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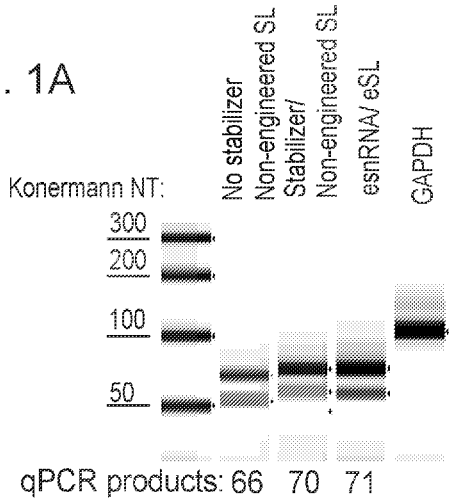
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(54) Title: COMPOSITIONS AND METHODS COMPRISING ENGINEERED SMALL NUCLEAR RNA (SNRNA)

(57) Abstract: SnRNA systems comprising engineered stem loops are disclosed herein.

FIG. 1A



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[Continued on next page]

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COMPOSITIONS AND METHODS COMPRISING ENGINEERED SMALL NUCLEAR RNA (SNRNA)

REFERENCE TO AN ELECTRONIC SEQUENCE LISTING

[01] The contents of the electronic sequence listing (LOCN_020_001WO_SeqList_ST26.xml; Size: 289,776 bytes; and Date of Creation: March 6, 2023) is herein incorporated by reference in its entirety.

RELATED APPLICATIONS

[02] This application claims priority to, and the benefit of U.S. Provisional Application No. 63/316,659 filed March 4, 2022 and U.S. Provisional Application No. 63/379,983 filed October 18, 2022. The contents of each of these applications are hereby incorporated by reference in their entireties.

FIELD OF THE DISCLOSURE

[03] The disclosure is directed to molecular biology, gene therapy, and compositions and methods for modifying expression and activity of RNA molecules.

BACKGROUND

[04] There are long-felt but unmet needs in the art for providing effective therapies for correcting dysfunctional messenger RNA.

[05] Small nuclear RNA (snRNA) is one of the smallest types of RNA with an average size of about 150 nucleotides. snRNAs are functional non-coding RNAs. Eucaryotic genomes code for a variety of non-coding RNA such as snRNA, a class of highly abundant RNA, localized in the nucleus with important functions in intron splicing and RNA processing. snRNA, in the pre-mRNA splicing process, are capable of forming ribonucleoprotein particles (snRNPs) along with other proteins. These snRNPs and additional proteins form a large particulate complex (spliceosome) bound to the unspliced pre-mRNA transcripts. In addition to splicing, snRNAs function in nuclear maturation of nascent transcripts, gene expression regulation, as a splice donor in non-canonical systems, and in 3' end processing of replication-dependent histone mRNAs. U7 snRNA can be programmed to bind and modulate mRNA without exogenous protein expression but there still exists a need to develop a highly specific mRNA-targeting therapeutic that minimizes immunogenic risk. Furthermore, the

small size of these programmed snRNAs creates an opportunity to develop single vector, highly specific (allele-specific), single target and multi-targeting gene therapy approaches.

[06] Accordingly, the disclosure provides compositions and methods comprising a new therapeutic RNA-targeting platform comprised of engineered snRNAs.

SUMMARY

[07] The disclosure provides gene therapy compositions comprising a new therapeutic RNA-targeting platform comprised of engineered snRNA (esnRNA) comprising an engineered snRNA stem loop (eSL).

[08] Disclosed herein are compositions comprising nucleic acid molecules, and vectors comprising the engineered snRNA (esnRNA).

[09] Disclosed herein is an RNA-targeting nucleic acid molecule comprising an engineered snRNA (esnRNA) system, wherein the esnRNA system comprises an engineered stem loop (eSL).

[010] In one embodiment, the esnRNA comprises a 5' interaction stabilizer domain (5'ISD).

[011] In one embodiment, the esnRNA comprises a targeting sequence (TS) (or spacer) that targets an RNA of interest. In another embodiment, the target RNA of interest is a microsatellite repeat RNA or a non-repeat RNA. In another embodiment, the microsatellite repeat RNA of interest is selected from the group consisting of CUG, CAG, GGGGCC, and CCCCGG. In one embodiment, the esnRNA comprises a targeting sequence (TS) that targets two target RNAs of interest which are GGGGCC and CCCCGG. In another embodiment, the two target RNAs of interest are a microsatellite repeat RNA and a non-repeat RNA. In another embodiment, the non-repeat RNA is a flanking sequence to the microsatellite repeat RNA. In another embodiment, the esnRNA comprises a targeting sequence (TS) that targets two or more RNAs of interest. In another embodiment the esnRNA comprises two or more targeting sequence (TS) that targets two or more RNAs of interest. In another embodiment, the esnRNA comprises a fusion of the two or more TSs.

[012] In one embodiment, the esnRNA comprises an Sm binding domain (SmBD). In one embodiment, the SmBD is selected from the group consisting of U1, U2, U4, and U5 snRNAs. In another embodiment, the SmBD is derived from a pseudo snRNA.

[013] In one embodiment, the esnRNA is operably linked to an snRNA promoter. In another embodiment, the snRNA promoter is a U7 promoter. In another embodiment, the U7 promoter is an endogenous U7 promoter. In another embodiment, the U7 promoter is a human U7 promoter (hU7) or a mouse U7 promoter (mU7). In another embodiment, the U7 promoter is an endogenous human U7 promoter of SEQ ID NO: 43. In one embodiment, the snRNA promoter is a U1 promoter. In another embodiment, the U1 promoter is a human U1 promoter or a mouse U1 promoter. In another embodiment, the snRNA promoter is selected from the group consisting of: a human U7 promoter, a human U1 promoter, a human U2 promoter, a human U4 promoter, a human U5 promoter, a human U6 promoter, a human 7sk promoter, a tRNA(Val) promoter, a mouse U1 promoter, and a mouse U7 promoter. In another embodiment, the vector comprises one or more esnRNAs, or one or more copies of the esnRNA driven by one or more snRNA promoters. In one embodiment, the vector comprises two copies (2x) of the esnRNA. In one embodiment, the vector comprises two snRNA promoters, wherein each promoter drives a copy of the 2x esnRNA. In another embodiment, the two snRNA promoters are the U7 promoter and the U1 promoter. In another embodiment, the two snRNA promoters are selected from the group consisting of: a human U7 promoter, a human U1 promoter, a human U2 promoter, a human U4 promoter, a human U5 promoter, a human U6 promoter, a human 7sk promoter, a tRNA(Val) promoter, a mouse U1 promoter, a mouse U2 promoter, a mouse U5 promoter, a mouse U6 promoter, a mouse U7 promoter, and a mouse H1 promoter. In another embodiment the two snRNA promoters are a mouse U7 promoter and a mouse U1 promoter.

[014] In one embodiment, the esnRNA is operably linked to an snRNA downstream terminator (DT). In another embodiment, the snRNA DT is a U7 DT.

[015] In one embodiment, the esnRNA comprises the eSL, the U7 promoter, the TS, the SmBD, the 5'ISD, and the DT. In another embodiment, the esnRNA comprises the eSL, the U7 promoter, the U1 promoter, the TS, the SmBD, the 5'ISD, and the DT.

[016]

[017] In one embodiment, the esnRNA comprises the eSL, the U7 promoter, the TS, the SmBD, the 5'ISD, and the DT. In another embodiment, the esnRNA comprises the eSL, the U7 promoter, the U1 promoter, the TS, the SmBD, the 5'ISD, and the DT.

[018] Also disclosed herein is a vector comprising the esnRNA. In some embodiments, the vector comprises multiple copies of the esnRNA. In some embodiments, the multiple copies of the esnRNA is 2, 3, or 4 copies (2x, 3x, or 4x) of the esnRNA. In some embodiments, the

multiple copies of the esnRNA is 4 or more copies (4x or more) of the esnRNA. In some embodiments, each esnRNA of the multiple copies of esnRNA is separated by a nucleic acid buffer sequence derived from human non-coding genomic sequences downstream of an snRNA. In one embodiment, the buffer sequence is derived from human genomic sequences downstream of U7. In one embodiment, the buffer sequence is selected from the group consisting of: buffer 1 (30bp, 100bp, or 500bp), buffer 2 (30bp, 100bp, or 500bp), buffer 3 (30bp, 100bp, or 500bp), and a combination thereof. In one embodiment, the vector is a viral vector or a non-viral vector. In another embodiment, the viral vector is an AAV vector. In another embodiment, the AAV vector is an scAAV vector or a ssAAV vector. In another embodiment, the AAV vector is an AAV9 vector. In another embodiment, the AAV9 vector is an ssAAV9 vector or an scAAV9 vector.

[019] Also disclosed herein is a method of targeting one or more target RNAs of interest and blocking, knocking down, editing, exon-skipping, exon inclusion or splicing the one or more target RNAs, comprising contacting an esnRNA of the disclosure with a cell comprising the one or more target RNAs.

[020] The disclosure provides aa RNA-targeting nucleic acid molecule comprising an engineered snRNA esnRNA, wherein the esnRNA system comprises an engineered stem loop (eSL) comprising one or more nucleic acid sequences selected from SEQ ID NO: 1-SEQ ID NO: 11, SEQ ID NO: 146 – SEQ ID NO: 148, SEQ ID NO: 163, or SEQ ID NO: 186-205.

[021] In some embodiments, the esnRNA comprises a targeting sequence (TS) that targets a target RNA of interest.

[022] In some embodiments, the target RNA is a pre-mRNA or mRNA sequence. In some embodiments, the target RNA of interest is a microsatellite repeat RNA. In some embodiments, the microsatellite repeat RNA is selected from the group consisting of CUG, CAG, and GGGGCC+CCCCGG.

[023] In some embodiments, the target RNA is a sequence encoding DMD. In some embodiments, the targeting sequence is selected from SEQ ID NO: 206 or SEQ ID NO: 207. In some embodiments, the targeting sequence comprises one or more nucleic acid sequences set forth in SEQ ID NO: 208 – SEQ ID NO: 227.

[024] In some embodiments, the esnRNA comprises two targeting sequences that target two RNAs of interest. In some embodiments, the two TSs are a fusion sequence.

[025] In some embodiments, the esnRNA comprises an Sm binding domain (SmBD) selected from the group consisting of a U1, U2, U4, and U5 SmBD.

[026] In some embodiments, the SmBD comprises a nucleic acid sequence set forth in any one of SEQ ID NO: 31 – SEQ ID NO: 38, or SEQ ID NO: 164.

[027] In some embodiments, the esnRNA comprises a 5' interaction stabilizer domain (5'ISD) comprising a nucleotide sequence selected any one of SEQ ID NO: 12 -SEQ ID NO: 23.

[028] In some embodiments, the esnRNA comprises a nucleic acid sequence set forth in any one of SEQ ID NO: 65 – SEQ ID NO: 119 or SEQ ID NO: 179 – SEQ ID NO: 185.

[029] The disclosure provides a vector comprising one or more esnRNA of the disclosure. In some embodiments, the viral vector is an AAV vector. In some embodiments, the esnRNA is operably linked to a promoter.

[030] In some embodiments, the esnRNA is operably linked to a U7 promoter or a U1 promoter.

[031] In some embodiments, the esnRNA is operably linked to a downstream terminator (DT). In some embodiments, the esnRNA is operably linked to a U7 downstream terminator or a U1 downstream terminator.

[032] In some embodiments, the vector comprises at least one, at least two, at least three, at least four, or at least five esnRNA. In some embodiments, the least one, at least two, at least three, at least four, or at least five esnRNA each target the same target RNA sequences.

[033] In some embodiments, the least one, at least two, at least three, at least four, or at least five esnRNA target two or more target RNA sequences In some embodiments, each esnRNA is separated by a buffer sequence. In some embodiments, the buffer sequence comprises a nucleic acid sequence set forth in any one SEQ ID NO: 24-SEQ ID NO: 30.

[034] In some embodiments, the vector comprises a nucleic acid sequence set forth in any one of SEQ ID NO: 123 – SEQ ID NO: 143, SEQ ID NO: 168 – SEQ ID NO: 178, or SEQ ID NO: 231 – SEQ ID NO: 233.

[035] A DMD exon 51 RNA-targeting nucleic acid molecule comprising a spacer sequence set forth in any one of SEQ ID NO: 206 – SEQ ID NO: 230.

[036] The disclosure provides a method of treating a disease or disorder in a subject comprising administering an RNA-targeting nucleic acid molecule of the disclosure or an AAV vector of the disclosure.

[037] In some embodiments, the disease or disorder is associated with a toxic repeat RNA sequence. In some embodiments, the toxic repeat RNA sequence is a CAG, CUG, GGCCCC, CCGGG, or GGCCC+CCGGGG RNA repeat.

[038] In some embodiments, the disease or disorder is myotonic dystrophy (DM1) or Huntington's disease (HD).

[039] In some embodiments, the disease or disorder is Duchenne Muscular Dystrophy. In some embodiments, the RNA-targeting nucleic acid molecule or AAV vector targets an RNA sequence encoding dystrophin (DMD).

[040] In some embodiments, the RNA sequence encoding DMD comprises an intronic or exonic sequence. In some embodiments, the exonic sequence comprises exon 51, or a flanking region thereof, of DMD. In some embodiments, the administration is administration is intravenous, intramuscular, subpial, intrathecal, intraparenchymal, intrathecal, intrastriatal, subcutaneous, intradermal, intraperitoneal, intratumoral, intravenous, intraocular, and/or parenteral administration.

BRIEF DESCRIPTION OF THE DRAWINGS

[041] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[042] FIG. 1A-D. FIG. 1A shows a tape station image of PCR products which increase in abundance for the engineered SL indicating increased stability of an esnRNA disclosed herein. Predicted PCR product size is shown below the image. FIG. 1B illustrates a schematic of the engineered snRNA (esnRNA) comprising the engineered stem loop (eSL) disclosed herein alongside non-engineered stem loops. FIG. 1C shows alternative mechanisms to protect the 5' end of the snRNA which forego the use of an interaction stabilizer domain (ISD). FIG 1D shows the approximate size of an snRNA cassette.

[043] FIG. 2A-C. FIG. 2A-2B shows FISH quantification and images of CUG RNA Foci of an esnRNA targeting CUG disclosed herein compared to NT (non-targeting) esnRNA. Y axis depicts percentage average foci per cell normalized to NT, and x axis depicts treatment. Cell nuclei was stained with DAPI and CUG RNA foci labeled with a specific labeled probe. FIG. 2C shows a schematic of the esnRNA MOA targeting and blocking CUG repeat expansions releasing MBLN and restoring splicing defects characteristic in DM1 disease.

[044] FIG. 3A-C. FIG. 3A shows qPCR results of a dose-dependent knockdown of CAG80 reporter mRNA to baseline levels. Y axis depicts CAG repeat RNA expression levels relative to reference gene GAPDH, and x axis depicts snRNA treatment CAG targeting

(CUG15) or non-targeting (nt) (using different doses 250 ng, 500 ng or 1000 ng). FIG. 3B shows a Western blot for CAG80 reporter poly-Q protein expression. Top lanes show CAG reporter poly-Q expression and bottom lane GAPDH loading control. FIG 3C shows CAG repeat expansions in mutant HTT in Huntington's disease and the esnRNA MOA blocking the CAG repeats.

[045] FIG. 4A-D. FIG. 4A shows a tape station image of the PCR product to detect USH2A exon 13 inclusion (top band) or exclusion (bottom band) after treatment with esnRNA. FIG.4C shows the quantification of percentage of exon 13 exclusion after esnRNA treatment compared to NT esnRNA control (shown in A). FIG 4B shows a schematic of the engineered snRNA comprising the eSL compared to the non-engineered snRNAs. FIG. 4D shows a schematic of splicing modulation in Usher's Syndrome and DMD (Duchenne Muscular Dystrophy).

[046] FIG. 5A-F shows PCR results for restoration of splicing isoforms for BIN1, DMD and LBD3 (mispliced in DM1 patient cells) after treatment with esnRNAs to target CUG repeats in DM1patient derived myotubes. Figures A-C show quantitation of the percentage restoration to the healthy splice isoform from the tape station images shown in Figures D-F. Y axis depicts percentage of correction, and x axis depicts treatment (knt, refers to non-targeting negative control; CAGx15 refers to CUG targeting esnRNA; unt refers to untreated).

[047] FIG. 6A-6B shows quantification of efficacy of esnRNA with alternative 5' interaction stabilizing domain (ISD) in knocking down CUG RNA foci, synthetic snRNA transfection in CTG480 HeLa cells followed by fluorescent in-situ hybridization for CUG RNA foci. (Light blue = alternative engineered stem loops with corresponding 5' ISDs. Dark blue = selected engineered stem loop and corresponding 5' ISD. sR220004 = non-targeting snRNA). Synthetic snRNAs were transfected at 33 nM (A) or 11 nM (B) dose.

[048] FIG. 7A-7B shows that different ISDs lead to varying levels of stability over time. FIG 7A and B show the relative abundance over time of synthetic engineered snRNAs with alternative 5' stabilizing domains. RNA was collected at 24 hr, 48 hr, and 72 hr time points after transfection of synthetic snRNAs with varying stabilizing domains to determine the relative stability of the snRNA.

[049] FIG. 8 shows levels of snRNA expression by qPCR in CTG480 HeLa cells when snRNAs are expressed under distinct PolIII and PolII promoters. Y axis depicts snRNA expression levels relative to GAPDH reference gene, and x axis depicts the different snRNAs

promoters used to express snRNAs (Pol II U1 and U7 promoters or PolIII: U6, tRNA and 7SK). Plasmids with varying promoters were transfected at two different doses (250 and 500 ng).

[050] FIG. 9A-9B shows quantification of CUG foci by RNA FISH in CTG480 HeLa cells after transfection of 500 ng (A) or 250 ng (B) engineered snRNA constructs with varying Pol III and Pol II promoters and respective DT sequences. Constructs with Pol II promoters (P02225 and P03557) driving expression of engineered snRNAs are more effective at depleting microsatellite repeat-containing foci than constructs with Pol III promoters driving snRNAs. Gray bars represent NT esnRNA and blue bars represent CUG targeting esnRNAs.

[051] FIG. 10 shows levels of snRNA expression by qPCR in HEK293T cells when snRNAs are expressed under PolIII (U6, tRNA and 7SK) or PolII promoters (U7 and U1) and contain the SmOpt or the U1 Sm binging sites.

[052] FIG. 11A-11B shows levels of snRNA expression relative to GAPDH reference gene after transfection into HEK293 cells. Primers specific for each snRNA (z) were used for qPCR to determine relative promoter strength. Y axis depicts snRNA expression levels relative to GAPDH and x axis depicts the snRNA spacer znt (non-targeting control, in A) and z38 (targeting spacer, B) when they are expressed under snRNA distinct promoters (U1, U2, U4, U5 and U7; unt refers to untreated).Primer sets specific to z-nt (FIG A) or z-38 (FIG B) were used.

[053] FIG. 12A-12B shows results for exon 51 skipping after transduction of human delta exon 52 myotubes with snRNA disclosed herein (A03980: 2x z38/42 fusion snRNA cassettes ; A03981: 2 snRNA cassettes, one with z42 TS and the other with z38 TS). FIG 12A shows a tape station image of PCR products representing the exon 51 included and excluded isoforms and a schematic showing expected fragment sizes. FIG 12B shows the quantification of the band intensities in FIG. 12A semi-quantitative PCR. Y axis depicts percentage of exon 51 skipping and x axis the treatment (either synthetic snRNA or AAV transduced for A03980 of A03981 with different MOIs).

[054] FIG. 13A-13B shows dystrophin staining and restoration of human delta exon 52 myotubes after treatment with snRNAs for exon 51 skipping. FIG 13A shows immunofluorescence for desmin or dystrophin in untreated myotubes, myotubes treated with synthetic snRNAs or myotubes treated with MOI of 1e6 or 5e6 of A03980 (2x z38/z42 fusion snRNA cassettes). FIG 13B shows immunofluorescence for desmin or dystrophin in

myotubes transduced with MOI of 1e6 or 5e6 of A03981 (2 snRNA cassettes with z42 TS and z38 TS).

[055] FIG. 14A illustrates the vector genome of A04569, which expresses 2 fusion snRNAs of identical sequence, as depicted in FIG. 14B. FIG. 14C shows that exon 51 Exon Splicing Enhancer (ESE)-targeting fusion snRNAs can be constructed such z38-targeting sequence is in the 5'-most position in the antisense sequence with z42-targeting sequence downstream of the z38 sequence (z73) or in the opposite orientation with z42-targeting sequence in the 5'-most position and z38 downstream (z187). In both cases, the antisense sequence of the snRNAs is composed of 2 targeting sequences, each of which targets a separate and unique ESE in exon 51 (FIG. 14C bottom diagram).

[056] FIG. 15A-D show the activity of exon 51 ESE-targeting fusion snRNAs in human skeletal myotubes with exon 52 deleted and del52hDMD/mdx mice. (A) tape station image and quantification of exon 51 skipping in human skeletal myotubes with *DMD* exon 52 deleted 24 hours after transfection of a low dose of synthetic snRNAs carrying the fusion antisense sequences z73 (z38/z42) and z187 (z42/z38). At a low dose, transfection of synthetic snRNA z187 induces higher levels of exon 51 skipping than z73. (FIG.15B) shows quantification of exon 51 skipping in human skeletal myotubes with DMD exon 52 deleted after transduction with AAV9-A04526 (carrying two esnRNA cassettes each expressing z73) and A04569 (carrying two cassettes each expressing z187) for 7 days with MOIs of 2.5e4, 1e5 and 5e5. (FIG. 15C) shows quantification of exon 51 skipping in the humanized exon 52-deleted DMD (del52hDMD/mdx) mouse model. Mice we injected retro-orbitally with 3e12 vector genomes of A04526 and A04569. Following 3 week survival, RNA was extracted from the tibialis anterior muscle (TA), the Gastrocnemius (Gc) and the heart. Semi-quantitative RT-PCR was performed to detect exon 51 included and excluded bands. (FIG. 15D) shows the quantification of dystrophin positive fibers 4 weeks after intramuscular delivery of a 3e11 vg/muscle dose of A04526 or an ESE-targeting Vivo-Morpholino (ViM) to the Gastrocnemius of del52hDMD/mdx mice. hDMD/mdx mice (gray bar) which expresses wildtype human dystrophin serves as a positive control for dystrophin expression. U = untreated.

[057] FIG. 16A-D show splicing reversal of DMD and LBD3 splice isoforms and knockdown of DMPK after treatment with snRNA targeting CUG repeats in patient derived myotubes (containing 1700 CUG repeats). DM1 patient fibroblasts were differentiated into myotubes by transduction with myoD Adenovirus vector (for 5 days). Then cells were

transduced with multiple MOIs of A04233 and A04234 (scAAV9 dual snRNAs targeting CUG repeats) and harvested 7 days post-transduction. FIG. 16A shows a tape station image of RT-PCR products using specific primers to detect DMD exon 78 inclusion (top band) and LBD3 exon 11 exclusion (bottom band) which are markers of splicing correction seem in normal WT cells. Quantification of DMD exon 78 inclusion (FIG. 16B) and LBD3 exon 11 exclusion (FIG. 16C). The x-axis depicts the treatment (vector and MOI). The y-axis depicts the percentage of splice correction, either exon inclusion for DMD exon 78 or exclusion for LBD3 exon 11 . FIG. 16D shows levels of DMPK RNA expression by ddPCR after treatment with snRNAs (AAV9 A04233 and AAV9 A04234) with different MOIs. The x-axis depicts the treatment. The y-axis depicts DMPK copies per 1000 copies of GAPDH reference gene normalized to UNT (untreated cells).

[058] FIG. 17A-B shows images and quantification of nuclear RNA foci from patient-derived myotubes transduced with different MOIs of AAV9 A04233 and AAV9 A04234. DM1 patient fibroblasts were differentiated into myotubes by transduction with myoD Adenovirus vector (for 5 days). Then cells were transduced with multiple MOIs of A04233 and A04234 (scAAV9 dual snRNAs targeting CUG repeats) and harvested 7 days post-transduction for RNA FISH (to detect CUG Foci). FIG. 17A shows images of CUG RNA foci obtained from untreated and treated myotubes with AAV9 snRNA vectors A04233 and A04234. Cell nuclei was stained with DAPI and CUG FISH was performed with a CUG labeled probe. Cells were processed 7 days post-transduction. FIG. 17B shows quantification for the average number of CUG foci per cell. The x-axis depicts the treatment and MOI used. The y-axis depicts average of CUG foci per cell normalized to UNT (untreated cells).

[059] FIG. 18A-C depicts the treatment, timeline and quantification of HTT mutant soluble protein after treatment with AAV-snRNA targeting CAG repeats. FIG. 18A shows the experimental design for the vector used AAV-A04390 (2x hU7/hU1 snRNA targeting CAG repeats), the 2 MOIs and the end point assay to detect mutant (mut) HTT soluble protein. FIG. 18B depicts the timeline for this experiment. HD patient iPSc (containing 66 CAG repeats) were differentiated into cortical neurons for 2 weeks and then transduced with AAV-A04390 snRNA vector for an additional 2 weeks. Then cortical neurons were harvested and mutant soluble HTT protein quantified by Meso scale discovery immunoassay (MSD, shown in Fig18C). The y-axis depicts fmol of mutant soluble HTT per mg of protein lysate, and the x-axis the treatment and MOI.

[060] FIG. 19A-B depicts the in vivo study design to target CAG repeats on R6/2 HD mouse model and quantification of mutant HTT soluble protein after treatment with AAV-snRNA targeting CAG repeats (A03081). FIG. 19A diagram shows dosage (2e10 vector genomes) of AAVrh10-snRNA (4x CAGx15 targeting snRNAs vector) administered by intrastriatal injection . Untreated or uninjected contralateral striatal side was used as a control. (FIG. 19B) shows quantification of mutant soluble HTT protein by Meso scale discovery immunoassay (MSD) on untreated and snRNA treated mice (n=10). The y-axis depicts fmol of mutant soluble HTT per mg of total protein lysate, and the x-axis the treatment.

[061] FIG. 20A depicts the differences between the snRNAs expressed from A04527 and A04526 with A04526 expressing engineered snRNAs that have a 5'ISD and engineered mouse SL and A04527 which has no 5'ISD and a mouse native SL. FIG. 20B shows a bar graph of the expression of z38/42 (in snRNA copies/nanogram) 2 days after transduction of CHO-Lec2 cells at an MOI of 1e6 for with AAV9-A04527 or A04526 virus.

DETAILED DESCRIPTION

[062] The disclosure provides gene therapy compositions comprising a new therapeutic RNA-targeting platform comprised of engineered snRNA (esnRNA) comprising an engineered snRNA stem loop (eSL).

[063] Disclosed herein are compositions comprising nucleic acid molecules, and vectors comprising the engineered snRNA (esnRNA).

[064] Small nuclear ribonucleic acids (snRNAs) are essential components of small nuclear ribonucleoprotein complexes (snRNPs) which, when assembled with additional proteins, form the large ribonucleoprotein complex known as the spliceosome, the cell machinery appointed to mediate the entire mRNA maturation process. The spliceosome is responsible for precursor mRNA splicing; the process that removes introns from RNA transcripts before protein production. An individual snRNA is generally about 250 nucleotides or less in size. For example, U1 snRNA is 164 nucleotides in length and is encoded by genes that occur in several copies within the human genome. U1 snRNA represents the ribonucleic component of the nuclear particle U1 snRNP. The U1 snRNA has a stem and loop tridimensional structure and within the 5' region there is a single-stranded sequence, generally about 9 nucleotides in length, capable of binding by complementary base pairing to the splicing donor site on the pre-mRNA molecule. (Horowitz et al., 1994, Trends Genet., 10(3):100-6.)

The various spliceosomal snRNAs have been designated as U1, U2, U4, U5, U6, U4ATAC, U6ATAC, U7, U11 and U12, due to the generous amount of uridylic acid they contain. (Mattaj et al., 1993, FASEB J, 15, 7:47-53.)

[065] snRNA systems can be used for treating toxic mutations. For example, antisense oligonucleotides that interfere with splice sites and regulatory elements within an exon containing toxic mutations can induce skipping of specific exons at the pre-RNA level. Such antisense sequences can be packaged in an snRNA sequence delivered using viral vectors carrying a nucleic acid sequence from which the snRNA can be transcribed. U7 snRNA is endogenously involved in histone pre-mRNA 3'-end processing, but can be converted into a versatile tool for splicing modulation by a small change in the binding site for Sm/Lsm proteins. One such therapeutic strategy for treating Duchenne muscular dystrophy has used modified U7 snRNA to convert an out-of-frame mutation into an in-frame mutation, which gives rise to internally deleted toxic RNA, but still functional dystrophin. (Goyenvalle et al., 2009, 17(7): 1234-1240.)

[066] Most U-rich snRNPs are complexes that mediate the splicing of pre-mRNAs. U7 snRNP is an exception. U7 is not involved in splicing but rather is a key factor in the unique 3'-end processing of replication-dependent histone mRNAs. By modifying the U7 snRNA histone binding sequence and the Sm motif, U7 can no longer be involved in processing the histone pre-mRNA and instead targets pre-mRNAs or smRNA for blocking or splicing modulation. In this manner, U7 snRNA can be used as an effective gene therapy platform. A U7 snRNA platform also has the additional advantages of being a compact size, having the capability to accumulate in the nucleus without causing cellular toxicity, and possesses little to no immunoreactivity. (Gadgil et al., 2021, J Gene Med, 23(4): e3321.)

[067] Disclosed herein is a newly engineered and redesigned snRNA platform (or known herein as an esnRNA platform) comprising an 1) engineered stem loop (eSL). Compensatory modifications made to the native stem loop sequence create an engineered stem loop (eSL) which more effectively communicates (folds and anneals) with the snRNA interaction stabilization domain (ISD) which in turn creates a snRNA platform with increased stability. See Figure 1. U7 snRNAs have been previously shown to be programmable to modulate mRNAs. Disclosed herein are programmed engineered snRNA improvements which are capable of being used as a gene therapy tool. These engineered snRNA systems are shown herein to lead to blocking microsatellite repeat expansions (shown herein for treating myotonic dystrophy (DM1) or Huntington's disease (HD)), exon skipping (for treating

DMD) and splicing modulation (shown herein for treating USH2A (Usher Syndrome type 2). In one embodiment, these snRNAs are human snRNAs. In another embodiment, these snRNAs are mouse snRNAs. In another embodiment, the snRNAs are a combination of human and mouse snRNAs. In one embodiment the U7 is a human U7 or a mouse U7. In another embodiment disclosed herein, engineered snRNA comprises varying types of snRNAs (U1-U12, etc.) by combining domains of endogenous snRNAs to fine tune stabilization of the platform and/or to reduce off-target effects. For example, in one embodiment, the engineered snRNA system comprises a combination of human or mouse U7 and human or mouse U1 snRNA components.

[068] Additional elements that can tune the processing and abundance of the RNA can be further engineered into the esnRNAs comprising eSLs. See Figure 1C. In one embodiment, additional elements that can tune the processing, stability, and abundance of the esnRNA can be further engineered into the esnRNAs at the 5' or 3' ends. In another embodiment, such elements may include but are not limited to stem loops, hairpins, G-C clamps, kissing loops, triplexes, quadruplexes, and protein binding sites.

[069] The esnRNA platform and portions thereof disclosed herein can be used in any therapeutic setting and context so long as a suitable spacer(s) (or TS(s)) is included in the design of the esnRNA therapeutic composition. In certain embodiments, a therapeutic esnRNA composition is used to treat a disease selected from the group consisting of Duchenne Muscular Dystrophy, DM1, and HD. In another embodiment, the esnRNA composition is used to treat DMD caused by exon 51 mutations

Engineered Stem Loops

[070] The engineered snRNA (esnRNA) system disclosed herein comprises an engineered stem loop (eSL) which includes compensatory modifications to a native snRNA stem loop. These modifications result in increased stability of the esnRNP compared to snRNP comprising an unmodified stem loop. An eSL disclosed herein can be derived from any snRNP such as U1-U12. In one embodiment, the eSL is a human or mouse U7 eSL. In one embodiment, the eSL is a human or mouse eSL. In some embodiments, the eSL is a human and mouse eSL. In some embodiments, the eSL is a non-human eSL selected from the group consisting of mouse, pig, sheep, goat, cow, dog, cat, horse, or a combination thereof. In some embodiments, the eSL is an eSL selected from the group consisting of human, mouse, pig, sheep, goat, cow, dog, cat, horse, or a combination thereof. In some embodiments, the eSL sequence is not a native stem loop sequence. In some embodiments, the nucleic acid

sequence of the eSL is at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% (or any percentage in between) is not a native stem loop sequence.

[071] In some embodiments, a human eSL comprises, consists essentially of, or consists of a nucleic acid sequence at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% (or any percentage in between) identical to one or more of the following nucleotide sequences:

ggctttctggctccttaccggaaagcc (SEQ ID NO: 1)),
ggctttctgggaggttaccggaaagcc (SEQ ID NO: 2),
ggctttctggcctccttaccggaaagcc (SEQ ID NO: 3),
ggctttctggggaggttaccggaaagcc (SEQ ID NO: 4),
ggctttctggctggctaccggaaagcc (SEQ ID NO: 5),
ggctttctggcttccccggaaagcc (SEQ ID NO: 6),
ggctttctggcttcttcccggaaagcc (SEQ ID NO: 7),
ggctttctggcaacttaccggaaagcc (SEQ ID NO: 8),
ggctttctggttcggtaccggaaagcc (SEQ ID NO: 9),
ggctttctggaagccttaccggaaagcc (SEQ ID NO: 10),
ggctttctggcttcttaccggaaagcc (SEQ ID NO: 11), or
GGCTTTCTGGCCTCCGCCGGAAAGCCCCT (SEQ ID NO: 186).

[072] In some embodiments, a murine eSL comprises, consists essentially of, or consists of a nucleic acid sequence at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% (or any percentage in between) identical to one or more of the following nucleotide sequences:

ggctttctggctccttaccggaaagcccct (SEQ ID NO: 163)
Ggttttctgacctccgtcggaaaacccct (SEQ ID NO: 146),
ggttttctgacctccttcggtcggaaaacccct (SEQ ID NO: 147),
Ggttttctgacctccgtcggaaaacc (SEQ ID NO: 148),
GGTTTTCTGACACTCCGTCGGAAAACCCCT (SEQ ID NO: 228),
GGTTTTCTGATCTCCATCGGAAAACCCCT (SEQ ID NO: 229), or
GGTTTTCCGACCTCCGTCGGAAAACCCCT (SEQ ID NO: 230).

[073] In some embodiments, a human or murine eSL comprises, consists essentially of, or consists of a nucleic acid sequence at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%,

97%, 98%, 99% or 100% (or any percentage in between) identical to one or more of the following nucleotide sequences:
GGCTTTCTGGCACTCCACCGGAAAGCCCCT (SEQ ID NO: 190),
GGCTTTCTGGCACTCCGCCGGAAAGCCCCT (SEQ ID NO: 191), or
GGCTTTCTGGCCTCCACCGGAAAGCCCCT (SEQ ID NO: 192).

[074] In some embodiments, a dog or cat eSL comprises, consists essentially of, or consists of a nucleic acid sequence at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% (or any percentage in between) identical to one or more of the following nucleotide sequences:
GGTTTTCCGGTCTCCACCGGAAAGCCCCC (SEQ ID NO: 193).

[075] In some embodiments, a cow, sheep, or goat eSL comprises, consists essentially of, or consists of a nucleic acid sequence at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% (or any percentage in between) identical to one or more of the following nucleotide sequences:
GGCTTTCCGGTCTCCACCGGAAAGCCCCT (SEQ ID NO: 194), or
GGCTTTCCGGCCTCCGCCGGAAAGCCCCT (SEQ ID NO: 195).

[076] In some embodiments, a pig eSL comprises, consists essentially of, or consists of a nucleic acid sequence at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% (or any percentage in between) identical to one or more of the following nucleotide sequences:
GGTTTTCCGGTCTCCACCGGAAAACCCTT (SEQ ID NO: 196),
GGTTTTCCGTGCTCCCACGGAAAACCCTT (SEQ ID NO: 197),
GGTTTTCCGGCCTCCGCCGGAAAACCCTT (SEQ ID NO: 198),
GGTTTTCCGTGACTCCCACGGAAAACCCTT (SEQ ID NO: 199), or
GGTTTTCCGGCACTCCGCCGGAAAACCCTT (SEQ ID NO: 200).

[077] In some embodiments, a horse eSL comprises, consists essentially of, or consists of a nucleic acid sequence at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% (or any percentage in between) identical to one or more of the following nucleotide sequences:
GGTCTTCCGGTCTCCTCCGGAAGGCCCCC (SEQ ID NO: 201), or
GGTCTTCCGGCTCCCCGGAAGGCCCCC (SEQ ID NO: 202).

[078] In some embodiments, a sheep eSL comprises, consists essentially of, or consists of a nucleic acid sequence at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%,

99% or 100% (or any percentage in between) identical to one or more of the following nucleotide sequences:
GGCTTTCCGTGCTCCCACGGAAAGCCCCT (SEQ ID NO: 203),
GGCTTTCCGTGACTCCCACGGAAAGCCCCT (SEQ ID NO: 204), or
GGCTTTCCGGCACTCCGCCGGAAAGCCCCT (SEQ ID NO: 205).

[079] In some embodiments, engineered stem loops provide for enhanced stability of an snRNA relative to an snRNA comprising a native stem loop. In some embodiments is a native snRNA stem loop comprises, consists essentially of, or consists of a nucleic acid sequence at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% (or any percentage in between) identical to one or more of the following nucleotide sequences:
Ggttttctgacttcggtcggaaaacccct (SEQ ID NO: 145),
ggttttctgacttcggtcggaaaacc (SEQ ID NO: 206),
Ggctttctggctttttaccggaaagcc (SEQ ID NO: 235), or
ggctttctggctttttaccggaaagccCCT (SEQ ID NO: 236).

5' Interaction stability domain

[080] The eSL disclosed herein possesses more effective folding and annealing properties with a 5' interaction stability domain (5'ISD) and this in turn results in increased stability of the esnRNA compared to a non-engineered snRNA. The 5' ISD has nucleotides that are complementary to the nucleotides within the engineered SL, and without wishing to be bound by theory, an interaction between the 5'ISD and eSL is predicted to form secondary structure that protects the 5' end of an snRNA. In some aspects, the 5' ISD anneals and/or hybridizes to an eSL of the disclosure. In some aspects, the 5'ISD is a sequence having complementarity and/or reverse complementarity to a sequence present in an eSL of the disclosure. In some aspects, a 5'ISD disclosed herein can be one of the 5'ISDs selected from the following nucleotide sequences:
ggagt (SEQ ID NO: 12),
cctct (SEQ ID NO: 13),
ggaggt (SEQ ID NO: 14),
cctcct (SEQ ID NO: 15),
agccag (SEQ ID NO: 16),
ggaag (SEQ ID NO: 17),
gaagaag (SEQ ID NO: 18),

gttg (SEQ ID NO: 19),
ccgaa (SEQ ID NO: 20),
taaggag (SEQ ID NO: 21),
gaag (SEQ ID NO: 22), or
ggctt (SEQ ID NO: 23).

Targeting Sequences

[081] The esnRNA systems can be programmed to comprise a targeting sequence (TS) (also termed spacer). In some aspects, the targeting sequence is a 5' targeting sequence (5'TS) (also termed spacer) that targets one or more RNAs of interest. In this context, 5' is in reference to the snRNA insert's 5' end and not necessarily to the overall vector configuration comprising the snRNA insert or inserts. And the TS can be located in or near the 5' end of the snRNA. In an alternative embodiment, the targeting sequence(s) (TS) can be located in or near a 3' position in the snRNA construct, thereby generating a 3' targeting sequence (3' TS), particularly if the snRNA construct is not a U7-based snRNA.

[082] Targeting sequences of the disclosure, including 5' TS, and 3'TS can be between about 1 and about 200 nucleotides in length. In some aspects, targeting sequences of the disclosure are between about 10 and about 150 nucleotides in length. In some aspects, targeting sequences of the disclosure are between about 10 and about 100 nucleotides in length. In some aspects, targeting sequences of the disclosure are between about 20 and about 60 nucleotides in length. In some aspects, targeting sequences of the disclosure are at least about 10, 20, 30, 40, 50, 60, or about 70 nucleotides in length.

[083] In one example, U7 snRNA can be programmed by replacing the histone mRNA binding sequence with a sequence complementary to a target of interest. In some aspects, esnRNA systems of the disclosure bind a target mRNA or pre-mRNA sequence of interest. The exemplary esnRNA systems shown herein lead to blocking or knocking down microsatellite repeat expansions (for treating myotonic dystrophy (DM1) or Huntington's disease (HD), hexanucleotide repeat expansion (for treating C9/ALS),splicing modulation (for treating USH2A (Usher Syndrome type 2)), or targeting one or more exon splicing enhancers (ESE) to induce exon skipping (for treating DMD, e.g., DMD exon 51 skipping). In one embodiment, the target RNA of interest is a microsatellite or hexanucleotide repeat RNA or a non-repeat RNA. In another embodiment, the repeat RNA of interest is selected

from the group consisting of CUG, CAG, GGGGCC, and CCCCGG. In one embodiment, the esnRNA comprises a targeting sequence (TS) that targets two target RNAs of interest are GGGGCC and CCCCGG. In another embodiment, the two target RNAs of interest are a microsatellite repeat RNA and a non-repeat RNA. In another embodiment, the non-repeat RNA is a flanking sequence to the repeat RNA.

[084] In some embodiments, esnRNA of the disclosure target a pre-mRNA or mRNA sequence encoding the DMD gene. DMD is a gene encoding the protein dystrophin. Mutations in DMD are associated with Duchene muscular dystrophy. In some embodiments, the DMD RNA sequence targeted by esnRNA compositions of the disclosure is an exon 51 DMD RNA sequence.

[085] Target sequences that bind DMD can comprise, consist essentially of, or consist of a nucleic acid sequence at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% (or any percentage in between) identical to one or more of the following nucleotide sequences set forth in the table which follows:

DMD exon 51 RNA Targeting Sequences

UID	Targeting Sequences	SEQ ID NO:
z38	TACCTCCAACATCAAGGAAGATGGCA	206
z42	GTAACCACAGGTTGTGTCACCAGAGTAACA	207
Fusion Sequences		
z70	catacCTTCTGCTTGATGATCATCTCGCACCAGAGTAACAGTCTGAGTAGGAGctaaa	208
z71	catacCTTCTGCTTGATGATCATCTCGTGCCGCTGCCCAATGCCATCCTGGAG	209
z72	catacCTTCTGCTTGATGATCATCTCGGCCCAATGCCATCCTGGAGTTCctg	210
z73(z38/z42)	TACCTCCAACATCAAGGAAGATGGCAGTAACCACAGGTTGTGTCACCAGAGTAACA	211
z74	AACATCAAGGAAGATGGCATTTCTAGGTAACCACAGGTTGTGTCACCAGAGTAACA	212
z75	AACATCAAGGAAGATGGCATTTCTAGTGCCGCTGCCCAATGCCATCCTGGAG	213
z76	TTTTTCTCATACCTTCTGCTTGATGTCTGAGTAGGAGCTAAAATATTTTGGG	214
Z187 (z42/z38)	GTAACCACAGGTTGTGTCACCAGAGTAACATACCTCCAACATCAAGGAAGATGGCA	215
z230	CGAGATGATCATCAAGCAGAAGgtatgCACCAGAGTAACAGTCTGAGTAGGAGctaaa	216
z231	CACCAGAGTAACAGTCTGAGTAGGAGctaaaTACCTCCAACATCAAGGAAGATGGCA	217
z232	TACCTCCAACATCAAGGAAGATGGCACACCAGAGTAACAGTCTGAGTAGGAGctaaa	218
z233	GTCTGAGTAGGAGctaaaatattttgggTACCTCCAACATCAAGGAAGATGGCA	219
z234	TACCTCCAACATCAAGGAAGATGGCAGTCTGAGTAGGAGctaaaatattttggg	220

z235	GTCTGAGTAGGAGctaaaatattttgggtttttctcatacCTTCTGCTTGAT	221
z237	cCTTCTGCTTGATGATCATCTCGGAGTAACAGTCTGAGTAGGAGc	222
z238	cCTTCTGCTTGATGATCATCTCGCCAGAGTAACAGTCTGAGTAGGAGc	223
z239	cCTTCTGCTTGATGATCATCTCGCAGTCTGAGTAGGAGctaaa	224
z240	ctcatacCTTCTGCTTGATGGAGTAACAGTCTGAGTAGGAGc	225
z241	ctcatacCTTCTGCTTGATGCCAGAGTAACAGTCTGAGTAGGAGc	226
z242	ctcatacCTTCTGCTTGATGCAGTCTGAGTAGGAGctaaa	227

[086] In one embodiment, TSs which are a fusion as in the above table can be a single TS sequence comprised within the fusion sequence.

[087] In another embodiment, the targeting sequences (TSs) that target two or more RNAs of interest. In another embodiment, the TSs which target two or more RNAs of interest are different sequences which target the same pre-mRNA molecule. In one embodiment, the spacers or TSs are a fusion sequence. In another embodiment, the fusion sequence is a spacer targeting DMD exon 51, wherein the fusion sequence is set forth in the table above.

[088] In some embodiments, CUG repeat targeting sequences comprise the nucleic acid sequence:
CAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAG (SEQ ID NO: 165).

[089] In some embodiments, CAG repeat targeting sequences comprise the nucleic acid sequence: CTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTG (SEQ ID NO: 167).

Sm Binding Domains

[090] The esnRNA systems disclosed herein utilize an Sm binding domain (SmBD). The Sm protein ring that assembles around the Sm binding domain (SmBD) to form an snRNP includes SmB/B', SmD1, SmD2, SmD3, SmE, SmF, and SmG. The U7 Sm binding site recruits endogenous RNA binding factors and can be replaced with a non-U7 snRNA to make the esnRNA more stable. In one embodiment, the SmBD is selected from the group consisting of U1, U2, U4, and U5 snRNAs. In another embodiment, the SmBD is derived from a pseudo snRNA. In another embodiment, the SmBD is a nucleotide sequence comprising SEQ ID NO: 31 (ATTTTT). In another embodiment, the SmBD comprises a nucleotide sequence selected from the group consisting of SEQ ID NO: 32 (AATTTTTGG), SEQ ID NO: 33 (AATTTGTGG), SEQ ID NO: 34 (AATTTGTGG), SEQ ID NO: 35 (AATTTCTGG), SEQ ID NO: 36 (GATTTTTGG), SEQ ID NO: 37 (AATTTTTGA), SEQ

ID NO: 38 (AATTTTTTG), SEQ ID NO: 161 (AATTTTTGGAGCA), and SEQ ID NO: 163 (AATTTTTGGAGTA) .

Promoter Sequences

[091] The esnRNA systems disclosed herein comprise an snRNA promoter from any of U1-U12. In one embodiment, the snRNA promoter is a U7 promoter. In another embodiment, the U7 promoter is a human U7 promoter (hU7) or a mouse U7 promoter (mU7). In another embodiment, the U7 promoter is an endogenous human U7 promoter comprising SEQ ID NO: 39:

TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGGCTGTGACTGGC
TGCTTTCTCAACCAATCAGCACCGAACTCATTTGCATGGGCTGAGAACAAATGTT
CGCGAACTCTAGAAATGAATGACTTAAGTAAGTTCCTTAGAATATTATTTTTCCT
ACTGAAAGTTACCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAAA
GTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATATCCCATCTTCTCTC
CAAACACATACGCA.

[092] In one embodiment, the snRNA promoter is a U1 promoter. In another embodiment, the U1 promoter is a human U1 promoter or a mouse U1 promoter.

[093] In another embodiment, an snRNA promoter drives a copy of an snRNA insert . In another embodiment, each copy of an snRNA insert is the same. In another embodiment, different snRNA promoters drive each copy of an snRNA insert. In one embodiment, a 2x snRNA comprises a mouse U7 promoter driving one copy of an snRNA insert and a mouse U1 promoter drives the other copy of an snRNA insert.

