGTGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	4427	Passenger Strand (DNA)	GCATCGACAAGGTAGACTC
	4488	Passenger Strand (RNA)	GCAUCGACAAGGUAGACUC
	4993	Passenger Strand (DNA) v2	GCATCGACAAGGTAGACTCCC
	4994	Passenger Strand (RNA) v2	GCAUCGACAAGGUAGACUCCC
	4362	Loop	TGTGACCTGG
	4436	Guide Strand (DNA)	TAGTCTACCATGTCGATGC
	4691	Guide Strand (RNA)	UAGUCUACCAUGUCGAUGC
	4915	Guide Strand (DNA) v2	TAGTCTACCATGTCGATGCTT
	4916	Guide Strand (RNA) v2	UAGUCUACCAUGUCGAUGCUU
	4374	3' Flanking	CTGTGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-114-579	4398	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAAGCTCCTCGCTGTTCGGTTCCCTGTGACCTGGTAACCGA ACTGCGAGGAGCTTCTGTGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA

	4428	Passenger Strand (DNA)	GCTCCTCGCTGTTCGGTTC
	4505	Passenger Strand (RNA)	GCUCCUCGCUGUUCGGUUC
	4997	Passenger Strand (DNA) v2	GCTCCTCGCTGTTCGGTTCCC
	4998	Passenger Strand (RNA) v2	GCUCCUCGCUGUUCGGUUCCC
	4362	Loop	TGTGACCTGG
	4437	Guide Strand (DNA)	TAACCGAACTGCGAGGAGC
	4700	Guide Strand (RNA)	UAACCGAACUGCGAGGAGC
	4919	Guide Strand (DNA) v2	TAACCGAACTGCGAGGAGCTT
	4920	Guide Strand (RNA) v2	UAACCGAACUGCGAGGAGCUU
	4374	3' Flanking	CTGTGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-114-586	4399	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAAGGCTTTGGCACGGGACTTCCCTGTGACCTGGTAAGTCC CGAGCCAAAGCCTTCTGTGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	4429	Passenger Strand (DNA)	GGCTTTGGCACGGGACTTC
	4483	Passenger Strand (RNA)	GGCUUUGGCACGGGACUUC
	5001	Passenger Strand (DNA) v2	GGCTTTGGCACGGGACTTCCC
	5002	Passenger Strand (RNA) v2	GGCUUUGGCACGGGACUUCCC
	4362	Loop	TGTGACCTGG
	4438	Guide Strand (DNA)	TAAGTCCCGAGCCAAAGCC
	4690	Guide Strand (RNA)	UAAGUCCCGAGCCAAAGCC
	4923	Guide Strand (DNA) v2	TAAGTCCCGAGCCAAAGCCTT
	4924	Guide Strand (RNA) v2	UAAGUCCCGAGCCAAAGCCUU
	4374	3' Flanking	CTGTGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-114-582	5039	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAACCTCGCAGTACGGTTAATCCCTGTGACCTGGTATTAAC CGAACTGCGAGGTTCTGTGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	5067	Passenger Strand (DNA)	CCTCGCAGTACGGTTAATC
	5068	Passenger Strand (RNA)	CCUCGCAGUACGGUUAAUC

	5069	Passenger Strand (DNA) v2	CCTCGCAGTACGGTTAATCCC
	5070	Passenger Strand (RNA) v2	CCUCGCAGUACGGUUAAUCCC
	4362	Loop	TGTGACCTGG
	5055	Guide Strand (DNA)	TATTAACCGAACTGCGAGG
	4694	Guide Strand (RNA)	UAUUAACCGAACUGCGAGG
	5056	Guide Strand (DNA) v2	TATTAACCGAACTGCGAGGTT
	5057	Guide Strand (RNA) v2	UAUUAACCGAACUGCGAGGUU
	4374	3' Flanking	CTGTGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-116-530	4400	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAAGACTGGAAGCGATGACAAGCCTGTGACCTGGTTTGTCA TCGCTTCCAGTCTTCTGTGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	4430	Passenger Strand (DNA)	GACTGGAAGCGATGACAAG
	4499	Passenger Strand (RNA)	GACUGGAAGCGAUGACAAG
	5005	Passenger Strand (DNA) v2	GACTGGAAGCGATGACAAGCC
	5006	Passenger Strand (RNA) v2	GACUGGAAGCGAUGACAAGCC
	4362	Loop	TGTGACCTGG
	4434	Guide Strand (DNA)	TTTGTCATCGCTTCCAGTC
	4697	Guide Strand (RNA)	UUUGUCAUCGCUUCCAGUC
	4907	Guide Strand (DNA) v2	TTTGTCATCGCTTCCAGTCTT
	4908	Guide Strand (RNA) v2	UUUGUCAUCGCUUCCAGUCUU
	4374	3' Flanking	CTGTGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-116-556	4401	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAACTTCCGCGAGAACGCCAAGCCTGTGACCTGGTTTGGCG TTCTCGCGGAAGTTCTGTGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	4431	Passenger Strand (DNA)	CTTCCGCGAGAACGCCAAG
	4510	Passenger Strand (RNA)	CUUCCGCGAGAACGCCAAG
	5009	Passenger Strand (DNA) v2	CTTCCGCGAGAACGCCAAGCC
	5010	Passenger Strand (RNA) v2	CUUCCGCGAGAACGCCAAGCC
	4362	Loop	TGTGACCTGG

	4435	Guide Strand (DNA)	TTTGGCGTTCTCGCGGAAG
	4701	Guide Strand (RNA)	UUUGGCGUUCUCGCGGAAG
	4911	Guide Strand (DNA) v2	TTTGGCGTTCTCGCGGAAGTT
	4912	Guide Strand (RNA) v2	UUUGGCGUUCUCGCGGAAGUU
	4374	3' Flanking	CTGTGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-116-564	4402	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAAGCATCGACATGGTAGACTGCCTGTGACCTGGTAGTCTA CCATGTCGATGCTTCTGTGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	4432	Passenger Strand (DNA)	GCATCGACATGGTAGACTG
	4489	Passenger Strand (RNA)	GCAUCGACAUGGUAGACUG
	5013	Passenger Strand (DNA) v2	GCATCGACATGGTAGACTGCC
	5014	Passenger Strand (RNA) v2	GCAUCGACAUGGUAGACUGCC
	4362	Loop	TGTGACCTGG
	4436	Guide Strand (DNA)	TAGTCTACCATGTCGATGC
	4691	Guide Strand (RNA)	UAGUCUACCAUGUCGAUGC
	4915	Guide Strand (DNA) v2	TAGTCTACCATGTCGATGCTT
	4916	Guide Strand (RNA) v2	UAGUCUACCAUGUCGAUGCUU
	4374	3' Flanking	CTGTGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-116-579	4403	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAAGCTCCTCGCAGTTCGGTTGCCTGTGACCTGGTAACCGA ACTGCGAGGAGCTTCTGTGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	4418	Passenger Strand (DNA)	GCTCCTCGCAGTTCGGTTG
	4503	Passenger Strand (RNA)	GCUCCUCGCAGUUCGGUUG
	4957	Passenger Strand (DNA) v2	GCTCCTCGCAGTTCGGTTGCC
	4958	Passenger Strand (RNA) v2	GCUCCUCGCAGUUCGGUUGCC
	4362	Loop	TGTGACCTGG
	4437	Guide Strand (DNA)	TAACCGAACTGCGAGGAGC
	4700	Guide Strand (RNA)	UAACCGAACUGCGAGGAGC

	4919	Guide Strand (DNA) v2	TAACCGAACTGCGAGGAGCTT
	4920	Guide Strand (RNA) v2	UAACCGAACUGCGAGGAGCUU
	4374	3' Flanking	CTGTGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-116-586	4404	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAAGGCTTTGGCTCGGGACTTGCCTGTGACCTGGTAAGTCC CGAGCCAAAGCCTTCTGTGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	4433	Passenger Strand (DNA)	GGCTTTGGCTCGGGACTTG
	4484	Passenger Strand (RNA)	GGCUUUGGCUCGGGACUUG
	5021	Passenger Strand (DNA) v2	GGCTTTGGCTCGGGACTTGCC
	5022	Passenger Strand (RNA) v2	GGCUUUGGCUCGGGACUUGCC
	4362	Loop	TGTGACCTGG
	4438	Guide Strand (DNA)	TAAGTCCCGAGCCAAAGCC
	4690	Guide Strand (RNA)	UAAGUCCCGAGCCAAAGCC
	4923	Guide Strand (DNA) v2	TAAGTCCCGAGCCAAAGCCTT
	4924	Guide Strand (RNA) v2	UAAGUCCCGAGCCAAAGCCUU
	4374	3' Flanking	CTGTGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-116-582	5043	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAACCTCGCAGTTCGGTTAATGCCTGTGACCTGGTATTAAC CGAACTGCGAGGTTCTGTGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	5071	Passenger Strand (DNA)	CCTCGCAGTTCGGTTAATG
	5072	Passenger Strand (RNA)	CCUCGCAGUUCGGUUAAUG
	5073	Passenger Strand (DNA) v2	CCTCGCAGTTCGGTTAATGCC
	5074	Passenger Strand (RNA) v2	CCUCGCAGUUCGGUUAAUGCC
	4362	Loop	TGTGACCTGG
	5055	Guide Strand (DNA)	TATTAACCGAACTGCGAGG
	4694	Guide Strand (RNA)	UAUUAACCGAACUGCGAGG
	5056	Guide Strand (DNA) v2	TATTAACCGAACTGCGAGGTT
	5057	Guide Strand (RNA) v2	UAUUAACCGAACUGCGAGGUU

	4374	3' Flanking	CTGTGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-102-587	5028	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAAGCTTTGGCTCGGGACTTCCCCTGTGACCTGGTGAAGTC CCGAGCCAAAGCTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	5075	Passenger Strand (DNA)	GCTTTGGCTCGGGACTTCC
	4477	Passenger Strand (RNA)	GCUUUGGCUCGGGACUUCC
	5076	Passenger Strand (DNA) v2	GCTTTGGCTCGGGACTTCCCC
	5077	Passenger Strand (RNA) v2	GCUUUGGCUCGGGACUUCCCC
	4362	Loop	TGTGACCTGG
	5078	Guide Strand (DNA)	TGAAGTCCCGAGCCAAAGC
	4687	Guide Strand (RNA)	UGAAGUCCCGAGCCAAAGC
	5079	Guide Strand (DNA) v2	TGAAGTCCCGAGCCAAAGCTT
	5080	Guide Strand (RNA) v2	UGAAGUCCCGAGCCAAAGCUU
	4373	3' Flanking	CTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-104-587	5032	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAAGCTTTGGCTCGGGACTTCACCTGTGACCTGGTGAAGTC CCGAGCCAAAGCTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	5081	Passenger Strand (DNA)	GCTTTGGCTCGGGACTTCA
	5082	Passenger Strand (RNA)	GCUUUGGCUCGGGACUUCA
	5083	Passenger Strand (DNA) v2	GCTTTGGCTCGGGACTTCACC
	5084	Passenger Strand (RNA) v2	GCUUUGGCUCGGGACUUCACC
	4362	Loop	TGTGACCTGG
	5078	Guide Strand (DNA)	TGAAGTCCCGAGCCAAAGC
	4687	Guide Strand (RNA)	UGAAGUCCCGAGCCAAAGC
	5079	Guide Strand (DNA) v2	TGAAGTCCCGAGCCAAAGCTT
	5080	Guide Strand (RNA) v2	UGAAGUCCCGAGCCAAAGCUU
	4373	3' Flanking	CTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-109-587	5036	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAAGCTTTGGCTCGGGACTTCTCCTGTGATTTGGTGAAGTC CCGAGCCAAAGCTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA

	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	5085	Passenger Strand (DNA)	GCTTTGGCTCGGGACTTCT
	5086	Passenger Strand (RNA)	GCUUUGGCUCGGGACUUCU
	5087	Passenger Strand (DNA) v2	GCTTTGGCTCGGGACTTCTCC
	5088	Passenger Strand (RNA) v2	GCUUUGGCUCGGGACUUCUCC
	4363	Loop	TGTGATTTGG
	5078	Guide Strand (DNA)	TGAAGTCCCGAGCCAAAGC
	4687	Guide Strand (RNA)	UGAAGUCCCGAGCCAAAGC
	5079	Guide Strand (DNA) v2	TGAAGTCCCGAGCCAAAGCTT
	5080	Guide Strand (RNA) v2	UGAAGUCCCGAGCCAAAGCUU
	4373	3' Flanking	CTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-114-587	5040	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAAGCTTTGGCTGGGGACTTCCCCTGTGACCTGGTGAAGTC CCGAGCCAAAGCTTCTGTGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	5089	Passenger Strand (DNA)	GCTTTGGCTGGGGACTTCC
	5090	Passenger Strand (RNA)	GCUUUGGCUGGGGACUUCC
	5091	Passenger Strand (DNA) v2	GCTTTGGCTGGGGACTTCCCC
	5092	Passenger Strand (RNA) v2	GCUUUGGCUGGGGACUUCCCC
	4362	Loop	TGTGACCTGG
	5078	Guide Strand (DNA)	TGAAGTCCCGAGCCAAAGC
	4687	Guide Strand (RNA)	UGAAGUCCCGAGCCAAAGC
	5079	Guide Strand (DNA) v2	TGAAGTCCCGAGCCAAAGCTT
	5080	Guide Strand (RNA) v2	UGAAGUCCCGAGCCAAAGCUU
	4374	3' Flanking	CTGTGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-116-587	5044	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAAGCTTTGGCTCGGGACTTCGCCTGTGACCTGGTGAAGTC CCGAGCCAAAGCTTCTGTGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	5093	Passenger Strand (DNA)	GCTTTGGCTCGGGACTTCG

	5094	Passenger Strand (RNA)	GCUUUGGCUCGGGACUUCG
	5095	Passenger Strand (DNA) v2	GCTTTGGCTCGGGACTTCGCC
	5096	Passenger Strand (RNA) v2	GCUUUGGCUCGGGACUUCGCC
	4362	Loop	TGTGACCTGG
	5078	Guide Strand (DNA)	TGAAGTCCCGAGCCAAAGC
	4687	Guide Strand (RNA)	UGAAGUCCCGAGCCAAAGC
	5079	Guide Strand (DNA) v2	TGAAGTCCCGAGCCAAAGCTT
	5080	Guide Strand (RNA) v2	UGAAGUCCCGAGCCAAAGCUU
	4374	3' Flanking	CTGTGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTCAGTGA
VOYTaumiR-127-587	5048	5' flanking to 3' flanking	GAAGCAAAGAAGGGGCAGAGGGAGCCCGTGAGCTGAGTGGGCCAGGGACTGGGAGAAGGAGTGAGGAGGCAGGGCCGGCATGCCTCTGCTGCTGGCCAGAGCTTTGGCTCGGGACTTCTCTGTCTGCACCTGTCACTAGTGAAGTCCCGAGCCAAAGCTTTGGCCGTGTAGTGCTACCCAGCGCTGGCTGCCTCCTCAGCATTGCAATTCCTCTCCCATCTGGGCACCAGTCAGCTACCCTGGTGGGAATCTGGGTAGCC
	4355	5' flanking	GAAGCAAAGAAGGGGCAGAGGGAGCCCGTGAGCTGAGTGGGCCAGGGACTGGGAGAAGGAGTGAGGAGGCAGGGCCGGCATGCCTCTGCTGCTGGCCAGA
	5085	Passenger Strand (DNA)	GCTTTGGCTCGGGACTTCT
	5086	Passenger Strand (RNA)	GCUUUGGCUCGGGACUUCU
	5097	Passenger Strand (DNA) v2	GCTTTGGCTCGGGACTTCTCT
	5098	Passenger Strand (RNA) v2	GCUUUGGCUCGGGACUUCUCU
	4366	Loop	GTCTGCACCTGTCACTAG
	5078	Guide Strand (DNA)	TGAAGTCCCGAGCCAAAGC
	4687	Guide Strand (RNA)	UGAAGUCCCGAGCCAAAGC
	5079	Guide Strand (DNA) v2	TGAAGTCCCGAGCCAAAGCTT
	5080	Guide Strand (RNA) v2	UGAAGUCCCGAGCCAAAGCUU
	4375	3' Flanking	TGGCCGTGTAGTGCTACCCAGCGCTGGCTGCCTCCTCAGCATTGCAATTCCTCTCCCATCTGGGCACCAGTCAGCTACCCTGGTGGGAATCTGGGTAGCC
VOYTaumiR-102-552	5029	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCTCTTCGGAAAGCTGACCTTCCGCGAGACCCTGTGACCTGGTTCTCGCGGAAGGTCAGCTTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCTCTTCGGAA
	5099	Passenger Strand (DNA)	AGCTGACCTTCCGCGAGAC
	4494	Passenger Strand (RNA)	AGCUGACCUUCCGCGAGAC

	5100	Passenger Strand (DNA) v2	AGCTGACCTTCCGCGAGACCC
	5101	Passenger Strand (RNA) v2	AGCUGACCUUCCGCGAGACCC
	4362	Loop	TGTGACCTGG
	5102	Guide Strand (DNA)	TTCTCGCGGAAGGTCAGCT
	4696	Guide Strand (RNA)	UUCUCGCGGAAGGUCAGCU
	5103	Guide Strand (DNA) v2	TTCTCGCGGAAGGTCAGCTTT
	5104	Guide Strand (RNA) v2	UUCUCGCGGAAGGUCAGCUUU
	4373	3' Flanking	CTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-104-552	5033	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAAAGCTGACCTTCCGCGAGAACCTGTGACCTGGTTCTCGC GGAAGGTCAGCTTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	5105	Passenger Strand (DNA)	AGCTGACCTTCCGCGAGAA
	5106	Passenger Strand (RNA)	AGCUGACCUUCCGCGAGAA
	5107	Passenger Strand (DNA) v2	AGCTGACCTTCCGCGAGAACC
	5108	Passenger Strand (RNA) v2	AGCUGACCUUCCGCGAGAACC
	4362	Loop	TGTGACCTGG
	5102	Guide Strand (DNA)	TTCTCGCGGAAGGTCAGCT
	4696	Guide Strand (RNA)	UUCUCGCGGAAGGUCAGCU
	5103	Guide Strand (DNA) v2	TTCTCGCGGAAGGTCAGCTTT
	5104	Guide Strand (RNA) v2	UUCUCGCGGAAGGUCAGCUUU
	4373	3' Flanking	CTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-109-552	5037	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAAAGCTGACCTTCCGCGAGATCCTGTGATTTGGTTCTCGC GGAAGGTCAGCTTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	5109	Passenger Strand (DNA)	AGCTGACCTTCCGCGAGAT
	5110	Passenger Strand (RNA)	AGCUGACCUUCCGCGAGAU
	5111	Passenger Strand (DNA) v2	AGCTGACCTTCCGCGAGATCC
	5112	Passenger Strand (RNA) v2	AGCUGACCUUCCGCGAGAUCC
	4363	Loop	TGTGATTTGG

	5102	Guide Strand (DNA)	TTCTCGCGGAAGGTCAGCT
	4696	Guide Strand (RNA)	UUCUCGCGGAAGGUCAGCU
	5103	Guide Strand (DNA) v2	TTCTCGCGGAAGGTCAGCTTT
	5104	Guide Strand (RNA) v2	UUCUCGCGGAAGGUCAGCUUU
	4373	3' Flanking	CTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-114-552	5041	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAAAGCTGACCTACCGCGAGACCCTGTGACCTGGTTCTCGC GGAAGGTCAGCTTTCTGTGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	5113	Passenger Strand (DNA)	AGCTGACCTACCGCGAGAC
	5114	Passenger Strand (RNA)	AGCUGACCUACCGCGAGAC
	5115	Passenger Strand (DNA) v2	AGCTGACCTACCGCGAGACCC
	5116	Passenger Strand (RNA) v2	AGCUGACCUACCGCGAGACCC
	4362	Loop	TGTGACCTGG
	5102	Guide Strand (DNA)	TTCTCGCGGAAGGTCAGCT
	4696	Guide Strand (RNA)	UUCUCGCGGAAGGUCAGCU
	5103	Guide Strand (DNA) v2	TTCTCGCGGAAGGTCAGCTTT
	5104	Guide Strand (RNA) v2	UUCUCGCGGAAGGUCAGCUUU
	4374	3' Flanking	CTGTGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-116-552	5045	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAAAGCTGACCTTCCGCGAGAGCCTGTGACCTGGTTCTCGC GGAAGGTCAGCTTTCTGTGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	5117	Passenger Strand (DNA)	AGCTGACCTTCCGCGAGAG
	5118	Passenger Strand (RNA)	AGCUGACCUUCCGCGAGAG
	5119	Passenger Strand (DNA) v2	AGCTGACCTTCCGCGAGAGCC
	5120	Passenger Strand (RNA) v2	AGCUGACCUUCCGCGAGAGCC
	4362	Loop	TGTGACCTGG
	5102	Guide Strand (DNA)	TTCTCGCGGAAGGTCAGCT
	4696	Guide Strand (RNA)	UUCUCGCGGAAGGUCAGCU

	5103	Guide Strand (DNA) v2	TTCTCGCGGAAGGTCAGCTTT
	5104	Guide Strand (RNA) v2	UUCUCGCGGAAGGUCAGCUUU
	4374	3' Flanking	CTGTGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-127-552	5049	5' flanking to 3' flanking	GAAGCAAAGAAGGGGCAGAGGGAGCCCGTGAGCTGAGTGGGCCAGG GACTGGGAGAAGGAGTGAGGAGGCAGGGCCGGCATGCCTCTGCTGC TGGCCAGAAGCTGACCTTCCGCGAGATCTGTCTGCACCTGTCACTA GTTCTCGCGGAAGGTCAGCTTTTGGCCGTGTAGTGCTACCCAGCGC TGGCTGCCTCCTCAGCATTGCAATTCCTCTCCCATCTGGGCACCAG TCAGCTACCCTGGTGGGAATCTGGGTAGCC
	4355	5' flanking	GAAGCAAAGAAGGGGCAGAGGGAGCCCGTGAGCTGAGTGGGCCAGG GACTGGGAGAAGGAGTGAGGAGGCAGGGCCGGCATGCCTCTGCTGC TGGCCAGA
	5109	Passenger Strand (DNA)	AGCTGACCTTCCGCGAGAT
	5110	Passenger Strand (RNA)	AGCUGACCUUCCGCGAGAU
	5121	Passenger Strand (DNA) v2	AGCTGACCTTCCGCGAGATCT
	5122	Passenger Strand (RNA) v2	AGCUGACCUUCCGCGAGAUCU
	4366	Loop	GTCTGCACCTGTCACTAG
	5102	Guide Strand (DNA)	TTCTCGCGGAAGGTCAGCT
	4696	Guide Strand (RNA)	UUCUCGCGGAAGGUCAGCU
	5103	Guide Strand (DNA) v2	TTCTCGCGGAAGGTCAGCTTT
	5104	Guide Strand (RNA) v2	UUCUCGCGGAAGGUCAGCUUU
	4375	3' Flanking	TGGCCGTGTAGTGCTACCCAGCGCTGGCTGCCTCCTCAGCATTGCA ATTCCTCTCCCATCTGGGCACCAGTCAGCTACCCTGGTGGGAATCT GGGTAGCC
VOYTaumiR-102-549	5030	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAAGCCGTCTTCCGCCAAGAGCCCTGTGACCTGGTCTCTTG GCGGAAGACGGCTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	5123	Passenger Strand (DNA)	GCCGTCTTCCGCCAAGAGC
	4527	Passenger Strand (RNA)	GCCGUCUUCCGCCAAGAGC
	5124	Passenger Strand (DNA) v2	GCCGTCTTCCGCCAAGAGCCC
	5125	Passenger Strand (RNA) v2	GCCGUCUUCCGCCAAGAGCCC
	4362	Loop	TGTGACCTGG
	5126	Guide Strand (DNA)	TCTCTTGGCGGAAGACGGC
	4718	Guide Strand (RNA)	UCUCUUGGCGGAAGACGGC
	5127	Guide Strand (DNA) v2	TCTCTTGGCGGAAGACGGCTT

	5128	Guide Strand (RNA) v2	UCUCUUGGCGGAAGACGGCUU
	4373	3' Flanking	CTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-104-549	5034	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAAGCCGTCTTCCGCCAAGAGACCTGTGACCTGGTCTCTTG GCGGAAGACGGCTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	5129	Passenger Strand (DNA)	GCCGTCTTCCGCCAAGAGA
	5130	Passenger Strand (RNA)	GCCGUCUUCCGCCAAGAGA
	5131	Passenger Strand (DNA) v2	GCCGTCTTCCGCCAAGAGACC
	5132	Passenger Strand (RNA) v2	GCCGUCUUCCGCCAAGAGACC
	4362	Loop	TGTGACCTGG
	5126	Guide Strand (DNA)	TCTCTTGGCGGAAGACGGC
	4718	Guide Strand (RNA)	UCUCUUGGCGGAAGACGGC
	5127	Guide Strand (DNA) v2	TCTCTTGGCGGAAGACGGCTT
	5128	Guide Strand (RNA) v2	UCUCUUGGCGGAAGACGGCUU
	4373	3' Flanking	CTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-109-549	5038	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAAGCCGTCTTCCGCCAAGAGTCCTGTGATTTGGTCTCTTG GCGGAAGACGGCTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	5133	Passenger Strand (DNA)	GCCGTCTTCCGCCAAGAGT
	5134	Passenger Strand (RNA)	GCCGUCUUCCGCCAAGAGU
	5135	Passenger Strand (DNA) v2	GCCGTCTTCCGCCAAGAGTCC
	5136	Passenger Strand (RNA) v2	GCCGUCUUCCGCCAAGAGUCC
	4363	Loop	TGTGATTTGG
	5126	Guide Strand (DNA)	TCTCTTGGCGGAAGACGGC
	4718	Guide Strand (RNA)	UCUCUUGGCGGAAGACGGC
	5127	Guide Strand (DNA) v2	TCTCTTGGCGGAAGACGGCTT
	5128	Guide Strand (RNA) v2	UCUCUUGGCGGAAGACGGCUU
	4373	3' Flanking	CTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA

VOYTaumiR-114-549	5042	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAAGCCGTCTTCGGCCAAGAGCCCTGTGACCTGGTCTCTTG GCGGAAGACGGCTTCTGTGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	5137	Passenger Strand (DNA)	GCCGTCTTCGGCCAAGAGC
	5138	Passenger Strand (RNA)	GCCGUCUUCGGCCAAGAGC
	5139	Passenger Strand (DNA) v2	GCCGTCTTCGGCCAAGAGCCC
	5140	Passenger Strand (RNA) v2	GCCGUCUUCGGCCAAGAGCCC
	4362	Loop	TGTGACCTGG
	5126	Guide Strand (DNA)	TCTCTTGGCGGAAGACGGC
	4718	Guide Strand (RNA)	UCUCUUGGCGGAAGACGGC
	5127	Guide Strand (DNA) v2	TCTCTTGGCGGAAGACGGCTT
	5128	Guide Strand (RNA) v2	UCUCUUGGCGGAAGACGGCUU
	4374	3' Flanking	CTGTGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-116-549	5046	5' flanking to 3' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAAGCCGTCTTCCGCCAAGAGGCCTGTGACCTGGTCTCTTG GCGGAAGACGGCTTCTGTGGAGCGCCTTGACAGCAGCCATGGGAGG GCCGCCCCCTACCTCAGTGA
	4354	5' flanking	GTGCTGGGCGGGGGGCGGCGGGCCCTCCCGCAGAACACCATGCGCT CTTCGGAA
	5141	Passenger Strand (DNA)	GCCGTCTTCCGCCAAGAGG
	5142	Passenger Strand (RNA)	GCCGUCUUCCGCCAAGAGG
	5143	Passenger Strand (DNA) v2	GCCGTCTTCCGCCAAGAGGCC
	5144	Passenger Strand (RNA) v2	GCCGUCUUCCGCCAAGAGGCC
	4362	Loop	TGTGACCTGG
	5126	Guide Strand (DNA)	TCTCTTGGCGGAAGACGGC
	4718	Guide Strand (RNA)	UCUCUUGGCGGAAGACGGC
	5127	Guide Strand (DNA) v2	TCTCTTGGCGGAAGACGGCTT
	5128	Guide Strand (RNA) v2	UCUCUUGGCGGAAGACGGCUU
	4374	3' Flanking	CTGTGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCT CAGTGA
VOYTaumiR-127-549	5050	5' flanking to 3' flanking	GAAGCAAAGAAGGGGCAGAGGGAGCCCGTGAGCTGAGTGGGCCAGG GACTGGGAGAAGGAGTGAGGAGGCAGGGCCGGCATGCCTCTGCTGC TGGCCAGAGCCGTCTTCCGCCAAGAGTCTGTCTGCACCTGTCACTA GTCTCTTGGCGGAAGACGGCTTTGGCCGTGTAGTGCTACCCAGCGC TGGCTGCCTCCTCAGCATTGCAATTCCTCTCCCATCTGGGCACCAG TCAGCTACCCTGGTGGGAATCTGGGTAGCC

	4355	5' flanking	GAAGCAAAGAAGGGGCAGAGGGAGCCCGTGAGCTGAGTGGGCCAGG GACTGGGAGAAGGAGTGAGGAGGCAGGGCCGGCATGCCTCTGCTGC TGGCCAGA
	5133	Passenger Strand (DNA)	GCCGTCTTCCGCCAAGAGT
	5134	Passenger Strand (RNA)	GCCGUCUUCCGCCAAGAGU
	5145	Passenger Strand (DNA) v2	GCCGTCTTCCGCCAAGAGTCT
	5146	Passenger Strand (RNA) v2	GCCGUCUUCCGCCAAGAGUCU
	4366	Loop	GTCTGCACCTGTCACTAG
	5126	Guide Strand (DNA)	TCTCTTGGCGGAAGACGGC
	4718	Guide Strand (RNA)	UCUCUUGGCGGAAGACGGC
	5127	Guide Strand (DNA) v2	TCTCTTGGCGGAAGACGGCTT
	5128	Guide Strand (RNA) v2	UCUCUUGGCGGAAGACGGCUU
	4375	3' Flanking	TGGCCGTGTAGTGCTACCCAGCGCTGGCTGCCTCCTCAGCATTGCA ATTCCTCTCCCATCTGGGCACCAGTCAGCTACCCTGGTGGGAATCT GGGTAGCC

AAV Particles Comprising Modulatory Polynucleotides

[0254] In some embodiments, the AAV particle comprises a viral genome comprising or encoding a modulatory polynucleotide. In such embodiments, a viral genome comprises or encodes a modulatory polynucleotide, e.g., an encoded modulatory polynucleotide comprising a passenger and guide strand for targeting a MAPT gene, mRNA, or protein described herein, is replicated and packaged into a viral particle. A target cell transduced with a viral particle comprising a modulatory polynucleotide may express the encoded sense and/or antisense sequences in a single cell.

[0255] Non-limiting examples of ITR to ITR sequences of AAV particles comprising a viral genome comprising a modulatory polynucleotide sequence are described, e.g., in Tables 10A, 10B, 11-18, and 26.

