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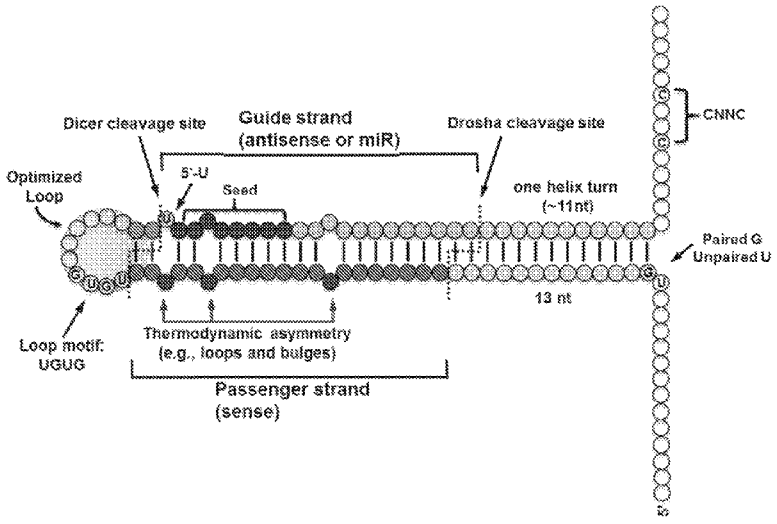
(54) Title: MODULATORY POLYNUCLEOTIDES

FIG. 1



(57) Abstract: The invention relates to compositions and methods for the preparation, manufacture and therapeutic use of modulatory polynucleotides.

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— *with sequence listing part of description (Rule 5.2(a))*

MODULATORY POLYNUCLEOTIDES

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 62/079,590, entitled Modulatory Polynucleotides, filed November 14, 2014, U.S. Provisional Patent Application No. 62/212,004, entitled Modulatory Polynucleotides, filed August 31, 2015, U.S. Provisional Patent Application No. 62/234,477, entitled Modulatory Polynucleotides, filed September 29, 2015; the contents of each of which are herein incorporated by reference in their entirety.

REFERENCE TO THE SEQUENCE LISTING

[0002] The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled 1014PCTSL.txt, created on November 12, 2015, which is 235,330 bytes in size. The information in the electronic format of the sequence listing is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0003] The invention relates to compositions, methods, processes, kits and devices for the design, preparation, manufacture and/or formulation of modulatory polynucleotides. In some embodiments such modulatory polynucleotides may be encoded by or within recombinant adeno-associated viruses (AAV) and may comprise artificial microRNAs, artificial pre-microRNAs and/or artificial pri-microRNAs.

BACKGROUND OF THE INVENTION

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

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

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

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

SUMMARY OF THE INVENTION

[0008] Described herein are compositions, methods, processes, kits and devices for the design, preparation, manufacture and/or formulation of modulatory polynucleotides.

[0009] In some embodiments such modulatory polynucleotides may be encoded by or contained within plasmids or vectors or recombinant adeno-associated viruses (AAV) and may comprise artificial microRNAs, artificial pre-microRNAs and/or artificial pri-microRNAs.

The present invention as claimed herein is described in the following items 1 to 25:

1. A modulatory polynucleotide comprising

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

(i) a 5' stem arm, said 5' stem arm comprising a passenger strand and a 5' spacer sequence located 5' to said passenger strand;

(ii) a loop region between 4-20 nucleotides in length;

(iii) a 3' stem arm, said 3' stem arm comprising a guide strand and a 3' spacer sequence located 3' to said guide strand;

(b) a first flanking region located 5' to said passenger strand, said first flanking region comprising said 5' spacer sequence and a 5' flanking sequence; and

(c) a second flanking region located 3' to said guide strand, said second flanking region comprising said 3' spacer region and a 3' flanking sequence, and wherein

said second flanking region comprises a nucleotide sequence which has at least 90% identity to SEQ ID NO: 11.

2. A modulatory polynucleotide comprising

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

(i) a 5' stem arm, wherein said 5' stem arm comprises a guide strand and a 5' spacer sequence located 5' to said guide strand;

(ii) a loop region between 4-20 nucleotides in length;

(iii) a 3' stem arm, wherein said 3' stem arm comprises a passenger strand and a 3' spacer sequence located 3' to said passenger strand;

(b) a first flanking region located 5' to said guide strand, said first flanking region comprising said 5' spacer sequence and a 5' flanking sequence; and

(c) a second flanking region located 3' to said passenger strand, said second flanking region comprising said 3' spacer region and a 3' flanking sequence, and wherein said second flanking region comprises a nucleotide sequence which has at least 90% identity to SEQ ID NO: 11.

3. The modulatory polynucleotide of any one of items 1-2, wherein the first flanking region comprises a nucleotide sequence which has at least 90% identity to SEQ ID NO: 2.

4. The modulatory polynucleotide of any one of items 1-2, wherein the first flanking region comprises a nucleotide sequence which has at least 95% identity to SEQ ID NO: 2.

5. The modulatory polynucleotide of any one of items 1-4, wherein the second flanking region comprises a nucleotide sequence which has at least 95% identity to SEQ ID NO: 11.

6. The modulatory polynucleotide of any one of items 1-4, wherein the second flanking region comprises the nucleotide sequence of SEQ ID NO: 11.

7. A modulatory polynucleotide comprising

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

(i) a 5' stem arm, wherein said 5' stem arm comprises a passenger strand and a 5' spacer sequence located 5' to said passenger strand;

(ii) a loop region between 4-20 nucleotides in length;

(iii) a 3' stem arm, wherein said 3' stem arm comprises a guide strand and a 3' spacer sequence located 3' to said guide strand;

(b) a first flanking region located 5' to said passenger strand, said first flanking region comprising said 5' spacer sequence and a 5' flanking sequence, and wherein said first flanking region comprises a nucleotide sequence which has at least 85% identity to SEQ ID NO: 2; and

(c) a second flanking region located 3' to said guide strand, said second flanking region comprising said 3' spacer region and a 3' flanking sequence.

8. A modulatory polynucleotide comprising

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

(i) a 5' stem arm, wherein said 5' stem arm comprises a guide strand and a 5' spacer sequence located 5' to said guide strand;

(ii) a loop region between 4-20 nucleotides in length;

(iii) a 3' stem arm, wherein said 3' stem arm comprises a passenger strand and a 3' spacer sequence located 3' to said passenger strand;

(b) a first flanking region located 5' to said guide strand, said first flanking region comprising said 5' spacer sequence and a 5' flanking sequence, and wherein said first flanking region comprises a nucleotide sequence which has at least 85% identity to SEQ ID NO: 2; and

(c) a second flanking region located 3' to said passenger strand, said second flanking region comprising said 3' spacer region and a 3' flanking sequence.

9. The modulatory polynucleotide of any one of items 7-8, wherein the first flanking region comprises a nucleotide sequence which has at least 90% identity to SEQ ID NO: 2.

10. The modulatory polynucleotide of any one of items 7-8, wherein the first flanking region comprises a nucleotide sequence which has at least 95% identity to SEQ ID NO: 2.

11. The modulatory polynucleotide of any one of items 7-8, wherein the first flanking region comprises the nucleotide sequence of SEQ ID NO: 2.

12. The modulatory polynucleotide of any one of items 1-11, wherein the modulatory polynucleotide is an artificial pri-miRNA.
13. The modulatory polynucleotide of any one of items 1-12, wherein the guide strand comprises a microRNA seed sequence at positions 2-7, 2-8 or 2-9.
14. The modulatory polynucleotide of any one of items 1-13, wherein the guide strand is between 15-30 nucleotides in length.
15. The modulatory polynucleotide of item 14, wherein the passenger strand is at least 70% complementary to the guide strand.
16. The modulatory polynucleotide of any one of items 1-15, wherein the guide strand is between 21-25 nucleotides in length.
17. The modulatory polynucleotide of item 16, wherein the guide strand is 22 nucleotides in length.
18. The modulatory polynucleotide of item 16, wherein the guide strand is 21 nucleotides in length.
19. The modulatory polynucleotide of any one of items 1-18, wherein the guide strand is at least 70% complementary to a target RNA.
20. The modulatory polynucleotide of item 19, wherein the target RNA is a mammalian coding mRNA in a neurologic cell, tissue or organ.
21. The modulatory polynucleotide of any one of items 1-20, wherein the passenger strand is between 15-30 nucleotides in length; wherein the 5' spacer sequence is between 8-20 nucleotides in length; wherein the guide strand is between 15-30 nucleotides in length; and wherein the 3' spacer sequence is between 8-20 nucleotides in length.
22. An adeno-associated virus (AAV) vector genome encoding the modulatory polynucleotide of any one of items 1-21.
23. A recombinant adeno-associated virus (AAV) comprising the AAV vector genome of item 22 and an AAV capsid.
24. The recombinant AAV of item 23, comprising a capsid selected from AAV1, AAV9, and AAVrh10.
25. The recombinant AAV of item 23, comprising an AAV1 capsid.

[0010] The details of various embodiments of the invention are set forth in the description below. Other features, and advantages of the invention will be apparent from the description and the drawings, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] The foregoing and other objects, features and advantages will be apparent from the following description of particular embodiments of the invention, as illustrated in the accompanying drawings in which like reference characters refer to the same parts throughout the different views. The drawings are not necessarily to scale, emphasis instead being placed upon illustrating the principles of various embodiments of the invention.

[0012] FIG. 1 is a schematic of an artificial pri-microRNA encoded in an AAV vector according to the present invention.

[0013] FIG. 2 is a histogram showing the activity of the pri-mRNA constructs encoded in AAV vectors.

[0014] FIG. 3 is a histogram showing the activity in HEK293T cells of the guide strand of the modulatory polynucleotides encoded in AAV vectors.

[0015] FIG. 4 is a histogram showing the activity in HEK293T cells of the passenger strand of the modulatory polynucleotides encoded in AAV vectors.

[0016] FIG. 5 is a histogram showing the activity in HeLa cells of the guide strand of the modulatory polynucleotides encoded in AAV vectors.

[0017] FIG. 6 is a histogram showing the activity in HeLa cells of the passenger strand of the modulatory polynucleotides encoded in AAV vectors.

[0018] FIG. 7 is a histogram for the quantification of expressed intracellular AAV DNA.

[0019] FIG. 8 is a histogram showing the activity in human motor neurons of the constructs encoded in AAV vectors.

[0020] FIG. 9 is a chart showing the dose-dependent silencing of SOD1 in U251MG cells.

[0021] FIG. 10 is a chart showing the dose-dependent silencing of SOD1 in human astrocyte cells.

[0022] FIG. 11 is a chart showing the time course of the silencing of SOD1 in U251MG cells.

[0023] FIG. 12 comprises Fig. 12A, Fig. 12B and Fig. 12C which are charts showing the dose-dependent effects of a construct. Fig. 12A shows the relative SOD1 expression. Fig. 12B shows the percent of guide strand. Fig. 12C shows the percent of the passenger strand.

[0024] FIG. 13 is a diagram showing the location of the modulatory polynucleotide (MP) in relation to the ITRs, the intron (I) and the polyA (P).

DETAILED DESCRIPTION

Compositions of the Invention

[0025] According to the present invention, modulatory polynucleotides are provided which function as artificial microRNAs. As used herein a "modulatory polynucleotide" is any nucleic acid polymer which functions to modulate (either increase or decrease) the level or amount of a target gene. Modulatory polynucleotides include precursor molecules which are processed inside the cell prior to modulation. Modulatory polynucleotides or the processed forms thereof may be encoded in a plasmid, vector, genome or other nucleic acid expression vector for delivery to a cell.

[0026] In some embodiments modulatory polynucleotides are designed as primary microRNA (pri-miRs) or precursor microRNAs (pre-miRs) which are processed within the cell to produce highly specific artificial microRNAs.

[0027] The modulatory polynucleotides, especially the artificial microRNAs of the invention, may be designed based on the sequence or structure scaffold of a canonical or known microRNA, pri-microRNA or pre-microRNA. Such sequences may correspond to any known microRNA or its precursor such as those taught in US Publication US2005/0261218 and US Publication US2005/0059005, the contents of which are incorporated herein by reference in their entirety.

[0028] microRNAs (or miRNA or miRs) are 19-25 nucleotide long noncoding RNAs that bind to the 3′UTR of nucleic acid molecules and down-regulate gene expression either by reducing

nucleic acid molecule stability or by inhibiting translation. The modulatory polynucleotides of the invention may comprise one or more microRNA sequences, microRNA seeds or artificial microRNAs, e.g., sequences which function as a microRNA.

[0029] A microRNA sequence comprises a "seed" region, i.e., a sequence in the region of positions 2-9 of the mature microRNA, which sequence has perfect Watson-Crick complementarity to the miRNA target sequence. A microRNA seed may comprise positions 2-8 or 2-7 or 2-9 of the mature microRNA. In some embodiments, a microRNA seed may comprise 7 nucleotides (e.g., nucleotides 2-8 of the mature microRNA), wherein the seed-complementary site in the corresponding miRNA target is flanked by an adenine (A) opposed to microRNA position 1. In some embodiments, a microRNA seed may comprise 6 nucleotides (e.g., nucleotides 2-7 of the mature microRNA), wherein the seed-complementary site in the corresponding miRNA target is flanked by an adenine (A) opposed to microRNA position 1. See for example, Grimson A, Farh KK, Johnston WK, Garrett-Engele P, Lim LP, Bartel DP; Mol Cell. 2007 Jul 6;27(1):91-105; each of which is herein incorporated by reference in their entirety. In naturally occurring microRNA, the bases of the microRNA seed have complete complementarity with the target sequence.

[0030] As taught herein, design parameters, or rules, have been identified and applied to design modulatory polynucleotides (e.g., artificial microRNAs) which have superior target gene modulatory properties with limited off target effects.

[0031] In one embodiment, the molecular scaffold of the modulatory polynucleotide described herein may be designed and optimized to create a modulatory polynucleotide that has the desired target gene modulatory properties. As a non-limiting example, the modulatory polynucleotide can have superior target gene modulatory properties with limited off target effects.

[0032] In one embodiment, the modulatory polynucleotides of the invention, such as artificial miRs, are comprised of modular elements or sequence motifs assembled according to a set of rules that result in highly specific target recognition and low guide/passenger ratio. Such modules or sequence motifs include, but are not limited to, double stranded regions, flanking regions, loops, optimized loops, UGUG loops, GU domains, spacers (to control proximal and distal motif or module spacing or to introduce structural elements such as turns, loops or bulges), CNNC motifs, and thermodynamic asymmetry regions which may embrace loops, bulges, mismatches, wobbles, and/or combinations thereof. Non limiting examples of rules which may be applied alone or in combination when constructing artificial miRs include those taught in Seitz et al. *Silence* 2011, 2:4; Gu, et al., *Cell* 151, 900–911, November 9, 2012; Schwartz, et al., *Cell*, Vol. 115, 199–208, October 17, 2003; Park, et al., *Nature,* Vol. 475, 101, 14 July 2011;

Ketley et al., 2013, *PLoS ONE* 8(6); Liu, et al., *Nucleic Acids Research*, 2008, Vol. 36, No. 9 2811–2824; Dow, et al., 2013, Nat Protoc. ; 7(2): 374–393. doi:10.1038/nprot.2011.446; Auyeung, et al., *Cell* 152, 844–858, February 14, 2013; Gu et al., *Cell* 2012 Nov 9, 151(4):900-11; Fellmann et al. Molecular Cell 41, 733-746, 2011; Han et al. Cell 125, 887-907, 2006; Betancur et al. Frontiers in Genetics, Vol. 3, Art. 127, 1-6 July 2012; Schwarz et al. Cell Vol 115, 199-208, 2003; the contents of each of which are herein incorporated by reference in their entirety.

[0033] In addition to the modules or sequence motifs, modulatory polynucleotides comprise at least one of or both a passenger and guide strand. The passenger and guide strand may be positioned or located on the 5' arm or 3' arm of a stem loop structure of the modulatory polynucleotide.

[0034] In one embodiment, the 3' stem arm of the modulatory polynucleotides may have 11 nucleotides downstream of the 3' end of the guide strand which have complementarity to the 11 of the 13 nucleotides upstream of the 5' end of the passenger strand in the 5' stem arm.

[0035] In one embodiment, the modulatory polynucleotides may have a cysteine which is 6 nucleotides downstream of the 3' end of the 3' stem arm of the modulatory polynucleotide.

[0036] In one embodiment, the modulatory polynucleotides comprise a miRNA seed match for the guide strand. In another embodiment, the modulatory polynucleotides comprise a miRNA seed match for the passenger strand. In yet another embodiment, the modulatory polynucleotides do no comprise a seed match for the guide or passenger strand.

[0037] In one embodiment, the modulatory polynucleotides may have almost no significant full-length off targets for the guide strand. In another embodiment, the modulatory polynucleotides may have almost no significant full-length off targets for the passenger strand. In yet another embodiment, the modulatory polynucleotides may have almost no significant full-length off targets for the guide strand or the passenger strand.

[0038] In one embodiment, the modulatory polynucleotides may have high activity *in vitro*. In another embodiment, the modulatory polynucleotides may have low activity *in vitro*. In yet another embodiment, the modulatory polynucleotides may have high guide strand activity and low passenger strand activity *in vitro*.

[0039] In one embodiment, the modulatory polynucleotides have a high guide strand activity and low passenger strand activity *in vitro*. The target knock-down (KD) by the guide strand may be at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, 99.5% or 100%. The target knock-down by the guide strand may be 60-65%, 60-70%, 60-75%, 60-80%, 60-85%, 60-90%, 60-95%, 60-99%, 60-99.5%, 60-100%, 65-70%, 65-75%, 65-80%, 65-85%, 65-90%, 65-95%, 65-99%,

65-99.5%, 65-100%, 70-75%, 70-80%, 70-85%, 70-90%, 70-95%, 70-99%, 70-99.5%, 70-100%, 75-80%, 75-85%, 75-90%, 75-95%, 75-99%, 75-99.5%, 75-100%, 80-85%, 80-90%, 80-95%, 80-99%, 80-99.5%, 80-100%, 85-90%, 85-95%, 85-99%, 85-99.5%, 85-100%, 90-95%, 90-99%, 90-99.5%, 90-100%, 95-99%, 95-99.5%, 95-100%, 99-99.5%, 99-100% or 99.5-100%. As a non-limiting example, the target knock-down (KD) by the guide strand is greater than 70%.

[0040] In one embodiment, the IC50 of the passenger strand for the nearest off target is greater than 100 multiplied by the IC50 of the guide strand for the target. As a non-limiting example, if the IC50 of the passenger strand for the nearest off target is greater than 100 multiplied by the IC50 of the guide strand for the target then the modulatory polynucleotide is said to have high guide strand activity and a low passenger strand activity *in vitro*.

[0041] In one embodiment, the 5' processing of the guide strand has a correct start (n) at the 5' end at least 75%, 80%, 85%, 90%, 95%, 99% or 100% of the time *in vitro* or *in vivo*. As a non-limiting example, the 5' processing of the guide strand is precise and has a correct start (n) at the 5' end at least 99% of the time *in vitro*. As a non-limiting example, the 5' processing of the guide strand is precise and has a correct start (n) at the 5' end at least 99% of the time *in vivo*.

[0042] In one embodiment, the guide-to-passenger (G:P) strand ratio is 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*. As a non-limiting example, the guide-to-passenger strand ratio is 80:20 *in vitro*. As a non-limiting example, the guide-to-passenger strand ratio is 80:20 *in vivo*.

[0043] In one embodiment, the integrity of the vector genome is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99% or more than 99% of the full length of the construct.

Modulatory Polynucleotides

[0044] In one embodiment, any of the known RNAi constructs or RNAi agents may serve as the starting construct for the design of the passenger and/or guide strand of a modulatory polynucleotides or artificial microRNAs of the invention. These include canonical siRNAs, small interfering RNAs (siRNA), double stranded RNAs (dsRNAs), inverted repeats, short hairpin RNAs (shRNAs), small temporally regulated RNAs (stRNA), clustered inhibitory RNAs (cRNAs), including radial clustered inhibitory RNA, asymmetric clustered inhibitory RNA, linear clustered inhibitory RNA, and complex or compound clustered inhibitory RNA, dicer substrates, DNA-directed RNAi (ddRNAi), single-stranded RNAi (ssRNAi), microRNA (miRNA) antagonists, microRNA mimics, microRNA agonists, blockmirs (a.k.a. Xmirs), microRNA mimetics, microRNA addbacks, supermiRs, the oligomeric constructs disclosed in PCT Publication WO/2005/013901 the contents of which are incorporated herein in their

entirety, tripartite RNAi constructs such as those disclosed in US Publication 20090131360, the contents of which are incorporated herein in their entirety, the solo-rxRNA constructs disclosed in PCT Publication WO/2010/011346, the contents of which are incorporated herein by reference in their entirety; the sd-rxRNA constructs disclosed in PCT Publication WO/2010/033247 the contents of which are incorporated herein by reference in their entirety, dual acting RNAi constructs which reduce RNA levels and also modulate the immune response as disclosed in PCT Publications WO/2010/002851 and WO/2009/141146 the contents of which are incorporated herein by reference in their entirety and antigene RNAs (agRNA) or small activating RNAs (saRNAs) which increase expression of the target to which they are designed disclosed in PCT Publications WO/2006/130201, WO/2007/086990, WO/2009/046397, WO/2009/149182, WO/2009/086428 the contents of which are incorporated herein by reference in their entirety.

[0045] Likewise, any pri- or pre-microRNA precursor of the above listed microRNA may also serve as the molecular scaffold of the modulatory polynucleotides of the invention.

[0046] In one embodiment, the starting construct may be derived from any relevant species such as, not limited to, mouse, rat, dog, monkey or human.

[0047] In one embodiment, the modulatory polynucleotide may be located in an expression vector downstream of a promoter such as, but not limited to, CMV, U6, CBA or a CBA promoter with a SV40 intron. Further, the modulatory polynucleotide may also be located upstream of the polyadenylation sequence in an expression vector. As a non-limiting example, the modulatory polynucleotide may be located within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 or more than 30 nucleotides downstream from the promoter and/or upstream of the polyadenylation sequence in an expression vector. As another non-limiting example, the modulatory polynucleotide may be located within 1-5, 1-10, 1-15, 1-20, 1-25, 1-30, 5-10, 5-15, 5-20, 5-25, 5-30, 10-15, 10-20, 10-25, 10-30, 15-20, 15-25, 15-30, 20-25, 20-30 or 25-30 nucleotides downstream from the promoter and/or upstream of the polyadenylation sequence in an expression vector. As a non-limiting example, the modulatory polynucleotide may be located within the first 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25% or more than 25% of the nucleotides downstream from the promoter and/or upstream of the polyadenylation sequence in an expression vector. As another non-limiting example, the modulatory polynucleotide may be located with the first 1-5%, 1-10%, 1-15%, 1-20%, 1-25%, 5-10%, 5-15%, 5-20%, 5-25%, 10-15%, 10-20%, 10-25%, 15-20%, 15-25%, or 20-25% downstream from the promoter and/or upstream of the polyadenylation sequence in an expression vector.

[0048] In one embodiment, the modulatory polynucleotide may be located upstream of the polyadenylation sequence in an expression vector. Further, the modulatory polynucleotide may be located downstream of a promoter such as, but not limited to, CMV, U6, CBA or a CBA promoter with a SV40 intron in an expression vector. As a non-limiting example, the modulatory polynucleotide may be located within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 or more than 30 nucleotides downstream from the promoter and/or upstream of the polyadenylation sequence in an expression vector. As another non-limiting example, the modulatory polynucleotide may be located within 1-5, 1-10, 1-15, 1-20, 1-25, 1-30, 5-10, 5-15, 5-20, 5-25, 5-30, 10-15, 10-20, 10-25, 10-30, 15-20, 15-25, 15-30, 20-25, 20-30 or 25-30 nucleotides downstream from the promoter and/or upstream of the polyadenylation sequence in an expression vector. As a non-limiting example, the modulatory polynucleotide may be located within the first 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25% or more than 25% of the nucleotides downstream from the promoter and/or upstream of the polyadenylation sequence in an expression vector. As another non-limiting example, the modulatory polynucleotide may be located with the first 1-5%, 1-10%, 1-15%, 1-20%, 1-25%, 5-10%, 5-15%, 5-20%, 5-25%, 10-15%, 10-20%, 10-25%, 15-20%, 15-25%, or 20-25% downstream from the promoter and/or upstream of the polyadenylation sequence in an expression vector.

[0049] In one embodiment, the modulatory polynucleotide may be located in a scAAV.

[0050] In one embodiment, the modulatory polynucleotide may be located in an ssAAV.

[0051] In one embodiment, the modulatory polynucleotide may be located near the 5' end of the flip ITR in an expression vector. In another embodiment, the modulatory polynucleotide may be located near the 3'end of the flip ITR in an expression vector. In yet another embodiment, the modulatory polynucleotide may be located near the 5' end of the flop ITR in an expression vector. In yet another embodiment, the modulatory polynucleotide may be located near the 3' end of the flop ITR in an expression vector. In one embodiment, the modulatory polynucleotide may be located between the 5' end of the flip ITR and the 3' end of the flop ITR in an expression vector. In one embodiment, the modulatory polynucleotide may be located between (e.g., half-way between the 5' end of the flip ITR and 3' end of the flop ITR or the 3' end of the flop ITR and the 5' end of the flip ITR), the 3' end of the flip ITR and the 5' end of the flip ITR in an expression vector. As a non-limiting example, the modulatory polynucleotide may be located within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 or more than 30 nucleotides downstream from the 5' or 3' end of an ITR (e.g., Flip or Flop ITR) in an expression vector. As a non-limiting example, the modulatory polynucleotide

may be located within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 or more than 30 nucleotides upstream from the 5' or 3' end of an ITR (e.g., Flip or Flop ITR) in an expression vector. As another non-limiting example, the modulatory polynucleotide may be located within 1-5, 1-10, 1-15, 1-20, 1-25, 1-30, 5-10, 5-15, 5-20, 5-25, 5-30, 10-15, 10-20, 10-25, 10-30, 15-20, 15-25, 15-30, 20-25, 20-30 or 25-30 nucleotides downstream from the 5' or 3' end of an ITR (e.g., Flip or Flop ITR) in an expression vector. As another non-limiting example, the modulatory polynucleotide may be located within 1-5, 1-10, 1-15, 1-20, 1-25, 1-30, 5-10, 5-15, 5-20, 5-25, 5-30, 10-15, 10-20, 10-25, 10-30, 15-20, 15-25, 15-30, 20-25, 20-30 or 25-30 upstream from the 5' or 3' end of an ITR (e.g., Flip or Flop ITR) in an expression vector. As a non-limiting example, the modulatory polynucleotide may be located within the first 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25% or more than 25% of the nucleotides upstream from the 5' or 3' end of an ITR (e.g., Flip or Flop ITR) in an expression vector. As another non-limiting example, the modulatory polynucleotide may be located with the first 1-5%, 1-10%, 1-15%, 1-20%, 1-25%, 5-10%, 5-15%, 5-20%, 5-25%, 10-15%, 10-20%, 10-25%, 15-20%, 15-25%, or 20-25% downstream from the 5' or 3' end of an ITR (e.g., Flip or Flop ITR) in an expression vector.

Molecular Scaffolds

[0052] In some embodiments the starting molecular scaffold of the modulatory polynucleotide is a known or wild type pri- or pre-microRNA. In other embodiments the molecular scaffold of the modulatory polynucleotides are designed *ab initio.* (See Cullen, *Gene Therapy* (2006) 13, 503–508 work with miR30; Chung, et al., *Nucleic Acids Research*, 2006, Vol. 34, No. 7 working with miR-155; the contents of which are herein incorporated by reference in their entirety).

[0053] As used herein a "molecular scaffold" is a framework or starting molecule that forms the sequence or structural basis against which to design or make a subsequent molecule.

[0054] Turning to FIG. 1. The modulatory polynucleotides of the present invention may be designed as a pri-miR as shown. In the figure, a pri-miR molecular scaffold is shown. The modulatory polynucleotide which comprises the payload (e.g., siRNA, miRNA or other RNAi agent described herein) comprises a leading 5' flanking sequence which may be of any length and may be derived in whole or in part from wild type microRNA sequence or be completely artificial.

[0055] Likewise, a 3' flanking sequence shown in the figure may mirror the 5' flanking sequence in size and origin. Either flanking sequence may be absent. The 3' flanking sequence may optionally contain one or more CNNC motifs, where "N" represents any nucleotide.

[0056] Forming the stem of the stem loop structure shown is a minimum of at least one payload sequence. In some embodiments the payload sequence comprises at least one nucleic acid sequence which is in part complementary or will hybridize to the target sequence. In some embodiments the payload is a wild type microRNA. In some embodiments the payload is an siRNA molecule or fragment of an siRNA molecule. In some embodiments the payload is a substantially double stranded construct which may comprise one or more microRNAs, artificial microRNAs or siRNAs.

[0057] In some embodiments the 5' arm of the stem loop comprises a passenger strand. This strand is also known as the sense strand in that it reflects an identity to a target. The passenger strand may be between 15-30 nucleotides in length. It may be 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 nucleotides in length.

[0058] In some embodiments the 3' arm of the stem loop comprises a guide strand. This strand is also known as the antisense strand in that it reflects homology to a target. The guide strand may be between 15-30 nucleotides in length, 21-25 nucleotides or 22 nucleotides in length. It may be 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 nucleotides in length. The guide strand, in some instances, comprises a "G" nucleotide at the 5' most end.

[0059] In some embodiments, where the guide strand comprises a microRNA, or artificial microRNAs, the guide strand may comprise one or more microRNA seed sequences. The seed sequence may be located at positions 2-7, 2-8 or 2-9 of the guide strand relative to the first 5' nucleotide of the guide strand or relative to a dicer cleavage site.

[0060] In other embodiments, the passenger strand may reside on the 3' arm while the guide strand resides on the 5' arm of the stem of the stem loop structure.

[0061] The passenger and guide strands may be completely complementary across a substantial portion of their length. In other embodiments the passenger strand and guide strand may be at least 70, 80, 90, 95 or 99% complementary across independently at least 50, 60, 70, 80, 85, 90, 95, or 99 % of the length of the strands.

[0062] Neither the identity of the passenger strand nor the homology of the guide strand need be 100% complementary to the target.

[0063] Separating the passenger and guide strand of the stem loop structure is a loop (also known as a loop motif). The loop may be of any length, between 4-30 nucleotides, between 4-20 nucleotides, between 4-15 nucleotides, between 5-15 nucleotides, between 6-12 nucleotides, 6 nucleotides, 7, nucleotides, 8 nucleotides, 9 nucleotides, 10 nucleotides, 11 nucleotides, and/or 12 nucleotides.

[0064] In some embodiments the loop comprises at least one UGUG motif. In some embodiments, the UGUG motif is located at the 5' terminus of the loop.

[0065] Spacer regions may be present in the modulatory polynucleotide to separate one or more modules from one another. There may be one or more such spacer regions present.

[0066] In one embodiment a spacer region of between 8-20, i.e., 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 nucleotides may be present between the passenger strand and a flanking sequence.

[0067] In one embodiment, the spacer is 13 nucleotides and is located between the 5' terminus of the passenger strand and a flanking sequence. In one embodiment a spacer is of sufficient length to form approximately one helical turn of the sequence.

[0068] In one embodiment a spacer region of between 8-20, i.e., 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 nucleotides may be present between the guide strand and a flanking sequence.

[0069] In one embodiment, the spacer sequence is between 10-13, i.e., 10, 11, 12 or 13 nucleotides and is located between the 3' terminus of the guide strand and a flanking sequence. In one embodiment a spacer is of sufficient length to form approximately one helical turn of the sequence.

[0070] In one embodiment the modulatory polynucleotide comprises at least one UG motif at the base of the stem whereby the G nucleotide is paired and the U nucleotide is unpaired. In some embodiments the unpaired U nucleotide is located in a flanking sequence.

[0071] In one embodiment, the modulatory polynucleotide comprises in the 5' to 3' direction, a 5' flanking sequence, a 5' arm, a loop motif, a 3' arm and a 3' flanking sequence. As a non-limiting example, the 5' arm may comprise a passenger strand and the 3' arm comprises the guide strand. In another non-limiting example, the 5' arm comprises the guide strand and the 3' arm comprises the passenger strand.

[0072] In one embodiment, the 5' arm, payload (e.g., passenger and/or guide strand), loop motif and/or 3' arm sequence may be altered (e.g., substituting 1 or more nucleotides, adding nucleotides and/or deleting nucleotides). The alteration may cause a beneficial change in the function of the construct (e.g., increase knock-down of the target sequence, reduce degradation of the construct, reduce off target effect, increase efficiency of the payload, and reduce degradation of the payload).

[0073] In one embodiment, the passenger strand sequence may be altered (e.g., substituting 1 or more nucleotides, adding nucleotides and/or deleting nucleotides). As a non-limiting example, the passenger strand sequence may comprise 1 or 2 substitutions within the last 4 nucleotides of the sequence (e.g., C substituted for a G). As another non-limiting example, the passenger strand

sequence may comprise 1 or 2 substitutions within the 7-15 nucleotides from the 5'end of the sequence (e.g., U substituted for an A or C substituted for a G).

[0074] In one embodiment, the 3' arm strand sequence may be altered (e.g., substituting 1 or more nucleotides, adding nucleotides and/or deleting nucleotides). As a non-limiting example, the sequence of the 3' arm may comprise 1 or 2 substitutions within the first 4 nucleotides of the sequence (e.g., A substituted for a U).

[0075] In one embodiment, the molecular scaffold of the payload construct may comprise a 5' flanking region, a loop motif and a 3' flanking region. Between the 5' flanking region and the loop motif may be a first payload region and between the loop motif and the 3' flanking region may be a second payload region. The first and second payload regions may comprise siRNA, miRNA or other RNAi agents, fragments or variants described herein. The first and second payload regions may also comprise a sequence which is the same, different or complementary to each other. As a non-limiting example, the first payload region sequence may be a passenger strand of a siRNA construct and the second payload region sequence may be a guide strand of an siRNA construct. The passenger and guide sequences may be substantially complementary to each other. As another non-limiting example, the first payload region sequence may be a guide strand of a siRNA construct and the second payload region sequence may be a passenger strand of an siRNA construct. The passenger and guide sequences may be substantially complementary to each other.

[0076] In one embodiment, the molecular scaffold of the modulatory polynucleotides described herein comprise a 5' flanking region, a loop region and a 3' flanking region. Non-limiting examples of the sequences for the 5' flanking region, loop region and the 3' flanking region which may be used in the molecular scaffolds described herein are shown in Tables 1-3.