[094] In other aspects, the snRNA promoter is a PolII promoter or a PolIII promoter. In other aspects, the snRNA promoter comprises, consists essentially of, or consists of a nucleic acid sequence at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% (or any percentage in between) identical to a promoter and/or promoter sequence listed in the Exemplary Promoter Table which follows:

Exemplary Promoter	Promoter Sequence
hU1	AAGGACCAGCTTCTTTGGGAGAGAACAGACGCAGGGGCGGGAGGGA AAAAGGGAGAGGCAGACGTCACTTCCCCTTGGCGGCTCTGGCAGCAG ATTGGTCGGTTGAGTGGCAGAAAGGCAGACGGGGACTGGGCAAGGC ACTGTCGGTGACATCACGGACAGGGCGACTTCTATGTAGATGAGGCA GCGCAGAGGCTGACGTCTTCGCCACTTGCTGCTTCACCACGAAGGAG TTCCCGTGCCCTGGGAGCGGGTTCAGGACCGCTGATCGGAAGTGAGA ATCCCAGCTGTGTGTCAGGGCTGGAAAGGGCTCGGGAGTGCGCGGGG

	CAAGTGACCGTGTGTGTAAAGAGTGAGGCGTATGAGGCTGTGTCGGG GCAGAGGCacaacgtttc (SEQ ID NO: 40)
hU2	CCACGCCCTCTGTGAAAGGGCGGGGCATGCAAATTCGAAATGAAAGC CCGGGAACGCCGGAAGAAGCACGGGTGTAAGATTTCCCTTTTCAAAG GCAGAGAATAAGAAATCAGCCCGAGAGTGTAAGGGCGTCAATAGCG CTGTGGACGAGACAGAGGGAATGGGGCAAGGAGCGAGGCTGGGGCT CTCACCGCGACTTGAATGTGGATGAGAGTGGGACGGTGACGGCGGGC GCGAAGGCGAGCGC (SEQ ID NO: 41)
hU4	TTCGCAGTCTCTGAATTAAGTCTATTAGCATGTTCCTCCCATAGTGCT TTGCTTCATATCAACAAAAACCTAGCTAAGTGAAATCAGCAACGATA TGCAGAAACCACCTACGCAGGTCACAAACATCTTTCTATGATTGTATA ATTTTCAAGCAAGCAATAAGTGAAGATTTTTCCATAGGCCCTAAACTC ACCTTTGCGAAATAGGAAGCTGGTTTATTGGGAGTGATGAGCAGGGG GCGTAACAAATT (SEQ ID NO: 42)
hU5	GCAGCAAGGCCTCCACTTCACCCCCTAAAGGTTGCCCCAAGAGCACC GTGTGACTGCTAAGGTATTTCCGGAGTCTAAAGACGATTATTCAGGTC TCATTTGCATACCCATAATACACTGCAAACAGTATTTTTTTCGGAAAA ACATTTATATATTGCTTGACATTTTTAAGTATGAGAATTTTGCATGCA GAATTTTTTTGTATAAACTTTCTCAGGTAGTAACCCTTGGGATTAGTA GACACCATCAGTGTACTAGGAATTGCAGTTACCCGAAAATTGAGTTA CAGAAGTAACTGGT (SEQ ID NO: 43)
hU6	Gtttattacagggacagcagagatccagtttggttaattaaggtaccgagggcctatttcccatgattccttcatatttg catatacgatacaaggctgttagagagataattagaattaatttgactgtaaacacaaagatattagtacaaaatacgt gacgtagaaagtaataatttcttgggtagtttgcagttttaaaattatgttttaaaatggactatcatatgcttaccgtaact tgaaagtatttcgatttcttggctttatatatcttgtggaaaggacgaaacacc (SEQ ID NO: 44)
h7sk	CTGCAGTATTTAGCATGCCCCACCCATCTGCAAGGCATTCTGGATAGT GTCAAAACAGCCGGAAATCAAGTCCGTTTATCTCAAACTTTAGCATTT TGGGAATAAATGATATTTGCTATGCTGGTTAAATTAGATTTTAGTTAA ATTTCCTGCTGAAGCTCTAGTACGATAAGTAACTTGACCTAAGTGTAA AGTTGAGATTTCCTTCAGGTTTATATAGCTTGTGCGCCGCCTGGGTAC CTC (SEQ ID NO: 45)
tRNA(Val)	CAGGACTAGTCTTTTAGGTCAAAAAGAAGAAGCTTTGTAACCGTTGG TTTCCGTAGTGTAGTGGTTATCACGTTCGCCTAACACGCGAAAGGTCC CCGGTTCGAAG (SEQ ID NO: 46)
mU1	TTGTTCCTCTTAGTGTTAATTCACACTAAAGACTGTGCATCCGACTCC TACATTTATGAAAGTAAATGCCTGTTGTTAGAACAAAAAAGGCTACA GAACAAAAAACAAAGCGAAATACCATCTGCTTTAGGTTCAGTGTGGT ATTTTCCCGCTGACAGGGAGGCGGGTTTTTGGGTACAGGAAACGAGT CACTATGGAGGCGGTACTATGTAGATGAGAATTCAGGTGCAAACTGG GAAAAGCAACTGCTTCCAAATATTTGTGATTTTTACAGTGTAGTTTTG GAAAAACTCTTAGCCTACCAATTCTTCTAAGTGTTTTAAAATGTGGGA

	GCCAGTACACATGAAGTTATAGAGTGTTTTAATGAGGCTTAAATATTT ACCGTAACTATGAAATGCTACGCATATCATGCTGTTCAGGCTCCGTGG CCACGCAACTC (SEQ ID NO: 47)
mU7+ extra 3'	TaacaacataggagctgtgattggctgttttcagccaatcagcactgActcatttgcatagcctttacaagcggtcac aaactcaagaaacgagcggttttaatagtcttttagaatattgtttatcgaaccgaataaggaactgtgctttgtgattca catatcagtggaggggtgtggaaatggcaccttgatctcaccctcatcgaaagtggagttgatgtcctTccctggct cgctacagacgcacttccgcaa (SEQ ID NO: 48)
mU7	taacaacataggagctgtgattggctgttttcagccaatcagcactgActcatttgcatagcctttacaagcggtcac aaactcaagaaacgagcggttttaatagtcttttagaatattgtttatcgaaccgaataaggaactgtgctttgtgattca catatcagtggaggggtgtggaaatggcaccttgatctcaccctcatcgaaagtggagttgatgtcctTccctggct cgctacagacgcacttccgc (SEQ ID NO: 151)
hU7	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGGCTGT GACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTTGCATGGGC TGAGAACAAATGTTCGCGAACTCTAGAAATGAATGACTTAAGTAAGT TCCTTAGAATATTATTTTTCCTACTGAAAGTTACCACATGCGTCGTTG TTTATACAGTAATAGGAACAAGAAAAAAGTCACCTAAGCTCACCCTC ATCAATTGTGGAGTTCCTTTATATCCCATCTTCTCTCCAAACACATAC GCA (SEQ ID NO: 39)
mU5	TGCCAACAGCTTTGAAATCCTCTGTGCTCTTGTGCCAATCCCACCCTC AGAACAGGGAGTCTGTCGGTTATGTTTTCGTCCTTTACAGTTCTTCGC CGTCTAATCCATTGGAAACCTCCTTTATTTAAAGGAAACCGTGTCCAA ATTCAGTGTACAGAGGTGCAAACCTCCGCCCCGCTCCTTGTAGGAAG CCCACGGGAACTGGGCCAATCGGACGGCGCTTACTCGGCTCATTTAC ATACCCATAACACACCGCGGCTAATGCAAATATTTTCGTGAAAAGAT CTTCCATTACTCGAAGTTTTAAAACTAAAAACAAAATATTATTTCAAA AGATCATGAAGAAATTTCTGTCGGTAACAGCAGTTTCAATTGATAAA TCACCATCACTTATCTAGGAGGTTCTGTTACTCTAGAAGTGAATTAAG CAGGACAGCTGT (SEQ ID NO: 152)
mU2	Gggcggggcatgcaaataactgctctgtggaactctgggagcaaaaacaaaaaactgcaaccaaaacttctcggc ctccttgaatcttacaggcttttcgtggcgtaaaggtggtgtactcaatgaagaggagagtctgtgttggctgcatgttt gagtcggttggttggtgactgtgaatTAAAGGTGTGGtcggtgttgagtgtatggggcgtgtgggcgtagt tcggt (SEQ ID NO: 153)
mU6	cgacgccgccatctctaggcccgcgccggccccctcgcacagacttgtgggagaagctcggctactcccctgccc cggttaatttgcatataatatttcctagtaactatagaggcttaatgtgcgataaaagacagataatctgttctttttaatac tagctacattttacatgataggcttggatttctataagagatacaaatactaaattattattttaaaaaacagcacaaaag gaaactcaccctaactgtaaagtaattgtgtgttttgagactataaatatcccttggagaaaagccttgttt (SEQ ID NO: 154)
mH1	CATgCAAATTACGCGCTgTGCTTTGTGGGAAATCACCCTAAACGTAAA ATTTATTCCTCTTTcGAGCCTTATAGTGGcGGCCGGTCTACACCCTAAA (SEQ ID NO: 155)

Terminator Sequences

[095] The esnRNA systems disclosed herein comprise an snRNA downstream terminator (DT). Downstream terminators define the end of a transcriptional unit, such as an esnRNA or

snRNA. In another embodiment the snRNA DT is a U7 DT comprising: CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGCAAAAATTATGG GTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCTTGGAG (SEQ ID NO: 49).

[096] In one embodiment, the esnRNA comprises the eSL, one or more promoters, the TS, the SmBD, the 5'ISD, and the DT. In one aspect, promoter and DT combinations are be mixed and matched.

[097] In another embodiment, the DT is selected from the exemplary DTs and/or DT sequences listed in the Exemplary DT Table below:

Exemplary DT	DT Sequence
hU1	ACTTTCTGGAGTTTCAAAAACAGACTGTACGCCAAGGGTCATATCTT TTT (SEQ ID NO: 50)
hU2	CCGGGGATACAACGTGTTTCCTAAAAGTAGAGGGAGGTAAGAGACG GTAG (SEQ ID NO: 51)
hU4	CTGAATTTTCTTGCAGTTGAACAACAGAGGCTTTTTTTGTGTGTGTGG GG (SEQ ID NO: 52)
hU5	ATATGTGGTAATCCAACAATAGAAATTATTTTTAAGTTTGTGTGTTCC TT (SEQ ID NO: 53)
hU6	TTTTTT (SEQ ID NO: 54)
h7sk	TTTTTT SEQ ID NO: 55)
tRNA(Val)	TTTTTT (SEQ ID NO: 56)
mU1	GTTTACTTGGTTTTAAAAATAGCTTGCACTAGCGATACGGAATATGG TTATTAGGTTTGTTAGGCATCATGTCGTGTCTTACTATAGAAAAATA ACGTAGTGTTCATTTTAGCCTGCCTGTATGTGTTAATTTGTCCTTATT GCGCATTGTTCTTGTTAAGTCTTCTGTAAGGAGTTGCGGGTTTCAAA CTGTCAGTCTGAGAGCA (SEQ ID NO: 57)
mU7+	Cccaatttcactggtctacaatgaaagcaaaacagttctcttccccgctccccggtgtgtgagaggggctttgatcc ttctctggtttcctaggaaacgcgtatgtgtac (SEQ ID NO: 58)
mU7	Cccaatttcactggtctacaatgaaagcaaaacagttctcttccccgctccccggtgtgtgagaggggctttgatcc ttctctggtttcctaggaaacgcgtatgtg (SEQ ID NO: 156)
hU7	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGCAAA AATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCTTGGAG (SEQ ID NO: 49)
hU7	CTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGCAAAAAT TATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCTTGGAG (SEQ ID NO: 234)

mU5	CCACATTTTGTGTTTAAAAATAGAAATATTTAAGTGAGATCAGTTTA AATCTGCTTTATCTAGGGTGTCTAACTGCTTGCATCTTTTTAACTTTT CCTTATTTGTGAGAAGGTCTGTAAAACTTATTATATGTTAGTACACT GTAGCTGTCTTCAGACACTCCAGAAGAGGGATTCAGATCACCTTACA GATGGTTTTGA (SEQ ID NO: 157)
mU2	CCCTCTGGGGAgtaaagttggttttaaagtcagagcatggtgattgtagggcagtccaacttttttaaatat gctgtg (SEQ ID NO: 158)
mU6	TTTTTT (SEQ ID NO: XX)
mH1	TTTTTT (SEQ ID NO: XX)

[098] In one embodiment, the esnRNA is delivered in an AAV vector.

[099] In some embodiments, the AAV vector comprises multiple copies of the esnRNA. In some embodiments, the multiple copies of the esnRNA are 2, 3, or 4 copies (2x, 3x, or 4x) of the esnRNA. In some embodiments, the multiple copies of the esnRNA are 4 or more copies of the esnRNA.

[0100] In some embodiments, each esnRNA of the multiple copies of esnRNA is separated by a nucleic acid buffer sequence derived from human non-coding genomic sequences downstream of an snRNA. In one embodiment, the buffer sequence is derived from human genomic sequences downstream of U7.

[0101] In one embodiment, the buffer sequence is selected from the group consisting of the following nucleic acid sequence:

buffer 1 (30bp) CAAACTACAGAGCCAAGTGCTATCCACAGA (SEQ ID NO: 24),

buffer 2 (30bp)

GAGCTTTCTGGGTTGCCATCTCAAGCAGAC(SEQ ID NO: 25),

buffer 3 (30bp) TACAAGGCCATCAGCTCATACTCACAATTG(SEQ ID NO: 26), and a combination thereof.

[0102] In another embodiment, the buffer sequence is selected from the group consisting of the following nucleic acid sequence:

buffer 1 (100bp)

CAAACTACAGAGCCAAGTGCTATCCACAGAGAGCTTTCTGGGTTGCCATCTCAAG CAGACTACAAGGCCATCAGCTCATACTCACAATTGACTTTGAGAG(SEQ ID NO: 27),

buffer 2 (100bp)

TTGACCACATACGTGCTCTTTCAAAGTTCTGTGTTTGAAGTTATGTTAGTAACAAC TGATGCCCATCCTGCAATGACAAATCCAATTCTCAGTGCAGCTC(SEQ ID NO: 28), and a combination thereof.

[0103] In another embodiment, the buffer sequence is selected from the group consisting of the following nucleic acid sequence:

buffer 1 (500bp)

CAAACTACAGAGCCAAGTGCTATCCACAGAGAGCTTTCTGGGTTGCCATCTCAAG
CAGACTACAAGGCCATCAGCTCATACTCACAATTGACTTTGAGAGTCATTTTCCA
ATGCTCCTACACACCCCTTCTTCACAATCCCCAACAAATCTGAGGCTGGAACTTG
GTACCATAACAATCATTACATTATTTCACCAGAAGTACACCTTGCCTGGAAGATT
GGCATTATAGCATCTTCTAACATTGTGAAAGTTAGTGACCAATGAGGAGATCCAA
GTCAGTTCCAGTTGGATTTCTCTATACTCTATAATAAATATATATGGTGTCTTCAA
CAATAGGACTTTGCCATCCAGTGATGCTAAAAATCAATAACAATGGCAATAACC
TGCCCTGTTTGGAAAGCCTCTGGCTTCCATGACTAACAATTCAAGGCAGGTCTCC
TATACCTAGTACTGAGATTTTTATTTGATAAACTATATCTTCTGGGAGGAGAAGC
ATTGT(SEQ ID NO: 29),

buffer 2 (500bp)

TTGACCACATACGTGCTCTTTCAAAGTTCTGTGTTTGAAGTTATGTTAGTAACAAC
TGATGCCCATCCTGCAATGACAAATCCAATTCTCAGTGCAGCTCTCTGAAATAGT
TTTGCTTTCTCTCTCTAGGTCTGTTCTATACTCCTAACTCTCCAGGAGTTTACAAG
GAATAAAATCTCTTCCAAATGCTTTCTGTTGCAACAACTGGACCATACTGAAAGC
TGAGGCCCACAATTGCAATCTAGGTTAGCAGGTAATCATTGTTGGTGAGGTCCTC
CCTTTCCCCAGGCTCGTGTTTGTATTGGGGAGCAGGAAATTTTTGCTAGAGCAGC
ACTGCCATCTCTCTACACTCCACCTGATTGGTGGGATGGACCAGAGAAATGGACA
TTCCCAACACAGTCCCTCCTTTCACATCTGCTCACCTGCCCACAGGATACTTTCCA
CCATGCATACTGGGCTCTGCACCAACCATTCAGCAGTGATGAAGAGGAAACTTG
AAC(SEQ ID NO: 30), and/or a combination thereof.

[0104] The 100bp and 500bp buffer 1 sequences are derived from a sequence starting 100bp downstream of the mus musculus U7 pseudogene 8 (Location Chromosome 14: 4,409,359-4,409,421 reverse strand. GRCm39:CM001007.3). The 100bp and 500bp buffer 2 sequences are derived from the sequence starting 130bp downstream of human U7 pseudogene 5 (Chromosome X: 140,451,148-140,451,208 forward strand. GRCh38:CM000685.2). Both 100bp buffers are the first 100bp of the corresponding 500bp buffer. The 30bp buffers 1, 2, and 3, are sequential 30bp sequences within "100bp buffer 1", downstream of the mus musculus U7 pseudogene 8. These downstream sequences were selected due to the lack of any known regulatory sites or genes within or nearby to the

sequence (using Gencode/Ensembl), in addition to lack of repetitive sequence, 40-60% GC content for total buffer, 40-60% GC content in the 20bp region at both ends of the buffer, and minimal sequence complexity.

esnRNA Sequences

[0105] Exemplary esnRNA sequences of the disclosure can comprise any combination of esnRNA features described herein. In some aspects, the esnRNA comprises, consists essentially of, or consists of a nucleic acid sequence at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% (or any percentage in between) identical to an esnRNA listed in the esnRNA Table which follows:

esnRNA sequences of the disclosure

ID	Description	Target Repeat or Gene Symbol	SEQ ID NO:	Sequence
	u7 snRNA CUG	CUG	65	ggagtCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGAATTTTTGGAGTAggctttctggctccttaccggaaagcc
	u7 snRNA NT	non-targeting	66	ggagtTCACCAGAAGCGTACCATACTCACGAAATTTTTGGAGTAggctttctggctccttaccggaaagcc
	u7 snRNA CAG	CAG	67	ggagtCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGAATTTTTGGAGTAggctttctggctccttaccggaaagcc
	z38/42 esnRNA targeting dystrophin exon 51	DMD exon 51	68	ggagtTACCTCCAACATCAAGGAAGATGGCAGTAACCACAGGTTGTGTCACCAGAGTAACAAATTTTTGGAGTAggctttctggctccttaccggaaagcc
	z42 esnRNA	DMD exon 51	69	ggagtGTAACCACAGGTTGTGTCACCAGAGTAACAAATTTTTGGAGTAggctttctggctccttaccggaaagcc
	z38 esnRNA	DMD exon 51	70	ggagtTACCTCCAACATCAAGGAAGATGGCAAATTTTTGGAGTAggctttctggctccttaccggaaagcc
sR2 20031	U7CUGx15-U1 Sm site_U7 term opt sl	CUG	71	ggagtCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGAATTTGTGGAGTAggctttctggctccttaccggaaagcc
sR2 20032	U7CUGx15-Sm mut 1_U7 term opt sl	CUG	72	ggagtCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGTCGAGTTGGAGTAggctttctggctccttaccggaaagcc
sR2 20033	U7CAGx15-no Sm_U7 term opt sl	CUG	73	ggagtCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGAGTAggctttctggctccttaccggaaagcc
sR2 20034	U7knt-U1 Sm site_U7 term opt sl	non-targeting	74	ggagtTCACCAGAAGCGTACCATACTCACGAAATTTGTGGAGTAggctttctggctccttaccggaaagcc
sR2 20035	U7knt-Sm mut 1_U7 term opt sl	non-targeting	75	ggagtTCACCAGAAGCGTACCATACTCACGATCGAGTTGGAGTAggctttctggctccttaccggaaagcc
sR2 20036	U7knt-no Sm_U7 term opt sl	non-targeting	76	ggagtTCACCAGAAGCGTACCATACTCACGAAGTAggctttctggctccttaccggaaagcc

sR2 20037	U7CAGx15-U1 Sm site_U7 term opt sl	CAG	77	ggagtCTGCTGCTG

sR2 20004	U7-nt	non-targeting	94	ggagtTCACCAGAAGCGTACCATACTCACGAAATTTTTGGAGTAggctttctggctccttaccggaaagcc
sR2 20097	U7 alt ISD SEQID16 non-targeting nt1	non-targeting	95	cctctTCACCAGAAGCGTACCATACTCACGAAATTTTTGGAGTAggctttctgggaggttaccggaaagcc
sR2 20098	U7 alt ISD SEQID17 non-targeting nt1	non-targeting	96	ggaggtTCACCAGAAGCGTACCATACTCACGAAATTTTTGGAGTAggctttctggcctccttaccggaaagcc
sR2 20099	U7 alt ISD SEQID18 non-targeting nt1	non-targeting	97	cctcctTCACCAGAAGCGTACCATACTCACGAAATTTTTGGAGTAggctttctggggaggttaccggaaagcc
sR2 20100	U7 alt ISD SEQID19 non-targeting nt1	non-targeting	98	agccagTCACCAGAAGCGTACCATACTCACGAAATTTTTGGAGTAggctttctggctggctaccggaaagcc
sR2 20101	U7 alt ISD SEQID20 non-targeting nt1	non-targeting	99	ggaagTCACCAGAAGCGTACCATACTCACGAAATTTTTGGAGTAggctttctggcttccccggaaagcc
sR2 20102	U7 alt ISD SEQID21 non-targeting nt1	non-targeting	100	gaagaagTCACCAGAAGCGTACCATACTCACGAAATTTTTGGAGTAggctttctggcttcttcccggaaagcc
sR2 20103	U7 alt ISD SEQID22 non-targeting nt1	non-targeting	101	gttgTCACCAGAAGCGTACCATACTCACGAAATTTTTGGAGTAggctttctggcaacttaccggaaagcc
sR2 20104	U7 alt ISD SEQID23 non-targeting nt1	non-targeting	102	ccgaaTCACCAGAAGCGTACCATACTCACGAAATTTTTGGAGTAggctttctggttcggtaccggaaagcc
sR2 20105	U7 alt ISD SEQID24 non-targeting nt1	non-targeting	103	taaggagTCACCAGAAGCGTACCATACTCACGAAATTTTTGGAGTAggctttctggctccttaccggaaagcc
sR2 20106	U7 alt ISD SEQID25 non-targeting nt1	non-targeting	104	gaagTCACCAGAAGCGTACCATACTCACGAAATTTTTGGAGTAggctttctggcttcttcccggaaagcc
sR2 20107	U7 alt ISD SEQID26 non-targeting nt1	non-targeting	105	ggcttTCACCAGAAGCGTACCATACTCACGAAATTTTTGGAGTAggctttctggaagccttaccggaaagcc
sR2 20108	U7 alt ISD SEQID27 non-targeting nt1	non-targeting	106	gaagTCACCAGAAGCGTACCATACTCACGAAATTTTTGGAGTAggctttctggcttcttaccggaaagcc
sR2 20010	U7-CUGx15	CUG	107	ggagtCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGAATTTTTGGAGTAggctttctggctccttaccggaaagcc
sR2 20109	U7 alt ISD SEQID16 CUGx15	CUG	108	cctctCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGAATTTTTGGAGTAggctttctgggaggttaccggaaagcc
sR2 20110	U7 alt ISD SEQID17 CUGx15	CUG	109	ggaggtCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGAATTTTTGGAGTAggctttctggcctccttaccggaaagcc
sR2 20111	U7 alt ISD SEQID18 CUGx15	CUG	110	cctcctCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGAATTTTTGGAGTAggctttctgggaggttaccggaaagcc
sR2 20112	U7 alt ISD SEQID19 CUGx15	CUG	111	agccagCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGAATTTTTGGAGTAggctttctggctggctaccggaaagcc
sR2 20113	U7 alt ISD SEQID20 CUGx15	CUG	112	ggaagCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGAATTTTTGGAGTAggctttctggcttccccggaaagcc

sR2 201 14	U7 alt ISD SEQID21 CUGx15	CUG	113	gaagaagCAGCAGCAGCAGCAGCAGCAGCAGCA GCAGCAGCAGCAGCAGAATTTTTGGAGTAggctttctgg cttcttcccggaaagcc
sR2 201 15	U7 alt ISD SEQID22 CUGx15	CUG	114	gttgCAGCAGCAGCAGCAGCAGCAGCAGCAGCA GCAGCAGCAGCAGAATTTTTGGAGTAggctttctggcaact taccggaaagcc
sR2 201 16	U7 alt ISD SEQID23 CUGx15	CUG	115	ccgaaCAGCAGCAGCAGCAGCAGCAGCAGCAGC AGCAGCAGCAGCAGAATTTTTGGAGTAggctttctggttcg gtaccggaaagcc
sR2 201 17	U7 alt ISD SEQID24 CUGx15	CUG	116	taaggagCAGCAGCAGCAGCAGCAGCAGCAGCA GCAGCAGCAGCAGCAGAATTTTTGGAGTAggctttctgg ctccttaccggaaagcc
sR2 201 18	U7 alt ISD SEQID25 CUGx15	CUG	117	gaagCAGCAGCAGCAGCAGCAGCAGCAGCAGC AGCAGCAGCAGCAGAATTTTTGGAGTAggctttctggcttc ttcccggaaagcc
sR2 201 19	U7 alt ISD SEQID26 CUGx15	CUG	118	ggcttCAGCAGCAGCAGCAGCAGCAGCAGCAGC AGCAGCAGCAGCAGAATTTTTGGAGTAggctttctggaag ccttaccggaaagcc
sR2 201 20	U7 alt ISD SEQID27 CUGx15	CUG	119	gaagCAGCAGCAGCAGCAGCAGCAGCAGCAGC AGCAGCAGCAGCAGAATTTTTGGAGTAggctttctggcttc ttaccggaaagcc
	DMD z42/38 reverse fusion	DMD exon 51	179	ggagtGTAACCACAGGTTGTGTCACCAGAGTAACAT ACCTCCAACATCAAGGAAGATGGCAaATTTTTGGA Gcaggttttctgacctccgtcggaaaaccccct
	DMD z38/42 forward fusion	DMD exon 51	180	ggagtTACCTCCAACATCAAGGAAGATGGCAGTAAC CACAGGTTGTGTCACCAGAGTAACAaATTTTTGGA Gcaggttttctgacctccgtcggaaaaccccct
	z42/38 reverse fusion no CCU tail	DMD exon 51	181	ggagtGTAACCACAGGTTGTGTCACCAGAGTAACAT ACCTCCAACATCAAGGAAGATGGCAaATTTTTGGA Gcaggttttctgacctccgtcggaaaacc
	z38/42 for fusion no ISD no eSL	DMD exon 51	182	TACCTCCAACATCAAGGAAGATGGCAGTAACCAC AGGTTGTGTCACCAGAGTAACAaATTTTTGGAGcagg ttttctgacttcggtcggaaaaccccct
	z38/42 forward fusion human loop with ISD and eSL	DMD exon 51	183	ggagtTACCTCCAACATCAAGGAAGATGGCAGTAAC CACAGGTTGTGTCACCAGAGTAACAAATTTTTGGA GTAggctttctggctccttaccggaaagcc
	z38/42 forward fusion human loop with ISD and eSL and added CCU tail	DMD exon 51	184	ggagtTACCTCCAACATCAAGGAAGATGGCAGTAAC CACAGGTTGTGTCACCAGAGTAACAAATTTTTGGA GTAggctttctggctccttaccggaaagccccct
	Z38/z42 forward fusion long mouse loop with 5' ISD and eSL	DMD exon 51	185	ggagtTACCTCCAACATCAAGGAAGATGGCAGTAAC CACAGGTTGTGTCACCAGAGTAACAaATTTTTGGA GcaGgttttctgacctccttcggtcggaaaaccccct

Vectors

[0106] Within the context of a recombinant expression vector, the terminology "operably linked" is intended to mean that the hybrid promoter is linked to an NOI in a manner

permitting expression of the nucleotide sequence in, for example, a host cell when the vector is introduced into (or in contact with) the host cell.

[0107] In some embodiments of the compositions and methods of the disclosure, a vector comprises the engineered snRNA. In some embodiments, the therapeutic snRNA is in a single or unitary vector.

[0108] In some embodiments of the compositions and methods of the disclosure, the RNA-binding snRNA systems are capable of targeting toxic CAG, CUG, GGCCCC, CCGGG, or GGCCC+CCGGGG RNA repeats (or flanking sequences thereof) are in a single vector. In some embodiments of the compositions and methods of the disclosure, the RNA-targeting systems are capable of targeting a non-repeat RNA of interest. In some embodiments of the compositions and methods of the disclosure, the RNA-targeting systems are capable of targeting one or more sequences of DMD. In some aspects, the snRNA systems are capable of targeting multiple (i.e., two or more) RNAs of interest. In some embodiments, the two or more RNAs of interest can be the same pre-mRNA molecule but different sequences within the pre-mRNA molecule.

[0109] One type of vector is a "plasmid," which refers to a circular double stranded DNA loop into which additional DNA segments can be inserted, such as by standard molecular cloning techniques. Another type of vector is a viral vector, wherein virally -derived DNA or RNA sequences are present in the vector for packaging into a virus (e.g., retroviruses, replication defective retroviruses, adenoviruses, replication defective adenoviruses, and adeno-associated viruses). Viral vectors also include polynucleotides carried by a virus for transfection into a host cell. In some embodiments, the vector is a lentivirus (such as an integration-deficient lentiviral vector) or adeno-associated viral (AAV) vector. Vectors are capable of autonomous replication in a host cell into which they are introduced such as e.g., bacterial vectors having a bacterial origin of replication and episomal mammalian vectors and other vectors such as, e.g., non-episomal mammalian vectors, are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome.

[0110] In some embodiments, vectors such as e.g., expression vectors, are capable of directing the expression of genes to which they are operatively-linked. Common expression vectors are often in the form of plasmids. In some embodiments, recombinant expression vectors comprise a nucleic acid provided herein such as e.g., an esnRNA in a form suitable for expression of a protein in a host cell. Recombinant expression vectors include one or

more regulatory elements, which may be selected on the basis of the host cells to be used for expression, that is operatively-linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory element(s) in a manner that allows for expression of the nucleotide sequence such as e.g., in an in vitro transcription/translation system or in a host cell when the vector is introduced into the host cell. Certain embodiments of a vector depend on factors such as the choice of the host cell to be transformed, and the level of expression desired. A vector can be introduced into host cells to thereby produce transcripts, proteins, or peptides, including fusion proteins or peptides, encoded by nucleic acids as described herein such as, e.g., snRNAs, CRISPR transcripts, proteins, enzymes, mutant forms thereof, fusion proteins thereof, etc.

Viral Vectors

[0111] In some embodiments of the compositions and methods of the disclosure, a vector of the disclosure is a viral vector. In some embodiments, the viral vector comprises a sequence isolated or derived from a retrovirus. In some embodiments, the viral vector comprises a sequence isolated or derived from a lentivirus. In some embodiments, the viral vector comprises a sequence isolated or derived from an adenovirus. In some embodiments, the viral vector comprises a sequence isolated or derived from an adeno-associated virus (AAV). In some embodiments, the viral vector is replication incompetent. In some embodiments, the viral vector is isolated or recombinant. In some embodiments, the viral vector is self-complementary.

Adeno-associated Virus Vectors

[0112] An "AAV vector" as used herein refers to a vector comprising, consisting essentially of, or consisting of one or more nucleic acid molecules and one or more AAV inverted terminal repeat sequences (ITRs). In some aspects, the nucleic acid molecule encodes for an esnRNA of the disclosure. Such AAV vectors can be replicated and packaged into infectious viral particles when present in a host cell that provides the functionality of rep and cap gene products, for example, by transfection of the host cell. In some aspects, AAV vectors contain a promoter, at least one nucleic acid that may encode at least one protein or RNA, and/or an enhancer and/or a terminator within the flanking ITRs that is packaged into the infectious AAV particle. The encapsidated nucleic acid portion may be referred to as the AAV vector genome. Plasmids containing AAV vectors may also contain elements for manufacturing

purposes, e.g., antibiotic resistance genes, origin of replication sequences etc., but these are not encapsidated and thus do not form part of the AAV particle.

[0113] In some aspects, an AAV vector can comprise at least one nucleic acid encoding an esnRNA composition of the disclosure. In some aspects, an AAV vector can comprise at least one regulatory sequence. In some aspects, an AAV vector can comprise at least one AAV inverted terminal (ITR) sequence. In some aspects, an AAV vector can comprise a first ITR sequence and a second ITR sequence. In some aspects, an AAV vector can comprise at least one promoter sequence. In some aspects, an AAV vector can comprise at least one enhancer sequence. In some aspects, an AAV vector can comprise at least one terminator sequence. In some aspects, an AAV vector can comprise at least one polyA sequence. In some aspects, an AAV vector can comprise at least one linker sequence. In some aspects, an AAV vector can comprise at least one buffer sequence. In some aspects, an AAV vector of the disclosure can comprise at least one nuclear localization signal, or nuclear export signal and/or both.

[0114] In some aspects, an AAV vector can comprise a first AAV ITR sequence, a promoter sequence, an esnRNA sequence, a terminator sequence and a second AAV ITR sequence. In some aspects, an AAV vector can comprise, in the 5' to 3' direction, a first AAV ITR sequence, a promoter sequence, an esnRNA sequence, a terminator sequence, and a second AAV ITR sequence.

[0115] In some aspects, an AAV vector can comprise a first AAV ITR sequence, a first promoter sequence, a first esnRNA sequence, a second promoter sequence, second esnRNA sequence, and a second AAV ITR sequence. In some aspects, an AAV vector can comprise a first AAV ITR sequence, a first promoter sequence, a first esnRNA sequence, a second promoter sequence, a second esnRNA sequence, a third promoter sequence, a third esnRNA sequence, and a second AAV ITR sequence. In some aspects, an AAV vector can comprise a first AAV ITR sequence, a first promoter sequence, a first esnRNA sequence, a second promoter sequence, second esnRNA sequence, and a second AAV ITR sequence. In some aspects, an AAV vector can comprise a first AAV ITR sequence, a first promoter sequence, a first esnRNA sequence, a second promoter sequence, a second esnRNA sequence, a third promoter sequence, a third esnRNA sequence, a fourth promoter sequence, a fourth esnRNA sequence, and a second AAV ITR sequence.

[0116] The term "adeno-associated virus" or "AAV" as used herein refers to a member of the class of viruses associated with this name and belonging to the genus Dependoparvovirus, family Parvoviridae. Adeno-associated virus is a single-stranded DNA virus that grows in

cells in which certain functions are provided by a co-infecting helper virus. General information and reviews of AAV can be found in, for example, Carter, 1989, Handbook of Parvoviruses, Vol. 1, pp. 169- 228, and Berns, 1990, Virology, pp. 1743-1764, Raven Press, (New York). It is fully expected that the same principles described in these reviews will be applicable to additional AAV serotypes characterized after the publication dates of the reviews because it is well known that the various serotypes are quite closely related, both structurally and functionally, even at the genetic level. (See, for example, Blacklowe, 1988, pp. 165-174 of Parvoviruses and Human Disease, J. R. Pattison, ed.; and Rose, Comprehensive Virology 3: 1-61 (1974)). For example, all AAV serotypes apparently exhibit very similar replication properties mediated by homologous rep genes; and all bear three related capsid proteins such as those expressed in AAV2. The degree of relatedness is further suggested by heteroduplex analysis which reveals extensive cross-hybridization between serotypes along the length of the genome; and the presence of analogous self-annealing segments at the termini that correspond to "inverted terminal repeat sequences" (ITRs). The similar infectivity patterns also suggest that the replication functions in each serotype are under similar regulatory control. Multiple serotypes of this virus are known to be suitable for gene delivery; all known serotypes can infect cells from various tissue types.

[0117] AAV possesses unique features that make it attractive as a vector for delivering foreign DNA to cells, for example, in gene therapy. AAV infection of cells in culture is noncytopathic, and natural infection of humans and other animals is silent and asymptomatic. Moreover, AAV infects many mammalian cells allowing the possibility of targeting many different tissues in vivo. Moreover, AAV transduces slowly dividing and non-dividing cells, and can persist essentially for the lifetime of those cells as a transcriptionally active nuclear episome (extrachromosomal element). The AAV proviral genome is inserted as cloned DNA in plasmids, which makes construction of recombinant genomes feasible. Furthermore, because the signals directing AAV replication and genome encapsidation are contained within the ITRs of the AAV genome, some or all of the internal approximately 4.3 kb of the genome (encoding replication and structural capsid proteins, rep-cap) may be replaced with foreign DNA to generate AAV vectors. The rep and cap proteins may be provided in trans. Another significant feature of AAV is that it is an extremely stable and hearty virus. It easily withstands the conditions used to inactivate adenovirus (56° to 65°C for several hours), making cold preservation of AAV less critical. AAV may even be lyophilized. Finally, AAV-infected cells are not resistant to superinfection.

[0118] Recombinant AAV (rAAV) genomes of the invention comprise, consist essentially of, or consist of a nucleic acid molecule encoding at least one esnRNA and one or more AAV ITRs flanking the nucleic acid molecule. Production of pseudotyped rAAV is disclosed in, for example, WO2001083692. Other types of rAAV variants, for example rAAV with capsid mutations, are also contemplated. *See, e.g.*, Marsic et al., Molecular Therapy, 22(11): 1900-1909 (2014). The nucleotide sequences of the genomes of various AAV serotypes are known in the art.

[0119] In some embodiments of the compositions and methods of the disclosure, the viral vector comprises a sequence isolated or derived from an adeno-associated virus (AAV). In some embodiments, the viral vector comprises an inverted terminal repeat sequence or a capsid sequence that is isolated or derived from an AAV of serotype AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAVrh10, AAV11 or AAV12. In some embodiments, the AAV serotype is AAVrh.74. In one embodiment, the AAV vector comprises a modified capsid. In one embodiment the AAV vector is an AAV2-Tyr mutant vector. In one embodiment the AAV vector comprises a capsid with a non-tyrosine amino acid at a position that corresponds to a surface-exposed tyrosine residue in position Tyr252, Tyr272, Tyr275, Tyr281, Tyr508, Tyr612, Tyr704, Tyr720, Tyr730 or Tyr673 of wild-type AAV2. See also WO 2008/124724 incorporated herein in its entirety. In some embodiments, the AAV vector comprises an engineered capsid. AAV vectors comprising engineered capsids include without limitation, AAV2.7m8, AAV9.7m8, AAV2 2tYF, and AAV8 Y733F). In some embodiments, the capsid is a ubiquitination resistant capsid. In another embodiment, the ubiquitination capsid is an AAV2 capsid comprising tyrosine (Y) and serine (S) mutations. In another embodiment, the AAV2 capsid comprises Y, S and threonine (T) mutations. In another embodiment, the AAV2 capsid includes, without limitation, AAV2 capsid mutants such as T455V, T491V, T550V, T659V, Y444+500+730F, and Y444+500+730F+T491V. In some embodiments, the viral vector is replication incompetent. In some embodiments, the viral vector is isolated or recombinant (rAAV). In some embodiments, the viral vector is self-complementary (scAAV). In some embodiments, the viral vector is single-stranded (ssAAV).

AAV ITR SEQUENCES

[0120] In some embodiments of the compositions and methods of the disclosure, an AAV inverted terminal repeat sequence can comprise any AAV ITR sequence known in the art. In some aspects, an AAV ITR sequence can comprise or consist of an AAV1 ITR sequence, an

AAV2 ITR sequence, an AAV3 ITR sequence, an AAV4 ITR sequence, an AAV5 ITR sequence, an AAV6 ITR sequence, an AAV7 ITR sequence, an AAV8 ITR sequence, an AAV9 ITR sequence, an AAV10 ITR sequence, an AAVrh10 ITR sequence, an AAV11 ITR sequence, an AAV12 ITR sequence, an AAV13 ITR sequence, or an AAVrh74 ITR sequence.

[0121] In some aspects, the ITR sequence can comprise a modified AAV ITR sequence.

[0122] In some aspects, an AAV ITR sequence can comprise, consist essentially of, or consist of a nucleic acid sequence at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% (or any percentage in between) identical to SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 162, or SEQ ID NO: 166.

[0123] In some aspects, a first AAV ITR sequence can comprise, consist essentially of, or consist of a nucleic acid sequence at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% (or any percentage in between) identical to SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 162, or SEQ ID NO: 166 and a second AAV ITR sequence can comprise, consist essentially of, or consist of a nucleic acid sequence at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% (or any percentage in between) identical to SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 162, or SEQ ID NO: 166. In some aspects, the first AAV ITR sequence is positioned at the 5' of a AAV vector. In some aspects, the second AAV ITR sequence is positioned at the 3' of a AAV vector.

[0124] In some embodiments of the compositions and methods of the disclosure, the viral vector comprises a sequence isolated or derived from an adeno-associated virus (AAV).

[0125] In some embodiments of the compositions and methods of the disclosure, a vector of the disclosure is a non-viral vector. In some embodiments, the vector comprises or consists of a nanoparticle, a micelle, a liposome or lipoplex, a polymersome, a polyplex or a dendrimer. In some embodiments, the vector is an expression vector or recombinant expression system. As used herein, the term "recombinant expression system" refers to a genetic construct for the expression of certain genetic material formed by recombination.

esnRNA Vector Constructs

[0126] Exemplary esnRNA AAV vectors of the disclosure can comprise one or more esnRNA sequences of the disclosure. In some aspects, the esnRNA AAV vector comprises, consists essentially of, or consists of a nucleic acid sequence at least 65%, 70%, 75%, 80%,

85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% (or any percentage in between) identical to a an esnRNA AAV vector listed in the esnRNA AAV vector Table which follows:

ID	Description	SEQ ID NO:
A02962	ss pAAV-4X U7(15XCUG) (derivative of P00369) targeting CUG repeats	120
A02963	ss pAAV-4X U7(NT1) (derivative of P00369)	121
A02967	ss pAAV-4X U7(15XCUG) targeting CUG repeats	122
A03079	sc pAAV-4X U7(15XCUG) (derivative of P00369) targeting CAG repeats	123
A03080	sc pAAV-4X U7(NT1) (derivative of P00369)	124
A03081	sc pAAV-4X U7(15XCTG) targeting CUG repeats	125
A02888	pAAV_1xU7(15xCUG)_CMV_GFP (no buffer) targeting CUG repeats	126
A02889	pAAV_1xU7(NT1)_CMV_GFP (no buffer)	127
A02925	pAAV_1xU7(15xCAG)_CMV_GFP (no buffer) targeting CAG repeats	128
A02894	pAAV_3xU7(15xCUG)_CMV_GFP (100bp buffer) targeting CUG repeats	129
A02895	pAAV_3xU7(NT1)_CMV_GFP (100bp buffer)	130
A02968	pAAV_3xU7(15XCAG)_CMV_GFP (100bp buffer) targeting CAG repeats	131
A02896	pAAV_3xU7(15xCUG)_CMV_GFP (500bp buffer)	132
A02897	pAAV_3xU7(NT1)_CMV_GFP (500bp buffer)	133
A02969	pAAV_3xU7(15xCAG)_CMV_GFP (500bp buffer) targeting CAG repeats	134
A03980	pAAV(ssAAV) U7promoter-esnRNA-z38/42-U7 termination-U1promoter-esnRNAz38/z42-U1 termination	135
A03981	pAAV(ssAAV)_U7promoter-esnRNA-z42-U7termination-U1promoter-esnRNA-z38-U1 termination	136
A04229	pAAV(scAAV) U7promoter-esnRNA-z38/42-U7 termination-U1promoter-esnRNAz38/z42-U1 termination-mut ITR	137
A04184	pAAV(ssAAV)-U7promoter-z38/42-U7term_U1promoter-z38/42-U1term_buffer combination sequencestuffer	138
A03681	pAAV(ssAAV)-U7 promoter-zCUGx15-U7 term_U1 promoter-zCUGx15-U1 term-eCMV-eGFP	139
A03682	pAAV(ssAAV)-U1 promoter-zCUGx15-U1 term_U7 promoter-zCUGx15-U7 term-eCMV-eGFP	140
A03683	pAAV(ssAAV)-U7 promoter-znt-U7 term_U1 promoter-znt-U1 term-eCMV-eGFP	141
A03864	pAAV(ssAAV)-U7 promoter-zCUGx15-U7 term_U1 promoter-zCUGx15-U1 term (minus GFP - derivative of 3681)	142
A04233	pAAV(scAAV)-U7promoter-zCUGx15-U7termination-U1promoter-zCUGx15-U1termination (derivative of A03681 no GFP in scAAV)	143
A04569	scAAVmU7p-z42/38 rev fus-mU7term_mU1p-z42/38 rev fus-mU1term; mouse loop with5' ISD and eSL	168
A04526	scAAVmU7p-z38/42 Forward fus-mU7term_mU1p-z38/42 forward fus-mU1term; mouseloop with5' ISD and eSL	169
A04771	scAAVmU7p-z42/38 reverse fus-mU7term_mU1p-z42/38 reverse fus-mU1term; mouseloop with 5' ISD and eSL no CCU tail	170
A04525	scAAV-mU7p-z38/42-mU7term_mU7p-z38/42-mU7term; mouse loop no ISD no eSL	171

A04527	scAAV-mU7p-z38/42-mU7term_mU1p-z38/42-mU1term; mouse loop no ISD no eSL	172
A04528	scAAV-mU7p-z38/42-mU7term_mU1p-z38/42-mU1term; human loop with ISD and eSL	173
A04529	scAAV-mU7p-z38/42-mU7term_mU1p-z38/42-mU1term; human loop with ISD and eSL with added CCU tail	174
A04537	scAAV-mU7p-z38/42-mU7term_mU1prom- p-z38/42-mU1term; long mouse loop with5' ISD and eSL	175
A04233	scAAV- hU7-CUGx15-hU1-CUGx15 (3'mut ITR)	176
A04234	scAAV- hU7-CUGx15-hU1-CUGx15 (5' mut ITR)	177
A04390	scAAV 5'mITR hU7-CAG15X-hU1-CAGx15	178
A04530	scAAV- mU7p-CUGx15-mU1p-CUGx15; mouseloop with ISD and eSL	231
A04940	scAAV- mU7p-CUGx10-mU1p-CUGx10; mouseloop with ISD and eSL no CCU	232
A04533	scAAV- mU7p-CAGx15-mU1p-CAGx15; mouseloop with ISD and eSL	233

[0127] An exemplary AAV vector of the disclosure comprises from 5' to 3': a first inverted terminal repeat (ITR) sequence, a U7 promoter sequence, a DMD exon 51 targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a U1 promoter sequence, a DMD exon 51 targeting U7 esnRNA sequence, a U1 downstream terminator sequence, and a second ITR sequence. In some aspects, a nucleic acid sequence encoding AAV vector A04569 encoding DMD exon 51 targeting snRNA sequences comprises SEQ ID NO: 168.

A04569: scAAVmU7p-z42/38 rev fus-mU7term_mU1p-z42/38 rev fus-mU1term; mouse loop with5' ISD and eSL

Plasmid Element	Nucleotide Sequence 5' to 3'
5' ITR	ctgcgcgctcgctcgctcactgaggccgcccgggcaaagcccgggcgtcgggcgacctttggtcgcccggcctcagtgagcgag cgagcgcgcagagagggagtggggtt (SEQ ID NO: 162)
Mouse U7 promoter	taacaacataggagctgtgattggctgttttcagccaatcagcactgActcatttgcatagcctttacaagcggtcacaaactcaagaaa cgagcggttttaatagtcttttagaatattgtttatcgaaccgaataaggaactgtgctttgtgattcacatatcagtggaggggtgtggaa atggcaccttgatctcaccctcatcgaaagtggagttgatgtcctTccctggctcgctacagacgcacttccgcaa (SEQ ID NO: 48)
ISD	ggagt (SEQ ID NO: 12)
Z42/z38 reverse fusion spacer	GTAACCACAGGTTGTGTCACCAGAGTAACATACCTCCAACATCAAGGAAGATGG CA (SEQ ID NO: 149)
SMOPT	aATTTTTGGAGca (SEQ ID NO: 161)
Mouse stem loop (eSL) short loop	ggttttctgacctccgtcggaaaacccct (SEQ ID NO: 146)
Mouse U7 terminator	cccaatttcactggtctacaatgaaagcaaaacagttctcttccccgctccccggtgtgtgagaggggctttgatccttctctggtttccta ggaaacgcgtatgtg (SEQ ID NO: 156)
Mouse U1 promoter	TTGTTCCTCTTAGTGTTAATTCACACTAAAGACTGTGCATCCGACTCCTACATTTA TGAAAGTAAATGCCTGTTGTTAGAACAAAAAAGGCTACAGAACAAAAAACAAA GCGAAATACCATCTGCTTTAGGTTCAGTGTGGTATTTTCCCGCTGACAGGGAGGC GGGTTTTTGGGTACAGGAAACGAGTCACTATGGAGGCGGTACTATGTAGATGAG AATTCAGGTGCAAACTGGGAAAAGCAACTGCTTCCAAATATTTGTGATTTTTACA GTGTAGTTTTGGAAAAACTCTTAGCCTACCAATTCTTCTAAGTGTTTTAAAATGT GGGAGCCAGTACACATGAAGTTATAGAGTGTTTTAATGAGGCTTAAATATTTACC

	GTAACTATGAAATGCTACGCATATCATGCTGTTCAGGCTCCGTGGCCACGCAACTC (SEQ ID NO: 47)
ISD	ggagt (SEQ ID NO: 12)
Z42/z38 reverse fusion spacer	GTAACCACAGGTTGTGTCACCAGAGTAACATACCTCCAACATCAAGGAAGATGGCA (SEQ ID NO: 149)
SMOPT	aATTTTTGGAGca (SEQ ID NO: 161)
Mouse stem loop (eSL) short loop	ggttttctgacctccgtcggaaaacccct (SEQ ID NO: 146)
Mouse U1 terminator	GTTTACTTGGTTTTAAAAATAGCTTGCACTAGCGATACGGAATATGGTTATTAGGTTTGTTAGGCATCATGTCGTGTCTTACTATAGAAAAATAACGTAGTGTTCATTTTAGCCTGCCTGTATGTGTTAATTTGTCCTTATTGCGCATTGTTCTTGTTAAGTCTTCTGTAAGGAGTTGCGGGTTTCAAACTGTCAGTCTGAGAGCA (SEQ ID NO: 57)
3' ITR	Aggaacccctagtgatggagttggccactccctctctgcgcgctcgctcgctcactgaggccgggcgaccaaaggtcgcccgacgcccgggctttgcccgggcggcctcagtgagcgagcgagcgcgcagctgcctgcagg (SEQ ID NO: 60)

[0128] An exemplary AAV vector of the disclosure comprises from 5' to 3': a first inverted terminal repeat (ITR) sequence, a U7 promoter sequence, a DMD exon 51 targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a U1 promoter sequence, a DMD exon 51 targeting U7 esnRNA sequence, a U1 downstream terminator sequence, and a second ITR sequence. In some aspects, a nucleic acid sequence encoding AAV vector A04526 encoding DMD exon 51 targeting snRNA sequences comprises SEQ ID NO: 169.

A04526: scAAVmU7p-z82/42 Forward fus-mU7term_mU1p-z38/42 forward fus-mU1term; mouseloop with5' ISD and eSL

Plasmid Element	**Nucleotide Sequence 5' to 3'**
5' ITR	ctgcgcgctcgctcgctcactgaggccgcccgggcaaagcccgggcgtcgggcgacctttggtcgcccggcctcagtgagcgagcgagcgcgcagagagggagtggggtt (SEQ ID NO: 162)
Mouse U7 promoter	taacaacataggagctgtgattggctgttttcagccaatcagcactgActcatttgcatagcctttacaagcggtcacaaactcaagaaacgagcggttttaatagtcttttagaatattgtttatcgaaccgaataaggaactgtgctttgtgattcacatatcagtggaggggtgtggaaatggcaccttgatctcaccctcatcgaaagtggagttgatgtcctTccctggctcgctacagacgcacttccgcaa (SEQ ID NO: 48)
ISD	ggagt (SEQ ID NO: 12)
Z38/z42 forward fusion spacer	TACCTCCAACATCAAGGAAGATGGCAGTAACCACAGGTTGTGTCACCAGAGTAACA (SEQ ID NO: 150)
SMOPT	aATTTTTGGAGca (SEQ ID NO: 161)
Mouse stem loop (eSL) short loop	ggttttctgacctccgtcggaaaacccct (SEQ ID NO: 146)
Mouse U7 terminator	cccaatttcactggtctacaatgaaagcaaaacagttctcttccccgctccccggtgtgtgagaggggctttgatccttctctggtttcctaggaaacgcgtatgtg (SEQ ID NO: 156)
Mouse U1 promoter	TTGTTCCTCTTAGTGTTAATTCACACTAAAGACTGTGCATCCGACTCCTACATTTATGAAAGTAAATGCCTGTTGTTAGAACAAAAAAGGCTACAGAACAAAAAACAAAGCGAAATACCATCTGCTTTAGGTTCAGTGTGGTATTTTCCCGCTGACAGGGAGGCGGGTTTTTGGGTACAGGAAACGAGTCACTATGGAGGCGGTACTATGTAGATGAGAATTCAGGTGCAAACTGGGAAAAGCAACTGCTTCCAAATATTTGTGATTTTTACAGTGTAGTTTTGGAAAAACTCTTAGCCTACCAATTCTTCTAAGTGTTTTAAAATGTGGGAGCCAGTACACATGAAGTTATAGAGTGTTTTAATGAGGCTTAAATATTTACCGTAACTATGAAATGCTACGCATATCATGCTGTTCAGGCTCCGTGGCCACGCAACTC (SEQ ID NO: 47)
ISD	ggagt (SEQ ID NO: 12)

Z38/z42 forward fusion spacer	TACCTCCAACATCAAGGAAGATGGCAGTAACCACAGGTTGTGTCACCAGAGTAA CA (SEQ ID NO: 150)
SMOPT	aATTTTTGGAGca (SEQ ID NO: 161)
Mouse stem loop (eSL) short loop	ggttttctgacctccgtcggaaaacccct (SEQ ID NO: 146)
Mouse U1 terminator	GTTTACTTGGTTTTAAAAATAGCTTGCACTAGCGATACGGAATATGGTTATTAGG TTTGTTAGGCATCATGTCGTGTCTTACTATAGAAAAATAACGTAGTGTTCATTTT AGCCTGCCTGTATGTGTTAATTTGTCCTTATTGCGCATTGTTCTTGTTAAGTCTTC TGTAAGGAGTTGCGGGTTTCAAACTGTCAGTCTGAGAGCA (SEQ ID NO: 57)
3' ITR	aggaacccctagtgatggagttggccactccctctctgcgcgctcgctcgctcactgaggccgggcgaccaaaggtcgcccgacgc ccgggctttgcccgggcggcctcagtgagcgagcgagcgcgcagctgcctgcagg (SEQ ID NO: 60)

[0129] An exemplary AAV vector of the disclosure comprises from 5' to 3': a first inverted terminal repeat (ITR) sequence, a U7 promoter sequence, a DMD exon 51 targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a U1 promoter sequence, a DMD exon 51 targeting U7 esnRNA sequence, a U1 downstream terminator sequence, and a second ITR sequence. In some aspects, a nucleic acid sequence encoding AAV vector A04771 encoding DMD exon 51 targeting snRNA sequences comprises SEQ ID NO: 170.