Table 10A. Exemplary Sequences of AAV Viral Genomes

ITR to ITR Construct Name	ITR to ITR SEQ ID NO	Modulatory Polynucleotide SEQ ID NO	ITR to ITR Construct Name	ITR to ITR SEQ ID NO	Modulatory Polynucleotide SEQ ID NO
VOYTAU1	4439	4380	VOYTAU40	5158	5040
VOYTAU2	4440	4381	VOYTAU41	5159	5041
VOYTAU3	4441	4382	VOYTAU42	5160	5042
VOYTAU4	4442	4383	VOYTAU43	5161	5035
VOYTAU5	4443	4384	VOYTAU44	5162	5036
VOYTAU6	4444	4385	VOYTAU45	5163	5037
VOYTAU7	4445	4386	VOYTAU46	5164	5038
VOYTAU8	4446	4387	VOYTAU47	5165	5031
VOYTAU9	4447	4388	VOYTAU48	5166	5032
VOYTAU10	4448	4389	VOYTAU49	5167	5033
VOYTAU11	4449	4390	VOYTAU50	5168	5034

VOYTAU12	4450	4391	VOYTAU51	5169	5027
VOYTAU13	4451	4392	VOYTAU52	5170	5028
VOYTAU14	4452	4393	VOYTAU53	5171	5029
VOYTAU15	4453	4394	VOYTAU54	5172	5030
VOYTAU16	4454	4395	VOYTAU55	5173	4405
VOYTAU17	4455	4396	VOYTAU56	5174	4380
VOYTAU18	4456	4397	VOYTAU57	5175	4381
VOYTAU19	4457	4398	VOYTAU58	5176	4383
VOYTAU20	4458	4399	VOYTAU59	5177	4384
VOYTAU21	4459	4400	VOYTAU60	5178	4385
VOYTAU22	4460	4401	VOYTAU61	5179	4386
VOYTAU23	4461	4402	VOYTAU62	5180	4388
VOYTAU24	4462	4403	VOYTAU63	5181	4389
VOYTAU25	4463	4404	VOYTAU64	5182	4390
VOYTAU26	4464	4405	VOYTAU65	5183	4391
VOYTAU27	4465	4406	VOYTAU66	5184	4393
VOYTAU28	4466	4407	VOYTAU67	5185	4394
VOYTAU29	4467	4408	VOYTAU68	5186	4395
VOYTAU30	4468	4409	VOYTAU69	5187	4396
VOYTAU31	5149	5047	VOYTAU70	5188	4398
VOYTAU32	5150	5048	VOYTAU71	5189	4399
VOYTAU33	5151	5049	VOYTAU72	5190	4400
VOYTAU34	5152	5050	VOYTAU73	5191	4401
VOYTAU35	5153	5043	VOYTAU74	5192	4403
VOYTAU36	5154	5044	VOYTAU75	5193	4404
VOYTAU37	5155	5045	VOYTAU76	5194	4406
VOYTAU38	5156	5046	VOYTAU77	5195	4408
VOYTAU39	5157	5039	VOYTAU78	5196	4409

Table 10B. Exemplary Sequences of AAV Viral Genomes

Name	SEQ ID NO	Sequence
VOYTAU55	5173	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG

		TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGAAGCAAAGAAGGGGCAGAGGGAGCCCGT GAGCTGAGTGGGCCAGGGACTGGGAGAAGGAGTGAGGAGGCAGGGCCGGCATGCCTCTGCTG CTGGCCAGAGACTGGAAGCGATGACAATCTGTCTGCACCTGTCACTAGTTTGTCATCGCTTC CAGTCTTTGGCCGTGTAGTGCTACCCAGCGCTGGCTGCCTCCTCAGCATTGCAATTCCTCTC CCATCTGGGCACCAGTCAGCTACCCTGGTGGGAATCTGGGTAGCCCTCGAGGGGTGGCATCC CTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTTGCCACTCCAGTGCCCACCAGCC TTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTAGGTGTCCTTCTATAATATTATG GGGTGGAGGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGAAGACAACCTGTAGGGCCTGCGG GGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCTTGGCTCACTGCAATCTCCGCCT CCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTTGTTGGGATTCCAGGCATGCATG ACCAGGCTCAGCTAATTTTTGTTTTTTTGGTAGAGACGGGGTTTCACCATATTGGCCAGGCT GGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGGCCTCCCAAATTGCTGGGATTAC AGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGCCTAGGGTTAATCATTAACTACA AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCC GGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGC GCGCAG
VOYTAU56	5174	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAAGACTGGAAGCGATGACAACCCTGTGACCTGGTTTGTC ATCGCTTCCAGTCTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTTGGTAGAGACGGG GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG
VOYTAU57	5175	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC

		CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAACTTCCGCGAGAACGCCAACCCTGTGACCTGGTTTGGC GTTCTCGCGGAAGTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTGGTAGAGACGGG GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG
VOYTAU58	5176	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAAGCTCCTCGCAGTTCGGTTCCCTGTGACCTGGTAACCG AACTGCGAGGAGCTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC

		AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTGGTAGAGACGGG GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG
VOYTAU59	5177	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAAGGCTTTGGCTCGGGACTTCCCTGTGACCTGGTAAGTC CCGAGCCAAAGCCTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTTGGTAGAGACGGG GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG
VOYTAU60	5178	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTAATTATTTTGTGCAGCGATGGG

		GGCGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAAGACTGGAAGCGATGACAAACCTGTGACCTGGTTTGTC ATCGCTTCCAGTCTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTGGTAGAGACGGG GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG
VOYTAU61	5179	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAACTTCCGCGAGAACGCCAAACCTGTGACCTGGTTTGGC GTTCTCGCGGAAGTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTGGTAGAGACGGG

		GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG
VOYTAU62	5180	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAAGCTCCTCGCAGTTCGGTTGCCTGTGACCTGGTAACCG AACTGCGAGGAGCTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTTGGTAGAGACGGG GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG
VOYTAU63	5181	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT

		TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAAGGCTTTGGCTCGGGACTTACCTGTGACCTGGTAAGTC CCGAGCCAAAGCCTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTTGGTAGAGACGGG GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG
VOYTAU64	5182	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAAGACTGGAAGCGATGACAATCCTGTGATTTGGTTTGTC ATCGCTTCCAGTCTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTTGGTAGAGACGGG GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG

VOYTAU65	5183	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAACTTCCGCGAGAACGCCAATCCTGTGATTTGGTTTGGC GTTCTCGCGGAAGTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTGGTAGAGACGGG GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG
VOYTAU66	5184	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG

		TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAAGCTCCTCGCAGTTCGGTTTCCTGTGATTTGGTAACCG AACTGCGAGGAGCTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTGGTAGAGACGGG GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG
VOYTAU67	5185	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAAGGCTTTGGCTCGGGACTTTCCTGTGATTTGGTAAGTC CCGAGCCAAAGCCTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTGGTAGAGACGGG GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG
VOYTAU68	5186	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT

		GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAAGACTGGAAGGGATGACAACCCTGTGACCTGGTTTGTC ATCGCTTCCAGTCTTCTGTGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTGGTAGAGACGGG GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG
VOYTAU69	5187	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAACTTCCGCGACAACGCCAACCCTGTGACCTGGTTTGGC GTTCTCGCGGAAGTTCTGTGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA

		GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTGGTAGAGACGGG GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG
VOYTAU70	5188	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAAGCTCCTCGCTGTTCGGTTCCCTGTGACCTGGTAACCG AACTGCGAGGAGCTTCTGTGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTGGTAGAGACGGG GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG
VOYTAU71	5189	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA

		GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAAGGCTTTGGCACGGGACTTCCCTGTGACCTGGTAAGTC CCGAGCCAAAGCCTTCTGTGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTGGTAGAGACGGG GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG
VOYTAU72	5190	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAAGACTGGAAGCGATGACAAGCCTGTGACCTGGTTTGTC ATCGCTTCCAGTCTTCTGTGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTTGGTAGAGACGGG GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC

		CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG
VOYTAU73	5191	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAACTTCCGCGAGAACGCCAAGCCTGTGACCTGGTTTGGC GTTCTCGCGGAAGTTCTGTGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTGGTAGAGACGGG GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG
VOYTAU74	5192	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT

		AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAAGCTCCTCGCAGTTCGGTTGCCTGTGACCTGGTAACCG AACTGCGAGGAGCTTCTGTGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTTGGTAGAGACGGG GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG
VOYTAU75	5193	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGCGCGCCAGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAAGGCTTTGGCTCGGGACTTGCCTGTGACCTGGTAAGTC CCGAGCCAAAGCCTTCTGTGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTTGGTAGAGACGGG GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG
VOYTAU76	5194	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG

		GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGAAGCAAAGAAGGGGCAGAGGGAGCCCGT GAGCTGAGTGGGCCAGGGACTGGGAGAAGGAGTGAGGAGGCAGGGCCGGCATGCCTCTGCTG CTGGCCAGACTTCCGCGAGAACGCCAATCTGTCTGCACCTGTCACTAGTTTGGCGTTCTCGC GGAAGTTTGGCCGTGTAGTGCTACCCAGCGCTGGCTGCCTCCTCAGCATTGCAATTCCTCTC CCATCTGGGCACCAGTCAGCTACCCTGGTGGGAATCTGGGTAGCCCTCGAGGGGTGGCATCC CTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTTGCCACTCCAGTGCCCACCAGCC TTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTAGGTGTCCTTCTATAATATTATG GGGTGGAGGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGAAGACAACCTGTAGGGCCTGCGG GGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCTTGGCTCACTGCAATCTCCGCCT CCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTTGTTGGGATTCCAGGCATGCATG ACCAGGCTCAGCTAATTTTTGTTTTTTTGGTAGAGACGGGGTTTCACCATATTGGCCAGGCT GGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGGCCTCCCAAATTGCTGGGATTAC AGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGCCTAGGGTTAATCATTAACTACA AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCC GGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGC GCGCAG
VOYTAU77	5195	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA

		TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGAAGCAAAGAAGGGGCAGAGGGAGCCCGT GAGCTGAGTGGGCCAGGGACTGGGAGAAGGAGTGAGGAGGCAGGGCCGGCATGCCTCTGCTG CTGGCCAGAGCTCCTCGCAGTTCGGTTTCTGTCTGCACCTGTCACTAGTAACCGAACTGCGA GGAGCTTTGGCCGTGTAGTGCTACCCAGCGCTGGCTGCCTCCTCAGCATTGCAATTCCTCTC CCATCTGGGCACCAGTCAGCTACCCTGGTGGGAATCTGGGTAGCCCTCGAGGGGTGGCATCC CTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTTGCCACTCCAGTGCCCACCAGCC TTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTAGGTGTCCTTCTATAATATTATG GGGTGGAGGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGAAGACAACCTGTAGGGCCTGCGG GGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCTTGGCTCACTGCAATCTCCGCCT CCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTTGTTGGGATTCCAGGCATGCATG ACCAGGCTCAGCTAATTTTTGTTTTTTTGGTAGAGACGGGGTTTCACCATATTGGCCAGGCT GGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGGCCTCCCAAATTGCTGGGATTAC AGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGCCTAGGGTTAATCATTAACTACA AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCC GGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGC GCGCAG
VOYTAU78	5196	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGAAGCAAAGAAGGGGCAGAGGGAGCCCGT GAGCTGAGTGGGCCAGGGACTGGGAGAAGGAGTGAGGAGGCAGGGCCGGCATGCCTCTGCTG CTGGCCAGAGGCTTTGGCTCGGGACTTTCTGTCTGCACCTGTCACTAGTAAGTCCCGAGCCA AAGCCTTTGGCCGTGTAGTGCTACCCAGCGCTGGCTGCCTCCTCAGCATTGCAATTCCTCTC CCATCTGGGCACCAGTCAGCTACCCTGGTGGGAATCTGGGTAGCCCTCGAGGGGTGGCATCC CTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTTGCCACTCCAGTGCCCACCAGCC TTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTAGGTGTCCTTCTATAATATTATG GGGTGGAGGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGAAGACAACCTGTAGGGCCTGCGG GGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCTTGGCTCACTGCAATCTCCGCCT CCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTTGTTGGGATTCCAGGCATGCATG ACCAGGCTCAGCTAATTTTTGTTTTTTTGGTAGAGACGGGGTTTCACCATATTGGCCAGGCT GGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGGCCTCCCAAATTGCTGGGATTAC AGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGCCTAGGGTTAATCATTAACTACA AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCC GGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGC GCGCAG
VOYTAU31	5149	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG

		GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGAAGCAAAGAAGGGGCAGAGGGAGCCCGT GAGCTGAGTGGGCCAGGGACTGGGAGAAGGAGTGAGGAGGCAGGGCCGGCATGCCTCTGCTG CTGGCCAGACCTCGCAGTTCGGTTAATTCTGTCTGCACCTGTCACTAGTATTAACCGAACTG CGAGGTTTGGCCGTGTAGTGCTACCCAGCGCTGGCTGCCTCCTCAGCATTGCAATTCCTCTC CCATCTGGGCACCAGTCAGCTACCCTGGTGGGAATCTGGGTAGCCCTCGAGGGGTGGCATCC CTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTTGCCACTCCAGTGCCCACCAGCC TTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTAGGTGTCCTTCTATAATATTATG GGGTGGAGGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGAAGACAACCTGTAGGGCCTGCGG GGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCTTGGCTCACTGCAATCTCCGCCT CCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTTGTTGGGATTCCAGGCATGCATG ACCAGGCTCAGCTAATTTTTGTTTTTTTGGTAGAGACGGGGTTTCACCATATTGGCCAGGCT GGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGGCCTCCCAAATTGCTGGGATTAC AGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGCCTAGGGTTAATCATTAACTACA AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCC GGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGC GCGCAG
VOYTAU32	5150	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA

		TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGAAGCAAAGAAGGGGCAGAGGGAGCCCGT GAGCTGAGTGGGCCAGGGACTGGGAGAAGGAGTGAGGAGGCAGGGCCGGCATGCCTCTGCTG CTGGCCAGAGCTTTGGCTCGGGACTTCTCTGTCTGCACCTGTCACTAGTGAAGTCCCGAGCC AAAGCTTTGGCCGTGTAGTGCTACCCAGCGCTGGCTGCCTCCTCAGCATTGCAATTCCTCTC CCATCTGGGCACCAGTCAGCTACCCTGGTGGGAATCTGGGTAGCCCTCGAGGGGTGGCATCC CTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTTGCCACTCCAGTGCCCACCAGCC TTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTAGGTGTCCTTCTATAATATTATG GGGTGGAGGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGAAGACAACCTGTAGGGCCTGCGG GGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCTTGGCTCACTGCAATCTCCGCCT CCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTTGTTGGGATTCCAGGCATGCATG ACCAGGCTCAGCTAATTTTTGTTTTTTTGGTAGAGACGGGGTTTCACCATATTGGCCAGGCT GGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGGCCTCCCAAATTGCTGGGATTAC AGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGCCTAGGGTTAATCATTAACTACA AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCC GGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGC GCGCAG
VOYTAU33	5151	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGAAGCAAAGAAGGGGCAGAGGGAGCCCGT GAGCTGAGTGGGCCAGGGACTGGGAGAAGGAGTGAGGAGGCAGGGCCGGCATGCCTCTGCTG CTGGCCAGAAGCTGACCTTCCGCGAGATCTGTCTGCACCTGTCACTAGTTCTCGCGGAAGGT CAGCTTTTGGCCGTGTAGTGCTACCCAGCGCTGGCTGCCTCCTCAGCATTGCAATTCCTCTC CCATCTGGGCACCAGTCAGCTACCCTGGTGGGAATCTGGGTAGCCCTCGAGGGGTGGCATCC CTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTTGCCACTCCAGTGCCCACCAGCC TTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTAGGTGTCCTTCTATAATATTATG GGGTGGAGGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGAAGACAACCTGTAGGGCCTGCGG GGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCTTGGCTCACTGCAATCTCCGCCT CCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTTGTTGGGATTCCAGGCATGCATG ACCAGGCTCAGCTAATTTTTGTTTTTTTGGTAGAGACGGGGTTTCACCATATTGGCCAGGCT GGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGGCCTCCCAAATTGCTGGGATTAC AGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGCCTAGGGTTAATCATTAACTACA AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCC GGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGC GCGCAG
VOYTAU34	5152	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG

		GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGAAGCAAAGAAGGGGCAGAGGGAGCCCGT GAGCTGAGTGGGCCAGGGACTGGGAGAAGGAGTGAGGAGGCAGGGCCGGCATGCCTCTGCTG CTGGCCAGAGCCGTCTTCCGCCAAGAGTCTGTCTGCACCTGTCACTAGTCTCTTGGCGGAAG ACGGCTTTGGCCGTGTAGTGCTACCCAGCGCTGGCTGCCTCCTCAGCATTGCAATTCCTCTC CCATCTGGGCACCAGTCAGCTACCCTGGTGGGAATCTGGGTAGCCCTCGAGGGGTGGCATCC CTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTTGCCACTCCAGTGCCCACCAGCC TTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTAGGTGTCCTTCTATAATATTATG GGGTGGAGGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGAAGACAACCTGTAGGGCCTGCGG GGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCTTGGCTCACTGCAATCTCCGCCT CCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTTGTTGGGATTCCAGGCATGCATG ACCAGGCTCAGCTAATTTTTGTTTTTTTGGTAGAGACGGGGTTTCACCATATTGGCCAGGCT GGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGGCCTCCCAAATTGCTGGGATTAC AGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGCCTAGGGTTAATCATTAACTACA AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCC GGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGC GCGCAG
VOYTAU35	5153	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA

		TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAACCTCGCAGTTCGGTTAATGCCTGTGACCTGGTATTAA CCGAACTGCGAGGTTCTGTGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTGGTAGAGACGGG GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG
VOYTAU36	5154	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAAGCTTTGGCTCGGGACTTCGCCTGTGACCTGGTGAAGT CCCGAGCCAAAGCTTCTGTGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTGGTAGAGACGGG GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG
VOYTAU37	5155	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT

		GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAAAGCTGACCTTCCGCGAGAGCCTGTGACCTGGTTCTCG CGGAAGGTCAGCTTTCTGTGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTGGTAGAGACGGG GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG
VOYTAU38	5156	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAAGCCGTCTTCCGCCAAGAGGCCTGTGACCTGGTCTCTT GGCGGAAGACGGCTTCTGTGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA

		AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTGGTAGAGACGGG GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG
VOYTAU39	5157	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAACCTCGCAGTACGGTTAATCCCTGTGACCTGGTATTAA CCGAACTGCGAGGTTCTGTGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTTGGTAGAGACGGG GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG
VOYTAU40	5158	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT

		TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAAGCTTTGGCTGGGGACTTCCCCTGTGACCTGGTGAAGT CCCGAGCCAAAGCTTCTGTGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTGGTAGAGACGGG GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG
VOYTAU41	5159	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAAAGCTGACCTACCGCGAGACCCTGTGACCTGGTTCTCG CGGAAGGTCAGCTTTCTGTGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTGGTAGAGACGGG GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG

		CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG
VOYTAU42	5160	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAAGCCGTCTTCGGCCAAGAGCCCTGTGACCTGGTCTCTT GGCGGAAGACGGCTTCTGTGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTGGTAGAGACGGG GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG
VOYTAU43	5161	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA

		ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAACCTCGCAGTTCGGTTAATTCCTGTGATTTGGTATTAA CCGAACTGCGAGGTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTTGGTAGAGACGGG GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG
VOYTAU44	5162	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAAGCTTTGGCTCGGGACTTCTCCTGTGATTTGGTGAAGT CCCGAGCCAAAGCTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTTGGTAGAGACGGG GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG
VOYTAU45	5163	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC

		CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAAAGCTGACCTTCCGCGAGATCCTGTGATTTGGTTCTCG CGGAAGGTCAGCTTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTGGTAGAGACGGG GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG
VOYTAU46	5164	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAAGCCGTCTTCCGCCAAGAGTCCTGTGATTTGGTCTCTT GGCGGAAGACGGCTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC

		AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTGGTAGAGACGGG GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG
VOYTAU47	5165	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAACCTCGCAGTTCGGTTAATACCTGTGACCTGGTATTAA CCGAACTGCGAGGTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTTGGTAGAGACGGG GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG
VOYTAU48	5166	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTAATTATTTTGTGCAGCGATGGG

		GGCGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAAGCTTTGGCTCGGGACTTCACCTGTGACCTGGTGAAGT CCCGAGCCAAAGCTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTGGTAGAGACGGG GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG
VOYTAU49	5167	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAAAGCTGACCTTCCGCGAGAACCTGTGACCTGGTTCTCG CGGAAGGTCAGCTTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTGGTAGAGACGGG

		GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG
VOYTAU50	5168	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAAGCCGTCTTCCGCCAAGAGACCTGTGACCTGGTCTCTT GGCGGAAGACGGCTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTTGGTAGAGACGGG GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG
VOYTAU51	5169	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT

		TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAACCTCGCAGTTCGGTTAATCCCTGTGACCTGGTATTAA CCGAACTGCGAGGTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTTGGTAGAGACGGG GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG
VOYTAU52	5170	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAAGCTTTGGCTCGGGACTTCCCCTGTGACCTGGTGAAGT CCCGAGCCAAAGCTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTTGGTAGAGACGGG GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG

VOYTAU53	5171	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAAAGCTGACCTTCCGCGAGACCCTGTGACCTGGTTCTCG CGGAAGGTCAGCTTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTGGTAGAGACGGG GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG
VOYTAU54	5172	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGG TCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGTAGCCATGCTCTAGGAAGA TCAATTCAATTCACGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGG GTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGC CTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTA ACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTT GGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAAT GGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATC TACGTATTAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCC CCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTTTTTAATTATTTTGTGCAGCGATGGG GGCGGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAG GCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGA GGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGCAAGCTTCGTT TAGTGAACCGTCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACAC CGGGACCGATCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGA TTCCCCGTGCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCT TTCTTCTTTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTT TCAGGGCAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGAT AATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTA ACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATG

		TTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCA TCACTTTGGCAAAGAATTGGGATTCGAACCGGTGTGCTGGGCGGGGGGCGGCGGGCCCTCCC GCAGAACACCATGCGCTCTTCGGAAGCCGTCTTCCGCCAAGAGCCCTGTGACCTGGTCTCTT GGCGGAAGACGGCTTCTGAGGAGCGCCTTGACAGCAGCCATGGGAGGGCCGCCCCCTACCTC AGTGACTCGAGGGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTT GCCACTCCAGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTA GGTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGA AGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCT TGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTT GTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTGGTAGAGACGGG GTTTCACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGG CCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTATCGATGC CTAGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCG CGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG CGGCCTCAGTGAGCGAGCGAGCGCGCAG

Table 10C. Exemplary Sequences of AAV Viral Genomes Components

Name	SEQ ID NO	Sequence
ITR	5197	CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTG GTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTG
ITR	5200	AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGC CGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGA GCGCGCAG
ITR	4469	CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCG GGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAAC TCCATCACTAGGGGTTCCT
ITR	4470	AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGC CGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGA GCGCGCAGCTGCCTGCAGG
CMVie (v1)	4472	CGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGGGTCATTAGTTCA TAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGCCTGGCTGACCG CCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTAACGCCAATAG GGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTTGGCAGTACA TCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAATGGCCCGCC TGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATCTACGTAT TAGTCATCGCTATTAC
CMVie (v2)	4471	GACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGGGTCATTAGTTCATAGCCC ATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGCCTGGCTGACCGCCCAAC GACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTAACGCCAATAGGGACTT TCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTTGGCAGTACATCAAGT GTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAATGGCCCGCCTGGCAT TATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATCTACGTATTAGTCA TCGCTATTACCATG
CMVie Enhancer-CBA Promoter (v1)	4473	CGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGGGTCATTAGTTCATAGCC CATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGCCTGGCTGACCGCCCAA CGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTAACGCCAATAGGGACT TTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTTGGCAGTACATCAAG TGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAATGGCCCGCCTGGCA TTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATCTACGTATTAGTC ATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCCCCCCCCTCCCC ACCCCCAATTTTGTATTTATTTATTTTTTTAATTATTTTGTGCAGCGATGGGGGCGGGGGGG GGGGGCGCGCGCCAGGCGGGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAGGCGGAGAGG

		TGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGAGGCGGCGG CGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGC
CBA Promoter	5199	CCACGTTCTGCTTCACTCTCCCCATCTCCCCCCCCTCCCCACCCCCAATTTTGTATTTATT TATTTTTTAATTATTTTGTGCAGCGATGGGGGCGGGGGGGGGGGGCGCGCGCCAGGCGGGG CGGGGCGGGGCGAGGGGCGGGGCGGGGCGAGGCGGAGAGGTGCGGCGGCAGCCAATCAGAG CGGCGCGCTCCGAAAGTTTCCTTTTATGGCGAGGCGGCGGCGGCGGCGCCCTATAAAAAG CGAAGCGCGCGGCGGGCGGGAGC
CMVie Enhancer-CBA Promoter (v2)	4474	CGCGTCGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGGGTCATTAGTTCA TAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGCCTGGCTGACCG CCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTAACGCCAATAG GGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTTGGCAGTACA TCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAATGGCCCGCC TGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATCTACGTAT TAGTCATCGCTATTACCATGTCGAGGCCACGTTCTGCTTCACTCTCCCCATCTCCCCCCCC TCCCCACCCCCAATTTTGTATTTATTTATTTTTTAATTATTTTGTGCAGCGATGGGGGCGG GGGGGGGGGGCGCGCGCCAGGCGGGGCGGGGCGAGGGGCGGGGCGGGGCGAGGCGG AGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCGCTCCGAAAGTTTCCTTTTATGGCGAGGC GGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGCGGCGGGCGGGAGC
hBG Intron	4475	TCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACACCGGGACCGA TCCAGCCTCCGCGGATTCGAATCCCGGCCGGGAACGGTGCATTGGAACGCGGATTCCCCGT GCCAAGAGTGACGTAAGTACCGCCTATAGAGTCTATAGGCCCACAAAAAATGCTTTCTTCT TTTAATATACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTTTCAGGG CAATAATGATACAATGTATCATGCCTCTTTGCACCATTCTAAAGAATAACAGTGATAATTT CTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTTCTGCATATAAATTGTAACTG ATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTATTT TATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATGTT CATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCAT CACTTTGGCAAAGAATT
hGH PolyA	4476	GGGTGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTTGCCACTCCAG TGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTAGGTGTCCTT CTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGGAAGACAACC TGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTGGCACAATCTTGGCTCA CTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTTGTTGGG ATTCCAGGCATGCATGACCAGGCTCAGCTAATTTTTGTTTTTTTGGTAGAGACGGGGTTTC ACCATATTGGCCAGGCTGGTCTCCAACTCCTAATCTCAGGTGATCTACCCACCTTGGCCTC CCAAATTGCTGGGATTACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTT

[0256] In some embodiments, the a viral genome described herein comprises the nucleotide sequence of any one of SEQ ID NOs: 4439-4468 or 5149-5196, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 99% or 100% identical to any one of SEQ ID NOs: 4439-4468 or 5149-5196. In some embodiments, the viral genome comprises the nucleotide sequence of any one of SEQ ID NOs: 4439-4468 or 5149-5196, or a nucleotide sequence at least 80% identical to any one of SEQ ID NOs: 4439-4468 or 5149-5196. In some embodiments, the viral genome comprises the nucleotide sequence of any one of SEQ ID NOs: 4439-4468 or 5149-5196, or a nucleotide sequence at least 85% identical to any one of SEQ ID NOs: 4439-4468 or 5149-5196. In some embodiments, the viral genome comprises the nucleotide sequence of any one of SEQ ID NOs: 4439-4468 or 5149-5196, or a nucleotide sequence at least 90% identical to any one of SEQ ID NOs: 4439-4468 or 5149-5196. In some embodiments, the viral genome comprises the nucleotide sequence of any one of SEQ ID NOs: 4439-4468 or 5149-5196, or a nucleotide sequence at least 95% identical to any one of SEQ ID NOs: 4439-4468 or 5149-5196. In some embodiments, the viral genome comprises the nucleotide

sequence of any one of SEQ ID NOs: 4439-4468 or 5149-5196, or a nucleotide sequence at least 99% identical to any one of SEQ ID NOs: 4439-4468 or 5149-5196.

[0257] In some embodiments, the AAV viral genome comprises the nucleotide sequence of SEQ ID NO: 5173, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto. In some embodiments, the AAV viral genome comprises the nucleotide sequence of SEQ ID NO: 5173, or a nucleotide sequence having at least one, two or three, but not more than 30, 20 or 10 different nucleotides relative to the nucleotide sequence of SEQ ID NO: 5173. In some embodiments, the AAV viral genome comprises the nucleotide sequence of SEQ ID NO: 5173.

[0258] In some embodiments, the AAV viral genome comprises the nucleotide sequence of SEQ ID NO: 5195, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto. In some embodiments, the AAV viral genome comprises the nucleotide sequence of SEQ ID NO: 5195, or a nucleotide sequence having at least one, two or three, but not more than 30, 20 or 10 different nucleotides relative to the nucleotide sequence of SEQ ID NO: 5195. In some embodiments, the AAV viral genome comprises the nucleotide sequence of SEQ ID NO: 5195.

[0259] In some embodiments, the AAV viral genome comprises the nucleotide sequence of SEQ ID NO: 5195, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto. In some embodiments, the AAV viral genome comprises the nucleotide sequence of SEQ ID NO: 5196, or a nucleotide sequence having at least one, two or three, but not more than 30, 20 or 10 different nucleotides relative to the nucleotide sequence of SEQ ID NO: 5196. In some embodiments, the AAV viral genome comprises the nucleotide sequence of SEQ ID NO: 5196.

[0260] In some embodiments, the AAV viral genome comprises the nucleotide sequence of SEQ ID NO: 5182, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto. In some embodiments, the AAV viral genome comprises the nucleotide sequence of SEQ ID NO: 5182, or a nucleotide sequence having at least one, two or three, but not more than 30, 20 or 10 different nucleotides relative to the nucleotide sequence of SEQ ID NO: 5182. In some embodiments, the AAV viral genome comprises the nucleotide sequence of SEQ ID NO: 5182.

[0261] In some embodiments, the AAV viral genome comprises the nucleotide sequence of SEQ ID NO: 5183, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto. In some embodiments, the AAV viral genome comprises the nucleotide sequence of SEQ ID NO: 5183, or a nucleotide sequence having at least one, two or three, but not more than 30, 20 or 10 different nucleotides relative to the nucleotide sequence of SEQ ID NO: 5183. In some embodiments, the AAV viral genome comprises the nucleotide sequence of SEQ ID NO: 5183.

[0262] In some embodiments, the AAV viral genome comprises the nucleotide sequence of SEQ ID NO: 5184, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99%

identical thereto. In some embodiments, the AAV viral genome comprises the nucleotide sequence of SEQ ID NO: 5184, or a nucleotide sequence having at least one, two or three, but not more than 30, 20 or 10 different nucleotides relative to the nucleotide sequence of SEQ ID NO: 5184. In some embodiments, the AAV viral genome comprises the nucleotide sequence of SEQ ID NO: 5184.

[0263] In some embodiments, the AAV viral genome comprises the nucleotide sequence of SEQ ID NO: 5185, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto. In some embodiments, the AAV viral genome comprises the nucleotide sequence of SEQ ID NO: 5185, or a nucleotide sequence having at least one, two or three, but not more than 30, 20 or 10 different nucleotides relative to the nucleotide sequence of SEQ ID NO: 5185. In some embodiments, the AAV viral genome comprises the nucleotide sequence of SEQ ID NO: 5185.

[0264] In some embodiments, the viral genome may comprise at least one inverted terminal repeat (ITR) region. In some embodiments, the AAV particle viral genome may comprise two inverted terminal repeat (ITR) regions, e.g., a 5' ITR region (e.g., an ITR region present 5' relative to the encoded modulatory polynucleotide) and a 3' ITR region (e.g., an ITR region present 3' relative to the encoded modulatory polynucleotide). In some embodiments, the ITR region comprises the nucleotide sequence of SEQ ID NO: 4469, 4470, 5197, or 5200; a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% identical to the nucleotide sequence of SEQ ID NO: 4469, 4470, 5197, or 5200; a nucleotide sequence comprising one, two, three, but no more than four different nucleotides relative to SEQ ID NO: 4469, 4470, 5197, or 5200; or a nucleotide sequence comprising one, two, three, but no more than four modifications relative to SEQ ID NO: 4469, 4470, 5197, or 5200. In some embodiments, the 5' ITR region comprises the nucleotide sequence of SEQ ID NO: 4469; a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% identical to the nucleotide sequence of SEQ ID NO: 4469; a nucleotide sequence comprising one, two, three, but no more than four different nucleotides relative to SEQ ID NO: 4469; or a nucleotide sequence comprising one, two, three, but no more than four modifications relative to SEQ ID NO: 4469. In some embodiments, the 3' ITR comprises the nucleotide sequence of SEQ ID NO: 4470; a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% identical to the nucleotide sequence of SEQ ID NO: 4470; a nucleotide sequence comprising one, two, three, but no more than four different nucleotides relative to SEQ ID NO: 4470; or a nucleotide sequence comprising one, two, three, but no more than four modifications relative to SEQ ID NO: 4470. In some embodiments, the 5' ITR region comprises the nucleotide sequence of SEQ ID NO: 5197; a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% identical to the nucleotide sequence of SEQ ID NO: 5197; a nucleotide sequence comprising one, two, three, but no more than four different nucleotides relative to SEQ ID NO: 5197; or a nucleotide sequence comprising one, two, three, but no more than four modifications relative to SEQ ID NO: 5197. In some embodiments, the 3' ITR comprises the nucleotide sequence of SEQ ID NO: 5200; a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95%,

or 99% identical to the nucleotide sequence of SEQ ID NO: 5200; a nucleotide sequence comprising one, two, three, but no more than four different nucleotides relative to SEQ ID NO: 5200; or a nucleotide sequence comprising one, two, three, but no more than four modifications relative to SEQ ID NO: 5200.

[0265] In some embodiments, the viral genome comprises an enhancer. In some embodiments, the enhancer region is a cytomegalovirus major immediate-early enhancer region (CMVie) enhancer. In some embodiments, the enhancer comprises the nucleotide sequence of SEQ ID NO: 4471; a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% identical to the nucleotide sequence of SEQ ID NO: 4471; a nucleotide sequence comprising one, two, three, but no more than four different nucleotides relative to SEQ ID NO: 4471; or a nucleotide sequence comprising one, two, three, but no more than four modifications relative to SEQ ID NO: 4471. In some embodiments, the enhancer comprises the nucleotide sequence of SEQ ID NO: 4472; a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% identical to the nucleotide sequence of SEQ ID NO: 4472; a nucleotide sequence comprising one, two, three, but no more than four different nucleotides relative to SEQ ID NO: 4472; or a nucleotide sequence comprising one, two, three, but no more than four modifications relative to SEQ ID NO: 4472.

[0266] In some embodiments, the viral genome comprises a promoter. In some embodiments, the promoter is a tissue specific promoter. In some embodiments, the promoter is a ubiquitous promoter. In some embodiments, the promoter comprises the nucleotide sequence of SEQ ID NO: 5199; a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% identical to the nucleotide sequence of SEQ ID NO: 5199; a nucleotide sequence comprising one, two, three, but no more than four different nucleotides relative to SEQ ID NO: 5199; or a nucleotide sequence comprising one, two, three, but no more than four modifications relative to SEQ ID NO: 5199.

[0267] In some embodiments, the viral genome comprises a promoter and enhancer, wherein the promoter and enhancer region comprises the nucleotide sequence of SEQ ID NO: 4474 or 4473; a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% identical to the nucleotide sequence of SEQ ID NO: 4474 or 4473; a nucleotide sequence comprising one, two, three, but no more than four different nucleotides relative to SEQ ID NO: 4474 or 4473; or a nucleotide sequence comprising one, two, three, but no more than four modifications relative to SEQ ID NO: 4474 or 4473.

[0268] In some embodiments, the viral genome comprises an intron. In some embodiments, the intron comprises the nucleotide sequence of SEQ ID NO: 4475; a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% identical to the nucleotide sequence of SEQ ID NO: 4475; a nucleotide sequence comprising one, two, three, but no more than four different nucleotides relative to SEQ ID NO: 4475; or a nucleotide sequence comprising one, two, three, but no more than four modifications relative to SEQ ID NO: 4475.

[0269] In some embodiments, the viral genome comprises a polyadenylation (polyA) signal sequence region. In some embodiments, the polyA signal sequence region comprises the nucleotide sequence of SEQ ID NO: 4476; a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% identical to the nucleotide sequence of SEQ ID NO: 4476; a nucleotide sequence comprising one, two, three, but no more than four different nucleotides relative to SEQ ID NO: 4476; or a nucleotide sequence comprising one, two, three, but no more than four modifications relative to SEQ ID NO: 4476.

[0270] In some embodiments, the viral genome comprises at least one ITR region (e.g., two ITR regions), an enhancer, a promoter sequence region, an intron, a modulatory polynucleotide, and a polyadenylation signal sequence region, e.g., as provided in Table 10C.

[0271] In some embodiments, the AAV particle viral genome comprises a 5' ITR region, a 3' ITR region, a CMV enhancer sequence, a CBA promoter sequence, an hBG intron, a modulatory polynucleotide, and a human growth hormone (hGH) polyA signal sequence region. In some embodiments, the viral genome comprises in 5' to 3' order: a 5' ITR, an enhancer (e.g., a CMVie enhancer or variant thereof), a promoter (e.g., a ubiquitous promoter, e.g., a CBA promoter or variant thereof), an intron (e.g., an hBG intron or variant thereof), a modulatory polynucleotide (e.g., a modulatory polynucleotide encoding an siRNA for targeting MAPT described herein, e.g., a modulatory polynucleotide as provided in Tables 9A and 9B or a variant thereof), a polyA signal sequence region (e.g., a hGH polyA signal sequence region or variant thereof), and a 3' ITR region. In some embodiments, the viral genome comprises one or more of the sequences provided in any one of Tables 10A, 10B, 11-18, or 26, or a variant thereof, e.g., a sequence at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% identical to any one of the sequences provided in Tables 10A, 10B,11-18, or 26; a nucleotide sequence comprising one, two, three, but no more than four different nucleotides relative to any one of the sequences provided in Tables 10A, 10B, 11-18, or 26; or a nucleotide sequence comprising one, two, three, but no more than four modifications relative to any one of the sequences provided in Tables 10A, 10B, 11-18, or 26.