Table 1. 5' Flanking Regions for Molecular Scaffold

5' Flanking Region Name	5' Flanking Region Sequence	5' Flanking Region SEQ ID
5F1	UUUAUGCCUCAUCCUCUGAGUGCUGAAGGC UUGCUGUAGGCUGUAUGCUG	1
5F2	GUGCUGGGCGGGGGGCGGCGGGCCCUCCCGC AGAACACCAUGCGCUCUUCGGAA	2
5F3	GAAGCAAAGAAGGGGCAGAGGGAGCCCGUG AGCUGAGUGGGCCAGGGACUGGGAGAAGGA GUGAGGAGGCAGGGCCGGCAUGCCUCUGCU GCUGGCCAGA	3
5F4	GUGCUGGGCGGGGGGCGGCGGGCCCUCCCGC AGAACACCAUGCGCUCUUCGGGA	4

Table 2. Loop Motif Regions for Molecular Scaffold

Loop Motif Region Name	Loop Motif Region Sequence	Loop Motif Region SEQ ID
L1	UGUGACCUGG	5
L2	UGUGAUUUGG	6
L3	UAUAAUUUGG	7
L4	CCUGACCCAGU	8
L5	GUCUGCACCUGUCACUAG	9

Table 3. 3'Flanking Regions for Molecular Scaffold

3' Flanking Region Name	3' Flanking Region Sequence	3' Flanking Region SEQ ID
3F1	AGUGUAUGAUGCCUGUUACUAGCAUUCACA UGGAACAAAUUGCUGCCGUG	10
3F2	CUGAGGAGCGCCUUGACAGCAGCCAUGGGA GGGCCGCCCCCUACCUCAGUGA	11
3F3	CUGUGGAGCGCCUUGACAGCAGCCAUGGGA GGGCCGCCCCCUACCUCAGUGA	12
3F4	UGGCCGUGUAGUGCUACCCAGCGCUGGCUGC CUCCUCAGCAUUGCAAUUCCUCUCCCAUCUG GGCACCAGUCAGCUACCCUGGUGGGAAUCU GGGUAGCC	13
3F5	GGCCGUGUAGUGCUACCCAGCGCUGGCUGCC UCCUCAGCAUUGCAAUUCCUCUCCCAUCUGG GCACCAGUCAGCUACCCUGGUGGGAAUCUG GGUAGCC	14
3F6	UCCUGAGGAGCGCCUUGACAGCAGCCAUGG GAGGGCCGCCCCCUACCUCAGUGA	810

[0077] Any of the regions described in Tables 1-3 may be used in the molecular scaffolds described herein.

[0078] In one embodiment, the molecular scaffold may comprise one 5' flanking region listed in Table 1. As a non-limiting example, the molecular scaffold may comprise the 5' flanking region 5F1, 5F2, 5F3 or 5F4.

[0079] In one embodiment, the molecular scaffold may comprise one loop motif region listed in Table 2. As a non-limiting example, the molecular scaffold may comprise the loop motif region L1, L2, L3, L4 or L5.

[0080] In one embodiment, the molecular scaffold may comprise one 3' flanking region listed in Table 3. As a non-limiting example, the molecular scaffold may comprise the 3' flanking region 3F1, 3F2, 3F3, 3F4, 3F5 or 3F6.

[0081] In one embodiment, the molecular scaffold may comprise at least one 5' flanking region and at least one loop motif region as described in Tables 1 and 2. As a non-limiting example, the molecular scaffold may comprise 5F1 and L1, 5F1 and L2, 5F1 and L3, 5F1 and L4, 5F1 and L5, 5F2 and L1, 5F2 and L2, 5F2 and L3, 5F2 and L4, 5F2 and L5, 5F3 and L1, 5F3 and L2, 5F3

and L3, 5F3 and L4, 5F3 and L5, 5F4 and L1, 5F4 and L2, 5F4 and L3, 5F4 and L4, or 5F4 and L5.

[0082] In one embodiment, the molecular scaffold may comprise at least one 3' flanking region and at least one loop motif region as described in Tables 2 and 3. As a non-limiting example, the molecular scaffold may comprise 3F1 and L1, 3F1 and L2, 3F1 and L3, 3F1 and L4, 3F1 and L5, 3F2 and L1, 3F2 and L2, 3F2 and L3, 3F2 and L4, 3F2 and L5, 3F3 and L1, 3F3 and L2, 3F3 and L3, 3F3 and L4, 3F3 and L5, 3F4 and L1, 3F4 and L2, 3F4 and L3, 3F4 and L4, 3F4 and L5, 3F5 and L1, 3F5 and L2, 3F5 and L3, 3F5 and L4, 3F5 and L5, 3F6 and L1, 3F6 and L2, 3F6 and L3, 3F6 and L4 or 3F6 and L5.

[0083] In one embodiment, the molecular scaffold may comprise at least one 5' flanking region and at least 3' flanking region as described in Tables 1 and 3. As a non-limiting example, the molecular scaffold may comprise 5F1 and 3F1, 5F1 and 3F2, 5F1 and 3F3, 5F1 and 3F4, 5F1 and 3F5, 5F1 and 3F6, 5F2 and 3F1, 5F2 and 3F2, 5F2 and 3F3, 5F2 and 3F4, 5F2 and 3F5, 5F2 and 3F6, 5F3 and 3F1, 5F3 and 3F2, 5F3 and 3F3, 5F3 and 3F4, 5F3 and 3F5, 5F3 and 3F6, 5F4 and 3F1, 5F4 and 3F2, 5F4 and 3F3, 5F4 and 3F4, 5F4 and 3F5, 5F4 and 3F6.

[0084] In one embodiment, the molecular scaffold may comprise at least one 5' flanking region, at least one loop motif region and at least one 3' flanking region. As a non-limiting example, the molecular scaffold may comprise 5F1, L1 and 3F1; 5F1, L1 and 3F2; 5F1, L1 and 3F3; 5F1, L1 and 3F4; 5F1, L1 and 3F5; 5F1, L1 and 3F6; 5F2, L1 and 3F1; 5F2, L1 and 3F2; 5F2, L1 and 3F3; 5F2, L1 and 3F4; 5F2, L1 and 3F5; 5F2, L1 and 3F6; 5F3, L1 and 3F1; 5F3, L1 and 3F2; 5F3, L1 and 3F3; 5F3, L1 and 3F4; 5F3, L1 and 3F5; 5F3, L1 and 3F6; 5F4, L1 and 3F1; 5F4, L1 and 3F2; 5F4, L1 and 3F3; 5F4, L1 and 3F4; 5F4, L1 and 3F5; 5F4, L1 and 3F6; 5F1, L2 and 3F1; 5F1, L2 and 3F2; 5F1, L2 and 3F3; 5F1, L2 and 3F4; 5F1, L2 and 3F5; 5F1, L2 and 3F6; 5F2, L2 and 3F1; 5F2, L2 and 3F2; 5F2, L2 and 3F3; 5F2, L2 and 3F4; 5F2, L2 and 3F5; 5F2, L2 and 3F6; 5F3, L2 and 3F1; 5F3, L2 and 3F2; 5F3, L2 and 3F3; 5F3, L2 and 3F4; 5F3, L2 and 3F5; 5F3, L2 and 3F6; 5F4, L2 and 3F1; 5F4, L2 and 3F2; 5F4, L2 and 3F3; 5F4, L2 and 3F4; 5F4, L2 and 3F5; 5F4, L2 and 3F6; 5F1, L3 and 3F1; 5F1, L3 and 3F2; 5F1, L3 and 3F3; 5F1, L3 and 3F4; 5F1, L3 and 3F5; 5F1, L3 and 3F6; 5F2, L3 and 3F1; 5F2, L3 and 3F2; 5F2, L3 and 3F3; 5F2, L3 and 3F4; 5F2, L3 and 3F5; 5F2, L3 and 3F6; 5F3, L3 and 3F1; 5F3, L3 and 3F2; 5F3, L3 and 3F3; 5F3, L3 and 3F4; 5F3, L3 and 3F5; 5F3, L3 and 3F6; 5F4, L3 and 3F1; 5F4, L3 and 3F2; 5F4, L3 and 3F3; 5F4, L3 and 3F4; 5F4, L3 and 3F5; 5F4, L3 and 3F6; 5F1, L4 and 3F1; 5F1, L4 and 3F2; 5F1, L4 and 3F3; 5F1, L4 and 3F4; 5F1, L4 and 3F5; 5F1, L4 and 3F6; 5F2, L4 and 3F1; 5F2, L4 and 3F2; 5F2, L4 and 3F3; 5F2, L4 and 3F4; 5F2, L4 and 3F5; 5F2, L4 and 3F6; 5F3, L4 and 3F1; 5F3, L4 and 3F2; 5F3, L4 and 3F3; 5F3, L4 and 3F4; 5F3, L4 and

3F5; 5F3, L4 and 3F6; 5F4, L4 and 3F1; 5F4, L4 and 3F2; 5F4, L4 and 3F3; 5F4, L4 and 3F4; 5F4, L4 and 3F5; 5F4, L4 and 3F6; 5F1, L5 and 3F1; 5F1, L5 and 3F2; 5F1, L5 and 3F3; 5F1, L5 and 3F4; 5F1, L5 and 3F5; 5F1, L5 and 3F6; 5F2, L5 and 3F1; 5F2, L5 and 3F2; 5F2, L5 and 3F3; 5F2, L5 and 3F4; 5F2, L5 and 3F5; 5F2, L5 and 3F6; 5F3, L5 and 3F1; 5F3, L5 and 3F2; 5F3, L5 and 3F3; 5F3, L5 and 3F4; 5F3, L5 and 3F5; 5F3, L5 and 3F6; 5F4, L5 and 3F1; 5F4, L5 and 3F2; 5F4, L5 and 3F3; 5F4, L5 and 3F4; 5F4, L5 and 3F5; or 5F4, L5 and 3F6.

[0085] In one embodiment, the molecular scaffold may comprise one or more linkers known in the art. The linkers may separate regions or one molecular scaffold from another. As a non-limiting example, the molecular scaffold may be polycistronic.

[0086] In one embodiment, the modulatory polynucleotide is designed using at least one of the following properties: loop variant, seed mismatch/bulge/wobble variant, stem mismatch, loop variant and vassal stem mismatch variant, seed mismatch and basal stem mismatch variant, stem mismatch and basal stem mismatch variant, seed wobble and basal stem wobble variant, or a stem sequence variant.

[0087] In one embodiment, the molecular scaffold may be located downstream of a promoter such as, but not limited to, CMV, U6, CBA or a CBA promoter with a SV40 intron. Further, the molecular scaffold may also be located upstream of the polyadenylation sequence. As a non-limiting example, the molecular scaffold may be located within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 or more than 30 nucleotides downstream from the promoter and/or upstream of the polyadenylation sequence. As another non-limiting example, the molecular scaffold may be located within 1-5, 1-10, 1-15, 1-20, 1-25, 1-30, 5-10, 5-15, 5-20, 5-25, 5-30, 10-15, 10-20, 10-25, 10-30, 15-20, 15-25, 15-30, 20-25, 20-30 or 25-30 nucleotides downstream from the promoter and/or upstream of the polyadenylation sequence. As a non-limiting example, the molecular scaffold may be located within the first 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25% or more than 25% of the nucleotides downstream from the promoter and/or upstream of the polyadenylation sequence. As another non-limiting example, the molecular scaffold may be located with the first 1-5%, 1-10%, 1-15%, 1-20%, 1-25%, 5-10%, 5-15%, 5-20%, 5-25%, 10-15%, 10-20%, 10-25%, 15-20%, 15-25%, or 20-25% downstream from the promoter and/or upstream of the polyadenylation sequence.

[0088] In one embodiment, the molecular scaffold may be located upstream of the polyadenylation sequence. Further, the molecular scaffold may be located downstream of a promoter such as, but not limited to, CMV, U6, CBA or a CBA promoter with a SV40 intron. As a non-limiting example, the molecular scaffold may be located within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 or more than 30

nucleotides downstream from the promoter and/or upstream of the polyadenylation sequence. As another non-limiting example, the molecular scaffold may be located within 1-5, 1-10, 1-15, 1-20, 1-25, 1-30, 5-10, 5-15, 5-20, 5-25, 5-30, 10-15, 10-20, 10-25, 10-30, 15-20, 15-25, 15-30, 20-25, 20-30 or 25-30 nucleotides downstream from the promoter and/or upstream of the polyadenylation sequence. As a non-limiting example, the molecular scaffold may be located within the first 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25% or more than 25% of the nucleotides downstream from the promoter and/or upstream of the polyadenylation sequence. As another non-limiting example, the molecular scaffold may be located with the first 1-5%, 1-10%, 1-15%, 1-20%, 1-25%, 5-10%, 5-15%, 5-20%, 5-25%, 10-15%, 10-20%, 10-25%, 15-20%, 15-25%, or 20-25% downstream from the promoter and/or upstream of the polyadenylation sequence.

[0089] In one embodiment, the molecular scaffold may be located in a scAAV.

[0090] In one embodiment, the molecular scaffold may be located in an ssAAV.

[0091] In one embodiment, the molecular scaffold may be located near the 5' end of the flip ITR. In another embodiment, the molecular scaffold may be located near the 3'end of the flip ITR. In yet another embodiment, the molecular scaffold may be located near the 5' end of the flop ITR. In yet another embodiment, the molecular scaffold may be located near the 3' end of the flop ITR. In one embodiment, the molecular scaffold may be located between the 5' end of the flip ITR and the 3' end of the flop ITR. In one embodiment, the molecular scaffold may be located between (e.g., half-way between the 5' end of the flip ITR and 3' end of the flop ITR or the 3' end of the flop ITR and the 5' end of the flip ITR), the 3' end of the flip ITR and the 5' end of the flip ITR. As a non-limiting example, the molecular scaffold may be located within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 or more than 30 nucleotides downstream from the 5' or 3' end of an ITR (e.g., Flip or Flop ITR). As a non-limiting example, the molecular scaffold may be located within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 or more than 30 nucleotides upstream from the 5' or 3' end of an ITR (e.g., Flip or Flop ITR). As another non-limiting example, the molecular scaffold may be located within 1-5, 1-10, 1-15, 1-20, 1-25, 1-30, 5-10, 5-15, 5-20, 5-25, 5-30, 10-15, 10-20, 10-25, 10-30, 15-20, 15-25, 15-30, 20-25, 20-30 or 25-30 nucleotides downstream from the 5' or 3' end of an ITR (e.g., Flip or Flop ITR). As another non-limiting example, the molecular scaffold may be located within 1-5, 1-10, 1-15, 1-20, 1-25, 1-30, 5-10, 5-15, 5-20, 5-25, 5-30, 10-15, 10-20, 10-25, 10-30, 15-20, 15-25, 15-30, 20-25, 20-30 or 25-30 upstream from the 5' or 3' end of an ITR (e.g., Flip or Flop ITR). As a non-limiting example, the molecular scaffold may be located within the first 1%, 2%, 3%, 4%,

5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25% or more than 25% of the nucleotides upstream from the 5' or 3' end of an ITR (e.g., Flip or Flop ITR). As another non-limiting example, the molecular scaffold may be located with the first 1-5%, 1-10%, 1-15%, 1-20%, 1-25%, 5-10%, 5-15%, 5-20%, 5-25%, 10-15%, 10-20%, 10-25%, 15-20%, 15-25%, or 20-25% downstream from the 5' or 3' end of an ITR (e.g., Flip or Flop ITR).

Expression Vector

[0092] In one embodiment, an expression vector (e.g., AAV vector) may comprise at least one of the modulatory polynucleotides comprising at least one of the molecular scaffolds described herein.

[0093] In one embodiment, an expression vector may comprise, from ITR to ITR recited 5' to 3', an ITR, a promoter, an intron, a modulatory polynucleotide, a polyA sequence and an ITR.

Genome Size

[0094] In one embodiment, the vector genome which comprises a nucleic acid sequence encoding the modulatory polynucleotides described herein may be a single stranded or double stranded vector genome. The size of the vector genome may be small, medium, large or the maximum size. Additionally, the vector genome may comprise a promoter and a polyA tail.

[0095] In one embodiment, the vector genome which comprises a nucleic acid sequence encoding the modulatory polynucleotides described herein may be a small single stranded vector genome. A small single stranded vector genome may be 2.7 to 3.5 kb in size such as about 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, and 3.5 kb in size. As a non-limiting example, the small single stranded vector genome may be 3.2 kb in size. Additionally, the vector genome may comprise a promoter and a polyA tail.

[0096] In one embodiment, the vector genome which comprises a nucleic acid sequence encoding the modulatory polynucleotides described herein may be a small double stranded vector genome. A small double stranded vector genome may be 1.3 to 1.7 kb in size such as about 1.3, 1.4, 1.5, 1.6, and 1.7 kb in size. As a non-limiting example, the small double stranded vector genome may be 1.6 kb in size. Additionally, the vector genome may comprise a promoter and a polyA tail.

[0097] In one embodiment, the vector genome which comprises a nucleic acid sequence encoding the modulatory polynucleotides described herein may be a medium single stranded vector genome. A medium single stranded vector genome may be 3.6 to 4.3 kb in size such as about 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2 and 4.3 kb in size. As a non-limiting example, the medium single stranded vector genome may be 4.0 kb in size. Additionally, the vector genome may comprise a promoter and a polyA tail.

[0098] In one embodiment, the vector genome which comprises a nucleic acid sequence encoding the modulatory polynucleotides described herein may be a medium double stranded vector genome. A medium double stranded vector genome may be 1.8 to 2.1 kb in size such as about 1.8, 1.9, 2.0, and 2.1 kb in size. As a non-limiting example, the medium double stranded vector genome may be 2.0 kb in size. Additionally, the vector genome may comprise a promoter and a polyA tail.

[0099] In one embodiment, the vector genome which comprises a nucleic acid sequence encoding the modulatory polynucleotides described herein may be a large single stranded vector genome. A large single stranded vector genome may be 4.4 to 6.0 kb in size such as about 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9 and 6.0 kb in size. As a non-limiting example, the large single stranded vector genome may be 4.7 kb in size. As another non-limiting example, the large single stranded vector genome may be 4.8 kb in size. As yet another non-limiting example, the large single stranded vector genome may be 6.0 kb in size. Additionally, the vector genome may comprise a promoter and a polyA tail.

[00100] In one embodiment, the vector genome which comprises a nucleic acid sequence encoding the modulatory polynucleotides described herein may be a large double stranded vector genome. A large double stranded vector genome may be 2.2 to 3.0 kb in size such as about 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9 and 3.0 kb in size. As a non-limiting example, the large double stranded vector genome may be 2.4 kb in size. Additionally, the vector genome may comprise a promoter and a polyA tail.

Promoters

[00101] A person skilled in the art may recognize that a target cell may require a specific promoter including but not limited to a promoter that is species specific, inducible, tissue-specific, or cell cycle-specific Parr et al., *Nat. Med.*3:1145-9 (1997); the contents of which are herein incorporated by reference in their entirety).

[00102] In one embodiment, the promoter is a promoter deemed to be efficient for the payload in the modulatory polynucleotide.

[00103] In one embodiment, the promoter is a promoter deemed to be efficient for the cell being targeted.

[00104] In one embodiment, the promoter is a weak promoter which provides expression of a payload for a period of time in targeted tissues such as, but not limited to, nervous system tissues. Expression may be for a period of 1 hour, 2, hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 1 day, 2 days, 3 days, 4 days,

5 days, 6 days, 1 week, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 2 weeks, 15 days, 16 days, 17 days, 18 days, 19 days, 20 days, 3 weeks, 22 days, 23 days, 24 days, 25 days, 26 days, 27 days, 28 days, 29 days, 30 days, 31 days, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 1 year, 13 months, 14 months, 15 months, 16 months, 17 months, 18 months, 19 months, 20 months, 21 months, 22 months, 23 months, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years or more than 10 years. Expression may be for 1-5 hours, 1-12 hours, 1-2 days, 1-5 days, 1-2 weeks, 1-3 weeks, 1-4 weeks, 1-2 months, 1-4 months, 1-6 months, 2-6 months, 3-6 months, 3-9 months, 4-8 months, 6-12 months, 1-2 years, 1-5 years, 2-5 years, 3-6 years, 3-8 years, 4-8 years or 5-10 years. As a non-limiting example, the promoter is a weak promoter for sustained expression of a payload in nervous tissues.

[00105] In one embodiment, the promoter may be a promoter which is less than 1 kb. The promoter may have a length of 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710, 720, 730, 740, 750, 760, 770, 780, 790, 800 or more than 800. The promoter may have a length between 200-300, 200-400, 200-500, 200-600, 200-700, 200-800, 300-400, 300-500, 300-600, 300-700, 300-800, 400-500, 400-600, 400-700, 400-800, 500-600, 500-700, 500-800, 600-700, 600-800 or 700-800.

[00106] In one embodiment, the promoter may be a combination of two or more components such as, but not limited to, CMV and CBA. Each component may have a length of 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710, 720, 730, 740, 750, 760, 770, 780, 790, 800 or more than 800. Each component may have a length between 200-300, 200-400, 200-500, 200-600, 200-700, 200-800, 300-400, 300-500, 300-600, 300-700, 300-800, 400-500, 400-600, 400-700, 400-800, 500-600, 500-700, 500-800, 600-700, 600-800 or 700-800. As a non-limiting example, the promoter is a combination of a 382 nucleotide CMV-enhancer sequence and a 260 nucleotide CBA-promoter sequence.

[00107] In one embodiment, the vector genome comprises at least one element to enhance the transgene target specificity and expression (See e.g., Powell et al. *Viral Expression Cassette Elements to Enhance Transgene Target Specificity and Expression in Gene Therapy*, 2015; the contents of which are herein incorporated by reference in their entirety). Non-limiting examples of elements to enhance the transgene target specificity and expression include promoters,

endogenous miRNAs, post-transcriptional regulatory elements (PREs), polyadenylation (PolyA) signal sequences and upstream enhancers (USEs), CMV enhancers and introns.

[00108] In one embodiment, the vector genome comprises at least one element to enhance the transgene target specificity and expression (See e.g., Powell et al. *Viral Expression Cassette Elements to Enhance Transgene Target Specificity and Expression in Gene Therapy*, 2015; the contents of which are herein incorporated by reference in their entirety) such as promoters. Promoters which promote expression in most tissues include, but are not limited to, human elongation factor 1α-subunit (EF1α), immediate-early cytomegalovirus (CMV), chicken β-actin (CBA) and its derivative CAG, the β glucuronidase (GUSB), or ubiquitin C (UBC). Tissue-specific expression elements can be used to restrict expression to certain cell types such as, but not limited to, nervous system promoters which can be used to restrict expression to neurons, astrocytes, or oligodendrocytes. Non-limiting example of tissue-specific expression elements for neurons include neuron-specific enolase (NSE), platelet-derived growth factor (PDGF), platelet-derived growth factor B-chain (PDGF-β), synapsin (Syn), methyl-CpG binding protein 2 (MeCP2), CaMKII, mGluR2, NFL, NFH, nβ2, PPE, Enk and EAAT2 promoters. A non-limiting example of tissue-specific expression elements for astrocytes include the glial fibrillary acidic protein (GFAP) and EAAT2 promoters. A non-limiting example of a tissue-specific expression element for oligodendrocytes is the myelin basic protein (MBP) promoter.

[00109] In one embodiment, the vector genome comprises a ubiquitous promoter. Non-limiting examples of ubiquitous promoters include CMV, CBA (including derivatives CAG, CBh, etc.), EF-1α, PGK, UBC, GUSB (hGBp), and UCOE (promoter of HNRPA2B1-CBX3). Yu et al. (Molecular Pain 2011, 7:63; the content of which is herein incorporated by reference in its entirety) evaluated the expression of eGFP under the CAG, EFIα, PGK and UBC promoters in rat DRG cells and primary DRG cells using lentiviral vectors and found that UBC showed weaker expression than the other 3 promoters and there was only 10-12% glial expression seen for all promoters. Soderblom et al. (E. Neuro 2015; the contents of which are herein incorporated by reference in its entirety) the expression of eGFP in AAV8 with CMV and UBC promoters and AAV2 with the CMV promoter after injection in the motor cortex. Intranasal administration of a plasmid containing a UBC or EFIα promoter showed a sustained airway expression greater than the expression with the CMV promoter (See e.g., Gill et al., Gene Therapy 2001, Vol. 8, 1539-1546; the contents of which are herein incorporated by reference in their entirety). Husain et al. (Gene Therapy 2009; the contents of which are herein incorporated by reference in their entirety) evaluated a HβH construct with a hGUSB promoter, a HSV-1LAT promoter and a NSE promoter and found that the HβH construct showed weaker expression than NSE in mouse brain.

Passini and Wolfe (J. Virol. 2001, 12382-12392, the contents of which are herein incorporated by reference in their entirety) evaluated the long term effects of the HβH vector following an intraventricular injection in neonatal mice and found that there was sustained expression for at least 1 year. Low expression in all brain regions was found by Xu et al. (Gene Therapy 2001, 8, 1323-1332; the contents of which are herein incorporated by reference in their entirety) when NF-L and NF-H promoters were used as compared to the CMV-lacZ, CMV-luc, EF, GFAP, hENK, nAChR, PPE, PPE + wpre, NSE (0.3 kb), NSE (1.8 kb) and NSE (1.8 kb + wpre). Xu et al. found that the promoter activity in descending order was NSE (1.8 kb), EF, NSE (0.3 kb), GFAP, CMV, hENK, PPE, NFL and NFH. NFL is a 650 nucleotide promoter and NFH is a 920 nucleotide promoter which are both absent in the liver but NFH is abundant in sensory proprioceptive neurons, brain and spinal cord and NFH is present in the heart. Scn8a is a 470 nucleotide promoter which expresses throughout the DRG, spinal cord and brain with particularly high expression seen in hippocampal neurons and cerebellar Purkinje cells, cortex, thalamus and hypothalamus (See e.g., Drews et al. 2007 and Raymond et al. 2004; the contents of each of which are herein incorporated by reference in their entireties).

[00110] In one embodiment, the vector genome comprises a UBC promoter. The UBC promoter may have a size of 300-350 nucleotides. As a non-limiting example, the UBC promoter is 332 nucleotides.

[00111] In one embodiment, the vector genome comprises a GUSB promoter. The GUSB promoter may have a size of 350-400 nucleotides. As a non-limiting example, the GUSB promoter is 378 nucleotides. As a non-limiting example, the construct may be AAV-promoter-CMV/globin intron-hFXN-RBG, where the AAV may be self-complementary and the AAV may be the DJ serotype.

[00112] In one embodiment, the vector genome comprises a NFL promoter. The NFL promoter may have a size of 600-700 nucleotides. As a non-limiting example, the NFL promoter is 650 nucleotides. As a non-limiting example, the construct may be AAV-promoter-CMV/globin intron-hFXN-RBG, where the AAV may be self-complementary and the AAV may be the DJ serotype.

[00113] In one embodiment, the vector genome comprises a NFH promoter. The NFH promoter may have a size of 900-950 nucleotides. As a non-limiting example, the NFH promoter is 920 nucleotides. As a non-limiting example, the construct may be AAV-promoter-CMV/globin intron-hFXN-RBG, where the AAV may be self-complementary and the AAV may be the DJ serotype.

[00114] In one embodiment, the vector genome comprises a scn8a promoter. The scn8a promoter may have a size of 450-500 nucleotides. As a non-limiting example, the scn8a promoter is 470 nucleotides. As a non-limiting example, the construct may be AAV-promoter-CMV/globin intron-hFXN-RBG, where the AAV may be self-complementary and the AAV may be the DJ serotype.

[00115] In one embodiment, the vector genome comprises a FXN promoter.

[00116] In one embodiment, the vector genome comprises a PGK promoter.

[00117] In one embodiment, the vector genome comprises a CBA promoter.

[00118] In one embodiment, the vector genome comprises a CMV promoter.

[00119] In one embodiment, the vector genome comprises a liver or a skeletal muscle promoter. Non-limiting examples of liver promoters include hAAT and TBG. Non-limiting examples of skeletal muscle promoters include Desmin, MCK and C5-12.

[00120] In one embodiment, the expression vector comprises an enhancer element, a promoter and/or a 5'UTR intron. The enhancer may be, but is not limited to, a CMV enhancer, the promoter may be, but is not limited to, a CMV, CBA, UBC, GUSB, NSE, Synapsin, MeCP2, and GFAP promoter and the 5'UTR/intron may be, but is not limited to, SV40, and CBA-MVM. As a non-limiting example, the enhancer, promoter and/or intron used in combination may be: (1) CMV enhancer, CMV promoter, SV40 5'UTR intron; (2) CMV enhancer, CBA promoter, SV 40 5'UTR intron; (3) CMV enhancer, CBA promoter, CBA-MVM 5'UTR intron; (4) UBC promoter; (5) GUSB promoter; (6) NSE promoter; (7) Synapsin promoter; (8) MeCP2 promoter and (9) GFAP promoter.

[00121] In one embodiment, the expression vector has an engineered promoter.

Introns

[00122] In one embodiment, the vector genome comprises at least one element to enhance the transgene target specificity and expression (See e.g., Powell et al. *Viral Expression Cassette Elements to Enhance Transgene Target Specificity and Expression in Gene Therapy*, 2015; the contents of which are herein incorporated by reference in 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).

[00123] In one embodiment, the intron may be 100-500 nucleotides in length. The intron may have a length of 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330,

340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490 or 500. The promoter may have a length between 80-100, 80-120, 80-140, 80-160, 80-180, 80-200, 80-250, 80-300, 80-350, 80-400, 80-450, 80-500, 200-300, 200-400, 200-500, 300-400, 300-500, or 400-500.

Introduction into cells

[00124] The modulatory polynucleotides of the invention can be introduced into host cells using any of a variety of approaches. Infection with a viral vector comprising the modulatory polynucleotide can be affected. Examples of suitable viral vectors include replication defective retroviral vectors, adenoviral vectors, adeno-associated vectors and lentiviral vectors.

[00125] According to the present invention, viral vectors for use in therapeutics and/or diagnostics comprise a virus that has been distilled or reduced to the minimum components necessary for transduction of a nucleic acid payload or cargo of interest.

[00126] 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.

[00127] As used herein, a "vector" is any molecule or moiety which transports, transduces or otherwise acts as a carrier of a heterologous molecule such as the modulatory polynucleotides of the invention. A "viral vector" is a vector which comprises one or more polynucleotide regions encoding or comprising payload molecules of interest, e.g., a transgene, a polynucleotide encoding a polypeptide or multi-polypeptide or a modulatory nucleic acid. Viral vectors of the present invention may be produced recombinantly and may be based on adeno-associated virus (AAV) parent or reference sequences. Serotypes which may be useful in the present invention include any of those arising from AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV9.47, AAV9(hu14), AAV10, AAV11, AAV12, AAVrh8, AAVrh10, AAV-DJ and AAV-DJ8.

[00128] In one embodiment, the serotype which may be useful in the present invention may be AAV-DJ8. The amino acid sequence of AAV-DJ8 may comprise two or more mutations in order to remove the heparin binding domain (HBD). As a non-limiting example, the AAV-DJ sequence described as SEQ ID NO: 1 in US Patent No. 7,588,772, the contents of which are herein incorporated by reference in their entirety, may comprise two mutations: (1) R587Q where arginine (R; Arg) at amino acid 587 is changed to glutamine (Q; Gln) and (2) R590T where arginine (R; Arg) at amino acid 590 is changed to threonine (T; Thr). As another non-limiting example, may comprise three mutations: (1) K406R where lysine (K; Lys) at amino acid 406 is changed to arginine (R; Arg), (2) R587Q where arginine (R; Arg) at amino acid 587 is

changed to glutamine (Q; Gln) and (3) R590T where arginine (R; Arg) at amino acid 590 is changed to threonine (T; Thr).

[00129] AAV vectors may also comprise self-complementary AAV vectors (scAAVs). scAAV vectors contain both DNA strands which anneal together to form double stranded DNA. By skipping second strand synthesis, scAAVs allow for rapid expression in the cell.

[00130] In one embodiment, the AAV vector used in the present invention is a scAAV.

[00131] In one embodiment, the modulatory polynucleotides may be introduced into cells from any relevant species, such as, but not limited to, human, dog, mouse, rat or monkey.

[00132] In one embodiment, the modulatory polynucleotides may be introduced into cells which are relevant to the disease to be treated. As a non-limiting example, the disease is ALS and the target cells are motor neurons and astrocytes.

[00133] In one embodiment, the modulatory polynucleotides may be introduced into cells which have a high level of endogenous expression of the target sequence.

[00134] In another embodiment, the modulatory polynucleotides may be introduced into cells which have a low level of endogenous expression of the target sequence.

[00135] In one embodiment, the cells may be those which have a high efficiency of AAV transduction.

[00136] In one embodiment, the cells which may be used for *in vitro* analysis of the modulatory polynucleotides include, but are not limited to, HEK293, HeLa, human primary astrocytes, human astrocyte cell line (U251MG), SH-SY5Y-neurons and human iPSC-derived motor neuron progenitors.

Target nucleic acids

[00137] The modulatory polynucleotides of the invention may be targeted to any gene or nucleic acid construct including coding and non-coding genes. Genes (DNA or mRNA) that encode human or primate proteins may be targeted. Further, non-coding genes may also be targeted, e.g., long noncoding RNAs (lncRNA).

[00138] Examples of such lncRNA molecules and RNAi constructs designed to target such lncRNA any of which may be targeted by or encoded in the modulatory polynucleotides, respectively are taught in International Publication, WO2012/018881 A2, the contents of which are incorporated herein by reference in their entirety.

[00139] In one embodiment, the modulatory polynucleotides of the invention may target any gene known in the art. As a non-limiting example, the gene may be SOD1.

[00140] In one embodiment, the modulatory polynucleotide may target a sequence 15-19 nucleotides in length. As a non-limiting example, the target may be any of the sequences

described in Table 1. As another non-limiting example, the target may be nucleotides 406-424 of NM_000454.4. As yet another non-limiting example, the target may be nucleotides 645-661 of NM_000454.4.

[00141] In one embodiment, the modulatory polynucleotide may target a sequence 21 nucleotides in length. In one aspect, the target may be any 21 mer sequence of NM_000454.4 or any gene known in the art. As a non-limiting example, the target may be nucleotides 521-541 of NM_000454.4. As another non-limiting example, the target may be nucleotides 639-659 of NM_000454.4. As another non-limiting example, the target may be nucleotides 640-660 of NM_000454.4. As another non-limiting example, the target may be nucleotides 645-665 of NM_000454.4. As another non-limiting example, the target may be nucleotides 664-684 of NM_000454.4.

[00142] In one embodiment, the modulatory polynucleotide may be designed to target any gene or mRNA in the human genome, e.g., genes associated with CNS disorders such as, but not limited to, Huntington's Disease, ALS and the like.

Pharmaceutical compositions

[00143] Although the descriptions of pharmaceutical compositions, e.g., those modulatory polynucleotides (including the encoding plasmids or expression vectors, such as viruses, e.g., AAV) comprising a payload to be delivered, provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are 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; mammals, including commercially relevant mammals such as cattle, pigs, horses, sheep, cats, dogs, mice, and/or rats; and/or birds, including commercially relevant birds such as poultry, chickens, ducks, geese, and/or turkeys.

[00144] 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 viral vector carrying the payload or to the modulatory polynucleotide payload molecule delivered by a viral vector as described herein.

[00145] 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.

[00146] Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition in accordance with the invention 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.

Formulation

[00147] The modulatory polynucleotides or viral vectors encoding them 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 viral vector to specific tissues or cell types).

[00148] Formulations of the present invention can include, without limitation, saline, lipidoids, liposomes, lipid nanoparticles, polymers, lipoplexes, core-shell nanoparticles, peptides, proteins, cells transfected with viral vectors (e.g., for transplantation into a subject), nanoparticle mimics and combinations thereof. Further, the viral vectors of the present invention may be formulated using self-assembled nucleic acid nanoparticles.

[00149] 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 associating the active ingredient with an excipient and/or one or more other accessory ingredients.

[00150] 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.

[00151] 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.