A04771: scAAVmU7p-z42/38 reverse fus-mU7term_mU1p-z42/38 reverse fus-mU1term; mouseloop with 5' ISD and eSL no CCU tail

Plasmid Element	Nucleotide Sequence 5' to 3'
5' ITR	ctgcgcgctcgctcgctcactgaggccgcccgggcaaagcccgggcgtcgggcgacctttggtcgcccggcctcagtgagcgagc gagcgcgcagagagggagtggggtt (SEQ ID NO: 162)
Mouse U7 promoter	taacaacataggagctgtgattggctgttttcagccaatcagcactgActcatttgcatagcctttacaagcggtcacaaactcaagaaac gagcggttttaatagtcttttagaatattgtttatcgaaccgaataaggaactgtgctttgtgattcacatatcagtggaggggtgtggaaatg gcaccttgatctcaccctcatcgaaagtggagttgatgtcctTccctggctcgctacagacgcacttccgcaa (SEQ ID NO: 48)
ISD	ggagt (SEQ ID NO: 12)
Z42/z38 reverse fusion spacer	GTAACCACAGGTTGTGTCACCAGAGTAACATACCTCCAACATCAAGGAAGATGGC A (SEQ ID NO: 149)
SMOPT	aATTTTTGGAGca (SEQ ID NO: 161)
Mouse stem loop (eSL) short loop no CCU	ggttttctgacctccgtcggaaaacc (SEQ ID NO: 148)
Mouse U7 terminator	cccaatttcactggtctacaatgaaagcaaaacagttcttccccgctccccggtgtgtgagaggggctttgatccttctctggtttcctag gaaacgcgtatgtg (SEQ ID NO: 156)
Mouse U1 promoter	TTGTTCCTCTTAGTGTTAATTCACACTAAAGACTGTGCATCCGACTCCTACATTTAT GAAAGTAAATGCCTGTTGTTAGAACAAAAAAGGCTACAGAACAAAAAACAAAGC GAAATACCATCTGCTTTAGGTTCAGTGTGGTATTTTCCCGCTGACAGGGAGGCGG GTTTTTGGGTACAGGAAACGAGTCACTATGGAGGCGGTACTATGTAGATGAGAAT TCAGGTGCAAACTGGGAAAAGCAACTGCTTCCAAATATTTGTGATTTTTACAGTGT AGTTTTGGAAAAACTCTTAGCCTACCAATTCTTCTAAGTGTTTTAAAATGTGGGAG CCAGTACACATGAAGTTATAGAGTGTTTTAATGAGGCTTAAATATTTACCGTAACT ATGAAATGCTACGCATATCATGCTGTTCAGGCTCCGTGGCCACGCAACTC (SEQ ID NO: 47)
ISD	ggagt (SEQ ID NO: 12)
Z42/z38 reverse fusion spacer	GTAACCACAGGTTGTGTCACCAGAGTAACATACCTCCAACATCAAGGAAGATGGC A (SEQ ID NO: 149)
SMOPT	aATTTTTGGAGca (SEQ ID NO: 161)

Mouse stem loop (eSL) short loop no CCU	ggttttctgacctccgtcggaaaacc (SEQ ID NO: 148)
Mouse U1 terminator	GTTTACTTGGTTTTAAAAATAGCTTGCACTAGCGATACGGAATATGGTTATTAGGT TTGTTAGGCATCATGTCGTGTCTTACTATAGAAAAATAACGTAGTGTTCATTTTAG CCTGCCTGTATGTGTTAATTTGTCCTTATTGCGCATTGTTCTTGTTAAGTCTTCTGT AAGGAGTTGCGGGTTTCAAACTGTCAGTCTGAGAGCA (SEQ ID NO: 57)
3' ITR	aggaacccctagtgatggagttggccactccctctctgcgcgctcgctcgctcactgaggccgggcgaccaaaggtcgcccgacgcc cgggctttgcccgggcggcctcagtgagcgagcgagcgcgcagctgcctgcagg (SEQ ID NO: 60)

[0130] An exemplary AAV vector of the disclosure comprises from 5' to 3': a first inverted terminal repeat (ITR) sequence, a U7 promoter sequence, a DMD exon 51 targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a U7 promoter sequence, a DMD exon 51 targeting U7 esnRNA sequence, a U7 downstream terminator sequence, and a second ITR sequence. In some aspects, a nucleic acid sequence encoding AAV vector A04525 encoding DMD exon 51 targeting snRNA sequences comprises SEQ ID NO: 171.

A04525: scAAV-mU7p-z38/42-mU7term_mU7p-z38/42-mU7term; mouse loop no ISD no eSL

Plasmid Element	**Nucleotide Sequence 5' to 3'**
5' ITR	ctgcgcgctcgctcgctcactgaggccgcccgggcaaagcccgggcgtcgggcgacctttggtcgcccggcctcagtgagcgagc gagcgcgcagagagggagtggggtt (SEQ ID NO: 162)
Mouse U7 promoter	taacaacataggagctgtgattggctgttttcagccaatcagcactgActcatttgcatagcctttacaagcggtcacaaactcaagaaac gagcggttttaatagtcttttagaatattgtttatcgaaccgaataaggaactgtgctttgtgattcacatatcagtggaggggtgtggaaatg gcaccttgatctcaccctcatcgaaagtggagttgatgtcctTccctggctcgctacagacgcacttccgcaa (SEQ ID NO: 48)
Z38/z42 forward fusion spacer	TACCTCCAACATCAAGGAAGATGGCAGTAACCACAGGTTGTGTCACCAGAGTAAC A (SEQ ID NO: 150)
SMOPT	aATTTTTGGAGca (SEQ ID NO: 161)
Mouse stem loop (WT) short loop	ggttttctgacttcggtcggaaaacccct (SEQ ID NO: 145)
Mouse U7 terminator	cccaatttcactggtctacaatgaaagcaaaacagttctcttccccgctccccggtgtgtgagaggggctttgatccttctctggtttcctag gaaacgcgtatgtg (SEQ ID NO: 156)
Mouse U7 promoter	taacaacataggagctgtgattggctgttttcagccaatcagcactgActcatttgcatagcctttacaagcggtcacaaactcaagaaac gagcggttttaatagtcttttagaatattgtttatcgaaccgaataaggaactgtgctttgtgattcacatatcagtggaggggtgtggaaatg gcaccttgatctcaccctcatcgaaagtggagttgatgtcctTccctggctcgctacagacgcacttccgcaa (SEQ ID NO: 48)
Z38/z42 forward fusion spacer	TACCTCCAACATCAAGGAAGATGGCAGTAACCACAGGTTGTGTCACCAGAGTAAC A (SEQ ID NO: 150)
SMOPT	aATTTTTGGAGca (SEQ ID NO: 161)
Mouse stem loop (WT) short loop	ggttttctgacttcggtcggaaaacccct (SEQ ID NO: 145)
Mouse U7 terminator	cccaatttcactggtctacaatgaaagcaaaacagttctcttccccgctccccggtgtgtgagaggggctttgatccttctctggtttcctag gaaacgcgtatgtg (SEQ ID NO: 156)
3' ITR	aggaacccctagtgatggagttggccactccctctctgcgcgctcgctcgctcactgaggccgggcgaccaaaggtcgcccgacgcc cgggctttgcccgggcggcctcagtgagcgagcgagcgcgcagctgcctgcagg (SEQ ID NO: 60)

[0131] An exemplary AAV vector of the disclosure comprises from 5' to 3': a first inverted terminal repeat (ITR) sequence, a U7 promoter sequence, a DMD exon 51 targeting U7

esnRNA sequence, a U7 downstream terminator sequence, a U1 promoter sequence, a DMD exon 51 targeting U7 esnRNA sequence, a U1 downstream terminator sequence, and a second ITR sequence. In some aspects, a nucleic acid sequence encoding AAV vector A04527 encoding DMD exon 51 targeting snRNA sequences comprises SEQ ID NO: 172.

A04527: scAAV-mU7p-z38/42-mU7term_mU1p-z38/42-mU1term; mouse loop no ISD no eSL

Plasmid Element	Nucleotide Sequence 5' to 3'
5' ITR	ctgcgcgctcgctcgctcactgaggccgcccgggcaaagcccgggcgtcgggcgacctttggtcgcccggcctcagtgagcgagc gagcgcgcagagagggagtggggtt (SEQ ID NO: 162)
Mouse U7 promoter	taacaacataggagctgtgattggctgttttcagccaatcagcactgActcatttgcatagcctttacaagcggtcacaaactcaagaaac gagcggttttaatagtctttagaatattgtttatcgaaccgaataaggaactgtgctttgtgattcacatatcagtggaggggtgtggaaatg gcaccttgatctcaccctcatcgaaagtggagttgatgtcctTccctggctcgctacagacgcacttccgcaa (SEQ ID NO: 48)
Z38/z42 forward fusion spacer	TACCTCCAACATCAAGGAAGATGGCAGTAACCACAGGTTGTGTCACCAGAGTAAC A (SEQ ID NO: 150)
SMOPT	aATTTTTGGAGca (SEQ ID NO: 161)
Mouse stem loop (WT) short loop	ggttttctgacttcggtcggaaaacccct (SEQ ID NO: 145)
Mouse U7 terminator	cccaatttcactggtctacaatgaaagcaaaacagttctcttccccgctccccggtgtgtgagaggggctttgatccttctctggtttcctag gaaacgcgtatgtg (SEQ ID NO: 156)
Mouse U1 promoter	TTGTTCCTCTTAGTGTTAATTCACACTAAAGACTGTGCATCCGACTCCTACATTTAT GAAAGTAAATGCCTGTTGTTAGAACAAAAAAGGCTACAGAACAAAAAACAAAGC GAAATACCATCTGCTTTAGGTTCAGTGTGGTATTTTCCCGCTGACAGGGAGGCGG GTTTTTGGGTACAGGAAACGAGTCACTATGGAGGCGGTACTATGTAGATGAGAAT TCAGGTGCAAACTGGGAAAAGCAACTGCTTCCAAATATTTGTGATTTTTACAGTGT AGTTTTGGAAAAACTCTTAGCCTACCAATTCTTCTAAGTGTTTTAAAATGTGGGAG CCAGTACACATGAAGTTATAGAGTGTTTTAATGAGGCTTAAATATTTACCGTAACT ATGAAATGCTACGCATATCATGCTGTTCAGGCTCCGTGGCCACGCAACTC (SEQ ID NO: 47)
Z38/z42 forward fusion spacer	TACCTCCAACATCAAGGAAGATGGCAGTAACCACAGGTTGTGTCACCAGAGTAAC A (SEQ ID NO: 150)
SMOPT	aATTTTTGGAGca (SEQ ID NO: 161)
Mouse stem loop (WT) short loop	ggttttctgacttcggtcggaaaacccct (SEQ ID NO: 145)
Mouse U1 terminator	GTTTACTTGGTTTTAAAAATAGCTTGCACTAGCGATACGGAATATGGTTATTAGGT TTGTTAGGCATCATGTCGTGTCTTACTATAGAAAAATAACGTAGTGTTCATTTTAG CCTGCCTGTATGTGTTAATTTGTCCTTATTGCGCATTGTTCTTGTTAAGTCTTCTGT AAGGAGTTGCGGGTTTCAAACTGTCAGTCTGAGAGCA (SEQ ID NO: 57)
3' ITR	aggaacccctagtgatggagttggccactccctctctgcgcgctcgctcgctcactgaggccgggcgaccaaaggtcgcccgacgcc cgggctttgcccgggcggcctcagtgagcgagcgagcgcgcagctgcctgcagg (SEQ ID NO: 60)

[0132] An exemplary AAV vector of the disclosure comprises from 5' to 3': a first inverted terminal repeat (ITR) sequence, a U7 promoter sequence, a DMD exon 51 targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a U1 promoter sequence, a DMD exon 51 targeting U7 esnRNA sequence, a U1 downstream terminator sequence, and a second ITR sequence. In some aspects, a nucleic acid sequence encoding AAV vector A04528 encoding DMD exon 51 targeting snRNA sequences comprises SEQ ID NO: 173.

A04528: scAAV-mU7p-z38/42-mU7term_mU1p-z38/42-mU1term; human loop with ISD and eSL

Plasmid Element	Nucleotide Sequence 5' to 3'
5' ITR	ctgcgcgctcgctcgctcactgaggccgcccgggcaaagcccgggcgtcgggcgacctttggtcgcccggcctcagtgagcgag cgagcgcgcagagagggagtggggtt (SEQ ID NO: 162)
Mouse U7 promoter	taacaacataggagctgtgattggctgttttcagccaatcagcactgActcatttgcatagcctttacaagcggtcacaaactcaagaaa cgagcggttttaatagtcttttagaatattgtttatcgaaccgaataaggaactgtgctttgtgattcacatatcagtggaggggtgtggaa atggcaccttgatctcaccctcatcgaaagtggagttgatgtcctTccctggctcgctacagacgcacttccgcaa (SEQ ID NO: 48)
ISD	ggagt (SEQ ID NO: 12)
Z38/z42 forward fusion spacer	TACCTCCAACATCAAGGAAGATGGCAGTAACCACAGGTTGTGTCACCAGAGTAA CA (SEQ ID NO: 150)
SMOPT	AATTTTTGGAGTA (SEQ ID NO: 164)
Human stem loop (eSL)	ggctttctggctccttaccggaaagcc (SEQ ID NO: 1)
Mouse U7 terminator	cccaatttcactggtctacaatgaaagcaaaacagttctcttccccgctccccggtgtgtgagaggggctttgatccttctctggtttccta ggaaacgcgtatgtg (SEQ ID NO: 156)
Mouse U1 promoter	TTGTTCCTCTTAGTGTTAATTCACACTAAAGACTGTGCATCCGACTCCTACATTTA TGAAAGTAAATGCCTGTTGTTAGAACAAAAAAGGCTACAGAACAAAAAACAAA GCGAAATACCATCTGCTTTAGGTTCAGTGTGGTATTTTCCCGCTGACAGGGAGGC GGGTTTTTGGGTACAGGAAACGAGTCACTATGGAGGCGGTACTATGTAGATGAG AATTCAGGTGCAAACTGGGAAAAGCAACTGCTTCCAAATATTTGTGATTTTTACA GTGTAGTTTTGGAAAAACTCTTAGCCTACCAATTCTTCTAAGTGTTTTAAAATGT GGGAGCCAGTACACATGAAGTTATAGAGTGTTTTAATGAGGCTTAAATATTTACC GTAACTATGAAATGCTACGCATATCATGCTGTTCAGGCTCCGTGGCCACGCAACT C (SEQ ID NO: 47)
ISD	ggagt (SEQ ID NO: 12)
Z38/z42 forward fusion spacer	TACCTCCAACATCAAGGAAGATGGCAGTAACCACAGGTTGTGTCACCAGAGTAA CA (SEQ ID NO: 150)
SMOPT	AATTTTTGGAGTA (SEQ ID NO: 164)
Human stem loop (eSL)	ggctttctggctccttaccggaaagcc (SEQ ID NO: 1)
Mouse U1 terminator	GTTTACTTGGTTTTAAAAATAGCTTGCACTAGCGATACGGAATATGGTTATTAGG TTTGTTAGGCATCATGTCGTGTCTTACTATAGAAAAATAACGTAGTGTTCATTTT AGCCTGCCTGTATGTGTTAATTTGTCCTTATTGCGCATTGTTCTTGTTAAGTCTTC TGTAAGGAGTTGCGGGTTTCAAACTGTCAGTCTGAGAGCA (SEQ ID NO: 57)
3' ITR	aggaaccctagtgatggagttggccactccctctctgcgcgctcgctcgctcactgaggccgggcgaccaaaggtcgcccgacgc ccgggctttgcccgggcggcctcagtgagcgagcgagcgcgcagctgcctgcagg (SEQ ID NO: 60)

[0133] An exemplary AAV vector of the disclosure comprises from 5' to 3': a first inverted terminal repeat (ITR) sequence, a U7 promoter sequence, a DMD exon 51 targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a U1 promoter sequence, a DMD exon 51 targeting U7 esnRNA sequence, a U1 downstream terminator sequence, and a second ITR sequence. In some aspects, a nucleic acid sequence encoding AAV vector A04529 encoding DMD exon 51 targeting snRNA sequences comprises SEQ ID NO: 174.

A04529: scAAV-mU7p-z38/42-mU7term_mU1p-z38/42-mU1term; human loop with ISD and eSL with added CCU tail

Plasmid Element	Nucleotide Sequence 5' to 3'
5' ITR	ctgcgcgctcgctcgctcactgaggccgcccgggcaaagcccgggcgtcgggcgacctttggtcgcccggcctcagtgagcgag cgagcgcgcagagagggagtgggggtt (SEQ ID NO: 162)
Mouse U7 promoter	taacaacataggagctgtgattggctgttttcagccaatcagcactgActcatttgcatagcctttacaagcggtcacaaactcaagaaa cgagcggttttaatagtcttttagaatattgtttatcgaaccgaataaggaactgtgctttgtgattcacatatcagtggaggggtgtggaa atggcaccttgatctcaccctcatcgaaagtggagttgatgtcctTccctggctcgctacagacgcacttccgcaa (SEQ ID NO: 48)
ISD	ggagt (SEQ ID NO: 12)
Z38/z42 forward fusion spacer	TACCTCCAACATCAAGGAAGATGGCAGTAACCACAGGTTGTGTCACCAGAGTAA CA (SEQ ID NO: 150)
SMOPT	AATTTTTGGAGTA (SEQ ID NO: 164)
Human stem loop (eSL) with CCU tail	ggctttctggctccttaccggaaagcccct (SEQ ID NO: 163)
Mouse U7 terminator	cccaatttcactggtctacaatgaaagcaaaacagttctcttccccgctccccggtgtgtgagaggggctttgatccttctctggtttccta ggaaacgcgtatgtg (SEQ ID NO: 156)
Mouse U1 promoter	TTGTTCCTCTTAGTGTTAATTCACACTAAAGACTGTGCATCCGACTCCTACATTTA TGAAAGTAAATGCCTGTTGTTAGAACAAAAAAGGCTACAGAACAAAAAACAAA GCGAAATACCATCTGCTTTAGGTTCAGTGTGGTATTTTCCCGCTGACAGGGAGGC GGGTTTTTGGGTACAGGAAACGAGTCACTATGGAGGCGGTACTATGTAGATGAG AATTCAGGTGCAAACTGGGAAAAGCAACTGCTTCCAAATATTTGTGATTTTTACA GTGTAGTTTTGGAAAAACTCTTAGCCTACCAATTCTTCTAAGTGTTTTAAAATGT GGGAGCCAGTACACATGAAGTTATAGAGTGTTTTAATGAGGCTTAAATATTTACC GTAACTATGAAATGCTACGCATATCATGCTGTTCAGGCTCCGTGGCCACGCAACT C (SEQ ID NO: 47)
ISD	ggagt (SEQ ID NO: 12)
Z38/z42 forward fusion spacer	TACCTCCAACATCAAGGAAGATGGCAGTAACCACAGGTTGTGTCACCAGAGTAA CA (SEQ ID NO: 150)
SMOPT	AATTTTTGGAGTA (SEQ ID NO: 164)
Human stem loop (eSL) with CCU tail	ggctttctggctccttaccggaaagcccct (SEQ ID NO: 163)
Mouse U1 terminator	GTTTACTTGGTTTTAAAAATAGCTTGCACTAGCGATACGGAATATGGTTATTAGG TTTGTTAGGCATCATGTCGTGTCTTACTATAGAAAAATAACGTAGTGTTCATTTT AGCCTGCCTGTATGTGTTAATTTGTCCTTATTGCGCATTGTTCTTGTTAAGTCTTC TGTAAGGAGTTGCGGGTTTCAAACTGTCAGTCTGAGAGCA (SEQ ID NO: 57)
3' ITR	aggaacccctagtgatggagttggccactccctctctgcgcgctcgctcgctcactgaggccgggcgaccaaaggtcgcccgacgc ccgggctttgcccgggcggcctcagtgagcgagcgagcgcgcagctgcctgcagg (SEQ ID NO: 60)

[0134] An exemplary AAV vector of the disclosure comprises from 5' to 3': a first inverted terminal repeat (ITR) sequence, a U7 promoter sequence, a DMD exon 51 targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a U1 promoter sequence, a DMD exon 51 targeting U7 esnRNA sequence, a U1 downstream terminator sequence, and a second ITR sequence. In some aspects, a nucleic acid sequence encoding AAV vector A04537 encoding DMD exon 51 targeting snRNA sequences comprises SEQ ID NO: 175.

A04537: scAAV-mU7p-z38/42-mU7term_mU1prom- p-z38/42-mU1term; long mouse loop with 5' ISD and eSL

Plasmid Element	Nucleotide Sequence 5' to 3'

5' ITR	ctgcgcgctcgctcgctcactgaggccgcccgggcaaagcccgggcgtcgggcgacctttggtcgcccggcctcagtgagcgag cgagcgcgcagagagggagtggggtt (SEQ ID NO: 162)
Mouse U7 promoter	taacaacataggagctgtgattggctgttttcagccaatcagcactgActcatttgcatagcctttacaagcggtcacaaactcaagaaa cgagcggttttaatagtcttttagaatattgtttatcgaaccgaataaggaactgtgctttgtgattcacatatcagtggaggggtgtggaa atggcaccttgatctcaccctcatcgaaagtggagttgatgtcctTccctggctcgctacagacgcacttccgcaa (SEQ ID NO: 48)
ISD	ggagt (SEQ ID NO: 12)
Z38/z42 forward fusion spacer	TACCTCCAACATCAAGGAAGATGGCAGTAACCACAGGTTGTGTCACCAGAGTAA CA (SEQ ID NO: 150)
SMOPT	aATTTTTGGAGca (SEQ ID NO: 161)
mouse stem loop (eSL) with CCU tail (long extended loop)	Ggttttctgacctccttcggtcggaaaacccct (SEQ ID NO: 147)
Mouse U7 terminator	Cccaatttcactggtctacaatgaaagcaaaacagttctcttccccgctccccggtgtgtgagaggggctttgatccttctctggtttcct aggaaacgcgtatgtg (SEQ ID NO: 156)
Mouse U1 promoter	TTGTTCCTCTTAGTGTTAATTCACACTAAAGACTGTGCATCCGACTCCTACATTTA TGAAAGTAAATGCCTGTTGTTAGAACAAAAAAGGCTACAGAACAAAAAACAAA GCGAAATACCATCTGCTTTAGGTTCAGTGTGGTATTTTCCCGCTGACAGGGAGGC GGGTTTTTGGGTACAGGAAACGAGTCACTATGGAGGCGGTACTATGTAGATGAG AATTCAGGTGCAAACTGGGAAAAGCAACTGCTTCCAAATATTTGTGATTTTTACA GTGTAGTTTTGGAAAAACTCTTAGCCTACCAATTCTTCTAAGTGTTTTAAAATGT GGGAGCCAGTACACATGAAGTTATAGAGTGTTTTAATGAGGCTTAAATATTTACC GTAACTATGAAATGCTACGCATATCATGCTGTTCAGGCTCCGTGGCCACGCAACT C (SEQ ID NO: 47)
ISD	ggagt (SEQ ID NO: 12)
Z38/z42 forward fusion spacer	TACCTCCAACATCAAGGAAGATGGCAGTAACCACAGGTTGTGTCACCAGAGTAA CA (SEQ ID NO: 150)
SMOPT	aATTTTTGGAGca (SEQ ID NO: 161)
mouse stem loop (eSL) with CCU tail (long extended loop)	ggttttctgacctccttcggtcggaaaacccct (SEQ ID NO: 147)
Mouse U1 terminator	GTTTACTTGGTTTTAAAAATAGCTTGCACTAGCGATACGGAATATGGTTATTAGG TTTGTTAGGCATCATGTCGTGTCTTACTATAGAAAAATAACGTAGTGTTCATTTT AGCCTGCCTGTATGTGTTAATTTGTCCTTATTGCGCATTGTTCTTGTTAAGTCTTC TGTAAGGAGTTGCGGGTTTCAAACTGTCAGTCTGAGAGCA (SEQ ID NO: 57)
3' ITR	aggaaccctagtgatggagttggccactccctctctgcgcgctcgctcgctcactgaggccgggcgaccaaaggtcgcccgacgc ccgggctttgcccgggcggcctcagtgagcgagcgagcgcgcagctgcctgcagg (SEQ ID NO: 60)

[0135] An exemplary AAV vector of the disclosure comprises from 5' to 3': a first inverted terminal repeat (ITR) sequence, a U7 promoter sequence, a CUG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a U1 promoter sequence, a CUG repeat targeting U7 esnRNA sequence, a U1 downstream terminator sequence, and a second ITR sequence. In some aspects, a nucleic acid sequence encoding AAV vector A04233 encoding CUG repeat targeting snRNA sequences comprises SEQ ID NO: 176.

A04233: scAAV- hU7-CUGx15-hU1-CUGx15 (3'mut ITR)

Plasmid Element	**Nucleotide Sequence 5' to 3'**
5' ITR	cctgcaggcagctgcgcgctcgctcgctcactgaggccgcccgggcgtcgggcgacctttggtcgcccggcctcagtgagcgagc gagcgcgcagagagggagtggccaactccatcactaggggttcct (SEQ ID NO: 59)
human U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGGCTGTGACTGGC TGCTTTCTCAACCAATCAGCACCGAACTCATTTGCATGGGCTGAGAACAAATGTT

	CGCGAACTCTAGAAATGAATGACTTAAGTAAGTTCCTTAGAATATTATTTTTCCT ACTGAAAGTTACCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAAA GTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATATCCCATCTTCTCTC CAAACACATACGCA (SEQ ID NO: 39)
ISD	ggagt (SEQ ID NO: 12)
CUG repeat targeting sequence	CAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAG (SEQ ID NO: 165)
SMOPT	AATTTTTGGAGTA (SEQ ID NO: 164)
Human stem loop (eSL)	ggctttctggctccttaccggaaagcc (SEQ ID NO: 1)
Human U7 terminator	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGCAAAAATTATGG GTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCTTGGAG (SEQ ID NO: 49)
Human U1 promoter	TAAGGACCAGCTTCTTTGGGAGAGAACAGACGCAGGGGCGGGAGGGAAAAAGG GAGAGGCAGACGTCACTTCCCCTTGGCGGCTCTGGCAGCAGATTGGTCGGTTGA GTGGCAGAAAGGCAGACGGGGACTGGGCAAGGCACTGTCGGTGACATCACGGA CAGGGCGACTTCTATGTAGATGAGGCAGCGCAGAGGCTGACGTCTTCGCCACTT GCTGCTTCACCACGAAGGAGTTCCCGTGCCCTGGGAGCGGGTTCAGGACCGCTG ATCGGAAGTGAGAATCCCAGCTGTGTGTCAGGGCTGGAAAGGGCTCGGGAGTGC GCGGGGCAAGTGACCGTGTGTGTAAAGAGTGAGGCGTATGAGGCTGTGTCGGGG CAGAGGCacaacgtttc (SEQ ID NO: 40)
ISD	ggagt (SEQ ID NO: 12)
spacer	CAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAG (SEQ ID NO: 165)
SMOPT	AATTTTTGGAGTA (SEQ ID NO: 164)
Human stem loop (eSL)	ggctttctggctccttaccggaaagcc (SEQ ID NO: 1)
human U1 terminator	ACTTTCTGGAGTTTCAAAAACAGACTGTACGCCAAGGGTCATATCTTTTT (SEQ ID NO: 50)
3'mut ITR	CCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGC CCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGA GGGA (SEQ ID NO: 61)

[0136] An exemplary AAV vector of the disclosure comprises from 5' to 3': a first inverted terminal repeat (ITR) sequence, a U7 promoter sequence, a CUG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a U1 promoter sequence, a CUG repeat targeting U7 esnRNA sequence, a U1 downstream terminator sequence, and a second ITR sequence. In some aspects, a nucleic acid sequence encoding AAV vector A04234 encoding CUG repeat targeting snRNA sequences comprises SEQ ID NO: 177.

A04234: scAAV- hU7-CUGx15-hU1-CUGx15 (5' mut ITR)

Plasmid Element	**Nucleotide Sequence 5' to 3'**
5' mut ITR	ctgcgcgctcgctcgctcactgaggccgcccgggcaaagcccgggcgtcgggcgacctttggtcgcccggcctcagtgagcgag cgagcgcgcagagagggagtggggtt (SEQ ID NO: 162)
human U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGGCTGTGACTGGC TGCTTTCTCAACCAATCAGCACCGAACTCATTTGCATGGGCTGAGAACAAATGTT CGCGAACTCTAGAAATGAATGACTTAAGTAAGTTCCTTAGAATATTATTTTTCCT ACTGAAAGTTACCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAAA GTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATATCCCATCTTCTCTC CAAACACATACGCA (SEQ ID NO: 39)

ISD	ggagt (SEQ ID NO: 12)
spacer	CAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAG (SEQ ID NO: 165)
SMOPT	AATTTTTGGAGTA (SEQ ID NO: 164)
Human stem loop (eSL)	ggctttctggctccttaccggaaagcc (SEQ ID NO: 1)
Human U7 terminator	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGCAAAAATTATGG GTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCTTGGAG (SEQ ID NO: 49)
Human U1 promoter	TAAGGACCAGCTTCTTTGGGAGAGAACAGACGCAGGGGCGGGAGGGAAAAAGG GAGAGGCAGACGTCACTTCCCCTTGGCGGCTCTGGCAGCAGATTGGTCGGTTGA GTGGCAGAAAGGCAGACGGGGACTGGGCAAGGCACTGTCGGTGACATCACGGA CAGGGCGACTTCTATGTAGATGAGGCAGCGCAGAGGCTGACGTCTTCGCCACTT GCTGCTTCACCACGAAGGAGTTCCCGTGCCCTGGGAGCGGGTTCAGGACCGCTG ATCGGAAGTGAGAATCCCAGCTGTGTGTCAGGGCTGGAAAGGGCTCGGGAGTGC GCGGGGCAAGTGACCGTGTGTGTAAAGAGTGAGGCGTATGAGGCTGTGTCGGGG CAGAGGCacaacgtttc (SEQ ID NO: 40)
ISD	ggagt (SEQ ID NO: 12)
spacer	CAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAG (SEQ ID NO: 165)
SMOPT	AATTTTTGGAGTA (SEQ ID NO: 164)
Human stem loop (eSL)	ggctttctggctccttaccggaaagcc (SEQ ID NO: 1)
human U1 terminator	ACTTTCTGGAGTTTCAAAAACAGACTGTACGCCAAGGGTCATATCTTTTT (SEQ ID NO: 50)
3'ITR	aaggaacccctagtgatggagttggccactccctctctgcgcgctcgctcgctcactgaggccgggcgaccaaaggtcgcccgacg cccgggctttgcccgggcggcctcagtgagcgagcgagcgcgccagc (SEQ ID NO: 166)

[0137] An exemplary AAV vector of the disclosure comprises from 5' to 3': a first inverted terminal repeat (ITR) sequence, a U7 promoter sequence, a CAG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a U1 promoter sequence, a CAG repeat targeting U7 esnRNA sequence, a U1 downstream terminator sequence, and a second ITR sequence. In some aspects, a nucleic acid sequence encoding AAV vector A04390 encoding CAG repeat targeting snRNA sequences comprises SEQ ID NO: 178.

A04390: scAAV 5'mITR hU7-CAG15X-hU1-CAGx15

Plasmid Element	**Nucleotide Sequence 5' to 3'**
5' mut ITR	ctgcgcgctcgctcgctcactgaggccgcccgggcaaagcccgggcgtcgggcgacctttggtcgcccggcctcagtgagcgag cgagcgcgcagagagggagtggggtt (SEQ ID NO: 162)
human U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGGCTGTGACTGGC TGCTTTCTCAACCAATCAGCACCGAACTCATTTGCATGGGCTGAGAACAAATGTT CGCGAACTCTAGAAATGAATGACTTAAGTAAGTTCCTTAGAATATTATTTTTCCT ACTGAAAGTTACCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAAA GTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATATCCCATCTTCTCTC CAAACACATACGCA (SEQ ID NO: 39)
ISD	ggagt (SEQ ID NO: 12)
CAG targeting sequence	CTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTG (SEQ ID NO: 167)
SMOPT	AATTTTTGGAGTA (SEQ ID NO: 164)

Human stem loop (eSL)	ggctttctggctccttaccggaaagcc (SEQ ID NO: 1)
Human U7 terminator	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGCAAAAATTATGG GTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCTTGGAG (SEQ ID NO: 49)
Human U1 promoter	TAAGGACCAGCTTCTTTGGGAGAGAACAGACGCAGGGGCGGGAGGGAAAAAGG GAGAGGCAGACGTCACTTCCCCTTGGCGGCTCTGGCAGCAGATTGGTCGGTTGA GTGGCAGAAAGGCAGACGGGGACTGGGCAAGGCACTGTCGGTGACATCACGGA CAGGGCGACTTCTATGTAGATGAGGCAGCGCAGAGGCTGACGTCTTCGCCACTT GCTGCTTCACCACGAAGGAGTTCCCGTGCCCTGGGAGCGGGTTCAGGACCGCTG ATCGGAAGTGAGAATCCCAGCTGTGTGTCAGGGCTGGAAAGGGCTCGGGAGTGC GCGGGGCAAGTGACCGTGTGTGTAAAGAGTGAGGCGTATGAGGCTGTGTCGGGG CAGAGGCacaacgtttc (SEQ ID NO: 40)
ISD	ggagt (SEQ ID NO: 12)
CAG targeting sequence	CTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTG (SEQ ID NO: 167)
SMOPT	AATTTTTGGAGTA (SEQ ID NO: 164)
Human stem loop (eSL)	ggctttctggctccttaccggaaagcc (SEQ ID NO: 1)
human U1 terminator	ACTTTCTGGAGTTTCAAAAACAGACTGTACGCCAAGGGTCATATCTTTTT (SEQ ID NO: 50)
3'ITR	aaggaacccctagtgatggagttggccactccctctctgcgcgctcgctcgctcactgaggccgggcgaccaaaggtcgcccgacg cccgggctttgcccgggcggcctcagtgagcgagcgagcgcgccagc (SEQ ID NO: 166)

[0138] An exemplary AAV vector of the disclosure comprises from 5' to 3': a first inverted terminal repeat (ITR) sequence, a U7 promoter sequence, a CUG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a U1 promoter sequence, a CUG repeat targeting U7 esnRNA sequence, a U1 downstream terminator sequence, and a second ITR sequence. In some aspects, a nucleic acid sequence encoding AAV vector A04530 encoding CUG repeat targeting snRNA sequences comprises SEQ ID NO: 231.

A04530: scAAV- mU7p-CUGx15-mU1p-CUGx15; mouseloop with ISD and eSL

Plasmid Element	**Nucleotide Sequence 5' to 3'**
5' mut ITR	ctgcgcgctcgctcgctcactgaggccgcccgggcaaagcccgggcgtcgggcgacctttggtc gcccggcctcagtgagcgagcgagcgcgcagagagggagtggggtt (SEQ ID NO: 162)
mouse U7 promoter	taacaacataggagctgtgattggctgttttcagccaatcagcactgActcatttgcatagcctttac aagcggtcacaaactcaagaaacgagcggttttaatagtcttttagaatattgtttatcgaaccgaata aggaactgtgctttgtgattcacatatcagtggaggggtgtggaaatggcaccttgatctcaccctc atcgaaagtggagttgatgtcctTccctggctcgctacagacgcacttccgcaa(SEQ ID NO: 48)
ISD	ggagt (SEQ ID NO: 12)
spacer	CAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAG CAGCAG (SEQ ID NO: 165)
SMOPT	aATTTTTGGAGca (SEQ ID NO: 161)
Mouse stem loop (eSL)	ggttttctgacctccgtcggaaaacccct (SEQ ID NO: 12)
Mouse U7 terminator	cccaatttcactggtctacaatgaaagcaaaacagttctcttccccgctccccggtgtgtgagaggg gctttgatccttctctggtttcctaggaaacgcgtatgtg (SEQ ID NO: 156)

Mouse U1 promoter	TTGTTCCTCTTAGTGTTAATTCACACTAAAGACTGTGCATCC GACTCCTACATTTATGAAAGTAAATGCCTGTTGTTAGAACA AAAAAGGCTACAGAACAAAAAACAAAGCGAAATACCATCT GCTTTAGGTTCAGTGTGGTATTTTCCCGCTGACAGGGAGGC GGGTTTTTGGGTACAGGAAACGAGTCACTATGGAGGCGGT ACTATGTAGATGAGAATTCAGGTGCAAACTGGGAAAAGCA ACTGCTTCCAAATATTTGTGATTTTTACAGTGTAGTTTTGGA AAAACTCTTAGCCTACCAATTCTTCTAAGTGTTTTAAAATG TGGGAGCCAGTACACATGAAGTTATAGAGTGTTTTAATGAG GCTTAAATATTTACCGTAACTATGAAATGCTACGCATATCA TGCTGTTCAGGCTCCGTGGCCACGCAACTC (SEQ ID NO: 47)
ISD	ggagt (SEQ ID NO: 12)
spacer	CAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAG CAGCAG (SEQ ID NO: 165)
SMOPT	aATTTTTGGAGca (SEQ ID NO: 161)
Mouse stem loop (eSL)	ggttttctgacctccgtcggaaaacccct (SEQ ID NO: 12)
Mouse U1 terminator	GTTTACTTGGTTTTAAAAATAGCTTGCACTAGCGATACGGA ATATGGTTATTAGGTTTGTTAGGCATCATGTCGTGTCTTACT ATAGAAAAATAACGTAGTGTTCATTTTAGCCTGCCTGTATG TGTTAATTTGTCCTTATTGCGCATTGTTCTTGTTAAGTCTTC TGTAAGGAGTTGCGGGTTTCAAACTGTCAGTCTGAGAGCA (SEQ ID NO: 57)
3'ITR	aggaacccctagtgatggagttggccactccctctctgcgcgctcgctcgctcactgaggccggg cgaccaaaggtcgcccgacgcccgggctttgcccgggcggcctcagtgagcgagcgagcgcg cagctgcctgcagg (SEQ ID NO: 60)

[0139] An exemplary AAV vector of the disclosure comprises from 5' to 3': a first inverted terminal repeat (ITR) sequence, a U7 promoter sequence, a CUG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a U1 promoter sequence, a CUG repeat targeting U7 esnRNA sequence, a U1 downstream terminator sequence, and a second ITR sequence. In some aspects, a nucleic acid sequence encoding AAV vector A04940 encoding CUG repeat targeting snRNA sequences comprises SEQ ID NO: 232.

A04940: scAAV- mU7p-CUGx10-mU1p-CUGx10; mouseloop with ISD and eSL no CCU

Plasmid Element	**Nucleotide Sequence 5' to 3'**
5' mut ITR	ctgcgcgctcgctcgctcactgaggccgcccgggcaaagcccgggcgtcgggcgacctttggtc gcccggcctcagtgagcgagcgagcgcgcagagagggagtggggtt (SEQ ID NO: 162)
mouse U7 promoter	taacaacataggagctgtgattggctgttttcagccaatcagcactgActcatttgcatagcctttac aagcggtcacaaactcaagaaacgagcggttttaatagtcttttagaatattgtttatcgaaccgaata aggaactgtgctttgtgattcacatatcagtggaggggtgtggaaatggcaccttgatctcaccctc

	atcgaaagtggagttgatgtcctTccctggctcgctacagacgcacttccgcaa (SEQ ID NO: 48)
ISD	ggagt (SEQ ID NO: 12)
spacer	CAGCAGCAGCAGCAGCAGCAGCAGCAG (SEQ ID NO: 165)
SMOPT	aATTTTTGGAGca (SEQ ID NO: 161)
Mouse stem loop (eSL)	ggttttctgacctccgtcggaaaacc (SEQ ID NO: 148)
Mouse U7 terminator	cccaatttcactggtctacaatgaaagcaaaacagttctcttccccgctccccggtgtgtgagaggg gctttgatccttctctggtttcctaggaaacgcgtatgtg (SEQ ID NO: 156)
Mouse U1 promoter	TTGTTCCTCTTAGTGTTAATTCACACTAAAGACTGTGCATCC GACTCCTACATTTATGAAAGTAAATGCCTGTTGTTAGAACA AAAAAGGCTACAGAACAAAAAACAAAGCGAAATACCATCT GCTTTAGGTTCAGTGTGGTATTTTCCCGCTGACAGGGAGGC GGGTTTTTGGGTACAGGAAACGAGTCACTATGGAGGCGGT ACTATGTAGATGAGAATTCAGGTGCAAACTGGGAAAAGCA ACTGCTTCCAAATATTTGTGATTTTTACAGTGTAGTTTTGGA AAAACTCTTAGCCTACCAATTCTTCTAAGTGTTTTAAAATG TGGGAGCCAGTACACATGAAGTTATAGAGTGTTTTAATGAG GCTTAAATATTTACCGTAACTATGAAATGCTACGCATATCA TGCTGTTCAGGCTCCGTGGCCACGCAACTC (SEQ ID NO: 47)
ISD	ggagt (SEQ ID NO: 12)
spacer	CAGCAGCAGCAGCAGCAGCAGCAGCAG (SEQ ID NO: 165)
SMOPT	aATTTTTGGAGca (SEQ ID NO: 161)
Mouse stem loop (eSL)	ggttttctgacctccgtcggaaaaccct (SEQ ID NO: 12)
Mouse U1 terminator	GTTTACTTGGTTTTAAAAATAGCTTGCACTAGCGATACGGA ATATGGTTATTAGGTTTGTTAGGCATCATGTCGTGTCTTACT ATAGAAAAATAACGTAGTGTTCATTTTAGCCTGCCTGTATG TGTTAATTTGTCCTTATTGCGCATTGTTCTTGTTAAGTCTTC TGTAAGGAGTTGCGGGTTTCAAACTGTCAGTCTGAGAGCA (SEQ ID NO: 57)
3'ITR	aggaacccctagtgatggagttggccactccctctctgcgcgctcgctcgctcactgaggccggg cgaccaaaggtcgcccgacgcccgggctttgcccgggcggcctcagtgagcgagcgagcgcg cagctgcctgcagg (SEQ ID NO: 60)

[0140] An exemplary AAV vector of the disclosure comprises from 5' to 3': a first inverted terminal repeat (ITR) sequence, a U7 promoter sequence, a CAG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a U1 promoter sequence, a CAG repeat targeting U7 esnRNA sequence, a U1 downstream terminator sequence, and a second

ITR sequence. In some aspects, a nucleic acid sequence encoding AAV vector A04533 encoding CAG repeat targeting snRNA sequences comprises SEQ ID NO: 233.

A04533: scAAV- mU7p-CAGx15-mU1p-CAGx15; mouseloop with ISD and eSL

Plasmid Element	Nucleotide Sequence 5' to 3'
5' mut ITR	ctgcgcgctcgctcgctcactgaggccgcccgggcaaagcccgggcgtcgggcgacctttggtc gcccggcctcagtgagcgagcgagcgcgcagagagggagtggggtt (SEQ ID NO: 162)
mouse U7 promoter	taacaacataggagctgtgattggctgttttcagccaatcagcactgActcatttgcatagcctttac aagcggtcacaaactcaagaaacgagcggttttaatagtcttttagaatattgtttatcgaaccgaata aggaactgtgctttgtgattcacatatcagtggaggggtgtggaaatggcaccttgatctcaccctc atcgaaagtggagttgatgtcctTccctggctcgctacagacgcacttccgcaa (SEQ ID NO: 48)
ISD	ggagt (SEQ ID NO: 12)
spacer	CTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTG CTG (SEQ ID NO: 167)
SMOPT	aATTTTTGGAGca (SEQ ID NO: 161)
Mouse stem loop (eSL)	ggttttctgacctccgtcggaaaacccct (SEQ ID NO: 12)
Mouse U7 terminator	cccaatttcactggtctacaatgaaagcaaaacagttctcttccccgctccccggtgtgtgagaggg gctttgatccttctctggtttcctaggaaacgcgtatgtg (SEQ ID NO: 156)
Mouse U1 promoter	TTGTTCCTCTTAGTGTTAATTCACACTAAAGACTGTGCATCC GACTCCTACATTTATGAAAGTAAATGCCTGTTGTTAGAACA AAAAAGGCTACAGAACAAAAAACAAAGCGAAATACCATCT GCTTTAGGTTCAGTGTGGTATTTTCCCGCTGACAGGGAGGC GGGTTTTTGGGTACAGGAAACGAGTCACTATGGAGGCGGT ACTATGTAGATGAGAATTCAGGTGCAAACTGGGAAAAGCA ACTGCTTCCAAATATTTGTGATTTTTACAGTGTAGTTTTGGA AAAACTCTTAGCCTACCAATTCTTCTAAGTGTTTTAAAATG TGGGAGCCAGTACACATGAAGTTATAGAGTGTTTTAATGAG GCTTAAATATTTACCGTAACTATGAAATGCTACGCATATCA TGCTGTTCAGGCTCCGTGGCCACGCAACTC (SEQ ID NO: 47)
ISD	ggagt (SEQ ID NO: 12)
spacer	CTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTG CTG (SEQ ID NO: 167)
SMOPT	aATTTTTGGAGca (SEQ ID NO: 161)
Mouse stem loop (eSL)	ggttttctgacctccgtcggaaaacccct (SEQ ID NO: 12)
Mouse U1 terminator	GTTTACTTGGTTTTAAAAATAGCTTGCACTAGCGATACGGA ATATGGTTATTAGGTTTGTTAGGCATCATGTCGTGTCTTACT ATAGAAAAATAACGTAGTGTTCATTTTAGCCTGCCTGTATG TGTTAATTTGTCCTTATTGCGCATTGTTCTTGTTAAGTCTTC

	TGTAAGGAGTTGCGGGTTTCAAACTGTCAGTCTGAGAGCA (SEQ ID NO: 57)
3' ITR	Aggaacccctagtgatggagttggccactccctctctgcgcgctcgctcgctcactgaggccgg gcgaccaaaggtcgcccgacgcccgggctttgcccgggcggcctcagtgagcgagcgagcgc gcagctgcctgcagg (SEQ ID NO: 60)

[0141] An exemplary AAV vector of the disclosure comprises from 5' to 3': a first inverted terminal repeat (ITR) sequence, a U7 promoter sequence, a CUG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, a U7 promoter sequence, a CUG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, a U7 promoter sequence, a CUG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, a U7 promoter sequence, a CUG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, and a second ITR sequence. In some aspects, a nucleic acid sequence encoding AAV vector A02962 encoding CUG repeat targeting snRNA sequences comprises SEQ ID NO: 120.A02962 ss pAAV-4X U7(15XCUG) (derivative of P00369) targeting CUG repeats

ITR	Cctgcaggcagctgcgcgctcgctcgctcactgaggccgcccgggcgtcgggcgacctttggtcgc ccggcctcagtgagcgagcgagcgcgcagagagggagtggccaactccatcactaggggttcct (SEQ ID NO: 59)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGG GCTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCAT TTGCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGA ATGACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAA AGTTACCACATGCGTCGTTGTTTATACAGTAATAGGAACAAG AAAAAAGTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCC TTTATATCCCATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCA GCAGCAGAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 65)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGT GCAAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTA AGCTTGGAG (SEQ ID NO: 49)
30bp buffer 1	CAAACTACAGAGCCAAGTGCTATCCACAGA (SEQ ID NO: 24)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGG GCTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCAT TTGCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGA ATGACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAA AGTTACCACATGCGTCGTTGTTTATACAGTAATAGGAACAAG AAAAAAGTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCC

	TTTATATCCCATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCA GCAGCAGAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 65)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGT GCAAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTA AGCTTGGAG (SEQ ID NO: 49)
30bp buffer 2	GAGCTTTCTGGGTTGCCATCTCAAGCAGAC (SEQ ID NO: 25)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGG GCTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCAT TTGCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGA ATGACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAA AGTTACCACATGCGTCGTTGTTTATACAGTAATAGGAACAAG AAAAAAGTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCC TTTATATCCCATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCA GCAGCAGAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 65)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGT GCAAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTA AGCTTGGAG (SEQ ID NO: 49)
30bp buffer 3	TACAAGGCCATCAGCTCATACTCACAATTG (SEQ ID NO: 26)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGG GCTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCAT TTGCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGA ATGACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAA AGTTACCACATGCGTCGTTGTTTATACAGTAATAGGAACAAG AAAAAAGTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCC TTTATATCCCATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCA GCAGCAGAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 65)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGT GCAAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTA AGCTTGGAG (SEQ ID NO: 49)
ITR	Aggaacccctagtgatggagttggccactccctctctgcgcgctcgctcgctcactgaggccgggcg accaaaggtcgcccgacgcccgggctttgcccgggcggcctcagtgagcgagcgagcgcgcagct gcctgcagg (SEQ ID NO: 60)

[0142] An exemplary AAV vector of the disclosure comprises from 5' to 3': a first inverted terminal repeat (ITR) sequence, a U7 promoter sequence, a non- targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, a U7 promoter sequence, a non- targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a

buffer sequence, a U7 promoter sequence, a non-targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, a U7 promoter sequence, a non-targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, and a second ITR sequence. In some aspects, a nucleic acid sequence encoding AAV vector A02963 encoding a non-targeting snRNA sequences comprises SEQ ID NO: 121.