Table 11. Sequence Regions in the ITR to ITR Sequence

Sequence Regions	VOYTAU1 (SEQ ID NO: 4439)		VOYTAU2 (SEQ ID NO: 4440)		VOYTAU3 (SEQ ID NO: 4441)		VOYTAU4 (SEQ ID NO: 4442)	
	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length
5' ITR	4469	141	4469	141	4469	141	4469	141
CMVie Enhancer	4472	382	4472	382	4472	382	4472	382
CBA Promoter	5199	267	5199	267	5199	267	5199	267
hBG Intron	4475	566	4475	566	4475	566	4475	566
Modulatory Polynucleotide	4380	158	4381	158	4382	158	4383	158
hGH PolyA	4476	477	4476	477	4476	477	4476	477
3' ITR	4470	141	4470	141	4470	141	4470	141

Table 12. Sequence Regions in the ITR to ITR Sequence

Sequence Regions	VOYTAU5 (SEQ ID NO: 4443)		VOYTAU6 (SEQ ID NO: 4444)		VOYTAU7 (SEQ ID NO: 4445)		VOYTAU8 (SEQ ID NO: 4446)	
	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length
5' ITR	4469	141	4469	141	4469	141	4469	141
CMVie Enhancer	4472	382	4472	382	4472	382	4472	382
CBA Promoter	5199	267	5199	267	5199	267	5199	267
hBG Intron	4475	566	4475	566	4475	566	4475	566
Modulatory Polynucleotide	4384	158	4385	158	4386	158	4387	158
hGH PolyA	4476	477	4476	477	4476	477	4476	477
3' ITR	4470	141	4470	141	4470	141	4470	141

Table 13. Sequence Regions in the ITR to ITR Sequence

Sequence Regions	VOYTAU9 (SEQ ID NO: 4447)		VOYTAU10 (SEQ ID NO: 4448)		VOYTAU11 (SEQ ID NO: 4449)		VOYTAU12 (SEQ ID NO: 4450)	
	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length
5' ITR	4469	141	4469	141	4469	141	4469	141
CMVie Enhancer	4472	382	4472	382	4472	382	4472	382
CBA Promoter	5199	267	5199	267	5199	267	5199	267
hBG Intron	4475	566	4475	566	4475	566	4475	566
Modulatory Polynucleotide	4388	158	4389	158	4390	158	4391	158
hGH PolyA	4476	477	4476	477	4476	477	4476	477
3' ITR	4470	141	4470	141	4470	141	4470	141

Table 14. Sequence Regions in the ITR to ITR Sequence

Sequence Regions	VOYTAU13 (SEQ ID NO: 4451)		VOYTAU14 (SEQ ID NO: 4452)		VOYTAU15 (SEQ ID NO: 4453)		VOYTAU16 (SEQ ID NO: 4454)	
	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length
5' ITR	4469	141	4469	141	4469	141	4469	141
CMVie Enhancer	4472	382	4472	382	4472	382	4472	382
CBA Promoter	5199	267	5199	267	5199	267	5199	267
hBG Intron	4475	566	4475	566	4475	566	4475	566
Modulatory Polynucleotide	4392	158	4393	158	4394	158	4395	158
hGH PolyA	4476	477	4476	477	4476	477	4476	477
3' ITR	4470	141	4470	141	4470	141	4470	141

Table 15. Sequence Regions in the ITR to ITR Sequence

Sequence Regions	VOYTAU17 (SEQ ID NO: 4455)		VOYTAU18 (SEQ ID NO: 4456)		VOYTAU19 (SEQ ID NO: 4457)		VOYTAU20 (SEQ ID NO: 4458)	
	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length
5' ITR	4469	141	4469	141	4469	141	4469	141
CMVie Enhancer	4472	382	4472	382	4472	382	4472	382
CBA Promoter	5199	267	5199	267	5199	267	5199	267
hBG Intron	4475	566	4475	566	4475	566	4475	566
Modulatory Polynucleotide	4396	158	4397	158	4398	158	4399	158
hGH PolyA	4476	477	4476	477	4476	477	4476	477
3' ITR	4470	141	4470	141	4470	141	4470	141

Table 16. Sequence Regions in the ITR to ITR Sequence

Sequence Regions	VOYTAU21 (SEQ ID NO: 4459)		VOYTAU22 (SEQ ID NO: 4460)		VOYTAU23 (SEQ ID NO: 4461)		VOYTAU24 (SEQ ID NO: 4462)	
	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length
5' ITR	4469	141	4469	141	4469	141	4469	141
CMVie Enhancer	4472	382	4472	382	4472	382	4472	382
CBA Promoter	5199	267	5199	267	5199	267	5199	267
hBG Intron	4475	566	4475	566	4475	566	4475	566
Modulatory Polynucleotide	4400	158	4401	158	4402	158	4403	158
hGH PolyA	4476	477	4476	477	4476	477	4476	477
3' ITR	4470	141	4470	141	4470	141	4470	141

Table 17. Sequence Regions in the ITR to ITR Sequence

Sequence Regions	VOYTAU25 (SEQ ID NO: 4463)		VOYTAU26 (SEQ ID NO: 4464)		VOYTAU27 (SEQ ID NO: 4465)		VOYTAU28 (SEQ ID NO: 4466)	
	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length
5' ITR	4469	141	4469	141	4469	141	4469	141
CMVie Enhancer	4472	382	4472	382	4472	382	4472	382
CBA Promoter	5199	267	5199	267	5199	267	5199	267
hBG Intron	4475	566	4475	566	4475	566	4475	566
Modulatory Polynucleotide	4404	158	4405	260	4406	260	4407	260
hGH PolyA	4476	477	4476	477	4476	477	4476	477
3' ITR	4470	141	4470	141	4470	141	4470	141

Table 18. Sequence Regions in the ITR to ITR Sequence

Sequence Regions	VOYTAU29 (SEQ ID NO: 4467)		VOYTAU30 (SEQ ID NO: 4468)		VOYTAU77 (SEQ ID NO: 5195)
	Region SEQ ID NO	Region length	Region SEQ ID NO	Region length	Region SEQ ID NO
5' ITR	4469	141	4469	141	5197
CMVie Enhancer	4472	382	4472	382	4471
CBA Promoter	5199	267	5199	267	5199
hBG Intron	4475	566	4475	566	4475
Modulatory Polynucleotide	4408	260	4409	260	4408
hGH PolyA	4476	477	4476	477	4476
3' ITR	4470	141	4470	141	5200

Table 26. Sequence Regions in the ITR to ITR Sequences

Sequence Regions	**VOYTAU55** (SEQ ID NO: 5173)	**VOYTAU78** (SEQ ID NO: 5196)	**VOYTAU64** (SEQ ID NO: 5182)	**VOYTAU65** (SEQ ID NO: 5183)	**VOYTAU66** (SEQ ID NO: 5184)	**VOYTAU67** (SEQ ID NO: 5185)
	Region SEQ ID NO:	**Region SEQ ID NO:**	**Region SEQ ID NO:**	**Region SEQ ID NO:**	**Region SEQ ID NO:**	**Region SEQ ID NO:**
5' ITR	5197	5197	5197	5197	5197	5197
CMVie Enhancer	4471	4471	4471	4471	4471	4471
CBA Promoter	5199	5199	5199	5199	5199	5199
hBG Intron	4475	4475	4475	4475	4475	4475
Modulatory Polynucleotide	4405	4409	4390	4391	4393	4394
hGH PolyA	4476	4476	4476	4476	4476	4476
3' ITR	5200	5200	5200	5200	5200	5200

[0272] In some embodiments, the present disclosure provides AAV particles comprising a viral genome described herein, and an AAV capsid protein, e.g., an AAV capsid variant described herein. In some embodiments, the present disclosure provides a vector comprising a viral genome described herein.

[0273] In other embodiments, an AAV particle comprising a nucleic acid sequence encoding a siRNA molecule is to deliver siRNA molecules to the central nervous system, e.g., as described in U.S. Pat. No. 6,180,613; the contents of which is herein incorporated by reference in its entirety.

Viral production

[0274] Cells for the production of AAV, *e.g.*, rAAV, particles may comprise, in some embodiments, mammalian cells (such as HEK293 cells) and/or insect cells (such as Sf9 cells).

[0275] In some embodiments, AAV production includes processes and methods for producing AAV particles and vectors which can contact a target cell to deliver a payload, *e.g.* a recombinant viral construct, which includes a nucleotide encoding a payload molecule. In certain embodiments, the viral vectors are

adeno-associated viral (AAV) vectors such as recombinant adeno-associated viral (rAAV) vectors. In certain embodiments, the AAV particles are adeno-associated viral (AAV) particles such as recombinant adeno-associated viral (rAAV) particles.

[0276] In some embodiments, disclosed herein is a vector comprising a viral genome described herein. In some embodiments, disclosed herein is a vector comprising a nucleotide sequence encoding a modulatory polynucleotide, e.g., a modulatory polynucleotide described herein. In some embodiments, the present disclosure provides a vector comprising a nucleotide sequence encoding an siRNA, e.g., an siRNA for targeting a MAPT gene, mRNA, and/or protein as described herein.

[0277] In some embodiments, disclosed herein is a cell comprising a viral genome, modulatory polynucleotide, siRNA, and/or AAV particle of the present disclosure. In some embodiments, the cell is a bacterial cell (e.g. an *E. coli* cell), a mammalian cell (e.g., a HEK293 cell or a CNS cell), or an insect cell (e.g., an Sf9 cell or an Sf21 cell).

[0278] In some embodiments, disclosed herein is a method of making a recombinant AAV particle of the present disclosure, the method comprising (i) providing a host cell comprising a viral genome described herein and incubating the host cell under conditions suitable to enclose the viral genome in an AAV capsid polypeptide, e.g., an AAV capsid variant, as described herein (e.g., an AAV capsid variant as provided in Table 1 or functional variant thereof), thereby making the recombinant AAV particle. In some embodiments, the method comprises prior to step (i), introducing a first nucleic acid comprising the viral genome into a cell. In some embodiments, the host cell comprises a second nucleic acid encoding the capsid protein. In some embodiments, the second nucleic acid is introduced into the host cell prior to, concurrently with, or after the first nucleic acid molecule. In some embodiments, the host cell is a bacterial cell, a mammalian cell (e.g., a HEK293 cell), or an insect cell (e.g., an Sf9 cell).

[0279] In some embodiments, disclosed herein is a method of making a viral genome. The method comprising providing a nucleic acid encoding a viral genome described herein and a backbone region suitable for replication of the viral genome in a cell, e.g., a bacterial cell (e.g., wherein the backbone region comprises one or both of a bacterial origin of replication and a selectable marker), and excising the viral genome from the backbone region, e.g., by cleaving the nucleic acid molecule at upstream and downstream of the viral genome. In some embodiments, the viral genome comprising a promoter operably linked to nucleic acid comprising a transgene encoding a polynucleotide (e.g., a MAPT targeting siRNA described herein), will be incorporated into an AAV particle produced in the cell. In some embodiments, the cell is a bacterial cell, a mammalian cell (e.g., a HEK293 cell), or an insect cell (e.g., an Sf9 cell).

[0280] In some embodiments, a vector used for AAV production comprises a nucleotide sequence encoding an AAV capsid protein, e.g., one, two, or all of a VP1 capsid protein, a VP2 capsid protein, or a VP3 capsid protein. In some embodiments, the nucleotide sequence encoding the capsid protein, e.g., the

VP1 capsid protein, comprises a canonical start codon (e.g., an ATG). In some embodiments, the nucleotide sequence encoding the AAV capsid protein, e.g., an AAV VP1 capsid protein, is a non-ATG start codon, e.g., a non-canonical start codon (e.g., ACG, TTG, or GTG), e.g., a start codon capable of altering the ratio of the viral capsid proteins in the production system.

[0281] In some embodiments, the vector(s) used for AAV production comprises a nucleotide sequence encoding an AAV rep protein, e.g., a Rep78 protein, a Rep52 protein, a Rep40 protein, and/or a Rep68 protein (e.g., a Rep78 and Rep52 protein). In some embodiments, the nucleotide sequence encoding the Rep protein comprises an ATG start codon. In some embodiments, the nucleotide sequence comprises a non-ATG start codon, e.g., a non-canonical stop codon, e.g., ACG, TTG, CTG or GTG.

[0282] In some embodiments, an AAV particle described herein is generated using a method described in WO 2022/187473, WO 2022/187548, WO 2021/041485, WO 2020/150556, WO 2020/081490, WO 2020/072844, WO 2020/023612, WO 2021/030125, WO 2020/223274, WO 2019/241486, WO2022032153, the contents of each of which are hereby incorporated by reference it their entirety.

Cells

[0283] In some embodiments, the present disclosure provides a cell comprising an AAV particle, a viral genome, a modulatory polynucleotide, and/or an siRNA targeting a MAPT gene, mRNA, and/or protein described herein.

[0284] Viral production disclosed herein describes processes and methods for producing an AAV particle, which comprise contacting a target cell to deliver a payload, e.g. a siRNA for targeting MAPT or an modulatory polynucleotide comprising a siRNA for targeting MAPT.

[0285] In some embodiments, the AAV particle of the present disclosure may be produced in insect cells (*e.g.*, Sf9 cells). In some embodiments, the AAV particle of the present disclosure may be produced using triple transfection. In some embodiments, the AAV particle of the present disclosure may be produced in mammalian cells. In some embodiments, the AAV particle of the present disclosure may be produced by triple transfection in mammalian cells. In some embodiments, the AAV particle of the present disclosure may be produced by triple transfection in HEK293 cells.

[0286] In some embodiments, the AAV particles may be produced in a viral replication cell that comprises an insect cell. Growing conditions for insect cells in culture, and production of heterologous products in insect cells in culture are well-known in the art, see U.S. Pat. No. 6,204,059, the contents of which are herein incorporated by reference in their entirety.

[0287] Any insect cell which allows for replication of parvovirus and which can be maintained in culture can be used in accordance with the present disclosure. Cell lines may be used from Spodoptera frugiperda, including, but not limited to the Sf9 or Sf21 cell lines, Drosophila cell lines, or mosquito cell lines, such as *Aedes albopictus* derived cell lines. Use of insect cells for expression of heterologous proteins is well

documented, as are methods of introducing nucleic acids, such as vectors, e.g., insect-cell compatible vectors, into such cells and methods of maintaining such cells in culture. See, for example, 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); and Samulski et al., U.S. Pat. No. 6,204,059, the contents of each of which is herein incorporated by reference in its entirety.

[0288] In certain embodiments, the AAV particles of the present disclosure may be produced in a viral production cell that includes a mammalian cell. Viral production cells may comprise mammalian cells such as A549, WEH1, 3T3, 10T1/2, BHK, MDCK, COS 1, COS 7, BSC 1, BSC 40, BMT 10, VERO, W138, HeLa, HEK293, HEK293T (293T), Saos, C2C12, L cells, HT1080, Huh7, HepG2, C127, 3T3, CHO, HeLa cells, KB cells, BHK and primary fibroblast, hepatocyte, and myoblast cells derived from mammals. Viral production cells can include cells derived from any mammalian species including, but not limited to, human, monkey, mouse, rat, rabbit, and hamster or cell type, including but not limited to fibroblast, hepatocyte, tumor cell, cell line transformed cell, etc.

Small scale production of AAV Particles

[0289] In some embodiments, viral production comprises processes and methods for producing an AAV particle, e.g., an AAV particle for contacting a target cell to deliver a payload, e.g. a siRNA for targeting MAPT or an modulatory polynucleotide comprising a siRNA for targeting MAPT.

[0290] In some embodiments, the AAV particles may be produced in a viral replication cell that comprises a mammalian cell. In some embodiments, the viral replication cell is a HEK293 cell, a COS cell, a HeLa cell, a KB cell, or a mammalian cell line as described in U.S. Pat. Nos. 6,156,303, 5,387,484, 5,741,683, 5,691,176, and 5,688,676; U.S. patent application 2002/0081721, and International Patent Applications WO 00/47757, WO 00/24916, and WO 96/17947, the contents of each of which are herein incorporated by reference in their entireties.

[0291] In some embodiments, an AAV particle is produced in a mammalian cell wherein all three VP proteins are expressed at a stoichiometry of about 1:1:10 (VP1:VP2:VP3). In some embodiments, the regulatory mechanisms that allow this controlled level of expression include the production of two mRNAs, one for VP1, and the other for VP2 and VP3, produced by differential splicing.

[0292] In some embodiments, an AAV particle is produced in a mammalian cells using a triple transfection method. In some embodiments, the method comprises providing a payload construct, parvoviral Rep and parvoviral Cap and a helper construct are comprised.

Baculovirus Production

[0293] In certain embodiments, processes of the present disclosure can include production of AAV

particles or viral vectors in a baculoviral system, e.g., an AAV viral production system. In certain embodiments, the AAV production system comprises an AAV expression construct. In some embodiments, the AAV expression construct comprises a baculovirus genome, e.g., a variant baculovirus genome, e.g., a variant baculovirus genome comprising a modification in at least one (e.g., at least two, three, four or more) non-essential genes. In some, embodiments, the AAV expression construct comprises at least one or two Rep-coding region and one, two, or three VP-coding regions. In some embodiments, the AAV production system further comprises an AAV payload construct. In some embodiments, the AAV payload construct encodes a payload described herein e.g., a modulatory polynucleotide comprising a siRNA for targeting MAPT or an siRNA for targeting MAPT. In some embodiments, the AAV expression construct, AAV payload construct, and/or AAV production system is as described and provided in WO 2022/187473, WO 2022/187548, WO 2021/041485, WO 2020/150556, WO 2020/081490, WO 2020/072844, WO 2020/023612, WO 2021/030125, WO 2020/223274, WO 2019/241486, WO2022032153, the contents of each of which are hereby incorporated by reference it their entirety.

[0294] In certain embodiments, BEVs are produced using a Bacmid Transfection agent, such as Promega FuGENE® HD, WFI water, or ThermoFisher Cellfectin® II Reagent. In certain embodiments, BEVs are produced and expanded in viral production cells, such as an insect cell.

[0295] In certain embodiments, the method utilizes seed cultures of viral production cells that include one or more BEVs, including baculovirus infected insect cells (BIICs). The seed BIICs have been transfected/transduced/infected with an Expression BEV which includes a viral expression construct, and also a Payload BEV which includes a payload construct. In certain embodiments, the seed cultures are harvested, divided into aliquots and frozen, and may be used at a later time to initiate transfection/transduction/infection of a naïve population of production cells. In certain embodiments, a bank of seed BIICs is stored at -80 °C or in LN2 vapor.

[0296] In some embodiments, the AAV expression constructs are capable of producing AAV particles in insect cells, including but not limited to *Spodoptera frugiperda* (Sf9) cells, provide high titers of viral vector product. Recombinant baculovirus encoding the viral expression construct and payload construct initiates a productive infection of viral vector replicating cells. Infectious baculovirus particles released from the primary infection secondarily infect additional cells in the culture, exponentially infecting the entire cell culture population in a number of infection cycles that is a function of the initial multiplicity of infection, *see* Urabe, M. *et al.* J Virol. 2006 Feb;80(4):1874-85, the contents of which are herein incorporated by reference in their entirety as related to the production and use of BEVs and viral particles.

[0297] In certain embodiments, stable viral producing cells permissive for baculovirus infection are engineered with at least one stable integrated copy of any of the elements necessary for AAV replication and vector production including, but not limited to, the entire AAV genome, Rep and Cap genes, Rep genes, Cap

genes, each Rep protein as a separate transcription cassette, each VP protein as a separate transcription cassette, the AAP (assembly activation protein), or at least one of the baculovirus helper genes with native or non-native promoters.

Large-scale production

[0298] In some embodiments, AAV particle production may be modified to increase the scale of production. Large scale viral production methods according to the present disclosure may include any of those taught in US Patent Nos. 5,756,283, 6,258,595, 6,261,551, 6,270,996, 6,281,010, 6,365,394, 6,475,769, 6,482,634, 6,485,966, 6,943,019, 6,953,690, 7,022,519, 7,238,526, 7,291,498 and 7,491,508 or International Publication Nos. WO1996039530, WO1998010088, WO1999014354, WO1999015685, WO1999047691, WO2000055342, WO2000075353 and WO2001023597, the contents of each of which are herein incorporated by reference in their entirety. Methods of increasing viral particle production scale typically comprise increasing the number of viral replication cells. In some embodiments, viral replication cells comprise adherent cells. To increase the scale of viral particle production by adherent viral replication cells, larger cell culture surfaces are required. In some cases, large-scale production methods comprise the use of roller bottles to increase cell culture surfaces. Other cell culture substrates with increased surface areas are known in the art. Examples of additional adherent cell culture products with increased surface areas include, but are not limited to CellSTACK®, CellCube® (Corning Corp., Corning, NY) and Nunc™ Cell Factory™ (Thermo Scientific, Waltham, MA.) In some cases, large-scale adherent cell surfaces may comprise from about 1,000 cm2 to about 100,000 cm2. In some cases, large-scale adherent cell cultures may comprise from about 107 to about 109 cells, from about 108 to about 1010 cells, from about 109 to about 1012 cells or at least 1012 cells. In some cases, large-scale adherent cultures may produce from about 109 to about 1012, from about 1010 to about 1013, from about 1011 to about 1014, from about 1012 to about 1015 or at least 1015 viral particles.

[0299] In some embodiments, large-scale viral production methods of the present disclosure may comprise the use of suspension cell cultures. Suspension cell culture allows for significantly increased numbers of cells. Typically, the number of adherent cells that can be grown on about 10-50 cm2 of surface area can be grown in about 1 cm3 volume in suspension.

[0300] Transfection of replication cells in large-scale culture formats may be carried out according to any methods known in the art. For large-scale adherent cell cultures, transfection methods may include, but are not limited to the use of inorganic compounds (e.g. calcium phosphate), organic compounds [e.g. polyethyleneimine (PEI)] or the use of non-chemical methods (e.g. electroporation.) With cells grown in suspension, transfection methods may include, but are not limited to the use of calcium phosphate and the use of PEI. In some cases, transfection of large-scale suspension cultures may be carried out according to the section entitled "Transfection Procedure" described in Feng, L. et al., 2008. Biotechnol Appl. Biochem.

50:121-32, the contents of which are herein incorporated by reference in their entirety. According to such embodiments, PEI-DNA complexes may be formed for introduction of plasmids to be transfected. In some cases, cells being transfected with PEI-DNA complexes may be 'shocked' prior to transfection. This comprises lowering cell culture temperatures to 4°C for a period of about 1 hour. In some cases, cell cultures may be shocked for a period of from about 10 minutes to about 5 hours. In some cases, cell cultures may be shocked at a temperature of from about 0°C to about 20°C.

[0301] In some cases, transfections may include one or more vectors for expression of an RNA effector molecule to reduce expression of nucleic acids from one or more AAV payload constructs. Such methods may enhance the production of viral particles by reducing cellular resources wasted on expressing payload constructs. In some cases, such methods may be carried according to those taught in US Publication No. US2014/0099666, the contents of which are herein incorporated by reference in their entirety.

[0302] AAV particles of the present disclosure may be prepared by any method known in the art, such as, but not limited to, mammalian cell production methods or insect cell production methods.

II. FORMULATION AND DELIVERY

Pharmaceutical compositions and formulation

[0303] The AAV particles of the present disclosure may be used to prepare a pharmaceutical composition.

[0304] It will be understood by the skilled artisan that the pharmaceutical compositions of the present disclosure are suitable for administration to humans, but that such compositions are also generally suitable for administration to any other animal, e.g., to non-human animals, e.g. non-human mammals. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with merely ordinary, if any, experimentation. Subjects to which administration of the pharmaceutical compositions is contemplated include, but are not limited to, humans and/or other primates.

[0305] In some embodiments, compositions are administered to humans, human patients or subjects. For the purposes of the present disclosure, the phrase "active ingredient" generally refers either to the synthetic siRNA duplexes, the vector, e.g., AAV vector, encoding the siRNA duplexes, or to the siRNA molecule delivered by a vector as described herein.

[0306] Formulations of the pharmaceutical compositions described herein may be prepared by any method known or hereafter developed in the art of pharmacology. In general, such preparatory methods include the step of bringing the active ingredient into association with an excipient and/or one or more other accessory ingredients, and then, if necessary and/or desirable, dividing, shaping and/or packaging the product into a desired single- or multi-dose unit.

[0307] Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition in accordance with the disclosure will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered.

[0308] The vector genomes comprising the nucleic acid sequence encoding the siRNA molecules of the present disclosure can be formulated using one or more excipients to: (1) increase stability; (2) increase cell transfection or transduction; (3) permit the sustained or delayed release; or (4) alter the biodistribution (e.g., target the AAV particles and/or vector genome to specific tissues or cell types such as brain and neurons).

[0309] Formulations of the present disclosure can include, without limitation, saline, lipidoids, liposomes, lipid nanoparticles, polymers, lipoplexes, core-shell nanoparticles, peptides, proteins, cells transfected with viral vectors such as, but not limited to, AAV particles (e.g., for transplantation into a subject), nanoparticle mimics and combinations thereof. Further, the viral vectors of the present disclosure (e.g., AAV particles) may be formulated using self-assembled nucleic acid nanoparticles.

[0310] A pharmaceutical composition in accordance with the present disclosure may be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a "unit dose" refers to a discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage such as, for example, one-half or one-third of such a dosage.

[0311] Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition in accordance with the present disclosure may vary, depending upon the identity, size, and/or condition of the subject being treated and further depending upon the route by which the composition is to be administered. For example, the composition may comprise between 0.1% and 99% (w/w) of the active ingredient. By way of example, the composition may comprise between 0.1% and 100%, e.g., between .5 and 50%, between 1-30%, between 5-80%, at least 80% (w/w) active ingredient.

[0312] In some embodiments, a pharmaceutically acceptable excipient may be at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% pure. In some embodiments, an excipient is approved for use for humans and for veterinary use. In some embodiments, an excipient may be approved by the United States Food and Drug Administration. In some embodiments, an excipient may be of pharmaceutical grade. In some embodiments, an excipient may meet the standards of the United States Pharmacopoeia (USP), the European Pharmacopoeia (EP), the British Pharmacopoeia, and/or the International Pharmacopoeia.

[0313] Excipients, which, as used herein, include, but are not limited to, any and all solvents, dispersion media, diluents, or other liquid vehicles, dispersion or suspension aids, surface active agents, isotonic agents,

thickening or emulsifying agents, preservatives, and the like, as suited to the particular dosage form desired. Various excipients for formulating pharmaceutical compositions and techniques for preparing the composition are known in the art (see Remington: The Science and Practice of Pharmacy, 21st Edition, A. R. Gennaro, Lippincott, Williams & Wilkins, Baltimore, MD, 2006; incorporated herein by reference in its entirety). The use of a conventional excipient medium may be contemplated within the scope of the present disclosure, except insofar as any conventional excipient medium may be incompatible with a substance or its derivatives, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutical composition.

[0314] Exemplary diluents include, but are not limited to, calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen phosphate, sodium phosphate lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, dry starch, cornstarch, powdered sugar, etc., and/or combinations thereof.

[0315] In some embodiments, the formulations may comprise at least one inactive ingredient. As used herein, the term "inactive ingredient" refers to one or more inactive agents included in formulations. In some embodiments, all, none or some of the inactive ingredients which may be used in the formulations of the present disclosure may be approved by the US Food and Drug Administration (FDA).

[0316] Formulations of vectors comprising the nucleic acid sequence for the siRNA molecules of the present disclosure may include cations or anions. In some embodiments, the formulations include metal cations such as, but not limited to, Zn2+, Ca2+, Cu2+, Mg+ and combinations thereof.

[0317] As used herein, "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form (e.g., by reacting the free base group with a suitable organic acid). Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. Representative acid addition salts include acetate, acetic acid, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzene sulfonic acid, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium,

methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. The pharmaceutically acceptable salts of the present disclosure include the conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present disclosure can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418, Pharmaceutical Salts: Properties, Selection, and Use, P.H. Stahl and C.G. Wermuth (eds.), Wiley-VCH, 2008, and Berge et al., Journal of Pharmaceutical Science, 66, 1-19 (1977); the content of each of which is incorporated herein by reference in its entirety.

[0318] The term "pharmaceutically acceptable solvate," as used herein, means a compound of the disclosure wherein molecules of a suitable solvent are incorporated in the crystal lattice. A suitable solvent is physiologically tolerable at the dosage administered. For example, solvates may be prepared by crystallization, recrystallization, or precipitation from a solution that includes organic solvents, water, or a mixture thereof. Examples of suitable solvents are ethanol, water (for example, mono-, di-, and tri-hydrates), N-methylpyrrolidinone (NMP), dimethyl sulfoxide (DMSO), N,N'-dimethylformamide (DMF), N,N'-dimethylacetamide (DMAC), 1,3-dimethyl-2-imidazolidinone (DMEU), 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone (DMPU), acetonitrile (ACN), propylene glycol, ethyl acetate, benzyl alcohol, 2-pyrrolidone, benzyl benzoate, and the like. When water is the solvent, the solvate is referred to as a "hydrate."

[0319] According to the present disclosure, the vector, e.g., AAV vector, comprising the nucleic acid sequence for the siRNA molecules of the present disclosure may be formulated for CNS delivery. Agents that cross the brain blood barrier (BBB) may be used. For example, some cell-penetrating peptides that can target the BBB endothelium may be used.

Inactive Ingredients

[0320] In some embodiments, formulations may comprise at least one excipient which is an inactive ingredient. As used herein, the term "inactive ingredient" refers to one or more inactive agents included in formulations. In some embodiments, all, none or some of the inactive ingredients which may be used in the formulations of the present disclosure may be approved by the US Food and Drug Administration (FDA).

[0321] Formulations of AAV particles and viral vectors carrying compositions described herein may include cations or anions. In some embodiments, the formulations include metal cations such as, but not limited to, Zn2+, Ca2+, Cu2+, Mg+ and combinations thereof. As a non-limiting example, formulations may

include polymers and compositions described herein complexed with a metal cation (See e.g., U.S. Pat. Nos. 6,265,389 and 6,555,525, each of which is herein incorporated by reference in its entirety).

Delivery

[0322] In some embodiments, the AAV particles and viral vector comprising compositions described herein may be administered or delivered using the methods for the delivery of AAV virions described in European Patent Application No. EP1857552, the contents of which are herein incorporated by reference in their entirety.

[0323] In some embodiments, the AAV particles and viral vector comprising compositions described herein may be administered or delivered using the methods for delivering proteins using AAV vectors described in European Patent Application No. EP2678433, the contents of which are herein incorporated by reference in their entirety.

[0324] In some embodiments, the AAV particles and viral vector comprising compositions described herein may be administered or delivered using the methods for delivering DNA molecules using AAV vectors described in US Patent No. US 5,858,351, the contents of which are herein incorporated by reference in their entirety.

[0325] In some embodiments, the AAV particles and viral vector comprising compositions described herein may be administered or delivered using the methods for delivering DNA to the bloodstream described in US Patent No. US 6,211,163, the contents of which are herein incorporated by reference in their entirety.

[0326] In some embodiments, the AAV particles and viral vector comprising compositions described herein may be administered or delivered using the methods for delivering AAV virions described in US Patent No. US 6,325,998, the contents of which are herein incorporated by reference in their entirety.

[0327] In some embodiments, the AAV particles and viral vector comprising compositions described herein may be administered or delivered using the methods for delivering a payload to the central nervous system described in US Patent No. US 7,588,757, the contents of which are herein incorporated by reference in their entirety.

[0328] In some embodiments, the AAV particles and viral vector comprising compositions described herein may be administered or delivered using the methods for delivering a payload described in US Patent No. US 8283151, the contents of which are herein incorporated by reference in their entirety.

[0329] In some embodiments, the AAV particles and viral vector comprising compositions described herein may be administered or delivered using the methods for delivering a payload using a glutamic acid decarboxylase (GAD) delivery vector described in International Patent Publication No. WO2001089583, the contents of which are herein incorporated by reference in their entirety.

[0330] In some embodiments, the AAV particles and viral vector comprising compositions described herein may be administered or delivered using the methods for delivering a payload to neural cells described

in International Patent Publication No. WO2012057363, the contents of which are herein incorporated by reference in their entirety.

Delivery to Cells

[0331] The present disclosure provides a method of delivering to a cell or tissue any of the above-described AAV polynucleotides or AAV genomes, comprising contacting the cell or tissue with said AAV polynucleotide or AAV genomes or contacting the cell or tissue with a particle comprising said AAV polynucleotide or AAV genome, or contacting the cell or tissue with any of the described compositions, including pharmaceutical compositions. The method of delivering the AAV polynucleotide or AAV genome to a cell or tissue can be accomplished in vitro, ex vivo, or in vivo.

Introduction into cells – AAV Vectors

[0332] The siRNA molecules (e.g., siRNA duplexes) of the present disclosure may be introduced into cells using any of a variety of approaches such as, but not limited to, viral vectors (e.g., AAV vectors or AAV particles). These viral vectors are engineered and optimized to facilitate the entry of siRNA molecule into cells that are not readily amendable to transfection. Also, some synthetic viral vectors possess an ability to integrate the shRNA into the cell genome, thereby leading to stable siRNA expression and long-term knockdown of a target gene. In this manner, viral vectors are engineered as vehicles for specific delivery while lacking the deleterious replication and/or integration features found in wild-type virus.

[0333] In some embodiments, the siRNA molecules of the present disclosure are introduced into a cell by contacting the cell with a composition comprising a lipophilic carrier and a vector, e.g., an AAV vector, comprising a nucleic acid sequence encoding the siRNA molecules of the present disclosure. In other embodiments, the siRNA molecule is introduced into a cell by transfecting or infecting the cell with a vector, e.g., an AAV vector, comprising nucleic acid sequences capable of producing the siRNA molecule when transcribed in the cell. In some embodiments, the siRNA molecule is introduced into a cell by injecting into the cell a vector, e.g., an AAV vector, comprising a nucleic acid sequence capable of producing the siRNA molecule when transcribed in the cell.

[0334] In some embodiments, prior to transfection, a vector, e.g., an AAV vector, comprising a nucleic acid sequence encoding the siRNA molecules of the present disclosure may be transfected into cells.

[0335] In other embodiments, the vectors, e.g., AAV vectors, comprising the nucleic acid sequence encoding the siRNA molecules of the present disclosure may be delivered into cells by electroporation (e.g. U.S. Patent Publication No. 20050014264; the content of which is herein incorporated by reference in its entirety).

[0336] Other methods for introducing vectors, e.g., AAV vectors, comprising the nucleic acid sequence for the siRNA molecules described herein may include photochemical internalization as described in U. S. Patent publication No. 20120264807; the content of which is herein incorporated by reference in its entirety.

[0337] In some embodiments, the formulations described herein may contain at least one vector, e.g., AAV vectors, comprising the nucleic acid sequence encoding the siRNA molecules described herein. In some embodiments, the siRNA molecules may target the MAPT transcript at one target site. In another embodiment, the formulation comprises a plurality of vectors, e.g., AAV vectors, each vector comprising a nucleic acid sequence encoding a siRNA molecule targeting the MAPT transcript at a different target site. The MAPT transcript may be targeted at 2, 3, 4, 5 or more than 5 sites.

[0338] In some embodiments, the vectors, e.g., AAV vectors, from any relevant species, such as, but not limited to, human, dog, mouse, rat or monkey may be introduced into cells.

[0339] In some embodiments, the vectors, e.g., AAV vectors, may be introduced into cells which are relevant to the disease to be treated. As a non-limiting example, the disease is Alzheimer's disease (AD), frontotemporal dementia (FTD), and/or Dravet syndrome (DS), and the target cells are neurons, e.g., interneurons, and astrocytes.

[0340] In some embodiments, the vectors, e.g., AAV vectors, may be introduced into cells which have a high level of endogenous expression of the target sequence.

[0341] In another embodiment, the vectors, e.g., AAV vectors, may be introduced into cells which have a low level of endogenous expression of the target sequence.

[0342] In some embodiments, the cells may be those which have a high efficiency of AAV transduction.

Delivery to Subjects

[0343] The present disclosure additionally provides a method of delivering to a subject, including a mammalian subject, any of the above-described AAV particles which comprises a vector genome encoding the sense, antisense and/or siRNA duplex described herein. As a non-limiting example, the mammalian subject may be a rodent, such as but not limited to, a transgenic mouse (e.g., htau, P301S, rTg4510, rTgTauEC, SCN1a-A1783V) or a non-transgenic (wild type) mouse. As another non-limiting example, the subject may be a non-human primate, such as but not limited to a rhesus macaque (*Macaca mulatta*). As yet another non-limiting example, the subject may be a human. In some embodiments, the human is a healthy human. In some embodiments, the human is a patient who has been diagnosed with a neurological disorder. In some embodiments, the human is a patient who has been diagnosed with or is suspected of having or is susceptible to a tauopathy. In some embodiments, the human is a patient who has been diagnosed with or is suspected of having or is susceptible to a epilepsy. Administration of any of the here within described AAV particles comprising a vector genome encoding a modulatory polynucleotide may be used to manage, prevent, slow the progression of, treat the symptoms associated with, and/or cure a disease afflicting the mammalian subject. The subject may be administered any of the described compositions, including pharmaceutical compositions.

[0344] In some embodiments, an AAV particle described herein, e.g., an AAV particle encoding an siRNA for targeting MAPT described herein, is administered via intravenous administration. In some embodiments, an AAV particle described herein, e.g., an AAV particle encoding an siRNA for targeting MAPT described herein, is administered via intracisternal magna administration.

[0345] The pharmaceutical compositions of AAV particles described herein may be characterized by one or more of bioavailability, therapeutic window and/or volume of distribution.