[00152] In some embodiments, the formulations described herein may contain at least one payload molecule. As a non-limiting example, the formulations may contain 1, 2, 3, 4 or 5 modulatory polynucleotide payload molecules. In one embodiment the formulation may contain a modulatory polynucleotide payload construct targeting proteins selected from categories such as, but not limited to, human proteins, veterinary proteins, bacterial proteins, biological proteins, antibodies, immunogenic proteins, therapeutic peptides and proteins, secreted proteins, plasma membrane proteins, cytoplasmic and cytoskeletal proteins, intracellular membrane bound proteins, nuclear proteins, proteins associated with human disease and/or proteins associated with non-human diseases. In one embodiment, the formulation contains at least three payload construct targeting proteins.

[00153] 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.

[00154] Excipients, which, as used herein, includes, but is 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.

[00155] 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.

Inactive Ingredients

[00156] In some embodiments, modulatory polynucleotide 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 invention may be approved by the US Food and Drug Administration (FDA).

[00157] Formulations of viral vectors carrying modulatory polynucleotide disclosed herein may include cations or anions. In one embodiment, 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 modulatory polynucleotides 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).

Administration

[00158] The viral vectors comprising modulatory polynucleotides of the present invention may be administered by any route which results in a therapeutically effective outcome. These include, but are not limited to enteral (into the intestine), gastroenteral, epidural (into the dura matter), oral (by way of the mouth), transdermal, peridural, intracerebral (into the cerebrum), intracerebroventricular (into the cerebral ventricles), 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), 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. In specific embodiments, compositions may be administered in a way which allows them to cross the blood-brain barrier, vascular barrier, or other epithelial barrier. In one embodiment, a formulation for a route of administration may include at least one inactive ingredient.

Dosing

[00159] The present invention provides methods comprising administering viral vectors and their modulatory polynucleotide payload or complexes in accordance with the invention to a

subject in need thereof. Viral vector pharmaceutical, imaging, diagnostic, or prophylactic compositions thereof, may be administered to a subject using any amount and any route of administration effective for preventing, treating, diagnosing, or imaging a disease, disorder, and/or condition (*e.g.*, a disease, disorder, and/or condition relating to working memory deficits). 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. Compositions in accordance with the invention 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 invention may be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective, prophylactically effective, or appropriate imaging dose level 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 specific modulatory polynucleotide payload 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.

[00160] In certain embodiments, viral vector pharmaceutical compositions in accordance with the present invention may be administered at modulatory polynucleotide dosage levels sufficient to deliver from about 0.0001 mg/kg to about 100 mg/kg, from about 0.001 mg/kg to about 0.05 mg/kg, from about 0.005 mg/kg to about 0.05 mg/kg, from about 0.001 mg/kg to about 0.005 mg/kg, from about 0.05 mg/kg to about 0.5 mg/kg, from about 0.01 mg/kg to about 50 mg/kg, from about 0.1 mg/kg to about 40 mg/kg, from about 0.5 mg/kg to about 30 mg/kg, from about 0.01 mg/kg to about 10 mg/kg, from about 0.1 mg/kg to about 10 mg/kg, or from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic, diagnostic, prophylactic, or imaging effect (see e.g., the range of unit doses described in International Publication No WO2013078199, herein incorporated by reference in its entirety). The desired modulatory polynucleotide dosage may be delivered more than once (e.g., more than one administration in a day). In certain embodiments, the desired modulatory polynucleotide 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 24 hour period. It may be administered as a single unit dose. In one embodiment, the viral vectors comprising the modulatory polynucleotides of the present invention are administered to a subject in split doses. They may be formulated in buffer only or in a formulation described herein.

[00161] In one embodiment, delivery of the compositions in accordance with the present invention to cells comprises a rate of delivery defined by [VG/hour = mL/hour * VG/mL] wherein VG is viral genomes, VG/mL is composition concentration, and mL/hour is rate of prolonged delivery.

[00162] In one embodiment, delivery of compositions in accordance with the present invention 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 $1x10^6$, $2x10^6$, $3x10^6$, $4x10^6$, $5x10^6$, $6x10^6$, $7x10^6$, $8x10^6$, $9x10^6$, $1x10^7$, $2x10^7$, $3x10^7$, $4x10^7$, $5x10^7$, $6x10^7$, $7x10^7$, $8x10^7$, $9x10^7$, $1x10^8$, $2x10^8$, $3x10^8$, $4x10^8$, $5x10^8$, $6x10^8$, $7x10^8$, $8x10^8$, $9x10^8$, $1x10^9$, $2x10^9$, $3x10^9$, $4x10^9$, $5x10^9$, $6x10^9$, $7x10^9$, $8x10^9$, $9x10^9$, $1x10^{10}$, $2x10^{10}$, $3x10^{10}$, $4x10^{10}$, $5x10^{10}$, $6x10^{10}$, $7x10^{10}$, $8x10^{10}$, $9x10^{10}$, $1x10^{11}$, $2x10^{11}$, $2.1x10^{11}$, $2.2x10^{11}$, $2.3x10^{11}$, $2.4x10^{11}$, $2.5x10^{11}$, $2.6x10^{11}$, $2.7x10^{11}$, $2.8x10^{11}$, $2.9x10^{11}$, $3x10^{11}$, $4x10^{11}$, $5x10^{11}$, $6x10^{11}$, $7x10^{11}$, $7.1x10^{11}$, $7.2x10^{11}$, $7.3x10^{11}$, $7.4x10^{11}$, $7.5x10^{11}$, $7.6x10^{11}$, $7.7x10^{11}$, $7.8x10^{11}$, $7.9x10^{11}$, $8x10^{11}$, $9x10^{11}$, $1x10^{12}$, $1.1\ x10^{12}$, $1.2x10^{12}$, $1.3x10^{12}$, $1.4x10^{12}$, $1.5x10^{12}$, $1.6x10^{12}$, $1.7x10^{12}$, $1.8x10^{12}$, $1.9x10^{12}$, $2x10^{12}$, $3x10^{12}$, $4x10^{12}$, $4.1x10^{12}$, $4.2x10^{12}$, $4.3x10^{12}$, $4.4x10^{12}$, $4.5x10^{12}$,$4.6x10^{12}$, $4.7x10^{12}$, $4.8x10^{12}$, $4.9x10^{12}$, $5x10^{12}$, $6x10^{12}$, $7x10^{12}$, $8x10^{12}$, $8.1x10^{12}$, $8.2x10^{12}$, $8.3x10^{12}$, $8.4x10^{12}$, $8.5x10^{12}$, $8.6x10^{12}$, $8.7x10^{12}$, $8.8\ x10^{12}$, $8.9x10^{12}$, $9x10^{12}$, $1x10^{13}$, $2x10^{13}$, $3x10^{13}$, $4x10^{13}$, $5x10^{13}$, $6x10^{13}$, $6.7x10^{13}$, $7x10^{13}$, $8x10^{13}$, $9x10^{13}$, $1x10^{14}$, $2x10^{14}$, $3x10^{14}$, $4x10^{14}$, $5x10^{14}$, $6x10^{14}$, $7x10^{14}$, $8x10^{14}$, $9x10^{14}$, $1x10^{15}$, $2x10^{15}$, $3x10^{15}$, $4x10^{15}$, $5x10^{15}$, $6x10^{15}$, $7x10^{15}$, $8x10^{15}$, $9x10^{15}$, or $1x10^{16}$ VG/subject.

[00163] In one embodiment, delivery of compositions in accordance with the present invention 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 $1x10^6$, $2x10^6$, $3x10^6$, $4x10^6$, $5x10^6$, $6x10^6$, $7x10^6$, $8x10^6$, $9x10^6$, $1x10^7$, $2x10^7$, $3x10^7$, $4x10^7$, $5x10^7$, $6x10^7$, $7x10^7$, $8x10^7$, $9x10^7$, $1x10^8$, $2x10^8$, $3x10^8$, $4x10^8$, $5x10^8$, $6x10^8$, $7x10^8$, $8x10^8$, $9x10^8$, $1x10^9$, $2x10^9$, $3x10^9$, $4x10^9$, $5x10^9$, $6x10^9$, $7x10^9$, $8x10^9$, $9x10^9$, $1x10^{10}$, $2x10^{10}$, $3x10^{10}$, $4x10^{10}$, $5x10^{10}$, $6x10^{10}$, $7x10^{10}$, $8x10^{10}$, $9x10^{10}$, $1x10^{11}$, $2x10^{11}$, $2.1x10^{11}$, $2.2x10^{11}$,

$2.3x10^{11}$, $2.4x10^{11}$, $2.5x10^{11}$, $2.6x10^{11}$, $2.7x10^{11}$, $2.8x10^{11}$, $2.9x10^{11}$, $3x10^{11}$, $4x10^{11}$, $5x10^{11}$, $6x10^{11}$, $7x10^{11}$, $7.1x10^{11}$, $7.2x10^{11}$, $7.3x10^{11}$, $7.4x10^{11}$, $7.5x10^{11}$, $7.6x10^{11}$, $7.7x10^{11}$, $7.8x10^{11}$, $7.9x10^{11}$, $8x10^{11}$, $9x10^{11}$, $1x10^{12}$, $1.1\ x10^{12}$, $1.2x10^{12}$, $1.3x10^{12}$, $1.4x10^{12}$, $1.5x10^{12}$, $1.6x10^{12}$, $1.7x10^{12}$, $1.8x10^{12}$, $1.9x10^{12}$, $2x10^{12}$, $3x10^{12}$, $4x10^{12}$, $4.1x10^{12}$, $4.2x10^{12}$, $4.3x10^{12}$, $4.4x10^{12}$, $4.5x10^{12}$,$4.6x10^{12}$, $4.7x10^{12}$, $4.8x10^{12}$, $4.9x10^{12}$, $5x10^{12}$, $6x10^{12}$, $7x10^{12}$, $8x10^{12}$, $8.1x10^{12}$, $8.2x10^{12}$, $8.3x10^{12}$, $8.4x10^{12}$, $8.5x10^{12}$, $8.6x10^{12}$, $8.7x10^{12}$, $8.8\ x10^{12}$, $8.9x10^{12}$, $9x10^{12}$, $1x10^{13}$, $2x10^{13}$, $3x10^{13}$, $4x10^{13}$, $5x10^{13}$, $6x10^{13}$, $6.7x10^{13}$, $7x10^{13}$, $8x10^{13}$, $9x10^{13}$, $1x10^{14}$, $2x10^{14}$, $3x10^{14}$, $4x10^{14}$, $5x10^{14}$, $6x10^{14}$, $7x10^{14}$, $8x10^{14}$, $9x10^{14}$, $1x10^{15}$, $2x10^{15}$, $3x10^{15}$, $4x10^{15}$, $5x10^{15}$, $6x10^{15}$, $7x10^{15}$, $8x10^{15}$, $9x10^{15}$, or $1x10^{16}$ VG/kg.

[00164] In one embodiment, about 10^5 to 10^6 viral genome (unit) may be administered per dose.

[00165] In one embodiment, delivery of the compositions in accordance with the present invention 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 $1x10^6$, $2x10^6$, $3x10^6$, $4x10^6$, $5x10^6$, $6x10^6$, $7x10^6$, $8x10^6$, $9x10^6$, $1x10^7$, $2x10^7$, $3x10^7$, $4x10^7$, $5x10^7$, $6x10^7$, $7x10^7$, $8x10^7$, $9x10^7$, $1x10^8$, $2x10^8$, $3x10^8$, $4x10^8$, $5x10^8$, $6x10^8$, $7x10^8$, $8x10^8$, $9x10^8$, $1x10^9$, $2x10^9$, $3x10^9$, $4x10^9$, $5x10^9$, $6x10^9$, $7x10^9$, $8x10^9$, $9x10^9$, $1x10^{10}$, $2x10^{10}$, $3x10^{10}$, $4x10^{10}$, $5x10^{10}$, $6x10^{10}$, $7x10^{10}$, $8x10^{10}$, $9x10^{10}$, $1x10^{11}$, $2x10^{11}$, $3x10^{11}$, $4x10^{11}$, $5x10^{11}$, $6x10^{11}$, $7x10^{11}$, $8x10^{11}$, $9x10^{11}$, $1x10^{12}$, $1.1x10^{12}$, $1.2x10^{12}$, $1.3x10^{12}$, $1.4x10^{12}$, $1.5x10^{12}$, $1.6x10^{12}$, $1.7x10^{12}$, $1.8x10^{12}$, $1.9x10^{12}$, $2x10^{12}$, $2.1x10^{12}$, $2.2x10^{12}$, $2.3x10^{12}$, $2.4x10^{12}$, $2.5x10^{12}$, $2.6x10^{12}$, $2.7x10^{12}$, $2.8x10^{12}$, $2.9x10^{12}$, $3x10^{12}$, $3.1x10^{12}$, $3.2x10^{12}$, $3.3x10^{12}$, $3.4x10^{12}$, $3.5x10^{12}$, $3.6x10^{12}$, $3.7x10^{12}$, $3.8x10^{12}$, $3.9x10^{12}$, $4x10^{12}$, $4.1x10^{12}$, $4.2x10^{12}$, $4.3x10^{12}$, $4.4x10^{12}$, $4.5x10^{12}$, $4.6x10^{12}$, $4.7x10^{12}$, $4.8x10^{12}$, $4.9x10^{12}$, $5x10^{12}$, $6x10^{12}$, $7x10^{12}$, $8x10^{12}$, $9x10^{12}$, $1x10^{13}$, $2x10^{13}$, $3x10^{13}$, $4x10^{13}$, $5x10^{13}$, $6x10^{13}$, $6.7x10^{13}$, $7x10^{13}$, $8x10^{13}$, $9x10^{13}$, $1x10^{14}$, $2x10^{14}$, $3x10^{14}$, $4x10^{14}$, $5x10^{14}$, $6x10^{14}$, $7x10^{14}$, $8x10^{14}$, $9x10^{14}$, $1x10^{15}$, $2x10^{15}$, $3x10^{15}$, $4x10^{15}$, $5x10^{15}$, $6x10^{15}$, $7x10^{15}$, $8x10^{15}$, $9x10^{15}$, or $1x10^{16}$ VG/mL.

Combinations

[00166] The viral vectors comprising the modulatory polynucleotide may be used in combination with one or more other therapeutic, prophylactic, diagnostic, or imaging agents. By "in combination with," it is not intended to imply that the agents must be administered at the same time and/or formulated for delivery together, although these methods of delivery are within the scope of the present disclosure. Compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. In general, each agent will be administered at a dose and/or on a time schedule determined for that agent. In

some embodiments, the present disclosure encompasses the delivery of pharmaceutical, prophylactic, diagnostic, or imaging compositions in combination with agents that may improve their bioavailability, reduce and/or modify their metabolism, inhibit their excretion, and/or modify their distribution within the body.

Delivery

[00167] In one embodiment, the viral vector comprising a modulatory polynucleotide 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.

[00168] In one embodiment, the viral vector comprising a modulatory polynucleotide 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.

[00169] In one embodiment, the viral vector comprising a modulatory polynucleotide may be administered or delivered using the methods for delivering DNA molecules using AAV vectors described in US Patent No. US 5858351, the contents of which are herein incorporated by reference in their entirety.

[00170] In one embodiment, the viral vector comprising a modulatory polynucleotide may be administered or delivered using the methods for delivering DNA to the bloodstream described in US Patent No. US 6211163, the contents of which are herein incorporated by reference in their entirety.

[00171] In one embodiment, the viral vector comprising a modulatory polynucleotide may be administered or delivered using the methods for delivering AAV virions described in US Patent No. US 6325998, the contents of which are herein incorporated by reference in their entirety.

[00172] In one embodiment, the viral vector comprising a modulatory polynucleotide may be administered or delivered using the methods for delivering DNA to muscle cells described in US Patent No. US 6335011, the contents of which are herein incorporated by reference in their entirety.

[00173] In one embodiment, the viral vector comprising a modulatory polynucleotide may be administered or delivered using the methods for delivering DNA to muscle cells and tissues described in US Patent No. US 6610290, the contents of which are herein incorporated by reference in their entirety.

[00174] In one embodiment, the viral vector comprising a modulatory polynucleotide may be administered or delivered using the methods for delivering DNA to muscle cells described in US

Patent No. US 7704492, the contents of which are herein incorporated by reference in their entirety.

[00175] In one embodiment, the viral vector comprising a modulatory polynucleotide may be administered or delivered using the methods for delivering a payload to skeletal muscles described in US Patent No. US 7112321, the contents of which are herein incorporated by reference in their entirety.

[00176] In one embodiment, the viral vector may be administered or delivered using the methods for delivering a payload to the central nervous system described in US Patent No. US 7588757, the contents of which are herein incorporated by reference in their entirety.

[00177] In one embodiment, the viral vector comprising a modulatory polynucleotide 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.

[00178] In one embodiment, the viral vector comprising a modulatory polynucleotide may be administered or delivered using the methods for delivering a payload for the treatment of Alzheimer disease described in US Patent No. US 8318687, the contents of which are herein incorporated by reference in their entirety.

[00179] In one embodiment, the viral vector comprising a modulatory polynucleotide may be administered or delivered using the methods for delivering a payload described in International Patent Publication No. WO2012144446, the contents of which are herein incorporated by reference in their entirety.

[00180] In one embodiment, the viral vector comprising a modulatory polynucleotide 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.

[00181] In one embodiment, the viral vector comprising a modulatory polynucleotide may be administered or delivered using the methods for delivering a payload described in International Patent Publication No. WO2001096587, the contents of which are herein incorporated by reference in their entirety.

[00182] In one embodiment, the viral vector comprising a modulatory polynucleotide may be administered or delivered using the methods for delivering a payload to muscle tissue described in International Patent Publication No. WO2002014487, the contents of which are herein incorporated by reference in their entirety.

[00183] In one embodiment, the viral vector comprising a modulatory polynucleotide 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.

[00184] The pharmaceutical compositions of viral vectors described herein may be characterized by one or more of bioavailability, therapeutic window and/or volume of distribution.

[00185] In one embodiment, the viral vectors 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.

[00186] In one embodiment, the viral vectors comprising a modulatory polynucleotide may be delivered to a subject via a single route administration.

[00187] In one embodiment, the viral vectors comprising a modulatory polynucleotide may be delivered to a subject via a multi-site route of administration. A subject may be administered the viral vectors comprising a modulatory polynucleotide at 2, 3, 4, 5 or more than 5 sites.

[00188] In one embodiment, a subject may be administered the viral vectors comprising a modulatory polynucleotide described herein using a bolus infusion.

[00189] In one embodiment, a subject may be administered the viral vectors 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.

[00190] In one embodiment, the catheter may be located at more than one site in the spine for multi-site delivery. The viral vectors comprising a modulatory polynucleotide may be delivered in a continuous and/or bolus infusion. Each site of delivery may be a different dosing regimen or the same dosing regimen may be used for each site of delivery. As a non-limiting example, the sites of delivery may be in the cervical and the lumbar region. As another non-limiting example, the sites of delivery may be in the cervical region. As another non-limiting example, the sites of delivery may be in the lumbar region.

[00191] In one embodiment, a subject may be analyzed for spinal anatomy and pathology prior to delivery of the viral vectors comprising a modulatory polynucleotide described herein. As a non-limiting example, a subject with scoliosis may have a different dosing regimen and/or catheter location compared to a subject without scoliosis.

[00192] In one embodiment, the orientation of the spine subject during delivery of the viral vectors comprising a modulatory polynucleotide may be vertical to the ground.

[00193] In another embodiment, the orientation of the spine of the subject during delivery of the viral vectors comprising a modulatory polynucleotide may be horizontal to the ground.

[00194] In one embodiment, the spine of the subject may be at an angle as compared to the ground during the delivery of the viral vectors comprising a modulatory polynucleotide subject. The angle of the spine of the subject as compared to the ground may be at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150 or 180 degrees.

[00195] In one embodiment, the delivery method and duration is chosen to provide broad transduction in the spinal cord. As a non-limiting example, intrathecal delivery is used to provide broad transduction along the rostral-caudal length of the spinal cord. As another non-limiting example, multi-site infusions provide a more uniform transduction along the rostral-caudal length of the spinal cord. As yet another non-limiting example, prolonged infusions provide a more uniform transduction along the rostral-caudal length of the spinal cord.

Bioavailability

[00196] Viral vectors comprising a modulatory polynucleotide of the present invention, when formulated into compositions with delivery/formulation agents or vehicles as described herein, may exhibit increased bioavailability as compared to compositions lacking delivery agents as described herein. As used herein, the term "bioavailability" refers to the systemic availability of a given amount of a particular agent administered to a subject. Bioavailability may be assessed by measuring the area under the curve (AUC) or the maximum serum or plasma concentration (C_{max}) of the unchanged form of a compound following administration of the compound to a mammal. AUC is a determination of the area under the curve plotting the serum or plasma concentration of a compound along the ordinate (Y-axis) against time along the abscissa (X-axis). Generally, the AUC for a particular compound may be calculated using methods known to those of ordinary skill in the art and as described in G. S. Banker, Modern Pharmaceutics, Drugs and the Pharmaceutical Sciences, v. 72, Marcel Dekker, New York, Inc., 1996, the contents of which are herein incorporated by reference in their entirety.

[00197] C_{max} values are maximum concentrations of compounds achieved in serum or plasma of a subject following administration of compounds to the subject. C_{max} values of particular compounds may be measured using methods known to those of ordinary skill in the art. As used herein, the phrases "increasing bioavailability" or "improving the pharmacokinetics," refer to actions that may increase the systemic availability of a viral vector of the present invention (as measured by AUC, C_{max}, or C_{min}) in a subject. In some embodiments, such actions may comprise co-administration with one or more delivery agents as described herein. In some embodiments, the bioavailability of viral vectors may increase by at least about 2%, at least about 5%, at least

about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95% or about 100%.

Therapeutic window

[00198] Viral vectors comprising a modulatory polynucleotide of the present invention, when formulated with one or more delivery agents as described herein, may exhibit increases in the therapeutic window of compound and/or composition administration as compared to the therapeutic window of viral vectors administered without one or more delivery agents as described herein. As used herein, the term "therapeutic window" refers to the range of plasma concentrations, or the range of levels of therapeutically active substance at the site of action, with a high probability of eliciting a therapeutic effect. In some embodiments, therapeutic windows of viral vectors when administered in a formulation may increase by at least about 2%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95% or about 100%.

Volume of distribution

[00199] Viral vectors comprising a modulatory polynucleotide of the present invention, when formulated with one or more delivery agents as described herein, may exhibit an improved volume of distribution (V_{dist}), e.g., reduced or targeted, relative to formulations lacking one or more delivery agents as described herein. V_{dist} relates the amount of an agent in the body to the concentration of the same agent in the blood or plasma. As used herein, the term "volume of distribution" refers to the fluid volume that would be required to contain the total amount of an agent in the body at the same concentration as in the blood or plasma: V_{dist} equals the amount of an agent in the body/concentration of the agent in blood or plasma. For example, for a 10 mg dose of a given agent and a plasma concentration of 10 mg/L, the volume of distribution would be 1 liter. The volume of distribution reflects the extent to which an agent is present in the extravascular tissue. Large volumes of distribution reflect the tendency of agents to bind to the tissue components as compared with plasma proteins. In clinical settings, V_{dist} may be used to determine loading doses to achieve steady state concentrations. In some embodiments, volumes of distribution of viral vector compositions of the present invention when co-administered with one or more delivery agents as described herein may decrease at least about 2%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about

30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%.

Kits and devices

[00200] The invention provides a variety of kits for conveniently and/or effectively carrying out methods of the present invention. Typically kits will comprise sufficient amounts and/or numbers of components to allow a user to perform multiple treatments of a subject(s) and/or to perform multiple experiments.

[00201] Any of the vectors, constructs, modulatory polynucleotides, polynucleotides or polypeptides of the present invention may be comprised in a kit. In some embodiments, kits may further include reagents and/or instructions for creating and/or synthesizing compounds and/or compositions of the present invention. In some embodiments, kits may also include one or more buffers. In some embodiments, kits of the invention may include components for making protein or nucleic acid arrays or libraries and thus, may include, for example, solid supports.

[00202] In some embodiments, kit components may be packaged either in aqueous media or in lyophilized form. The container means of the kits will generally include at least one vial, test tube, flask, bottle, syringe or other container means, into which a component may be placed, and preferably, suitably aliquotted. Where there are more than one kit component, (labeling reagent and label may be packaged together), kits may also generally contain second, third or other additional containers into which additional components may be separately placed. In some embodiments, kits may also comprise second container means for containing sterile, pharmaceutically acceptable buffers and/or other diluents. In some embodiments, various combinations of components may be comprised in one or more vial. Kits of the present invention may also typically include means for containing compounds and/or compositions of the present invention, e.g., proteins, nucleic acids, and any other reagent containers in close confinement for commercial sale. Such containers may include injection or blow-molded plastic containers into which desired vials are retained.

[00203] In some embodiments, kit components are provided in one and/or more liquid solutions. In some embodiments, liquid solutions are aqueous solutions, with sterile aqueous solutions being particularly preferred. In some embodiments, kit components may be provided as dried powder(s). When reagents and/or components are provided as dry powders, such powders may be reconstituted by the addition of suitable volumes of solvent. In some embodiments, it is envisioned that solvents may also be provided in another container means. In some embodiments, labeling dyes are provided as dried powders. In some embodiments, it is contemplated that 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 120, 120, 130, 140, 150, 160, 170, 180,

190, 200, 300, 400, 500, 600, 700, 800, 900, 1000 micrograms or at least or at most those amounts of dried dye are provided in kits of the invention. In such embodiments, dye may then be resuspended in any suitable solvent, such as DMSO.

[00204] In some embodiments, kits may include instructions for employing kit components as well the use of any other reagent not included in the kit. Instructions may include variations that may be implemented.

Devices

[00205] In some embodiments, compounds and/or compositions of the present invention may be combined with, coated onto or embedded in a device. Devices may include, but are not limited to, dental implants, stents, bone replacements, artificial joints, valves, pacemakers and/or other implantable therapeutic device.

[00206] The present invention provides for devices which may incorporate viral vectors that encode one or more modulatory polynucleotide payload molecules. These devices contain in a stable formulation the viral vectors which may be immediately delivered to a subject in need thereof, such as a human patient.

[00207] Devices for administration may be employed to deliver the viral vectors comprising a modulatory polynucleotide of the present invention according to single, multi- or split-dosing regimens taught herein.

[00208] Method and devices known in the art for multi-administration to cells, organs and tissues are contemplated for use in conjunction with the methods and compositions disclosed herein as embodiments of the present invention. These include, for example, those methods and devices having multiple needles, hybrid devices employing for example lumens or catheters as well as devices utilizing heat, electric current or radiation driven mechanisms.

[00209] The modulatory polynucleotides of the present invention may be used in the treatment, prophylaxis or amelioration of any disease or disorder characterized by aberrant or undesired target expression.

DEFINITIONS

[00210] At various places in the present specification, substituents of compounds of the present disclosure are disclosed in groups or in ranges. It is specifically intended that the present disclosure include each and every individual subcombination of the members of such groups and ranges.

[00211] *About:* As used herein, the term "about" means +/- 10% of the recited value.

[00212] *Administered in combination:* As used herein, the term "administered in combination" or "combined administration" means that two or more agents are administered to a subject at the

same time or within an interval such that there may be an overlap of an effect of each agent on the patient. In some embodiments, they are administered within about 60, 30, 15, 10, 5, or 1 minute of one another. In some embodiments, the administrations of the agents are spaced sufficiently closely together such that a combinatorial (*e.g.*, a synergistic) effect is achieved.

[00213] *Animal:* As used herein, the term "animal" refers to any member of the animal kingdom. In some embodiments, "animal" refers to humans at any stage of development. In some embodiments, "animal" refers to non-human animals at any stage of development. In certain embodiments, the non-human animal is a mammal (*e.g.*, a rodent, a mouse, a rat, a rabbit, a monkey, a dog, a cat, a sheep, cattle, a primate, or a pig). In some embodiments, animals include, but are not limited to, mammals, birds, reptiles, amphibians, fish, and worms. In some embodiments, the animal is a transgenic animal, genetically-engineered animal, or a clone.

[00214] *Approximately:* As used herein, the term "approximately" or "about," as applied to one or more values of interest, refers to a value that is similar to a stated reference value. In certain embodiments, the term "approximately" or "about" refers to a range of values that fall within 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less in either direction (greater than or less than) of the stated reference value unless otherwise stated or otherwise evident from the context (except where such number would exceed 100% of a possible value).

[00215] *Associated with:* As used herein, the terms "associated with," "conjugated," "linked," "attached," and "tethered," when used with respect to two or more moieties, means that the moieties are physically associated or connected with one another, either directly or via one or more additional moieties that serves as a linking agent, to form a structure that is sufficiently stable so that the moieties remain physically associated under the conditions in which the structure is used, *e.g.*, physiological conditions. An "association" need not be strictly through direct covalent chemical bonding. It may also suggest ionic or hydrogen bonding or a hybridization based connectivity sufficiently stable such that the "associated" entities remain physically associated.

[00216] *Bifunctional:* As used herein, the term "bifunctional" refers to any substance, molecule or moiety which is capable of or maintains at least two functions. The functions may affect the same outcome or a different outcome. The structure that produces the function may be the same or different.

[00217] *Biocompatible*: As used herein, the term "biocompatible" means compatible with living cells, tissues, organs or systems posing little to no risk of injury, toxicity or rejection by the immune system.

[00218] *Biodegradable*: As used herein, the term "biodegradable" means capable of being broken down into innocuous products by the action of living things.

[00219] *Biologically active*: As used herein, the phrase "biologically active" refers to a characteristic of any substance that has activity in a biological system and/or organism. For instance, a substance that, when administered to an organism, has a biological effect on that organism, is considered to be biologically active. In particular embodiments, a modulatory polynucleotide of the present invention may be considered biologically active if even a portion of the polynucleotides is biologically active or mimics an activity considered biologically relevant.

[00220] *Induced pluripotent stem cells*: As used herein, "induced pluripotent stem cells" are cells that may be induced to form any of several distinct cell types.

[00221] *Compound:* As used herein, the term "compound," is meant to include all stereoisomers, geometric isomers, tautomers, and isotopes of the structures depicted.

[00222] The compounds described herein can be asymmetric (*e.g.*, having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present disclosure that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically active starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present disclosure. Cis and trans geometric isomers of the compounds of the present disclosure are described and may be isolated as a mixture of isomers or as separated isomeric forms.

[00223] Compounds of the present disclosure also include tautomeric forms. Tautomeric forms result from the swapping of a single bond with an adjacent double bond and the concomitant migration of a proton. Tautomeric forms include prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge.

[00224] Compounds of the present disclosure also include all of the isotopes of the atoms occurring in the intermediate or final compounds. "Isotopes" refers to atoms having the same atomic number but different mass numbers resulting from a different number of neutrons in the nuclei. For example, isotopes of hydrogen include tritium and deuterium.

[00225] The compounds and salts of the present disclosure can be prepared in combination with solvent or water molecules to form solvates and hydrates by routine methods.

[00226] *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.

[00227] In some embodiments, two or more sequences are said to be "completely conserved" if they are 100% identical to one another. In some 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 some 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 some 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 some 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.

[00228] *Controlled Release:* As used herein, the term "controlled release" refers to a pharmaceutical composition or compound release profile that conforms to a particular pattern of release to effect a therapeutic outcome.

[00229] *Cyclic or Cyclized:* As used herein, the term "cyclic" refers to the presence of a continuous loop. Cyclic molecules need not be circular, only joined to form an unbroken chain of subunits.

[00230] *Cytostatic*: As used herein, "cytostatic" refers to inhibiting, reducing, suppressing the growth, division, or multiplication of a cell (*e.g.*, a mammalian cell (*e.g.*, a human cell)), bacterium, virus, fungus, protozoan, parasite, prion, or a combination thereof.

[00231] *Cytotoxic*: As used herein, "cytotoxic" refers to killing or causing injurious, toxic, or deadly effect on a cell (*e.g.*, a mammalian cell (*e.g.*, a human cell)), bacterium, virus, fungus, protozoan, parasite, prion, or a combination thereof.

[00232] *Delivery:* As used herein, "delivery" refers to the act or manner of delivering a compound, substance, entity, moiety, cargo or payload.

[00233] *Delivery Agent*: As used herein, "delivery agent" refers to any substance which facilitates, at least in part, the *in vivo* delivery of a modulatory polynucleotide to targeted cells.

[00234] *Destabilized:* As used herein, the term "destable," "destabilize," or "destabilizing region" means a region or molecule that is less stable than a starting, wild-type or native form of the same region or molecule.

[00235] *Detectable label:* As used herein, "detectable label" refers to one or more markers, signals, or moieties which are attached, incorporated or associated with another entity that is readily detected by methods known in the art including radiography, fluorescence, chemiluminescence, enzymatic activity, absorbance and the like. Detectable labels include radioisotopes, fluorophores, chromophores, enzymes, dyes, metal ions, ligands such as biotin, avidin, streptavidin and haptens, quantum dots, and the like. Detectable labels may be located at any position in the peptides or proteins disclosed herein. They may be within the amino acids, the peptides, or proteins, or located at the N- or C- termini.

[00236] *Diastereomer:* As used herein, the term "diastereomer," means stereoisomers that are not mirror images of one another and are non-superimposable on one another.

[00237] *Digest*: As used herein, the term "digest" means to break apart into smaller pieces or components. When referring to polypeptides or proteins, digestion results in the production of peptides.

[00238] *Distal:* As used herein, the term "distal" means situated away from the center or away from a point or region of interest.

[00239] *Dosing regimen*: As used herein, a "dosing regimen" is a schedule of administration or physician determined regimen of treatment, prophylaxis, or palliative care.

[00240] *Enantiomer:* As used herein, the term "enantiomer" means each individual optically active form of a compound of the invention, having an optical purity or enantiomeric excess (as determined by methods standard in the art) of at least 80% (i.e., at least 90% of one enantiomer and at most 10% of the other enantiomer), preferably at least 90% and more preferably at least 98%.

[00241] *Encapsulate:* As used herein, the term "encapsulate" means to enclose, surround or encase.

[00242] *Engineered:* As used herein, embodiments of the invention are "engineered" when they are designed to have a feature or property, whether structural or chemical, that varies from a starting point, wild type or native molecule.

[00243] *Effective Amount:* As used herein, the term "effective amount" of an agentis that amount sufficient to effect beneficial or desired results, for example, clinical results, and, as

such, an "effective amount" depends upon the context in which it is being applied. For example, in the context of administering an agent that treats cancer, an effective amount of an agent is, for example, an amount sufficient to achieve treatment, as defined herein, of cancer, as compared to the response obtained without administration of the agent.

[00244] *Exosome:* As used herein, "exosome" is a vesicle secreted by mammalian cells or a complex involved in RNA degradation.

[00245] *Expression*: As used herein, "expression" of a nucleic acid sequence refers to one or more of the following events: (1) production of an RNA template from a DNA sequence (*e.g.*, by transcription); (2) processing of an RNA transcript (*e.g.*, by splicing, editing, 5′ cap formation, and/or 3′ end processing); (3) translation of an RNA into a polypeptide or protein; and (4) post-translational modification of a polypeptide or protein.

[00246] *Feature:* As used herein, a "feature" refers to a characteristic, a property, or a distinctive element.

[00247] *Formulation*: As used herein, a "formulation" includes at least one modulatory polynucleotide and a delivery agent.

[00248] *Fragment:* A "fragment," as used herein, refers to a portion. For example, fragments of proteins may comprise polypeptides obtained by digesting full-length protein isolated from cultured cells.

[00249] *Functional*: As used herein, a "functional" biological molecule is a biological molecule in a form in which it exhibits a property and/or activity by which it is characterized.