A02963 ss pAAV-4X U7(NT1) (derivative of P00369)

ITR	Cctgcaggcagctgcgcgctcgctcgctcactgaggccgcccgggcgtcgggcgacctttggtcgcc cggcctcagtgagcgagcgagcgcgcagagagggagtggccaactccatcactaggggttcct (SEQ ID NO: 59)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGG CTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTT GCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATG ACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTT ACCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAA AGTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATAT CCCATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtTCACCAGAAGCGTACCATACTCACGAAATTTTTGGAGTAgg ctttctggctccttaccggaaagcc (SEQ ID NO: 66)
U7 Downstrea m (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTG CAAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGC TTGGAG (SEQ ID NO: 49)
30bp buffer 1	CAAACTACAGAGCCAAGTGCTATCCACAGA (SEQ ID NO: 24)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGG CTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTT GCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATG ACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTT ACCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAA AGTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATAT CCCATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtTCACCAGAAGCGTACCATACTCACGAAATTTTTGGAGTAgg ctttctggctccttaccggaaagcc (SEQ ID NO: 66)
U7 Downstrea m (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTG CAAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGC TTGGAG (SEQ ID NO: 49)
30bp buffer 2	GAGCTTTCTGGGTTGCCATCTCAAGCAGAC (SEQ ID NO: 25)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGG CTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTT GCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATG ACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTT ACCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAA

	AGTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATAT CCCATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtTCACCAGAAGCGTACCATACTCACGAAATTTTTGGAGTAgg ctttctggctccttaccggaaagcc (SEQ ID NO: 66)
U7 Downstrea m (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTG CAAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGC TTGGAG (SEQ ID NO: 49)
30bp buffer 3	TACAAGGCCATCAGCTCATACTCACAATTG (SEQ ID NO: 26)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGG CTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTT GCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATG ACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTT ACCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAA AGTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATAT CCCATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtTCACCAGAAGCGTACCATACTCACGAAATTTTTGGAGTAgg ctttctggctccttaccggaaagcc (SEQ ID NO: 66)
U7 Downstrea m (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTG CAAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGC TTGGAG (SEQ ID NO: 49)
ITR	Aggaacccctagtgatggagttggccactccctctctgcgcgctcgctcgctcactgaggccgggcga ccaaaggtcgcccgacgcccgggctttgcccgggcggcctcagtgagcgagcgagcgcgcagctgc ctgcagg (SEQ ID NO: 60)

[0143] An exemplary AAV vector of the disclosure comprises from 5' to 3': a first inverted terminal repeat (ITR) sequence, a U7 promoter sequence, a CAG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, a U7 promoter sequence, a CAG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, a U7 promoter sequence, a CAG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, a U7 promoter sequence, a CAG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, and a second ITR sequence. In some aspects, a nucleic acid sequence encoding AAV vector A02967 encoding a CAG repeat targeting snRNA sequences comprises SEQ ID NO: 122.

[0144] A02967 ss pAAV-4X U7(15XCAG) targeting CAG repeats

ITR	Cctgcaggcagctgcgcgctcgctcgctcactgaggccgcccgggcgtcgggcgacctttggtcgc ccggcctcagtgagcgagcgagcgcgcagagagggagtggccaactccatcactaggggttcct (SEQ ID NO: 59)

U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGG GCTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCAT TTGCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGA ATGACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAA GTTACCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAA AAAAGTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTT ATATCCCATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGC TGCTGAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 67)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTG CAAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAG CTTGGAG (SEQ ID NO: 49)
30bp buffer 1	CAAACTACAGAGCCAAGTGCTATCCACAGA (SEQ ID NO: 24)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGG GCTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCAT TTGCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGA ATGACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAA GTTACCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAA AAAAGTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTT ATATCCCATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGC TGCTGAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 67)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTG CAAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAG CTTGGAG (SEQ ID NO: 49)
30bp buffer 2	GAGCTTTCTGGGTTGCCATCTCAAGCAGAC (SEQ ID NO: 25)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGG GCTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCAT TTGCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGA ATGACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAA GTTACCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAA AAAAGTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTT ATATCCCATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGC TGCTGAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 67)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTG CAAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAG CTTGGAG (SEQ ID NO: 49)
30bp buffer 3	TACAAGGCCATCAGCTCATACTCACAATTG (SEQ ID NO: 26)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGG GCTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCAT TTGCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGA ATGACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAA GTTACCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAA

	AAAAGTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTT ATATCCCATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGC TGCTGAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 67)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTG CAAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAG CTTGGAG (SEQ ID NO: 49)
ITR	Aggaacccctagtgatggagttggccactccctctctgcgcgctcgctcgctcactgaggccgggcg accaaaggtcgcccgacgcccgggctttgcccgggcggcctcagtgagcgagcgagcgcgcagct gcctgcagg (SEQ ID NO: 60)

[0145] An exemplary AAV vector of the disclosure comprises from 5' to 3': a first inverted terminal repeat (ITR) sequence, a U7 promoter sequence, a CUG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, a U7 promoter sequence, a CUG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, a U7 promoter sequence, a CUG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, a U7 promoter sequence, a CUG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, and a second ITR sequence. In some aspects, a nucleic acid sequence encoding AAV vector A03079 encoding a CUG repeat targeting snRNA sequences comprises SEQ ID NO: 123.

A03079 sc pAAV-4X U7(15XCUG) (derivative of P00369) targeting CUG repeats

ITR	Cctgcaggcagctgcgcgctcgctcgctcactgaggccgcccgggcgtcgggcgacctttggtcgcc cggcctcagtgagcgagcgagcgcgcagagagggagtggccaactccatcactaggggttcct (SEQ ID NO: 59)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGG CTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTT GCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATG ACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTT ACCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAA AGTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATAT CCCATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAG CAGCAGAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 65)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGC AAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCT TGGAG (SEQ ID NO: 49)
30bp buffer 1	CAAACTACAGAGCCAAGTGCTATCCACAGA (SEQ ID NO: 24)

U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGG CTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTT GCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATG ACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTT ACCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAA AGTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATAT CCCATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAG CAGCAGAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 65)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGC AAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCT TGGAG (SEQ ID NO: 49)
30bp buffer 2	GAGCTTTCTGGGTTGCCATCTCAAGCAGAC (SEQ ID NO: 25)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGG CTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTT GCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATG ACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTT ACCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAA AGTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATAT CCCATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAG CAGCAGAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 65)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGC AAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCT TGGAG (SEQ ID NO: 49)
30bp buffer 3	TACAAGGCCATCAGCTCATACTCACAATTG (SEQ ID NO: 26)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGG CTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTT GCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATG ACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTT ACCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAA AGTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATAT CCCATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAG CAGCAGAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 65)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGC AAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCT TGGAG (SEQ ID NO: 49)
ITR	CCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGA CCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAG TGAGCGAGCGAGCGCGCAGAGAGGGA (SEQ ID NO: 61)

[0146] An exemplary AAV vector of the disclosure comprises from 5' to 3': a first inverted terminal repeat (ITR) sequence, a U7 promoter sequence, a non-targeting U7 esnRNA

sequence, a U7 downstream terminator sequence, a buffer sequence, a U7 promoter sequence, a non-targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, a U7 promoter sequence, a non-targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, a U7 promoter sequence, a non-targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, and a second ITR sequence. In some aspects, a nucleic acid sequence encoding AAV vector A03080 encoding a non-repeat targeting snRNA sequences comprises SEQ ID NO: 124.

A03080 sc pAAV-4X U7(NT1) (derivative of P00369)

ITR	Cctgcaggcagctgcgcgctcgctcgctcactgaggccgcccgggcgtcgggcgacctttggtcgccc ggcctcagtgagcgagcgagcgcgcagagagggagtggccaactccatcactaggggttcct (SEQ ID NO: 59)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGG CTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTT GCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATG ACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTTA CCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAAA GTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATATCC CATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtTCACCAGAAGCGTACCATACTCACGAAATTTTTGGAGTAggc tttctggctccttaccggaaagcc (SEQ ID NO: 66)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGC AAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCT TGGAG (SEQ ID NO: 49)
30bp buffer 1	CAAACTACAGAGCCAAGTGCTATCCACAGA (SEQ ID NO: 24)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGG CTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTT GCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATG ACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTTA CCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAAA GTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATATCC CATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtTCACCAGAAGCGTACCATACTCACGAAATTTTTGGAGTAggc tttctggctccttaccggaaagcc (SEQ ID NO: 66)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGC AAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCT TGGAG (SEQ ID NO: 49)
30bp buffer 2	GAGCTTTCTGGGTTGCCATCTCAAGCAGAC (SEQ ID NO: 25)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGG CTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTT GCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATG ACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTTA CCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAAA

	GTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATATCC CATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtTCACCAGAAGCGTACCATACTCACGAAATTTTTGGAGTAggc tttctggctccttaccggaaagcc (SEQ ID NO: 66)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGC AAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCT TGGAG (SEQ ID NO: 49)
30bp buffer 3	TACAAGGCCATCAGCTCATACTCACAATTG (SEQ ID NO: 26)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGG CTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTT GCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATG ACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTTA CCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAAA GTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATATCC CATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtTCACCAGAAGCGTACCATACTCACGAAATTTTTGGAGTAggc tttctggctccttaccggaaagcc (SEQ ID NO: 66)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGC AAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCT TGGAG (SEQ ID NO: 49)
ITR	CCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGA CCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGT GAGCGAGCGAGCGCGCAGAGAGGGA (SEQ ID NO: 61)

[0147] An exemplary AAV vector of the disclosure comprises from 5' to 3': a first inverted terminal repeat (ITR) sequence, a U7 promoter sequence, a CAG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, a U7 promoter sequence, a CAG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, a U7 promoter sequence, a CAG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, a U7 promoter sequence, a CAG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, and a second ITR sequence. In some aspects, a nucleic acid sequence encoding AAV vector A03081 encoding a CAG repeat targeting snRNA sequences comprises SEQ ID NO: 125.

A03081 sc pAAV-4X U7(15XCAG) targeting CAG repeats

ITR	Cctgcaggcagctgcgcgctcgctcgctcactgaggccgcccgggcgtcgggcgacctttggtcgccc ggcctcagtgagcgagcgagcgcgcagagagggagtggccaactccatcactaggggttcct (SEQ ID NO: 59)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGG CTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTT GCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATG ACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTTA CCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAAA

	GTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATATCC CATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTG CTGAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 67)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGC AAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCT TGGAG (SEQ ID NO: 49)
30bp buffer 1	CAAACTACAGAGCCAAGTGCTATCCACAGA (SEQ ID NO: 24)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGG CTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTT GCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATG ACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTTA CCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAAA GTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATATCC CATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTG CTGAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 67)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGC AAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCT TGGAG (SEQ ID NO: 49)
30bp buffer 2	GAGCTTTCTGGGTTGCCATCTCAAGCAGAC (SEQ ID NO: 25)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGG CTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTT GCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATG ACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTTA CCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAAA GTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATATCC CATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTG CTGAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 67)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGC AAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCT TGGAG (SEQ ID NO: 49)
30bp buffer 3	TACAAGGCCATCAGCTCATACTCACAATTG (SEQ ID NO: 26)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGG CTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTT GCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATG ACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTTA CCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAAA GTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATATCC CATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTG CTGAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 67)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGC AAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCT TGGAG (SEQ ID NO: 49)

ITR	CCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGA CCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGT GAGCGAGCGAGCGCGCAGAGAGGGA (SEQ ID NO: 61)

[0148] An exemplary AAV vector of the disclosure comprises from 5' to 3': a first inverted terminal repeat (ITR) sequence, a U7 promoter sequence, a CUG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a CMV promoter sequence, a sequence encoding green fluorescent protein (GFP), a sv40 polyA sequence, and a second ITR sequence. In some aspects, a nucleic acid sequence encoding AAV vector A02888 encoding a CUG repeat targeting snRNA sequence comprises SEQ ID NO: 126.

A02888 pAAV_1xU7(15xCUG)_CMV_GFP (no buffer) targeting CUG repeats

ITR	Cctgcaggcagctgcgcgctcgctcgctcactgaggccgcccgggcgtcgggcgacctttggtcgccc ggcctcagtgagcgagcgagcgcgcagagagggagtggccaactccatcactaggggttcct (SEQ ID NO: 59)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGG CTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTT GCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATG ACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTTA CCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAAA GTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATATCC CATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAG CAGCAGAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 65)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGC AAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCT TGGAG (SEQ ID NO: 49)
CMV promoter	Cgttacataacttacggtaaatggcccgcctggctgaccgcccaacgacccccgcccattgacgtcaata atgacgtatgttcccatagtaacgccaatagggactttccattgacgtcaatgggtggagtatttacggtaaa ctgcccacttggcagtacatcaagtgtatcatatgccaagtacgccccctattgacgtcaatgacggtaaat ggcccgcctggcattatgcccagtacatgaccttatgggactttcctacttggcagtacatctacgtattagtc atcgctattaccatggtgatgcggttttggcagtacatcaatgggcgtggatagcggtttgactcacgggga tttccaagtctccaccccattgacgtcaatgggagtttgttttggcaccaaaatcaacgggactttccaaaatg tcgtaacaactccgccccattgacgcaaatgggcggtaggcgtgtacggtgggaggtctatataagcaga gct (SEQ ID NO: 62)
eGFP	ATGgtgagcaagggcgaggagctgttcaccggggtggtgcccatcctggtcgagctggacggcgac gtaaacggccacaagttcagcgtgtccggcgagggcgagggcgatgccacctacggcaagctgaccct gaagttcatctgcaccaccggcaagctgcccgtgccctggcccaccctcgtgaccaccctgacctacggc gtgcagtgcttcagccgctaccccgaccacatgaagcagcacgacttcttcaagtccgccatgcccgaag gctacgtccaggagcgcaccatcttcttcaaggacgacggcaactacaagacccgcgccgaggtgaagt tcgagggcgacaccctggtgaaccgcatcgagctgaagggcatcgacttcaaggaggacggcaacatc ctggggcacaagctggagtacaactacaacagccacaacgtctatatcatggccgacaagcagaagaac ggcatcaaggtgaacttcaagatccgccacaacatcgaggacggcagcgtgcagctcgccgaccactac

	cagcagaacacccccatcggcgacggccccgtgctgctgcccgacaaccactacctgagcacccagtc cgccctgagcaaagaccccaacgagaagcgcgatcacatggtcctgctggagttcgtgaccgccgccg ggatcactctcggcatggacgagctgtacaagTAA (SEQ ID NO: 63)
SV40 Poly A	Aacttgtttattgcagcttataatggttacaaataaagcaatagcatcacaaatttcacaaataaagcatttttttt cactgcattctagttgtggtttgtccaaactcatcaatgtatctta (SEQ ID NO: 64)
ITR	Aggaacccctagtgatggagttggccactccctctctgcgcgctcgctcgctcactgaggccgggcgac caaaggtcgcccgacgcccgggctttgcccgggcggcctcagtgagcgagcgagcgcgcagctgcct gcagg (SEQ ID NO: 60)

[0149] An exemplary AAV vector of the disclosure comprises from 5' to 3': a first inverted terminal repeat (ITR) sequence, a U7 promoter sequence, a non-targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a CMV promoter sequence, a sequence encoding green fluorescent protein (GFP), a sv40 polyA sequence, and a second ITR sequence. In some aspects, a nucleic acid sequence encoding AAV vector A02889 encoding a non-targeting repeat targeting snRNA sequence comprises SEQ ID NO: 127.

A02889 pAAV_1xU7(NT1)_CMV_GFP (no buffer)

ITR	Cctgcaggcagctgcgcgctcgctcgctcactgaggccgcccgggcgtcgggcgacctttggtcgccc ggcctcagtgagcgagcgagcgcgcagagagggagtggccaactccatcactaggggttcct (SEQ ID NO: 59)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGG CTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTT GCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATG ACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTTA CCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAAA GTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATATCC CATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtTCACCAGAAGCGTACCATACTCACGAAATTTTTGGAGTAggc tttctggctccttaccggaaagcc (SEQ ID NO: 66)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGC AAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCT TGGAG (SEQ ID NO: 49)
CMV promoter	Cgttacataacttacggtaaatggcccgcctggctgaccgcccaacgacccccgcccattgacgtcaata atgacgtatgttcccatagtaacgccaatagggactttccattgacgtcaatgggtggagtatttacggtaaa ctgcccacttggcagtacatcaagtgtatcatatgccaagtacgccccctattgacgtcaatgacggtaaat ggcccgcctggcattatgcccagtacatgaccttatgggactttcctacttggcagtacatctacgtattagtc atcgctattaccatggtgatgcggttttggcagtacatcaatgggcgtggatagcggtttgactcacgggga tttccaagtctccaccccattgacgtcaatgggagtttgttttggcaccaaaatcaacgggactttccaaaatg tcgtaacaactccgccccattgacgcaaatgggcggtaggcgtgtacggtgggaggtctatataagcaga gct (SEQ ID NO: 62)
eGFP	ATGgtgagcaagggcgaggagctgttcaccggggtggtgcccatcctggtcgagctggacggcgac gtaaacggccacaagttcagcgtgtccggcgagggcgagggcgatgccacctacggcaagctgaccct gaagttcatctgcaccaccggcaagctgcccgtgccctggcccaccctcgtgaccaccctgacctacggc gtgcagtgcttcagccgctaccccgaccacatgaagcagcacgacttcttcaagtccgccatgcccgaag

	gctacgtccaggagcgcaccatcttcttcaaggacgacggcaactacaagacccgcgccgaggtgaagt tcgagggcgacaccctggtgaaccgcatcgagctgaagggcatcgacttcaaggaggacggcaacatc ctggggcacaagctggagtacaactacaacagccacaacgtctatatcatggccgacaagcagaagaac ggcatcaaggtgaacttcaagatccgccacaacatcgaggacggcagcgtgcagctcgccgaccactac cagcagaacaccccatcggcgacggccccgtgctgctgcccgacaaccactacctgagcacccagtc cgccctgagcaaagaccccaacgagaagcgcgatcacatggtcctgctggagttcgtgaccgccgccg ggatcactctcggcatggacgagctgtacaagTAA (SEQ ID NO: 63)
SV40 Poly A	Aacttgtttattgcagcttataatggttacaaataaagcaatagcatcacaaatttcacaaataaagcatttttttt cactgcattctagttgtggtttgtccaaactcatcaatgtatctta (SEQ ID NO: 64)
ITR	Aggaacccctagtgatggagttggccactccctctctgcgcgctcgctcgctcactgaggccgggcgac caaaggtcgcccgacgcccgggctttgcccgggcggcctcagtgagcgagcgagcgcgcagctgcct gcagg (SEQ ID NO: 60)

[0150] An exemplary AAV vector of the disclosure comprises from 5' to 3': a first inverted terminal repeat (ITR) sequence, a U7 promoter sequence, a CAG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a CMV promoter sequence, a sequence encoding green fluorescent protein (GFP), a sv40 polyA sequence, and a second ITR sequence. In some aspects, a nucleic acid sequence encoding AAV vector A02925 encoding a CAG repeat targeting repeat targeting snRNA sequence comprises SEQ ID NO: 128.

A02925 pAAV_1xU7(15xCAG)_CMV_GFP (no buffer) targeting CAG repeats

ITR	Cctgcaggcagctgcgcgctcgctcgctcactgaggccgcccgggcgtcgggcgacctttggtcgccc ggcctcagtgagcgagcgagcgcgcagagagggagtggccaactccatcactaggggttcct (SEQ ID NO: 59)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGG CTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTT GCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATG ACTTAAGTAAGTTCCTTAGAATATTATTTTCCTACTGAAAGTTA CCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAAA GTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATATCC CATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTG CTGAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 67)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGC AAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCT TGGAG (SEQ ID NO: 49)

CMV promoter	Cgttacataacttacggtaaatggcccgcctggctgaccgcccaacgacccccgcccattgacgtcaata atgacgtatgttcccatagtaacgccaatagggactttccattgacgtcaatgggtggagtatttacggtaaa ctgcccacttggcagtacatcaagtgtatcatatgccaagtacgccccctattgacgtcaatgacggtaaat ggcccgcctggcattatgcccagtacatgaccttatgggactttcctacttggcagtacatctacgtattagtc atcgctattaccatggtgatgcggttttggcagtacatcaatgggcgtggatagcggtttgactcacgggga tttccaagtctccaccccattgacgtcaatgggagtttgttttggcaccaaaatcaacgggactttccaaaatg tcgtaacaactccgccccattgacgcaaatgggcggtaggcgtgtacggtgggaggtctatataagcaga gct (SEQ ID NO: 62)
eGFP	ATGgtgagcaagggcgaggagctgttcaccggggtggtgcccatcctggtcgagctggacggcgac gtaaacggccacaagttcagcgtgtccggcgagggcgagggcgatgccacctacggcaagctgaccct gaagttcatctgcaccaccggcaagctgcccgtgccctggcccaccctcgtgaccaccctgacctacggc gtgcagtgcttcagccgctaccccgaccacatgaagcagcacgacttcttcaagtccgccatgcccgaag gctacgtccaggagcgcaccatcttcttcaaggacgacggcaactacaagacccgcgccgaggtgaagt tcgagggcgacaccctggtgaaccgcatcgagctgaagggcatcgacttcaaggaggacggcaacatc ctggggcacaagctggagtacaactacaacagccacaacgtctatatcatggccgacaagcagaagaac ggcatcaaggtgaacttcaagatccgccacaacatcgaggacggcagcgtgcagctcgccgaccactac cagcagaacaccccatcggcgacggccccgtgctgctgcccgacaaccactacctgagcacccagtc cgccctgagcaaagaccccaacgagaagcgcgatcacatggtcctgctggagttcgtgaccgccgccg ggatcactctcggcatggacgagctgtacaagTAA (SEQ ID NO: 63)
SV40 Poly A	Aacttgtttattgcagcttataatggttacaaataaagcaatagcatcacaaatttcacaaataaagcatttttttt cactgcattctagttgtggtttgtccaaactcatcaatgtatctta (SEQ ID NO: 64)
ITR	Aggaacccctagtgatggagttggccactccctctctgcgcgctcgctcgctcactgaggccgggcgac caaaggtcgcccgacgcccgggctttgcccgggcggcctcagtgagcgagcgagcgcgcagctgcct gcagg (SEQ ID NO: 60)

[0151] An exemplary AAV vector of the disclosure comprises from 5' to 3': a first inverted terminal repeat (ITR) sequence, a U7 promoter sequence, a CUG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, a U7 promoter sequence, a CUG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, a U7 promoter sequence, a CUG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a CMV promoter sequence, a sequence encoding green fluorescent protein (GFP), a sv40 polyA sequence, and a second ITR sequence. In some aspects, a nucleic acid sequence encoding AAV vector A02894 encoding a CUG repeat targeting repeat targeting snRNA sequence comprises SEQ ID NO: 129.

A02894 pAAV_3xU7(15xCUG)_CMV_GFP (100bp buffer) targeting CUG repeats

ITR	Cctgcaggcagctgcgcgctcgctcgctcactgaggccgcccgggcgtcgggcgacctttggtcgccc ggcctcagtgagcgagcgagcgcgcagagagggagtggccaactccatcactaggggttcct (SEQ ID NO: 59)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGG CTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTT GCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATG

	ACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTTA CCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAAA GTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATATCC CATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAG CAGCAGAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 65)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGC AAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCT TGGAG (SEQ ID NO: 49)
100bp buffer 1	CAAACTACAGAGCCAAGTGCTATCCACAGAGAGCTTTCTGGGTT GCCATCTCAAGCAGACTACAAGGCCATCAGCTCATACTCACAAT TGACTTTGAGAG (SEQ ID NO: 31)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGG CTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTT GCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATG ACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTTA CCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAAA GTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATATCC CATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAG CAGCAGAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 65)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGC AAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCT TGGAG (SEQ ID NO: 49)
100bp buffer 2	TTGACCACATACGTGCTCTTTCAAAGTTCTGTGTTTGAAGTTATG TTAGTAACAACTGATGCCCATCCTGCAATGACAAATCCAATTCT CAGTGCAGCTC (SEQ ID NO: 28)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGG CTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTT GCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATG ACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTTA CCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAAA GTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATATCC CATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAG CAGCAGAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 65)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGC AAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCT TGGAG (SEQ ID NO: 49)

CMV promoter	Cgttacataacttacggtaaatggcccgcctggctgaccgcccaacgacccccgcccattgacgtcaata atgacgtatgttcccatagtaacgccaatagggactttccattgacgtcaatgggtggagtatttacggtaaa ctgcccacttggcagtacatcaagtgtatcatatgccaagtacgccccctattgacgtcaatgacggtaaat ggcccgcctggcattatgcccagtacatgaccttatgggactttcctacttggcagtacatctacgtattagtc atcgctattaccatggtgatgcggttttggcagtacatcaatgggcgtggatagcggtttgactcacgggga tttccaagtctccaccccattgacgtcaatgggagtttgttttggcaccaaaatcaacgggactttccaaaatg tcgtaacaactccgccccattgacgcaaatgggcggtaggcgtgtacggtgggaggtctatataagcaga gct (SEQ ID NO: 62)
eGFP	ATGgtgagcaagggcgaggagctgttcaccggggtggtgcccatcctggtcgagctggacggcgac gtaaacggccacaagttcagcgtgtccggcgagggcgagggcgatgccacctacggcaagctgaccct gaagttcatctgcaccaccggcaagctgcccgtgccctggcccaccctcgtgaccaccctgacctacggc gtgcagtgcttcagccgctaccccgaccacatgaagcagcacgacttcttcaagtccgccatgcccgaag gctacgtccaggagcgcaccatcttcttcaaggacgacggcaactacaagacccgcgccgaggtgaagt tcgagggcgacaccctggtgaaccgcatcgagctgaagggcatcgacttcaaggaggacggcaacatc ctggggcacaagctggagtacaactacaacagccacaacgtctatatcatggccgacaagcagaagaac ggcatcaaggtgaacttcaagatccgccacaacatcgaggacggcagcgtgcagctcgccgaccactac cagcagaacaccccatcggcgacggccccgtgctgctgcccgacaaccactacctgagcacccagtc cgccctgagcaaagaccccaacgagaagcgcgatcacatggtcctgctggagttcgtgaccgccgccg ggatcactctcggcatggacgagctgtacaagTAA (SEQ ID NO: 63)
SV40 Poly A	Aacttgtttattgcagcttataatggttacaaataaagcaatagcatcacaaatttcacaaataaagcatttttttt cactgcattctagttgtggtttgtccaaactcatcaatgtatctta (SEQ ID NO: 64)
ITR	Aggaacccctagtgatggagttggccactccctctctgcgcgctcgctcgctcactgaggccgggcgac caaaggtcgcccgacgcccgggctttgcccgggcggcctcagtgagcgagcgagcgcgcagctgcct gcagg (SEQ ID NO: 60)

[0152] An exemplary AAV vector of the disclosure comprises from 5' to 3': a first inverted terminal repeat (ITR) sequence, a U7 promoter sequence, a non-targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, a U7 promoter sequence, a non-targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, a U7 promoter sequence, a non-targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a CMV promoter sequence, a sequence encoding green fluorescent protein (GFP), a sv40 polyA sequence, and a second ITR sequence. In some aspects, a nucleic acid sequence encoding AAV vector A02895 encoding a non-targeting snRNA sequence comprises SEQ ID NO: 130.

A02895 pAAV_3xU7(NT1)_CMV_GFP (100bp buffer)

ITR	Cctgcaggcagctgcgcgctcgctcgctcactgaggccgcccgggcgtcgggcgacctttggtcgccc ggcctcagtgagcgagcgagcgcgcagagagggagtggccaactccatcactaggggttcct (SEQ ID NO: 59)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGG CTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTT GCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATG ACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTTA

	CCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAAA GTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATATCC CATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtTCACCAGAAGCGTACCATACTCACGAAATTTTTGGAGTAggc tttctggctccttaccggaaagcc (SEQ ID NO: 66)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGC AAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCT TGGAG (SEQ ID NO: 49)
100bp buffer 1	CAAACTACAGAGCCAAGTGCTATCCACAGAGAGCTTTCTGGGTT GCCATCTCAAGCAGACTACAAGGCCATCAGCTCATACTCACAAT TGACTTTGAGAG (SEQ ID NO: 27)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGG CTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTT GCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATG ACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTTA CCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAAA GTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATATCC CATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtTCACCAGAAGCGTACCATACTCACGAAATTTTTGGAGTAggc tttctggctccttaccggaaagcc (SEQ ID NO: 66)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGC AAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCT TGGAG (SEQ ID NO: 49)
100bp buffer 2	TTGACCACATACGTGCTCTTTCAAAGTTCTGTGTTTGAAGTTATG TTAGTAACAACTGATGCCCATCCTGCAATGACAAATCCAATTCT CAGTGCAGCTC (SEQ ID NO: 28)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGG CTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTT GCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATG ACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTTA CCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAAA GTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATATCC CATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtTCACCAGAAGCGTACCATACTCACGAAATTTTTGGAGTAggc tttctggctccttaccggaaagcc (SEQ ID NO: 66)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGC AAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCT TGGAG (SEQ ID NO: 49)
CMV promoter	Cgttacataacttacggtaaatggcccgcctggctgaccgcccaacgacccccgcccattgacgtcaata atgacgtatgttcccatagtaacgccaatagggactttccattgacgtcaatgggtggagtatttacggtaaa ctgcccacttggcagtacatcaagtgtatcatatgccaagtacgccccctattgacgtcaatgacggtaaat ggcccgcctggcattatgcccagtacatgaccttatgggactttcctacttggcagtacatctacgtattagtc atcgctattaccatggtgatgcggttttggcagtacatcaatgggcgtggatagcggtttgactcacgggga tttccaagtctccaccccattgacgtcaatgggagtttgttttggcaccaaaatcaacgggactttccaaaatg tcgtaacaactccgccccattgacgcaaatgggcggtaggcgtgtacggtgggaggtctatataagcaga gct (SEQ ID NO: 62)
eGFP	ATGgtgagcaagggcgaggagctgttcaccggggtggtgcccatcctggtcgagctggacggcgac gtaaacggccacaagttcagcgtgtccggcgagggcgagggcgatgccacctacggcaagctgaccct

	gaagttcatctgcaccaccggcaagctgcccgtgccctggcccaccctcgtgaccaccctgacctacggc gtgcagtgcttcagccgctaccccgaccacatgaagcagcacgacttcttcaagtccgccatgcccgaag gctacgtccaggagcgcaccatcttcttcaaggacgacggcaactacaagacccgcgccgaggtgaagt tcgagggcgacaccctggtgaaccgcatcgagctgaagggcatcgacttcaaggaggacggcaacatc ctggggcacaagctggagtacaactacaacagccacaacgtctatatcatggccgacaagcagaagaac ggcatcaaggtgaacttcaagatccgccacaacatcgaggacggcagcgtgcagctcgccgaccactac cagcagaacaccccatcggcgacggccccgtgctgctgcccgacaaccactacctgagcacccagtc cgccctgagcaaagaccccaacgagaagcgcgatcacatggtcctgctggagttcgtgaccgccgccg ggatcactctcggcatggacgagctgtacaagTAA (SEQ ID NO: 63)
SV40 Poly A	Aacttgtttattgcagcttataatggttacaaataaagcaatagcatcacaaatttcacaaataaagcatttttttt cactgcattctagttgtggtttgtccaaactcatcaatgtatctta (SEQ ID NO: 64)
ITR	Aggaacccctagtgatggagttggccactccctctctgcgcgctcgctcgctcactgaggccgggcgac caaaggtcgcccgacgcccgggctttgcccgggcggcctcagtgagcgagcgagcgcgcagctgcct gcagg (SEQ ID NO: 60)

[0153] An exemplary AAV vector of the disclosure comprises from 5' to 3': a first inverted terminal repeat (ITR) sequence, a U7 promoter sequence, a CAG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, a U7 promoter sequence, a CAG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, a U7 promoter sequence, a CAG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a CMV promoter sequence, a sequence encoding green fluorescent protein (GFP), a sv40 polyA sequence, and a second ITR sequence. In some aspects, a nucleic acid sequence encoding AAV vector A02968 encoding a CAG repeat targeting repeat targeting snRNA sequence comprises SEQ ID NO: 131.

A02968 pAAV_3xU7(15XCAG)_CMV_GFP (100bp buffer) targeting CAG repeats

ITR	Cctgcaggcagctgcgcgctcgctcgctcactgaggccgcccgggcgtcgggcgacctttggtcgcc cggcctcagtgagcgagcgagcgcgcagagagggagtggccaactccatcactaggggttcct (SEQ ID NO: 59)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGG CTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTT GCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATG ACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTT ACCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAA AGTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATAT CCCATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCT GCTGAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 67)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGC AAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCT TGGAG (SEQ ID NO: 49)

100bp buffer 1	CAAACTACAGAGCCAAGTGCTATCCACAGAGAGCTTTCTGGGT TGCCATCTCAAGCAGACTACAAGGCCATCAGCTCATACTCACA ATTGACTTTGAGAG (SEQ ID NO: 27)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGG CTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTT GCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATG ACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTT ACCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAA AGTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATAT CCCATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCT GCTGAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 67)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGC AAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCT TGGAG (SEQ ID NO: 49)
100bp buffer 2	TTGACCACATACGTGCTCTTTCAAAGTTCTGTGTTTGAAGTTAT GTTAGTAACAACTGATGCCCATCCTGCAATGACAAATCCAATT CTCAGTGCAGCTC (SEQ ID NO: 28)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGG CTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTT GCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATG ACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTT ACCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAA AGTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATAT CCCATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCT GCTGAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 67)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGC AAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCT TGGAG (SEQ ID NO: 49)
CMV promoter	Cgttacataacttacggtaaatggcccgcctggctgaccgcccaacgacccccgcccattgacgtcaat aatgacgtatgttcccatagtaacgccaatagggactttccattgacgtcaatgggtggagtatttacggta aactgcccacttggcagtacatcaagtgtatcatatgccaagtacgccccctattgacgtcaatgacggta aatggcccgcctggcattatgcccagtacatgaccttatgggactttcctacttggcagtacatctacgtatt agtcatcgctattaccatggtgatgcggttttggcagtacatcaatgggcgtggatagcggtttgactcacg gggatttccaagtctccaccccattgacgtcaatgggagtttgttttggcaccaaaatcaacgggactttcc aaaatgtcgtaacaactccgccccattgacgcaaatgggcggtaggcgtgtacggtgggaggtctatata agcagagct (SEQ ID NO: 62)
eGFP	ATGgtgagcaagggcgaggagctgttcaccggggtggtgcccatcctggtcgagctggacggcga cgtaaacggccacaagttcagcgtgtccggcgagggcgagggcgatgccacctacggcaagctgacc ctgaagttcatctgcaccaccggcaagctgcccgtgccctggcccaccctcgtgaccaccctgacctac ggcgtgcagtgcttcagccgctaccccgaccacatgaagcagcacgacttcttcaagtccgccatgccc gaaggctacgtccaggagcgcaccatcttcttcaaggacgacggcaactacaagacccgcgccgaggt gaagttcgagggcgacaccctggtgaaccgcatcgagctgaagggcatcgacttcaaggaggacggc aacatcctggggcacaagctggagtacaactacaacagccacaacgtctatatcatggccgacaagcag aagaacggcatcaaggtgaacttcaagatccgccacaacatcgaggacggcagcgtgcagctcgccg

	accactaccagcagaacacccccatcggcgacggccccgtgctgctgcccgacaaccactacctgagc acccagtccgccctgagcaaagaccccaacgagaagcgcgatcacatggtcctgctggagttcgtgac cgccgccgggatcactctcggcatggacgagctgtacaagTAA (SEQ ID NO: 63)
SV40 Poly A	Aacttgtttattgcagcttataatggttacaaataaagcaatagcatcacaaatttcacaaataaagcatttttt tcactgcattctagttgtggtttgtccaaactcatcaatgtatctta (SEQ ID NO: 64)
ITR	Aggaacccctagtgatggagttggccactccctctctgcgcgctcgctcgctcactgaggccgggcga ccaaaggtcgcccgacgcccgggctttgcccgggcggcctcagtgagcgagcgagcgcgcagctgc ctgcagg (SEQ ID NO: 60)

[0154] An exemplary AAV vector of the disclosure comprises from 5' to 3': a first inverted terminal repeat (ITR) sequence, a U7 promoter sequence, a CUG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, a U7 promoter sequence, a CUG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, a U7 promoter sequence, a CUG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a CMV promoter sequence, a sequence encoding green fluorescent protein (GFP), a sv40 polyA sequence, and a second ITR sequence. In some aspects, a nucleic acid sequence encoding AAV vector A02896 encoding a CUG repeat targeting repeat targeting snRNA sequence comprises SEQ ID NO: 132.

A02896 pAAV_3xU7(15xCUG)_CMV_GFP (500bp buffer)

ITR	Cctgcaggcagctgcgcgctcgctcgctcactgaggccgcccgggcgtcgggcgacctttggtcgccc ggcctcagtgagcgagcgagcgcgcagagagggagtggccaactccatcactaggggttcct (SEQ ID NO: 59)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGG CTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTT GCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATG ACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTTA CCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAAA GTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATATCC CATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAG CAGCAGAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 65)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGC AAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCT TGGAG (SEQ ID NO: 49)
500bp buffer 1	CAAACTACAGAGCCAAGTGCTATCCACAGAGAGCTTTCTGGGTT GCCATCTCAAGCAGACTACAAGGCCATCAGCTCATACTCACAAT TGACTTTGAGAGTCATTTTCCAATGCTCCTACACACCCCTTCTTC ACAATCCCCAACAAATCTGAGGCTGGAACTTGGTACCATAACAA TCATTACATTATTTCACCAGAAGTACACCTTGCCTGGAAGATTG GCATTATAGCATCTTCTAACATTGTGAAAGTTAGTGACCAATGA GGAGATCCAAGTCAGTTCCAGTTGGATTTCTCTATACTCTATAAT

	AAATATATATGGTGTCTTCAACAATAGGACTTTGCCATCCAGTG ATGCTAAAAATCAATAACAATGGCAATAACCTGCCCTGTTTGGA AAGCCTCTGGCTTCCATGACTAACAATTCAAGGCAGGTCTCCTA TACCTAGTACTGAGATTTTTATTTGATAAACTATATCTTCTGGGA GGAGAAGCATTGT (SEQ ID NO: 29)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGG CTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTT GCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATG ACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTTA CCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAAA GTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATATCC CATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAG CAGCAGAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 65)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGC AAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCT TGGAG (SEQ ID NO: 49)
500bp buffer 2	TTGACCACATACGTGCTCTTTCAAAGTTCTGTGTTTGAAGTTATG TTAGTAACAACTGATGCCCATCCTGCAATGACAAATCCAATTCT CAGTGCAGCTCTCTGAAATAGTTTTGCTTTCTCTCTCTAGGTCTG TTCTATACTCCTAACTCTCCAGGAGTTTACAAGGAATAAAATCT CTTCCAAATGCTTTCTGTTGCAACAACTGGACCATACTGAAAGC TGAGGCCCACAATTGCAATCTAGGTTAGCAGGTAATCATTGTTG GTGAGGTCCTCCCTTTCCCCAGGCTCGTGTTTGTATTGGGGAGC AGGAAATTTTTGCTAGAGCAGCACTGCCATCTCTCTACACTCCA CCTGATTGGTGGGATGGACCAGAGAAATGGACATTCCCAACAC AGTCCCTCCTTTCACATCTGCTCACCTGCCCACAGGATACTTTCC ACCATGCATACTGGGCTCTGCACCAACCATTCAGCAGTGATGAA GAGGAAACTTGAAC (SEQ ID NO: 30)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGG CTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTT GCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATG ACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTTA CCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAAA GTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATATCC CATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAG CAGCAGAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 65)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGC AAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCT TGGAG (SEQ ID NO: 49)

CMV promoter	Cgttacataacttacggtaaatggcccgcctggctgaccgcccaacgacccccgcccattgacgtcaata atgacgtatgttcccatagtaacgccaatagggactttccattgacgtcaatgggtggagtatttacggtaaa ctgcccacttggcagtacatcaagtgtatcatatgccaagtacgccccctattgacgtcaatgacggtaaat ggcccgcctggcattatgcccagtacatgaccttatgggactttcctacttggcagtacatctacgtattagtc atcgctattaccatggtgatgcggttttggcagtacatcaatgggcgtggatagcggtttgactcacgggga tttccaagtctccaccccattgacgtcaatgggagtttgttttggcaccaaaatcaacgggactttccaaaatg tcgtaacaactccgccccattgacgcaaatgggcggtaggcgtgtacggtgggaggtctatataagcaga gct (SEQ ID NO: 62)
eGFP	ATGgtgagcaagggcgaggagctgttcaccggggtggtgcccatcctggtcgagctggacggcgac gtaaacggccacaagttcagcgtgtccggcgagggcgagggcgatgccacctacggcaagctgaccct gaagttcatctgcaccaccggcaagctgcccgtgccctggcccaccctcgtgaccaccctgacctacggc gtgcagtgcttcagccgctaccccgaccacatgaagcagcacgacttcttcaagtccgccatgcccgaag gctacgtccaggagcgcaccatcttcttcaaggacgacggcaactacaagacccgcgccgaggtgaagt tcgagggcgacaccctggtgaaccgcatcgagctgaagggcatcgacttcaaggaggacggcaacatc ctggggcacaagctggagtacaactacaacagccacaacgtctatatcatggccgacaagcagaagaac ggcatcaaggtgaacttcaagatccgccacaacatcgaggacggcagcgtgcagctcgccgaccactac cagcagaacaccccatcggcgacggccccgtgctgctgcccgacaaccactacctgagcacccagtc cgccctgagcaaagaccccaacgagaagcgcgatcacatggtcctgctggagttcgtgaccgccgccg ggatcactctcggcatggacgagctgtacaagTAA (SEQ ID NO: 63)
SV40 Poly A	Aacttgtttattgcagcttataatggttacaaataaagcaatagcatcacaaatttcacaaataaagcatttttttt cactgcattctagttgtggtttgtccaaactcatcaatgtatctta (SEQ ID NO: 64)
ITR	Aggaacccctagtgatggagttggccactccctctctgcgcgctcgctcgctcactgaggccgggcgac caaaggtcgcccgacgcccgggctttgcccgggcggcctcagtgagcgagcgagcgcgcagctgcct gcagg (SEQ ID NO: 60)

[0155] An exemplary AAV vector of the disclosure comprises from 5' to 3': a first inverted terminal repeat (ITR) sequence, a U7 promoter sequence, a non-targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, a U7 promoter sequence, a non-targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, a U7 promoter sequence, a non-targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a CMV promoter sequence, a sequence encoding green fluorescent protein (GFP), a sv40 polyA sequence, and a second ITR sequence. In some aspects, a nucleic acid sequence encoding AAV vector A02897 encoding a non-targeting repeat targeting snRNA sequence comprises SEQ ID NO: 133.

A02897 pAAV_3xU7(NT1)_CMV_GFP (500bp buffer)

ITR	Cctgcaggcagctgcgcgctcgctcgctcactgaggccgcccgggcgtcgggcgacctttggtcgcc cggcctcagtgagcgagcgagcgcgcagagagggagtggccaactccatcactaggggttcct (SEQ ID NO: 59)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGG CTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTT GCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATG

	ACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTT ACCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAA AGTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATAT CCCATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtTCACCAGAAGCGTACCATACTCACGAAATTTTTGGAGTAgg ctttctggctccttaccggaaagcc (SEQ ID NO: 66)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGC AAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCT TGGAG (SEQ ID NO: 49)
500bp buffer 1	CAAACTACAGAGCCAAGTGCTATCCACAGAGAGCTTTCTGGGT TGCCATCTCAAGCAGACTACAAGGCCATCAGCTCATACTCACA ATTGACTTTGAGAGTCATTTTCCAATGCTCCTACACACCCCTTC TTCACAATCCCCAACAAATCTGAGGCTGGAACTTGGTACCATA ACAATCATTACATTATTTCACCAGAAGTACACCTTGCCTGGAAG ATTGGCATTATAGCATCTTCTAACATTGTGAAAGTTAGTGACCA ATGAGGAGATCCAAGTCAGTTCCAGTTGGATTTCTCTATACTCT ATAATAAATATATATGGTGTCTTCAACAATAGGACTTTGCCATC CAGTGATGCTAAAAATCAATAACAATGGCAATAACCTGCCCTG TTTGGAAAGCCTCTGGCTTCCATGACTAACAATTCAAGGCAGG TCTCCTATACCTAGTACTGAGATTTTTATTTGATAAACTATATCT TCTGGGAGGAGAAGCATTGT (SEQ ID NO: 29)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGG CTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTT GCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATG ACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTT ACCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAA AGTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATAT CCCATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtTCACCAGAAGCGTACCATACTCACGAAATTTTTGGAGTAgg ctttctggctccttaccggaaagcc (SEQ ID NO: 66)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGC AAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCT TGGAG (SEQ ID NO: 49)
500bp buffer 2	TTGACCACATACGTGCTCTTTCAAAGTTCTGTGTTTGAAGTTAT GTTAGTAACAACTGATGCCCATCCTGCAATGACAAATCCAATT CTCAGTGCAGCTCTCTGAAATAGTTTTGCTTTCTCTCTCTAGGTC TGTTCTATACTCCTAACTCTCCAGGAGTTTACAAGGAATAAAAT CTCTTCCAAATGCTTTCTGTTGCAACAACTGGACCATACTGAAA GCTGAGGCCCACAATTGCAATCTAGGTTAGCAGGTAATCATTG TTGGTGAGGTCCTCCCTTTCCCCAGGCTCGTGTTTGTATTGGGG AGCAGGAAATTTTTGCTAGAGCAGCACTGCCATCTCTCTACACT CCACCTGATTGGTGGGATGGACCAGAGAAATGGACATTCCCAA CACAGTCCCTCCTTTCACATCTGCTCACCTGCCCACAGGATACT TTCCACCATGCATACTGGGCTCTGCACCAACCATTCAGCAGTGA TGAAGAGGAAACTTGAAC (SEQ ID NO: 30)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGG CTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTT GCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATG ACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTT

	ACCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAA AGTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATAT CCCATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtTCACCAGAAGCGTACCATACTCACGAAATTTTTGGAGTAgg ctttctggctccttaccggaaagcc (SEQ ID NO: 66)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGC AAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCT TGGAG (SEQ ID NO: 49)
CMV promoter	Cgttacataacttacggtaaatggcccgcctggctgaccgcccaacgacccccgcccattgacgtcaat aatgacgtatgttcccatagtaacgccaatagggactttccattgacgtcaatgggtggagtatttacggta aactgcccacttggcagtacatcaagtgtatcatatgccaagtacgcccccctattgacgtcaatgacggta aatggcccgcctggcattatgcccagtacatgaccttatgggactttcctacttggcagtacatctacgtatt agtcatcgctattaccatggtgatgcggttttggcagtacatcaatgggcgtggatagcggtttgactcacg gggatttccaagtctccaccccattgacgtcaatgggagtttgttttggcaccaaaatcaacgggactttcc aaaatgtcgtaacaactccgccccattgacgcaaatgggcggtaggcgtgtacggtgggaggtctatata agcagagct (SEQ ID NO: 62)
eGFP	ATGgtgagcaagggcgaggagctgttcaccggggtggtgcccatcctggtcgagctggacggcga cgtaaacggccacaagttcagcgtgtccggcgagggcgagggcgatgccacctacggcaagctgacc ctgaagttcatctgcaccaccggcaagctgcccgtgccctggcccaccctcgtgaccaccctgacctac ggcgtgcagtgcttcagccgctaccccgaccacatgaagcagcacgacttcttcaagtccgccatgccc gaaggctacgtccaggagcgcaccatcttcttcaaggacgacggcaactacaagacccgcgccgaggt gaagttcgagggcgacaccctggtgaaccgcatcgagctgaagggcatcgacttcaaggaggacggc aacatcctggggcacaagctggagtacaactacaacagccacaacgtctatatcatggccgacaagcag aagaacggcatcaaggtgaacttcaagatccgccacaacatcgaggacggcagcgtgcagctcgccg accactaccagcagaacaccccatcggcgacggccccgtgctgctgcccgacaaccactacctgagc acccagtccgccctgagcaaagaccccaacgagaagcgcgatcacatggtcctgctggagttcgtgac cgccgccgggatcactctcggcatggacgagctgtacaagTAA (SEQ ID NO: 63)
SV40 Poly A	Aacttgtttattgcagcttataatggttacaaataaagcaatagcatcacaaatttcacaaataaagcatttttt tcactgcattctagttgtggtttgtccaaactcatcaatgtatctta (SEQ ID NO: 64)
ITR	Aggaacccctagtgatggagttggccactccctctctgcgcgctcgctcgctcactgaggccgggcga ccaaaggtcgcccgacgcccgggctttgcccgggcggcctcagtgagcgagcgagcgcgcagctgc ctgcagg (SEQ ID NO: 60)

[0156] An exemplary AAV vector of the disclosure comprises from 5' to 3': a first inverted terminal repeat (ITR) sequence, a U7 promoter sequence, a CAG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, a U7 promoter sequence, a CAG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, a U7 promoter sequence, a CAG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a CMV promoter sequence, a sequence encoding green fluorescent protein (GFP), a sv40 polyA sequence, and a second ITR sequence. In some aspects, a nucleic acid sequence encoding AAV vector A02969 encoding a CAG repeat targeting repeat targeting snRNA sequence comprises SEQ ID NO: 134.