III. ADMINISTRATION AND DOSING

Administration

[0346] The AAV particles comprising a nucleic acid sequence encoding the siRNA molecules of the present disclosure may be administered by any route which results in a therapeutically effective outcome. These include, but are not limited to, within the parenchyma of an organ such as, but not limited to, a brain (e.g., intraparenchymal), spinal cord (intraparenchymal), corpus striatum (intrastriatal), enteral (into the intestine), gastroenteral, epidural, oral (by way of the mouth), transdermal, peridural, intracerebral (into the cerebrum), intracerebroventricular (into the cerebral ventricles), subpial (under the pia), epicutaneous (application onto the skin), intradermal, (into the skin itself), subcutaneous (under the skin), nasal administration (through the nose), intravenous (into a vein), intravenous bolus, intravenous drip, intraarterial (into an artery), intramuscular (into a muscle), intracardiac (into the heart), intraosseous infusion (into the bone marrow), intrathecal (into the spinal canal), intraganglionic (into the ganglion), intraperitoneal, (infusion or injection into the peritoneum), intravesical infusion, intravitreal, (through the eye), intracavernous injection (into a pathologic cavity) intracavitary (into the base of the penis), intravaginal administration, intrauterine, extra-amniotic administration, transdermal (diffusion through the intact skin for systemic distribution), transmucosal (diffusion through a mucous membrane), transvaginal, insufflation (snorting), sublingual, sublabial, enema, eye drops (onto the conjunctiva), in ear drops, auricular (in or by way of the ear), buccal (directed toward the cheek), conjunctival, cutaneous, dental (to a tooth or teeth), electro-osmosis, endocervical, endosinusial, endotracheal, extracorporeal, hemodialysis, infiltration, interstitial, intra-abdominal, intra-amniotic, intra-articular, intrabiliary, intrabronchial, intrabursal, intracartilaginous (within a cartilage), intracaudal (within the cauda equine), intracisternal (within the cisterna magna cerebellomedularis), intracorneal (within the cornea), dental intracornal, intracoronary (within the coronary arteries), intracorporus cavernosum (within the dilatable spaces of the corporus cavernosa of the penis), intradiscal (within a disc), intraductal (within a duct of a gland), intraduodenal (within the duodenum), intradural (within or beneath the dura), intraepidermal (to the epidermis), intraesophageal (to the esophagus), intragastric (within the stomach), intragingival (within the gingivae), intraileal (within the distal portion of the small intestine), intralesional (within or introduced directly to a localized lesion), intraluminal (within a lumen of a tube), intralymphatic (within the lymph), intramedullary (within the marrow cavity of a bone),

intrameningeal (within the meninges), intraocular (within the eye), intraovarian (within the ovary), intrapericardial (within the pericardium), intrapleural (within the pleura), intraprostatic (within the prostate gland), intrapulmonary (within the lungs or its bronchi), intrasinal (within the nasal or periorbital sinuses), intraspinal (within the vertebral column), intrasynovial (within the synovial cavity of a joint), intratendinous (within a tendon), intratesticular (within the testicle), intrathecal (within the cerebrospinal fluid at any level of the cerebrospinal axis), intrathoracic (within the thorax), intratubular (within the tubules of an organ), intratumor (within a tumor), intratympanic (within the aurus media), intravascular (within a vessel or vessels), intraventricular (within a ventricle), iontophoresis (by means of electric current where ions of soluble salts migrate into the tissues of the body), irrigation (to bathe or flush open wounds or body cavities), laryngeal (directly upon the larynx), nasogastric (through the nose and into the stomach), occlusive dressing technique (topical route administration which is then covered by a dressing which occludes the area), ophthalmic (to the external eye), oropharyngeal (directly to the mouth and pharynx), parenteral, percutaneous, periarticular, peridural, perineural, periodontal, rectal, respiratory (within the respiratory tract by inhaling orally or nasally for local or systemic effect), retrobulbar (behind the pons or behind the eyeball), soft tissue, subarachnoid, subconjunctival, submucosal, topical, transplacental (through or across the placenta), transtracheal (through the wall of the trachea), transtympanic (across or through the tympanic cavity), ureteral (to the ureter), urethral (to the urethra), vaginal, caudal block, diagnostic, nerve block, biliary perfusion, cardiac perfusion, photopheresis or spinal.

[0347] In specific embodiments, compositions of AAV particles comprising a nucleic acid sequence encoding the siRNA molecules of the present disclosure may be administered in a way which facilitates entry to cells of the central nervous system (e.g., cells of the brain and spinal cord). The cells of the brain may be localized within one or specific brain areas. Non-limiting examples of brain areas may be the frontal, temporal, or parietal lobes, basal ganglia, thalamus, cerebellum and brainstem.

[0348] In specific embodiments, compositions of AAV particles comprising a nucleic acid sequence encoding the siRNA molecules of the present disclosure may be administered in a way which facilitates the vectors or siRNA molecule to enter the central nervous system and penetrate into cortical neurons, hippocampal neurons, entorhinal neurons, cholinergic neurons, interneurons, dentate gyrus granule cells, glial cells, and oligodendrocytes.

[0349] In some embodiments, the AAV particles comprising a nucleic acid sequence encoding the siRNA molecules of the present disclosure may be administered by intramuscular (IM) injection. In some embodiments, the AAV particles comprising a nucleic acid sequence encoding the siRNA molecules of the present disclosure may be administered by intraperitoneal (IP) injection. In some embodiments, the AAV particles comprising a nucleic acid sequence encoding the siRNA molecules of the present disclosure may be administered by intracerebroventricular (ICV) injection. In some embodiments, the AAV particles comprising

a nucleic acid sequence encoding the siRNA molecules of the present disclosure may be administered via intraparenchymal (IPa) injection into the spinal cord and/or brain. In some embodiments, the AAV particles comprising a nucleic acid sequence encoding the siRNA molecules of the present disclosure may be administered via intra-cisterna magna (ICM) injection. In some embodiments, the AAV particles comprising a nucleic acid sequence encoding the siRNA molecules of the present disclosure may be administered by via intrathecal (IT) injection. In some embodiments, the AAV particles comprising a nucleic acid sequence encoding the siRNA molecules of the present disclosure may be administered via subpial injection. In some embodiments, the AAV particles comprising a nucleic acid sequence encoding the siRNA molecules of the present disclosure may be administered via ICM injection and any other route of administration described herein. As a non-limiting example, the AAV particles comprising a nucleic acid sequence encoding the siRNA molecules of the present disclosure may be administered via combined ICM and IPa, e.g. intrathalamic, injection.

[0350] In some embodiments, an AAV particle described herein (e.g., an AAV particle comprising an AAV capsid polypeptide, e.g., an AAV capsid variant) may be administered to a subject by systemic administration. In some embodiments, the systemic administration is intravenous administration. In another embodiment, the systemic administration is intraarterial administration. In some embodiments, an AAV particle of the present disclosure may be administered to a subject by intravenous administration. In some embodiments, the intravenous administration may be achieved by subcutaneous delivery. In some embodiments, the AAV particle is administered to the subject via focused ultrasound (FUS), e.g., coupled with the intravenous administration of microbubbles (FUS-MB) or MRI-guided FUS coupled with intravenous administration, e.g., as described in Terstappen et al. (Nat Rev Drug Discovery, doi.org/10.1038/s41573-021-00139-y (2021)), the contents of which are incorporated herein by reference in its entirety. In some embodiments, the AAV particle, e.g., an AAV particle described herein, is administered to the subject intravenously. In some embodiments, the subject is a human.

[0351] In some embodiments, AAV particles that express siRNA duplexes of the present disclosure may be administered to a subject by peripheral injections (e.g., intravenous) and/or intranasal delivery. It was disclosed in the art that the peripheral administration of AAV particles for siRNA duplexes can be transported to the central nervous system, for example, to the neurons (e.g., U. S. Patent Publication Nos. 20100240739; and 20100130594; the content of each of which is incorporated herein by reference in their entirety).

[0352] In other embodiments, compositions comprising at least one AAV particle comprising a nucleic acid sequence encoding the siRNA molecules of the present disclosure may be administered to a subject by intracranial delivery (See, e.g., U. S. Pat. No. 8,119,611; the content of which is incorporated herein by reference in its entirety).

[0353] The AAV particle comprising a nucleic acid sequence encoding the siRNA molecules of the present disclosure may be administered in any suitable form, either as a liquid solution or suspension, as a solid form suitable for liquid solution or suspension in a liquid solution. The siRNA duplexes may be formulated with any appropriate and pharmaceutically acceptable excipient.

[0354] The AAV particle comprising a nucleic acid sequence encoding the siRNA molecules of the present disclosure may be administered in a therapeutically effective amount, e.g., an amount that is sufficient to alleviate and/or prevent at least one symptom associated with the disease, or provide improvement in the condition of the subject.

[0355] In some embodiments, the AAV particle may be administered to the CNS in a therapeutically effective amount to improve function and/or survival for a subject with AD, FTD, and/or DS.

[0356] In some embodiments, an siRNA for targeting MAPT; or AAV particle or pharmaceutical composition described herein comprising or encoding a siRNA for inhibiting MAPT can be administered or used to treat mild cognitive impairment (MCI), neurodegenerative disease, Alzheimer's disease (AD), frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), frontotemporal lobar degeneration (FTLD), frontotemporal dementia (FTD), chronic traumatic encephalopathy (CTE), progressive supranuclear palsy (PSP), Down's syndrome, Pick's disease, corticobasal degeneration (CBD), corticobasal syndrome, amyotrophic lateral sclerosis (ALS), a prion disease, Creutzfeldt-Jakob disease (CJD), multiple system atrophy, tangle-only dementia, stroke, and progressive subcortical gliosis.

[0357] In some embodiments, an siRNA that targets MAPT described herein or an AAV particle comprising a payload, e.g., a siRNA that binds to MAPT described herein, can be used to treat a traumatic brain injury (TBI), e.g., as described in Edwards et al. "Traumatic Brain Injury Induces Tau Aggregation and Spreading," *J. Neurotrauma*, 2020, 37(1):80-92, the contents of which are hereby incorporated by reference in their entirety.

[0358] In some embodiments, the AAV particle may be administered to a subject in a therapeutically effective amount for the siRNA duplexes or dsRNA to target cortical neurons. In another embodiment, the AAV particle may be administered to a subject in a therapeutically effective amount for the siRNA duplexes or dsRNA to target cholinergic neurons. In yet another embodiment, the AAV particle may be administered to a subject in a therapeutically effective amount for the siRNA duplexes or dsRNA to target interneurons. In yet another embodiment, the AAV particle may be administered to a subject in a therapeutically effective amount for the siRNA duplexes or dsRNA to target glial cells.

[0359] In some embodiments, the siRNA duplexes or dsRNA may target MAPT transcript and reduce the levels of RNA transcript and/or resultant protein product(s). As another non-limiting example, the siRNA duplexes or dsRNA target MAPT transcript and can suppress or inhibit or silence MAPT transcript and reduce tau mediated toxicity.

[0360] In some embodiments, the AAV particle may be administered via intracerebroventricular (ICV) injection in a therapeutically effective amount to transduce cortical neurons, interneurons, hippocampal neurons, entorhinal neurons, cholinergic neurons, and/or glial cells such as, but not limited to, oligodendrocytes and/or astrocytes. As a non-limiting example, the vector may be administered via intraventricular injection into the lateral ventricle.

[0361] In some embodiments, the AAV particle may be administered via intracisternal injection in a therapeutically effective amount to transduce cortical neurons, interneurons, hippocampal neurons, entorhinal neurons, cholinergic neurons, and/or glial cells such as, but not limited to, oligodendrocytes and/or astrocytes. As a non-limiting example, the vector may be administered via intraventricular injection into the cisterna magna. In some embodiments, the AAV particle may be administered using intrathecal (IT) infusion in a therapeutically effective amount to transduce cortical neurons, interneurons, hippocampal neurons, entorhinal neurons, cholinergic neurons, and/or glial cells such as, but not limited to, oligodendrocytes and/or astrocytes. As a non-limiting example, the vector may be administered into the lumbar spinal cord. In some embodiments, the AAV particle may be administered using intramuscular (IM) infusion in a therapeutically effective amount to transduce cortical neurons, interneurons, hippocampal neurons, entorhinal neurons, cholinergic neurons, and/or glial cells such as, but not limited to, oligodendrocytes and/or astrocytes. As a non-limiting example, the vector may be administered into the deltoid. In some embodiments, the AAV particle may be administered to the CNS in a therapeutically effective amount for the siRNA duplexes or dsRNA to target cells in various brain areas. As a non-limiting example, the brain areas may be the hippocampus, cortex, thalamus, brainstem, striatum, and cerebellum. In some embodiments, the AAV particle may be administered to the CNS in a therapeutically effective amount for the siRNA duplexes or dsRNA to target cells in the olfactory bulb. In some embodiments, the AAV particle may be administered to the CNS in a therapeutically effective amount for the siRNA duplexes or dsRNA to target cells in the liver.

[0362] In some embodiments, the AAV particle comprising a modulatory polynucleotide may be formulated. As a non-limiting example, the baricity and/or osmolality of the formulation may be optimized to ensure optimal drug distribution in the central nervous system or a region or component of the central nervous system.

[0363] In some embodiments, the AAV particle comprising a modulatory polynucleotide may be delivered to a subject via a single route administration. In some embodiments, the AAV particle comprising a modulatory polynucleotide may be delivered to a subject via a multi-site route of administration. A subject may be administered the AAV particle comprising a modulatory polynucleotide at 2, 3, 4, 5 or more than 5 sites. In some embodiments, a subject may be administered the AAV particle comprising a modulatory polynucleotide described herein using a bolus injection. In some embodiments, the efficacy of administration of the AAV particle comprising a modulatory polynucleotide using a bolus injection may be measured by

monitoring the gene transfer to the spinal cord, brain stem, or cortex. The biodistribution and cellular tropism may be monitored by any methods known in the art, such as, but not limited to, immunostaining, and the vector genome levels may be measured by digital PCR.

[0364] In some embodiments, a subject may be administered the AAV particle comprising a modulatory polynucleotide described herein using sustained delivery over a period of minutes, hours or days. The infusion rate may be changed depending on the subject, distribution, formulation or another delivery parameter.

[0365] In some embodiments, the AAV particle described herein is administered via putamen and caudate infusion. As a non-limiting example, the dual infusion provides a broad striatal distribution as well as a frontal and temporal cortical distribution.

[0366] In some embodiments, an AAV particle or pharmaceutical composition described herein is administered intravenously.

[0367] In some embodiments, the selection of subjects for administration of the AAV particle described herein and/or the effectiveness of the dose, route of administration and/or volume of administration may be evaluated using imaging of the perivascular spaces (PVS) which are also known as Virchow-Robin spaces. PVS surround the arterioles and venules as they perforate brain parenchyma and are filled with cerebrospinal fluid (CSF)/interstitial fluid. PVS are common in the midbrain, basal ganglia, and centrum semiovale. While not wishing to be bound by theory, PVS may play a role in the normal clearance of metabolites and have been associated with worse cognition and several disease states including Parkinson's disease. PVS are usually normal in size but they can increase in size in a number of disease states. Potter et al. (Cerebrovasc Dis. 2015 Jan; 39(4): 224–231; the contents of which are herein incorporated by reference in its entirety) developed a grading method where they studied a full range of PVS and rated basal ganglia, centrum semiovale and midbrain PVS. They used the frequency and range of PVS used by Mac and Lullich et al. (J Neurol Neurosurg Psychiatry. 2004 Nov;75(11):1519-23; the contents of which are herein incorporated by reference in its entirety) and Potter et al. gave 5 ratings to basal ganglia and centrum semiovale PVS: 0 (none), 1 (1-10), 2 (11-20), 3 (21-40) and 4 (>40) and 2 ratings to midbrain PVS: 0 (non-visible) or 1 (visible). The user guide for the rating system by Potter et al. can be found at: sbirc.ed.ac.uk/documents/epvs-rating-scale-user-guide.pdf, the contents of which are hereby incorporated by reference in their entirety.

[0368] In some embodiments, administration of an siRNA or modulatory polynucleotide for targeting MAPT or an AAV viral genome encoding an siRNA or modulatory polynucleotide for targeting MAPT described herein results in a reduction of tau pathology, e.g., a decrease in a biomarker of tau pathology (e.g., ^{18}F-flortaucipir, plasma ptau 181, or ^{18}F-PM-PBB3), e.g., as measured by a PET scan or PET scan in combination with Braak neuropathological staging and/or serum biomarker staining.

Dosing

[0369] The pharmaceutical compositions of the present disclosure may be administered to a subject using any amount effective for reducing, preventing and/or treating a disease and/or disorder. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the disease, the particular composition, its mode of administration, its mode of activity, and the like.

[0370] The compositions of the present disclosure are typically formulated in unit dosage form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of the compositions of the present disclosure may be decided by the attending physician within the scope of sound medical judgment. The specific therapeutic effectiveness for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the siRNA duplexes employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts.

[0371] As a non-limiting example, the dose may be determined based on the total volume of CSF of a subject. For example, cynomolgus monkeys have a total estimated cerebrospinal fluid (CSF) volume of approximately 6 to 12 mL and humans have a total estimated CSF of approximately 120 to 150 mL, a factor of at least 10 to 12-fold. Therefore, a factor of 10x to 12x may be used to determine a human dose based on the dose to a cynomolgus monkey. In some embodiments, the factor is 10x. In another embodiment the factor is 11x. In yet another embodiment, the factor is 12x. In yet another embodiment, the factor may be, but is not limited to, 10x, 10.1x, 10.2x, 10.3x, 10.4x, 10.5x, 10.6x, 10.7x, 10.8x, 10.9x, 11x, 11.1x, 11.2x, 11.3x, 11.4x, 11.5x, 11.6x, 11.7x, 11.8x, 11.9x, 12x, 12.1x, 12.2x, 12.3x, 12.4x, and 12.5x.

[0372] In some embodiments, the age and sex of a subject may be used to determine the dose of the compositions of the present disclosure. As a non-limiting example, a subject who is older may receive a larger dose (e.g., 5-10%, 10-20%, 15-30% ,20-50%, 25-50% or at least 1%, 2%, 3%, 4%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more than 90% more) of the composition as compared to a younger subject. As another non-limiting example, a subject who is younger may receive a larger dose (e.g., 5-10%, 10-20%, 15-30%, 20-50%, 25-50% or at least 1%, 2%, 3%, 4%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more than 90% more) of the composition as compared to an older subject. As yet another non-limiting example, a subject who is female may receive a larger dose (e.g., 5-10%, 10-20%, 15-30% ,20-50%, 25-50% or at least 1%, 2%, 3%, 4%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more than 90% more) of the composition as compared to a male subject. As yet another non-limiting example, a subject who is male may receive a larger dose (e.g., 5-10%, 10-20%, 15-30% ,20-50%, 25-50% or

at least 1%, 2%, 3%, 4%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more than 90% more) of the composition as compared to a female subject

[0373] In some specific embodiments, the doses of AAV particles for delivering siRNA duplexes of the present disclosure may be adapted depending on the disease condition, the subject and the treatment strategy.

[0374] In some embodiments, delivery of the compositions in accordance with the present disclosure to cells comprises a rate of delivery defined by [VG/hour = mL/hour * VG/mL] wherein VG is vector genomes, VG/mL is composition concentration, and mL/hour is rate of prolonged delivery.

[0375] In some embodiments, delivery of compositions in accordance with the present disclosure to cells may comprise a total concentration per subject between about $1x10^6$ VG and about $1x10^{16}$ VG. In some embodiments, delivery may comprise a composition concentration of about $1x10^6$, $2x10^6$, $3x10^6$, $4x10^6$, $5x10^6$, $6x10^6$, $7x10^6$, $8x10^6$, $9x10^6$, $1x10^7$, $2x10^7$, $3x10^7$, $4x10^7$, $5x10^7$, $6x10^7$, $7x10^7$, $8x10^7$, $9x10^7$, $1x10^8$, $2x10^8$, $3x10^8$, $4x10^8$, $5x10^8$, $6x10^8$, $7x10^8$, $8x10^8$, $9x10^8$, $1x10^9$, $2x10^9$, $3x10^9$, $4x10^9$, $5x10^9$, $6x10^9$, $7x10^9$, $8x10^9$, $9x10^9$, $1x10^{10}$, $2x10^{10}$, $3x10^{10}$, $4x10^{10}$, $5x10^{10}$, $6x10^{10}$, $7x10^{10}$, $8x10^{10}$, $9x10^{10}$, $1x10^{11}$, $1.1x10^{11}$, $1.2x10^{11}$, $1.3x10^{11}$, $1.4x10^{11}$, $1.5x10^{11}$, $1.6x10^{11}$, $1.7x10^{11}$, $1.8x10^{11}$, $1.9x10^{11}$, $2x10^{11}$, $2.1x10^{11}$, $2.2x10^{11}$, $2.3x10^{11}$, $2.4x10^{11}$, $2.5x10^{11}$, $2.6x10^{11}$, $2.7x10^{11}$, $2.8x10^{11}$, $2.9x10^{11}$, $3x10^{11}$, $4x10^{11}$, $5x10^{11}$, $6x10^{11}$, $7x10^{11}$, $7.1x10^{11}$, $7.2x10^{11}$, $7.3x10^{11}$, $7.4x10^{11}$, $7.5x10^{11}$, $7.6x10^{11}$, $7.7x10^{11}$, $7.8x10^{11}$, $7.9x10^{11}$, $8x10^{11}$, $9x10^{11}$, $1x10^{12}$, $1.1\ x10^{12}$, $1.2x10^{12}$, $1.3x10^{12}$, $1.4x10^{12}$, $1.5x10^{12}$, $1.6x10^{12}$, $1.7x10^{12}$, $1.8x10^{12}$, $1.9x10^{12}$, $2x10^{12}$, $2.1x10^{12}$, $2.2x10^{12}$, $2.3x10^{12}$, $2.4x10^{12}$, $2.5x10^{12}$, $2.6x10^{12}$, $2.7x10^{12}$, $2.8x10^{12}$, $2.9x10^{12}$, $3x10^{12}$, $3.1x10^{12}$, $3.2x10^{12}$, $3.3x10^{12}$, $3.4x10^{12}$, $3.5x10^{12}$, $3.6x10^{12}$, $3.7x10^{12}$, $3.8x10^{12}$, $3.9x10^{12}$, $4x10^{12}$, $4.1x10^{12}$, $4.2x10^{12}$, $4.3x10^{12}$, $4.4x10^{12}$, $4.5x10^{12}$,$4.6x10^{12}$, $4.7x10^{12}$, $4.8x10^{12}$, $4.9x10^{12}$, $5x10^{12}$, $6x10^{12}$, $6.1x10^{12}$, $6.2x10^{12}$, $6.3x10^{12}$, $6.4x10^{12}$, $6.5x10^{12}$, $6.6x10^{12}$, $6.7x10^{12}$, $6.8x10^{12}$, $6.9x10^{12}$, $7x10^{12}$, $8x10^{12}$, $8.1x10^{12}$, $8.2x10^{12}$, $8.3x10^{12}$, $8.4x10^{12}$, $8.5x10^{12}$, $8.6x10^{12}$, $8.7x10^{12}$, $8.8\ x10^{12}$, $8.9x10^{12}$, $9x10^{12}$, $1x10^{13}$, $1.1x10^{13}$, $1.2x10^{13}$, $1.3x10^{13}$, $1.4x10^{13}$, $1.5x10^{13}$, $1.6x10^{13}$, $1.7x10^{13}$, $1.8x10^{13}$, $1.9x10^{13}$, $2x10^{13}$, $3x10^{13}$, $4x10^{13}$, $5x10^{13}$, $6x10^{13}$, $6.7x10^{13}$, $7x10^{13}$, $8x10^{13}$, $9x10^{13}$, $1x10^{14}$, $2x10^{14}$, $3x10^{14}$, $4x10^{14}$, $5x10^{14}$, $6x10^{14}$, $7x10^{14}$, $8x10^{14}$, $9x10^{14}$, $1x10^{15}$, $2x10^{15}$, $3x10^{15}$, $4x10^{15}$, $5x10^{15}$, $6x10^{15}$, $7x10^{15}$, $8x10^{15}$, $9x10^{15}$, or $1x10^{16}$ VG/subject.

[0376] In some embodiments, delivery of compositions in accordance with the present disclosure to cells may comprise a total concentration per subject between about $1x10^6$ VG/kg and about $1x10^{16}$ VG/kg. In some embodiments, delivery may comprise a composition concentration of about $1x10^6$, $2x10^6$, $3x10^6$, $4x10^6$, $5x10^6$, $6x10^6$, $7x10^6$, $8x10^6$, $9x10^6$, $1x10^7$, $2x10^7$, $3x10^7$, $4x10^7$, $5x10^7$, $6x10^7$, $7x10^7$, $8x10^7$, $9x10^7$, $1x10^8$, $2x10^8$, $3x10^8$, $4x10^8$, $5x10^8$, $6x10^8$, $7x10^8$, $8x10^8$, $9x10^8$, $1x10^9$, $2x10^9$, $3x10^9$, $4x10^9$, $5x10^9$, $6x10^9$, $7x10^9$, $8x10^9$, $9x10^9$, $1x10^{10}$, $2x10^{10}$, $3x10^{10}$, $4x10^{10}$, $5x10^{10}$, $6x10^{10}$, $7x10^{10}$, $8x10^{10}$, $9x10^{10}$, $1x10^{11}$, $1.1x10^{11}$, $1.2x10^{11}$, $1.3x10^{11}$, $1.4x10^{11}$, $1.5x10^{11}$, $1.6x10^{11}$, $1.7x10^{11}$, $1.8x10^{11}$, $1.9x10^{11}$, $2x10^{11}$, $2.1x10^{11}$, $2.2x10^{11}$, $2.3x10^{11}$, $2.4x10^{11}$, $2.5x10^{11}$, $2.6x10^{11}$, $2.7x10^{11}$, $2.8x10^{11}$, $2.9x10^{11}$, $3x10^{11}$, $4x10^{11}$, $5x10^{11}$, $6x10^{11}$, $7x10^{11}$, $7.1x10^{11}$, $7.2x10^{11}$, $7.3x10^{11}$, $7.4x10^{11}$, $7.5x10^{11}$, $7.6x10^{11}$, $7.7x10^{11}$, $7.8x10^{11}$, $7.9x10^{11}$, $8x10^{11}$, $9x10^{11}$, $1x10^{12}$,

1.1 x10^{12}, 1.2x10^{12}, 1.3x10^{12}, 1.4x10^{12}, 1.5x10^{12}, 1.6x10^{12}, 1.7x10^{12}, 1.8x10^{12}, 1.9x10^{12}, 2x10^{12}, 2.1x10^{12}, 2.2x10^{12}, 2.3x10^{12}, 2.4x10^{12}, 2.5x10^{12}, 2.6x10^{12}, 2.7x10^{12}, 2.8x10^{12}, 2.9x10^{12}, 3x10^{12}, 3.1x10^{12}, 3.2x10^{12}, 3.3x10^{12}, 3.4x10^{12}, 3.5x10^{12}, 3.6x10^{12}, 3.7x10^{12}, 3.8x10^{12}, 3.9x10^{12}, 4x10^{12}, 4.1x10^{12}, 4.2x10^{12}, 4.3x10^{12}, 4.4x10^{12}, 4.5x10^{12},4.6x10^{12}, 4.7x10^{12}, 4.8x10^{12}, 4.9x10^{12}, 5x10^{12}, 6x10^{12}, 6.1x10^{12}, 6.2x10^{12}, 6.3x10^{12}, 6.4x10^{12}, 6.5x10^{12}, 6.6x10^{12}, 6.7x10^{12}, 6.8x10^{12}, 6.9x10^{12}, 7x10^{12}, 8x10^{12}, 8.1x10^{12}, 8.2x10^{12}, 8.3x10^{12}, 8.4x10^{12}, 8.5x10^{12}, 8.6x10^{12}, 8.7x10^{12}, 8.8 x10^{12}, 8.9x10^{12}, 9x10^{12}, 1x10^{13}, 1.1x10^{13}, 1.2x10^{13}, 1.3x10^{13}, 1.4x10^{13}, 1.5x10^{13}, 1.6x10^{13}, 1.7x10^{13}, 1.8x10^{13}, 1.9x10^{13}, 2x10^{13}, 3x10^{13}, 4x10^{13}, 5x10^{13}, 6x10^{13}, 6.7x10^{13}, 7x10^{13}, 8x10^{13}, 9x10^{13}, 1x10^{14}, 2x10^{14}, 3x10^{14}, 4x10^{14}, 5x10^{14}, 6x10^{14}, 7x10^{14}, 8x10^{14}, 9x10^{14}, 1x10^{15}, 2x10^{15}, 3x10^{15}, 4x10^{15}, 5x10^{15}, 6x10^{15}, 7x10^{15}, 8x10^{15}, 9x10^{15}, or 1x10^{16} VG/kg.

[0377] In some embodiments, about 10^5 to 10^6 vector genome (unit) may be administered per dose.

[0378] In some embodiments, delivery of the compositions in accordance with the present disclosure to cells may comprise a total concentration between about 1x10^6 VG/mL and about 1x10^{16} VG/mL. In some embodiments, delivery may comprise a composition concentration of about 1x10^6, 2x10^6, 3x10^6, 4x10^6, 5x10^6, 6x10^6, 7x10^6, 8x10^6, 9x10^6, 1x10^7, 2x10^7, 3x10^7, 4x10^7, 5x10^7, 6x10^7, 7x10^7, 8x10^7, 9x10^7, 1x10^8, 2x10^8, 3x10^8, 4x10^8, 5x10^8, 6x10^8, 7x10^8, 8x10^8, 9x10^8, 1x10^9, 2x10^9, 3x10^9, 4x10^9, 5x10^9, 6x10^9, 7x10^9, 8x10^9, 9x10^9, 1x10^{10}, 2x10^{10}, 3x10^{10}, 4x10^{10}, 5x10^{10}, 6x10^{10}, 7x10^{10}, 8x10^{10}, 9x10^{10}, 1x10^{11}, 1.1x10^{11}, 1.2x10^{11}, 1.3x10^{11}, 1.4x10^{11}, 1.5x10^{11}, 1.6x10^{11}, 1.7x10^{11}, 1.8x10^{11}, 1.9x10^{11}, 2x10^{11}, 3x10^{11}, 4x10^{11}, 5x10^{11}, 6x10^{11}, 7x10^{11}, 8x10^{11}, 9x10^{11}, 1x10^{12}, 1.1x10^{12}, 1.2x10^{12}, 1.3x10^{12}, 1.4x10^{12}, 1.5x10^{12}, 1.6x10^{12}, 1.7x10^{12}, 1.8x10^{12}, 1.9x10^{12}, 2x10^{12}, 2.1x10^{12}, 2.2x10^{12}, 2.3x10^{12}, 2.4x10^{12}, 2.5x10^{12}, 2.6x10^{12}, 2.7x10^{12}, 2.8x10^{12}, 2.9x10^{12}, 3x10^{12}, 3.1x10^{12}, 3.2x10^{12}, 3.3x10^{12}, 3.4x10^{12}, 3.5x10^{12}, 3.6x10^{12}, 3.7x10^{12}, 3.8x10^{12}, 3.9x10^{12}, 4x10^{12}, 4.1x10^{12}, 4.2x10^{12}, 4.3x10^{12}, 4.4x10^{12}, 4.5x10^{12}, 4.6x10^{12}, 4.7x10^{12}, 4.8x10^{12}, 4.9x10^{12}, 5x10^{12}, 6x10^{12}, 6.1x10^{12}, 6.2x10^{12}, 6.3x10^{12}, 6.4x10^{12}, 6.5x10^{12}, 6.6x10^{12}, 6.7x10^{12}, 6.8x10^{12}, 6.9x10^{12}, 7x10^{12}, 8x10^{12}, 9x10^{12}, 1x10^{13}, 1.1x10^{13}, 1.2x10^{13}, 1.3x10^{13}, 1.4x10^{13}, 1.5x10^{13}, 1.6x10^{13}, 1.7x10^{13}, 1.8x10^{13}, 1.9x10^{13}, 2x10^{13}, 3x10^{13}, 4x10^{13}, 5x10^{13}, 6x10^{13}, 6.7x10^{13}, 7x10^{13}, 8x10^{13}, 9x10^{13}, 1x10^{14}, 2x10^{14}, 3x10^{14}, 4x10^{14}, 5x10^{14}, 6x10^{14}, 7x10^{14}, 8x10^{14}, 9x10^{14}, 1x10^{15}, 2x10^{15}, 3x10^{15}, 4x10^{15}, 5x10^{15}, 6x10^{15}, 7x10^{15}, 8x10^{15}, 9x10^{15}, or 1x10^{16} VG/mL.

[0379] In certain embodiments, the desired siRNA duplex dosage may be delivered using multiple administrations (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations). When multiple administrations are employed, split dosing regimens such as those described herein may be used. As used herein, a "split dose" is the division of single unit dose or total daily dose into two or more doses, e.g., two or more administrations of the single unit dose. As used herein, a "single unit dose" is a dose of any modulatory polynucleotide therapeutic administered in one dose/at one time/single route/single point of contact, i.e., single administration event. As used herein, a "total daily dose" is an amount given or prescribed in a 24-hour period. It may be administered as a single unit dose. In some

embodiments, the AAV particles comprising the modulatory polynucleotides of the present disclosure are administered to a subject in split doses. They may be formulated in buffer only or in a formulation described herein.

[0380] In some embodiments, the dose, concentration and/or volume of the composition described herein may be adjusted depending on the contribution of the thalamus to cortical and subcortical distribution after administration. The administration may be intracerebroventricular (ICV), intrathalamic, intraparenchymal into the spinal cord, subpial, and/or intrathecal administration.

[0381] In some embodiments, the dose, concentration and/or volume of the composition described herein may be adjusted depending on the cortical and neuraxial distribution following administration by intravenous, intracerebroventricular, intrathalamic, intraparenchymal into the spinal cord, subpial, and/or intrathecal delivery.

IV. METHODS AND USES OF THE COMPOSITIONS OF THE DISCLOSURE

[0382] The present disclosure relates to modulatory polynucleotides, e.g., RNA or DNA molecules, which may be used as therapeutic agents as RNA interference mediated gene silencing can specifically inhibit targeted gene expression.

[0383] Described herein are double stranded RNA (dsRNA) molecules (e.g., small interfering RNA, siRNA) targeting MAPT mRNA, pharmaceutical compositions comprising such dsRNA molecules, as well as processes of their design. The present disclosure also provides methods of their use for inhibiting MAPT gene expression, MAPT transcript expression and/or MAPT protein production, which may be used for treating neurodegenerative disease, such as, but not limited to tauopathies, and other indications described here. Such indications may include, but are not limited to mild cognitive impairment (MCI), neurodegenerative disease, Alzheimer's disease (AD), frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), frontotemporal lobar degeneration (FTLD), frontotemporal dementia (FTD), chronic traumatic encephalopathy (CTE), progressive supranuclear palsy (PSP), Down's syndrome, Pick's disease, corticobasal degeneration (CBD), corticobasal syndrome, amyotrophic lateral sclerosis (ALS), a prion disease, Creutzfeldt-Jakob disease (CJD), multiple system atrophy, tangle-only dementia, stroke, and progressive subcortical gliosis. As a non-limiting example, the tauopathy is Alzheimer's disease (AD). As a non-limiting example, the tauopathy is frontotemporal dementia (FTD). As a non-limiting example, the tauopathy is Frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17). As a non-limiting example, the tauopathy is progressive supranuclear palsy (PSP). As a non-limiting example, the tauopathy is central nervous system trauma. As a non-limiting example, the tauopathy is chronic traumatic encephalopathy (CTE). As a non-limiting example, the tauopathy is traumatic brain injury (TBI). As a non-limiting example, the tauopathy is prion disease. As a non-limiting example, the tauopathy is neurodegeneration. As a non-limiting

example, the tauopathy is stroke. As a non-limiting example, the tauopathy is an epilepsy or a variant thereof, such as, but not limited to, Dravet syndrome (DS).

[0384] In particular, the AAV particles comprising modulatory polynucleotides comprising a nucleic acid sequence encoding the siRNA molecules of the present disclosure may be delivered into specific types of targeted cells, including neurons such as cortical neurons, hippocampal neurons (e.g., dentate gyrus granule cell neurons), entorhinal neurons, cholinergic neurons, and interneurons (e.g., inhibitory interneurons), or glial cells such as oligodendrocytes, astrocytes and microglia.

[0385] In some embodiments, the present disclosure provides methods for treating, or ameliorating Alzheimer's disease (AD), frontotemporal dementia (FTD), and/or Dravet syndrome (DS) associated with abnormal tau RNA and/or protein products in a subject in need of treatment, the method comprising administering to the subject a pharmaceutically effective amount of at least one siRNA duplex or a nucleic acid encoding a siRNA duplex targeting the MAPT transcript, delivering said siRNA duplex (or encoded duplex) into targeted cells, inhibiting MAPT transcript expression and production of toxic proteins, and ameliorating symptoms of AD and/or FTD in the subject.

[0386] In some embodiments, the siRNA molecules or the AAV particles encoding such siRNA molecules may be introduced directly into the central nervous system of the subject, for example, by intraparenchymal (IPa), subpial, intrathecal, intracranial injection or intravenous (IV) administration.