[00250] *Homology*: As used herein, the term "homology" refers to the overall relatedness between polymeric molecules, *e.g.* between nucleic acid molecules (*e.g.* DNA molecules and/or RNA molecules) and/or between polypeptide molecules. In some embodiments, polymeric molecules are considered to be "homologous" to one another if their sequences are at least 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% identical or similar. The term "homologous" necessarily refers to a comparison between at least two sequences (polynucleotide or polypeptide sequences). In accordance with the invention, two polynucleotide sequences are considered to be homologous if the polypeptides they encode are at least about 50%, 60%, 70%, 80%, 90%, 95%, or even 99% for at least one stretch of at least about 20 amino acids. In some embodiments, homologous polynucleotide sequences are characterized by the ability to encode a stretch of at least 4–5 uniquely specified amino acids. For polynucleotide sequences less than 60 nucleotides in length, homology is determined by the ability to encode a stretch of at least 4–5 uniquely specified amino acids. In accordance with the invention, 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.

[00251] *Identity*: As used herein, the term "identity" refers to the overall relatedness between polymeric molecules, *e.g.*, between polynucleotide molecules (*e.g.* DNA molecules and/or RNA molecules) and/or between polypeptide molecules. Calculation of the percent identity of two polynucleotide sequences, for example, can be performed by aligning the two sequences for optimal comparison purposes (*e.g.*, gaps can be introduced in one or both of a first and a second nucleic acid sequences for optimal alignment and non-identical sequences can be disregarded for comparison purposes). In certain embodiments, the length of a sequence aligned for comparison purposes is at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or 100% of the length of the reference sequence. The nucleotides at corresponding nucleotide positions are then compared. When a position in the first sequence is occupied by the same nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which needs to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. For example, the percent identity between two nucleotide sequences can be determined using methods such as those described in Computational Molecular Biology, Lesk, A. M., ed., Oxford University Press, New York, 1988; Biocomputing: Informatics and Genome Projects, Smith, D. W., ed., Academic Press, New York, 1993; Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press, 1987; Computer Analysis of Sequence Data, Part I, Griffin, A. M., and Griffin, H. G., eds., Humana Press, New Jersey, 1994; and Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991; each of which is incorporated herein by reference. 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)).

[00252] *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.

[00253] *Isomer:* As used herein, the term "isomer" means any tautomer, stereoisomer, enantiomer, or diastereomer of any compound of the invention. It is recognized that the compounds of the invention can have one or more chiral centers and/or double bonds and, therefore, exist as stereoisomers, such as double-bond isomers (i.e., geometric E/Z isomers) or diastereomers (e.g., enantiomers (i.e., (+) or (-)) or cis/trans isomers). According to the invention, the chemical structures depicted herein, and therefore the compounds of the invention, encompass all of the corresponding stereoisomers, that is, both the stereomerically pure form (e.g., geometrically pure, enantiomerically pure, or diastereomerically pure) and enantiomeric and stereoisomeric mixtures, e.g., racemates. Enantiomeric and stereoisomeric mixtures of compounds of the invention can typically be resolved into their component enantiomers or stereoisomers by well-known methods, such as chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, or crystallizing the compound in a chiral solvent. Enantiomers and stereoisomers can also be obtained from stereomerically or enantiomerically pure intermediates, reagents, and catalysts by well-known asymmetric synthetic methods.

[00254] *In vitro*: As used herein, the term "*in vitro*" refers to events that occur in an artificial environment, *e.g.*, in a test tube or reaction vessel, in cell culture, in a Petri dish, *etc.*, rather than within an organism (*e.g.*, animal, plant, or microbe).

[00255] *In vivo*: As used herein, the term "*in vivo*" refers to events that occur within an organism (*e.g.*, animal, plant, or microbe or cell or tissue thereof).

[00256] *Isolated*: As used herein, the term "isolated" refers to a substance or entity that has been separated from at least some of the components with which it was associated (whether in nature or in an experimental setting). Isolated substances may have varying levels of purity in reference to the substances from which they have been associated. Isolated substances and/or

entities may be separated from at least about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, or more of the other components with which they were initially associated. In some embodiments, isolated agents are more than about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or more than about 99% pure. As used herein, a substance is "pure" if it is substantially free of other components.

[00257] *Substantially isolated*: By "substantially isolated" is meant that the compound is substantially separated from the environment in which it was formed or detected. Partial separation can include, for example, a composition enriched in the compound of the present disclosure. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compound of the present disclosure, or salt thereof. Methods for isolating compounds and their salts are routine in the art.

[00258] *Linker:* As used herein, a linker refers to a group of atoms, e.g., 10-1,000 atoms, and can be comprised of the atoms or groups such as, but not limited to, carbon, amino, alkylamino, oxygen, sulfur, sulfoxide, sulfonyl, carbonyl, and imine. The linker can be attached to a modified nucleoside or nucleotide on the nucleobase or sugar moiety at a first end, and to a payload, e.g., a detectable or therapeutic agent, at a second end. The linker may be of sufficient length as to not interfere with incorporation into a nucleic acid sequence. The linker can be used for any useful purpose, such as to form modulatory polynucleotide multimers (e.g., through linkage of two or more modulatory polynucleotides molecules) or modulatory polynucleotides conjugates, as well as to administer a payload, as described herein. Examples of chemical groups that can be incorporated into the linker include, but are not limited to, alkyl, alkenyl, alkynyl, amido, amino, ether, thioether, ester, alkylene, heteroalkylene, aryl, or heterocyclyl, each of which can be optionally substituted, as described herein. Examples of linkers include, but are not limited to, unsaturated alkanes, polyethylene glycols (e.g., ethylene or propylene glycol monomeric units, e.g., diethylene glycol, dipropylene glycol, triethylene glycol, tripropylene glycol, tetraethylene glycol, or tetraethylene glycol), and dextran polymers and derivatives thereof., Other examples include, but are not limited to, cleavable moieties within the linker, such as, for example, a disulfide bond (-S-S-) or an azo bond (-N=N-), which can be cleaved using a reducing agent or photolysis. Non-limiting examples of a selectively cleavable bond include an amido bond can be cleaved for example by the use of tris(2-carboxyethyl)phosphine (TCEP), or other reducing agents, and/or photolysis, as well as an ester bond can be cleaved for example by acidic or basic hydrolysis.

[00259] *MicroRNA (miRNA) binding site:* As used herein, a microRNA (miRNA) binding site represents a nucleotide location or region of a nucleic acid transcript to which at least the "seed" region of a miRNA binds.

[00260] *Modified:* As used herein "modified" refers to a changed state or structure of a molecule of the invention. Molecules may be modified in many ways including chemically, structurally, and functionally.

[00261] *Naturally occurring:* As used herein, "naturally occurring" means existing in nature without artificial aid.

[00262] *Neutralizing antibody*: As used herein, a "neutralizing antibody" refers to an antibody which binds to its antigen and defends a cell from an antigen or infectious agent by neutralizing or abolishing any biological activity it has.

[00263] *Non-human vertebrate:* As used herein, a "non human vertebrate" includes all vertebrates except *Homo sapiens*, including wild and domesticated species. Examples of non-human vertebrates include, but are not limited to, mammals, such as alpaca, banteng, bison, camel, cat, cattle, deer, dog, donkey, gayal, goat, guinea pig, horse, llama, mule, pig, rabbit, reindeer, sheep water buffalo, and yak.

[00264] *Off-target:* As used herein, "off target" refers to any unintended effect on any one or more target, gene, or cellular transcript.

[00265] *Open reading frame:* As used herein, "open reading frame" or "ORF" refers to a sequence which does not contain a stop codon in a given reading frame.

[00266] *Operably linked:* As used herein, the phrase "operably linked" refers to a functional connection between two or more molecules, constructs, transcripts, entities, moieties or the like.

[00267] *Optionally substituted:* Herein a phrase of the form "optionally substituted X" (*e.g.*, optionally substituted alkyl) is intended to be equivalent to "X, wherein X is optionally substituted" (*e.g.*, "alkyl, wherein the alkyl is optionally substituted"). It is not intended to mean that the feature "X" (*e.g.* alkyl) *per se* is optional.

[00268] *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.

[00269] *Patient:* As used herein, "patient" refers to a subject who may seek or be in need of treatment, requires treatment, is receiving treatment, will receive treatment, or a subject who is under care by a trained professional for a particular disease or condition.

[00270] *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.

[00271] *Pharmaceutically acceptable excipients:* The phrase "pharmaceutically acceptable excipient," as used herein, refers any ingredient other than the compounds described herein (for example, a vehicle capable of suspending or dissolving the active compound) and having the properties of being substantially nontoxic and non-inflammatory in a patient. Excipients may include, for example: antiadherents, antioxidants, binders, coatings, compression aids, disintegrates, dyes (colors), emollients, emulsifiers, fillers (diluents), film formers or coatings, flavors, fragrances, glidants (flow enhancers), lubricants, preservatives, printing inks, sorbents, suspensing or dispersing agents, sweeteners, and waters of hydration. Exemplary excipients include, but are not limited to: butylated hydroxytoluene (BHT), calcium carbonate, calcium phosphate (dibasic), calcium stearate, croscarmellose, crosslinked polyvinyl pyrrolidone, citric acid, crospovidone, cysteine, ethylcellulose, gelatin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, maltitol, mannitol, methionine, methylcellulose, methyl paraben, microcrystalline cellulose, polyethylene glycol, polyvinyl pyrrolidone, povidone, pregelatinized starch, propyl paraben, retinyl palmitate, shellac, silicon dioxide, sodium carboxymethyl cellulose, sodium citrate, sodium starch glycolate, sorbitol, starch (corn), stearic acid, sucrose, talc, titanium dioxide, vitamin A, vitamin E, vitamin C, and xylitol.

[00272] *Pharmaceutically acceptable salts*: The present disclosure also includes pharmaceutically acceptable salts of the compounds described herein. 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), each of which is incorporated herein by reference in its entirety.

[00273] *Pharmaceutically acceptable solvate*: The term "pharmaceutically acceptable solvate," as used herein, means a compound of the invention 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."

[00274] *Pharmacokinetic:* As used herein, "pharmacokinetic" refers to any one or more properties of a molecule or compound as it relates to the determination of the fate of substances administered to a living organism. Pharmacokinetics is divided into several areas including the extent and rate of absorption, distribution, metabolism and excretion. This is commonly referred to as ADME where: (A) Absorption is the process of a substance entering the blood circulation; (D) Distribution is the dispersion or dissemination of substances throughout the fluids and tissues of the body; (M) Metabolism (or Biotransformation) is the irreversible transformation of parent

compounds into daughter metabolites; and (E) Excretion (or Elimination) refers to the elimination of the substances from the body. In rare cases, some drugs irreversibly accumulate in body tissue.

[00275] *Physicochemical:* As used herein, "physicochemical" means of or relating to a physical and/or chemical property.

[00276] *Preventing*: As used herein, the term "preventing" 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.

[00277] *Prodrug*: The present disclosure also includes prodrugs of the compounds described herein. As used herein, "prodrugs" refer to any substance, molecule or entity which is in a form predicate for that substance, molecule or entity to act as a therapeutic upon chemical or physical alteration. Prodrugs may by covalently bonded or sequestered in some way and which release or are converted into the active drug moiety prior to, upon or after administered to a mammalian subject. Prodrugs can be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compounds. Prodrugs include compounds wherein hydroxyl, amino, sulfhydryl, or carboxyl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, sulfhydryl, or carboxyl group respectively. Preparation and use of prodrugs is discussed in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are hereby incorporated by reference in their entirety. In some embodiments, the pri-miRs of the invention may be prodrugs of the pre-miRs. Likewise either pri- or pre-miRs may be prodrugs of the artificial miRs which are processed from them.

[00278] *Proliferate:* As used herein, the term "proliferate" means to grow, expand or increase or cause to grow, expand or increase rapidly. "Proliferative" means having the ability to proliferate. "Anti-proliferative" means having properties counter to or inapposite to proliferative properties.

[00279] *Prophylactic*: As used herein, "prophylactic" refers to a therapeutic or course of action used to prevent the spread of disease.

[00280] *Prophylaxis:* As used herein, a "prophylaxis" refers to a measure taken to maintain health and prevent the spread of disease.

[00281] *Protein cleavage site*: As used herein, "protein cleavage site" refers to a site where controlled cleavage of the amino acid chain can be accomplished by chemical, enzymatic or photochemical means.

[00282] *Protein cleavage signal:* As used herein "protein cleavage signal" refers to at least one amino acid that flags or marks a polypeptide for cleavage.

[00283] *Protein of interest:* As used herein, the terms "proteins of interest" or "desired proteins" include those provided herein and fragments, mutants, variants, and alterations thereof.

[00284] *Proximal:* As used herein, the term "proximal" means situated nearer to the center or to a point or region of interest.

[00285] *Purified:* As used herein, "purify," "purified," "purification" means to make substantially pure or clear from unwanted components, material defilement, admixture or imperfection.

[00286] *Sample:* As used herein, the term "sample" or "biological sample" refers to a subset of its tissues, cells or component parts (e.g. body fluids, including but not limited to blood, mucus, lymphatic fluid, synovial fluid, cerebrospinal fluid, saliva, amniotic fluid, amniotic cord blood, urine, vaginal fluid and semen). A sample further may include a homogenate, lysate or extract prepared from a whole organism or a subset of its tissues, cells or component parts, or a fraction or portion thereof, including but not limited to, for example, plasma, serum, spinal fluid, lymph fluid, the external sections of the skin, respiratory, intestinal, and genitourinary tracts, tears, saliva, milk, blood cells, tumors, organs. A sample further refers to a medium, such as a nutrient broth or gel, which may contain cellular components, such as proteins or nucleic acid molecule.

[00287] *Signal Sequences:* As used herein, the phrase "signal sequences" refers to a sequence which can direct the transport or localization of a protein.

[00288] *Single unit dose*: As used herein, a "single unit dose" is a dose of any therapeutic administered in one dose/at one time/single route/single point of contact, i.e., single administration event.

[00289] *Similarity*: As used herein, the term "similarity" refers to the overall relatedness between polymeric molecules, *e.g.* between polynucleotide molecules (*e.g.* DNA molecules and/or RNA molecules) and/or between polypeptide molecules. Calculation of percent similarity of polymeric molecules to one another can be performed in the same manner as a calculation of

percent identity, except that calculation of percent similarity takes into account conservative substitutions as is understood in the art.

[00290] *Split dose*: As used herein, a "split dose" is the division of single unit dose or total daily dose into two or more doses.

[00291] *Stable:* As used herein "stable" refers to a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and preferably capable of formulation into an efficacious therapeutic agent.

[00292] *Stabilized:* As used herein, the term "stabilize", "stabilized," "stabilized region" means to make or become stable.

[00293] *Stereoisomer:* As used herein, the term "stereoisomer" refers to all possible different isomeric as well as conformational forms which a compound may possess (e.g., a compound of any formula described herein), in particular all possible stereochemically and conformationally isomeric forms, all diastereomers, enantiomers and/or conformers of the basic molecular structure. Some compounds of the present invention may exist in different tautomeric forms, all of the latter being included within the scope of the present invention.

[00294] *Subject:* As used herein, the term "subject" or "patient" refers to any organism to which a composition in accordance with the invention may be administered, *e.g.*, for experimental, diagnostic, prophylactic, and/or therapeutic purposes. Typical subjects include animals (*e.g.*, mammals such as mice, rats, rabbits, non-human primates, and humans) and/or plants.

[00295] *Substantially*: As used herein, the term "substantially" refers to the qualitative condition of exhibiting total or near-total extent or degree of a characteristic or property of interest. One of ordinary skill in the biological arts will understand that biological and chemical phenomena rarely, if ever, go to completion and/or proceed to completeness or achieve or avoid an absolute result. The term "substantially" is therefore used herein to capture the potential lack of completeness inherent in many biological and chemical phenomena.

[00296] *Substantially equal*: As used herein as it relates to time differences between doses, the term means plus/minus 2%.

[00297] *Substantially simultaneously*: As used herein and as it relates to plurality of doses, the term means within 2 seconds.

[00298] *Suffering from*: An individual who is "suffering from" a disease, disorder, and/or condition has been diagnosed with or displays one or more symptoms of a disease, disorder, and/or condition.

[00299] *Susceptible to*: An individual who is "susceptible to" a disease, disorder, and/or condition has not been diagnosed with and/or may not exhibit symptoms of the disease, disorder, and/or condition but harbors a propensity to develop a disease or its symptoms. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition (for example, cancer) may be characterized by one or more of the following: (1) a genetic mutation associated with development of the disease, disorder, and/or condition; (2) a genetic polymorphism associated with development of the disease, disorder, and/or condition; (3) increased and/or decreased expression and/or activity of a protein and/or nucleic acid associated with the disease, disorder, and/or condition; (4) habits and/or lifestyles associated with development of the disease, disorder, and/or condition; (5) a family history of the disease, disorder, and/or condition; and (6) exposure to and/or infection with a microbe associated with development of the disease, disorder, and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition will develop the disease, disorder, and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition will not develop the disease, disorder, and/or condition.

[00300] *Sustained release:* As used herein, the term "sustained release" refers to a pharmaceutical composition or compound release profile that conforms to a release rate over a specific period of time.

[00301] *Synthetic*: The term "synthetic" means produced, prepared, and/or manufactured by the hand of man. Synthesis of polynucleotides or polypeptides or other molecules of the present invention may be chemical or enzymatic.

[00302] *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, preferably a mammal, more preferably a human and most preferably a patient.

[00303] *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.

[00304] *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.

[00305] *Therapeutically effective outcome*: As used herein, the term "therapeutically effective outcome" means an outcome that is sufficient in a subject suffering from or susceptible to an infection, disease, disorder, and/or condition, to treat, improve symptoms of, diagnose, prevent, and/or delay the onset of the infection, disease, disorder, and/or condition.

[00306] *Total daily dose:* As used herein, a "total daily dose" is an amount given or prescribed in 24 hour period. It may be administered as a single unit dose.

[00307] *Transfection*: As used herein, the term "transfection" refers to methods to introduce exogenous nucleic acids into a cell. Methods of transfection include, but are not limited to, chemical methods, physical treatments and cationic lipids or mixtures.

[00308] *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.

[00309] *Unmodified*: As used herein, "unmodified" refers to any substance, compound or molecule prior to being changed in any way. Unmodified may, but does not always, refer to the wild type or native form of a biomolecule. Molecules may undergo a series of modifications whereby each modified molecule may serve as the "unmodified" starting molecule for a subsequent modification.

EQUIVALENTS AND SCOPE

[00310] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments in accordance with the invention described herein. The scope of the present invention is not intended to be limited to the above Description, but rather is as set forth in the appended claims.

[00311] In the claims, articles such as "a," "an," and "the" may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include "or" between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention 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 invention includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process.

[00312] It is also noted that the term "comprising" is intended to be open and permits but does not require the inclusion of additional elements or steps. When the term "comprising" is used herein, the term "consisting of" is thus also encompassed and disclosed.

[00313] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Methods and materials are described herein for use in the present disclosure; other, suitable methods and materials known in the art can also be used.

[00314] 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 invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[00315] In addition, it is to be understood that any particular embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of the claims. Since such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the compositions of the invention (*e.g.*, any nucleic acid or protein encoded thereby; any method of production; any method of use; *etc.*) can be excluded from any one or more claims, for any reason, whether or not related to the existence of prior art.

[00316] All cited sources, for example, references, publications, databases, database entries, and art cited herein, are incorporated into this application by reference, even if not expressly stated in the citation. In case of conflicting statements of a cited source and the instant application, the statement in the instant application shall control.

[00317] Section and table headings are not intended to be limiting.

EXAMPLES

Example 1. Design of modulatory polynucleotides (artificial pri- or pre-microRNAs)

[00318] Artificial pri- or pre-microRNAs are designed as shRNA or stem loop structures encoding an artificial miR (or artificial siRNA) having at least one strand that can at least partially hybridize with a target nucleic acid, e.g., RNA or DNA and one or more of the following features (a) UG motif at the base of basal stem, (b) a UGUG motif at the 5' end of the

miRNA loop, (c) Uridine at the 5' end of guide strand, (d) a loop structure derived from a canonical microRNA such as miR-22 (e) a CNNC at the 3' flanking sequence, (f) flanking regions from a canonical microRNA such as let-7b and/or (g) one or more bulges and mismatches as between the passenger and guide strand.

[00319] Once designed, the sequence is engineered or synthesized or inserted in a plasmid or vector and administered to a cell or organism. Suitable plasmids or vectors are any which transduce or transfect the target cell.

[00320] Adeno-associated viral vectors (AAV), viral particles or entire viruses may be used.

[00321] Administration results in the processing of the modulatory polynucleotide to generate the artificial microRNA which alters expression levels of the target nucleic acid.

[00322] Effective knockdown of a target may be determined by methods in the art and will show little if any off-target effects.

[00323] Effective passenger-guide strand duplexes of the modulatory polynucleotides, e.g., pri- or pre-microRNAs demonstrate greater than 95% guide to passenger strand ratio when processing is measured.

Example 2. Passenger-Guide strand optimization

[00324] In order to achieve target knockdown or modulation of target expression which is specific and potent, the passenger and guide strands that will form the duplex stem of the stem-loop structure of the pri- or pre-microRNA of the invention may be optimized separately, for example as siRNA (small interfering RNAs).

[00325] siRNAs are designed against a target nucleic acid of choice as canonical siRNAs having a 19 base pair central duplex with a 3' dinucleotide overhang on the 3' end of the strands of the duplex and where the antisense strand has perfect complementarity to the target nucleic acid over the 19 nucleotide region.

[00326] Alternatively, siRNAs are designed whereby the sense strand (passenger strand) comprises less than 19 nucleotide identity to the target nucleic acid.

[00327] Modifications to the sense-antisense (passenger-guide) strand duplex base pairing is made to introduce bulges or mismatches. Insertions or deletions or mismatches may be incorporated at the 5' or 3' terminus of the sense strand and these insertions or deletions may or may not be mirrored on the guide strand.

[00328] The resulting siRNA are tested by standard methods known in the art for target knockdown and other relevant physiologic and pharmacokinetic properties and for degree of off-target effects.

[00329] siRNA exhibiting sufficient target knockdown with few off target effects are then engineered, either with or without further modifications, as the passenger and guide strands of the pri- or pre-microRNAs of the invention.

Example 3. Passenger-Guide strand design for SOD1

[00330] In engineering optimal passenger and guide strands for the pri- and/or pre-microRNAs of the invention, a series of 19-mer sense strand (passenger strand) sequences were chosen from the sequence of superoxide dismutase 1 (SOD1; GenBank Reference NM_000454.4). The sequence of the SOD1 mRNA (shown as DNA) is

GTTTGGGGCCAGAGTGGGCGAGGCGCGGAGGTCTGGCCTATAAAGTAGTCGCGGAG
ACGGGGTGCTGGTTTGCGTCGTAGTCTCCTGCAGCGTCTGGGGTTTCCGTTGCAGTC
CTCGGAACCAGGACCTCGGCGTGGCCTAGCGAGTTATGGCGACGAAGGCCGTGTGC
GTGCTGAAGGGCGACGGCCCAGTGCAGGGCATCATCAATTTCGAGCAGAAGGAAAG
TAATGGACCAGTGAAGGTGTGGGGAAGCATTAAAGGACTGACTGAAGGCCTGCATG
GATTCCATGTTCATGAGTTTGGAGATAATACAGCAGGCTGTACCAGTGCAGGTCCTC
ACTTTAATCCTCTATCCAGAAAACACGGTGGGCCAAAGGATGAAGAGAGGCATGTT
GGAGACTTGGGCAATGTGACTGCTGACAAAGATGGTGTGGCCGATGTGTCTATTGA
AGATTCTGTGATCTCACTCTCAGGAGACCATTGCATCATTGGCCGCACACTGGTGGT
CCATGAAAAAGCAGATGACTTGGGCAAAGGTGGAAATGAAGAAAGTACAAAGACA
GGAAACGCTGGAAGTCGTTTGGCTTGTGGTGTAATTGGGATCGCCCAATAAACATTC
CCTTGGATGTAGTCTGAGGCCCCTTAACTCATCTGTTATCCTGCTAGCTGTAGAAAT
GTATCCTGATAAACATTAAACACTGTAATCTTAAAAGTGTAATTGTGTGACTTTTTC
AGAGTTGCTTTAAAGTACCTGTAGTGAGAAACTGATTTATGATCACTTGGAAGATTT
GTATAGTTTTATAAAACTCAGTTAAAATGTCTGTTTCAATGACCTGTATTTTGCCAGA
CTTAAATCACAGATGGGTATTAAACTTGTCAGAATTTCTTTGTCATTCAAGCCTGTG
AATAAAAACCCTGTATGGCACTTATTATGAGGCTATTAAAAGAATCCAAATTCAAAC
TAAAAAAAAAAAAAAAAAA (SEQ ID NO: 15).

[00331] The 19mers, along with the 5' most position of the sense strand are shown in Table 4 along with the antisense strand which is the reverse complement of the sense strand.

[00332] The 19mers served as the core starting sequences for the design of the siRNA to be tested.

Table 4. SOD1 19mers

Start Position of sense strand in	Sense Strand, e.g., Passenger Strand (5′-3′)	SEQ ID NO	Antisense Strand, e.g., Guide Strand (5′-3′)	SEQ ID NO

NM_000454.4				
26	CGGAGGUCUGGCCUAUAAA	16	UUUAUAGGCCAGACCUCCG	17
27	GGAGGUCUGGCCUAUAAAG	18	CUUUAUAGGCCAGACCUCC	19
28	GAGGUCUGGCCUAUAAAGU	20	ACUUUAUAGGCCAGACCUC	21
29	AGGUCUGGCCUAUAAAGUA	22	UACUUUAUAGGCCAGACCU	23
30	GGUCUGGCCUAUAAAGUAG	24	CUACUUUAUAGGCCAGACC	25
32	UCUGGCCUAUAAAGUAGUC	26	GACUACUUUAUAGGCCAGA	27
33	CUGGCCUAUAAAGUAGUCG	28	CGACUACUUUAUAGGCCAG	29
34	UGGCCUAUAAAGUAGUCGC	30	GCGACUACUUUAUAGGCCA	31
35	GGCCUAUAAAGUAGUCGCG	32	CGCGACUACUUUAUAGGCC	33
36	GCCUAUAAAGUAGUCGCGG	34	CCGCGACUACUUUAUAGGC	35
37	CCUAUAAAGUAGUCGCGGA	36	UCCGCGACUACUUUAUAGG	37
74	GUCGUAGUCUCCUGCAGCG	38	CGCUGCAGGAGACUACGAC	39
76	CGUAGUCUCCUGCAGCGUC	40	GACGCUGCAGGAGACUACG	41
77	GUAGUCUCCUGCAGCGUCU	42	AGACGCUGCAGGAGACUAC	43
78	UAGUCUCCUGCAGCGUCUG	44	CAGACGCUGCAGGAGACUA	45
149	AUGGCGACGAAGGCCGUGU	46	ACACGGCCUUCGUCGCCAU	47
153	CGACGAAGGCCGUGUGCGU	48	ACGCACACGGCCUUCGUCG	49
157	GAAGGCCGUGUGCGUGCUG	50	CAGCACGCACACGGCCUUC	51
160	GGCCGUGUGCGUGCUGAAG	52	CUUCAGCACGCACACGGCC	53
177	AGGGCGACGGCCCAGUGCA	54	UGCACUGGGCCGUCGCCCU	55
192	UGCAGGGCAUCAUCAAUUU	56	AAAUUGAUGAUGCCCUGCA	57
193	GCAGGGCAUCAUCAAUUUC	58	GAAAUUGAUGAUGCCCUGC	59
195	AGGGCAUCAUCAAUUUCGA	60	UCGAAAUUGAUGAUGCCCU	61
196	GGGCAUCAUCAAUUUCGAG	62	CUCGAAAUUGAUGAUGCCC	63
197	GGCAUCAUCAAUUUCGAGC	64	GCUCGAAAUUGAUGAUGCC	65
198	GCAUCAUCAAUUUCGAGCA	66	UGCUCGAAAUUGAUGAUGC	67
199	CAUCAUCAAUUUCGAGCAG	68	CUGCUCGAAAUUGAUGAUG	69
206	AAUUUCGAGCAGAAGGAAA	70	UUUCCUUCUGCUCGAAAUU	71
209	UUCGAGCAGAAGGAAAGUA	72	UACUUUCCUUCUGCUCGAA	73
210	UCGAGCAGAAGGAAAGUAA	74	UUACUUUCCUUCUGCUCGA	75
239	AAGGUGUGGGGAAGCAUUA	76	UAAUGCUUCCCCACACCUU	77
241	GGUGUGGGGAAGCAUUAAA	78	UUUAAUGCUUCCCCACACC	79
261	GACUGACUGAAGGCCUGCA	80	UGCAGGCCUUCAGUCAGUC	81
263	CUGACUGAAGGCCUGCAUG	82	CAUGCAGGCCUUCAGUCAG	83
264	UGACUGAAGGCCUGCAUGG	84	CCAUGCAGGCCUUCAGUCA	85
268	UGAAGGCCUGCAUGGAUUC	86	GAAUCCAUGCAGGCCUUCA	87
269	GAAGGCCUGCAUGGAUUCC	88	GGAAUCCAUGCAGGCCUUC	89
276	UGCAUGGAUUCCAUGUUCA	90	UGAACAUGGAAUCCAUGCA	91
278	CAUGGAUUCCAUGUUCAUG	92	CAUGAACAUGGAAUCCAUG	93
281	GGAUUCCAUGUUCAUGAGU	94	ACUCAUGAACAUGGAAUCC	95
284	UUCCAUGUUCAUGAGUUUG	96	CAAACUCAUGAACAUGGAA	97
290	GUUCAUGAGUUUGGAGAUA	98	UAUCUCCAAACUCAUGAAC	99
291	UUCAUGAGUUUGGAGAUAA	100	UUAUCUCCAAACUCAUGAA	101
295	UGAGUUUGGAGAUAAUACA	102	UGUAUUAUCUCCAAACUCA	103
296	GAGUUUGGAGAUAAUACAG	104	CUGUAUUAUCUCCAAACUC	105
316	AGGCUGUACCAGUGCAGGU	106	ACCUGCACUGGUACAGCCU	107

317	GGCUGUACCAGUGCAGGUC	108	GACCUGCACUGGUACAGCC	109
329	GCAGGUCCUCACUUUAAUC	110	GAUUAAAGUGAGGACCUGC	111
330	CAGGUCCUCACUUUAAUCC	112	GGAUUAAAGUGAGGACCUG	113
337	UCACUUUAAUCCUCUAUCC	114	GGAUAGAGGAUUAAAGUGA	115
350	CUAUCCAGAAAACACGGUG	116	CACCGUGUUUUCUGGAUAG	117
351	UAUCCAGAAAACACGGUGG	118	CCACCGUGUUUUCUGGAUA	119
352	AUCCAGAAAACACGGUGGG	120	CCCACCGUGUUUUCUGGAU	121
354	CCAGAAAACACGGUGGGCC	122	GGCCCACCGUGUUUUCUGG	123
357	GAAAACACGGUGGGCCAAA	124	UUUGGCCCACCGUGUUUUC	125
358	AAAACACGGUGGGCCAAAG	126	CUUUGGCCCACCGUGUUUU	127
364	CGGUGGGCCAAAGGAUGAA	128	UUCAUCCUUUGGCCCACCG	129
375	AGGAUGAAGAGAGGCAUGU	130	ACAUGCCUCUCUUCAUCCU	131
378	AUGAAGAGAGGCAUGUUGG	132	CCAACAUGCCUCUCUUCAU	133
383	GAGAGGCAUGUUGGAGACU	134	AGUCUCCAACAUGCCUCUC	135
384	AGAGGCAUGUUGGAGACUU	136	AAGUCUCCAACAUGCCUCU	137
390	AUGUUGGAGACUUGGGCAA	138	UUGCCCAAGUCUCCAACAU	139
392	GUUGGAGACUUGGGCAAUG	140	CAUUGCCCAAGUCUCCAAC	141
395	GGAGACUUGGGCAAUGUGA	142	UCACAUUGCCCAAGUCUCC	143
404	GGCAAUGUGACUGCUGACA	144	UGUCAGCAGUCACAUUGCC	145
406	CAAUGUGACUGCUGACAAA	146	UUUGUCAGCAGUCACAUUG	147
417	CUGACAAAGAUGGUGUGGC	148	GCCACACCAUCUUUGUCAG	149
418	UGACAAAGAUGGUGUGGCC	150	GGCCACACCAUCUUUGUCA	151
469	CUCAGGAGACCAUUGCAUC	152	GAUGCAAUGGUCUCCUGAG	153
470	UCAGGAGACCAUUGCAUCA	154	UGAUGCAAUGGUCUCCUGA	155
475	AGACCAUUGCAUCAUUGGC	156	GCCAAUGAUGCAAUGGUCU	157
476	GACCAUUGCAUCAUUGGCC	158	GGCCAAUGAUGCAAUGGUC	159
480	AUUGCAUCAUUGGCCGCAC	160	GUGCGGCCAAUGAUGCAAU	161
487	CAUUGGCCGCACACUGGUG	162	CACCAGUGUGCGGCCAAUG	163
494	CGCACACUGGUGGUCCAUG	164	CAUGGACCACCAGUGUGCG	165
496	CACACUGGUGGUCCAUGAA	166	UUCAUGGACCACCAGUGUG	167
497	ACACUGGUGGUCCAUGAAA	168	UUUCAUGGACCACCAGUGU	169
501	UGGUGGUCCAUGAAAAAGC	170	GCUUUUUCAUGGACCACCA	171
504	UGGUCCAUGAAAAAGCAGA	172	UCUGCUUUUUCAUGGACCA	173
515	AAAGCAGAUGACUUGGGCA	174	UGCCCAAGUCAUCUGCUUU	175
518	GCAGAUGACUUGGGCAAAG	176	CUUUGCCCAAGUCAUCUGC	177
522	AUGACUUGGGCAAAGGUGG	178	CCACCUUUGCCCAAGUCAU	179
523	UGACUUGGGCAAAGGUGGA	180	UCCACCUUUGCCCAAGUCA	181
524	GACUUGGGCAAAGGUGGAA	182	UUCCACCUUUGCCCAAGUC	183
552	GUACAAAGACAGGAAACGC	184	GCGUUUCCUGUCUUUGUAC	185
554	ACAAAGACAGGAAACGCUG	186	CAGCGUUUCCUGUCUUUGU	187
555	CAAAGACAGGAAACGCUGG	188	CCAGCGUUUCCUGUCUUUG	189
562	AGGAAACGCUGGAAGUCGU	190	ACGACUUCCAGCGUUUCCU	191
576	GUCGUUUGGCUUGUGGUGU	192	ACACCACAAGCCAAACGAC	193
577	UCGUUUGGCUUGUGGUGUA	194	UACACCACAAGCCAAACGA	195
578	CGUUUGGCUUGUGGUGUAA	196	UUACACCACAAGCCAAACG	197
579	GUUUGGCUUGUGGUGUAAU	198	AUUACACCACAAGCCAAAC	199
581	UUGGCUUGUGGUGUAAUUG	200	CAAUUACACCACAAGCCAA	201
583	GGCUUGUGGUGUAAUUGGG	202	CCCAAUUACACCACAAGCC	203
584	GCUUGUGGUGUAAUUGGGA	204	UCCCAAUUACACCACAAGC	205
585	CUUGUGGUGUAAUUGGGAU	206	AUCCCAAUUACACCACAAG	207