A02969 pAAV_3xU7(15xCAG)_CMV_GFP (500bp buffer) targeting CAG repeats

ITR	Cctgcaggcagctgcgcgctcgctcgctcactgaggccgcccgggcgtcgggcgacctttggtcgccc ggcctcagtgagcgagcgagcgcgcagagagggagtggccaactccatcactaggggttcct (SEQ ID NO: 59)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGG CTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTT GCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATG ACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTTA CCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAAA GTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATATCC CATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTG CTGAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 67)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGC AAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCT TGGAG (SEQ ID NO: 49)
500bp buffer 1	CAAACTACAGAGCCAAGTGCTATCCACAGAGAGCTTTCTGGGTT GCCATCTCAAGCAGACTACAAGGCCATCAGCTCATACTCACAAT TGACTTTGAGAGTCATTTTCCAATGCTCCTACACACCCCTTCTTC ACAATCCCCAACAAATCTGAGGCTGGAACTTGGTACCATAACAA TCATTACATTATTTCACCAGAAGTACACCTTGCCTGGAAGATTG GCATTATAGCATCTTCTAACATTGTGAAAGTTAGTGACCAATGA GGAGATCCAAGTCAGTTCCAGTTGGATTTCTCTATACTCTATAAT AAATATATATGGTGTCTTCAACAATAGGACTTTGCCATCCAGTG ATGCTAAAAATCAATAACAATGGCAATAACCTGCCCTGTTTGGA AAGCCTCTGGCTTCCATGACTAACAATTCAAGGCAGGTCTCCTA TACCTAGTACTGAGATTTTTATTTGATAAACTATATCTTCTGGGA GGAGAAGCATTGT (SEQ ID NO: 29)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGG CTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTT GCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATG ACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTTA CCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAAA GTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATATCC CATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTG CTGAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 67)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGC AAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCT TGGAG (SEQ ID NO: 49)
500bp buffer 2	TTGACCACATACGTGCTCTTTCAAAGTTCTGTGTTTGAAGTTATG TTAGTAACAACTGATGCCCATCCTGCAATGACAAATCCAATTCT CAGTGCAGCTCTCTGAAATAGTTTTGCTTTCTCTCTCTAGGTCTG TTCTATACTCCTAACTCTCCAGGAGTTTACAAGGAATAAAATCT CTTCCAAATGCTTTCTGTTGCAACAACTGGACCATACTGAAAGC TGAGGCCCACAATTGCAATCTAGGTTAGCAGGTAATCATTGTTG GTGAGGTCCTCCCTTTCCCCAGGCTCGTGTTTGTATTGGGGAGC AGGAAATTTTTGCTAGAGCAGCACTGCCATCTCTCTACACTCCA

	CCTGATTGGTGGGATGGACCAGAGAAATGGACATTCCCAACAC AGTCCCTCCTTTCACATCTGCTCACCTGCCCACAGGATACTTTCC ACCATGCATACTGGGCTCTGCACCAACCATTCAGCAGTGATGAA GAGGAAACTTGAAC (SEQ ID NO: 30)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGG CTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTT GCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATG ACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTTA CCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAAA GTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATATCC CATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
U7 snRNA	ggagtCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTG CTGAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 67)
U7 Downstream (terminator)	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGC AAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCT TGGAG (SEQ ID NO: 49)
CMV promoter	Cgttacataacttacggtaaatggcccgcctggctgaccgcccaacgacccccgcccattgacgtcaata atgacgtatgttcccatagtaacgccaatagggactttccattgacgtcaatgggtggagtatttacggtaaa ctgcccacttggcagtacatcaagtgtatcatatgccaagtacgccccctattgacgtcaatgacggtaaat ggcccgcctggcattatgcccagtacatgaccttatgggactttcctacttggcagtacatctacgtattagtc atcgctattaccatggtgatgcggttttggcagtacatcaatgggcgtggatagcggtttgactcacgggga tttccaagtctccaccccattgacgtcaatgggagtttgttttggcaccaaaatcaacgggactttccaaaatg tcgtaacaactccgccccattgacgcaaatgggcggtaggcgtgtacggtgggaggtctatataagcaga gct (SEQ ID NO: 62)
eGFP	ATGgtgagcaagggcgaggagctgttcaccggggtggtgcccatcctggtcgagctggacggcgac gtaaacggccacaagttcagcgtgtccggcgagggcgagggcgatgccacctacggcaagctgaccct gaagttcatctgcaccaccggcaagctgcccgtgccctggcccaccctcgtgaccaccctgacctacggc gtgcagtgcttcagccgctaccccgaccacatgaagcagcacgacttcttcaagtccgccatgcccgaag gctacgtccaggagcgcaccatcttcttcaaggacgacggcaactacaagacccgcgccgaggtgaagt tcgagggcgacaccctggtgaaccgcatcgagctgaagggcatcgacttcaaggaggacggcaacatc ctggggcacaagctggagtacaactacaacagccacaacgtctatatcatggccgacaagcagaagaac ggcatcaaggtgaacttcaagatccgccacaacatcgaggacggcagcgtgcagctcgccgaccactac cagcagaacaccccatcggcgacggccccgtgctgctgcccgacaaccactacctgagcacccagtc cgccctgagcaaagaccccaacgagaagcgcgatcacatggtcctgctggagttcgtgaccgccgccg ggatcactctcggcatggacgagctgtacaagTAA (SEQ ID NO: 63)
SV40 Poly A	Aacttgtttattgcagcttataatggttacaaataaagcaatagcatcacaaatttcacaaataaagcatttttttt cactgcattctagttgtggtttgtccaaactcatcaatgtatctta (SEQ ID NO: 64)
ITR	Aggaacccctagtgatggagttggccactccctctctgcgcgctcgctcgctcactgaggccgggcgac caaaggtcgcccgacgcccgggctttgcccgggcggcctcagtgagcgagcgagcgcgcagctgcct gcagg (SEQ ID NO: 60)

[0157] An exemplary AAV vector of the disclosure comprises from 5' to 3': a first inverted terminal repeat (ITR) sequence, a U7 promoter sequence, a DMD exon 51 targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a U1 promoter sequence, a DMD exon 51 targeting U7 esnRNA sequence, a U1 downstream terminator sequence, and a

second ITR sequence. In some aspects, a nucleic acid sequence encoding AAV vector A03980 encoding a DMD exon 51 targeting snRNA sequences comprises SEQ ID NO: 135.

A03980: pAAV(ssAAV) U7promoter-esnRNA-z38/42-U7 termination-U1promoter-esnRNAz38/z42-U1 termination

ITR	cctgcaggcagctgcgcgctcgctcgctcactgaggccgcccgggcgtcgggcgacctttggtcgcccggcctcagtgagcgagcgagcgcgcagagagggagtggccaactccatcactaggggttcct (SEQ ID NO: 59)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGGCTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTTGCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATGACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTTACCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAAAGTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATATCCCATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
z38/42 esnRNA (DMD exon 51)	ggagtTACCTCCAACATCAAGGAAGATGGCAGTAACCACAGGTTGTGTCACCAGAGTAACAAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 68)
U7 termination	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGCAAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCTTGGAG (SEQ ID NO: 49)
U1 promoter	TAAGGACCAGCTTCTTTGGGAGAGAACAGACGCAGGGGCGGGAGGGAAAAAGGGAGAGGCAGACGTCACTTCCCCTTGGCGGCTCTGGCAGCAGATTGGTCGGTTGAGTGGCAGAAAGGCAGACGGGGACTGGGCAAGGCACTGTCGGTGACATCACGGACAGGGCGACTTCTATGTAGATGAGGCAGCGCAGAGGCTGACGTCTTCGCCACTTGCTGCTTCACCACGAAGGAGTTCCCGTGCCCTGGGAGCGGGTTCAGGACCGCTGATCGGAAGTGAGAATCCCAGCTGTGTGTCAGGGCTGGAAAGGGCTCGGGAGTGCGCGGGGCAAGTGACCGTGTGTGTAAAGAGTGAGGCGTATGAGGCTGTGTCGGGGCAGAGGCacaacgtttc (SEQ ID NO: 40)
z38/42 esnRNA (DMD exon 51)	ggagtTACCTCCAACATCAAGGAAGATGGCAGTAACCACAGGTTGTGTCACCAGAGTAACAAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 68)
U1 termination	ACTTTCTGGAGTTTCAAAAACAGACTGTACGCCAAGGGTCATATCTTTTT (SEQ ID NO: 50)
ITR	aggaacccctagtgatggagttggccactccctctctgcgcgctcgctcgctcactgaggccgggcgaccaaaggtcgcccgacgcccgggctttgcccgggcggcctcagtgagcgagcgagcgcgcagctgcctgcagg (SEQ ID NO: 60)

[0158] An exemplary AAV vector of the disclosure comprises from 5' to 3': a first inverted terminal repeat (ITR) sequence, a U7 promoter sequence, a DMD exon 51 targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a U1 promoter sequence, a DMD exon 51 targeting U7 esnRNA sequence, a U1 downstream terminator sequence, and a second ITR sequence. In some aspects, a nucleic acid sequence encoding AAV vector A03981 encoding a DMD exon 51 targeting snRNA sequences comprises SEQ ID NO: 136.

A03981: pAAV(ssAAV)_U7promoter-esnRNA-z42-U7termination-U1promoter-esnRNA-z38-U1 termination

ITR	cctgcaggcagctgcgcgctcgctcgctcactgaggccgcccgggcgtcgggcgacctttggtcgcccggcc tcagtgagcgagcgagcgcgcagagagggagtggccaactccatcactaggggttcct (SEQ ID NO: 59)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGGCTG TGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTTGCATGG GCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATGACTTAAGTA AGTTCCTTAGAATATTATTTTTCCTACTGAAAGTTACCACATGCGTC GTTGTTTATACAGTAATAGGAACAAGAAAAAAGTCACCTAAGCTCA CCCTCATCAATTGTGGAGTTCCTTTATATCCCATCTTCTCTCCAAAC ACATACGCA (SEQ ID NO: 39)
z42 esnRNA (DMD exon 51)	ggagtGTAACCACAGGTTGTGTCACCAGAGTAACAAATTTTTGGAGTA ggctttctggctccttaccggaaagcc (SEQ ID NO: 69)
U7 termination	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGCAA AAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCTTGGAG (SEQ ID NO: 49)
U1 promoter	TAAGGACCAGCTTCTTTGGGAGAGAACAGACGCAGGGGCGGGAGG GAAAAAGGGAGAGGCAGACGTCACTTCCCCTTGGCGGCTCTGGCAG CAGATTGGTCGGTTGAGTGGCAGAAAGGCAGACGGGGACTGGGCA AGGCACTGTCGGTGACATCACGGACAGGGCGACTTCTATGTAGATG AGGCAGCGCAGAGGCTGACGTCTTCGCCACTTGCTGCTTCACCACG AAGGAGTTCCCGTGCCCTGGGAGCGGGTTCAGGACCGCTGATCGGA AGTGAGAATCCCAGCTGTGTGTCAGGGCTGGAAAGGGCTCGGGAGT GCGCGGGGCAAGTGACCGTGTGTGTAAAGAGTGAGGCGTATGAGG CTGTGTCGGGGCAGAGGCacaacgtttc (SEQ ID NO: 40)
z38 esnRNA (DMD exon 51)	ggagtTACCTCCAACATCAAGGAAGATGGCAAATTTTTGGAGTAggctttc tggctccttaccggaaagcc (SEQ ID NO: 70)
U1 termination	ACTTTCTGGAGTTTCAAAAACAGACTGTACGCCAAGGGTCATATCTT TTT (SEQ ID NO: 50)
ITR	aggaacccctagtgatggagttggccactccctctctgcgcgctcgctcgctcactgaggccgggcgaccaaa ggtcgcccgacgcccgggctttgcccgggcggcctcagtgagcgagcgagcgcgcagctgcctgcagg (SEQ ID NO: 60)

[0159] An exemplary AAV vector of the disclosure comprises from 5' to 3': a first inverted terminal repeat (ITR) sequence, a U7 promoter sequence, a DMD exon 51 targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a U1 promoter sequence, a DMD exon 51 targeting U7 esnRNA sequence, a U1 downstream terminator sequence, and a second ITR sequence. In some aspects, a nucleic acid sequence encoding AAV vector A04229 encoding a DMD exon 51 targeting snRNA sequences comprises SEQ ID NO: 137.

[0160] A04229: pAAV(scAAV) U7promoter-esnRNA-z38/42-U7 termination-U1promoter-esnRNAz38/z42-U1 termination-mut ITR

ITR	cctgcaggcagctgcgcgctcgctcgctcactgaggccgcccgggcgtcgggcgacctttggtcgcccggc ctcagtgagcgagcgagcgcgcagagagggagtggccaactccatcactaggggttcct (SEQ ID NO: 59)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGGCT GTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTTGCAT GGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATGACTTAA GTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTTACCACATGC GTCGTTGTTTATACAGTAATAGGAACAAGAAAAAAGTCACCTAAG CTCACCCTCATCAATTGTGGAGTTCCTTTATATCCCATCTTCTCTCC AAACACATACGCA (SEQ ID NO: 39)
z38/42 esnRNA (DMD exon 51)	ggagtTACCTCCAACATCAAGGAAGATGGCAGTAACCACAGGTTGTG TCACCAGAGTAACAAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 68)
U7 termination	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGCAA AAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCTTGGA G (SEQ ID NO: 49)
U1 promoter	TAAGGACCAGCTTCTTTGGGAGAGAACAGACGCAGGGGCGGGAGG GAAAAAGGGAGAGGCAGACGTCACTTCCCCTTGGCGGCTCTGGCA GCAGATTGGTCGGTTGAGTGGCAGAAAGGCAGACGGGGACTGGGC AAGGCACTGTCGGTGACATCACGGACAGGGCGACTTCTATGTAGA TGAGGCAGCGCAGAGGCTGACGTCTTCGCCACTTGCTGCTTCACCA CGAAGGAGTTCCCGTGCCCTGGGAGCGGGTTCAGGACCGCTGATC GGAAGTGAGAATCCCAGCTGTGTGTCAGGGCTGGAAAGGGCTCGG GAGTGCGCGGGGCAAGTGACCGTGTGTGTAAAGAGTGAGGCGTAT GAGGCTGTGTCGGGGCAGAGGCacaacgtttc (SEQ ID NO: 40)
z38/42 esnRNA (DMD exon 51)	ggagtTACCTCCAACATCAAGGAAGATGGCAGTAACCACAGGTTGTG TCACCAGAGTAACAAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 68)
U1 termination	ACTTTCTGGAGTTTCAAAAACAGACTGTACGCCAAGGGTCATATCT TTTT (SEQ ID NO: 50)
mITR	CCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACC AAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAG CGAGCGAGCGCGCAGAGAGGGA (SEQ ID NO: 61)

[0161] An exemplary AAV vector of the disclosure comprises from 5' to 3': a first inverted terminal repeat (ITR) sequence, a U7 promoter sequence, a DMD exon 51 targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, a U1 promoter sequence, a DMD exon 51 targeting U7 esnRNA sequence, a U1 downstream terminator sequence, a buffer sequence, and a second ITR sequence. In some aspects, a nucleic acid sequence encoding AAV vector A04184 encoding a DMD exon 51 targeting snRNA sequences comprises SEQ ID NO: 138.

A04184: pAAV(ssAAV)-U7promoter-z38/42-U7term_U1promoter-z38/42-U1term_buffer combination sequence

ITR	cctgcaggcagctgcgcgctcgctcgctcactgaggccgcccgggcgtcgggcgacctttggtcgccc ggcctcagtgagcgagcgagcgcgcagagagggagtggccaactccatcactaggggttcct (SEQ ID NO: 59)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGG CTGTGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTT GCATGGGCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATG ACTTAAGTAAGTTCCTTAGAATATTATTTTTCCTACTGAAAGTT ACCACATGCGTCGTTGTTTATACAGTAATAGGAACAAGAAAAA AGTCACCTAAGCTCACCCTCATCAATTGTGGAGTTCCTTTATAT CCCATCTTCTCTCCAAACACATACGCA (SEQ ID NO: 39)
z38/42 esnRNA (DMD exon 51)	ggagtTACCTCCAACATCAAGGAAGATGGCAGTAACCACAGGTTG TGTCACCAGAGTAACAAATTTTTGGAGTAggctttctggctccttaccggaaa gcc (SEQ ID NO: 68)
U7 termination	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGC AAAAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCT TGGAG (SEQ ID NO: 49)
U1 promoter	TAAGGACCAGCTTCTTTGGGAGAGAACAGACGCAGGGGCGGGA GGGAAAAAGGGAGAGGCAGACGTCACTTCCCCTTGGCGGCTCT GGCAGCAGATTGGTCGGTTGAGTGGCAGAAAGGCAGACGGGG ACTGGGCAAGGCACTGTCGGTGACATCACGGACAGGGCGACTT CTATGTAGATGAGGCAGCGCAGAGGCTGACGTCTTCGCCACTT GCTGCTTCACCACGAAGGAGTTCCCGTGCCCTGGGAGCGGGTT CAGGACCGCTGATCGGAAGTGAGAATCCCAGCTGTGTGTCAGG GCTGGAAAGGGCTCGGGAGTGCGCGGGGCAAGTGACCGTGTGT GTAAAGAGTGAGGCGTATGAGGCTGTGTCGGGGCAGAGGCacaa cgtttc (SEQ ID NO: 40)
z38/42 esnRNA (DMD exon 51)	ggagtTACCTCCAACATCAAGGAAGATGGCAGTAACCACAGGTTG TGTCACCAGAGTAACAAATTTTTGGAGTAggctttctggctccttaccggaaa gcc (SEQ ID NO: 68)
U1 termination	ACTTTCTGGAGTTTCAAAAACAGACTGTACGCCAAGGGTCATAT CTTTTT (SEQ ID NO: 50)
Buffer combo sequence	CAAACTACAGAGCCAAGTGCTATCCACAGAGAGCTTTCTGGGT TGCCATCTCAAGCAGACTACAAGGCCATCAGCTCATACTCACA ATTGACTTTGAGAGTCATTTTCCAATGCTCCTACACACCCCTTCT TCACAATCCCCAACAAATCTGAGGCTGGAACTTGGTACCATAA CAATCATTACATTATTTCACCAGAAGTACACCTTGCCTGGAAGA TTGGCATTATAGCATCTTCTAACATTGTGAAAGTTAGTGACCAA TGAGGAGATCCAAGTCAGTTCCAGTTGGATTTCTCTATACTCTA TAATAAATATATATGGTGTCTTCAACAATAGGACTTTGCCATCC AGTGATGCTAAAAATCAATAACAATGGCAATAACCTGCCCTGT TTGGAAAGCCTCTGGCTTCCATGACTAACAATTCAAGGCAGGTC TCCTATACCTAGTACTGAGATTTTTATTTGATAAACTATATCTTC TGGGAGGAGAAGCATTGTTTGACCACATACGTGCTCTTTCAAA GTTCTGTGTTTGAAGTTATGTTAGTAACAACTGATGCCCATCCT GCAATGACAAATCCAATTCTCAGTGCAGCTCTCTGAAATAGTTT TGCTTTCTCTCTCTAGGTCTGTTCTATACTCCTAACTCTCCAGGA GTTTACAAGGAATAAAATCTCTTCCAAATGCTTTCTGTTGCAAC AACTGGACCATACTGAAAGCTGAGGCCCACAATTGCAATCTAG GTTAGCAGGTAATCATTGTTGGTGAGGTCCTCCCTTTCCCCAGG

	CTCGTGTTTGTATTGGGGAGCAGGAAATTTTTGCTAGAGCAGCA CTGCCATCTCTCTACACTCCACCTGATTGGTGGGATGGACCAGA GAAATGGACATTCCCAACACAGTCCCTCCTTTCACATCTGCTCA CCTGCCCACAGGATACTTTCCACCATGCATACTGGGCTCTGCAC CAACCATTCAGCAGTGATGAAGAGGAAACTTGAACCCATGCAG AGTACCTCTAGAGAAAAGTTTCTAAAGTTGGTTTTGCCTTGCTT AGAAAGGAGGTCAAAGGTGAAGCCTAGGAGAAACATTCAGCA ATGTTGCACAAAGACATGAGAATAAATGATTTTAGCATCCTGA AATGAAGAGCATAGTGATCTCACCATAGCTACCCACCTACCCA GAGAACTTCCAGGCTTTCACTGTCTCTTTTCTGAATCACCCACA TTACAGAATATCAGTCATTGTGTAATTAGATAACAGATTGTGAG GTGCCCAAACAGAAACAAACTTTACAGGAGGAGAGAGAAAAT CAAGGTGATGACTATGGAGAACAAAATGAGAAGGAGAGGTGG AGTTCCTGCTGCATGAACACCTATCCTGCTATAGAGCCCATTTC TTCCATAAATAATACAACTCTGTAACTCCATAGGTCAGAAAGA AACAGTGTTCTGTGTCTTCCCATCTAGCACCACAAACCCCCACA AGATTAATTTGTTTCTAGGGACCCTTAAATCTCTATCAAAATTC TGGAAACCTCTACTTTAGAAAATCTTATATTTATTATTCAGGCT ACTTTCCAGAGTGATAAGCTACTGAGTCTCCTAAGTGTCATCTA TGGTACACAGGGATAAGATCAGGAATAAACCTGGG (SEQ ID NO: 144)
ITR	aggaacccctagtgatggagttggccactccctctctgcgcgctcgctcgctcactgaggccgggcgac caaaggtcgcccgacgcccgggctttgcccgggcggcctcagtgagcgagcgagcgcgcagctgcct gcagg (SEQ ID NO: 60)

[0162] An exemplary AAV vector of the disclosure comprises from 5' to 3': a first inverted terminal repeat (ITR) sequence, a U7 promoter sequence, a CUG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, a U1 promoter sequence, a CUG repeat targeting U7 esnRNA sequence, a U1 downstream terminator sequence, an eCMV promoter sequence, a sequence encoding GFP, a polyA sequence, and a second ITR sequence. In some aspects, a nucleic acid sequence encoding AAV vector A03681 encoding a CUG repeat targeting snRNA sequences comprises SEQ ID NO: 139.

A03681: pAAV(ssAAV)-U7 promoter-zCUGx15-U7 term_U1 promoter-zCUGx15-U1 term-eCMV-eGFP

ITR	cctgcaggcagctgcgcgctcgctcgctcactgaggccgcccgggcgtcgggcgacctttggtcgcccggcct cagtgagcgagcgagcgcgcagagagggagtggccaactccatcactaggggttcct (SEQ ID NO: 59)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGGCTG TGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTTGCATGG GCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATGACTTAAGTA AGTTCCTTAGAATATTATTTTTCCTACTGAAAGTTACCACATGCGTCG TTGTTTATACAGTAATAGGAACAAGAAAAAAGTCACCTAAGCTCAC CCTCATCAATTGTGGAGTTCCTTTATATCCCATCTTCTCTCCAAACAC ATACGCA (SEQ ID NO: 39)

zCUGx15 esnRNA	ggagtCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAG CAGAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 65)
U7 termination	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGCAAA AATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCTTGGAG (SEQ ID NO: 49)
U1 promoter	TAAGGACCAGCTTCTTTGGGAGAGAACAGACGCAGGGGCGGGAGGG AAAAAGGGAGAGGCAGACGTCACTTCCCCTTGGCGGCTCTGGCAGC AGATTGGTCGGTTGAGTGGCAGAAAGGCAGACGGGGACTGGGCAAG GCACTGTCGGTGACATCACGGACAGGGCGACTTCTATGTAGATGAG GCAGCGCAGAGGCTGACGTCTTCGCCACTTGCTGCTTCACCACGAAG GAGTTCCCGTGCCCTGGGAGCGGGTTCAGGACCGCTGATCGGAAGT GAGAATCCCAGCTGTGTGTCAGGGCTGGAAAGGGCTCGGGAGTGCG CGGGGCAAGTGACCGTGTGTGTAAAGAGTGAGGCGTATGAGGCTGT GTCGGGGCAGAGGCacaacgtttc (SEQ ID NO: 40)
zCUGx15 esnRNA	ggagtCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAG CAGAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 65)
U1 termination	ACTTTCTGGAGTTTCAAAAACAGACTGTACGCCAAGGGTCATATCTT TTT (SEQ ID NO: 50)
eCMV promoter	cgttacataacttacggtaaatggcccgcctggctgaccgcccaacgacccccgcccattgacgtcaataatgac gtatgttcccatagtaacgccaatagggactttccattgacgtcaatgggtggagtatttacggtaaactgcccactt ggcagtacatcaagtgtatcatatgccaagtacgccccctattgacgtcaatgacggtaaatggcccgcctggcatt atgcccagtacatgaccttatgggactttcctacttggcagtacatctacgtattagtcatcgctattaccatg (SE Q ID NO: 62)
eGFP	ATGgtgagcaagggcgaggagctgttcaccggggtggtgcccatcctggtcgagctggacggcgacgtaaa cggccacaagttcagcgtgtccggcgagggcgagggcgatgccacctacggcaagctgaccctgaagttcatct gcaccaccggcaagctgcccgtgccctggcccaccctcgtgaccaccctgacctacggcgtgcagtgcttcagc cgctaccccgaccacatgaagcagcacgacttcttcaagtccgccatgcccgaaggctacgtccaggagcgcac catcttcttcaaggacgacggcaactacaagacccgcgccgaggtgaagttcgagggcgacaccctggtgaacc gcatcgagctgaagggcatcgacttcaaggaggacggcaacatcctggggcacaagctggagtacaactacaa cagccacaacgtctatatcatggccgacaagcagaagaacggcatcaaggtgaacttcaagatccgccacaaca tcgaggacggcagcgtgcagctcgccgaccactaccagcagaacaccccatcggcgacggccccgtgctgc tgcccgacaaccactacctgagcacccagtccgccctgagcaaagaccccaacgagaagcgcgatcacatggt cctgctggagttcgtgaccgccgccgggatcactctcggcatggacgagctgtacaagTAA (SEQ ID NO: 63)
SV40 pA	aacttgtttattgcagcttataatggttacaaataaagcaatagcatcacaaatttcacaaataaagcatttttttcactg cattctagttgtggtttgtccaaactcatcaatgtatctta (SEQ ID NO: 64)
ITR	aggaacccctagtgatggagttggccactccctctctgcgcgctcgctcgctcactgaggccgggcgaccaaag gtcgcccgacgcccgggctttgcccgggcggcctcagtgagcgagcgagcgcgcagctgcctgcagg (SE Q ID NO: 60)

[0163] An exemplary AAV vector of the disclosure comprises from 5' to 3': a first inverted terminal repeat (ITR) sequence, a U1 promoter sequence, a CUG repeat targeting U7 esnRNA sequence, a U1 downstream terminator sequence, a buffer sequence, a U7 promoter sequence, a CUG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, an eCMV promoter sequence, a sequence encoding GFP, a polyA sequence, and a second ITR sequence. In some aspects, a nucleic acid sequence encoding AAV vector A03682 encoding a CUG repeat targeting snRNA sequences comprises SEQ ID NO: 140.

A03682: pAAV(ssAAV)-U1 promoter-zCUGx15-U1 term_U7 promoter-zCUGx15-U7 term-eCMV-eGFP

ITR	cctgcaggcagctgcgcgctcgctcgctcactgaggccgcccgggcgtcgggcgacctttggtcgcccggcc tcagtgagcgagcgagcgcgcagagagggagtggccaactccatcactaggggttcct (SEQ ID NO: 59)
U1 promoter	TAAGGACCAGCTTCTTTGGGAGAGAACAGACGCAGGGGCGGGAGG GAAAAAGGGAGAGGCAGACGTCACTTCCCCTTGGCGGCTCTGGCAG CAGATTGGTCGGTTGAGTGGCAGAAAGGCAGACGGGGACTGGGCA AGGCACTGTCGGTGACATCACGGACAGGGCGACTTCTATGTAGATG AGGCAGCGCAGAGGCTGACGTCTTCGCCACTTGCTGCTTCACCACG AAGGAGTTCCCGTGCCCTGGGAGCGGGTTCAGGACCGCTGATCGGA AGTGAGAATCCCAGCTGTGTGTCAGGGCTGGAAAGGGCTCGGGAGT GCGCGGGGCAAGTGACCGTGTGTGTAAAGAGTGAGGCGTATGAGG CTGTGTCGGGGCAGAGGCacaacgtttc (SEQ ID NO: 40)
zCUGx15 esnRNA	ggagtCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAG CAGAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 65)
U1 termination	ACTTTCTGGAGTTTCAAAAACAGACTGTACGCCAAGGGTCATATCTT TTT (SEQ ID NO: 50)
U7 promoter	AATCCAGGTCTCCGGGCTTAACAACAACGAAGGGGCTGTGACTGGC TGCTTTCTCAACCAATCAGCACCGAACTCATTTGCATGGGCTGAGA ACAAATGTTCGCGAACTCTAGAAATGAATGACTTAAGTAAGTTCCT TAGAATATTATTTTTCCTACTGAAAGTTACCACATGCGTCGTTGTTT ATACAGTAATAGGAACAAGAAAAAAGTCACCTAAGCTCACCCTCAT CAATTGTGGAGTTCCTTTATATCCCATCTTCTCTCCAAACACATACG CA (SEQ ID NO: 39)
zCUGx15 esnRNA	ggagtCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAG CAGAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 65)
U7 termination	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGCAA AAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCTTGGAG (SEQ ID NO: 49)
eCMV promoter	cgttacataacttacggtaaatggcccgcctggctgaccgcccaacgacccccgcccattgacgtcaataatgac gtatgttcccatagtaacgccaatagggactttccattgacgtcaatgggtggagtatttacggtaaactgcccactt ggcagtacatcaagtgtatcatatgccaagtacgccccctattgacgtcaatgacggtaaatggcccgcctggca ttatgcccagtacatgaccttatgggactttcctacttggcagtacatctacgtattagtcatcgctattaccatg (SEQ ID NO: 62)
eGFP	ATGgtgagcaagggcgaggagctgttcaccggggtggtgcccatcctggtcgagctggacggcgacgtaa acggccacaagttcagcgtgtccggcgagggcgagggcgatgccacctacggcaagctgaccctgaagttca tctgcaccaccggcaagctgcccgtgccctggcccaccctcgtgaccaccctgacctacggcgtgcagtgcttc agccgctaccccgaccacatgaagcagcacgacttcttcaagtccgccatgcccgaaggctacgtccaggagc gcaccatcttcttcaaggacgacggcaactacaagacccgcgccgaggtgaagttcgagggcgacaccctggt gaaccgcatcgagctgaagggcatcgacttcaaggaggacggcaacatcctggggcacaagctggagtacaa ctacaacagccacaacgtctatatcatggccgacaagcagaagaacggcatcaaggtgaacttcaagatccgc cacaacatcgaggacggcagcgtgcagctcgccgaccactaccagcagaacaccccatcggcgacggccc cgtgctgctgcccgacaaccactacctgagcacccagtccgccctgagcaaagaccccaacgagaagcgcga tcacatggtcctgctggagttcgtgaccgccgccgggatcactctcggcatggacgagctgtacaagTAA (SEQ ID NO: 63)

SV40 pA	aacttgtttattgcagcttataatggttacaaataaagcaatagcatcacaaatttcacaaataaagcatttttttcactg cattctagttgtggtttgtccaaactcatcaatgtatctta (SEQ ID NO: 64)
ITR	aggaacccctagtgatggagttggccactccctctctgcgcgctcgctcgctcactgaggccgggcgaccaaa ggtcgcccgacgcccgggctttgcccgggcggcctcagtgagcgagcgagcgcgcagctgcctgcagg (S EQ ID NO: 60)

[0164] An exemplary AAV vector of the disclosure comprises from 5' to 3': a first inverted terminal repeat (ITR) sequence, a U7 promoter sequence, a non-targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, a U1 promoter sequence, a non-targeting U7 esnRNA sequence, a U1 downstream terminator sequence, an eCMV promoter sequence, a sequence encoding GFP, a polyA sequence, and a second ITR sequence. In some aspects, a nucleic acid sequence encoding AAV vector A03683 encoding a non-targeting snRNA sequences comprises SEQ ID NO: 141.

A03683: pAAV(ssAAV)-U7 promoter-znt-U7 term_U1 promoter-znt-U1 term-eCMV-eGFP

ITR	cctgcaggcagctgcgcgctcgctcgctcactgaggccgcccgggcgtcgggcgacctttggtcgcccggcc tcagtgagcgagcgagcgcgcagagagggagtggccaactccatcactaggggttcct (SEQ ID NO: 59)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGGCTG TGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTTGCATGG GCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATGACTTAAGTA AGTTCCTTAGAATATTATTTTTCCTACTGAAAGTTACCACATGCGTC GTTGTTTATACAGTAATAGGAACAAGAAAAAAGTCACCTAAGCTCA CCCTCATCAATTGTGGAGTTCCTTTATATCCCATCTTCTCTCCAAAC ACATACGCA (SEQ ID NO: 39)
z-nt esnRNA	ggagtTCACCAGAAGCGTACCATACTCACGAAATTTTTGGAGTAggctttct ggctccttaccggaaagcc (SEQ ID NO: 66)
U7 termination	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGCAA AAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCTTGGAG (SEQ ID NO: 49)
U1 promoter	TAAGGACCAGCTTCTTTGGGAGAGAACAGACGCAGGGGCGGGAGG GAAAAAGGGAGAGGCAGACGTCACTTCCCCTTGGCGGCTCTGGCAG CAGATTGGTCGGTTGAGTGGCAGAAAGGCAGACGGGGACTGGGCA AGGCACTGTCGGTGACATCACGGACAGGGCGACTTCTATGTAGATG AGGCAGCGCAGAGGCTGACGTCTTCGCCACTTGCTGCTTCACCACG AAGGAGTTCCCGTGCCCTGGGAGCGGGTTCAGGACCGCTGATCGGA AGTGAGAATCCCAGCTGTGTGTCAGGGCTGGAAAGGGCTCGGGAGT GCGCGGGGCAAGTGACCGTGTGTGTAAAGAGTGAGGCGTATGAGG CTGTGTCGGGGCAGAGGCacaacgtttc (SEQ ID NO: 40)
z-nt esnRNA	ggagtTCACCAGAAGCGTACCATACTCACGAAATTTTTGGAGTAggctttct ggctccttaccggaaagcc (SEQ ID NO: 66)
U1 termination	ACTTTCTGGAGTTTCAAAAACAGACTGTACGCCAAGGGTCATATCTT TTT (SEQ ID NO: 50)

eCMV promoter	cgttacataacttacggtaaatggcccgcctggctgaccgcccaacgacccccgcccattgacgtcaataatgac gtatgttcccatagtaacgccaatagggactttccattgacgtcaatgggtggagtatttacggtaaactgcccactt ggcagtacatcaagtgtatcatatgccaagtacgccccctattgacgtcaatgacggtaaatggcccgcctggca ttatgcccagtacatgaccttatgggactttcctacttggcagtacatctacgtattagtcatcgctattaccatg (S EQ ID NO: 62)
eGFP	ATGgtgagcaagggcgaggagctgttcaccggggtggtgcccatcctggtcgagctggacggcgacgtaa acggccacaagttcagcgtgtccggcgagggcgagggcgatgccacctacggcaagctgaccctgaagttca tctgcaccaccggcaagctgcccgtgccctggcccaccctcgtgaccaccctgacctacggcgtgcagtgcttc agccgctaccccgaccacatgaagcagcacgacttcttcaagtccgccatgcccgaaggctacgtccaggagc gcaccatcttcttcaaggacgacggcaactacaagacccgcgccgaggtgaagttcgagggcgacaccctggt gaaccgcatcgagctgaagggcatcgacttcaaggaggacggcaacatcctggggcacaagctggagtacaa ctacaacagccacaacgtctatatcatggccgacaagcagaagaacggcatcaaggtgaacttcaagatccgc cacaacatcgaggacggcagcgtgcagctcgccgaccactaccagcagaacaccccatcggcgacggccc cgtgctgctgcccgacaaccactacctgagcacccagtccgccctgagcaaagaccccaacgagaagcgcga tcacatggtcctgctggagttcgtgaccgccgccgggatcactctcggcatggacgagctgtacaagTAA (SEQ ID NO: 63)
SV40 pA	aacttgtttattgcagcttataatggttacaaataaagcaatagcatcacaaatttcacaaataaagcatttttttcactg cattctagttgtggtttgtccaaactcatcaatgtatctta (SEQ ID NO: 64)
ITR	Aggaacccctagtgatggagttggccactccctctctgcgcgctcgctcgctcactgaggccgggcgaccaaa ggtcgcccgacgcccgggctttgcccgggcggcctcagtgagcgagcgagcgcgcagctgcctgcagg (SEQ ID NO: 60)

[0165] An exemplary AAV vector of the disclosure comprises from 5' to 3': a first inverted terminal repeat (ITR) sequence, a U7 promoter sequence, a CUG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, a U1 promoter sequence, a CUG repeat targeting U7 esnRNA sequence, a U1 downstream terminator sequence, and a second ITR sequence. In some aspects, a nucleic acid sequence encoding AAV vector A03684 encoding a CUG repeat targeting snRNA sequences comprises SEQ ID NO: 142.

A03864: pAAV(ssAAV)-U7 promoter-zCUGx15-U7 term_U1 promoter-zCUGx15-U1 term (minus GFP - derivative of 3681)

ITR	cctgcaggcagctgcgcgctcgctcgctcactgaggccgcccgggcgtcgggcgacctttggtcgcccggcc tcagtgagcgagcgagcgcgcagagagggagtggccaactccatcactaggggttcct (SEQ ID NO: 59)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGGCTG TGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTTGCATGG GCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATGACTTAAGTA AGTTCCTTAGAATATTATTTTTCCTACTGAAAGTTACCACATGCGTC GTTGTTTATACAGTAATAGGAACAAGAAAAAAGTCACCTAAGCTCA CCCTCATCAATTGTGGAGTTCCTTTATATCCCATCTTCTCTCCAAAC ACATACGCA (SEQ ID NO: 39)
zCUGx15 esnRNA	ggagtCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAG CAGAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 65)

U7 termination	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGCAA AAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCTTGGAG (SEQ ID NO: 49)
U1 promoter	TAAGGACCAGCTTCTTTGGGAGAGAACAGACGCAGGGGCGGGAGG GAAAAAGGGAGAGGCAGACGTCACTTCCCCTTGGCGGCTCTGGCAG CAGATTGGTCGGTTGAGTGGCAGAAAGGCAGACGGGGACTGGGCA AGGCACTGTCGGTGACATCACGGACAGGGCGACTTCTATGTAGATG AGGCAGCGCAGAGGCTGACGTCTTCGCCACTTGCTGCTTCACCACG AAGGAGTTCCCGTGCCCTGGGAGCGGGTTCAGGACCGCTGATCGGA AGTGAGAATCCCAGCTGTGTGTCAGGGCTGGAAAGGGCTCGGGAGT GCGCGGGGCAAGTGACCGTGTGTGTAAAGAGTGAGGCGTATGAGG CTGTGTCGGGGCAGAGGCacaacgtttc (SEQ ID NO: 40)
zCUGx15 esnRNA	ggagtCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAG CAGAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 65)
U1 termination	ACTTTCTGGAGTTTCAAAAACAGACTGTACGCCAAGGGTCATATCTT TTT (SEQ ID NO: 50)
ITR	aggaacccctagtgatggagttggccactccctctctgcgcgctcgctcgctcactgaggccgggcgaccaaa ggtcgcccgacgcccgggctttgcccgggcggcctcagtgagcgagcgagcgcgcagctgcctgcagg (SEQ ID NO: 60)

[0166] An exemplary AAV vector of the disclosure comprises from 5' to 3': a first inverted terminal repeat (ITR) sequence, a U7 promoter sequence, a CUG repeat targeting U7 esnRNA sequence, a U7 downstream terminator sequence, a buffer sequence, a U1 promoter sequence, a CUG repeat targeting U7 esnRNA sequence, a U1 downstream terminator sequence, and a second ITR sequence. In some aspects, a nucleic acid sequence encoding AAV vector A04233 encoding a CUG repeat targeting snRNA sequences comprises SEQ ID NO: 143.

A04233: pAAV(scAAV)-U7promoter-zCUGx15-U7termination-U1promoter-zCUGx15-U1termination (derivative of A03681 no GFP in scAAV)

ITR	cctgcaggcagctgcgcgctcgctcgctcactgaggccgcccgggcgtcgggcgacctttggtcgcccggcc tcagtgagcgagcgagcgcgcagagagggagtggccaactccatcactaggggttcct (SEQ ID NO: 59)
U7 promoter	TACTGCCGAATCCAGGTCTCCGGGCTTAACAACAACGAAGGGGCTG TGACTGGCTGCTTTCTCAACCAATCAGCACCGAACTCATTTGCATGG GCTGAGAACAAATGTTCGCGAACTCTAGAAATGAATGACTTAAGTA AGTTCCTTAGAATATTATTTTTCCTACTGAAAGTTACCACATGCGTC GTTGTTTATACAGTAATAGGAACAAGAAAAAAGTCACCTAAGCTCA CCCTCATCAATTGTGGAGTTCCTTTATATCCCATCTTCTCTCCAAAC ACATACGCA (SEQ ID NO: 39)
zCUGx15 esnRNA	ggagtCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAG CAGAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 65)
U7 termination	CCTCTTATGATGTTTGTTGCCAATGATAGATTGTTTTCACTGTGCAA AAATTATGGGTAGTTTTGGTGGTCTTGATGCAGTTGTAAGCTTGGAG (SEQ ID NO: 49)

U1 promoter	TAAGGACCAGCTTCTTTGGGAGAGAACAGACGCAGGGGCGGGAGG GAAAAAGGGAGAGGCAGACGTCACTTCCCCTTGGCGGCTCTGGCAG CAGATTGGTCGGTTGAGTGGCAGAAAGGCAGACGGGGACTGGGCA AGGCACTGTCGGTGACATCACGGACAGGGCGACTTCTATGTAGATG AGGCAGCGCAGAGGCTGACGTCTTCGCCACTTGCTGCTTCACCACG AAGGAGTTCCCGTGCCCTGGGAGCGGGTTCAGGACCGCTGATCGGA AGTGAGAATCCCAGCTGTGTGTCAGGGCTGGAAAGGGCTCGGGAGT GCGCGGGGCAAGTGACCGTGTGTGTAAAGAGTGAGGCGTATGAGG CTGTGTCGGGGCAGAGGCacaacgtttc (SEQ ID NO: 40)
zCUGx15 esnRNA	ggagtCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAG CAGAATTTTTGGAGTAggctttctggctccttaccggaaagcc (SEQ ID NO: 65)
U1 termination	ACTTTCTGGAGTTTCAAAAACAGACTGTACGCCAAGGGTCATATCTT TTT (SEQ ID NO: 50)
mITR	CCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCA AAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCG AGCGAGCGCGCAGAGAGGGA (SEQ ID NO: 61)

Promoter Sequences

[0167] Gene therapy and RNA-targeting snRNA gene therapy compositions of the disclosure comprise promoter sequences derived from an snRNA.

[0168] A "promoter" is a control sequence that is a region of a polynucleotide sequence at which initiation and rate of transcription are controlled. It may contain genetic elements at which regulatory proteins and molecules may bind such as RNA polymerase and other transcription factors.

[0169] In some embodiments of the compositions and methods of the disclosure, an expression vector, viral vector or non-viral vector provided herein, includes without limitation, an expression control element. An "expression control element" as used herein refers to any sequence that regulates the expression of a coding sequence, such as a gene. Exemplary expression control elements include but are not limited to promoters, enhancers, microRNAs, post-transcriptional regulatory elements, polyadenylation signal sequences, and introns. Expression control elements may be constitutive, inducible, repressible, or tissue-specific, for example. A "promoter" is a control sequence that is a region of a polynucleotide sequence at which initiation and rate of transcription are controlled. It may contain genetic elements at which regulatory proteins and molecules may bind such as RNA polymerase and other transcription factors. An "enhancer" is a region of DNA that can be bound by activating proteins to increase the likelihood or frequency of transcription.

[0170] In some embodiments of the compositions and methods of the disclosure, an expression vector, viral vector or non-viral vector provided herein, includes without

limitation, vector elements such as a buffer sequence derived human genomic sequences downstream from an snRNA and as such will have the capability to encoding multiple snRNAs from a single construct.

[0171] In some embodiments, with the incorporation of coding sequences into the compositions disclosed herein, multicistronic vectors can simultaneously express two or more separate proteins from the same mRNA. The two strategies most widely used for constructing multicistronic configurations are through the use of an IRES or a 2A self-cleaving site. An "IRES" refers to an internal ribosome entry site or portion thereof of viral, prokaryotic, or eukaryotic origin which are used within polycistronic vector constructs. In some embodiments, an IRES is an RNA element that allows for translation initiation in a cap-independent manner. The term "self-cleaving peptides" or "sequences encoding self-cleaving peptides" or "2A self-cleaving site" refer to linking sequences which are used within vector constructs to incorporate sites to promote ribosomal skipping and thus to generate two polypeptides from a single promoter, such self-cleaving peptides include without limitation, T2A, and P2A peptides or other sequences encoding the self-cleaving peptides.

[0172] In another embodiment, the vector configurations can comprise linker(s), signal sequence(s), and/or tag(s).

[0173] In some embodiments, the vector is a viral vector. In some embodiments, the vector is an adenoviral vector, an adeno-associated viral (AAV) vector, or a lentiviral vector. In some embodiments, the vector is a retroviral vector, an adenoviral/retroviral chimera vector, a herpes simplex viral I or II vector, a parvoviral vector, a reticuloendotheliosis viral vector, a polioviral vector, a papillomaviral vector, a vaccinia viral vector, or any hybrid or chimeric vector incorporating favorable aspects of two or more viral vectors. In some embodiments, the vector further comprises one or more expression control elements operably linked to the polynucleotide. In some embodiments, the vector further comprises one or more selectable markers. In some embodiments, the AAV vector has low toxicity. In some embodiments, the AAV vector does not incorporate into the host genome, thereby having a low probability of causing insertional mutagenesis. In some embodiments, the AAV vector can encode a range of total polynucleotides from 4.5 kb to 4.75 kb. In some embodiments, exemplary AAV vectors that may be used in any of the herein described compositions, systems, methods, and kits can include an AAV1 vector, a modified AAV1 vector, an AAV2 vector, a modified AAV2 vector, an AAV2-Tyr mutant vector, an AAV3 vector, a modified AAV3 vector, an AAV4 vector, a modified AAV4 vector, an AAV5 vector, a modified AAV5

vector, an AAV6 vector, a modified AAV6 vector, an AAV7 vector, a modified AAV7 vector, an AAV8 vector, an AAVrh8 vector, an AAV9 vector, an AAV.rh10 vector, a modified AAV.rh10 vector, an AAVrh.74, an AAV.rh32/33 vector, a modified AAV.rh32/33 vector, an AAV.rh43 vector, a modified AAV.rh43 vector, an AAV.rh64R1 vector, and a modified AAV.rh64R1 vector, an AAV-Tyr mutant vector, AAV-Tyr-Ser mutant vector, AAV-Tyr-Ser-Thr mutant vector and any combinations or equivalents thereof. In some embodiments, the lentiviral vector is an integrase-competent lentiviral vector (ICLV). In some embodiments, the lentiviral vector can refer to the transgene plasmid vector as well as the transgene plasmid vector in conjunction with related plasmids (e.g., a packaging plasmid, a rev expressing plasmid, an envelope plasmid) as well as a lentiviral-based particle capable of introducing exogenous nucleic acid into a cell through a viral or viral-like entry mechanism.

[0174] Lentiviral vectors are well-known in the art (see, e.g., Trono D. (2002) Lentiviral vectors, New York: Spring-Verlag Berlin Heidelberg and Durand et al. (2011) *Viruses* 3(2):132-159 doi: 10.3390/v3020132). In some embodiments, exemplary lentiviral vectors that may be used in any of the herein described compositions, systems, methods, and kits can include a human immunodeficiency virus (HIV) 1 vector, a modified human immunodeficiency virus (HIV) 1 vector, a human immunodeficiency virus (HIV) 2 vector, a modified human immunodeficiency virus (HIV) 2 vector, a sooty mangabey simian immunodeficiency virus (SIV_{SM}) vector, a modified sooty mangabey simian immunodeficiency virus (SIV_{SM}) vector, a African green monkey simian immunodeficiency virus (SIV_{AGM}) vector, a modified African green monkey simian immunodeficiency virus (SIV_{AGM}) vector, an equine infectious anemia virus (EIAV) vector, a modified equine infectious anemia virus (EIAV) vector, a feline immunodeficiency virus (FIV) vector, a modified feline immunodeficiency virus (FIV) vector, a Visna/maedi virus (VNV/VMV) vector, a modified Visna/maedi virus (VNV/VMV) vector, a caprine arthritis-encephalitis virus (CAEV) vector, a modified caprine arthritis-encephalitis virus (CAEV) vector, a bovine immunodeficiency virus (BIV), or a modified bovine immunodeficiency virus (BIV).

Nucleic Acids

[0175] An NOI (nucleotide sequence of interest) includes, without limitation, any nucleotide sequence or transgene capable of being delivered by a vector. NOIs can be synthetic, derived from naturally occurring DNA or RNA, codon optimized, recombinant

RNA/DNA, cDNA, partial genomic DNA, and/or combinations thereof. The NOI can be a coding region or partial coding region, but need not be a coding region. An NOI can be RNA/DNA in a sense or anti-sense orientation. An NOI can be an snRNA. NOIs are also referred herein, without limitation, as transgenes, heterologous sequences, genes, therapeutic genes. An NOI may also encode an RNA (ribonucleoprotein complex) a POI (protein of interest), a partial POI, a mutated version or variant of a POI. A POI may be analogous to or correspond to a wild-type protein. A POI may also be a fusion protein or ribonucleoprotein complex such as an snRNP. In some aspects, RNA sequences disclosed herein may be represented as DNA sequences and it is within the ability of the skilled artisan to derive the sequence of an RNA sequence from a DNA sequence.

Codon Optimization

[0176] In some embodiments, NOIs or transgenes or GOIs such as nucleic acid sequences encoding RNA-targeting snRNAs of the disclosure are codon optimized nucleic acid sequences. In some embodiments, the codon optimized sequence exhibits at least 5%, at least 10%, at least 20%, at least 30%, at least 50%, at least 75%, at least 100%, at least 200%, at least 300%, at least 500%, or at least 1000% increased transcription or translation in a human subject relative to a wild-type or non-codon optimized nucleic acid sequence.

[0177] In some aspects, a codon optimized nucleic acid sequence exhibits increased stability. In some aspects, a codon optimized nucleic acid sequence exhibits increased stability through increased resistance to hydrolysis. In some embodiments, the codon optimized sequence exhibits at least 5%, at least 10%, at least 20%, at least 30%, at least 50%, at least 75%, at least 100%, at least 200%, at least 300%, at least 500%, or at least 1000% increased stability relative to a wild-type or non-codon optimized nucleic acid sequence. In some embodiments, the codon optimized sequence exhibits at least 5%, at least 10%, at least 20%, at least 30%, at least 50%, at least 75%, at least 100%, at least 200%, at least 300%, at least 500%, or at least 1000% increased resistance to hydrolysis in a human subject relative to a wild-type or non-codon optimized nucleic acid sequence.

[0178] In some aspects, a codon optimized nucleic acid sequence can comprise no donor splice sites. In some aspects, a codon optimized nucleic acid sequence can comprise no more than about one, or about two, or about three, or about four, or about five, or about six, or about seven, or about eight, or about nine, or about ten donor splice sites. In some aspects, a codon optimized nucleic acid sequence comprises at least one, or at least two, or at least three, or at least four, or at least five, or at least six, or at least seven, or at least eight, or at

least nine, or at least ten fewer donor splice sites as compared to a non-codon optimized nucleic acid sequence.