[0387] In some embodiments, the pharmaceutical composition of the present disclosure is used as a solo therapy. In other embodiments, the pharmaceutical composition of the present disclosure is used in combination therapy. 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.

[0388] 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 neuron degeneration.

[0389] In some embodiments, the present disclosure provides methods for treating, or ameliorating Alzheimer's disease (AD), frontotemporal dementia (FTD), and/or Dravet syndrome (DS) by administering to a subject in need thereof a therapeutically effective amount of an siRNA or AAV particle described herein.

Alzheimer's disease

[0390] Alzheimer Disease (AD) is a debilitating neurodegenerative disease currently afflicting more than 35 million people worldwide, with that number expected to double in coming decades. Symptomatic treatments have been available for many years, but these treatments do not address the underlying

pathophysiology. Recent clinical trials using these and other treatments have largely failed and, to date, no known cure has been identified.

[0391] The AD brain is characterized by the presence of two forms of pathological aggregates, the extracellular plaques composed of β-amyloid (Aβ) and the intracellular neurofibrillary tangles (NFT) comprised of hyperphosphorylated microtubule associated protein tau. Based on early genetic findings, β-amyloid alterations were thought to initiate disease, with changes in tau considered downstream. Thus, most clinical trials have been Aβ-centric. Although no mutations of the MAPT gene have been linked to AD, such alterations have been shown to result in a family of dementias known as tauopathies, demonstrating that changes in tau can contribute to neurodegenerative processes. Tau is normally a very soluble protein known to associate with microtubules based on the extent of its phosphorylation. Hyperphosphorylation of tau depresses its binding to microtubules and microtubule assembly activity. In tauopathies, the tau becomes hyperphosphorylated, misfolds and aggregates as NFT of paired helical filaments (PHF), twisted ribbons or straight filaments. In AD, NFT pathology, rather than plaque pathology, correlates more strongly with neuropathological markers such as neuronal loss, synaptic deficits, severity of disease and cognitive decline. NFT pathology marches through the brain in a stereotyped manner and animal studies suggest a trans-cellular propagation mechanism along neuronal connections.

[0392] Several approaches have been proposed for therapeutically interfering with the progression of tau pathology to prevent or hasten downstream molecular, cellular, and/or cognitive consequences. Given that NFT are composed of hyperphosphorylated, misfolded and aggregated tau, each pathological form has yielded a set of avidly pursued targets. Tau reduction has also been a goal of many treatment strategies as continued- or over-production of tau, and specifically mutant tau, may exacerbate disease progression, e.g., by contributing to already impaired neuronal trafficking processes, or accelerating NFT formation. Introducing agents that limit phosphorylation, block misfolding, prevent aggregation, or reduce tau expression have all generated promising results, however the success of these strategies has been limited. As such, there is presently no known effective treatment for tauopathies. Thus, there remains a need in the art for effectively reducing, preventing and/or treating tauopathies.

[0393] The delivery of vectored RNAi targeting MAPT of present disclosure may be used to treat subjects suffering from AD and other tauopathies. In some cases, methods of the present disclosure may be used to treat subjects suspected of developing AD or other tauopathies.

Frontotemporal dementia

[0394] Frontotemporal dementia (FTD), also referred to as frontotemporal lobar degeneration (FTLD), is a neurological condition often associated with AD. FTD represents a group of brain disorders that result from the progressive degeneration of the temporal and frontal lobes of the brain. FTD is the second most common form of early-onset (<65 years) dementia after Alzheimer's disease (AD). Common signs and symptoms of

FTD include significant changes in behavior and personality (such as lack of judgment and inhibition, apathy, and repetitive compulsive behavior), impairment or loss of speech and language function, and movement disorders (such as rigidity, muscle spasms and muscle weakness).

[0395] The prevalence of FTD in the United States was estimated to around 60,000 cases (Knopman and Roberts. J Mol Neurosci. 2011;45(3):330-5). Signs and symptoms typically manifest in late adulthood, more commonly between the ages of 45 and 65, approximately equally affecting men and women. The course of the disease ranges from 2 to over 20 years, with a mean course of 8 years from the onset of symptoms.

[0396] Clinicopathological and genetic data have long supported the concept that AD and FTD may represent an overlapping continuum of disease with a shared underlying pathogenesis (Lillo and Hodges, J Clin Neurosci. 2009;16(9):1131-5; Neumann et al., Science. 2006;314(5796):130-3). They often co-occur in a family, and the prevalence of frontal lobe impairment in AD populations may approach 50%. Similarly, as many as half of FTD patients develop clinical symptoms of motor neuron dysfunction (Blitterswijk et al., Curr Opin Neurol. 2012; 25(6): 689–700). Both diseases commonly show accumulations of abnormal proteins including the DNA/RNA binding protein TDP-43 (Neumann et al., Science. 2006;314(5796):130-3).

Frontotemporal dementia and parkinsonism linked to chromosome 17

[0397] Although Alzheimer's disease is, in part, characterized by the presence of tau pathology, no known mutations in the MAPT gene have been causally linked to the disease. Mutations in the MAPT gene have been shown to lead to an autosomal dominantly inherited tauopathy known as frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) and demonstrate that alterations in tau can lead to neurodegenerative changes in the brain. Mutations in the MAPT gene that lead to FTDP-17 are thought to influence splicing patterns, thereby leading to an elevated proportion of tau with four microtubule binding domains (rather than three). These molecules are considered to be more amyloidogenic, meaning they are more likely to become hyperphosphorylated and more likely to aggregate into NFT (Hutton, M. et al., 1998, Nature 393(6686):702-5). Although physically and behaviorally, FTDP-17 patients can appear quite similar to Alzheimer's disease patients, at autopsy FTDP-17 brains lack the prominent Aβ plaque pathology of an AD brain (Gotz, J. et al., 2012, British Journal of Pharmacology 165(5):1246-59). Therapeutically targeting tau protein may ameliorate and prevent degenerative changes in the brain and potentially lead to improved cognitive ability.

[0398] As of today, there is no treatment to prevent, slow the progression, or cure FTDP-17. Medication may be prescribed to reduce aggressive, agitated or dangerous behavior. There remains a need for therapy affecting the underlying pathophysiology, such as RNAi therapies targeting tau protein.

[0399] In some embodiments, the vectored RNAi delivery of the present disclosure may be used to treat subjects suffering from FTDP-17. In some cases, methods of the present disclosure may be used to treat subjects suspected of developing FTDP-17.

Chronic traumatic encephalopathy

[0400] Unlike the genetically linked tauopathies, chronic traumatic encephalopathy (CTE) is a degenerative tauopathy linked to repeated head injuries. The disease was first described in boxers who behaved "punch drunk" and has since been identified primarily in athletes that engage in American football, ice hockey, wrestling and other contact sports. The brains of those suffering from CTE are characterized by distinctive patterns of brain atrophy accompanied by accumulation of hyperphosphorylated species of aggregated tau in NFT. In CTE, pathological changes in tau are accompanied by a number of other pathobiological processes, such as inflammation (Daneshvar, D.H. et al., 2015 Mol Cell Neurosci 66(Pt B): 81-90). Targeting the tau may provide reprieve from the progression of the disease and may allow cognitive improvement.

[0401] As of today, there is no medical therapy to treat or cure CTE. The condition is only diagnosed after death, due to lack of *in vivo* techniques to identify CTE specific biomarkers. There remains a need for therapy affecting the underlying pathophysiology, such as vectored RNAi therapies targeting tau protein.

[0402] In some embodiments, the vectored RNAi delivery methods of the present disclosure may be used to treat subjects suffering from CTE. In some cases, methods of the present disclosure may be used to treat subjects suspected of developing CTE.

Prion diseases

[0403] Prion diseases, also known as transmissible spongiform encephalopathies (TSEs), are a group of rare progressive conditions affecting the nervous system. The related conditions are rare and are typically caused by mutations in the PRNP gene which enables production of the prion protein. Gene mutations lead to an abnormally structured prion protein. Alternatively, the abnormal prion may be acquired by exposure from an outside source, e.g. by consumption of beef products containing the abnormal prion protein. Abnormal prions are misfolded, causing the brain tissue to degenerate rapidly. Prion diseases include, but are not limited to, Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker syndrome (GSS), fatal insomnia (FFI), variably protease-sensitive prionopathy (VPSPr), and kuru. Prion diseases are rare. Approximately 350 cases of prion diseases are diagnosed in the US annually.

[0404] CJD is a degenerative brain disorder characterized by problems with muscular coordination, personality changes including mental impairment, impaired vision, involuntary muscle jerks, weakness and eventually coma. The most common categories of CJD are sporadic, hereditary (familial) due to a genetic mutation, and acquired. Sporadic CJD is the most common form affecting people with no known risk factors for the disease. The acquired form of CJD is transmitted by exposure of the brain and nervous system tissue to the prion. As an example, variant CJD (vCDJ) is linked to a bovine spongiform encephalopathy (BSE), also known as a 'mad cow' disease. CJD is fatal and patients typically die within one year of diagnosis.

[0405] Prion diseases are associated with an infectious agent consisting of an alternative conformational isoform of the prion protein, PrPSc. PrPSc replication is considered to occur through an induction of the infectious prion in the normal prion protein (PrPC). The replication occurs without a nucleic acid.

[0406] As of today, there is no therapy to manage or cure CJD, or other prion diseases. Typically, treatment is aimed at alleviating symptoms and increasing comfortability of the patient, e.g. with pain relievers. There remains a need for therapy affecting the underlying pathophysiology, such as vectored RNAi therapies targeting the prion protein.

[0407] In some embodiments, vectored RNAi delivery methods of the present disclosure may be used to treat subjects suffering from a prion disease. In some cases, methods of the present disclosure may be used to treat subjects suspected of developing a prion disease.

Neurodegeneration and stroke

[0408] Neurodegenerative diseases and other diseases of the nervous system share many common features. Neurodegenerative diseases, in particular, are a group of conditions characterized by progressive loss of neuronal structure and/or function, ultimately leading to neuronal cell death. Neurons are the building blocks of the nervous system(s) and are generally unable to reproduce and/or be replaced, and therefore neuron damage and/or death is especially devastating. Other, non-degenerating diseases that lead to neuronal cell loss, such as stroke, have similarly debilitating outcomes. Targeting molecules that contribute to the deteriorating cell structure or function may prove beneficial generally for treatment of nervous system diseases, neurodegenerative disease and/or stroke.

[0409] Many neurodegenerative diseases are associated with aggregation of misfolded proteins, including, but not limited to, alpha synuclein, tau, amyloid β, prion proteins, TDP-43, and huntingtin (see, e.g. De Genst et al., 2014, Biochim Biophys Acta;1844(11):1907-1919, and Yu et al., 2013, Neurotherapeutics.; 10(3): 459–472, references therein). The aggregation results from disease-specific conversion of soluble proteins to an insoluble, highly ordered fibrillary deposit. This conversion is thought to prevent the proper disposal or degradation of the misfolded protein, thereby leading to further aggregation. In some embodiments, the vectored RNAi delivery of the present disclosure is utilized to target the aforementioned antigens (e.g., misfolded or aggregated proteins).

[0410] AAV Particles and methods of using the AAV particles described in the present disclosure may be used to prevent, manage and/or treat tauopathies. As a non-limiting example, the AAV particles of the present disclosure comprise a nucleic acid sequence encoding at least one of the sequences described in Table 5.

Dravet syndrome and epilepsy

[0411] Dravet syndrome (DS), also known as severe myoclonic epilepsy of infancy (SMEI), is a type of early-onset epilepsy that manifests as intractable epilepsy and neurodevelopmental delays, with genetic basis in the mutation of the voltage-gated calcium channel, alpha-1 subunit (SCN1A) gene on chromosome 2q24

(see, e.g., Anwar et al., Cureus. 2019 Jun; 11(6): e5006 and Claes et al., Am J Hum Genet. 2001 Jun;68(6):1327-32. Epub 2001 May 15, the contents of each of which are incorporated herein by reference in their entirety). While more than 90% of these mutations are thought to be de novo (sporadic), familial mutations (e.g., missense) account for only 5-10% of cases. DS is rare, with incidence estimated at 1 in 15000 to 1 in 40,000, arising in males and females in equal proportion (see, e.g., Wu at al., Pediatrics. 2015 Nov; 136(5): e1310–e1315; Rosander et al., Dev Med Child Neurol. 2015 Jul;57(7):628-633; and, Hurst Epilepsia. 1990 Jul-Aug;31(4):397-400, the contents of each of which are incorporated herein by reference in their entirety).

[0412] Age of onset for DS typically occurs in the first year of life at ~6 months (1-18 months, range) with 10-20% mortality by the age of 10 (Shmuely et al., Epilepsy Behav. 2016 Nov;64(Pt A):69-74, the contents of which are incorporated herein by reference in their entirety). Indeed, it is estimated that 14-20% of DS patients succumb to sudden unexpected death in epilepsy (SUDEP), the cause of which is largely unknown, but that may be associated with cardiac or respiratory complications (Genton et al., 2011, Epilepsia. 2011 Apr;52 Suppl 2:44-9 the contents of which are incorporated herein by reference in their entirety). During adulthood, DS commonly manifests as persistent motor and cognitive functions (see, e.g., Anwar et al., Cureus. 2019 Jun; 11(6): e5006, the contents of which are incorporated herein by reference in their entirety). Several different seizure categories have been identified in DS patients such as, but not limited to, convulsive, myoclonic, absence, focal, obtundation status, and tonic seizures. In addition to pleomorphic seizure activity, motor dysfunction may include ataxia, tremors, dysarthria, pyramidal, and extrapyramidal signs. Most patients also exhibit cognitive, visual and visuomotor, and language impairment. Psychiatric conditions including aggressiveness, agitation, obsessiveness, perseveration, and hoarding behavior may also occur in DS patients.

[0413] Due to its intractable nature, treatment options for DS are somewhat limited, but may include anti-epileptic drugs, cannabinoids, ketogenic diet therapy, and surgery (e.g., deep brain stimulation). Despite the development of a number antiepileptic drugs over the course of the past few decades, the efficacy of such treatments has not substantially improved, in particular, as several patients suffer from seizures that are drug-refractory (Pérez-Pérez et al., Epilepsy Behav. 2019 Aug 1:106430, the contents of which are incorporated herein by reference in their entirety). DS is among the most drug-resistant forms of epilepsy (see, e.g., Chiron Dev Med Child Neurol. 2011 Apr;53 Suppl 2:16-8, the contents of which are incorporated herein by reference in their entirety). Thus, there remains a need in the art for effectively reducing, preventing, and/or treating epilepsies or variants thereof, such as, but not limited to, DS and other intractable childhood epilepsies.

[0414] Several lines of evidence suggest that antiepileptic effects of tau reduction and/or ablation may offer a new avenue for the treatment of drug-resistant epilepsy. Indeed, the genetic ablation of tau has been shown to reduces hyperexcitability in AD mouse lines, induced seizure models, and genetic *in vivo* models of

epilepsy alike. For instance, a ~50% reduction of tau by has been shown to improve survival, reduce seizure frequency, decrease neuronal hyperexcitability, and rescue behavioral impairment in a mouse model of DS (Gheyara et al., Ann Neurol. 2014 Sep;76(3):443-56, the contents of which are incorporated herein by reference in their entirety). In two chemically induced seizure mouse models, antisense oligonucleotide (ASO)-mediated reduction of tau tightly tracked with attenuation of seizure severity (Devos et al., J Neurosci. 2013 Jul 31;33(31):12887-97, the contents of which are incorporated herein by reference in their entirety). Levels of tau protein in cerebrospinal fluid (CSF) has also been linked to epilepsy severity, including in both AD and epileptic patients (see, e.g., Tábuas-Pereira et al., Epilepsy Behav. 2019 Sep;98(Pt A):207-209, the contents of which are incorporated herein by reference in their entirety). Though as yet not fully understood, possible contributing mechanisms to support of tau (MAPT) knockdown as a genetic modifier for epilepsy, include: enhanced activity of inhibitory neurons; reduced N-methyl-D-aspartate receptor (NMDAR)-dependent excitotoxicity; and, reduced mossy fiber sprouting (Roberson et al., J Neurosci. 2011 Jan 12;31(2):700-11; Miyamoto et al., Mol Neurodegener. 2017 May 19;12(1):41; and, Cavarsan et al., Front Neurol. 2018 Nov 30;9:1023, the contents of each of which are incorporated herein by reference in their entirety). Together, tau reduction may be therapeutically beneficial for DS and other epilepsies, including those that frequently occur in AD.

[0415] In some embodiments, the vectored RNAi delivery methods of the present disclosure may be used to treat subjects suffering from DS, or other epilepsy or variant thereof. In some cases, methods of the present disclosure may be used to treat subjects suspected of developing DS, or other epilepsy or variant thereof.

Animal models

[0416] Vectored RNAi delivery methods of the present disclosure (e.g., delivery of the siRNA or the AAV particles of the present disclosure) may be used to inhibit or suppress expression of MAPT transcript in a subject, including a non-human animal. In some embodiments, the non-human animal may be a rodent, such as, but not limited to, a mouse. As a non-limiting example, the mouse may be a transgenic mouse. Non-limiting examples of a transgenic mice include htau, P301S, rTg4510, and rTgTauEC transgenic mice.

[0417] In some embodiments, delivery of the siRNA or AAV particles of the present disclosure may be used to prevent, manage and/or treat tauopathy in the P301S mouse model of tauopathy, as described by Allen et al., J Neurosci. 2002 Nov 1;22(21):9340-51, the contents of which are incorporated herein by reference in their entirety; or the htau mouse model of tauopathy, as described in Andorfer et al., J Neurochem. 2003 Aug;86(3):582-90 and WO199620218, the contents of which are incorporated herein by reference in their entirety). In some embodiments, sarkosyl insoluble paired helical filament (PHF) tau, or like substance, from Alzheimer's disease (AD) and/or other tauopathy disease brain or biofluid, may be introduced, e.g., via injection, into a brain area, e.g. the hippocampus, of htau mice, using methods similar to those previously described by Hu et al., Alzheimer's Dement. 2016 Oct;12(10):1066-1077 and Gerson et al., J Neurotrauma.

2016 Nov 15;33(22):2034-2043, the contents of each of which are incorporated herein by reference in their entirety. In some embodiments, aged htau mice may be monitored for the onset of cognitive deficits as previously described by Polydoro et al., 2009 and Geiszler et al., 2016 (Polydoro et al., J Neurosci. 2009 Aug 26;29(34):10741-9 and Geiszler et al., Neuroscience. 2016 Aug 4;329:98-111, the contents of each of which are incorporated herein by reference in their entirety). In some embodiments, tau immunoreactivity may be measured in the seeding and in the first and secondary synaptic brain areas using anti-tau antibodies, such as but not limited to the AT100 antibody ($pSer^{212}/pSer^{214}$; ThermoFisher, Waltham, MA; described in United States Patent No US6121003, the contents of which are herein incorporated in their entirety).

[0418] In some embodiments, brain lysate from mice may be tested for tau seeding activity using a biosensor as described by, e.g., Gui et al., Sensors (Basel). 2017 Jul; 17(7):1623 and Frost et al., J Biol Chem. 2009 May 8;284(19):12845-52, the contents of each of which are incorporated herein by reference in their entirety; or Frost et al., J Biol Chem. 2009 May 8;284(19):12845-52, the contents of which are incorporated herein by reference in their entirety.

[0419] In some embodiments, delivery of the siRNA or AAV particles of the present disclosure may be used to inhibit or suppress expression of MAPT transcript in a subject, including a non-human animal. The non-human animal may be a non-human primate (NHP), such as but not limited to, a rhesus macaque (*Macaca mulatta*). In some embodiments, delivery of the siRNA or AAV particles of the present disclosure may be used to inhibit or suppress expression of MAPT transcript in non-human animals, such as but not limited to, htau mice, P301S mice, and/or NHPs.

V. DEFINITIONS

[0420] Unless stated otherwise, the following terms and phrases have the meanings described below. The definitions are not meant to be limiting in nature and serve to provide a clearer understanding of certain aspects of the present disclosure.

[0421] 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.

[0422] It is also noted that the term "comprising" is intended to be open and permits but does not require the inclusion of additional elements or steps. When the term "comprising" is used herein, the term "consisting of" and "consisting essentially thereof" is thus also encompassed and disclosed.

[0423] 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.

[0424] *Adeno-associated virus (AAV):* As used herein, the term "adeno-associated virus" or "AAV" refers to members of the dependovirus genus or a variant, e.g., a functional variant, thereof. In some embodiments, the AAV is wildtype, or naturally occurring. In some embodiments, the AAV is recombinant.

[0425] *AAV Particle:* As used herein, an "AAV particle" refers to an AAV capsid, e.g., an AAV capsid variant, and a polynucleotide, e.g., a viral genome. In some embodiments, the viral genome of the AAV particle comprises at least one payload region and at least one ITR. In some embodiments, an AAV particle of the disclosure is an AAV particle comprising an AAV variant. In some embodiments, the AAV particle is capable of delivering a nucleic acid, e.g., a payload region, encoding a payload to cells, typically, mammalian, e.g., human, cells. In some embodiments, an AAV particle of the present disclosure may be produced recombinantly. In some embodiments, an AAV particle may be derived from any serotype, described herein or known in the art, including combinations of serotypes (e.g., "pseudotyped" AAV) or from various genomes (e.g., single stranded or self-complementary). In some embodiments, the AAV particle may be replication defective and/or targeted. It is to be understood that reference to the AAV particle of the disclosure also includes pharmaceutical compositions thereof, even if not explicitly recited.

[0426] *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.

[0427] *Antisense strand:* As used herein, the term "antisense strand" or "the first strand" or "the guide strand" of a siRNA molecule refers to a strand that is substantially complementary to a target sequence. In some embodiments, the antisense strand 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 the gene targeted for silencing. In some embodiments, the antisense strand is 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.

[0428] *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. When referring to a measurable value such as an amount, a temporal duration, and the like, the term is meant to encompass is meant to encompass variations of ±20% or in some instances ±10%, or in some instances ±5%, or in some instances

±1%, or in some instances ±0.1% from the specified value, as such variations are appropriate to perform the disclosed methods.

[0429] *Capsid*: As used herein, the term "capsid" refers to the exterior, e.g., a protein shell, of a virus particle, e.g., an AAV particle, that is substantially (e.g., >50%, >90%, or 100%) protein. In some embodiments, the capsid is an AAV capsid comprising an AAV capsid protein described herein, e.g., a VP1, VP2, and/or VP3 polypeptide. The AAV capsid protein can be a wild-type AAV capsid protein or a variant, e.g., a structural and/or functional variant from a wild-type or a reference capsid protein, referred to herein as an "AAV capsid variant." In some embodiments, the AAV capsid variant described herein has the ability to enclose, e.g., encapsulate, a viral genome and/or is capable of entry into a cell, e.g., a mammalian cell. In some embodiments, the AAV capsid variant described herein may have modified tropism compared to that of a wild-type AAV capsid, e.g., the corresponding wild-type capsid.

[0430] *Complementary and substantially complementary:* As used herein, the term "complementary" refers to the ability of polynucleotides to form base pairs with one another. Base pairs are typically formed by hydrogen bonds between nucleotide units in antiparallel polynucleotide strands. Complementary polynucleotide strands can form base pairs in the Watson-Crick manner (e.g., A to T, A to U, C to G), or in any other manner that allows for the formation of duplexes. As persons skilled in the art are aware, when using RNA as opposed to DNA, uracil rather than thymine is the base that is considered to be complementary to adenine. However, when a U is denoted in the context of the present disclosure, the ability to substitute a T is implied, unless otherwise stated. Perfect complementarity or 100% complementarity refers to the situation in which each nucleotide unit of one polynucleotide strand can form a hydrogen bond with a nucleotide unit of a second polynucleotide strand. Less than perfect complementarity refers to the situation in which some, but not all, nucleotide units of two strands can form hydrogen bond with each other. For example, for two 20-mers, if only two base pairs on each strand can form a hydrogen bond with each other, the polynucleotide strands exhibit 10% complementarity. In the same example, if 18 base pairs on each strand can form hydrogen bonds with each other, the polynucleotide strands exhibit 90% complementarity. The term "complementary" as used herein can encompass fully complementary, partially complementary, or substantially complementary. As used herein, the term "substantially complementary" means that the siRNA has a sequence (e.g., in the antisense strand) which is sufficient to bind the desired target mRNA, and to trigger the RNA silencing of the target mRNA. "Fully complementary", "perfect complementarity", or "100% complementarity" refers to the situation in which each nucleotide unit of one polynucleotide or oligonucleotide strand can base-pair with a nucleotide unit of a second polynucleotide or oligonucleotide strand.

[0431] *Conservative amino acid substitution*: As used herein, a "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain.

Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine).

[0432] *Conserved*: As used herein, the term "conserved" refers to nucleotides or amino acid residues of a polynucleotide sequence or polypeptide sequence, respectively, that are those that occur unaltered in the same position of two or more sequences being compared. Nucleotides or amino acids that are relatively conserved are those that are conserved amongst more related sequences than nucleotides or amino acids appearing elsewhere in the sequences.

[0433] In certain embodiments, two or more sequences are said to be "completely conserved" if they are 100% identical to one another. In certain embodiments, two or more sequences are said to be "highly conserved" if they are at least 70% identical, at least 80% identical, at least 90% identical, or at least 95% identical to one another. In certain embodiments, two or more sequences are said to be "highly conserved" if they are about 70% identical, about 80% identical, about 90% identical, about 95%, about 98%, or about 99% identical to one another. In certain embodiments, two or more sequences are said to be "conserved" if they are at least 30% identical, at least 40% identical, at least 50% identical, at least 60% identical, at least 70% identical, at least 80% identical, at least 90% identical, or at least 95% identical to one another. In certain embodiments, two or more sequences are said to be "conserved" if they are about 30% identical, about 40% identical, about 50% identical, about 60% identical, about 70% identical, about 80% identical, about 90% identical, about 95% identical, about 98% identical, or about 99% identical to one another. Conservation of sequence may apply to the entire length of a polynucleotide or polypeptide or may apply to a portion, region or feature thereof.

[0434] *Encapsulate:* As used herein, the term "encapsulate" means to enclose, surround or encase. As an example, a capsid protein, e.g., an AAV capsid variant, often encapsulates a viral genome. In some embodiments, encapsulate within a capsid, e.g., an AAV capsid variant, encompasses 100% coverage by a capsid, as well as less than 100% coverage, e.g., 95% or less. For example, gaps or discontinuities may be present in the capsid so long as the viral genome is retained in the capsid, e.g., prior to entry into a cell.

[0435] *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 AD, an effective amount of an agent is, for example, an amount sufficient to achieve treatment, as defined herein, of AD, as compared to the response obtained without administration of the agent.

[0436] *Expression*: As used herein, "expression" of a nucleic acid sequence refers to production of an RNA template from a DNA sequence (*e.g.*, by transcription). In some embodiments, expression further comprises one or more of: (1) processing of an RNA transcript (*e.g.*, by splicing, editing, 5′ cap formation, and/or 3′ end processing); (2) translation of an RNA into a polypeptide or protein; and (3) post-translational modification of a polypeptide or protein.

[0437] *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. In some embodiments, a fragment is a nucleic acid fragment.

[0438] *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 certain 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 present 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 certain 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 present 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.

[0439] *Identity*: As used herein, "identity" refers to the subunit sequence identity between two polymeric molecules, e.g., between two nucleic acid molecules, such as, two DNA molecules or two RNA molecules, or between two polypeptide molecules. When a subunit position in both of the two molecules is occupied by the same monomeric subunit; e.g., if a position in each of two DNA molecules is occupied by adenine, then they are identical at that position. The identity between two sequences is a direct function of the number of matching positions; e.g., if half (e.g., five positions in a polymer ten subunits in length) of the positions in two sequences are identical, the two sequences are 50% identical; if 90% of the positions (e.g., 9 of 10), are matched, the two sequences are 90% identical. 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)).

[0440] *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.

[0441] *Isolated*: As used herein, the term "isolated" refers to a substance or entity that is altered or removed from the natural state, e.g., altered or removed from at least some of the components with which it is associated in the natural state. For example, a nucleic acid or a peptide naturally present in a living animal is

not "isolated," but the same nucleic acid or peptide partially or completely separated from the coexisting materials of its natural state is "isolated." An isolated nucleic acid or protein can exist in substantially purified form, or can exist in a non-native environment such as, for example, a host cell. Such polynucleotides could be part of a vector and/or such polynucleotides or polypeptides could be part of a composition, and still be isolated in that such vector or composition is not part of the environment in which it is found in nature. In some embodiments, an isolated nucleic acid is recombinant or may be incorporated into a vector.

[0442] *MicroRNA (miRNA) binding site:* As used herein, a "miR binding site" comprises a nucleic acid sequence (whether RNA or DNA, e.g., differ by "U" of RNA or "T" in DNA) that is capable of binding, or binds, in whole or in part to a microRNA (miR), e.g., through complete or partial hybridization. Typically, such binding occurs between the miR and the miR binding site in the reverse complement orientation. In some embodiments, the miR binding site is transcribed from the AAV viral genome encoding the miR binding site.

[0443] In some embodiments, a miR binding site may be encoded or transcribed in series. Such a "miR binding site series" or "miR BSs" may include two or more miR binding sites having the same or different nucleic acid sequence.

[0444] Spacer: As used here, a "spacer" is generally any selected nucleic acid sequence of, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides in length, which is located between two or more consecutive miR binding site sequences. Spacers may also be more than 10 nucleotides in length, e.g., 20, 30, 40, or 50 or more than 50 nucleotides.

[0445] *Modulatory polynucleotide:* As used herein, a "modulatory polynucleotide" is any nucleic acid sequence(s) which functions to modulate (either increase or decrease) the level or amount of a target gene expression, transcript expression and/or protein production.

[0446] *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).

[0447] *Nucleic Acid:* "nucleic acid," "nucleic acid molecule," "polynucleotide," or "polynucleotide molecule" refers to deoxyribonucleic acids (DNA) or ribonucleic acids (RNA) and polymers thereof in either single- or double-stranded form. Unless specifically limited, the term encompasses nucleic acids containing known analogues of natural nucleotides that have similar binding properties as the reference nucleic acid and are metabolized in a manner similar to naturally occurring nucleotides. In some embodiments, a "nucleic acid," "nucleic acid molecule," "polynucleotide," or "polynucleotide molecule" comprise a nucleotide/nucleoside derivative or analog. Unless otherwise indicated, a particular nucleic acid sequence also implicitly encompasses conservatively modified variants thereof (for example, degenerate codon substitutions, for example, conservative substitutions), alleles, orthologs, SNPs, and complementary sequences as well as the sequence explicitly indicated. Specifically, degenerate codon substitutions, for

example, conservative substitutions may be achieved by generating sequences in which the third position of one or more selected (or all) codons is substituted with mixed-base and/or deoxyinosine residues (Batzer et al., Nucleic Acid Res. 19:5081 (1991); Ohtsuka et al., J. Biol. Chem. 260:2605-2608 (1985); and Rossolini et al., Mol. Cell. Probes 8:91-98 (1994)).

[0448] *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.

[0449] *Polypeptide:* As used herein, "polypeptide" means a polymer of amino acid residues (natural or unnatural) linked together most often by peptide bonds. The term, as used herein, refers to proteins, polypeptides, and peptides of any size, structure, or function. If the polypeptide is a peptide, it will be at least about 2, 3, 4, or at least 5 amino acid residues long. Thus, polypeptides include gene products, naturally occurring polypeptides, synthetic polypeptides, homologs, orthologs, paralogs, fragments and other equivalents, variants, and analogs of the foregoing. A polypeptide may be a single molecule or may be a multi-molecular complex such as a dimer, trimer or tetramer. They may also comprise single chain or multichain polypeptides and may be associated or linked. The term polypeptide may also apply to amino acid polymers in which one or more amino acid residues are an artificial chemical analogue of a corresponding naturally occurring amino acid.

[0450] *Polypeptide variant:* The term "polypeptide variant" refers to molecules which differ in their amino acid sequence from a native or reference sequence. The amino acid sequence variants may possess substitutions, deletions, and/or insertions at certain positions within the amino acid sequence, as compared to a native or reference sequence. In some embodiments, a variant comprises a sequence having at least about 50%, at least about 80%, or at least about 90%, identical (homologous) to a native or a reference sequence.

[0451] *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.

[0452] *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.

[0453] *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.

[0454] *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.

[0455] 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.

[0456] *RNA/DNA:* 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. In some embodiments, 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).

[0457] *RNA interfering:* As used herein, the term "RNA interfering" or "RNAi" refers to a sequence specific regulatory mechanism that mediates cleavage of an RNA transcript, e.g., via an RNA-induced silencing complex (RISC) pathway. In some embodiments RNAi is mediated by RNA molecules which results in the inhibition or interfering or "silencing" of the expression of a corresponding protein-coding gene. In some embodiments, 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. In some embodiments, dsRNA molecules can be introduced into cells exogenously. In some embodiments, 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, e.g., small interfering RNAs (siRNAs).

[0458] *Sample:* As used herein, the term "sample" or "biological sample" refers to a subset of its tissues, cells, nucleic acids, or component parts (e.g., body fluids, including but not limited to blood, serum, mucus,

lymphatic fluid, synovial fluid, cerebrospinal fluid, saliva, amniotic fluid, amniotic cord blood, urine, vaginal fluid, and semen).

[0459] *Self-complementary viral particle*: As used herein, a "self-complementary viral particle" is a particle included of at least two components, a protein capsid and a polynucleotide sequence encoding a self-complementary genome enclosed within the capsid.

[0460] *Sense Strand:* As used herein, the term "sense strand" or "second strand" or "passenger strand" or "sense sequence" of a siRNA molecule refers to a strand that is complementary to the antisense strand. In some embodiments, the antisense and sense strands of a siRNA molecule are hybridized to form a duplex structure, e.g., an siRNA.

[0461] *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. In certain embodiments, a siRNA molecule includes 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, such as 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, such as 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 siRNA duplex.

[0462] *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 such as chimpanzees and other apes and monkey species, and humans) and/or plants.

[0463] *Substantially Complementary:* As used herein, the term "substantially complementary" means that the siRNA has a sequence (e.g., in the antisense strand) which is sufficient to bind the desired target mRNA, and to trigger the RNA silencing of the target mRNA.

[0464] *Targeted Cells:* As used herein, "targeted cells" 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, such as a mammal, a human, or a human patient.

[0465] *Tauopathy:* As used herein, tauopathies and/or tau-associated diseases, refers to a heterogeneous group of neurodegenerative diseases characterized by the dysfunction and/or aggregation of the microtubule-associated protein tau (MAPT). MAPT may also be referred to as "Tau" herein.

[0466] *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.

[0467] *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.

[0468] *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.

[0469] *Variant:* As used herein, the term "variant" refers to a polypeptide or polynucleotide that has an amino acid or a nucleotide sequence that is substantially identical, e.g., having at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity to a reference sequence. In some embodiments, the variant is a functional variant.

[0470] *Functional Variant*: As used herein, the term "functional variant" refers to a polypeptide variant or a polynucleotide variant that has at least one activity of the reference sequence.

[0471] *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. Vectors of the present disclosure may be produced recombinantly. The heterologous molecule may be a polynucleotide and/or a polypeptide.

[0472] *Viral Genome:* As used herein, the term "viral 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.

[0473] The present disclosure is further illustrated by the following non-limiting examples.

VI. EXAMPLES

Example 1. Design and synthesis of siRNA sequences targeting the human MAPT transcript

Evaluation of MAPT transcripts

[0474] siRNAs (19mers and 21mers) were generated from human microtubule associated protein tau (MAPT), transcript variant 4, NCBI RefSeq transcript sequence NM_016841.4 (SEQ ID NO: 3947). Subsequent analysis included: evaluation of full match (FM) 19mer and 17mer (without considering positions 1 and 19), and of 19mer and 17mer with single mismatch (SMM) for determination of cross-creativity with human (Hu), rhesus (Rh) and cynomolgus (Cyno) monkey, rat (Rt), and mouse (Ms) transcript (including miRNA seed); evaluation of predicted specificity in human, mouse, rat, and non-human primate (NHP), including separate analysis of sense and antisense strands; and, analysis of a human single nucleotide polymorphism (SNP) database (NCBI-DB-SNP) to identify siRNA targeting regions with known SNPs, including information of positions of SNPs within the target, as well as minor allele frequency (MAF) in available case data. A subset of siRNAs was selected for synthesis.