587	UGUGGUGUAAUUGGGAUCG	208	CGAUCCCAAUUACACCACA	209
588	GUGGUGUAAUUGGGAUCGC	210	GCGAUCCCAAUUACACCAC	211
589	UGGUGUAAUUGGGAUCGCC	212	GGCGAUCCCAAUUACACCA	213
593	GUAAUUGGGAUCGCCCAAU	214	AUUGGGCGAUCCCAAUUAC	215
594	UAAUUGGGAUCGCCCAAUA	216	UAUUGGGCGAUCCCAAUUA	217
595	AAUUGGGAUCGCCCAAUAA	218	UUAUUGGGCGAUCCCAAUU	219
596	AUUGGGAUCGCCCAAUAAA	220	UUUAUUGGGCGAUCCCAAU	221
597	UUGGGAUCGCCCAAUAAAC	222	GUUUAUUGGGCGAUCCCAA	223
598	UGGGAUCGCCCAAUAAACA	224	UGUUUAUUGGGCGAUCCCA	225
599	GGGAUCGCCCAAUAAACAU	226	AUGUUUAUUGGGCGAUCCC	227
602	AUCGCCCAAUAAACAUUCC	228	GGAAUGUUUAUUGGGCGAU	229
607	CCAAUAAACAUUCCCUUGG	230	CCAAGGGAAUGUUUAUUGG	231
608	CAAUAAACAUUCCCUUGGA	232	UCCAAGGGAAUGUUUAUUG	233
609	AAUAAACAUUCCCUUGGAU	234	AUCCAAGGGAAUGUUUAUU	235
610	AUAAACAUUCCCUUGGAUG	236	CAUCCAAGGGAAUGUUUAU	237
611	UAAACAUUCCCUUGGAUGU	238	ACAUCCAAGGGAAUGUUUA	239
612	AAACAUUCCCUUGGAUGUA	240	UACAUCCAAGGGAAUGUUU	241
613	AACAUUCCCUUGGAUGUAG	242	CUACAUCCAAGGGAAUGUU	243
616	AUUCCCUUGGAUGUAGUCU	244	AGACUACAUCCAAGGGAAU	245
621	CUUGGAUGUAGUCUGAGGC	246	GCCUCAGACUACAUCCAAG	247
633	CUGAGGCCCCUUAACUCAU	248	AUGAGUUAAGGGGCCUCAG	249
635	GAGGCCCCUUAACUCAUCU	250	AGAUGAGUUAAGGGGCCUC	251
636	AGGCCCCUUAACUCAUCUG	252	CAGAUGAGUUAAGGGGCCU	253
639	CCCCUUAACUCAUCUGUUA	254	UAACAGAUGAGUUAAGGGG	255
640	CCCUUAACUCAUCUGUUAU	256	AUAACAGAUGAGUUAAGGG	257
641	CCUUAACUCAUCUGUUAUC	258	GAUAACAGAUGAGUUAAGG	259
642	CUUAACUCAUCUGUUAUCC	260	GGAUAACAGAUGAGUUAAG	261
643	UUAACUCAUCUGUUAUCCU	262	AGGAUAACAGAUGAGUUAA	263
644	UAACUCAUCUGUUAUCCUG	264	CAGGAUAACAGAUGAGUUA	265
645	AACUCAUCUGUUAUCCUGC	266	GCAGGAUAACAGAUGAGUU	267
654	GUUAUCCUGCUAGCUGUAG	268	CUACAGCUAGCAGGAUAAC	269
660	CUGCUAGCUGUAGAAAUGU	270	ACAUUUCUACAGCUAGCAG	271
661	UGCUAGCUGUAGAAAUGUA	272	UACAUUUCUACAGCUAGCA	273
666	GCUGUAGAAAUGUAUCCUG	274	CAGGAUACAUUUCUACAGC	275
667	CUGUAGAAAUGUAUCCUGA	276	UCAGGAUACAUUUCUACAG	277
668	UGUAGAAAUGUAUCCUGAU	278	AUCAGGAUACAUUUCUACA	279
669	GUAGAAAUGUAUCCUGAUA	280	UAUCAGGAUACAUUUCUAC	281
673	AAAUGUAUCCUGAUAAACA	282	UGUUUAUCAGGAUACAUUU	283
677	GUAUCCUGAUAAACAUUAA	284	UUAAUGUUUAUCAGGAUAC	285
692	UUAAACACUGUAAUCUUAA	286	UUAAGAUUACAGUGUUUAA	287
698	ACUGUAAUCUUAAAAGUGU	288	ACACUUUUAAGAUUACAGU	289
699	CUGUAAUCUUAAAAGUGUA	290	UACACUUUUAAGAUUACAG	291
700	UGUAAUCUUAAAAGUGUAA	292	UUACACUUUUAAGAUUACA	293
701	GUAAUCUUAAAAGUGUAAU	294	AUUACACUUUUAAGAUUAC	295
706	CUUAAAAGUGUAAUUGUGU	296	ACACAAUUACACUUUUAAG	297
749	UACCUGUAGUGAGAAACUG	298	CAGUUUCUCACUACAGGUA	299
770	UUAUGAUCACUUGGAAGAU	300	AUCUUCCAAGUGAUCAUAA	301
772	AUGAUCACUUGGAAGAUUU	302	AAAUCUUCCAAGUGAUCAU	303
775	AUCACUUGGAAGAUUUGUA	304	UACAAAUCUUCCAAGUGAU	305
781	UGGAAGAUUUGUAUAGUUU	306	AAACUAUACAAAUCUUCCA	307

800	UAUAAAACUCAGUUAAAAU	308	AUUUUAACUGAGUUUUAUA	309
804	AAACUCAGUUAAAAUGUCU	310	AGACAUUUUAACUGAGUUU	311
819	GUCUGUUUCAAUGACCUGU	312	ACAGGUCAUUGAAACAGAC	313
829	AUGACCUGUAUUUUGCCAG	314	CUGGCAAAAUACAGGUCAU	315
832	ACCUGUAUUUUGCCAGACU	316	AGUCUGGCAAAAUACAGGU	317
833	CCUGUAUUUUGCCAGACUU	318	AAGUCUGGCAAAAUACAGG	319
851	UAAAUCACAGAUGGGUAUU	320	AAUACCCAUCUGUGAUUUA	321
854	AUCACAGAUGGGUAUUAAA	322	UUUAAUACCCAUCUGUGAU	323
855	UCACAGAUGGGUAUUAAAC	324	GUUUAAUACCCAUCUGUGA	325
857	ACAGAUGGGUAUUAAACUU	326	AAGUUUAAUACCCAUCUGU	327
858	CAGAUGGGUAUUAAACUUG	328	CAAGUUUAAUACCCAUCUG	329
859	AGAUGGGUAUUAAACUUGU	330	ACAAGUUUAAUACCCAUCU	331
861	AUGGGUAUUAAACUUGUCA	332	UGACAAGUUUAAUACCCAU	333
869	UAAACUUGUCAGAAUUUCU	334	AGAAAUUCUGACAAGUUUA	335
891	UCAUUCAAGCCUGUGAAUA	336	UAUUCACAGGCUUGAAUGA	337
892	CAUUCAAGCCUGUGAAUAA	338	UUAUUCACAGGCUUGAAUG	339
906	AAUAAAAACCCUGUAUGGC	340	GCCAUACAGGGUUUUUAUU	341
907	AUAAAAACCCUGUAUGGCA	342	UGCCAUACAGGGUUUUUAU	343
912	AACCCUGUAUGGCACUUAU	344	AUAAGUGCCAUACAGGGUU	345
913	ACCCUGUAUGGCACUUAUU	346	AAUAAGUGCCAUACAGGGU	347
934	GAGGCUAUUAAAAGAAUCC	348	GGAUUCUUUUAAUAGCCUC	349
944	AAAGAAUCCAAAUUCAAAC	350	GUUUGAAUUUGGAUUCUUU	351
947	GAAUCCAAAUUCAAACUAA	352	UUAGUUUGAAUUUGGAUUC	353

[00333] The core starting sense-antisense pairs of Table 4 above were then engineered as duplex siRNA. In doing so the 3' most nucleotide of the sense strand was, in all cases, changed to a cytidine (C) nucleotide leaving then only 18 nucleotides with identity to the target.

[00334] Then a dinucleotide terminus at the 3' end of each of the sense and antisense strands was added producing the duplexes of Table 5.

Table 5. siRNA duplexes to SOD1

Start	duplex ID	SS ID	sense strand sequence (5′-3′)	SEQ ID NO	AS ID	antisense strand sequence (5′-3′)	SEQ ID NO
26	D-2741	7414	CGGAGGUCUGGCC UAUAACdTdT	354	7415	UUUAUAGGCCAG ACCUCCGdTdT	355
27	D-2742	7416	GGAGGUCUGGCCU AUAAACdTdT	356	7417	UUUUAUAGGCCA GACCUCCdTdT	357
28	D-2743	7418	GAGGUCUGGCCUA UAAAGCdTdT	358	7419	UCUUUAUAGGCC AGACCUCdTdT	359
29	D-2744	7420	AGGUCUGGCCUAU AAAGUCdTdT	360	7421	UACUUUAUAGGC CAGACCUdTdT	361
30	D-2745	7422	GGUCUGGCCUAUA AAGUACdTdT	362	7423	UUACUUUAUAGG CCAGACCdTdT	363
32	D-2746	7424	UCUGGCCUAUAAA GUAGUCdTdT	364	7425	UACUACUUUAUA GGCCAGAdTdT	365
33	D-2747	7426	CUGGCCUAUAAAG UAGUCCdTdT	366	7427	UGACUACUUUAU AGGCCAGdTdT	367
34	D-2748	7428	UGGCCUAUAAAGU AGUCGCdTdT	368	7429	UCGACUACUUUA UAGGCCAdTdT	369

35	D-2749	7430	GGCCUAUAAAGUAGUCGCCdTdT	370	7431	UGCGACUACUUUAUAGGCCdTdT	371
36	D-2750	7432	GCCUAUAAAGUAGUCGCGCdTdT	372	7433	UCGCGACUACUUUAUAGGCdTdT	373
37	D-2751	7434	CCUAUAAAGUAGUCGCGGCdTdT	374	7435	UCCGCGACUACUUUAUAGGdTdT	375
74	D-2752	7436	GUCGUAGUCUCCUGCAGCCdTdT	376	7437	UGCUGCAGGAGACUACGACdTdT	377
76	D-2753	7438	CGUAGUCUCCUGCAGCGUCdTdT	378	7439	UACGCUGCAGGAGACUACGdTdT	379
77	D-2754	7440	GUAGUCUCCUGCAGCGUCCdTdT	380	7441	UGACGCUGCAGGAGACUACdTdT	381
78	D-2755	7442	UAGUCUCCUGCAGCGUCUCdTdT	382	7443	UAGACGCUGCAGGAGACUAdTdT	383
149	D-2756	7444	AUGGCGACGAAGGCCGUGCdTdT	384	7445	UCACGGCCUUCGUCGCCAUdTdT	385
153	D-2757	7446	CGACGAAGGCCGUGUGCGCdTdT	386	7447	UCGCACACGGCCUUCGUCGdTdT	387
157	D-2758	7448	GAAGGCCGUGUGCGUGCUCdTdT	388	7449	UAGCACGCACACGGCCUUCdTdT	389
160	D-2759	7450	GGCCGUGUGCGUGCUGAACdTdT	390	7451	UUUCAGCACGCACACGGCCdTdT	391
177	D-2760	7452	AGGGCGACGGCCCAGUGCCdTdT	392	7453	UGCACUGGGCCGUCGCCCUdTdT	393
192	D-2761	7454	UGCAGGGCAUCAUCAAUUCdTdT	394	7455	UAAUUGAUGAUGCCCUGCAdTdT	395
193	D-2762	7456	GCAGGGCAUCAUCAAUUUCdTdT	396	7457	UAAAUUGAUGAUGCCCUGCdTdT	397
195	D-2763	7458	AGGGCAUCAUCAAUUUCGCdTdT	398	7459	UCGAAAUUGAUGAUGCCCUdTdT	399
196	D-2764	7460	GGGCAUCAUCAAUUUCGACdTdT	400	7461	UUCGAAAUUGAUGAUGCCCdTdT	401
197	D-2765	7462	GGCAUCAUCAAUUUCGAGCdTdT	402	7463	UCUCGAAAUUGAUGAUGCCdTdT	403
198	D-2766	7464	GCAUCAUCAAUUUCGAGCCdTdT	404	7465	UGCUCGAAAUUGAUGAUGCdTdT	405
199	D-2767	7466	CAUCAUCAAUUUCGAGCACdTdT	406	7467	UUGCUCGAAAUUGAUGAUGdTdT	407
206	D-2768	7468	AAUUUCGAGCAGAAGGAACdTdT	408	7469	UUUCCUUCUGCUCGAAAUUdTdT	409
209	D-2769	7470	UUCGAGCAGAAGGAAAGUCdTdT	410	7471	UACUUUCCUUCUGCUCGAAdTdT	411
210	D-2770	7472	UCGAGCAGAAGGAAAGUACdTdT	412	7473	UUACUUUCCUUCUGCUCGAdTdT	413
239	D-2771	7474	AAGGUGUGGGGAAGCAUUCdTdT	414	7475	UAAUGCUUCCCCACACCUUdTdT	415
241	D-2772	7476	GGUGUGGGGAAGCAUUAACdTdT	416	7477	UUUAAUGCUUCCCCACACCdTdT	417
261	D-2773	7478	GACUGACUGAAGGCCUGCCdTdT	418	7479	UGCAGGCCUUCAGUCAGUCdTdT	419
263	D-2774	7480	CUGACUGAAGGCCUGCAUCdTdT	420	7481	UAUGCAGGCCUUCAGUCAGdTdT	421
264	D-2775	7482	UGACUGAAGGCCUGCAUGCdTdT	422	7483	UCAUGCAGGCCUUCAGUCAdTdT	423
268	D-2776	7484	UGAAGGCCUGCAUGGAUUCdTdT	424	7485	UAAUCCAUGCAGGCCUUCAdTdT	425
269	D-2777	7486	GAAGGCCUGCAUGGAUUCCdTdT	426	7487	UGAAUCCAUGCAGGCCUUCdTdT	427
276	D-2778	7488	UGCAUGGAUUCCAUGUUCCdTdT	428	7489	UGAACAUGGAAUCCAUGCAdTdT	429

278	D-2779	7490	CAUGGAUUCCAUGUUCAUCdTdT	430	7491	UAUGAACAUGGAAUCCAUGdTdT	431
281	D-2780	7492	GGAUUCCAUGUUCAUGAGCdTdT	432	7493	UCUCAUGAACAUGGAAUCCdTdT	433
284	D-2781	7494	UUCCAUGUUCAUGAGUUUCdTdT	434	7495	UAAACUCAUGAACAUGGAAdTdT	435
290	D-2782	7496	GUUCAUGAGUUUGGAGAUCdTdT	436	7497	UAUCUCCAAACUCAUGAACdTdT	437
291	D-2783	7498	UUCAUGAGUUUGGAGAUACdTdT	438	7499	UUAUCUCCAAACUCAUGAAdTdT	439
295	D-2784	7500	UGAGUUUGGAGAUAAUACCdTdT	440	7501	UGUAUUAUCUCCAAACUCAdTdT	441
296	D-2785	7502	GAGUUUGGAGAUAAUACACdTdT	442	7503	UUGUAUUAUCUCCAAACUCdTdT	443
316	D-2786	7504	AGGCUGUACCAGUGCAGGCdTdT	444	7505	UCCUGCACUGGUACAGCCUdTdT	445
317	D-2787	7506	GGCUGUACCAGUGCAGGUCdTdT	446	7507	UACCUGCACUGGUACAGCCdTdT	447
329	D-2788	7508	GCAGGUCCUCACUUUAAUCdTdT	448	7509	UAUUAAAGUGAGGACCUGCdTdT	449
330	D-2789	7510	CAGGUCCUCACUUUAAUCCdTdT	450	7511	UGAUUAAAGUGAGGACCUGdTdT	451
337	D-2790	7512	UCACUUUAAUCCUCUAUCCdTdT	452	7513	UGAUAGAGGAUUAAAGUGAdTdT	453
350	D-2791	7514	CUAUCCAGAAAACACGGUCdTdT	454	7515	UACCGUGUUUUCUGGAUAGdTdT	455
351	D-2792	7516	UAUCCAGAAAACACGGUGCdTdT	456	7517	UCACCGUGUUUUCUGGAUAdTdT	457
352	D-2793	7518	AUCCAGAAAACACGGUGGCdTdT	458	7519	UCCACCGUGUUUUCUGGAUdTdT	459
354	D-2794	7520	CCAGAAAACACGGUGGGCCdTdT	460	7521	UGCCCACCGUGUUUUCUGGdTdT	461
357	D-2795	7522	GAAAACACGGUGGGCCAACdTdT	462	7523	UUUGGCCCACCGUGUUUUCdTdT	463
358	D-2796	7524	AAAACACGGUGGGCCAAACdTdT	464	7525	UUUUGGCCCACCGUGUUUUdTdT	465
364	D-2797	7526	CGGUGGGCCAAAGGAUGACdTdT	466	7527	UUCAUCCUUUGGCCCACCGdTdT	467
375	D-2798	7528	AGGAUGAAGAGAGGCAUGCdTdT	468	7529	UCAUGCCUCUCUUCAUCCUdTdT	469
378	D-2799	7530	AUGAAGAGAGGCAUGUUGCdTdT	470	7531	UCAACAUGCCUCUCUUCAUdTdT	471
383	D-2800	7532	GAGAGGCAUGUUGGAGACCdTdT	472	7533	UGUCUCCAACAUGCCUCUCdTdT	473
384	D-2801	7534	AGAGGCAUGUUGGAGACUCdTdT	474	7535	UAGUCUCCAACAUGCCUCUdTdT	475
390	D-2802	7536	AUGUUGGAGACUUGGGCACdTdT	476	7537	UUGCCCAAGUCUCCAACAUdTdT	477
392	D-2803	7538	GUUGGAGACUUGGGCAAUCdTdT	478	7539	UAUUGCCCAAGUCUCCAACdTdT	479
395	D-2804	7540	GGAGACUUGGGCAAUGUGCdTdT	480	7541	UCACAUUGCCCAAGUCUCCdTdT	481
404	D-2805	7542	GGCAAUGUGACUGCUGACCdTdT	482	7543	UGUCAGCAGUCACAUUGCCdTdT	483
406	D-2806	7544	CAAUGUGACUGCUGACAACdTdT	484	7545	UUUGUCAGCAGUCACAUUGdTdT	485
417	D-2807	7546	CUGACAAAGAUGGUGUGGCdTdT	486	7547	UCCACACCAUCUUUGUCAGdTdT	487
418	D-2808	7548	UGACAAAGAUGGUGUGGCCdTdT	488	7549	UGCCACACCAUCUUUGUCAdTdT	489

469	D-2809	7550	CUCAGGAGACCAUUGCAUCdTdT	490	7551	UAUGCAAUGGUCUCCUGAGdTdT	491
470	D-2810	7552	UCAGGAGACCAUUGCAUCCdTdT	492	7553	UGAUGCAAUGGUCUCCUGAdTdT	493
475	D-2811	7554	AGACCAUUGCAUCAUUGGCdTdT	494	7555	UCCAAUGAUGCAAUGGUCUdTdT	495
476	D-2812	7556	GACCAUUGCAUCAUUGGCCdTdT	496	7557	UGCCAAUGAUGCAAUGGUCdTdT	497
480	D-2813	7558	AUUGCAUCAUUGGCCGCACdTdT	498	7559	UUGCGGCCAAUGAUGCAAUdTdT	499
487	D-2814	7560	CAUUGGCCGCACACUGGUCdTdT	500	7561	UACCAGUGUGCGGCCAAUGdTdT	501
494	D-2815	7562	CGCACACUGGUGGUCCAUCdTdT	502	7563	UAUGGACCACCAGUGUGCGdTdT	503
496	D-2816	7564	CACACUGGUGGUCCAUGACdTdT	504	7565	UUCAUGGACCACCAGUGUGdTdT	505
497	D-2817	7566	ACACUGGUGGUCCAUGAACdTdT	506	7567	UUUCAUGGACCACCAGUGUdTdT	507
501	D-2818	7568	UGGUGGUCCAUGAAAAGCdTdT	508	7569	UCUUUUUCAUGGACCACCAdTdT	509
504	D-2819	7570	UGGUCCAUGAAAAAGCAGCdTdT	510	7571	UCUGCUUUUUCAUGGACCAdTdT	511
515	D-2820	7572	AAAGCAGAUGACUUGGGCCdTdT	512	7573	UGCCCAAGUCAUCUGCUUUdTdT	513
518	D-2821	7574	GCAGAUGACUUGGGCAAACdTdT	514	7575	UUUUGCCCAAGUCAUCUGCdTdT	515
522	D-2822	7576	AUGACUUGGGCAAAGGUGCdTdT	516	7577	UCACCUUUGCCCAAGUCAUdTdT	517
523	D-2823	7578	UGACUUGGGCAAAGGUGGCdTdT	518	7579	UCCACCUUUGCCCAAGUCAdTdT	519
524	D-2824	7580	GACUUGGGCAAAGGUGGACdTdT	520	7581	UUCCACCUUUGCCCAAGUCdTdT	521
552	D-2825	7582	GUACAAAGACAGGAAACGCdTdT	522	7583	UCGUUUCCUGUCUUUGUACdTdT	523
554	D-2826	7584	ACAAAGACAGGAAACGCUCdTdT	524	7585	UAGCGUUUCCUGUCUUUGUdTdT	525
555	D-2827	7586	CAAAGACAGGAAACGCUGCdTdT	526	7587	UCAGCGUUUCCUGUCUUUGdTdT	527
562	D-2828	7588	AGGAAACGCUGGAAGUCGCdTdT	528	7589	UCGACUUCCAGCGUUUCCUdTdT	529
576	D-2829	7590	GUCGUUUGGCUUGUGGUGCdTdT	530	7591	UCACCACAAGCCAAACGACdTdT	531
577	D-2830	7592	UCGUUUGGCUUGUGGUGUCdTdT	532	7593	UACACCACAAGCCAAACGAdTdT	533
578	D-2831	7594	CGUUUGGCUUGUGGUGUACdTdT	534	7595	UUACACCACAAGCCAAACGdTdT	535
579	D-2832	7596	GUUUGGCUUGUGGUGUAACdTdT	536	7597	UUUACACCACAAGCCAAACdTdT	537
581	D-2833	7598	UUGGCUUGUGGUGUAAUUCdTdT	538	7599	UAAUUACACCACAAGCCAAdTdT	539
583	D-2834	7600	GGCUUGUGGUGUAAUUGGCdTdT	540	7601	UCCAAUUACACCACAAGCCdTdT	541
584	D-2835	7602	GCUUGUGGUGUAAUUGGGCdTdT	542	7603	UCCCAAUUACACCACAAGCdTdT	543
585	D-2836	7604	CUUGUGGUGUAAUUGGGACdTdT	544	7605	UUCCCAAUUACACCACAAGdTdT	545
587	D-2837	7606	UGUGGUGUAAUUGGGAUCCdTdT	546	7607	UGAUCCCAAUUACACCACAdTdT	547
588	D-2838	7608	GUGGUGUAAUUGGGAUCGCdTdT	548	7609	UCGAUCCCAAUUACACCACdTdT	549

589	D-2839	7610	UGGUGUAAUUGGGAUCGCCdTdT	550	7611	UGCGAUCCCAAUUACACCAdTdT	551
593	D-2840	7612	GUAAUUGGGAUCGCCCAACdTdT	552	7613	UUUGGGCGAUCCCAAUUACdTdT	553
594	D-2841	7614	UAAUUGGGAUCGCCCAAUCdTdT	554	7615	UAUUGGGCGAUCCCAAUUAdTdT	555
595	D-2842	7616	AAUUGGGAUCGCCCAAUACdTdT	556	7617	UUAUUGGGCGAUCCCAAUUdTdT	557
596	D-2843	7618	AUUGGGAUCGCCCAAUAACdTdT	558	7619	UUUAUUGGGCGAUCCCAAUdTdT	559
597	D-2844	7620	UUGGGAUCGCCCAAUAAACdTdT	560	7621	UUUUAUUGGGCGAUCCCAAdTdT	561
598	D-2845	7622	UGGGAUCGCCCAAUAAACCdTdT	562	7623	UGUUUAUUGGGCGAUCCCAdTdT	563
599	D-2846	7624	GGGAUCGCCCAAUAAACACdTdT	564	7625	UUGUUUAUUGGGCGAUCCCdTdT	565
602	D-2847	7626	AUCGCCCAAUAAACAUUCCdTdT	566	7627	UGAAUGUUUAUUGGGCGAUdTdT	567
607	D-2848	7628	CCAAUAAACAUUCCCUUGCdTdT	568	7629	UCAAGGGAAUGUUUAUUGGdTdT	569
608	D-2849	7630	CAAUAAACAUUCCCUUGGCdTdT	570	7631	UCCAAGGGAAUGUUUAUUGdTdT	571
609	D-2850	7632	AAUAAACAUUCCCUUGGACdTdT	572	7633	UUCCAAGGGAAUGUUUAUUdTdT	573
610	D-2851	7634	AUAAACAUUCCCUUGGAUCdTdT	574	7635	UAUCCAAGGGAAUGUUUAUdTdT	575
611	D-2852	7636	UAAACAUUCCCUUGGAUGCdTdT	576	7637	UCAUCCAAGGGAAUGUUUAdTdT	577
612	D-2853	7638	AAACAUUCCCUUGGAUGUCdTdT	578	7639	UACAUCCAAGGGAAUGUUUdTdT	579
613	D-2854	7640	AACAUUCCCUUGGAUGUACdTdT	580	7641	UUACAUCCAAGGGAAUGUUdTdT	581
616	D-2855	7642	AUUCCCUUGGAUGUAGUCCdTdT	582	7643	UGACUACAUCCAAGGGAAUdTdT	583
621	D-2856	7644	CUUGGAUGUAGUCUGAGGCdTdT	584	7645	UCCUCAGACUACAUCCAAGdTdT	585
633	D-2857	7646	CUGAGGCCCCUUAACUCACdTdT	586	7647	UUGAGUUAAGGGGCCUCAGdTdT	587
635	D-2858	7648	GAGGCCCCUUAACUCAUCCdTdT	588	7649	UGAUGAGUUAAGGGGCCUCdTdT	589
636	D-2859	7650	AGGCCCCUUAACUCAUCUCdTdT	590	7651	UAGAUGAGUUAAGGGGCCUdTdT	591
639	D-2860	7652	CCCCUUAACUCAUCUGUUCdTdT	592	7653	UAACAGAUGAGUUAAGGGGdTdT	593
640	D-2861	7654	CCCUUAACUCAUCUGUUACdTdT	594	7655	UUAACAGAUGAGUUAAGGGdTdT	595
641	D-2862	7656	CCUUAACUCAUCUGUUAUCdTdT	596	7657	UAUAACAGAUGAGUUAAGGdTdT	597
642	D-2863	7658	CUUAACUCAUCUGUUAUCCdTdT	598	7659	UGAUAACAGAUGAGUUAAGdTdT	599
643	D-2864	7660	UUAACUCAUCUGUUAUCCCdTdT	600	7661	UGGAUAACAGAUGAGUUAAdTdT	601
644	D-2865	7662	UAACUCAUCUGUUAUCCUCdTdT	602	7663	UAGGAUAACAGAUGAGUUAdTdT	603
645	D-2866	7664	AACUCAUCUGUUAUCCUGCdTdT	604	7665	UCAGGAUAACAGAUGAGUUdTdT	605
654	D-2867	7666	GUUAUCCUGCUAGCUGUACdTdT	606	7667	UUACAGCUAGCAGGAUAACdTdT	607
660	D-2868	7668	CUGCUAGCUGUAGAAAUGCdTdT	608	7669	UCAUUUCUACAGCUAGCAGdTdT	609

661	D-2869	7670	UGCUAGCUGUAGAAAUGUCdTdT	610	7671	UACAUUUCUACAGCUAGCAdTdT	611
666	D-2870	7672	GCUGUAGAAAUGUAUCCUCdTdT	612	7673	UAGGAUACAUUUCUACAGCdTdT	613
667	D-2871	7674	CUGUAGAAAUGUAUCCUGCdTdT	614	7675	UCAGGAUACAUUUCUACAGdTdT	615
668	D-2872	7676	UGUAGAAAUGUAUCCUGACdTdT	616	7677	UUCAGGAUACAUUUCUACAdTdT	617
669	D-2873	7678	GUAGAAAUGUAUCCUGAUCdTdT	618	7679	UAUCAGGAUACAUUUCUACdTdT	619
673	D-2874	7680	AAAUGUAUCCUGAUAAACCdTdT	620	7681	UGUUUAUCAGGAUACAUUUdTdT	621
677	D-2875	7682	GUAUCCUGAUAAACAUUACdTdT	622	7683	UUAAUGUUUAUCAGGAUACdTdT	623
692	D-2876	7684	UUAAACACUGUAAUCUUACdTdT	624	7685	UUAAGAUUACAGUGUUUAAdTdT	625
698	D-2877	7686	ACUGUAAUCUUAAAAGUGCdTdT	626	7687	UCACUUUUAAGAUUACAGUdTdT	627
699	D-2878	7688	CUGUAAUCUUAAAAGUGUCdTdT	628	7689	UACACUUUUAAGAUUACAGdTdT	629
700	D-2879	7690	UGUAAUCUUAAAAGUGUACdTdT	630	7691	UUACACUUUUAAGAUUACAdTdT	631
701	D-2880	7692	GUAAUCUUAAAAGUGUAACdTdT	632	7693	UUUACACUUUUAAGAUUACdTdT	633
706	D-2881	7694	CUUAAAAGUGUAAUUGUGCdTdT	634	7695	UCACAAUUACACUUUUAAGdTdT	635
749	D-2882	7696	UACCUGUAGUGAGAAACUCdTdT	636	7697	UAGUUUCUCACUACAGGUAdTdT	637
770	D-2883	7698	UUAUGAUCACUUGGAAGACdTdT	638	7699	UUCUUCCAAGUGAUCAUAAdTdT	639
772	D-2884	7700	AUGAUCACUUGGAAGAUUCdTdT	640	7701	UAAUCUUCCAAGUGAUCAUdTdT	641
775	D-2885	7702	AUCACUUGGAAGAUUUGUCdTdT	642	7703	UACAAAUCUUCCAAGUGAUdTdT	643
781	D-2886	7704	UGGAAGAUUUGUAUAGUUCdTdT	644	7705	UAACUAUACAAAUCUUCCAdTdT	645
800	D-2887	7706	UAUAAAACUCAGUUAAAACdTdT	646	7707	UUUUUAACUGAGUUUUAUAdTdT	647
804	D-2888	7708	AAACUCAGUUAAAAUGUCCdTdT	648	7709	UGACAUUUUAACUGAGUUUdTdT	649
819	D-2889	7710	GUCUGUUUCAAUGACCUGCdTdT	650	7711	UCAGGUCAUUGAAACAGACdTdT	651
829	D-2890	7712	AUGACCUGUAUUUUGCCACdTdT	652	7713	UUGGCAAAAUACAGGUCAUdTdT	653
832	D-2891	7714	ACCUGUAUUUUGCCAGACCdTdT	654	7715	UGUCUGGCAAAAUACAGGUdTdT	655
833	D-2892	7716	CCUGUAUUUUGCCAGACUCdTdT	656	7717	UAGUCUGGCAAAAUACAGGdTdT	657
851	D-2893	7718	UAAAUCACAGAUGGGUAUCdTdT	658	7719	UAUACCCAUCUGUGAUUUAdTdT	659
854	D-2894	7720	AUCACAGAUGGGUAUUAACdTdT	660	7721	UUUAAUACCCAUCUGUGAUdTdT	661
855	D-2895	7722	UCACAGAUGGGUAUUAAACdTdT	662	7723	UUUUAAUACCCAUCUGUGAdTdT	663
857	D-2896	7724	ACAGAUGGGUAUUAAACUCdTdT	664	7725	UAGUUUAAUACCCAUCUGUdTdT	665
858	D-2897	7726	CAGAUGGGUAUUAAACUUCdTdT	666	7727	UAAGUUUAAUACCCAUCUGdTdT	667
859	D-2898	7728	AGAUGGGUAUUAAACUUGCdTdT	668	7729	UCAAGUUUAAUACCCAUCUdTdT	669

861	D-2899	7730	AUGGGUAUUAAAC UUGUCCdTdT	670	7731	UGACAAGUUUAA UACCCAUdTdT	671
869	D-2900	7732	UAAACUUGUCAGA AUUUCCdTdT	672	7733	UGAAAUUCUGAC AAGUUUAdTdT	673
891	D-2901	7734	UCAUUCAAGCCUG UGAAUCdTdT	674	7735	UAUUCACAGGCU UGAAUGAdTdT	675
892	D-2902	7736	CAUUCAAGCCUGU GAAUACdTdT	676	7737	UUAUUCACAGGC UUGAAUGdTdT	677
906	D-2903	7738	AAUAAAAACCCUG UAUGGCdTdT	678	7739	UCCAUACAGGGU UUUUAUUdTdT	679
907	D-2904	7740	AUAAAAACCCUGU AUGGCCdTdT	680	7741	UGCCAUACAGGG UUUUUAUdTdT	681
912	D-2905	7742	AACCCUGUAUGGC ACUUACdTdT	682	7743	UUAAGUGCCAUA CAGGGUUdTdT	683
913	D-2906	7744	ACCCUGUAUGGCA CUUAUCdTdT	684	7745	UAUAAGUGCCAU ACAGGGUdTdT	685
934	D-2907	7746	GAGGCUAUUAAAA GAAUCCdTdT	686	7747	UGAUUCUUUUAA UAGCCUCdTdT	687
944	D-2908	7748	AAAGAAUCCAAAU UCAAACdTdT	688	7749	UUUUGAAUUUGG AUUCUUUdTdT	689
947	D-2909	7750	GAAUCCAAAUUCA AACUACdTdT	690	7751	UUAGUUUGAAUU UGGAUUCdTdT	691

[00335] The siRNA are then annealed and tested for SOD1 knockdown.

Example 4. Pri and pre-microRNAs targeting SOD1

[00336] The passenger-guide strand duplexes of the SOD1 siRNA found to be efficacious from the experiments in Example 3 are engineered into expression vectors and transfected into cells of the central nervous system or neuronal cell lines. Even though overhang utilized in the siRNA knockdown study is a canonical dTdT for siRNA, the overhang in the synthetic pri- or pre-miR may comprise any dinucleotide overhang.

[00337] The cells used may be primary cells or derived from induced pluripotent stem cells (iPS cells).

[00338] SOD1 knockdown is then measured and deep sequencing performed to determine the exact passenger and guide strand processed from each pri- or pre-microRNA administered in the expression vector.

[00339] A guide to passenger strand ratio is calculated to determine the efficiency of knockdown, e.g., of RNA Induced Silencing Complex (RISC) processing.

[00340] The N-terminus is sequenced to determine the cleavage site and to determine the percent homogeneous cleavage of the target. It is expected that cleavage will be higher than 90 percent.