[0179] Without wishing to be bound by theory, the removal of donor splice sites in the codon optimized nucleic acid sequence can unexpectedly and unpredictably increase expression of protein of interest *in vivo*, as cryptic splicing is prevented. Moreover, cryptic splicing may vary between different subjects, meaning that the expression level of a protein comprising donor splice sites may unpredictably vary between different subjects. Such unpredictability is unacceptable in the context of human therapy. Accordingly, the codon optimized nucleic acid sequences which lacks donor splice sites, unexpectedly and surprisingly allows for increased expression of the protein in human subjects and regularizes expression of the protein across different human subjects.

[0180] In some aspects, a codon optimized nucleic acid sequence can have a GC content that differs from the GC content of the non-codon optimized nucleic acid sequence encoding the RNA-targeting snRNA. In some aspects, the GC content of a codon optimized nucleic acid sequence is more evenly distributed across the entire nucleic acid sequence, as compared to the non-codon optimized nucleic acid sequence.

[0181] Without wishing to be bound by theory, by more evenly distributing the GC content across the entire nucleic acid sequence, the codon optimized nucleic acid sequence exhibits a more uniform melting temperature ("Tm") across the length of the transcript. The uniformity of melting temperature results unexpectedly in increased expression of the codon optimized nucleic acid in a human subject, as transcription and/or translation of the nucleic acid sequence occurs with less stalling of the polymerase and/or ribosome.

[0182] In some aspects, a codon optimized nucleic acid sequence can have fewer repressive microRNA target binding sites as compared to the non-codon optimized nucleic acid sequence. In some aspects, a codon optimized nucleic acid sequence can have at least one, or at least two, or at least three, or at least four, or at least five, or at least six, or at least seven, or at least eight, or at least nine, or at least ten, or at least ten fewer repressive microRNA target binding sites as compared to the non-codon optimized nucleic acid sequence.

[0183] Without wishing to be bound by theory, by having fewer repressive microRNA target binding sites, the codon optimized nucleic acid sequence unexpectedly exhibits increased expression in a human subject.

[0184] Provided herein are the nucleic acid sequences encoding the gene therapy compositions or RNA-targeting snRNA systems for use in gene transfer and expression

techniques described herein. It should be understood, although not always explicitly stated that the sequences provided herein can be used to provide the expression product as well as substantially identical sequences that encode an RNA or express and produce a protein that has the same biological properties. These "biologically equivalent" or "biologically active" or "equivalent" polypeptides are encoded by equivalent polynucleotides as described herein. They may possess at least 60%, or alternatively, at least 65%, or alternatively, at least 70%, or alternatively, at least 75%, or alternatively, at least 80%, or alternatively at least 85%, or alternatively at least 90%, or alternatively at least 95% or alternatively at least 98%, identical primary amino acid sequence to the reference polypeptide when compared using sequence identity methods run under default conditions. Specific polypeptide sequences are provided as examples of particular embodiments. Modifications to the sequences to amino acids with alternate amino acids that have similar charge. Additionally, an equivalent polynucleotide is one that hybridizes under stringent conditions to the reference polynucleotide or its complement or in reference to a polypeptide, a polypeptide encoded by a polynucleotide that hybridizes to the reference encoding polynucleotide under stringent conditions or its complementary strand. Alternatively, an equivalent polypeptide or protein is one that is expressed from an equivalent polynucleotide.

[0185] The NOIs or nucleic acid sequences (e.g., polynucleotide sequences) disclosed herein may be codon-optimized which is a technique well known in the art. Codon optimization refers to the fact that different cells differ in their usage of particular codons. This codon bias corresponds to a bias in the relative abundance of particular tRNAs in the cell type. By altering the codons in the sequence to match with the relative abundance of corresponding tRNAs, it is possible to increase expression. It is also possible to decrease expression by deliberately choosing codons for which the corresponding tRNAs are known to be rare in a particular cell type. Codon usage tables are known in the art for mammalian cells, as well as for a variety of other organisms. Based on the genetic code, nucleic acid sequences coding for, e.g., an esnRNA, esnRNA can be generated. In some embodiments, such a sequence is optimized for expression in a host or target cell, such as a host cell used to express the esnRNA or a cell in which the disclosed methods are practiced (such as in a mammalian cell, e.g., a human cell). Codon preferences and codon usage tables for a particular species can be used to engineer isolated nucleic acid molecules encoding an esnRNA that takes advantage of the codon usage preferences of that particular species. For example, the esnRNA disclosed herein can be designed to have codons that are preferentially

used by a particular organism of interest. In one example, an esnRNA nucleic acid sequence is optimized for expression in human cells, such as one having at least 70%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 98%, or at least 99% sequence identity to its corresponding wild-type or originating nucleic acid sequence. In some embodiments, an isolated nucleic acid molecule encoding at least one esnRNA (which can be part of a vector) includes at least one esnRNA coding sequence that is codon optimized for expression in a eukaryotic cell, or at least one esnRNA coding sequence codon optimized for expression in a human cell. In one embodiment, such a codon optimized esnRNA coding sequence has at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to its corresponding wild-type or originating sequence. In another embodiment, a eukaryotic cell codon optimized nucleic acid sequence encodes esnRNA having at least 85%, at least 90%, at least 92%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to its corresponding wild-type or originating sequence. In another embodiment, a variety of clones containing functionally equivalent nucleic acids may be routinely generated, such as nucleic acids which differ in sequence but which encode the same esnRNA sequence. Silent mutations in the coding sequence result from the degeneracy (i.e., redundancy) of the genetic code, whereby more than one codon can encode the same amino acid residue. Thus, for example, leucine can be encoded by CTT, CTC, CTA, CTG, TTA, or TTG; serine can be encoded by TCT, TCC, TCA, TCG, AGT, or AGC; asparagine can be encoded by AAT or AAC; aspartic acid can be encoded by GAT or GAC; cysteine can be encoded by TGT or TGC; alanine can be encoded by GCT, GCC, GCA, or GCG; glutamine can be encoded by CAA or CAG; tyrosine can be encoded by TAT or TAC; and isoleucine can be encoded by ATT, ATC, or ATA. Tables showing the standard genetic code can be found in various sources (see, for example, Stryer, 1988, Biochemistry, 3.sup.rd Edition, W.H. 5 Freeman and Co., NY).

[0186] "Hybridization" refers to a reaction in which one or more polynucleotides react to form a complex that is stabilized via hydrogen bonding between the bases of the nucleotide residues. The hydrogen bonding may occur by Watson-Crick base pairing, Hoogstein binding, or in any other sequence-specific manner. The complex may comprise two strands forming a duplex structure, three or more strands forming a multi-stranded complex, a single self-hybridizing strand, or any combination of these. A hybridization reaction may constitute

a step in a more extensive process, such as the initiation of a PC reaction, or the enzymatic cleavage of a polynucleotide by a ribozyme.

[0187] Examples of stringent hybridization conditions include: incubation temperatures of about 25°C to about 37°C; hybridization buffer concentrations of about 6x SSC to about 10x SSC; formamide concentrations of about 0% to about 25%; and wash solutions from about 4x SSC to about 8x SSC. Examples of moderate hybridization conditions include: incubation temperatures of about 40°C to about 50°C; buffer concentrations of about 9x SSC to about 2x SSC; formamide concentrations of about 30% to about 50%; and wash solutions of about 5x SSC to about 2x SSC. Examples of high stringency conditions include: incubation temperatures of about 55°C to about 68°C; buffer concentrations of about lx SSC to about 0.1x SSC; formamide concentrations of about 55% to about 75%; and wash solutions of about lx SSC, 0.1x SSC, or deionized water. In general, hybridization incubation times are from 5 minutes to 24 hours, with 1, 2, or more washing steps, and wash incubation times are about 1, 2, or 15 minutes. SSC is 0.15 M NaCl and 15 mM citrate buffer. It is understood that equivalents of SSC using other buffer systems can be employed.

[0188] "Homology" or "identity" or "similarity" refers to sequence similarity between two peptides or between two nucleic acid molecules. Homology can be determined by comparing a position in each sequence which may be aligned for purposes of comparison. When a position in the compared sequence is occupied by the same base or amino acid, then the molecules are homologous at that position. A degree of homology between sequences is a function of the number of matching or homologous positions shared by the sequences. An "unrelated" or "non-homologous" sequence shares less than 40% identity, or alternatively less than 25% identity, with one of the sequences of the present invention.

Cells

[0189] In some embodiments of the compositions and methods of the disclosure, a cell of the disclosure is a prokaryotic cell.

[0190] In some embodiments of the compositions and methods of the disclosure, a cell of the disclosure is a eukaryotic cell. In some embodiments, the cell is a mammalian cell. In some embodiments, the cell is a bovine, murine, feline, equine, porcine, canine, simian, or human cell. In some embodiments, the cell is a non-human mammalian cell such as a non-human primate cell.

[0191] In some embodiments, a cell of the disclosure is a somatic cell. In some embodiments, a cell of the disclosure is a germline cell. In some embodiments, a germline cell of the disclosure is not a human cell.

[0192] In some embodiments of the compositions and methods of the disclosure, a cell of the disclosure is a stem cell. In some embodiments, a cell of the disclosure is an embryonic stem cell. In some embodiments, an embryonic stem cell of the disclosure is not a human cell. In some embodiments, a cell of the disclosure is a multipotent stem cell or a pluripotent stem cell. In some embodiments, a cell of the disclosure is an adult stem cell. In some embodiments, a cell of the disclosure is an induced pluripotent stem cell (iPSC). In some embodiments, a cell of the disclosure is a hematopoietic stem cell (HSC).

[0193] In some embodiments of the compositions and methods of the disclosure, a somatic cell of the disclosure is a neuronal cell. In one embodiment, a cell or cells of a patient treated with compositions disclosed herein include, without limitation, central nervous system (neurons), peripheral nervous system (neurons), peripheral motor neurons, and/or sensory neurons. In one embodiment, a neuronal cell is a glial cell.

[0194] In some embodiments of the compositions and methods of the disclosure, a somatic cell of the disclosure is a fibroblast or an epithelial cell. In some embodiments, an epithelial cell of the disclosure forms a squamous cell epithelium, a cuboidal cell epithelium, a columnar cell epithelium, a stratified cell epithelium, a pseudostratified columnar cell epithelium or a transitional cell epithelium. In some embodiments, an epithelial cell of the disclosure forms a gland including, but not limited to, a pineal gland, a thymus gland, a pituitary gland, a thyroid gland, an adrenal gland, an apocrine gland, a holocrine gland, a merocrine gland, a serous gland, a mucous gland and a sebaceous gland. In some embodiments, an epithelial cell of the disclosure contacts an outer surface of an organ including, but not limited to, a lung, a spleen, a stomach, a pancreas, a bladder, an intestine, a kidney, a gallbladder, a liver, a larynx or a pharynx. In some embodiments, an epithelial cell of the disclosure contacts an outer surface of a blood vessel or a vein.

[0195] In some embodiments of the disclosure, a somatic cell is an ocular cell. An ocular cell includes, without limitation, corneal epithelial cells, keratyocytes, retinal pigment epithelial (RPE) cells, lens epithelial cells, iris pigment epithelial cells, conjunctival fibroblasts, non-pigmented ciliary epithelial cells, trabecular meshwork cells, ocular choroid fibroblasts, conjunctival epithelial cells, In some embodiments, an ocular cell is a retinal cell or a corneal cell. In one embodiment, a retinal cell is a photoreceptor cell or a retinal pigment

epithelial cell. In another embodiment, a retinal cell is a ganglion cell, an amacrine cell, a bipolar cell, a horizontal cell, a Müller glial cell, a rod cell, or a cone cell. In some embodiments of the compositions and methods of the disclosure, a somatic cell of the disclosure is a primary cell.

[0196] In some embodiments of the compositions and methods of the disclosure, a somatic cell of the disclosure is a cultured cell.

[0197] In some embodiments of the compositions and methods of the disclosure, a somatic cell of the disclosure is in vivo, in vitro, ex vivo or in situ.

[0198] In some embodiments of the compositions and methods of the disclosure, a somatic cell of the disclosure is autologous or allogeneic.

Methods of Use

[0199] The disclosure provides a method of encoding an RNA or expressing an NOI in a cell using the snRNA systems disclosed herein. In one embodiment, the disclosure provides a method of modifying an RNA or the activity of a protein encoded by an RNA molecule comprising contacting the composition of the disclosure and the target RNA molecule under conditions suitable for binding to the RNA molecule.

[0200] The disclosure provides a method of modifying the level of expression of an RNA molecule of the disclosure or a protein encoded by the RNA molecule comprising contacting the composition of the disclosure and a cell comprising the RNA molecule under conditions suitable for binding to the RNA molecule. In some embodiments, the cell is in vivo, in vitro, ex vivo or in situ. In some embodiments, the composition of the disclosure comprises a vector comprising snRNA sequences. In some embodiments, the vector is an AAV.

[0201] The disclosure provides a method of modifying the level of expression of an RNA molecule of the disclosure or a protein encoded by the RNA molecule comprising contacting the composition of the disclosure and the RNA molecule under conditions suitable for knocking down, blocking, splicing, multi-targeting, or editing the target RNA. In some embodiments, the vector is an AAV.

[0202] The disclosure provides a method of modifying a target RNA or an activity of a protein encoded by an RNA molecule comprising contacting the composition and a cell comprising the RNA molecule under conditions suitable knocking down, blocking, splicing, multi-targeting, or editing the target RNA. In some embodiments, the cell is in vivo, in vitro,

ex vivo or in situ. In some embodiments, the composition comprises a vector comprising the snRNA sequences disclosed herein. In some embodiments, the vector is an AAV.

[0203] The disclosure provides a method of treating a disease or disorder comprising administering to a subject a therapeutically effective amount of an snRNA composition of the disclosure.

[0204] The disclosure provides a method of treating a disease in a patient in need of such treatment comprising administering to the patient a therapeutically effective amount of an snRNA composition of the disclosure, wherein the composition comprises a vector comprising snRNA sequences disclosed herein, wherein the composition modifies, reduces, destroys, knocks down or ablates a level of expression of a toxic repeat RNA (compared to the level of expression of a toxic repeat RNA treated with a non-targeting (NT) control or compared to no treatment). In another embodiment, the level of reduction is 1-fold or greater. In another embodiment, the level of reduction is 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold or 10-fold. In another embodiment, the level of reduction is 10-fold or greater. In another embodiment, the level of reduction is between 10-fold and 20-fold. In another embodiment, the level of reduction is 11-fold, 12-fold, 13-fold, 14-fold, 15-fold, 16-fold, 17-fold, 18-fold, 19-fold, or 20-fold. In another embodiment, the gene therapy compositions disclosed herein when administered to a patient lead to 20%-100% destruction of the toxic repeat RNA. In one embodiment, the % elimination of the toxic repeat RNA is any of 20-99%, 25%-99%, 50%-99%, 80%-99%, 90%-99%, 95%-99%. In one embodiment, the % elimination is 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%. In another embodiment, % elimination is complete elimination or 100% elimination of the toxic repeat RNA.

[0205] The disclosure provides a method of treating a disease or disorder in a subject comprising administering an RNA-targeting nucleic acid molecule (i.e. an esnRNA of the disclosure) or an AAV vector comprising an esnRNA of the disclosure.

[0206] In some aspects, the disease or disorder is associated with a toxic repeat RNA sequence. In some aspects, the toxic repeat RNA sequence is a CAG, CUG, GGCCCC, CCGGG, or GGCCC+CCGGGG RNA repeat.

[0207] In some aspects, the disease or disorder is myotonic dystrophy (DM1) or Huntington's disease (HD).

[0208] In some aspects, the disease or disorder is Duchenne Muscular Dystrophy. In some aspects, the RNA-targeting nucleic acid molecule or AAV vector targets an RNA sequence

encoding dystrophin (DMD). In some aspects, the RNA sequence encoding DMD comprises an intronic or exonic sequence. In some aspects, the exonic sequence comprises exon 51, or a flanking region thereof, of DMD.

[0209] In some embodiments of the methods of the disclosure, a subject of the disclosure has been diagnosed with a disease to be treated. In some embodiments, the subject of the disclosure presents at least one sign or symptom of a disorder or disease to be treated. In some embodiments, the subject of the disclosure presents at least one sign or symptom of a disease.

[0210] In some embodiments of the methods of the disclosure, a subject of the disclosure is female. In some embodiments of the methods of the disclosure, a subject of the disclosure is male. In some embodiments, a subject of the disclosure has two XX or XY chromosomes. In some embodiments, a subject of the disclosure has two XX or XY chromosomes and a third chromosome, either an X or a Y.

[0211] In some embodiments of the methods of the disclosure, a subject of the disclosure is a neonate, an infant, a child, an adult, a senior adult, or an elderly adult. In some embodiments of the methods of the disclosure, a subject of the disclosure is at least 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 31 days old. In some embodiments of the methods of the disclosure, a subject of the disclosure is at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 months old. In some embodiments of the methods of the disclosure, a subject of the disclosure is at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100 or any number of years or partial years in between of age.

[0212] In some embodiments of the methods of the disclosure, a subject of the disclosure is a mammal. In some embodiments, a subject of the disclosure is a non-human mammal.

[0213] In some embodiments of the methods of the disclosure, a subject of the disclosure is a human.

[0214] In some embodiments of the methods of the disclosure, a therapeutically effective amount comprises a single dose of a composition of the disclosure. In some embodiments, a therapeutically effective amount comprises a therapeutically effective amount comprises at least one dose of a composition of the disclosure. In some embodiments, a therapeutically effective amount comprises a therapeutically effective amount comprises one or more dose(s) of a composition of the disclosure.

[0215] In some embodiments of the methods of the disclosure, a therapeutically effective amount eliminates a sign or symptom of the disease or disorder. In some embodiments, a therapeutically effective amount reduces a severity of a sign or symptom of the disease or disorder.

[0216] In some embodiments of the methods of the disclosure, a therapeutically effective amount eliminates the disease or disorder.

[0217] In some embodiments of the methods of the disclosure, a therapeutically effective amount prevents an onset of a disease or disorder. In some embodiments, a therapeutically effective amount delays the onset of a disease or disorder. In some embodiments, a therapeutically effective amount reduces the severity of a sign or symptom of the disease or disorder. In some embodiments, a therapeutically effective amount improves a prognosis for the subject.

[0218] In some embodiments of the methods of the disclosure, a composition of the disclosure is administered to the subject via intracerebral administration. In some embodiments, the composition of the disclosure is administered to the subject by an intrastriatal route. In some embodiments, the composition of the disclosure is administered to the subject by a stereotaxic injection or an infusion. In some embodiments, the composition is administered to the brain. In some embodiments of the methods of the disclosure, a composition of the disclosure is administered to the subject locally.

In some embodiments, the compositions disclosed herein are formulated as pharmaceutical compositions. Briefly, pharmaceutical compositions for use as disclosed herein may comprise a protein(s) or a polynucleotide encoding the protein(s), optionally comprised in an AAV, which is optionally also immune orthogonal, in combination with one or more pharmaceutically or physiologically acceptable carriers, diluents or excipients. Such compositions may comprise buffers such as neutral buffered saline, phosphate buffered saline and the like; carbohydrates such as glucose, mannose, sucrose or dextrans, mannitol; proteins; polypeptides or amino acids such as glycine; antioxidants; chelating agents such as EDTA or glutathione; adjuvants (e.g., aluminum hydroxide); and preservatives. Compositions of the disclosure may be formulated for routes of administration, such as e.g., oral, enteral, topical, transdermal, intranasal, and/or inhalation; and for routes of administration via injection or infusion such as, e.g., intravenous, intramuscular, subpial, intrathecal, intraparenchymal, intrathecal, intrastriatal, subcutaneous, intradermal, intraperitoneal, intratumoral, intravenous, intraocular, and/or parenteral administration. In

certain embodiments, the compositions of the present disclosure are formulated for intracerebral or intrastriatal administration.

EXAMPLES

Example 1: esnRNA Targeting CUG Repeats in DM1 Cell Model

[0219] Materials and Methods:

[0220] CTG480 HeLa cells were seeded at 100,000 cells/ml in 12 well plate. Next day snRNAs were transfected using lipofectamine (2 µL P3000 and 2.5 µl lipofectamine per sample). 24 h our later cells were trypsinized and ½ of the cells seeded in chamber slides for FISH and the other ½ in a 24-well plate for RNA analysis.

[0221] Next day RNA was extracted for RNA analysis and cells were fixed for FISH. For FISH CUG foci was labeled with CUG fluorescent probe, and the cell nuclei was stained with DAPI.

[0222] Purpose: To determine whether engineered snRNPs comprising the engineered stem loop are capable of knocking down CUG expansions and therefore decrease the number of RNA foci in a DM1 cell model.

[0223] Rationale: The U7 snRNA can be programmed to target mRNAs by replacing its histone mRNA annealing sequence with a sequence complementary to a target of interest. U7 with 15x CAG repeats has been shown by others to reduce CUG repeat expansions, which cause DM1 (François et al NSMB 2011). We optimized this snRNA system by engineering the stem loop (SEQ ID NO: 1) to better stabilize the secondary structure of U7 snRNA in cells. We compared our engineered U7 stem loop to the U7 stem loop known in the art (François et al NSMB 2011). The constructs contain 15x CAG repeats and an optimized Sm binding domain, which further helps to stabilize the programmed U7. The CUG-targeting constructs were tested to determine whether they can deplete CUG foci by binding to and blocking CUG repeats in an appropriate cell model and compared to U7s that contained a non-targeting (NT) sequence. See Figures 1A-D and 2A-C.

[0224] Constructs and controls were transiently transfected into HeLa(CTG480) which has 480 CTG repeats inserted into its genome by CRISPR to model DM1 and express CUG foci as shown by in-situ hybridization. Cells were seeded and fixed onto chamber slides, and RNA in-situ hybridization was performed on the cells using a probe for CUG and dapi for nuclear staining. The co-localization of the CUG probe and DAPI signal was quantified using Halo.

[0225] Treatment with 15xCAG esnRNA constructs (to target/block CUG repeats) significantly decreased CUG RNA foci.

[0226] Compared to their respective non-targeting control, the non-engineered snRNA and esnRNA constructs led to a 39% and 68% reduction in average # foci/cell, respectively.

Example 2: esnRNA targeting CAG repeats

[0227] Materials and Methods:

[0228] HEK293T cells were seeded at 150,000 cells/ml in a 12 well plate. Next day snRNAs were transfected using lipofectamine (2 µL P3000 and 2.5 µl lipofectamine per sample). Cells were transfected with the CAG reporter construct (containing 80 CAG repeats) and increasing doses (from 100 to 1000 ng) of the snRNA plasmids targeting CAG repeats (referred as CUG-15) or the control non-targeting (nt).

[0229] RNA was extracted for RNA analysis 48 h post transfection using the QiaCube Connect. qRT-PCR was performed to detect the expression levels of the CAG reporter and normalized to the expression levels of the GAPDH reference gene.

[0230] Another set of cells was used for Western blot analysis with a myc tag antibody to detect the protein levels of Poly-Q CAG containing reporter. GAPDH was used as loading control.

[0231] Purpose: Mutant HTT is caused by the existence of microsatellite repeats in exon one of HTT. Here, we explored whether engineered snRNPs comprising the engineered stem loop are capable of knocking down CAG microsatellite repeat RNA in a CAG80 reporter assay.

[0232] Rationale:

[0233] The U7 snRNA can be programmed to target mRNAs by replacing its histone mRNA annealing sequence with a sequence complementary to a target of interest. The esnRNA system reprogrammed to target CAG repeats comprises an eSL of SEQ ID NO: 1 to better stabilize the secondary structure of U7 snRNA in cells. The constructs contain 15x CUG repeats to target CAG expansions. These constructs also contained an optimized Sm binding domain, which further helps to stabilize the programmed U7. The CAG-targeting constructs were tested to determine whether they can knock down CAG repeats and poly-Q containing protein compared to eSLs that contained a non-targeting sequence.

[0234] Complete knockdown of detectable PolyQ protein was achieved by the highest 3 doses of U7. An almost complete knockdown was achieved at the lowest U7 dose.

Accordingly, we show herein a dose-dependent knockdown of CAG80 reporter mRNA to baseline levels. See Figures 3A-3C.

Example 3: esnRNA modulation of USH2A minigene exon 13 splicing

[0235] Materials and Methods:

[0236] HEK293T cells were seeded at 150,000/ ml in 12 well plate. Next day cells were transfected with 50 ng of USH2A minigene with a total of 250 ng, 500 ng, 1 ug of pcDNA expressing non-targeting esnRNA or USH2A exon 13-targeting esnRNA with lipofectamine.

[0237] Cells were harvested 48 h post-transfection. RNA was extracted using Qiacube connect, reverse transcribed, and semiquantitative PCR performed with primers that anneal to USH2A exon 12 and 14.

[0238] Quantitation of U7 was performed by PCR with primers annealing to the non-targeting esnRNA.

[0239] Rationale: USH2A exon 13 mutations lead to Usher Syndrome Type 2A. Exon 13 is an in-frame exon and a therapeutic strategy includes skipping exon 13. We designed esnRNAs comprising an eSL disclosed herein that target and anneal to exon splicing enhancers on exon 13 of USH2A and block the inclusion of exon 13. Our programmed esnRNA system to target USH2A exon 13 results in efficient exon 13 skipping on minigene. PCR results suggest higher steady state levels of the esnRNA system compared to non-engineered SL. See Figures 4A-4D. See also Figure 1A.

Example 4: Splicing Correction by esnRNA-Mediated CUG-Repeat Blocking in DM1 Patient Myotubes

[0240] Materials and Methods:

[0241] DM1 patient myotubes containing 2600 CUG repeats in the 3'UTR of *DMPK* were differentiated for 13 days before introduction of esnRNA comprising eSL disclosed herein targeting 15xCUG repeats. RNA was extracted from cells 24 hours after treatment, RNA was reverse transcribed and semiquantitative PCR was performed to DM1 disease splicing biomarkers *LDB3* exon 11, *BIN1* exon 11 and *DMD* exon 78. Analysis of splicing isoforms was performed by calculating the percentage of the healthy splice isoform (*LDB3* exon 11 excluded, *BIN1* exon 11 included and *DMD* exon 78 included) over the total signal from both the disease and healthy isoforms.

[0242] Rationale:

[0243] DM1 is caused by CUG repeat expansions in the 3'UTR of the DMPK gene that sequesters MBNL protein and as a result lead to dysregulation of alternative splicing. esnRNAs comprising an eSL disclosed herein were programmed to target CUG (15xCUGs) and this resulted in a dose dependent increase in healthy splice isoforms for all three tested disease splicing biomarkers compared to the non-targeting control. See Figures 5A-5F. See also Figure 2C.

Example 5: Testing Alternative 5' Stabilizing Motifs in U7-based eSLs and ISDs.

[0244] Efficacy of CUGx15 targeting snRNAwith alternative 5' interaction stabilizing domain (ISD) in reducing RNA foci was shown and determined by synthetic snRNA transfection in CTG480 HeLa cells followed by fluorescent in-situ hybridization for CUG RNA foci. See FIG. 6A-6B. (Light blue = alternative engineered stem loops with corresponding 5' ISDs. Dark blue = selected engineered stem loop and corresponding 5' ISD. sR220004 = non-targeting snRNA.)

[0245] Expression levels of non-targeting snRNAs with alternative 5' stabilizing domains at 24 hr, 48 hr, and 72 hr time points after transfection of synthetic snRNA were evaluated. See FIG. 7A-7B. sR220004 had the highest expression at all time points. sR220088 had no detectable expression. eSL/5'ISD found in 004 was selected for future constructs. sR220004 and sR220091 had the highest retention of expression at 48hr and 72hr time points.

Example 6: U7 snRNA Efficacy and Expression by PolIII and PolII Promoters

[0246] snRNA expression was evaluated by qPCR in CTG480 HeLa cells when snRNA expression was driven by different human PolIII and PolII promoters. See FIG. 8. The U1 promoter drives the highest level of snRNAs, followed by the U7 promoter. The PolIII promoters U6 and 7SK had low expression, and the PolIII tRNA promoter had lowest expression.

[0247] CUG foci quantification was evaluated by RNA FISH in CTG480 HeLa cells. See FIG. 9A-9B. Only U1 and U7 promoters were clearly efficacious in reducing the number of CUG foci, with U1 being more efficacious than U7 (blue=CUG-targeting; grey = non-targeting).

UID	Promoter, target
P03490	tRNA (CUGx15)

P03462	U6 (CUGx15)
P03465	7SK (CUGx15)
P03557	U1 (CUGx15)
P02225	U7 (CUGx15)
P03491	tRNA (nt)
P03463	U6 (nt)
P03466	7SK (nt)
P03561	U1 (nt)
P02313	U7 (nt)

[0248] snRNA expression was determined by qPCR in HEK293T cells (see FIG. 10). Expression of U7 snRNAs under PolIII promoters increased up to 25x when SmOpt was converted to U1 Sm binding site. Expression by PolII U1 and U7 promoters decreased when Sm site was converted to U1 Sm. Expression by U1 and U7 promoters are superior to Pol III promoters.

[0249] snRNA transfection into HEK293T cells was conducted. See FIG. 11A-11B. Here znt esnRNA and z38 esnRNA expression was driven by distinct snRNA promoters. Those constructs were transfected into HEK293T cells. 48 h post-transfection RNA was extracted and cDNA was made. Primers specific for each snRNA (z) were used for qPCR to determine snRNA expression and relative promoter strength.

Example 7: esnRNA Constructs Result in DMD Exon Skipping of Exon 51 in Patient Myotubes.

[0250] Transduction of human delta exon 52 myotubes with snRNA disclosed herein was conducted. See FIG. 12A-12B. Quantification of the band intensities using amplification primers determined % exon 51 skipping.

[0251] Human delta exon 52 myotubes were transduced with AAV9 carrying snRNAs disclosed herein. Immunofluorescence was performed to desmin and dystrophin. Dystrophin can be detected after treatment with exon 51-targeting snRNAs. See FIG. 13A-13B.

Example 8: Exon 51 Skipping Skeletal Myotubes and a DMD Mouse Model

[0252] Human skeletal myotubes with exon 52 deleted were transfected with exon 51 RNA-targeting snRNAs carrying fusion antisense sequences (z73=z38/z42) and z187=z42/z38) which target exon splicing enhancers (ESEs). 24 hours after transfection of a low dose of the snRNAs exon 51 skipping levels were quantified (tape station image Fig. 15A). Human

skeletal myotubes (with DMD exon 52 deleted) were transduced with AAV9-A04526 (2x z73) and A04569 (2x z187). The myotubes were transduced for 7 days with MOIs of 2.5e4, 1e5 and 5e5. AAV9-based exon 51 skipping was quantified (Fig. 15B). Mice carrying hDMD with exon 52 deleted (del52hDMD/mdx) were injected retro-orbitally with 3e12 vector genomes of A04526 and A04569. Following 3-week survival, RNA was extracted from the tibialis anterior muscle (TA), the Gastrocnemius (Gc) and the heart. Semi-quantitative RT-PCR was performed to detect exon 51 included and excluded bands. (Fig. 15C) shows quantification of exon 51 skipping in the humanized DMD mouse model. Intramuscular delivery of a 3e11 vg/muscle dose of A04526 or an exon 51 ESE-targeting Morpholino (ViM) to the Gastrocnemius of del52hDMD/mdx mice. Fig. 15D shows the quantification of dystrophin positive fibers after 4 weeks. hDMD/mdx mice (gray bar) which expresses wildtype human dystrophin serves as a positive control for dystrophin expression. U = untreated.

Example 9: AAV9-based Splicing Reversal and CUG Repeat Knockdown in DM1 Patient-Derived Myotubes

[0253] DM1 patient fibroblasts were differentiated into myotubes by transduction with myoD Adenovirus vector (for 5 days). Myotubes were transduced with MOIs of 5e4, 2e5 and 1e6 of A04233 and A04234 (scAAV9 with dual snRNA cassettes targeting CUG repeats) and harvested 7 days post-transduction. Splicing reversal of DMD and LBD3 RNAs and knockdown of DMPK after treatment with U7 snRNA targeting CUG repeats in patient derived myotubes (containing 1700 CUG repeats). See Figs. 16A-D. Cell nuclei were stained with DAPI and CUG FISH was performed with a CUG labeled probe. Cells were processed 7 days post-transduction for quantification of average number of CUG foci per cell. See Figs. 17A-B.

Example 10: AAV9-based HTT Knockdown in HD Patient Cells and HD Mouse Model

[0254] HD patient iPSc (containing 66 CAG repeats) were differentiated into cortical neurons for 2 weeks and then transduced with 2 different MOIs of AAV-A04390 snRNA vector (2x snRNA cassette targeting CAG repeats) for an additional 2 weeks. Then cortical neurons were harvested and mutant soluble HTT quantified by Meso scale discovery immunoassay. See Figs. 18A-18C. Then, an in vivo study was designed to target CAG repeats in an R6/2 HD mouse model. An AAV-snRNA vector targeting CAG repeats (A03081: AAVrh10-snRNA (4x snRNAs with CAGx15 TS)) was administered intrastriatal

at 2e10 vector genomes and post-treatment mutant soluble HTT protein was quantified via Meso scale discovery immunoassay (MSD) on untreated and snRNA treated mice (n=10). See Figs. 19A-B.

Example 11: Higher levels of expression with engineered stem loop snRNA vectors compared to native stem loop snRNA vectors.

[0255] CHO-Lec2 cells were transduced at an MOI of 1e6 with AAV9-A04527 vector (native stem loop expressing z38/42 targeting DMD exon 51 ESEs) or AAV9-A04526 vector (engineered stem loop expressing z38/42 targeting DMD exon 51 ESEs). Expression of z38/42 is higher in cells transduced with engineered snRNA vector compared to expression of z38/42 in cells transduced with native stem loop snRNA vector. See Figs. 20A-B.

INCORPORATION BY REFERENCE

[0256] Every document cited herein, including any cross referenced or related patent or application is hereby incorporated herein by reference in its entirety unless expressly excluded or otherwise limited. The citation of any document is not an admission that it is prior art with respect to any invention disclosed or embodimented herein or that it alone, or in any combination with any other reference or references, teaches, suggests or discloses any such invention. Further, to the extent that any meaning or definition of a term in this document conflicts with any meaning or definition of the same term in a document incorporated by reference, the meaning or definition assigned to that term in this document shall govern.

OTHER EMBODIMENTS

[0257] While particular embodiments of the disclosure have been illustrated and described, various other changes and modifications can be made without departing from the spirit and scope of the disclosure. The scope of the appended claims includes all such changes and modifications that are within the scope of this disclosure.

CLAIMS

What is claimed is:

1. An RNA-targeting nucleic acid molecule comprising an engineered snRNA esnRNA, wherein the esnRNA system comprises an engineered stem loop (eSL) comprising one or more nucleic acid sequences selected from SEQ ID NO: 1-SEQ ID NO: 11, SEQ ID NO: 146 – SEQ ID NO: 148, SEQ ID NO: 163, or SEQ ID NO: 186-205.
2. The RNA-targeting nucleic acid molecule of claim 1, wherein the esnRNA comprises a targeting sequence (TS) that targets a target RNA of interest.
3. The RNA-targeting nucleic acid molecule of claim 2, wherein the target RNA is pre-mRNA or mRNA sequence.
4. The RNA-targeting nucleic acid molecule of claim 2, wherein the target RNA of interest is a microsatellite repeat RNA.
5. The RNA-targeting nucleic acid molecule of claim 4, wherein the microsatellite repeat RNA is selected from the group consisting of CUG, CAG, and GGGGCC+CCCCGG.
6. The RNA-targeting nucleic acid molecule of claim 2, wherein the target RNA is a sequence encoding DMD.
7. The RNA-targeting nucleic acid molecule of claim 6, wherein the targeting sequence is selected from SEQ ID NO: 206 or SEQ ID NO: 207.
8. The RNA-targeting nucleic acid molecule of claim 6, wherein the targeting sequence comprises one or more nucleic acid sequences set forth in SEQ ID NO: 208 – SEQ ID NO: 227.
9. The RNA-targeting nucleic acid molecule of claim 1, wherein the esnRNA comprises two targeting sequences that target two RNAs of interest.
10. The RNA-targeting nucleic acid molecule of claim 9, wherein the two TSs are a fusion sequence.
11. The RNA-targeting nucleic acid molecule of claim 1, wherein the esnRNA comprises an Sm binding domain (SmBD) selected from the group consisting of a U1, U2, U4, and U5 SmBD.

12. The RNA-targeting nucleic acid molecule of claim 11, wherein the SmBD comprises a nucleic acid sequence set forth in any one of SEQ ID NO: 31 – SEQ ID NO: 38, or SEQ ID NO: 164.
13. The RNA-targeting nucleic acid molecule of claim 1, wherein the esnRNA comprises a 5' interaction stabilizer domain (5'ISD) comprising a nucleotide sequence selected any one of SEQ ID NO: 12 -SEQ ID NO: 23.
14. The RNA targeting nucleic acid of claim 1, wherein the esnRNA comprises a nucleic acid sequence set forth in any one of SEQ ID NO: 65 – SEQ ID NO: 119 or SEQ ID NO: 179 – SEQ ID NO: 185.
15. A vector comprising one or more esnRNA of claim 1.
16. The vector of claim 15, wherein the viral vector is an AAV vector.
17. The AAV vector of claim 16, wherein the snRNA is operably linked to a promoter.
18. The AAV vector of claim 16, wherein the snRNA is operably linked to a U7 promoter or a U1 promoter.
19. The AAV vector of claim 6, wherein the snRNA is operably linked to a downstream terminator (DT).
20. The AAV vector of claim 16, wherein the snRNA is operably linked to a U7 downstream terminator or a U1 downstream terminator.
21. The AAV vector of claim 16, wherein the vector comprises at least one, at least two, at least three, at least four, or at least five esnRNA.
22. The AAV vector of claim 21, wherein the least one, at least two, at least three, at least four, or at least five esnRNA each target the same target RNA sequences.
23. The AAV vector of claim 21, wherein the least one, at least two, at least three, at least four, or at least five esnRNA target two or more target RNA sequences
24. The AAV vector of claim 21, wherein each esnRNA is separated by a buffer sequence.
25. The AAV vector of claim 24, wherein the buffer sequence comprises a nucleic acid sequence set forth in any one SEQ ID NO: 24-SEQ ID NO: 30.
26. The AAV vector of claim 20, wherein the vector comprises a nucleic acid sequence set forth in any one of SEQ ID NO: 123 – SEQ ID NO: 143, SEQ ID NO: 168 – SEQ ID NO: 178, or SEQ ID NO: 231 – SEQ ID NO: 233.
27. A method of targeting one or more target RNAs of interest and blocking, knocking down, editing, exon-skipping or splicing the one or more target RNAs,

comprising contacting the esnRNA of claim 1 with a cell comprising the one or more target RNAs.

28. A DMD exon 51 RNA-targeting nucleic acid molecule comprising a spacer sequence set forth in any one of SEQ ID NO: 206 – SEQ ID NO: 230.
29. A method of treating a disease or disorder in a subject comprising administering an RNA-targeting nucleic acid molecule of claim 1 or an AAV vector of claim 15.
30. The method of claim 29, wherein the disease or disorder is associated with a toxic repeat RNA sequence.
31. The method of claim 29, wherein the toxic repeat RNA sequence is a CAG, CUG, GGCCCC, CCGGG, or GGCCC+CCGGGG RNA repeat.
32. The method of claim 29, wherein the disease or disorder is myotonic dystrophy (DM1) or Huntington's disease (HD).
33. The method of claim 29, wherein the disease or disorder is Duchenne Muscular Dystrophy.
34. The method of claim 33, wherein the RNA-targeting nucleic acid molecule or AAV vector targets an RNA sequence encoding dystrophin (DMD).
35. The method of claim 34, wherein the RNA sequence encoding DMD comprises an intronic or exonic sequence.
36. The method of claim 35, wherein the exonic sequence comprises exon 51, or a flanking region thereof, of DMD.
37. The method of claim 29, wherein the administration is administration is intravenous, intramuscular, subpial, intrathecal, intraparenchymal, intrathecal, intrastriatal, subcutaneous, intradermal, intraperitoneal, intratumoral, intravenous, intraocular, and/or parenteral administration.

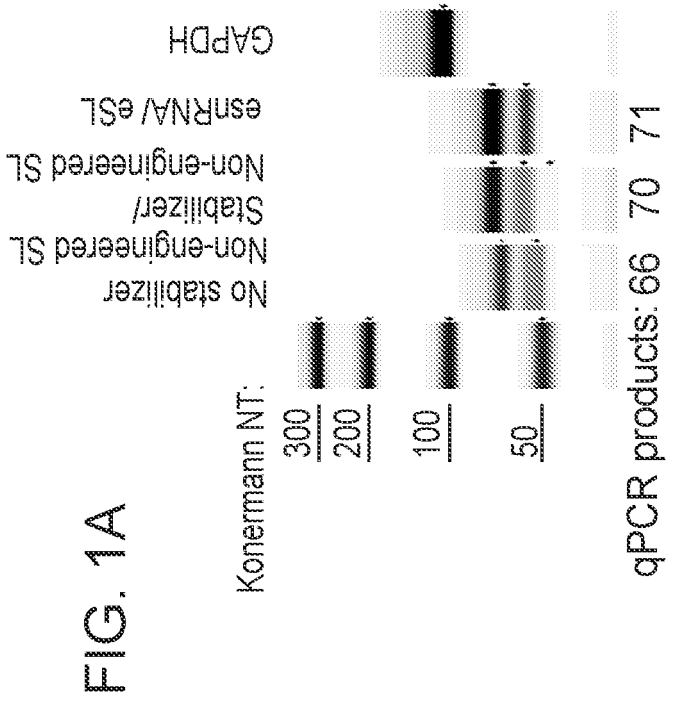


FIG. 1A

FIG. 1B

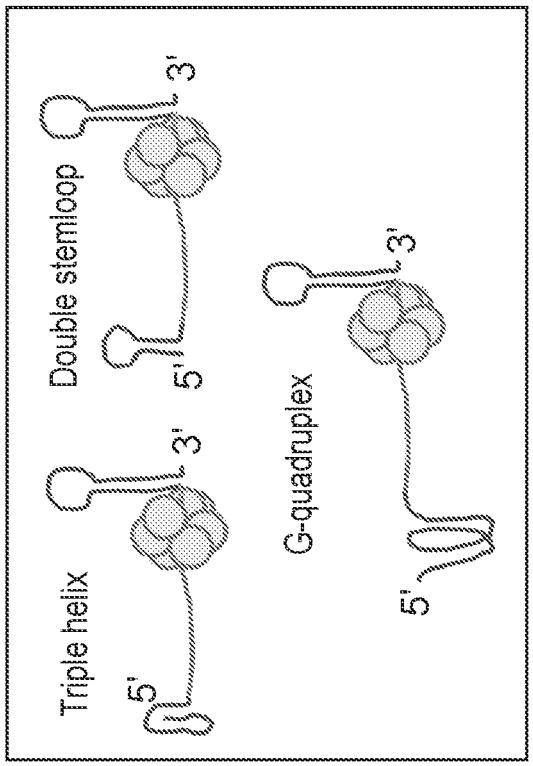


FIG. 1C

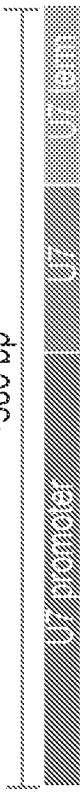


FIG. 1D

FIG. 2A

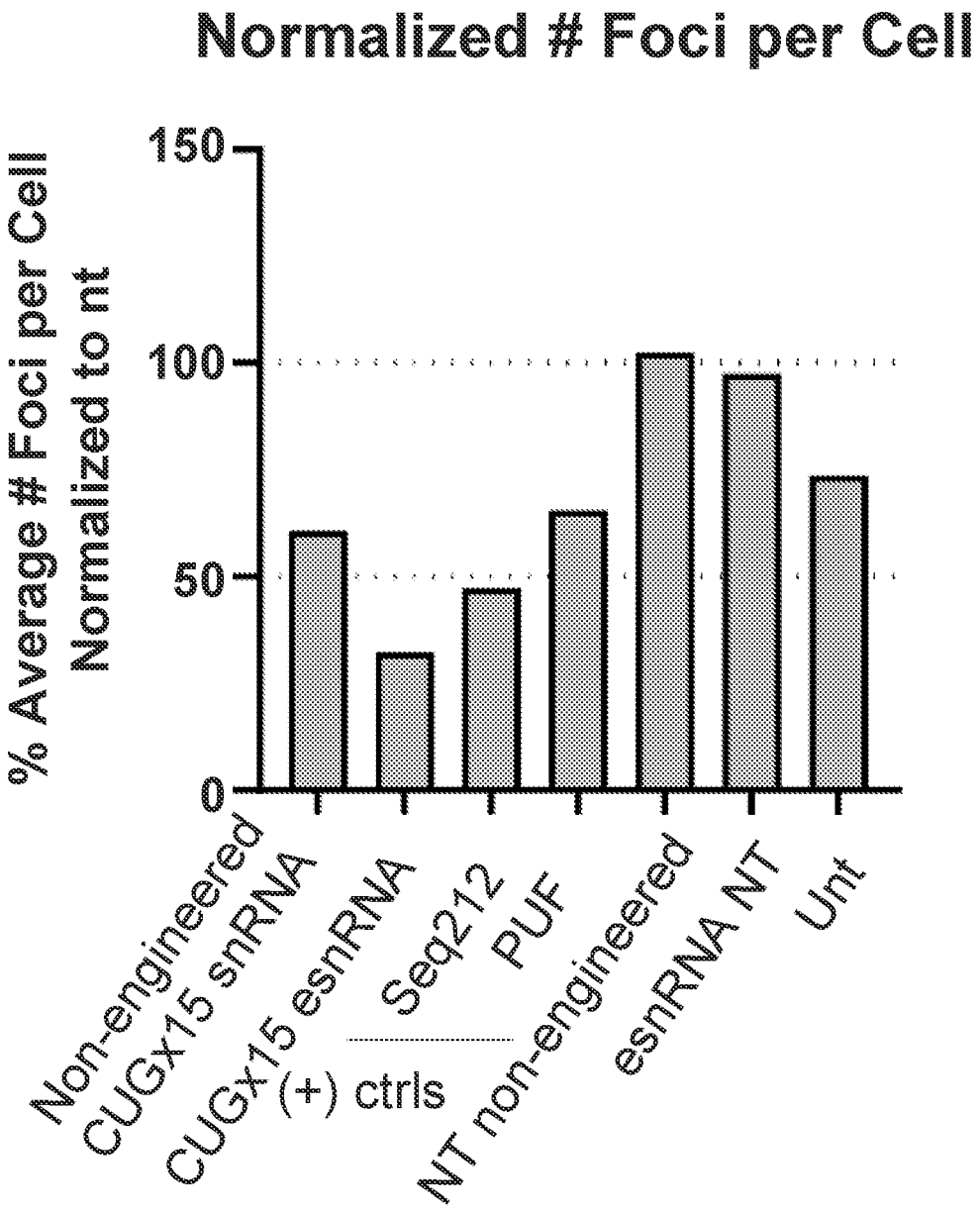

Normalized # Foci per Cell
% Average # Foci per Cell
Normalized to nt
150
100
50
0
Non-engineered CUGx15 snRNA
CUGx15 esnRNA
Seq212 PUF
NT non-engineered
esnRNA NT
Unt
(+) ctrls

FIG. 2B

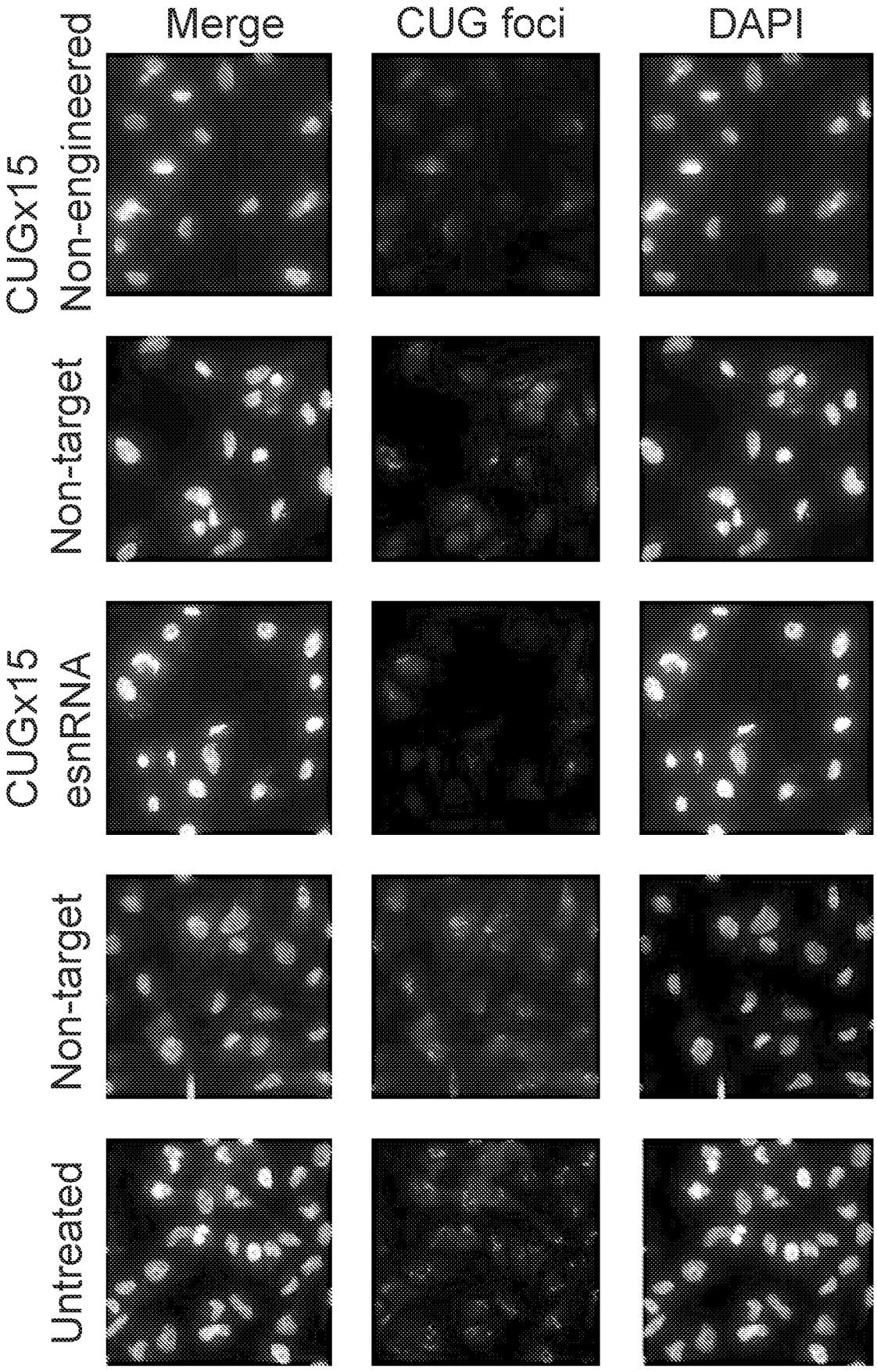

Merge
CUG foci
DAPI
CUGx15 Non-engineered
Non-target
CUGx15 esnRNA
Non-target
Untreated

FIG. 2C

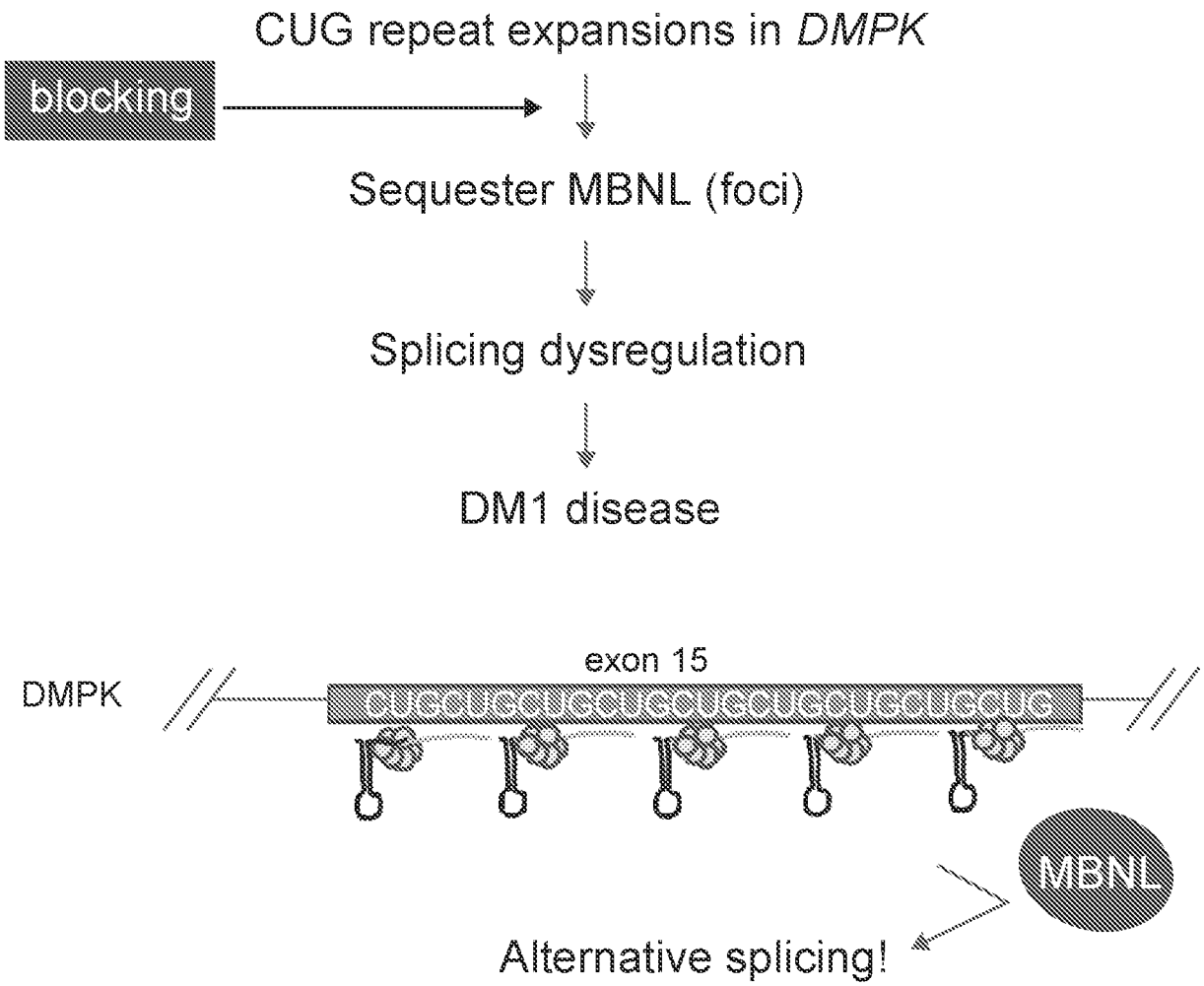

CUG repeat expansions in *DMPK*
blocking
Sequester MBNL (foci)
Splicing dysregulation
DM1 disease
DMPK
exon 15
CUGCUGCUGCUGCUGCUGCUGCUGCUG
MBNL
Alternative splicing!