[0475] Cross-reactivity determination analysis was based on Human MAPT, transcript variant 4, NCBI RefSeq transcript sequence NM_016841.4 (SEQ ID NO: 3947). Analysis of siRNA cross-reactivity was performed for transcript variants and different species; for 19mers and 17mers with a full match (FM), and for 19mers and 17mers with a single mismatch (SMM).

[0476] An alignment was created by performing a BLASTn search with Human MAPT, transcript variant 4, NCBI RefSeq transcript sequence NM_016841.4 (SEQ ID NO: 3947) versus human, NHP (cynomolgus and rhesus), rat and mouse MAPT protein-coding transcript sequences. Table 9 provides information for MAPT transcript sequences corresponding to each species. Transcripts used for cross-reactivity determination analyses were limited to those longer than 5,000 bp. Sequences are identified in the Table 19 using NCBI RefSeq Accession and/or Ensembl ID identifier codes.

Table 19. MAPT transcripts

Species	Transcript No. (Accession/ID)	19mer cross-reactive with NM_016841.4	19mer in common	Type
Hu	NM_001123066.3	5401	5120	mRNA
Hu	NM_001123067.3	5448	5120	mRNA
Hu	NM_001203251.1	5461	5120	mRNA
Hu	NM_001203252.1	5460	5120	mRNA
Hu	NM_005910.5	5447	5120	mRNA
Hu	NM_016834.4	5463	5120	mRNA
Hu	NM_016835.4	5418	5120	mRNA

Hu	NM_016841.4	5476	5120	mRNA
Hu	XM_005257362.4	5198	5120	mRNA
Hu	XM_005257364.4	5119	5120	mRNA
Hu	XM_005257365.4	5211	5120	mRNA
Hu	XM_005257366.3	5256	5120	mRNA
Hu	XM_005257367.4	5212	5120	mRNA
Hu	XM_005257368.4	5225	5120	mRNA
Hu	XM_005257369.4	5213	5120	mRNA
Hu	XM_005257370.4	5278	5120	mRNA
Hu	XM_005257371.4	5229	5120	mRNA
Hu	ENST00000446361	5171	5120	known PRT coding
Hu	ENST00000262410	5418	5120	known PRT coding
Hu	ENST00000351559	5447	5120	known PRT coding
Hu	ENST00000344290	5401	5120	known PRT coding
Hu	ENST00000535772	5460	5120	known PRT coding
Hu	ENST00000340799	5448	5120	known PRT coding
Hu	ENST00000571311	289	-	known PRT coding
Hu	ENST00000570299	856	-	known PRT coding
Hu	ENST00000334239	1089	-	known PRT coding
Hu	ENST00000420682	1013	-	known PRT coding
Hu	ENST00000415613	966	-	known PRT coding
Hu	ENST00000571987	983	-	known PRT coding
Hu	ENST00000574436	1012	-	known PRT coding
Hu	ENST00000431008	1025	-	known PRT coding
Hu	ENST00000576518	1145	-	known PRT coding
Hu	ENST00000572440	50	-	known retained
Hu	ENST00000576238	0	-	known retained
Hu	ENST00000577017	38	-	known processed
Rh	XM_015119945.1	2184	2175	mRNA
Rh	XM_015119946.1	2198	2175	mRNA
Rh	XM_015119947.1	2193	2175	mRNA
Rh	XM_015119948.1	2260	2175	mRNA
Rh	XM_015119949.1	2207	2175	mRNA
Rh	XM_015119950.1	2181	2175	mRNA
Rh	XM_015119952.1	2185	2175	mRNA
Rh	XM_015119953.1	2188	2175	mRNA
Rh	XM_015119954.1	2286	2175	mRNA
Rh	XM_015119955.1	2286	2175	mRNA
Rh	XM_015119956.1	2299	2175	mRNA
Rh	XM_015119957.1	2290	2175	mRNA
Rh	XM_015119958.1	2299	2175	mRNA
Rh	XM_015119959.1	2303	2175	mRNA
Rh	XM_015119960.1	2166	2175	mRNA
Rh	ENSMMUT00000068911	2184	2175	novel PRT coding
Rh	ENSMMUT00000005862	2032	2175	novel PRT coding
Rh	ENSMMUT00000005853	496	-	known PRT coding
Rh	ENSMMUT00000001151	500	-	known PRT coding
Rh	ENSMMUT00000005859	557	-	known PRT coding
Rh	ENSMMUT00000005855	527	-	known PRT coding
Cyno	NM_001123066.3*	2105	2223	mRNA

Cyno	NM_001123067.3*	2148	2223	mRNA
Cyno	NM_005910.5*	2148	2223	mRNA
Cyno	NM_016834.4*	2152	2223	mRNA
Cyno	NM_016835.4*	2122	2223	mRNA
Cyno	NM_016841.4*	2165	2223	mRNA
Cyno	XM_005584531.2	2178	2223	mRNA
Cyno	XM_005584536.1	2227	2223	mRNA
Cyno	XM_005584537.1	2244	2223	mRNA
Cyno	XM_005584538.2	2178	2223	mRNA
Cyno	XM_005584539.2	2182	2223	mRNA
Cyno	XM_005584540.1	2270	2223	mRNA
Cyno	XM_005584541.2	2270	2223	mRNA
Cyno	XM_005584542.1	2283	2223	mRNA
Cyno	XM_005584543.2	2274	2223	mRNA
Cyno	XM_005584544.2	2283	2223	mRNA
Cyno	XM_005584545.2	2287	2223	mRNA
Cyno	XM_015437937.1	2195	2223	mRNA
Cyno	XM_015437938.1	2191	2223	mRNA
Cyno	XM_015437939.1	2208	2223	mRNA
Cyno	XM_015437940.1	2189	2223	mRNA
Cyno	XM_015437941.1	2206	2223	mRNA
Cyno	XM_015437942.1	2219	2223	mRNA
Cyno	XM_015437943.1	2193	2223	mRNA
Rt	NM_017212.2	179	225	mRNA
Rt	XM_008768268.2	177	225	mRNA
Rt	XM_008768269.2	177	225	mRNA
Rt	XM_008768270.2	179	225	mRNA
Rt	XM_008768271.2	178	225	mRNA
Rt	XM_008768272.2	177	225	mRNA
Rt	XM_008768273.2	179	225	mRNA
Rt	XM_008768277.2	176	225	mRNA
Rt	XM_008768278.2	178	225	mRNA
Rt	XM_008768279.2	178	225	mRNA
Rt	XM_008768280.2	180	225	mRNA
Rt	XM_008768281.2	181	225	mRNA
Rt	XM_008768282.2	177	225	mRNA
Rt	XM_017597175.1	176	225	mRNA
Rt	ENSRNOT00000006947	179	225	known PRT coding
Rt	ENSRNOT00000045127	71	-	known PRT coding
Rt	ENSRNOT00000092428	0	-	known PRT coding
Rt	ENSRNOT00000050070	66	-	known PRT coding
Rt	ENSRNOT00000092483	5	-	known processed
Rt	ENSRNOT00000042984	51	-	known PRT coding
Ms	NM_001038609.2	213	218	mRNA
Ms	NM_001285454.1	181	218	mRNA
Ms	NM_001285455.1	213	218	mRNA
Ms	NM_001285456.1	215	218	mRNA
Ms	NM_010838.4	213	218	mRNA
Ms	XM_006532407.3	213	218	mRNA
Ms	XM_006532408.3	215	218	mRNA

Ms	XM_006532409.2	215	218	mRNA
Ms	XM_006532410.3	213	218	mRNA
Ms	XM_017314315.1	207	218	mRNA
Ms	ENSMUST00000106992	213	218	known PRT coding
Ms	ENSMUST00000106988	69	-	known PRT coding
Ms	ENSMUST00000106989	69	-	known PRT coding
Ms	ENSMUST00000146353	0	-	known PRT coding
Ms	ENSMUST00000145227	8	-	known PRT coding
Ms	ENSMUST00000106993	100	-	known PRT coding
Ms	ENSMUST00000100347	75	-	known PRT coding
Ms	ENSMUST00000138384	8	-	known PRT coding
Ms	ENSMUST00000144836	48	-	known PRT coding
Ms	ENSMUST00000126820	46	-	known PRT coding
Ms	ENSMUST00000132245	0	-	known PRT coding
Ms	ENSMUST00000132977	0	-	known PRT coding

[0477] Without considering specificity prediction, 1891-3581 siRNAs were cross-reactive with human and NHP. For siRNAs predicted to be specific in human, 666-1382 siRNAs were cross-reactive with human and NHP. For siRNAs predicted to be specific in human and NHP, 517-1042 siRNAs were cross-reactive with human and NHP.

Evaluation of siRNA candidates

[0478] siRNA off-target genes were predicted for human, rhesus monkey, cynomolgus monkey, mouse, rat, and dog. Off-target frequency was calculated as the number of predicted off-targets (genes) with 0, 1, 2, 3, or 4 mismatches relative to positions 2-18 of an siRNA, where 0 indicated no predicted off-target identified with the indicated number of mismatches. Criterion for off-target frequency was less than or equal to 20 (optimally less than or equal to10) off-targets with 2 mismatches to the antisense strand. In general, the off-target frequency was used for refined ranking within siRNA candidate sets.

[0479] A specificity score was assigned to each siRNA strand. The specificity score accounted for the likelihood of unintended downregulation of any other transcript by full or partial complementarity of a siRNA strand (up to 4 mismatches within positions 2-18), and was based on the number and position of mismatches. Thus, the specificity score described the predicted most likely off-target(s) for all predicted off-targets corresponding to antisense and sense strands of each siRNA; where 0 indicated a perfect match. Criterion for the antisense and sense strand was a specificity score greater than or equal to 2 and greater than or equal to 1, respectively.

[0480] siRNA strands were analyzed for the presence of human, rhesus monkey, rat, mouse, rabbit, dog, and/or pig microRNA (miRNA) seed regions. siRNAs can function in a miRNA-like manner via base-pairing with complementary sequences within the 3'-UTR of mRNA molecules. The complementarity typically encompasses the 5'-bases 2-7 of the miRNA, which corresponds to the seed region. To circumvent siRNA action at functional miRNA binding sites, siRNA strands containing natural miRNA seed regions were

excluded. Seed regions identified in miRNAs from human, rhesus monkey, dog, pig, mouse, and rat were classified as conserved. Mature miRNAs for *Homo sapiens* (2588), *Macaca mulatta* (914), *Mus Musculus* (1915), *Rattus norvegicus* (765), *Canis familiaris* (453), and *Sus scrofa* (411) were used for miRNA seed region conservation analyses. *Oryctolagus cuniculus* miRNAs were excluded as identified mature miRNAs (886) were not validated in depth.

[0481] Specificity categories were assigned to siRNAs (antisense [AS] and sense strand [SS], independently of each other) based on combined specificity score and miRNA seed analysis. For specificity category, lower numbers were selected, as 1 represented high specificity. Requisite specificity categories were AS1 or AS2, and SS1, SS2 or SS3

[0482] For assessment of SNPs, the total number of human MAPT SNPs described was 433. MAFs were assigned to 158 SNPs and 35 SNPs had a MAF greater than or equal to 1% in target sites (range, 0.0106-0.2025%).

[0483] Among the 19mers, 1891 human and NHP (cynomolgus) cross-reactive siRNAs were identified, of which 517 siRNAs were specific in human and NHP, and 19 siRNAs were highly specific in human. Among the 17mers, 2077 human and NHP cross-reactive siRNAs were identified, of which 564 siRNAs were specific in human and NHP, and 20 siRNAs were highly specific in human. The siRNAs were further filtered and sub-sorted by factors such as presence of human miRNA seeds, presence of rhesus monkey miRNA seeds, presence of conserved (human, mouse, rat) miRNA seeds, off-target frequency value, presence of SNPs with minor allele frequency (MAF) greater than or equal to 1% in target sites, and, predicted siRNA activity

siRNA selection

[0484] Together, siRNAs were selected on the basis of several factors, including: cross-reactivity (with 19mer in human MAPT mRNA, and with 17mer/19mer in NHP MAPT mRNA); specificity category for human and NHP; miRNA seeds, which may not be identical to those of a known human miRNA, nor may it be conserved between human, mouse, and rat; off-target frequency (less than or equal to 15 human off-targets matched with 2 mismatches by antisense strand); and, human SNPs.

[0485] 191 siRNA duplexes predicted to be specific in human, monkey and mouse, including several siRNAs predicted to be active, were selected. The siRNA duplexes and their corresponding sense and antisense strand sequences are provided in Table 4, where the antisense and sense strand sequence comprise dTdT overhangs at the 3' end of each sequence; and in Table 5 where the sense and antisense strand sequences do not comprise a dTdT overhang. The target sites of these siRNAs were distributed along the human MAPT transcript. Position 1 of the antisense strand was engineered to a U and position 19 of the sense strand was engineered to a C, in order to unpair the duplex at this position.

Example 2. Initial *in vitro* siRNA screening and hit identification

[0486] The MAPT siRNA duplexes designed in Example 1 and provided in Table 4 and 5, were screened for inhibition of tau (MAPT) expression (e.g., mRNA inhibition) in HEK293 cells at a duple concentration of either 0.1 nM or 10 nM. The 191 siRNA duplexes were designed to target the coding region of MAPT or the 3' UTR region.

[0487] The percent MAPT mRNA remaining relative to control in the HEK293 cells post-treatment with the 191 siRNA duplexes at the 0.1 nM and 10 nM concentrations is provided in Table 20. As shown in Table 20, approximately 20 siRNA sequences reduced tau mRNA levels by approximately 60% at the 0.1 nM concentration and 80% at the 10 nM concentration. The siRNA duplexes of D-001 (SEQ ID NO: 4143 and 3952 or 4477 and 4687), D-002 (SEQ ID NO: 4144 and 3953 or 4478 and 4688), D-003 (SEQ ID NO: 4145 and 3954 or 4479 and 4689, D-004 (SEQ ID NO: 4146 and 3955 or 4480 and 4690), D-009 (SEQ ID NO: 4151 and 3956 or 4485 and 4691), D-014 (SEQ ID NO: 4156 and 3957 or 4490 and 4692), D-015 (SEQ ID NO: 4157 and 3958 or 4491 and 4693), D-016 (SEQ ID NO: 4158 and 3959 or 4492 and 4694), D-017 (SEQ ID NO: 4159 and 3960 or 4493 and 4695), D-018 (SEQ ID NO: 4160 and 3961 or 4494 and 4696), D-019 (SEQ ID NO: 4161 and 3692 or 4495 and 4697), D-026 (SEQ ID NO: 4168 and 3965 or 4502 and 4700), D-030 (SEQ ID NO: 4172 and 3966 or 4506 and 4701), D-035 (SEQ ID NO: 4177 and 3967 or 4511 and 4702), D-038 (SEQ ID NO: 4180 and 3970 or 4514 and 4705), D-043 (SEQ ID NO: 4185 and 3975 or 4519 and 4710), D-045 (SEQ ID NO: 4187 and 3977 or 4521 and 4712), D-047 (SEQ ID NO: 4189 and 3979 or 4523 and 4714), D-049 (SEQ ID NO: 4191 and 3981 or 4525 and 4716), and D-051 (SEQ ID NO: 4193 and 3983 or 4527 and 4718) resulted in the greatest knockdown of MAPT mRNA (Table 20). The sequences of having the indicated duplex IDs in Table 20 are provided in Table 4. Table 5 includes the corresponding siRNA sequences without the dTdT overhangs.

Table 20. Percentage of tau mRNA remaining following transfection of siRNA duplexes

siRNA Duplex ID	% tau mRNA remaining relative to control, 0.1 nM	% tau mRNA remaining relative to control, 10 nM	siRNA Duplex ID	% tau mRNA remaining relative to control, 0.1 nM	% tau mRNA remaining relative to control, 10 nM
D-002	26	15	D-071	64	60
D-019	30	15	D-107	64	60
D-026	30	15	D-120	64	60
D-003	30	15	D-208	64	60
D-017	30	15	D-161	64	60
D-014	32	16	D-066	64	61
D-043	33	17	D-143	65	61
D-004	33	17	D-065	65	61
D-015	34	17	D-091	65	62
D-016	34	17	D-101	65	62
D-030	35	18	D-210	66	62
D-009	35	18	D-112	66	63
D-001	35	18	D-138	66	63

D-045	36	19	D-094	66	63
D-047	36	19	D-149	66	64
D-038	36	19	D-083	66	64
D-051	36	20	D-102	66	64
D-018	36	20	D-067	66	64
D-035	38	20	D-132	66	64
D-049	38	21	D-172	66	65
D-056	40	21	D-164	67	65
D-096	40	22	D-139	67	65
D-069	40	22	D-198	67	65
D-024	41	23	D-113	67	66
D-039	41	23	D-140	67	66
D-040	42	23	D-133	67	66
D-044	42	23	D-158	67	66
D-122	43	23	D-068	68	67
D-085	43	24	D-144	68	67
D-053	44	25	D-146	69	67
D-052	44	25	D-199	69	68
D-041	45	25	D-177	69	68
D-050	45	26	D-165	70	69
D-114	46	27	D-180	70	69
D-042	46	27	D-196	70	69
D-036	47	27	D-075	70	70
D-126	48	28	D-203	70	71
D-048	51	28	D-108	71	71
D-055	51	28	D-159	71	71
D-025	52	28	D-191	71	73
D-097	52	28	D-193	71	73
D-037	53	29	D-154	71	74
D-076	53	29	D-088	72	74
D-104	53	30	D-109	72	74
D-057	54	33	D-197	72	74
D-086	54	34	D-202	73	74
D-061	54	34	D-092	73	75
D-127	54	34	D-121	74	75
D-115	54	35	D-173	74	75
D-046	55	36	D-150	74	75
D-116	55	38	D-194	74	76
D-098	55	38	D-155	74	76
D-054	56	40	D-178	75	76
D-077	56	41	D-124	75	78
D-059	56	42	D-186	75	78
D-128	56	42	D-151	75	78
D-078	57	42	D-134	75	78
D-117	57	43	D-166	75	78
D-099	57	43	D-181	75	79
D-062	57	44	D-152	75	79
D-079	57	44	D-141	75	79
D-168	57	45	D-084	76	79
D-072	57	45	D-182	76	81

D-058	57	46	D-183	76	81
D-070	57	46	D-187	77	82
D-080	58	46	D-162	77	83
D-093	58	47	D-142	77	83
D-060	58	47	D-188	77	84
D-105	58	48	D-200	77	84
D-169	59	49	D-095	78	85
D-129	59	49	D-204	81	85
D-153	59	50	D-179	81	85
D-130	59	51	D-103	81	85
D-110	60	51	D-209	83	85
D-087	60	51	D-205	84	85
D-064	60	52	D-201	85	86
D-100	61	52	D-184	85	88
D-118	61	52	D-192	86	90
D-163	61	52	D-135	87	90
D-081	61	53	D-125	87	90
D-073	61	53	D-195	88	91
D-082	61	53	D-189	88	92
D-145	61	53	D-156	89	92
D-111	61	54	D-174	90	93
D-170	62	55	D-190	91	94
D-089	62	56	D-160	91	94
D-123	62	56	D-063	92	96
D-148	62	56	D-207	93	96
D-119	62	56	D-147	93	97
D-106	62	56	D-185	97	97
D-136	63	57	D-157	97	101
D-137	63	58	D-206	98	101
D-090	63	59	D-175	100	104
D-131	63	59	D-167	106	112
D-074	64	59	D-176	111	124
D-171	64	59			

[0488] Of the siRNAs designed and provided in Table 4 and tested as shown in Table 20, 10 siRNAs were selected for further evaluation *in vitro*, which included D-001 (SEQ ID NO: 4143 and 3952 or 4477 and 4687), D-004 (SEQ ID NO: 4146 and 3955 or 4480 and 4690), D-009 (SEQ ID NO: 4151 and 3956 or 4485 and 4691), D-016 (SEQ ID NO: 4158 and 3959 or 4492 and 4694), D-018 (SEQ ID NO: 4160 and 3961 or 4494 and 4696), D-019 (SEQ ID NO: 4161 and 3692 or 4495 and 4697), D-026 (SEQ ID NO: 4168 and 3965 or 4502 and 4700), D-030 (SEQ ID NO: 4172 and 3966 or 4506 and 4701), D-045 (SEQ ID NO: 4187 and 3977 or 4521 and 4712), D-051 (SEQ ID NO: 4193 and 3983 or 4527 and 4718). The IC50 values and maximum inhibition in five different cells lines were determined for each of these 10 siRNAs (**Table 25**). The five cell lines used were MCF-7 cells (breast cancer cells), HEK293 cells (epithelial like cells from the kidneys), BT-474 cells (cells that exhibit epithelial morphology that was isolated from a solid, invasive ductal carcinoma of the breast cancer), LNCap cells (androgen-sensitive human prostate adenocarcinoma cells

derived from the left supraclavicular lymph node metastasis), and SH-SY5Y cells (cloned neuroblastoma cell line). High potency was observed in the BT-474 cells, with IC50 values in the 7-21 pM range and maximum inhibition values between 80-90% (**Table 25**). Similar data was observed in the HEK293 and LNCap cell lines (**Table 25**).

Table 25. IC50 and Maximum Inhibition of MAPT targeting siRNAs in HEK293 cells, BT-474 cells, LNCap cells, SH-SY5Y cells, and MCF-7 cells

	HEK293 Cells		BT-474 Cells		LNCap Cells		MCF-7 Cells	
Duplex	IC50 (nM)	Maximum Inhibition	IC50 (nM)	Maximum Inhibition	IC50 (nM)	Maximum Inhibition	IC50 (nM)	Maximum Inhibition
D-026	0.026	81.7	0.011	90.7	0.005	86.3	0.063	68.6
D-019	0.098	76.1	0.007	86.5	0.010	81.3	0.058	65.8
D-004	0.109	80.1	0.062	86.1	0.024	84.7	1.822	58.7
D-016	0.023	76.2	0.035	88.0	0.016	84.8	1.072	65.6
D-009	0.020	84.9	0.010	90.8	0.011	86.5	0.574	65.4
D-030	0.078	74.8	0.115	83.8	0.082	80.5	124.980	51.7
D-001	0.038	81.8	0.021	90.7	0.010	87.4	5.528	56.2
D-045	0.064	76.7	0.019	86.6	0.030	83.4	13.662	56.1
D-018	0.056	81.8	0.028	85.2	0.039	84.2	0.248	61.4
D-051	0.144	77.7	0.040	83.7	0.025	83.6	2.676	56.8

Example 3. Design and evaluation of vectorized miRNAs

[0489] Ten of the MAPT siRNA sequences demonstrating high potency (e.g., increased knockdown of MAPT mRNA) based on strong cross-cell activity and diversity as shown in Example 2 and **Table 25**, were selected for design of miRNA constructs comprising a passenger strand (sense) and a guide strand (antisense) as well as a scaffold comprising a 5' flanking region, loop region, and a 3' flanking region. The scaffolds used in these constructs included: (i) a 5' flanking region of SEQ ID NO: 4354 (DNA) or 4879 (RNA), a loop region of SEQ ID NO: 4362 (DNA) or 4887 (RNA), and a 3' flanking region of SEQ ID NO: 4373 (DNA) or 4898 (RNA); (ii) a 5' flanking region of SEQ ID NO: 4354 (DNA) or 4879 (RNA), a loop region of SEQ ID NO: 4363 (DNA) or 4888 (RNA), and a 3' flanking region of SEQ ID NO: 4373 (DNA) or 4898 (RNA); (iii) a 5' flanking region of SEQ ID NO: 4354 (DNA) or 4879 (RNA), a loop region of SEQ ID NO: 4362 (DNA) or 4887 (RNA), and a 3' flanking region of SEQ ID NO: 4374 (DNA) or 4899 (RNA); or (iv) a 5' flanking region of SEQ ID NO: 4355 (DNA) or 4880 (RNA), a loop region of SEQ ID NO: 4366 (DNA) or 4891 (RNA), and a 3' flanking region of SEQ ID NO: 4375 (DNA) or 4900 (RNA). The miRNA constructs also referred to herein as modulatory polynucleotides were designed and generated to have the scaffolds, passenger strand, and guide strand as indicated in Tables 9A and 9B above. From 5' to 3', these modulatory polynucleotides comprised the indicated 5' flanking region, the indicated passenger strand, the indicated loop region, the indicated guide strand, and the indicated 3' flanking region (Table 9A and 9B).

[0490] The modulatory polynucleotides VOYTaumiR-127-530 (SEQ ID NO: 4405), VOYTaumiR-127-556 (SEQ ID NO: 4406), VOYTaumiR-127-564 (SEQ ID NO: 4407), VOYTaumiR-127-579 (SEQ ID NO:

4408), and VOYTaumiR-127-586 (SEQ ID NO: 4409) were tested to determine guide and passenger strand activity using the DUAL-GLO® luciferase assay (Promega) in HEK293 cells. These constructs were vectorized in a self-complementary AAV genome under the control of a CBA promoter and transfected into cells with reporter plasmids that comprised the target regions of the guide and passenger strands being investigated arranged in tandem. Approximately 48-hours post transfection, cells were lysed and the Renilla and firefly luciferase activity was measured and relative activity was obtained by normalizing the Renilla luciferase level to the control firefly luciferase level (relative R/F luc activity % over amiR-NTC). A higher luciferase signal indicates low activity and a low luciferase signal indicates increased knockdown and activity. Of the constructs tested with respect to the guide strand, less than 50% normalized R/F luciferase activity was observed for the guide strands tested, with the guide strand of VOYTaumiR-127-530 showing the greatest knockdown and activity. The guide strands of VOYTaumiR-127-556 (SEQ ID NO: 4406), VOYTaumiR-127-564 (SEQ ID NO: 4407), VOYTaumiR-127-579 (SEQ ID NO: 4408), and VOYTaumiR-127-586 (SEQ ID NO: 4409) also all showed high, comparable levels of knockdown and activity. With respect to the passenger strand activity, VOYTaumiR-127-530 (SEQ ID NO: 4405), VOYTaumiR-127-564 (SEQ ID NO: 4407), VOYTaumiR-127-579 (SEQ ID NO: 4408), and VOYTaumiR-127-586 (SEQ ID NO: 4409), all showed low levels of passenger strand activity as indicated by a high normalized R/F luciferase activity. The ability of these modulatory polynucleotides to knockdown MAPT mRNA expression was also investigated. The percentage of MAPT mRNA remaining was quantified by qPCR and normalized to the TBP gene. VOYTaumiR-127-530 (SEQ ID NO: 4405) demonstrated a 92.3% knockdown (7.7% MAPT mRNA remaining), VOYTaumiR-127-556 (SEQ ID NO: 4406) demonstrated a 66% knockdown (34% MAPT mRNA remaining), VOYTaumiR-127-564 (SEQ ID NO: 4407) demonstrated a 90.4% knockdown (9.6% MAPT mRNA remaining), VOYTaumiR-127-579 (SEQ ID NO: 4408) demonstrated an 86.5% knockdown (13.5% MAPT mRNA remaining), and VOYTaumiR-127-586 (SEQ ID NO: 4409) demonstrated a 76.3% knockdown (23.7% MAPT mRNA remaining) of MAPT mRNA. The mRNA knockdown results correlated with the results observed in the guide/passenger strand activity assay.

[0491] The modulatory polynucleotides VOYTaumiR-102-530 (SEQ ID NO: 4380), VOYTaumiR-102-556 (SEQ ID NO: 4381), VOYTaumiR-102-579 (SEQ ID NO: 4383), VOYTaumiR-102-586 (SEQ ID NO: 4384), VOYTaumiR-104-530 (SEQ ID NO: 4385), VOYTaumiR-104-556 (SEQ ID NO: 4386), VOYTaumiR-104-579 (SEQ ID NO: 4388), VOYTaumiR-104-586 (SEQ ID NO: 4389), VOYTaumiR-109-530 (SEQ ID NO: 4390), VOYTaumiR-109-556 (SEQ ID NO: 4391), VOYTaumiR-109-579 (SEQ ID NO: 4393), VOYTaumiR-109-586 (SEQ ID NO: 4394), VOYTaumiR-114-530 (SEQ ID NO: 4395), VOYTaumiR-114-556 (SEQ ID NO: 4396), VOYTaumiR-114-579 (SEQ ID NO: 4398), VOYTaumiR-114-586 (SEQ ID NO: 4399), VOYTaumiR-116-530 (SEQ ID NO: 4400), VOYTaumiR-116-556 (SEQ ID NO: 4401), VOYTaumiR-116-579 (SEQ ID NO: 4403), VOYTaumiR-116-586 (SEQ ID NO: 4404),

VOYTaumiR-127-530 (SEQ ID NO: 4405), VOYTaumiR-127-556 (SEQ ID NO: 4406), VOYTaumiR-127-579 (SEQ ID NO: 4408), and VOYTaumiR-127-586 (SEQ ID NO: 4409) were also tested to determine guide strand activity using the DUAL-GLO® luciferase assay (Promega) in HEK293 cells, as compared to a non-targeting control (NTC) construct. These constructs were vectorized and transfected into cells with reporter plasmids that comprised the target regions of the guide strand being investigated arranged in tandem. Approximately 48-hours post transfection, cells were lysed and the Renilla and firefly luciferase activity was measured and relative activity was obtained by normalizing the Renilla luciferase level to the non-targeting control firefly luciferase level (relative R/F luc activity % over NTC). A higher luciferase signal indicates low activity and a low luciferase signal indicates increased knockdown and activity. As shown in **FIG. 1**, greater than 75% knockdown was observed for all the guide strands of the vectorized modulatory polynucleotides targeting MAPT tested and no knockdown was observed for the non-targeting control construct.

[0492] Vectorized modulatory polynucleotides VOYTaumiR-102-530 (SEQ ID NO: 4380), VOYTaumiR-102-556 (SEQ ID NO: 4381), VOYTaumiR-102-579 (SEQ ID NO: 4383), VOYTaumiR-102-586 (SEQ ID NO: 4384), VOYTaumiR-104-530 (SEQ ID NO: 4385), VOYTaumiR-104-556 (SEQ ID NO: 4386), VOYTaumiR-104-579 (SEQ ID NO: 4388), VOYTaumiR-104-586 (SEQ ID NO: 4389), VOYTaumiR-109-530 (SEQ ID NO: 4390), VOYTaumiR-109-556 (SEQ ID NO: 4391), VOYTaumiR-109-579 (SEQ ID NO: 4393), VOYTaumiR-109-586 (SEQ ID NO: 4394), VOYTaumiR-114-530 (SEQ ID NO: 4395), VOYTaumiR-114-556 (SEQ ID NO: 4396), VOYTaumiR-114-579 (SEQ ID NO: 4398), VOYTaumiR-114-586 (SEQ ID NO: 4399), VOYTaumiR-116-530 (SEQ ID NO: 4400), VOYTaumiR-116-556 (SEQ ID NO: 4401), VOYTaumiR-116-579 (SEQ ID NO: 4403), VOYTaumiR-116-586 (SEQ ID NO: 4404), VOYTaumiR-127-530 (SEQ ID NO: 4405), VOYTaumiR-127-556 (SEQ ID NO: 4406), VOYTaumiR-127-579 (SEQ ID NO: 4408), and VOYTaumiR-127-586 (SEQ ID NO: 4409) or a vectorized non-target control were also transfected into HEK293 cells at 1 μg/well to measure knockdown of MAPT mRNA by qPCR at 48 hours post-transfection. The amount of MAPT mRNA remaining was determined and the fold-change in MAPT mRNA remaining for each vectorized modulatory polynucleotide relative to the non-target control (NTC) was calculated as shown on the Y-axis of **FIG. 2**. A number of modulatory polynucleotides tested lead to a fold change of at least 0.5 in MAPT mRNA remaining relative to the non-target control, including VOYTaumiR-127-530 (SEQ ID NO: 4405), VOYTaumiR-127-556 (SEQ ID NO: 4406), VOYTaumiR-109-556 (SEQ ID NO: 4391), and VOYTaumiR-109-579 (SEQ ID NO: 4393) (**FIG. 2**). Several modulatory polynucleotides led to a fold change of at least 0.7 in MAPT mRNA remaining relative to the non-target control, including VOYTaumiR-127-579 (SEQ ID NO: 4408), VOYTaumiR-127-586 (SEQ ID NO: 4409), VOYTaumiR-116-556 (SEQ ID NO: 4401), VOYTaumiR-109-530 (SEQ ID NO: 4390), VOYTaumiR-109-586 (SEQ ID NO: 4394), VOYTaumiR-104-556 (SEQ ID NO: 4386), and VOYTaumiR-104-586 (SEQ ID NO: 4389) (**FIG. 2**).

[0493] Several of the modulatory polynucleotides that demonstrated a fold change of at least 0.5-0.7 in MAPT mRNA remaining relative to the non-target control as shown in **FIG. 2** were selected for subsequent testing in a dose-response study, including VOYTaumiR-127-530 (SEQ ID NO: 4405), VOYTaumiR-127-556 (SEQ ID NO: 4406), VOYTaumiR-127-579 (SEQ ID NO: 4408), VOYTaumiR-127-586 (SEQ ID NO: 4409), VOYTaumiR-109-530 (SEQ ID NO: 4390), VOYTaumiR-109-556 (SEQ ID NO: 4391), VOYTaumiR-109-579 (SEQ ID NO: 4393), VOYTaumiR-109-586 (SEQ ID NO: 4394), VOYTaumiR-116-579 (SEQ ID NO: 4403), VOYTaumiR-104-556 (SEQ ID NO: 4386), and VOYTaumiR-104-586 (SEQ ID NO: 4389). These modulatory polynucleotides or a non-target control construct were transfected into HEK293 cells at a concentration of 0.05 μg per well, 0.16 μg per well, 0.5 μg per well, or 1.5 μg per well. Cells were harvested at 48 hours post-transfection, and the MAPT mRNA levels remaining were determined. The fold change in MAPT mRNA levels remaining post-transfection with the vectorized modulatory polynucleotides relative to the non-targeting control (NTC) was calculated (**FIG. 3**). As provided in **FIG. 3**, a strong dose response in MAPT mRNA inhibition was observed for at least VOYTaumiR-127-530 (SEQ ID NO: 4405), VOYTaumiR-127-586 (SEQ ID NO: 4409), VOYTaumiR-109-530 (SEQ ID NO: 4390), VOYTaumiR-109-556 (SEQ ID NO: 4391), VOYTaumiR-109-579 (SEQ ID NO: 4393), and VOYTaumiR-109-586 (SEQ ID NO: 4394).

[0494] The ability of additional modulatory polynucleotides to inhibit MAPT mRNA was investigated in HEK293 cells, including VOYTaumiR-102-582 (SEQ ID NO: 5027), VOYTaumiR-104-582 (SEQ ID NO: 5031), VOYTaumiR-109-582 (SEQ ID NO: 5035), VOYTaumiR-114-582 (SEQ ID NO: 5039), VOYTaumiR-127-582 (SEQ ID NO: 5047), VOYTaumiR-102-587 (SEQ ID NO: 5028), VOYTaumiR-109-587 (SEQ ID NO: 5036), VOYTaumiR-114-587 (SEQ ID NO: 5040), VOYTaumiR-104-552 (SEQ ID NO: 5033), VOYTaumiR-104-549 (SEQ ID NO: 5034), and VOYTaumiR-116-549 (SEQ ID NO: 5046). These constructs were vectorized and transfected into cells at a concentration of 0.50 μg per well or 1 μg per well. VOYTaumiR-127-530 (SEQ ID NO: 4405), VOYTaumiR-109-530 (SEQ ID NO: 4390), and an antisense oligonucleotide (ASO) targeting MAPT were included as positive controls, and a plasmid encoding GFP or a non-targeting control (NTC) were included as negative controls (**FIG. 4**). Cells were harvested at 48 hours post-transfection, and the MAPT mRNA levels remaining were determined. The fold change in MAPT mRNA levels remaining post-transfection with the vectorized modulatory polynucleotides relative to the non-targeting control was also calculated (**FIG. 4**). As shown in **FIG. 4**, the eleven vectorized modulatory polynucleotides targeting MAPT (VOYTaumiR-102-582, VOYTaumiR-104-582, VOYTaumiR-109-582, VOYTaumiR-114-582, VOYTaumiR-127-582, VOYTaumiR-102-587, VOYTaumiR-109-587, VOYTaumiR-114-587, VOYTaumiR-104-552, VOYTaumiR-104-549, and VOYTaumiR-116-549) transfected at 1.0 μg per well, resulted in approximately a 50% knockdown of MAPT mRNA. Even when transfected at 0.5 μg per well, seven of the vectorized modulatory polynucleotides (VOYTaumiR-102-582,

VOYTaumiR-104-582, VOYTaumiR-109-582, VOYTaumiR-114-582, VOYTaumiR-127-582, VOYTaumiR-104-552, VOYTaumiR-104-549, and VOYTaumiR-116-549) tested resulted in approximately 40-50% knockdown of MAPT mRNA.