[00341] HeLa cells are co-transfected in a parallel study to analyze in vitro knockdown of SOD1. A luciferase construct is used as a control to determine off-target effects.

[00342] Deep sequencing is again performed.

Example 5. Pri and pre-microRNAs targeting SOD1

[00343] According to the present invention, pri and pre-microRNAs were designed. These are given in Tables 6A, 6B, 7A and 7B. The sequences are described in the 5' to 3' direction and the regions of the stem-loop structure are broken out in the table in that order. In Tables 7A and 7B, the "miR" component of the name of the sequence does not necessarily correspond to the sequence numbering of miRNA genes (e.g., VOYmiR-101 is the name of the sequence and does not necessarily mean that miR-101 is part of the sequence).

Table 6A. Pre-miR sequences (5'-3')

	Pre-miR sequence (5' to 3')					
Name and Folded Energy (E)	**Passenger**	**SEQ ID NO**	**Loop**	**SEQ ID NO**	**Guide**	**SEQ ID NO**
VOYpre-001_D-2806_Starting construct (18 native nucleotides and position 19 is C; 3' terminal CC dinucleotide) E= -33.8	CAAUGU GACUGC UGACAA CCC	692	UGUGA CCUGG	5	UUUGUCA GCAGUCAC AUUGUU	693
VOYpre-002_D-2806_p19MMU (position 19 U to form mismatch) E= -34.2	CAAUGU GACUGC UGACAA UCC	694	UGUGA CCUGG	5	UUUGUCA GCAGUCAC AUUGUU	693
VOYpre-003_D-2806_p19GUpair (position 19 is G to form GU pair) E= -38.1	CAAUGU GACUGC UGACAA GCC	695	UGUGA CCUGG	5	UUUGUCA GCAGUCAC AUUGUU	693
VOYpre-004_D-2806_p19AUpair (position 19 is A to form AU pair) E= -38.1	CAAUGU GACUGC UGACAA ACC	696	UGUGA CCUGG	5	UUUGUCA GCAGUCAC AUUGUU	693
VOYpre-005_D-2806_CMM (central mismatch) E= -33.0	CAAUGU GACAGC UGACAA ACC	697	UGUGA CCUGG	5	UUUGUCA GCAGUCAC AUUGUU	693
VOYpre-006_D-2806_p19DEL (position 19 deleted) E= -34.0	CAAUGU GACUGC UGACAA CC	698	UGUGA CCUGG	5	UUUGUCA GCAGUCAC AUUGUU	693
VOYpre-007_D-2806_p19ADD (nucleotide added at position 19; addition is U; keep C and terminal CC dinucleotide) E= -32.8	CAAUGU GACUGC UGACAA UCCC	699	UGUGA CCUGG	5	UUUGUCA GCAGUCAC AUUGUU	693
VOYpre-008_D-2806_Uloop (increase U content of loop) E= -33.8	CAAUGU GACUGC UGACAA CCC	692	UGUGA UUUGG	6	UUUGUCA GCAGUCAC AUUGUU	693

VOYpre-009_D-2806_AUloop (increase AU content of loop) E= -33.8	CAAUGUGACUGCUGACAACCC	692	UAUAAUUUGG	7	UUUGUCAGCAGUCACAUUGUU	693
VOYpre-010_D-2806_mir-22-loop (swap in loop from miR-22) E= -30.0	CAAUGUGACUGCUGACAACAC	700	CCUGACCCAGU	8	UUUGUCAGCAGUCACAUUGUU	693

Table 6B. Pre-miR sequences (5'-3')

Name and Folded Energy (E)	**Guide**	**SEQ ID NO**	**Loop**	**SEQ ID NO**	**Passenger**	**SEQ ID NO**
VOYpre-011_D-2806_passenger-guide strand swap with terminal 3' C on passenger strand E= -36.1	UUUGUCAGCAGUCACAUUGUC	701	UGUGACCUGG	5	CAAUGUGACUGCUGACAAAUC	702
VOYpre-012_D-2806_ passenger-guide strand swap with terminal 3' C on passenger strand E= -35.4	UUUGUCAGCAGUCACAUUGUC	701	UGUGACCUGG	5	CAAUGUGACUGCUGACAAUUC	703
VOYpre-013_D-2806_ passenger-guide strand swap with terminal 3' C on passenger strand E= -34.7	UUUGUCAGCAGUCACAUUGAC	704	CCUGACCCAGU	8	CAAUGUGACUGCUGACAAAUC	702

Table 7A. Pri-miR sequences (5'-3')

Pri-miR construct components 5' to 3'						
Name and Folded Energy (E)	**5' Flanking SEQ ID NO**	**Passenger SEQ ID NO**	**Loop SEQ ID NO**	**Guide SEQ ID NO**	**3' Flanking SEQ ID NO**	**5' Flanking to 3' Flanking SEQ ID NO**
VOYmiR-101_pre-001 hsa-mir-155; D-2806 E= -63.7	1	692	5	693	10	747
VOYmiR-102_pre-001 Engineered; D-2806; let-7b stem E= -106.0	2	692	5	693	11	748
VOYmiR-103_pre-002 Engineered; D-2806_p19MMU; let-7b stem E= -106.4	2	694	5	693	11	749
VOYmiR-104_pre-003 Engineered; D-2806_p19GUpair; let-7b stem E= -110.3	2	695	5	693	11	750

VOYmiR-105_pre-004 Engineered; D-2806_p19AUpair; let-7b stem E= -110.3	2	696	5	693	11	751
VOYmiR-106_pre-005 Engineered; D-2806_CMM; let-7b stem E= -105.2	2	697	5	693	11	752
VOYmiR-107_pre-006 Engineered; D-2806_p19DEL; let-7b stem E= -106.2	2	698	5	693	11	753
VOYmiR-108_pre-007 Engineered; D-2806_p19ADD; let-7b stem E= -105.0	2	705	5	693	11	754
VOYmiR-109_pre-008 Engineered; D-2806_Uloop; let-7b stem E= -106.0	2	692	6	693	11	755
VOYmiR-110_pre-009 Engineered; D-2806_AUloop; let-7b stem E= -106.0	2	692	7	693	11	756
VOYmiR-111_pre-010 Engineered; D-2806_mir-22-loop; let-7b stem E= -102.2	2	700	8	693	11	757
VOYmiR-112_pre-001 Engineered; PD; D-2806; let-7b basal-stem instability E= -102.3	2	692	5	693	12	758
VOYmiR-113_pre-002 Engineered; D-2806_p19MMU; let-7b basal-stem instability E= -102.7	2	694	5	693	12	759
VOYmiR-114_pre-005 Engineered; D-2806_CMM; let-7b basal-stem instability E= -101.5	2	697	5	693	12	760

VOYmiR-115_pre-010 Engineered; D-2806_mir-22-loop; let-7b basal-stem instability E= -98.5	2	700	8	693	12	761
VOYmiR-116_pre-003 Engineered; D-2806_p19GUpair; let-7b basal-stem instability E= -110.1	2	695	5	693	12	762
VOYmiR-117_pre-001 Engineered; D-2757; let-7b stem E= -106.9	2	706	5	707	11	763
VOYmiR-118_pre-001 Engineered; D-2823; let-7b stem E= -108.7	2	708	5	709	11	764
VOYmiR-119_pre-001 Engineered; D-2866; let-7b stem	2	710	5	711	11	765
VOYmiR-127	3	692	9	693	13	766
VOYmiR-102.860	2	712	5	713	11	767
VOYmiR102.861	2	714	5	715	11	768
VOYmiR-102.866	2	716	5	711	11	769
VOYmiR-102.870	2	717	5	718	11	770
VOYmiR-102.823	2	719	5	709	11	771
VOYmiR-104.860	2	720	5	713	11	772
VOYmiR-104.861	2	721	5	715	11	773
VOYmiR-104.866	2	722	5	711	11	774
VOYmiR-104.870	2	723	5	718	11	775
VOYmiR-104.823	2	724	5	709	11	776
VOYmiR-109.860	2	712	6	713	11	777
VOYmiR-104.861	2	714	6	715	11	778
VOYmiR-104.866	2	716	6	711	11	779
VOYmiR-109.870	2	717	6	718	11	780
VOYmiR-109.823	2	719	6	709	11	781
VOYmiR-114.860	2	725	5	713	12	782
VOYmiR-114.861	2	726	5	715	12	783
VOYmiR-114.866	2	727	5	711	12	784
VOYmiR-114.870	2	728	5	718	12	785
VOYmiR-114.823	2	729	5	709	12	786
VOYmiR-116.860	2	720	5	713	12	787
VOYmiR-116.861	2	721	5	715	12	788
VOYmiR-116.866	2	730	5	711	12	789
VOYmiR-116.870	2	723	5	718	12	790
VOYmiR-116.823	2	724	5	709	12	791
VOYmiR-127.860	3	731	9	713	13	792
VOYmiR-127.861	3	714	9	715	13	793
VOYmiR-127.866	3	716	9	711	13	794
VOYmiR-127.870	3	717	9	718	13	795
VOYmiR-127.823	3	732	9	709	13	796

Table 7B. Pri-miR sequences (5'-3')

Name	5' Flanking SEQ ID NO	Guide SEQ ID NO	Loop SEQ ID NO	Passenger SEQ ID NO	3' Flanking SEQ ID NO	5' Flanking to 3' Flanking SEQ ID NO
VOYmiR-120	4	733	5	734	810	797

Example 6. Pri and pre-microRNAs targeting SOD1; in vivo study

[00344] *In vivo* studies are performed to test the efficacy of the pri- or pre-microRNA constructs of Example 5.

[00345] Table 8 outlines the experimental design variables to be explored.

[00346] The design of the modulatory nucleic acids (pri or pre-microRNA) includes a loop region derived from miR30, a stem region is derived from let7 and various combinations of passenger strands that vary in bulge, mismatch, and asymmetry regions.

Table 8. Experimental Design

Variable	Options
AAV Serotype	AAVrh10, AAV9
Species	NHP (non human primate), pig, sheep, rodent
Route of delivery	IT-lumbar,-thoracic, -cervical; CM Single site, multi-site
Vector concentration	$1x10^{13}$ vg/mL
Rate of infusion	Bolus (0.3-1 mL/min), 1 mL/hr
Duration of infusion	1-3 min, 1 hour, 10 hours
Total dose	$3x10^{13}$ vg (vector genomes)
Position of animal	Prone, upright
Catheter	Implanted, acute/adjustable
Labelling of vector	No label, MRI – Gadolinium; PET - ^{124}I or -zirconium

Example 7. pri-miRNA constructs in AAV-miRNA vectors

[00347] The passenger-guide strand duplexes of the SOD1 siRNA listed in Table 7 are engineered into AAV-miRNA expression vectors. The construct from ITR to ITR, recited 5' to 3', comprises a mutant ITR, a promoter (either a CMV, a U6 or the CB6 promoter (which includes a CMVie enhancer, a CBA promoter and an SV40 intron), the pri-miRNA construct from Table 7, a rabbit globin polyA and wildtype ITR. *In vitro* and *in vivo* studies are performed to test the efficacy of the AAV-miRNA expression vectors.

Example 8. Activity of pri-miRNA constructs in HeLa cells

[00348] Seven of the pri-miRNA constructs described in Example 7 (VOYmiR-103, VOYmiR-105, VOYmiR-108, VOYmiR-114, VOYmiR-119, VOYmiR-120, and VOYmiR-127) and a control of double stranded mCherry were transfected in HeLa to test the activity of the constructs.

A. Passenger and Guide Strand Activity

[00349] The seven pri-miRNA constructs and a control of double stranded mCherry were transfected into HeLa cells. After 48 hours the endogenous mRNA expression was evaluated. All seven of the pri-miRNA constructs showed high activity of the guide strand with 75-80% knock-down and low to no activity of the passenger strand. Guide strands of miRNA candidate vectors showed high activity, yielding 75-80% knockdown of SOD1, while passenger strands demonstrated little to no activity.

B. Activity of miRNA on SOD1

[00350] The seven pri-miRNA constructs and a control of double stranded mCherry (dsmCherry) were transfected into HeLa cells at a MOI of 1e4 vg/cell, 1e3 vg/cell, or 1e2 vg/cell. After 72 hours the endogenous mRNA expression was evaluated. All seven of the pri-miRNA constructs showed efficient knock-down at 1e3 vg/cell. Most of the pri-miRNA constructs showed high activity (75-80% knock-down) as shown in FIG. 2.

Example 9. Activity of pri-miRNA constructs

[00351] Thirty of the pri-miRNA constructs described in Example 7 (VOYmiR-102.860, VOYmiR-102.861, VOYmiR-102.866, VOYmiR-102.870, VOYmiR-102.823, VOYmiR-104.860, VOYmiR-104.861, VOYmiR-104.866, VOYmiR-104.870, VOYmiR-104.823, VOYmiR-109.860, VOYmiR-109.861, VOYmiR-109.866, VOYmiR-109.870, VOYmiR-109.823, VOYmiR-114.860, VOYmiR-114.861, VOYmiR-114.866, VOYmiR-114.870, VOYmiR-114.823, VOYmiR-116.860, VOYmiR-116.861, VOYmiR-116.866, VOYmiR-116.870, VOYmiR-116.823, VOYmiR-127.860, VOYmiR-127.861, VOYmiR-127.866, VOYmiR-127.870, VOYmiR-127.823) and a control of VOYmiR-114 and double stranded mCherry were transfected in cells to test the activity of the constructs.

A. Passenger and Guide Strand Activity in HEK293

[00352] The thirty pri-miRNA constructs and two controls were transfected into HEK293T cells. After 24 hours the endogenous mRNA expression was evaluated. Most of the pri-mRNA constructs showed high activity of the guide strand (FIG. 3) and low to no activity of the passenger strand (FIG. 4).

B. Passenger and Guide Strand Activity in HeLa

[00353] The thirty pri-miRNA constructs and two controls were transfected into HeLa cells. After 48 hours the endogenous mRNA expression was evaluated. Most of the pri-mRNA constructs showed high activity of the guide strand (FIG. 5) and low to no activity of the passenger strand (FIG. 6).

C. HeLa and HEK293 correlation

[00354] The knock-down of the thirty pri-miRNA were similar between the HeLa and HEK293 cells. The thirty pri-miRNA constructs showed knock-down for the guide strand of the constructs (See FIG. 3 and FIG. 5). Most of the guide strands of the pri-miRNA constructs showed 70-90% knock-down.

D. Capsid Selection

[00355] The top pri-miRNA constructs from the HeLa and HEK293 are packaged in AAVs and will undergo HeLa infection. To determine the best AAV to package for the constructs, mCherry packaged in either AAV2 or AAV-DJ8 was infected into HeLa cells at a MOI of 10 vg/cell, 1e2 vg/cell, 1e3 vg/cell, 1e4 vg/cell or 1e5 vg/cell and the expression was evaluated at 40 hours. AAV2 was selected as the capsid to package the top pri-miR constructs.

E. AAV2 Production

[00356] The top pri-miRNA constructs from the HeLa and HEK293 are packaged in AAV2 (1.6 kb) and a control of double stranded mCherry (dsmCherry) was also packaged. The packaged constructsunderwent Idoixanol purification prior to analysis. The AAV titer is shown in Table 9.

Table 9. AAV Titer

Construct	AAV Titer (genomes per ul)
VOYmir-102.860	5.5E+08
VOYmir-102.861	1.0E+09
VOYmir-102.823	9.1E+08
VOYmir-104.861	1.2E+09
VOYmir-104.866	8.0E+08
VOYmir-104.823	5.7E+08
VOYmir-109.860	3.1E+08
VOYmir-109.861	8.9E+08
VOYmir-109.866	6.0E+08
VOYmir-109.823	6.0E+08
VOYmir-114.860	4.7E+08
VOYmir-114.861	3.7E+08
VOYmir-114.866	1.0E+09
VOYmir-144.823	1.7E+09
VOYmir-116.860	1.0E+09
VOYmir-116.866	9.1E+08
VOYmir-127.860	1.2E+09
VOYmir-127.866	9.0E+08
dsmCherry	1.2E+09

[00357] The effect of transduction on SOD1 knock-down in HeLa cells is shown in FIG. 7. In addition, in HeLa cells, a larger MOI (1.0E+04 compared to 1.0E+05) did not show increased knock-down for every construct.

F. Activity of constructs in Human Motor Neuron Progenitors (HMNPs)

[00358] The top 18 pri-miRNA constructs as described in Example 9E and a control of mCherry were infected into human motor neuron progenitor (HMNP) cells at a MOI of 10E5.

After 48 hours the endogenous mRNA expression was evaluated. About half of the constructs gave greater than 50% silencing of SOD1 in HMNPs and 4 of those gave greater than 70% silencing (FIG. 8).

G. Construct Selection for In Vivo Studies

[00359] The top twelve pri-miRNA packaged constructs are selected which had a major effect on the target sequence and a minor effect on the cassette. These constructs packaged in AAV-rh10 capsids are formulated for injection and administered in mammals to study the *in vivo* effects of the constructs.

H. Activity in Various Cell Lines

[00360] The activity of the pri-miRNA packaged constructs was tested in HeLa, SH-SY5Y, U87MG and primary human astrocyte cells. The activity in HeLa cells ranged from 1 to 5 pM. The activity in SH-SY5Y cells ranged from 13 to 17 pM. The activity in U87MG cells was about 1 pM. The activity in primary human astrocyte cells ranged from 49 to 123 pM.

Example 10. *In Vitro* Study of Pri-miRNAs

[00361] The 18 pri-miRNAs and mCherry control described in Example 9D packaged in AAV2 were used for this study. For this study, HEK293T cells (Fisher Scientific, Cat.# HCL4517) in culture medium (500 ml of DMEM/F-12 GLUTAMAX™ supplement (Life Technologies, Cat#. 10565-018), 50 ml FBS (Life Technologies, Cat#. 16000-044, lot:1347556), 5 ml MEM Non-essential amino acids solution (100x) (Cat.# 11140-050) and 5 ml HEPES (1M) (Life Technologies, Cat#. 15630-080)), U251MG cells (P18) (Sigma, Cat#. 09063001-1VL) in culture medium (500 ml of DMEM/F-12 GLUTAMAX™ supplement (Life Technologies, Cat#. 10565-018), 50 ml FBS (Life Technologies, Cat#. 16000-044, lot:1347556), 5 ml MEM Non-essential amino acids solution (100x) (Cat.# 11140-050) and 5 ml HEPES (1M) (Life Technologies, Cat#. 15630-080)) or normal human astrocyte (HA) (Lonza, Cat#CC-2565) in culture medium (ABM Basal Medium 500 ml (Lonza, Cat#. CC-3186) supplemented with AGM SingleQuot Kit Suppl. & Growth Factors (Lonza, Cat#. CC-4123)) were used to test the constructs. HEK293T cells (5x10E4 cells/well in 96 well plate), U251MG cells (2x10E4 cells/well in 96 well plate) and HA cells (2x10E4 cells/well in 96 well plate) were seeded and the MOI used for infection of cells was 1.0E+05. After 48 hours the cells were analyzed and the results are shown in Table 10.

Table 10. Relative SOD1 mRNA level

Construct	Relative SOD1 mRNA Level (%) (Normalized to GAPDH)		
	HEK293T	U251MG	HA
VOYmiR-102.823	19.5	49.6	87.3
VOYmiR-102.860	1.7	5.3	19.2

VOYmiR-102.861	1.1	13.9	42.6
VOYmiR-104.823	49.9	69.6	102.7
VOYmiR-104.861	1.0	10.7	36.3
VOYmiR-104.866	12.3	54.6	85.5
VOYmiR-109.823	23.0	46.1	84.6
VOYmiR-109.860	1.9	8.3	35.6
VOYmiR-109.861	1.9	22.7	57.3
VOYmiR-109.866	4.1	38.5	67.9
VOYmiR-114.823	19.3	44.7	82.3
VOYmiR-114.860	1.4	4.7	17.6
VOYmiR-114.861	1.1	9.7	48.1
VOYmiR-114.866	4.0	38.7	78.2
VOYmiR-116.860	1.1	4.8	15.8
VOYmiR-116.866	5.5	40.2	73.7
VOYmiR-127.860	1.0	2.1	7.4
VOYmiR-127.866	1.0	15.4	43.8
mCherry	100.0	100.2	100.1

[00362] Greater than 80% knock-down was seen in the HEK293T cells for most constructs. More than half of the constructs showed greater than 80% knock-down in the U251MG cells and in the HA cells.

Example 11. Dose Dependent SOD1 Lowering

[00363] Four of the top 18 pri-miRNA constructs as described in Example 9E and a control of mCherry were transfected into a human astrocyte cell line (U251MG) or a primary human astrocyte (HA) at an MOI of 1.0E+02, 1.0E+03, 1.0E+04, 1.0E+05 or 1.0E+06. After 48 hours the endogenous mRNA expression and the dose-dependent silencing was evaluated and are shown in FIG. 9 (U251MG) and FIG. 10 (HA). For all constructs, the increase in dose also correlated to an increase in the amount of SOD1 mRNA that was knocked-down.

Example 12. Time Course of SOD1 Knock-Down

[00364] Two pri-miRNA constructs (VOYmiR-120 and VOYmiR-122), a negative control and a positive control of SOD1 siRNA were transfected into a human astrocyte cell line (U251MG). The relative SOD1 mRNA was determined for 60 hours as shown in FIG. 11. 70-75% knock-down of hSOD1 was seen for both pri-miR constructs after Nucleofector transfection, with the greatest knock-down seen in the 12-24 hour window.

Example 13. SOD1 Knock-Down and Stand Percentages

[00365] VOYmiR-104 was transfected into HeLa cells at concentrations of 50pM, 100 pM and 150 pM and compared to untreated (UT) cells. The relative SOD1 mRNA, the percent of the guide strand and the percent of the passenger strand was determined at 36, 72, 108 and 144 hours as shown in FIGs. 12A-12C. The highest concentration (150pM) showed the greatest reduction in expression, but all three doses showed a significant reduction in the expression of SOD1.

Example 14. Pri-miRNAs targeting SOD1

[00366] Pri-miRNAs were designed for Dog SOD1 and the constructs are given in Table 11. Dog SOD1 is 100% conserved with human in the region targeted in the present invention. The sequences are described in the 5' to 3' direction and the regions of the stem-loop structure are broken out in the table in that order. In Table 11, the "miR" component of the name of the sequence does not necessarily correspond to the sequence numbering of miRNA genes (e.g., dVOYmiR-102 is the name of the sequence and does not necessarily mean that miR-102 is part of the sequence).

Table 11. Dog Pri-miR sequences (5'-3')

Pri-miR construct components 5' to 3'						
Name	**5' Flanking SEQ ID NO**	**Passenger SEQ ID NO**	**Loop SEQ ID NO**	**Guide SEQ ID NO**	**3' Flanking SEQ ID NO**	**5' Flanking to 3' Flanking SEQ ID NO**
dVOYmiR-102.788	2	735	5	736	11	798
dVOYmiR-102.805	2	737	5	738	11	799
dVOYmiR-104.788	2	739	5	736	11	800
dVOYmiR-104.805	2	740	5	738	11	801
dVOYmiR-109.788	2	741	6	736	11	802
dVOYmiR-109.805	2	742	6	738	11	803
dVOYmiR-114.788	2	743	5	736	12	804
dVOYmiR-114.805	2	744	5	738	12	805
dVOYmiR-116.788	2	741	5	736	12	806
dVOYmiR-116.805	2	742	5	738	12	807
dVoymiR-127.788	3	741	9	745	14	808
dVoymiR-127.805	3	742	9	746	14	809

Example 15. Effect of the Position of Modulatory Polynucleotides

A. Effect on viral titers

[00367] A modulatory polynucleotide (VOYmiR-114 or VOYmiR-126) was inserted into an expression vector (genome size approximately 2400 nucleotides; scAAV) at six different locations as shown in FIG. 13. In FIG. 13, "ITR" is the inverted terminal repeat, "I" represents intron, "P" is the polyA and "MP" is the modulatory polynucleotide. The viral titers were evaluated using TaqMan PCR for the 6 position and for a control (construct without a modulatory polynucleotide; scAAV) and the results are shown in Table 12.

Table 12. Viral Titers

Modulatory Polynucleotide	Modulatory Polynucleotide Position	Virus Titer (VG per 15-cm dish)
VOYmiR-114	Position 1	5.5E+10
VOYmiR-114	Position 2	5.5E+10
VOYmiR-114	Position 3	4.5E+10
VOYmiR-114	Position 4	3.7E+10
VOYmiR-114	Position 5	6.5E+10
VOYmiR-114	Position 6	2.5E+10
VOYmiR-126	Position 1	1.6E+10
VOYmiR-126	Position 2	3.2E+10
VOYmiR-126	Position 3	6.0E+10
VOYmiR-126	Position 4	1.6E+10
VOYmiR-126	Position 5	9.5E+09
VOYmiR-126	Position 6	6.0E+10
-	Control	2.1E+11

B. Effect on genome integrity

[00368] A modulatory polynucleotide (VOYmiR-114) was inserted into an expression vector (genome size 2400 nucleotides; scAAV) at six different locations and a control without a modulatory polynucleotide (scAAV) as shown in FIG. 13. In FIG. 13, "ITR" is the inverted terminal repeat, "I" represents intron, "P" is the polyA and "MP" is the modulatory polynucleotide. Viral genomes were extracted from purified AAV preparations and run on a neutral agarose gel. Truncated genomes were seen in all constructs and the approximate percent of the truncated genomes (percent of the total) is shown in Table 13.

Table 13. Truncated Genomes

Construct	% of total
Position 1	50
Position 2	42
Position 3	49
Position 4	34
Position 5	33
Position 6	59
Control	9

[00369] Position 6 had the greatest number of truncated genomes with Position 4 and 5 having the least amount of truncated genomes.

C. Effect on knock-down efficiency

[00370] A modulatory polynucleotide (VOYmiR-114) was inserted into an expression vector (AAV2) (genome size 2400 nucleotides; scAAV) at six different locations as shown in FIG. 13. In FIG. 13, "ITR" is the inverted terminal repeat, "I" represents intron, "P" is the polyA and "MP" is the modulatory polynucleotide. Transduction of HeLa cells was conducted at 1 x 10^4

vg/cell, 1 x 10^3 vg/cell and 1 x 10^2 vg/cell. The SOD1 mRNA expression (as % of control (eGFP)) was determined 72 hours post-infection and the results are shown in Table 14.

Table 14. SOD1 Expression

Construct	SOD1 mRNA expression (% of control)		
	1 x 10^4 vg/cell	1 x 10^3 vg/cell	1 x 10^2 vg/cell
Position 1	40	59	69
Position 2	31	46	75
Position 3	50	66	81
Position 4	21	34	55
Position 5	49	52	67
Position 6	31	37	62
Control (eGFP)	100	100	94

[00371] Position 3 had the highest SOD1 mRNA expression (as % of control) and Position 4 had the lowest SOD1 mRNA expression (as % of control).

Example 16. Effect of Genome Size

A. Effect on viral titers

[00372] A modulatory polynucleotide (VOYmiR-114) was inserted into an expression vector (genome size 2 kb; scAAV) at positions 1, 2, 5 and 6 as shown in FIG. 13. In FIG. 13, "ITR" is the inverted terminal repeat, "I" represents intron, "P" is the polyA and "MP" is the modulatory polynucleotide. A double stranded control without a modulatory polynucleotide (genome size 1.6 kb; scAAV ctrl) and a double stranded expression vector (scAAV miR114; ITR (105 nucleotide) – Promoter (~900 nucleotides)-modulatory polynucleotide (158 nucleotides)- polyA sequence (127 nucleotides) and ITR) was compared as well as a control (eGFP; scAAV) with no modulatory polynucleotide. The viral titers were evaluated using TaqMan PCR and the results are shown in Table 15.

Table 15. Viral Titers

Construct	Size	Virus Titer (VG per 15-cm dish)
Position 1	2 kb	9.5E+10
Position 2	2 kb	1.2E+11
scAAV miR114	1.6 kb	1.1E+11
Position 5	2 kb	2.4E+10
Position 6	2 kb	1.1E+11
Control	2 kb	2.2E+11

[00373] The lowest viral titers were seen with the position 5 construct and the greatest was with the position 2 construct.

B. Effect on genome integrity

[00374] A modulatory polynucleotide (VOYmiR-114) was inserted into an expression vector (genome size 2 kb; scAAV) at positions 1, 2, 5 and 6 as shown in FIG. 13. In FIG. 13, "ITR" is the inverted terminal repeat, "I" represents intron, "P" is the polyA and "MP" is the modulatory

polynucleotide. A double stranded control without a modulatory polynucleotide (genome size 1.6 kb; scAAV ctrl) and a double stranded expression vector (scAAV miR114; ITR (105 nucleotide) – Promoter (~900 nucleotides)-modulatory polynucleotide (158 nucleotides)- polyA sequence (127 nucleotides) and ITR) was compared as well as a control (eGFP; scAAV) with no modulatory polynucleotide. Truncated genomes were seen in all constructs and the approximate percent of the truncated genomes (percent of the total) is shown in Table 16.

Table 16. Truncated Genomes

Construct	Size	% of total
Position 1	2 kb	34
Position 2	2 kb	30
scAAV miR114	1.6 kb	20
Position 5	2 kb	21
Position 6	2 kb	46
Control	2 kb	5

[00375] All constructs were determined to have some truncated genomes.

[00376] An additional study was conducted to determine the effect of different modulatory polynucleotides. VOYmiR-114 and VOYmiR-126 were inserted into separate expression vectors (genome size 1.6 kb; scAAV) with the modulatory polynucleotide near the 3' ITR (forward orientation). For the VOYmiR-114 construct the distance between the 5' end of the vector genome (1526 nucleotides) and the center of the modulatory polynucleotide (middle of the flexible loop) is 1115 nucleotides. For the VOYmiR-126 construct the distance between the 5' end of the vector genome (1626 nucleotides) and the center of the modulatory polynucleotide (middle of the flexible loop) is 1164 nucleotides.

[00377] For the VOYmiR-114 construct, the viral titer (VG per 15-cm dish) was about 1.1E+11. For the VOYmiR-126 construct, the intron probe viral titer (VG per 15-cm dish) was about 1.2E+12. The control was about 2.1E+11 (VG per 15-cm dish). VOYmir-114 had about 20% truncated genomes, VOYmiR-126 has about 15% truncated genomes and the control had about 5% truncated genomes.

Example 17. Effect of Single Stranded Constructs

A. Effect on viral titers

[00378] A modulatory polynucleotide (VOYmiR-114) was inserted into an expression vector (genome size 4.7 kb; ssAAV) at positions 1, 3 and 5 as shown in FIG. 13 and there was a control also tested without a modulatory polynucleotide (genome size 2 kb; ssAAV). In FIG. 13, "ITR" is the inverted terminal repeat, "I" represents intron, "P" is the polyA and "MP" is the modulatory polynucleotide. The viral titers were evaluated using TaqMan PCR and the results are shown in Table 17.

Table 17. Viral Titers

Construct	Virus Titer (VG per 15-cm dish)
Position 1	5.0E+11
Position 3	7.5E+11
Position 5	3.5E+11
Control	2.5E+11

[00379] Position 3 showed the greatest viral titers followed by position 1 and then position 5.

B. Effect on genome integrity

[00380] A modulatory polynucleotide (VOYmiR-114) was inserted into an expression vector (genome size 4.7 kb; ssAAV) at positions 1, 3 and 5 as shown in FIG. 13 and there was a control also tested without a modulatory polynucleotide (genome size 2 kb; ssAAV). In FIG. 13, "ITR" is the inverted terminal repeat, "I" represents intron, "P" is the polyA and "MP" is the modulatory polynucleotide. Viral genomes were extracted from purified AAV preparations and run on a neutral agarose gel. Truncated genomes were seen in all constructs and the approximate percent of the truncated genomes (percent of the total) is shown in Table 18.

Table 18. Truncated Genomes

Construct	% of total
Position 1	48
Position 3	30
Position 5	72
Control	0

[00381] Position 5 had the greatest number of truncated genomes with Position 3 having the least amount of truncated genomes.

C. Effect on knock-down efficiency

[00382] A modulatory polynucleotide (VOYmiR-114) was inserted into an expression vector (genome size 4.7 kb; ssAAV) at positions 1, 3 and 5 as shown in FIG. 13 and there was a single stranded control without a modulatory polynucleotide (genome size 2 kb; ssAAV ctrl), a double stranded control without a modulatory polynucleotide (genome size 1.6 kb; scAAV ctrl) and a double stranded expression vector (scAAV miR114; ITR (105 nucleotide) – Promoter (~900 nucleotides)-modulatory polynucleotide (158 nucleotides)- polyA sequence (127 nucleotides) and ITR). In FIG. 13, "ITR" is the inverted terminal repeat, "I" represents intron, "P" is the polyA and "MP" is the modulatory polynucleotide. Transduction of HeLa cells was conducted at 1 x 10^4 vg/cell, 1 x 10^3 vg/cell and 1 x 10^2 vg/cell. The SOD1 mRNA expression (as % of control (eGFP)) was determined 72 hours post-infection and the results are shown in Table 19.

Table 19. SOD1 Expression

Construct	SOD1 mRNA expression (% of control)

	1 x 10^4 vg/cell	1 x 10^3 vg/cell	1 x 10^2 vg/cell
Position 1	62	85	87
Position 3	77	93	99
Position 5	59	82	84
ssAAV ctrl	100	101	108
scAAV ctrl	95	97	102
scAAV miR114	23	33	62

[00383] Position 3 had the highest SOD1 mRNA expression (as % of control), then position 1 and the single stranded constructs with the lowest SOD1 mRNA expression (as % of control) was Position 5. None of the single stranded constructs had knock-down efficiency that was as low as the double stranded control with a modulatory polynucleotide.

Example 18. SOD1 Knock-Down *in vivo*

[00384] To evaluate the *in vivo* biological activity of pri-miRNAs, self-complementary pri-miRNAs (VOYmiR-114.806, VOYmiR127.806, VOYmiR102.860, VOYmiR109.860, VOYmiR114.860, VOYmiR116.860, VOYmiR127.860, VOYmiR102.861, VOYmiR104.861, VOYmiR109.861, VOYmiR114.861, VOYmiR109.866, VOYmiR116.866, or VOYmiR127.866) are packaged in AAV-DJ with a CBA promoter.

[00385] In mice, these packaged pri-miRNAs or a control of vehicle only (phosphate-buffered saline with 5% sorbitol and 0.001% F-68) were administered by a 10 minute intrastriatal infusion. Female or male Tg(SOD1)3Cje/J mice (Jackson Laboratory, Bar Harbor, ME), which express human SOD1, and of approximately 20-30 g body weight, receive unilateral injections of 5 uL test article which is targeted to the striatum (anteroposterior +0.5 mm, mediolateral + 2 mm, relative to bregma; dorsoventral 3.8 mm, relative to skull surface). Test articles are injected (5 animals per test article) at 0.5 uL/min. using pre-filled, pump-regulated Hamilton micro-syringes (1701 model, 10 µl) with 33 gauge needles. At 1, 2, 3, 4 or 6 weeks following the injection, animals are sacrificed, brains are removed, and ipsilateral striata encompassing the infusion site from a 1 mm coronal slab, as well as striatal tissue from the adjacent 1 mm coronal slabs are dissected and flash frozen. Mouse tissue samples are lysed, and human SOD1 protein levels, and SOD1 and mouse GAPDH (mGAPDH) mRNA levels are quantified. SOD1 protein levels are quantified by ELISA (eBioscience (Affymetrix, San Diego, CA)), and total protein levels are quantified by BCA analysis (ThermoFisher Scientific, Waltham, MA). For each tissue sample, the level of SOD1 protein normalized to total protein is calculated as an average of 2 determinations. These normalized SOD1 protein levels are further normalized to the vehicle group, then averaged to obtain a group (treatment) average. SOD1 and mGAPDH mRNA levels are quantified by qRT-PCR. For each tissue sample, the ratio of SOD1/mGAPDH (normalized SOD1 mRNA level) is calculated as an average of 3 determinations. These ratios are then

averaged to obtain a group (treatment) average. These group averages are further normalized to the vehicle group.