FIG. 3A

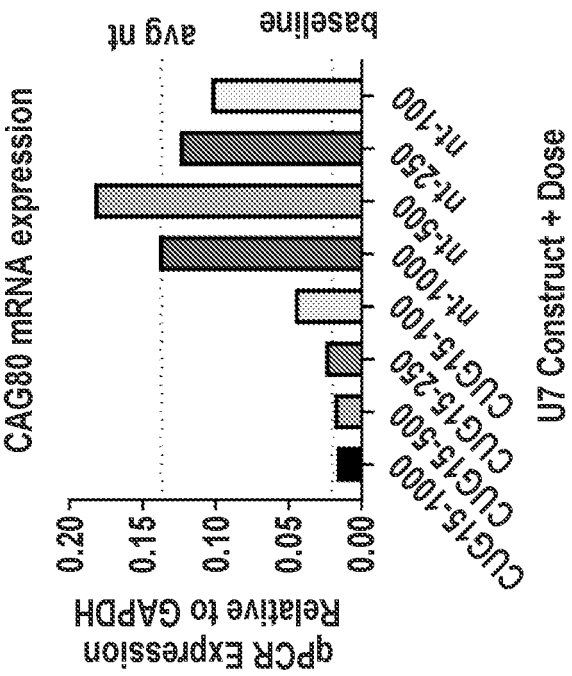


FIG. 3B

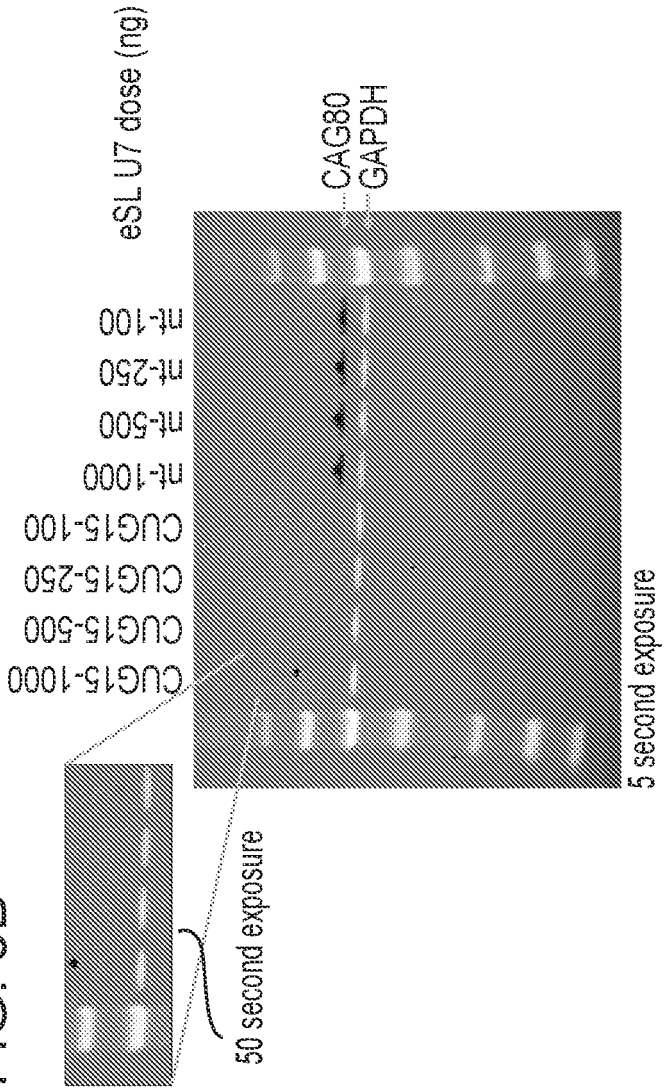
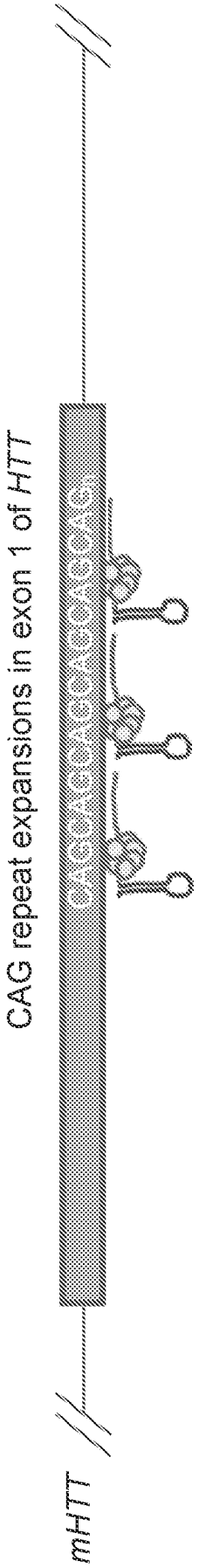
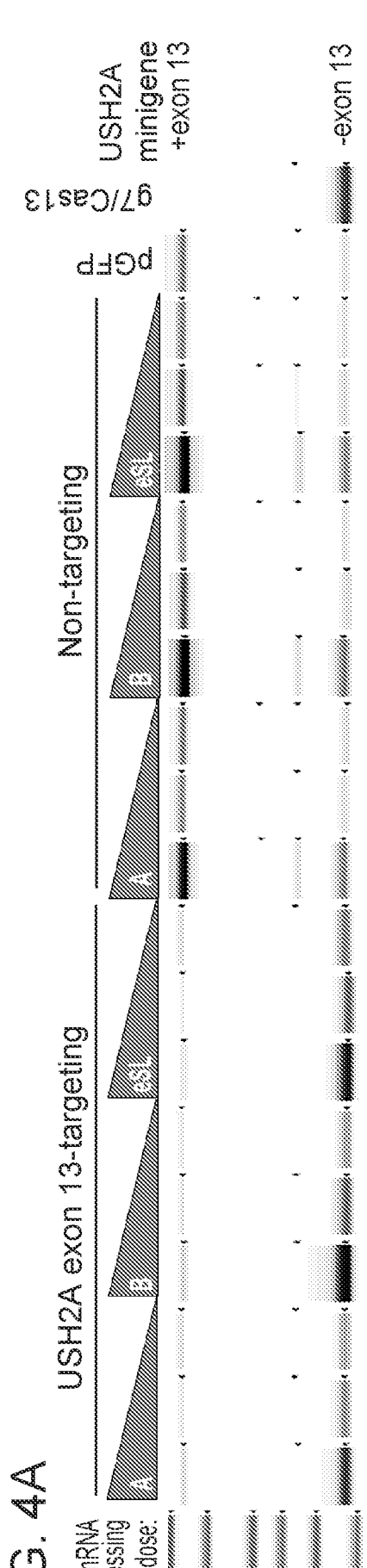
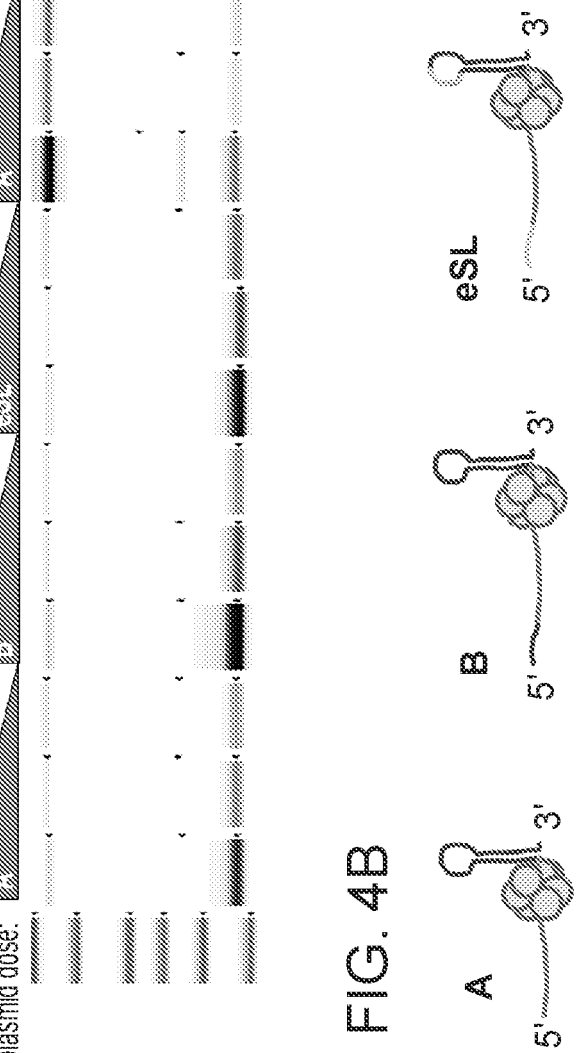


FIG. 3C




FIG. 4A
snRNA expressing plasmid dose:
USH2A exon 13-targeting
Non-targeting
pGFP
g7/Cas13
USH2A minigene +exon 13
-exon 13
A
B
eSL


FIG. 4B
A
B
eSL
5'
3'

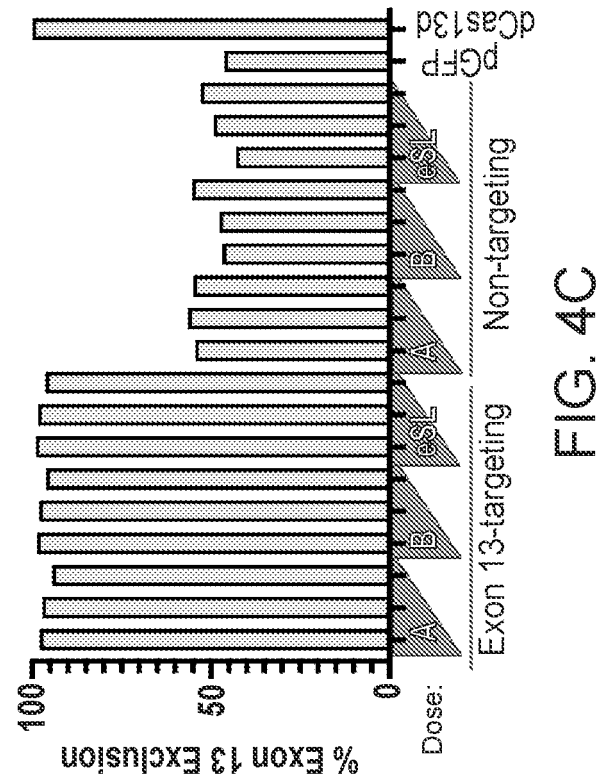
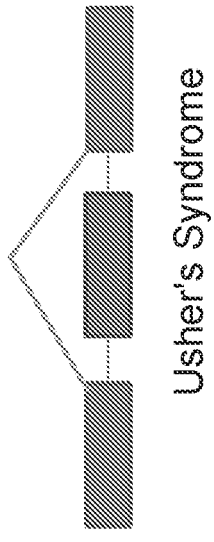

% Exon 13 Exclusion
100
50
0
Dose:
A
B
eSL
Exon 13-targeting
Non-targeting
pGFP
dCas13d

FIG. 4C


FIG. 4D
Splicing modulation
Usher's Syndrome

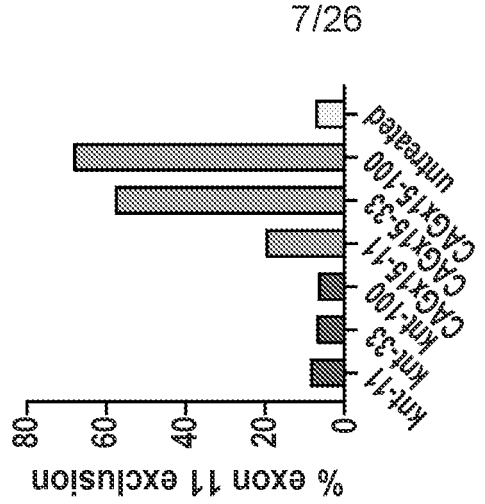


FIG. 5A

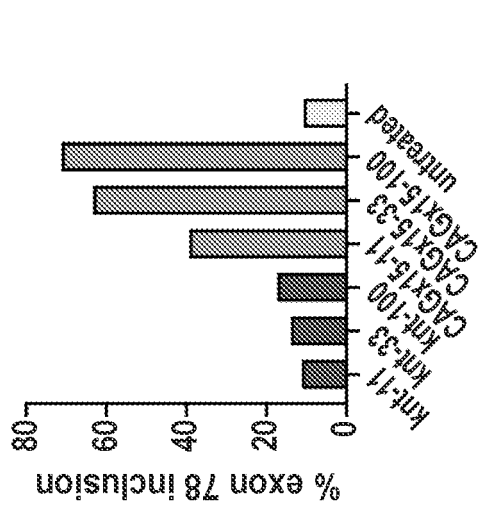


FIG. 5B

FIG. 5C

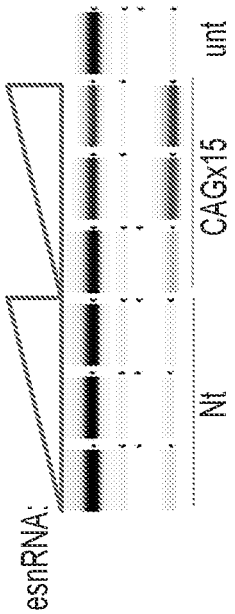
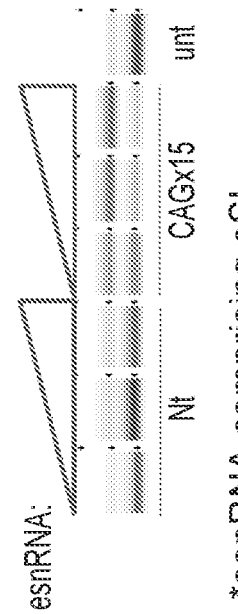


FIG. 5D



*esnRNA comprising eSL

FIG. 5E

FIG. 5F

FIG. 6A

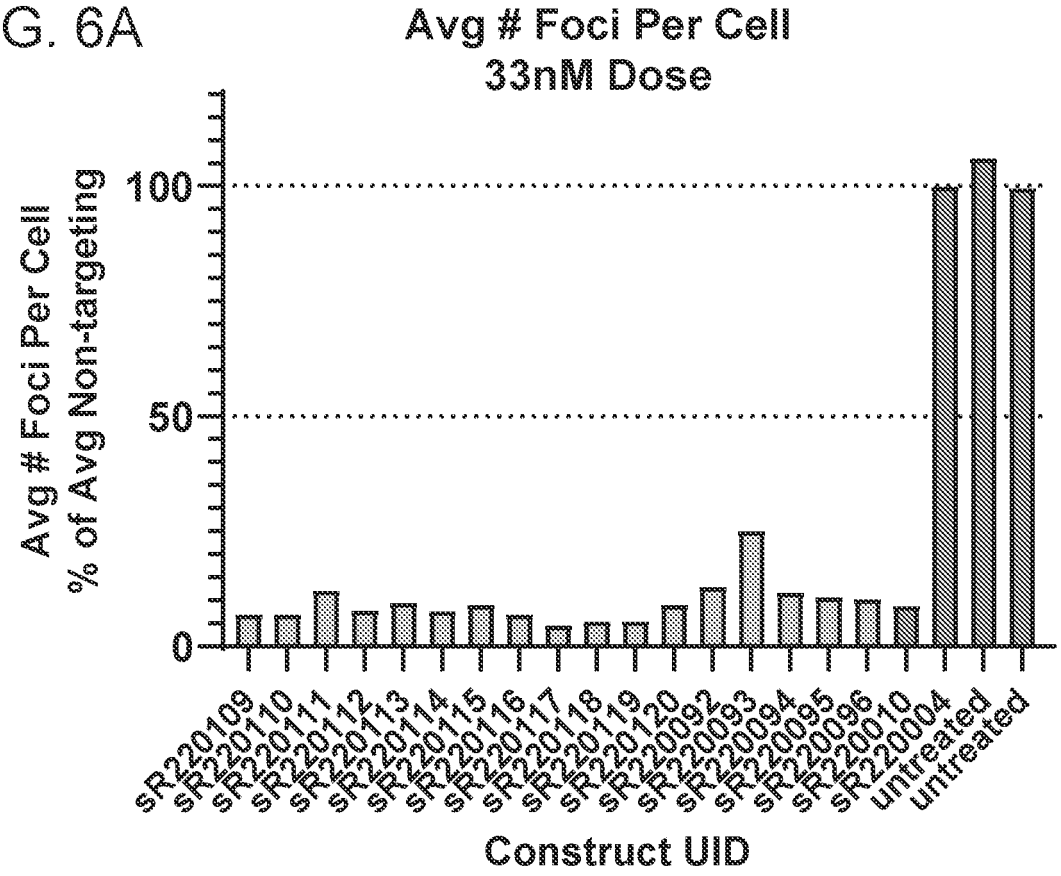

Avg # Foci Per Cell
33nM Dose
Avg # Foci Per Cell
% of Avg Non-targeting
100
50
0
SR220109
SR220110
SR220111
SR220112
SR220113
SR220114
SR220115
SR220116
SR220117
SR220118
SR220119
SR220120
SR220092
SR220093
SR220094
SR220095
SR220096
SR220010
SR220004
untreated
untreated
Construct UID

FIG. 6B

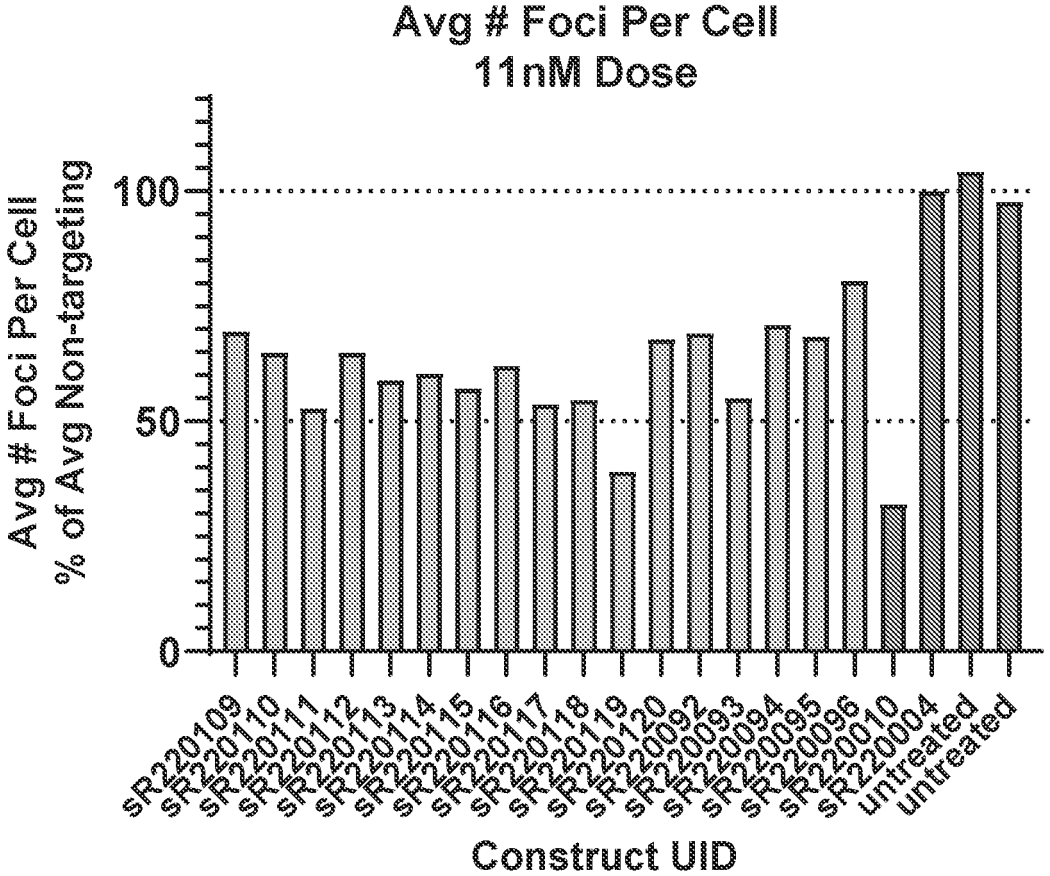

Avg # Foci Per Cell
11nM Dose
Avg # Foci Per Cell
% of Avg Non-targeting
100
50
0
SR220109
SR220110
SR220111
SR220112
SR220113
SR220114
SR220115
SR220116
SR220117
SR220118
SR220119
SR220120
SR220092
SR220093
SR220094
SR220095
SR220096
SR220010
SR220004
untreated
untreated
Construct UID

FIG. 7A

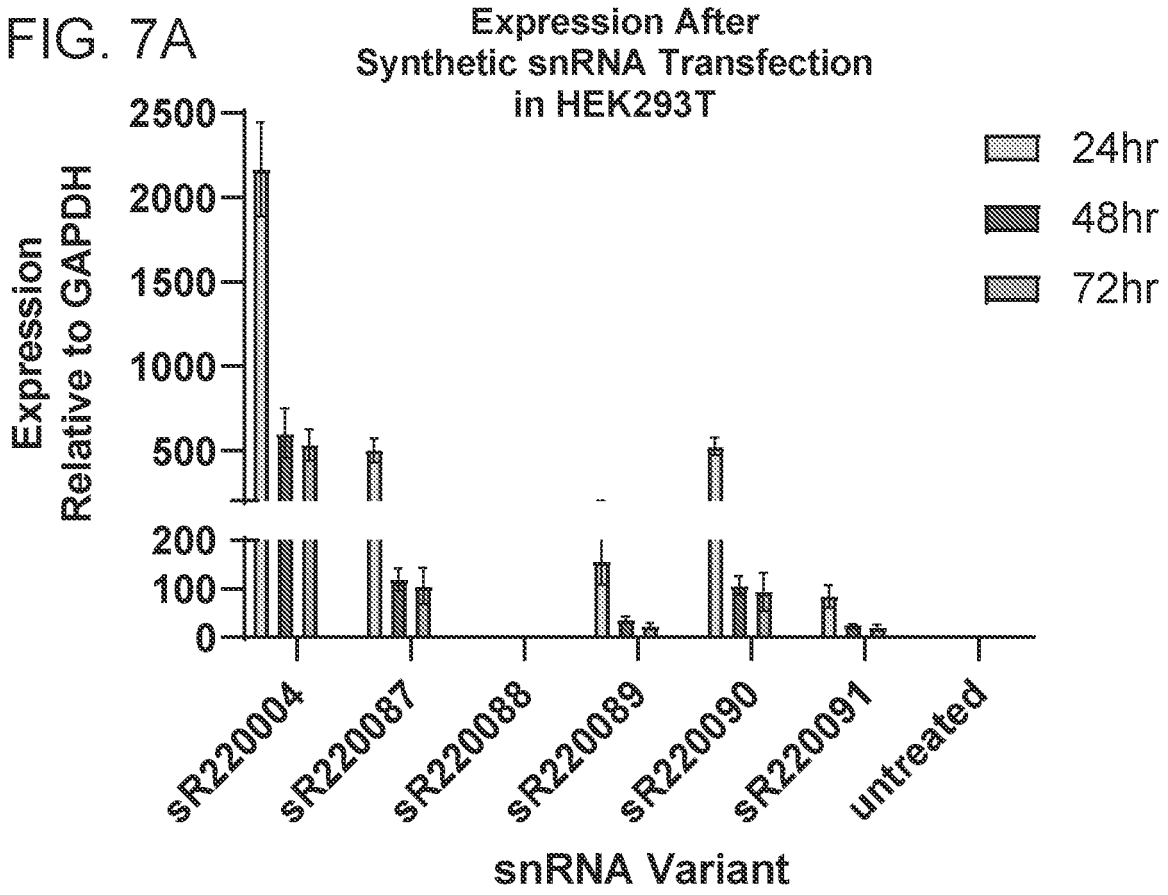

Expression After
Synthetic snRNA Transfection
in HEK293T
Expression
Relative to GAPDH
2500
2000
1500
1000
500
200
100
0
24hr
48hr
72hr
sR220004
sR220087
sR220088
sR220089
sR220090
sR220091
untreated
snRNA Variant

FIG. 7B

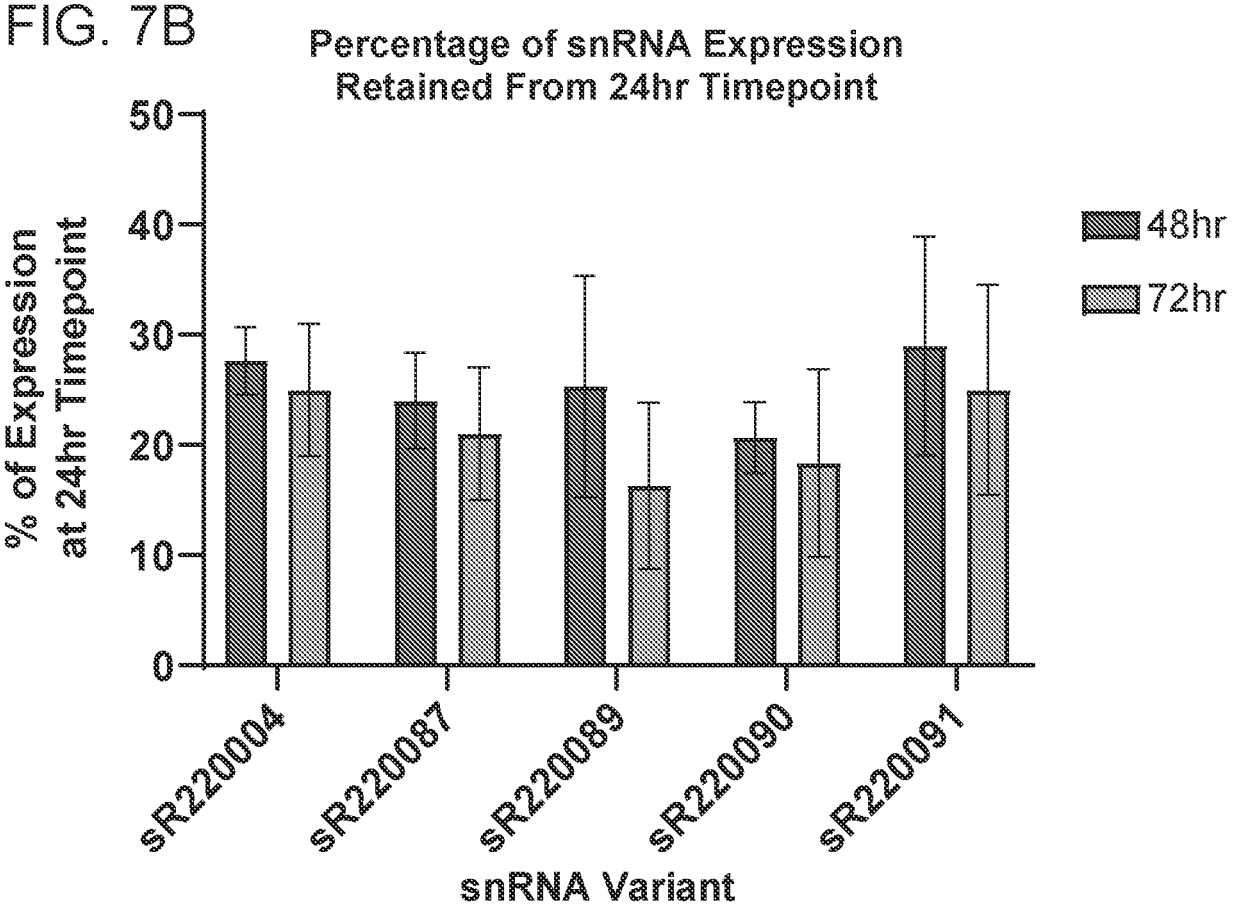

Percentage of snRNA Expression
Retained From 24hr Timepoint
% of Expression
at 24hr Timepoint
50
40
30
20
10
0
48hr
72hr
sR220004
sR220087
sR220089
sR220090
sR220091
snRNA Variant

FIG. 8

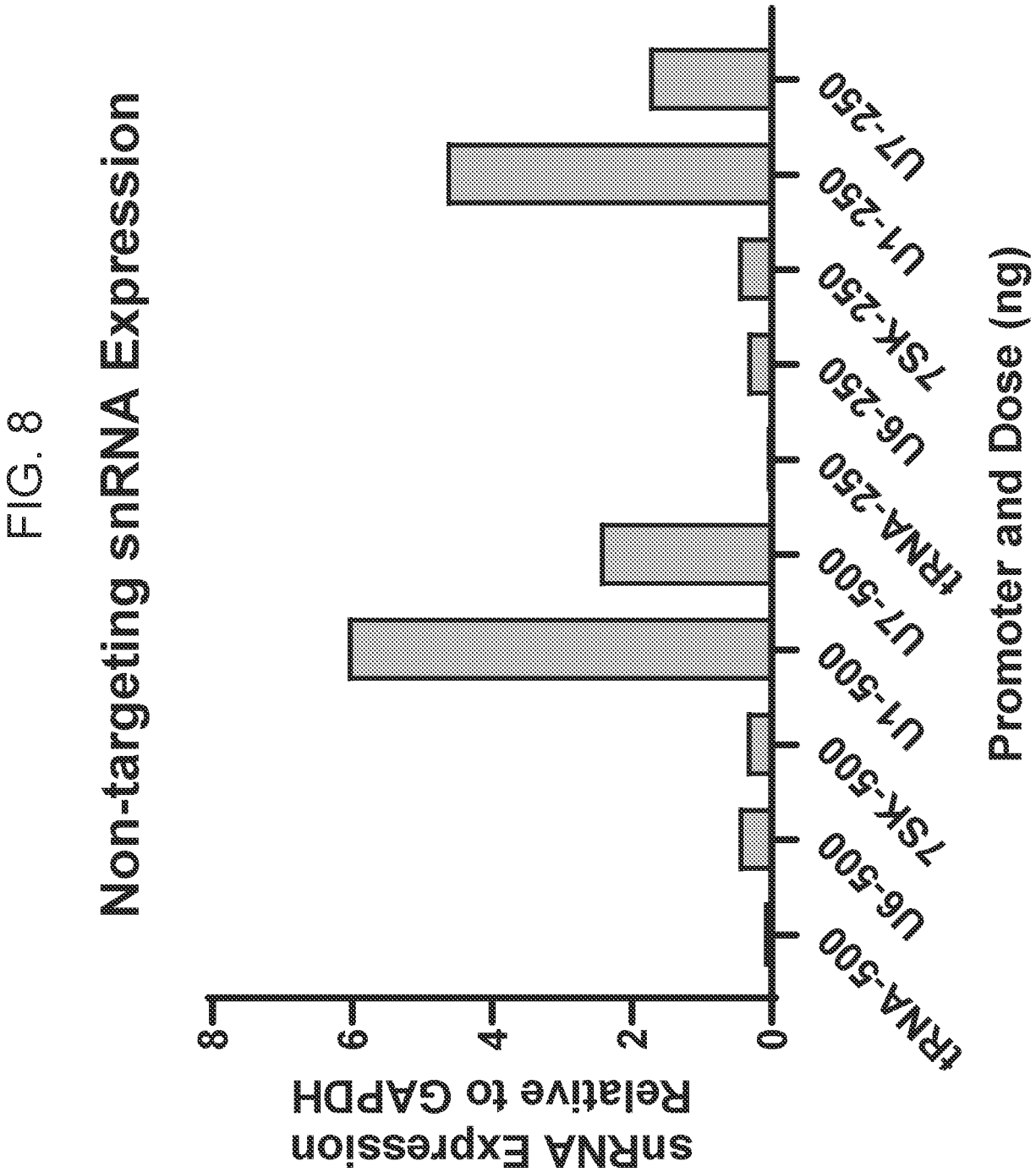

Non-targeting snRNA Expression
snRNA Expression
Relative to GAPDH
0
2
4
6
8
tRNA-500
U6-500
7SK-500
U1-500
U7-500
tRNA-250
U6-250
7SK-250
U1-250
U7-250
Promoter and Dose (ng)

FIG. 9A

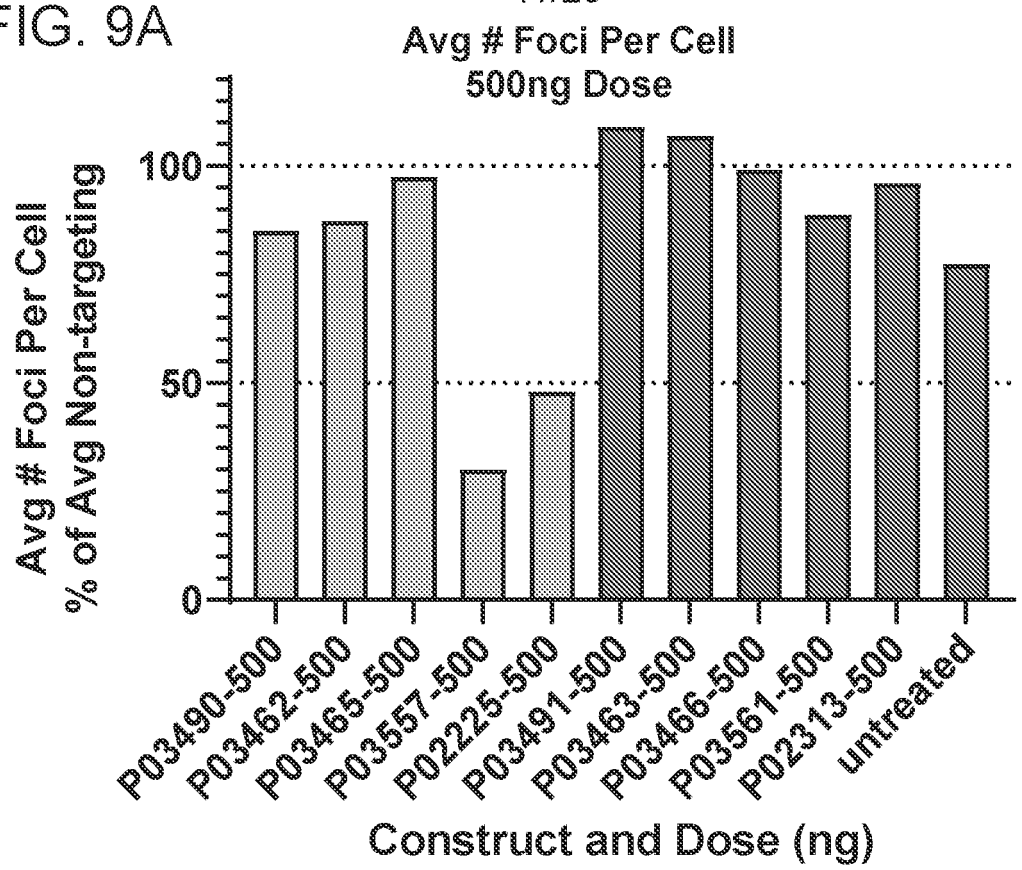

Avg # Foci Per Cell
500ng Dose
Avg # Foci Per Cell
% of Avg Non-targeting
100
50
0
P03490-500
P03462-500
P03465-500
P03557-500
P02225-500
P03491-500
P03463-500
P03466-500
P03561-500
P02313-500
untreated
Construct and Dose (ng)

FIG. 9B

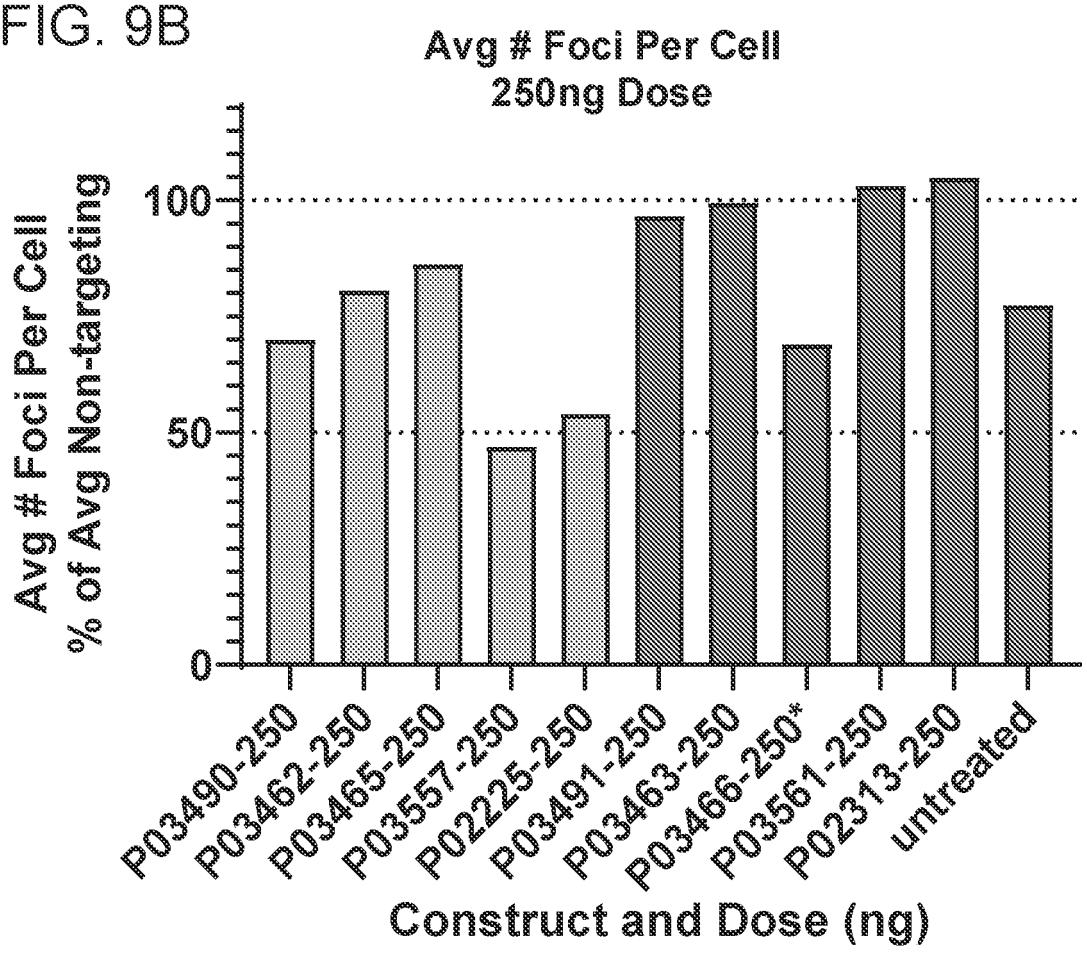

Avg # Foci Per Cell
250ng Dose
Avg # Foci Per Cell
% of Avg Non-targeting
100
50
0
P03490-250
P03462-250
P03465-250
P03557-250
P02225-250
P03491-250
P03463-250
P03466-250*
P03561-250
P02313-250
untreated
Construct and Dose (ng)

FIG. 10

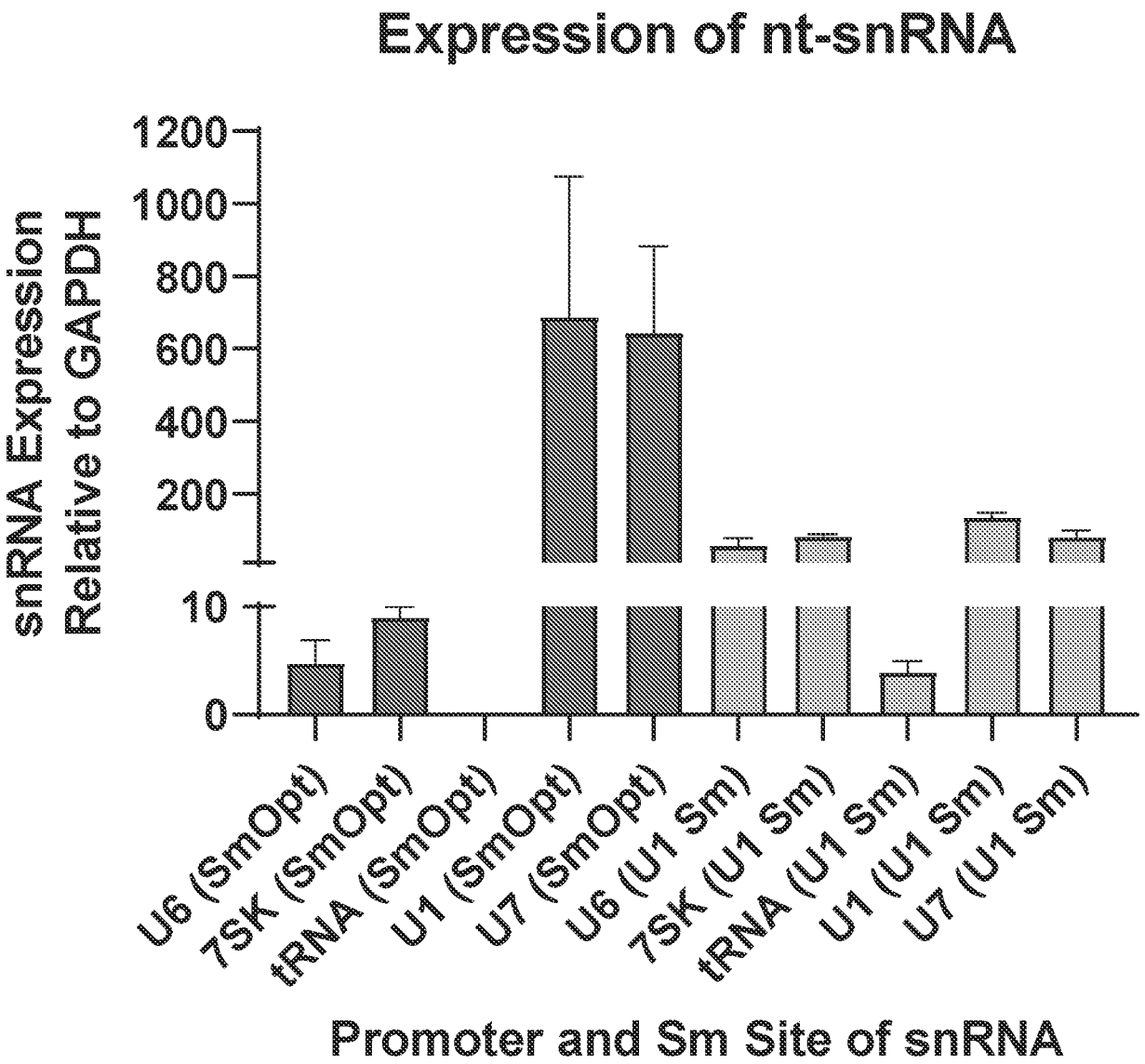

Expression of nt-snRNA
snRNA Expression
Relative to GAPDH
1200
1000
800
600
400
200
10
0
U6 (SmOpt)
7SK (SmOpt)
tRNA (SmOpt)
U1 (SmOpt)
U7 (SmOpt)
U6 (U1 Sm)
7SK (U1 Sm)
tRNA (U1 Sm)
U1 (U1 Sm)
U7 (U1 Sm)
Promoter and Sm Site of snRNA

FIG. 11B

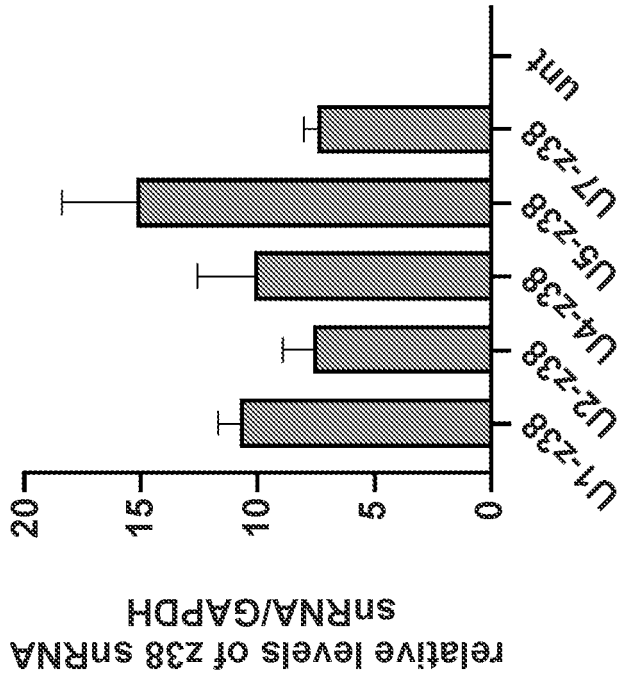


FIG. 11A

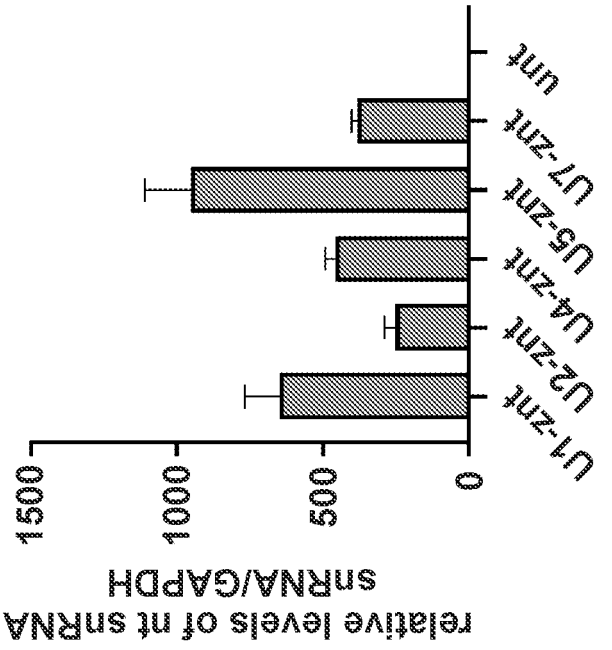
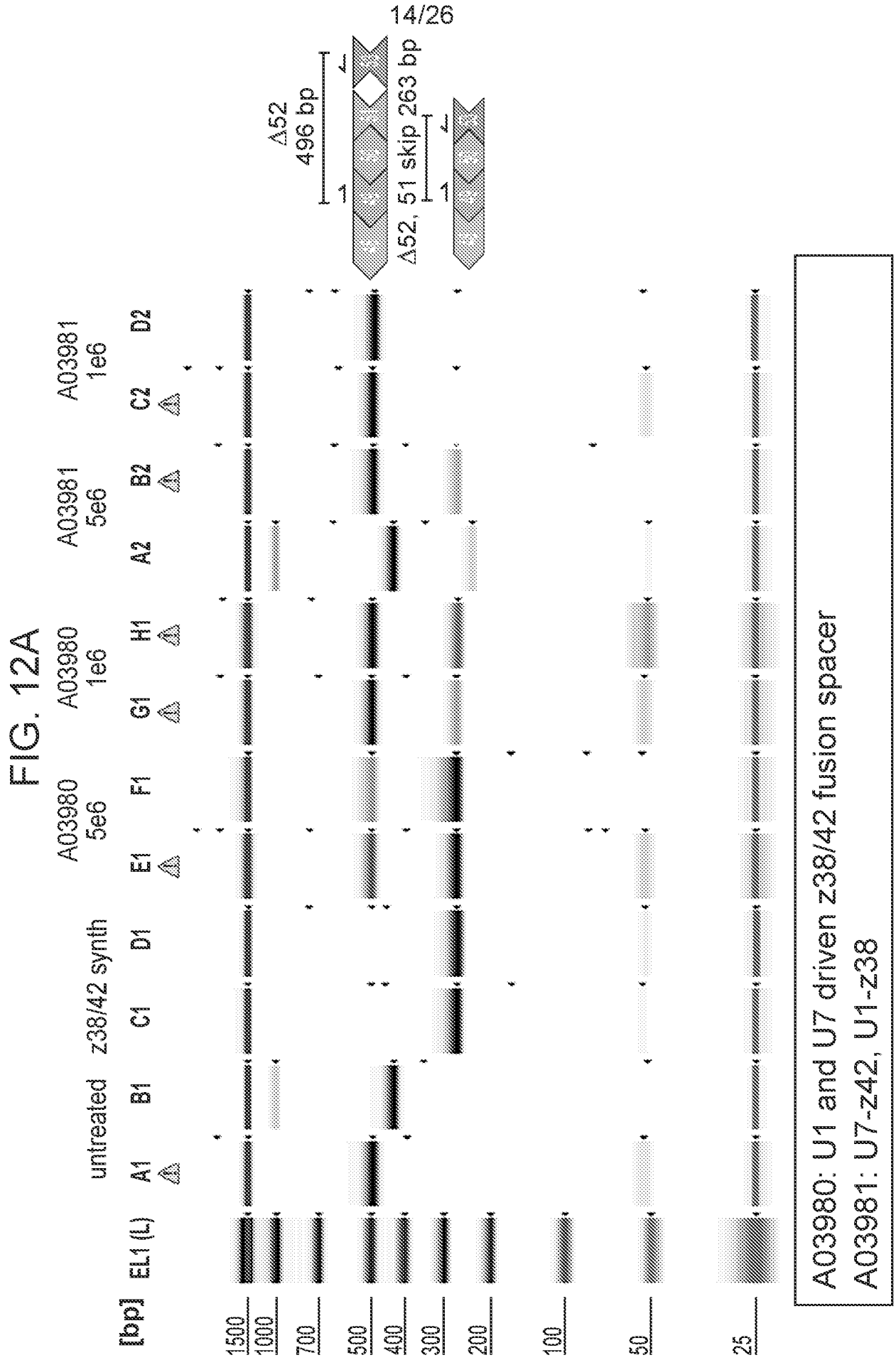