[0495] Taken together, these data demonstrate several modulatory polynucleotides for targeting MAPT that demonstrated high knockdown of MAPT mRNA, high guide strand activity, and/or low passenger strand activity that could be used to treat tauopathies, e.g. tauopathies with aberrant expression of MAPT.

Example 4. Viral genomes encoding siRNA molecules

[0496] Modulatory polynucleotides comprising a molecular scaffold and encoding siRNA duplexes (siRNA molecules) comprising guide (antisense) strands targeting the MAPT transcript and passenger (sense) strands, were engineered into single stranded or self-complementary AAV viral genomes.

[0497] The single stranded AAV viral genomes in 5' to 3' order, comprised a 5' inverted terminal repeat (ITR) comprising SEQ ID NO: 4469, a CMVie enhancer comprising SEQ ID NO: 4472, a CBA promoter comprising SEQ ID NO: 5199, an hBG intron comprising SEQ ID NO: 4475, a modulatory polynucleotide comprising any one of SEQ ID NOs: 4380-4409, a human growth hormone (hGH) polyadenylation (PolyA) signal sequence comprising SEQ ID NO: 4476, and a 3' ITR comprising SEQ ID NO: 4470. The single stranded viral genomes comprise the nucleotide sequences of any one of SEQ ID NOs: 4439-4468 and are provided in Table 10A and Tables 11-18.

[0498] The self-complementary AAV viral genomes, in 5' to 3' order, comprised a 5' inverted terminal repeat (ITR) comprising SEQ ID NO: 5197, a CMVie enhancer comprising SEQ ID NO: 4171, a CBA promoter comprising SEQ ID NO: 5199, an hBG intron comprising SEQ ID NO: 4475, a modulatory polynucleotide comprising any one of SEQ ID NOs: 4380-4409 or 5027-5050, a human growth hormone (hGH) polyadenylation (PolyA) signal sequence comprising SEQ ID NO: 4476, and a 3' ITR comprising SEQ ID NO: 5200. The self-complementary viral genomes comprise the nucleotide sequences of any one of SEQ ID NOs: 5149-5196 and are provided in Table 10A, Table 10B, and Table 26.

Example 5. Tau knock-down in *in vivo* animal studies

***In vivo* rodent studies**

[0499] To evaluate *in vivo* biological activity of AAV particles comprising vector genomes that encode MAPT siRNA, select AAV particles are delivered to rodents, such as transgenic mice (e.g., htau, P301S, rTg4510, rTgTauEC, SCN1a-A1783V) and non-transgenic (wild type) mice, via ICM, IM, IP, ICV, IPa (e.g., intrathalamic) or IT administration routes at a number of doses within a set dose range. A control group is treated with, e.g., vehicle, which can be PBS. The administration may include one or more injections over a period of time. Following test article administration, behavioral tests that may include the Morris water-, Y-,T- or radial arm-maze, or object recognition or open field tests, are performed at several time intervals across the lifespan. At a predetermined day post-dosing, animals are euthanized, and brain tissue punches (e.g.,

sampled from frontal and temporal lobes, basal ganglia, cerebellum, parietal lobe and brainstem) are collected and snap frozen. Tissue punches are homogenized, and the total RNA is purified. Relative MAPT expression (mRNA) is determined by quantification methods, e.g. qRT-PCR. MAPT expression is normalized to housekeeping gene expression, and then further normalized to the vehicle control group. Tissue samples, including brain and spinal cord, in addition to other peripheral organs, are also used to quantify tau protein, e.g., using immunohistochemical and western blot approaches.

In vivo htau mouse studies

[0500] The htau mouse model of tauopathy, the natural history of which has been previously described in detail by Andorfer et al., 2003 (Andorfer et al., J Neurochem. 2003 Aug;86(3):582-90, the contents of which are incorporated herein by reference in their entirety), is identified for studies, such as but not limited to, pharmacology and efficacy studies, due to both favorable cognitive and behavioral phenotypes.

[0501] The htau mouse transgene contains the coding sequence, intronic regions, and regulatory elements of the human microtubule-associated protein tau (MAPT) gene. Although no endogenous mouse MAPT is detected (the htau mouse was generated on a mouse tau knockout background), all six isoforms (including both 3R and 4R forms) of human MAPT are expressed. Htau mice develop tau pathology in a time course and distribution that is comparable to that occurring in the early stages of human Alzheimer's disease (AD). Hyperphosphorylated MAPT is detected in cell bodies and dendrites by 3 months of age. Accumulation of hyperphosphorylated tau begins by 6 months, but increases further by 13- and 15-months of age. Aggregated tau and PHFs are detectable in htau mice aged 9 months via sarkosyl-insolubility. The majority of tau pathology in htau mice is found in neocortex and hippocampus, while minimal tau pathology is found in brain stem and spinal cord. Consequently, there are no overt gross motor or behavioral disturbances. Tau pre-tangle, such as CP13 ($pSer^{202}$) immunoreactivity can be observed in CA1 and CA3 at 4 months of age. At 12 months of age, htau mice display prominent hippocampal CP13 and PHF-1 ($pSer^{396}/pSer^{404}$; described in International Publication WO199620218, the contents of which are herein incorporated in their entirety) immunoreactivity, resembling that observed in human AD at a moderate stage of tau pathology. Htau mice also develop learning and memory deficits in an age-dependent manner. For instance, object recognition memory and spatial memory are impaired in the aged htau mice (12 months of age). These deficits have not been observed in younger (4-month) htau mice.

Paired helical filament (PHF) seeding

[0502] To circumvent an extended drug screening timeline resulting from prolonged disease progression in htau mice, which do not exhibit cognitive deficits until an advanced age (12 months old), sarkosyl insoluble paired helical filament (PHF) tau from Alzheimer's disease (AD) or other tauopathy disease brain or biofluid, is injected into the hippocampus of htau mice (n = 10-15 mice), using methods similar to those previously described (see e.g., Hu et al., Alzheimer's Dement. 2016 Oct;12(10):1066-1077 and Gerson et al.,

J Neurotrauma. 2016 Nov 15;33(22):2034-2043, the contents of each of which are incorporated herein by reference in their entirety).

[0503] The amount of PHF for injection and the time course (4, 8, and 12 weeks) for the development of seeding activity, in other words, the initiation of tau pathology, as well as for the development of cognitive deficits, such as those that may be measured by spatial memory (e.g., Morris water maze) and/or novel object recognition tests, is determined.

[0504] Age-matched htau and wild type (control) mice may be used. Aged htau mice (12 months old; n = 10-15) are monitored for the onset of cognitive deficits as previously described by Polydoro et al., 2009 and Geiszler et al., 2016 (Polydoro et al., J Neurosci. 2009 Aug 26;29(34):10741-9 and Geiszler et al., Neuroscience. 2016 Aug 4;329:98-111, the contents of each of which are incorporated herein by reference in their entirety).

[0505] The htau PHF seeding model may be used to test whether tau miRNA administration may have a therapeutic effect post-symptomatically. As a nonlimiting example, the seeding may occur prior to miRNA administration.

Olfactory bulb propagation

[0506] PHF tau isolated from AD and/or FTLD patients is injected into the olfactory bulb (seeding) in 4-month-old htau female mice. Propagation of tau pathology from olfactory bulb to the first (e.g., piriform cortex, entorhinal cortex) and second (e.g. medial thalamus, hippocampus) synaptic connections are assessed following a given time interval, e.g., 12-16 weeks post-injection. Tau immunoreactivity is measured in the seeding and in the first and secondary synaptic brain areas using anti-tau antibodies, such as but not limited to the AT100 antibody ($pSer^{212}/pSer^{214}$; ThermoFisher, Waltham, MA; described in United States Patent No US6121003, the contents of which are herein incorporated in their entirety). Pilot experiments have been performed using AD isolated PHF. This model may be used to test anti-tau miRNA of the present disclosure in therapeutic setting.

In vivo target engagement and potency

[0507] Identified miRNAs, such as those described in Example 2, are evaluated *in vivo* for target engagement. Mice (htau; 10 per dose group) are injected via intra-cisterna magna (ICM) with or without additional direct intraparenchymal (IPa) delivery routes at 2 months of age. Initial doses may include $5x10^8$, $5x10^9$, and/or $5x10^{10}$ vg/mouse for ICM or intra-thalamic injections. Mice may be euthanized at set intervals following dosing, such as but not limited to, 4-, 8- and 12- weeks post-dose. Hippocampus, cortex, thalamus, olfactory bulb, brainstem, striatum, cerebellum, spinal cord and liver are collected, and human tau levels from the transgene are quantified by quantitative reverse transcription polymerase chain reaction (RT-qPCR) and/or branched DNA, enzyme-linked immunosorbent assays (ELISAs) and/or immunohistochemistry (IHC).

[0508] Constructs showing >50% decrease in tau mRNA/protein expression are tested in a time-response study. Briefly, htau mice (n = 6-10 mice) are injected with an ICM or intra-thalamic injection of tau miRNA constructs, tissue is collected at various time-points (e.g. 4-, 8- and 12-weeks), and human tau mRNA and protein levels are quantified.

[0509] Dose and time-point for optimal knock-down/suppression of expression are determined.

In vivo efficacy of AAV particle administration

[0510] AAV particles showing >50% decrease of human tau protein in brain areas such as hippocampus, cortex, thalamus, brainstem, cerebellum and olfactory bulb are tested in P301S, as described by Allen et al., 2002 (Allen et al., 2002, J Neurosci. 2002 Nov 1;22(21):9340-51, the contents of which are incorporated herein by reference in their entirety), and/or htau mice, e.g., htau seeding and/or propagation models, are selected for efficacy studies. Mice (n = 8-12) are injected with AAV particles (ICM) with or without direct IPa administration into the thalamus) at various doses and evaluated for multiple efficacy outcomes. Nervous system tissue regions such as hippocampus, cortex, thalamus, olfactory bulb, brainstem, striatum, cerebellum, spinal cord, as well as the liver, are collected, and human tau levels are quantified by RT-qPCR and/or branched DNA, ELISAs and/or IHC. Brain lysate from mice in the treatment and control groups are tested for tau seeding activity using biosensor cells, as described by Frost et al., 2009 (Frost et al., J Biol Chem. 2009 May 8;284(19):12845-52, the contents of where are incorporated herein by reference in their entirety). Versus the control group, no or minimal tau seeding activity (e.g., tau aggregation) may be observed in brain lysate isolated from treatment groups demonstrating efficacy in decreasing tau pathology.

[0511] A comparison of the *in vivo* efficacy of AAV anti-tau miRNAs versus anti-tau antisense oligonucleotides (ASOs) and/or vectorized anti-tau antibody efficacy is performed. Whether efficacy of AAV anti-tau miRNA treatment is equivalent, superior, or inferior compared to efficacy comparators, e.g., anti-tau ASO and/or vectorized anti-tau antibody, as described above (Example 1), and/or is additive with anti-tau ASO or vectorized anti-tau antibody in combination, is determined. Thus, anti-tau ASOs or vectorized anti-tau antibody will be run in parallel and together with AAV anti-tau miRNAs to provide a head-to-head comparator, as well as to inform whether co-treating provides synergy.

[0512] Based on *in vivo* efficacy data, up to 3 constructs are selected for additional studies. Data obtained in this example will include a minimally efficacious dose (MED) for *in vivo* efficacy, data related to therapeutic index (efficacious dose and tolerability findings). These data, in combination with target engagement data are used to drive additional experimental design and/or parameters, e.g., dose selection.

***In vivo* non-human primate (NHP) studies**

[0513] In non-human primates, AAV particles or vehicle are delivered via IM, IP, ICV, IPa or IT administration routes at a number of doses within a set dose range. The administration may include one or more injections over a period of time. Clinical signs are documented and behavioral tests, e.g. the delayed

response task, are performed. At a pre-set day and time following the administration, animals are sacrificed, and select tissues harvested for bioanalytical and histological evaluation. Brain regions included in evaluation may include frontal and temporal lobes, as well as many other brain regions, such as but not limited to, basal ganglia, cerebellum, parietal lobe and brainstem. Hence, entire brain regions would be assessed, including deep structures and cerebellum. Tau protein and mRNA levels are assessed for tau/MAPT suppression following administration of AAV particles comprising vector genomes that encode MAPT siRNA versus vehicle.

Route of administration (ROA) and capsid evaluation

[0514] Multiple routes of administration (ROA) using different capsids will be evaluated for comparison against AAV9 intra-cisterna magna (ICM) and thalamic intraparenchymal (IPa) administration.

[0515] Up to 4 different capsids, e.g., VOY101, AAV9, AVrh10, and AAV1 are selected. A single transgene tool construct is used for biodistribution studies. This may include a tool of vectorized anti-tau antibody and/or another well-validated transgene target.

[0516] NHP receive ICM and/or intrathalamic IPa injections of transgene tool construct at various doses. At a pre-selected time-point (e.g., 1-2 months post injection), NHPs are euthanized and brain, spinal cord, and peripheral tissues are collected. Tissue punches from multiple brain regions are collected from the left hemisphere and vector genome and anti-tau antibody or frataxin transgene mRNA levels are quantified from the same sample. Additionally, the right hemisphere is utilized for IHC (or in situ hybridization, ISH) analysis of tool construct expression.

Example 6. Evaluation of vectorized MAPT siRNAs *in vivo* in mice

[0517] This Example investigates the ability of the modulatory polynucleotide VOYTaumiR-127-530 (SEQ ID NO: 4405) and/or VOYTaumiR-127-579 (SEQ ID NO: 4408) to inhibit and reduce expression of MAPT (human tau) *in vivo* at varying doses. These constructs also demonstrated increased activity *in vitro* as shown in Example 3.

[0518] In a first study, AAV particles were generated with the VOY9P39 capsid (SEQ ID NO: 5147) or the VOY101 (SEQ ID NO: 1) encapsulating the VOYTaumiR-127-530 modulatory polynucleotide (SEQ ID NO: 4405) driven by a CBA promoter encoded by a self-complementary viral genome. The self-complementary viral genome comprised the nucleotide sequence of SEQ ID NO: 5173. The AAV particles comprising the VOY9P39 capsid encoding the VOYTaumiR-127-530 modulatory polynucleotide were intravenously administered to hTau mice (female; 12-13 weeks old, n=6) at increasing doses of 3e12 vg/kg (low), 1e13 vg/kg (mid), or 3e13 vg/kg (high). AAV particles comprising the VOY101 capsid encoding the VOYTaumiR-127-530 modulatory polynucleotide or an mCherry reporter control; or AAV particles comprising the VOY9P39 capsid encoding a non-targeting control or an mCherry reporter control were intravenously administered to hTau mice at a dose of 3e13 vg/kg. A group of mice also received a non

treatment vehicle control (n=6). The in-life period was four weeks and brains, livers, spinal cord, serum, and/or CSF were collected from the mice to measure tau knockdown (mRNA and protein levels) and biodistribution. The body weight and cage side observations for all mice throughout the study were normal and no significant changes were observed.

[0519] **Table 21** and **FIGs. 5A-5E**, provide the AAV biodistribution observed in the cortex, hippocampus, brainstem, thalamus, and liver following intravenous administration of the AAV particles comprising the VOY9P39 or VOY101 capsid protein encoding the VOYTaumiR-127-530 modulatory polynucleotide, the non-targeting control (NTC), or the mCherry reporter control construct. Good biodistribution was observed in all brain regions investigated. Additionally, a dose dependent increase was observed in the biodistribution (vg copies per diploid cells (vg/dg)) in the cortex, hippocampus, brainstem, and thalamus in the mice that received the increasing doses of the AAV particles comprising the VOY9P39 capsid encoding the VOYTaumiR-127-530 modulatory polynucleotide (**Table 21** and **FIGs. 5A-5D**). Low levels of vg/dg (biodistribution) were observed in the liver of the mice when administered the AAV particles comprising the VOY9P39 capsid (**Table 21** and **FIG. 5E**).

Table 21. Biodistribution (vg/dg) in the brain of mice post-intravenous injection of AAV particles comprising the VOY9P39 or VOY101 capsid protein encoding the VOYTaumiR-127-530 modulatory polynucleotide, non-target control, or the mCherry reporter control

Payload	Capsid	Dose (vg/kg)	VG/DG				
			Cortex	Hippocampus	Brainstem	Thalamus	Liver
mCherry Reporter Control	VOY9P39	3e13	45.5	27.1	61.2	49.6	5.6
Non-Target Control	VOY9P39	3e13	38.4	20.7	47.7	39.6	2.2
VOYTaumiR-127-530	VOY9P39	3e12	14.3	5.6	18.6	13.8	0.4
VOYTaumiR-127-530	VOY9P39	1e13	21.9	9.1	30.6	24.7	0.9
VOYTaumiR-127-530	VOY9P39	3e13	57.5	22.6	66.5	55.8	5.5
mCherry Reporter Control	VOY101	3e13	63.3	33.3	74.0	66.5	22.0
VOYTaumiR-127-530	VOY101	3e13	46.5	28.0	59.5	48.5	27.4

[0520] The ability of vectorized VOYTaumiR-127-530 modulatory polynucleotide (SEQ ID NO: 4405) to reduce MAPT mRNA expression was also determined in the cortex, hippocampus, thalamus, and brainstem of mice at 4 weeks post intravenous administration. The amount of MAPT mRNA remaining after treatment was measured by qPCR and normalized to a housekeeping gene (endogenous XPNPEP1) and the fold-change in MAPT mRNA remaining in the groups receiving the increasing doses of the VOYTaumiR-127-530 modulatory polynucleotide relative to the vehicle was determined. As shown in **FIGs. 6A-6D**, MAPT mRNA was reduced in all mice that received AAV particles encoding the VOYTaumiR-127-530 modulatory polynucleotide, relative to the groups that received the non-targeting control or the mCherry reporter control. Additionally, AAV particles encoding the VOYTaumiR-127-530 modulatory polynucleotide comprising the VOY9P39 capsid protein or the VOY1010 capsid protein led to comparable levels of MAPT mRNA knockdown in the brain tissues investigated (**FIGs. 6A-6D**). As shown in **FIGs. 6A-6D**, a trending dose

response was observed in MAPT mRNA knockdown in the cortex, hippocampus, thalamus, and brainstem when mice were intravenously administered AAV particles comprising the VOY9P39 capsid and encoding the VOYTaumiR-127-530 modulatory polynucleotide at 3e12 vg/kg, 1e13 vg/kg, or 3e13 vg/kg. The fold-change in MAPT mRNA remaining in the groups receiving the increasing doses of the VOYTaumiR-127-530 modulatory polynucleotide relative to the vehicle or non-target control is shown in **Table 22**. The percent MAPT knockdown was calculated in the hippocampus, cortex and brainstem and is provided in **Table 23**. At least a 70% knockdown and up to a 90% knockdown was observed in the brain following treatment with the VOYTaumiR-127-530 modulatory polynucleotide targeting MAPT at the highest dose tested (3e13 vg/kg) **(Table 23)**. Even at the low dose of 3e12 vg/kg, 44-76% knockdown of MAPT mRNA was observed in different regions of the mouse brain four weeks post treatment with vectorized VOYTaumiR-127-530, which targets MAPT **(Table 23)**.

Table 22. Fold change in MAPT mRNA levels in the brain of mice post-intravenous injection of AAV particles encoding the VOYTaumiR-127-530 modulatory polynucleotide relative to MAPT mRNA levels in the brain of mice receiving the vehicle control or AAV particles encoding a non-target control

			Fold Change relative to Vehicle			
Payload	**Capsid**	**Dose (vg/kg)**	**Cortex**	**Hippocampus**	**Thalamus**	**Brainstem**
Vehicle	N/A	N/A	1.00	1.00	1.00	1.00
VOYTaumiR-127-530	VOY9P39	3e12	0.24	0.42	0.27	0.25
VOYTaumiR-127-530	VOY9P39	1e13	0.17	0.32	0.28	0.21
VOYTaumiR-127-530	VOY9P39	3e13	0.10	0.27	0.18	0.13
			Fold Change relative to Non-Target Control			
Payload	**Capsid**	**Dose (vg/kg)**	**Cortex**	**Hippocampus**	**Thalamus**	**Brainstem**
Non-Target Control	VOY9P39	3e13	1.00	1.00	1.00	1.00
VOYTaumiR-127-530	VOY9P39	3e12	0.24	0.53	0.38	0.21
VOYTaumiR-127-530	VOY9P39	1e13	0.17	0.41	0.40	0.18
VOYTaumiR-127-530	VOY9P39	3e13	0.10	0.34	0.26	0.11

Table 23. Percent knockdown of MAPT mRNA in the brain of mice post-intravenous injection of AAV particles comprising the VOY9P39 capsid and encoding the VOYTaumiR-127-530 modulatory polynucleotide

			Percent Knockdown of mRNA levels		
Payload	**Capsid**	**Dose (vg/kg)**	**Cortex**	**Hippocampus**	**Brainstem**
VOYTaumiR-127-530	VOY9P39	3e12	76%	44%	75%
VOYTaumiR-127-530	VOY9P39	1e13	84%	64%	79%
VOYTaumiR-127-530	VOY9P39	3e13	90%	69%	87%

[0521] A linear regression was performed to determine the relationship between viral genome levels and MAPT mRNA levels remaining relative to the vehicle in the brain regions at 4 weeks post-intravenous treatment with the AAV particles comprising the VOY9P39 capsid and encoding the VOYTaumiR-127-530 modulatory polynucleotide. A negative correlation was observed between the MAPT mRNA levels and the viral genome levels. The R^2 value in the cortex was 0.7172 ($p<0.0001$); the R^2 value in the hippocampus was

0.4143 (p=0.0053); the R^2 value in the thalamus was 0.4907 (p=0.0017); and the R^2 value in the brainstem was 0.8667 (p<0.0001).

[0522] Total tau protein levels in the cortex, thalamus, and brainstem following treatment with the AAV particles comprising the VOY9P39 capsid and encoding the VOYTaumiR-127-530 modulatory polynucleotide were determined by AlphaLISA. As shown in **FIGs.7A-7D** and **Table 24**, knockdown in total tau protein level was observed across all brain regions, with the cortex, thalamus, and brainstem showing significant reductions. This knockdown was specific for total tau protein, as no decrease in beta-actin protein levels were observed in the cortex by Western blot.

Table 24. Percent knockdown of MAPT protein and total MAPT protein remaining relative to the vehicle control in the brain of mice post-intravenous injection of AAV particles comprising the VOY9P39 capsid and encoding the VOYTaumiR-127-530 modulatory polynucleotide

			Percent Knockdown of Protein			
Payload	**Capsid**	**Dose (vg/kg)**	**Cortex**	**Hippocampus**	**Thalamus**	**Brainstem**
VOYTaumiR-127-530	VOY9P39	3e12	65%	37%	65%	65%
VOYTaumiR-127-530	VOY9P39	1e13	72%	17%	53%	63%
VOYTaumiR-127-530	VOY9P39	3e13	74%	46%	60%	64%
			Tau Protein Levels Remaining relative to Vehicle Control			
Payload	**Capsid**	**Dose (vg/kg)**	**Cortex**	**Hippocampus**	**Thalamus**	**Brainstem**
Vehicle	N/A	N/A	1.0	1.0	1.0	1.0
VOYTaumiR-127-530	VOY9P39	3e12	0.35	0.63	0.43	0.36
VOYTaumiR-127-530	VOY9P39	1e13	0.29	0.83	0.47	0.38
VOYTaumiR-127-530	VOY9P39	3e13	0.27	0.54	0.40	0.36

[0523] Small RNA processing analysis via high throughput small RNA deep sequencing to measure guide to passenger ratio, abundance of guide and passenger strands relative to the total endogenous pool of miRNAs (saturation level of the endogenous miRNA pathway), and precision of processing at the 5'-end of the guide strand was also performed on RNA isolated from the cortex 4 weeks post-intravenous treatment with the AAV particles comprising the VOY9P39 capsid and encoding the VOYTaumiR-127-530 modulatory polynucleotide. **Table 25** shows the level of mature exogenous MAPT targeting polynucleotides relative to the total endogenous pool of miRNAs to ensure a lack of overharnessing of the endogenous miRNA biogenesis pathway, where a lower percentage is more favorable to prevent any effects related to endogenous miRNA pathway saturation. The guide to passenger strand level is also provided in **Table 25**. A higher guide to passenger strand ratio is more favorable for potency and selectivity and to minimize any passenger strand effects. **Table 25** also shows the 5' end processing of the modulatory polynucleotides evaluated. The 5' end processing of the modulatory polynucleotides indicates that the constructs are being processed correctly at the 5' end and a higher value is more favorable. As the seed region is used for recognition of the target mRNA and starts at a fixed position relative to the 5' end of the guide strand, accurate processing of the 5' end of the guide strand is needed. Both doses of VOYTaumiR-127-530 tested led to 89-90% in the 5' end processing.

Table 25. Guide to passenger ratio, abundance of guide and passenger strands relative to the total endogenous pool of miRNAs (% endogenous), and precision of processing at the 5'-end of the guide strand for the VOYTaumiR-127-530 modulatory polynucleotides in the cortex 4-weeks post-intravenous injection in mice

Payload	Capsid	Dose (vg/kg)	%Endogenous	Guide/Passenger Ratio	5' Precision Processing (%)
VOYTaumiR-127-530	VOY9P39	3e12	2.79%	34.59	91.77%
VOYTaumiR-127-530	VOY9P39	3e13	5.67%	29.60	89.16%
Vehicle	N/A	N/A	0.005%	N/A	97.08%

[0524] In a second study, AV particles were generated with the VOY9P39 capsid (SEQ ID NO: 5147) encapsulating the VOYTaumiR-127-530 modulatory polynucleotide (SEQ ID NO: 4405), the VOYTaumiR-127-579 (SEQ ID NO: 4408) modulatory polynucleotide, or a non-target control (NTC) modulatory polynucleotide driven by a CBA promoter encoded by a self-complementary viral genome. The self-complementary viral genome encoding VOYTaumiR-127-530 comprised the nucleotide sequence of SEQ ID NO: 5173; and the self-complementary viral genome encoding VOYTaumiR-127-579 comprised the nucleotide sequence of SEQ ID NO: 5195. The AAV particles comprising the VOY9P39 capsid encoding the VOYTaumiR-127-530 modulatory polynucleotide were intravenously administered to hTau mice (female; 17-18 weeks old, n=6) at a high dose of 1e13 vg/kg or a low dose of 1e12 vg/kg. The AAV particles comprising the VOY9P39 capsid encoding the VOYTaumiR-127-579 modulatory polynucleotide or the non-target control construct were intravenously administered to hTau mice (female; 17-18 weeks old, n=6) at the high dose of 1e13 vg/kg. The in-life period was four weeks and brains were collected from the mice to measure tau knockdown.

[0525] The amount of MAPT mRNA remaining after treatment was measured by qPCR and normalized to a housekeeping gene (endogenous XPNPEP1) in the cortex, hippocampus, thalamus, and brainstem. The fold-change in MAPT mRNA remaining in the groups receiving the VOYTaumiR-127-530 or VOYTaumiR-127-579 modulatory polynucleotide relative to the vehicle was determined (**FIGs. 8A-8D**). As shown in **FIGs. 8A-8D**, MAPT mRNA was reduced across all brain regions investigated, including the cortex, hippocampus, thalamus, and brainstem, at 4 weeks post-treatment with AAV particles encoding the VOYTaumiR-127-530 or VOYTaumiR-127-579 modulatory polynucleotide. Additionally, a dose response was observed in these brain regions in the mice that received the high and low dose of AAV particles encoding the VOYTaumiR-127-530 modulatory polynucleotide (**FIGs. 8A-8D**).

[0526] Taken together, these *in vivo* data demonstrate good biodistribution and/or knock down of MAPT following intravenous administration of AAV particles encoding the VOYTaumiR-127-530 modulatory polynucleotide or the VOYTaumiR-127-579 modulatory polynucleotide which target MAPT.

VII. EQUIVALENTS AND SCOPE

[0527] The disclosures of each and every patent, patent application, and publication cited herein are hereby incorporated herein by reference in their entirety. While this invention has been disclosed with reference to certain embodiments, it is apparent that further embodiments and variations of this invention may be devised by others skilled in the art without departing from the true spirit and scope of the invention. The appended claims are intended to be construed to include all such embodiments and equivalent variations.

We claim:

1. A short interfering ribonucleic acid (siRNA) for inhibiting expression of microtubule-associated protein tau (MAPT) which comprises a sense strand sequence and an antisense strand sequence, wherein:

(i) the antisense strand sequence comprises at least 20 or 21 contiguous nucleotides of any one of SEQ ID NOs: 4908, 4920, 4924, 5057, 4916, 4912, 5080, 5104, or 5128; and

(ii) the sense strand sequence comprises at least 20 or 21 contiguous nucleotides of any one of SEQ ID NOs: 4906, 4926, 4946, 4966, 4986, 5006, 4918, 4938, 4958, 4978, 4998, 4922, 4942, 4962, 4982, 5002, 5022, 5054, 5060, 5064, 5066, 5070, 5074, 4914, 4934, 4954, 4974, 4994, 5014, 4910, 4930, 4950, 4970, 4990, 5010, 5077, 5084, 5088, 5092, 5096, 5098, 5101, 5108, 5112, 5116, 5120, 5122, 5125, 5132, 5136, 5140, 5144, or 5146;

wherein the sense strand sequence and the antisense strand sequence comprise a region of complementarity of at least 15, 16, 17, 18, 19, or 20 nucleotides.

2. An adeno-associated virus (AAV) viral genome comprising a nucleotide sequence positioned between two inverted terminal repeats (ITRs), wherein the nucleotide sequence encodes an siRNA for inhibiting MAPT, wherein the siRNA comprises a sense strand sequence and an antisense strand sequence, wherein:

(i) the antisense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides of any one of SEQ ID NOs: 4908, 4920, 4924, 5057, 4916, 4912, 5080, 5104, or 5128; and

(ii) the sense strand sequence comprises at least 19, 20, or 21 contiguous nucleotides of any one of SEQ ID NOs: 4906, 4926, 4946, 4966, 4986, 5006, 4918, 4938, 4958, 4978, 4998, 4922, 4942, 4962, 4982, 5002, 5022, 5054, 5060, 5064, 5066, 5070, 5074, 4914, 4934, 4954, 4974, 4994, 5014, 4910, 4930, 4950, 4970, 4990, 5010, 5077, 5084, 5088, 5092, 5096, 5098, 5101, 5108, 5112, 5116, 5120, 5122, 5125, 5132, 5136, 5140, 5144, or 5146;

wherein the sense strand sequence and the antisense strand sequence comprise a region of complementarity of at least 15, 16, 17, 18, 19, or 20 nucleotides.

3. The siRNA of claim 1, or the AAV viral genome of claim 2, wherein:

(i) the antisense strand comprises at least 20 contiguous nucleotides of any one of SEQ ID NOs: 4908, 4920, 4924, or 4912; and/or the sense strand comprises at least 20 contiguous nucleotides of any one of SEQ ID NOs: 4906, 4926, 4946, 4966, 4986, 5006, 4918, 4938, 4958, 4978, 4998, 4922, 4942, 4962, 4982, 5002, 5022, 4910, 4930, 4950, 4970, 4990, or 5010;

(ii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4908 and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4906, 4926, 4946, 4966, 4986, or 5006;

(iii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4920 and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4918, 4938, 4958, 4978, or 4998;

(iv) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4924 and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4922, 4942, 4962, 4982, 5002, or 5022;

(v) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4912 and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4910, 4930, 4950, 4970, 4990, or 5010;

(vi) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4916 and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 4914, 4934, 4954, 4974, 4994, or 5014;

(vii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5104; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 5101, 5108, 5112, 5116, 5120, or 5122;

(viii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5128; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 5125, 5132, 5136, 5140, 5144, or 5146;

(ix) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5080; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 5077, 5084, 5088, 5092, 5096, or 5098; or

(x) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5057; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of any one of SEQ ID NOs: 5054, 5060, 5064, 5066, 5070, or 5074.

4. The siRNA of claim 1 or 3, or the AAV viral genome of claim 2 or 3, wherein:

(i) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4908 and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4906;

(ii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4920 and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4918;

(iii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4924 and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4922;

(iv) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4908 and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4966;

(v) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4912 and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4970;

(vi) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4920 and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4978;

(vii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4924 and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4982;

(viii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4912; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4910;

(ix) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4916; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4914;

(x) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5057; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5054;

(xi) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4908; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4926;

(xii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4912; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4930;

(xiii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4916; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4934;

(xiv) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4920; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4938;

(xv) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4924; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4942;

(xvi) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5057; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5060;

(xvii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4908; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4946;

(xviii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4912; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4950;

(xix) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4916; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4954;

(xx) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4920; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4958;

(xxi) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4924; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4962;

(xxii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5057; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5064;

(xxiii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4916; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4974;

(xxiv) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5057; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5066;

(xxv) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4908; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4986;

(xxvi) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4912; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4990;

(xxvii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4916; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4994;

(xxviii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4920; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4998;

(xxix) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4924; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5002;

(xxx) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5057; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5070;

(xxxi) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4908; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5006;

(xxxii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4912; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5010;

(xxxiii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4916; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5014;

(xxxiv) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4920; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4958;

(xxxv) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 4924; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5022;

(xxxvi) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5057; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5074;

(xxxvii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5080; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5077;

(xxxviii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5080; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5084;

(xxxix) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5080; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5088;

(xl) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5080; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5092;

(xli) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5080; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5096;

(xlii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5080; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5098;

(xliii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5104; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5101;

(xliv) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5104; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5108;

(xlv) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5104; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5112;

(xlvi) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5104; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5116;

(xlvii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5104; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5120;

(xlviii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5104; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5122;

(xlix) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5128; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5125;

(l) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5128; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5132;

(li) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5128; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5136;

(lii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5128; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5140;

(liii) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5128; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5144; or

(liv) the antisense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5128; and the sense strand sequence comprises at least 20 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 5146.

5. The siRNA of any one of claims 1, 3, or 4, or the AAV viral genome of any one of claims 2-4, wherein:

(i) the antisense strand comprises the nucleotide sequence of any one of SEQ ID NOs: 4908, 4920, 4924, or 4912; and/or the sense strand comprises at the nucleotide sequence of any one of SEQ ID NOs: 4906, 4926, 4946, 4966, 4986, 5006, 4918, 4938, 4958, 4978, 4998, 4922, 4942, 4962, 4982, 5002, 5022, 4910, 4930, 4950, 4970, 4990, or 5010;

(ii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4908 and the sense strand sequence comprises the nucleotide sequence of any one of SEQ ID NOs: 4906, 4926, 4946, 4966, 4986, or 5006;

(iii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4920 and the sense strand sequence comprises the nucleotide sequence of any one of SEQ ID NOs: 4918, 4938, 4958, 4978, or 4998;

(iv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4924 and the sense strand sequence comprises the nucleotide sequence of any one of SEQ ID NOs: 4922, 4942, 4962, 4982, 5002, or 5022;

(v) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4912 and the sense strand sequence comprises the nucleotide sequence of any one of SEQ ID NOs: 4910, 4930, 4950, 4970, 4990, or 5010;

(vi) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4916 and the sense strand sequence comprises the nucleotide sequence of any one of SEQ ID NOs: 4914, 4934, 4954, 4974, 4994, or 5014;

(vii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5104; and the sense strand sequence comprises the nucleotide sequence of any one of SEQ ID NOs: 5101, 5108, 5112, 5116, 5120, or 5122;

(viii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5128; and the sense strand sequence comprises the nucleotide sequence of any one of SEQ ID NOs: 5125, 5132, 5136, 5140, 5144, or 5146;

(ix) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5080; and the sense strand sequence comprises the nucleotide sequence of any one of SEQ ID NOs: 5077, 5084, 5088, 5092, 5096, or 5098; or

(x) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5057; and the sense strand sequence comprises the nucleotide sequence of any one of SEQ ID NOs: 5054, 5060, 5064, 5066, 5070, or 5074.