[00386] In non-human primates, test articles ($1 \times 10^{13} - 3 \times 10^{13}$vg of pri-miRNA packaged in AAV-DJ with a CBA promoter) or vehicle are administered by intrathecal lumbar bolus. Female cynomolgus monkeys (Macaca fascicularis, CR Research Model Houston, Houston, TX) of approximately 2.5-8.5 kg body weight, receive implanted single intrathecal catheters with the tip of the catheter located at the lumbar spine. Test articles are administered (4 animals per test article) comprising three 1 mL bolus injections (1 mL/minute), at approximately 60 minute intervals. At 4 to 6 weeks following the administration, animals are sacrificed, and selected tissues harvested for bioanalytical and histological evaluation. SOD1 protein and mRNA levels are assessed for suppression after treatment with pri-miRNA packaged in AAV-DJ with a CBA promoter, relative to the vehicle group.

Example 19. SOD1 Knock-Down *in vivo* using VOYmiR-114.806

[00387] In Tg(SOD1)3Cje/J mice, VOYmiR-114.806 packaged in AAVDJ with a CBA promoter is administered as described in Example 18. The mice were administered by unilateral intrastriatal administration a dose of 3.7×10^9 vg. After 1 or 2 weeks, there was no significant reduction in normalized SOD1 protein levels; normalized SOD1 protein levels were 98±11% (standard deviation) and 98±10% of the vehicle control group after 1 and 2 weeks, respectively. By week 3, VOYmiR-114.806 reduced the normalized SOD1 protein level to 84±9.0% of the vehicle control group, which was statistically significant ($p<0.05$, One-way ANOVA with Dunnett's post-hoc analysis). By weeks 4 and 6, VOYmiR-114.806 reduced the normalized SOD1 protein level to 73±7.9% ($p < 0.0001$) and 75±7.4% ($p<0.0001$), respectively, of the vehicle control group. These results demonstrate that VOYmiR-114.806 packaged in AAV-DJ with a CBA promoter, is efficacious *in vivo* in down-modulating SOD1 protein levels. In addition, these results demonstrate that a total intrastriatal dose as low as 3.7×10^9 vg of VOYmiR-114.806 packaged in AAVDJ with a CBA promoter resulted in significant down-modulation of SOD1 protein levels.

[00388] While the present invention has been described at some length and with some particularity with respect to the several described embodiments, it is not intended that it should be limited to any such particulars or embodiments or any particular embodiment, but it is to be construed with references to the appended claims so as to provide the broadest possible interpretation of such claims in view of the prior art and, therefore, to effectively encompass the intended scope of the invention.

[00389] All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, section headings, the materials, methods, and examples are illustrative only and not intended to be limiting.

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

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

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CLAIMS

1. A modulatory polynucleotide comprising

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

(i) a 5' stem arm, said 5' stem arm comprising a passenger strand and a 5' spacer sequence located 5' to said passenger strand;

(ii) a loop region between 4-20 nucleotides in length;

(iii) a 3' stem arm, said 3' stem arm comprising a guide strand and a 3' spacer sequence located 3' to said guide strand;

(b) a first flanking region located 5' to said passenger strand, said first flanking region comprising said 5' spacer sequence and a 5' flanking sequence; and

(c) a second flanking region located 3' to said guide strand, said second flanking region comprising said 3' spacer region and a 3' flanking sequence, and wherein said second flanking region comprises a nucleotide sequence which has at least 90% identity to SEQ ID NO: 11.

2. A modulatory polynucleotide comprising

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

(i) a 5' stem arm, wherein said 5' stem arm comprises a guide strand and a 5' spacer sequence located 5' to said guide strand;

(ii) a loop region between 4-20 nucleotides in length;

(iii) a 3' stem arm, wherein said 3' stem arm comprises a passenger strand and a 3' spacer sequence located 3' to said passenger strand;

(b) a first flanking region located 5' to said guide strand, said first flanking region comprising said 5' spacer sequence and a 5' flanking sequence; and

(c) a second flanking region located 3' to said passenger strand, said second flanking region comprising said 3' spacer region and a 3' flanking sequence, and wherein said second flanking region comprises a nucleotide sequence which has at least 90% identity to SEQ ID NO: 11.

3. The modulatory polynucleotide of any one of claims 1-2, wherein the first flanking region comprises a nucleotide sequence which has at least 90% identity to SEQ ID NO: 2.

4. The modulatory polynucleotide of any one of claims 1-2, wherein the first flanking region comprises a nucleotide sequence which has at least 95% identity to SEQ ID NO: 2.

5. The modulatory polynucleotide of any one of claims 1-4, wherein the second flanking region comprises a nucleotide sequence which has at least 95% identity to SEQ ID NO: 11.

6. The modulatory polynucleotide of any one of claims 1-4, wherein the second flanking region comprises the nucleotide sequence of SEQ ID NO: 11.

7. A modulatory polynucleotide comprising

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

(i) a 5' stem arm, wherein said 5' stem arm comprises a passenger strand and a 5' spacer sequence located 5' to said passenger strand;

(ii) a loop region between 4-20 nucleotides in length;

(iii) a 3' stem arm, wherein said 3' stem arm comprises a guide strand and a 3' spacer sequence located 3' to said guide strand;

(b) a first flanking region located 5' to said passenger strand, said first flanking region comprising said 5' spacer sequence and a 5' flanking sequence, and wherein said first flanking region comprises a nucleotide sequence which has at least 85% identity to SEQ ID NO: 2; and

(c) a second flanking region located 3' to said guide strand, said second flanking region comprising said 3' spacer region and a 3' flanking sequence.

8. A modulatory polynucleotide comprising

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

(i) a 5' stem arm, wherein said 5' stem arm comprises a guide strand and a 5' spacer sequence located 5' to said guide strand;

(ii) a loop region between 4-20 nucleotides in length;

(iii) a 3' stem arm, wherein said 3' stem arm comprises a passenger strand and a 3' spacer sequence located 3' to said passenger strand;

(b) a first flanking region located 5' to said guide strand, said first flanking region comprising said 5' spacer sequence and a 5' flanking sequence, and wherein said first flanking region comprises a nucleotide sequence which has at least 85% identity to SEQ ID NO: 2; and

(c) a second flanking region located 3' to said passenger strand, said second flanking region comprising said 3' spacer region and a 3' flanking sequence.

9. The modulatory polynucleotide of any one of claims 7-8, wherein the first flanking region comprises a nucleotide sequence which has at least 90% identity to SEQ ID NO: 2.

10. The modulatory polynucleotide of any one of claims 7-8, wherein the first flanking region comprises a nucleotide sequence which has at least 95% identity to SEQ ID NO: 2.

11. The modulatory polynucleotide of any one of claims 7-8, wherein the first flanking region comprises the nucleotide sequence of SEQ ID NO: 2.

12. The modulatory polynucleotide of any one of claims 1-11, wherein the modulatory polynucleotide is an artificial pri-miRNA.

13. The modulatory polynucleotide of any one of claims 1-12, wherein the guide strand comprises a microRNA seed sequence at positions 2-7, 2-8 or 2-9.

14. The modulatory polynucleotide of any one of claims 1-13, wherein the guide strand is between 15-30 nucleotides in length.

15. The modulatory polynucleotide of claim 14, wherein the passenger strand is at least 70% complementary to the guide strand.

16. The modulatory polynucleotide of any one of claims 1-15, wherein the guide strand is between 21-25 nucleotides in length.

17. The modulatory polynucleotide of claim 16, wherein the guide strand is 22 nucleotides in length.

18. The modulatory polynucleotide of claim 16, wherein the guide strand is 21 nucleotides in length.

19. The modulatory polynucleotide of any one of claims 1-18, wherein the guide strand is at least 70% complementary to a target RNA.

20. The modulatory polynucleotide of claim 19, wherein the target RNA is a mammalian coding mRNA in a neurologic cell, tissue or organ.

21. The modulatory polynucleotide of any one of claims 1-20, wherein the passenger strand is between 15-30 nucleotides in length; wherein the 5' spacer sequence is between 8-20 nucleotides in length; wherein the guide strand is between 15-30 nucleotides in length; and wherein the 3' spacer sequence is between 8-20 nucleotides in length.

22. An adeno-associated virus (AAV) vector genome encoding the modulatory polynucleotide of any one of claims 1-21.

23. A recombinant adeno-associated virus (AAV) comprising the AAV vector genome of claim 22 and an AAV capsid.

24. The recombinant AAV of claim 23, comprising a capsid selected from AAV1, AAV9, and AAVrh10.

25. The recombinant AAV of claim 23, comprising an AAV1 capsid.

FIG. 1

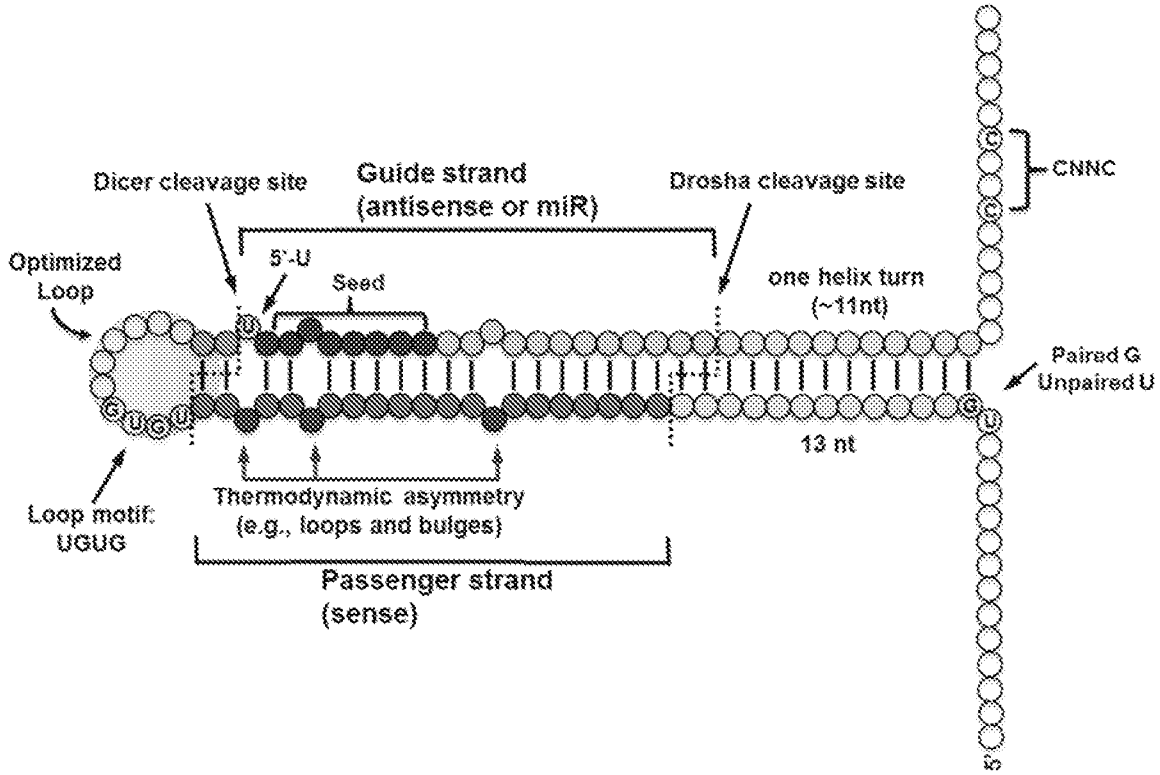

Dicer cleavage site
Guide strand
(antisense or miR)
Drosha cleavage site
CNNC
Optimized
Loop
5'-U
Seed
one helix turn
(~11nt)
Paired G
Unpaired U
13 nt
Loop motif:
UGUG
Thermodynamic asymmetry
(e.g., loops and bulges)
Passenger strand
(sense)
5'

FIG. 2

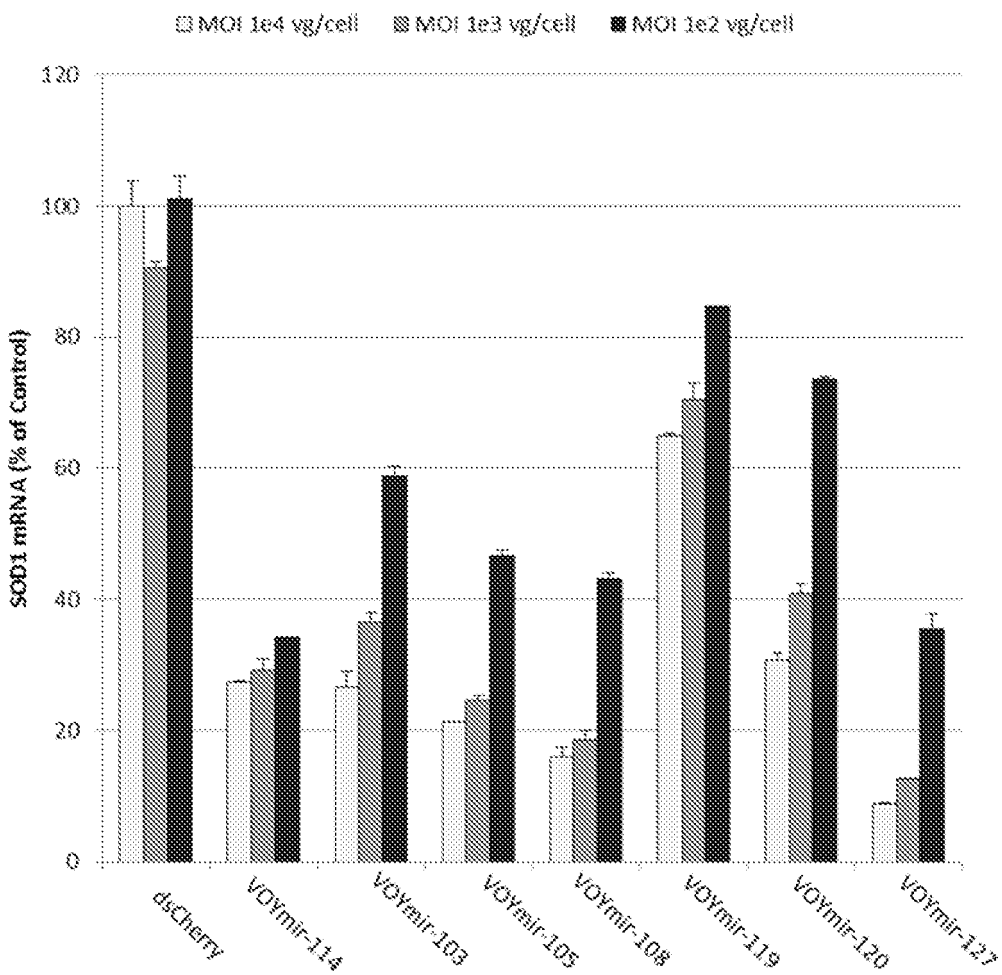

MOI 1e4 vg/cell
MOI 1e3 vg/cell
MOI 1e2 vg/cell
SOD1 mRNA (% of Control)
120
100
80
60
40
20
0
dsCherry
VOYmir-114
VOYmir-103
VOYmir-105
VOYmir-108
VOYmir-119
VOYmir-120
VOYmir-127

FIG. 3

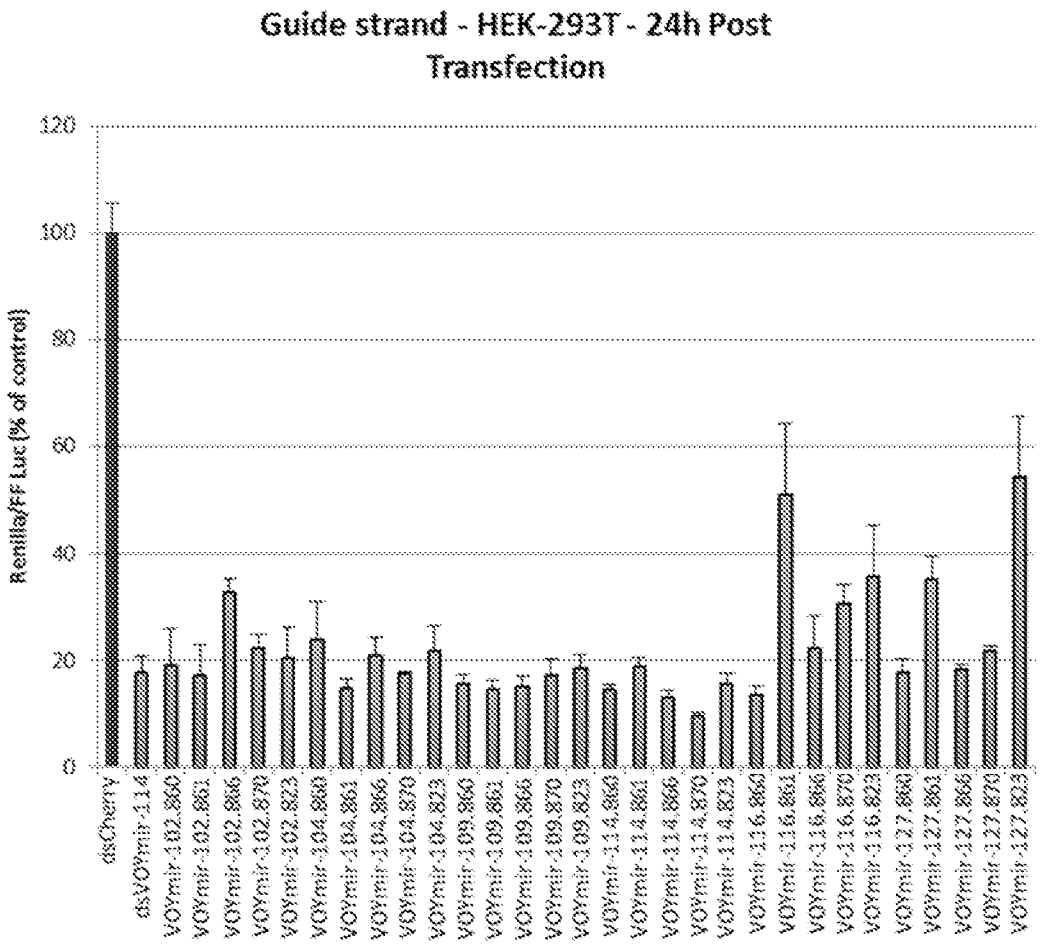

Guide strand - HEK-293T - 24h Post Transfection
Renilla/FF Luc (% of control)
120
100
80
60
40
20
0
dsCherry
dsVOYmir-114
VOYmir-102.860
VOYmir-102.861
VOYmir-102.866
VOYmir-102.870
VOYmir-102.823
VOYmir-104.880
VOYmir-104.861
VOYmir-104.866
VOYmir-104.870
VOYmir-104.823
VOYmir-109.856
VOYmir-109.861
VOYmir-109.866
VOYmir-109.870
VOYmir-109.823
VOYmir-114.865
VOYmir-114.861
VOYmir-114.866
VOYmir-114.870
VOYmir-114.823
VOYmir-116.865
VOYmir-116.861
VOYmir-116.866
VOYmir-116.870
VOYmir-116.823
VOYmir-127.860
VOYmir-127.863
VOYmir-127.866
VOYmir-127.870
VOYmir-127.823

FIG. 4

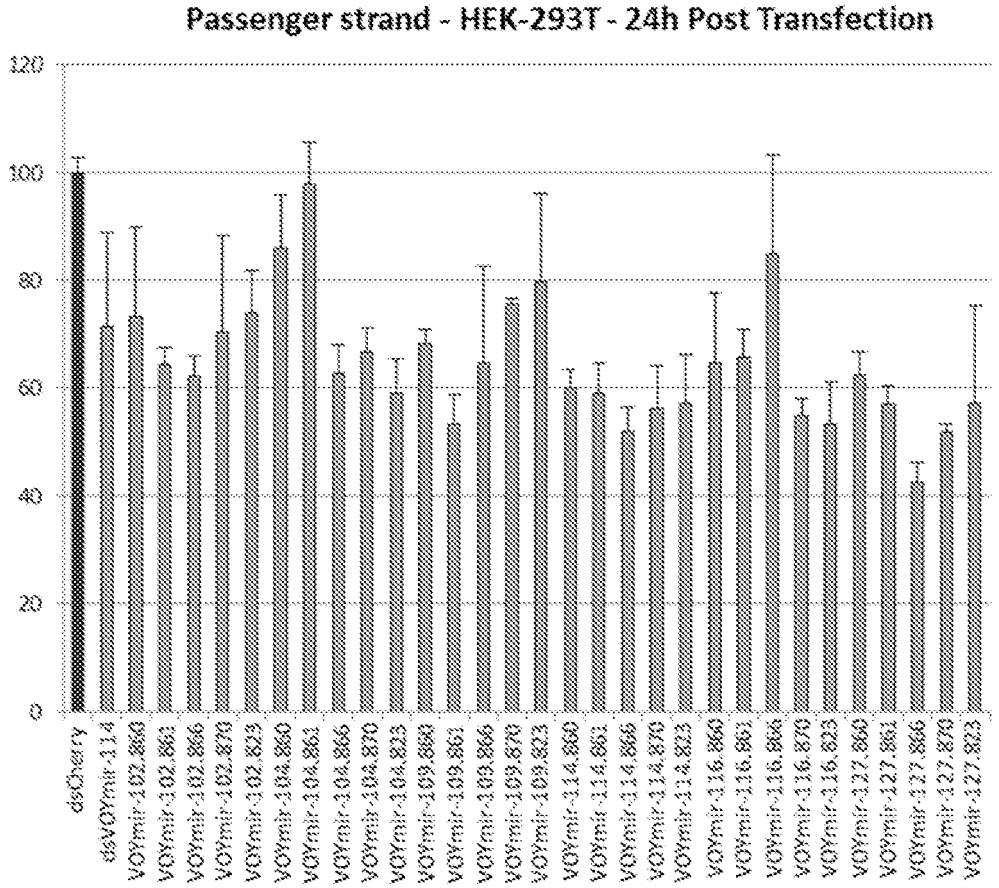

Passenger strand - HEK-293T - 24h Post Transfection
120
100
80
60
40
20
0
dsCherry
dsVOYmir-114
VOYmir-102.860
VOYmir-102.861
VOYmir-102.866
VOYmir-102.870
VOYmir-102.823
VOYmir-104.860
VOYmir-104.861
VOYmir-104.866
VOYmir-104.870
VOYmir-104.823
VOYmir-109.860
VOYmir-109.861
VOYmir-109.866
VOYmir-109.870
VOYmir-109.823
VOYmir-114.860
VOYmir-114.861
VOYmir-114.866
VOYmir-114.870
VOYmir-114.823
VOYmir-116.860
VOYmir-116.861
VOYmir-116.866
VOYmir-116.870
VOYmir-116.823
VOYmir-127.860
VOYmir-127.861
VOYmir-127.866
VOYmir-127.870
VOYmir-127.823

FIG. 5

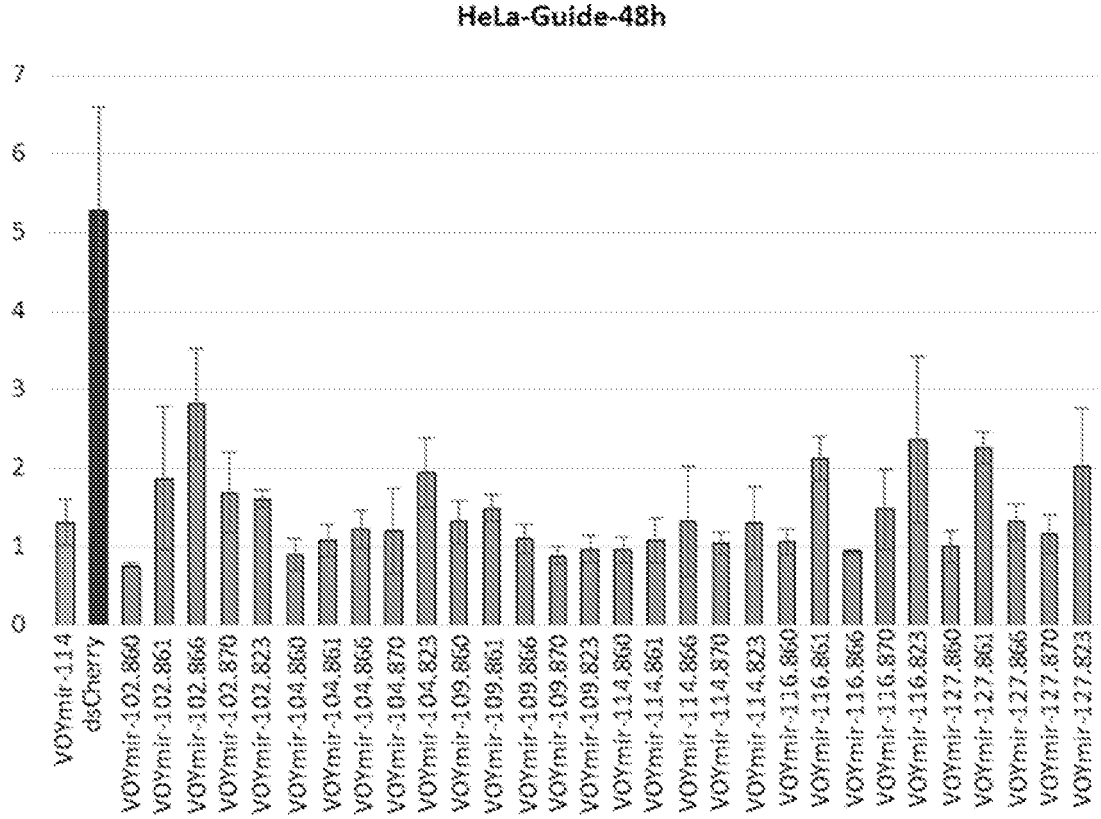

HeLa-Guide-48h
7
6
5
4
3
2
1
0
VOYmir-114
dsCherry
VOYmir-102.860
VOYmir-102.861
VOYmir-102.866
VOYmir-102.870
VOYmir-102.823
VOYmir-104.860
VOYmir-104.861
VOYmir-104.866
VOYmir-104.870
VOYmir-104.823
VOYmir-109.860
VOYmir-109.861
VOYmir-109.866
VOYmir-109.870
VOYmir-109.823
VOYmir-114.860
VOYmir-114.861
VOYmir-114.866
VOYmir-114.870
VOYmir-114.823
VOYmir-116.860
VOYmir-116.861
VOYmir-116.866
VOYmir-116.870
VOYmir-116.823
VOYmir-127.860
VOYmir-127.861
VOYmir-127.866
VOYmir-127.870
VOYmir-127.823

FIG. 6

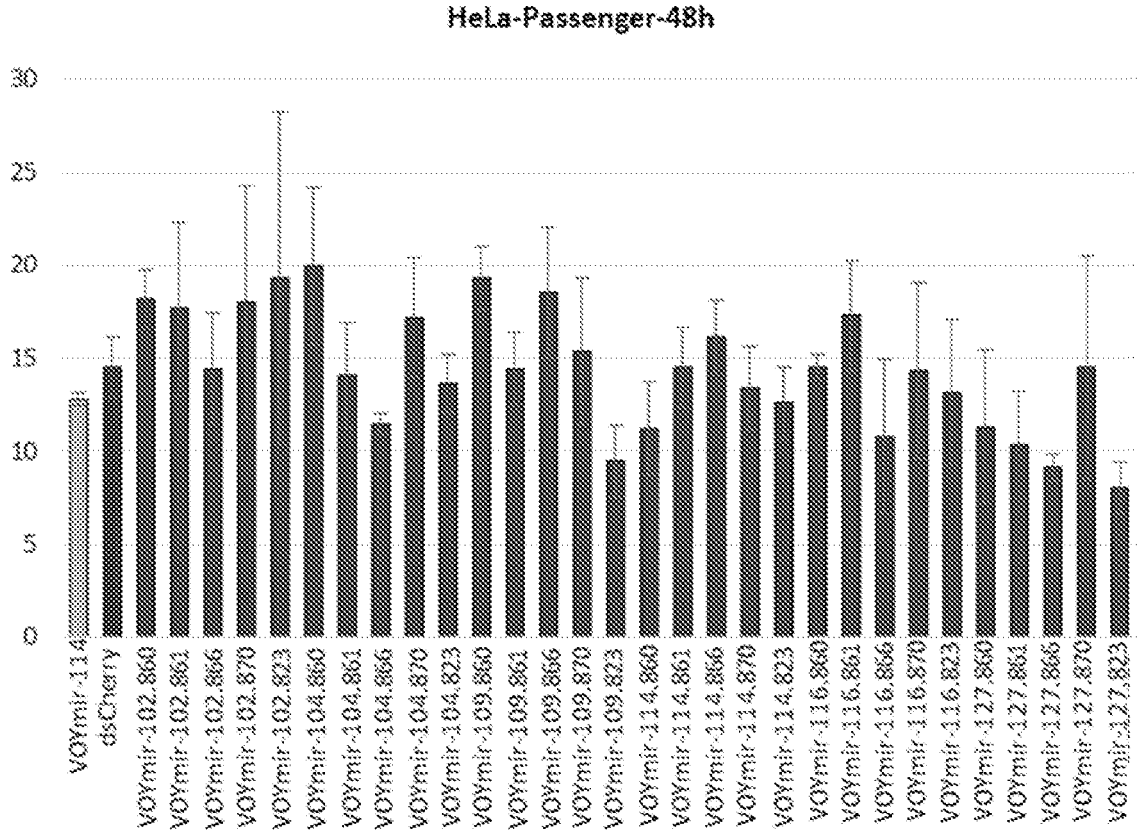

HeLa-Passenger-48h
30
25
20
15
10
5
0
VOYmir-114
dsCherry
VOYmir-102.860
VOYmir-102.861
VOYmir-102.866
VOYmir-102.870
VOYmir-102.823
VOYmir-104.860
VOYmir-104.861
VOYmir-104.866
VOYmir-104.870
VOYmir-104.823
VOYmir-109.860
VOYmir-109.861
VOYmir-109.866
VOYmir-109.870
VOYmir-109.823
VOYmir-114.860
VOYmir-114.861
VOYmir-114.866
VOYmir-114.870
VOYmir-114.823
VOYmir-116.860
VOYmir-116.861
VOYmir-116.866
VOYmir-116.870
VOYmir-116.823
VOYmir-127.860
VOYmir-127.861
VOYmir-127.866
VOYmir-127.870
VOYmir-127.823

FIG. 7

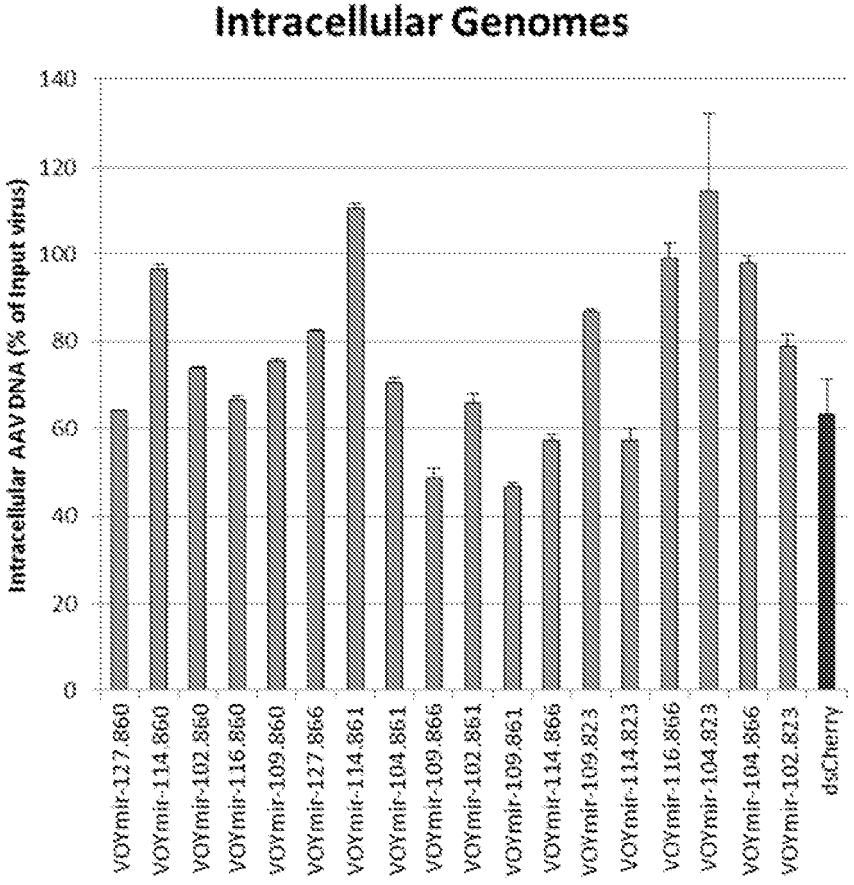

Intracellular Genomes
Intracellular AAV DNA (% of input virus)
140
120
100
80
60
40
20
0
VOYmir-127.860
VOYmir-114.860
VOYmir-102.860
VOYmir-116.860
VOYmir-109.860
VOYmir-127.866
VOYmir-114.861
VOYmir-104.861
VOYmir-109.866
VOYmir-102.861
VOYmir-109.861
VOYmir-114.866
VOYmir-109.823
VOYmir-114.823
VOYmir-116.866
VOYmir-104.823
VOYmir-104.866
VOYmir-102.823
dsCherry