FIG. 12A


[bp]
EL1 (L)
untreated
A1
B1
z38/42 synth
C1
D1
A03980 5e6
E1
F1
A03980 1e6
G1
H1
A03981 5e6
A2
B2
A03981 1e6
C2
D2
1500
1000
700
500
400
300
200
100
50
25
Δ52 496 bp
Δ52, 51 skip 263 bp
A03980: U1 and U7 driven z38/42 fusion spacer
A03981: U7-z42, U1-z38

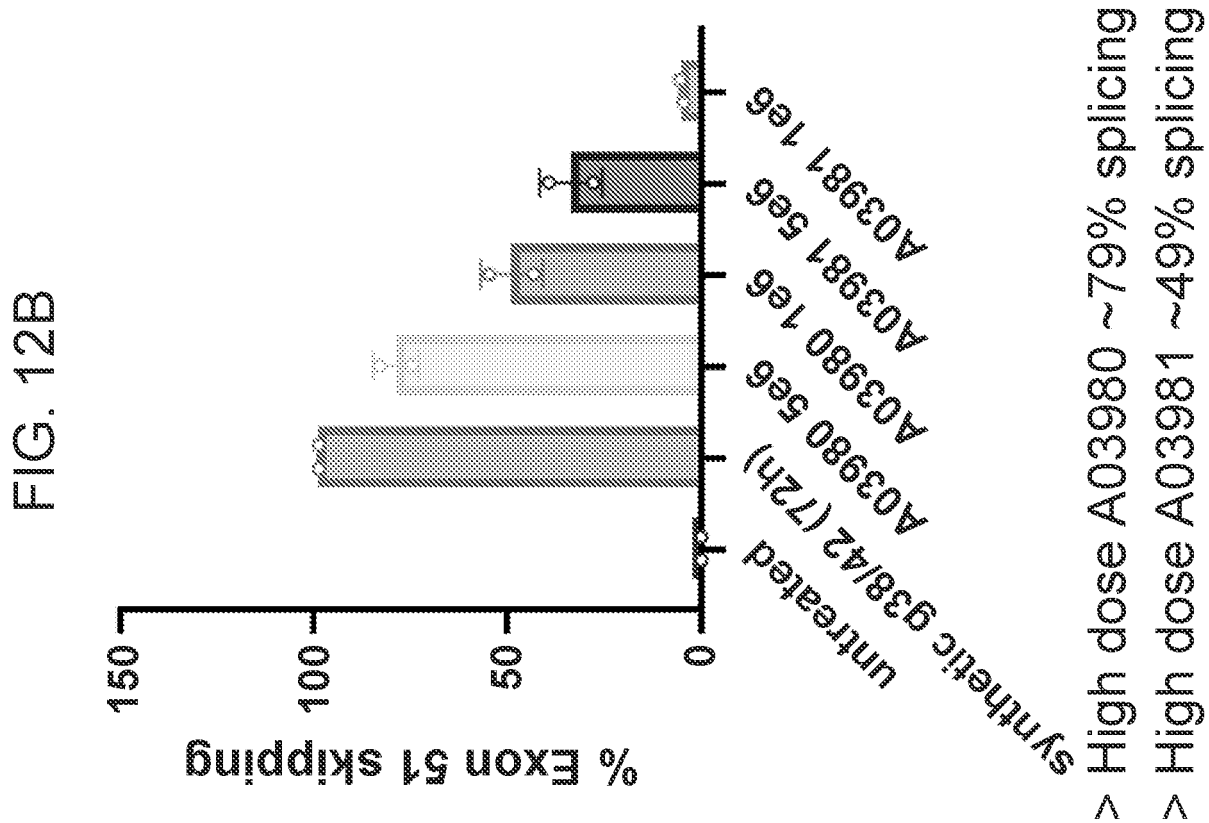

% Exon 51 skipping
150
100
50
0
untreated
synthetic 938/42 (72h)
A03980 5e6
A03980 1e6
A03981 5e6
A03981 1e6
> High dose A03980 ~79% splicing
> High dose A03981 ~49% splicing

FIG. 12B

FIG. 13A

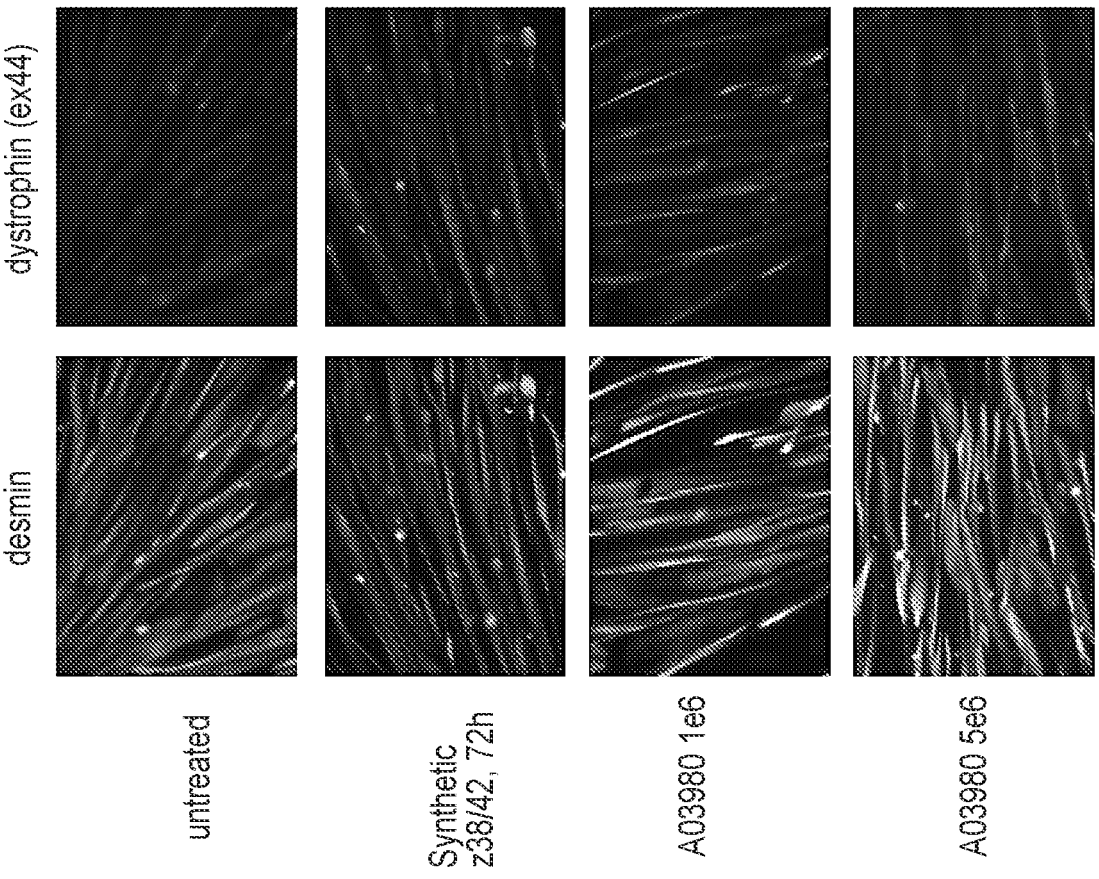


FIG. 13B

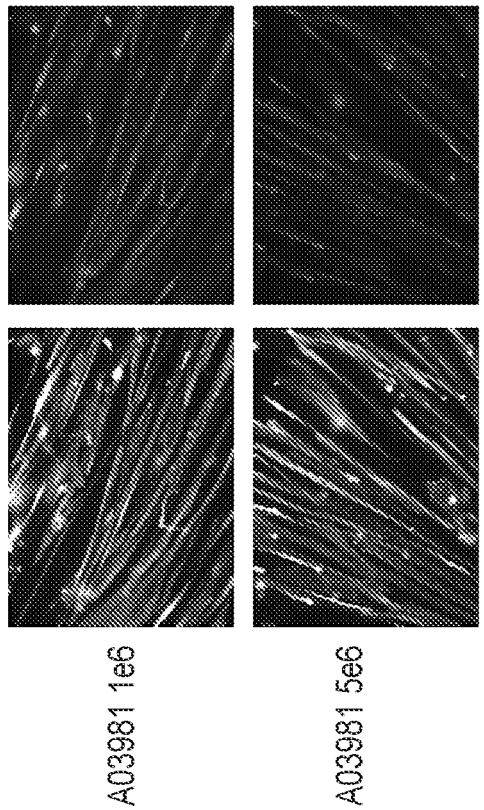


FIG. 14A

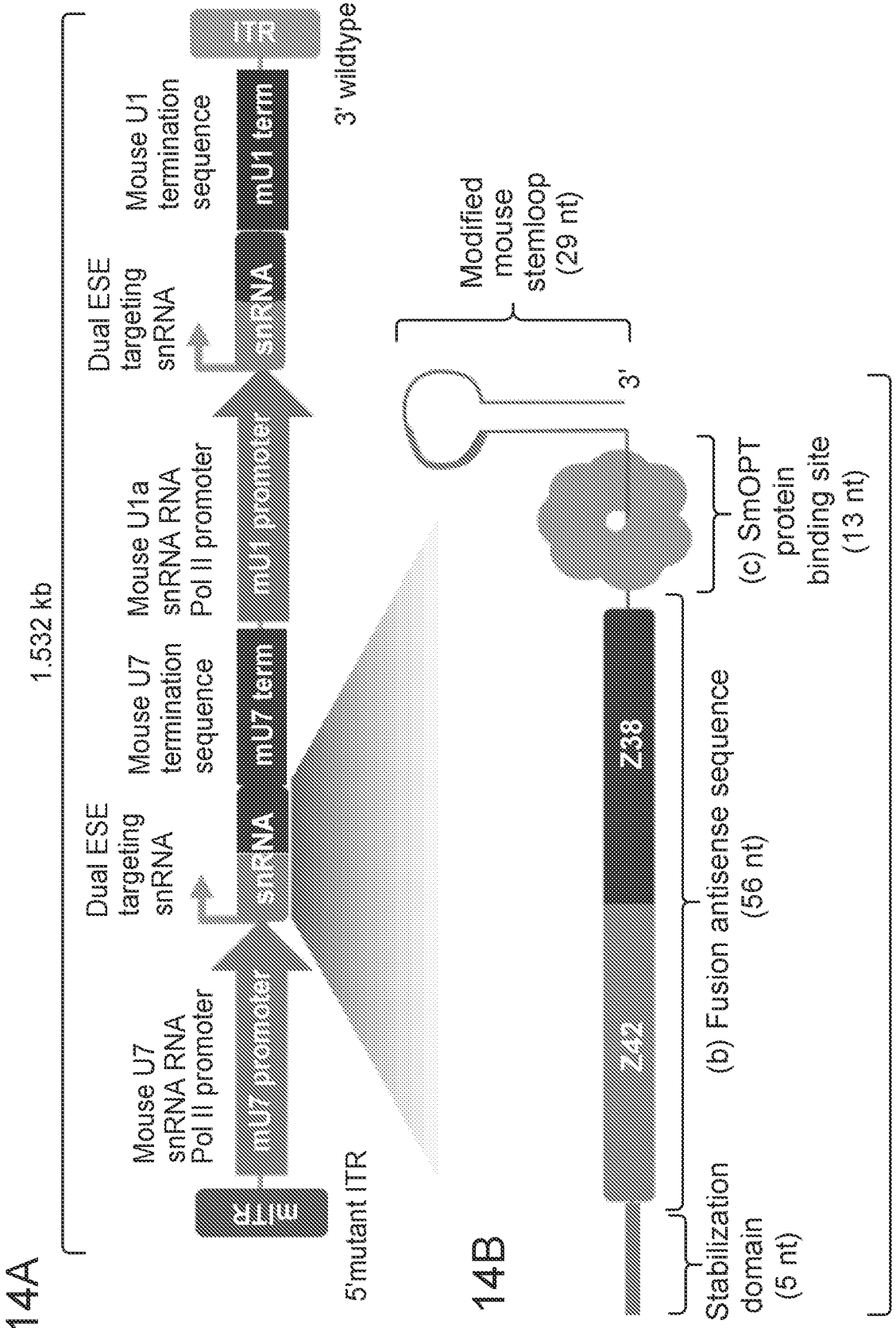


FIG. 14B

FIG. 14C

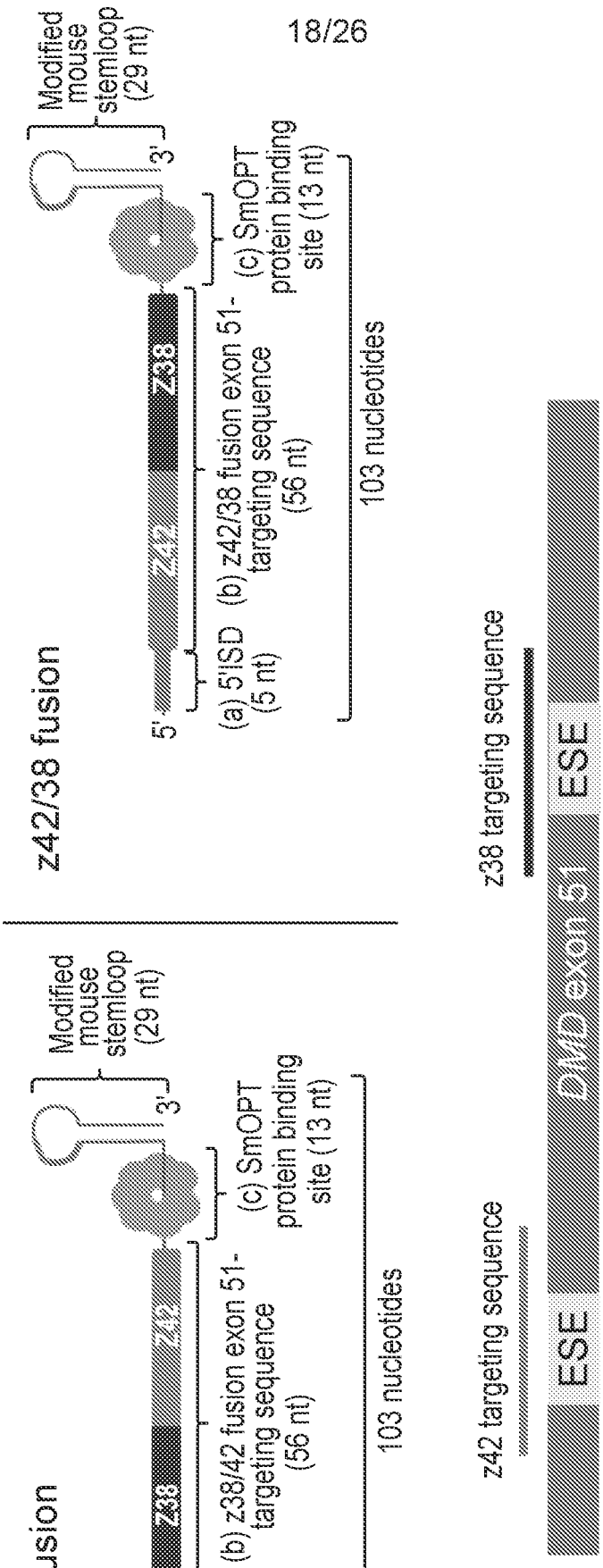

z38/42 fusion
5'
(a) 5'ISD (5 nt)
Z38
Z42
(b) z38/42 fusion exon 51-targeting sequence (56 nt)
3'
Modified mouse stemloop (29 nt)
(c) SmOPT protein binding site (13 nt)
103 nucleotides
z42/38 fusion
5'
(a) 5'ISD (5 nt)
Z42
Z38
(b) z42/38 fusion exon 51-targeting sequence (56 nt)
3'
Modified mouse stemloop (29 nt)
(c) SmOPT protein binding site (13 nt)
103 nucleotides
z42 targeting sequence
z38 targeting sequence
ESE
DMD exon 51
ESE

FIG. 15B

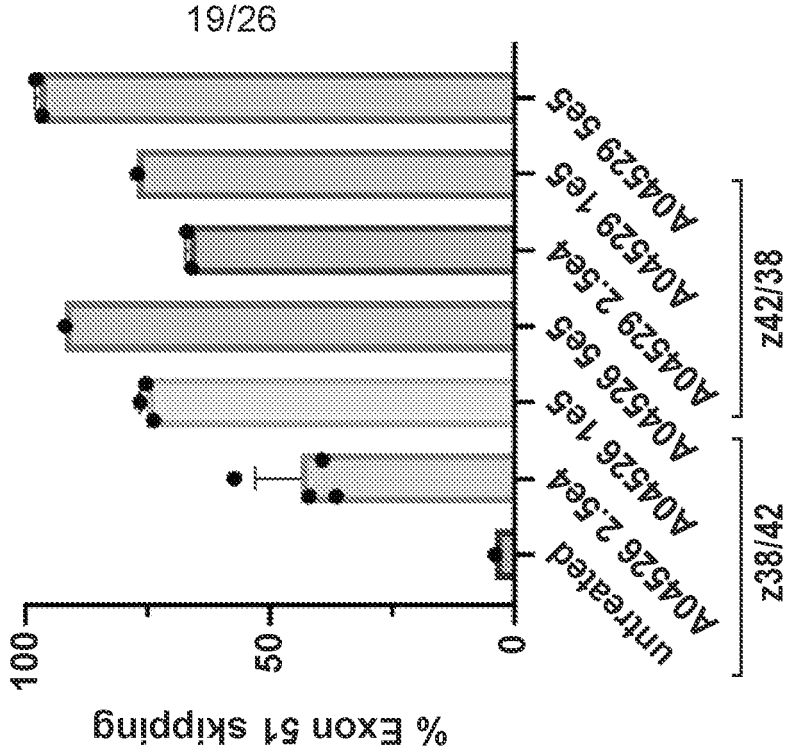


FIG. 15A

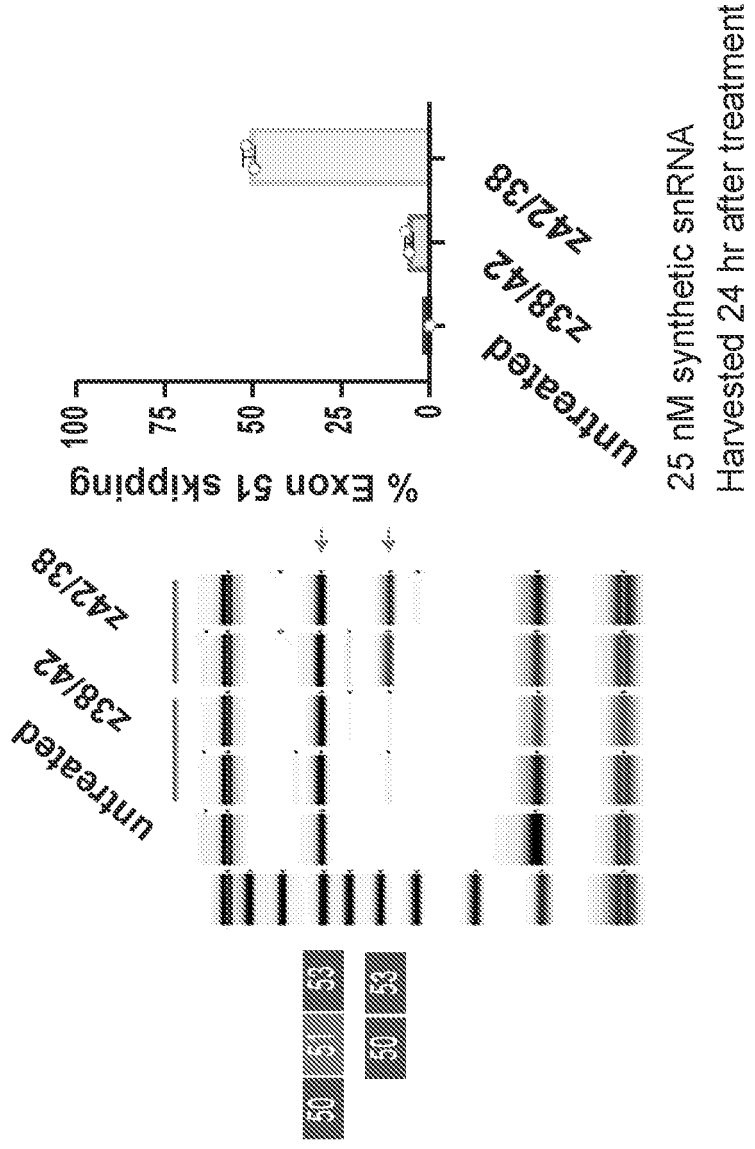


FIG. 15C

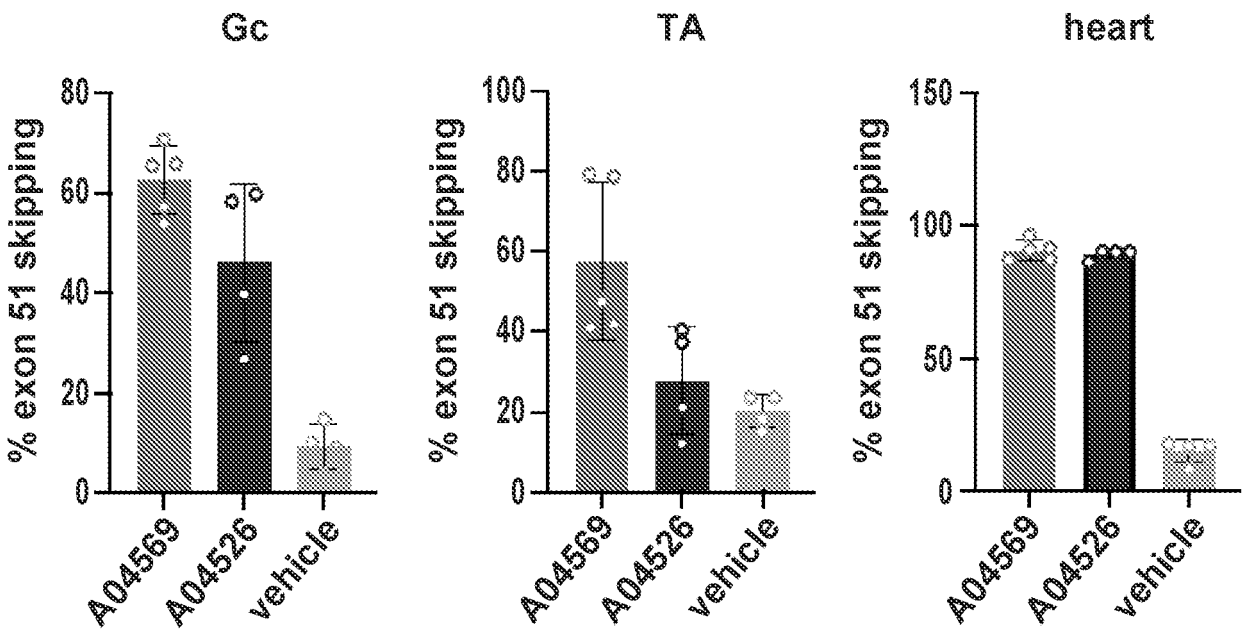
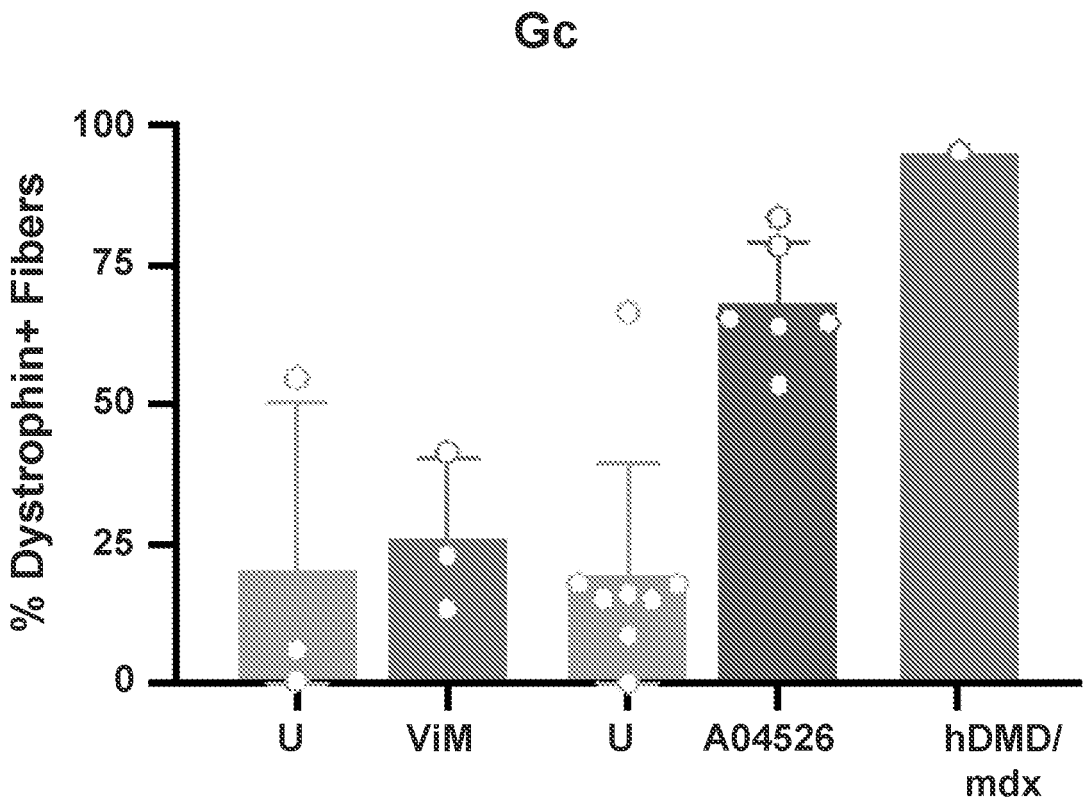


FIG. 15D



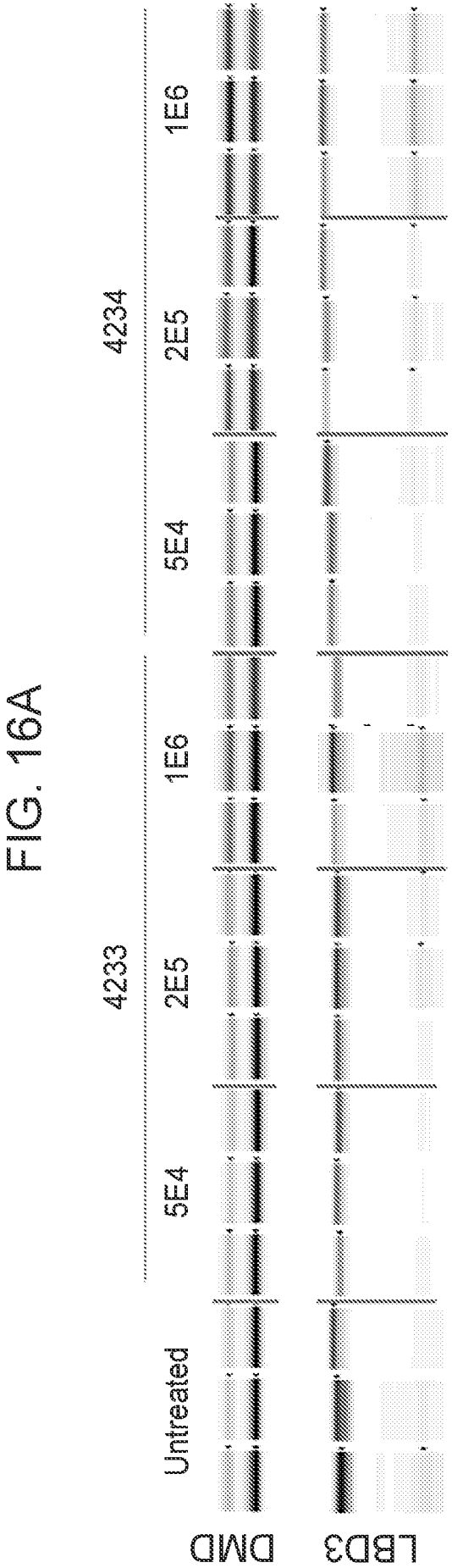


FIG. 16A

FIG. 16B

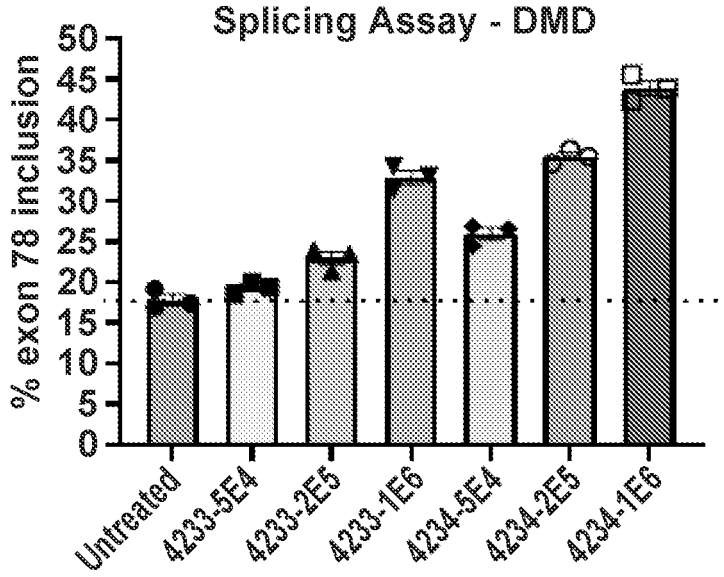


FIG. 16C

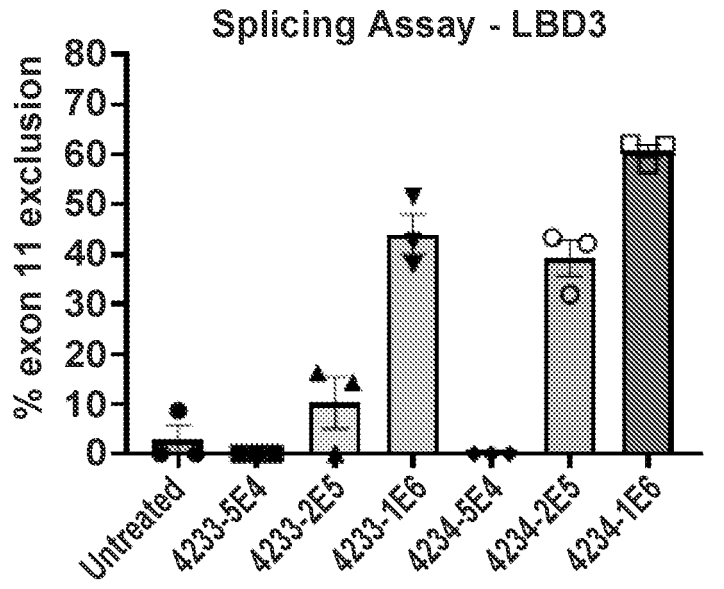


FIG. 16D

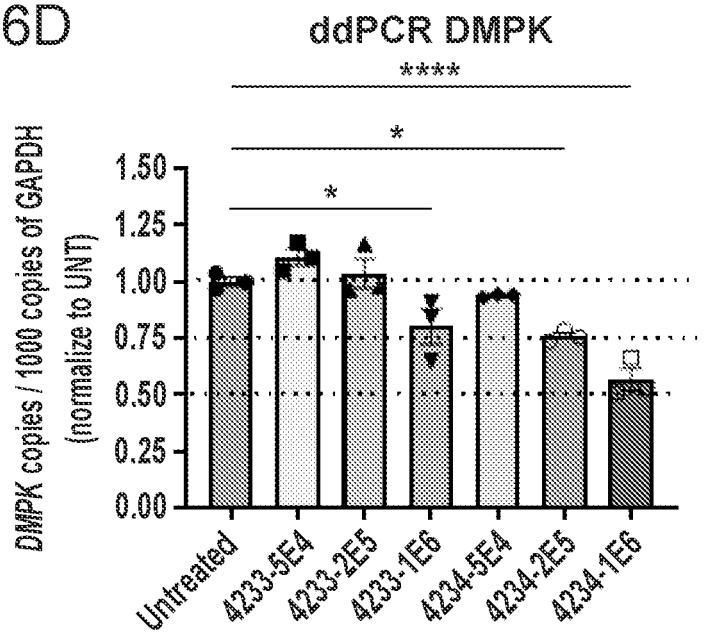


FIG. 17A

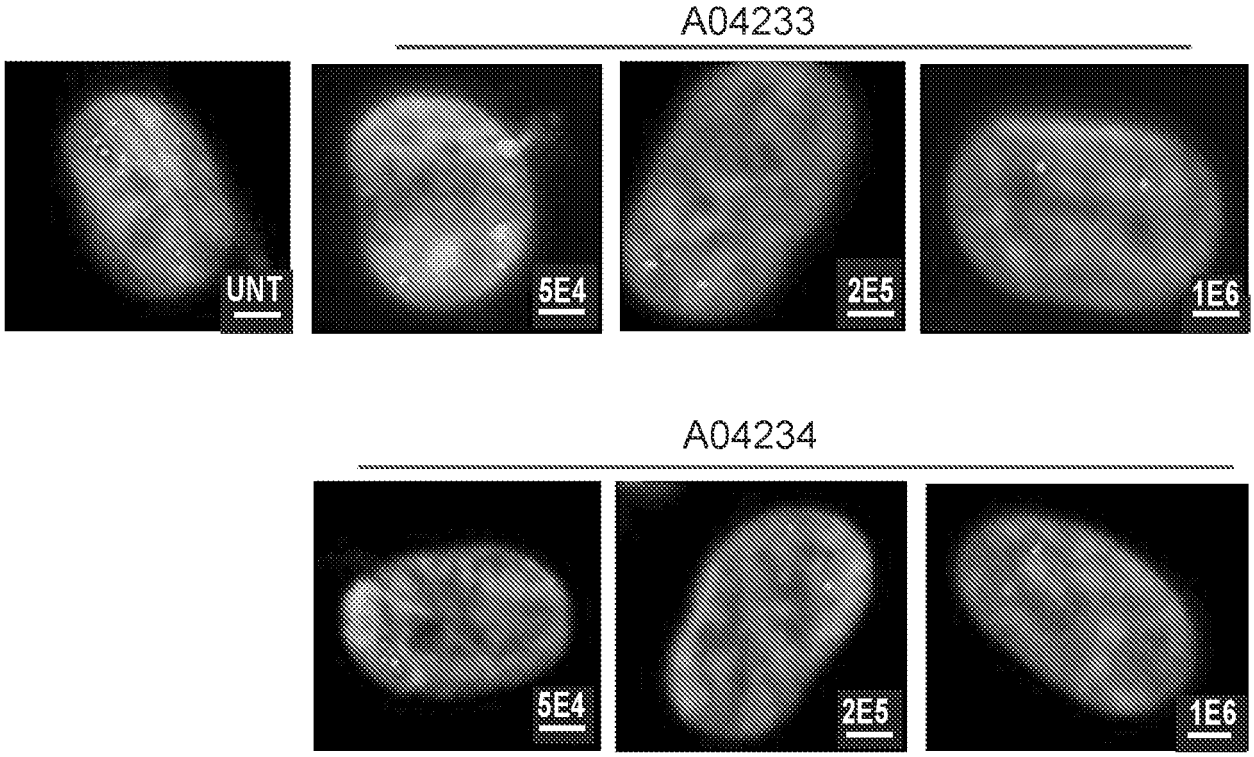


FIG. 17B

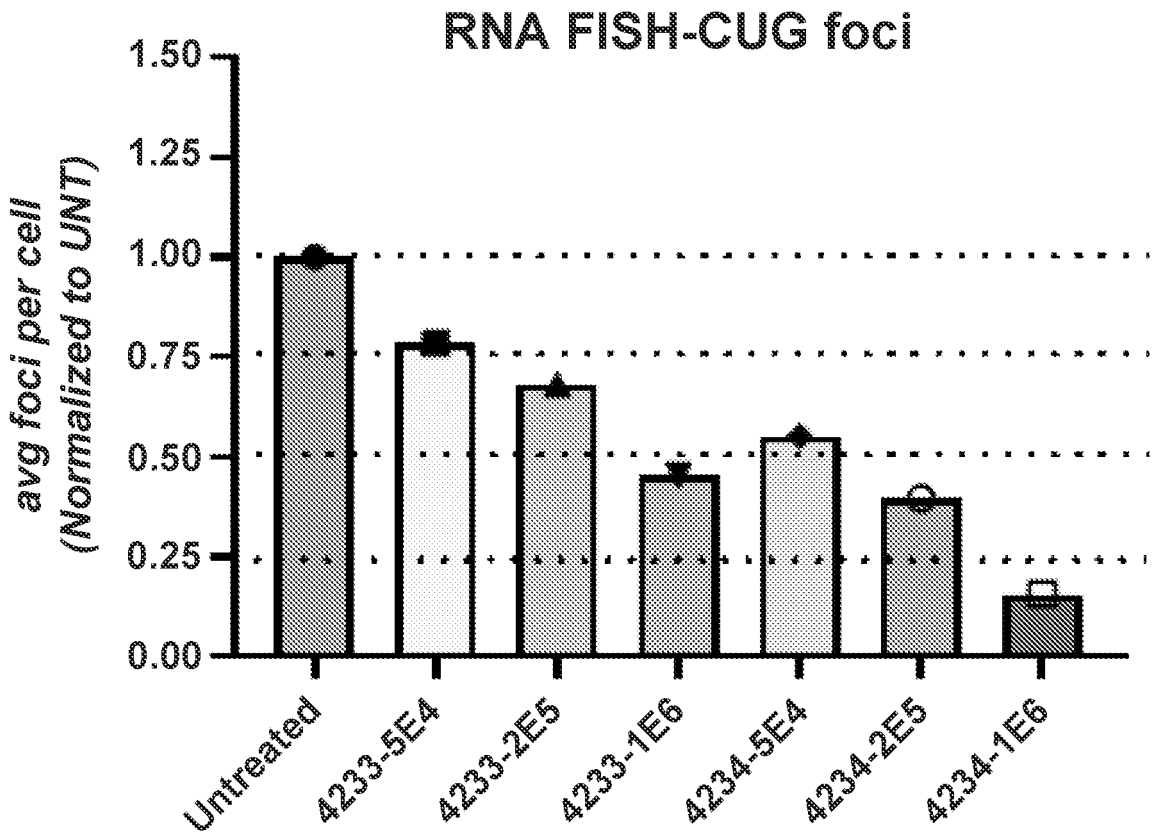


FIG. 18A

Vector	MOI	Readouts
A04390: hU7p_U7CAG15_ hU1p_U7CAG15 snRNA	MOI 1e6, 1e5	MSD for soluble HTT 2 weeks post-transduction

FIG. 18B

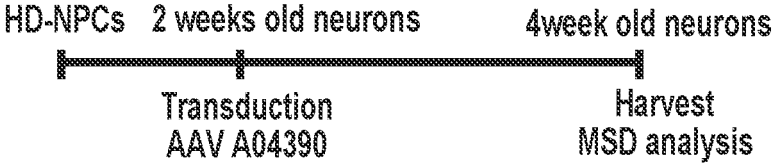


FIG. 18C

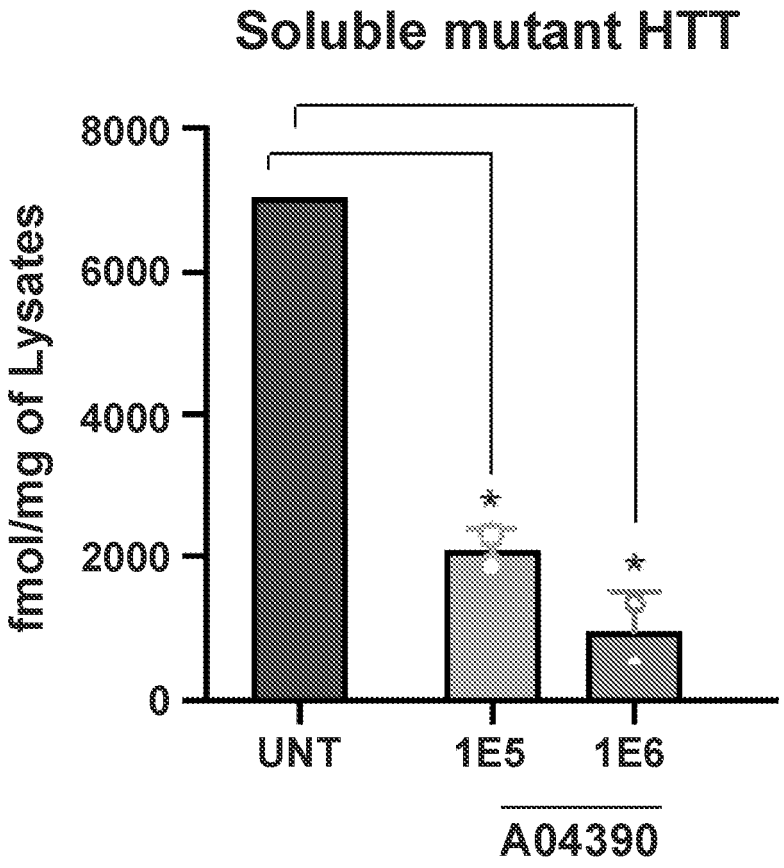


FIG. 19B

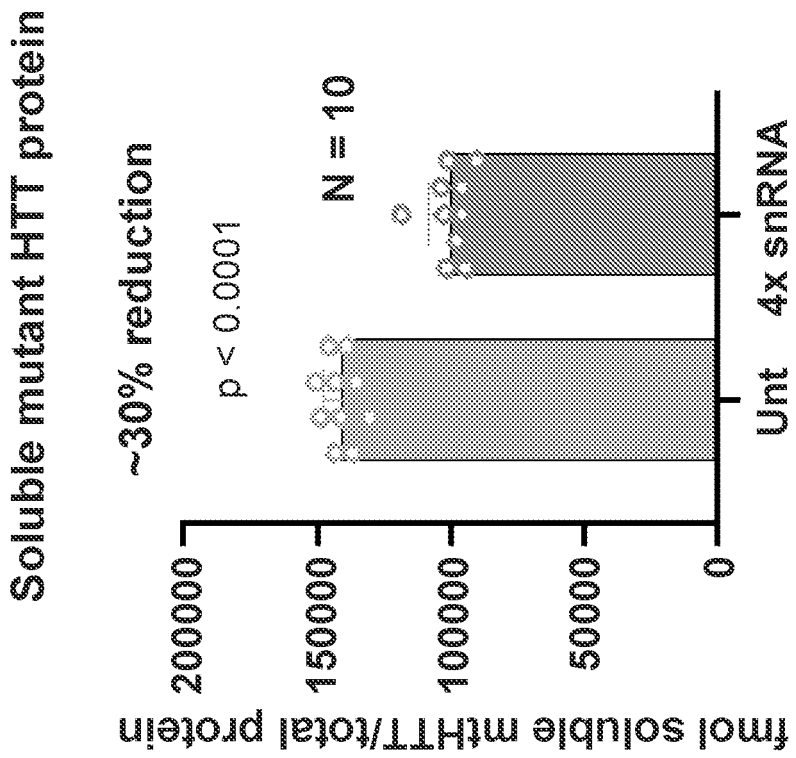


FIG. 19A

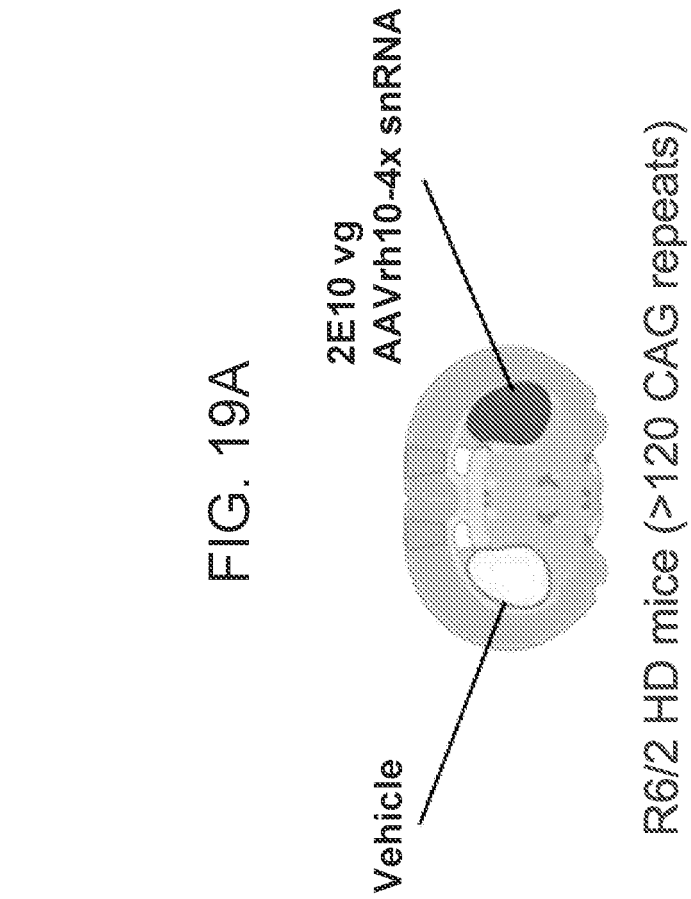


FIG. 20A

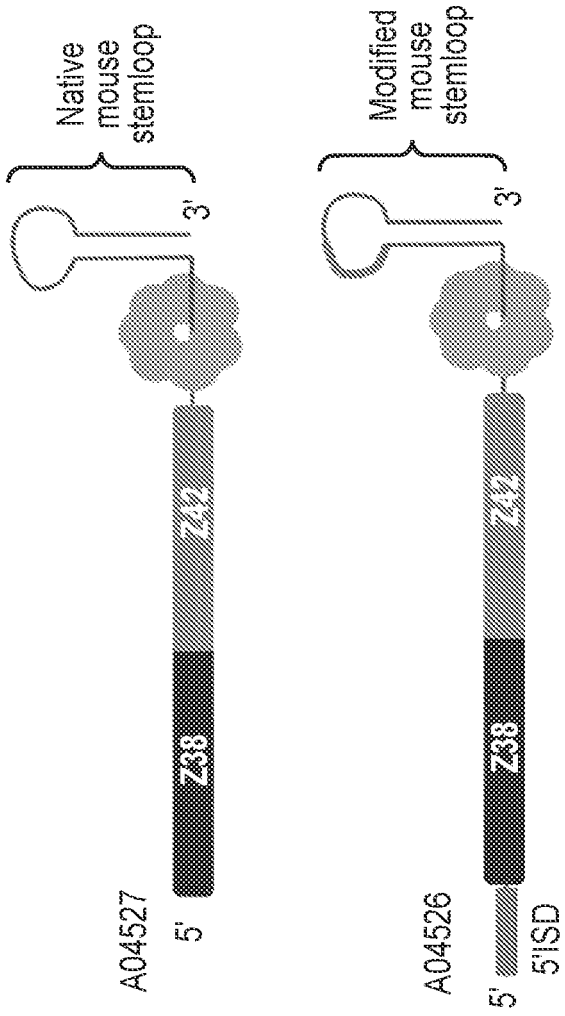
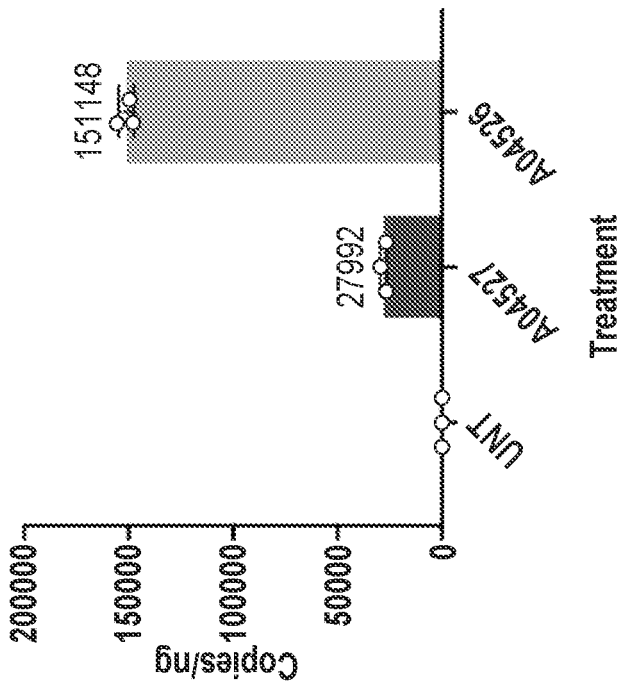


FIG. 20B



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