6. The siRNA of any one of claims 1 or 3-5, or the AAV viral genome of any one of claims 2-5, wherein:

(i) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4908 and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4906;

(ii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4920 and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4918;

(iii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4924 and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4922;

(iv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4908 and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4966;

(v) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4912 and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4970;

(vi) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4920 and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4978;

(vii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4924 and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4982;

(viii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4912; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4910;

(ix) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4916; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4914;

(x) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5057; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5054;

(xi) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4908; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4926;

(xii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4912; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4930;

(xiii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4916; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4934;

(xiv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4920; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4938;

(xv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4924; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4942;

(xvi) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5057; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5060;

(xvii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4908; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4946;

(xviii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4912; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4950;

(xix) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4916; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4954;

(xx) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4920; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4958;

(xxi) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4924; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4962;

(xxii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5057; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5064;

(xxiii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4916; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4974;

(xxiv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5057; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5066;

(xxv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4908; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4986;

(xxvi) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4912; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4990;

(xxvii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4916; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4994;

(xxviii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4920; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4998;

(xxix) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4924; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5002;

(xxx) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5057; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5070;

(xxxi) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4908; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5006;

(xxxii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4912; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5010;

(xxxiii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4916; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5014;

(xxxiv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4920; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4958;

(xxxv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4924; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5022;

(xxxvi) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5057; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5074;

(xxxvii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5080; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5077;

(xxxviii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5080; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5084;

(xxxix) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5080; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5088;

(xl) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5080; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5092;

(xli) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5080; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5096;

(xlii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5080; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5098;

(xliii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5104; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5101;

(xliv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5104; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5108;

(xlv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5104; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5112;

(xlvi) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5104; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5116;

(xlvii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5104; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5120;

(xlviii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5104; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5122;

(xlix) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5128; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5125;

(l) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5128; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5132;

(li) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5128; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5136;

(lii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5128; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5140;

(liii) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5128; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5144; or

(liv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5128; and the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 5146.

7. The siRNA of any one of claims 1 or 3-6, or the AAV viral genome of any one of claims 2-6, wherein:

(i) the nucleotide sequence encoding the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4907 and the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4905;

(ii) the nucleotide sequence encoding the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4919 and the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4917;

(iii) the nucleotide sequence encoding the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4923 and the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4921;

(iv) the nucleotide sequence encoding the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4907 and the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4965;

(v) the nucleotide sequence encoding the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4911 and the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4969;

(vi) the nucleotide sequence encoding the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4919 and the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4977; or

(vii) the nucleotide sequence encoding the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4923 and the nucleotide sequence encoding the sense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4981.

8. The siRNA of any one of claims 1 or 3-7, or the AAV viral genome of any one of claims 2-7, wherein:

(i) the sense strand sequence, the antisense strand sequence, or both the sense strand sequence and the antisense strand sequence comprise at least 15-30, 19-21, or 25-30 nucleotides in length, e.g., 17, 18, 20, 21, 22, 25, or 30 nucleotides in length;

(ii) the sense strand sequence, the antisense strand sequence, or both the sense strand sequence and the antisense strand sequence comprise an overhang, e.g., an overhang at the 5' end of the sense strand sequence and/or at the 3' end of the antisense strand sequence, of 1 or 2 nucleotides;

(iii) the sense strand and the antisense strand comprise one mismatch; and/or

(iv) the antisense strand and the target sequence comprise one mismatch.

9. A modulatory polynucleotide comprising the siRNA of any one of claims 1 or 3-8.

10. The AAV viral genome of any one of claims 2-8, wherein the viral genome further encodes a modulatory polynucleotide comprising the sense and antisense strand of the siRNA.

11. The modulatory polynucleotide of claim 9 or the AAV viral genome of claim 10, wherein the modulatory polynucleotide further comprises one, two, three or all of:

(i) a 5' flanking region;

(ii) a loop region; and

(iii) a 3' flanking region.

12. The modulatory polynucleotide of claim 11 or the AAV viral genome of claim 11, wherein:

(A) (i) the 5' flanking region comprises the nucleotide sequence of any one of SEQ ID NOs: 4878-4886; a nucleotide sequence at least 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of any of SEQ ID NOs: 4878-4886; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of any of SEQ ID NOs: 4878-4886;

(ii) the loop region comprises the nucleotide sequence of any of SEQ ID NOs: 4887-4896; a nucleotide sequence at least 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto; a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of any of SEQ ID NOs: 4887-4896; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of any of SEQ ID NOs: 4887-4896; and/or

(iii) the 3' flanking region comprises the nucleotide sequence of any one of SEQ ID NOs: 4897-4904; a nucleotide sequence at least 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of any of SEQ ID NOs: 4897-4904; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of any of SEQ ID NOs: 4897-4904; and/or

(B) (i) the nucleotide sequence encoding the 5' flanking region comprises the nucleotide sequence of any of SEQ ID NOs: 4353-4361, a nucleotide sequence at least 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of any of SEQ ID NOs: 4353-4361; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of any of SEQ ID NOs: 4353-4361;

(ii) the nucleotide sequence encoding the loop region comprises the nucleotide sequence of any of SEQ ID NOs: 4362-4371; a nucleotide sequence at least 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto; a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of any of SEQ ID NOs: 4362-4371; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of any of SEQ ID NOs: 4362-4371; and/or

(iii) the nucleotide sequence encoding the 3' flanking region comprises the nucleotide sequence of any of SEQ ID NOs: 4372-4379; a nucleotide sequence at least 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of any of SEQ ID NOs: 4372-4379; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of any of SEQ ID NOs: 4372-4379.

13. The modulatory polynucleotide of any one of claims 9, 11, or 12, or the AAV viral genome of any one of claims 10-12, wherein the modulatory polynucleotide comprises:

(A) (i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4879, a nucleotide sequence at least 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4879, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4879; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4879;

(ii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4887, a nucleotide sequence at least 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4887, a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4887; or a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4887; and

(iii) a 3' flanking region of SEQ ID NO: 4898, a nucleotide sequence at least 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4898, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4898, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4898;

(B) (i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4879, a nucleotide sequence at least 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4879, a

nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4879; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4879;

(ii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4888, a nucleotide sequence at least 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4888, a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4888; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4888; and

(iii) a 3' flanking region of SEQ ID NO: 4898, a nucleotide sequence at least 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4898, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4898, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4898;

(C) (i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4879, a nucleotide sequence at least 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4879, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4879; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4879;

(ii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4887, a nucleotide sequence at least 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4887, a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4887; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4887; and

(iii) a 3' flanking region of SEQ ID NO: 4899, a nucleotide sequence at least 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4899, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4899, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4899; or

(D) (i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4880, a nucleotide sequence at least 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4880, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides

relative to the nucleotide sequence of SEQ ID NO: 4880; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4880;

(ii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4891, a nucleotide sequence at least 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4891, a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4891; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4891; and

(iii) a 3' flanking region of SEQ ID NO: 4900, a nucleotide sequence at least 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4900, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4900, or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to SEQ ID NO: 4900.

14. The modulatory polynucleotide of any one of claims 9 or 11-13 or the AAV viral genome of any one of claims 10-13, wherein the modulatory polynucleotide comprises in 5' to 3' order:

(i) the 5' flanking region, sense strand sequence, loop region, antisense strand sequence, and 3' flanking region; or

(ii) the 5' flanking region, antisense strand sequence, loop region, sense strand sequence, and 3' flanking region.

15. The modulatory polynucleotide of any one of claims 9 or 11-14 or the AAV viral genome of any one of claims 10-14, wherein the modulatory polynucleotide comprises in 5' to 3' order:

(A) (i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4880; a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4880; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4880; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4880;

(ii) the sense strand sequence of SEQ ID NO: 4906;

(iii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4891; a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4891; a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ

ID NO: 4891; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4891;

(iv) the antisense strand sequence of SEQ ID NO: 4908; and

(v) a 3' flanking region comprising the nucleotide sequence of SEQ ID NO: 4900; a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4900; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4900; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to SEQ ID NO: 4900;

(B) (i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4880; a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4880; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4880; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4880;

(ii) the sense strand sequence of SEQ ID NO: 4918;

(iii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4891; a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4891; a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4891; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4891;

(iv) the antisense strand sequence of SEQ ID NO: 4920; and

(v) a 3' flanking region comprising the nucleotide sequence of SEQ ID NO: 4900; a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4900; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4900; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to SEQ ID NO: 4900;

(C) (i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4880; a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4880; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4880; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4880;

(ii) the sense strand sequence of SEQ ID NO: 4922;

(iii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4891; a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4891; a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4891; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4891;

(iv) the antisense strand sequence of SEQ ID NO: 4924; and

(v) a 3' flanking region comprising the nucleotide sequence of SEQ ID NO: 4900; a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4900; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4900; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to SEQ ID NO: 4900;

(D) (i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4879, a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4879, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4879; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4879;

(ii) the sense strand sequence of SEQ ID NO: 4966;

(iii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4888, a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4888, a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4888; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4888;

(iv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4908; and

(v) a 3' flanking region of SEQ ID NO: 4898, a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4898, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4898, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4898;

(E) (i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4879, a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4879, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4879; or a nucleotide sequence comprising one, two,

three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4879;

(ii) the sense strand sequence of SEQ ID NO: 4970;

(iii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4888, a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4888, a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4888; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4888;

(iv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4912; and

(v) a 3' flanking region of SEQ ID NO: 4898, a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4898, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4898, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4898;

(F) (i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4879, a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4879, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4879; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4879;

(ii) the sense strand sequence of SEQ ID NO: 4978;

(iii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4888, a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4888, a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4888; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4888;

(iv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4920; and

(v) a 3' flanking region of SEQ ID NO: 4898, a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4898, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4898, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4898; or

(G) (i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4879, a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4879, a nucleotide

sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4879; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4879;

(ii) the sense strand sequence of SEQ ID NO: 4982;

(iii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4888, a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4888, a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4888; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4888;

(iv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4924; and

(v) a 3` flanking region of SEQ ID NO: 4898, a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4898, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4898, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4898.

16. The modulatory polynucleotide of any one of claims 9 or 11-15 or the AAV viral genome of any one of claims 10-15, wherein the nucleotide sequence encoding the modulatory polynucleotide comprises in 5' to 3' order:

(A) (i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4355; a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4355; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4355; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4355;

(ii) the sense strand sequence of SEQ ID NO: 4905;

(iii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4366; a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4366; a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4366; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4366;

(iv) the antisense strand sequence of SEQ ID NO: 4907; and

(v) a 3' flanking region comprising the nucleotide sequence of SEQ ID NO: 4375; a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4375; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4375; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to SEQ ID NO: 4375;

(B) (i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4355; a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4355; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4355; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4355;

(ii) the sense strand sequence of SEQ ID NO: 4917;

(iii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4366; a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4366; a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4366; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4366;

(iv) the antisense strand sequence of SEQ ID NO: 4919; and

(v) a 3' flanking region comprising the nucleotide sequence of SEQ ID NO: 4375; a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4375; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4375; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to SEQ ID NO: 4375;

(C) (i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4355; a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4355; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4355; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4355;

(ii) the sense strand sequence of SEQ ID NO: 4921;

(iii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4366; a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4366; a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ

ID NO: 4366; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4366;

(iv) the antisense strand sequence of SEQ ID NO: 4923; and

(v) a 3' flanking region comprising the nucleotide sequence of SEQ ID NO: 4375; a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4375; a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4375; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to SEQ ID NO: 4375;

(D) (i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4354, a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4354, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4354; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4354;

(ii) the sense strand sequence of SEQ ID NO: 4965;

(iii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4363, a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4363, a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4363; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4363;

(iv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4907; and

(v) a 3' flanking region of SEQ ID NO: 4373, a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4373, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4373, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4373;

(E) (i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4354, a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4354, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4354; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4354;

(ii) the sense strand sequence of SEQ ID NO: 4969;

(iii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4363, a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4363, a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4363; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4363;

(iv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4911; and

(v) a 3' flanking region of SEQ ID NO: 4373, a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4373, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4373, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4373;

(F) (i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4354, a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4354, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4354; or a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4354;

(ii) the sense strand sequence of SEQ ID NO: 4977;

(iii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4363, a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4363, a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4363; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4363;

(iv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4919; and

(v) a 3' flanking region of SEQ ID NO: 4373, a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4373, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4373, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4373; or

(G) (i) a 5' flanking region comprising the nucleotide sequence of SEQ ID NO: 4354, a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4354, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4354; or a nucleotide sequence comprising one, two,

three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4354;

(ii) the sense strand sequence of SEQ ID NO: 4981;

(iii) a loop region comprising the nucleotide sequence of SEQ ID NO: 4363, a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4363, a nucleotide sequence comprising one, two, three, or four, but no more than five different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4363; or a nucleotide sequence comprising one, two, three, or four, but no more than five modifications relative to the nucleotide sequence of SEQ ID NO: 4363;

(iv) the antisense strand sequence comprises the nucleotide sequence of SEQ ID NO: 4923; and

(v) a 3' flanking region of SEQ ID NO: 4373, a nucleotide sequence at least 85%, 90%, 95% 96%, 97%, 98%, 99% identical to SEQ ID NO: 4373, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten different nucleotides relative to the nucleotide sequence of SEQ ID NO: 4373, a nucleotide sequence comprising one, two, three, four, five, six, or seven, but no more than ten modifications relative to the nucleotide sequence of SEQ ID NO: 4373.

17. The modulatory polynucleotide of any one of claims 9 or 11-16, or the AAV viral genome of any one of claims 10-16, wherein the nucleotide sequence encoding the modulatory polynucleotide comprises the nucleotide sequence of any one of SEQ ID NOs: 4405, 4408, 4409, 4390, 4391, 4393, 4394, 4380-4389, 4392, 4395-4404, 4406, or 4407, or nucleotide sequence at least 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto.

18. An AAV viral genome comprising a promoter operably linked to a nucleic acid encoding the modulatory polynucleotide of any one of claims 9 or 11-17 or the siRNA of any one of claims 1 or 3-8.

19. The AAV viral genome of any one of claims 3-8 or 10-17, wherein the AAV viral genome further comprises a promoter operably linked to the nucleotide sequence encoding the sense strand sequence and the antisense strand sequence or the nucleotide sequence encoding the modulatory polynucleotide.

20. The AAV viral genome of claim 18 or 19, wherein the promoter:

(i) is a ubiquitous promoter;

(ii) is a cell or tissue specific promoter;

(iii) is chosen from human elongation factor 1α-subunit (EF1α), cytomegalovirus (CMV) immediate-early enhancer and/or promoter, chicken β-actin (CBA) and its derivative CAG, β glucuronidase (GUSB), or ubiquitin C (UBC), neuron-specific enolase (NSE), platelet-derived growth factor (PDGF), platelet-derived

growth factor B-chain (PDGF-β), intercellular adhesion molecule 2 (ICAM-2), synapsin (Syn), methyl-CpG binding protein 2 (MeCP2), Ca2+/calmodulin-dependent protein kinase II (CaMKII), metabotropic glutamate receptor 2 (mGluR2), neurofilament light chain (NFL) or neurofilament heavy chain (NFH), β-globin minigene nβ2, preproenkephalin (PPE), enkephalin (Enk) and excitatory amino acid transporter 2 (EAAT2), glial fibrillary acidic protein (GFAP), myelin basic protein (MBP), a cardiovascular promoter (e.g., αMHC, cTnT, and CMV-MLC2k), a liver promoter (e.g., hAAT, TBG), a skeletal muscle promoter (e.g., desmin, MCK, C512) or a functional fragment, e.g., a truncation, or a functional variant thereof;

(iii) is a CBA promoter or variant thereof;

(iv) comprises the nucleotide sequence of any one of the nucleotide sequences provided in Table 2; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to any one of the nucleotide sequences provided in Table 2; or a nucleotide sequence with at least 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity to any one of the nucleotide sequences provided in Table 2; or

(v) comprises the nucleotide sequence of SEQ ID NO: 5199; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5199; or a nucleotide sequence with at least 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO: 5199.

21. The AAV viral genome of any one of claims 2-8 or 10-20, wherein the AAV viral genome further comprises:

(i) at least one or two inverted terminal repeat (ITR) sequences, optionally wherein the AAV viral genome comprises an ITR sequence positioned 5' relative to the nucleic acid encoding the modulatory polynucleotide or siRNA and/or an ITR sequence positioned 3' relative to the nucleic acid encoding the modulatory polynucleotide or siRNA;

(ii) a polyadenylation (polyA) signal sequence;

(iii) an enhancer, a Kozak sequence, an intron region, and/or an exon region; and/or

(iv) a nucleotide sequence encoding a microRNA (miR) binding site, e.g., a miR binding site that modulates, e.g., reduces expression of payload encoded by the viral genome in a cell or tissue where the corresponding miRNA is expressed; optionally wherein the encoded miR binding site modulates, e.g., reduces expression of the encoded payload in a cell or tissue of the DRG, liver, heart, hematopoietic lineage, or a combination thereof

22. The AAV viral genome of claim 21, wherein:

(i) the ITR positioned 5' relative to the nucleic acid encoding the modulator polynucleotide or siRNA comprises the nucleotide sequence of SEQ ID NO: 5197 or 4469; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5197 or 4469; or a nucleotide sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO: 5197 or 4469;

(ii) the ITR positioned 3' relative to the nucleic acid encoding the modulator polynucleotide or siRNA comprises the nucleotide sequence of SEQ ID NO: 5200 or 4470; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5200 or 4470; or a nucleotide sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO: 5200 or 4470;

(iii) the polyA signal sequence comprises the nucleotide sequence of SEQ ID NO: 4476; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4476; or a nucleotide sequence with at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, or 99%) sequence identity to SEQ ID NO: 4476;

(iv) the enhancer comprises a CMVie enhancer or variant thereof;

(v) the enhancer comprises the nucleotide sequence of SEQ ID NO: 4471 or 4472; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4471 or 4472; or a nucleotide sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO: 4471 or 4472; and/or

(vi) the intron comprises the nucleotide sequence of SEQ ID NO: 4475; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4475; or a nucleotide sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO: 4475.

23. The AAV viral genome of any one of claims 2-8 or 10-22, wherein the AAV viral genome is self-complementary or single stranded.

24. The AAV viral genome of any one of claims 2-8 or 10-23, wherein the AAV viral genome further comprises a nucleotide sequence encoding a Rep protein, e.g., a non-structural protein, wherein the Rep protein comprises a Rep78 protein, a Rep68, Rep52 protein, and/or a Rep40 protein (e.g., a Rep78 and a Rep52 protein).

25. The AAV viral genome of any one of claims 2-8 or 10-24, which comprises in 5' to 3' order:

(A) (i) an ITR, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 5197; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5197; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5197;

(ii) an enhancer, wherein the enhancer comprises the nucleotide sequence of SEQ ID NO: 4471; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4471; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4471;

(iii) a promoter, wherein the promoter comprises the nucleotide sequence of SEQ ID NO: 5199; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5199; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5199;

(iv) an intron, wherein the intro comprises the nucleotide sequence of SEQ ID NO: 4475; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4475; or a nucleotide sequence at least 80%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4475;

(v) a nucleotide sequence encoding a modulatory polynucleotide, wherein the nucleotide sequence comprises any one of SEQ ID NOs: 4380-4409 or 5027-5050, or nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto;

(vi) a polyA signal sequence, wherein the polyA signal sequence comprises the nucleotide sequence of SEQ ID NO: 4476; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4476; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4476; and

(vii) an ITR, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 5200; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5200; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5200; or

(B) (i) an ITR, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 4469; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4469; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4469;

(ii) an enhancer, wherein the enhancer comprises the nucleotide sequence of SEQ ID NO: 4472; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten

modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4472; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4472;

(iii) a promoter, wherein the promoter comprises the nucleotide sequence of SEQ ID NO: 5199; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5199; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5199;

(iv) an intron, wherein the intro comprises the nucleotide sequence of SEQ ID NO: 4475; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4475; or a nucleotide sequence at least 80%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4475;

(v) a nucleotide sequence encoding a modulatory polynucleotide, wherein the nucleotide sequence comprises any one of SEQ ID NOs: 4380-4409 or 5027-5050, or nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto;

(vi) a polyA signal sequence, wherein the polyA signal sequence comprises the nucleotide sequence of SEQ ID NO: 4476; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4476; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4476; and

(vii) an ITR, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 4470; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4470; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4470.

26. The AAV viral genome of any one of claims 2-8 or 10-25, which comprises in 5' to 3' order:

(A) (i) an ITR, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 5197; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5197; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5197;

(ii) an enhancer, wherein the enhancer comprises the nucleotide sequence of SEQ ID NO: 4471; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4471; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4471;

(iii) a promoter, wherein the promoter comprises the nucleotide sequence of SEQ ID NO: 5199; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten

modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5199; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5199;

(iv) an intron, wherein the intro comprises the nucleotide sequence of SEQ ID NO: 4475; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4475; or a nucleotide sequence at least 80%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4475;

(v) a nucleotide sequence encoding a modulatory polynucleotide, wherein the nucleotide sequence comprises SEQ ID NO: 4405, or nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto;

(vi) a polyA signal sequence, wherein the polyA signal sequence comprises the nucleotide sequence of SEQ ID NO: 4476; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4476; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4476; and

(vii) an ITR, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 5200; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5200; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5200;

(B) (i) an ITR, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 5197; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5197; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5197;

(ii) an enhancer, wherein the enhancer comprises the nucleotide sequence of SEQ ID NO: 4471; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4471; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4471;

(iii) a promoter, wherein the promoter comprises the nucleotide sequence of SEQ ID NO: 5199; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5199; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5199;

(iv) an intron, wherein the intro comprises the nucleotide sequence of SEQ ID NO: 4475; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4475; or a nucleotide sequence at least 80%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4475;

(v) a nucleotide sequence encoding a modulatory polynucleotide, wherein the nucleotide sequence comprises SEQ ID NO: 4408, or nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto;

(vi) a polyA signal sequence, wherein the polyA signal sequence comprises the nucleotide sequence of SEQ ID NO: 4476; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4476; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4476; and

(vii) an ITR, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 5200; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5200; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5200;

(C) (i) an ITR, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 5197; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5197; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5197;

(ii) an enhancer, wherein the enhancer comprises the nucleotide sequence of SEQ ID NO: 4471; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4471; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4471;

(iii) a promoter, wherein the promoter comprises the nucleotide sequence of SEQ ID NO: 5199; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5199; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5199;

(iv) an intron, wherein the intro comprises the nucleotide sequence of SEQ ID NO: 4475; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4475; or a nucleotide sequence at least 80%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4475;

(v) a nucleotide sequence encoding a modulatory polynucleotide, wherein the nucleotide sequence comprises SEQ ID NO: 4409, or nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto;

(vi) a polyA signal sequence, wherein the polyA signal sequence comprises the nucleotide sequence of SEQ ID NO: 4476; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4476; or a

nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4476; and

(vii) an ITR, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 5200; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5200; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5200;

(D) (i) an ITR, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 5197; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5197; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5197;

(ii) an enhancer, wherein the enhancer comprises the nucleotide sequence of SEQ ID NO: 4471; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4471; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4471;

(iii) a promoter, wherein the promoter comprises the nucleotide sequence of SEQ ID NO: 5199; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5199; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5199;

(iv) an intron, wherein the intro comprises the nucleotide sequence of SEQ ID NO: 4475; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4475; or a nucleotide sequence at least 80%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4475;

(v) a nucleotide sequence encoding a modulatory polynucleotide, wherein the nucleotide sequence comprises SEQ ID NO: 4390, or nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto;

(vi) a polyA signal sequence, wherein the polyA signal sequence comprises the nucleotide sequence of SEQ ID NO: 4476; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4476; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4476; and

(vii) an ITR, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 5200; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5200; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5200;

(E) (i) an ITR, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 5197; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5197; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5197;

(ii) an enhancer, wherein the enhancer comprises the nucleotide sequence of SEQ ID NO: 4471; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4471; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4471;

(iii) a promoter, wherein the promoter comprises the nucleotide sequence of SEQ ID NO: 5199; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5199; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5199;

(iv) an intron, wherein the intro comprises the nucleotide sequence of SEQ ID NO: 4475; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4475; or a nucleotide sequence at least 80%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4475;

(v) a nucleotide sequence encoding a modulatory polynucleotide, wherein the nucleotide sequence comprises SEQ ID NO: 4391, or nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto;

(vi) a polyA signal sequence, wherein the polyA signal sequence comprises the nucleotide sequence of SEQ ID NO: 4476; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4476; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4476; and

(vii) an ITR, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 5200; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5200; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5200;

(F) (i) an ITR, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 5197; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5197; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5197;

(ii) an enhancer, wherein the enhancer comprises the nucleotide sequence of SEQ ID NO: 4471; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten

modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4471; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4471;

(iii) a promoter, wherein the promoter comprises the nucleotide sequence of SEQ ID NO: 5199; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5199; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5199;

(iv) an intron, wherein the intro comprises the nucleotide sequence of SEQ ID NO: 4475; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4475; or a nucleotide sequence at least 80%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4475;

(v) a nucleotide sequence encoding a modulatory polynucleotide, wherein the nucleotide sequence comprises SEQ ID NO: 4393, or nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto;

(vi) a polyA signal sequence, wherein the polyA signal sequence comprises the nucleotide sequence of SEQ ID NO: 4476; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4476; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4476; and

(vii) an ITR, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 5200; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5200; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5200; or

(G) (i) an ITR, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 5197; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5197; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5197;

(ii) an enhancer, wherein the enhancer comprises the nucleotide sequence of SEQ ID NO: 4471; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4471; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4471;

(iii) a promoter, wherein the promoter comprises the nucleotide sequence of SEQ ID NO: 5199; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5199; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5199;

(iv) an intron, wherein the intro comprises the nucleotide sequence of SEQ ID NO: 4475; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4475; or a nucleotide sequence at least 80%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4475;

(v) a nucleotide sequence encoding a modulatory polynucleotide, wherein the nucleotide sequence comprises SEQ ID NO: 4394, or nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto;

(vi) a polyA signal sequence, wherein the polyA signal sequence comprises the nucleotide sequence of SEQ ID NO: 4476; a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 4476; or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4476; and

(vii) an ITR, wherein the ITR comprises the nucleotide sequence of SEQ ID NO: 5200; a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 5200; or a nucleotide sequence comprising at least one, two, three, four, five, six, or seven but no more than ten modifications, e.g., substitutions, insertions, or deletions, relative to SEQ ID NO: 5200.

27. The AAV viral genome of any one of claims 2-8 or 10-26, which comprises the nucleotide sequence of any one of SEQ ID NOs: 5173, 5195, 5196, 5182, 5183, 5184, 5185, 5149-5172, 5174-5181, 5186-5194 or 4439-4468, or a nucleotide sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 99% or 100% identical to any one of SEQ ID NOs: 5173, 5195, 5196, 5182, 5183, 5184, 5185, 5149-5172, 5174-5181, 5186-5194 or 4439-4468.

28. An AAV particle comprising the AAV viral genome of any one of claims 2-8 or 10-27, an AAV viral genome encoding the modulatory polynucleotide of any one of claims 9 or 11-17, or a viral genome encoding the siRNA of any one of claims 1 or 3-8, and an AAV capsid protein.

29. The AAV particle of claim 28, wherein the AAV capsid protein comprises:

(i) an AAV5 capsid protein or a variant thereof, an AAV9 capsid protein or a variant thereof, VOY101 capsid protein or a variant thereof, a PHPeB capsid protein or a variant thereof, a PHP.B capsid protein or a variant thereof, a PHP.N capsid protein or a variant thereof, an AAV1 capsid protein or a variant thereof, an AAV2 capsid protein or a variant thereof, an AAVrh10 capsid protein or a variant thereof, or VOY9P39 capsid protein or a variant thereof;

(ii) an AAV9 capsid protein or a variant thereof;

(iii) an AAV5 capsid protein or variant thereof;

(iv) an amino acid sequence provided in Table 1 or an amino acid sequence at least 85%, 90%, 92%, 95%, 97%, 98%, or 99% identical thereto; or

(v) the nucleotide sequence encoding the AAV capsid protein comprises any one of the nucleotide sequences in Table 1, or a nucleotide sequence at least 85%, 90%, 92%, 95%, 97%, 98%, or 99% identical thereto.

30. A vector comprising the AAV viral genome of any one of claims 2-8 or 10-27, a nucleotide sequence encoding the modulatory polynucleotide of any one of claims 9 or 11-17, or a nucleotide sequence encoding the siRNA of any one of claims 1 or 3-8.

31. A cell comprising the AAV particle of claim 28 or 29, the AAV viral genome of any one of claims 2-8 or 10-27, the modulatory polynucleotide of any one of claims 9 or 11-17, or the siRNA of any one of claims 1 or 3-8, optionally wherein, the cell is:

(a) a mammalian cell or an insect cell;

(b) a cell of a brain region or a spinal cord region (e.g., a CNS cell);

(c) a cell of the cortex, hippocampus, thalamus, or brain stem; or

(d) a neuron, a glial cell, or an oligodendrocyte.

32. A method of making an AAV particle, comprising:

(i) providing a host cell comprising the AAV viral genome of any one of claims 2-8 or 10-27, an AAV viral genome encoding the modulatory polynucleotide of any one of claims 9 or 11-17, or a viral genome encoding the siRNA of any one of claims 1 or 3-8;

(ii) incubating the host cell under conditions suitable to enclose the viral genome in an AAV capsid protein;

thereby making the AAV particle.

33. A pharmaceutical composition comprising the AAV particle of claim 28 or 29, the AAV viral genome of any one of claims 2-8 or 10-27, the modulatory polynucleotide of any one of claims 9 or 11-17, or the siRNA of any one of claims 1 or 3-8, and a pharmaceutically acceptable excipient.

34. A method of delivering an siRNA for inhibiting MAPT expression to a cell, comprising administering to the cell an effective amount of the pharmaceutical composition of claim 33, the AAV particle of claim 28 or 29, the AAV viral genome of any one of claims 2-8 or 10-27, the modulatory polynucleotide of any one of

claims 9 or 11-17, or the siRNA of any one of claims 1 or 3-8, thereby delivering the siRNA for inhibiting MAPT expression to the cell.

35. The method of claim 34, wherein the cell is:

(a) a mammalian cell or an insect cell;

(b) a cell of a brain region or a spinal cord region (e.g., a CNS cell);

(c) a cell of the cortex, hippocampus, thalamus, or brain stem;

(d) a neuron, a glial cell, or an oligodendrocyte; and/or

(e) in a subject.

36. The method of claim 35, wherein the subject has or has been diagnosed with having a genetic disorder (e.g., a monogenic disorder or a polygenic disorder); a neurological disorder (e.g., a neurodegenerative disorder); a disorder associated with tau expression, e.g., aberrant tau expression; and/or a tauopathy.

37. A method of treating a subject having or diagnosed with having a genetic disorder (e.g., a monogenic disorder or a polygenic disorder); a neurological disorder (e.g., a neurodegenerative disorder); a disorder associated with tau expression, e.g., aberrant tau expression; and/or a tauopathy, the method comprising administering to the subject an effective amount of the pharmaceutical composition of claim 33, the AAV particle of claim 28 or 29, the AAV viral genome of any one of claims 2-8 or 10-27, the modulatory polynucleotide of any one of claims 9 or 11-17, or the siRNA of any one of claims 1 or 3-8.

38. The method of claim 36 or 37, wherein the genetic disorder, neurological disorder (e.g., neurodegenerative disorder), disorder associated with tau expression (e.g., aberrant tau expression), and/or tauopathy is Alzheimer's disease (AD), Frontotemporal dementia (FTD), frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), frontotemporal lobar degeneration (FTLD), Dravet syndrome (DS), neurodegenerative disease, traumatic brain injury (TBI), chronic traumatic encephalopathy (CTE), progressive supranuclear palsy (PSP), Down's syndrome, Pick's disease, corticobasal degeneration (CBD), corticobasal syndrome, amyotrophic lateral sclerosis (ALS), Prion diseases, CJD, Multiple system atrophy, mild cognitive impairment, Tangle-only dementia, or Progressive subcortical gliosis.

39. The method of claim 37 or 38, wherein treating comprises prevention of progression of the genetic disorder, neurological disorder (e.g., neurodegenerative disorder), disorder associated with tau expression (e.g., aberrant tau expression), and/or tauopathy in the subject in the subject.

40. The method of any one of claims 37-39, further comprising performing a blood test, an imaging test (e.g., a PET scan or a PET scan in combination with biomarker, e.g., serum biomarker staining), a CNS biopsy sample, or an aqueous cerebral spinal fluid biopsy, optionally wherein the blood test, imaging test, biopsy sample, or aqueous cerebral spinal fluid biopsy is performed prior to, during, or after treatment with the AAV particle, modulatory polynucleotide, siRNA, or pharmaceutical composition.

41. The method of any one of claims 37-4, wherein the pharmaceutical composition, AAV particle, modulatory polynucleotide, and siRNA are administered to the subject:

(i) intravenously, via intra-cisterna magna injection (ICM), intracerebrally, intrathecally, intracerebroventricularly, via intraparenchymal administration, or intramuscularly;

(ii) via focused ultrasound (FUS), e.g., coupled with the intravenous administration of microbubbles (FUS-MB), or MRI-guided FUS coupled with intravenous administration;

(iii) intravenously.

42. The pharmaceutical composition of claim 33, the AAV particle of claim 28 or 29, the AAV viral genome of any one of claims 2-8 or 10-27, the modulatory polynucleotide of any one of claims 9 or 11-17, or the siRNA of any one of claims 1 or 3-8, for use in a method of delivering an siRNA for inhibiting MAPT expression to a cell.

43. The pharmaceutical composition of claim 33, the AAV particle of claim 28 or 29, the AAV viral genome of any one of claims 2-8 or 10-27, the modulatory polynucleotide of any one of claims 9 or 11-17, or the siRNA of any one of claims 1 or 3-8, for use in the manufacture of a medicament.

44. The pharmaceutical composition of claim 33, the AAV particle of claim 28 or 29, the AAV viral genome of any one of claims 2-8 or 10-27, the modulatory polynucleotide of any one of claims 9 or 11-17, or the siRNA of any one of claims 1 or 3-8, for use in the treatment of a genetic disorder, neurological disorder (e.g., neurodegenerative disorder), disorder associated with tau expression (e.g., aberrant tau expression), and/or tauopathy.

45. Use of the pharmaceutical composition of claim 33, the AAV particle of claim 28 or 29, the AAV viral genome of any one of claims 2-8 or 10-27, the modulatory polynucleotide of any one of claims 9 or 11-17, or the siRNA of any one of claims 1 or 3-8, in the manufacture of a medicament for delivering an siRNA for inhibiting MAPT expression to a cell.

46. Use of the pharmaceutical composition of claim 33, the AAV particle of claim 28 or 29, the AAV viral genome of any one of claims 2-8 or 10-27, the modulatory polynucleotide of any one of claims 9 or 11-17, or the siRNA of any one of claims 1 or 3-8, in the manufacture of a medicament.

47. Use of the pharmaceutical composition of claim 33, the AAV particle of claim 28 or 29, the AAV viral genome of any one of claims 2-8 or 10-27, the modulatory polynucleotide of any one of claims 9 or 11-17, or the siRNA of any one of claims 1 or 3-8, in the manufacture of a medicament for treating a genetic disorder, neurological disorder (e.g., neurodegenerative disorder), disorder associated with tau expression (e.g., aberrant tau expression), and/or tauopathy.