FIG. 8

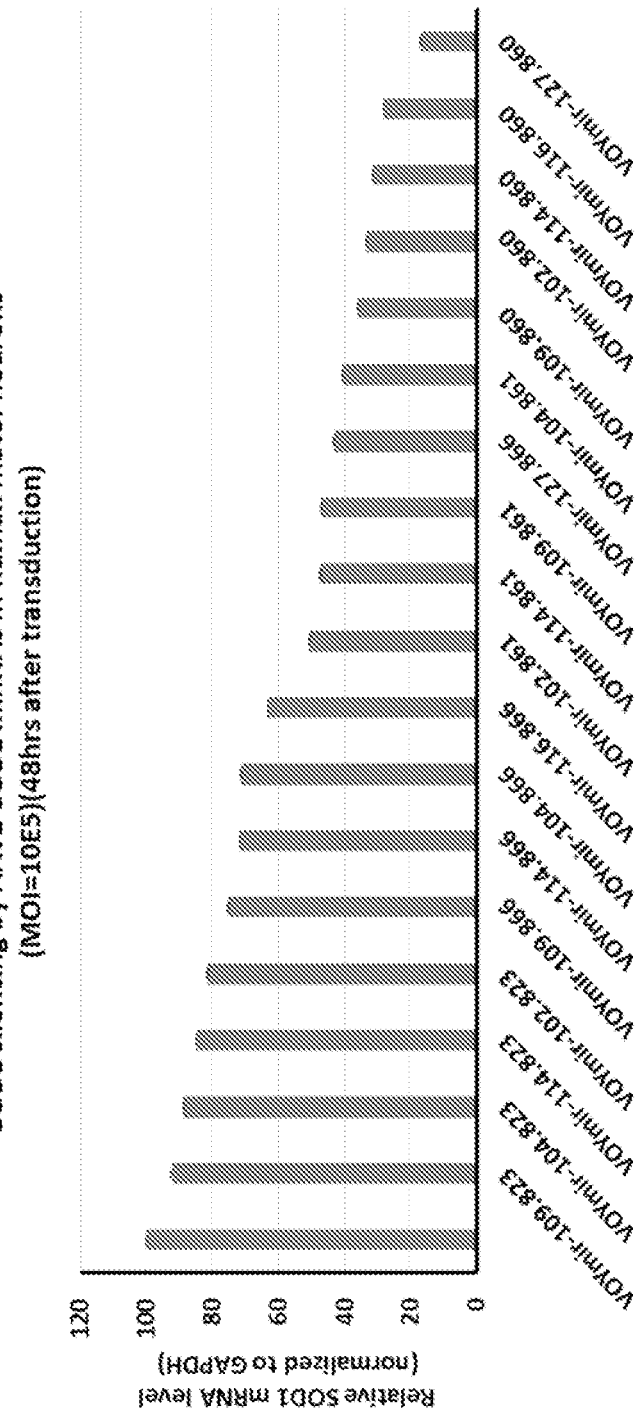

SOD1 silencing by AAV2-SOD1 miRNAs in human motor neurons
(MOI=10E5)(48hrs after transduction)
Relative SOD1 mRNA level
(normalized to GAPDH)
120
100
80
60
40
20
0
VOVmir-109.823
VOVmir-104.823
VOVmir-114.823
VOVmir-102.823
VOVmir-109.866
VOVmir-114.866
VOVmir-104.866
VOVmir-116.866
VOVmir-102.861
VOVmir-114.861
VOVmir-109.861
VOVmir-127.866
VOVmir-104.861
VOVmir-109.860
VOVmir-102.860
VOVmir-114.860
VOVmir-116.860
VOVmir-127.860

FIG. 9

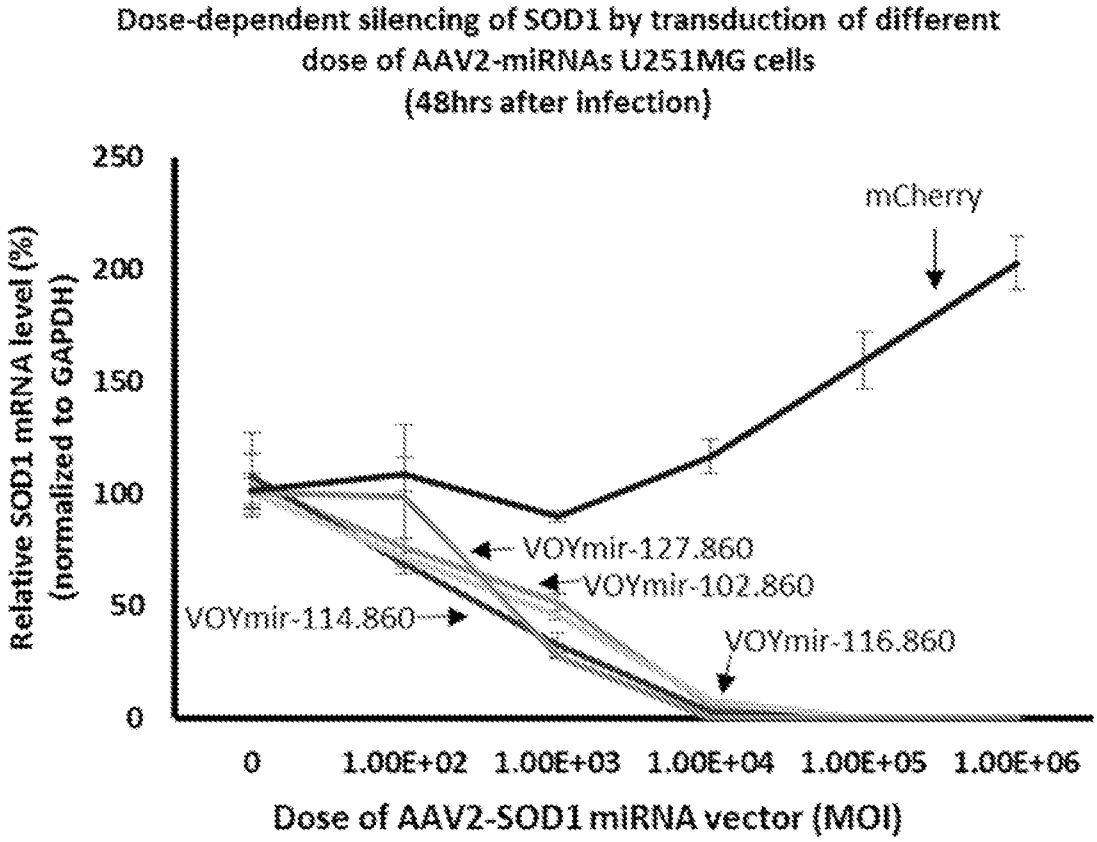

Dose-dependent silencing of SOD1 by transduction of different dose of AAV2-miRNAs U251MG cells (48hrs after infection)
Relative SOD1 mRNA level (%) (normalized to GAPDH)
250
200
150
100
50
0
mCherry
VOYmir-127.860
VOYmir-102.860
VOYmir-114.860
VOYmir-116.860
0
1.00E+02
1.00E+03
1.00E+04
1.00E+05
1.00E+06
Dose of AAV2-SOD1 miRNA vector (MOI)

FIG. 10

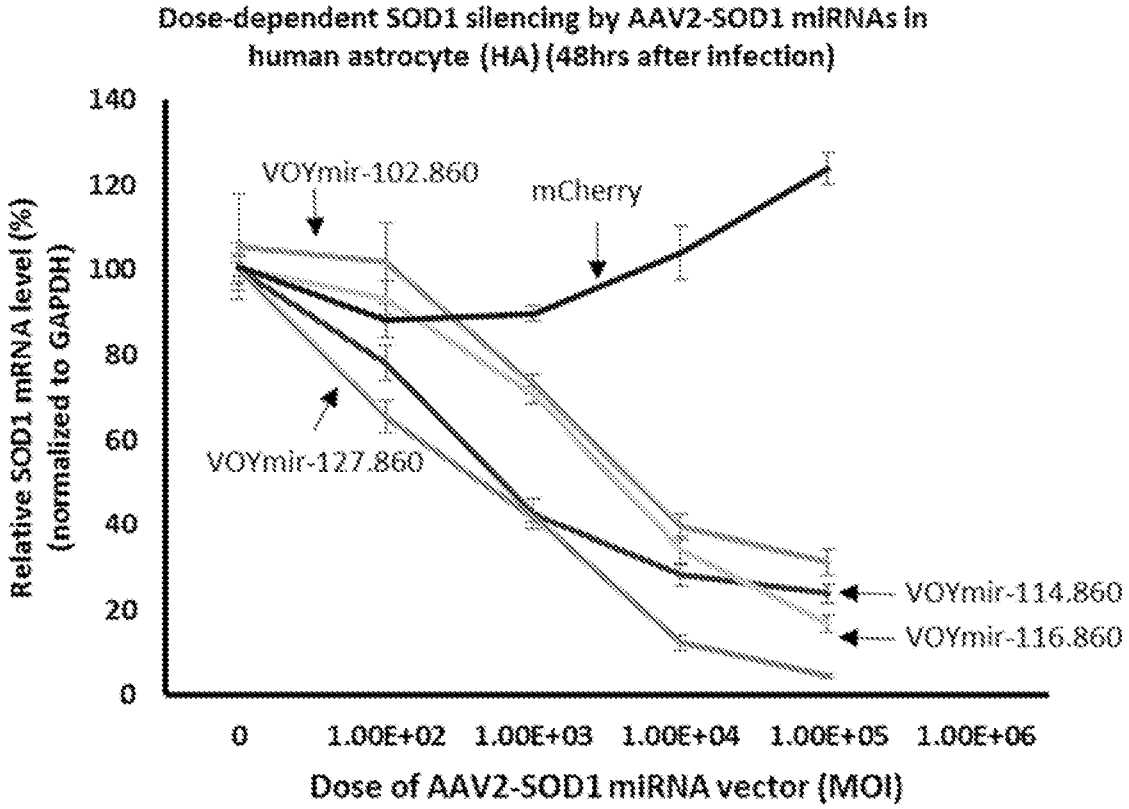

Dose-dependent SOD1 silencing by AAV2-SOD1 miRNAs in human astrocyte (HA) (48hrs after infection)
Relative SOD1 mRNA level (%) (normalized to GAPDH)
140
120
100
80
60
40
20
0
VOYmir-102.860
mCherry
VOYmir-127.860
VOYmir-114.860
VOYmir-116.860
0
1.00E+02
1.00E+03
1.00E+04
1.00E+05
1.00E+06
Dose of AAV2-SOD1 miRNA vector (MOI)

FIG. 11

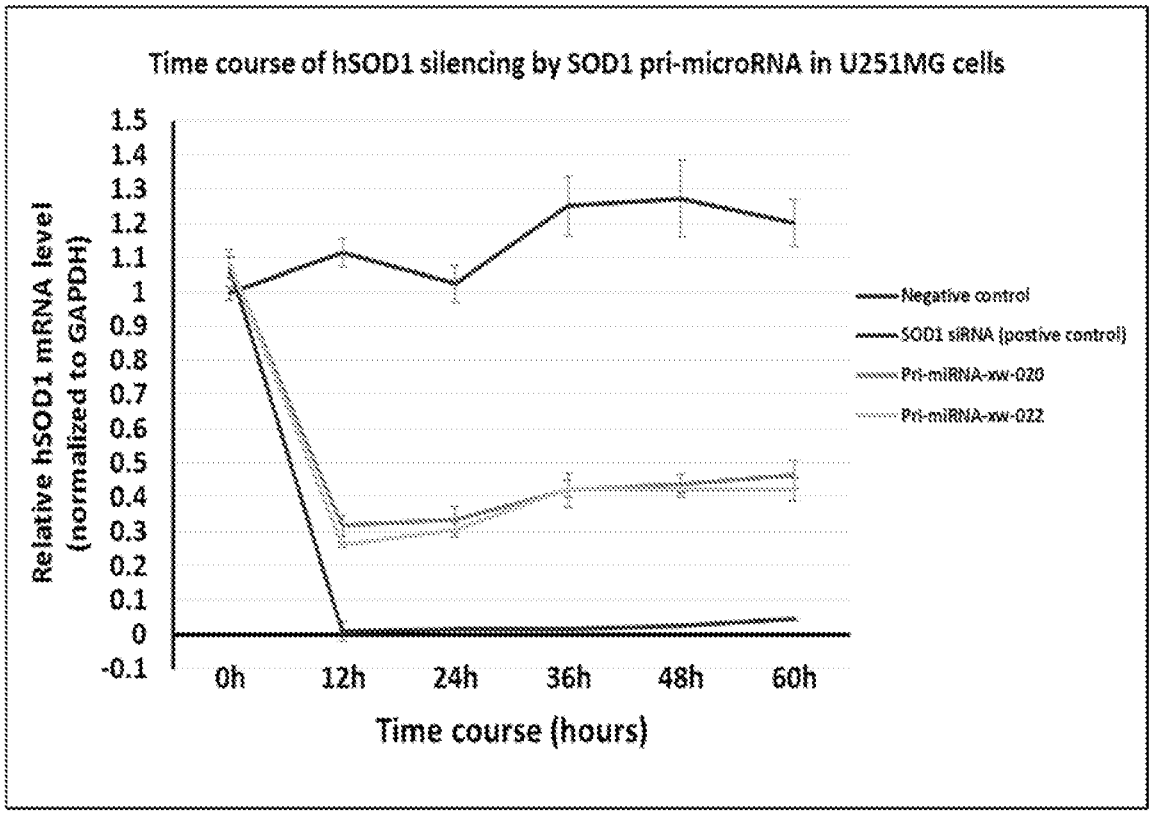

Time course of hSOD1 silencing by SOD1 pri-microRNA in U251MG cells
Relative hSOD1 mRNA level (normalized to GAPDH)
1.5
1.4
1.3
1.2
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
0h
12h
24h
36h
48h
60h
Time course (hours)
Negative control
SOD1 siRNA (postive control)
Pri-miRNA-sw-020
Pri-miRNA-sw-022

FIG. 12A

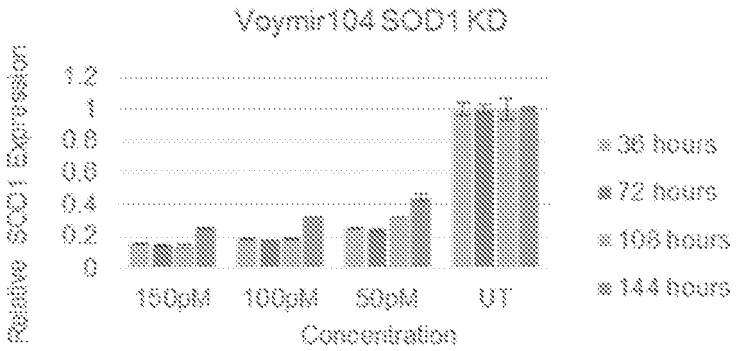


FIG. 12B

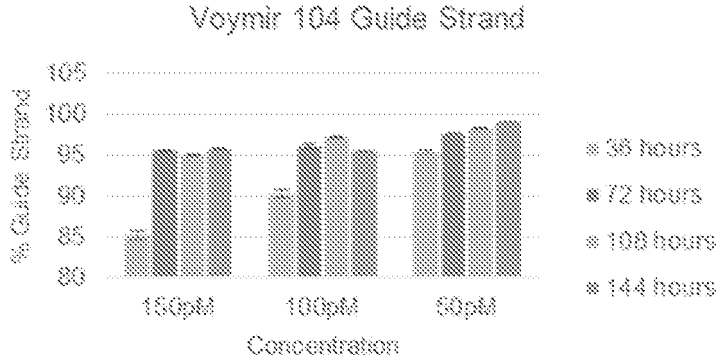


FIG. 12C

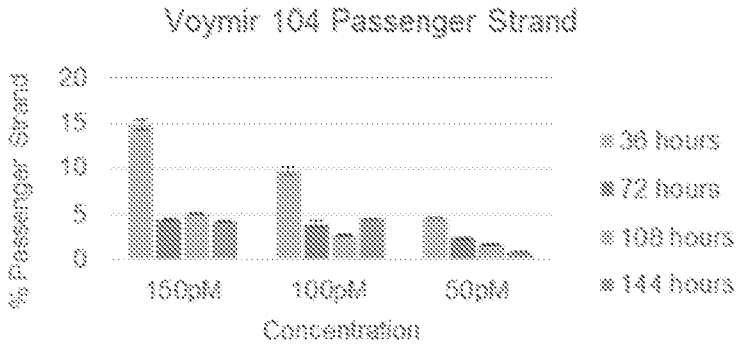
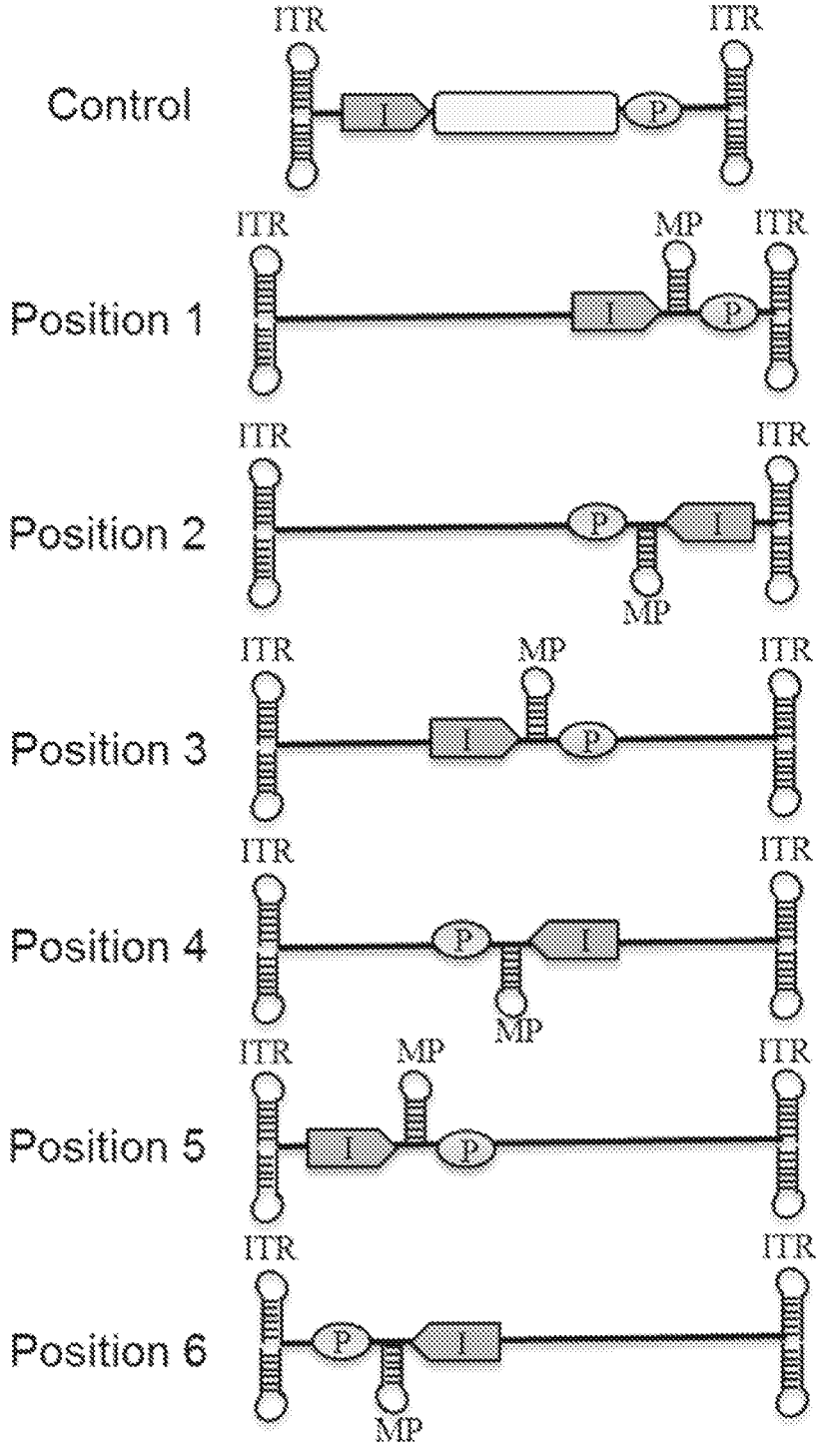


FIG. 13


Control
ITR
I
P
ITR
Position 1
ITR
MP
ITR
Position 2
ITR
Position 3
Position 4
Position 5
Position 6

SEQUENCE LISTING

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gugaggaggc agggccggca ugccucugcu gcuggccaga 100

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oligonucleotide

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oligonucleotide

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<213> Artificial Sequence

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<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic oligonucleotide

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<210> 13
<211> 100
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic

polynucleotide

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ugggcaccag ucagcuaccc uggugggaau cuggguagcc 100

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<212> DNA
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ccaggacctc ggcgtggcct agcgagttat ggcgacgaag gccgtgtgcg tgctgaaggg 180

cgacggccca gtgcagggca tcatcaattt cgagcagaag gaaagtaatg gaccagtgaa 240

ggtgtgggga agcattaaag gactgactga aggcctgcat ggattccatg ttcatgagtt 300

tggagataat acagcaggct gtaccagtgc aggtcctcac tttaatcctc tatccagaaa 360

acacggtggg ccaaaggatg aagagaggca tgttggagac ttgggcaatg tgactgctga 420

caaagatggt gtggccgatg tgtctattga agattctgtg atctcactct caggagacca 480

ttgcatcatt ggccgcacac tggtggtcca tgaaaaagca gatgacttgg gcaaaggtgg 540

aaatgaagaa agtacaaaga caggaaacgc tggaagtcgt ttggcttgtg gtgtaattgg 600

gatcgcccaa taaacattcc cttggatgta gtctgaggcc ccttaactca tctgttatcc 660

tgctagctgt agaaatgtat cctgataaac attaaacact gtaatcttaa aagtgtaatt 720

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<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 713
uaacagauga guuaaggggu u 21

<210> 714
<211> 21
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 714
cccuuaacuc aucuguuacc c 21

<210> 715
<211> 21
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 715
uuaacagaug aguuaagggu u 21

<210> 716
<211> 21
<212> RNA
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<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 716
aacucaucug uuaucuugcc c 21

<210> 717
<211> 21
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<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 717
gcuguggaaa uguaucuucc c 21

<210> 718
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<212> RNA
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<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 718
uaggauacau uucuacagcu u 21

<210> 719
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<212> RNA
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<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 719
ugacuugggc aaaggugagc c 21

<210> 720
<211> 21
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 720
ccccuuaacu caucuguugc c 21

<210> 721
<211> 21
<212> RNA

<213> Artificial Sequence

<220>
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oligonucleotide

<400> 721
cccuuaacuc aucuguuagc c 21

<210> 722
<211> 21
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 722
aacucaucug uuaucuuagc c 21

<210> 723
<211> 21
<212> RNA
<213> Artificial Sequence

<220>
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oligonucleotide

<400> 723
gcuguggaaa uguaucuugc c 21

<210> 724
<211> 21
<212> RNA
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<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 724
ugacuugggc aaagguaggc c 21

<210> 725
<211> 21
<212> RNA
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<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 725
ccccuuaaca caucuguuac c 21

<210> 726

<211> 21
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 726
cccuuaacug aucuguuaac c 21

<210> 727
<211> 21
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 727
aacucaucuc uuaucuugcc c 21

<210> 728
<211> 21
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 728
gcuguggaau uguaucuugc c 21

<210> 729
<211> 21
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 729
ugacuugggg aaaggugagc c 21

<210> 730
<211> 21
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 730
aacucaucug uuaucuuggc c 21

<210> 731
<211> 21
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 731
ccccuuaacu cauuuguucc c 21

<210> 732
<211> 21
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 732
ugacuugggc aaagguagcc c 21

<210> 733
<211> 21
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 733
uuugucagca gucacauugu c 21

<210> 734
<211> 19
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 734
caaugugacu gcugacaaa 19

<210> 735
<211> 21
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 735

gcagguccuc acuuuaaugc c 21

<210> 736
<211> 21
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic oligonucleotide

<400> 736
gauuaaagug aggaccugcu u 21

<210> 737
<211> 21
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic oligonucleotide

<400> 737
ggcaauguga cugcugaccc c 21

<210> 738
<211> 21
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic oligonucleotide

<400> 738
ugucagcagu cacauugccu u 21

<210> 739
<211> 21
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic oligonucleotide

<400> 739
gcagguccuc acuuuaauuc c 21

<210> 740
<211> 21
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic oligonucleotide

<400> 740
ggcaauguga cugcugaugc c 21

<210> 741
<211> 21
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 741
gcagguccuc acuuuaaucc c 21

<210> 742
<211> 21
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 742
ggcaauguga cugcugauac c 21

<210> 743
<211> 21
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 743
gcagguccug acuuuaaucc c 21

<210> 744
<211> 21
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 744
ggcaaugugu cugcugauac c 21

<210> 745
<211> 22
<212> RNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 745
gauuaaagug aggaccugcu uu 22

<210> 746
<211> 22
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 746
ugucagcagu cacauugccu uu 22

<210> 747
<211> 152
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 747
uuuaugccuc auccucugag ugcugaaggc uugcuguagg cuguaugcug caaugugacu 60

gcugacaacc cugugaccug guuugucagc agucacauug uuaguguaug augccuguua 120

cuagcauuca cauggaacaa auugcugccg ug 152

<210> 748
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 748
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaacaaugu 60

gacugcugac aacccuguga ccugguuugu cagcagucac auuguucuga ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 749
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 749
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaacaaugu 60

gacugcugac aauccuguga ccugguuugu cagcagucac auuguucuga ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 750
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 750
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaacaaugu 60

gacugcugac aagccuguga ccugguuugu cagcagucac auuguucuga ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 751
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 751
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaacaaugu 60

gacugcugac aaaccuguga ccugguuugu cagcagucac auuguucuga ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 752
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 752
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaacaaugu 60

gacagcugac aaaccuguga ccugguuugu cagcagucac auuguucuga ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 753
<211> 157
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 753
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaacaaugu 60

gacugcugac aaccugugac cugguuuguc agcagucaca uuguucugag gagcgccuug 120

acagcagcca ugggagggcc gcccccuacc ucaguga 157

<210> 754
<211> 159
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 754
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaacaaugu 60

gacugcugac aaucccugug accugguuug ucagcaguca cauuguucug aggagcgccu 120

ugacagcagc caugggaggg ccgcccccua ccucaguga 159

<210> 755
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 755
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaacaaugu 60

gacugcugac aacccuguga uuugguuugu cagcagucac auuguucuga ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 756
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 756
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaacaaugu 60

gacugcugac aacccuauaa uuugguuugu cagcagucac auuguucuga ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 757
<211> 159
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 757
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaacaaugu 60

gacugcugac aacacccuga cccaguuuug ucagcaguca cauuguucug aggagcgccu 120

ugacagcagc caugggaggg ccgcccccua ccucaguga 159

<210> 758
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 758
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaacaaugu 60

gacugcugac aacccuguga ccugguuugu cagcagucac auuguucugu ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 759
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 759
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaacaaugu 60

gacugcugac aauccuguga ccugguuugu cagcagucac auuguucugu ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 760
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 760
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaacaaugu 60

gacagcugac aaaccuguga ccugguuugu cagcagucac auuguucugu ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 761
<211> 159
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 761
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaacaaugu 60

gacugcugac aacacccuga cccaguuuug ucagcaguca cauuguucug uggagcgccu 120

ugacagcagc caugggaggg ccgcccccua ccucaguga 159

<210> 762
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 762
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaacaaugu 60

gacugcugac aagccuguga ccugguuugu cagcagucac auuguucugu ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 763
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 763
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaacgacga 60

aggccgugug cgcccuguga ccuggucgca cacggccuuc gucguucuga ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 764
<211> 158
<212> RNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 764
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaaugacuu 60

gggcaaaggu ggcccuguga ccugguccac cuuugcccaa gucauucuga ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 765
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 765
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaaaacuca 60

ucuguuaucc ugcccuguga ccuggucagg auaacagaug aguuuucuga ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 766
<211> 260
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 766
gaagcaaaga aggggcagag ggagcccgug agcugagugg gccagggacu gggagaagga 60

gugaggaggc agggccggca ugccucugcu gcuggccaga caaugugacu gcugacaacc 120

cgucugcacc ugucacuagu uugucagcag ucacauuguu uggccgugua gugcuaccca 180

gcgcuggcug ccuccucagc auugcaauuc cucucccauc ugggcaccag ucagcuaccc 240

uggugggaau cuggguagcc 260

<210> 767
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 767
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaaccccuu 60

aacucaucug uucccuguga ccuggguaaca gaugaguuaa gggguucuga ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 768
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 768
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaacccuua 60

acucaucugu uacccuguga ccugguuaac agaugaguua aggguucuga ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 769
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 769
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaaaacuca 60

ucuguuaucu ugcccuguga ccuggucagg auaacagaug aguuuucuga ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 770
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 770
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaagcugug 60

gaaauguauc uucccuguga ccugguagga uacauuucua cagcuucuga ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 771
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 771
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaaugacuu 60

gggcaaaggu gagccuguga ccugguccac cuuugcccaa gucauucuga ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 772
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 772
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaaccccuu 60

aacucaucug uugccuguga ccugguaaca gaugaguuaa gggguucuga ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 773
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 773
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaacccuua 60

acucaucugu uagccuguga ccugguuaac agaugaguua aggguucuga ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 774
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 774
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaaaacuca 60

ucuguuaucu uagccuguga ccuggucagg auaacagaug aguuuucuga ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 775
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 775
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaagcugug 60

gaaauguauc uugccuguga ccugguagga uacauuucua cagcuucuga ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 776
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 776
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaaugacuu 60

gggcaaaggu aggccuguga ccugguccac cuuugcccaa gucauucuga ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 777
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 777
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaaccccuu 60

aacucaucug uucccuguga uuugguaaca gaugaguuaa gggguucuga ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 778
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 778
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaacccuua 60

acucaucugu uacccuguga uuugguuaac agaugaguua aggguucuga ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 779
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 779
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaaaacuca 60

ucuguuaucu ugcccuguga uuuggucagg auaacagaug aguuuucuga ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 780
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 780
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaagcugug 60

gaaauguauc uucccuguga uuugguagga uacauuucua cagcuucuga ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 781
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 781
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaaugacuu 60

gggcaaaggu gagccuguga uuugguccac cuuugcccaa gucauucuga ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 782
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 782
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaaccccuu 60

aacacaucug uuaccuguga ccugguaaca gaugaguuaa gggguucugu ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 783
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 783
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaacccuua 60

acugaucugu uaaccuguga ccugguuaac agaugaguua aggguucugu ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 784
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 784
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaaaacuca 60

ucucuuaucu ugcccuguga ccuggucagg auaacagaug aguuuucugu ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 785
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 785
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaagcugug 60

gaauuguauc uugccuguga ccugguagga uacauuucua cagcuucugu ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 786
<211> 158
<212> RNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 786
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaaugacuu 60

ggggaaaggu gagccuguga ccugguccac cuuugcccaa gucauucugu ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 787
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 787
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaaccccuu 60

aacucaucug uugccuguga ccugguaaca gaugaguuaa gggguucugu ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 788
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 788
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaacccuua 60

acucaucugu uagccuguga ccugguuaac agaugaguua aggguucugu ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 789
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 789
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaaaacuca 60

ucuguuaucu uggccuguga ccuggucagg auaacagaug aguuuucugu ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 790

<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 790
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaagcugug 60

gaaauguauc uugccuguga ccugguagga uacauuucua cagcuucugu ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 791
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 791
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaaugacuu 60

gggcaaaggu aggccuguga ccugguccac cuuugcccaa gucauucugu ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 792
<211> 260
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 792
gaagcaaaga aggggcagag ggagcccgug agcugagugg gccagggacu gggagaagga 60

gugaggaggc agggccggca ugccucugcu gcuggccaga ccccuuaacu cauuuguucc 120

cgucugcacc ugucacuagu aacagaugag uuaagggguu uggccgugua gugcuaccca 180

gcgcuggcug ccuccucagc auugcaauuc cucucccauc ugggcaccag ucagcuaccc 240

uggugggaau cuggguagcc 260

<210> 793
<211> 260
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 793
gaagcaaaga aggggcagag ggagcccgug agcugagugg gccagggacu gggagaagga 60

gugaggaggc agggccggca ugccucugcu gcuggccaga cccuuaacuc aucuguuacc 120

cgucugcacc ugucacuagu uaacagauga guuaaggguu uggccgugua gugcuaccca 180

gcgcuggcug ccuccucagc auugcaauuc cucucccauc ugggcaccag ucagcuaccc 240

uggugggaau cuggguagcc 260

<210> 794
<211> 260
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 794
gaagcaaaga aggggcagag ggagcccgug agcugagugg gccagggacu gggagaagga 60

gugaggaggc agggccggca ugccucugcu gcuggccaga aacucaucug uuaucuugcc 120

cgucugcacc ugucacuagu caggauaaca gaugaguuuu uggccgugua gugcuaccca 180

gcgcuggcug ccuccucagc auugcaauuc cucucccauc ugggcaccag ucagcuaccc 240

uggugggaau cuggguagcc 260

<210> 795
<211> 260
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 795
gaagcaaaga aggggcagag ggagcccgug agcugagugg gccagggacu gggagaagga 60

gugaggaggc agggccggca ugccucugcu gcuggccaga gcuguggaaa uguaucuucc 120

cgucugcacc ugucacuagu aggauacauu ucuacagcuu uggccgugua gugcuaccca 180

gcgcuggcug ccuccucagc auugcaauuc cucucccauc ugggcaccag ucagcuaccc 240

uggugggaau cuggguagcc 260

<210> 796
<211> 260
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 796
gaagcaaaga aggggcagag ggagcccgug agcugagugg gccagggacu gggagaagga 60

gugaggaggc agggccggca ugccucugcu gcuggccaga ugacuugggc aaagguagcc 120

cgucugcacc ugucacuagu ccaccuuugc ccaagucauu uggccgugua gugcuaccca 180

gcgcuggcug ccuccucagc auugcaauuc cucucccauc ugggcaccag ucagcuaccc 240

uggugggaau cuggguagcc 260

<210> 797
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 797
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc gggauuuguc 60

agcagucaca uugucuguga ccuggcaaug ugacugcuga caaauccuga ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 798
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 798
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaagcaggu 60

ccucacuuua augccuguga ccugggauua aagugaggac cugcuucuga ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 799
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 799
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaaggcaau 60

gugacugcug accccuguga ccugguguca gcagucacau ugccuucuga ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 800
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 800
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaagcaggu 60

ccucacuuua auuccuguga ccugggauua aagugaggac cugcuucuga ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 801
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 801
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaaggcaau 60

gugacugcug augccuguga ccugguguca gcagucacau ugccuucuga ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 802
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 802
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaagcaggu 60

ccucacuuua aucccuguga uuugggauua aagugaggac cugcuucuga ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 803
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 803
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaaggcaau 60

gugacugcug auaccuguga uuugguguca gcagucacau ugccuucuga ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 804
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 804
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaagcaggu 60

ccugacuuua aucccuguga ccugggauua aagugaggac cugcuucugu ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 805
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 805
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaaggcaau 60

gugucugcug auaccuguga ccugguguca gcagucacau ugccuucugu ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 806
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 806
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaagcaggu 60

ccucacuuua aucccuguga ccugggauua aagugaggac cugcuucugu ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 807
<211> 158
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic

polynucleotide

<400> 807
gugcugggcg gggggcggcg ggcccucccg cagaacacca ugcgcucuuc ggaaggcaau 60

gugacugcug auaccuguga ccugguguca gcagucacau ugccuucugu ggagcgccuu 120

gacagcagcc augggagggc cgcccccuac cucaguga 158

<210> 808
<211> 260
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 808
gaagcaaaga aggggcagag ggagcccgug agcugagugg gccagggacu gggagaagga 60

gugaggaggc agggccggca ugccucugcu gcuggccaga gcagguccuc acuuuaaucc 120

cgucugcacc ugucacuagg auuaaaguga ggaccugcuu uggccgugua gugcuaccca 180

gcgcuggcug ccuccucagc auugcaauuc cucucccauc ugggcaccag ucagcuaccc 240

uggugggaau cuggguagcc 260

<210> 809
<211> 260
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 809
gaagcaaaga aggggcagag ggagcccgug agcugagugg gccagggacu gggagaagga 60

gugaggaggc agggccggca ugccucugcu gcuggccaga ggcaauguga cugcugauac 120

cgucugcacc ugucacuagu gucagcaguc acauugccuu uggccgugua gugcuaccca 180

gcgcuggcug ccuccucagc auugcaauuc cucucccauc ugggcaccag ucagcuaccc 240

uggugggaau cuggguagcc 260

<210> 810
<211> 54
<212> RNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic oligonucleotide

<400> 810
uccugaggag cgccuugaca gcagccaugg gagggccgcc cccuaccuca guga 54